



REVIEW ON AZADIRACHTA INDICA LEAVES RELATED TO ITS ACTION AGAINST ACNE VULGARIS

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Review Paper

Received: 12.05.2021

Revised: 18.05.2021

Accepted: 07.06.2021

ABSTRACT

Acne vulgaris is a common dermatological disease with huge psychological burden. The pathophysiology of acne include various factors among them bacterial colonisation and inflammation are supreme culprit in the causation of disease. The leaves of *Azadirachta indica* possesses both antibacterial and anti-inflammatory actions against the causative micro-organism which supports the use of *Azadirachta indica* leaves in traditional system of medicine

No. of Pages: 6

References: 63

Keywords: Acne vulgaris, *Azadirachta indica*, *Barg-e-neem*, *Propionibacterium acnes*, anti-inflammatory.

INTRODUCTION

Acne vulgaris is chronic, often self-limiting inflammatory disease of pilosebaceous unit, manifesting generally in adolescence with pleomorphic lesions like comedones, papules, pustules, nodules and cysts (1). Acne vulgaris globally targets 650 million people or around 9.4% population, hence making it eighth most prevalent disease worldwide. There is 22% rise in DALYs (Disability-adjusted life years) in global burden of disease study 2010 due to acne vulgaris since 1990(2).

Although basic cause of acne is unknown; (3) its pathophysiology is based upon several factors, which include excessive sebum production, alteration of the quality of sebum lipids, dysregulation of the hormone microenvironment, neuropeptide interaction, hyperkeratinization, *Propionibacterium acnes* colonization and inflammation(4)(5)(6).

Propionibacterium acnes and other micro-organisms involved in Pathogenesis

The role of micro-organisms in the pathogenesis of acne vulgaris is commonly associated with inflammatory acne lesion. According to Studies, most common micro-organisms involved in acne vulgaris are *Propionibacterium acnes*, *Staphylococcus epidermidis* and *Staphylococcus aureus*(7).

The *Propionibacterium acnes* is a Gram-positive anaerobic non-motile, pleomorphic, rod-shaped bacterium which is considered to be skin commensal, commonly resides in sebaceous follicles. The presence of *P. acnes* is beneficial due to its ability to lower the pH of skin by acidic fermentation of products, thus protecting the follicles against colonization by harmful pathogens (8). The virulence factors involved in *Propionibacterium acnes* include neuraminidases, sialidases and endo-glycoceramidases(9). The bio-film is also excreted by *P. acnes* which is glycocalyx polymer and it contributes to its persistence and immunogenicity (10). It plays significant

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role in the development of inflammatory acne. The bacterial overgrowth can lead to precipitation of innate immune response and, in some cases follicular wall rupture may occur which initiates host inflammatory reaction. *P. acnes* releases many enzymes, such as proteinases, lipases, hyaluronidases and chemotactic factors(11) and may direct immune reactions by modulation of the T-helper cell (TH1/TH2) response and induction of monocyte-derived dendritic cell maturation(12).

Staphylococcus epidermidis is a Gram-negative aerobic bacterium, also considered as skin commensal and colonizes various areas of the skin but sometimes it acts as an opportunistic micro-organism by breaching the skin surface and entering the bloodstream (13). The lipases, fatty acid modifying enzyme, polysaccharide intercellular adhesion (PIA), and poly-glutamic acid are the virulence factors in *Staphylococcus epidermidis*(14).

Staphylococcus aureus, is an opportunistic Gram-positive pathogen, implicated in pathogenesis of acne vulgaris and is associated with pus from acne. Their co-existence with other microbes in acne lesions has been reported (15) (16). The virulence factors of *S. aureus* involved in the pathogenesis of acne are adhesins, fibronectin binding protein, proteases, lipases, and hyaluronidases (17). Presence of *S. aureus* in the oropharynx and nose are higher in patients with acne than controls without acne(18)(9).

All these microorganisms implicated, have been isolated from the pustular lesions of acne vulgaris. In a study conducted by Yousif *et al.*, 27.08% *Staphylococcus epidermidis* (aerobic bacterium) and 13.02% *Propionibacterium acnes* (anaerobic bacteria) were isolated from inflamed and discharging pus from 160 acne patients(19). Another study identified the involved pathogen from samples of 80 patients and out of 71.24% isolated aerobic organisms 54.38% were *Staphylococcus epidermidis* and among 26.25% isolated anaerobes 57.14% were *Propionibacterium acnes* (20). Various other studies have demonstrated the presence of *S. aureus* in pustular lesions of acne and sensitivity test has shown multiple antibiotic resistance of the organism(21)(22) (23). In another study five strains of *S. aureus* and 11 strains of *S. epidermidis* were isolated from 25 samples from acne patients (7). The results of all these mentioned studies imply that these three micro-organisms viz., *Propionibacterium acnes*, *Staphylococcus epidermidis* and *Staphylococcus aureus*, are commonly involved in acne infection.

Inflammation

The role of *P. acnes* in the aetiology of inflammatory acne has been recognized for more than a century. It stimulates host innate immune response with activation of Toll-like receptors (TLRs) which are in response against pathogen.

TLRs are present on keratinocytes, monocytes/macrophages, langerhans cells, T and B lymphocytes, mast cells and endothelial cells. TLR activation further leads to activation of nuclear factors, which promotes gene expression responsible for production of cytokines, chemokines and adhesion molecules. *P. acnes* activates TLR-2, resulting in increased levels of IL-8, IL-12, tumour necrosis factor-(alpha), and IL-1 (beta) (24) (25) (26). In cultured human epidermal keratinocytes, TLRs, activation also induces human b-defensin-2 (and IL-8) expressions which are a family of antimicrobial peptides produced in the skin against microbial infection and are implicated in clinically inflammatory acne lesion formation. The properties of b-defensins include modification of cell migration and maturation, induction of cytokines, and chemo-attraction of immune-competent cells (27)(28).

Recent data also suggests that inflammatory events in acne vulgaris could occur even before the microcomedones formation, which is supported by the fact that uninvolved skin from acne patients contains elevated levels of CD3+ and CD4+ T cells in the perifollicular and papillary dermis and increased macrophage numbers similar to those seen in papules(29).

Studies of *Azadirachta indica* leaves related to its action against *Acne vulgaris*

Anti-bacterial activity of *Azadirachta indica* against *P. acne*

Barg-e-Neem (*Azadirachta indica*) possesses antibacterial action against *P. Acnes* (Acne causing bacteria). In an in-vitro study aqueous, ethanolic and petroleum ether extract have exhibited antibacterial action. The zone of inhibition of *Azadirachta indica* was 14 mm for 5mg/ disc, 14 mm for 7 mg/ disc, 15 mm for 10 mg/ disc in aqueous extract. In ethanolic extract the zone of inhibition was 14 mm for 5mg/ disc, 15 mm for 7 mg/disc, 15 mm for 10 mg/ disc. The zone of inhibition for ethanolic extract was 9 mm for 5mg/ disc, 12 mm for 7 mg/ disc, 15 mm for 10 mg/ disc in Petroleum ether extract. Thus, results of the study revealed that *Barg-e-Neem* has potential antibacterial activity and both aqueous and ethanolic extract are equally significant against *Propionibacterium acnes*(30).

Anti-bacterial activity of *Azadirachta indica* against *Staphylococcus aureus* and *Staphylococcus epidermidis*

In an in-vitro study antibacterial activity of ethanolic and methanolic extract of *Azadirachta indica* leaves was assessed against various opportunistic bacterial strains including *Staphylococcus aureus* and *Staphylococcus epidermidis*. The minimum inhibitory concentration (MIC) of methanolic extract of 50gm of *Azadirachta indica* leaves against *S. aureus* was 12mm and against *S. eidermidis* was 10 mm. Similarly ethanolic extract of 50 g of *Azadirachta indica*

leaves has 11 mm and 18 mm MIC against *S. aureus* and *S. epidermidis* respectively. Thus, indicating its great potential against these opportunist infections which also play role in pathogenesis of acne(31).

Topical anti-inflammatory activity of *Azadirachta indica* Barg-e-Neem (*Azadirachta indica*) also possesses topical anti-inflammatory action. The study was conducted to assess to anti-inflammatory activity by inducing skin oedema test using turpentine oil. The percentage of inhibition of the inflammation was 45.23% for petroleum ether extract 26.34% for chloroform extract and 9.16% for ethyl alcohol. All extracts, except the ethyl alcohol extract, showed significant inhibition of the inflammation compared to control. The study concluded that petroleum ether extract has the maximum capability to inhibit the process of inflammation, and it has comparable anti-inflammatory activity of diclofenac gel (49.82%), the drug used as reference(32).

In an in-vitro study conducted by Kaur *et al.*, rat peritoneal macrophage exposure to nimbidin inhibited phagocytosis and phorbol-12-myristate-13-acetate (PMA) stimulated respiratory burst in these cells. It also inhibited nitric oxide (NO) and prostaglandin E2 (PGE2) production in lipopolysaccharide (LPS) stimulated macrophages but interleukin 1 (IL-1) inhibited mildly. In addition, nimbidin led to degranulation of neutrophilic lysosomes and release of myeloperoxidase, beta-glucuronidase and lysozyme. Thus, the results concluded that nimbidin suppresses the functions of macrophages and neutrophils relevant to inflammation (33).

Antioxidant activity of *Azadirachta indica*

The antioxidant activity was evaluated in young flowers and leaves. The parameter of oxidative stress, malondialdehyde (MDA), was reduced by 46.0% in flower extract and 50.6% in leaf-based extracts.(34)

Skin renewal activity

The effect of various extract of *Azadirachta indica* was assessed on skin renewal rate. The maximum increase in skin renewal was 27.5% shown by hydro-alcoholic macerate extract followed by hydro-alcoholic 23.75% and alcohol extract 23.12%(35).

CONCLUSION

The potential of the leaves of *Azadirachta indica* is evident through the above mentioned preclinical data which supports its action against the pathophysiology of acne vulgaris. Thus the use of *Azadirachta indica* leaves in traditional medicine is quite close to antibacterial and anti-inflammatory approach of contemporary medicine.

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