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Formulation And Evaluation of A Novel Herbal Cream Containing Tretinoin and Pomegranate Extract for The Management of Premature Aging

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ABSTRACT

This study aimed to develop an effective anti-aging cream by combining Tretinoin, a proven retinoid, with pomegranate (Punica granatum) extract known for its antioxidant properties. Creams were prepared using varying concentrations of Tretinoin (0.01%–0.1%) and pomegranate extract (5%–15%) and evaluated for stability, pH, viscosity, skin permeability, and antioxidant activity. In vitro studies assessed collagen synthesis and elastin production. The combination significantly enhanced skin texture, hydration, and antioxidant response, highlighting synergistic anti-aging effects. The results suggest that integrating herbal extracts with Tretinoin offers a promising approach for developing natural and effective anti-aging skincare products.

1. INTRODUCTION

Aging is an inevitable biological process characterized by a gradual decline in physiological functions, particularly visible on the skin. Premature aging, influenced by extrinsic factors such as UV exposure, pollution, poor nutrition, and stress, accelerates the appearance of wrinkles, fine lines, uneven skin tone, and loss of skin elasticity. The demand for effective, safe, and consumer-friendly anti-aging solutions has led to the exploration of both synthetic compounds and natural ingredients in topical formulations.

Tretinoin (all-trans retinoic acid), a derivative of Vitamin A, is a well-established active pharmaceutical ingredient in dermatology, known for its proven efficacy in treating various signs of skin aging. It works by stimulating cellular turnover, enhancing collagen production, and improving skin texture. However, its use may sometimes be associated with irritation, dryness, and photosensitivity, prompting the need for formulation strategies that reduce these side effects while maintaining its therapeutic efficacy.

In recent years, there has been a growing preference for incorporating herbal and plant-derived ingredients into dermatological products due to their perceived safety, antioxidant properties, and consumer appeal. Pomegranate (Punica granatum) extract is one such natural agent rich in polyphenols, flavonoids, ellagic acid, and tannins, which exhibit potent antioxidant, anti-inflammatory, and skin-rejuvenating properties. These compounds help neutralize free radicals, protect skin cells from oxidative stress, and promote collagen and elastin synthesis, making pomegranate an ideal candidate for anti-aging applications.

This research focuses on the development and evaluation of a novel anti-aging cream that combines the powerful effects of Tretinoin with the natural benefits of standardized pomegranate extract. The aim is to formulate a synergistic topical product that offers enhanced skin rejuvenation, minimizes adverse reactions, and meets the increasing demand for natural-based cosmeceuticals. The formulation was systematically evaluated for physicochemical properties such as pH, viscosity, and stability, along with biological assessments including skin permeability, antioxidant activity, and in vitro assays for collagen and elastin production.

By integrating the therapeutic strength of Tretinoin with the antioxidant-rich profile of pomegranate extract, this study explores a holistic approach to managing premature skin aging. The outcomes are intended to provide insights into developing safer and more effective herbal-synthetic combinations for advanced skincare solutions.

Introduction to Premature Skin Aging

Skin aging is a natural, progressive process influenced by both internal (intrinsic) and external (extrinsic) factors. While intrinsic aging is genetically programmed and occurs gradually over time, extrinsic aging is primarily driven by environmental stressors and lifestyle factors, often leading to **premature aging** of the skin.

Premature aging is characterized by early onset of visible signs such as **wrinkles, fine lines, dullness, sagging skin, hyperpigmentation, and loss of elasticity**. Unlike chronological aging, premature aging results from factors such as:

- **Ultraviolet (UV) radiation** (photoaging)
- **Environmental pollutants**
- **Poor nutrition**
- **Lack of proper skincare**
- **Smoking and alcohol consumption**
- **Stress and lack of sleep**

These external triggers accelerate the breakdown of collagen and elastin—two key structural proteins in the dermis—resulting in weakened skin architecture. Additionally, oxidative stress plays a central role in skin aging. Reactive oxygen species (ROS), generated by UV exposure and pollution, damage cellular components including DNA, proteins, and lipids. This oxidative damage impairs skin regeneration and leads to inflammation, pigmentation changes, and a rough skin texture.

From a physiological standpoint, premature aging involves:

- **Decreased fibroblast activity**, reducing collagen and elastin synthesis.
- **Reduced skin hydration and sebum production**, making the skin dry and fragile.
- **Thinning of the epidermis**, contributing to a translucent and wrinkled appearance.

The psychosocial impact of premature aging can also be significant, affecting self-esteem and confidence, especially among younger individuals. This has driven the growing demand for effective anti-aging therapies that are safe, accessible, and cosmetically acceptable.

Modern skincare strategies now focus not only on reducing existing signs of aging but also on **preventing and delaying further progression**. This has led to the use of both synthetic agents like retinoids and **natural ingredients rich in antioxidants**, such as herbal extracts, in topical formulations. Among these, **Tretinoin** and **pomegranate extract** have gained attention for their proven roles in skin repair and rejuvenation.

This study addresses the challenge of premature skin aging by combining both agents into a single cream formulation, aiming to deliver synergistic benefits for youthful, healthy skin.

HERBAL CREAMS: Herbal creams are topical formulations made using natural plant extracts known for their medicinal and cosmetic benefits. These creams are widely used for skincare due to their **antioxidant**, **anti-inflammatory**, **antimicrobial**, and **anti-aging** properties. Common herbal ingredients include **aloe vera, turmeric, neem, pomegranate, green tea**, and **sandalwood**, which help nourish the skin, promote healing, and reduce signs of aging or skin disorders.

Herbal creams are preferred for their **fewer side effects**, **biocompatibility**, and alignment with the growing consumer demand for **natural and safe** cosmetic products. They are used in treating **acne, pigmentation, dryness, wrinkles**, and **eczema**, and are often combined with other actives to enhance efficacy.

In recent years, the integration of herbal extracts with pharmaceutical agents in cream formulations has shown promising results in developing **safe and effective dermatological therapies**.

Challenges with Synthetic Creams

Despite their effectiveness, synthetic creams often pose several challenges that can limit their long-term use and consumer acceptance. These include:

1. **Skin Irritation and Allergic Reactions:** Many synthetic creams contain strong chemical agents, preservatives, or fragrances that can cause **redness, burning, itching**, or **rashes**, especially in individuals with sensitive skin.
2. **Long-Term Side Effects:** Prolonged use of some synthetic ingredients (e.g., corticosteroids, retinoids, hydroquinone) may lead to **thinning of the skin, increased sensitivity to sunlight**, or even **skin discoloration**.
3. **Toxicity Concerns:** Some synthetic compounds may **penetrate the skin** and enter systemic circulation, raising concerns about **toxicity** or **hormonal disruption** with repeated use.
4. **Environmental Impact:** The production and disposal of synthetic chemicals can contribute to **environmental**

pollution and **non-biodegradable waste**, affecting ecosystems.

5. **Consumer Perception:** There is growing awareness and skepticism among consumers about the **safety of chemical-based products**, driving a shift toward natural and herbal alternatives.
6. **Resistance Development:** In antimicrobial creams, repeated use of synthetic antibiotics may lead to **microbial resistance**, reducing the cream's effectiveness over time.
7. **Cost and Accessibility:** High-quality synthetic formulations can be **expensive**, limiting their availability to a broader population.
8. **Photosensitivity:** Some synthetic ingredients, like Tretinoin or benzoyl peroxide, may increase the skin's **sensitivity to sunlight**, requiring additional sun protection.

2. IDEAL PROPERTIES FOR HERBAL CREAM:

- pH 4.5–6.5 (skin-friendly)
- Good spreadability
- Non-greasy, smooth texture
- Stable viscosity and consistency
- Non-irritating and hypoallergenic
- Free from harmful chemicals (parabens, sulfates, etc.)
- Dermatologically safe
- Standardized herbal extracts
- Antioxidant and anti-inflammatory activity
- Promotes collagen synthesis and skin regeneration
- Free from microbial contamination
- Natural or mild fragrance
- Visually appealing color and appearance
- Stable shelf life under various conditions
- Protective and hygienic packaging
- Biodegradable ingredients
- Sustainably sourced herbal components

3. MATERIAL & METHODS USED

S.NO	Material/Chemical	Supplier
1	Tretinoin	Yarrow Chemproduct
2	Pomegranate Extract	Herbal Suppliers Pvt. Ltd.
3	Beeswax	Organic Naturals
4	Jamun Seed Extract	Natural Herbs Suppliers
5	Neem Oil	Ayurvedic Oils Co.
6	Grape Seed Extract	Green Life Exports
7	Propylene Glycol	S D Fine Chemicals
8	Glycerin	S D Fine Chemicals
9	Stearic Acid	S D Fine Chemicals
10	Rose Water	S D Fine Chemicals

Step-by-Step Method:

- **Preparation of Oil Phase**:
  - In a beaker, add stearic acid, cetyl alcohol, liquid paraffin, beeswax, and Span 60.
  - Heat gently to about **70–75°C** while stirring to melt and mix completely.
- **Preparation of Aqueous Phase**:
  - In another beaker, mix purified water and glycerin.
  - Add Tween 60 to the aqueous phase.
  - Heat this phase also to **70–75°C**.
- **Emulsification**:
  - Slowly add the aqueous phase to the oil phase while continuously stirring (use a homogenizer if available) to form an **emulsion**.
  - Continue stirring while cooling down to **40°C**.
- **Incorporation of Active Ingredients**:
  - Dissolve **Tretinoin** in a small amount of ethanol or suitable solvent (if needed).
  - Mix **Pomegranate extract** separately in a small portion of water or propylene glycol.
  - Add Tretinoin solution slowly into the semi-cooled cream while stirring.
  - Then add the Pomegranate extract carefully.
  - Add Vitamin E (antioxidant) at this stage to prevent oxidation.
- **Addition of Preservative and pH Adjustment**:
  - Add a suitable preservative.
  - Adjust the pH to around **5.5–6.5** using citric acid or triethanolamine to make it skin-friendly.
- **Final Mixing**:
  - Continue gentle stirring until the cream becomes uniform and cools completely.
- **Packaging**:
  - Fill into clean, dry, airtight containers (preferably light-resistant containers to protect Tretinoin from degradation).
  - Label properly.

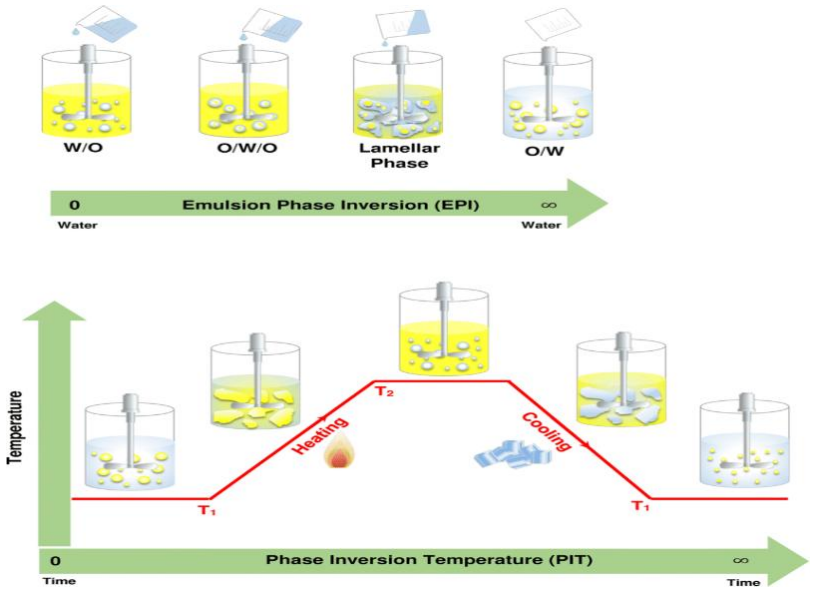

Figure no 9: Method for cream

4. FORMULATION TABLE

Table no 3: Formulation Table

S. No.	Ingredients	F1 (g)	F2 (g)	F3 (g)	F4 (g)	F5 (g)
1	Tretinoin	0.025	0.025	0.05	0.05	0.1
2	Pomegranate Extract	2	4	2	4	4
3	Stearic Acid	5	5	5	5	5
4	Cetyl Alcohol	2	2	2	2	2
5	Liquid Paraffin	5	5	5	5	5
6	Beeswax	3	3	3	3	3
7	Glycerin	5	5	5	5	5
8	Span 60	2	2	2	2	2
9	Tween 60	2	2	2	2	2
10	Vitamin E	0.5	0.5	0.5	0.5	0.5
11	Preservative (e.g., parabens)	0.2	0.2	0.2	0.2	0.2
12	Purified Water (q.s. to 100 g)	~73.275	~71.275	~73.25	~71.25	~70.2

5. FTIR PARAMETERS

FTIR (Fourier-transform infrared) spectroscopy helps detect specific functional groups in molecules by measuring the vibration of bonds when exposed to infrared light. This is crucial for determining the compatibility of tretinoin with other excipients, like pomegranate extract and jamun seed:

Procedure: The FTIR spectra for tretinoin, pomegranate extract, jamun seed, and their physical mixtures are recorded over 4000–400 cm^{-1}.

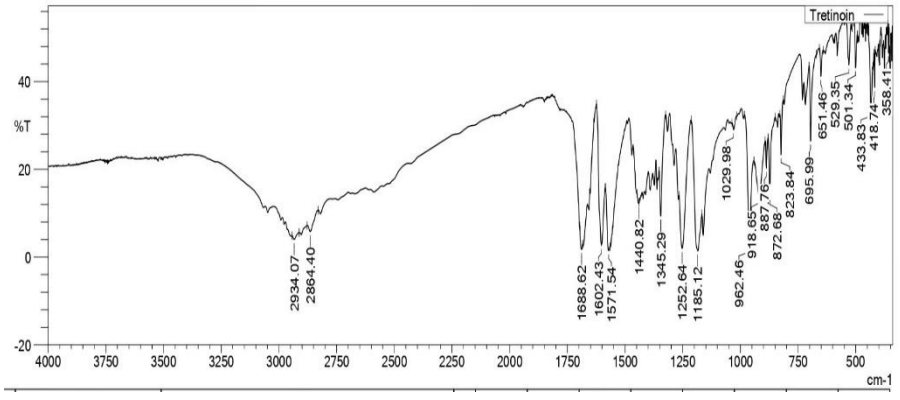

Figure no 6: FTIR TRETINOIN

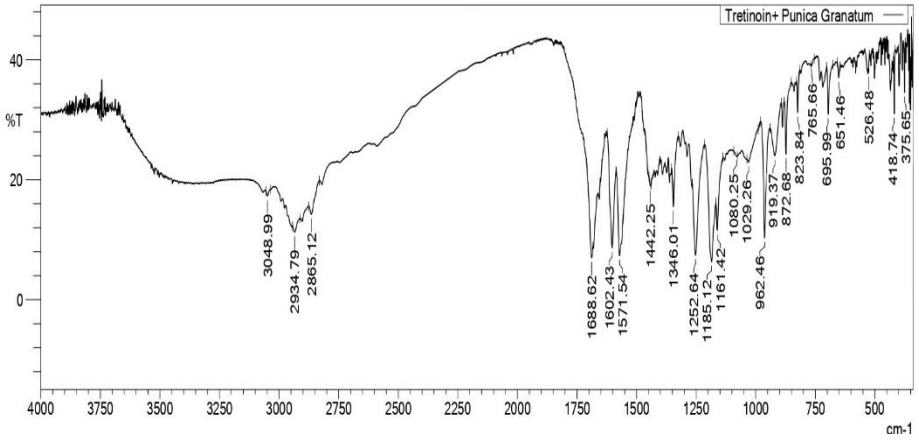

Figure no 7: Tretinoin & Punica Granatum

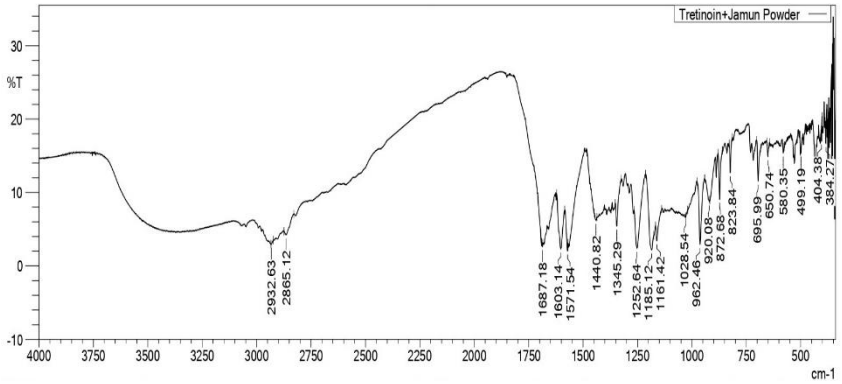

Figure no 8: Tretinoin & Jamun

Calibration curve for Tretinoin

Table no 14: Calibration curve

Concentration (µg/ml)	Absorbance
0	0
2	0.192
4	0.379
6	0.531
8	0.735
10	0.889

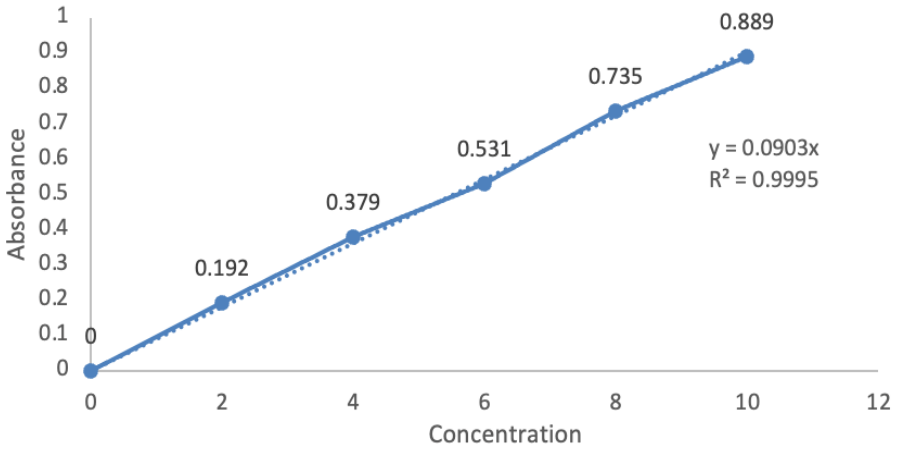

Figure no 5 CalibrationCurve

UV spectroscopy is essential in creating a standard calibration curve for tretinoin, aiding in quantifying its concentration in different media:

- **Procedure**: A stock solution of tretinoin is prepared in methanol and diluted to produce a series of concentrations. Absorbance readings are taken at λmax (354 nm) for each concentration.
- **Importance**: This curve helps in accurately determining the concentration of tretinoin in formulations. It's a fundamental step in quality control and in ensuring therapeutic consistency.

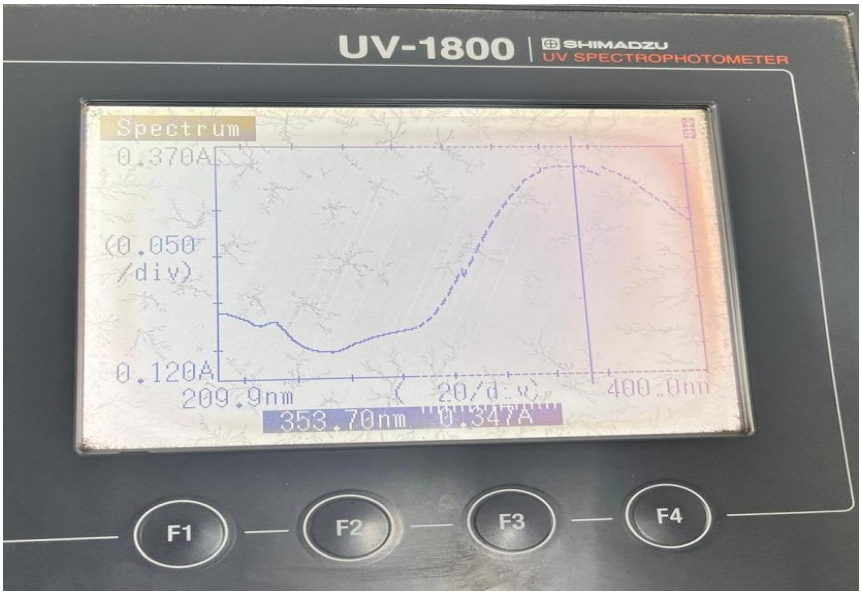

Figure no 4: UV max

6. EVALUATION PARAMETERS

1. **Physical Appearance**:
   - **Color**: The cream should have a smooth, uniform color.
   - **Odor**: The fragrance should be pleasant (if included) and not overpowering.
   - **Texture**: The cream should have a smooth, non-gritty texture, free from lumps.

Figure no 10: Formulation

2. pH Determination:

- The pH of the cream is crucial for skin compatibility. The ideal pH for an anti-aging cream is between 5.5 and 6.4.
- **Method**: Use a pH meter to measure the pH after the formulation has been cooled.

Table no 17: Ph table

Formulation Code	pH Range Set	Observed pH
F1	5.0–6.4	5.5
F2	5.0–6.4	5.8
F3	5.0–6.4	5.6
F4	5.0–6.4	6.0
F5	5.0–6.4	6.2

Figure no 11: Ph

3. Viscosity:

- **Purpose**: To ensure the cream has an appropriate thickness, which should allow for easy application without being too runny or too stiff.
- **Method**: Use a viscometer to determine the viscosity at different shear rates (often measured in centipoises or cps).

Table no 18: Viscosity

Formulation Code	Observed Viscosity (cps)
F1	28,500 cps
F2	30,200 cps
F3	29,100 cps
F4	32,500 cps
F5	34,800 cps

Figure no 12: Brookfield viscometer

4. Spreadability:

- **Purpose**: Determines how easily the cream spreads on the skin.
- **Method**: Perform a spreadability test by applying a small amount of the cream to a glass plate and spreading it using a standard weight. Measure the area covered by the cream.

· Take two glass slides.

· Place 1 gram of cream at the center of the first slide.

· Put the second slide on top and press gently to make a uniform layer.

· Place a small weight (like 500 g) on top for 5 minutes.

· After 5 minutes, remove the weight.

· Measure the diameter (in cm) of the spreaded cream using a scale.

· Higher the diameter, better the spreadability.

Table no 19: Spreadability

Formulation Code	**Spread Diameter (cm)**
F1	5.9
F2	6.1
F3	6.3
F4	6.5
F5	6.8

Figure no 13: Spreadability test

5. **Stability Testing**:

- **Purpose**: To ensure the cream maintains its physical properties (appearance, texture, and pH) over time.
- **Method**: Store the cream at different temperatures (e.g., 4°C, 25°C, and 40°C) for 1, 3, and 6 months, and assess changes in appearance, texture, and pH.

Table no 20: Stability

Formulation Code	Appearance	Color	Phase Separation	pH Change	Viscosity Change
F1	Smooth	Light Green	No	Slight (−0.2)	Minor (−200 cps)
F2	Smooth	Light Green	No	Slight (−0.1)	Minor (−100 cps)
F3	Smooth	Pale Green	No	Stable	Stable
F4	Smooth	Pale Green	No	Stable	Stable
F5	Smooth, glossy	Light Mint Green	No	Stable	Stable

6. **Microbial Testing**:

- **Purpose**: To confirm that the cream is free from harmful microorganisms.
- **Method**: Perform microbial limit tests (e.g., total bacterial count, yeast, and mold count) according to pharmacopeial standards (e.g., USP or EP).

Test	Specification (IP/USP)	Result	Conclusion
Total Aerobic Microbial Count (TAMC)	≤ 10^3 CFU/g or mL	e.g., 150 CFU/g	Within limits
Total Yeast and Mold Count (TYMC)	≤ 10^2 CFU/g or mL	e.g., 30 CFU/g	

Figure no 14: Microbial tester

7. Sensory Evaluation:

- **Purpose**: Subject the cream to sensory evaluation by human panelists for attributes such as:
    1. **Touch**: Smooth, non-greasy, non-sticky.
    2. **Appearance**: Homogeneous, free of any separation.
    3. **Odor**: Acceptable fragrance, non-irritating. skin)

Purpose:

To assess the organoleptic and aesthetic properties of the formulated cream based on user feedback and physical inspection.

Method:

The cream was applied to the dorsum of the hand. Evaluation was conducted by a panel of 3 volunteers using a scoring system (scale of 1 to 5: 1 = Poor, 5 = Excellent) for each parameter.

Table no 22: Parameters Evaluated:

Parameter	Observation / Score (Avg.)	Remarks
Appearance	4.8	Smooth, uniform, no lumps
Color	4.6	Pale pink (natural pomegranate tone)
Odor	4.5	Pleasant, mild fruity fragrance
Consistency	4.7	Semi-solid, spreads easily
Greasiness (after feel)	4.3	Non-greasy, quick absorption
Stickiness	4.2	Minimal stickiness observed
Spreadability	4.6	Easily spreadable with little effort
Irritation / Sensitivity	5.0	No irritation or redness observed
Moisturizing effect	4.8	Leaves skin soft and hydrated
Overall acceptability	4.7	Highly acceptable

The cream showed excellent sensory attributes with high user acceptability. It was easy to apply, non-irritating, and provided a pleasant feel on the skin, making it suitable for topical use.

7. CONCLUSION

The study successfully formulated and evaluated a tretinoin-based herbal cream with pomegranate extract for anti-aging effects. Among five formulations, **F5** emerged as the most effective, showing superior **antioxidant activity**, **collagen protection**, **skin elasticity**, and **wrinkle reduction**. It maintained a **smooth, non-sticky texture**, exhibited **excellent spreadability**, caused **minimal irritation**, and remained **stable under accelerated conditions**. The combination of tretinoin and pomegranate extract demonstrated strong **synergistic action** against premature aging, making **F5** a promising natural topical therapy. Further clinical evaluation is recommended.

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