

Contact Dermatitis in Saffron Workers: Clinical Profile and Identification of Contact Sensitizers in a Saffron-Cultivating Area of Kashmir Valley of North India

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Background: Saffron, a bulbous perennial plant belonging to Iridaceae family, is the most expensive cultivated herb that is widely used for industrial and nonindustrial purposes. However, besides its attractive and valuable properties, contact dermatitis due to saffron is an uncommon reported entity.

Objectives: The aims of this study were to determine the clinical pattern patch-testing profile of contact dermatitis in saffron workers and to identify the most common allergens/sensitizers.

Material and Methods: One hundred ten saffron workers were patch-tested with 39 allergens, which included Indian standard series antigens, plant series antigens, and extracts from different parts of saffron flower.

Results: The allergens in Indian standard series accounted for 52.44% of positive reactions. Plant series and different parts of saffron accounted for 47.56% of the positive reactions. Among those patients with positive responses to the supplemental saffron allergens, 83.3% were of present or past relevance.

Conclusions: The data observed in the present study confirm that the saffron dermatitis is a distinct clinical entity with characteristic clinical presentation and has a strong significance as an occupational allergen in those handling this plant. Patch testing with different parts of saffron flower has a role to play in finding out the etiological cause.

Saffron plant (*Crocus Sativus L.*) is a bulbous perennial plant, belonging to the Iridaceae family and to the genus *Crocus*.¹ It is widely cultivated in Iran, India, Greece, Italy, and Spain and is regarded as the most expensive cultivated herb, also known as red gold in producing countries. This reverence emanates from the facts that main management techniques and cultivation are carried out manually, a huge quantity of flowers is needed to obtain a single gram of it, and it is widely used as a spice and dye as well as in preparation of perfumes and cosmetics.²⁻⁴ Saffron has been extensively used in traditional medicine, as well as in modern medicine, making it a big storehouse of many health benefits.⁵⁻¹⁰ In

morphology, saffron plant consists of corm, leaves, flowers consisting of 3 violet sepals and 3 similar petals together, anther, and stigma (Fig. 1). Growth pattern of the saffron plant can be divided into 3 stages, namely, flowering during autumn (October-November), vegetative stage throughout winter, and formation of corms (Table 1).¹ Besides undeniably attractive and valuable properties, various adverse effects due to saffron such as cardiovascular, hematologic, anaphylactic reactions, and pollen food syndrome have been reported.¹¹⁻¹³ Due to the need for manual labor at all stages of cultivation, cutaneous adverse effects such as allergic contact dermatitis and airborne contact dermatitis (ABCD) due to saffron, particularly during saffron-growing and saffron-harvesting season in those who come in contact with this plant have also been reported.^{14,15} The aims of this study were to study the clinical pattern and patch-testing profile of contact dermatitis in saffron workers and to identify and determine the most common allergens/sensitizers causing contact dermatitis in them.

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MATERIALS AND METHODS

The present study was conducted in collaboration with Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir in the saffron-cultivating area of Pampore in Kashmir.

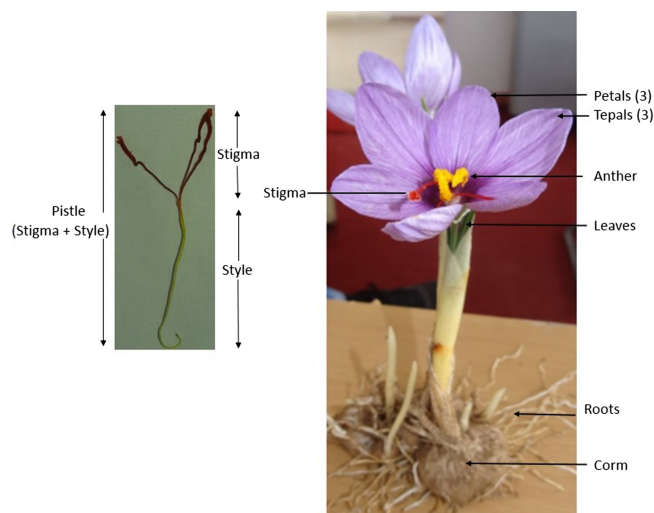


Figure 1. Morphology of the saffron flower.

Study Population

The study population comprised 110 saffron workers with history and clinical evidence of contact dermatitis caused by either saffron flower or exacerbating during saffron-growing and saffron-harvesting season. A detailed history was taken, and thorough clinical examination was carried out in each patient.

Patch Testing

All patients were patch-tested with Indian standard series (ISS) antigens obtained from Systopic laboratories and approved by Contact and Occupational Dermatitis Forum of India (Table 2), plant series antigens obtained from Chemotechnique Diagnostic

TABLE 1. Growth Pattern of Saffron Plant and Nature of Work During Each Stage

Life Stages of Saffron Plant	Worker's Job
Formation of corms	
Withering of leaves (May)	Corm formation/planting: outdoor activity done manually
Cormlets uprooting (July-August)	
Corm planting (September-October)	
Flowering	
During autumn (October-November)	Collection of saffron flower: outdoor activity done manually
	Stigma excision: indoor activity done manually
Vegetative stage	
Throughout winter under snow (December-April)	No major outdoor saffron-growing activity done; mostly involved in marketing and packaging of harvested saffron
Production of new corms	

TABLE 2. ISS Recommended by Contact and Occupational Dermatitis Forum of India (Systopic)

Allergens	Concentration, %
Vaseline	100.0
Wool alcohols	30.0
Balsam of Peru	25.0
Formaldehyde	1.1
Mercaptobenzothiazole	2.0
Potassium dichromate	0.5
Nickel sulfate	5.0
Cobalt chloride	1.0
Colophony	20.0
Epoxy resin	1.0
Paraben mix	15.0
Phenylenediamine	1.0
Parthenium	0.1
Neomycin sulfate	20.0
Benzocaine	5.0
Chlorocresol	1.0
Fragrance mix	8.0
Thiuram mix	1.0
Nitrofurazone	1.0
Black rubber mix	0.6

(Sweden) and marketed by Systopic Laboratories (India) (Table 3), and extracts from different parts of saffron plant that included corm, leaves, flower, stigma, and anther. Thirty-eight antigens were applied to the upper back of each patient, and patch-test readings and interpretation were done according to criteria laid by International Contact Dermatitis Research Group on days 2 and 4.¹⁶ An assessment of the relevance of each patch positive reaction to the patient's presenting dermatitis was also made. To rule out any irritant reactions caused by saffron plant extract, patch testing was also performed in 20 healthy controls.

TABLE 3. Plants Series Antigens (Chemotechnique)

Allergens	Concentration, %
<i>Anthemis nobilis</i> extract	1.0
Diallyl disulfide	1.0
<i>Arnica montana</i> extract	0.5
<i>Taraxacum officinale</i>	2.5
<i>Achillea millefolium</i> extract	1.0
<i>Propolis</i>	10.0
<i>Chrysanthemum cinerariaefolium</i>	1.0
Sesquiterpene lactone mix	0.1
α -Methylene- γ -butyrolactone	0.01
<i>Tanacetum vulgare</i> extract	1.0
Alantolactone	0.033
Lichen acid mix	0.3
Parthenolide	0.1
<i>Chamomilla recutita</i> extract	1.0

TABLE 4. Clinical Patterns in Allergic Contact Dermatitis to Saffron Plant (N = 110)

Clinical Pattern	n (%)
Chronic hand eczema	83 (75.50)
Hands plus forearms/arms	11 (10)
Face plus forearms plus hands (exposed areas)	4 (3.60)
Face	2 (1.80)

Preparation of Saffron Plant Extract

Saffron corms and whole saffron flowers are composed of tepals, stamens, leaves, and pistils collected from the saffron-cultivating area of Pampore in Kashmir. The saffron plant extract was prepared according to the method recommended by Hjorth and Wilkinson¹⁷ for other bulbous plants. An extract of each part was prepared by shaking with acetone (80% in water) for 90 minutes. After vacuum evaporation, the extract was kept in a desiccator. One percent of the extract in 70% ethanol was used for patch testing.

Saffron samples were analyzed according to ISO 3632 trade standard (ISO/TS 3636,2003). High-performance liquid chromatography (HPLC) was performed to evaluate the composition of saffron flower. The details of this standard procedure are presented in a study published by co-authors previously.¹⁸

RESULTS

One hundred ten patients (males, 72; females, 38) clinically suspected of having contact dermatitis due to saffron flower were enrolled in the study. Twenty consecutive healthy controls were also patch-tested with saffron extract to rule out any irritant reactions caused by the saffron plant extract.

The majority of the cases (40%, 44/110) belonged to the age group of 31 to 40 years. The mean age of the study group was 39.5 years with an SD of 13.8 (39.5 [13.8]).

Itching was the most common symptom that was seen in 81% (89/110) of the patients. History of atopy and palmoplantar hyperhidrosis was observed in 21.8% and 15.45% of patients, respectively.



Figure 2. Hand eczema involving the tips of the thumbs and index fingers of both hands.



Figure 3. Close-up view of the same patient showing erythema, crusting, and fissures.

Morphology of the lesions varied according to the phase of dermatitis. Erythema, papulovesicles, erosions, oozing, and crusting were observed during the acute stage, whereas lichenification, fissures, and hyperpigmentation were the most common morphological patterns present during the chronic stage.

Hand eczema was the most common clinical pattern identified. Pattern of the dermatitis corresponded to the area of hands coming in contact with the saffron plant and was symmetric in most of the cases. The tips of index finger and thumb were the most frequent part involved. Most of the cases had involvement of hands without impact on any other body surface areas; however, spread to other areas, which included the face, legs, and abdomen, was observed (Table 4, Figs. 2–4).

Eighty-two reactions were observed to 38 allergens applied for patch testing. Thirty of these 82 reactions were doubtful, and second reading on D6/7 was performed to evaluate for occurrence



Figure 4. Chronic hand eczema symmetrically involving the tips of the thumbs and index fingers, and palms of both hands, after contact with stigma.

TABLE 5. Results of Patch Testing With Saffron Plant Extract and Characteristics of the 15 Patients Who Tested Positive

Patient Number	Sex	Clinical Pattern	Morphological Part	Patch-Test Reading	Relevance	ISS	Plant Series
1	M	Hand eczema	Corm Pistil	+ +	Old Current	—	—
2	M	Hand eczema	Pistil	+	Old	—	<i>Arnica montana</i> extract
3	F	Hand eczema	Corm	++	Not known	—	
4	M	Hand eczema	Corm	+	Current	Nickel	
5	M	Hand eczema plus forearm	Stamen Corm	+ +	Old Current	—	—
6	F	Hand eczema	Corm Pistil	+ ++	Old	—	—
7	F	Hand eczema	Pistil	+	Old	—	—
8	M	Hand eczema	Pistil	+	Current	Cobalt	<i>Anthemis nobilis</i> extract
9	M	Hand eczema plus forearm	Corm	+	Not known	—	
10	M		Petal	+	Old	—	—
11	F	Hands, forearm and face	Corm	+	Old	Balsam of Peru	—
12	F	Hand eczema	Stamen	+	Old	—	—
13	M	Hand eczema	Corm	++	Current	—	α -Methylene- γ -butyrolactone
14	M	Hand eczema	Corm	+	Current	—	
15	M	Hand eczema	Pistil	+	Old	Potassium dichromate	—

of delayed positive reactions. However, none of these reactions was positive and therefore they were not included. Of the 52 positive reactions, 29 were observed to ISS antigens, 18 were observed to different parts of saffron flower, and 5 were observed to plant series antigens.

Of the 18 positive reactions observed in 15 patients, corm was the most common morphological part causing contact dermatitis (9 reactions), followed by stigma (6 reactions), anther (2 reactions), and sepals/petals (1 reaction). Fifteen (83.3%) of 18 positive patch tests to saffron plant were clinically relevant (Table 5).

Composition of saffron flower extracted by HPLC is demonstrated in Tables 6 and 7.

DISCUSSION

Saffron is widely grown in Pampore province of Kashmir, North India. All stages of saffron cultivation and management are carried out manually, and the resultant friction, trauma and its causes can contribute to major source of primary sensitization, which eventually

results in contact dermatitis. Dermatitis may occur at any stage of saffron flower cultivation and even during the final stage of packing for storage or commercial use. Cultivation of the saffron plant is usually a family labor activity done by seasonal workers, often women and children, who leave their jobs if seriously sensitized. Saffron is grown by corms. There is no seed setting in saffron owing to its triploid nature making it sterile. The corms are planted directly into the soil, and flowers emerge from the corms in the month of October. Greenhouses are not needed for saffron, and the flowers are harvested manually by simple picking with hands. Saffron picking in Kashmir is not mechanized.¹⁸ The cutaneous adverse effects of saffron reported so far have been seen in those who are engaged in family enterprises and small firms. However, these studies are confined to few anecdotal reports only.^{14,15} Due to lack of studies, general frequency of saffron contact dermatitis is unknown.

In our study, 52 positive patch-test reactions to 38 antigens applied were observed. Of 20 antigens in ISS, 29 positive reactions were recorded (nickel, 7; cobalt, 6; PPD, 4; potassium dichromate,

TABLE 6. Saffron Flower Composition (Range in g/100 g on Dry Weight Basis) (Photometric Absorption Unit)

Flower Part	Ash	Protein	Lipids	Carbohydrates	Reducing Sugars
Tepal	6–6.2	8–8.2	1.9–2.1	59–68.9	35.9–45
Stamen	10.9–11.6	23.9–24.1	10.6–10.8	33–33.8	4.0–4.5
Style	8–8.6	11.4–11.8	3.2–3.7	68–71.2	14.2–16.2
Pistil	6.5–7	13.5–13.8	8.5–8.6	62.2–62.3	15.9–16.9

TABLE 7. Mineral Composition (Range in g/100 g on Dry Weight Basis)

Minerals	Tepals	Stamens	Style	Stigma
P	0.21–0.24	0.57–0.59	0.29–0.30	0.33
Mg	0.09–0.10	0.30–0.31	0.18	0.13–0.14
Ca	0.12–0.13	0.21–0.22	0.34–0.35	0.10–0.11
Fe	0.02–0.03	0.02–0.03	0.04	0.01
K	1.31–1.37	3.75–3.80	1.79–1.83	1.47–1.49
Na	0.01	0.01	0.01–0.02	0.01
Glucose	11.10–11.18	5.70–5.75	8.10–8.30	7.35–7.45
Fructose	0.40–0.61	1.30–1.38	0.50–0.58	0.35–0.43
Sucrose	0.18–0.25	—	—	—
Maltose	0.11–0.16	—	0.05–0.08	—
Inositol	0.23–0.29	0.69–0.76	—	0.34–0.39
Sorbitol	—	0.10–0.13	—	0.23–0.26
Mannitol	0.71–0.79	—	—	—

4; formaldehyde, 3; parthenium, 2; balsam of Peru, 1; MBT, 1; neomycin, 1). These figures were comparable with local data published earlier.¹⁹

Fifteen workers showed reaction to at least 1 allergen from a different saffron extract. Eighteen reactions were observed. Sensitivity to corm (9 of 18 reactions) was found to be the most common cause of dermatitis due to saffron flower followed by stigma (6 reactions) and anther (2 reactions), and a single reaction was observed caused by sepals. To our knowledge, this is the first study to report contact dermatitis caused by saffron corms/bulbs. In an attempt to study occupational allergy in saffron workers, Feo et al¹⁴ carried out prick test and RAST, with saffron pollen, stamen, and pistil extracts, in 50 workers and evaluated the cutaneous and specific antibody responses. Three of them were sensitized to saffron pollen and stamen proteins, giving prick and RAST positive values. Furthermore, using SDS-PAGE immunoblotting and high-resolution gel-filtration chromatography, these authors were able to detect 15.5 kd allergen with prololinic nature in pollen and stamens. No allergenic components were demonstrated in pistils. However, in this study, prick test and RAST test were done with stamens, pistils, and pollen. Corms/bulbs and sepals/petals were not included.

A single case report of ABCD caused by saffron bulb was reported in a 72-year-old female by Martinez et al.¹⁵ The authors were able to demonstrate a positive patch-test result to saffron bulbs. In our study, we did not come across any patients with ABCD due to saffron.

Saffron corm/bulbs were the most common sensitizer in our study. Bulbs of some other plants are well known to cause various well-recognized skin problems. These include tulip fingers resulting from tulip bulbs,^{20,21} lily rash or daffodil itch,^{22,23} and hyacinth itch^{17,24} resulting from irritant dermatitis due to calcium oxalate crystals present in narcissus and hyacinth bulbs respectively, hyperkeratotic lesions, and fissures in fingers, sometimes even resembling psoriasis due to a contact allergy to diallyl disulfide from bulbs of *Allium* genus, which includes onions and garlic.

Stigma/pistil was the second most frequent part of saffron flower causing contact dermatitis in our study (6 reactions). This is

in contrast to the study done by Feo et al¹⁴ in which no reaction/allergenic components could be demonstrated in pistils. Anther/stamen were next in frequency in our study (2 reactions). This is in accordance with the previous study by Feo et al.¹⁴ A single positive reaction was observed to sepals/petals.

As established by HPLC analysis and depicted in Tables 6 and 7, saffron flower is a rich source of proteins, vitamins (riboflavin and thiamine), potassium, iron, copper, zinc, sodium, and manganese. Protein contact dermatitis (PCD) is a well-recognized clinical entity, which usually presents a chronic and recurrent eczema with often episodic acute exacerbations occurring after contact with the offending allergen.^{25,26} The pathogenesis of PCD is still elusive. Since the introduction of this term by Hjorth and Roed-Petersen in 1976 in Danish food handlers,²⁷ over the years, the studies have shown conflicting results indicating the role of both type I and type IV allergic skin reactions, which is supported by the positive patch-test results, prick tests, and RAST.^{28–30}

Wuthrich et al¹² reported a 21-year-old farmer who developed a severe anaphylactic reaction a few minutes after eating a yellow rice prepared in saffron and mushrooms. These authors were able to demonstrate positive skin test and RAST to saffron and suggested that saffron was the cause of the life-threatening anaphylactic reaction. Positive skin tests including patch tests and RAST to saffron extracts were confirmed by other authors also.^{13–15}

As far as we know, there are no publications on the association of PCD as a causative mechanism of saffron dermatitis. Our study found the possible role of PCD as a causative mechanism in contact dermatitis due to saffron, which should be confirmed by future comprehensive and in-depth studies focusing on patch testing, skin prick test, and RAST. Doing so may further increase the yield of positive reactions and hence the diagnosis and better management.

Henceforth, saffron has a strong significance as an occupational allergen in those handling the saffron plant in different geographical regions of the world, and therefore, saffron dermatitis needs to be recognized as a separate entity. Further studies are also needed to confirm and verify these points as well as to isolate and quantify the allergens/sensitizers of different parts of the saffron plant for standardization and inclusion in patch test/RAST series.

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