IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Azadirachta Indica (Neem) a Potential Alternative for the Treatment of Acne: A Systematic Review of Randomized Controlled Trial

Shubham Sharma[1]*, Khushboo Kumari[2], Hitesh Gupta[2], and Rabinda Ku. Sah[2]

[1]MarksMan Healthcare Communications, J1309, Amethyst Tower, PBEL City, Peeramcheruvu Village, Rajendra Nagar Mandal, Hyderabad, Telangana, 500091, India

[2] Indian Institute of Public Health Gandhinagar (IIPHG), Gandhinagar, 382042, India

***Correspondence:**
Shubham Sharma

Abstract

Introduction: Modern science has improved mankind's life expectancy, but is often limited to better off of society. Acne is a physiologically harmful skin condition that primarily affects adolescents and has negative side effects from contemporary treatment. Neem an age-old traditional tree from India used to treat skin ailments, lacks contemporary evidence in the treatment of acne. Hence, we aimed to sieve the efficacy and safety of neem in acne in a systematic manner. **Methods:** This review systematically searched for randomized control trials in four databases in the last ten years to determine the efficacy and safety of neem in acne treatment. Data from these trials are presented in two MS Excel grids, and the methodology of each study is assessed. **Results:** Twenty-five full-text articles were screened of which only two articles got included following inclusion criteria. The two single-blind, randomized clinical trials were conducted in India, having a study duration of 6 weeks, with a total of 121 acne patients. Azadirachta indica (neem) application reported a positive efficacy in the subjective and objective outcome, along with non-serious adverse events. **Conclusion:** Neem safety and effectiveness in acne is difficult to be generalized due to limited trials, hence both clinicians and patients should be cautious. Double-blind, enhanced duration, and with a higher sample size trial is suggested.

Keywords: Acne, azadirachta indica, randomized control trial, review

PROSPERO Registration: CRD42022359779

Introduction

Panacea for all, the goal of modern technology, allopathic medication, and bio-active molecules, has led to improvement in mankind's life expectancy, good health, and better quality of life. Such overwhelming progression is more often limited to the better off of the society in even developed countries, whereas such luxuries are food for thought in underdeveloped or developing countries. Due to restrictions on the availability and economic factors related to modern medication, the majority of second and third-world countries utilize natural resources for the treatment of mild to moderate ailments, due to easy availability and affordability. India, with recognized indigenous systems of medicine viz., Ayurveda, Homeopathy, Naturopathy Siddha, Unani, and Yoga, and its lush flora and fauna, has been a trailblazer in the production, utilization, and export of herbal medication.[1-4] Azadirachta Indica, an indigenous plant of India, commonly known as neem, has been used from generation to treat various skin ailments, with modern-day utility in other pharmacological features, such as antidiabetic, hypolipidemic, hepatoprotective, antipyretic, antifertility, hypoglycaemic, etc.[5-6] In traditional Ayurveda Mukhadushika (acne vulgaris) was characterized by the eruptions like Shalmali thorn, on the face during adolescence caused by vitiated Kapha, Vata, and Rakta. Modern science reports acne vulgaris (gram-positive bacteria) as a non-fatal (in its natural course of the disease) chronic inflammatory skin disease affecting the majority of teenage and young adults, with disproportionately less common in higher age groups (> 25 years).[7-8] Acne is often self-limiting and subdues over time, but in some patients, it takes a severe form and results in scarring and hyperpigmentation of the skin. This morphological impairment during such a tender age results in emotional scars, hampering an individual's confidence causing physical, social, and psychological suffering, and reducing self-esteem and emotional distress.[8-11] A plethora of modern therapeutics are available for the treatment of acne: a) topical and systemic- antibiotics (erythromycin and clindamycin), retinoids (adapalene, tretinoin, and isotretinoin), benzoyl peroxide, and azelaic acid; b) hormonal therapy- inhibitors of androgen production by the ovaries (oral contraceptives), androgen receptor inhibitors (cyproterone acetate and spironolactone) and adrenal glands (glucocorticoids) approach.[12-13] Such therapies provide outcomes quickly but are prone to severe adverse events like teratogenicity, skin allergy, drug resistance, less economical, adherence, and relapse.[14] As a result of such adversity, people are going back to nature for treatment of their skin ailment, as natural ingredients are easily available and have minimal side effects.[4] In-vitro analysis of neems steam, bark, leaves, and seeds have reported to be highly effective in inhibiting the growth of both gram-positive and gram-negative bacteria.[15] The after scars of acne may lead to hyperpigmentation and can cause dark patches on the skin, which may require separate treatment along with general medication for acne.[16] Azadirachta indica active constituents (limonoids, flavonoids, and diterpenoid) in the animal study has been reported to be effective against melanogenesis, which is a biosynthetic pathway responsible for melanin production in human skin.[5,17] This property of neem can be effectively harnessed for the treatment of dark patches after acne is cured. The interesting property of Azadirachta indica can be a potential alternative to minimize the increase in bacterial resistance to existing antimicrobials, eliminate or attenuate the potential adverse effects of conventional therapies, encourage adherence to therapy, and address inadequate responses to acne treatment.

Several studies (traditional review, systematic review, and meta-analysis) have reported the significance of traditional approach, medicinal plants, and photochemical in the treatment of acne vulgaris,[11,14,18-19] with less emphasis on Azadirachta indica. This motivated us to conduct a systematic review of randomized controlled trials, which focus on reviewing the available studies on neem with a potential anti-acne effect.

Methods

The systematic search was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy and selection criteria A structured quest was carried out following the registration of review protocol in the international prospective register of systematic reviews (PROSPERO Regd. No. CRD42022359779). To capture the contemporary efficacy and safety of neem in treatment of acne, only peer-reviewed published RCTs in the past 10 years (1st Jan 2012 till 1st Jan 2022) were included. We implore to identify the effectiveness of acne (either in combination or stand alone) in treatment of acne either in adolescence (≥12 years) or adults (≥18 years) in both sexes. We carried the search after login in Clinicaltrials.gov, Cochrane, Google Scholar, and Pubmed using the MeSH/keywords 'acne', 'azadirachta indica', and 'neem', by applying Boolean operators. The keyword 'Acne' was used instead of 'acne vulgaris' as it is more general and commonly used. Since this article is focused on efficacy and safety of neem in acne vulgaris, articles that discussed other forms of acne (such as acne rosacea), polymorphisms associated with

acne, acne due to medical conditions, and any other irrelevant articles were excluded (S1_ Search strategy with key words and MeSH).

Data extraction and quality To follow the inclusion exclusion of this article corresponding title/abstract (L1) and full text (L2) screening excel grid was prepared. Further to capture relevant information (L3) from included articles excel grid was prepared by all reviewers. After the consensus on excel grid, two reviewers KS and HG, following independent L1 and L2 screening captured data from included articles. All discrepancies at all levels were resolved by third reviewer SS. Modification in the acne condition prior-post application of neem was assessed via., subjective (Acne lesion, QOL score, Patients global assessment (PGA)), objective assessment (Global acne severity (GEA), Global acne grading system (GAGS), Cook's acne grading scale), and through adverse events. The pre-post mean difference was reported along with p values to represent direction of effectiveness in interpreting the tests, where needed range values and proportion were used. The quality of included RCTs was assessed by two independent authors (KS and HG) through risk of bias (ROB) assessment (Selection bias Random sequence generation; Selection bias Allocation concealment; Performance bias Blinding (participants and personnel); Detection bias Blinding (outcome assessment); Attrition bias Incomplete outcome data; Reporting bias Selective reporting; and Other bias Other sources of bias), using Cochrane risk of bias tool for RCTs in RevMan 5.1 software. Descriptive characteristics of the study populations were reported using range values and proportions (S2_ PICOT). The two included RCT were single blinded, two-arm, active control studies.
For trials which were extracted from Clinicaltrial.gov, or from COCHRANE registry having studies linked to Clinicaltrial.gov. Authors of such trials were contacted through mail (available in trial website) if the study result or outcome data was not available on the website or in peer reviewed journals.

Result
Search outcome

The search resulted in an initial hit of 813 articles. Undergoing level 1(title/abstract) screening and removing duplicates, 780 articles were excluded, and 33 articles were included for level 2 (full text screening). We removed 8 studies due to unavailability of full text or Clinicaltrial.gov trials, further 23 studies were excluded as they failed to meet the inclusion criteria. Finally, two RCTs were included for the review. This is represented in (Figure_1).

Characterisation of included studies The sieving due to inclusion and exclusion criteria resulted in the selection of 2 randomized, active controlled, single-blinded trials. The 2 trials had a study duration of 6 weeks each, having a combined sample size of 119 acne patients (grade was not reported), and both the studies were conducted in India. As a result of attrition, 19 patients were excluded from the analysis, and 100 (84%) patients were analyzed for outcomes. The distribution of 100 acne patients as per their sexes was: 38 males and 62 females. One of the studies was registered in clinical trials (CTRI/2017/12/010974), with 71 patients equally distributed through block randomization in two arms. Azadirachta indica was an active constituent of Ṭila-i Muhāsā, which the patients were suggested to apply over acne-affected skin.[20] Forty-eight acne affected patients were randomized to either intervention or active control arm. Zimade Muhasa (Azadirachta indica a major constituent) was recommended to be applied over acne affected skin as an intervention.[21] Benzoyl peroxide (5%) was used by patients as an active control in both the trials.[20,21] The trials were of moderate quality based on the quality assessment through risk of bias assessment tool for RCT (Figure_2).

Efficacy and safety outcomes

Subjective assessment In acne patients the patient global assessment (PGA) score reduced significantly ($p<0.001$) in both groups, representing better efficacy of treatment. The reduction was better in the intervention arm compared to the control arm at 6 weeks of trial.[20] Acne lesions assessed by comedones, papules, pustules, nodules, cysts, pigmentation and scars reduced significantly ($p<0.05$) in all parameters in the intervention arm. In the control arm only comedones ($p<0.001$) and papules ($p<0.001$) reduced significantly, whereas other acne

lesions reported non-significant reduction ($p>0.05$) at 6th week of trial. Quality of life (QoL) score evaluated by Cardiffe disability index questionnaire reduced significantly in both groups ($p<0.01$), describing better QoL. Although fairness results were not in number or statistics, along with acne lesions and QoL the reduction was profound in the intervention arm[21]

Objective assessment

Global acne grading scale (GAGS) score was used to assess clinical severity in which a lower score represents a higher improvement. The GAGS score reduced significantly ($p<0.0001$) in both groups. Cook's acne grading scale (using photographic standards) score was reduced in both groups, with a grade 0 (better improvement) in patients more in the intervention arm.[20] Global acne severity score reduced significantly ($p<0.001$) in both groups, with slight better results in the intervention arm.[21]

Adverse events

Haematological and biochemical safety parameters similar in both groups, and other adverse events (dryness, itching and burning) were observed in 3, 9 patients of intervention and control arm respectively at 6th week compared to baseline.[20] There were no significant difference ($p>0.05$) observed in the appearance of adverse events (dryness, peeling, burning, itching) in both the groups.[21] Descriptive details of all findings is provided in Table 1, and 2.

Discussion

This systematic review consisted of 2 complete RCTs, both of which reported higher efficacy and safety of Azadirachta indica (with other natural ingredients) compared to benzoyl peroxide in the treatment of acne. The duration of the study was 6 weeks, and both trials commenced in India. The two trials had 61 patients in the intervention arm and 60 patients in the control arm, whereas only 100 patients (82.6%) from both trials were analyzed for the outcomes. Both trials reported improvement in subjective and objective assessment with reduced adverse events when neem along with other natural ingredients was applied in acne patients. [20,21] Rajaiah Yogesh et al, conducted a single arm, four weeks, clinical trial reporting similar improvement in 120 acne patients of grade 2-3 (as per IGA) when intervened with purifying neem and turmeric face wash (with mild surfactant).[22] Yet another single-arm, three weeks, clinical trial of 31 acne patients were advised to apply Ṭila-i Muhasa (with neem as one of the active ingredients) which reported a similar reduction of acne in patients.[23] Such studies strengthen the hypothesis that natural products can be used together to act in a synergistic manner. For instance, aloe potentiates the anti-acne benefits of basil oil in a dose-dependent manner even if it is ineffective as a monotherapy.[24] Benzoyl peroxide an antibacterial and anti-inflammatory agent is an effective topical agent for the treatment of acne,[25] but antibiotics are associated with the development of bacterial resistance hence the use of antibiotics for acne is discouraged in clinical practice.[25,26] Despite various scientific studies, the complete pathogenesis and treatment of acne remain unclear, and a single, primary cause has not been identified. Some studies have reported that acne involves the combination of four factors, including hyperkeratinization, excess sebum production, overgrowth of bacteria, and inflammation.[27,28] Therefore the antimicrobial, anti-keratinization, anti-inflammatory and antioxidant effects properties of the natural ingredients may have been implicated.[29,30] Pre-clinical and in-vitro studies have been utilized to provide a summary of potential explanations for why neem and other natural ingredients may have benefited patients with acne (Table_3). [5,17,31-45] Natural products are often thought to be secure and free of side effects. As some natural items that are administered topically or taken orally frequently fall outside of the Food and Drug Administration's pharmaceutical restrictions. This can result in a lack of oversight and contaminated herbal supplements.[18] An observational case-control study conducted by Singh et al, reported patients consuming acne cosmetics (which included natural products), without the consultation of clinicians, and may experience worsening of their acne.[46] Some researchers have recently conducted parallel arm RCTs to emphasise the value of neem and other botanical treatments for acne, but they have not yet released the findings.[47-48]

This study is the first to systematically scrutinize RCTs to assess the effectiveness and safety of neem in treating acne in studies published in the last ten years. Although the review summaries the neem is effective in acne treatment, is prone to certain limitations: a) a small number of studies (n=2) limiting the quantification of outcomes; b) sample size was not determined in both trials; c) neem was combined with other natural products hence neem can be effective if applied alone is questionable; d) possibility of publication bias, as only positive outcomes are reported, and research with negative results may not be published.

Conclusion

In this review, it was revealed that neem (Azadirachta indica), a tree that is widely available in India, can alleviate acne when used topically in the form of a cream. The findings are not generalizable due to the smaller sample size, hence clinicians and patients should be cautious while suggesting or applying the topical application of neem products for acne. A double-blind, long-term clinical trial, with adequate sample size, its additional applications and to assess the plausible obnoxious effects are recommended.

Supplementary files

S1_Search Strategy with Keywords and MeSH

S2_PICOT

Data Availability Statement

Data extracted from the studies will be made available by the corresponding author upon request.

Acknowledgment

We are thankful to Dr. Chiranjivi Adhikari, a Phd scholar from India for his guidance and suggestion during the protocol preparation.

Reference:

1. More B. Overview of medicine-its importance and impact. DJ Int J Med Res. 2016;1:1–8.

2. Sen S, Chakraborty R. Revival, modernization and integration of Indian traditional herbal medicine in clinical practice: Importance, challenges and future. *Journal of traditional and complementary medicine*. 2017;7(2):234-244.

3.Sharma A, Shanker C, Tyagi LK, Singh M, Rao CV. Herbal medicine for market potential in India: an overview. *Acad J Plant Sci*. 2008;1(2):26-36.

4. Verma S, Singh S. Current and future status of herbal medicines. *Veterinary world*. 2008;1(11):347.

5. Baby AR, Freire TB, Marques G de A, et al. Azadirachta indica (Neem) as a Potential Natural Active for Dermocosmetic and Topical Products: A Narrative Review. *Cosmetics*. 2022;9(3):58.

6. Saleem S, Muhammad G, Hussain MA, Bukhari SNA. A comprehensive review of phytochemical profile, bioactives for pharmaceuticals, and pharmacological attributes of Azadirachta indica. *Phytotherapy research*. 2018;32(7):1241-1272.

7. Gevariya J, Kamaliya S, Vaghela D. A Case Report: Management of Mukhadushika (Acne Vulgaris) with Ayurveda. *International Journal of Ayurvedic Medicine*. 12(1):148-152.

8. Brajac I, Bilić-Zulle L, Tkalčić M, Lončarek K, Gruber F. Acne vulgaris: myths and misconceptions among patients and family physicians. *Patient education and counseling*. 2004;54(1):21-25.

9. Nguyen R, Su J. Treatment of acne vulgaris. *Paediatrics and Child Health*. 2011;21(3):119-125.

10. Safizadeh H, Shamsi-Meymandy S, Naeimi A. Quality of life in Iranian patients with acne. *Dermatology research and practice*. 2012;2012.

11. Sinha P, Srivastava S, Mishra N, Yadav NP. New perspectives on antiacne plant drugs: contribution to modern therapeutics. *BioMed research international*. 2014;2014.

12. Fox L, Csongradi C, Aucamp M. Jeanetta Du Plessis, and Minja Gerber. 2016."Treatment Modalities for Acne." *Molecules*. 21(8).

13. Savage LJ, Layton AM. Treating acne vulgaris: systemic, local and combination therapy. *Expert review of clinical pharmacology*. 2010;3(4):563-580.

14. Proença AC, Luís Â, Duarte AP. The Role of Herbal Medicine in the Treatment of Acne Vulgaris: A Systematic Review of Clinical Trials. *Evidence-Based Complementary and Alternative Medicine*. 2022;2022.

15. Biswas K, Chattopadhyay I, Banerjee RK, Bandyopadhyay U. Biological activities and medicinal properties of neem (Azadirachta indica). *Current science*. Published online 2002:1336-1345.

16. Elbuluk N, Grimes P, Chien A, et al. The pathogenesis and management of acne-induced post-inflammatory hyperpigmentation. *American journal of clinical dermatology*. 2021;22(6):829-836.

17. Akihisa T, Zhang J, Manosroi A, Kikuchi T, Manosroi J, Abe M. Limonoids and other secondary metabolites of Azadirachta indica (neem) and Azadirachta indica var. siamensis (Siamese neem), and their bioactivities. *Studies in Natural Products Chemistry*. 2021;68:29-65.

18. Fisk WA, Lev-Tov HA, Sivamani RK. Botanical and phytochemical therapy of acne: a systematic review. *Phytotherapy research*. 2014;28(8):1137-1152.

19. rights are reserved by Pradnya A, Bhagat J. Efficacy of Jalaukawacharana Therapy in Acne-A Literature Review and Meta Analysis.

20. Azahar M, Uddin Q, Kazmi MH, Khatoon F, Husain N. Therapeutic Evaluation of a Topical Unani Formulation, Tila-i Muhāsā in Buthūr Labaniyya (Acne Vulgaris): A Randomized, Controlled Clinical Study. *CELLMED*. 2020;10(2):15-1.

21. Tabasum H, Ahmad T, Anjum F, Rehman H. The effect of Unani antiacne formulation (Zimade Muhasa) on acne vulgaris: A single-blind, randomized, controlled clinical trial. *Journal of Pakistan Association of Dermatologists*. 2014;24(4):319-326.

22. Rajaiah Yogesh H, Gajjar T, Patel N, Kumawat R. Clinical study to assess efficacy and safety of Purifying Neem Face Wash in prevention and reduction of acne in healthy adults. *Journal of cosmetic dermatology*. 2022;21(7):2849-2858.

23. Doni M, Patel MI, Khalid M, Husain N, Khan MQ, Ayesha B. Therapeutic evaluation of herbal formulation in acne vulgaris and its influence on quality of life—A single-arm clinical trial. *Journal of Herbal Medicine*. 2022;34:100577.

24. Orafidiya L, Agbani E, Oyedele A, Babalola O, Onayemi O, Aiyedun F. The effect of aloe vera gel on the anti-acne properties of the essential oil of Ocimum gratissimum Linn leaf–a preliminary clinical investigation. *International Journal of Aromatherapy*. 2004;14(1):15-21.

25. Zeind CS, Carvalho MG. *Applied Therapeutics: The Clinical Use of Drugs*. Wolters Kluwer; 2018.

26. Rathi SK. Acne vulgaris treatment: the current scenario. *Indian journal of dermatology*. 2011;56(1):7.

27. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *The Lancet*. 2012;379(9813):361-372.

28. Strutton G, Rubin AI, Weedon D. *Weedon's Skin Pathology*. Churchill Livingstone; 2010.

29. Shivanand P, Nilam M, Viral D. Herbs play an important role in the field of cosmetics. *International Journal of PharmTech Research*. 2010;2(1):632-639.

30. Basak PY, Gultekin F, Kilinc I. The role of the antioxidative defense system in papulopustular acne. *The Journal of dermatology*. 2001;28(3):123-127.

31. Benisheikh A, Muhammad FM, Kelluri H, Aliyu ZM, Mallam UB, Jibrin MW. Phytochemical extraction and antimicrobial studies on crude leaf extract of Azadirachta indica (Neem) in semi-arid region of Borno State, Nigeria. *International Journal of Research and Review*. 2019;6(12):516-522.

32. Patel P, Bhalodia Y, Gohil T, Malavia S, Devmurari V. In-vitro antioxidant activity of Azadirachta Indica leaves. *J Advances Pharmacy Healthcare Res*. 2011;1(3):22-27.

33. Dinda A, Das D, Ghosh G, Kumar S. Analgesic and anti-inflammatory activity of hydro-alcoholic extract of Azadirachta indica leaf. *Pharmacologyonline*. 2011;3:477-484.

34. Durrani F, Sultan A, Jan M, Chand N, Durrani Z. Immunomodulatory and growth promoting effects of Neem (Azadirachta indica) leaves infusion in broiler chicks. *Sarhad J Agric*. 2008;24(4):655-659.

35. Kamlesh J, Lakhotiya C, Milind J. Skin renewal effect of different extracts of leaves of Azadirachta indica. *International Journal of PharmTech Research*. 2009;1(4):1350-1353.

36. Ganaie AA, Mishra RP, Allaie AH. Antioxidant activity of some extracts of Iris ensata. *J Pharmacogn Phytochem*. 2018;7:230-235.

37. Bobby M, Krupanidhi S, Peele KA, et al. Screening of Antifungal Potential of Leaf Extracts from Albizia lebbeck (L.) Benth. *Current Trends in Biotechnology & Pharmacy*. 2019;13(4).

38. Babu NP, Pandikumar P, Ignacimuthu S. Anti-inflammatory activity of Albizia lebbeck Benth., an ethnomedicinal plant, in acute and chronic animal models of inflammation. *Journal of ethnopharmacology*. 2009;125(2):356-360.

39. Maya C, Kumar SA, Rajesh K, Bhupendra C, Kovidendra K, Vipin A. Comparative immunomodulator activity of leaves and bark of albizia lebbeck (LINN.) benth. *Int J Res Dev Pharm L Sci*. 2012;1(1):21-23.

40. Bobbarala V, Vadlapudi V. Abrus precatorius L. seed extracts antimicrobial properties against clinically important bacteria. *International journal of pharmtech research*. 2009;1(4):1115-1118.

41. Pal RS, Ariharasivakumar G, Girhepunjhe K, Upadhay A. In-vitro antioxidative activity of phenolic and flavonoid compounds extracted from seeds of Abrus precatorius. *Int J Pharm Pharm Sci*. 2009;1(2):136-140.

42. Anam E. Anti-inflammatory activity of compounds isolated from the aerial parts of Abrus precatorius (Fabaceae). *Phytomedicine*. 2001;8(1):24-27.

43. Tilwari A, Shukla NP, Pathirissery UD. Immunomodulatory activity of the aqueous extract of seeds of Abrus precatorius Linn (Jequirity) in mice. *Iranian Journal of Immunology*. 2011;8(2):96-103.

44. Ibrahim SR, Mohamed GA, Al-Musayeib NM. New constituents from the rhizomes of Egyptian Iris germanica L. *Molecules*. 2012;17(3):2587-2598.

45. Nazir N, Koul S, Qurishi MA, et al. Immunomodulatory activity of isoflavones isolated from Iris germanica (Iridaceae) on T-lymphocytes and cytokines. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*. 2009;23(3):428-433.

46. Singh S, Mann BK, Tiwary NK. Acne cosmetica revisited: a case-control study shows a dose-dependent inverse association between overall cosmetic use and post-adolescent acne. *Dermatology*. 2013;226(4):337-341.

47. Uddin Md. Shahab, Application of Poly-herbal Powder for Treating Acne Vulgaris . ClinicalTrials.gov identifier: NCT04949932. Updated July 2, 2021. Accessed December 20, 2022. https://clinicaltrials.gov/ct2/show/study/NCT04949932

48. Lahkar Mangala, To Evaluate The Efficacy of Neem Caplets in the Treatment of Acne Vulgaris: A Double Blind Comparative Study. https://trialsearch.who.int/ identifier: CTRI/2011/06/001806. Accessed December 20, 2022. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2011/06/001806

Figure 1 and 2

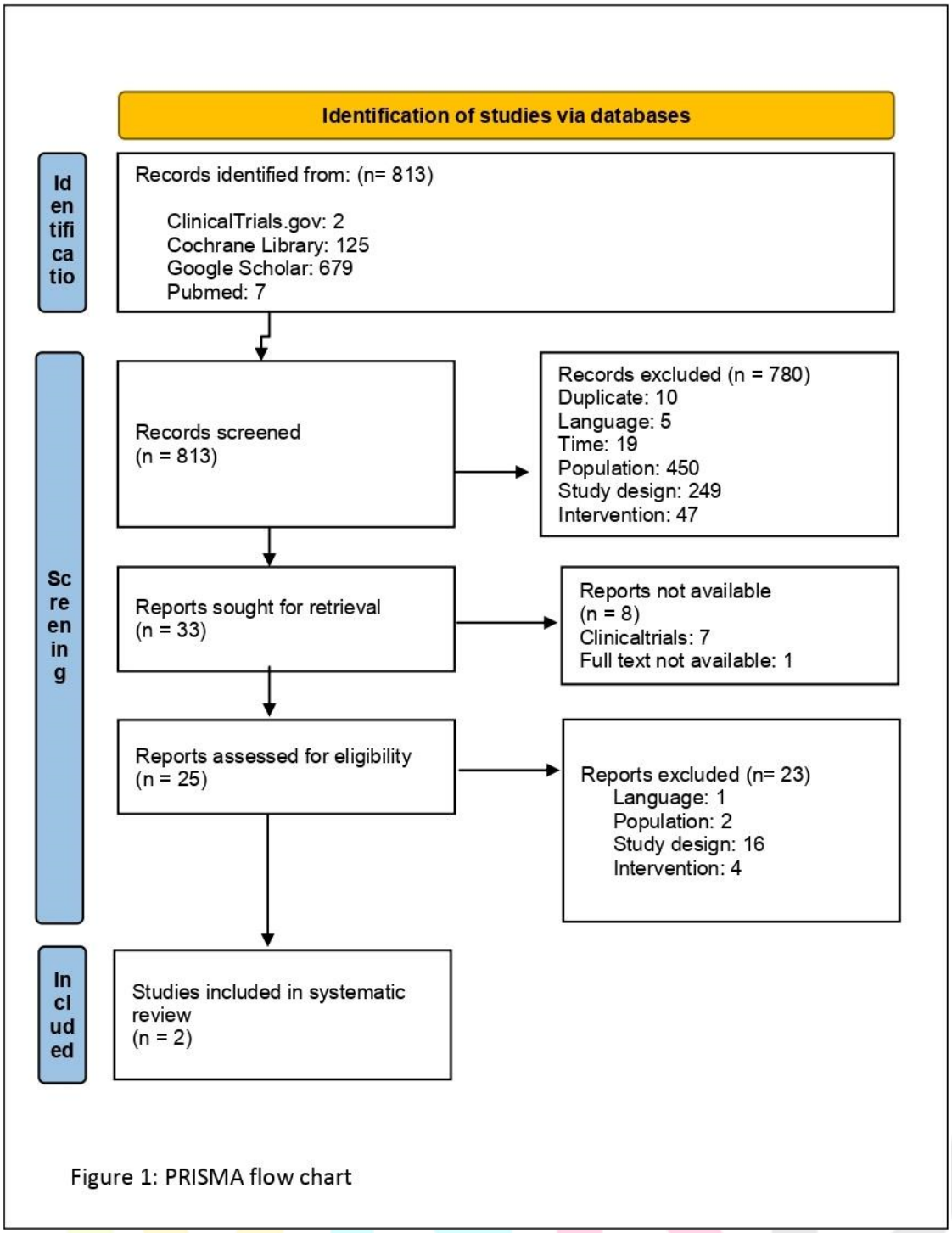

Figure 1: PRISMA flow chart

Figure 2_Risk of bias assessment

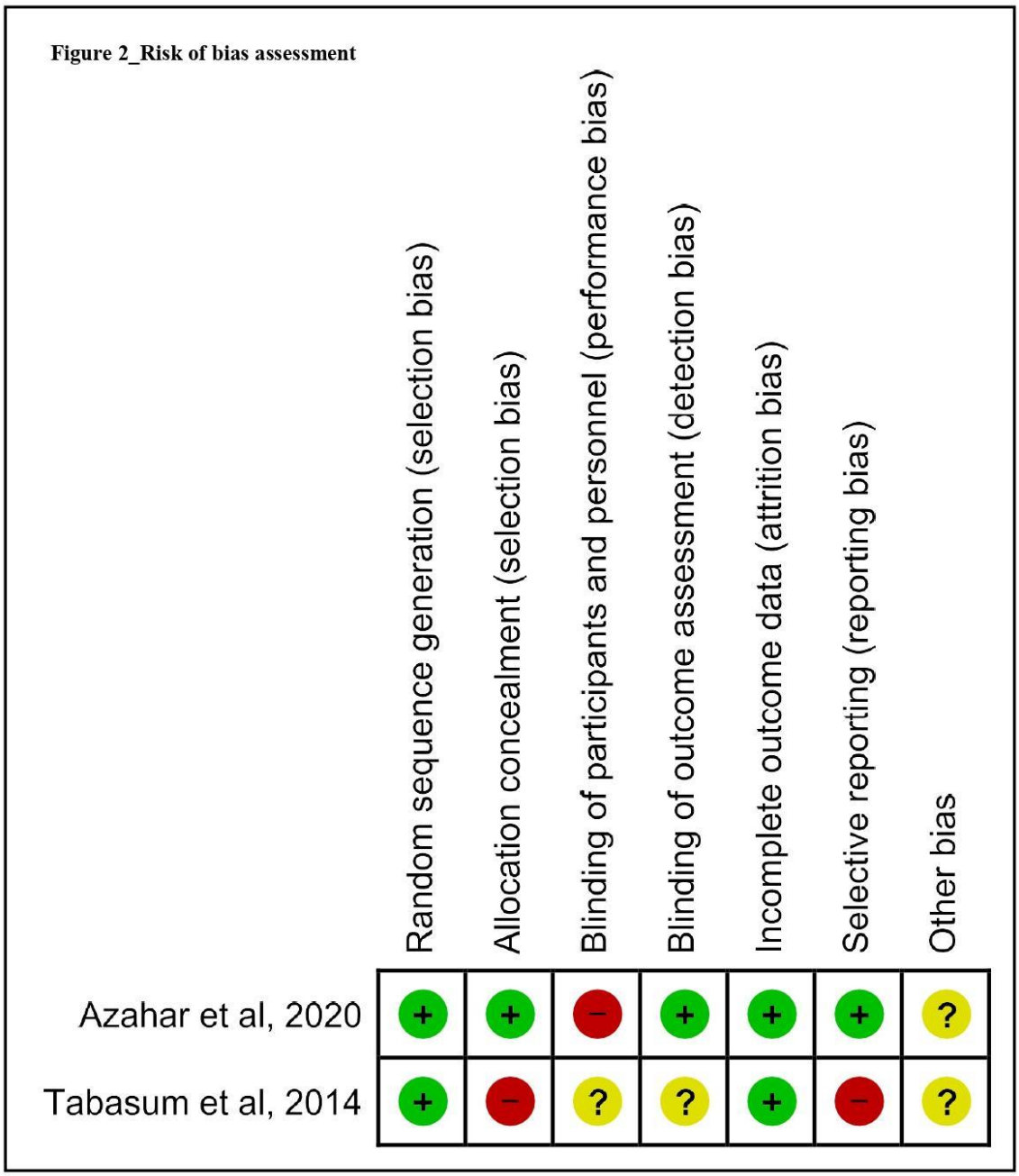

Table 1, 2, and 3

Table 1: Qualitative description of included study

S. No.	Author, Year	Title	Trial no.	Country	Blinding	Randomization method	Patients N (n), enrolled patients (analysed patients)		Time	Exposure		Acne grade	Inclusion	Exclusion	Strength and limitation
							Intervention	Comparator		Intervention	Comparator				
1	Azahar et al, 2020 (20)	Therapeutic Evaluation of a Topical Unani Formulation, Tila-i Muhāsā in Buthūr Labaniyya (Acne Vulgaris): A Randomized, Controlled Clinical Study	CTRI/2017/12/010974	India	Single-blind (assessor blinded)	Block randomization (block size 4)	37 (30)	36 (30)	6 weeks	Ṭila-i Muhāsā fine powdered (Iris ensata, Albizia lebbeck, and Azadirachta indica) • Apply paste (fine powder mixed with lukewarm water) on the acne-affected skin of the prewashed & dried face at night • Wash face with lukewarm water in morning	Benzoyl peroxide gel (5%) • Apply gel on the acne-affected skin of the prewashed & dried face at night • Wash face with lukewarm water in morning	NA	• Patients (12-40 years) with acne vulgaris • Outpatient of CRIUM, Hyderabad (between August, 2018 and April, 2019)	• Patients below or over 12-40 years respectively • Pregnant and lactating women • Patients on corticosteroid therapy, anticonvulsant therapy or taking oral contraceptives • Patients with mental retardation, renal, hepatic, or severe cardiac co-morbidities and unable to attend treatment schedule regularly • Patients with any systemic disease or concomitant disorders (acne rosacea, acne fulminans, acne necrotica, psoriasis, eczema	Strength • Both group similar at baseline characteristics, signifying proper randomization • Equal attrition of patients in both group • Trial registered • Strength of composition in intervention (Ṭila-i Muhāsā) provided • Patients with < 75% compliance not evaluated Limitation • No detail for sample size determination • Short trial period (6 weeks), difficult to access long term efficacy

S. No.	Author, Year	Title	Trial no.	Country	Blinding	Randomization method	Patients N (n), enrolled patients (analysed patients)		Time	Exposure		Acne grade	Inclusion	Exclusion	Strength and limitation
							Intervention	Comparator		Intervention	Comparator				
														etc) • Patients who had used any topical and systemic treatments in previous 4 weeks	
2	Tabasum et al, 2014 (21)	The effect of Unani antiacne formulation (Zimade Muhasa) on acne vulgaris: A single-blind, randomized, controlled clinical trial	NA	India	Single blind	Computer generated randomization	24 (20)	24 (20)	6 weeks	Zimade Muhasa fine powdered (Iris germanica var. florentina, Azadirachta indica, Abrus precatorius, Albizia lebbeck and lake salt) • Apply paste (2 gm formulation mixed with luke warm) daily overnight on clean face	Benzoyl peroxide gel (5%) • Apply daily overnight over clean face	NA	• Patients (13-40 years) suffering from acne • Outpateints at National Institute of Unani Medicine, Bangalore (Between February 2012 to January 2013)	• Patients below or over 12-40 years respectively • Pregnant and lactating women • Patients on corticosteroid therapy, anticonvulsant therapy or taking oral contraceptives • Patients with any systemic disease or concomitant disorders (acne rosacea, acne fulminans, acne necrotica, psoriasis, eczema etc)	Strength • Both group similar at baseline characteristics, signifying proper randomization • Equal attrition of patients in both group • Patients with < 80% compliance not evaluated Limitation • No detail for sample size determination • No trial registration • Strength of composition in intervention (Zimade Muhasa) not provided • Short trial period (6 weeks), difficult to access long term efficacy

Table 2: Outcome description of included study

S. No.	Author, Year	Exposure		Subjective assessment		Objective assessment		Adverse events	
		Intervention	Comparator	Grading scale	Outcome	Grading scale	Outcomes	Adverse effects	Outcome
1	Azahar et al, 2020 (20)	Ṭila-i Muhāsā fine powdered (Iris ensata, Albizia lebbeck, and **Azadirachta indica**) • Apply paste (fine powder mixed with lukewarm water) on the acne-affected skin of the prewashed & dried face at night • Wash face with lukewarm water in morning	Benzoyl peroxide gel (5%) • Apply gel on the acne-affected skin of the prewashed & dried face at night • Wash face with lukewarm water in morning	• Patients global assessment (PGA): 0 - 100 mm horizontal visual analogue scale	• Significantly reduced ($p<0.001$) in both group, with slight better result in active control group	• Global acne grading system (GAGS): 1-18 (mild) - 31-38 (sever) • Cooks acne grading scale (using photographic standards): 0 (better) - 8 (worse)	• GAGS score reduced significantly in both groups ($p<0.0001$) • Cooks score reduced in both group, with higher patients in 0 grade for intervention	• Haematological and biological test (haemogram, urine examination, liver function tests and kidney function tests) • Dryness, itching and burning	• Haematological and biochemical safety parameters similar in both groups at 6 week compared to baseline • Other adverse events were 3 in intervention and 9 in control group
2	Tabasum et al, 2014 (21)	Zimade Muhasa fine powdered (Iris germanica var. florentina, **Azadirachta indica**, Abrus precatorius, Albizia lebbeck and lake salt) • Apply paste (2 gm formulation mixed with luke warm) daily overnight on clean face	Benzoyl peroxide gel (5%) • Apply daily overnight over clean face	• Acne lesion [comedones, papules, pustules, nodules, cysts, pigmentation and scars]:arbitary 4 point grading scale (0 (no symptoms) - 3 (severe symptoms)) • QOL (cardiffe disability index questionnaire): higher score reporting greater QoL impairment •	• In intervention group acne lesion reduced significantly ($p<0.05$) at 6 week compared to baseline • In control group only comedones ($p<0.001$) and papules ($p<0.001$) reduced significantly, whereas other acne lesion reported non-significant reduction	• Global acne severity (GEA) devised by Global evaluation acne group: 1 (almost clear) - 3 (moderate severe)	• Significantly reduced ($p<0.001$) in both group, with slight better result in intervention group	• Dryness, peeling, burning, itching	• No Significant difference ($p>0.05$) of adverse events in both group

S. No.	Author, Year	Exposure		Subjective assessment		Objective assessment		Adverse events	
		Intervention	Comparator	Grading scale	Outcome	Grading scale	Outcomes	Adverse effects	Outcome
				Fairness: assessed by a 5-point arbitrary grading score	(p>0.05) • QoL reduced significantly (p<0.001) in both group, with better result in intervention group • Fairness improved in intervention arm				

Table 3: Possible anti acne properties of neem and other natural ingredients

Natural ingredients/Properties	**Antimicrobial activity**	**Anti oxidant/free radical scavenging activity**	**Anti-inflammatory**	**Immunomudulatory**	**Skin renewal (epidermal turnover)**	**Skin whitening**
Azadirachta indica (leaves)	31	32	33	34	35	5,17
Iris ensata (roots)	36	36	-	-	-	-
Alibizia lebbeck (stem-bark)	37	37	38	39	-	-
Abrus precatorius (seed)	40	41	42	43	-	-
Iris germanica florentina	44	-	44	45	-	-

Supplementary files

Table S1: Search outcomes in four databases (ClinicalTrials.gov, Cochrane, Google Scholar, Pubmed)[1]

S. No.	Database	MeSH/keywords	Strategy	Hits
1	ClinicalTrial.gov (09/10/2022)	Acne, Neem, Azadirachta Indica	Advance search: • Condition or disease: Acne • Other terms: Neem Or azadirachta indica • No filters applied	2
2	Cochrane (05/10/2022, 19:52:37)	Acne, Neem, Azadirachta Indica	Advanced search>Search manager:	
	#1: Neem			127
	#2: Azadirachta indica			78
	#3: Acne			5224
	#4: #1 OR #2 AND #3			129
3	Google Search (09/10/2022)	Acne, Neem, Azadirachta Indica	Normal search: • Neem OR azadirachta indica AND acne • Filter applied for time (2012-2022)	2390
	*Initial 679 articles included			679
4	Pubmed (09/10/2022, 07:47:33)	Acne, Neem, Azadirachta Indica	Advanced search:	
	#1: "Neem"[All Fields]			1648
	#2: "azadirachta"[MeSH Terms] OR "azadirachta"[All Fields] OR ("azadirachta"[All Fields] AND "indica"[All Fields]) OR "azadirachta indica"[All Fields]			1697
	#3: "acne vulgaris"[MeSH Terms] OR ("acne"[All Fields] AND "vulgaris"[All Fields]) OR "acne vulgaris"[All Fields] OR "acne"[All Fields]			21001
	#4: "Neem"[All Fields] OR ("azadirachta"[MeSH Terms] OR "azadirachta"[All Fields] OR ("azadirachta"[All Fields] AND "indica"[All Fields]) OR "azadirachta indica"[All Fields])			2390
	#5: ("acne vulgaris"[MeSH Terms] OR ("acne"[All Fields] AND "vulgaris"[All Fields]) OR "acne vulgaris"[All Fields] OR "acne"[All Fields]) AND ("Neem"[All Fields] OR ("azadirachta"[MeSH Terms] OR "azadirachta"[All Fields] OR ("azadirachta"[All Fields] AND "indica"[All Fields]) OR "azadirachta indica"[All Fields]))			7

[1] All searches in respective database done after login.

Table S2: PICOT

PICOT	
Population (Pop)	Inclusion: Adolescent (>=12 years), adults (>=18 years), both sexes with acne/pimple (all types)
	Exclusion: Pre-clinical trials, animal studies
Intervention (Int)	Azadirachta Indica/Neem (either from leave, fruits, barks or other parts), topical or oral formulation, either alone or in combination with or without pharmaceutical active or herbal consituents
Comparators (Com)	Different composition, formulation of neem or placebo and other active treatment
Outcome (Out)	• Improvement or no new appearance of inflammatory and non-inflammatory acne, lesions, comedones, papules, pustules, erythema, nodules and itching • Improvement of skin hydration • Redution in sebum concentration • Adverse events
Study design (Stu)	Inclusion: RCT, only paper in english Exclusion: Conference paper, review article, letter to editor, observational study
Time (Tim)	10 years (1st Jan 2012 till 1st Jan 2022)
Sample size (Sam)	>= 10 participants
Hierarchy of exclusion	Duplicate>Language>Time>Population>Study design>Intervention