Will the polyphenol and adapalene combination be a good strategy on acne vulgaris?

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A B S T R A C T
Acne vulgaris is a common disease which affects about 85% of the population. Various topical drugs are available, but the retinoid derivatives are mostly taken into consideration. They are used as a first-line treatment drugs. However, they also have few side effects. Whereas, adapalene which is a third generation topical retinoid has fewer side effects compared to other derivatives. In this, we hypothesize that the combination therapy of adapalene and flavonoid could improve the efficacy and thereby it can also decrease the treatment time. Since, flavonoids possess multiple activities we assume that it can improve the action of the drug by showing a synergistic activity. Moreover, when we incorporate these two drugs in nanoemulgel, it can easily penetrate into the skin and produce its therapeutic action. Hence, we assume that if this hypothesis proves to be correct then this method will be an effective one in treating acne (pustule).

Introduction
Acne is also called as acne vulgaris. It is a chronic inflammatory skin disease which occurs mostly in teens and adolescents having the age ranging from 12 to 24 [1]. They commonly occur at the following parts (i.e.) face, neck, upper chest, upper back, etc. It is not a life-threatening disease but it affects the patient both psychologically as well as psychosocially [2]. According to the Global Burden of Disease study, about 85% of the population is affected by this disease. In addition to this, the Global burden of disease study also states that acne is the eighth most prevalent disease in the world as of 2010 [12]. Additionally, it is said that the US is mostly affected by acne. And about 40-50 million Americans has been affected by this particular disease. Acne can be classified based on its severity as mild, moderate and severe form and it can also be classified based on the inflammatory and non-inflammatory conditions like blackheads, whiteheads (non-inflammatory condition) and papules, pustules, nodules and, cyst (an inflammatory condition). Many factors are responsible for the occurrence of acne [17]. But, mainly there are 4 mechanisms responsible for the formation of acne and they are: 1. Hyper-proliferation of the follicular epithelial cells, 2. Excess sebum production from the sebaceous gland due to the hormones, 3. Propionibacterium acne, and 4. various inflammatory mediators.

According to the literature, people with white skin are more prone to acne compared to black skin, the reason for this condition is that the white skin people are having sensitive skin whereas, the people with dark skin tone are having a tough skin and they are less sensitive to sunlight. Additionally, women are more prone to this condition as compared to that of men because of various reasons like using of cosmetic products which thereby blocks the skin pores, having less sensitive skin as compared to that of men and hormonal changes, etc. There are various factors responsible for the occurrence of acne; supporting this statement several articles have been published. According to the French studies with the adolescents, the following data has been established: Gender, overweight and physical activity doesn’t have any influence of acne whereas; chocolate consumption, smoking, sweating, squeezing of pimples and using of cosmetic products have an influence on acne. But, these factors vary in every article.

Even though acne is not a life-threatening disease, it affects the patient both psychologically as well as psychosocially. Patients enter into psychological problems like low self-esteem, self-image, frustration, and embarrassment. In addition to this, they also experience some of the psychosocial problems like having self-consciousness during their inter-personal relationship, feeling helplessness, lack of interest in academics as well as in their jobs and using of camouflage in order to mask their appearance [14]. Various treatment options are available to treat acne. Novel treatments are also available to treat acne in order to reduce the side effects of the drug and to improve the efficacy of the
Pathogenesis of acne: Fig. 1 is a schematic diagram representing the pathophysiology of acne. As discussed earlier, there are 4 factors responsible for acne. Apart from these 4 factors, additional factors are also depicted in the Fig. 1.

All the medications act by a different mechanism. But, the main aim of all these medications is to decrease the inflammation and bacterial load, decreasing the retention hyperkeratosis and reducing the production of sebum. In addition to this, the treatment method should also reduce the scars. Topical retinoids act by decreasing the formation of microcomedones, reducing the keratinocyte proliferation and creating a harsh and difficult environment for the micro-organism. On the other hand, antibiotics focus only on the bacteria which are causing the disease. When we go for topical treatment then the absorption of drug depends on varieties of factors like surface area, quantity applied, time and duration of application, selection of vehicle and the area on to which the formulation has been applied. When there is no therapeutic effect observed after applying topical medication and consuming oral formulations then, in that case, we consider it as a severe form of acne. This form of acne can be treated by other alternative treatment methods like hormone-based therapy, light-based therapy, vaccines etc.

All the treatment options are depicted in the Fig. 2. While comparing all the above treatment, the topical treatment is mostly preferred because of their ease of administration and they act directly on the affected area.

Side effects associated with current treatment options: Even though acne vulgaris can be treated with various drugs, all the topical treatments are having side effects and they are represented in the Fig. 3.
Acne vulgaris is a common skin disease, it can be divided into three types depending upon the severity like mild, moderate and severe. Acne vulgaris is not a life-threatening disease but it affects the patient’s self-esteem and confidence. There are various treatment options available as depicted in Fig. 2. But, all these drugs have side effects in one or the other way. Commonly seen side effects are dryness, erythema, irritation, and photosensitivity. In this work, we hypothesize the use of selected polyphenols in enhancing the efficacy of the frontline drug Adapalene by producing a synergistic activity and thereby reducing the unwanted effects of the same. Moreover, polyphenols are obtained naturally; it will not produce any side effects compared to other marketed products. Formulating topical gel as the carrier for the drug of choice/test can directly act on the skin which can be easily applied to the affected area.

Nanotechnology in treating acne: We are incorporating nanotechnology in our formulation in order to develop a nanoemulgel (by using spontaneous emulsification method) so that we can improve the penetration of the drug into the skin and thereby improve the efficacy.
of the treatment. And the nanoemulgel is more stable as compared to that of emulgel. In addition to this, we can also improve the bioavailability of the drug.

Topical retinoids are preferred as the first-line drug in the treatment of acne vulgaris. Different topical retinoid derivatives are available and they can be sorted as Tretinoin, Isotretinoin and Adapalene etc. From these three drugs, we have selected adapalene as our choice of drug. The reason for choosing Adapalene as our drug is because it is less irritating and doesn’t have a photosensitivity reaction. Whereas, when we consider isotretinoin, and tretinoin, the concentration of the drug is less as compared to that of adapalene at the same time they are also having more side effects as compared to adapalene [15]. Studies revealed that a concentration of 0.1% of adapalene and 0.025% of tretinoin are having similar efficacy. But however, we can reduce the concentration of adapalene when we go for a combination therapy. Adapalene is marketed along with clindamycin. But, the problem in this is, since there is an antibiotic, the bacteria may become resistant to the drug. While coming to our formulation we are combining the drug (Adapalene) along with a polyphenol (flavanoid). We expect that this combination can give a better efficacy as compared to that of monotherapy or even a combination therapy which is available in market and moreover it will not have any drug resistance activity.

Flavonoids and its activities: Flavonoids are the natural products obtained from fruits, vegetables and even in certain beverages like tea, cocoa and wine etc. They are having a polyphenolic structure. In addition, they are also having a wide spectrum of health-promoting effects because they possess different activities like anti-oxidant, anti-inflammatory, anti-carcinogenic and anti-mutagenic [16]. Flavonoids also inhibit several enzymes such as cyclooxygenase, lipoxygenase and xanthine oxidase (XO). Depending upon the number of the carbon atom, unsaturation and the oxidation of the basic structure, it can be classified as flavones, flavonols, catachins, and neoflavonoids etc. Different types of flavonoids can be obtained from a variety of fruits and vegetables such as apple, onion, grapes, berries, celery, and parsley etc. Researches support the anti-inflammatory activity by inhibiting the COX-2 enzyme (which is responsible for the synthesis of prostaglandin and causes inflammation) [5]. Certain flavonoids like hesperidin, apigenin, luteolin, and quercetin are reported to have anti-inflammatory activity. It is reported that along with inhibition of COX-2 enzyme they also inhibit other inflammatory mediators like cytokines and chemokines [6]. Its anti-bacterial activity depends upon several factors like their ability to inactivate the bacterial adhesins, enzymes. Sometimes the microbial membranes are also disrupted by some of the flavonoids [6]. Based on these research facts, we propose to use flavonoids obtained from some fruits which might play a role in improving the efficacy of the drug.

In our work, we are going to formulate a combination product. Selected drug Adapalene acts on the affected area by normalizing the epithelial cell differentiation and decreasing the comedone formation. And the mechanism of action of the combination therapy is represented in Fig. 5.

The progression of acne vulgaris is depicted in the Fig. 4. In the normal skin, when there is an excess of sebum production as well as the formation of keratinous material, they both clog the pore of the skin. After which the bacteria starts growing and leads to the formation of whiteheads. When this process continues, then the orifice of the follicle opens and leads to the formation of blackheads (Black color is due to the oxidized lipids and the melanin). Further, the enlargement of comedone results in rupturing of the follicle and finally resulting in papule, pustule and more severe form of acne like nodules or cyst [7]. Mechanism of action [8,5,13]: Fig. 5 depicts the mechanism of action. In which when the prepared formulation is applied to the affected area, both polyphenol and adapalene acts differently on the skin. 1. Polyphenol like Hesperidin, resveratrol, and apigenin has anti-bacterial and anti-inflammatory property [18]. So, by either way, they’ll act on the affected skin. 2. Drug (adapalene) has a wide range of mechanism. In which the first one is binding to the RAR (Retinoic acid receptor) and then again combining with RXR (retinoid X receptor) in order to regulate the gene transcription. Additionally, they also have other properties like anti-inflammatory and anti-seborrheic activities.

Evaluation of hypothesis

Induction of acne vulgaris: For the induction of acne, there is no particular animal model available. But, mostly acne is induced in laboratory animals like rat, mouse, and rabbit. In a study, they stated that the HR-1 mouse was having more inflammatory action as compared to other mouse strain (VDR k/o, BALB/c, SCID). They have observed the inflammation after injecting 10⁶ colony forming unit/µl of Propionibacterium acnes suspension [9]. The reason for this is that the expression of inflammatory mediators was more in HR-1 mice as compared to that of other mouse strain. In another study, acne was induced by injecting the Propionibacterium acnes into the ears of female Sprague Dawley rats. The thickness of the ear was compared in both cases (i.e.) saline injected ear and p.acne injected ear and they observed that the bacteria injected ear was 2–3 times thicker than saline solution [10]. Acne can also be induced by using chemicals as an alternative way to micro-organism. The rabbit was chosen to induce pustules (a moderate form of acne). In this particular study, they have used 8 chemicals out of which 2 chemicals gave a reproducible results. They have used Sodium lauryl sulphate and mercuric chloride at different concentrations to induce pustules at different areas of the rabbit. Researchers state that this action is due to the primary irritancy caused by the chemicals [11].

Efficacy of the formulation: The main aim of our work is to treat acne with a combination therapy for improved efficacy. Efficacy of the treatment with prepared formulation can be improved since, we are combining the drug with polyphenol. Both adapalene and polyphenol can be combined and incorporated into a lipid-based gel in order to develop nanoemulsion gel. When we administer this formulation on the affected area, both drug as well as polyphenol exhibit different actions in order to treat acne. As seen in Figure-5 Adapalene is having various activities like anti-inflammatory, anti-seborrheic activity, and normalizing cellular differentiation. When we come to flavonoids they are having a wide range of activities like anti-inflammatory, anti-carcinogenic, anti-oxidative effect, anti-bacterial effect, anti-aging, neuroprotective effect etc. Because of this, we expect that the polyphenol may exhibit a synergistic activity on the drug thereby improving the treatment efficacy and decreasing the time of treatment.

Characterization and evaluation of the formulation: The prepared nanoemulgel formulation will be subjected to characterization like:

1. Particle size,
2. Polydispersity index,
3. Zeta potential,
4. Viscosity,
5. pH,
6. Spreadability and
7. Extrudability.

After characterizing the formulation, we’ll be going for ex-vivo [19] and in-vivo evaluation studies. And all these studies are given in the short in the Figs. 6 and 7 [20].

Discussion

Retinoid derivatives are used as the first line drug in the treatment of acne vulgaris. But, most of the retinoid derivatives are having side effects. Flavonoids are used in the formulation because they possess a wide variety of activities like anti-inflammatory, anti-bacterial and anti-oxidant activities. Acne vulgaris occurs due to the hormonal changes which thereby increase the sebum production (acts as a growth medium
for the bacteria “Propionibacterium acne”) and epithelial proliferation. Once the bacterium gets activated it leads to the release of inflammatory mediators and consequently, it causes the inflammation. Adapalene being a retinoid derivative shows its activity by normalizing the differentiation of epithelial cells and by decreasing the sebum level. In addition, it has also got anti-inflammatory activity. Adapalene acts by binding to specific receptor RAR (Retinoic acid receptor) and RXR (Retinoid X receptor). In this framework, we assume that the flavonoid will possess a synergistic activity along with the drug and it can also decrease the dose or the concentration of the drug. Once when the concentration of the drug is decreased then it may diminish the side effect which is raised by the drug. In addition to this, we can also improve the efficacy and decrease the time period which is required for the treatment. Application of nanoemulsion in our formulation would also improve the penetration capacity of the compound. Since, acne is a skin disease we can directly target the affected area. In addition to this, the nanoemulsion gel is also helpful in retaining the drug on the affected area for the prolonged period of time. Moreover, when we compare the emulsion and nanoemulsion, nanoemulsions are having more stability because of its nano size. Once the formulation is done, then we’ll be going for the ex-vivo as well as in-vivo studies in order to determine the characteristics of the formulated compound. The ex-vivo study will be useful in determining the cumulative drug release. After the ex-vivo study, in-vivo studies will be carried out. In the case of in-vivo studies, an animal model will be induced with acne and then it will be treated with the prepared formulation. In addition to the treatment, the efficacy of the marketed (combination therapy), as well as the prepared formulation, will also be compared. After considering all these aspects we assume that this formulation will be an effective tool in the management of disease under the research.

Fig. 4. . Schematic diagram representing the evolution of acne vulgaris (From normal skin to the severe form of acne).

Fig. 5. . Schematic diagram representing the mechanism of action of the prepared formulation on the affected area.
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