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RESEARCH ARTICLE

Allergic contact dermatitis caused by farnesol: clinical relevance

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Abstract

Context: The fragrance material farnesol is cited as an infrequent but important cause of allergic contact dermatitis (ACD). It is included in the fragrance mix II patch series and requires labeling in the European Union if it is used in a consumer product.

Objective: To review the existing literature to determine the causative role of farnesol in clinical contact allergy.

Materials and methods: Survey of the literature on farnesol studies; predictive and clinical elicitation tests in case reports, reviews, and abstracts.

Results: Predictive animal studies demonstrated in most cases that farnesol was a nonsensitizer. However, 2 local lymph node assays (LLNAs) indicated strong sensitization potential. Predictive human test data indicated a low potential, if any, for sensitization in human tests with farnesol at 10% or 12%. A few clinical reports indicated low-level allergy or questionable reactions to farnesol, with 5% being the most commonly used. There were also reports in which no reactions were seen.

Discussion: Predictive testing on farnesol in animals shows conflicting results depending on the study methodology used. Human predictive patch-test data also had gaps that prevented it from being definitive in pointing to a causative relationship between farnesol and contact dermatitis. The real sensitizing potential of a material can best be determined by evaluating the clinical and epidemiological data so as to help resolve the conflicting animal and human predictive test data.

Conclusions: This literature and scoring exercise showed that predictive and clinical elicitation data do not document a clear causative determination that farnesol is a frequent contact allergen. Detailed clinical relevance and patient studies should clarify the clinical problem farnesol represents.

Keywords: Patch testing; farnesol; fragrance mix; fragrance; cosmetics; clinical relevance; skin sensitization

Introduction

Farnesol is a natural organic compound found in many essential oils, including neroli, tuberose, rose, balsam, lemongrass, and musk. It is also a component of vitamin K, so it is becoming more widely used in topical consumer products, especially skin care formulations (1). Farnesol is also used in cosmetics to emphasize the floral notes of fragrances and as a natural microbicide (2) in deodorants and antiperspirants (3). It has been cited as a frequent cause of

allergic contact dermatitis (ACD) and is one of the 6 compounds composing fragrance mix II (FM II), which has been recommended for diagnostic contact allergy testing since 2005 (4). Farnesol is one of the 26 fragrance compounds requiring labeling in the European Union (EU) because of a presumed sensitization potential (5). This article reviews the published and unpublished studies on the sensitization potential of farnesol: 2,6,10-dodecatrien-1-ol, 3,7,11-trimethyl, farnesyl alcohol, trimethyl dodecatrienol, 3,7,11-trimethyl-2,6,10-dodecatrien-1-ol (Chemical Abstract

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Service [CAS] No.: 4602-84-0, European Inventory of Existing Commercial Chemical Substances [EINECS] No.: 225-004-1).

Materials and methods

Medical literature was searched using the electronic databases PubMed, Medline, Biosis, Web of Science (ISI), Academic Search Premier (EBSCO), PsycINFO, and National Center for Biotechnology Information (NCBI). Search terms included *farnesol*, *contact allergy*, *fragrance*, *contact dermatitis*, *hypersensitivity*, *perfume*, and *patch test(s)*. Study reports were obtained where allowed. If the primary report was not obtainable, an abstract was reviewed but not scored because of lack of adequate details. The Research Institute for Fragrance Materials, Inc. (RIFM) kindly made available copies of unpublished studies performed by itself or its members.

A semiquantitative analysis of these reports was made using the methodology outlined by Hostynek and Maibach (6), which is based on work by Benezra et al (7). The methodology follows a stepwise system that attempts to rule out many of the confounding factors inherent in each test method. It offers a logical progression of questions the clinician can use to assess results, including the assignment of an overall confidence score to the study on a 0–5-point scale. The criteria for evaluating a substance's allergenic potential from predictive patch-test reports included the following: 1) was the test material clearly identified, 2) were details of the test conditions provided, 3) were the tests sufficiently maximized, 4) were there adequate controls, 5) was the number of test subjects sufficient, and 6) were the results presented in sufficient detail? The principles for evaluating clinical patch-test reports included the following: 1) is the report a primary case report or a general review, 2) is information provided on the number and

condition of patients, 3) are the conditions of the patch test given, 4) are the results reported in sufficient detail, 5) is it possible to determine whether patients reacted to other materials, 6) can cross-reactions be ruled out, 7) can excited skin syndrome (ESS) be ruled out, 8) has the substance been tested in use tests, and, finally, 9) have the substance and the allergy been linked to a specific consumer product or exposure situation (6)? The scoring system for the predictive patch tests and clinical elicitation tests is provided in Table 1.

All studies were evaluated using the weight-of-evidence approach described above (6,7). Authors reviewed and scored each publication separately, then reviewed the scoring together and, if a discrepancy arose, the reasoning was discussed in detail until a resolution on the score could be reached. This double-review process allowed for consensus decision and overall good practice for the performance of a systematic review.

This article is a continuation of evaluations done by Hostynek and Maibach on other skin fragrance compounds that have been cited as important fragrance allergens (8–13).

Results

Predictive tests on animals

Six animal tests have been reported (Table 2). The degree of confidence for each test has also been designated following the criteria of Hostynek and Maibach (6) based on the Benezra et al. system (7).

Two Freund's complete adjuvant tests (FCATs) were done by Hausen et al. (14,15). Both classified farnesol as a weak sensitizer.

In 2 local lymph node assays (LLNAs), both concluded farnesol was a skin sensitizer based on EC3 (concentration of test chemical required to provoke a

Table 1. Assignment of degree of confidence for predictive and clinical elicitation reports.

Test qualification	Degree of confidence/numerical score
Meets all criteria	5
Meets criteria, but number of positives ^a /cases ^b is marginal	4
Meets criteria, but some parameters are questionable	3
Controls not apparent or small number of subjects*/Evidence does not unambiguously indicate causative role**	2
Fails several criteria; results are not considered reliable	1
Fails all criteria	0

^aPredictive test report criteria.

^bClinical elicitation report criteria.

Criteria: vehicle-treated and untreated controls; test concentration sufficient for response; use of appropriate vehicle; adequate compound purity; significant number of cases used.

3-fold increase in lymph node cell proliferation) values (16,17).

The remaining guinea pig maximization tests (GPMTs) concluded that farnesol was a nonsensitizer (18,19).

One study summary obtained from RIFM was listed as a cross-sensitization test on guinea pigs with farnesyl acetate (20). The summary lacked sufficient detail to determine test protocol details, concentration, or vehicle. No score was given to this report and it is included for review only.

Predictive tests on human volunteers

Human maximization tests (HMTs) from the mid- to late 1970s by Epstein and Kligman and unpublished synopses were submitted to RIFM and reviewed. Scoring and score criteria are included in Table 2. Overall, the tests had several deficiencies, including lack of maximization and data on controls (21–33).

Clinical elicitation tests on patients

Farnesol, a component of FM II, is included in routine diagnostic patch testing. More specific testing of eczematous patients with reactions or previous histories has been done (Table 3). These reports are examined using the criteria outlined by Hostynek and Maibach (6) to further determine the strength of causation linking adverse reactions directly to farnesol.

Tests producing reactions

Several studies showed positive reactions in those referred with a working diagnosis of ACD.

Two patients with eczema had positive reactions to farnesol, but relevance to a cosmetic product was not established (3).

One woman with axillary dermatitis used deodorant that did not contain farnesol, so clinical relevance was not established (34).

Twenty-two subjects with possible ACD had positive reactions to farnesol. Five of those subjects also reacted to other materials; however, no repeated open application test (ROAT) or provocative use testing (PUT) was done, so clinical relevance was not established (2).

In an occupational exposure study, 1 subject with chronic hand eczema was evaluated. Upon further investigation, the occupational nature was likely irritant, as there was little evidence linking causality to

any product from either the home or occupational setting (35).

A multicenter study was conducted with 2 concentrations of FM II (36). If a positive reaction to FM II was demonstrated, the individual compounds were tested. Cross-reactions occurred, so clinical relevance could not be established.

A case report described a woman with axillary dermatitis who underwent patch testing with the standard series and her deodorant (37). Review of the deodorant did not detect farnesol. Therefore, the reaction was not consistent with a product and was more likely due to a cross-reaction.

Two subjects in a multicenter study reacted to farnesol (38). They reacted positively to more than 1 material. The presence of ESS was a concern with multiple material reactions (39), and no further ROAT/PUT was performed. No causative link to an actual product use was made.

Patch testing with the 26 labeled fragrance allergens identified 38 subjects with positive results (40). These patients also reacted to other materials. No ESS testing was done, nor ROAT/PUT. The relevance of cosmetic exposure was not established.

Another multicenter study in Europe showed positive reactions to farnesol (41). Subjects underwent patch testing with FM I and 14 other fragrance materials. Subjects reacted to multiple compounds, and ESS was not excluded, nor was further ROAT or PUT done to establish a link to relevance. Causality was tentative at best.

A primary study evaluating lavender oil in Japan was done that also included farnesol as a test material (42). Farnesol was not screened for its presence in cosmetic products or for its relevance to reactions. The report's focus was lavender oil, so no further data were provided.

Patients with contact allergy to *Myroxylon pereirae* (balsam of Peru) were patch tested (43). Farnesol was present as a trace constituent of *M. pereirae*, but no further link to relevance or product use was established.

A range-finding study showed positive reactions to patch testing with farnesol (44). No relevance to clinical outcomes was explored and no further testing was conducted.

One case report of a woman with axillary dermatitis identified positive reactions that were linked to her deodorant and its farnesol constituent when it was broken out and patch tested further (45).

Tests producing no reactions

For negative studies, there is no causative link to make, so no study confidence scores were

assigned. Such reports are still noteworthy when reviewing the final profile for farnesol, so they are included in the reference section for further review (46–48).

Abstracts or reports in another language that were not translated

Several abstracts and other articles were found in which data on farnesol were lacking, could not be

Table 2. Predictive testing of farnesol.

Reference ^a	Test material identified	Type of test	Test conditions provided?	Was test fully maximized?	Were there adequate controls?	Was number of subjects sufficient?	Were results presented in adequate detail?	Final rating
14	Yes	FCAT	Yes	No, at 3%	No data	Only 10	Yes	3
15	Yes	FCAT	No	Yes	No data	No data	No	2
16	Yes	LLNA	Yes	Yes	Yes	4/dose	Yes	5
17	Yes	LLNA	Yes	Yes	Yes	4/dose	Yes	5
18	Yes	GPMT	Yes	Yes	Yes	20	Yes	5
19	Yes	GPMT	Yes	Yes	Yes	20	Yes	5
20	No	Cross-sensitization test—guinea pig	No—limited in RIFM summary	No data	No data	Only 10	No	NA
21	Yes	HMT	Yes—via RIFM summary	No, 12% only	Yes	35	Yes	3
22	Yes	HMT	Yes—via RIFM summary	No, 12% only	No data	25	Yes	2
23	Yes	HMT	Yes—via RIFM summary	No, 12% only	No data	25	No	2
24	Yes	HMT for cross-reactivity	Yes—via RIFM summary	No, 12% only	No data	1—positive to cinnamic alcohol	Yes	2
25	Yes	HMT	Yes—via RIFM summary	No, 12% only	No data	25	Yes	2
26	Yes	HMT	Yes—via RIFM summary	No, 12% only	No data	25	Yes	2
27	Yes	HMT	Yes—via RIFM summary	No, 12% only	No data	25	Yes	2
28	Yes	HMT	Yes—via RIFM summary	No, 12% only	No data	26	No	2
29	Yes	HMT	Yes—via RIFM summary	No, 10% only	No data	25	No	2
30	Yes	HMT	Yes—via RIFM summary	No, 10% only	No data	25	Yes	2
31	Yes	HMT	Yes—via RIFM summary	No, 10% only	No data	25	No	2
32	Yes	HRIPT	Yes	No, 5% only	No data	108	No	2
33	Yes	HRIPT	Yes	No, 5% only	No data	103	No	2

^aFor complete reference citations, see the reference list.

FCAT = Freund's complete adjuvant test; GPMT = guinea pig maximization test; HMT = human maximization test; HRIPT = human repeated insult patch test; LLNA = local lymph node assay; NA = not applicable; RIFM = Research Institute for Fragrance Materials.

Table 3. Clinical elicitation patch tests for farnesol.

Reference ^a	Report type ^b	Number and conditions of patients ^c	Conditions of patch testing given ^d	Patients' reacting scores ^e	Is irritancy unlikely?	Reaction to other materials? ^f	Cross-reaction (s) likely? ^g	Excited skin unlikely?	ROAT or PUT used? ^h	Linked to specific product?	Final score
3	Primary	8,521: Ecz	Yes, Dose, V = ?	2: Score?	No	Yes, 54% with multiple	Poss.	No	No	No	2
34	Primary	1: Ecz	Yes, Dose, V = ?	1: = +, ?	No	Yes, FM, cosmetic ingredients	Poss.	No	No	Other positive scores linked to fragrance in deodorant	2
2	MC	2,021: Ecz	Yes, 5% Pet	13/2,021 ?, 17/2, 021 +, 2/2,021 follicular 5/2,021 ++	No	Yes, <i>M. pereirae</i> resin and propolis	Poss.	No	No	No	2
35	Primary	1: Ecz, FM +, FM II +	No, Dose, V = ?	No	No	History of sensitization to epoxy resin, balsam of Peru, fragrance mixes	Poss.	No	No	Skin protection cream implied	2
36	MC	1,701: Ecz	Yes, 2.5% Pet, 5% Pet	20/1,701 irr, 4/1,701 + at 2.5%, 30/1,701 irr, 5/1,701 +, 1/1,701 ++ to +++ at 5%	No	Yes	Poss.	No	ROAT to FM, FM II, constituents to FM II	No	3
37	Primary	1: Ecz	No, 5% EtOH	+	No	Yes, balsam of Peru	Poss.	No	No	Other positive scores linked to fragrance in deodorant	3
38	MC	182: Ecz	Yes, 4% Pet	1.1% positivity rate, no scores	No	Yes, multiple to standard and fragrance series	Poss.	No	No	No	2
40	MC	4,238: Ecz	Yes, 5% Pet	30/4,238 +, 8/4,238 ++/+ +++	No	Yes, multiple fragrances and nickel	Poss.	No	No	No	2
41	MC	1,855: Ecz	Yes, 5% Pet	21/1,855 doubtful, 10/1,855 +	No	Yes, other FM I materials	Poss.	No	No	No	2

Table 3. continued on next page

Table 3. Continued.

Reference ^a	Report type ^b	Number and conditions of patients ^c	Conditions of patch testing given? ^d	Patients' reacting scores ^e	Is irritancy unlikely?	Reaction to other materials? ^f	Cross-reaction (s) likely? ^g	Excited skin unlikely?	ROAT or PUT used? ^h	Linked to specific product?	Final score
42	Primary	1,483: Ecz	Yes, 5% Pet	1.1% positivity rate, no scores	No	Yes, other fragrance	Poss.	No	No	No, focus of test was lavender oil	2
43	Primary	102: balsam of Peru +	Yes, 5% Pet	4/102 +	No	Yes, other balsam of Peru constituents	Yes	No	No	No, attempted to link to specific habits	2
44	MC	466: Ecz	No, 0%, 2%, 5%, 10% Pet	5/454 +?, 2/454 +, 1/454 irr at 2%, 5/456 +?, 7/456 +, 4/456 irr at 5%, 9/457 +?, 7/457 +, 2/457 irr at 10%-	No	No	No	No	No	No	2
45	Primary	1: Ecz	No, 1% Pet	1/1 ++	No	Yes, nickel sulfate, <i>M. pereirae</i> , oak moss absolute	Poss.	No	No	Yes, deodorant	3

^aFor complete reference citations, see the reference list.^bPrimary = primary report of cases; MC = multicenter study, may be reported separately; Review = primary reports cited.^cEcz = eczematous; Frag A = fragrance allergic; FM + = fragrance mix positive; FM II + = fragrance mix II positive.^dDose, V = ? = dose and vehicle unknown; Pet = petrolatum; Acet = acetone; EtOH = ethanol.^eScore? = intensity of reaction not recorded; +/– or +? = doubtful; + = mild, erythema only; ++ to +++ = more severe; irr = irritation.^fFM = fragrance mix; *M. pereirae* = *Myroxylon pereirae* (balsam of Peru).^gPoss. = cross-reactions possible but cannot be determined.^hPUT = provocative use testing; ROAT = repeated open application test.

translated, or were incomplete. No confidence scores could be assigned. They are listed in the reference section (5,49–56).

Discussion

Predictive testing on farnesol in animals showed conflicting results among the studies with high levels of confidence. The 2 LLNAs both indicated that farnesol was a skin sensitizer. The 2 GPMTs both indicated that farnesol was a nonsensitizer. The remaining FCATs had lower levels of confidence, but they both concluded that farnesol was a weak sensitizer. Such conflicting data are not uncommon. To make sense of these results, we must look at the test types more closely for information on their possible clinical relevance.

The LLNA was specifically developed as an alternative to the GPMT to evaluate and identify chemicals that lead to skin sensitization (57). Initial testing to validate the LLNA compared existing sensitization data in guinea pigs and humans and found these data to correlate approximately 90% of the time. Recent concerns have been raised about interpreting the test. Namely, there are data suggesting that the vehicle greatly affects the test outcome, either heightening or dampening the response. Irritant chemicals can give false-positive results and therefore an erroneous classification of a sensitizer (58). Both study reports on farnesol used the Organisation for Economic Co-operation and Development (OECD) guideline, which recommends an acetone/olive oil vehicle (AOO) (4:1) (59). This could be problematic because when AOO was tested alone, it gave a stimulation index (SI) of greater than 3. This adds doubt to the interpretation of the 2 LLNAs on farnesol.

The GPMT has been used extensively to determine the risk of skin sensitization to many types of chemicals. Magnusson and Kligman (60), who developed the test procedure, noted its shortcomings in cases when there were reactions to the test material. However, they found that when results showed no reactions to indicate animal sensitization, they could definitively establish a reliable estimate of safety in consumer use. Such results indicated an allergenic potential so low that “no imaginable human exposure is likely to be attended by a significant incidence of sensitization” (61). There were no animals sensitized to farnesol in either GPMT. These results may suggest to the reader that the “best” method for determining sensitization potential would be to use animal testing. This is not what we are concluding. The confidence scores assigned were only in relation to evaluating the study protocol, not the positive or negative results. One must look closely at the

overall profile to determine the relevance of patch-test results. There was no one method we found that served as a stand-alone predictor of ACD. In the case of the GPMT, a review of various guinea pig test methods attempted to correlate results to mice data from the LLNA and human data from the human repeated insult patch test (HRIPT). The authors of the review concluded that overall there was a trend for false-positive results with animal data as compared with human assays (62,63). Other research also compared the LLNA to the HMT to determine the capacity of each to predict allergy potency. The authors quantitatively showed that the LLNA was only 80% as accurate as the HMT in predicting potency for the allergens they studied (64).

The human predictive patch-test data on farnesol also had limitations that resulted in lower confidence scores. The HRIPT and HMT have been used for many years and have been refined over time to avoid confounders in the protocol. Politano and Api outlined HRIPT guidelines specifically in regard to its use with fragrance materials. They recommended a procedure to use to strengthen the validity of this method (65). McNamee and colleagues also outlined key factors that were critical to address when conducting and interpreting the HRIPT (66).

One issue with HRIPT testing for contact allergy is the concern raised by those who think any use of human volunteers for patch testing is unethical (67). Though we recognize the contentious nature of both animal and human testing, society can either expose the total consumer population or instead seek smaller numbers of volunteers providing informed consent such as the subjects utilized in the HRIPT. We know of no example of a clinical disease that has evolved from properly conducted irritation and sensitization testing. We agree with recommendations to have rigorous review of any type of test method employed for testing of contact allergy and to use it only when necessary. Human patch testing will continue to play an important role in the overall determination of ACD (65,66,68).

The real sensitizing potential of a material can best be determined by evaluating the clinical and epidemiological data (61) so as to help resolve the conflicting animal and human predictive test data. Though the criteria noted for review seem best able to qualify data from case studies but seem not to be relevant to epidemiological studies, that is not the case. The same criteria are relevant to epidemiological studies, but unfortunately they are rarely used in practice as few epidemiological studies include retests and use tests in their design. The only such report originated from the International Contact Dermatitis Research Group (ICDRG) and has not been repeated (69).

Of the reports citing clinical data, none definitively linked the patient's allergic condition to farnesol in a particular product of use. A strong confidence score of 5 was not assigned to any report. This was because no reports adequately addressed all criteria needed to determine causation. Though in some cases it did appear that farnesol was causing an allergic response in a specific product or deodorant, causality could not be determined because in all cases, other materials also gave positive responses (34,37,44). The materials most often linked to a positive farnesol reaction were *M. pereirae* (balsam of Peru), propolis, nickel, and oak moss absolute (5,34,35,37,40,43,45). This link should be further studied to determine whether there is a special chemical or response mechanism leading to a pattern of cross-reactivity between farnesol and these other materials.

Conclusions

Data from predictive animal studies showed in most test cases that farnesol was a nonsensitizer. However, 2 LLNAs indicated strong sensitization potential. Predictive human test data indicated mostly a low potential, if any, for sensitization in HMT or HRIPT testing of farnesol at 10% or 12%, usually using sodium lauryl sulfate (SLS) pretreatment. These test results were mostly in summary form, so little correlation could be made to actual causality. Most of the reports did not have control groups or positive reaction follow-up for ROAT or PUT determination. The clinical reports indicated some + and -/+ or questionable reactions to farnesol at varying concentrations, with 5% being the most commonly used. However it has been noted that such clinical studies on previously sensitized subjects were not able to definitely point to one material as the cause of the patient's condition (13). This can be said of the farnesol data as well. Despite being required for labeling in the EU and as a component of FM II, it requires more data to demonstrate that farnesol is a major causative allergen in consumer use products. This could be done by performing serial dilution testing at levels that match actual consumer product exposure using the published results of fragrance use estimations (70). The ROAT or PUT methodologies, as have been used and documented in previous publications (71–73), would help determine a dose/response profile for each fragrance material. The second step would be to then do in-use testing for 2 to 4 weeks at the actual product concentration, not the patch-test concentration. This would help to correlate consumer use data, clinical relevance, and patch-test results.

Identifying clinical relevance of positive patch test results to fragrance materials is a challenge. The complexity and proprietary nature of fragrances, and their use of multiple complex natural and synthetic substances, make it even more difficult to determine the true cause of allergy. This process of determining causation can be made easier by following the step-wise system such as that proposed by Hostynek and Maibach (6). This system attempts to exclude many of the confounding factors such as ESS, multiple cross-reactions, and irritancy. It offers a logical progression of questions the clinician can use to assess patch test results.

Farnesol is included in the standard FM II series and is required for labeling on cosmetics in the EU. Whether or not there is a scientific basis for such inclusions, both may provide further data on farnesol's causal role in ACD via future tracking. Also, rigorous prospective clinical correlation patch studies could be undertaken to give clearer data on farnesol's role in ACD. The recent assistance from the International Fragrance Association (IFRA) in providing breakdown samples for patch testing should help accelerate our knowledge of clinical relevance (74).

Declaration of interest

The authors report no declarations of interest.

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