

Tolerability and benefit of a tetramethoxyluteolin-containing skin lotion

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Theoharis C Theoharides,^{1,2,3} Julia M Stewart¹
and Irene Tsilioni¹

Abstract

As many as 40% of people have sensitive skin and at least half of them suffer from pruritus associated with allergies, atopic dermatitis (AD), chronic urticaria (CU), cutaneous mastocytosis (CM), and psoriasis. Unfortunately, the available topical formulations contain antihistamines that are often not as effective as those containing corticosteroids. Certain natural flavonoids have anti-inflammatory actions. We recently reported that the natural flavonoid tetramethoxyluteolin has potent antiallergic and anti-inflammatory actions in vitro and in vivo. This flavonoid was formulated in a skin lotion along with olive fruit extract and was first tested for tolerability in 25 patients with mastocytosis or mast cell activation syndrome and very sensitive skin who reported back through a questionnaire. The skin lotion was then used by eight patients, four with AD and four with psoriasis, who had not received any topical treatment for at least 2 months, twice daily for 2 weeks. The use of this tetramethoxyluteolin formulation resulted in significant improvement of the skin lesions and could be useful adjuvant treatment for allergic and inflammatory skin conditions.

Keywords

allergy, atopic dermatitis, inflammation, luteolin, mast cells, psoriasis, tetramethoxyluteolin

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Introduction

Approximately 40% of people have dry, sensitive skin. Of those, over 20% have medical conditions that involve skin allergies and/or inflammation, often accompanied by pruritus (itching). These include allergies, atopic dermatitis (AD), chronic urticaria (CU), multiple chemical sensitivity disorder, and psoriasis.^{1,2} In particular, patients with mast cell (MC) disease such as mastocytosis or mast cell activation syndrome (MCAS) have sensitive skin, suffer from skin rashes, and react by flushing in response to many different triggers. All of these conditions involve skin MCs,³ which are stimulated by allergens through high affinity surface IgE receptors (FcεRI), as well as environmental triggers such as bacteria, mold, viruses, stress,

heavy metals, preservatives, pesticides, and other toxins, releasing numerous pruritogenic molecule

¹Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston, MA, USA

²Sackler School of Graduate Biomedical Sciences and Tufts University School of Medicine, Boston, MA, USA

³Department of Internal Medicine, Tufts Medical Center and Tufts University School of Medicine, Boston, MA, USA

Corresponding author:

Theoharis C Theoharides, Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, 136 Harrison Avenue, J304, Boston, MA 02111, USA.
Email: Theoharis.theoharides@tufts.edu



mediators such as histamine, interleukin (IL)-31, prostaglandins, and tryptase.⁴

Pruritus is typically addressed by oral antihistamines that are helpful in allergic cases, but less so in the diseases mentioned above. Unfortunately, there are surprisingly few topical preparations that address the skin conditions previously described. These include the antihistaminic creams, diphenhydramine (Benadryl; available only in the United States) and dimetindene (Fenistil; available only in Europe), as well as one containing the antipsychotic promethazine (Phenergan; available only in Europe) and the tricyclic antidepressant doxepin (Zonalon; available only in the United States).

There are still no clinically effective MC inhibitors.⁵ Disodium cromoglycate (cromolyn) inhibits rodent peritoneal MC histamine release,⁶ but it does not effectively inhibit either murine⁷ or human⁸ MCs.

There are also various topical cortisone preparations as well as the skin lotion tacrolimus (Protopic) used in AD.⁹ A “home-made” test formulation of the “MC inhibitor” disodium cromoglycate (cromolyn) was reported to reduce itching in humans, but apparently by inhibiting the sensory nerves and *not* skin MCs.¹⁰ There is therefore a need for the development of novel, effective antiallergic and anti-inflammatory topical preparations.

Materials and methods

A skin lotion (GentleDerm[®], Serial Number: 86442451) was formulated to contain tetramethoxyluteolin (>98% purity; Skyherb Technologies Co, Ltd, Hangzhou, China, under exclusive agreement with BiomedAdvice, LLC) mixed with olive fruit extract to provide added benefit¹¹ and increase absorption through the skin.

A sample of GentleDerm[®] (Serial Number: 86442451) (4 oz) was given to 25 patients with mastocytosis or MCAS during the 2015 annual meeting of the Mastocytosis Society with the request to try out on any part of their body every day until it was used up or until they may experience any sensitivity or other adverse effect. Two weeks later, a questionnaire (Figure 1) was sent electronically to assess tolerability.

Subsequently, the skin lotion was given to eight patients with different skin conditions (Table 1), who were directed to apply the skin lotion to the

relevant affected area twice per day (a.m. and p.m.) for 1 month. The selected areas were examined by one of the authors, TCT and were photographed by the patients before and at the end of the treatment period.

Results

This formulation was pilot-tested for tolerability on 25 Caucasian patients with mastocytosis or MCAS who could not tolerate any cosmetics. Patients were each given a 4 oz jar and were directed to apply the lotion to any skin area (face, chest, arms, legs, or scalp, but no open wounds) twice per day for 2 weeks. An electronic survey (Figure 1) was sent to all patients asking for any skin symptoms associated with the use of this lotion. The survey was returned by 18/25 patients (70.5%; 1 male and 17 females); of these volunteers, 52.94% used the lotion once per day and 47.06% twice per day. The lotion was used for 6 weeks by 47.06%, for 5 weeks by 11.76%, and the rest for 1–5 weeks. No patient reported any irritation (Figure 1). Even though the intent of the lotion was to determine tolerability, 72.22% reported benefit that was apparent in 28.57% of volunteers even after they stopped applying the lotion.

This skin lotion was then used by eight patients with either AD or psoriasis as shown in Table 1. These patients had not received any systemic or local therapy for at least 1 month prior to use of the test skin lotion. All patients applied the lotion on their skin lesions twice daily for 1 month. All patients had significant improvement as shown in Figure 2.

Discussion

Our present findings indicate that a tetramethoxyluteolin-containing skin formulation could improve skin allergic and inflammatory conditions. Additional features of this skin lotion include the antioxidant¹² and skin protective effects of olive fruit extract (Table 2).^{11,13}

Tetramethoxyluteolin belongs to the family of natural flavonoids with antioxidant and anti-inflammatory properties.¹⁴ The four methyl groups in 5,7,3',4'-tetramethoxyflavone (methoxyluteolin) instead of the hydroxyl groups of the structurally related flavonol, luteolin, make it easier for this flavone to penetrate the skin and render it also metabolically more stable.^{15,16}

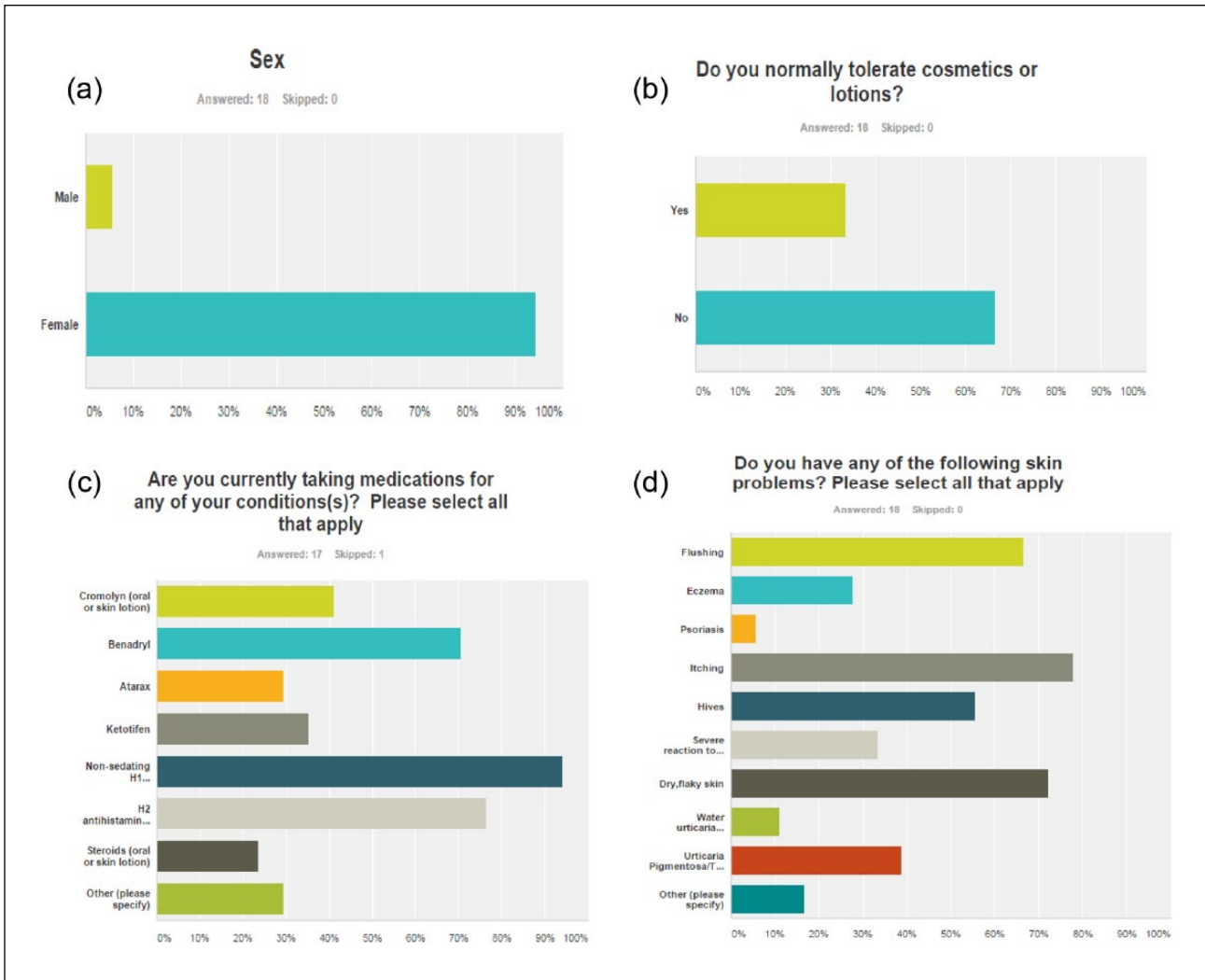


Figure 1. Questionnaire results.

Table 1. Patient demographics and diagnoses.

Patient	Age (years)	Sex	Diagnoses
A	51	F	AD
B	43	F	AD
C	39	F	AD
D	42	F	AD
E	39	F	Psoriasis
F	47	M	Psoriasis
G	38	M	Psoriasis
H	16	F	Psoriasis

AD: atopic dermatitis.

Tetramethoxyluteolin was more potent MC inhibitor than luteolin,¹⁷ which inhibits MCs,¹⁸ pruritus,¹⁹ and activation of keratinocytes.²⁰ Luteolin could inhibit flushing.²¹ Moreover, luteolin-7-glucoside was recently reported to inhibit

keratinocytes, skin inflammation, and psoriasis in a mouse model.²² Luteolin and its structurally related flavonol quercetin (5,7,11,3',4'-pentahydroxyflavonol) inhibit histamine, IL-6, IL-8, tumor necrosis factor (TNF), and tryptase release from human MCs.^{18,23} Moreover, quercetin was shown to be better inhibitor than cromolyn of human MC cytokine release and of contact dermatitis than in humans.⁸

Luteolin also inhibits microglial activation and proliferation,²⁴ especially IL-6 release,²⁵ and is neuroprotective.²⁶ An oral luteolin formulation significantly improved symptoms in over 60% of children with autism^{27,28} many of which have AD, CU, or CM.²⁹ We recently reported that tetramethoxyluteolin inhibits human microglia proliferation³⁰ and so do flavonoids from safflower

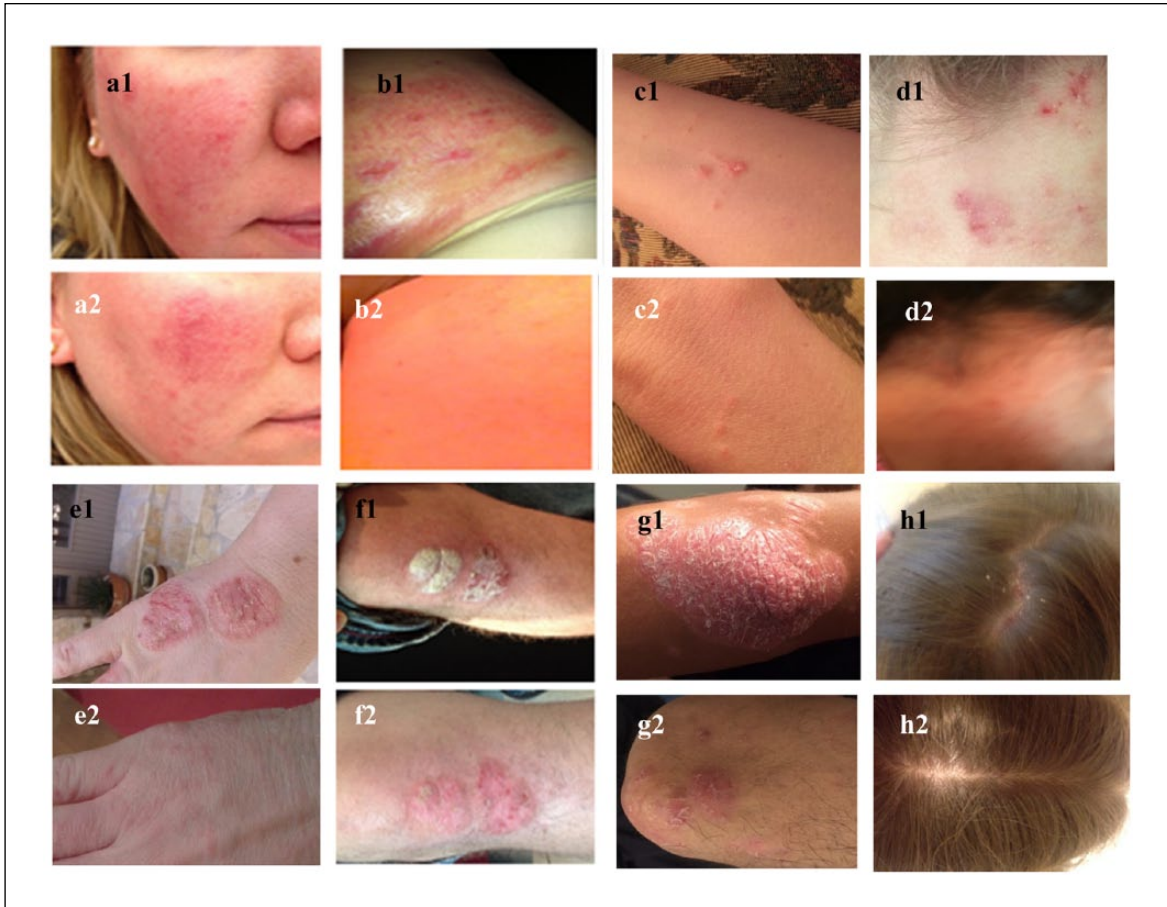


Figure 2. Photographs of lesional skin areas. Areas were photographed before (upper panels, a1–d1; e1–h1) and after (lower panels, a2–d2; e2–h2) using this lotion twice daily for 4 weeks. (a–d) atopic dermatitis: (a) face, (b) abdomen, (c) arm, and (d) back of neck. (e–h) psoriasis: (e) hand, (f) knee, (g) elbow, and (h) top of head.

Table 2. Ingredients and benefits of GentleDerm.

Ingredients	Actions
Tetramethoxyluteolin	Antiallergic, anti-inflammatory
Olive fruit extract	Antioxidant, skin protector
Oregano extract	Antioxidant
Chamomile extract	Antioxidant, skin protector
Honey	Antibacterial
Electrolytes	Hydration

yellow.³¹ Flavonoids are generally considered safe^{32,33} and now being increasingly discussed³⁴ for the treatment of neurodegenerative disorders.³⁴

This pilot case series studies confirm that this tetramethoxyluteolin-containing skin lotion is well tolerated and could provide significant benefit for patients with dry, irritated, or sensitive skin, especially AD, CM, CU, and psoriasis. (Table 3) It is important to confirm these findings by well-designed, double-blind, placebo-controlled, clinical trials.

Table 3. Learning points.

Skin allergy and inflammation are present in many conditions including atopic dermatitis (AD), chronic urticaria (CU), cutaneous mastocytosis (CM), and psoriasis.

The few topical skin formulations contain antihistaminics or corticosteroids.

The natural flavonoid tetramethoxyluteolin has potent antiallergic and anti-inflammatory actions.

A skin lotion containing tetramethoxyluteolin formulated in olive fruit extract was well tolerated by patients sensitive skin.

This skin lotion improved skin lesions in patients with AD, CM, and psoriasis.

Skin lotion containing tetramethoxyluteolin could be used for the treatment of allergic and inflammatory skin conditions.

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Medicine) for checking the purity of tetramethoxyluteolin with NMR and LC-MS.

Declaration of conflicting interests

The composition of this tetramethoxyluteolin containing formulation is covered by US patents 6689748; 6984667, 7906153, 8268365 and is trademarked as GentleDerm® (Serial Number:86442451) awarded to TCT. GentleDerm® (Serial Number:86442451) is produced to specifications decided by BiomedAdvice, LLC directed by TCT.

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