

# Management and Treatment of Acne Vulgaris

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**Abstract:** With the present-day fast lifestyle leading to stressful conditions, coupled with increase in dietary intake of fast foods, the incidence of acne vulgaris may evolve as a major medical problem in the near future. Acne vulgaris can have physiological manifestations such as eruptions which tend to impair the appearance of a person as also psychological manifestations such as feeling of ugliness, depression, low self-esteem etc. Acne vulgaris can be prevented by maintaining self-hygiene and application of topical products which prevent the development of conditions favourable for formation of acne vulgaris. Cosmetics can also help in treatment of acne vulgaris once they are formed. The prevention and treatment of acne vulgaris assume tremendous significance since untreated acne vulgaris can leave permanent scars which may be difficult to remove.

**Keywords:** Acne vulgaris, treatments, inflammation, skin microbiota in acne.

## Introduction:

Acne which is an inflammatory disorder of pilosebaceous unit that occurs during adolescence which causes characteristic lesions with open (black) and closed (white) comedones, which may progress into inflammatory lesions (papules, pustules, nodules and cyst) <sup>(1)</sup>. Acne in general is a form of eruption on the skin mainly in the facial area which tends to affect the appearance of an individual. Acne is common among both males and female genders and mostly affects people in their adolescence. Acne has both physiological as well as psychological effects on the person. While the physiological effects are mainly soreness accompanied with pain, the psychological effects are anxiety, depression and low self-esteem. In one of the studies, it was also reported that 8.8 % of women dealing with acne reported suffering from depression which was twice the number of men. <sup>(2)</sup> With proper care, development of acne can be prevented with the help of conventional therapies as well as alternative therapies containing new agents under development for the treatments that are available for curing acne once the skin condition arise.

## Acne Vulgaris:

All the types of acne are disorders of pilosebaceous units, which are composed of hair follicles, sebaceous glands and hair. <sup>(3)</sup> These skin condition that is formed when a hair follicle becomes plugged with oil, dirt, and dead skin cells. This accumulation causes the formation of whiteheads, blackheads, pimples or cysts. Acne has been found to be more common in teenagers but it may affect people of all ages. Based on age, acne can be neonatal, infantile, mid-childhood and preadolescent. This classification is based on a panel convened by the American Acne and Rosacea Society.

Neonatal acne is also called baby acne or neonatal cephalic pustulosis and expresses itself in new born babies, in about two weeks after birth and does not usually leave scars. Infantile acne affects children of ages six weeks to one year and is more common in boys than in girls, at a ratio of 3:1. Mid-childhood acne affects children from ages 1-6 years and is rather rare, and may result in

hyper-androgenism, and therefore a visit to an endocrinologist must be made. Preadolescent acne expresses itself in the first signs of puberty, between ages 7 to 12 years or up to menarche in females and is the most common age group that is affected by this skin condition, usually affecting the T-zone of the face. Adult acne or post-adolescent acne onsets in the teenage years or after the age of 25 and can be persistent. The scarring of the skin may depend on the severity of the acne. <sup>(4)</sup>

Whiteheads are closed plugged pores on skin while blackheads are open plugged pores. Both, whiteheads and blackheads are non-inflammatory. Whiteheads are formed when the follicular wall bulges. Blackheads on the other hand, are formed when the pore is open and is congested with oil and bacteria which turns brown when exposed to air. While whiteheads and blackheads are non-inflammatory in nature, papules, pimples, pustules, nodules and cysts cause inflammation of the skin. Papules are small, red and tender bumps on the skin, pimples or pustules are papules which contain pus, showing as a white tip, nodules are large, solid and painful lumps under the skin and cysts are cystic lesions that are under the skin, painful and pus filled. While whiteheads and blackheads may be treated with cosmetics and physical procedures, the latter four which are inflammatory in nature are harder to treat and may need medical attention. <sup>(5)</sup>

### **Formation of Acne vulgaris:**

Acne vulgaris is the formation of comedones, papules, nodules or cysts as a result of obstruction and inflammation of pilosebaceous units which consist of hair follicle and their accompanying sebaceous gland causing increased sebum production. These obstructions are also contributed to by keratin retention and growth of bacteria which results in inflammation. One of the major pathogenic factors involved in acne vulgaris is hyper-keratinization. The sebaceous follicles get obstructed and result in abnormal keratinization of infundibular epithelium. The increase in sebaceous gland secretion due to androgens and microbial colonization of pilosebaceous units by *P. acnes* leads to the formation of perifollicular inflammation. Increased activity of the sebaceous glands results in the proliferation of *P. acnes* which is anaerobic in nature, retains sebum from pilosebaceous ducts. These anaerobic organisms consist of ribosome rich cytoplasm with thick cell wall producing various biologically active mediators that results into inflammation by promoting leukocyte migration and follicular rupture. In case of inflamed lesions, several neutrophils and macrophages infiltrate surrounding hair follicles causing phagocytosis of *P. acnes*. For examination of neurogenic factors involved in pathogenesis of acne vulgaris, one can quantitatively assess the effect of neuropeptides on morphology of sebaceous glands by in vitro analysis using electron microscopy <sup>[6]</sup>. In general *Propionibacterium acnes* (*P. acnes*), an anaerobic bacterium is believed to play a vital role in the formation of acne vulgaris on the skin. The accumulated sebum gets oxidized in a process called sebum peroxidation. The oxidative damage thus caused by the free radicals lowers the oxygen supply to the area and *P. acnes* being anaerobic, thrives in this environment. <sup>(7)</sup>

The mechanism of acne formation involves pathogenic factors like seborrhea, sebum retention and inflammation in the respective sequence. The sebum retention is caused by hyper-keratinization of the infra infundibulum of the sebaceous duct. This is due to the stimulation of sebaceous gland by androgens which may be due to the excessive sensitivity of sebaceous end-organs to androgens. The corresponding inflammation is related to the inflammatory role of various enzymes of *P. acnes* and to the chemotaxis of neutrophils. <sup>(8)</sup>

*P. acnes* plays a vital role in acne pathogenesis. One mechanism is through the Toll-like receptors (TLRs).

There are four distinct stages or steps to the formation of acne vulgaris on the skin. These are:

1. Androgen that act on the sebaceous gland to increase sebum production – Stimulation of sebaceous gland is due to the potent androgen 5 $\alpha$ -DHT as the sebaceous gland cells consist of all the necessary enzymes required for the conversion of testosterone to 5 $\alpha$ -DHT. 5 $\alpha$ -reductase type I Isozyme catalyzes the conversion of testosterone to 5 $\alpha$ -DHT in peripheral

tissues by a NADPH dependent reaction, expressed where cytoplasm and cell membrane compartment is present in skin cell. This is particularly more frequent in facial sebocytes. <sup>(9)</sup>

2. This increase in sebum facilitates the growth and proliferation of the bacterium *P. acnes* – The increase in sebum excretion has a major role in pathophysiology of acne vulgaris. Other than this, there are other functions of sebaceous gland which are also responsible for acne development such as sebaceous proinflammatory lipids, production of different cytokines, various neuropeptides like corticotrophin releasing hormone produce by sebocytes and substance P (belonging to tachykinin family of peptides found in peripheral and central nervous systems) in nerve endings of healthy glands of acne patients. <sup>(10)</sup>
3. There is impairment in the follicular desquamation – This causes the desquamated matter to plug the opening of the follicle. Linoleic acid is responsible for regulating interleukin (IL)-8 secretions which regulates the inflammatory responses regarding acne vulgaris. The deficiency of Linoleic acid can cause impairment in the follicular epithelium barrier, allowing other fatty acids produced by bacterial lipase activity or sebocytes metabolism to penetrate the epithelium, leading to the deficiency of essential lipids <sup>(11)</sup>
4. The presence of *P. acnes* causes conversion of sebum to free fatty acids in greater amounts – *P. acnes* is known to releases lipase that produce fatty acids by digesting sebum, which results into inflammation of the skin. At least 12 putative lipases are encoded in the genome of *P. acnes* but only two of them (GehA and GehB) possess a signal peptide for secretion. They are 42% identical on protein level. GehA is thought to be the main enzyme responsible for hydrolysis of sebum triglycerides, resulting in production of free fatty acids, and is considered as the inflammatory agent. It increases adhesion between *P. acnes* and the cells of hair follicle, promoting colonization of *P. acnes*. Whereas, GehB is shown to be associated with healthy skin and beneficial effect of lipase. However, there are possibilities that different lipases play distinctive roles in regard to health and disease <sup>(12)</sup>

In males, the androgens target the sebaceous gland and acne may be caused by excessive sensitivity of the gland to androgens. In women however, an ovarian or adrenal hyperandrogenism may be the cause.

#### **Conditions Favourable for Acne Formation:**

Typical areas for appearance of acne are forehead, face, chest, shoulders and upper back as they contain relatively more pilosebaceous units. This means that acne prone skin is typically oily in nature. There are certain triggers for the formation of acne on skin or those that may worsen it. Factors such as hormonal changes, diet, stress and certain medications may in fact worsen the acne condition. Acne vulgaris can also be hereditary in some cases.

The hormone, androgen increases during puberty which affects the sebaceous glands causing them to enlarge, thus producing more sebum. This is a common occurrence. In males suffering from acne vulgaris, the skin may exhibit high levels of 5 $\alpha$ -reductase which causes increase in the conversion rate of testosterone to a more active dihydrotestosterone. Hyperandrogenic conditions like excess of adrenal androgen and 21-hydroxylase deficiency and polycystic ovarian syndrome may aid with the development of acne. Many females undergo hormonal changes in later stages of life, which can lead to acne breakouts. Premenstrual breakouts are common in women. Medications that include steroids such as corticosteroids, testosterone or lithium also contribute to acne formation on skin. <sup>(13)</sup>

A diet rich in carbohydrate foods, such as breads, pasta, cereal made of wheat flour, chips, sodas, sugar sweetened beverages, sweeteners such as maple syrup, honey and cane sugar and high glycemic foods may worsen acne. Different receptors are expressed

by the sebaceous gland, responsible for inducing sebum. Studies have identified the receptors which get activated by dietary substances. Free fatty acids and cholesterol present in diet are known to stimulate the peroxisome proliferator-activated receptor (PPAR  $\alpha$ ,  $\beta$  and  $\gamma$ ) and (IGF)-1 which is an insulin-like growth factor receptor is stimulated by sugar and, leptin receptor by fat. Bodyweight is regulated by adipocytes which is secreted by leptin hormone and known to link lipid metabolism with inflammation in various cell types. This result suggests that leptin plays the major role in inducing inflammation and altering lipid profile in sebocytes and can be a link between diet and inflammatory acne development.<sup>(10)</sup> Application of oily, occlusive cosmetic products like face creams, lotions may also contribute to acne.

Acne vulgaris not only affects the skin but also may take a toll on the emotional health of an individual. This is due to the fact that acne may result in discolored skin and permanent scarring on the areas that it affects. It may also leave open pores on the skin. Studies have shown that people suffering from acne vulgaris can develop signs of depression, anxiety, low self-esteem, poor self-image and an overall low quality of life.<sup>(14)</sup>

Even though acne vulgaris is not a fatal or life-threatening skin condition, it does impact more than just the skin of a person. Untreated acne vulgaris can result in permanent scarring of the skin. Untreated cases of severe acne such as cystic may result in more severity such as acne conglobate which is characterized by nodules of cysts under the skin which is a very painful condition.

Other effects of acne vulgaris include post inflammatory hyperpigmentation and excoriated acne. The former is the change in skin color after the acne has healed and the inflammation from the acne is gone. It results in hyperpigmentation due to the quantity of melanin deposits in that area. These are temporary blemishes on the skin and heal over time, usually without the aid of treatment or medication. Excoriated acne, however, is another specific kind of acne which results when the papules, pimples in the affected area are popped, picked at or squeezed. This condition is characterized by an intense urge to pick and scratch at the lesions even if they are small whiteheads or blackheads.

Acne vulgaris is known to grow in the following four grades:

Grade I – Simple non inflammatory acne consisting of comedones and a few papules.

Grade II – Here comedones, papules as well as a few pustules are observed.

Grade III – Larger inflammatory papules, pustules and a few cysts are observed.

Grade IV – Here, cysts are seen to become confluent.<sup>(15)</sup>

### **Acne vulgaris treatment:**

#### **Physical treatments:**

Physical ways of dealing with blackheads and whiteheads include extraction with the help of an extractor which can be helped with association of steaming. Such facilities and procedures are offered at spas and performed by professionals.

As an alternative to topical and oral treatments for acne vulgaris, laser and radiofrequency had been discovered in the recent years. Lasers are believed to reduce inflammatory acne lesions by targeting the factors such as *P. acnes* bacterium, activity of sebaceous gland and inflammation reduction. The Pulsed Dye Laser which is known for dermal remodeling and collagen production, is used for acne scarring.<sup>(16)</sup>

Pulsed dye laser is mostly used for collagen production and can also reduce inflammatory acne. Recent studies have found that it has no effect on degree of *P.acnes* colonization or sebum production in the skin and found to have significant upregulation of

transforming growth factor  $\beta$ , and potent inhibitor of inflammation. This is likely due to its local anti-inflammatory effects. The combination of radiofrequency and pulsed light device has been used for treating acne. Recent clinical study has shown improvement in acne with reduction in both perifollicular inflammation and sebaceous glands with reduction by 47 percent in mean acne lesion counts. Another study has also shown 75 percent reduction in inflammatory acne lesion in more than 90 percent of patients.<sup>(16)</sup>

Use of intense pulsed light for acne vulgaris treatment is based on the production of singlet oxygen ( $O_2$ ) post photo activation of porphyrins that are synthesized by *P. acnes* and then stored. An intense pulsed light provides a source which offers irradiation at a specific wavelength which can be modified by filters. In one such study with 19 patients suffering from mild to moderate acne, the patients were exposed to wavelengths ranging from 430 nm to 1100 nm with an energy density of 3.5 J/cm<sup>2</sup>, pulse width of 35 milliseconds.<sup>(17)</sup> Differences were seen in non-inflammatory as well as inflammatory cases with a decrease in lesions up to 79 percent in non-inflammatory and 74 percent in inflammatory cases one month after the final treatment.

An infrared diode laser can effectively reduce inflammatory acne lesion with conjugation of a dynamic cooling device and with a flux rate of 14 J/cm<sup>2</sup>. Because of the safety this procedure offers along with its efficacy, it has become a common treatment for acne. Radiofrequency combined with pulsed light device has also been used to treat acne with two weekly sessions for 4 weeks. A reduction of 47 percent in mean acne lesion was observed in 32 patients.<sup>(16)(18)</sup>

### **Chemical treatments:**

For mild acne vulgaris, first line treatments include benzoyl peroxide or a topical retinoid. A combination of such along with an antibiotic can also be used. For moderate acne vulgaris, the first line of treatment includes a combination of benzoyl peroxide along with topical antibiotic such as erythromycin or clindamycin. Whereas, the first line treatment for severe acne vulgaris includes an oral antibiotic, benzoyl peroxide a topical antibiotic and a topical retinoid. Isotretinoin, which is an effective retinoid against severe, nodular or cystic acne. In case of females, spironolactone can also be considered as a mode of treatment.<sup>(5)</sup> Even though, topical and oral antibiotics are very effective against acne vulgaris, an individual exposed to its prolonged use may develop a resistance to it.

### **Combination of Physical and Chemical treatments:**

Lasers such as Potassium Titanyl Phosphate Vascular Laser have shown to be effective against acne vulgaris. It is said to work by selective photo-thermolysis of blood vessels or photodynamic effect on *P. acnes* and sebaceous gland. In a study the Erbium Glass Laser has shown to be effective against acne with 78 percent reduction in lesions after four sessions at 4-week intervals. *P. acnes* produces an endogenous coproporphyrins and photo-porphyrins in the metabolic process. When these are exposed to visible light—red, blue or green, these endogenous porphyrins get excited and generate a reactive singlet oxygen species which damages the cell membrane of the bacterium.<sup>(19)</sup>

Photodynamic therapy (PDT) has also been used for treating acne. PDT involves light sensitive medication and a light source which is used to destroy any abnormal cells. With this procedure, bactericidal activity has been observed.<sup>(20)</sup> It involves the exogenous 5-aminolevulinic acid which is a porphyrin precursor and is converted intracellularly into photoporphyrin IX which is its photoreactive species. Indocyanine green, a dye that binds albumin and is known to be selectively absorbed by the sebaceous gland had also been used for treating acne. Although, Photodynamic therapy has a good efficacy rate, it is said to be characterized by pain and eruptions of pustules and cysts and phototoxicity. Methyl aminolevulinate, a methyl ester of 5-aminolevulinic acid has shown a decrease in post treatment adverse effects.<sup>(16)</sup> PDT involves the use of photosensitizer in combination with light and oxygen. Mechanism of PDT action is considered due to the reduction of sebum excretion and Cutibacterium acnes colonization along with its

immunomodulatory effects. Red light is most commonly used along with intense pulsed light. Where both inflammatory and noninflammatory lesions response to PDT treatment in clinical studies. <sup>(21)</sup>

Acne patches or pimple patches have also been introduced into the market which have been embraced widely. These are anti-acne in nature and are like stickers that can be applied over the acne lesion or bump to help disinfect it and reduce their size considerably. They are beneficial in the manner that they create a barrier between the outer environment and the lesion to protect them from worsening. The patches have shown to help reducing mild acne but it cannot be held as an alternative or substitute for medical treatments, especially in cases as severe as cystic acne. These patches are formulated and manufactured with active ingredients which target acne spots and minimize them. They are beneficial as they act as a shield from the environment and prevent an individual from picking at the lesion from time to time. They contain a hydrocolloid component which absorbs the pus and reduces the inflammation and keeps the area moist. <sup>(22)</sup>

### **Skin Microbiota in Acne and Probiotic Treatment:**

In general, 60% of the species comes under genera staphylococcus (firmicutes), Corynebacterium and Propionibacterium (actinobacteria). In the oily areas of the skin, lipophilic species of propionibacterium and cutibacterium predominate. Whereas, in the moist regions, staphylococcus and Corynebacterium species can be seen and in dry areas of the skin, a mixture of all the four phyla can be seen. <sup>(23)</sup> It has been stated that  $10^6$  aerobic bacteria can be present per  $\text{cm}^2$  in moist skin and  $10^2 - 10^6$  anaerobes are present in per  $\text{cm}^2$  in dry skin. <sup>(24)</sup>

Probiotics can be used for the acne treatment by topical application that can alter the skin microbiota and help in improving skin immune response. This also helps in improving the skin barrier and production in antimicrobial peptides. For example, streptococcus thermophiles can enhance ceramides which helps to trap water in our skin and phytosphingosine, which is a ceramide sphingolipid shows antimicrobial activity against *C. acnes* and thus is found to have a positive effect against acnegenic condition. <sup>(25)</sup> There are several techniques that describe the mechanism of antimicrobial peptides where it states that these peptides contact microorganisms and exert their action. One such model is *the toroidal type*, where integration between antimicrobial peptides and lipid chains takes place in such a way that the hydrophilic regions of these peptide face inside the pore and hydrophobic region is in contact with the phospholipid which helps in the union between the external and internal membrane. Another mechanism is the *carpet type model* where translocation of membrane takes place in peptide-pathogenic contact where peptide aggregation takes place on the membrane and generates tension, this is similar to the micelle formation in a detergent. High molecular weight peptides which are found in natural killer cells and cytotoxic T-cell have a broad-spectrum bactericidal action against *P. acnes* which has 5 alpha helicoidal regions made up of 74 amino acids in which disulfide bonds are contained. This polypeptide has the most relevant fragment having 31-50 sequence with antibacterial and anti-inflammatory effects. Another example is, CEN1HC-Br antimicrobial peptide obtained from sea urchin having heterodimeric peptide of 30 amino acids with disulfide intramolecular bridge which attributes antimicrobial activity against *P. acnes*. <sup>(26)</sup>

Research study also have demonstrated positive effect for the tropical probiotic treatment of acne vulgaris. One such study where Enterococcus faecalis strain was used for the lotion treatment for eight weeks has shown the positive effect in pustule type acne lesion. Another study where Nitrosomonas eutropha was used for 12 weeks, showed reduction in acne severity and inflammatory lesions. <sup>(23)</sup> Bacteriotherapy is mostly used for the treatment where one or multiple pure cultures are used in which:

1. Probiotics where living microorganisms are used which give beneficial effect.
2. Thermo killed bacteria (Postbiotics) where bacterial cell, enzymes and excreted bacterial product are used but the bacteria do not replicate.
3. Cell lysates (Postbiotics) where physically killed bacteria are used in which cell wall and cell content are present. Here, the bacteria do not replicate anymore but the enzymes are still active.

In microbiome products, fermented products are also used in which bacteria are not added but the supernatant which contain antioxidant, amino acid, lipids are used. Studies have also shown beneficial impact of using beneficial bacteria on human skin and its potential as a cosmetic ingredient. <sup>(27)</sup>

### **Cosmetics involved in Prevention and Treatment of Acne Vulgaris:**

Acne vulgaris is a very common condition of the skin, affecting both males and females. It may arise at any age, though puberty is a very common stage for acne vulgaris to affect an individual.

### **Preventive cosmetics for acne vulgaris:**

Acne vulgaris is a common occurrence in oily skin. A person with oily skin is very prone to acne and thus the term, “Acne prone skin”. These individuals are encouraged to use non- comedogenic and non-acnegenic products. The class of non-comedogenic products contain ingredients specifically that do not clog pores. As acne vulgaris is a skin condition that expresses itself when the pores of the skin are clogged or plugged, it is essential to do what needs to be done to help them keep open and airy. It may also be important for people with acne prone skin to opt for non-comedogenic, skin care and make up cosmetic products. They must opt for products carrying ingredients such as essential oils like grapeseed oil, sunflower oil, neem oil, rosehip seed oil, sweet almond oil, hempseed oil, benzoyl peroxide, resorcinol, aloe vera which are non-comedogenic in nature. They should strictly avoid cosmetic products containing comedogenic ingredients such as acetylated and ethoxylated lanolins, almond oil, ascorbyl palmitate, avocado oil, beeswax, capric acid, isopropyl myristate and its derivatives such as isopropyl palmitate, myristyl myristate, propylene glycol-2 myristyl propionate, D&C Red dyes.

A very common misconception about non-comedogenic cosmetic products is that they do not contain oils of any kind, natural, mineral or synthetic and are always water-based. When in fact, non-comedogenic products even though may be water based, they do contain oils, but these oils are non-comedogenic in nature, meaning they do not settle in the pores. It is one of the distinguishing points between a non-comedogenic and a non-acnegenic product, the latter being oil- free. There is no standardized scale to measure the non-comedogenic factor of such a product. So, on a scale of 1 to 5, if a product ranks at 0 – 2 in terms of how much pores have been clogged by the product, it gets labeled as a non-comedogenic product. <sup>(28) (29)</sup>

### **Topical treatment for acne vulgaris:**

People suffering from mild or moderate cases acne vulgaris sometimes prefer to self-medicate, turning to over-the-counter drugs and products. Noticing this behavior of consumers, many cosmetic, personal wellness and skin care brands have designated the term “Anti Acne Products” to a particular group of products. These products are developed and marketed as such and are formulated with ingredients that are effective against acne vulgaris such as Salicylic acid, Benzoyl peroxide, Niacinamide, Glycolic acid, Zinc salt of pyrrolidone carboxylic acid, Alpha hydroxy acids (AHAs), Beta hydroxy acids (BHAs), Retinoids, Lactic acid and Sulfur. An array of products has been developed under Anti acne products such as creams, lotions, serums, face-washes, scrubs, face packs, gels, foams, sheets, exfoliators and soaps. Some brands also offer an entire regimen or routine specifically for acne prone skin.

### **Natural, herbal and home remedies for acne vulgaris:**

Indians have always had a knack for home remedies for various skin and health conditions. Acne vulgaris is no exception to this. Many people who suffer from acne vulgaris have been known to opt for such remedies rather than medications or cosmetics as a first line approach. Natural, herbal and fruit extracts and oils such as Neem leaf oils, Tea tree oil, Aloe vera gel and extracts, Pear extracts etc. have been included in many anti acne formulations. These have greatly helped overcome the issue of attaining resistance from prolonged use of antibiotics. Nigella sativa (Black seeds) have been used as an approach to treat acne vulgaris. A clinical trial was done to evaluate the efficacy of N. sativa hydrogel against acne vulgaris. It was observed that the hydrogel product was able to

show decrease in the amount of acne lesions.<sup>(30)</sup> There are also some raw remedial approaches for prevention and treatment that are carried out at home. Ingredients like Apple cider vinegar, Cinnamon, Honey, Witch hazel, Green tea, Aloe vera are generally used to treat acne at home, many of these ingredients are antibacterial and anti-microbial in nature. Apple cider vinegar contains organic acid such as citric acid, which can kill bacteria and suppress inflammation and lactic acid improves acne scars. It has been found to kill *P. acnes*. Honey and Cinnamon are able to fight bacteria and decrease inflammation. A study in 2017 showed that a combination of Cinnamon bark extract and Honey had antibacterial action on *P. acnes*. Green tea is very rich in antioxidants and contains compounds that help against acne when consumed or applied on skin.<sup>(31)</sup> It is likely to act against acne as the polyphenols in green tea are able to fight bacteria and reduce inflammation. The main antioxidant in green tea epigallocatechin-3-gallate (EGCG) has been observed to cause decline in sebum production and inhibits the growth of *P. acnes* as shown through research<sup>(32)</sup> Another such ingredient is Aloe vera, which naturally contains salicylic acid and sulfur both of which are very commonly used in anti-acne cosmetic products. Tea tree oil has also been used for the treating acne, having anti-inflammatory and antibacterial properties. It is advised to use Tea tree oil in diluted form as it is comedogenic in nature and may be slightly irritant on its own, in conjugation with a non-comedogenic agent as a carrier oil.<sup>(33)</sup>

### **Topical Ingredients used for alleviating acne:**

Some ingredients have been extensively used in formulation of products which help to prevent and treat acne vulgaris. These include sulfur, benzoyl peroxide, salicylic acid, retinoids, derivatives of vitamin A, adapalene and tretinoin (Retin A).

Benzoyl peroxide is an effective topical agent, having been used since many years in these formulations in concentrations of 2.5 to 10%. It has been incorporated in creams, gels, lotions etc. Benzoyl peroxide is a broad-spectrum antibiotic agent, and has an advantage due to its effective oxidizing activity. It is anti-inflammatory, comedolytic, keratolytic and is very effective against mild to moderate acne vulgaris.<sup>(34)</sup> It acts on the epithelial cells of the skin, increasing the over cellular turnover rate. It helps in the peeling of the skin and thus, aiding with resolving comedones. Benzoyl peroxide is metabolized in the epidermis upper layer to benzoic acid and free oxygen radicals. The former lowers the skin pH and the latter disrupts microbial cell membrane as it has broad-spectrum antimicrobial activity. It also has shown to be keratoplastic by inhibiting epidermal metabolism and DNA synthesis. It also helps in reducing metabolism of sebaceous gland cell but reduction in sebum is not well known. Reduction in free fatty acid in sebum is due to the antibacterial effect as lipases are responsible for free fatty acids production. Benzoyl peroxide also shows follicular flushing action.<sup>(35)</sup>

Salicylic acid is oil soluble, so naturally it can help with the breakdown of oils and sebum that have collected in the pores over time to cause acne vulgaris and unclog them for good. It can be used in anti-acne as well as non-comedogenic products as it works by breaking down the sebum to clean out the pores. It is a good ingredient for persons with oily and acne prone skin, where the cells tend to stick close, and clog pores, this ingredient works by dissolving the oily material that holds the cells so close, thus relieving them. In higher concentrations it can help heal pustules and redness, being anti-inflammatory in nature.<sup>(34)</sup>

Alpha hydroxy acids (AHAs) can treat acne by reducing inflammation and washing away the dead skin cells. They help stimulate the growth of new skin by reducing the concentration of calcium ions in the skin which aids in shedding of the cells at the surface and therefore aid with healing acne scarring. AHAs are able to reduce the epidermis pH and inhibit the action of transferases and kinases, interfering with formation of ionic bonds, helping to stimulate the process of desquamation.<sup>(36)</sup> The most common AHAs used in cosmetics are glycolic acid and lactic acid. Beta hydroxy acids (BHAs) are oil soluble which allows them easy penetration into deeper layers of skin. They are capable of unclogging the pores and even control oil level in the skin. They are also good exfoliators and skin peeling agents, so they can wash away the dead skin cells easily and improve the overall appearance of the



skin. Salicylic acid, as mentioned above is a BHA along with citric acid. Both are commonly used in acne concerning cosmetic products. <sup>(34)</sup> Chemical peels may contain up to 50% of salicylic acid. Superficial chemical peels have also been used to treat acne vulgaris and its scarring. <sup>(37)</sup>

Azelaic acid belongs to the dicarboxylic acid family and is an exfoliant with antibacterial and antioxidant properties. It is available in concentrations up to 10 percent to 20 percent in creams or serums. It can be used for both facial acne and body acne in a foaming formulation. It can be a little drying in nature and therefore it is advised to be used in combination with a hydrating agent. It works by loosening the acne prone skin, and targeting *P. acnes*, inhibiting its growth. The antimicrobial activity of Azelaic acid is due to its ability to inhibit microbial cellular protein synthesis. It also reduces dark spots and is therefore effective for acne scarring as well. <sup>(38)</sup>

Retinoids are derivatives of vitamin A which are widely used in acne concerning formulations. They work by binding to nuclear receptors and trigger them to normalize the cell turnover cycle. Retinoids also target abnormal follicular epithelial hyperproliferation and reduces follicular plugging and micro-comedones. Some retinoids that are currently being used in cosmetics concerning acne vulgaris are Tretinoin, Adapalene, Tazarotene, Isotretinoin, Metretinide, Retinaldehyde, and B-Retinoyl Glucuronide. The concentration of retinoids used in formulations depends on their tolerability by the skin.

The exact mechanism for treatment of topical tretinoin function is not completely understood but the medication is thought to be through binding of retinoic acid receptors (RARs) alpha, beta and gamma along with retinoid X receptors (RXRs) by inflammatory mediators blocking. This leads to the increase in production of procollagen to augment collagen type I and III formations. The positive effect of Tretinoin is to modify the abnormal follicular formation which is because of the excessive keratinization of epithelial cells as tretinoin promotes cornified cell detachment and enhances shedding. This increases the mitotic activity which increases the loosely bond corneocytes turnover. This results into expulsion of comedogenic contents with reduction of micro-comedo precursor lesion of acne.

Retinoic acid usually binds to retinoic acid receptor alpha, a steroid thyroid hormone receptor which forms the heterodimers with RXR and retinoic acid which responds to the genes involved in cell differentiation. Topical dosages of tretinoin consist of 0.1%, 0.08%, and 0.04% applied once daily. <sup>(39)</sup>

Adapalene, (6-[3-(1-adamanty)-4-methoxyphenyl]-2-naphthoic acid) causes an anti-inflammatory effect by inhibiting the activity of lipoxygenase, as it is lipophilic in nature. It has an affinity for the retinoid acid receptor (RAR) which is present in the epithelial cells. Once this Adapalene-RAR complex is formed, it binds with the retinoid X receptor (RXR). With gene transcription, it then binds at specific DNA sites which causes effects such as keratinization and anti-inflammatory properties. It is an advantage that Adapalene is effective at less concentrations. It was found that Adapalene absorption through skin is in low amounts. About 0.25ng/ml of it was found in plasma of patients of acne vulgaris being treated topically with Adapalene chronically. <sup>(40)</sup>

Studies done on the topical acne treatment where (ADA) adapalene loaded PAMAM dendrimer were used and compared with the commercial gel product “Differin” gel, which targeted the pilosebaceous units—especially hair follicles. Results found that the PAMAM dendrimer gel formulation in lower ADA doses compared with a commercial product showed improved follicular localization and skin deposition of ADA. Overall, it was considered to be safe which minimizes the side effect and provides efficiency in topical treatment for dermatological diseases such as acne vulgaris even in the reduced doses of administration. Thus we can say, the improvement in the delivery of topical drug in nanoform can give effective result with no side effect. <sup>(41)</sup>

Tazarotene is an acetylenic class of retinoids. A pro-drug that is converted to its active form, cognate carboxylic acid of tazarotene. Tazarotenic acid binds to all three members of retinoic acid receptor RAR alpha, RAR beta and RAR gamma. The therapeutic effect of tazarotene for acne is considered due to its anti-hyperproliferative and anti-inflammatory effects. Topical application of tazarotene reduces the expression of hyperproliferative keratins K6 and K16, which are increased in a comedogenic condition. It also suppresses the activator protein 1, resulting in reducing expression of several matrix metalloproteinases from keratinocytes which are increased in the condition of acne vulgaris. It has also shown the inhibition of TLR-2 induced innate response which triggers inflammation in acne, by decreasing the expression of Toll-like receptor (TLR) 2 and reducing the ligand binding with *P. acnes*. It results into increased epidermal turnover, normalized epidermal cellular differentiation and downregulates the expression of epidermal growth factor receptor, all of which result in reduction of hyperpigmentation and decreased hyperkeratinization. <sup>(42)</sup>

Isotretinoin mechanism of action is said to be only treatment that has implication for entire pathogenesis of acne. In general, retinoid plays a role through nuclear interaction with retinoic acid receptors (RARs), which are ligand-dependent transcription factors. Thus, regulation of gene transcription mainly occurs by the interaction of retinoid composition with receptor. Overall retinoid contributes to decreasing corneocyte adhesion, supporting cellular proliferation and follicular renewal, induction of cell apoptosis and immune regulation. Isotretinoin may alter comedogenesis through these mechanisms, by reducing sebum production and colonization of *P. acnes* and giving anti-inflammatory effects. It also affects comedogenesis by decreasing hyper-keratinization. The mechanism is still not known. It is also said that isotretinoin does not have direct antimicrobial activity. It reduces the sebum excretion and size of pilosebaceous ducts which in turn reduces the favorable environment for *P. acnes*. Isotretinoin also improves the host defense mechanisms and modifies chemotaxis monocytes which produce anti-inflammatory effects. Thus, reducing *P. acnes* population and resulting in decreasing acne inflammation. <sup>(43)</sup>

Other topical retinoids have been used for more than 30 years which target the microcomedo-precursor lesion of acne. These can be used as a first line treatment or with the combination to treat mild to moderate inflammatory acne. Its effectiveness is very well documented as it targets abnormal follicular epithelial hyperproliferation, it also reduces follicular plugging and micro-comedones along with non-inflammatory and inflammatory acne lesions. Their biological effectiveness is due to nuclear hormone receptors such as retinoic acid receptor RAR and retinoids X receptor RXR with three subtypes  $\alpha$ ,  $\beta$ , and  $\gamma$  and cytosolic binding proteins. <sup>(44)</sup>

Almost all anti-acne cosmetic formulations contain antibacterial agents which inhibit the action and growth of *P. acnes* and reduce inflammation. Some such antibiotics are erythromycin and clindamycin which are popularly used in many high-end cosmetic products for acne vulgaris. They are both effective against inflammatory acne in combination of concentration of 1-4%. Some other ingredients that are used in these formulations are niacinamide (Vitamin B<sub>3</sub>), Vitamin C, various types of clays and charcoal. <sup>(45)</sup>

### **Conclusion:**

With the emerging trends of consumption of fast foods by adolescents, the incidence of acne vulgaris may become a major medical problem in our society in the recent future. In this context, the importance of self-hygiene and healthy diet as preventive measures for acne vulgaris cannot be over emphasized. Cosmetics including both chemical and herbal play a vital role in prevention and treatment of acne vulgaris. Oral and topical medications for acne vulgaris are essential in severe cases to avoid complications arising due to untreated acne vulgaris.

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