



Novel Approaches In Herbal Medicament For Acne Vulgaris



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Abstract

Acne vulgaris is usually skin disorder occurs more often in adolescence during puberty, regardless of sex. The major pathogenic factors involved are hyper keratinization, obstruction of sebaceous follicles resulting from abnormal keratinization of the infundibular epithelium, stimulation of sebaceous gland secretion by androgens, and microbial colonization of pilosebaceous units by *Propionibacterium acnes*, which promotes perifollicular inflammation. The available traditional formulations often cause side various effects such as skin irritation, dryness, peeling, itching, low patient compliance and decreased therapeutic efficacy. Novel drug delivery systems are promising option for improved acne treatment outcome, as they can weaken the side effects caused by the therapeutic agents or can modulate their properties and at the same time offering possibilities for modified release and enhanced skin penetration of the drug substances. The cosmetics industries implement nanotechnology in their formulations. This review focuses on overview/causes/pathogenesis of acne vulgaris and novel nanoparticulated carrier systems that can be used for acne treatment.

Keywords: Acne Vulgaris; Keratinization; Skin disorder; Skin irritation; Dryness; Peeling; Itching

Introduction

Skin is the most exposed part of the human body. Constant day-to-day exposure of human skin to ultraviolet (UV) radiations, pollution, dust, chemicals etc leads to the number of skin disorders such as acne, pimples, hyperpigmentation and sunburn marks. Acne vulgaris (acne) is most typical follicular skin disease that principally affects the pilosebaceous follicular unit of the face, neck, and trunk. The numbers of topical and systematic therapies using synthetic ingredients are available for so long to cure acne vulgaris. Acne vulgaris (acne) is common chronic skin disorder occurring in adolescence and in young adulthood that involves various pathogenetic factors like blockage or inflammation of pilosebaceous units, abrupt increase in body androgens, epidermic hyperproliferation, blocking of sebaceous glands of skin, microbial establishment of pilosebaceous entities [1,2]. The over activate sebaceous glands stimulated by androgen causes proliferation of *P. acnes*, an anaerobe present within the retained sebum in the pilosebaceous ducts. On skin, the characterization of acne is observed by both inflammatory (papules, pustules and nodules) and non-inflammatory (comedones, open and closed) lesions.

Acquisition of antibiotic resistance by these microorganisms and adverse effects associated with the current treatment regimens requires the introduction of novel therapeutic agents for acne vulgaris. Clinically, acne is usually observed on the face, upper part of the chest, and the back of subjects who possess greater numbers of oil glands (Figure 1). Common therapies that are used for the treatment of acne include topical, systemic, hormonal, herbal and combination therapy. Consumption of herbal medicinal plants is common amongst patients affected by acne and infectious skin diseases. Herbal plants have a long history of use and have been shown to possess low side effects. Nano-technological approaches such as particulate (solid lipid nanoparticles and microspheres), vesicular (liposomes and niosomes), colloidal drug delivery systems (micro-emulsion and nano-emulsion), and miscellaneous systems (aerosol foams and micro-sponges) have an important place in acne therapy [3]. These approaches have an immense opportunity for the designing of novel, low-dose, targeted and effective treatment systems for treatment of acne vulgaris. In this review, we specially focus on the different nanotechnological approaches for an effective treatment of acne.



Figure 1: Acne on the face.

Symptoms of acne

Non inflammatory acne

- Whiteheads
- Blackheads

Inflammatory acne

- Papules
- Pustules

- Nodules

Social symptoms

- Loss of self confidence
- Anxiety and depression
- May withdraw from society.

Causes of acne vulgaris

Following are various factors causing acne and some of them are shown in are shown in Figure 2.



Figure 2: Causes of Acne Vulgaris.

a. Hormonal Stimulation - Androgen are the hormones that increase in boys and girls during puberty causes the sebaceous glands to enlarge and make more sebum resulting in acne.

b. Medications - Various medications containing corticosteroids, testosterone or lithium causes acne.

c. Diet - Studies indicates that consuming carbohydrate-rich and fat rich foods worsen the appearance acne.

d. Stress - Stress can show synergistic effect on acne condition by further worsening it.

Pathogenesis of acne

As discussed earlier, acne is associated to hormones, sebum, follicle fallout, bacteria, and inflammation, which initiates the pilosebaceous units of the dermis. The major factors that cause acne include [4]:

a. Enhanced sebum production: The one of the most important factors involved in the development of acne lesions is enhanced sebum production rate. The role of sebum in the pathogenesis of acne is its major or associative role in comedogenics and also providing the substrate for P. acnes growth. Figure 1 shows the basic mechanism involved in pathogenesis of acne.

b. Follicular hyper keratinization: Blocking of the pilosebaceous canal further leads the expansion of acne lacerations. The hindrance is produced by the growth of supporter-keratinized cells within the channel forms an impaction blocking the flow of sebum because of an irregularity in the sebaceous lipids resulting in a relative hyper proliferation of corneocytes. Comedones formation may be due to a localized deficiency of linoleic acid in pilosebaceous duct.

c. Abnormal bacterial function: Skin surface in acne

disposed to areas are colonized with Staphylococcus epidermidis and P. acnes. P. acnes that supports the inflammation through stimulation of various chemotactic factors and separation the comedones.

Physical and psychological consequences

In adolescent stage the self-esteem of a person is developed, whereas conditions like anxiety, depression, or any other problem which may require medical advice can lead to a decrease in self-esteem. Though acne is not life-threatening disease but it has major physical and psychological consequences such as permanent scarring, depression, anxiety and suicidal tendency. Thus it can unenthusiastically and can affect the patients` quality of life, early and aggressive therapy is critical with successful treatment promoting much more than just cosmetic benefits. Up to date, various clinical guidelines for management of acne have been proposed. A stepwise approach to acne management involves topical agents for mild to moderate acne.

Herbal treatment of acne

Herbal remedies were used to clear up acne and other skin conditions well before modern treatments existed. Despite the lack of research on many herbal solutions, anecdotal evidence is plentiful. Herbal remedies tend to have fewer side effects than modern treatments. Some herbs have antibacterial, anti-inflammatory, and antiseptic properties. These properties may help reduce acne-causing bacteria and inflammation, and heal blemishes [5]. Various herbal-marketed formulations of acne vulgaris are tabulated in Table 1. Herbal novel drug are better because of their less toxicity and better therapeutic action. They reduce toxicity by decrease dose frequency. Herbal therapies include naturally derived drugs from active plant extracts, essential oils, phytomolecules and extracts.

Table 1: Marketed formulations for acne vulgaris.

| S.NO | Marketed product | Herbs used | Brand |
|------|--|---|-----------------------|
| 1 | Vaadi Herbal Anti Acne Cream Clove & Neem Extract. | Clove oil, tea tree oil, neem and orange extract. | Vaadi Herbals. |
| 2 | Biotique Bio Myristica Spot Corrector Anti-Acne Sustainable Face Pack. | White sandalwood oil, multani mitti powder, jaiphal powder, turmeric root, pipali root. | Biotique. |
| 3 | Patanjali Neem Tulsi Face Wash. | Aloe-vera, tulsi, neem. | Patanjali. |
| 4 | Khadi Organique Acne Pimple Cream with Neem & Basil. | Neem extract, basil extract, teatree oil, calendula extract, cinnamon bark extract, lavender extract, turmeric. | Khadi Organique. |
| 5 | Indus Valley Seaweed Teatree Calming Acne Gel | Rose water, aloe-vera, wheatgerm oil, almond oil, grapefruit seed extract, niroli oil, rose oil. | Indus Cosmeceuticals. |
| 6 | Himalaya Herbal Anti Acne Cream | Aloe-vera, lentil, silk cotton oil, nirgundi, shalmali. | Himalaya. |
| 7 | Mamaearth Tea Tree Spot Gel Face Cream with Tea Tree For Acne | Tea tree. | Mamaearth. |
| 8 | Soundarya Herbs Anti-Acne Anti-Pimple Herbal Gel | Aloe-vera, neem, papaya. | Soundarya. |
| 9 | WOW Skin Science Anti Acne Face Wash, | Tea tree essential oil, neem extract. | WOW SKIN SCIENCE. |
| 10 | Lotus Herbals Tea Tree & Cinnamon Anti-Acne Oil Control Face Wash. | Tea tree oil, cinnamon, oak. | Lotus Herbals. |

Medicinal herbs used in acne vulgaris

Many herbal plants seems to have in vitro inhibitory effects on the growth of microbes (Figure 3). But due to limited clinical evidences about the effectiveness and safety of these plants in the treatment of skin infections, chemical drugs seem to still be the

first choice of treatment for acne. However, the efficacy and safety of synthetic drugs are under question in the treatment of acne and other skin infections. Some plants reviewed in paper have shown promising results. Table 2 shows different parts of herbal plant that can be used for acne treatment

Table 2: Medicinal plants used in acne treatment.

| S.no | Medicinal plants | Family | Part used |
|------|-------------------------|------------------|----------------------------|
| 1 | Aloe barbadensis | Asphodelaceae | Powder and complex extract |
| 2 | Commiphora mukul | Buseraceae | Gugulipid |
| 3 | Terminalia chebula | Combretaceae | Extracts |
| 4 | Hemidesmus indicus | Apocynaceae | Extracts |
| 5 | Withania somnifera | Solanaceae | Extracts |
| 6 | Butyrospermum paradoxum | Sapotaceae | Oil |
| 7 | Hippophae rhamnoides L. | Elaegnaceae | Fruit extracts |
| 8 | Melaleuca alternifolia | Myrtaceae | Oil |
| 9 | Lens culinaris | Fabaceae | Powder and complex extract |
| 10 | Curcuma longa | Zingiberaceae | Extracts |
| 11 | Azadirachta indica | Meliaceae | Extracts |
| 12 | Aloe vera | Xanthorrhoeaceae | Extracts |

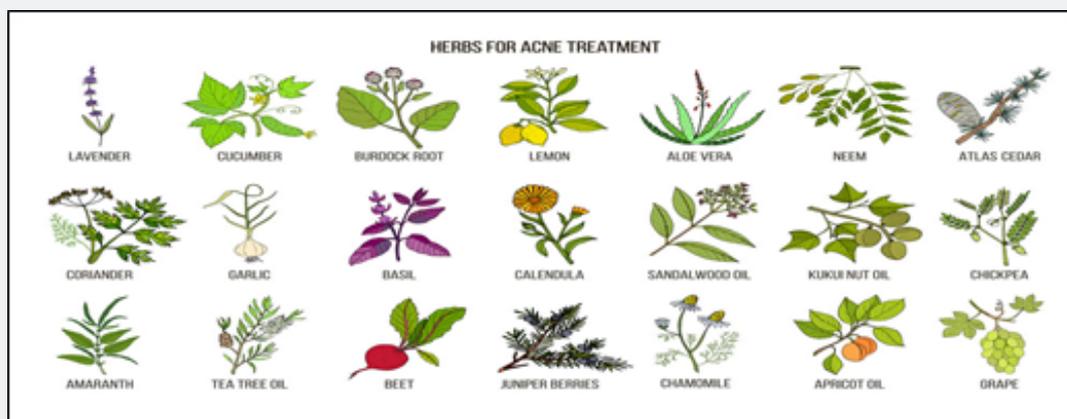


Figure 3: Herbal plants used in treatment of Acne Vulgaris.

a. Manjistha - is herb popular in Ayurvedic medicine. It's thought to support your lymphatic system, which is critical to healthy skin. Research shows that manjistha has anti-inflammatory, antibacterial, and antiandrogenic abilities that may help prevent and treat acne.

b. Neem - Traditional therapeutic uses of neem include treating skin conditions such as acne, eczema, and psoriasis.

c. Tea tree - Tea tree is a herb used to treat skin problems and wounds. It has antiseptic and anti-inflammatory abilities that may reduce the number of acne lesions.

d. Witch hazel - Witch hazel contain treat acne by removing excess skin oil. It also has anti-inflammatory effects and can reduce redness and bruising. Witch hazel is often used alone or as a base for homemade acne remedies.

Novel nanoparticulate approaches for Acne Vulgaris

In spite of numerous treatments available for acne, many patients did not respond well to the treatment. Drugs that are used for treatment of acne show frequent limitations and side effects (skin irritation, redness, dryness etc) leading to reduce patient compliance. Thus novel nanoparticulate approaches of

anti-acne agents are introduced with an attempt to reduce their side effects by increasing drug effectiveness (dermal localization effect)/patient compliance as they are not only safe and effective but also cosmetically available. Novel drug delivery agents or novel carriers are gaining large recognition, as they are highly efficient to transfer the drug across the skin. Various novel carriers include niosomes, liposome, emulsomes, transferosomes, micro

emulsion, nano emulsion, and nano lipid carriers (Figure 4)[6]. Novel delivery strategy for existing drug and their modification represent acne treatment changes, in addition to the development of new herbal medication that target regulatory pathways in acne patho-physiology. Novel drug delivery system also reduces the medication problem in terms of penetration, retention, sustained release and therapeutic efficacy [7].

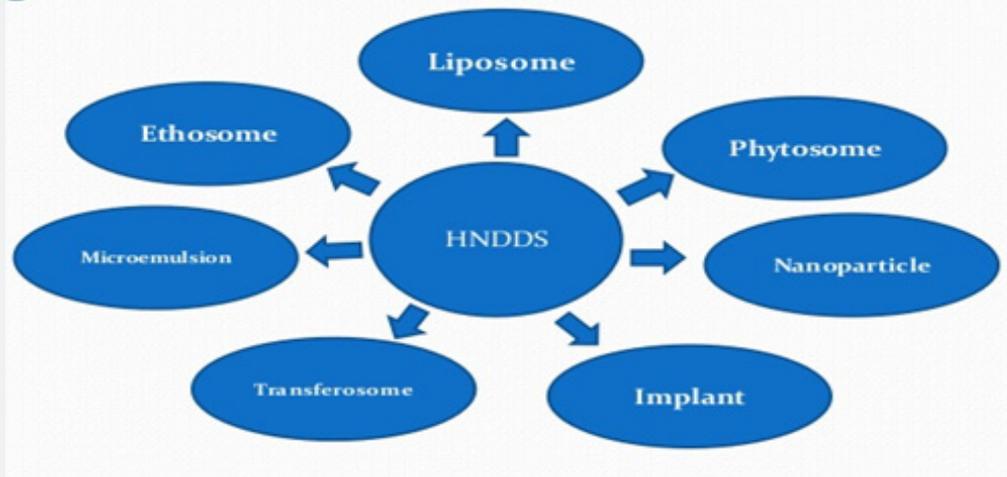


Figure 4: Types of carriers in Herbal Novel Drug Delivery System.

Types of novel drug delivery systems used for acne treatment include:

i. Microsphere: Microspheres are micro particulate technology that improves the treatment tolerability, encourages adherence, and contributes to better long-term therapeutic outcomes. Microspheres removes the quick delivery of high concentrations of drug to the application site and instead facilitates controlled release of potentially irritating drugs. It is associated with improved treatment outcomes and minimal irritation [8].

ii. Liposomes: Liposomes are spherical vesicles whose membrane consists of amphiphilic lipids (i.e., lipids that are hydrophilic on one side and lipophilic on the other side) that enclose an aqueous core, similar to the bilayer membranes of living cells. They are currently used as vehicles in pharmaceuticals and cosmetics for a controlled and optimized delivery to deep skin layers. Liposomes improves efficacy of incorporated synthetic and herbal drugs; reduces high drug application frequency; extends the therapeutic value by reducing toxicity and enhancing the bioavailability. Amphiphilic nature of liposomes enables the delivery of two types of substances once they are applied on the skin; each differs in its effects on skin permeability, which may enhance the desired therapeutic benefit [9]. E.g. liposomal herbal medication for acne is liposomal encapsulated rhodomlyrtone.

iii. Niosome: In dermatological disorders such as acne, niosomes acts as an unique drug delivery system with an aim to

increase the drug’s residence time in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. They increases epidermal properties by reducing trans-epidermal water loss and by increasing smoothness via replenishing lost skin lipids [10].

iv. Surfactant-free emulsions: In field of dermatology emulsifier-free formulations are innovative area. Mostly cosmetic or skin care products are emulsions, i.e. mixture of two or more immiscible. As a result, they require the addition of surfactants (emulsifiers) that stabilize the formulation and increase its shelf life. Once these surfactant agents are applied on the skin, they tend to emulsify and remove the natural lipids of the epidermis. Accordingly, the pharmaceutical industry has been developing surfactant-free emulsions as alternatives to conventional formulations using stabilizers, such as polymeric emulsifiers or solid particles. Emulsions, being free of surfactants or other potentially irritant agents, can be a good option for the delivery of active ingredients to the skin, represents a better alternative for the treatment of acne [11].

v. Micro-emulsion: They are translucent mixtures of oil, surfactant, co-surfactant, and water, in which either the oil globules are dispersed in water (o/w) or water globule are dispersed in oils (w/o). Various researches have revealed the significance of micro-emulsion for dermal and transdermal delivery both in-vitro and in-vivo. Due to the high solubilization capacity, a large quantity of drug can be incorporated in this formulation [12].

vi. Nano-emulsion: Nano-emulsions are also called “ultrafine emulsions” because of the formation of submicron range droplets which may seem to be transparent and translucent with a bluish color. The small-size droplets give them characteristic stability against creaming, sedimentation, flocculation, and coalescence. It facilitates effective transport of drugs to the skin [13].

vii. Aerosols foams: Aerosol foams have converted an increasingly standard type of topical formulation for a variety of skin conditions including acne vulgaris. The vehicle base of the foam can have a liquid or semi-solid consistency that shares the same physicochemical characteristics of conventional vehicles like creams, lotions, and gels, but it maintains desirable properties such as moisturizing, fast-drying effects, or higher drug bioavailability. The aerosol base is dispensed through a gas pressurized can that discharges the foam. The product characteristics (i.e., texture, bubble size and thickness, viscosity, stability, and spreadability) are determined by the type of formulation and the dispensing container that are selected to suit the specific treatment needs [14].

viii. Microsponges: They are biologically inert particles prepared of synthetic polymers with the capacity to store a volume of an active agent up to their own weight. Additionally, the particles assist to defend the entrapped active compound from physical and environmental degradation. The microsphere technology can be utilized in a variety of formulations, but is more frequently manufactured as gels. Once applied on the skin, microsponges slowly release the active agents [15].

ix. Fullerenes: They are hollow spherical molecules that are composed entirely of carbon and are thought to be potentially potent antioxidants. On contact with the skin, fullerenes migrate intracellularly through the skin. Thus it can be said that fullerenes “traps” active compounds and then releases them into the epidermis of the skin after the application [16].

x. Solid Lipids nanoparticles (SLNs): Solid Lipid nanoparticles have been introduced as likely attractive and profitable options due to their natural components. SLNs have been identified as an alternate carrier system to liposomes, emulsions and polymeric nanoparticles. Lipid components of SLNs are solid at both body and ambient temperature and can be very much purified triglycerides, complex glyceride mixtures or even waxes. SLNs improve the stability, capacity loading and prevent the drug expulsion during storage. They are noticeable from SLNs by the composition of the solid matrix [17].

Advantages of nanocarriers are:

- Improved stability of active substance.
- Excellent entrapment efficiency.
- Maintain the physicochemical properties of entrapped drug.

- Excellent penetration enhancers.
- Improved skin tolerance.
- Targeted drug delivery action.
- Minimizes the side effects.
- Accommodate drug molecules with a wide range of solubility.
- Incorporates both lipophilic and hydrophilic drugs.
- Increased stability due to less hydrolysis and oxidation.
- Rapid and efficient drug penetration.
- Increases the rate and extent of absorption of the drug.
- Modifies/sustained drug release mechanism

Various researches regarding herbal medicament in acne vulgaris

H Bisht et al [18] discussed acne vulgaris as a common skin disorder found in adolescent age group. It is a cutaneous disorder of the pilo-sebaceous unit involving the abnormalities in the production of sebum. Various medicinal plants extracts and its formulations are used for treatment of acne [18]. Sonali Syal [19] discussed high risk and side effects associated with synthetic drugs used in anti-acne therapies. Different internal and external herbal remedies are considered to be a more effective and safe alternative for the treatment for acne vulgaris. It is developed as natural and safe approaches to fight acne due to their enhanced effectiveness [19]. Nirmani Wishwakala Nawarathne et al [20] developed novel gel formulations from seeds of *Nigella sativa* L. and evaluated the antibacterial potential against some acne-causing bacterial species. The antibacterial potency of this formulation against *S. aureus* exceeded the marketed synthetic product used as the positive control. During the storage period no change in color, odour, homogeneity, consistency, and pH was observed, while the antibacterial potency was retained. The potent antibacterial activity in topical gel formulations developed from the ethyl acetate extract of *N. sativa* signposts their suitability as alternatives to existing antiacne agents in the management of acne vulgaris [20].

Singh N et al [21] discussed the psychological problem of decreased self-esteem that hinders the quality of life of teenagers due to acne. A topical formulation must be cheap, acceptable, stable and effective [21]. Pal RS et al [22] discussed the new cosmeceutical possibilities by fusing with traditional Indian medicine for developing new anti-aging cosmeceutical with natural ingredients for topical applications. The future for beauty-from-within functional cosmetics is bright, because of multifunctional benefits in the area of anti-oxidant cellular protection and skin health with anti-inflammatory and anti-stress properties [22]. Sarangi KM and Padhi S [23] highlighted the current condition for the development of novel herbal formulations such as nanoparticles,

nanocapsules, liposomes, phytosomes, emulsions, microspheres, transfersomes, and ethosomes and summarize their biological activity/ applications [23]. Baghel S et al [24] reviewed novel technologies of drug delivery system for plant based medicine. The main goal for development of the herbal nanocarriers is to sustained drug action, at predetermined rate, to maintain a relative constant, effective drug level in body with less harmful effects and increase bioavailability [24]. Ramesh V and Kumar R [25] reviewed effectiveness of novel drug delivery system for herbal drugs for its safe, effective, convenient and economically affordable qualities. Liposomal formulations have successfully used in the treatment of various dermatological diseases. The drug loaded liposomes methods can be easily upgraded for commercial scale and has offered an excellent opportunity and hope in raising the in-vivo bioavailability of herbal drugs [25].

Nadica Sibinowska et al [26] discussed use of various novel carrier systems of drug in field of modern cosmetology, with an urgent need to formulate efficient, safe and acceptable cosmetic products. The novelistic drug delivery systems can help overcome the limitations of conventional formulations used in acne treatment, offering several advantages such as possibility for controlled release of the active substances, improved stability and reduction of side-effects, therefore, improving the patients' compliance to the treatment [26]. Nasari H et al [5] discussed various herbal plants that can be used alone or as adjuvant with other therapeutic measures or in mild to moderate situations [5]. Patel SD et al [27] discussed acne as a epidermal pleomorphic disorder of the pilosebaceous unit involving malfunctions in sebum production. The work focuses on the treatment of acne using herbal drugs and various drug delivery systems as a carrier. Though they have very little number of clinical trials, many successful results have been recorded [27]. Sinha P et al [28] reviewed numerous drug therapies for the management of acne, but high antibiotic resistance and epidermal toxicities with current medications are the challenging factor. Herbal remedies are always considered as a safe alternative against acne over synthetic drugs. But there are certain issues allied to natural therapies, such as it is necessary to define the quality and safety of plant extracts [28].

Sousa I [29] discussed and evaluated the pathogenic pathways associated to the mechanisms of action of novel molecules, which are currently under investigation for the treatment of acne vulgaris. In future, more effective treatments with lesser side effects are expected. The author believes that there will likely be a decline in the use of antibiotics for controlling *P. acnes* colonization and targeting the inflammation cascade [29]. Mullaicharam AR and Fatma AE reviewed anti-acne property of plant extract for acne vulgaris. Natural remedies are more acceptable in the belief that they are safer with fewer side effects than synthetic drugs, so herbal anti-acne cream proved to be non-toxic, safe and effective formulation [30]. Yarnell E and Abascal K [31] reviewed natural therapies for acne vulgaris, with antimicrobial, inflammation-modulating, anticomedogenic and hormone-balancing actions.

Natural substitutes are gaining greater research support and have much to offer clinically [31].

Conclusion

Acne vulgaris is common skin problem affecting millions of people. There are many important aspects considered for treatment of acne. In adolescence, acne can have negative psychological effect on affected individual. Herbs are natural source of medicament, which is used for acne treatment, without, or least side effects. Various studies are conducted for teenagers and other people to escape from acne. There are sufficient data to support use of herbs in clinical practices as they are prove to be useful in acne treatment. An overall herbal medicament has much to offer to improve the ability to deal with complex issue acne present. The use of novel herbal carrier systems of active substances is gaining popularity in modern cosmetology, due to the need for formulation of efficient, acceptable and safe cosmetic products. The encapsulation of herbal anti-acne moiety in carrier system represent better way to minimize side effects while maintaining their efficacy. Currently very few medicaments based on micro-sized and nano-sized application system have been approved and introduced to the market. Therefore, the main focus of researchers in the field of acne treatment has been the estimating the potential of different novel drug delivery systems as carriers for anti-acne herbal medicaments. In the last few decades, there has been a major increase in the number of patents with many patients rising acne as their problem and some of these original herbal formulations are becoming commercially available. The novel drug delivery systems can help to overcome the restraints of usual formulations used in acne treatment, offering numerous advantages such as better controlled release of the active drug, improved stability and reduction of drug related side-effects, therefore, improving the patients compliance and satisfaction towards anti-acne therapy.

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