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Title: Phytodermatitis in East and Southeast of Turkey: A Prospective Study

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Phyto dermatitis in East and Southeast of Turkey: A Prospective Study

ABSTRACT

Objective: Some plants may cause cutaneous side effects called phyto dermatitis due to skin contact. Plants that cause phyto dermatitis vary according to countries and regions. The aim of this study was to examine the phyto dermatitis cases seen in Turkey's east and southeast and compare them with phyto dermatitis cases seen previously in the literature in these provinces and to revise the literature.

Material and Methods: In this study, 34 patients with phyto dermatitis were prospectively evaluated. The demographic and clinical characteristics of the patients such as age, sex, affected areas, dermatitis type and plant name were recorded.

Results: Phytophotodermatitis (PPD) developed in 7 (20,5%) of 34 patients. PPDs occurred after contact of *Heracleum persicum*, *Ferula orientalis* and *Chaerophyllum macropodum* Boiss. Two (5.8%) patients developed allergic contact dermatitis due to *Xanthium strumarium*. Irritant contact dermatitis (ICD) developed in 25 patients (73.5%). ICD was most frequently associated with *Tragopogon porrifolius* (8 patients). In other patients, ICD was developed due to *Ranunculus arvensis*, *Mentha pulegium*, *Euphorbia helioscopia*, *Heracleum persicum*, *Malva sylvestris*, *Mandragora autumnalis*, *Plantago major* and *Rheum ribes*.

Conclusion: In our study, we determined the cases of PPD caused by *F. orientalis* and *Chaerophyllum macropodum* Boiss, which were not previously described in the literature, and ICD which was caused by *R. ribes*. Clinicians should be aware that cutaneous reactions due to these plants may develop. Our study is the first comprehensive and prospective study on phyto dermatitis in Turkey. More studies are needed to determine causes and prevalence of phyto dermatitis in Turkey.

Keywords: Allergic contact dermatitis; Phytophotodermatitis; Irritant contact dermatitis; Turkey

INTRODUCTION

Plants have been used for medical purposes since ancient times. Their use in alternative therapies is becoming increasingly popular worldwide. Some plants may cause cutaneous side effects called phytodermatitis due to skin contact^{1,2}.

Phytodermatitis is classified as phytophotodermatitis (PPD), irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). PPD is a type of phototoxic dermatitis due to psoralene, a photosensitive substance found in plants³. ICD is developing after unintended contact with the plant or due to the use of some plants as an alternative treatment method. This reaction develops due to substances such as ranunculin, mandragorine, triterpenoids, guaianolides, malvin and polyphenols found in plants^{1,4-7}.

Phytodermatitis often occurs due to plants belonging to the family Asteraceae, Urticaceae, Alliaceae, Primulaceae, Hennadiaceae and Cactaceae. The incidence of phytodermatitis and the plants that cause phytodermatitis vary according to the countries and regions^{2,3,7-9}.

The aim of this study was to examine the phytodermatitis cases seen in Turkey's east (Van province) and southeast (Sanliurfa province) and compare them with phytodermatitis cases seen previously in the literature in these provinces and to revise the literature.

MATERIAL AND METHOD

Thirty – four patients who were admitted to Van Training and Research Hospital, Şanlıurfa Training and Research Hospital and Harran University Medical Faculty Dermatology outpatient clinics and diagnosed as phytodermatitis between September 2015 and October 2018 were evaluated prospectively. The demographic and clinical characteristics of the patients such as age, sex, affected areas, type of dermatitis and plant name were recorded. Plants that cause phytodermatitis were evaluated by the Department of Botany. In order to confirm the diagnosis in patients who were thought to have ICD and ACD with clinical findings, we made patch test with different parts of the plants such as flowers, leaves and stems. In addition, in patients who were thought to have PPD with clinical findings, we made a photopatch test with different parts such as flowers, leaves and stems. Statistical analysis was performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) program.

RESULTS

Twenty-three (67.6%) of the patients were male and 11 (32.4%) were female. The mean age was 31.9 (range 9 to 67 years). The lesions were located on the forearm of 16 patients, on the legs of 5 patients, on the knee of 3 patients, on the hand of 3 patients, on the back of 2 patients, on the abdomen of 1 patient, on the face of 1 patient, on the foot of 1 patient, on the forearm-neck of 1 patient and on the leg-abdomen-back skin of 1 patient.

In total, 7 (20.5%) of 34 patients were diagnosed with PPD. PPD occurred after contact of *Heracleum persicum* in 3 patients, *Ferula orientalis* in 3 patients, and *Chaerophyllum macropodium* Boiss in 1 patient. ACD developed in 2 (5.8%) patients. All cases of ACD caused due to *Xanthium strumarium*.

ICD developed in twenty-five (73.5%) patients. ICD was most frequently associated with *Tragopogon porrifolius* (8 patients). In other patients, ICD was developed due to *Ranunculus*

arvensis (5 patients), *Mentha pulegium* (3 patients), *Euphorbia helioscopia* (3 patients), *Heracleum persicum* (2 patients), *Malva sylvestris* (1 patient), *Mandragora autumnalis* (1 patient), *Plantago major* (1 patient) and *Rheum ribes* (1 patient).

The general characteristics of the plants and the resulting skin reactions are indicated in Table 1. (Table 1)

DISCUSSION

PPD is a photosensitive reaction that occurs after oral ingestion of plants or after contact to skin and exposure to sunlight. PPD is caused by plants belonging to a small number of families such as apiaceae, rutaceae and moraceae. Children and gardeners are particularly at risk for PPD⁹⁻¹¹. In two separate studies conducted in eastern Turkey, it was reported that the PPD was developed due to *Chenopodium album* belonging to the Chenopodiaceae family and *Plantago lanceolata* belonging to the Plantaginaceae family^{2,12}. In our study, PPD, was developed due to *Heracleum persicum* (Figure 1), *Ferula orientalis* and *Chaerophyllum macropodium* Boiss which are belonging to Apiaceae family.

The Apiaceae family is a family of flowering plants that includes aromatic fragrant plants^{6,11,13}. Most of the members of this family are psoralen rich and have been shown to cause phototoxic reactions⁹. The known phytochemical components of *H. persicum* are terpenoids, triterpenes, furocoumarins, flavonoids and alkaloids^{6,13}. *F. orientalis*, another member of the Apiaceae family, is frequently used for the treatment of headache, arthritis and diabetes. *F. orientalis* contains α -pinene, β -pinene, camphene, sabinene and naphthalene¹¹. Previous cases of PPD due to *H. persicum* have been reported in the literature⁹. However, as far as we know, there are no cases of PPD due to *F. orientalis* and *Chaerophyllum macropodium* Boiss.

ACD, another phyto dermatitis due to plants, develops frequently in the USA due to toxic ivy of the toxicodendron species¹⁴. In a study by Uce Ozkol et al conducted in eastern Turkey, ACD occurred in two patients due to *Eryngium billardieri* belonging to Apiaceae family². There were no ACD cases due to toxicodendron species in our study. In our study, ACD developed in two patients due to *X. strumarium* belonging to Asteraceae family (Figure 2). Guin identified ACD cases in one or more localized areas due to *Xanthium* species. This reaction is due to sesquiterpene lactone, the major allergic component found in the extracts of the plants⁴.

Another cutaneous reaction due to plants is ICD. In the east and southeast of Turkey, complementary and alternative treatment methods are frequently used by patients and ICD cases may have been seen. In a study conducted in the east of Turkey, the most common cause of ICD was found as *R. kotschy*². In our study, ICD was most frequently related to *T. porrifolius* (Figure 3) belonging to Asteraceae family. ICD case related to *R. kotschy* was not seen.

The Asteraceae family, including *T. porrifolius*, is the second largest flowering plant family¹⁵. ICD due to plants belonging to this family is frequently seen. Major allergenic compounds of these plants are sesquiterpene lactones such as alantolactone, dehydrocostuslactone, costunolide, guaianolides, germacranolides, eudesmanolides, usually found in the leaves and in the liquid portion of the pollen^{8,9,16}.

The other plants that caused ICD in our study were *R. arvensis*, *M. pulegium*, *E. helioscopia*, *H. persicum*, *M. sylvestris*, *M. autumnalis*, *P. major* and *R. ribes*.

Members of the Ranunculaceae family, including *R. arvensis*, are herbaceous plants with five-leaf yellow flowers, especially seen in spring and summer¹. This plant is applied topically to the painful area in alternative medicine and covered with a nylon. This plant grows in Eastern

Anatolia and Southeastern Anatolia in our country. *Ranunculus* species contain ranunculin having irritant properties. Ranunculin is the precursor to protoanemonin, a toxic substance, and the actual toxic effect is thought to be caused by protoanemonin. With skin contact of the plant, ranunculin is transformed to protoanemonin. When applied to the skin surface, subepidermal dissociation and bulla formation are seen by the destruction of the sulfur bonds^{1,17}.

In a study of 25 patients with phytocontact dermatitis caused by the species of the *Ranunculaceae* family conducted by Akbulut et al., 5 cases were reported to be associated with *R. arvensis*. The authors stated that most of the cases are middle aged and older women, the lesions are usually seen in the knees and legs and the patients use these plants because of complaints such as arthritis and myalgia¹. In our study, the patients who developed ICD due to *R. arvensis* were middle and advanced elderly.(Figure 4) The lesions had been usually located on the knees and legs, and the patients had been developed lesions 8-12 hours after using this plant topically for arthritis and myalgia.

The *Lamiaceae* family is found in the group of perennials and is known as aromatic plants. *M. pulegium* is a flowering plant belonging to the family *Lamiaceae*. *M. pulegium* shows toxic effects to the liver when taken orally, menthofuran is responsible of the toxic effect¹⁸. There is a case of ACD due to *M. pulegium*, confirmed with positive patch test and negative prick test. Limonene, the first cyclic intermediate in the biosynthesis of monoterpenes in *M. pulegium*, was reported to be responsible for this reaction¹⁹. In addition, a case of urticaria associated with *M. pulegium* was reported and menthol was thought to be responsible for this reaction²⁰. In our study, ICD developed in 3 patients due to *M. pulegium*(Figure 5). In these cases, *M. pulegium* was applied topically to the abdomen, back and leg area and covered with nylon and kept for at least 8 hours. In all three cases, bullous lesions developed and postinflammatory hyperpigmentation remained after treatment.

Euphorbiaceae is a family of flowering plants, mostly herbaceous²¹. *E. helioscopia* produces a typical milky peduncle that can cause bullous lesions and toxic reactions after contact with the skin. The structure of 12-deoxyphorbol-13-phenylacetal-20-acetate is responsible for chemical irritation²². Five cases of ICD due to *E. helioscopia* were reported in the southeast of Turkey. All of these cases were pediatric patients and after the contact with the plant, bullous lesions developed^{21,22}. In our study, ICD developed due to *E. helioscopia* in 3 patients(Figure 6). Three cases were children, the lesions were formed on the forearm skin after contact with the plant. Since our patients were evaluated at least 1 week after lesion formation, bullous lesions were not seen, only postinflammatory hyperpigmentation was observed.

M. sylvestris in Malvaceae family is an herbaceous plant that opens bright yellow flowers between April and July. Anti-inflammatory, hepatoprotective, antioxidant and antimicrobial effects of *M. sylvestris* have been reported^{23,24}. In leaves and flowers of *M. sylvestris*, flavonoids, malvin, malvone A, coumarins, polyphenols and tannins are found²³. To the best of our knowledge, only one case of ICD due to *M. sylvestris* has been reported in the literature. This 76-year-old patient applied *M. sylvestris* to her legs topically because of her rheumatic complaints and three days later bullous lesions developed²⁴. In our case, because of back pain, *M. sylvestris* was applied topically to the lumbar region and 12 hours later, erythematous localized vesicular lesions developed(Figure 7).

Mandragora species belonging to Solanaceae family have sedative, aphrodisiac, analgesic and anesthetic properties²⁵. *Mandragora* species include alkaloids such as mandragorine, hyoscyamine, scopolamine, apoatropine and atropine⁵. The cases of poisoning caused by the systemic use of *M. autumnalis* have been reported²⁶. In addition, a case of ICD in the knee due to topical application of *M. autumnalis* has been reported in our region². In our study, ICD developed in the knees of a patient due to topical application of *M. autumnalis*(Figure 8).

P. major is a plant belonging to Plantaginaceae family growing in temperate regions. *P. major* contains caffeic acid derivatives include glycosides, alkaloids, volatile compounds, triterpenoids, phenolic acids and flavonoids²⁷. In our region, two cases of ICD due to topical application of *P. major* were reported²⁸. In our study, ICD developed in one patient due to topical application of *P. major*(Figure 9).

R. ribes is a perennial herbaceous wild plant belonging to the Polygonaceae family. It is the only species of *Rheum* grown in our country. It grows in the Eastern Anatolia Region of our country. It contains plenty of vitamin A, C and E, oxalic acid and selenium²⁹. *R. ribes* is consumed as food in the Van province in spring. To the best of our knowledge, there are no reported cases of phytodermatitis reported in the literature due to *R. ribes*. In our study, ICD developed in the forearm of a child patient after contact with *R. ribes*.

In conclusion, we aimed to investigate phytodermatitis cases in Eastern and Southeastern Anatolia of Turkey and the plants causing phytodermatitis in the literature. In our study, we identified *F. orientalis* and *Chaerophyllum macropodium* Boiss-related PPD and *R. ribes*-related ICD which were not previously described in the literature. Clinicians should be aware that cutaneous reactions due to these plants may develop. Our study is the first comprehensive prospective study on phytodermatitis in Turkey. More studies are needed to determine causes and prevalence of phytodermatitis in Turkey.

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Figures and Table legends

Figure 1: Phytophotodermatitis and irritant contact dermatitis due to *H. persicum* and image of the plant.

Figure 2: Allergic contact dermatitis due to *X. strumarium*.

Figure 3: Irritant contact dermatitis due to *T. porrifolius* and image of the plant.

Figure 4: Irritant contact dermatitis due to *R. arvensis* and image of the plant.

Figure 5: Irritant contact dermatitis due to *M. pulegium* and image of the plant.

Figure 6: Irritant contact dermatitis due to *E. helioscopia* and image of the plant.

Figure 7: Irritant contact dermatitis due to *M. sylvestris* and image of the plant.

Figure 8: Irritant contact dermatitis due to *M. autumnalis*.

Figure 9: Irritant contact dermatitis due to *P. major* and image of the plant.

Table 1: The general characteristics of the plants and the resulting skin reactions

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Plant Name	The Plant Family	Content of the Plant	Exposure	Type of Dermatitis
X. strumarium	Asteraceae	Sesquiterpene lactones	Topically and occlusion	ACD
T. porrifolius	Asteraceae	Sesquiterpene lactones	Topically and occlusion	ACD
P. major	Plantaginaceae	Glycosides, alkaloids, volatile compounds, triterpenoid, phenolic acid, flavonoid	Topically and occlusion	ICD
M. autumnalis	Solanaceae	Mandragorine, hyoscyamine, scopolamine, apoatropine, atropin	Topically and occlusion	ICD
M. sylvestris	Malvaceae	Flavonoids, malvin, malvone A, polysaccharides, coumarins, polyphenols, tannins	Topically and occlusion	ICD
H. persicum	Apiaceae	Terpenoid, triterpen, furocoumarins, flavonoid, alkaloid	Topically and sun exposure, Topically	PPD and ICD
F. orientalis	Apiaceae	α -pinene, β -pinene, camphene, sabinene, naphthalene	Topically and sun exposure	PPD
C. macropodium Boiss	Apiaceae	Furocoumarins	Topically and sun exposure	PPD
M. pulegium	Lamiaceae	Limonen, menthol	Topically and occlusion	ICD
R. arvensis	Ranunculaceae	Ranunculin, protoanemonin	Topically and occlusion	ICD
E. helioscopia	Euphorbiaceae	12-deoxyphorbol-13-phenylacetal-20-acetate	Topically	ICD
R. ribes	Polygonaceae	Vitamin A, ascorbic acid, Vitamin E, oxalic acid and selenium	Topically	ICD
PPD: Phytophotodermatitis, ICD: Irritant contact dermatitis, ACD: Allergic contact dermatitis				









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