

Beyond Pleiotropy: A Call for Target Deconvolution and Chemopreventive Repositioning of Alkaloids in CRC [Letter]

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Dear editor,

We read with great interest the comprehensive review by Guo et al on traditional Chinese medicine-derived alkaloids in colorectal cancer therapy.¹ The authors have made a commendable effort to integrate a large and rapidly expanding literature to map the multi-layered mechanisms, from Wnt/ β -catenin and PI3K/Akt regulation to autophagy, ferroptosis, and gut microbiota remodeling, that position these natural compounds as promising adjuvants in CRC therapy. The inclusion of nanoformulation strategies and the critical discussion of pharmacokinetic barriers further distinguish this review as a timely resource for the field.

However, we wish to raise a conceptual point that we believe merits deeper consideration, as it may fundamentally shape how we evaluate the translational potential of these alkaloids. Throughout the manuscript, the authors highlight the “multi-target, multi-pathway” nature of alkaloid action as a core therapeutic advantage. While this characterization is mechanistically accurate, we respectfully note that in the context of CRC's established genomic heterogeneity and clonal evolution, this pleiotropy may represent a translational advantage rather than an ineligible asset, especially when long-term application of adjuvant therapy or prophylaxis is considered.²

The authors themselves acknowledge that the majority of preclinical evidence derives from xenograft and cell-line models, which, as they note, lack the mutational heterogeneity and microenvironmental complexity of human CRC. We would extend this observation to its logical conclusion: in a tumour with concurrent APC, KRAS, and TP53 mutations that each driving distinct, often non-overlapping, pathway dependencies, a compound that simultaneously modulates Wnt, MAPK, PI3K/AKT, and TGF- β signalling may exert selective pressures across multiple clones simultaneously.³ This could, paradoxically, accelerate the emergence of polyclonal resistance, a phenomenon well described in the targeted therapy literature but rarely discussed in the context of natural product research. The authors' own data on BBR's ability to modulate gut microbiota and suppress inflammatory signalling, while impressive, do not address whether prolonged exposure might select for microbiota compositions that metabolically inactivate the drug or promote compensatory oncogenic pathway upregulation.⁴

This concern is not merely theoretical. The review cites the 6-year follow-up of the BBR adenoma recurrence trial, showing persistent protective effects. Yet the mechanistic basis for this durability remains unclear. Is it sustained microbiota remodelling? Epigenetic reprogramming? Or, more provocatively, does BBR preferentially suppress a specific adenoma-initiating clone while leaving others dormant—an effect that might be reversed upon drug cessation⁵? The long-term safety data in this trial are encouraging, but they do not address whether patients who eventually recur carry tumours with distinct mutation profiles compared to those who do not. Without such genomic stratification, we cannot confidently attribute the observed benefit to the mechanisms delineated in Figure 4 of the review.

We would therefore propose that future research directions, while aligned with the authors' recommendations for nanodelivery and organoid models, should incorporate three additional priorities. First, mechanistic studies should move beyond pathway-level descriptions to identify the primary molecular target responsible for each alkaloid's anti-CRC activity. The field would benefit from chemical proteomics approaches such as thermal shift analysis or activity-based protein profiling to decompose "multitarget" claims into a hierarchy of direct and indirect effects. Second, patient-derived organoid biobanks with matched genomic and transcriptomic data should be employed to test whether the sensitivity to specific alkaloids correlates with particular mutational signatures. This would enable rational patient selection rather than the current "one-size-fits-all" approach to preclinical evaluation. Third, longitudinal studies in preclinical models should explicitly examine whether alkaloid treatment alters the clonal architecture of tumours over time, and whether this is associated with differential responses to subsequent standard-of-care therapies.

We also note that the review, while comprehensive in its coverage of apoptosis, autophagy, and proliferation, does not extensively discuss the potential for alkaloids to modulate DNA damage repair pathways or the tumour-immune interface beyond STAT3 and NF- κ B. Given the growing interest in combining natural products with immune checkpoint inhibitors, and the authors' own mention of immunogenic cell death induced by camptothecin, we believe this represents a fertile area for future mechanistic exploration. For instance, do alkaloids such as BBR or matrine influence PD-L1 expression via the JAK/STAT axis, and could this potentiate or antagonise anti-PD-1 therapy⁵? The answer would have immediate translational relevance.

Finally, we commend the authors for their honest appraisal of the limitations—solubility, bioavailability, toxicity, and drug-drug interactions. The proposed framework of "drug development optimisation, clinical validation, and precise application" is sensible. However, we would suggest that the clinical development pathway for these compounds may need to diverge from the conventional cytotoxic paradigm. Given their favourable long-term safety profile and the compelling epidemiological data linking inflammation to CRC initiation, alkaloids such as BBR are arguably better positioned as chemopreventive agents in high-risk populations rather than as therapeutic agents for established metastatic disease. Such a reorientation would be consistent with the observed mechanisms of microbiota modulation, inflammation suppression, and early pathway disruption, but it would also mitigate concerns about polyclonal resistance in advanced, hypermutated tumors. The authors touch on this in their discussion but do not fully develop the argument; we believe it warrants explicit emphasis.

In summary, Guo et al have provided a valuable and scholarly synthesis. Our commentary is offered in a spirit of constructive engagement, aiming to sharpen the conceptual framework within which the translational potential of TCM-derived alkaloids is evaluated. We look forward to seeing how the field addresses these challenges in the coming years, and we hope that our perspective may stimulate further discussion and hypothesis-driven experimentation.

Disclosure

The authors declare no competing interests in this communication.

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