

FORMULATION AND EVALUATION OF HERBAL CREAM BY USING PERILLA FRUTESCENS ON ALLERGIC SKIN REACTION

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Abstract

The various skin conditions including allergic contact dermatitis to atopic eczemas have become a major health challenge across the globe. The currently available pharmacological approaches such as topical steroids and antihistamine drugs have been associated with serious side effects on prolonged administration. This development has brought about an increased interest in Phytotherapy. Perilla frutescens (L.) Britt. (Lamiaceae) is a traditional phytoherb which has been known to posseses anti-inflammatory, antioxidant and anti-allergic characteristics. The current literature will focus on the strategies of formulation and the considerations of evaluating perilla cream. The article will provide information about active ingredients in Perilla which include rosmarinic acid, luteolin, and apigenin as well as their mechanism in the regulation of Type I and Type IV hypersensitivity.

Keywords: Perilla frutescens, allergic contact dermatitis, herbal cream formulation, rosmarinic acid, mast cell stabilization, natural anti-allergic agents, topical drug delivery

Introduction:

The plant Perilla frutescens comes under the family Lamiaceae (earlier termed as Labiatae) and goes by the name perilla. Perilla is a widespread annual herb that finds extensive growth in countries from Asia, including India, China, Japan, Korea, and Thailand. The plant has a fragrant quality and produces a distinct mint-like smell. A popular variant of Perilla frutescens, known as Perilla frutescens var. crispa, which goes by the name of “shiso,” is largely cultivated in Japan. This herb naturally exists in the regions of China, Korea, Japan, and the Himalayan ranges of India and Nepal. In India, Perilla can be found in places such as Uttarakhand, Himachal Pradesh, Kashmir, Sikkim, Manipur, Mizoram, and Meghalaya. Its commercial value has

resulted in its cultivation even in other countries like Russia, Europe, and the United States. The *perilla frutescens* herb contains several biologically active phytochemicals like rosmarinic acid, luteolin, quercetin, catechin, caffeic acid, and ferulic acid. Moreover, the seeds of the herb contain phytosterols, tocopherols, squalene, and polyunsaturated fatty acids. Though the plant is consumed as a functional food in various parts of the world, in some places, it has not been used much because of lack of cultivation of this herb. There are a number of biological activities associated with the *perilla frutescens*, such as antimicrobial activity, anti-allergy, anti-inflammation, anticancer, antiviral activity, antioxidant, and antidepressant effects.



Fig. *perilla frutescens*

Conventional pharmacological management has traditionally relied on topical corticosteroids as first-line therapy. While undeniably effective for acute flare suppression, prolonged corticosteroid use carries well-documented risks including skin atrophy, telangiectasia, striae, perioral dermatitis, and systemic absorption with chronic application. Topical calcineurin inhibitors offer an alternative but raise concerns about long-term safety and carry boxed warnings regarding potential malignancy risk. Oral antihistamines address pruritus but do not resolve underlying inflammation. These limitations have created a therapeutic gap that herbal medicine is increasingly positioned to fill.

Phytochemical Profile and Anti-Allergic Effect of the Herb

The efficacy of *P.frutescens* in managing skin allergy lies in its distinctive chemical constitution:

Active Ingredients

Rosmarinic acid: A polyphenol with the ability to inhibit the action of C3-convertase and block the lipoxygenase pathway.

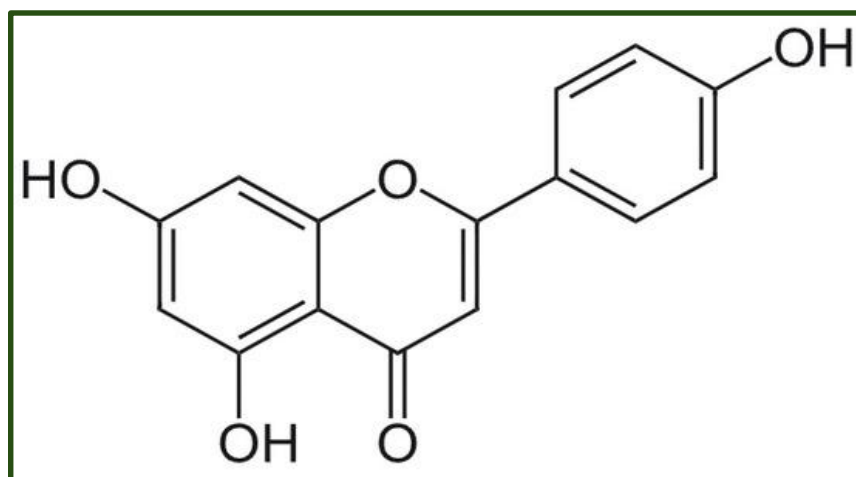
Luteolin: Luteolin is the most common and extensively studied bioactive flavonoid present in plants. Belonging to the chemical family of flavones, it possesses powerful antioxidant, anti-inflammatory, and neuroprotective effects. It is usually extracted from the leaves, bark, and peel of different edible plants and medicinal herbs. A flavonoid that acts as a vascular impermeability inhibitor and suppresses IgE antibody production.

1. Chemical Structure and Properties:

Chemical formula: $C_{15}H_{10}O_6$.

Structure: It comprises two aromatic benzene rings (A and B) and one hetero-ring system (pyrone, C).

It is the hydroxyl groups present on carbons 3', 4', 5, and 7 that make luteolin highly reactive. This is due to the ability of the molecule to donate electrons to neutralize free radicals.



2. Mechanism of Action

Luteolin is not only a nutrient but also works as a biological regulator in the human body. Luteolin performs some significant roles, namely:

A. Anti-Inflammatory Actions

Luteolin blocks the secretion of inflammatory cytokines including Interleukin-6 (IL-6) and Tumor Necrosis Factor- α (TNF- α). In doing so, Luteolin suppresses the NF- κ B pathway, which is known as the “master” switch for inflammation in humans.

B. Antioxidant Properties

It acts as a scavenger of reactive oxygen species (ROS). As it reduces the ROS effect on the human body, it protects the cells from oxidative stress which causes cellular senescence.

C. Nervous System Protection

The research studies have shown that luteolin passes through the blood-brain barrier. It decreases the brain fog and neuroinflammation by suppressing the activation of microglia (immune cells in the brain). That is why luteolin is under consideration in the treatment of Alzheimer’s and multiple sclerosis.

D. Anti-Allergic Activity

As was said about *Perilla frutescens*, Luteolin has strong mast cell stabilization properties. Luteolin prevents the histamine release from the mast cells causing itching, swelling, and redness as the allergic symptoms.

4. Therapeutic Applications

Due to the multiple actions exerted by luteolin, it is being researched on as a potential remedy for:

Anti-Cancer Agent: It causes programmed cell death in several types of cancer cells.

Glucose Metabolism: Some studies suggest that it can play a role in improving insulin sensitivity and glucose utilization.

Mode of action:

The therapeutic effect of the drug developed from *Perilla frutescens* in allergic skin diseases is achieved through a multi-target pharmacologic strategy and not by a mere single mechanism of action. The effect is exerted on multiple levels during the course of allergic inflammation.

The mode of action is described below in the following biochemical pathway:

1. Stabilization of Mast Cells

An allergic reaction occurs because of the degranulation of mast cells. When an allergen penetrates the skin, it attaches itself to IgE antibodies on the surface of the mast cells.

Effect: Luteolin and Rosmarinic acid, present in Perilla extract, stabilize the membrane of the mast cells.

Effect of the Action: They stop the cells from bursting and releasing histamine, prostaglandins, and leukotrienes. As a result, this will reduce redness, warmth, and severe itching.

2. Inhibiting Pro-inflammatory Enzymes

The extracts of Perilla have been found to be natural inhibitors of the enzymes that cause the formation of inflammation-related chemicals.

COX-2 and LOX Inhibition: The ingredients inhibit the function of Cyclooxygenase-2 and Lipoxygenase.

Effect of the Action: By blocking their actions, the formula stops the production of PGE₂ and LTB₄, the chief causes of edema (swelling) and pain.

3. Inhibition of Cytokine Signaling (NF- κ B Pathway)

At a genetic level, the compound hinders cytokine signaling by interfering with pro-inflammatory signals in the cell.

The Action: It blocks nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) from entering the nucleus of the cell.

The Effect: Because NF- κ B is known as the “master regulator” for inflammation, preventing it from activating would prevent pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and IL-6 from being made.

4. Suppression of T-Cell Activation

Often, allergic contact dermatitis involves T-cell hypersensitivity.

The Action: Perilla extract can help regulate the balance between Th1 and Th2 responses.

The Result: It is able to block excess Th2 response, leading to decreased levels of IgE, which is found to be elevated in chronic allergies such as atopic dermatitis.

5. Skin Barrier Repair and Antioxidant Protection

Oxidative stress is common in allergic skin conditions.

Antioxidant Scavenging: Perilla leaf extract contains rosmarinic acid, an antioxidant that acts as a powerful ROS scavenger.

Ingredients category	Example	Function
Active Ingredients	Perilla frutescence	Anti allergic agent
Oil phase	Cetyl alcohol, stearic acid	Consistency and emolliency
Aqueous phase	Distilled water	Solvents
Emulsifier	Span80, tween 80	Stabilize the emulsion
Humectant	Glycerin, propylene glycol	Prevent skin dehydration
Preservatives	Methyl paraben	Prevent microbial growth

Preparation Method:

Perilla cream preparation involves using the standardized technique used in preparing creams based on emulsions. In order to stabilize the bioactive components such as perillaldehyde and rosmarinic acid, cold incorporation or heat-controlled fusion techniques are applied.

Step 1: Preparation of Perilla frutescens Extract

Before cream formulation, the active ingredients have to be extracted from the raw materials:

Harvesting & Drying: Fresh leaves are harvested, cleaned, and dried under the shade to avoid their destruction due to exposure to heat.

Extraction: The powder is extracted using maceration or Soxhlet technique with a solvent mixture such as 70% ethanol or methanol. This step is done to extract polar phenols such as luteolin.

Concentration: The resultant solution is then filtered and concentrated using rotary evaporator under controlled temperature up to 40^oC.

2. Chemical Composition of Cream Base

This formulation is prepared as Oil in Water (O/W) emulsion type because this is preferable for allergy prone skin type.

Phase	Ingredients	Role
Oil phase	Stearic acid, cetyl alcohol, White soft paraffin	Provides the emollient base and structure
Aqueous phase	Distilled water, propylene glycol, glycerin	Act as vehicle and humectant. (moisture retainer)
Emulsifier	Tween 80	Reduce surface tension to blend oil and water
Preservatives	Methyl paraben, propyl paraben	Prevent microbial contamination

3. Process for Formulating Cream (Fusion Technique)

This process is conducted through two different processes to ensure homogeneity:

Step A: Oil Phase Formulation

The stearic acid, cetyl alcohol, and paraffin oils are mixed in a clean porcelain dish. They are heated to around 70^oC – 75^oC by placing the dish in hot water until the components melt.

Step B: Aqueous Phase Formulation

The glycerin, water, and preservatives are combined in a beaker and heated up to 75°C. It is essential to heat the two phases at the same temperature to avoid early solidification when combining them.

C. Emulsification

The aqueous solution is gradually added to the oil while continuously stirring with either a mechanical stirrer or a glass rod. The stirrer should continue running in one direction for the emulsion to form and air bubbles to be avoided.

D. Perilla Extract Addition

After the emulsion starts cooling (at around 35°C - 40°C), the Perilla extract and its volatile elements such as Perillaldehyde are introduced.

Note: For the volatile components not to evaporate or break down, adding the extract at a lower temperature is essential.

4. Homogenization and Storage

The cream is stirred until it cools down to room temperature and acquires the desired semisolid texture. Afterwards, it undergoes homogenization by a homogenizer machine to decrease the size of the internal droplets and improve the cream's stability and texture. The cream is then poured into lightproof containers.

5. Quality Control Check (Initial)

After the cream is prepared, it is tested for:

Homogeneity: Absence of any visual evidence of separation between oil and water.

Texture: Must be smooth and free from any gritty particles.

Appearance and Aroma: The color varies from pale green to light brown (according to the concentration of extracts) and the smell is herbaceous.

Parameters of Evaluation:

In order to prove that the herbal cream is ready for use in clinics, it has to be tested in terms of physicochemical and biological parameters.

Physicochemical Testing

Organoleptic Characteristic: Test of color, smell, and appearance.

pH Value: The pH level of the cream should be within the range of 5.5 and 7.0 since it is similar to the pH of human skin.

Spreadability: Determined by calculating the time it takes for two glass plates to part with the cream between them ($S = M \cdot L / T$).

Viscosity: Evaluated using Brookfield Viscometer.

Pharmacological evaluation:

The pharmacological evaluation for a herbal cream made from *Perilla frutescens* consists of several steps that seek to establish its safety, assess its biological activity, and confirm that it has bioactive ingredients in it.

1. In Vitro Anti-Inflammatory Action

The effectiveness of the cream in terms of inhibiting inflammation is tested in laboratory settings before conducting the experiments on live subjects.

Albumin Denaturation Test: When a person suffers from inflammation, the first thing that happens is protein denaturation. For this test, the cream is heated along with egg albumin. Higher levels of inhibition of denaturation demonstrate that the cream is able to protect the structure of proteins just like it does with the anti-inflammatory action.

HRBC Membrane Stabilizing: Similar to lysosomal membranes, the membranes of Human Red Blood Cells (HRBC) also get affected when there is inflammation. If the cream prevents HRBC bursting under hypotonic condition, it means that it is capable of stabilizing lysosomal membranes too.

2. In Vitro Antioxidant Potential

In case of allergic reaction, oxidative stress plays an important role.

DPPH Radical Scavenging Assay: This assay determines the capability of the antioxidant present in the cream such as Rosmarinic acid to eliminate free radicals. The degree of discoloration, from violet to yellow, is analyzed using a spectrophotometer, and then the IC_{50} value is obtained.

3. In Vivo Safety Test (Toxicity)

First of all, safety should always be our foremost priority when dealing with skin formulations, especially for allergenic skin.

Acute Skin Irritation Test: Based on OECD guidelines, the formulation is applied to shaved skin in the back region of an animal model (generally Albino rabbits or Wistar rats).

Observation: After 24, 48, and 72 hours, the area of application is checked for erythema or edema formation. A “Primary Irritation Index” should also be noted, and for this to pass safety, the score must be close to zero.

4. Mechanisms for Anti-Allergy Effectiveness

The effectiveness of the cream in combating certain types of allergic reactions can be demonstrated using biological models that target the condition.

Passive Cutaneous Anaphylaxis (PCA): PCA is an allergic response that results from the IgE mechanism. It involves evaluating the reduction in the size of "blue spots" (the result of leakage of dye after contact with the allergen) in the skin of subjects.

DNFB-Induced Contact Dermatitis: DNFB is used to induce a reaction akin to the eczematous condition. Ear swelling and the degree of cellular influx is compared in both the experimental and control groups.

5. Anti-Microbial Screening

An allergic skin is very prone to secondary infection such as *Staphylococcus aureus*.

Skin samples are obtained after the completion of all in vivo tests

Zones of Inhibition: This test uses the Agar Well Diffusion technique. The zones of inhibition (areas with no growth of bacteria around the cream) are measured in millimeters to indicate the degree of antimicrobial properties of the cream.

6. Histopathological Examination

Skin samples are obtained after the completion of all in vivo tests.

Pathology Analysis: A decrease in the epidermis thickness and decreased numbers of mast cells and eosinophils should be observed in the dermis layer. Successful Perilla cream should have normal skin without allergy symptoms.

7. Summary of Evaluation Criteria

Test type	Parameters	Desired result
In Vitro	Protein denaturation	>70% inhibition
Safety	Draize skin score	0(Non irritant)
Efficacy	Ear swelling	Significant reduction vs control
Microbial	Preservatives efficacy	No growth of <i>S.aureus</i> or <i>C albicans</i>

Conclusion:

Perilla frutescens represents a compelling source of anti-allergic phytochemicals with demonstrated activity relevant to skin allergic reactions. The scientific evidence—spanning traditional use documentation, phytochemical characterization, in vitro mechanistic studies, and limited in vivo efficacy data—supports further investment in formulation development. The major bioactive constituents (rosmarinic acid, apigenin, luteolin, PDMF) exhibit multiple complementary mechanisms: mast cell stabilization through FcεRI and MRGPRX2 inhibition, NF-κB-mediated anti-inflammatory effects, and antioxidant protection. This multi-targeted profile offers theoretical advantages over single-mechanism synthetic agents. Formulation of Perilla frutescens extracts into stable, elegant, and effective creams presents challenges typical of botanical products—standardization, preservation, stability, and sensory properties—but these challenges are surmountable with systematic application of modern pharmaceutical science. The growing patient preference for natural products, combined with legitimate safety concerns about long-term corticosteroid use, creates a receptive market for evidence-based herbal alternatives.

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