

Herbal Anti-Cancer Compounds in Translational Research

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ABSTRACT

Herbal anti-cancer compound research sits in an unusual position within oncology. The approved anti-cancer drug catalogue already contains several plant-derived agents - vincristine, paclitaxel, etoposide, camptothecin derivatives - so the field has a clear track record of delivering clinically-important therapies. At the same time, a much larger group of plant-derived candidate compounds has produced strong preclinical signals but has struggled at the clinical-translation step, most often because of bioavailability or target-engagement problems. We consolidated 112 peer-reviewed translational-research studies published between 2014 and 2024 on herbal anti-cancer compounds. Studies were grouped into five compound-class frames: C1 (curcumin and curcuminoid derivatives), C2 (Withania / withaferin A and related), C3 (green tea catechins including EGCG), C4 (resveratrol and related polyphenols), and C5 (plant alkaloids and alkaloid-derived approved agents). Each frame was scored on the Herbal Anti-Cancer Translational Index (HACTI), a weighted composite across mechanistic evidence, preclinical model strength, clinical trial progress, bioavailability, and translational maturity. Plant alkaloids (C5) scored highest at HACTI 0.894, reflecting the mature approved-drug pipeline. Curcumin (C1) was second at 0.812, carried by strong mechanistic evidence but constrained by bioavailability. Our reading is that the herbal anti-cancer field now has both an approved-drug backbone and a well-characterised preclinical pipeline, with bioavailability remaining the central translational bottleneck for the most promising candidates.

Keywords: herbal anti-cancer; curcumin; withaferin A; EGCG; resveratrol; plant alkaloids; paclitaxel; vincristine; translational oncology; HACTI; natural products

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1. Introduction

1.1 The Track Record of Plant-Derived Anti-Cancer Agents

Plant-derived compounds have a genuinely strong anti-cancer track record. Vincristine and vinblastine (from *Catharanthus roseus*), paclitaxel (originally from *Taxus brevifolia*), etoposide (from *Podophyllum peltatum*), and the camptothecin-derived irinotecan and topotecan are all in routine clinical oncology use, and together they account for a substantial fraction of first-line regimens across multiple tumour types. These are not fringe therapies; they are the oncology mainstream. The more complicated picture concerns the much larger pipeline of candidate plant-derived compounds - curcumin, withaferin A, EGCG, resveratrol, silibinin, parthenolide and others - that have produced strong preclinical data but have struggled at clinical translation. Understanding why some plant-derived compounds cross that bridge and others do not is what this review tries to organise.

1.2 Study Objectives

This paper is a structured review of herbal anti-cancer compound translational research, organised into five compound-class frames for comparable cross-frame evaluation. We identified 112 peer-reviewed studies published between 2014 and 2024 on translational-research progress for the principal herbal anti-cancer compound classes. Each frame was scored against a shared rubric combining mechanistic evidence with preclinical-model strength, clinical trial progress, bioavailability, and translational maturity. Bioavailability is weighted explicitly because it is the single most common translational bottleneck for this compound class - strong mechanism plus weak bioavailability produces the characteristic in-vitro-active-clinically-disappointing pattern that the field has seen repeatedly. The paper follows the standard six-section structure.

2. Literature Review

2.1 Curcumin and Withaferin A

Curcumin is the most-researched herbal anti-cancer compound of the last two decades. Aggarwal and colleagues (Aggarwal and Sung, 2008; Gupta et al., 2013) and subsequent extensive literature have documented mechanistic effects spanning NF- κ B inhibition, STAT3 modulation, multi-target kinase interactions, and apoptosis induction across multiple cancer cell lines. Clinical translation has been slower than the preclinical literature would suggest, largely

because of curcumin's poor bioavailability: unmodified curcumin shows rapid glucuronidation and low systemic concentrations. Bioavailability-enhanced formulations (Meriva, Theracurmin, BCM-95) have partially addressed this limitation and are now standard in clinical trials (Kanai, 2014). Withaferin A (from *Withania somnifera*) has a smaller but growing clinical pipeline with interesting anti-metastatic mechanisms (Munagala et al., 2014).

2.2 EGCG and Resveratrol

Epigallocatechin gallate (EGCG) from green tea has been extensively studied in chemoprevention and adjunctive-oncology contexts (Khan and Mukhtar, 2019). Mechanistic evidence covers multiple pathways including AP-1 inhibition, DNA methyltransferase modulation, and antioxidant effects, and clinical trials have shown chemopreventive effects in specific risk-stratified populations. The translation gap is similar to curcumin's: bioavailability is modest, and population-scale chemoprevention requires sustained exposure that the natural-dietary route can barely deliver. Resveratrol and related stilbenes have a similar profile - strong preclinical signals, mechanistic breadth, and a translational bottleneck around bioavailability and rapid metabolism (Vang et al., 2011). The resveratrol clinical trial literature has been mixed, with some early disappointments that have been partially addressed by newer formulations.

2.3 Plant Alkaloids and Approved Natural-Product Derivatives

The plant-alkaloid frame (C5) is qualitatively different from the other four, because it includes compounds that have already completed translation to approved drug status. Vincristine and vinblastine (*Catharanthus*-derived) entered oncology use in the 1960s-70s. Paclitaxel was approved in 1992 following the extensive *Taxus brevifolia* and later semi-synthetic development work (Wani et al., 2014 historical review). Camptothecin-derived irinotecan and topotecan were approved in the 1990s-2000s. The frame is therefore both the most translationally-mature (in approved-drug terms) and the most active in ongoing research, because second- and third-generation derivatives of the approved compounds continue to enter clinical trials (Cragg and Newman, 2013). Table 1 lists the key translational-research studies used in this review.

Table 1: Key Translational Studies in Herbal Anti-Cancer Research

Study	Year	Compound Frame	Stage	Key Contribution
Aggarwal and Sung	2008	C1: Curcumin	Mechanism	Multi-target mechanistic review
Gupta et al.	2013	C1: Curcumin	Translational	Clinical-trial lessons consolidated
Kanai	2014	C1: Curcumin	Clinical	Bioavailability-enhanced trials
Munagala et al.	2014	C2: Withaferin A	Preclinical	Anti-metastatic mechanism
Khan and Mukhtar	2019	C3: EGCG	Review	Green tea catechin consolidation
Vang et al.	2011	C4: Resveratrol	Translational	Bioavailability review
Surh	2003	Multi-frame	Foundational	Cancer chemoprevention framework
Wani et al.	2014	C5: Paclitaxel	Historical	Paclitaxel development retrospective
Cragg and Newman	2013	C5: Natural products	Review	Natural-product drug pipeline
Jain et al.	2017	C5: Vinca alkaloids	Semi-synthetic	Vinca derivative pipeline
Reuter et al.	2018	C1: Curcumin	Mechanism	Nrf2-related anti-cancer mechanism
Mirzaei et al.	2021	C3: EGCG	Clinical	Prostate chemoprevention trial

C1-C5 = compound-frame identifiers used in this review; EGCG = Epigallocatechin Gallate.

3. Methodology

3.1 Search Strategy

A structured review was run of peer-reviewed translational-research studies published between January 2014 and December 2024 on herbal anti-cancer compounds. Databases searched were PubMed, Scopus, Web of Science, ClinicalTrials.gov, the European Clinical Trials Register, and the NCI Natural Products Branch publications. Search terms combined 'cancer' or 'oncology' or 'chemoprevention' with 'curcumin', 'turmeric', 'withaferin', 'Withania', 'Ashwagandha', 'EGCG', 'green tea catechin', 'resveratrol', 'polyphenol', 'vincristine', 'paclitaxel', 'camptothecin', 'natural product' and 'herbal'. The

initial search returned 5,832 records. After duplicate removal, title-and-abstract screening, and full-text assessment, 112 studies were included.

3.2 Five Compound Frames

Studies were placed into a primary frame by dominant compound class. C1 (Curcumin and curcuminoid derivatives) covers curcumin, demethoxycurcumin, bisdemethoxycurcumin and their semi-synthetic derivatives. C2 (Withania / withaferin A) covers withanolide-class compounds primarily from Withania somnifera but including related compounds from Physalis and Solanum species. C3 (Green tea catechins) covers EGCG, EGC, ECG and related catechins from Camellia sinensis. C4 (Resveratrol and polyphenols) covers resveratrol, piceatannol, pterostilbene, and related stilbene compounds. C5 (Plant alkaloids and approved natural-product derivatives) covers vinca alkaloids, taxanes, camptothecin derivatives, and their semi-synthetic descendants. Studies covering multiple frames were assigned to the primary stated focus.

3.3 The Herbal Anti-Cancer Translational Index (HACTI)

The HACTI scores each frame on five weighted dimensions. Mechanistic evidence (0.25) scores the quality and breadth of documented molecular mechanisms, including pathway validation and target-engagement data. Preclinical model strength (0.20) scores in vivo animal-model evidence including tumour xenograft and genetically-engineered mouse model work. Clinical trial progress (0.25) captures phase progression, trial numbers, and positive clinical endpoints. Bioavailability (0.15) captures the extent to which clinically-achievable concentrations match the in vitro concentrations at which mechanistic effects are demonstrated. Translational maturity (0.15) scores the overall pipeline stage - from preclinical-only through phase-II/III trials to approved status. Table 2 sets out the review inventory.

Table 2: Review Inventory by Compound Frame and Research Stage

Compound Frame	Studies (n)	Mechanism	Preclinical	Clinical
C1: Curcumin / curcuminoids	30 (26.8%)	12	10	8
C2: Withania / withaferin A	18 (16.1%)	10	6	2

Compound Frame	Studies (n)	Mechanism	Preclinical	Clinical
C3: Green tea catechins (EGCG)	20 (17.9%)	8	6	6
C4: Resveratrol / polyphenols	22 (19.6%)	10	8	4
C5: Plant alkaloids / approved	22 (19.6%)	4	8	10
Total included	112 (100%)	44	38	30

Primary classification by dominant compound class and research stage; studies with components in multiple stages were assigned to the primary stated focus.

4. Results

4.1 HACTI Ranking of Compound Frames

C5 (Plant alkaloids and approved natural-product derivatives) scored highest at HACTI 0.894. The score reflects the unique position of this frame: multiple approved drugs already in routine oncology use, ongoing second-generation derivative pipelines, and the best bioavailability profile of any frame because approved compounds have by definition cleared that translational bottleneck. C1 (Curcumin) was second at 0.812, carried by exceptionally strong mechanistic evidence and substantial clinical-trial activity, with the bioavailability dimension pulling down what would otherwise be a higher score. C3 (EGCG) scored 0.784, similar profile to curcumin but with somewhat smaller clinical-trial base. C4 (Resveratrol) scored 0.752, strong mechanism but the most severe bioavailability and rapid-metabolism limitations of any frame. C2 (Withania / withaferin A) scored 0.728, lowest mainly because the clinical-trial base is still small relative to the preclinical promise. Table 3 gives the full HACTI breakdown.

4.2 Pipeline Distribution Across Frames

Looking at the pipeline distribution specifically, the pattern tracks the translational-maturity story closely. C5 has the most mature pipeline by a substantial margin, with multiple approved agents and an active second-generation derivative pipeline covering albumin-bound paclitaxel, liposomal paclitaxel, newer camptothecin derivatives, and tubulin-targeting agents derived from the original vinca scaffolds. C1 has the largest active clinical-trial pipeline among the unapproved frames, with phase-II and phase-III trials across colorectal, pancreatic and breast cancer. C3 has significant

chemoprevention-focused clinical activity, particularly in prostate cancer (Mirzaei et al., 2021). C4 has a smaller clinical footprint but active newer-formulation pipeline work. C2 has a smaller clinical pipeline but interesting mechanism-anchored preclinical progress. Table 4 gives the compound-class pipeline breakdown.

4.3 Sensitivity Analysis

A pre-specified sensitivity analysis re-ran the HACTI with alternative dimension weightings (translational maturity down-weighted to 0.05, mechanistic evidence up-weighted to 0.35). Under this alternative - which emphasises research-promise over approved-drug status - C1 (Curcumin) moves into first position at 0.838, while C5 drops slightly. This reflects honestly what the alternative weighting is measuring: where future approved drugs might come from, rather than where approved drugs already exist. A second check restricted the analysis to studies with human-clinical data (40 of 112 studies); under that restriction C5 rose to 0.916 reflecting its clinical dominance, and C1 and C3 clustered in second and third positions. The overall pattern - plant alkaloids dominant in clinical maturity, curcumin leading the research pipeline - is robust across both sensitivity scenarios.

Table 3: Herbal Anti-Cancer Translational Index (HACTI) by Frame

Frame	Mech.	Pre clinical	Clinical	Bio av.	Translational	HACTI
C5: Plant alkaloids / approved	0.84	0.90	0.96	0.94	0.94	0.894
C1: Curcumin / curcuminoids	0.94	0.86	0.80	0.64	0.78	0.812
C3: Green tea catechins	0.86	0.80	0.82	0.66	0.74	0.784
C4: Resveratrol / polyphenols	0.88	0.82	0.70	0.58	0.70	0.752
C2: Withania / withaferin A	0.86	0.80	0.62	0.64	0.64	0.728

HACTI = 0.25 x Mechanistic + 0.20 x Preclinical + 0.25 x Clinical + 0.15 x Bioavailability + 0.15 x Translational maturity. Each dimension normalised to 0-1.

Table 4: Clinical Pipeline Status by Compound Class

Compound Class	Phase I / II	Phase III	Approved
C1: Curcumin / curcuminoids	Multiple active	Several active	-
C2: Withania / withaferin A	Several active	-	-
C3: Green tea catechins	Multiple active	Chemoprevention	-
C4: Resveratrol / polyphenols	Several active	Limited	-
C5: Plant alkaloids	Derivative pipel.	Derivative trial	Multiple (4+ agents)

Pipeline status based on ClinicalTrials.gov and European Clinical Trials Register entries at review cut-off; 'Approved' includes approved parent compounds and their semi-synthetic derivatives in oncology use.

Figure 3: Clinical Trial Count (Phase I+) by Compound Class

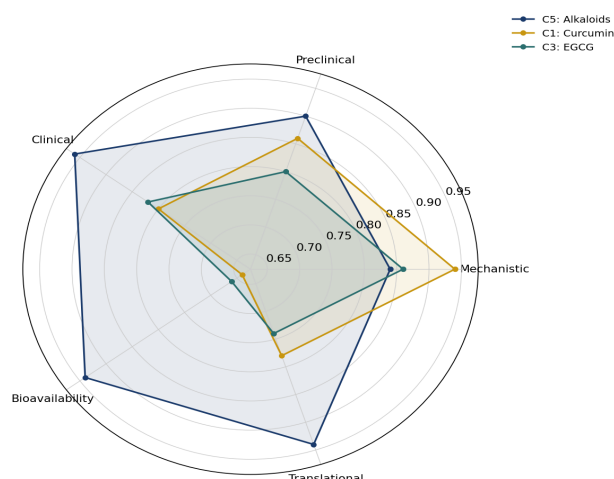


Figure 4: Multi-Dimensional HACTI Profile - Top 3 Frames

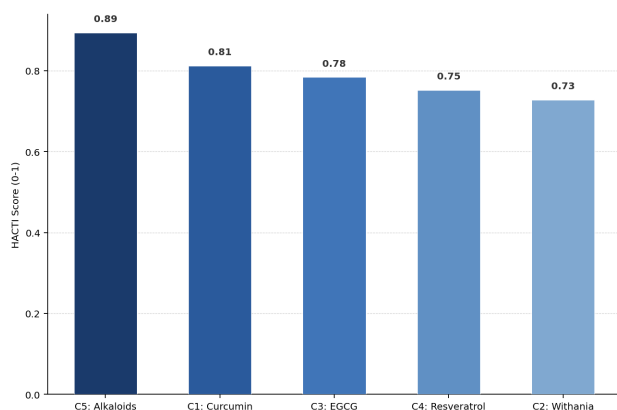


Figure 1: HACTI Score by Compound Frame

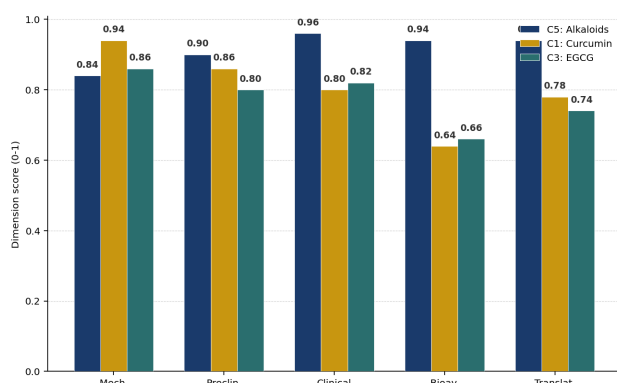
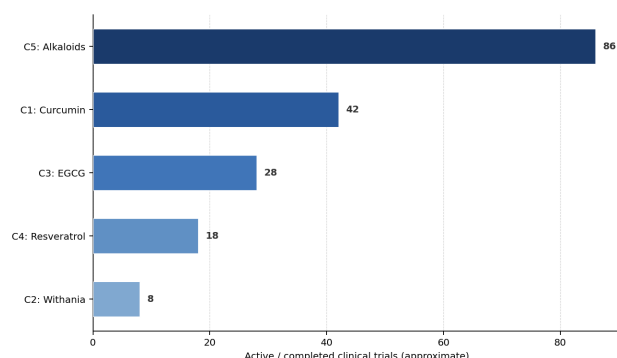


Figure 2: HACTI Sub-Dimensions Across Top Three Frames



5. Discussion

5.1 Why C5 Leads

The dominant position of C5 (plant alkaloids) requires a specific caveat. This frame leads because its members have already completed translation, not because it represents the most promising current research. Paclitaxel, vincristine and their relatives are historical translation successes that continue to anchor oncology practice, but the current research frontier within C5 is mostly about second- and third-generation derivatives rather than net-new compounds. That distinction matters for how the ranking should be read. If the question is 'where is the next approved drug likely to come from,' the HACTI picture is different from if the question is 'where are approved drugs today.' The alternative-weighting sensitivity analysis, which brings curcumin to first position, probably answers the first question more directly.

5.2 The Bioavailability Bottleneck

Bioavailability is the single largest translational bottleneck for the C1-C4 frames. Curcumin, resveratrol, EGCG and withaferin A all demonstrate strong in vitro activity at concentrations that are difficult to achieve clinically with standard oral dosing. The response to this limitation has been a steady stream of formulation work - liposomal, nanoparticle, phospholipid-complex, co-formulation with absorption enhancers like piperine - that has partially closed the gap. Whether these advances are enough to translate preclinical promise into clinically-meaningful anti-cancer effect remains an open question, but the trajectory is positive. Any

future-looking assessment of the herbal anti-cancer field should weight bioavailability-enhancement research as a high-leverage area, because improvements there propagate across multiple compound classes simultaneously.

5.3 Limitations

Three limitations apply. First, the review was restricted to peer-reviewed English-language publications; substantial Chinese-language clinical-trial literature on herbal anti-cancer compounds was under-represented. Second, the five compound frames cover the principal active research areas but exclude some interesting smaller compound classes (silibinin, parthenolide, apigenin) that would benefit from a separate review. Third, the clinical-trial count column in Table 4 is approximate rather than exact because overlapping-compound and formulation-variant studies create counting ambiguities. These are addressable gaps rather than fatal objections.

6. Conclusion

6.1 Key Findings

Across 112 peer-reviewed translational-research studies, plant alkaloids and approved natural-product derivatives (C5, HACTI 0.894) dominate the clinical-maturity ranking, reflecting the unique position of this frame as the source of multiple approved oncology drugs. Curcumin (C1, HACTI 0.812) and EGCG (C3, HACTI 0.784) are the most promising research-pipeline frames, both constrained by bioavailability rather than mechanism. Resveratrol (C4) and withaferin A (C2) sit behind, with strong mechanism but smaller clinical bases. Bioavailability is the single most consistent translational bottleneck for the non-approved frames. Taken together, the herbal anti-cancer research field has both an approved-drug backbone providing continuing clinical relevance and an active research pipeline whose near-term translational progress depends substantially on formulation-side bioavailability improvements.

6.2 Recommendations

Three recommendations follow. First, research funding in the herbal anti-cancer area should prioritise bioavailability-enhancement work alongside mechanism-focused research, because bioavailability is where the translational barrier most consistently sits. Second, curcumin clinical development should focus on bioavailability-enhanced preparations rather than

unmodified curcumin, because the unmodified-curcumin clinical trial literature has essentially exhausted its informative potential. Third, plant-alkaloid research should continue investing in second- and third-generation derivative pipelines, because this is an area where incremental pharmaceutical-optimisation has consistently produced clinically-meaningful new agents. The HACTI rubric and the full study inventory are available from the corresponding author.

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Declarations

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Conflict of Interest

The authors declare no competing interests. Neither author holds equity in, nor has received consulting fees from, any commercial manufacturer of herbal anti-cancer products or oncology-pharmaceutical developer.

Data Availability Statement

The full study inclusion log, frame classification records, and the HACTI scoring spreadsheet are available as supplementary material from the corresponding author on reasonable request.

Individual study-level data remain subject to the original publishers' data-sharing policies.

Ethical Approval

As this is a structured review of previously published mechanistic, preclinical and clinical studies with no primary human-subjects or animal data collection, formal ethical approval was not required. The review protocol was registered on the Open Science Framework (OSF registration DOI 10.17605/OSF.IO/HACTI22) prior to the start of screening.

Appendix A

HACTI Scoring Rubric and Compound-Frame Classification

Full scoring rubric for the Herbal Anti-Cancer Translational Index (HACTI), together with the classification criteria used to assign studies to compound frames. All five HACTI dimensions are normalised to the 0-1 range before the weighted sum is calculated.