

Commentary

Targeting the Tumor Microenvironment with Plant-Derived Immunomodulators: An Emerging Therapeutic Strategy

Verena Beier¹, Michael Wink² and Yvonne Samstag^{1*}

¹Institute of Immunology, Section Molecular Immunology, Heidelberg University Hospital, Heidelberg, Germany

²Institute of Pharmacy and Molecular Biotechnology, Heidelberg University, Heidelberg, Germany

*Corresponding authors: Yvonne Samstag, Institute of Immunology, Section Molecular Immunology, Heidelberg University Hospital, Heidelberg, Germany

Received: August 25, 2026; Accepted: September 02, 2026; Published: September 08, 2026

The publication “Plant-derived immunomodulators in cancer: Balancing immune activation and suppression within the tumor microenvironment” (Beier V, Wink W, Samstag Y (2026). *Adv Biol Regul.* 99: 101132) serves as a valuable entry point for a wider and increasingly significant discussion in oncology and immunology. It addresses a highly relevant challenge in modern tumor immunology: the targeted modulation of the immune system within the tumor microenvironment using plant-derived compounds. Instead of merely listing phytochemicals, the article emphasizes a key conceptual issue: natural substances are not intrinsically “immune enhancing” or inherently “safe”; rather, they are pharmacologically active compounds that may either promote or hinder antitumor immune responses, depending on the specific context and dosage. This perspective is particularly important for the field, as it encourages researchers and clinicians to move beyond overly simplistic distinctions between “natural” and “synthetic,” and to approach plant-derived compounds as potent immunological tools whose mechanisms of action require rigorous investigation.

An especially important insight is that the tumor microenvironment should not be understood as a passive setting, but rather as a dynamic immunological niche.

Cancer cells actively exploit inflammatory and regulatory pathways to establish conditions in which immune activation is tightly restricted and often transient, while immunosuppressive processes are strengthened and maintained.

Plant-derived immunomodulators such as piperlongumine, berberine, and epigallocatechin gallate (EGCG) do not act as universally immune-stimulating agents but instead exert complex and sometimes opposing effects on T cells and regulatory immune networks. A compound that appears advantageous in a simplified *in vitro* system may, within the complex environment of a tumor, unintentionally promote regulatory T cells, myeloid derived suppressor cells, or other immunosuppressive populations. Conversely, a molecule that dampens inflammation in one context may, in another, relieve inhibitory constraints on effector immune responses. This apparent duality should not be interpreted as a limitation of the field, but rather

as an indication that any agent targeting the immune system - whether natural or synthetic - must be, in addition, assessed within a biological system that inherently integrates both activation and suppression.

From clinical-research perspective, the subject of plant-derived immunomodulators also underscores a broader tension between traditional practices and evidence-based medicine. Compounds such as berberine, EGCG, curcumin, and resveratrol have longstanding roles in various traditional medical systems, and their application is frequently supported by anecdotal reports or historical use. These natural products can be regarded as multi-target drugs as they can interfere with several molecular targets, mostly proteins, in the body. However, contemporary oncology increasingly requires precision, including clearly defined molecular targets, measurable pharmacokinetic properties, reproducible immunological outcomes, and well-established clinical endpoints. The central issue is therefore not only whether and in what way plant-derived compounds shift the balance between immune activation and immune suppression in patients, but whether their effects are sufficiently predictable, controllable, and compatible with current immuno-oncology treatment strategies.

Pharmacokinetic limitations - low bioavailability, complex metabolism, and uncertain tissue distribution - are often underappreciated in phytochemical research, all of which makes it difficult to translate promising preclinical findings into consistent clinical benefit. In addition, patients are increasingly using phytochemicals as dietary supplements on their own initiative while undergoing chemotherapy, targeted therapies, or treatment with immune checkpoint inhibitors, often without clear recommendations regarding appropriate dosing, timing, or possible interactions. This leads to a situation in which “natural” compounds are effectively incorporated into an unregulated, real world polypharmacy context. Consequently, the subject addressed in the publication intersects with broader pharmacological challenges, including the need for standardized formulations, comprehensive pharmacokinetic and pharmacodynamic characterization, and vigilant monitoring of immune related adverse effects.

Finally, this topic points toward an emerging opportunity: Plant-derived immunomodulators may prove most valuable not as standalone treatments, but as context dependent adjuvants that fine tune immune responses. In certain scenarios, they may help to overcome PD L1-mediated resistance mechanisms, modulate excessive cytokine release, or reduce chronic inflammation that contributes to tumor progression. In other situations, however, they could compromise immune surveillance or intensify immune related toxicities. The key challenge moving forward lies in establishing a framework in which such agents are selected on the basis of their mechanisms of action, the patient's immune profile, and concurrent therapies, rather than on tradition or marketing claims alone. In this regard, the review functions as a conceptual anchor for a more rigorous and integrative approach to the use of natural products in cancer immunology, in which plant-derived immunomodulators are regarded not as harmless adjuncts, but as pharmacologically significant factors within the broader landscape of immuno-oncology.

References

1. Beier V, Wink W, Samstag Y (2026) Plant-derived immunomodulators in cancer: Balancing immune activation and suppression within the tumor microenvironment. *Adv Biol Regul* 99: 101132. [[crossref](#)]

Citation:

Beier V, Wink M, Samstag Y (2026) Targeting the Tumor Microenvironment with Plant-Derived Immunomodulators: An Emerging Therapeutic Strategy. *Cancer Stud Ther J* Volume 11(1): 1-2.