

Pharmacological Evaluation of Plant-Derived Analgesic and Anti-Inflammatory Agents: A Review of *Azadirachta indica* and *Holarrhena Antidysenterica*

Payal L. Sonawane¹, Purva D. Rokade², Lina R. Bhoje³, Priyanka B. Waje⁴, Gauraja S. Kothawade⁵,
Dr. Rishikesh S. Bachhav⁶, Dr. Santosh A. Deshmukh⁷

^{1,2,3,4,5}, Student, Department Of Pharmacology, Kalyani Charitable Trust's Ravindra Gambhirrao Sapkal College Of Pharmacy, Anjaneri, Nashik

⁶, Principal, Department Of Pharmacology, Kalyani Charitable Trust's Ravindra Gambhirrao Sapkal College Of Pharmacy, Anjaneri, Nashik, India.

⁷, Associate Professor, Department Of Pharmacology, Kalyani Charitable Trust's Ravindra Gambhirrao Sapkal College Of Pharmacy, Anjaneri, Nashik, India.

Abstract

In recent years, growing interest in plant-derived therapeutics has led to studies of medicinal plants with analgesic and anti-inflammatory activity. *Azadirachta indica* (Neem) and *Holarrhena antidysenterica* (Kutaj) have been used medicinally in Ayurvedic and Unani medicine for inflammatory conditions, pain and gastrointestinal diseases. The current review summarizes the phytochemical profiles, pharmacological effects, and understanding of both plants. *A. indica* contains high concentrations of limonoids, flavonoids, and phenolics that regulate inflammatory mediators such as prostaglandins, tumor necrosis factor- α (TNF- α), and interleukins, and exhibit antioxidant and immunomodulatory properties. The anti-inflammatory, anti-analgesic, and neuroprotective activity of *H. antidysenterica* is mediated by modulation of ion channels, enzymatic pathways, and immune responses, a property attributed to the presence of steroidal alkaloids such as conessine. The preclinical data show a dose-dependent anti-pain effect on paw edema and inflammatory markers, similar to that of well-known chemical analgesics at high doses. These phytochemicals are synergic and polypharmacological and are good candidates for alternative-based therapeutics. The review also highlights the importance of standardization of extraction, pharmacokinetic characterization, and clinical validation to guarantee the efficacy and safety of the use in human application.

Keywords: *Azadirachta indica*, *Holarrhena antidysenterica*, Analgesic activity, anti-inflammatory activity, Phytochemicals, Limonoids, Steroidal alkaloids, Ethnopharmacology, Natural therapeutics, Polypharmacology.

Introduction

The use of conventional synthetic analgesics and anti-inflammatory drugs has many associated adverse effects, including gastrointestinal toxicity and renal impairment, which warrants the search for safe botanical drugs (Rao et al., 2016, p. 256). *Azadirachta indica* and *Holarrhena antidysenterica* are traditional medicinal plants that have been shown to have anti-inflammatory and anti-nociceptive properties with promising effects on inflammatory pathways and nociceptive responses (Alyas et al., 2023; Oktavia et al., 2022, p. 245). *Holarrhena antidysenterica* has a dual effect on peripheral and central pathways of pain, but *Azadirachta indica* has shown high efficacy in acute inflammatory models, and has been considered as a suitable alternative to aspirin as it has fewer side effects (Kewlani et al., 2021; Bhuiyan et al., 2020; Ganapathy et al., 2010). Recent

pharmacological studies have highlighted the ability of *A. indica* leaves to modulate nociception via ATP-sensitive channel and opioid receptor pathways (Mali et al., 2019).

Ethnobotanical Profiles

Azadirachta indica, a member of Meliaceae family, is widely used in traditional Indian medicine for its therapeutic versatility where it is used as a treatment for skin ailments, hypertension and a variety of infectious diseases (Mali et al., 2019). In addition to the systemic applications, the phytochemical composition of the plant (rich in flavonoids and phenolics) is responsible for its ability to modulate the activity of enzymes involved in the inflammatory process, such as those of cyclooxygenase and lipoxygenase pathways (Mali et al., 2019). Moreover, existing studies have shown that its constituents can actively influence key molecular targets, including NF- κ B, p53, and the PI3K/Akt signaling pathway, which are essential for anti-inflammatory and (anti)cancer care, respectively (Mali et al., 2019). Historical use of *Holarrhena antidysenterica* for gastrointestinal health has sparked interest in its potential synergistic effects with other bioactive plants to optimize analgesic effects, highlighting the need for further research to better understand its therapeutic mechanisms and clinical applications (Aggarwal et al., 2025).

Botanical Characteristics

Azadirachta indica is a medium-to-large sized evergreen tree with pinnate leaves and bitter drupe fruits with the bioactive limonoids that give the tree its pharmacological properties (Hemdan et al., 2023, p. 2). *Holarrhena antidysenterica*, on the other hand, is a member of the Apocynaceae family and is often used as a deciduous shrub or small tree, rich in steroidal alkaloids, the compounds responsible for its traditional medicinal uses in treating gastrointestinal inflammation and dysentery. The secondary metabolites in *H. antidysenterica* provide an additional pharmacological basis that complements the enzyme-inhibitory activity of *A. indica*, particularly in regulating prostaglandin-mediated inflammatory responses (Kewlani et al., 2021). In addition, the variety of secondary metabolites allows the use of a comprehensive strategy for managing pain, which includes both anti-oxidative and anti-inflammatory effects, by simultaneously targeting the expression of pro-inflammatory mediators (Mali et al., 2019; Rao, 2026).

Traditional Medicinal Uses

In Ayurvedic and Unani systems, it is widely used and its leaves, bark and seeds are the main treatments for pyrexia, dermal complications and inflammatory disorders (Alzohairy, 2016; Saleem et al., 2018). The wide range of therapeutic activity is mainly due to the complex chemical composition, including azadirachtin, nimbidin, and nimbolide, which are responsible for immunomodulatory and antioxidant activities (Goyal, 2026; Rao, 2026). The bioactive secondary metabolites work together to inhibit cyclooxygenase expression and reduce cytokine production, thereby regulating inflammatory responses (Umar et al., 2014). On the other hand, *Holarrhena antidysenterica* was traditionally used for diarrhoeal conditions and inflammatory bowel disease, owing to its exclusive recipe of different alkaloids that helps to maintain the integrity of the gastric mucosa (Gite & Abukalam, 2024; Loganathan et al., 2021, p. 119). In recent pharmacologic research, it was also confirmed to be effective against systemic infections caused by pathogenic bacteria such as *Escherichia coli* and *Staphylococcus aureus* (Bala et al., 2022, p. 221).

Phytochemical Composition

The therapeutic potentials of *A. indica* are attributed to its high contents of limonoids, saponins and flavonoids, which are potent anti-inflammatory agents (Krishnaiah et al., 2009, p. 70; Kumatia et al., 2024, p. 3). By contrast, the pharmacological activity of *Holarrhena antidysenterica* is mainly attributed to the presence of 68 alkaloids, including conessine, kurchine, and holarrhimine, which have remarkable anti-inflammatory and

antioxidant properties (Kundu et al., 2024; Mohammad et al., 2025). These steroidal alkaloids have therapeutic effects which involve modulating cholinergic signaling and also have a neuroprotective effect that goes beyond their localized anti-diarrheal effects (Thawkar et al., 2024). Furthermore, the extracts modulate the proinflammatory cell signaling and apoptotic pathways, thus giving broad mechanistic support to their use in treating chronic immune-mediated disorders (Abba & Dogara, 2021, p. 16; Goyal6, 2026).

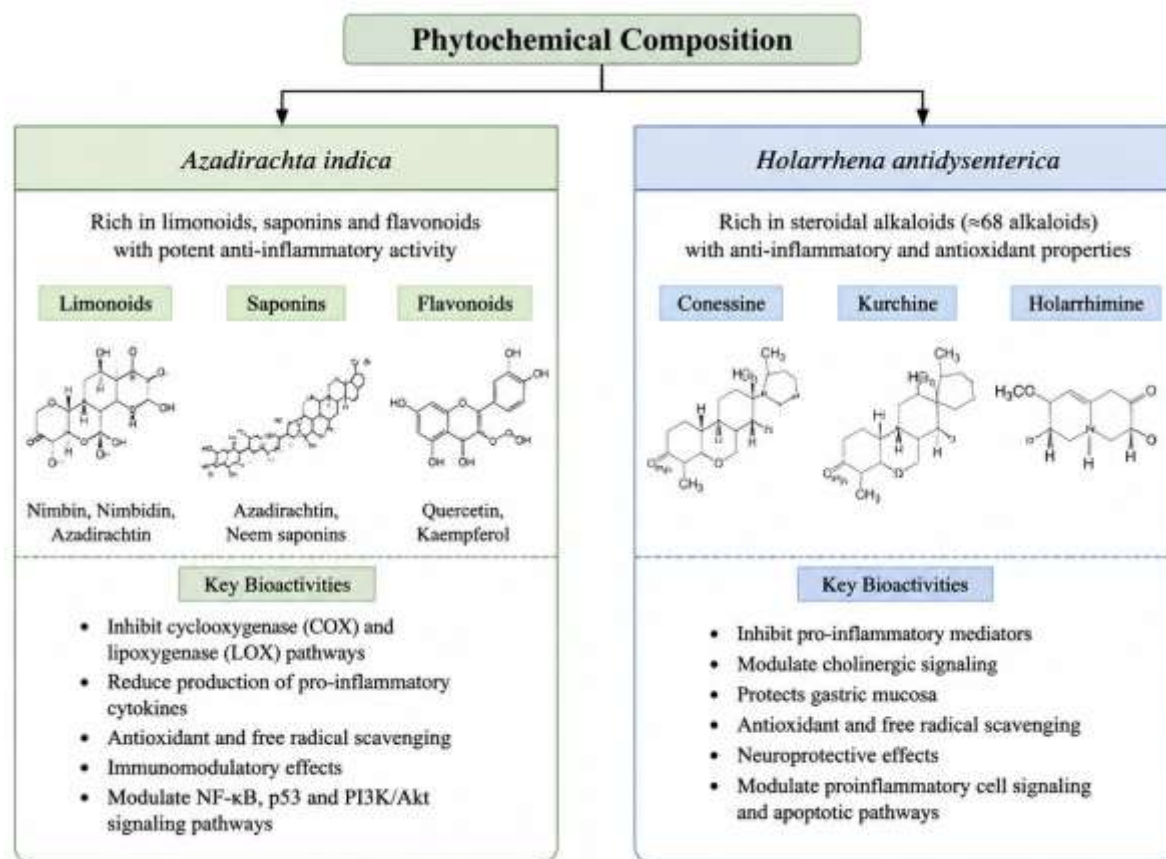


Figure 1: Comparative Phytochemical Composition and Bioactivity Profile of *Azadirachta indica* and *Holarrhena antidysenterica*

The figure illustrates the comparative phytochemical composition and key bioactive constituents of *Azadirachta indica* (Neem) and *Holarrhena antidysenterica*. Neem is rich in limonoids, saponins, and flavonoids such as nimbin, nimbidin, quercetin, and kaempferol, which contribute to its strong anti-inflammatory, antioxidant, immunomodulatory, and enzyme-inhibitory effects. In contrast, *Holarrhena antidysenterica* contains steroidal alkaloids including conessine, kurchine, and holarrhimine, which exhibit potent anti-inflammatory, antioxidant, neuroprotective, and cholinergic-modulating activities. Together, the two plants act through multiple molecular pathways, including COX/LOX inhibition, cytokine suppression, oxidative stress reduction, and apoptotic regulation, supporting their traditional medicinal use for pain and inflammatory disorders.

Active Secondary Metabolites

Limonoids like nimbin, nimbidin and azadirachtin are the key phytochemicals involved in the action of *Azadirachta indica* that inhibit the expression of tumour necrosis factor alpha (TNF- α), interleukins (IL-6) and intermediate nitric oxide (iNOS) (Aggarwal et al., 2011, p. 1603; Nagaraj & Samiappan, 2019, p. 1769). Furthermore, flavonoids present in the plant matrix act as strong inhibitors of prostaglandin biosynthesis and of specific enzymatic activities, such as protein kinases and phosphodiesterases, which directly affect inflammatory signaling pathways (Alamry et al., 2024, p. 22018). Concurrently, the alkaloid content in *Holarrhena antidysenterica* offers action through the regulatory of ion channels and enzymatic receptors, hence

its significant role in reducing gastrointestinal-associated inflammatory upset. They play a role in modulating host immune pathways, such as phagocytosis and MHC class II antigen expression (Alhazmi et al., 2021, p. 637561).

Pharmacological Activities

The anti-inflammatory and analgesic activity of *Azadirachta indica* is evident in its ability to inhibit protein denaturation, as reported by Sambasivan (2025), who observed inhibition of up to 66.4% at certain experimental concentrations. Furthermore, the presence of a major limonoid compound in the leaf extract, called "gedunin," supports the attenuation of pain, pyrexia, and swellings by enhancing overall immunomodulatory responses (E. et al., 2007, p. 2870). At the same time, the pharmacological testing of *H. antidysenterica* revealed a high level of anti-inflammatory activity against the microbes, primarily due to the synergistic effect of its steroidal alkaloids on markers of lipid peroxidation (Gumastha et al., 2026). In addition, both plant species have strong antioxidant properties that prevent cell damage and *A. indica* has been reported to show potential in chemopreventive pathways through its ability to induce apoptosis in malignant cell lines (Ashok et al. 2024; Schumacher et al. 2010, p. 149).

Analgesic Potential Mechanisms

The peripheral and central regulation of nociceptive signaling involved in the analgesic effects of these botanical agents is primarily attributed to the downregulation of prostaglandin E2 and the attenuation of oxidative stress-induced neuroinflammation (Rajendran et al., 2024, p. 1). Further, molecular docking studies have pointed out nimbolide and nimbandiol as active molecules which could inhibit the pro-inflammatory cytokines, such as tumor necrosis factor (TNF- α) and interleukins (IL-6) (Khadam et al., 2024; Kumar et al., 2025). Moreover, these phytochemicals have demonstrated efficacy and are known to inhibit the production of cytokines and adhesion molecules, which are key components of the pathophysiology of chronic inflammatory conditions (Anna et al., 2021, p. 257). Specifically, fruit extracts of *A. indica* have been shown to exert anti-inflammatory effects by reducing paw edema in experimental models and to possess significant analgesic properties, supporting the traditional use of *A. indica* for inflammatory distress (Razzak et al., 2025).

Antiinflammatory Efficacy Evidence

The bioefficacy of the extracts from the leaves of *A. indica* has been shown in vivo to significantly reduce paw edema in carrageenan-induced inflammation and cotton pellet-induced granuloma formation in a manner comparable to the current pharmacological standards (Kharwar et al., 2020, p. 909). Likewise, extracts of *H. antidysenterica* have demonstrated potent antinociceptive and anti-inflammatory effects in formalin- and acetic acid-induced pain models, resulting in anti-inflammatory activity, such as suppression of local tissue swelling, by neutralizing the phlogistic agents (Asiri et al., 2024, p. 1351827). In addition, empirical evidence indicates that synergistic pharmacological interactions among these botanical extracts may lead to superior therapeutic effects compared with any single extract (Anis et al., 2026). The observed effects are in line with the well-established understanding that various phytochemical classes such as alkaloids, flavonoids, and terpenoids exhibit polypharmacological action by modulating multiple components of the arachidonic acid cascade and reactive oxygen species signaling pathways (Rudrapal et al., 2023, p. 8658; Sasidharan & J, 2021, p. 206).

Toxicological Safety Profiles

For an accurate assessment, the aforementioned phytochemicals should be evaluated for potential adverse effects, such as hepatotoxicity or nephrotoxicity, that may occur with high-dose consumption (Aladejana, 2023, p. 957). Existing investigations have pointed out that parameters of toxicity that describe acute toxicity (such as median lethal dose or prolonged sub-chronic exposure studies) are important to define safe therapeutic windows for clinical application (Ibrahim et al., 2023, p. 415). In recent times, the need to standardize these

plant products has been highlighted to reduce the risk of side effects from secondary metabolites, which is of primary importance for integrating these botanical agents into contemporary therapeutic systems (Patil et al., 2019, p. 4369).

Table 1: Toxicological Safety Profile of *Azadirachta indica* and *Holarrhena antidysenterica*

Parameter	<i>Azadirachta indica</i> (Neem)	<i>Holarrhena antidysenterica</i> (Kutaj)	Literature Evidence
Acute Toxicity (LD50)	Generally safe at therapeutic doses; toxicity observed only at very high doses	Considered relatively safe in moderate doses; higher doses may cause mild toxicity	Ibrahim et al., 2023
Hepatotoxicity Risk	Rare cases reported with excessive or prolonged use; associated with high-dose extracts	Limited reports; generally low hepatotoxic potential	Aladejana, 2023
Nephrotoxicity Risk	No significant nephrotoxicity at normal doses; caution at high doses	No strong evidence of kidney toxicity in experimental studies	Patil et al., 2019
Sub-chronic Exposure	Long-term use may alter liver enzymes and metabolic markers in high doses	Mild physiological changes observed in prolonged use studies	Ibrahim et al., 2023
Safety Margin	Wide therapeutic window at low–moderate doses	Moderate safety margin depending on alkaloid concentration	Aladejana, 2023
Standardization Requirement	Required to avoid variability in limonoid content and toxicity risk	Required due to variability in steroidal alkaloid concentration	Patil et al., 2019
Overall Safety Profile	Generally safe but dose-dependent toxicity possible	Generally safe with caution at high concentrations	Combined literature consensus

Adverse Effect Assessment

Excessive dosage of *A. indica* has been noted to cause transient alteration in the level of serum transaminase while *H. antidysenterica* should be dosed carefully due to its potential for gastrointestinal irritation (Ezung et al., 2024, p. 1680). As with any therapeutic, researchers state that a standardized extraction process should be used to ensure the therapeutic index remains within non-toxic ranges (Vincent et al., 2024). In addition, longitudinal studies are required to demonstrate the absence of systemic toxicity and the physiological stability of these bioactive compounds over the duration of administration, for extended periods (Moraes et al., 2017, p. 202; Uroko et al., 2023, p. 2). Given the diverse biological activities of these plants, the molecular pharmacokinetic profile should be clarified in future pharmacological studies to optimize therapeutic efficacy and reduce toxicity (Sherif et al., 2024, p. 1326483).

Future Research Perspectives

Further studies are required to elucidate the pharmacokinetic parameters and the exact molecular mechanisms of these secondary metabolites to develop a standardized therapeutic guideline based on evidence from the developed research (Semwal et al., 2023, p. 1257019). In particular, incorporating

pharmacokinetic/pharmacodynamic (PK/PD) parameters, including maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC), will be crucial to defining a therapeutic window and facilitating clinical translatability (Tie et al., 2025, p. 1657842). Additionally, investigators need to focus on long-term safety monitoring and follow rigorous reporting guidelines, including the CONSORT statement, to confirm the benefit-risk balance of these medicinal products (Wang et al., 2022, p. 154591). Future studies are also required to include standardized microscopic analysis, physicochemical evaluation, and characterization of the chemical fingerprints of these herbal products to improve the authentication and reliability of each batch and ensure consistent efficacy (Noviana et al., 2022, p. 853038). Furthermore, understanding how the plant interacts with drugs is crucial because some compounds can affect the mechanisms by which traditional medicines are metabolized, potentially impacting patient safety (Balkrishna et al., 2024, p. 39). Furthermore, it remains an urgent need to translate these promising preclinical results into proven clinical practice through well-designed randomized controlled trials (Addissouky et al., 2023, p. 61; Attiq et al., 2017, p. 768).

References

1. Abba, A., & Dogara, A. M. (2021). Ethnomedicinal Survey of Plants used for Management of Inflammatory Diseases in Ringim Local Government, Jigawa State, Nigeria. *Ethnobotany Research and Applications*, 22. <https://doi.org/10.32859/era.22.47.1-27>
2. Addissouky, T. A., Ali, M. M. A., Sayed, I. E. T. E., & Wang, Y. (2023). Recent Advances in Diagnosing and Treating *Helicobacter pylori* through Botanical Extracts and Advanced Technologies. *Archives of Pharmacology and Therapeutics*, 5(1), 53–66. <https://doi.org/10.33696/pharmacol.4.045>
3. Aggarwal, B. B., Prasad, S., Reuter, S., Kannappan, R., Yadav, V. R., Park, B., Kim, J. H., Gupta, S. C., Phromnoi, K., Sundaram, C., Prasad, S., Chaturvedi, M. M., & Sung, B. (2011). Identification of Novel Anti-inflammatory Agents from Ayurvedic Medicine for Prevention of Chronic Diseases: “Reverse Pharmacology” and “Bedside to Bench” Approach. *Current Drug Targets*, 12(11), 1595–1653. <https://doi.org/10.2174/138945011798109464>
4. Aggarwal, I., Upadhyay, S., & Kumar, A. (2025). PHARMACOLOGICAL EVALUATION OF COMBINED MIXTURE OF FRACTIONS FOR ANALGESIC AND ANTI-INFLAMMATORY POTENTIAL IN RODENT MODELS. *Asian Journal of Pharmaceutical and Clinical Research*, 143–146. <https://doi.org/10.22159/ajpcr.2025v18i12.57268>
5. Aladejana, E. B. (2023). Biological Properties of Polyherbal Formulations: A Review of their Antimicrobial, Anti-Inflammatory, Antioxidant, and Toxicological Activities. *Pharmacognosy Journal*, 15(5), 933–963. <https://doi.org/10.5530/pj.2023.15.178>
6. Alamry, K. A., Hussein, M. A., Khan, A., & Asiri, A. M. (2024). Anticoagulation activity of sulfated carboxymethyl cellulose/Azadirachta indica leaf powder-based bio-composite. *RSC Advances*, 14(30), 22017–22027. <https://doi.org/10.1039/d4ra02893g>
7. Alhazmi, H. A., Najmi, A., Javed, S. A., Sultana, S., Bratty, M. A., Makeen, H. A., Meraya, A. M., Ahsan, W., Mohan, S., Taha, M. M. E., & Khalid, A. (2021). Medicinal Plants and Isolated Molecules Demonstrating Immunomodulation Activity as Potential Alternative Therapies for Viral Diseases Including COVID-19. *Frontiers in Immunology*, 12, 637553–637553. <https://doi.org/10.3389/fimmu.2021.637553>

8. Alyas, S., Zahra, N., Khadam, A., SULTANA, R., ZAHID, B., Tariq, R., Akhtar, R., RAFIQUE, H., & Ahmad, S. S. (2023). STUDY OF ANTI-INFLAMMATORY, ANTIPYRETIC AND ANALGESIC EFFECTS OF AZADIRACHTA INDICA LEAVES EXTRACT IN ALBINO RATS. *Biological and Clinical Sciences Research Journal*, 2023(1), 257–257. <https://doi.org/10.54112/bcsrj.v2023i1.257>
9. Alzohairy, M. A. (2016). Therapeutics Role of Azadirachta indica (Neem) and Their Active Constituents in Diseases Prevention and Treatment. *Evidence-Based Complementary and Alternative Medicine*, 2016(1), 7382506–7382506. <https://doi.org/10.1155/2016/7382506>
10. Anis, M., Baig, S. G., Farrukh, U., Ahmad, F. M., Mansoor, N., & Mahmood, Z. A. (2026). Exploring The Therapeutic Potential Of A Polyherbal Combination For Pain And Inflammation. *Pakistan Journal of Pharmaceutical Sciences*, 39(3), 657–666. <https://doi.org/10.36721/pjps.2026.39.3.reg.14596.1>
11. Anna, K. Q., Ayensu, I., Emmanuel, O., Nana, A. M.-G., Yakubu, J., & Phoebe, E. G. (2021). In-vivo anti-inflammatory activity of different parts of Adansonia Digitata. *Journal of Medicinal Plants Research*, 15(6), 252–259. <https://doi.org/10.5897/jmpr2020.7079>
12. Ashok, B., Jadhav, Prof. P. V., & Shirsa, prof. A. B. (2024). Azadirachta indica: A Medicinal Plant with Many Uses for Immunity, Cancer, and Digestive Disorders. *International Journal of Pharmaceutical Research and Applications*, 9(5), 431–434. <https://doi.org/10.35629/4494-0905431434>
13. Asiri, S., Shabnam, M., Zafar, R., Alshehri, O. M., Alshehri, M. A., Sadiq, A., Mahnashi, M. H., & Jan, M. S. (2024). Evaluation of Habenaria aitchisonii Reichb. for antioxidant, anti-inflammatory, and antinociceptive effects with in vivo and in silico approaches. *Frontiers in Chemistry*, 12, 1351827–1351827. <https://doi.org/10.3389/fchem.2024.1351827>
14. Attiq, A., Jalil, J., & Husain, K. (2017). Annonaceae: Breaking the Wall of Inflammation. *Frontiers in Pharmacology*, 8, 752–752. <https://doi.org/10.3389/fphar.2017.00752>
15. Bala, K., Melkani, I., SINGH, A. P., Singh, A. P., & Kaur, J. (2022). Holarrhena antidysenterica in Inflammatory Bowel Disease: a potential review. *Journal of Drug Delivery and Therapeutics*, 12(4), 221–226. <https://doi.org/10.22270/jddt.v12i4.5458>
16. Balkrishna, A., Sharma, N., Srivastava, D., Kukreti, A., Srivastava, S., & Arya, V. (2024). Exploring the Safety, Efficacy, and Bioactivity of Herbal Medicines: Bridging Traditional Wisdom and Modern Science in Healthcare. *Future Integrative Medicine*, 3(1), 35–49. <https://doi.org/10.14218/fim.2023.00086>
17. Bhuiyan, Md. M. R., Bhuiya, N. M. M. A., Hasan, Md. N., & Nahar, U. J. (2020). In vivo and in silico evaluation of antinociceptive activities of seed extract from the Holarrhena antidysenterica plant. *Heliyon*, 6(5). <https://doi.org/10.1016/j.heliyon.2020.e03962>
18. E., O. I., McGaw, L. J., Naidoo, V., & Eloff, J. N. (2007). Inflammation: the foundation of diseases and disorders. A review of phytomedicines of South African origin used to treat pain and inflammatory conditions. *AFRICAN JOURNAL OF BIOTECHNOLOGY*, 6(25), 2868–2885. <https://doi.org/10.5897/ajb2007.000-2457>
19. Ezung, B., Kalivarathan, R., Khusro, A., Agastian, P., Almutairi, B. O., & Arokiyaraj, S. (2024). In vitro assessment on anti-inflammatory and anti-lipidemic properties of selected plant species. *BioResources*, 19(1), 1680–1695. <https://doi.org/10.15376/biores.19.1.1680-1695>

20. Ganapathy, P. S. S., Ramachandra, Y., & Padmalatha, S. (2010). *Anti-inflammatory and Analgesic Activities of Holarrhena antidysenterica Wall. Leaf Extract in Experimental Animal Models*. [http://www.globalsciencebooks.info/Online/GSBOOnline/images/2010/IJBPS_4\(1&2\)/IJBPS_4\(2\)101-103o.pdf](http://www.globalsciencebooks.info/Online/GSBOOnline/images/2010/IJBPS_4(1&2)/IJBPS_4(2)101-103o.pdf)
21. Gite, D. U., & Abukalam, K. M. (2024). Azadirachta indica (Neem) and its Active Ingredients' Therapeutic Significance in the Prevention and Treatment of Diseases. *International Journal of Advanced Research in Science Communication and Technology*, 261–271. <https://doi.org/10.48175/ijarsct-19418>
22. Goyal⁶, Dr. K. S., Ms. Minata², Dr. Arvind Kumar³, Mr. Anurag Kumar⁴, Mr. Zuber Ahamad⁵, Himanshu. (2026a). NEEM (AZADIRACHTA INDICA) AS A MEDICINAL PLANT: PHARMACOLOGICAL INSIGHTS AND THERAPEUTIC POTENTIAL. *Zenodo (CERN European Organization for Nuclear Research)*. <https://doi.org/10.5281/zenodo.18480732>
23. Goyal⁶, Dr. K. S., Ms. Minata², Dr. Arvind Kumar³, Mr. Anurag Kumar⁴, Mr. Zuber Ahamad⁵, Himanshu. (2026b). NEEM (AZADIRACHTA INDICA) AS A MEDICINAL PLANT: PHARMACOLOGICAL INSIGHTS AND THERAPEUTIC POTENTIAL. *Zenodo (CERN European Organization for Nuclear Research)*. <https://doi.org/10.5281/zenodo.18480731>
24. Gumastha, P., Khare, S., Deshmukh, N. C., & Chakraborty, M. (2026). Comparative analysis of medicinal plant alkaloids: A chemical and pharmacological study of Moringa oleifera and Azadirachta indica (Neem). *Journal of Medicinal Plants Studies*, 14(1), 239–245. <https://doi.org/10.22271/plants.2026.v14.i1c.2034>
25. Hemdan, B. A., Mostafa, A., Elbatanony, M. M., El-Feky, A. M., Paunova-Krasteva, T., Stoitsova, S., El-Liethy, M. A., El-Taweel, G. E., & Mraheil, M. A. (2023). Bioactive Azadirachta indica and Melia azedarach leaves extracts with anti-SARS-CoV-2 and antibacterial activities. *PLoS ONE*, 18(3). <https://doi.org/10.1371/journal.pone.0282729>
26. Ibrahim, R. M., Abdel-Baki, P. M., Elmasry, G. F., El-Rashedy, A. A., & Mahdy, N. E. (2023). Combinative effects of akarkara root-derived metabolites on anti-inflammatory and anti-alzheimer key enzymes: integrating bioassay-guided fractionation, GC-MS analysis, and in silico studies. *BMC Complementary Medicine and Therapies*, 23(1), 413–413. <https://doi.org/10.1186/s12906-023-04210-6>
27. Kewlani, A., Bhalerao, S., Bhide, H., Deshpande, T., Tilak, A. V., & Dharkar, N. (2021). Comparison of Anti-Inflammatory Efficacy of Ocimum Sanctum, Azadirachta Indica and their Combination with Aspirin in Chemically Induced Acute Inflammation. *Biomedical & Pharmacology Journal*, 14(3), 1509–1518. <https://doi.org/10.13005/bpj/2252>
28. Kewlani, A., Bhalerao, S., Math, P., Dhole, M., & Barde, A. (2021). Evaluation of efficacy of Ocimum sanctum, Azadirachta indica, and their combination in comparison with aspirin on acute inflammatory pain. *National Journal of Physiology Pharmacy and Pharmacology*, 0, 1–1. <https://doi.org/10.5455/njppp.2021.11.03098202131032021>
29. Khadam, A., Alyas, S., Zahra, N., Ahmad, S., Sarwar, A., Khan, A. A., Aziz, T., Alharbi, M., & Alasmari, A. F. (2024). Influence of Azadirachta indica leaf extracts on tumor necrosis factor- α and interleukin-6 in albino rats and its computational analysis. *Cellular and Molecular Biology*, 70(11), 95–100. <https://doi.org/10.14715/cmb/2024.70.11.14>

30. Kharwar, R. N., Sharma, V. K., Mishra, A., Kumar, J., Singh, D. K., Verma, S., Gond, S. K., Kumar, A., Kaushik, N., Bharadwaj, R., & Kusari, S. (2020). Harnessing the Phytotherapeutic Treasure Troves of the Ancient Medicinal Plant *Azadirachta indica* (Neem) and Associated Endophytic Microorganisms. *Planta Medica*, 86, 906–940. <https://doi.org/10.1055/a-1107-9370>
31. Krishnaiah, D., Devi, T. L., Bono, A., & Sarbatly, R. (2009). Studies on phytochemical constituents of six Malaysian medicinal plants. *Journal of Medicinal Plants Research*, 3(2), 67–72. <https://doi.org/10.5897/jmpr.9001153>
32. Kumar, V., Kumar, A., Monika, K., Gupta, M. K., Rajpoot, A. K., & Singh, B. K. (2025). Qualitative Chemical Evaluation of Chloroform Extract of *Azadirachta Indica* Leaves for Analgesic and Antipyretics Activities: In silico and AdmetStudies. *Current Functional Foods*, 3. <https://doi.org/10.2174/0126668629372093250612111334>
33. Kumatia, E. K., Zoiku, F. K., Baffour, K., Anokye-Kumatia, A. B., & Asase, A. (2024). Phytochemical analysis, cytotoxicity, anti-trypanosomal, anti-oxidant and anti-inflammatory activities of *Clausena anisata* fruit, *Azadirachta indica* leaf and stem bark extracts. In *Research Square*. <https://doi.org/10.21203/rs.3.rs-5425137/v1>
34. Kundu, M. K., MALLICK, S. M. B., Rahman, A., Islam, Md. R., & Reza, M. S. (2024). AntiDiarrhea and Central Nerval System Activity of Methanolic Extract of *Holarrhenna antidysenterica* (L.). In *Research Square*. <https://doi.org/10.21203/rs.3.rs-4007319/v1>
35. Loganathan, T., Barathinivas, A., Soorya, C., Balamurugan, S., Nagajothi, T. G., & Jayakumararaj, R. (2021). GCMS Profile of Bioactive Secondary Metabolites with Therapeutic Potential in the Ethanolic Leaf Extracts of *Azadirachta indica*—: A Sacred Traditional Medicinal Plant of INDIA. *Journal of Drug Delivery and Therapeutics*, 11, 119–126. <https://doi.org/10.22270/jddt.v11i4-s.4967>
36. Mali, A. S., Thorat, M. B., Ghadge, D. M., Nikam, K. A., Sawant, S. D., Shaikh, F. I., Vhatkar, N. M., Shinde, S., Dhongade, K. D., & Tamboli, M. A. (2019a). *Antinociceptive and antioxidant activities of methanolic extract of leaves of Azadirachta indica in vivo*. <https://doi.org/10.7287/peerj.preprints.27847>
37. Mali, A. S., Thorat, M. B., Ghadge, D. M., Nikam, K. A., Sawant, S. D., Shaikh, F. I., Vhatkar, N. M., Shinde, S., Dhongade, K. D., & Tamboli, M. A. (2019b). *Antinociceptive and antioxidant activities of methanolic extract of leaves of Azadirachta indica in vivo*. <https://doi.org/10.7287/peerj.preprints.27847v1>
38. Mali, A. S., Thorat, M. B., Ghadge, D. M., Nikam, K. A., Sawant, S. D., Shaikh, F. I., Vhatkar, N. M., Shinde, S., Dhongade, K. D., & Tamboli, M. A. (2019c). *Antinociceptive and antioxidant activities of methanolic extract of leaves of Azadirachta indica in vivo*. <https://doi.org/10.7287/peerj.preprints.27847v2>
39. Mali, A. S., Thorat, M. B., Ghadge, D. M., Nikam, K. A., Sawant, S. D., Shaikh, F. I., Vhatkar, N., Shinde, S., Gonghade, K. D., & Tamboli, M. A. (2019a). Antinociceptive and Antioxidant Activities of Methanolic Extract of Leaves of *Azadirachta Indica* (Neem). In *Preprints.org*. <https://doi.org/10.20944/preprints201907.0145.v1>
40. Mali, A. S., Thorat, M. B., Ghadge, D. M., Nikam, K. A., Sawant, S., Shaikh, F. I., Vhatkar, N., Shinde, S., Gonghade, K. D., & Tamboli, M. A. (2019b). Antinociceptive and Antioxidant

Activities of Methanolic Extract of Leaves of Azadirachta Indica (Neem). In *bioRxiv (Cold Spring Harbor Laboratory)*. Cold Spring Harbor Laboratory. <https://doi.org/10.1101/694505>

41. Mohammad, R. S., Rahman, M. A., Yusuf, M. S., & Karim, S. A. (2025). Therapeutic Potential of Inderjo Talkh (*Holarrhena antidysenterica*) in Unani Medicine: An In-Depth Study. *Journal of Drug Delivery and Therapeutics*, 15(4), 165–171. <https://doi.org/10.22270/jddt.v15i4.7073>
42. Moraes, M. A., Bruna, C. S. S., Rodrigo, L. F., Elita, S., Alves, M. S., Célia, H. Y., Mírian, P. R., Glauciemar, D.-V.-V., Ana, L., Aílson, da L. A. de A., & Orlando, V. de S. (2017). Pharmacological potential of *Palicourea rigida* kunth: A possible participation of flavonoid compounds. *Journal of Medicinal Plants Research*, 11(10), 194–206. <https://doi.org/10.5897/jmpr2016.6320>
43. Nagaraj, A., & Samiappan, S. (2019). Presentation of Antibacterial and Therapeutic Anti-inflammatory Potentials to Hydroxyapatite via Biomimetic With *Azadirachta indica*: An in vitro Anti-inflammatory Assessment in Contradiction of LPS-Induced Stress in RAW 264.7 Cells. *Frontiers in Microbiology*, 10, 1757–1757. <https://doi.org/10.3389/fmicb.2019.01757>
44. Noviana, E., Indrayanto, G., & Rohman, A. (2022). Advances in Fingerprint Analysis for Standardization and Quality Control of Herbal Medicines. *Frontiers in Pharmacology*, 13, 853023–853023. <https://doi.org/10.3389/fphar.2022.853023>
45. Oktavia, S. N., Ifora, I., & Fauziah, F. (2022). Anti-inflammatory, Analgesic, and Antipyretic Potential of *Azadirachta indica*: A Review. *Journal of Drug Delivery and Therapeutics*, 12, 245–254. <https://doi.org/10.22270/jddt.v12i3-s.5502>
46. Patil, K. R., Mahajan, U. B., Unger, B. S., Goyal, S. N., Belemkar, S., Surana, S. J., Ojha, S., & Patil, C. R. (2019). Animal Models of Inflammation for Screening of Anti-inflammatory Drugs: Implications for the Discovery and Development of Phytopharmaceuticals. *International Journal of Molecular Sciences*, 20(18), 4367–4367. <https://doi.org/10.3390/ijms20184367>
47. Rajendran, P., Renu, K., Abdallah, B. M., Ali, E. M., Veeraraghavan, V. P., Sivalingam, K., Rustagi, Y., Abdelsalam, S. A., Ibrahim, R. I. H., & Al-Ramadan, S. Y. (2024). Nimbolide: promising agent for prevention and treatment of chronic diseases (recent update). *Food & Nutrition Research*, 68. <https://doi.org/10.29219/fnr.v68.9650>
48. Rao, L. T. N., Jadhav Pooja Shriram, Kudande Sakshi Santosh and Prof. C. V. N. (2026a). A REVIEW OF BIOACTIVE CONSTITUENTS, PHARMACOLOGICAL AND THERAPEUTIC POTENTIAL OF NEEM (*AZADIRACHTA INDICA*). *Zenodo (CERN European Organization for Nuclear Research)*. <https://doi.org/10.5281/zenodo.18150563>
49. Rao, L. T. N., Jadhav Pooja Shriram, Kudande Sakshi Santosh and Prof. C. V. N. (2026b). A REVIEW OF BIOACTIVE CONSTITUENTS, PHARMACOLOGICAL AND THERAPEUTIC POTENTIAL OF NEEM (*AZADIRACHTA INDICA*). *Zenodo (CERN European Organization for Nuclear Research)*. <https://doi.org/10.5281/zenodo.18150562>
50. Rao, T. C. S., Renuka, P., Akhil, P., Divya, P., & P, D. P. (2016). EVALUATION OF THE ANTI-INFLAMMATORY ACTIVITY OF COMBINATION OF ETHANOL EXTRACTS OF *AZADIRACHTA INDICA* (NEEM) AND *LAWSONIA INERMIS* (HENNA). *Asian Journal of Pharmaceutical and Clinical Research*, 9(5), 256–256. <https://doi.org/10.22159/ajpcr.2016.v9i5.13474>

51. Razzak, M., Riaz, A., Rajput, M. A., Wahid, S., Alqahtani, A. S., Khan, S., Nawaz, M., & Ahmed, A. (2025). Pharmacological insights into Azadirachta indica fruit: GC-MS Profiling and evaluation of key bioactivities on experimental animals. *PubMed*, 38(1), 139–150. <https://pubmed.ncbi.nlm.nih.gov/40188472>
52. Rudrapal, M., Eltayb, W. A., Rakshit, G., El-Arabey, A. A., Khan, J., Aldosari, S. M., Alshehri, B., & Abdalla, M. (2023). Dual synergistic inhibition of COX and LOX by potential chemicals from Indian daily spices investigated through detailed computational studies. *Scientific Reports*, 13(1), 8656–8656. <https://doi.org/10.1038/s41598-023-35161-0>
53. Saleem, S., Muhammad, G., Hussain, M. A., & Bukhari, S. N. A. (2018). A comprehensive review of phytochemical profile, bioactives for pharmaceuticals, and pharmacological attributes of Azadirachta indica. *Phytotherapy Research*, 32(7), 1241–1272. <https://doi.org/10.1002/ptr.6076>
54. Sambasivan³, A. J., Parvathy Prasad^{*2}, Aiswarya. (2025). Therapeutic Potential of Azadirachta indica Leaf Extract. *Zenodo (CERN European Organization for Nuclear Research)*. <https://doi.org/10.5281/zenodo.18085652>
55. Sasidharan, S., & J, H. N. (2021). In-vivo studies to manifest the potent antiinflammatory and analgesic effect of the topical formulation, Pankajakasthuri orthoherb cream/ thermagel upon single application in wistar albino rats. *Pharmacy & Pharmacology International Journal*, 9(5), 201–208. <https://doi.org/10.15406/ppij.2021.09.00345>
56. Schumacher, M., Cerella, C., Reuter, S., Dicato, M., & Diederich, M. (2010). Anti-inflammatory, pro-apoptotic, and anti-proliferative effects of a methanolic neem (Azadirachta indica) leaf extract are mediated via modulation of the nuclear factor- κ B pathway. *Genes & Nutrition*, 6(2), 149–160. <https://doi.org/10.1007/s12263-010-0194-6>
57. Semwal, P., Rauf, A., & Simal-Gándara, J. (2023). Editorial: High altitude medicinal plants and their bioactive compounds for the prevention of oxidative stress-induced diseases and disorders. *Frontiers in Pharmacology*, 14, 1257018–1257018. <https://doi.org/10.3389/fphar.2023.1257018>
58. Sherif, A. E., Alam, R., Asif, M., Khan, K.-R., & Rehman, M. S. U. (2024). Evaluation of the anti-inflammatory, antinociceptive, and antipyretic potential of ethanolic extract of Aristida depressa Retz through in vitro, in vivo, and in silico models. *Frontiers in Pharmacology*, 15, 1326482–1326482. <https://doi.org/10.3389/fphar.2024.1326482>
59. Thawkar, M. M., Jeurkar, M. M., Saktel, M. G., & Mohitkar, S. P. (2024). Phyto-Pharmacology Profile Of Holarrhena Antidysenterica: A Review. *Journal Of Advanced Zoology*, 1294–1299. <https://doi.org/10.53555/jaz.v45i2.4123>
60. Tie, Y., Liu, H., Zhang, T., Meng, T., & Liang, Q. (2025). Natural products alleviate viral pneumonia by modulating inflammatory and oxidative-stress pathways. *Frontiers in Pharmacology*, 16, 1657829–1657829. <https://doi.org/10.3389/fphar.2025.1657829>
61. Umar, M. I., Asmawi, M. Z., Sadikun, A., Majid, A. M. S. A., Atangwho, I. J., Ahamed, M. B. K., Altaf, R., & Ahmad, A. (2014). Multi-constituent synergism is responsible for anti-inflammatory effect of Azadirachta indica leaf extract. *Pharmaceutical Biology*, 52(11), 1411–1422. <https://doi.org/10.3109/13880209.2014.895017>
62. Uroko, R. I., Ijioma, S. N., Ogbonna, H. N., Aguwamba, C., & Ugwuanyi, K. C. (2023). Evaluation of the Anti-diarrhoeal, Anti-inflammatory, and Analgesic Effects of the Polyherbal

Formulation, Aju Mbaise in Experimental Rats. In *Research Square*. <https://doi.org/10.21203/rs.3.rs-2877604/v1>

63. Vincent, O. M., Joseph, O. N. M., Simon, M. E., Moriasi, G., & Jared, O. and O. M. (2024). Safety, Analgesic, and Anti-Inflammatory Effects of Aqueous and Methanolic Leaf Extracts of *Hypericum revolutum* subsp. *keniense*. *International Journal of Innovative Science and Research Technology (IJISRT)*, 3005–3015. <https://doi.org/10.38124/ijisrt/ijisrt24mar1443>

64. Wang, X., Ma, Y., Xu, Q., Shikov, A. N., Pozharitskaya, O. N., Flisyuk, E. V., Liu, M., Li, H., Vargas-Murga, L., & Duez, P. (2022). Flavonoids and saponins: What have we got or missed? *Research Portal (King's College London)*, 109, 154580–154580. <https://doi.org/10.1016/j.phymed.2022.154580>