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✦Commentary

From poisonous botanicals to precision anticancer leads: non-edible medicinal plants in oncology drug discovery

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Abstract

Some of the most pharmacologically powerful plant metabolites come from species that are not edible, largely because evolution optimized them for defense rather than safety. In oncology, where many effective therapies are intrinsically hazardous, toxicity should be treated less as a disqualifier and more as a development constraint that can sometimes be engineered. This commentary argues for a shift from "toxic plant equals interesting cytotoxicity" to precision toxic phytomedicine: mechanism-anchored discovery, reproducible chemistry, rational selectivity assessment, and exposure control through modern delivery and prodrug strategies. The frontier opportunity is not to promote poisonous botanicals as therapies, but to convert their chemical aggression into clinically manageable, target-selective anticancer leads. Historically, oncology has already benefited from toxic plant-derived anticancer pharmacology, showing that toxicity does not preclude clinical value when exposure and mechanism are carefully controlled. The key issue is therefore not whether toxic botanicals are safe in their raw form, but whether their defense metabolites can be translated into reproducible, target-informed, and clinically manageable anticancer leads.

Toxicity is not the enemy; uncontrolled exposure is

Cancer drug development has always been about managed harm: shifting the therapeutic index so tumor cells experience lethal target engagement while normal tissues stay below dose-limiting injury. In this commentary, "toxic plants" refers to non-edible medicinal species whose therapeutic use is constrained by narrow therapeutic windows or recognized toxicological liabilities, and whose bioactivity is dominated by potent defense metabolites rather than nutritional phytochemicals. That framing changes how toxic plants should be interpreted as a discovery space. Modern metabolomics-centric reviews emphasize that progress in natural product drug discovery increasingly depends on workflows that connect chemistry to mechanism and translational feasibility rather than relying on screening-only narratives, by which we mean reports that stop at cytotoxicity signals without establishing selectivity, reproducible chemistry, target/pathway relevance, or a realistic route toward therapeutic use [1,2]. A common objection is that toxicity makes plant-derived leads scientifically unhelpful or clinically unrealistic. In reality, oncology repeatedly converts potent toxins into medicines by controlling exposure, selecting the right context, and engineering delivery, so toxicity is a translational constraint that must be addressed through selectivity evidence, mechanism, dose control, and exposure engineering rather than a reason to dismiss the chemical space outright [3,4].

This perspective is not without precedent. Modern oncology already includes plant-derived anticancer agents and derivatives that emerged from highly bioactive botanical chemistry, showing that potent plant defense metabolites can become clinically useful when chemistry, selectivity, and exposure are rigorously controlled. Vinca alkaloids isolated from Catharanthus roseus illustrate how potent plant defense metabolites can become clinically useful anticancer drugs [5], while podophyllotoxin-inspired development shows that a toxic phytochemical scaffold can be transformed into therapeutically valuable derivatives [6]. These examples do not justify the use of poisonous plants as remedies; rather, they show that toxic botanical metabolites can function as starting points for mechanism-guided drug discovery when chemistry, selectivity, and exposure are rigorously controlled.

The frontier stance: precision toxic phytomedicine

What makes a toxic phytochemical valuable now is not merely that it kills cancer cells in vitro, but that it does so with interpretable selectivity, mechanistic coherence, and a plausible route toward a usable therapeutic index. This is also where computational methods move from hype to utility. Reviews describe how artificial intelligence and machine learning can accelerate natural product programs via dereplication, prioritization, activity prediction, and mechanism inference, improving the odds that only the most tractable toxic scaffolds proceed to costly optimization and in vivo validation [7]. Here, dereplication refers to the early recognition of already known compounds within complex extracts so that discovery efforts can focus on genuinely novel or strategically valuable chemistry rather than repeatedly re-isolating familiar metabolites. For toxic plant research, this distinction is particularly important because apparent novelty or potency may sometimes reflect rediscovery of known toxic constituents rather than a credible new translational opportunity.

Stop listing plants; build a pipeline that can survive peer review

The field does not need more inventories of "promising toxic plants." It needs a repeatable pipeline that progresses in a biologically and translationally coherent order: authenticated source material, reproducible chemistry, in vitro anticancer activity, mechanistic anchoring, explicit selectivity evidence, early liability assessment, followed by in vivo validation and only then an exposure-control strategy. Functional metabolomics has matured into a practical framework for connecting chemistry to phenotype, shifting from correlation toward stronger causal interpretation and prioritization of bioactive natural products [2,8]. In parallel, learning directly from large-scale MS/MS repositories is improving molecular representation and annotation, an important advance for toxic plants where compositional variability and hidden isomers can derail reproducibility [9]. This level of rigor is increasingly the baseline expectation for claims that aspire to translation [2].

Table 1. Translational playbook for developing toxic plant metabolites into anticancer candidates

Development checkpoint	What "good" looks like	Why it matters for toxic plants
Botanical identity and sourcing	Authenticated taxonomy, voucher specimen, transparent sourcing metadata	Prevents misidentification and reduces cross-batch variability that can shift both efficacy and toxicity
Chemical reproducibility	Quantitative marker standardization plus LC–MS fingerprint; stability and impurity profiling	Toxicity often depends on minor constituents; reproducible chemistry is a safety prerequisite
In vitro anticancer activity	Robust activity in tumor-relevant models, concentration-response behavior, and replication across models	Establishes that the signal is real and not an artifact before deeper mechanistic work
Mechanistic anchoring	Target/pathway evidence, resistance mapping, target engagement, not only cytotoxicity	Avoids black-box kill claims and supports precision positioning and rational combinations
Selectivity evidence	Direct comparison with non-malignant cells or tissues, therapeutic-window logic, and evidence that activity is not simply nonspecific toxicity	Distinguishes potent hazards from tractable candidates with plausible therapeutic windows
Early liability assessment	Metabolic stability, CYP and transporter liabilities, reactive metabolite flags	Reduces late-stage failure and improves safety planning for combinations common in oncology
In vivo credibility	PK/PD alignment, preliminary therapeutic-index assessment, dose-limiting toxicity characterization, and reproducible efficacy after sufficient in vitro selectivity and mechanism data	Demonstrates that potency survives biological complexity without unacceptable harm
Exposure-control strategy	Delivery, targeting, or activation concept introduced after mechanistic and in vivo proof-of-concept to improve tumor exposure, reduce peak off-target injury, and widen the therapeutic index	Converts potent toxin into usable candidate by managing where and when toxicity occurs

Exposure engineering after proof-of-concept: how validated toxic leads may become usable therapies

For many toxic plant metabolites, potency is not the only question; sequence matters. Advanced delivery or prodrug strategies should not be treated as a shortcut around weak biological evidence. They become relevant only after a phytochemical or standardized fraction has shown reproducible anticancer activity, acceptable selectivity, and credible mechanistic anchoring. At that stage, the key translational question is whether exposure can be controlled in a way that improves the in vivo therapeutic index by reducing off-target injury while preserving tumor-relevant drug levels.

Nano-enabled delivery has long been discussed as a route to improve solubility, pharmacokinetics, and delivery efficiency for phytochemicals, but formulation novelty is not enough. The standard should be simple: does the approach widen the therapeutic index in vivo, reduce peak off-target exposure, and preserve or enhance tumor exposure? Prodrug strategies offer a conceptually clean route to preferential activation or release under tumor-associated conditions, aiming to convert systemic hazard into localized effect [10]. Ligand-directed targeting adds another lever, with antibody–drug conjugates offering a clinically validated proof-of-principle that highly potent cytotoxins can be used safely when targeting, linker chemistry, and payload properties are engineered together [3,4].

The credibility gate: standardization and reproducibility

Toxic botanicals face an extra scientific burden: small compositional shifts can change both efficacy and toxicity. This is a primary reason botanical oncology claims fail to translate, because the same activity may not reproduce across batches, geographies, seasons, or extraction conditions. Functional metabolomics approaches and integrated activity profiling frameworks strengthen reproducibility by improving chemical annotation, linking molecules to phenotypes, and encouraging higher reporting standards [2,8]. Representation learning from massive MS/MS repositories can also reduce misassignment risk and improve dereplication, which matters when a minor constituent can drive toxicity [9].

Ethics and public health: separating drug development from self-medication

Any serious discussion of toxic plants must make one boundary explicit: raw poisonous botanicals are not medicines. Their potency makes them pharmacologically interesting, while their toxicity makes them vulnerable to misinformation and harmful self-experimentation. The responsible scientific stance is controlled development with standardized material, dose-finding, safety pharmacology, and clinical monitoring. Targeted toxin delivery paradigms are instructive here, not because toxic plants should become antibody conjugates by default, but because oncology already demonstrates how potent toxins can be harnessed safely through design and control [3].

Take-home message

Toxic plants are not direct anticancer therapies in their raw botanical form; rather, they are a high-potency chemical library from which clinically relevant anticancer leads may emerge. The frontier opportunity is to convert evolutionary defense chemistry into oncology tools through

mechanism-anchored and AI-assisted discovery, reproducible chemotype standardization, and exposure engineering using prodrug activation, targeted delivery paradigms, and rigorous PK/PD design. When toxicity is managed rather than ignored, non-edibility can become a feature rather than a flaw in the search for the next generation of cancer therapeutics. The field's most credible next step is to treat toxic botanicals as sources of precision anticancer leads and to prioritize three early requirements: reproducible chemotype standardization, mechanism-linked biomarkers, and evidence that controlled exposure can improve the therapeutic index in vivo.

Competing interests

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