REVIEW ARTICLE

INTERNATIONAL JOURNAL OF RECENT RESEARCH IN PHARMACY

IJRRP

ACNE- PATHOGENESIS, TYPES, CAUSES AND REMEDIAL TREATMENT FOR ACNE

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Received- 04/December/2020 **Revised-** 20/December/2020 **Accepted-** 15/January/2021 **Published-** 31/January/2021

ABSTRACT

Acne, from the Greek word "Akme" means peak or apex, is genetic or acquired affections of the pilosebaceous units. The correct name for acne is Acne vulgaris. Acne is a disease that affects 80% of adolescents and young adults. Acne vulgaris is one of the most common dermatological disorders that afflict people in their adolescence. Acne vulgaris or simply known as acne is a human skin disease characterized by skin with scaly red skin (seborrhea), blackheads and whiteheads (comedones), pinheads (papules), large papules (nodules), pimples and scarring. Acne vulgaris is a disease of pilosebaceous unit characterized by the formation of open and closed comedones, papules, pustules, nodules, and cysts. Acne affects skin having dense sebaceous follicles in areas including face, chest and back. The present review focuses on an epidemiology, etiology, pathogenesis, diagnosis, and management of acne with the pharmaceutical dosage forms. Various allopathic medicines for acne treatment includes benzoyl peroxide, antibiotics, antiseborrheic medications, sulfur and sodium sulphacetamide, anti-androgen medications, salicylic acid, hormonal treatments, alpha hydroxy acid, retinoids, azelaic acid, keratolytic soaps and nicotinamide and herbal medicine like neem, tea tree oil, turmeric, raw papaya fruit, lemon, mint etc. Currently laser and light devices and minor subcision surgery have been also performed for acne treatment.

KEYWORDS: Acne, Epidemiology, Etiology, Pathogenesis, Diagnosis, and Management of acne

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INTRODUCTION

Acne, from the Greek word "Akme" means peak or apex, is genetic or acquired affections of the pilosebaceous units. The correct name for acne is Acne vulgaris. Acne is a disease that affects 80% of adolescents and young adults. Acne vulgaris is characterized by different areas of scaly red skin (seborrhea), pinheads (papules), blackheads and whiteheads (come¬dones), large papules (nodules), and sometimes scarring (piples). Severe acne is usually inflammatory; however, it may also be non-inflammatory [(1)].

Acne vulgaris is an inflammatory multifactorial disease caused by hormonal, microbiological and immunological factors. It affects all age groups, i.e., teenagers (85%), 25–34-year-olds (8%) and 35–44-year-olds (3%). It is characterized by open and closed comedones (blackheads and white-heads) and inflammatory lesions like papules, pustules and nodules [(2,3)]. *Propionibacterium acnes*, *Staphylococcus aureus* and *Staphylococcus epidermidis* are the organisms that proliferate rapidly [(4)] and cause the development of acne. The severity of this skin disorder generally increases with age and time. People normally get affected by it with the onset of puberty.

Overview of Acne Pathogenesis

The pathogenesis of acne (a common skin disease, which manifests in the pilosebaceous follicle) is attributed to multiple factors such as increased sebum production, alteration of the quality of sebum lipids, regulation of cutaneous steroidogenesis, androgen activity, follicular hyperkeratinisation and the proliferation of *P.*

acnes within the follicle [5,6]. It is believed that adrenal androgens stimulate the lipid production of sebaceous glands and produce more of follicular epithelium, which later becomes cohesive. The cells further adhere to one another and form micro-comedone, which is the precursor to all types of acne lesions [7]. The follicle then gets colonized by normal bacteria flora of the skin, which includes *P. acnes, S. aureus* and *S. epidermidis.* They can produce a variety of enzymes, including lipase and protease, to hydrolyze sebum and release inflammatory compounds to stimulate immunological response (degranulation of mast cells and neutrophil chemotaxis) resulting in the development of inflammatory acne lesions [8].

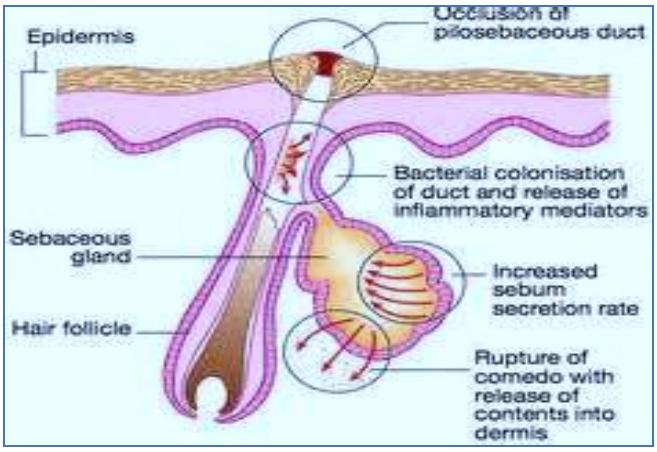

Figure 1: Pathogenesis of Acne

Propionibacterium acnes

The primary micro-organism responsible for the development of inflammatory as well as non-inflammatory acne is *P. acnes* [9]. *P. acnes* belongs to a family of anaerobic, non-spore forming gram-positive and non-motile bacterium [10]. Three species of *Propionibacterium*, namely, *P. acnes, P. avidum and P. granulosum* are recognized as commensals of the human skin [11]. They act as immunostimulators which can produce a variety of biologically active molecules and enzymes such as lipases, proteases and chemotactic factors, which are involved in the development of inflammatory acne [12].

Hormonal Factors

Hormonal factors, particularly androgens, appear to be important in the pathogenesis of acne vulgaris. The sebaceous glands, in case of acne, are more sensitive to normal blood levels of androgens, and are stimulated to produce more sebum. Unfortunately, puberty leads to an increase in the production of sebum, which in some cases is caused by increased levels of testosterone in both males and females [13]. For example, testosterone stimulates the sebaceous glands accompanying the hair follicles. In response, these glands become enlarged and begin to secrete more sebum than usual. Testosterone also stimulates the cell lining to release more keratin, an insoluble protein which is the primary constituent of the hair and the epidermis.

Together, the sebum and keratin block a skin pore resulting in comedones, also known as blackhead. These are open comedones, having black appearance and are caused due to the oxidation of tyrosine to melanin by tyrosinase, whereas white heads are referred to as closed comedones. Bacteria proliferate in the clogged pores and the body typically responds by releasing enzymes to break down the sebum [14]. These enzymes cause the pore to inflame. This, eventually, may result in pustules or pimples and is especially prevalent on the face, back and shoulders where a larger number of sebaceous glands exist.

Sebum

Sebum production is stimulated by androgens and is believed to be responsible for the development of acne vulgaris [15]. *Acne vulgaris* and sebum production in both sexes correlate with serum dihydroepiandrosterone sulfate (DHEAS) levels during puberty. DHEAS is an adrenal precursor for the synthesis of more potent androgens, such as testosterone and dihydrotesto-sterone (DHT).

Although increased serum androgen levels correlate with the presence of severe nodular acne in men and women, these levels are often within the normal range in case of mild to moderate acne. The sebaceous glands possess the steroid metabolizing enzymes needed to convert DHEAS to DHT. Even in acne patients, lipoperoxides are present because of the peroxidation of squalene and due to decreased level of vitamin E, which is a major sebum anti-oxidant [16].

Lipoperoxides and monounsaturated fatty acids (MUFAs) are capable of inducing alteration in keratinocytes proliferation and differentiation, whereas peroxides are also capable of inducing the production of pro-inflammatory cytokines and activation of peroxisome (PPARs) proliferator-activated receptors [17].

Nutrition:

Acne is driven by hormones and growth factors [particularly insulin-like growth factor (IGF- 1)] acting on the sebaceous glands and the keratinocytes. Dairy products contain steroid precursors of DHT, which are responsible for the functioning of sebaceous glands [18]. Drinking of milk causes a direct rise in IGF-1 through a disproportionate increase in blood sugar and serum insulin levels [19]. High glycemic load foods also cause IGF-1-mediated elevations in DHT, which in turn leads to the formation of acne [20]. Moreover, vitamin A, which is required for normal follicular function, is often found deficient in teenagers. Therefore, they are more prone to acne.

Cytokines:

In normal sebaceous glands, cytokines are generally present but their release increases significantly in a stressed environment. Cytokines like IL-1 a, tumor necrosis factor (TNF-a), IL-6 and IL-8 get released into supernatant only in unstressed sebocyte culture. However, in vivo studies indicate that IL-6 is barely detectable in the sebaceous glands of healthy skin. In case of acne patients, a weak expression has been found in the unaffected portion of skin but a stronger one in the affected portion. It has also been found that IL-8 exhibits a stronger expression in sebocytes of acne afflicted patients than in those of healthy controls [20].

Epidemiology:

Acne vulgaris or common acne affects approximately 80% of young adults between the ages of 12 and 24 years. The incidence of acne peaks at 18 years of age and it usually continues for four or five years. Acne also affects 80% of adults aged 25 to 34 years and 3% of adults aged 35 to 44 years. Experts believe that the prevalence of acne among older people is increasing, although the reasons for this are uncertain [21].

Salient Causes for the Development of Acne:

Acne appears when the pores on the skin are blocked either with oil, dead skin, or bacteria or both. Each pore on the skin is the opening to a follicle which is made up of a hair and a sebaceous oily gland. The oil gland releases natural substance called sebum which lubricate and protects the skin passes up to the hair root, through the pores, and skin. At this juncture acne is spread out due to one or more problems occurred in this lubrication process due to increased oil production and plug the follicular pore. If it is covered by a thin layer of skin, the said plug either appears to be a whitehead or if it is exposed to the air, the darker exposed portion of the plug is termed as blackhead. The plugged hair follicle gradually emerged as a bump.

As the follicle expands, the wall become rupture, allowing normal skin bacteria enter into the deeper layers of the skin, duly creating inflammation as a result of which the surface of the skin produces a pustule and deeper inflammation become pimple and if penetrates more deeper a cyst is formed which may leave incurable permanent scars on the skin. Due to excess production of oil, a pore clogged by dead skin cells, as well as bacteria are caused to the development of pimples [22].

Sign and Symptoms of Acne

It includes papules, nodules (large papules), seborrhea (increased oil-sebum secretion), comedones, pustules and scarring [23]. The appearance of acne varies with skin color and it is also associated with psychological and social problems [24].

Types of Acne

According to the criteria of age, acne can be classified as neonatal acne, infant acne, puberty acne and acne in the adult. Different types of acne **(Table 1)** have different degrees of severity [25].

Treatment of Acne

Though acne vulgaris is not a life-threatening disease, it is a distressing skin condition which causes significant psychological disability. The estimated annual worldwide expenditure on acne OTC medication is $100 million. Severe cystic acne leads to purulent discharge and recurrent bleeding. Patients experience anger and are at increased risk of depression, anxiety and suicidal ideation because of their social appearance. Moreover, they are mainly teenagers or young adults who experience embarrassment in their peer group after the occurrence and development of scar. It has been reported that scarring may affect up to 95% of the patients with acne [26]. Therefore, acne patients look forward to a topical product that is not only safe and effective but also cosmetically acceptable and easy to apply.

Table 1: Types of acne and its characterization

S. No.	Type of Acne	Characterization
1	Acne vulgaris	Shows presence of black spots, white spots, papules and/or pustules.
2	Acne congloblata	Very severe type of acne with presence of some nodules and cutaneous injuries.
3	Acne papulopustular	Characterized by the presence of pustules and papules.
4	Acne excorie	More common in females than males and can be a sign of stress or depression and is characterized by the presence of scratched or picked pimples.
5	Acne mechanics	Originates by reaction to a constant pressure on the skin, friction, heat or when the skin is always covered.
6	Chloroacne	Cutaneous rash characterized by many comedones due to the exposition of chlorinated or chemical or herbicides agents.
7	Acne steroid	Acne that appears after a long exposition to the corticosteroids

Acne Therapies and Their Limitations

There is a large and expanding market for over-the-counter (OTC) medications. Currently, acne therapy is based on the treatment of excess sebum production, keratinization disorders and increase in the number of *P. acnes* [27]. A number of antibiotics and chemotherapeutic agents are applied topically or taken orally, such as benzoyl peroxide, erythromycin, clindamycin or tetracycline, etc., to control the bacteria. Depending on clinical type and severity of the disease, currently, acne is being treated either by monotherapy or by a combination therapy of chemotherapeutic agents [28]. Currently available treatments have many unwanted side effects, such as skin dryness, puritis, burning sensation, erythema, occasional hyperpigmentation, local irritation and photosensitization [29]. There are a variety of therapies available that are frequently administered in combination to target concurrent multiple pathogenic factors, which are listed along with their side effects **Table 2**.

Table 2: Overview of Reported Therapies

S. No.	Category	Active Ingredient and Mode of Administration	Mechanism of Action	Side Effects
1	Retinoid	Isotretinoin (Topical)	Suppress TLR's expression and inhibit IL and IFN production	Headache, effect on CNS, teratogenic effects, irritation [30]
2	Retinoid and macrolide	Tretinoin and erythromycin (Topical)	Synergistic effect	Headache, effects on CNS, teratogenic effects, GI irritation [31]
3	Retinoid and macrolide	Tretinoin and clindamycin phosphate (Topical)	Synergistic effect	Stomach pain, effects on CNS, teratogenic effects [32]
4	Retinoic acid derivative	Adapalene (Topical)	Comedolytic effect, anti-inflammatory	Irritation, dryness and itchy skin [33]
5	Retinoic acid derivative	Tazarotene (Topical)	Reduces lesions and inflammation	Erythema, pruritis, burning, stinging [34]
6	Antibacterial	Benzoyl peroxide (Topical)	Inhibits *S. aureus* and *P. acnes*	Erythema, contact dermatitis, dryness, bleaching of clothes [35]
7	Keratolytic and anti-inflammatory	Salicylic acid (Topical)	Inhibits prostaglandins, mild keratolytic and anti- inflammatory	Dryness, skin irritation [36]
8	Lincosamide antibiotic	Clindamycin, erythromycin, tetracycline (Topical)	Bacteriostatic for *P. acnes*	GI irritation due to erythromycin. Tetracycline causes dizziness and tinnitus, not to be taken by pregnant or lactating mother [37]
9	Antibiotic and antibacterial	Clindamycin and benzoyl peroxide (Topical)	Synergistic effect	Abdominal pain, bloody diarrhoea, colitis [38]
10	Antibiotic and retinoid	Clindamycin and retinoid (Topical)	Synergistic effect	Diarrhoea, abdominal pain, colitis [39]
11	Antibiotic and retinoic acid derivative	Clindamycin, adapalene (Topical)	Synergistic effect	Erythema, scaling, dryness, burning [40]
12	Naturally occurring comedolytic	Azelaic acid (Topical)	Inhibition of (ROS), reduction of inflamed pustules, papules *P. acnes* sensitive	Scaling, pruritis, mild burning sensation [41]
13	Antibacterial and anti-inflammatory	Dapsone (Topical)	Reduction in inflammation and lesions	Dryness, redness and peeling of the skin [42]
14	Nitroimidazole antibiotic	Metronidazole (Topical)	*P. acnes* not sensitive;	Skin redness, dryness, burning,

			anti- inflammatory	irritation, stinging [43]
15	Antibacterial and Keratolytic	Sodium sulfacetamide and sulfur (Topical)	Antimicrobial effect	Exfoliative dermatitis [44]
16	Anti- androgens	Spironolactone, flutamine and cyproterone acetate (Oral)	Inhibitors of 5- a-reductase enzyme	Nausea, vomiting, breakthrough bleeding, weight gain, and breast tenderness [45]
17	Antibiotics	Tetracycline HCl and oxytetracycline (Oral)	Antimicrobial effects on *P. acnes* and inhibitory effects on cytokines	GI tract upset lupus erythematous. Tetracycline causes dizziness and tinnitus. and should not to be taken by pregnant or lactating mother [46]
18	Antibiotics	Doxycycline and minocycline (Oral)	Antimicrobial effects on *P. acnes* and inhibitory effects on cytokines	Pigmentation in the skin, headache, dizziness, ataxia, photosensitivity and drowsiness [47]
19	Macrolide antibiotic	Azithromycin (Oral)	Antimicrobial	Nausea, vomiting and dermatological reactions [48]
20	Retinoid	Isotretinoin (Oral)	Inhibits *P. acnes* growth	Dryness, itching, peeling, headache, flare, teratogenic effects [49]

Herbal Treatments for Acne

Modern acne therapy has been designed to interrupt the pathogenic pathway at one or more points. Both topical and systemic therapies are available for the treatment of acne. Topical therapy includes comedolytic agents and antibiotics and various anti-inflammatory drugs. Systemic therapy includes antibiotics, zinc and hormones [50]. With the excessive use of antibiotics for long periods has lead to the increased resistance in acne causing bacteria against a number of antibiotics used of treat acne.

A long term therapy is required for the treatment of acne so there are more chances of occurrence of adverse effects due to this medication. Some of the reported adverse effects reported are lupus erythematosus, serum sickness like reaction, autoimmune hepatitis, pigmentation of skin, alveolar bone pneumonitis [51]. These leads to an increased interest among patients seeking alternative treatment for such conditions. World Health Organization (WHO) noted that majority of world's population depends on traditional medicine of primary healthcare.

Herbal therapy for skin disorders has been used for thousands of years. Specific herbs and their uses developed regionally, based on locally available plants and through trade in ethnobotanical remedies. Systems of herbal use developed regionally in Europe, the Middle East [52], Africa, India [53], China, Japan, Australia, and the Americas. In India, records of Ayurvedic medicine date back to about 3000 BC.

To overcome the problem of antibiotic resistance, medicinal plants have been extensively studied as alternative treatments for diseases. So, our aim and objective are to develop safe and effective polyherbal formulation for effective management of acne.

1) Tea Tree Oil

Tea tree oil, also known as melaleuca oil, is a monoterpene-rich, lipophilic, essential oil derived by steam distillation of leaves and terminal branchlets of the Australian native plant *Melaleuca alternifolia* (Myrtaceae) [54]. Tea tree oil consists of a complex mixture of hydrocarbons and terpenes [54]. The oil consists of approximately 100 components, including terpinen-4-01, 1, 8-cineole, a-terpineol, terpinolene and a- and y-terpinene, making up 90% of the oil. Clinical studies with tea tree oil products have shown efficacy for a number of superficial diseases including acne, oral candidiasis, tinea, onychomycosis and molluscum contagiosum [54, 55].

Figure 2: Tea tree oil

2) Neem

The neem tree (*Azadirachta indica*) is a tropical evergreen tree native to India. In India, neem is known as "the village pharmacy" because of its healing versatility, and it has been used in

Ayurvedic medicine for more than 4,000 years due to its medicinal properties. The bark, leaves, seeds and latex have been used for the treatment of many skin problems due to the presence of medicinal properties. The main chemical components are tri-terpenoids and tetra-nor triterpene in seed oil; nimbolin A and B, nimbin, gedunin, tannin and volatile oil in the barks and leaves. It is showed anti-inflammatory, anti-microbial and antibacterial properties [56, 57].

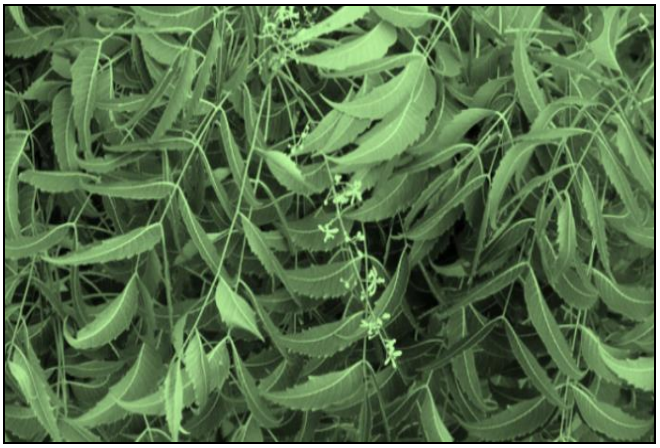

Figure 3: Neem

3) Liquorice

It is commonly known as Mulethi. Liquorice roots are particularly rich in flavanoids [58]. The root contains 5-10% glycyrrhizin, licochalcone, glabridin, glbrene and showed antimicrobial activity [59]. It is used for skin irritation and in cosmetics for acne and sunburn [60, 61].

Figure 4: liquorice

4) Turmeric

Turmeric (*Curcuma longa* L.) belongs to the family Zingiberaceae includes more than 80 species of rhizomatous perennial herbs and has widespread existence in the tropics of Asia, Africa, and Australia [62]. *C. longa* revealed the presence of many rich sources of polyphenolic curcuminoids, i.e., curcumin, demethoxy-curcumin, and bisdemethoxycurcumin [64]. Curcumin (diferuloylmethane), the main yellow bioactive component of turmeric has been shown to have a wide spectrum of biological actions. These include its anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, antifertility, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, antifibrotic, antivenom, antiulcer, hypotensive and hypo cholesteremic activities. Curcuminoids contain curcumin the principal curcuminoids (about 80%), and other two curcuminoids are demethoxycurcumin (about 12%) and bisdemethoxycurcumin [63, 64]. Turmeric paste is used to treat common eye infections and to dress wounds, treat bites, burns, acne, and various skin diseases [65].

Figure 5: Curcuma longa

5) Raw Papaya Fruit

It is a natural acne remedy for the removal of dead skin cells as well as excess lipids from skin surface keeping it soft. Papaya also contains an enzyme papain, which reduces inflammation and aids to stop pus formation.

Figure 6: Raw papaya fruit

6) Tomato

Tomatoes are naturally rich in antioxidants and vitamin-C and A. Tomatoes are used for acne

remedy because these are available at any food store. First slice a small tomato in half. Rub the opened half over areas of the skin where acne is present. Massage the juice on skin for few seconds is very easy application. Eventually rinse face with warn water. Apply twice a day for getting decorous results.

Figure 7: Tomato

7) Lemons:

Lemon act as an exfoliant, disinfectant and skin lightener to decrease the appearance of new pimples forming and scars. Lemon juice works as a disinfectant. It will kill bacteria that cause acne. Lemon juice can also stimulate circulation to the skin which will get essential nutrients from body to aid fight acne.

Figure 8: Lemons

8) Bananas Peels:

It contains something substance known as lutein, one of the powerful antioxidant which decreases the swelling and inflammation, and helps healthy cell growth of the skin of one banana peel is required.

9) Mint:

It has menthol content, which works as a natural anti-inflammatory and pain killer but it cannot cure acne yet it acts as helping agent to lessen the redness spot on the skin.

Figure 9: Bananas peels

Figure 10: Mint

CONCLUSION:

Despite recent scientific investigations, researchers are still not able to arrive at correct conclusions scientifically about acnes on the various parts of the body. But the proper option is to abandon all things that may cause or worsen the acne by keeping face and body skin clean every day. Diet, lifestyle and herbs can be an important part of natural remedies. Born of Acne cannot be cured. After its emergeit can be controlled with treatment.

The main goal of acne treatment is to decrease or clear up the spots through treatments or skin care to inhibit sebum production, bacterial growth, shedding of skin cells and unclogging pores. Acne comes and goes, between the age of twelve and twenty-three, but some people develop severe acnes because of production of higher level of androgens in their systems but men are more sufferers from acne than women. The continued resistance of mainstream dermatology to the possibility of this approach does not optimally

serve patients who might be significantly helped by natural therapies. There are sufficient pilot data to warrant larger trials on various herbal medicines in isolation and combined with each other and other natural therapies. The data are also sufficient to support a recommendation for use of these herbs in clinical practice. This is particularly true, given how safe they are. Overall, herbal medicine has much to offer to improve our ability to deal with the complex issue's acne presents.

ACKNOWLEDGEMENT

Authors are thankful to Dr. Pushpendra Kannojia (Principal), BIU College of Pharmacy, Bareilly International University, Bareilly for his valuable suggestion in writing this paper.

CONFLICT OF INTEREST

None

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How to cite this article:

Singh B, Mishra P, Kannojia P, Bijauliya RK and Singh PK. "Acne- pathogenesis, types, causes and remedial treatment for acne". International Journal of Recent Research in Pharmacy (IJRRP), 2021; 2(1A), pp. 01-09.