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Review Paper

Advance In Herbal Nano-Emulsion Gel Innovation of Clove Oil and Curcumin in Treatment of Acne

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ABSTRACT

Acne is a long-lasting disorder of skin affected the many people globally, especially young and teenagers adults. Follicular hyperkeratinisation, increased the sebum production, bacterial cloning, & inflammation. Acne is caused through the bacterial replication that causes the severe physical discomfort. Some chemicals substance and antibiotics are used as traditional treatment of acne symptoms they are effective but they shows side effects likes irritation, dryness etc., and in few cases these are rising bacterial resistance. Interesting in natural treatment that are providing safe and effective acne treatment. Among such herbal bioactive are clove oil and curcumin are used due to their potent such as antioxidant, antimicrobial and anti-inflammatory properties. Clove is obtained from the plant of syzygium aromaticum and eugenol is present in the clove as bioactive compound that show the anti-bacterial activity which is caused acne. Eugenol is also give an effect against swelling, inflammation and cavity infection. Curcumin is a bioactive chemical substance are obtained from the plant of Curcuma longa which are used in the prevention of post- inflammatory hyperpigmentation. In addition of curcumin and clove oil medication is give the synergistic effect on the acne. The clinical effect of clove oil and curcumin are limited due to their less solubility in the water and less permeation into the skin during at topical uses. Advance in the nanotechnology remove their limitation through the nanoemulgel Formulation. Nanoemulgel medication are increases the penetration of skin and increases the solubility of lipophilic

INTRODUCTION

A prevalent long-term inflammatory skin condition is acne vulgaris. About 80% of teenagers and adults have this. These conditions are impacts

on skin that can cause effects that are either inflammatory or not. Open blackheads, closed whiteheads, and inflammatory lesions such as nodules, pustules, and papules are the hallmarks of

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acne, a chronic inflammatory dermatitis. Acne has a wide range of harmful impacts on teenagers.

This results in irritation, mental strain, abnormality, and sometimes irreversible injury to the skin. In addition to lowering the patient's physiological and social welfare, it may cause sufferers to feel anxious and ashamed. Acne can be brought on by or made worse by a number of factors. In addition to harmful substances, including androgenic chemicals such as hormones and pore-clogging skincare, genes, male gender, young age, anxiety, and smoke are some of these causes. A previous study indicates that hereditary impact, along with comedogenic hormones (particularly androgens), produces abnormal oil production that exacerbates pimples. Acne can be classified into numerous categories, contains:

- **Fungus pimples (also called pityrosporum follicle inflammation),**
- **acne caused by hormonal changes, or**
- **cystic acne**
- **Nodular pimples**

Acne cysts: Deeply underneath the skin, pus-filled acne cysts (pimples) are the result of cystic acne, or pimples. Acne cysts are frequently large and painful. Cystic acne should be treated by a dermatologist to reduce the risk of infection and scarring. Skin can be cleared up with the use of pharmaceutical topical remedies and medications. Pimples that are painful and packed with pus develop deep under the skin in people with cystic acne, a form of inflammatory acne. Eczema is caused by sebum & cellular debris plugging up pores. Bacteria that infiltrate the pores of people with cystic acne also cause edema, or inflammation. Acne that is cystic is the most severe kind. In addition to being painful, acne cysts are more prone to leave scars.

Fungal acne (pityrosporum folliculitis): When a fungus known as *Malassezia* yeast infects hair follicles, it can lead to fungal acne, a common skin

disorder. The illness is also known as *Pityrosporum folliculitis* or *Malassezia folliculitis*. Clusters of tiny, itchy, red pimples called papules appear on your skin as a result of fungal acne. Occasionally, the lumps enlarge somewhat and develop into whiteheads, which are tiny pockets of pus that are either white or yellow (pustules). Common acne is sometimes mistaken for fungal acne, also known as *Malassezia folliculitis*, which is an infection of the hair follicles. It results in clumps of tiny, red, irritating pimples on your skin. Antifungal drugs can cure the infection, and there are methods to avoid and alleviate the symptoms that resemble a rash.

Hormonal acne: Adults between the ages of 20 and 50 are susceptible to hormonal acne, Adult hormonal acne is distinguished through breakouts that might include painful cysts, whiteheads, and blackheads. This is a greasy substance that skin pores overproduce, clogged vessels leading to blisters. Which are linked to hormonal acne. Hormonal acne can be treated to stop future breakouts, even though it is frequently unavoidable.

Nodular pimples: Severe acne is known as nodular acne. Nodules, or hard lumps or knots, form deep beneath your skin as a result. The nodules appear as red pimples on the skin and begin beneath the surface. There is typically no blackhead or whitehead in the middle of these lumps. The duration of the nodules may be weeks or even months. They cause excruciating pain. Infection and inflammation result from a bacterium called *Cut bacterium acnes* (*C. acnes*) becoming trapped beneath your skin in these nodules.

A dermatologist, a medical professional who specializes in skin care, has to treat pigmented pimples. That type of pimple can cause serious, long-lasting scarring if left untreated. By getting therapy as soon as possible, you can lower your chance of scarring. Inflammatory acne includes



nodules. It causes substantial, painful lumps under the skin as well as red pimples on the skin's surface. Nodular acne has to be treated by a medical professional. This kind of acne is not self-treatable. Severe scarring may result if left untreated. Topical creams and oral prescription drugs can be beneficial.

Symptom of acne: The severity of illness determines the indicators of pimples

- **Black heads (wholly clogged holes) and Whiteheads (closed clogged porosity)**

- **Tiny red, sensitive lumps**
- **Pustules, or pimples, are papules with pus at their tips.**
- **Nodules are large, solid, painful lumps under the skin**
- **Cystic lesions are painful, pus-filled lumps beneath the skin.**

Acne usually affects the skin of the face, forehead, the chest, upper back, & shoulder:

Table. 1.1 Treatment of acne

Therapy Type	Examples	Indications
Surface treatment	Therapeutic antibiotics, benzyl peroxide, and antioxidants	Light to medium pimples
Orally	COCs, spironolactone	Moderate to severe acne
Procedural	Chemical peels, light therapy, micro needling	Adjunct or resistant cases
Emerging/Innovative	Biologics, probiotics, immunotherapy	Severe/resistant, research phase

As we know that mostly acne is occurring due to hormonal changes, life style, stress, bacterial infection. Then the acne can be cured and treated with the help of clove oil and curcumin.

Skin: Skin is a complex tissue that provides the human body's primary defense against the external environment while also helping to maintain proper hydration under both healthy and diseased conditions. Skin contains three important layers, each of which has anatomical and functional roles: (a) epidermis (b) dermis (c) subcutaneous. The

actual epidermis includes that non-living outer part called the deeper viable epidermis and the stratum corneum. Skin is the largest part of the human body, covers about 20 square feet, and makes up roughly 16% of total body weight. Its structure and properties can vary widely between individuals and even between different areas on the same person. The skin's surface typically has a slightly acidic pH of around 4.7, although this can fluctuate between 4 and 6 depending on factors like age, sex, and body site.

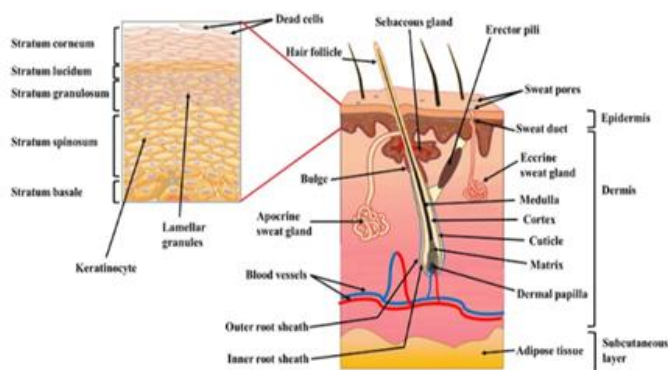


Fig. 1.1- Structure of Skin

Penetration pathways across the skin: In general, substances can pass through the skin using one of several different pathways.

- **Intercellular pathway through lipid domains:** The rate at which substances are absorbed through the skin depends on their polarity — whether they are **lipophilic** (fat-loving) or **hydrophilic** (water-loving). Typically, lipophilic compounds are absorbed more efficiently and can pass through the **stratum corneum (SC)** with ease, whereas hydrophilic substances have more difficulty penetrating this barrier. The movement of these two types of molecules through the SC occurs via different diffusion mechanisms. Overall, the SC mainly allows **small, uncharged molecules** to pass through the skin more easily.

- **Intracellular pathway through the corneocytes by diffusion process:** Hydrophilic (or polar) molecules mainly pass through the **intracellular pathway**, as water makes up a large part of the cell's structure. However, their movement is slowed down by the **multiple lipid bilayers**, which act as the main barrier to their permeation.
- **Transappendageal pathway through skin appendages:** This pathway is created by skin appendages like **hair follicles**, **sebaceous glands**, and **sweat glands**, which form small openings or channels in the skin. It allows substances to pass through the skin **without having to cross the stratum corneum's lipid layers**.

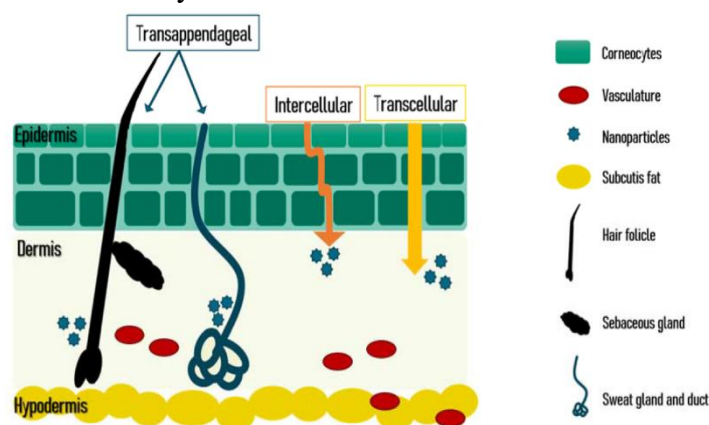


Fig. 1.2: Diagram of the pathway of permeate into the skin and out of the skin.

Clove oil: The dried flower buds of the *Syzygium aromaticum* clove plant are used to make clove oil. And belongs to the Myrtaceae family. It is

commonly obtained by steam dehydration from the buds, although the stem and leave of the plant may also serve as alternative sources for oil

production. Clove trees originally come from Indonesia, but they are now grown widely in many tropical regions. Large-scale cultivation takes place in the Brazil, Zanzibar, and Sumatra & Amboina. These plants are commonly obtained in Sri Lanka, India, and Madagascar & Penang.

Application of clove oil: Clove is valued for its antiseptic, aromatic, stimulant, and carminative properties, and is a common flavoring agent. This oil commonly applied as a local anesthetic and for disinfecting root canals. It has the ability to

eliminate intestinal parasites and shows strong antimicrobial activity against various bacteria and fungi, making it useful in treating diarrhea, worm infestations, and other digestive disorders. Clove oil is well known for relieving toothache, and a few drops taken with water can help reduce nausea or vomiting. Consuming cloves is also traditionally considered to enhance libido. The main active compound, eugenol, serves as a mild local anesthetic when used in small amounts.

Table 1.2: List of biochemical content in dried clove.

Sr. no.	Biochemical	Amount
I.	Eugenol	70–85% of essential oil (major active)
II.	Eugenyl	11-16%
III.	Caryophyllene	6-12%
IV.	Tannins	10–13% of dried clove
V.	Carbohydrates	60–65%
VI.	Fixed oils	15–20%
VII.	Proteins	~5–6%

Clove oil also promotes intestinal movement, acts as a powerful germicide, and works as a stimulating expectorant in respiratory conditions. Preparations like clove infusion and clove water are often used as carriers for alkaloids and aromatic substances.

Curcumin: Curcumin is a member of the diarylheptanoid class compounds, is one of several curcuminoids obtained of the rhizome of the Indian native plant *Curcuma longa* and widely known as turmeric. Turmeric is century's traditional Asian medical systems because of their therapeutic advantages. Because of its potent anti-inflammatory and antioxidant qualities, curcumin has been studied for its potential use in treating diseases like depression, cancer, and Alzheimer's. That are taken through turmeric in the diet or as a supplement, though it's natural absorption in the body is limited.

Application of curcumin:

These are have many medicinal uses -

- 1) It has anti-inflammatory properties helps to reduce swelling and pain.
- 2) These are used in the treatment of arthritis and bowel disease.
- 3) It has antioxidant properties that remove the free radicals from the body.
- 4) It is also has quality to reduce tumor cell growth and help in the treatment of cancer.
- 5) These are have ability to enhance body immune system.

Table.3.1- list of phytochemicals present in turmeric

Sr.no.	Biochemicals	Amount
1.	Curcumin	3.1% - 3-4%
2.	Anthocyanin	19.0 – 36%
3.	Phenol	0.14 - 0.61%
4.	Tannin	0.31 - 0.75%
5.	Proteins	3.6-6.8%
6.	Sugar	20.5-43.4%
7.	Oil	3.7-5.3%

Nano-emulsion gel (nanoemulgel): Advance in the nanotechnology remove their limitation



through the nanoemulgel Formulation. Nanoemulgel medication are increases the penetration of skin and increases the solubility of lipophilic substances. The medication of advance Nano-emulsion gel is formulated through the clove oil and curcumin has more efficacy, safe and potent. **Hydrophobic or poorly water-soluble medications are especially well-suited for delivery using nanoemulgels.** Especially in dermatological treatments such as anti-inflammatory, antimicrobial, analgesic, and anti-acne therapies.

Formulation Principles of Nanoemulgel:

- 1. Selection of Drug:** The active drug chosen for nanoemulgel formulation is usually poorly soluble in water and lipophilic, requiring improved dermal penetration. Such drugs benefit from the enhanced solubilization and permeation offered by nano-sized droplets. Examples include essential oils, curcumin, anti-inflammatory agents, and antifungal compounds.
- 2. Oil Stage:** This phase dissolves the medication and creates the scattered nano-droplets into formulation. Oils with strong drug-solubilizing properties are selected to ensure efficient loading of the active ingredient. Common oils include clove oil, eucalyptus oil, and isopropyl myristate.
- 3. Surfactant and Co-Surfactant:** Surfactants are necessary to stabilize the nanodroplets and reduce interfacial tension in order to stop coalescence. Co-surfactants enhance the stability and flexibility of the nano emulsion system in conjunction with surfactant. Tween 20, Tween 80, PEG 400, and propylene glycol are typical stabilizer.
- 4. Aqueous Phase:** The aqueous phase typically consists of distilled or deionized water, forming the continuous phase of the Nano-emulsion and aiding in uniform dispersion.
- 5. Preparation of Nano-emulsion:** It is possible to create Nano-emulsions by using:
 - Highly energetic techniques like homogenization under high pressure and ultrasonication are used which physically break down droplet size.
 - Low-energies techniques such as spontaneously Emulsification and phase inversion, which rely on the system's intrinsic physicochemical properties.
- 6. Desired Final Characteristics:** The resulting nanoemulgel should exhibit:
 - A **smooth and uniform texture**
 - Viscosity
 - Controlled medication release
 - Distribution of active ingredients
 - Not phase instability



Figure. 1.3- Nanoemulgel preparation diagram

Rational for nanoemulgel formulation:

Nanoemulgel formulation system are improve the medication treatment as penetration, therapeutics efficacy and stability. The Nano-sized particle into the nanoemulgel formulation increase the better diffusion through the skin layer resulting better absorption.

This formulation is beneficial for those medication which are hydrophobic or less soluble in water such as oil phases of Nano emulsion. This gel structure is increase the smoothness, freely spreading and that are given patient satisfaction when use these medication. The gel matrix giving the continuous and regulated release the active medicine. Nano-emulgel are more effective and better method of topically used medication.

Clove oil emulsion preclinical studies: The preclinical study on clove oil Nano emulgel medication as an innovation on topical delivery system are develop to increases the efficacy and therapeutics effect of clove oil.

In vivo animal method are given significant effect against skin inflammation, the nanoemulgel formulation are also give antimicrobial activity, and effective against bacteria which caused acne. These are given antifungal effect along with such medication (fluconazole). The Nano-emulgel particle size is mainly 340nm, good spread ability and stable various storage condition.

Overall, clove oil Nano-emulgel are phytomedical used for treatment of infectious and inflammatory skin. This formulation improve the patient's compliance and reduce the side effect.

Curcumin nanoemulgel: Curcumin nano-emulgel are better surface spreading formulation which increase the solubility of curcumin and penetration of skin. These are mainly used for skin condition like wound healing, treatment of psoriasis and infection.

Preclinical study of cumarin nanoemulgel is indicate these have good rheological quality and

suitable for skin. These are increases the penetration of skin and these quality of curcumin nanoemulgel make it safe and effective.

Combined curcumin and clove oil treatment for acne: A formulation containing both clove oil and curcumin are beneficial for treatment for acne because both are given better therapeutics effect together. Eugenol is present into clove and these has strong antiseptic & antibacterial effect against acne causing bacteria and inhibit the growth of microbes such as propionibacterium, it also has mild pain reduce action. Curcumin is present in the turmeric which has strong antibacterial and anti-inflammatory activity, it remove redness of skin, swelling, pigmentation& wound healing. When these are mixed together in nanoemulgel their effect and penetration power are increases. The nanoemulgel are more relevant has long time contact with skin, better spreading ability and these medication has controlled release action. This combined formulation has better action against infection of skin, acne and given effective herbal treatment.

Properties of physiochemical:

Lipophilic (fat-loving) molecules Compared to hydrophilic (water-loving) ones, they often permeate the skin more readily. Similarly, **non-polar substances** are absorbed Fluids, particularly organic liquids, are superior to polar ones., tend to be absorbed more effectively than solids.

Multiple partitions and dispersion control the **percutaneous absorption mechanisms**, and it can also be affected by the skin **thickness and properties** which vary based on the location of the body. High concentrations of a drug are generally more effective in penetrating the skin when they stay in touch with it for an extended period of time, allowing for almost maximal absorption.



For this reason, an ideal substance for **transdermal delivery** should have certain **physicochemical properties** that favor effective absorption through the skin.

- **Partition coefficient:** The process of a substance penetrating and passing through the skin happens in **multiple steps**. This begins with the material being released from its formulation and then separating into the stratum corneum's lipid.

After that, substance **diffuses through the lipid environment** of the SC. Skin absorption tends to increase when the substance has moderate **lipophilicity**, typically an optimal **Log P of 2–3**.

Molecular size: The molecular size of these depended on the Stokes-Einstein-

$$D = \frac{KBT}{6\pi\eta r}$$

Where η is the solvent's viscosity, **D** is the diffusion coefficient, **T** is the medium's absolute temperature, **r** is the spherical particles' radius, and **KB** is the Boltzmann constant.

- **Solubility:** A permeant's solubility in the intercellular lipid pathways influences its diffusion coefficient in the stratum corneum. Lipophilic molecules, which dissolve well in these lipid regions, generally show enhanced skin permeation. But the concentration of the permeant dissolved in the formulation vehicle also affects the overall permeation rate. When a substance is poorly soluble in the carrier, it quickly partitions into the SC, leading to depletion of the permeant in the vehicle and a subsequent decline in flux. Therefore, To successfully control skin penetration, an ideal permeant should have a high diffusion coefficient and moderate water solubility

Skin penetration enhancement: A range of Methods and approaches have been developed to get around the protective qualities of the skin. Enabling drugs to more easily penetrate and reach the skin's microcirculation. These penetration

enhancement methods are generally divided these falls into two primary sections: biochemical approaches, which use substances like alcohols, polyols, surfactants, and essential oils, and physical techniques, which include iontophoresis, electricity, and microoperation.

Role of surfactants in the manufacturing of Nano-emulsion: surfactants aid in the stabilization of emulsion mixtures for reducing the interfacial tension between two liquids that are immiscible, thereby promoting and maintaining emulsion formation.

Surfactants can stabilize emulsions through a variety of different mechanisms.

1. Lower the tension between the two surfaces.
2. Keep identical electrically charged droplets away from one another.
3. The development of mesophases, or liquid crystalline phases, which provide the system a more stable conformation.
4. The rigid macromolecules' adsorbed on the surfaces of fine split particle.

There are three types of ionic surfactants: amphoteric, cationic, and anionic. Cationic surfactants generate positively charged ions in aqueous solutions, anionic surfactants release negatively charged ions, and amphoteric surfactants can dissociate into positive and negative ions. Selecting a suitable surfactant type is crucial and should be based on the desired emulsion system. Non-ionized surfactants are commonly employed in topical products owing to their low toxicity and less tendency for irritating the skin. Examples such as Tween 80 and Span 80 serve important functions in maintaining formulation stability and enhancing skin permeation.

Role of HLB: Apart from their ionic classification, the hydrophilic-lipophilic balance



(HLB) of surfactants can also be used to classify them.

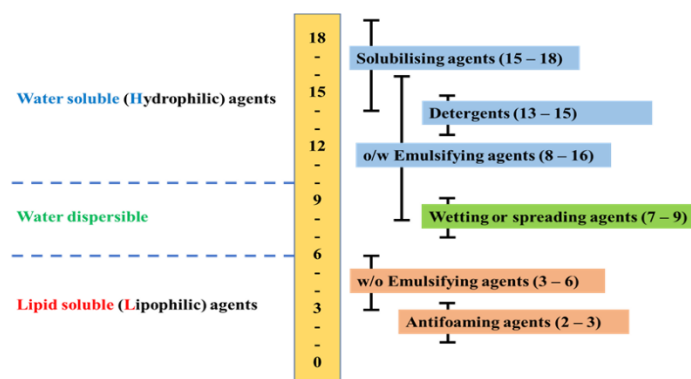


Fig. 1.4: HLB scale values

It is also crucial to consider the chemical structure of the surfactant. Often, a combination of surfactants is used, as each contributes unique properties beneficial to the formulation.

Phase inversion emulsification methods: This method depends on phase transitions that happen during emulsification as a result of the surfactant's (emulsifier's) spontaneous changes in curvature. Variations in composition or temperature can cause these changes. Thus, there are two approaches to produce emulsification: the phase inversion temperature (PIT) method, which involves changing the temperature while maintaining a constant composition, or the phase inversion composition (PIC) method, which involves changing the composition at a constant temperature.

For instance, a synthetic surfactant in the PIT technique is hydrophilic at low temperatures and lipophilic at high temperatures. An oil-in-water (o/w) emulsion is created when the polar groups control the surface area below the transition temperature. The hydrocarbon chains occupy the surface above the transition temperature, creating a water-in-oil (w/o) emulsion. A kinetically stable Nano-emulsion with a small polydispersity index (PDI) is then produced by rapid cooling; however,

Ostwald ripening is a frequent problem with this technique.

Advantages of Advanced Herbal Nanoemulgel Formulations:

- 1. Enhance bioavailability and solubility:** More herbal ingredients are less water soluble, limiting their therapeutic action, but nanoemulgel formulations increase the solubility and bioavailability when these are placed on the surface of skin.
- 2. Increase penetration of skin:** The nanoemulgel formulation increases the penetration ability of skin.
- 3. Sustained and controlled release:** This formulation with gel matrix gives sustained & controlled release of drug and long-time action with more efficacy.
- 4. Synergistic action:** Herbal Nano-emulsion gel combined gives the synergistic effect as strong antimicrobial and anti-inflammatory action.
- 5. Decrease side effect:** The nanoemulgel reduces side effects on the skin such as redness, irritation, or burning. Herbal Nanoemulgel shows less side effect action.
- 6. Increase stability of herbal bioactive:** Some herbal formulations are light sensitive or less

stability but the Nano- emulgel are more stable to other herbal medication.

7. **Non-greasy formulation:** Nano-emulsion gel is non-greasy in nature which is suitable for skin and easily enters into the skin.

CONCLUSION

Acne is a disorder of skin which are effecting more population in the world. Treatment of acne uses retinoid, chemical agents and antibiotics are effective but it have some draw back such as antibiotics resistance, skin irritation and dryness. These negative consequences are remove to uses their alternate as herbal formulation. Clove oil and curcumin are together as herbal medication has anti-microbial, anti-inflammation, and antioxidant properties. These formulation is suitable treatment for acne. The medication of advance Nano-emulsion gel is formulated through the clove oil and curcumin has more efficacy, safe and potent. Clove is obtained from the plant of *syzygium aromaticum* and eugenol is present in the clove as bioactive compound that show the anti-bacterial activity which is caused acne. Eugenol is also give an effect against swelling, inflammation and cavity infection. Curcumin is a bioactive chemical substance are obtained from the plant of *Curcuma longa* which are used in the prevention of post-inflammatory hyperpigmentation. In addition of curcumin and clove oil medication is give the synergistic effect on the acne. The clinical effect of clove oil and curcumin are limited due to their less solubility in the water and less permeation into the skin during at topical uses.

Advance innovation in the nanotechnology remove their limitation through the nanoemulgel Formulation. Nanoemulgel medication are increases the penetration of skin and increases the solubility of lipophilic substances.

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