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Formulation and Evaluation of Orange Peel Combined with Salicylic acid Gel for acne treatment

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Abstract
The purpose of this study was to create and assess a gel that treats acne by mixing salicylic acid and orange-peel extract. Salicylic acid is a frequently utilized chemical that aids in pore unclogging and dead skin cell removal. Natural antibacterial and antioxidant components found in orange peel may help lower acne-causing germs. To moisturize and calm the skin, *Aloe Vera* was used. Several criteria, including pH, spreadibility, homogeneity, and stability, were assessed after the gel was produced using Carbopol -934. The findings demonstrated that the gel was stable without phase separation, had a smooth texture, and had an appropriate pH of 6.1. This study suggest that the formulation might work well and safely for mild to moderate acne. This study focuses on formulating and evaluating a stable, pH-balanced anti-acne gel combining salicylic acid, orange peel extract, and *Aloe Vera* for exfoliating, antibacterial, and soothing effects.

Keywords: Acne vulgaris, orange peel, salicylic acid, gel formulation, herbal cosmetics, topical therapy, Cutibacteria

Introduction

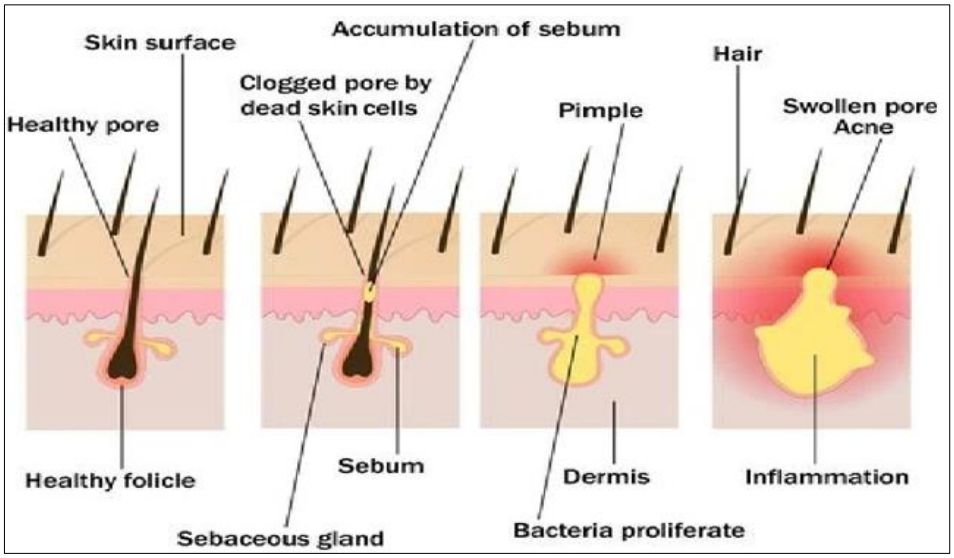

Fig 1: Acne formation

Acne: The name acne comes from the Greek word "akme," which means "peak or apex" and refers to gemnetic or acquired affections of the pilosebaceous units. Acne vulgaris is the proper term for acne. It is typified by the development of both inflammatory and non-inflammatory lesions of the sebaceous glands and hair follicles, which are together known as the pilosebaceous unit. There are five types of acne: comedonal, papular, pustular, cystic, and nodular [1]. Acne vulgaris, a hormone-mediated inflammation of the sebaceous glands and hair follicles, causes giant papules (nodules), blackheads and whiteheads (comedones),

pinhead-sized papules (papules), scaly red skin (seborrhea), and rarely scarring (pimples) [2].

It's a skin disorder that impacts nearly everyone and affects a lot of people. The adrenal glands of both sexes produce male chemicals that trigger it, and it typically affects adolescents and young adults. This condition is primarily seen on the face, chest, and back. The symptoms include discomfort, erythema, papules, pustules (pimples), pain, and loss of function. In 2015, 650 million people worldwide suffered from acne, which was ranked as the seventh most common illness globally. Provocative hyperpigmentation is more common in people of hazier ethnicities, and it is more severe in people with a favourable family history [3].

Acne can manifest as comedones, papules, pustules, cysts, or inflammatory nodules, and in more severe cases, it can progress to deep, purulent lesions [4]. The bacteria that causes acne vulgaris is called Propionibacterium acnes. Acne is brought on by these germs (Propionibacterium acnes) penetrating the skin. Studies have shown that eating foods high in carbohydrates, like bread, bagels, and chips, can exacerbate acne. If following dietary restrictions will benefit those with acne, more research is needed [45].

Acne vulgaris can be classified as either inflammatory or non-inflammatory. While comedones are a characteristic of non-inflammatory acne, inflammatory acne manifests as papules, pustules, nodules, and cysts [2]. Keratin-filled plugs called comedones are found on the epidermis' outermost layer; they can further develop into open or closed comedones. Blackheads and whiteheads are the names for open and closed comedones, respectively. A solid, fluid-free lesion is called a papule. A build-up of inflammatory cells and enhanced follicular inflammation result in the pustule, a pus-filled lesion. A lesion on the deeper, keratin-filled layer of skin is called a cyst. An extensive, solid lesion packed with fluid and keratin that results from inflammation and follicular wall breakdown is called a nodule [4].

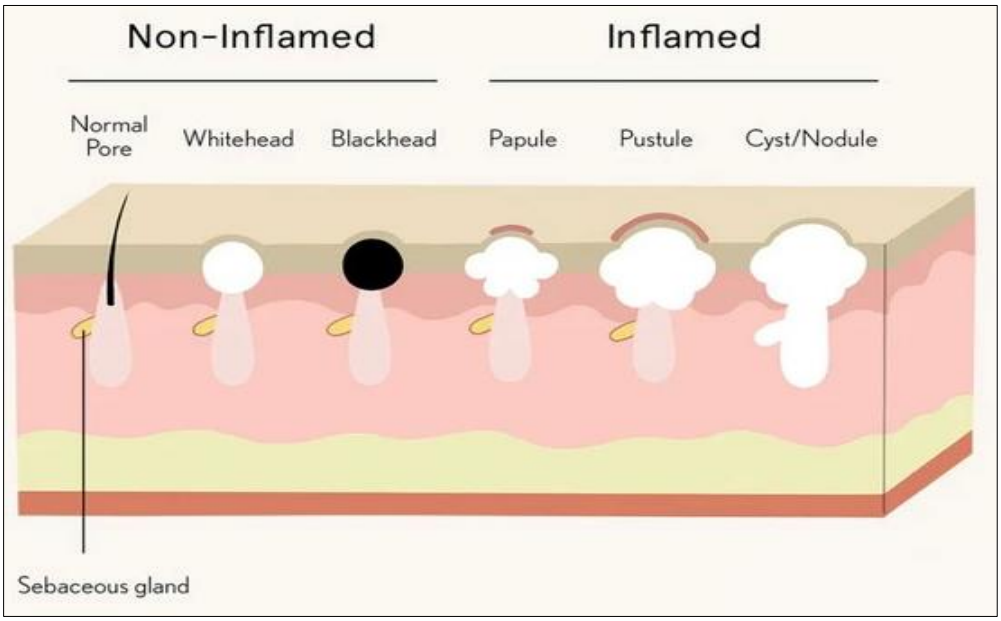

Fig 2: Acne types

In general, acne can be divided into three categories: mild, moderate, and severe. Non-inflammatory closed and open comedones with minimal inflammatory lesions are the

Hall marks of mild acne, which is usually restricted to the face. More inflammatory papules and pustules on the face, together with frequently minor truncal illness, are signs of moderate acne. And last, the presence of nodules and cysts indicates severe acne. Often, broad truncal illness coexists with face lesions in these situations [30].

The production and secretion of sebum by the androgen-sensitive sebaceous glands is one of the causes of acne. When a girl or boy reaches puberty, their levels of androgens rise. Changes in hormones associated with pregnancy, birth control pill use or cessation, stress, skin irritation, and heredity [1].

There are four main causes of acne

a) Excessive production of sebum by sebaceous glands;
b) Inhibition of keratinization within pilosebaceous follicles;
c) Fast growth and multiplication of bacteria like Propionibacterium acnes; and
d) An inflammatory immune response and swelling fortification surrounding pilosebaceous follicles [9].

There are numerous over-the-counter acne solutions available to treat mild to moderate acne or sporadic breakouts, such as gels, cleansing lotions, foams and towelettes, leave-on products, and treatment kits. Depending on their active ingredients (benzoyl peroxide, salicylic acid, sulfur, and α hydroxyl acids), acne products can work in different ways. Some eliminate microorganisms that cause inflammation, while others remove excess oil from the skin or accelerate skin cell turnover [7]. Several topical medications, including as retinoids, nystatin, salicylic acid, and antibiotics like erythromycin, clindamycin, and minocycline, are used as part of chemotherapy to treat bacterial skin conditions and acne. Furthermore, anti-inflammatory drugs are advised to reduce inflammation-related pain and itching. Nevertheless, serious side effects and adverse drug responses are common with these antimicrobial chemotherapy medications [14].

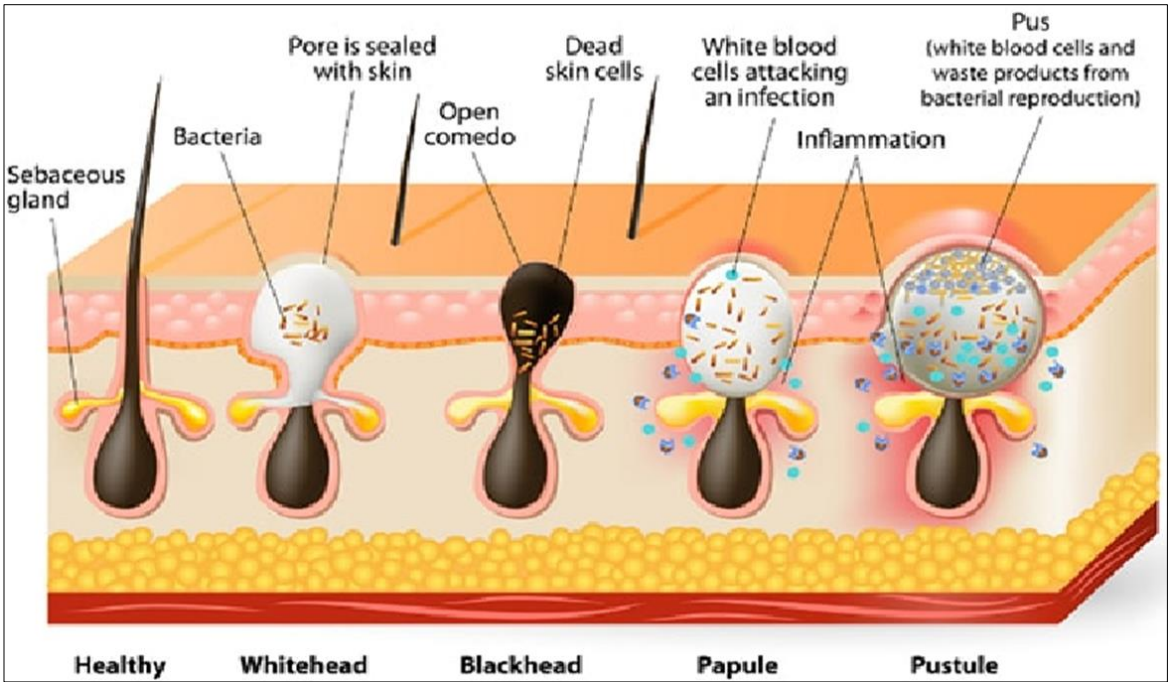

Fig 3: Progression of Acne Lesions from Healthy Pores to Pustule Formation

The majority of the time, acne is a disorder that fluctuates in severity and distribution rather than being an acute illness. Despite treatment, acne can still leave scars and have detrimental psychological repercussions, thus it is usually necessary to cure it for months to years [48].

To solve this issue, a variety of synthetic antibiotic medications are employed, including minocycline, doxycycline, and clindamycin. When using benzyl peroxide plus retinoids, topical therapy is typically the initial line of treatment. However, given the rising prevalence of antibiotics and their adverse effects, attention should be directed toward the investigation of herbal medications [5].

The four main causes of acne physiopathology are hyper cornification of the pilosebaceous duct, inflammation, P. acnes colonization, and increased sebum production. Recent studies indicate that these aspects are far more interconnected than previously thought [18].

In contrast to current formulations that have significant adverse effects such skin dryness, rashes, wrinkles, erythema, pruritis, skin eruption, and resistance development, herbal remedies are gaining popularity [6]. Numerous studies have documented the antibacterial and anti-inflammatory properties of natural chemicals produced from plants. According to new research, essential oils and/or the main components they contain may be a viable substitute for conventional acne treatments [7].

Background of Acne

- A Look Back at Acne Prevention from the Greek word "akme," which means "point or spot," the English term "acne" seems to have evolved. While there are very old texts about acne that date back to Eber's Papyrus, it wasn't until Fuchs came up with the term "acne vulgaris" and Erasmus Wilson distinguished it from acne rosacea that it was clearly characterized. Acne has roots that can be traced back to three popular ancient civilizations: the Greeks, Romans, and Egyptians.
- It has been noted in some Egyptian texts that pharaohs had acne and had tried to treat it. The term "aku-t" is mentioned in Ebers Papyrus, which was subsequently translated as "boils, blains, sores, pustules, or any inflammatory swelling." It is said to be treated with honey and some concoctions of animal origin. It was believed by ancient Egyptians in the third century that lying was the root cause of acne. According to the anti-acne treatments found in his tomb, Tutankhamun, the Egyptian pharaoh of the 18th dynasty, suffered from acne. According to historical accounts, this condition was recognized by both Aristotle and Hippocrates. This circumstance was also thoroughly addressed by Aristotle [26].
- The medical writings of the Greeks, the European pioneer in mid-19th century dermatology, Hebra (1816-1880, Vienna), noted that the Hippocratic texts contained no mention of acne. Given its prevalence, Hebra deduced that Greek doctors did not consider acne to be a medical condition. It is actually believed that Celsus and Galen were the first to describe a cutaneous condition that consists of sores on young people's faces that, to a modern reader, would resemble acne. To emphasize how diverse the lesions were, he gave it the name "varus" or "varius."
- The term "acne" was most likely first used in the sixth century by Aetius Amidenus, a physician in Constantinople, who called the lesions on the face that develop at the "acme" of life-puberty-"ionthos" (ίονθωξ,) or "acnae." Aetius' treatise suggests that αχμη (acne) originated from a mistake of αχμη (akme), as the term "acme," which was used as a colloquial term, had no official spelling until the 12th century [20].
- The first English-language dermatology textbook was written by Daniel Turner (1667-1741), a surgeon who later became a fellow of the College of Physicians of London. In 1723, Yale College awarded Turner an honorary MD in recognition of his donation of books to the library, which was the first medical degree awarded in the American colonies. He was the first to highlight dietary limitations as a treatment for acne. He reasoned that the lesion, which he called a varus or pimple, was caused by "alimentary juices by some accident lodged

in the pores of the skin and growing, as it finds liberty, into a little tubercle, or unequal rising above the surface, which after some time hardening, proves troublesome by disfiguring the face."

- In his 1783 work Doctrin a de Morbis Cutaneis (The Science of Skin Diseases), Vienna native Joseph Jakob Plenck (1735-1807) linked frequent acne in youth to a high-fat diet and abundant semen production. Additionally, he mentioned that acne went away in later adolescence and that marriage was widely believed to be a treatment for acne [31].
- Because people in ancient Rome thought that a sulfur mixture in mineral baths could lift and cleanse the skin's pores, acne was treated with baths. In his surviving medical treatise De Medicina, Roman encyclopedist Aulus Cornelius Celsus (25 BC-50 AD) made reference to this procedure. In 3 AD, Cassius deduced that this condition is called "akmas" because it is associated with puberty. Theodosius' court physician in the fourth century AD suggested that acne sufferers use a handkerchief to wipe their "pimples" while gazing at a falling star, as this would cause the pimples to "fall from the body."
- In the sample books of renowned Greco-Arabic (Unani) thinkers, a dermatological ailment known as "Busoore labaniya" was recorded. This condition bears clinical similarities to modern-day acne vulgaris. Sebaceous glands were vividly described by Rabban Tabari (770-850 AD) in his renowned work "Firdous al Hikmah" (Paradise of Wisdom). Many formulas for the treatment of minor facial eruptions (funsi) have been described by Sabit Bin Qurrah (836-901 AD). In his brilliant work Al Hawi (The Virtuous Life), Zakariya Razi (850-923 AD), also known as Rhazes, described how to treat Busoore labaniya (acne) that appears over the face and nose.

  Avicenna, also known as Ibn Sina (980-1037), described the etiopathogenesis and clinical manifestation of Busoore labaniya (acne) in his renowned work "Al Qanoon fil tib" (The Cannon of Medicine) [32].

Epidemiology: About 9.4% of people have acne, according to a 2010 study. Approximately 90% of people experience it during their adolescence and occasionally into adulthood. The prevalence of moderate to severe cases is around 20%. In remote settings, acne is rare. The prevalence is higher in girls (9.8%) than in males (9.0%). Approximately 1% of males and 5% of females over 40 experience difficulties. Although it is unclear whether race influences disease rates, it affects people from all ethnic groups [27]. Most epidemiological research on acne were conducted in the United States and the United Kingdom between the middle and end of the 20th century. A population-based research of more than 20,000 Americans whose acne was assessed by dermatologists or residents was the biggest of these. Comparable smaller studies with a sample size of around a tenth was conducted in the United Kingdom

Fig 4: Face acne

According to studies conducted during that time period, the late teens were the age at which acne incidence peaked, and as people aged, the prevalence gradually decreased. Patients who had more severe forms of acne were more likely to be male [41]. Acne prevalence varies by nation and age group; estimates range from 35% to nearly 100% of teenagers having acne at some stage [42].

Etiology: The development of acne is brought on by sebum (microcomedo), hyperkeratinization, keratin plug production, and follicular blockage. The production of sebum increases along with the enlargement of sebaceous glands caused by increased androgen production [21]. Acne vulgaris has been linked to Staphylococcus aureus and Propionibacterium acnes. Their precise roles in the development of acne are unclear, though. Certain P. acnes strains are found in normal skin, while others are seen in long-term acne problems. Therefore, it is unknown if these strains are acquired pathogenically or are engaged in this syndrome [22]. Certain foods, such as foods high in carbohydrates, such bread, bagels, and chips, have been shown in studies to exacerbate acne. Further research is necessary to determine whether following dietary restrictions may benefit those with acne [40]. Acne is most frequently found on the face, back, chest, and upper arms-areas of the body with larger, more numerous sebaceous glands. The majority of acne sufferers have a variety of acne lesions at different stages of development when they first appear (see comedone and inflamatory lesions) [24]. Comedones, pustules, scarring, seborrhea (increased secretion of oil and sebum), papules, and nodules (big papules) are all included. Skin colour affects how acne looks, and it's also linked to social and psychological issues. Acne scars are caused by inflammation in the dermis, which is produced when a cut heals and collagen deposits in one area [27].

Table 1: Types of Acne Scars and Their Distinct Characteristics

Scars	Characteristics
Box car scars	Like chickenpox scars, angular scars can be minor or deep on the cheeks.
Ice pick scars	Most often, deep pits are an indication of acne scarring.
Rolling scars	Skin with a wave-like look
Hypertrophic scars	Keloid or thick scars
Pigmented scars	Genuine scars, Alteration in the pigmentation of the skin, an angry red mark caused by cystic or nodular acne

Pathophysiology: There are both internal and extrinsic factors for acne vulgaris, making its pathophysiology complicated. But the root reason is aberrant desquamation of epithelial cells and excessive sebum production. The formation of the microcomedo, or follicular canal blockage, is one of the first factors in the development of acne lesions. The accumulation of keratin and sebum in the follicle is caused by hyperkeratosis of the follicular lining and increased cohesiveness of corneocytes.

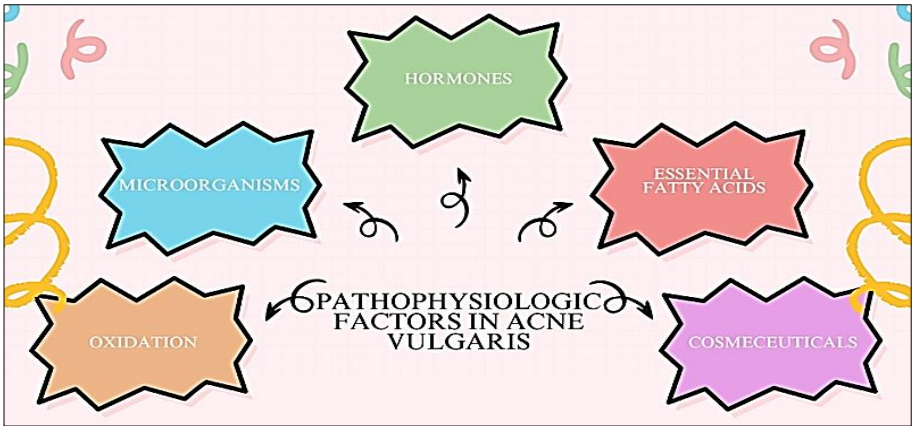

Fig 5: Key Pathophysiologic Factors Contributing to Acne Vulgaris

This forms a comedo, or plug, over the duct of the sebaceous gland. The comedo enlarges behind a tiny follicular aperture to the skin as these cells fill the follicle one by one [24]. The pilosebaceous units' activation by circulating androgens is thought to constitute the initiating event. A comedone forms when sebum production causes retention hyperkeratosis, which dilates and plugs the follicular infundibulum. When Propionibacterium acnes colonizes the follicle and the follicular plugging occurs, inflammatory mediators are released into the skin [44]. According to a small case series of 60 women, people with darker complexion had a higher density of P. acnes. There has been little research to draw firm conclusions about the size and activity of sebaceous glands in black and white participants, and the findings of a number of these studies have been inconsistent. Puberty causes an increase in sebum production, and it starts earlier for Black people [43]. It is also impacted by social and environmental pollution, as well as changes in dietary habits and lifestyle, such as increased air pollution, eating sweets, staying up late, and using social media and networks. Acne is therefore becoming more common every year [46].

Microcomedones, the antecedents of all acne lesions, are the result of sebaceous follicle obstruction, which is the earliest morphologic alteration or initial pathologic event. Although the exact process underlying the creation of microcomedo is unknown, there is solid evidence that ductal keratinocytes are hyperproliferating [47]. Androgens cause acne by causing the production of sebum, which in turn causes the formation of comedones. Sebum production associated with androgen is connected to changes in the skin's natural flora. Acne vulgaris is linked to conditions like congenital adrenal hyperplasia, polycystic ovarian syndrome, and endocrine tumors that cause the body to produce high levels of androgens [27].

Diagnosis

In most cases, acne can be diagnosed clinically. The face is the primary area affected (99%), with the back (60%) and chest (15%) being less affected. In younger patients, comedones, or non-inflammatory lesions, appear before inflammatory lesions. Many inflammatory lesions originate from non-inflammatory lesions, and they might be superficial or deep [50]. Selecting the best treatment depends on correctly classifying the type of lesion. The 1990 Consensus Conference on Acne Classification advocated a worldwide assessment of lesions and associated side effects, such as discomfort, bleeding, and drainage. Three other factors are used to grade acne: psychological impact, failure to respond to prior therapies, and occupational disability [47]. External factors including drugs, occupational exposures, or mechanical obstructions like helmets or shirt collars can cause or exacerbate acne [51].

The following scales used to grade acne vulgaris severity

- **Pillsbury scale:** It ranks acne from 1 (least severe) to 4 (most severe) according to severity.
- **Cook's acne grading scale:** From 0 (least severe) to 8 (most severe), it uses pictures to assign a severity rating.
- **Leeds Acne Grading Method:** This method uses a scale of 0 to 10 to count and classify inflammatory and non-inflammatory abnormalities. Whiter than whiteheads from acne and most frequently found near the eyes.
- Dermatitis of the perioral area.
- The majority of Pityrosporum folliculitis cases occur on the trunk [27].

Treatment: There are two methods of treating acne: topical and systemic.

The way each patient reacts to the treatment can differ significantly from one another.

A number of acne treatments are typically available, and the best outcomes are achieved when the therapies are categorized separately based on clinical assessments [25]. There isn't a single method for treating acne, and dermatologists have quite different tastes when it comes to the drugs they prescribe. Most therapies either break down the comedo or reduce the bacterial load [24].

- **Topical Retinoid:** For patients who just have comedones, retinoid therapy is the cornerstone. Between 40% and 70% of inflammatory lesions and comedones can be reduced by them [22]. By affecting

epithelial cell maturation and turnover and lowering follicular plugging, they normalize follicular desquamation. Due to its dual comedolytic and anticomedogenic properties, retinoid therapy is useful for treating inflammatory papules, open comedones, and closed comedones [24]. Tretinoin, the first retinoid used to treat acne, has been widely used for more than 40 years. Because it is photolabile, it works well for mild to moderate inflammatory and comedonal acne, especially when administered at night [34]. Adapalene was produced as a retinoid-like activity agent with anti-inflammatory and comedolytic properties. The main formulations are gel and cream, which have been found to be more effective than tretinoin. Tararotene, another retinoid-like activity agent, has been introduced. It quickly transforms into its active form, tazarotenic acid. Nevertheless, it affected non-inflammatory lesions more than inflammatory ones [23]. Retinoids will remain crucial in the treatment of acne because they inhibit the inflammatory response that P. acnes causes in individuals with acne, which is in turn controlled by vitamin A (retinol is a derivative of vitamin A) and vitamin D [37].

- **Azelaic Acid:** Azelaic acids found in nature include comedolytic action, antibacterial qualities against P. acnes, which include normalizing keratinization, anti-inflammatory effects on neutrophil function, and skin-lightening qualities [23]. An RCT involving individuals with mild acne showed that 20% azelaic acid reduced inflammatory lesions by 72%, compared to 47% with a placebo. Oral tetracycline and topical azelaic acid 20% were tested in two RCTs. Azelaic acid and oral tetracycline reduced the number of inflammatory lesions by 83% and 86%, respectively, in one trial, and 79% in another [28]. Through the stimulation of peroxisome proliferator-activated receptor-γ and the suppression of proinflammatory cytokines, azelaic acid may help lessen inflammation [34]. Among the benefits of 20% azelaic acid include its ability to cure post-inflammatory dyspigmentation and its potential for safe use during pregnancy. 20% azelaic acid is generally well accepted, however in people with dark skin, it can produce burning, stinging, and hypopigmentation [52].
- **Salicylic Acid:** A beta hydroxyl molecule with bacteriostatic, fungistatic, and anti-inflammatory qualities is salicylic acid. When applied topically, it keeps pores clear and exfoliates the skin to lessen acne. It is an effective treatment for mild pimples and comedoneal acne because it breaks the connections that hold dead skin cells together, allowing them to shed more effectively [38]. Although salicylic acid is safe to use, it can occasionally irritate, itchy, and dry out the skin. The primary usage of it is to treat moderate acne [35]. The primary usage of it is to treat moderate acne. There are many over-the-counter medications for treating acne, most of which contain salicylic acid [12]. Both α- and β-hydroxy acids have the ability to cause skin irritation that is dependent on pH. Therefore, during acne treatment, pH adjustment and formulation design optimization are essential to prevent additional skin irritation [29]. When it comes to treating acne, a 2% salicylic acid wash is somewhat more effective than a topical retinoid. Despite its long history of use, there aren't many carefully planned studies examining its effectiveness and safety [49].
- **Benzoyl Peroxide:** Benzoyl peroxide, an antimicrobial agent with a high affinity that inhibits S. aureus and P. acnes, was used to a variety of formulations, primarily gels [23]. Benzoyl peroxide use is currently not associated with any indications of bacterial resistance. As a result, the drug is frequently used in combination with topical antibiotics to lower the risk of resistance [24]. For acne, benzoyl peroxide (BP) is thought to be a successful topical therapy. It works more effectively on non-inflammatory lesions but seems to work similarly to topical antibiotics on inflammatory lesions [34]. Benzoyl peroxide is concentrated in pilosebaceous units and is well absorbed into the epidermis. The systemic circulation receives around 2% of the administered dose after it has been converted to benzoic acid in the skin. It is broken down into benzoic acid and then eliminated in the urine as benzoate [36].
- **Hormonal Treatment:** Regardless of the underlying hormonal imbalances, hormonal medications are an effective second-line treatment for acne in women. Antiandrogen medication can be beneficial even if there is no androgen excess. Based on clinical observations, hormone therapy appears to be particularly effective for deep-seated nodules on the neck and lower face [49]. These hormones are frequently used as oral contraceptive tablets. These hormone-based birth control pills prevent the formation of sebum, which is initially triggered by testosterone. It lowers the quantity of physiologically active free testosterone in women's bodies by increasing the synthesis of sex hormone-binding globulin [35]. Combination oral contraceptives have FDA approval for treating acne in women over 15 who also want to use contraception, are antiandrogenic, and are effective in treating comedonal and inflammatory acne in menarcheal females [52]. Nowadays, a number of OCs have been shown to be effective in treating acne. They all have less than 35 µg of estrogen. The US Food and Drug Administration has not authorized any androgen-receptor blockers for use in acne therapy [28].
- **Neem:** Commonly referred to as neem, Azadirachta indica (family Meliaceae) is a medicinal plant that is used extensively to cure a variety of illnesses and is found in Bangladesh, Nepal, India, and Pakistan. Neem has gained popularity in modern medicine and has been used extensively in Ayurveda, Unani, Homoeopathic, and Siddha treatment [8]. Because of its therapeutic qualities, the bark, leaves, seeds, and latex have all been used to treat a variety of skin conditions. Studies have indicated that it works well to treat acne. The ethanolic extract of Azadirachta indica showed anti-acne potential in an anti-acne trial by preventing P. acne from growing [25].
- ***Aloe Vera*:** Ayurvedic medicines contain *Aloe Vera* extract as a component. Acne lesions were greatly decreased. The medicinal application of Aloe spp. in South Africa was consistent with this Asian dermatological treatment. A. Vera, however, had no effect on the suppression of proinflammatory cytokines and ROS brought on by P. acnes [23]. A randomized double-blind clinical experiment involving 60 individuals with mild-to-moderate acne found that

topical use of 50% *Aloe Vera* gel with tretinoin cream was considerably more effective than tretinoin and vehicle and was well tolerated over the course of eight weeks [22]. For the topical treatment of mild acne vulgaris, the study found that an aqueous extract of *Garcinia mangostana* and *Aloe Vera* may be combined to create an aqueous-based gel solution [39].

- **Orange Peel:** A number of bioactive substances, including carotenoids, flavonoids, minerals, vitamins, polyphenols, and omegas, are thought to be abundant in orange peel. These substances have anti-cancer, anti-diabetic, allergy-preventive, and antibacterial qualities. Catechol, dimethoxyphenol, cyclohexane, coumarin, acetic acid, stigmasterol, sitosterol, and vitamin E are among the substances in orange peel that provide antioxidant qualities [40].

Gels: Gels are semi-rigid systems in which a three-dimensional network of interlacing particles or solvated macromolecules of the dispersed phase limits the dispersing medium's motion. "Gel" is derived from "gelatin," and the words "gel" and "jelly" can be traced back to the Latin word "gelu," which means "frost," and "gel are," which means "freeze" or "congeal" [10]. To provide the most effective cutaneous and percutaneous medication delivery, gels are used. Enzymatic activity and drug interactions with food and beverages can be avoided using gels. They can be used to provide medications orally when the oral route is not suitable [11].

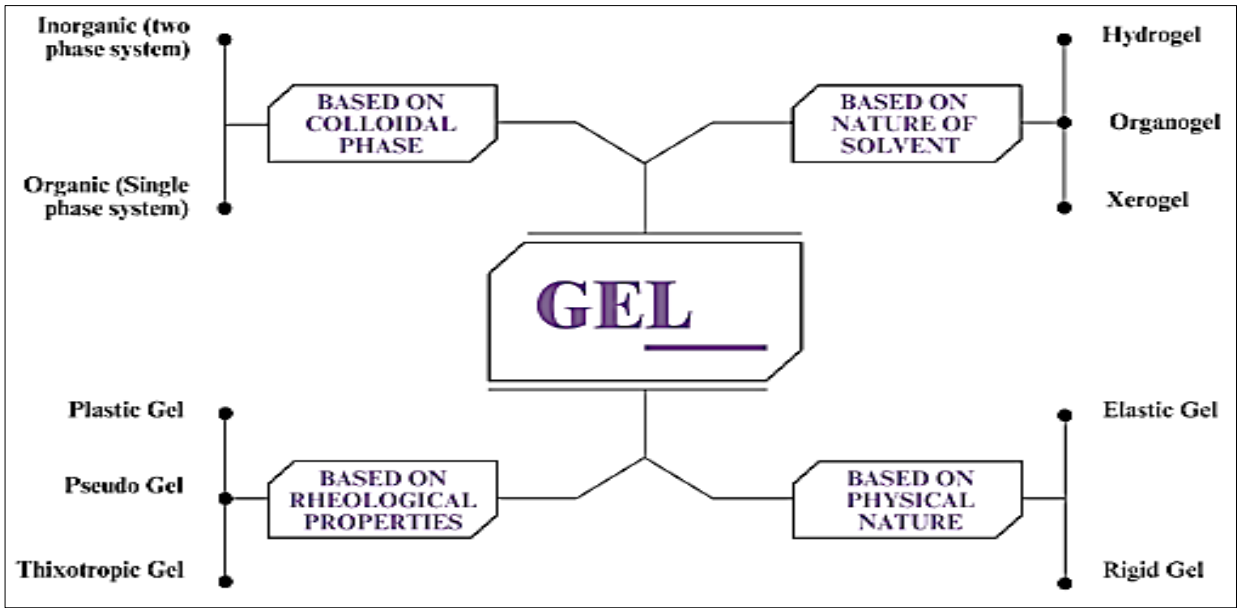

Fig 6: Classification of Gels Based on Colloidal Phase, Solvent Nature, Rheological Properties, and Physical Nature

Gels are semisolids with a high solvent to gelling agent ratio that range from translucent to opaque. Gelling agents combine or entangle when dissolved in the right solvent to create a three-dimensional colloidal network structure. Through solvent molecule trapping and immobilization, this network restricts fluid flow [1]. The structural components that make up the gel network might be either organic macromolecules, mostly polymers, or inorganic particles [13]. According to the USP, gels are a semisolid system composed of a dispersion of either big organic molecules or tiny inorganic particles that are surrounded and penetrated by liquid [16].

The majority of anti-acne creams on the market contain a number of ingredients that could have negative side effects for the user, even though gel-based, oil-free formulations are always preferable [15]. Aluminium hydroxide gel is one of the viscous oral solutions that have been dispensed using gels. Direct medication release and quicker absorption are two major benefits of topical gel delivery at pathological sites as opposed to creams and ointments [11]. represent a more recent family of dosage forms derived from the encapsulation of a sizable amount of hydro alcoholic or aqueous liquid in a network of colloidal solid particles. In general, gel formulations provide faster medication release than ointments and creams. Gels are frequently chosen because of their higher patient acceptance and user-friendliness [33].

Properties

- It is ideal for the gelling agent to be safe, inert, and incapable of reacting with other ingredients in the formulation.
- When the gelling ingredient is stored, it should have a reasonable solid-like consistency that breaks quickly when subjected to shear pressures from squeezing the tube, shaking the bottle, or applying topically [10].
- It should have an appropriate antimicrobial to guard against microbial assault.
- Avoid using sticky topical gel [13].
- It must not come into contact with any other formulation ingredients.
- The gel should not irritate the skin or any surrounding tissue when administered [17].
- The gel should keep its rheological characteristics while being stored.
- It should be emollient, thixotropic, and non-greasy [33].

Characteristic

- **Swelling:** Gels are capable of swelling, absorbing liquids as their volume increases. This might be viewed

as the first stage of disintegration. In order to replace gel-gel interactions with gel-solvent interactions, the solvent permeates the gel matrix [10]. The amount and strength of connections between individual gelling agent molecules determine how much swelling occurs [13].

- **Syneresis (weeping):** Many gels frequently emit a fluid substance and constrict spontaneously when left standing. Syneresis is the term for this effect. When the gelling agent concentration drops, the degree of syneresis increases [16]. As the concentration of the gelling agent decreases, the degree of syneresis is shown to increase. Syneresis indicates that the original gel was thermodynamically unstable [17].
- **Ageing:** Colloidal systems often aggregate slowly on their own. The term "aging" refers to this process [10]. A denser network of the gelling agent gradually forms in gels as they age [13]. Since fluid medium is lost from the freshly formed gel, Theimer proposes that this process is identical to the original gelling process and continues beyond the initial gelation [19].
- **Structure:** The development of a network by the interconnection of particles from the gelling chemicals is responsible for the hardness of a gel [17]. The types of particles and forces at play affect the gel's characteristics as well as the network's structure [33].
- **Rheology:** Gelling agent solutions and flocculated solid dispersions are pseudo plastic, meaning they show non-Newtonian flow behaviour, which is defined by a drop-in viscosity as the shear rate increases [16]. The breakdown of inter-particulate connection caused by applied shear stress disrupts the fragile structure of inorganic particles scattered in water, resulting in a higher tendency to flow [10]. Likewise, when shear stress is applied to macromolecules, the molecules align themselves in the direction of the tension, straightening up and reducing flow resistance [19].

Material & Method

The ingredients used in the formulation were selected based on their dermatological benefits and suitability for topical application. Each component contributes uniquely to the gel's stability and therapeutic effectiveness. The detailed composition is presented in the table below

Table 2: Composition, Quantity, and Functions of Ingredients in an Orange Peel-Based Topical Gel Formulation.

S.no	Ingredients	Quantity	Function
1	Salicylic Acid	1 gm	Keratolytic Agent; Causes Pores to Open and Dead Skin Cells to Be Exfoliated.
2	Carbopol (934)	1 gm	Gelling Agent; Gives It Viscosity and Structure.
3	Orange Peel	1 gm	Natural Antioxidant and Exfoliate.
4	Methyl Parabehan	0.25 gm	Preserve to Stop The Growth of Microorganisms.
5	*Aloe Vera* Gel	7 gm	Moisturizes and Calms the Skin.
6	Triethanolamine	2-3 drop	pH Adjuster (5.5-6.0) for Skin Compatibility.
7	Water	Qs. to 50 ml	Primary Solvent and Vehicle.

Herbal ingredients and their therapeutic benefits

Aloe Vera

Drug Profile

Kingdom: Plantae
Order: Asparagales
Family: Asphodelaceae
Genus: Aloe
Species: A. Vera
Botanical Name: *Aloe Vera*

Fig 7: Aloe Vera

Aloe Vera is a type of succulent plant that belongs to the genus Aloe. In many regions of the world, aloe, which contains 500 varieties, is considered an invasive plant. The Arabian Peninsula is the native home of this evergreen perennial, which grows wild in arid, subtropical, and tropical climates worldwide. It is primarily grown for commercial use as a centuries-old topical treatment [54].

Orange Peel

Drug profile

Kingdom: Plantae
Order: Sapindales
Family: Rutaceae
Genus: Citrus
Species: C. sinensis
Botanical Name: *Citrus sinensis*

Fig 8: Orange Peel Powder

Oranges, which are consumed all over the world, are a significant source of polyphenolic chemicals and vitamin C. Flavonoids-of which flavanones are the most prevalent and hydroxycinnamic acids (HCAs) are the primary phenolic chemicals found in oranges. Numerous medicinal benefits, such as anti-inflammatory, antihypertensive, diuretic, analgesic, and hypolipidemic actions, are attributed to citrus flavonoids, particularly hesperidin [55].

Method of preparation

Carbopol dispersion

- Stir 1 g of Carbopol 934 constantly in 40 mL of distilled water.
- For complete swelling, let it soak at room temperature for the entire night.

Orange Peel Extraction

- Combine 1 gram of powdered orange peel with 5 ml of ethanol.
- For five minutes, agitate vigorously or ultrasonically.
- Filter if necessary to get rid of coarse particles**.**

Fig 9: Preparation of Orange Peel Gel with GPS-Tagged

Salicylic Acid Solution

- 30 ml of distilled water has taken to heat at about 60 degrees Celsius.
  While stirring, dissolve 1 gram of salicylic acid in the heated water.
- If using, add 0.2 g of methyl parabean mix until it dissolves**.**

Fig 10: Salicylic Acid Sample with Gel Preparation

Combining Active Ingredients

Thoroughly combine the 7 g *Aloe Vera* Gel, Orange Peel extract, and Salicylic Acid solution.

Mix with Carbopol

To prevent air entrapment, gradually add this active combination to the Carbopol dispersion while stirring gently.

pH Adjustment

Drop by drop, gradually add triethanolamine until the pH reaches 5.5-6.0 and the gel is noticeably smoother and thicker.

Volume makeup & packaging

- To get 50 mL, add warm distilled water.
- Label appropriately after transferring to a sterile, airtight container.

Evaluation of Gel

- **Organoleptic Properties:** The resulting gel formulation was evaluated for a number of physical characteristics, including colour and odour [53].
- **Spreadability:** It is a term used to describe how easily gel spreads over a surface when applied to skin or an affected area. The spreading value of a formulation also affects how effective it is as a treatment. Spread ability is measured in seconds, or the amount of time it takes for two slides to separate from gel when a specific stress is applied between them. It is determined by applying the formula [1].
- **Washability:** The ease and extent of washing with water were manually assessed after the formulations were applied to the skin [1].
- **pH:** A digital pH meter that had been calibrated was used to monitor the formulation's aqueous solution (1%) at a steady temperature [5].
- **Grittiness:** By applying the product to the skin, any gritty particles were detected [53].
- **Homogenity:** The prepared gel formulation's homogeneity and appearance were examined physically [15].
- **Viscosity:** Cone and Plate viscometers were used to measure the formulated batches' viscosity [15].
- **Stability Studies:** The stability study is conducted by keeping the drug substance in their proposed pack or prototype container in the case of bulk drugs in sufficient number in room temperature away from light [5].

Results

Table 3: Organoleptic Evaluation

S.NO.	Properties	Result
1.	Colour	Orange
2.	Odour	Characteristic odour
4.	Texture	Smooth Homogenous
5.	Homogeneity	Good
6.	Washability	Good

Table 4: Physiochemical Evaluation

S.NO.	Properties	Result
1.	Homogeneity	Good
2.	pH	6.1
3.	Spreadibility	2 cm

Table 5: Stability Studies

S.NO	Properties	Result
1.	Visual Appearance	Orange
2.	Phase Separation	Nil
3.	Homogeneity	Good
4.	Grittiness	Nil

Discussion

In order to cure acne, a topical herbal-synthetic gel was developed. Due to its capacity to exfoliate and unclog pores, salicylic acid is frequently found in acne treatments. Orange peel extract was selected because to its inherent antioxidant and antibacterial properties. *Aloe Vera* was included to enhance hydration and lessen skin irritation.

The gel has good physical qualities and was simple to make. It was skin-friendly with a pH of 6.1, had a smooth and even texture, and distributed easily. The formulation is stable since stability testing revealed no phase separation. The gel's combination of synthetic and natural chemicals may provide less harmful side effects while effectively treating acne. It also bolsters the rising demand for skincare products made with herbs.

Conclusion

A topical gel including salicylic acid, orange peel extract, and *Aloe Vera* was effectively created and assessed in this study to treat acne. The combination was selected because to its ability to provide both skin-friendly qualities and therapeutic efficacy. While orange peel offered inherent antibacterial and antioxidant properties, salicylic acid functioned as an efficient exfoliate. By adding calming and hydrating properties of *Aloe Vera*, it decreases the likelihood of skin discomfort. Good physical and chemical characteristics were displayed by the finished gel, which included a uniformly smooth texture, a pH of 6.1, and no indications of phase separation over storage. According to these results, the formulation is both stable and appropriate for topical use. Future researchers could explore enhanced delivery systems, long-term clinical efficacy, varied concentrations of active ingredients, and synergistic effects with other botanicals for improved treatment of different acne severities.

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