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FORMULATION AND EVALUATION OF *NATURAL* HERBAL ANTI-ACNE AS GEL DELIVERY SYSTEMS

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ABSTRACT

The objective of this study was to produce a Carbopol 940 based gel formula containing an Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum sanctum extract and evaluate their anti-acne potential. The ethanolic extract was derived from the dried leaves of Aloe barbadensis, Allium sativum, Camellia, sinensis and Ocimum sanctum and was subjected to a phytochemical evaluation. Three gel formulations of Carbopol 940 containing Aloe barbadensis, Allium sativum Camellia sinensis and Ocimum sanctum extract in three different concentrations, i.e., 0.5, 1, and 2% w/w were prepared. These gels were evaluated for their physical appearance, antimicrobial activity, skin irritability, pH, spread ability, and wash ability. The prepared formulas were stable, greenish and homogeneous. None of them showed irritation to the skin. The spread ability (g.cm/sec) and pH of all three formulations were 11.76, 11.50, 12.03,6-7 respectively. Gel-III exhibited the highest antimicrobial potential against Propionibacterium acne, It was revealed from the acne healing studies that the elimination time for the acne treated with Gel-III was two weeks. A formulation gel containing 2%w/w extract showed better antimicrobial activity, physicochemical characteristics, and pharmacological parameters than the other formulations. It can be concluded that the acne healing process was faster with the gel formulation containing 2% w/w of the Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum sanctum extract, proposing that this formulation is a promising candidate for acne healing.

KEYWORDS: Aloe barbadensis, Allium sativum, Camellia sinensis, Ocimum sanctum, Gel, Anti acne.

INTRODUCTION

Lot of teenagers will have pimples at some point some only have a few small pimples that soon go away. Others develop persistent and clearly visible acne. This can be very distressing, particularly in puberty. However, there are a number of things that can be done about acne. Although patience is needed, this is about acne in teenagers and younger known as “Common acne” or “Acne vulgaris.”

Acne, from the Greek word “Akme", means peak or apex, is genetic or acquired affections of the pilosebaceous units.[1] Acne is also called as “Acne vulgaris” in medical terminology.[2] Acne is basically the involvement of sebaceous gland which comprised pustules and papules, means solid lesions occur on the skin or puss occurs on the skin. Normally, this sebaceous gland protects and moistures the skin and is very important for the skin. However, due to certain changes such as extreme dirt, dust, or germs infections, it harms the skin.[3]

Day-to-day exposure of human skin causes to number of problems such as acne, pimples, pigmentations, and sunburns marks.[4] Typically begins around puberty and early adolescence, it tends to present earlier in females 12 or 13 years then in males 14 or 15 years because of late onset of puberty in males. Acne has been estimated to affect 95–100% of 16–17-year-old boys and 83–85% of 16–17-year-old girls' acne is a pleomorphic disease that occurs on the face 99%, back 60%, and chest 15%. The individual lesions of acne vulgaris are divisible into three types: noni flamed lesions, inflamed lesions, and scars.[5]

Acne develops as a result of blockage of follicles, hyper keratinization and keratin plug formation and sebum (microcomedo). With increased androgen production, sebaceous glands are enlarged and sebum production is increased. The microcomedo may enlarge to form an open come do (blackhead) or closed come do. Comedones occur as a result of clogging of sebaceous glands with sebum, naturally occurring oil and dead skin cells.[6] The naturally occurring commensal bacterium Propionibacterium acnes can cause inflammation and inflammatory lesions like infected pustules or nodules and papules in the dermis around the microcomedo or comedone resulting in redness, scarring or hyperpigmentation.[6,7]

It includes different factors such as high-humidity, Prolonged sweating, Increase in skin hydration, exposure to dirt or vaporized cooking oil or certain chemicals like petroleum derivatives.

Drugs like Phenytoin, Isoniazid, Phenobarbital, Lithium, Ethionamide, Steroids, Azathioprine, Quinine and Rifampin causes acne.[8]

Menstrual cycles and puberty may also cause acne. During puberty, increase in androgens level causes the enlargement of follicular glands and sebum production is also increased.[6,9] Anabolic steroids produce similar effect.[10] Several hormones are linked with acne like the androgen's testosterone, dihydrotestosterone, dehydroepiandrosterone sulfate and insulin like growth factor 1 (IGP -I). In later years development of acne vulgaris is uncommon but rosacea incidence will increase which is having similar symptoms in older age groups. Acne vulgaris in adult women may be due to underlying condition such as; pregnancy, Cushing's syndrome, hirsutism or polycystic ovary syndrome. Acne climacterica refers to menopause associated acne, occurs as production of the anti-acne ovarian hormones estradiol and progesterone allowing the acne genic hormone testosterone to continuously exert its effects.

The genetics of acne susceptibility is polygenic as the disease does not follow classic Mendelian inheritance pattern. There are multiple candidates for genes related to acne which includes polymorphisms in Tumor necrosis factor-alpha, Interleukin-1 alpha, CYP1A1.[11]

Studies shows that increased stress levels are associated with increased acne severity.[12] The National Institutes of Health (USA) shows that stress can cause acne flare.[13] In Singapore, study of adolescents observed positive correlation between stress levels and acne severity.[14]

Propionibacterium acnes (P. acnes) are anaerobic bacterium species that mostly causes acne. Staphylococcus aureus has been discovered to play an important role since normal pores colonized only by Propionibacterium acnes.[15] Specific clonal sub strains of P. acnes are also associated with normal skin health and long-term acne problems. These strains have the capability of changing, perpetuating or adapting to the abnormal cycle of inflammation, oil production and inadequate sloughing activities of acne pores. For at least 87 years, one virulent strain of Propionibacterium acnes has been circulating around Europe.[16] Antibiotics resistance has been continuously increasing to P. acnes in vitro.[17]

The relationship between acne and diet remains unclear although high glycemic diet is associated with worsening of acne.[18-20] There is a positive association between the milk consumption and prevalence of acne increases.[20-22] Reports showed that consumption of chocolate and salt are not associated with development of acne.[20] Chocolate contains large amount of sugar that can lead to high glycemic load. It might be possible that acne is linked with obesity and insulin metabolism.[23]

Acne is linked with the parasitic mite Demodex but it is not clear whether Demodex or Demodex associated bacteria causes the effects.[24-26]

Mild acne can occur across all ages and in all skin types. Acne falls into the "mild" category if you have fewer than 20 whiteheads or blackheads, fewer than 15 inflamed bumps, or fewer than 30 total lesions. Mild acne is usually treated with over-the-counter topical medicine. It may take up to eight weeks to see a significant improvement.[27]

The negligible adverse effects of herbal drugs compared with modern medicines have become another important aspect in the treatment of this condition. Acne can be cured by herbal either consuming internally and externally or with both.[28] Topical treatment is preferable choice of consumers as ease of application, safe, and efficacious for their efficacy in the treatment of acne but still many herbs remained untouched by the scientist. The review focuses the benefits of herbal medicines for the treatment of acne[28] as shown in Table 1.

Table 1: Herbs Containing Anti-Acne Constituents (Plant Profile).

Herb	Common Names	Part Used	Traditional Uses	Reported Biological Activities	Active Constituents	Reference
Aloe barbadensis	Aloe Vera	Leaves	Applied topically to treat skin ailments, seborrheic dermatitis, psoriasis Vagaries, genital herpes, skin burns, and Acne valgaris	Antioxidant. Anti-inflammatory, Antimicrobial, Anti-acne effect in vivo	Aloin. emodin.	[29-34]
Allium sativum	Garlic	Bulb	Used to treat a variety of diseases around the world, including high blood pressure, infections, and snakebites, and it has also been used	Anti- bacterial, Anthelimintic, Rubefacient, may treat cardiovascular diseases, elevated cholesterol and blood presser.	Allicin. Allin. Carbohydarates, volatile oil, s-allyl mercapto cysteine, s-allyl cysteine.	[35-36]

			to ward off evil spirits and antimicrobial effects			
Camellia sinensis L.	Green tea	Leaves	Protection and miniaturization of the skin and hair.	Antimicrobial, Anti-inflammatory Anti-acne in vivo, Antioxidant, 5 alpha reductases inhibitory	Epigallocatechin -3 gallate. EGCG, EC, GCG, ECG, EGC and GA,	[37-43]
Ocimum basilicum L.	Sweet basil	Leaves	Wound, acne and vitiligo.	Antimicrobial. Anti-inflammatory, Antioxidant.	Neral, citral, alpha humulene, Beta caryophyllaceous, linalool, and germacrene -d.	[44-47]

In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.[48-102]

OBJECTIVE OF STUDY

The Objective of this study was to formulate and evaluate of natural anti-acne herbal gel with four herbal extracts that have antimicrobial activity against P.acne and have no adverse effects.

MATERIALS AND METHODS

Plant Materials and Preparation of Extract

Aloe barbadensis (Aloe vera leaves), *Allium sativum bulbs* (Garlic bulb), *Camellia sinensis* leaves (Grean Tea leaves) and *Ocimum basilicum* leaves (Sweat Basil leaves). Carbopol 940 (Corel Pharma Chem, India), Propylene glycol 400 (SK, Picglobal company, South Korea), Methyl paraben (Aseschem, India), Triethanolamine. (Aseschem, India).

Plants Collection

Aloe barbadensis leaves: Aloe Vera leaves were harvested from Jaref, Sana'a, cleaned from foreign materials, washed with water, dried in the shade for 72 hours, coarsely grinded, weighed, and stored in a dark airtight jar.

Allium sativum bulbs: Allium sativum bulbs were obtained from a local spice shop, cleaned from foreign materials, coarsely grinded, weighed, and stored in a dark airtight jar.

Camellia sinensis leaves: Camellia sinensis leaves were obtained from a local spice shop, cleaned from foreign materials, coarsely grinded, weighed, and stored in a dark airtight jar.

Ocimum basilicum leaves: Ocimum basilicum leaves were obtained from a local spice shop, cleaned from foreign materials, coarsely grinded, weighed, and stored in a dark airtight jar.

Equipment

Grinder (Lejieyin, China), Orbital Shaker (Pioway Medical Lap Equipment Company, China), Rotary Evaporator (Biobase biodustry Company, China), Electronic thermostatic drying oven (Jiangsu Jinyi Instrument Technology Company, China), Digital Mixer (Jiangsu Zhengji Instrument, China), Rotational Viscometer (Nanjing T-Bota Scientech Instrument and Equipment Company, China), pH Meter (Changzhou Xiangtian Experimental Instrument Factory, China).

Extraction Procedure of Aloe Barbadensis Leaves, Allium Sativum Bulbs, Camellia Sinensis Leaves and Ocimum Basilicum Leaves

250g of each herbal drugs were weighed and added to the conical flask containing five times volume of 96% of ethanol as a ratio (1:5), then soaked for 10 days, then filtered. Filtrates were allowed to evaporate in Rotary evaporator until the desired concentrations were obtained.[103] After Rotary evaporator the extracts were leave in oven at 40℃ for a week for becomes more concentrate.

Gel Formulation

The gel was prepared by using 0.5%, 1% and 2% concentration of the Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum basilicum extract. In a separate beaker, Carbopol 940 was dispersed uniformly in distilled water with continuous stirring, avoiding air entrapment and allowed to soak for few hours. In another beaker, methylparaben was dissolved in the remaining amount of distilled water by gently heating. To this solution, the herbal extracts were added and triturated well. The above mixture was then added to the carbopol mixture and stirred well. Finally, propylene glycol and triethanolamine were added and the pH was adjusted to 6.8-7. The prepared formulation was filled in a suitable

container.[1,104] Various formulation batches were prepared the composition of formulations was shown in Table 2.

Table 2: Composition of Gel Formulation.

	Ingredients name	Quantity per 100 g (in grams)			Role of Ingredients
		Gel -I	Gel-II	Gel- III	
1	**Aloe Barbadensis**	0.125%	0.25%	0.5%	Active Ingredient.
2	**Allium Sativum**	o.125%	0.25%	0.5%	Active Ingredient.
3	**Camellia Sinensis**	0.125	0.25%	0.5%	Active Ingredient.
4	**Ocimum Hasilium**	0.125%	0.25%	0.5%	Active Ingredient.
5	**Carbopol 940**	2%	2%	2%	Gelling Agent
6	**Propylene Glycol 400**	2%	2%	2%	Humectant, Solvent
7	**Methyl Paraben**	0.1%	0.1%	0.1%	Preservative
8	**Triethanolamina**	2%	2%	2%	Stabilizer or Neutralizer
9	**Distilled Water**	q.s	q.s	q.s	Vehicle

Evaluation of Gel

Physical Evaluation

The formulated gels were evaluated for various parameters as follows:

Colour: The colour of the prepared gels was examined by the naked eye against a white and black background.[105]

Odour: By dissolving the prepared gels in water, the odour of the gels was tested by smelling.[105]

Homogeneity: By applying the prepared gels to a transparent glass plate, the presence or absence of particles that have not been mixed homogeneously was examined using visual inspection.[106]

Consistency: By applying the prepared gels to a transparent glass plate, the presence or absence of coarse particles was examined using visual inspection.[106]

Wash Ability: Formulations were applied on hand which was observed under running water.[1]

pH Test: The pH of the gels was detected with a digital pH meter. An amount of 0.5 g of gel was dissolved in 50 ml of distilled water and stored for two hours. Each formulation's pH was measured in triplicate and the average values were taken.[107]

Spread-ability: The gel was weighed to be as high as 0.5 g and then placed on graph paper coated with glass. Then, we put another glass above the gel mass. The gel diameter was calculated by measuring the diameter length of several sides. Then we added an additional load of 150 g, allowed the mixture to stand for one minute, and measured the diameter of the gel as before[108] The spread ability was recorded using the following formula: S=M*L/T Where: S- spread ability, M- mass in grams, L- length in centimeter, T- time in seconds.

Viscosity Study: The measurement of viscosity of the prepared gel was done using Brookfield digital Viscometer. The viscosity was measured using spindle no. 64 at 10 rpm and 250°C. Before measurement deaeration of gel was done and the gel was filled in appropriate wide mouth container. Samples of the gels were allowed to settle over 30 min at the assay temperature (25 ± 10°C) before the measurements.[105]

Pharmacological Evaluation

Skin Irritation Test: Skin irritation test for gel formulation was conducted over skin of human volunteers, the prepared gel formulation was applied on the skin of hand, face, nick and observed for any type of undesirable effect.[107]

Acne Healing Activity of Gel Formulations: Adults aged from 17 to 23-year-old were divided into three groups, having 2 adults each Group I, II, and III received Gel-I containing 0.5% w/w of Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum basilicum extract, Gel-II containing 1% w/w of Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum basilicum extract, and Gel-III containing 2% w/w of Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum basilicum extract. No other medicine was given to the adults during the entire study. The study was evaluated for two to four weeks.

RESULTS AND DISCUSSION

This study evaluated the anti-acne potential of herbal gels. Three different concentrations of an Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum basilicum extract were used to prepare gel formulations with Carbopol940, Propylene glycol 400, Methyl parapen and Triethanolamine as shown in Table 2.

The formulations were evaluated for the physical parameters like colour, odour, homogeneity and consistency and other parameters like PH value, washability, viscosity, and spreadability as shown in Table 3.

A pharmacological evaluation, like a skin irritation test, revealed that the herbal gels were safe to apply on the skin. An anti-acne study was carried out to show that the herbal gels can heal the acne without severe adverse effects.

Evaluation of Gel Formulations

All the formulations were light green. The spreadability indicates the extent to which the gel readily spreads on application to the skin or the affected part. The bioavailability efficiency of a gel formulation also depends on its spreading value. All the formulations had a neutral pH from range of 6.8 to 7 which was compatible with normal skin physiology. The results of the evaluation are also shown in Table 3.

Table 3: Physical Parameters Evaluation of Gel Formulation.

Formulation Code	Color	Consistency	pH	Spread Ability (g.cm/sec)	Viscosity (cps)	Homogeneity
Gel-I	Light Green	Absence of coarse particles	6.79	11.76	1357	Homogenous
Gel-II	Light Green	Absence of coarse particles	6.87	11.50	1370	Homogenous
Gel-III	Light Green	Absence of coarse particles	6.95	12.03	1587	Homogenous

Skin Irritation Test: All gel formulations when applied on the skin were safe and there was no irritation or sensitivity to the skin.

Acne Healing Activity of Gel Formulations: Gel-III containing 2% w/w (0.5% Aloe barbadensis, 0.5% Allium sativum, 0.5% Camellia sinensis and 0.5% Ocimum basilicum extract) showed a better healing activity when compared with Gel-I and Gel-II.

The adults' skin treated with the 2% w/w of Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum basilicum extract healed in two weeks compared to those who treated with 1% w/w(0.25% Aloe barbadensis,0.25% Allium sativum, 0.25% Camellia sinensis and 0.25% Ocimum basilicum extract) and 0.5% w/w(0.125% Aloe barbadensis, 0.125% Allium

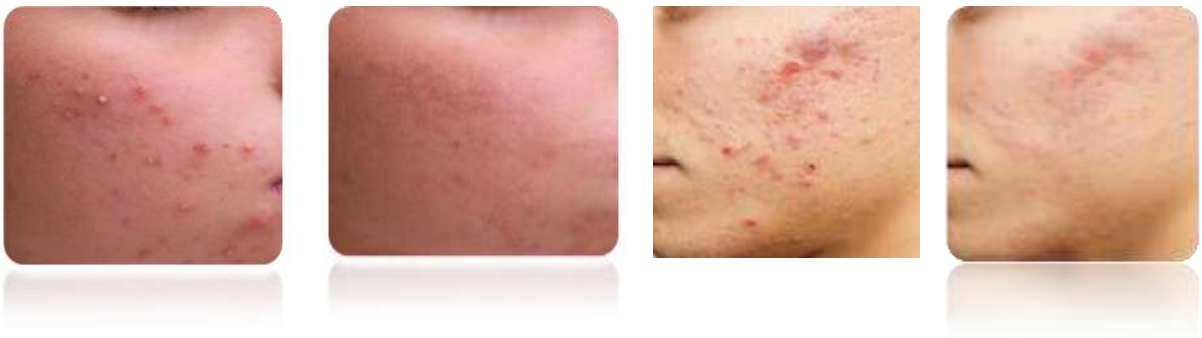
sativum,0.125% Camellia sinensis and0.125% Ocimum basilicum extract)where the healing occurred in four weeks and five weeks, respectively as shown in Figures 1- 3.

(1) Before **(1) After 5 weeks** **(2) Before** **(2) After 5 weeks**

Fig. 1: Adults Treated with Gel-I Containing 0.5% w/w of Herbal Extract.

(1) Before **(1) After 4 weeks** **(2) Before** **(2) After 4 weeks**

Fig. 2: Adults Treated with Gel-III Containing 2% w/w of Herbal Extract.



(1) Before **(1) After 5 weeks** **(2) Before** **(2) After 5 weeks**

Fig. 3: Adults Treated with Gel-I Containing 0.5% w/w of Herbal Extract.

Acne vulgaris is a highly common skin disorder that affects substantially all individuals at least once during life. The incidence of acne peaks at teenage, but fundamental numbers of

men and women between 20-40 years of age are also affected by the disorder. Acne can have important negative psychosocial consequences for the affected individual, including diminished self-esteem, social withdrawal due to embarrassment and depression.[109]

Herbal medication are considered safer than allopathic medicines as allopathic medicines are associated with adverse effects such as like contact allergy, local irritation, scaling, photosensitivity, itching, pruritus, redness, skin peeling, xerosis of the skin etc.[109]

The present research work deals with formulation and evaluation of herbal Anti- Acne gels. The Plant material used for the formulations were ethanolic extract of leaves of Aloe barbadensis, Allium sativum, Camellia sinensis, Ocimum sanctum. Although various topical herbal formulations for acne are available in the market, we propose to make use all these herbs in one formulation for the first time in the developed formulations. The plants have been reported in literature having good antimicrobial, anti-inflammatory, refreshing activity, cleansing agent, dirt absorbent, and antioxidant.[110]

CONCLUSION

According to the present study, the acne elimination improves with the increasing concentration of the herbal extract. Among these formulations, gels containing an Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum sanctum extracts in the concentration of 0.5%, 1% and 2% w/w, a formulation gel containing 2% w/w extracts of Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum sanctum showed better wound healing and antimicrobial effects. It can be concluded that the extracts of Aloe barbadensis, Allium sativum, Camellia sinensis and Ocimum sanctum (2% w/w) was a better candidate for acne spots healing than Gel-II and Gel-II better than Gel-I.

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