

Nature's pharmacy at risk: Unveiling the hidden molecular secrets of phytotherapy in the age of globalization

Phytotherapy—the use of medicinal plants as a cure—is one of the oldest forms of therapies used worldwide. The historian Herodotus documented the first reports of herbal medicine dating back to the third millennium BC. Paracelsus, the physician, philosopher, and reformer of medicine, also found great healing power in plants and formulated “All meadows, all mountains and hills are pharmacies,” which refers to his holistic approach to a healthy environment for sustainable health. In our days, the inclination toward natural agents among patients, doctors, and pharmaceutical companies is not reflected by the number of scientific publications. Indeed, publications including the term “phytotherapy” in PubMed reached their peak the year 2012 with 2660 scientific reports and have since then been rapidly declining. In 2023, only 536 scientific reports on “phytotherapy” were cited PubMed. This apparent loss of interest is contradicts reports by the World Health Organization (WHO) stating that around 80% of the global population still relies on botanical drugs. Moreover, a plethora of biologically active compounds present in synthetically prepared drugs were identified from medicinal plants.

A comprehensive review of human drugs introduced since 1981 suggests that out of 847 small molecule-based drugs, 43 were natural products, 232 were derived from natural products, and 572 were prepared synthetically. However, 262 of the 572 synthetic compounds had a natural product-inspired pharmacophore or could be considered natural product analogs.¹ This observation highlights the continued importance of natural entities as a fundamental source of inspiration for the creation of novel target therapeutic agents.

Integrative medicine embracing existing areas of traditional medicine systems—above all in the field of naturopathy and complementary medicine—with established methods of conventional medicine as holistic, evidence-based and patient-centered elements—not only in Asian countries but also in Western societies.²

Indeed, patients and parents of children with atopic dermatitis commonly resort to complementary and alternative medicine. However, these alternative methods often lack evidence-based validation and their molecular mechanisms of action remain poorly understood. Several natural agents have become popular for their expected activity in the treatment of atopic dermatitis, such as oral Chinese herbal products and topical agents coconut oil, colloidal oatmeal, sunflower oil, and mustard oil. Some compounds present in traditional Chinese medicine have been demonstrated to exert potent anti-inflammatory properties for AD as shown in a meta-analysis

of the efficacy and safety of Chinese herbal medicine for treating atopic dermatitis.³ The modern daily dermatological practice offers a variety of phytotherapeutic approaches. In dermatotherapy, for example, synthetic (e.g., topicals containing Tamol) as well as natural tanning agents (e.g., black tea) are available. Phytotherapeutic-based, authorized preparations include green tea extracts with the main active ingredients identified as epigallocatechin and podophyllotoxin from the lignan group of substances—both of which are authorized for the treatment of genital warts.⁴

In the journal *Allergy*, to date, phytotherapy and medicinal products have only been reported as substances that can potentially induce allergic reactions, Type I and Type IV allergies. The publication by Franzten et al.⁵ stands representative of 27 publications in the last 40 years. Therefore, a recent study of Kwon et al.⁶ is not only a novelty in content but also for the journal as it is the first publication on the mode of action of a novel plant extract that can modulate AD-related cell types. The anti-inflammatory activity of compounds isolated from the *Forsythia velutina* Nakai extract (FVE) was validated in different immune cell types. Dimatairesinol, a main active compound from FVE, showed the most potent inhibitory effects across various immune cells. Considering the quantitative composition of each compound, the anti-AD effects of FVE were attributed to synergistic interactions among constituents, such as arctiin, arctigenin, and matairesinol. These findings underscore, that components in extracts can have synergistic or even additive effects, as also shown for other medicinal plants.⁷ In the study by Kwon et al.,⁶ the therapeutic potential of orally administration of plant extract was evaluated using a 2,4-dinitrochlorobenzene (DNCB)-induced mouse model of AD. The authors postulate that their findings provide valuable insight into the development of *multi-target* therapies for atopic dermatitis. They further suggest that this study could be used as a guideline for a potential botanical mixture as a drug for AD patients, particularly for those who are unresponsive to conventional regimens. This notion warrants support from further representative studies. A limitation of this study was the use of a DNCB-induced mouse model as it is not the best-fitting AD model available. In a study by Matsuoka et al. repeated administration of *Dermatophagoides* extract induced IgE-associated atopic eczema/dermatitis syndrome (AEDS)-like lesions on the skin of NC mice and was suggested as a model of the disease.⁸ Furthermore, FVE could be used in a human clinical study.

AD in general is a multifaceted disease that has to be stratified⁹ for the development of tailored therapeutic management that goes far beyond anti-inflammatory drugs but also includes personalized basic therapy and patient education.¹⁰⁻¹² So, why not combine FVE with other targeted treatments, such as anti-IL4/IL13 of JAK-inhibitors to increase the efficacy.¹³ This question would be challenged by the limited support in conducting clinical studies on the efficacy of medicinal products.

The definition of science-based evidence is open to debate. Is a therapy that has been used successfully for centuries evidence enough? In molecular, precision medicine, we strive to understand the mode of action and pursue "One drug, One receptor, One effect" as a perfect cure. Biologicals for psoriasis and atopic dermatitis have shown that the latter can work.¹⁴ Phytotherapy and integrative medicine take a different approach: the basic prerequisite for understanding phytotherapy is the realization that a combination of medicinal plant constituents used acts as an overall material and structural composition, and that this overall effect is greater than the sum of its individual plant constituents. The publication by Kwon et al. exactly tries to address this topic. Future work on the mode of action of medicinal plants should be supported by network pharmacology, molecular docking, and experimental validation as well as the use of AI.¹⁵

It is clear that on a global scale, herbal medicine will remain a main pillar in therapy, especially in underdeveloped countries. The loss of biodiversity presents a threat to the availability of medicinal plants.¹⁶ This decline in biodiversity is largely the result of rapid and sometimes unplanned industrialization, indiscriminate deforestation, overexploitation of natural resources, pollution, and finally global climate change.¹⁸ Therefore, it is of utmost importance that plant biodiversity be preserved, to identify novel lead compounds with medicinal properties for future drug development.^{16,17} This is particularly important for developing nations. Well-planned bioprospecting, coupled with nondestructive commercialization, could aid in the conservation of biodiversity, ultimately benefiting mankind in the long run.


This editorial aims to achieve two key goals: first, to highlight the notable research conducted by Kwon et al.,⁶ and second, to emphasize the urgent need to evaluate and enhance the ethnoecological knowledge related to the use of wild plants for medicinal purposes. In this context, it is crucial to analyze the molecular mechanisms of phytotherapeutics to fully understand their efficacy and safety. Biodiversity is increasingly under threat from the expanding challenges of globalization, jeopardizing both the preservation of traditional knowledge and the diverse biological systems that are integral to this knowledge. It is imperative to bridge scientific inquiry with traditional practices to safeguard and nurture this precious biological and cultural heritage for future generations.

CONFLICT OF INTEREST STATEMENT

I declare that I have no conflicts of interest in relation to this work.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Claudia Traidl-Hoffmann^{1,2,3} 

¹Environmental Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany

²CK CARE, Christine Kühne Center for Allergy Research and Education, Davos, Switzerland

³Institute of Environmental Medicine, Helmholtz Center Munich, Augsburg, Germany

Correspondence

Claudia Traidl-Hoffmann, University of Augsburg, Lehrstuhl für Umweltmedizin, Neusässer Straße 47, 86156 Augsburg, Germany.

Email: claudia.traidl-hoffmann@tum.de and claudia.traidl-hoffmann@uni-a.de

ORCID

Claudia Traidl-Hoffmann  <https://orcid.org/0000-0001-5085-5179>

REFERENCES

- Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. *J Nat Prod*. 2016;79(3):629-661.
- Hon KL, Chu S, Leung AKC, Wong A. Atopic dermatitis: conventional and integrative medicine. *Curr Pediatr Rev*. 2022;18(2):84-96.
- Jia J, Gu SX, Mo X, Liu J, Chen D. An updated systematic review and meta-analysis of efficacy and safety of Chinese herbal medicine for treating atopic dermatitis. *J Dermatolog Treat*. 2023;34(1):2268766.
- Zink A, Traidl-Hoffmann C. Green tea in dermatology – myths and facts. *J Dtsch Dermatol Ges*. 2015;13(8):768-775.
- Frantzen B, Brocker EB, Trautmann A. Immediate-type allergy caused by poppy seed. *Allergy*. 2000;55(1):97-98.
- Kwon Y, Kang YJ, Kwon J, et al. Forsythia velutina Nakai extract: a promising therapeutic option for atopic dermatitis through multiple cell type modulation. *Allergy*. 2024;79(5):1242-1257.
- Steiert SA, Zissler UM, Chaker AM, et al. Anti-inflammatory effects of the petasin phyto drug Ze339 are mediated by inhibition of the STAT pathway. *Biofactors*. 2017;43(3):388-399.
- Matsuoka H, Maki N, Yoshida S, et al. A mouse model of the atopic eczema/dermatitis syndrome by repeated application of a crude extract of house-dust mite *Dermatophagoides farinae*. *Allergy*. 2003;58(2):139-145.
- Bieber T, Traidl-Hoffmann C, Schappi G, Lauener R, Akdis C, Schmid-Grendlmeier P. Unraveling the complexity of atopic dermatitis: the CK-CARE approach toward precision medicine. *Allergy*. 2020;75(11):2936-2938.
- Ring J, Akdis C, Behrendt H, et al. Davos declaration: allergy as a global problem. *Allergy*. 2012;67(2):141-143.
- Ring J, Akdis C, Lauener R, et al. Global allergy forum and second Davos declaration 2013 allergy: barriers to cure – challenges and actions to be taken. *Allergy*. 2014;69(8):978-982.
- Werfel T, Allam JP, Biedermann T, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2016;138(2):336-349.

13. Simpson EL, Bruin-Weller M, Flohr C, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the international eczema council. *J Am Acad Dermatol*. 2017;77(4):623-633.
14. Bieber T. Disease modification in inflammatory skin disorders: opportunities and challenges. *Nat Rev Drug Discov*. 2023;22(8):662-680.
15. Liu C, Liu Y, Liu Y, et al. Network pharmacology, molecular docking and experimental verification revealing the mechanism of Fule cream against childhood atopic dermatitis. *Curr Comput Aided Drug Des*. 2023. doi:[10.2174/0115734099257922230925074407](https://doi.org/10.2174/0115734099257922230925074407).
16. Applequist WL, Brinckmann JA, Cunningham AB, et al. Scientists' warning on climate change and medicinal plants. *Planta Med*. 2020;86(1):10-18.
17. Nadeau KC, Agache I, Jutel M, et al. Climate change: a call to action for the United Nations. *Allergy*. 2022;77(4):1087-1090.
18. Agache I, Sampath V, Aguilera J, et al. Climate change and global health: A call to more research and more action. *Allergy*. 2022;77(5):1389-1407. doi:[10.1111/all.15229](https://doi.org/10.1111/all.15229).