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Review Article

A comprehensive review of herbal treatment of the species of spinach over the stages of acne vulgaris for research methodologies

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ABSTRACT

Acne is the inflammatory response of increased levels of hormones. Generally seen on the face as well as back, characterized by pimples, black heads, white heads and pustules. It may get severe if remains untreated. Acne directly correlates with the psychological conditions such as low self confidence to socialize, low self esteem, etc. Acne is most common in citizens thriving in central and peninsular regions of India especially teenagers. Spinach is found to be rich in antioxidants. This review was designed to generalize the use of spinach which is rich in flavonoids, phenolic acids, tocopherol; to determine its antioxidant properties as a herbal therapy for the developing stages of acne incorporating topical use; As a staple vegetable of the Indian diet, spinach can be exploited for its anti oxidant properties in the prophylaxis of acne. The review also involves, detailed information regarding the pathophysiology, receptors as well as the effect of acne on the patient's mentality.

Keywords: Acne vulgaris, *Spinach oleracea*, *Basella alba*, Herbal gel, Herbal cosmetics, Antioxidants

INTRODUCTION

The skin is the largest organ in the body and has a surface area of 1.5-2 square meters in adults. In certain areas, it contains accessory structures; glands, hair and nails. Epidermis is the most superficial layer and is composed of stratified keratinised squamous epithelium. It is thickest in palms and soles. There are no blood vessels or nerve endings in the epidermis, but its deeper layers are bathed in interstitial fluid from the dermis provides; oxygen and nutrients and drains away the lymph.

Sweat glands are widely distributed on the skin but the major location is on the facial region.[1] Also, the sebaceous glands are generally present at most of the locations of body but abundantly on the face and scalp. That's why the acnes are more prone to develop on the face and neck of the human body. But these glands are completely absent in some areas such as eyelids, borders of lip, labia minora and female areola. These sebaceous glands contain more lipid droplets called as sebum in the cytoplasm; arranged into lobules of the upper segment of the hair follicle. Lipid filled cells are then formed by basaloid cells which further expelled into infundibular segment of the hair follicle through sebaceous duct.[2] Because of this sebaceous gland produce lipids, then there is a chance for the formation of acne by the combination of dead skin and largely secreted oil.

ACNE VULGARIS

Acne vulgaris this is the most common skin disease having psychological disstress and disfigurement followed by formation of comedones which may recurrent and chronic. Erythemus papules and pustules may develop on the face, neck, trunk and proximal upper extremities which will get converted into scars later. This condition is most common at time of puberty because of

hormonal imbalance; but uncommonly seen in neonatal period and develop de novo in adulthood. Formation of acne is common in boys and in girls. At age of 12-16; 40-95% chances are there in boys; similarly from 61-83% chances are there in girls at the same age gap.[3] As the self defence mechanism, body will secrete antimicrobial peptides which gives the protection. These peptides are most commonly produced by; keratinocytes, sebocytes, neutrophils and sweat glands.[4] A study from Saudi Arabia, 2018 states that approximately 9.4% of world's population are suffering from acne vulgaris.[5] People suffering from this disease, usually feel like isolated, excluded from society and used to make their life limited. As per a review of such cases it was found that there is a direct impact of acne vulgaris on the psycho-social health of individual as like depression, frustration, suicidal thoughts, alcohol abuse, anxiety, psychosomatic embarrassment and social inhibition. Also, it was proved that, quality of life is slightly lower in the patients suffering from acne than the normal one.[6] A study states that high levels of ACTH, adrenal androgens and glucocorticoids during stress will give negative effect on cutaneous permeability, epidermal liposynthesis and antimicrobial defence. Substance P which is neuroactive substance; may stimulate sebaceous gland proliferation and causes acne lesions. A drug; isotretinoin, is useful against severe acne infection, but still it's frequent dose causes depression while less frequent dose causes suicidal thoughts and psychoses. Such conditions will interrupt hippocampus, corpus striatum and frontal cortex, mainly orbitofrontal cortex which has pathophysiology as that of depression. Also, now a days, teenagers are addicted to internet, because of it, they prefer to stay alone and a study states that, high levels of loneliness is the major reason behind acne for teenagers.[7] Patients reported outcomes gives a view of physical, functional and psychological impact of acne scars from patient's perspective.[8] Hormonal imbalance is the reason for increased risk of acne in women than men. Specifically adult women has a complex pathogenesis for acne; as an evidence of hyperandrogenism disorders such as poly-cystic ovary syndrome and hormone based treatments like oral contraceptives, decreased breast size etc. A survey shows that women get depressed quickly than men. Dairy consumption, improper diet, genetics, family history, overweight, irregular menstrual cycles, obesity, oily or mixed skin, greasy food, stress, sur exposure, smoking, occlusive cosmetic use, environmental factors are some major causes for getting acne.[9] Anyhow acne is not lethal disease; it will get cure after good treatment but still it will damage to the appearance of skin. Acne marks or acne scars could be there if it's not treated correctly. In adolescent patients, because of constant change in the hormonal levels; like in females, constantly there will be lot of changes in oestrogen and progesterone levels, this is very threatening period for getting acne.[10] For proliferation and differentiation of the sebaceous glands, substance P is essential. It will increase the lipogenesis in the sebocytes. But the peripheral nerves secretes this substance P and it will act as a response of stress. So the study shows that there is a correlation between stress scale and serum substance P levels in Acne vulgaris.[11] Inflammation is the end point of the acne cycle, followed by seborrhoea, hyperkeratosis and bacterial hyper-proliferation. If there is any bacterial growth within this inflammation, it will create a complex problem for the treatment. Formation of acne to the formation of acne lesions, process is having very interlinking, multi-factorial and complex. Pro inflammatory factors like, Toll like receptors, interleukin-1 and 8, Human beta defensin 4 and matrix metalloprotease are upregulated in acne affected skin to stimulate anti-inflammatory mediators.[12]

Types of acne

Clinical classification of acne includes-Grade 1: mild, grade 2: moderate, grade 3: severe, grade 4: cysts.

Reasons which makes acne at worst conditions

The increase in the hormonal levels during puberty, leads to acne production. The oil secreted by sebaceous gland may develops various kind of bacterial infections, resulting redness and inflammation. Acne production is irrespective with pollution, dirt, sexual activity or by chocolates. Using various soaps/ excessive scrubbing can worsen the acne or the infection associated with the acne. Squeezing of the acne pores will cause the scars.[13]

Results of study confirm that people with acne vulgaris are more experience to depression, loneliness, they also suggest that they are more vulnerable to internet addiction. In order to stop acne vulgaris patients from becoming addicted to internet, loneliness and sadness should evaluated, if discovered, treated psychologically.[7]

Table 1: Role of lipids in acne.

Endogenous lipids	Exogenous lipids	Sebaceous lipids
Mostly consist of a combination of ceramids, cholesterol and FFAs. The features are because of epidermal lipids that can shield the body from microbial invasion.	These are externally taken lipids, especially membrane lipids, cholesterol, linoleic acid and FFAs. It may affects barrier homeostasis and may slow healing of skin barrier because it exacerbates trans-cutaneous water loss.	Sebum production is high during acne. Sebaceous lipids are mostly made of triglycerides, which bacteria can hydrolyze into FFAs and glycerol. Types of sebaceous glands: sapienic acid, wax esters, squalene stearic acid, oleic acid and palmitoleic acid

Pathophysiology of acne

Role of essential free fatty acids in acne

These are the essential free fatty acid which can not be synthesized within the human body, hence it has to taken through the meals and diet. Free fatty acids such as linoleic acid, alpha linoleic acid may influence the acne development by lowering in FFAs. It may also damage the skin.[13]

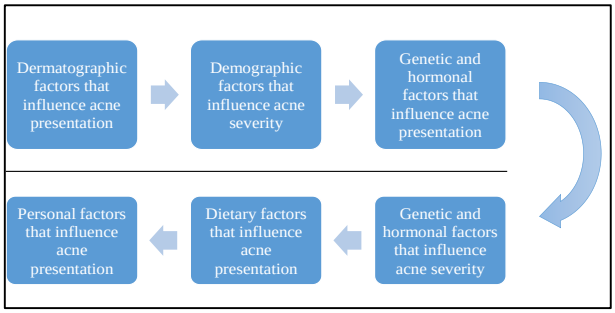

Figure 1: Parameters to be considered for acne development.[14,15]

Table 2: Receptors of acne.

Receptors of acne	Role
Histamine receptor	Squalene concentrations within human sebaceous glands, cells are dramatically reduced by histamine 1 receptor antagonist diphenhydramine. If the generation of cAMP is mediated by H1 receptor antagonist; insulin's reduction in adipocyte cAMP rates may also decrease in lipid lipid cell such as sebocytes. H1 antihistamines can be useful in management of acne.
Retinoic receptor	These receptors are relating to the superfamily of steroid/thyroid hormone have been generated in human sebocytes, exert their pleiotropic effect on cell development.
Fibroblast growth factor receptors	A potential cause of acne vulgaris has been identified as androgen producing FGFR2b signaling over- expression in acne skin. Additionally, the progression of acne may also be influenced by the FGFR2b signaling pathway in dermal - epithelial contact within the process of comedogenesis, sebaceous gland proliferation, pilosebaceous follicle homeostasis.
Forkhead box O1 receptor	It has been demonstrated that retinoids actively elevates Fox O protein, Particularly Fox O1 mediates negative effects as like hypertriglyceridemia brought on by isotretinoin.
Androgen receptors	Sebocytes function include altered lipid production, Sebocyte proliferation & sebocyte differentiation are governed by endocrine process. By reacting with the nuclear androgen receptors, androgen elevates the size of active sebaceous glands. Sebaceous glands have been found to contain highest density of ARs. It produces more sebum when androgens are present.
Epidermal growth factor receptor	It is associated with the receptors present on the keratinocyte surface, hair follicle cells etc. The signals are beneficial for skin development and homeostasis. Due to general use of topical EGF treatments in clinical dermatology and cosmetics, including one reports' significant concentration of such recombinant human EGF, the clinical severity for mild to severe acne has grown.

Prevention of acne

Cutibacterium acnes has a large number of bio-synthetic gene clusters and lipases that help produce and release antibacterial and immunomodulatory chemicals, which allows it to change its local environment. The complexity of the condition, as determined by several gradings, affects the recommended course of treatment for acne today. Skin barrier change is linked to systemic and topical drugs such retinoids, topical antibiotics, and benzoyl peroxide, which may also cause skin dryness and irritation in some patients. Skin irritation can be reduced with OTC acne medications and skincare products including anti comedogenic cleansers and moisturizers. Dry skin that is prone to irritation typically characterizes mature women with facial acne. They might gain from nonprescription acne treatments that are especially formulated for them, like as cleansers and moisturizers that address their issue. Air pollution causes oxidative damage which aggravates dys-seborrhea, which could also result in microcomedones, which is an additional exposome factor that may cause acne. Hence, the proper and rational use of antioxidants can helps in the prevention of acne formation.[12]

RECENT DEVELOPMENTS IN ACNE PREVENTION

Approximately 95% population is suffering from the acne problem, although the drugs such as Antibiotics, acids,

benzoyl peroxide, and retinoids are the most commonly used. The scientist and many pharmaceutical companies are leading for the formulation of the novel drugs and the novel formulation to prevent and cure the acne. These advancements are essential because the conventional drug delivery for these drugs gives various undesired side effects as well as the problems associated with undesired penetration in stratum corneum, short retention time, poor aqueous solubility etc. Currently, dermatologists and plastic surgeons frequently perform daily, uncomplicated chemical peeling procedures in a therapeutic context to treat aggressive acne vulgaris. In order to smooth out rough areas, promote product component penetration, and increase collagen formation, various superficial chemical peels usually applied to the skin. In addition to treating a portion of active lesions, applying superficial chemical peels to treat active acne can break down corneosomes, exfoliate the epidermis' outermost layers, stimulate activity of skin's enzymes, and cause epidermolysis.[16,17]

Table 3: The recent advancements and the treatments for acne.

Type of the treatment	Description	Drawbacks
Systemic treatment	First line treatment for the management of the of severe acne. It involves oral administration of antibiotics, retinoids and hormonal treatments.	GI upset, vaginal candidisis, Pigmentation of skin and teeth, menstrual irregulations, melasma, vascular thrombosis, dehydration of skin, psychological disorders.
Topical treatment	1st line treatment for the management of the mild and moderate acne. It involves the drugs like benzoyl peroxide, herbal agents or combination of topical agents. It is safer than systemic medications.	Erythma, itching, dryness of the skin, irritant dermatitis, burning sensations, skin irritation, allergy.
Other treatments	It includes surgical removal of acne, photo-dynamic treatment, photo-thermal therapy, chemical peeling, laser therapy etc.	Costly, skin irritations, skin itching

VACCINE TREATMENT OF ACNE[18]

The main principle of such vaccine treatment is to produce vaccines with the half killed micro organisms which are the causative agents of acne. When these vaccines are injected into patient's body, the tissues will tend to produce the antibodies against the foreign microorganisms. Even, the patients tissue will get stimulated in the production of antibodies with respect to the foreign materials. So, the amount of antibodies will be more than the normal and the prevention will be successful.

Correlation between acne and immunity

The main cell types of the epidermis, keratinocytes and sebocytes, actively contribute to innate immunity as a source of antimicrobial peptides and cytokines that gives inflammation whenever the epithelium is exposed to damaged/pathogen-associated molecular patterns , which are primarily represented by toll-like receptor 2, 4, and 6 ligands as well as protease activated receptor-2 phylotypes of acne and the kind of skin appear to have various effects on how the innate immune system is activated.[19]

Role of free radicals on the development of acne

Our understanding of free radical chemistry as well as its potential role in both age-related disease and dysfunction as well as normal essential biology has advanced incredibly quickly over the past several years. Oxidative stress, which is brought on by oxygen radicals, is thought to play a major role in a number of CNS degenerative illnesses also the natural ageing process. It is simple for the reactive oxygen species created during typical metabolic activities to start the per-oxidation of membrane phospholipids, which results in the buildup of lipid peroxides.

USE OF ANTIOXIDANTS ON SKIN

After the utilization of oxygen by body it will give free radicals as a by-product. Hence body requires antioxidant to fight against free radicals. Generally, free radicals will give a chain reaction which will damage the physiology of skin by forming acne or inflammation like condition. Antioxidants contain one unpaired electron in their outermost orbit; to this unpaired electron, free radical will try to attach to gain stability. Antioxidants plays very important role in the protection of skin, promotes cell growth as well as prevents from ageing. Vitamins like vit. A, vit. C and vit. E has antioxidant property.[20]

Spinach oleracea

Spinacia oleracea is a vegetable plant and grown in many places. As it is rich in magnesium it is included in routinely diet. It is useful in energy metabolism, maintaining muscle and nerve function, heart rhythm, maintains BP and also useful in maintaining immunity. These leaves are the rich source of antioxidants, minerals and vitamins. *Spinacia oleracea* belongs to the family Amaranthacae; order Caryophyllales and Kingdom

Plantae. It is useful in the treatment of the diseases of brain, blood, asthma, leprosy, biliousness, urinary calculi, difficulties in breathing, inflammation of liver and jaundice. *Spinacia oleracea* contains 23 calories per 100 gm and calcium as 99 mg per 100 gm.[21] Result of the study of cooked and uncooked leaves of *Spinacia oleracea* states the presence of antioxidants via methanolic extract method. Anti-oxidants present in *Spinacia oleracea* will stimulate cell growth. The phenolic compounds such as flavonoids, phenolic acids and tocopherols are effective H+ donors which makes the spinach productive antioxidant.[21]

Basella alba

The *Basella alba* is majorly found in India and Indonesia where, it is naturally grown in tropical Asia and tropical Africa. *Basella alba* is a perennial vine that grows quickly and can withstand great heat; it is widely grown as a cool and interesting vegetable. Fruits are spherical, meaty, without a stem, purple in colour, and fleshy. It is called as "Poi" and is widespread throughout India, with the exception of the hills. The plant is really a herbaceous, silky, twining, branching, succulent vine that grows to a length among many meters. Green or purple stems are seen. The leaves are cordate, heart-shaped, and 5 to 12 cm long with a pointy tip on the stalk.[22]

Basically Malabar spinach is used to cure cancer, viral infections, inflammation, high cholesterol levels, ulcers, microbial infections, glycaemia and wounds etc. Also, to cure infections that causes diarrhoea, dysentery; juice of Malabar spinach is useful. As it is rich in Vitamin C, it is useful as laxative in children as well as in pregnant women.[22]

Collection and cultivation of spinach

Due to the lack of minerals, growing spinach on acidic soil is difficult but is possible with careful fertilizer management.[23]

The study was capable of comparing leaf tissues of the same developmental stage instead of chronological age by analyzing the growth kinetics of spinach plants (*Spinacia oleracea* L. cv. Savoy) cultivated at 50C or 16°C. For the 50C and 160C plants, the secondary leaf pairs were fully expanded at 32 and 92 days of plant maturity, respectively. Leaf area, dry weight, dry weight per area, & leaf thickness all increased during growth at 50C. Despite these modifications, the growth temperature had no effect on the pigment content and composition, room-temperature in vivo fluorescence, apparent quantum yield, or light-saturated rates of CO_2 exchange or O_2 evolution.

Spinach is a cold-tolerant plant which has frequently been utilized in research on freezing and cold tolerance. In comparison between spinach that has been cold-hardened and spinach that has not, photosynthetic characteristics and responsiveness to low temperature-induced photo inhibition have also been examined.[24]

Antioxidant property of spinach

Antioxidant is the major factor in maintaining the health and disease prevention. A study concluded the structure of flavanol present in spinach is patulein and presence of spinacetin in spinach leaves. Extraction of glycosides was in methanolic extract of spinach was reported. These are glucuronide and oxygenated flavanol. These flavanols are acylated and glucuronides are highly water soluble than glycosides. Anti oxidative effects are responsible for a variety of biological processes, including defence against mutagenesis, carcinogenesis, and ageing, among others. A number of effective water-soluble natural antioxidants have recently been found in spinach leaves, and we have detailed their possible biological activity. A low molecular weight fraction of the water extract from spinach leaves that reveal antioxidant activity and a second fraction made up of components over 1000 MW that are water insoluble were the two primary fractions, according to earlier research from lab. Furthermore, the reverse phase C18 column HPLC profile showed that little of the initial fraction was eluted from the column. Initially examined about the solubility of the antioxidants found in the aqueous spinach extract in different solvents because the antioxidants described looked to comprise simultaneously hydrophobic and hydrophilic components.[25]

CONCLUSION

As the various species of spinach contains ample number of antioxidants such as flavonoids, phenolic acids and tocopherols, which are useful as antioxidants. These antioxidants can be used to prevent the oxidation process which may give rise to the acne formation. As there are no such cosmetic products are available with spinach, the use of spinach leaves as herbal cosmetic will be a novel formulation.

As a future scope of this information, various cosmetic products such as herbal gels, herbal ointments, herbal creams can be manufactured.

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