REVIEW ARTICLE

CANDIDATE PHYTOCHEMICAL AND BOTANICAL PRODUCTS IN BREAST CANCER: HUMAN EVIDENCE, DRUG DELIVERY, SAFETY AND TRANSLATIONAL READINESS: A CRITICAL NARRATIVE REVIEW

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ABSTRACT

Phytochemical and botanical products are frequently proposed during breast-cancer care, but plant name, formulation, dose, systemic exposure and intended clinical role are often poorly defined. This critical narrative review evaluates curcumin/turmeric, epigallocatechin-3-gallate (EGCG)/green-tea extract, quercetin, resveratrol and Withania somnifera as bounded case studies linking human evidence to delivery science, safety and regulatory development. PubMed/MEDLINE, ClinicalTrials.gov, current breast-cancer guidance, and official regulatory and quality documents were searched through 30 July 2026; reproducible search strategies and an evidence map are supplied in the supplement. Human clinical, pharmacokinetic, interaction and organ-safety evidence was prioritised, followed by representative breast-cancer delivery studies. Study design, exact product definition, endpoint hierarchy, precision, missing data, sponsor involvement, active-moiety uncertainty and route-specific translational limitations were appraised qualitatively. Curcumin has the broadest human evidence base, but findings remain inconsistent: a 686-patient radiodermatitis trial was negative, a small docetaxel trial stopped for futility, and positive chemotherapy studies require independent replication and product-specific pharmacokinetic confirmation. A small 2025 trial suggested less tamoxifen-associated fatty-liver progression, but it does not resolve the separate finding that curcumin plus piperine reduced endoxifen exposure. Concentrated green-tea extract has a reproducible hepatic safety boundary and food-dependent exposure; green tea can also alter transporter substrates even when one small tamoxifen study did not detect an interaction. Quercetin and resveratrol evidence is dominated by healthy-volunteer pharmacokinetics or biomarker outcomes, whereas Withania supportive-care evidence is non-randomised and must be balanced against reported idiosyncratic liver injury. Solubilising and nano-enabled systems can increase exposure or improve preclinical tumour control, yet these gains do not establish clinical benefit and may introduce carrier, infusion, immune, stability and manufacturing risks. A credible programme should begin with authenticated product identity and a quality target product profile, connect critical material and process attributes to exposure and safety, and apply predefined interaction, nonclinical and clinical go/no-go criteria. No reviewed product currently supports routine use to prevent recurrence or improve survival.

Keywords: breast cancer, botanical products, phytochemicals, curcumin, EGCG, nanomedicine, pharmacokinetics, herb-drug interactions, quality by design, translational medicine

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1. INTRODUCTION

Female breast cancer remains one of the most commonly diagnosed malignancies worldwide, and contemporary treatment is selected according to stage, tumour biology, genomic risk, prior therapy, comorbidity and patient preference.[1],[2] This clinical heterogeneity is directly relevant to botanical products: a small change in the exposure of tamoxifen, a taxane, an anticoagulant or a hepatotoxic agent may have different consequences in curative, adjuvant, metastatic and survivorship settings. An ingested or injected botanical product is therefore not a neutral lifestyle choice when it is used during active oncology care.

Integrative oncology also includes non-pharmacological interventions. A 2025 living guideline supports selected exercise, mindfulness, psychological and mind-body approaches for defined patient-reported outcomes in breast-cancer survivors.[3] Those interventions should not be conflated with botanical drug products. A behavioural intervention requires evidence-based

delivery, practitioner competence and outcome monitoring; a chemical or botanical product additionally requires authenticated identity, composition, reproducible manufacture, analytical control, biopharmaceutics, interaction assessment and product-specific clinical testing.

The distinction is not semantic. Complementary-medicine use has been associated with greater refusal of conventional cancer treatment and poorer survival, with treatment refusal substantially mediating the association.[4] The present review therefore evaluates phytochemical and botanical candidates only as potential supportive or adjunctive products that must not delay, replace or reduce evidence-based oncology. “Natural”, “traditional”, “food derived” and “nano-enabled” are descriptors; none establishes efficacy, pharmaceutical quality or compatibility with anticancer therapy.

Several recurrent reasoning errors motivate this review. First, evidence is often transferred from a purified compound to a crude extract, or from one carrier to another, without demonstrating pharmaceutical equivalence. Second, a rise in plasma “total compound” is treated as proof that the pharmacologically active species has increased. Third, cell-line potency or xenograft inhibition is interpreted as clinical efficacy even when the route is intratumoural, the comparator is not dose normalised, or carrier toxicity and whole-body distribution are unknown. Fourth, safety statements are generalised across dose, food state, duration, co-medications and route.

The review asks: for selected phytochemical and botanical products used or proposed in breast-cancer populations, what do human clinical, pharmacokinetic, interaction and safety data establish; what pharmaceutical problems do delivery systems solve or fail to solve; and what minimum quality, nonclinical and clinical package is required for credible translation? Its distinctive contribution is a candidate-level map connecting intended indication, product identity, active moiety, formulation attributes, exposure, interaction liability, clinical endpoints and explicit go/no-go decisions.

2. METHODS

2.1 Review design and scope

This was a structured critical narrative review developed with reference to SANRA and PRISMA-S reporting principles.[5],[6] It was not registered as a systematic review, no pooled meta-analysis was planned, and it does not claim exhaustive retrieval of every preclinical nanocarrier report. The unit of analysis was the defined product-formulation-indication combination rather than the plant name alone. The methods were designed to maximise auditability while preserving a deliberately bounded translational question.

2.2 Candidate-selection framework

The scope was restricted to five case studies. Candidates were retained when at least two of the following were present: (i) human breast-cancer, survivor or high-risk evidence; (ii) human pharmacokinetic, interaction or organ-safety evidence relevant to oncology; and (iii) a breast-cancer formulation or delivery literature. Curcumin/turmeric and EGCG/green-tea extract met all three criteria. Quercetin and resveratrol connected human pharmacokinetics or biomarkers to preclinical delivery. Withania somnifera was retained as a complex-botanical comparator because it has supportive-care evidence in breast-cancer patients and exposes identity, fingerprint and batch-comparability problems that are not captured by single-compound models. The review is not a ranking of all botanical products used by patients.

2.3 Information sources and search update

PubMed/MEDLINE was searched from database inception to 30 July 2026. ClinicalTrials.gov was searched for interventional breast-cancer studies of the five candidates. Official sources included current breast-cancer guidance, the U.S. Food and Drug Administration (FDA), the International Council for Harmonisation (ICH), the European Food Safety Authority (EFSA) and the International Committee of Medical Journal Editors (ICMJE). Backward citation checking was used for pivotal human studies and delivery reports. Full PubMed strings, source dates, candidate logic and selected registry records are provided in Supplementary Tables S1-S4.

2.4 Eligibility and evidence hierarchy

Eligible human evidence included randomised and non-randomised breast-cancer trials, high-risk or survivor studies with explicitly limited endpoints, healthy-volunteer formulation pharmacokinetics, clinically relevant interaction studies and organ-safety reports. Representative preclinical studies had to define the active, carrier, route and at least one formulation characteristic, comparator or in-vivo outcome. Mechanistic-only publications, uncharacterised mixtures, unrelated cancer models presented as direct breast-cancer evidence, retracted records and unverifiable citations were excluded. Registry entries were treated as trial-status evidence, not efficacy evidence.

Evidence was prioritised in the following order: replicated patient-relevant clinical outcomes; randomised clinical evidence with meaningful endpoints; human interaction and organ-safety evidence; formulation-specific human pharmacokinetics; biomarker studies; clinically relevant in-vivo delivery studies; and mechanistic or cell-based evidence. A large, well-conducted negative study was given more inferential weight than a small positive pilot for the same indication. Statistical significance was not treated as clinical importance, and surrogate or exploratory outcomes were labelled as such.

2.5 Critical appraisal and synthesis

Randomised studies were appraised qualitatively for randomisation, allocation concealment where reported, masking, missing data, prespecification, endpoint hierarchy, effect size, precision, follow-up, adverse-event reporting, selective emphasis and sponsor involvement. Non-randomised studies were appraised for confounding, selection, exposure definition, co-interventions, outcome measurement and temporal ambiguity. Human pharmacokinetic studies were assessed for exact product definition, dose, analyte, assay, sampling duration, food state, comparator, period or carryover effects, sample size, confidence intervals and commercial involvement.

Preclinical delivery studies were assessed for route feasibility, dose normalisation, free-active and empty-carrier controls, physicochemical characterisation, pharmacokinetics and biodistribution, randomisation and blinding, repeat-dose safety, batch information, stability and scale-up relevance. The labels in Figure 2 are an author synthesis rather than a formal GRADE rating. Screening and extraction were not performed independently in duplicate; this is explicitly acknowledged as a limitation.

2.6 Translational analysis

For each candidate, the synthesis asked six linked questions: What is the final product? Which molecular species or mixture is expected to mediate activity? Can that species be measured reproducibly in the dosage form and biological matrix? Does the formulation create a clinically relevant exposure or target-engagement change? What interaction, organ or carrier risks accompany that change? Is there a patient-relevant endpoint capable of establishing net benefit? This sequence prevents a formulation metric from substituting for pharmacology or clinical proof.

3. DEFINITIONS AND CLINICAL-REGULATORY BOUNDARY

3.1 Product nomenclature and pharmaceutical equivalence

A phytochemical is a chemically defined or analytically measurable plant-derived constituent. A botanical product is a preparation derived from one or more plant materials and may contain multiple active or marker constituents. A standardised

extract is standardised only to the extent that its species, plant part, extraction process, marker range, chromatographic fingerprint, contaminants, stability and batch comparability are documented. FDA botanical guidance recognises that complex mixtures may require a "totality of evidence" approach, but it does not remove the need for quality control or clinically comparable batches.[7]

Pharmaceutical equivalence cannot be assumed between turmeric powder, a curcuminoid extract, a piperine-containing capsule, a micelle, a phospholipid complex and an intravenous liposome. The same principle applies to green tea as a beverage, a decaffeinated catechin mixture and purified EGCG; to free quercetin and a lecithin complex; and to different Withania species, plant parts and extraction solvents. A formulation claim applies to the studied product and manufacturing process, not automatically to another product bearing the same plant name.

3.2 Nominal dose, measured exposure and active moiety

The nominal milligram dose is not the same as delivered active moiety. For poorly soluble polyphenols, oral absorption may be dissolution limited, yet the measured plasma signal may consist predominantly of glucuronide or sulfate conjugates. For nanocarriers, "total drug" may combine free, protein-bound and carrier-associated fractions with different tissue access and toxicity. For complex botanicals, one marker can demonstrate consistency without proving that the marker is the sole pharmacologically active constituent. A meaningful programme must therefore predefine the analyte, biological matrix, sampling window and exposure metric that will be linked to pharmacodynamic activity.

A nanocarrier is an engineered delivery system whose structural and size-dependent properties can alter release, absorption, biodistribution, clearance or safety. FDA guidance emphasises product-specific assessment of nanomaterial attributes, while liposome guidance separates encapsulated and unencapsulated drug, release, leakage, pharmacokinetics and CMC controls.[8],[9] These distinctions are especially important when exposure enhancement is promoted as a benefit: a carrier may increase systemic or organ exposure without improving tumour target engagement or therapeutic index.

3.3 Intended clinical role and evidence threshold

The word "adjunctive" should describe an intended development role rather than an established benefit. Three conditions are necessary: standard therapy is not delayed or replaced; the indication and endpoint are explicit; and the final clinical product is compositionally and biopharmaceutically linked to the evidence. A short-duration product intended to reduce radiodermatitis, a chronic oral product used during endocrine therapy and an intravenous product combined with chemotherapy require different risk tolerances, interaction programmes and clinical endpoints.

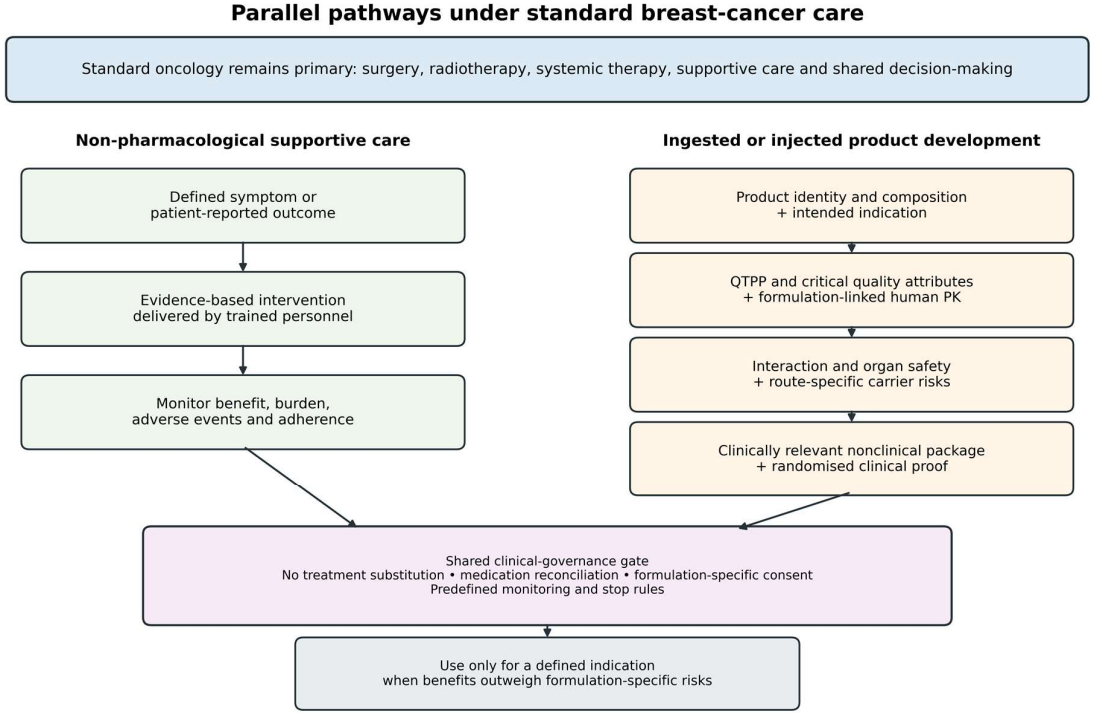

Figure 1: Parallel pathways for non-pharmacological supportive care and candidate phytochemical or botanical products in breast cancer. QTPP, quality target product profile; CQA, critical quality attribute; PK, pharmacokinetics. The product pathway is author proposed and should be adapted to route, indication and regulatory classification.

4. HUMAN CLINICAL EVIDENCE BY CANDIDATE

4.1 Curcumin and turmeric products

Curcumin is poorly water soluble, chemically labile under some conditions and extensively conjugated after oral administration. Its clinical literature demonstrates why product and endpoint discipline are essential. A 30-patient pilot reported less severe radiation dermatitis with 6 g/day of a defined curcuminoid product, but the much larger multicentre double-blind trial of 686 patients did not detect a clinically meaningful reduction at the end of radiotherapy; pain and quality-of-life outcomes were also not improved.[10],[11] The large negative study should dominate inference for that oral product and indication rather than being averaged narratively with the pilot.

A small 2025 triple-blind trial addressed a different supportive question: prevention of ultrasound-defined fatty-liver progression during the first six months of tamoxifen. Among 44 patients, worsening of fatty-liver grade was reported less often with 500 mg/day curcumin than placebo.[12] The finding is clinically interesting but remains preliminary because the sample was small, imaging was a surrogate rather than a clinical liver endpoint, the exact formulation and exposure-response

relationship require scrutiny, and the result does not neutralise separate evidence that some curcumin products can reduce endoxifen exposure.

Anticancer efficacy findings are inconsistent. In a 150-patient double-blind study, weekly intravenous CUC-1 plus paclitaxel increased short-term objective response four weeks after treatment, but follow-up was brief, attrition affected completed-treatment analyses, and time-to-event evidence was not sufficiently mature to establish durable benefit.[13] By contrast, an open-label phase II study adding oral curcumin to docetaxel stopped for futility after an interim analysis of 37 participants; objective response and time-to-event endpoints did not favour the curcumin arm.[14]

A 2025 randomised study of 120 patients reported higher response rates and favourable time-to-event outcomes with a curcuminoid-piperine product added to chemotherapy.[15] The publication substantially increases the need for independent replication, not the certainty of routine use. The product included a bioenhancer with known interaction potential; the regimen, tumour subtypes, allocation process, endpoint hierarchy, missing-data handling and chemotherapy balance must be evaluated together; and the study should be replicated with prespecified pharmacokinetic and safety margins. Taken together, curcumin has testable signals, but no replicated evidence of recurrence or survival benefit across clinically comparable products.

4.2 EGCG and concentrated green-tea extract

No reviewed trial established that purified EGCG or concentrated green-tea extract improves breast-cancer treatment efficacy. The large Minnesota prevention trial enrolled postmenopausal women with high breast density and primarily addressed risk biomarkers and safety, not treatment or recurrence. In the liver-safety analysis, moderate-or-worse liver abnormalities occurred substantially more often with concentrated extract than placebo.[16] EFSA concluded that supplemental green-tea catechins, particularly exposures at or above 800 mg/day EGCG, are associated with transaminase elevations and that a universally safe supplemental dose could not be identified.[17]

The prevention context matters. A biomarker change in high-risk participants does not establish reduced cancer incidence, and a safety estimate in otherwise healthy women may underestimate vulnerability during polypharmacy, chemotherapy, liver metastases or pre-existing hepatic disease. Formulations that increase catechin exposure should therefore incorporate food-state control, liver-test eligibility, stopping rules, symptom education and an explicit maximum exposure rather than treating bioavailability as an unqualified advantage.

4.3 Quercetin

Quercetin has low aqueous solubility, extensive conjugation and variable oral absorption, but no direct breast-cancer efficacy trial was identified in the selected human corpus. A branded lecithin-based phytosome increased plasma exposure in 12 healthy volunteers, demonstrating a formulation effect rather than clinical benefit.[18] The study was funded by the manufacturer and all listed authors were employees; this does not invalidate the result, but it raises the importance of independent replication, transparent assay methods and product comparability. A development claim should specify whether total quercetin, free aglycone or a conjugate pool is the relevant exposure.

4.4 Resveratrol

Oral resveratrol is absorbed but rapidly metabolised, producing low systemic exposure to unchanged parent compound.[19] In women at increased breast-cancer risk, a 39-participant study reported changes in selected promoter-methylation biomarkers rather than incidence, recurrence, response or survival.[20] Biomarker modulation can justify mechanistic work but cannot define a therapeutic indication without evidence that the marker is reproducibly linked to a clinically meaningful outcome.

Dose-escalation pharmacokinetics in healthy volunteers showed that even gram-level oral doses produced parent resveratrol concentrations below many concentrations used in cell studies, while sulfate and glucuronide metabolites were substantially more abundant.[21] A delivery programme must therefore specify whether the parent, a metabolite, local gastrointestinal exposure or a reversible tissue conjugate pool is expected to mediate activity. Without that active-moiety hypothesis, higher "total resveratrol" can be analytically impressive but pharmacologically uninterpretable.

4.5 Withania somnifera

A prospective open-label non-randomised study of 100 breast-cancer patients reported lower chemotherapy-related fatigue and better quality-of-life measures with a root extract dosed at 2 g every eight hours.[22] The study was vulnerable to selection, expectation and performance bias; product composition and concomitant care limit generalisability; and the exploratory overall-survival difference was not statistically significant. The report is hypothesis generating for supportive care, not evidence for tumour control.

Withania also illustrates why a long history of use cannot substitute for product-specific safety surveillance. Case series from the United States, Iceland and India describe a reproducible pattern of idiosyncratic liver injury, often cholestatic or mixed, with prolonged jaundice and severe outcomes in some patients with pre-existing liver disease.[23],[24] These reports do not quantify population incidence, but they establish a plausible clinical hazard that should influence exclusion criteria, baseline liver assessment, stopping rules and post-marketing pharmacovigilance for any oncology product.

4.6 Cross-candidate interpretation: why evidence cannot be pooled by plant name

Across the five candidates, the dominant methodological problem is clinical and pharmaceutical heterogeneity rather than a simple shortage of positive trials. Products carrying the same familiar name can differ in extraction solvent, marker composition, impurity profile, crystalline form, particle size, carrier, bioenhancer, food instructions and route. These differences can change dissolution, absorption, parent-to-metabolite ratios, interaction potential and organ exposure. Consequently, a meta-analysis or narrative statement that pools "curcumin", "green tea", "quercetin", "resveratrol" or "ashwagandha" without product-level stratification risks combining non-equivalent interventions. The appropriate unit of inference is the defined investigational product used in a defined population and regimen, not the botanical name alone.

Endpoint hierarchy is equally important. Radiation dermatitis, fatigue, ultrasound-defined fatty-liver grade, methylation biomarkers, response rate, progression-free survival and overall survival answer different questions and should not be arranged on a single continuum of "anticancer effect". Supportive-care endpoints can be clinically valuable when measured with validated instruments and prespecified minimum important differences, but they do not imply tumour control. Biomarkers can support biological plausibility or dose selection, but a biomarker must be analytically valid, responsive to the intervention and credibly linked to patient benefit before it can serve as a surrogate. Objective response in metastatic disease may justify further study, yet it remains vulnerable to assessment timing, missing imaging, post-randomisation exclusions and imbalance in concurrent systemic therapy.

The small-study problem is amplified by selective publication and flexible analysis. Several positive reports are single-centre, use modest samples, include multiple secondary outcomes, provide limited product characterisation or emphasise per-protocol findings. A large negative multicentre trial should therefore not be diluted by counting it as one study against several small positive studies. The synthesis in this review privileges prespecified primary endpoints, intention-to-treat

analyses, confidence intervals, clinically interpretable effect sizes, complete adverse-event reporting and consistency across independently manufactured batches. Absence of statistical significance is not proof of equivalence, but a non-significant result with wide intervals cannot be converted into evidence of benefit by highlighting a favourable subgroup or later time point.

Future trials should use a core product dossier alongside the clinical protocol. At minimum, the dossier should identify botanical source or chemical active, manufacturing process, quantitative marker or active range, fingerprint, impurities, dissolution or release, stability, packaging, batch numbers and concomitant bioenhancers. The protocol should define interaction exclusions, food state, adherence, rescue treatments, endpoint hierarchy, clinically important difference, missing-data strategy and product-specific safety stopping rules. Publishing this information would allow later reviewers to distinguish replication from superficial similarity and would make negative trials scientifically useful by showing whether pharmacologically relevant exposure was actually achieved.

Table 1: Direct human clinical evidence and critical appraisal. Appraisal is author proposed and is not a formal Cochrane RoB 2 or GRADE assessment.

Product / study	Design and population	Exact product and dose	Endpoint / follow-up	Quantitative result	Safety	Qualitative appraisal	Funding / conflicts
Curcumin; radiodermatitis pilot[10]	Randomised, double-blind; n=30 receiving breast radiotherapy	Curcumin C3 Complex; 6 g/day	Dermatitis severity at end of radiotherapy	Mean RDS 2.6 vs 3.4; p=0.008; moist desquamation 28.6% vs 87.5%; p=0.002	Short exposure; small sample	High imprecision; pilot effect not replicated in larger trial	Product donated; report sponsor role
Curcumin; radiodermatitis[11]	Multisite randomised, double-blind; n=686	Oral curcumin 6 g/day vs placebo	Primary dermatitis score; symptoms and quality of life	Coefficient 0.044 (95% CI -0.101 to 0.188); p=0.552; no significant pain or quality-of-life benefit	No major product-specific signal reported	Strongest direct evidence for this indication; negative primary result	Public/academic network; full funding statement reported
Curcumin; tamoxifen-associated fatty liver[12]	Triple-blind randomised placebo-controlled; n=44 ER-positive patients starting tamoxifen	Curcumin 500 mg/day for 6 months	Ultrasound-defined NAFLD grade and laboratory measures	Worsened NAFLD grade 13.6% vs 54.5%; p=0.03	No curcumin-related adverse effects reported	Promising but small; imaging surrogate, short duration and formulation/exposure details limit inference	Single-centre; verify full product and funding details
Intravenous curcumin plus paclitaxel[13]	Randomised, double-blind; n=150 advanced/metastatic breast cancer	CUC-1 300 mg IV weekly plus paclitaxel 80 mg/m² for 12 weeks	Objective response; 24-week safety and time-to-event follow-up	ITT objective response 51% vs 33%; p<0.01 at 4 weeks after treatment	No major overall safety difference reported; fatigue favoured curcumin	Some/high concerns: short follow-up, attrition, selective endpoint emphasis and commercial context	BRIU/Phytomed affiliations; commercial relationships material
Oral curcumin plus docetaxel[14]	Multicentre randomised open-label phase II; interim n=37	Oral curcumin plus docetaxel vs docetaxel	Objective response, survival and progression outcomes	Objective response 55.6% vs 73.7%; p=0.25; no survival or progression benefit; stopped for futility	Reported safe in tested regimen	Directly negative but imprecise because of early stopping and small sample	Academic multicentre; confirm full sponsor role
Curcuminoids plus piperine plus chemotherapy[15]	Randomised study; n=120 locally advanced/metastatic disease	95% curcuminoids 1 g/day plus 1% piperine for 12-24 weeks	Response and time-to-event outcomes	Publication reports higher response and favourable time-to-event outcomes	Publication reports tolerability; detailed adverse-event extraction is essential	Requires independent replication, allocation and endpoint audit, and product-specific interaction study	No specific funding in abstract; product provenance must be fully reported
Resveratrol biomarker study[20]	Randomised biomarker trial; n=39 women at increased risk	Trans-resveratrol 5 or 50 mg twice daily for 12 weeks	Breast-tissue promoter methylation	Selected biomarker associations; no cancer clinical outcome	Short exposure; not a treatment-safety conclusion	High indirectness and imprecision for prevention or treatment	Assay multiplicity and funding should remain visible
Withania root extract[22]	Prospective open-label non-randomised; n=100 during chemotherapy	Root extract 2 g every 8 hours	Fatigue, quality of life; exploratory 24-month survival	Symptom signals; overall survival 72% vs 56%, p=0.176	Product-specific tolerability reported; systematic hepatic monitoring unclear	High risk of confounding, performance and measurement bias	Product standardisation and sponsor role require full reporting

5. HUMAN PHARMACOKINETICS, INTERACTIONS AND FORMULATION SAFETY

5.1 Curcumin and turmeric: exposure and interaction are formulation specific

Tamoxifen depends on CYP2D6-mediated formation of the active metabolite endoxifen. In a crossover study, curcumin 1,200 mg three times daily reduced endoxifen AUC by 7.7% (95% CI -15.4% to 0.7%; p=0.07), whereas curcumin plus piperine 10 mg three times daily reduced it by 12.4% (95% CI -21.9% to -1.9%; p=0.02).[25] The clearer piperine-containing signal demonstrates that “bioenhancement” can be undesirable when it changes a co-administered anticancer drug. The point estimate with curcumin alone also argues against claiming equivalence merely because conventional significance was not reached in a very small study.

A prospective sequential-cycle study of 60 breast-cancer patients found that 2 g/day turmeric reduced model-estimated paclitaxel AUC and maximum concentration by 7.7% and 12.1%, respectively.[26] The authors considered the magnitude unlikely to be clinically important, but the non-randomised period design, model-derived estimates and single product do not establish safety for other formulations. For narrow-therapeutic-index or exposure-sensitive oncology drugs, the acceptable no-effect boundary should be prespecified rather than inferred after observing the result.

Healthy-volunteer studies demonstrate large formulation effects but also analytic complexity. In a 12-participant crossover comparison of eight oral formulations, micelles and a gamma-

cyclodextrin complex markedly increased measured exposure relative to native curcumin, but free curcumin was not detected and the plasma signal was predominantly conjugated.[27] A separate 15-participant crossover study reported higher Cmax and AUC with micellar curcumin but no effect in the tested ex-vivo inflammatory assay.[28] Cross-study fold comparisons are invalid because product, dose, analyte, deconjugation method, food state, sampling and comparator differ.

Parenteral delivery changes both the magnitude and type of risk. In a phase I study of 32 patients with advanced solid tumours, weekly liposomal curcumin reached a maximum tolerated dose of 300 mg/m² over six hours; haemolysis and haemoglobin reductions were clinically important concerns, and no objective RECIST responses were reported.[29] Higher systemic delivery therefore created an infusion and red-cell safety burden without demonstrating antitumour benefit. Any parenteral curcumin programme requires separate assays for total, free and encapsulated drug, haemocompatibility, release kinetics and carrier-related reactions.

5.2 EGCG: food state, nonlinear exposure, hepatic risk and transporters

EGCG exposure is sensitive to dose and food state. In healthy volunteers, fasting administration of a defined catechin mixture increased free EGCG peak concentration more than threefold relative to administration with a light meal and also increased nausea at the highest dose.[30] Ten days of purified EGCG showed more-than-dose-proportional exposure at 800 mg/day, suggesting saturation of elimination or recirculation at the upper dose.[31] These findings explain why the same nominal dose may have different safety profiles depending on formulation and instructions for use.

In 14 tamoxifen-treated patients, a defined green-tea regimen containing 300 mg EGCG twice daily did not detect a material change in endoxifen exposure.[32] This result applies to that small study, product and dosing condition. It is not evidence that all green-tea products are interaction free. Green tea or EGCG has reduced exposure to transporter substrates such as nadolol and fexofenadine in healthy-volunteer studies, supporting an intestinal transporter mechanism that is not captured by CYP-only screening.[33],[34] A risk-based programme should therefore consider uptake and efflux transporters as well as metabolic enzymes.

5.3 Quercetin and resveratrol: formulation gains and interaction uncertainty

The quercetin-phytosome study establishes that complexation with lecithin can substantially change oral exposure, but the clinical relevance remains undefined because only 12 healthy volunteers were studied and no pharmacodynamic or oncology endpoint was measured.[18] Repeated quercetin altered diclofenac pharmacokinetics in another 12-participant study, consistent with CYP2C9 modulation.[35] A final oncology product should therefore undergo a staged interaction programme: composition-confirmed in-vitro enzyme and transporter testing, model-informed interpretation where feasible, and a clinical study when predicted exposure changes or the co-medication risk justify it.

Resveratrol shares the active-moiety problem. Single-dose and dose-escalation studies show low parent exposure and much higher conjugate concentrations.[19],[21] Repeated 500 mg/day resveratrol approximately doubled diclofenac exposure in a small sequential healthy-volunteer study, indicating clinically relevant CYP2C9 inhibition under the tested conditions.[36] This indirect interaction does not predict the effect on every anticancer drug, but it refutes the assumption that a dietary polyphenol is pharmacokinetically inert.

5.4 Withania and complex-botanical safety

For Withania, the absence of a well-defined human pharmacokinetic programme is itself a development gap. Withanolides are often used as markers, but commercial products can differ in species, plant part, extraction, marker profile and co-ingredients. The reported liver-injury phenotype is idiosyncratic rather than clearly dose dependent, which makes routine short healthy-volunteer studies insufficient to exclude risk.[23],[24] Product development should include authenticated raw material, orthogonal chemical identification, targeted and untargeted fingerprints, exclusion of adulterants, baseline hepatic criteria, symptom-triggered testing and active pharmacovigilance.

5.5 Practical interpretation of a negative interaction study

A small study that does not detect an interaction should not be described as proving safety. Interpretation should report the confidence interval around the exposure ratio, the prespecified no-effect range, within-subject variability, genotype or phenotype distribution, adherence, food state, final product and duration. FDA clinical interaction guidance provides a risk-based framework for CYP- and transporter-mediated studies.[37] In oncology, the consequence of decreased exposure may be loss of efficacy, whereas increased exposure may amplify neutropenia, neuropathy, bleeding, QT effects or hepatic injury; the clinically relevant direction depends on the victim drug.

Table 2: Human pharmacokinetic, interaction and organ-safety evidence. Fold changes are study specific and should not be compared across products.

Product / question	Design / population	Product and dose	Analyte / endpoint	Result	Interpretation	Sponsor / conflicts
Curcumin ± piperine with tamoxifen[25]	16 evaluable breast-cancer patients; crossover	Curcumin 1,200 mg TID; piperine 10 mg TID	Endoxifen AUC and Cmax	-7.7% AUC with curcumin (p=0.07); -12.4% with piperine (p=0.02)	Formulation-specific interaction; piperine-containing products are higher priority	No declared competing interest
Turmeric with paclitaxel[26]	60 breast-cancer patients; sequential treatment cycles	Turmeric 2 g/day for 21 days	Modelled paclitaxel PK	AUCinf -7.7%; Cmax -12.1%	Magnitude may be small, but period design and model uncertainty limit generalisation	Academic; supplement and product assay should be verified
Eight curcumin formulations[27]	12 healthy volunteers; randomised crossover	Single 207 mg curcuminoid dose across formulations	24-hour plasma exposure to analytes	Micelles 57-fold and gamma-cyclodextrin 30-fold vs native in study-specific analysis	Predominantly conjugates; not efficacy; cross-product ranking invalid	TISSO/AQUANOVA relationships reported
Micellar curcumin[28]	15 healthy volunteers; crossover	105 mg/day for 7 days	Cmax/AUC and ex-vivo assay	Cmax approximately 39-fold and AUC approximately 14-fold vs native; no ex-vivo anti-inflammatory effect	Small PK study; exposure did not establish pharmacodynamic benefit	AQUANOVA supplied product; authors reported no conflict
Liposomal curcumin[29]	Phase I; 32 advanced solid-tumour patients	IV 100-300 mg/m² weekly	MTD, PK and response	MTD 300 mg/m² over 6 hours; no objective responses	Haemolysis and haemoglobin decrease; infusion and CMC burden	SignPath funded; one author company executive
Green-tea extract with tamoxifen[32]	14 breast-cancer patients; crossover/steady state	1 g BID extract containing 300 mg EGCG	Endoxifen AUC, Cmax and trough	AUC -0.4% (95% CI -8.6 to 8.5); p=0.92	Did not detect interaction; small and product specific	Academic; product supply should be reported
EGCG food effect[30]	30 healthy volunteers; randomised crossover	Polyphenon E containing 400, 800 or 1,200 mg EGCG	Free and total catechin exposure	Fasting increased free EGCG Cmax >3.5-fold; nausea more frequent at high fasted dose	Administration instructions are a CQA-linked safety variable	NCI-supported clinical study
Repeated purified EGCG[31]	36 healthy men; randomised double-blind	200, 400 or 800 mg/day for 10 days	Plasma kinetics and tolerability	More-than-dose-proportional exposure at 800 mg/day	Potential capacity-limited elimination; short duration cannot define long-term safety	Industry research setting
Green-tea extract safety[16],[17]	1,021 women with normal baseline liver tests; safety analysis plus authoritative review	Concentrated extract; prevention setting	Moderate-or-worse liver abnormalities	26/513 (5.1%); odds ratio 7.0 vs placebo	Hepatic monitoring and stopping rules required	NIH-supported trial; EFSA independent opinion
Green tea and transporter substrates[33],[34]	Small healthy-volunteer crossover studies	EGCG-rich or green-tea extract	Nadolol and fexofenadine exposure	Marked reductions in substrate exposure under tested conditions	Transporter effects can occur despite negative CYP-focused studies	Product and food-state specific
Quercetin phytosome[18]	12 healthy volunteers; crossover	Branded lecithin complex	Plasma quercetin exposure	Up to approximately 20-fold increase	No breast-cancer endpoint; small study	Indena funded; all authors employees
Quercetin-diclofenac interaction[35]	12 healthy volunteers	Quercetin 500 mg BID for 10 days	Diclofenac PK / CYP2C9 activity	Significant exposure alteration reported	Indirect to oncology; final-product studies required	Full conflict statement should be checked
Oral resveratrol[19],[21]	Healthy-volunteer single-dose and dose-escalation studies	Oral resveratrol up to gram doses	Parent and metabolite exposure	High absorption, low parent bioavailability and higher conjugate exposure	Active moiety and tissue target engagement remain uncertain	Early phase pharmacology studies
Resveratrol-diclofenac interaction[36]	12 healthy volunteers; sequential study	Resveratrol 500 mg/day for 10 days	Diclofenac PK / CYP2C9	Diclofenac AUC approximately doubled	Clinically relevant indirect interaction signal	Small single-centre study; requires product-specific confirmation
Withania-associated liver injury[23],[24]	International and Indian case series	Single-ingredient or analytically evaluated products	Clinical phenotype and causality	Predominantly cholestatic/mixed injury; severe outcomes in vulnerable patients	Incidence unknown, but reproducible hazard supports baseline assessment and stopping rules	Independent clinical case ascertainment

6. PRECLINICAL DELIVERY SYSTEMS AND THE TRANSLATIONAL GAP

6.1 What delivery platforms can solve

Micelles, cyclodextrin complexes, phospholipid complexes, polymeric nanoparticles, nanoemulsions, liposomes and solid-lipid systems can address discrete pharmaceutical problems: apparent solubility, dissolution rate, chemical stability, intestinal transfer, controlled release, residence time, intracellular entry or co-delivery. They do not solve an undefined active moiety, an invalid biological target, an interaction liability, a clinically infeasible route or the absence of a meaningful endpoint. Carrier selection should begin with the QTPP and limiting mechanism rather than with the novelty of the material.

For oral products, the useful question is not whether a nanoparticle can enter a cancer cell in vitro, but whether the dosage form remains stable through manufacture and storage, disperses reproducibly in gastrointestinal fluids, survives or intentionally releases during digestion, produces a predictable parent/metabolite exposure profile, and remains compatible with food and co-medications. For parenteral products, the key questions include free-drug leakage, dilution stability, protein binding, haemocompatibility, complement activation, infusion rate, organ distribution, persistence and clearance.

6.2 What representative breast-cancer studies show

Representative breast-cancer studies demonstrate technical feasibility across curcumin micelles, folate-targeted EGCG-PLGA nanoparticles, quercetin polymeric nanoparticles, curcumin solid-lipid nanoparticles and a resveratrol lipid system.[38],[39],[40],[41],[42] Recurrent limitations include intratumoural or peritumoural dosing, cell-only evaluation, short xenograft follow-up, incomplete dose normalisation, absent empty-carrier controls, limited pharmacokinetics and biodistribution, and little information on repeated manufacture or stability. Particle size and drug loading are descriptors, not a cross-product efficacy relationship.

6.3 Tumour delivery, organ exposure and biological identity

Cancer nanomedicine has produced clinically useful products, but translation is constrained by heterogeneous tumour perfusion, vascular access, extracellular matrix, stromal and immune barriers, mononuclear-phagocyte uptake and patient-to-patient variation.[43],[44] The frequently cited low mean delivery to tumours should not be interpreted as a universal constant: later analyses show substantial dependence on particle, model, route, sampling time, tumour type and denominator.[45],[46],[47] Whole-body distribution and therapeutic index are therefore more informative than tumour accumulation alone.

Once a particle contacts biological fluids, adsorbed proteins and other biomolecules can change its effective biological identity. Protein-corona results are highly sensitive to sample preparation and analytical workflow; a multicentre study demonstrated that standardisation materially improved inter-laboratory agreement.[48] This is not an academic detail. Corona composition can affect cellular uptake, clearance, complement activation, ligand accessibility and assay interpretation, and it can differ between healthy animals, tumour-bearing animals and patients receiving chemotherapy.

6.4 Reproducibility and minimum reporting

MIRIBEL recommends minimum reporting across material characterisation, biological characterisation and experimental protocols, while ARRIVE 2.0 defines essential reporting for in-vivo studies.[49],[50] For botanical nanocarriers, the minimum dataset should additionally include source and assay of the active, batch number, marker or impurity profile, free versus encapsulated fraction, recovery after separation, stability during the experiment, vehicle and empty-carrier controls, dose normalisation, randomisation, blinding, sample-size rationale and complete adverse observations. Without these data, apparent superiority may reflect dose, vehicle, analytical recovery or selection bias rather than delivery.

6.5 Route and scale-up realism

A route used only to prove mechanism can be scientifically useful, but it should not be described as translationally ready. Intratumoural and peritumoural injections bypass absorption and systemic distribution and may exaggerate local exposure. Conversely, an intravenous formulation can require sterile manufacture, endotoxin and particulate control, infusion infrastructure and management of acute reactions. Scale-up may alter mixing energy, particle-size distribution, drug loading, release and residual solvent; a “same composition” batch is not necessarily a comparable product unless critical attributes are bridged analytically and biopharmaceutically.

6.6 Requirements for a translationally informative preclinical package

A decision-enabling preclinical package should separate formulation performance from pharmacological efficacy. Physicochemical characterisation should be performed on the actual dosing batch and after dilution into the administration medium, because serum proteins, salts, pH and shear can change size distribution, aggregation, release and free-active fraction. The package should report assay recovery and mass balance, not only encapsulation efficiency. Free active, empty carrier, physical mixture and vehicle controls are needed where feasible, with doses normalised by active content and administration schedule. A carrier that appears superior only because it delivers a larger effective dose has not demonstrated a delivery advantage.

Pharmacokinetic and biodistribution studies should quantify the molecular species relevant to the proposed mechanism. For oral products this may require parent, major conjugates and deconjugated total analyte under fed and fasted conditions. For parenteral nanocarriers, plasma and tissue assays should distinguish free or releasable active from carrier-associated and total active using validated separation procedures. Sampling must cover distribution, release and elimination phases, and tissue concentrations should be interpreted with blood-volume correction and recovery controls. Fluorescent carrier labels can be useful for localisation, but label signal is not a substitute for quantifying intact carrier or pharmacologically available active.

Efficacy experiments should be randomised, blinded where practicable and prospectively powered for a prespecified primary outcome. Both sexes should be considered when biologically relevant, and models should reflect the intended molecular subtype, immune context, metastatic site and treatment line. Testing a delivery system only in a rapidly growing subcutaneous xenograft provides limited information about micrometastatic, bone, brain or immune-mediated disease. Standard-of-care combination arms are essential when the intended clinical use is adjunctive. Follow-up should be long enough to identify rebound growth and delayed toxicity, and full individual-level data should be retained for transparent reanalysis.

Safety studies must be route and product specific. Oral programmes require gastrointestinal tolerance, liver monitoring and interaction assessment at clinically relevant repeated exposure. Intravenous programmes additionally require haemocompatibility, complement activation, cytokine response, infusion reaction monitoring, organ histopathology, immunotoxicity, repeated-dose recovery and device or diluent compatibility. A no-observed-adverse-effect level alone is insufficient when the therapeutic hypothesis depends on chronic administration or when the carrier accumulates in liver, spleen or mononuclear phagocyte compartments. Translation should proceed only when the exposure associated with efficacy is separated from the exposure associated with carrier or active-moiety toxicity by a credible margin.

Table 3: Representative breast-cancer delivery studies selected to illustrate recurring translational barriers; this is not an exhaustive inventory.

Platform	Active / carrier	Reported formulation attributes	Model / route	Claimed result	Principal translational limitation
POCA4C6-curcumin micelles[38]	Curcumin; phosphorylated calixarene micelle	3.86 ± 0.32 nm; PDI 0.125 ± 0.078; loading 17.10 ± 1.25%	BT-549 cells and TNBC xenografts; intratumoural	Growth inhibition versus controls	Clinically impractical route; short safety window; carrier contribution and systemic PK unresolved
Folate-EGCG PLGA nanoparticles[39]	EGCG; ligand-targeted PLGA	169 ± 5.6 nm; PDI 0.063 ± 0.04; loading 3.33 ± 0.28%; encapsulation 52.3 ± 2.05%	MDA-MB-231/MCF-7 cells and xenografts	Improved targeting/activity in model	Ligand density, off-target folate uptake, systemic PK, stability, repeat-dose safety and scale-up needed
MPEG-PLA quercetin nanoparticles[40]	Quercetin; polymeric nanoparticle	155.3 ± 3.2 nm; PDI 0.20 ± 0.05; zeta -3.14 mV; loading 5.3 ± 1.1%	MDA-MB-231 xenograft; peritumoural	Sustained release and tumour-growth inhibition	Peritumoural route, modest loading, biodistribution and chronic safety limit translation
Curcumin solid-lipid nanoparticles[41]	Curcumin; cholesterol-based solid-lipid system	166.4 ± 3.5 nm; encapsulation 76.9 ± 1.9%; QbD optimisation	MDA-MB-231 in vitro	Uptake, cytotoxicity and apoptosis	Cell-only evidence; no in-vivo PK, biodistribution, systemic safety or scale-up validation
TPGS-resveratrol solid-lipid nanoparticles[42]	Resveratrol; TPGS-containing lipid carrier	Approximately 203 nm; zeta -25.6 ± 1.3 mV; loading 32.4 ± 2.6%	Drug-resistant breast-cancer cells and xenografts	Improved tumour inhibition versus free active	Excipient contribution, dose normalisation, route, long-term safety and batch reproducibility require clarification

7. PRODUCT DEVELOPMENT: FROM QTPP TO CLINICAL PROOF

7.1 Begin with a quality target product profile

The quality target product profile (QTPP) should define the intended indication, patient population, route, dose, duration, release behaviour, exposure target, storage, administration setting and safety constraints. A product for short-term radiodermatitis prevention has a different QTPP from a chronic product used during endocrine therapy or an intravenous carrier combined with chemotherapy. ICH Q8(R2), Q9(R1), Q10, Q12 and Q13 provide the development, quality-risk, pharmaceutical-system, lifecycle and manufacturing framework.[51],[52],[53],[54],[55]

The QTPP should include a clinical "non-interference" requirement where the product is used with curative or disease-controlling therapy. For example, an oral curcuminoid product intended during tamoxifen could specify a prespecified margin for endoxifen exposure, a prohibition or defined limit for piperine, a liver-safety plan, acceptable pill burden and a minimum adherence target. A parenteral product would additionally specify infusion time, free-drug fraction, haemocompatibility, reaction rate, osmolality, sterile presentation and device compatibility.

7.2 Raw materials and critical material attributes

For a chemically defined active, critical material attributes include identity, purity, stereochemistry where relevant, solid state, particle form, degradants, residual solvents and water content. For a botanical extract, they additionally include authenticated species and plant part, geographic and cultivation controls, harvest and storage, extraction solvent and ratio, marker range, chromatographic fingerprint, pesticides, elemental impurities, microbial burden, mycotoxins and adulterants. FDA botanical guidance permits flexibility for complex mixtures but expects control of raw materials, process and clinical-batch consistency.[7]

Botanical variability cannot be solved by measuring one marker alone. A marker may support identity or consistency while failing to represent pharmacological activity. Orthogonal testing can combine macroscopic or microscopic identity, DNA methods where appropriate, chromatographic or spectroscopic fingerprints and quantitative markers. Where the active constituents are unknown, clinical-batch comparability should rely on a justified multivariate fingerprint and process controls rather than a single nominal withanolide or curcuminoid percentage.

7.3 Formulation variables, critical process parameters and control strategy

Carrier materials may introduce molecular-weight distribution, lipid composition, oxidation, ligand density, residual monomer, catalyst or solvent, endotoxin and functional excipient variability. Critical process parameters may include mixing order, temperature, pH, energy input, solvent removal, filtration, homogenisation, extrusion, sterilisation, lyophilisation, fill conditions, hold time and redispersion. The relationship between these parameters and product CQAs should be evaluated through development studies or design-of-experiments rather than by selecting a single "optimised" batch from multiple trials.

Product CQAs may include particle-size distribution and polydispersity, morphology, surface charge where mechanistically relevant, active loading, encapsulation efficiency, free and carrier-associated fractions, release, dissolution, aggregation, osmolality and pH, sterility, endotoxin, visible and subvisible particles, redispersibility, container interaction and in-use stability. A target value without an acceptance range and validated method is not a control strategy.

7.4 Analytical and bioanalytical method lifecycle

Analytical procedures should be stability indicating and developed and validated using ICH Q14 and Q2(R2) principles.[56],[57] For multicomponent botanicals, assay specificity may require a combination of targeted quantitation, fingerprint similarity, mass balance and orthogonal impurity tests. For nanocarriers, separation of free from associated active can itself disturb the equilibrium; method recovery, dilution, filtration, centrifugation and storage should therefore be validated against the intended question.

Human bioanalysis should follow ICH M10 principles and distinguish the relevant parent, metabolite and formulation fractions.[58] Sample collection must account for rapid conjugation, ex-vivo instability, light sensitivity and adsorption to tubes. Enzymatic deconjugation can estimate "total" analyte but may obscure the actual circulating species. A robust PK report should show both the measured species and the rationale linking that species to pharmacological activity.

7.5 Stability, packaging and in-use performance

Stability studies should address the attributes most likely to change clinical performance, not only assay potency. ICH Q1A(R2) and Q1B provide general stability and photostability principles.[59],[60] Curcumin and resveratrol products may

require light and oxygen control; catechins are susceptible to oxidation; phospholipids and some polymers can generate degradants; and botanical powders can gain moisture or support microbial growth. For reconstituted, diluted or infusion products, in-use stability should evaluate particle size, leakage, precipitation, potency, degradants and compatibility over the complete administration period.

Container-closure selection is part of product design. Moisture and oxygen transmission, sorption, leachables, headspace, light protection and dose-delivery accuracy can affect exposure. For complex extracts, long-term stability should include fingerprint and marker drift as well as microbiological and contaminant controls. Elemental-impurity risk should be assessed using source, process and excipient knowledge, with ICH Q3D(R2) as a risk-based reference.[61]

7.6 Nonclinical package and safety translation

Nonclinical studies should be proportionate to the intended indication, route and duration. An oral supportive-care product may require gastrointestinal, hepatic and interaction-focused evaluation, whereas a parenteral nanocarrier additionally requires haemocompatibility, complement activation, immunotoxicity, distribution, persistence, repeated-dose toxicity and local tolerance. For an anticancer product, ICH S9 provides a context for nonclinical development, but a botanical carrier with a new excipient or prolonged use can create questions beyond those addressed by the active alone.[62]

Clinically relevant route, dose and schedule are essential. Free-active and empty-carrier controls should be included; exposures should be measured rather than inferred from administered dose; and tumour, liver, spleen, kidney, lung, blood and excreta should be considered where relevant. Repeat-dose studies should use at least one batch representative of the planned clinical process. If the effect is seen only with intratumoural dosing or without dose-normalised comparators, the programme should be redesigned before further efficacy claims.

7.7 Clinical development and estimands

Early clinical development should answer product-specific questions in sequence: tolerability and food effect; parent/metabolite or free/associated pharmacokinetics; interaction risk; target engagement; dose and schedule; and then patient-relevant efficacy. A supportive-care trial should prespecify the symptom construct, minimum clinically important difference, missing-data strategy, rescue medication and adherence. An anticancer trial should define the estimand, endpoint hierarchy, imaging schedule, treatment discontinuation, subsequent therapy and duration of follow-up. ICH E6(R3) reinforces risk-proportionate quality and reliable trial data.[63]

Table 4 :Author-proposed candidate-level QTPP-QbD map. The final set of attributes must be justified by the intended product, route and indication.

Candidate product	Illustrative QTPP	Critical quality attributes	Critical material attributes	Critical process parameters	Control and evidence strategy
Oral curcuminoid product during tamoxifen	Defined supportive indication; oral; chronic; no clinically relevant reduction in endoxifen exposure	Curcuminoid identity/ratio; piperine absence or amount; dissolution; parent/conjugate exposure; stability	Extract fingerprint; excipient/solubiliser grade; contaminants	Extraction, complexation, drying, blending and encapsulation	Batch fingerprint plus dissolution; endoxifen interaction study; hepatic/GI monitoring; adherence and pill burden
Concentrated EGCG product	Defined supportive/prevention endpoint; oral; exposure below hepatic-toxicity boundary	EGCG/catechin profile; oxidation products; dissolution; food effect; caffeine; liver-safety markers	Leaf/extract source; catechin fingerprint; contaminants	Extraction, oxygen/light control, drying and packaging	Stability-indicating catechin assay; fed/fasted instructions; liver eligibility and stop rules; transporter-risk plan
Quercetin phytosome	Oral product with target exposure and no priority oncology interaction	Complexation efficiency; free quercetin; phospholipid oxidation; dispersion; parent/metabolite PK	Quercetin purity; lecithin composition and oxidation	Complexation, solvent removal, particle formation and drying	Sponsor-independent PK; CYP/transporter programme; oxidative stability; clinical target-engagement endpoint
Resveratrol nanoformulation	Route and active moiety defined; clinically relevant exposure and target engagement	Isomer ratio; photodegradation; loading/free active; release; parent/metabolite/tissue exposure	Trans-resveratrol purity; carrier grade	Light/oxygen control; encapsulation; sterilisation if parenteral	Photostability; active-moiety assay; comparative PK/PD; distribution and repeat-dose safety
Withania standardised extract	Defined symptom endpoint; oral; consistent multicomponent product	Species/part; withanolide range; full fingerprint; contaminants; dissolution; batch comparability	Botanical source, harvest, storage and extraction solvent	Extraction, concentration, drying, blending and packaging	Orthogonal identity; fingerprint specifications; interaction screen; hepatic risk management; randomised symptom trial

8. TRANSLATIONAL READINESS AND GO/NO-GO DECISIONS

8.1 Candidate-level readiness

Figure 2 summarises the present evidence by product and domain without converting qualitative judgements into a misleading numerical score. Curcumin has the most human formulation and interaction evidence and multiple clinical trials, but efficacy remains inconsistent and product dependent. EGCG has a clearer hepatic and food-effect boundary than efficacy signal. Quercetin and resveratrol remain at healthy-volunteer PK, interaction, biomarker and preclinical stages. Withania has preliminary supportive-care evidence, major product-definition uncertainty and a clinically relevant liver-injury signal. None is ready for routine use to reduce recurrence or mortality.

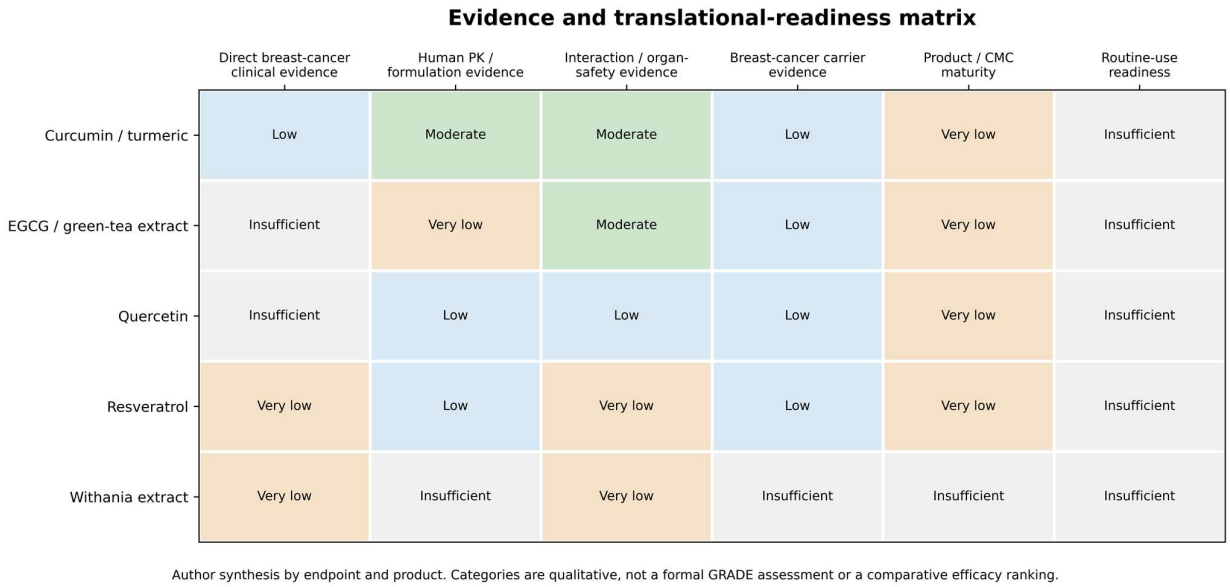

Figure 2: Qualitative evidence and translational-readiness matrix. "Moderate", "low", "very low" and "insufficient" are author-synthesis labels based on directness, design, precision, product definition and consistency; they are not a formal GRADE assessment and should not be used to rank efficacy.

8.2 Oral and parenteral development pathways

For oral products, the first go/no-go question is whether the final dosage form produces a reproducible, interpretable exposure under intended food conditions without compromising co-medications. A large rise in total conjugates without target engagement is not a reason to proceed. The second question is whether the chronic safety and adherence burden is acceptable for the intended population. Long-duration supportive products require a lower tolerance for uncertainty than short-course investigational products in advanced disease.

For parenteral products, translation requires an advantage sufficient to justify infusion, sterile manufacture and carrier-related risk. Dose-normalised comparison with free active, complete plasma and organ pharmacokinetics, haemocompatibility, complement and infusion assessments, repeated-dose toxicology, dilution and device compatibility, and a clinically feasible administration schedule should precede efficacy claims. Complement activation-related reactions are recognised risks for some liposomal, micellar and polymeric systems and must be tested as a product attribute rather than presumed from carrier class alone.[64],[65]

8.3 Explicit stopping and redesign rules

A programme should stop or redesign when the active moiety is undefined; the clinical batch cannot be linked to the evidence; clinically relevant exposure cannot be achieved without organ or carrier toxicity; a priority interaction changes anticancer-drug exposure beyond a prespecified margin; the route used in efficacy models is not clinically feasible; the carrier has no advantage over free active after dose-normalised PK; or a randomised trial fails its patient-relevant primary endpoint. Conversely, progression requires reproducible batches, a defined exposure target, acceptable safety margins, clinically relevant route and a trial capable of changing care.

Table 5: Practical clinical screening and monitoring framework for candidate botanical products. This table is not a prescribing recommendation and should be adapted to local guidance and the patient's oncology regimen.

Clinical question	Information to obtain	Higher-risk findings	Suggested action before or during use
What exactly is the product?	Brand, plant species/part, extract ratio, marker content, carrier, piperine/other bioenhancers, batch and dose	Uncharacterised powder or mixture; product differs from cited trial	Do not transfer efficacy or safety claims; obtain label/certificate or avoid use during active therapy
Which anticancer and supportive drugs are co-administered?	Endocrine therapy, taxanes, anticoagulants, antiplatelets, hepatotoxic agents and transporter-sensitive drugs	Tamoxifen plus piperine-containing curcumin; multiple hepatic risks; narrow therapeutic index	Pharmacist/oncologist review; product-specific interaction evidence; consider therapeutic or laboratory monitoring
What is the intended benefit?	Specific symptom, prevention biomarker, tumour response or survival claim; expected time to benefit	Vague "detoxification", cure, recurrence or survival promise	Reframe as investigational; do not replace or delay standard care
What baseline risk is present?	Liver disease, anaemia/haemolysis risk, allergy/infusion history, pregnancy, frailty and renal function	Pre-existing chronic liver disease with Withania or concentrated EGCG; IV carrier risk	Avoid or use only in governed research; document baseline and stopping criteria
How will harm and non-response be detected?	Liver tests, symptoms, adherence, concomitant-drug toxicity, validated patient-reported outcome and planned review date	No monitoring or indefinite continuation	Set review/stop date; discontinue for toxicity, interaction concern or absent meaningful benefit

Table 6: Author-proposed translational go/no-go framework.

Development gate	Minimum evidence to progress	No-go or redesign trigger
Product identity	Orthogonal identity, quantitative markers/fingerprint, impurity and contaminant controls, batch comparability	Unresolved identity, adulteration, unstable fingerprint or non-comparable clinical batch
Formulation performance	Reproducible CQAs, release/dissolution, stability and scale-relevant process understanding	Benefit depends on non-scalable process or attributes drift during storage, dilution or sterilisation
Exposure / active moiety	Validated assay; parent, metabolite and formulation fraction defined; exposure linked to target engagement	Only total conjugate signal rises, with no plausible pharmacodynamic bridge
Interaction / safety	Priority enzyme/transporter study; organ and route-specific monitoring; prespecified no-effect boundary	Clinically important reduction in anticancer exposure, hepatotoxicity, haemolysis or immune reaction
Nonclinical translation	Clinically feasible route; free-active and empty-carrier controls; comparative PK/biodistribution; repeat-dose safety	Effect only after intratumoural/peritumoural dosing or without dose-normalised comparator
Clinical proof	Randomised design; prespecified meaningful endpoint; adequate follow-up; transparent missing data and harms	Futility, inconsistent replication, selective short-term response or no benefit beyond PK

9. CLINICAL IMPLICATIONS AND SHARED DECISION-MAKING

Clinicians should ask specifically about powders, extracts, concentrated teas, branded complexes, “bioenhancers”, gummies, oils and injectable products. The question “Do you use supplements?” often misses products perceived as food or traditional medicine. Medication reconciliation should record exact product, dose, schedule, food instructions, start date and reason for use. Photographs of the label and batch information are often more useful than the plant name alone.

Communication should separate uncertainty from dismissal. Patients may seek control, symptom relief or cultural continuity, and an abrupt rejection can reduce disclosure. A clinically useful response acknowledges the goal, explains whether human evidence addresses that goal, identifies interaction or organ risks, and agrees on a monitoring and stopping plan. The non-negotiable boundary is that a botanical product must not replace curative or disease-controlling therapy or be presented as proven to prevent recurrence or improve survival.

Concentrated green-tea products warrant liver-risk discussion, particularly with fasting instructions or hepatic comorbidity. Piperine-containing curcumin should not be assumed compatible with tamoxifen. Withania should be considered in the differential diagnosis of new cholestatic or mixed liver injury. An absence of interaction in a small study of one product should be communicated as limited evidence, not universal safety. Injectable products and high-exposure nanoformulations belong within formal clinical development rather than unsupervised complementary use.

10. DISCUSSION

10.1 Principal findings and contribution

The central finding is not merely that bioavailability differs. Each candidate must be evaluated as a linked chain: source and composition; formulation and CQAs; parent, metabolite and formulation-fraction exposure; interaction and organ safety; target engagement; and patient-relevant outcome. Breaking any link invalidates extrapolation. This chain explains why large pharmacokinetic gains in healthy volunteers, tumour-cell uptake and xenograft inhibition can coexist with negative, inconsistent or unreplicated clinical results.

Curcumin provides the clearest example. The evidence includes a large negative radiodermatitis trial, a small positive pilot, a preliminary fatty-liver prevention signal, a negative futility trial, two positive chemotherapy studies with replication and interpretation requirements, a tamoxifen interaction signal, small formulation studies and parenteral haemolytic toxicity. A class-wide statement that “curcumin is effective” or “curcumin is safe” is scientifically untenable. The studied product, route, indication, co-medications and endpoint must be named.

10.2 Why higher bioavailability may fail to improve benefit

Higher systemic exposure can fail for at least six reasons. The measured analyte may not be active; the target may not be engaged at tolerable exposure; the mechanism observed in cells may not be dominant in human tumours; organ or carrier toxicity may narrow the therapeutic index; drug interactions may offset benefit; or the clinical endpoint may be insensitive, inappropriate or dominated by effective standard therapy. Delivery science is most valuable when it identifies and solves a verified limiting step, not when it is used to rescue an inadequately defined biological claim.

Carrier papers should therefore be interpreted as product-development evidence. Particle size, loading, encapsulation and cell cytotoxicity are necessary but insufficient. A formulation that increases tumour exposure but also increases liver and spleen exposure, complement activation, infusion burden or manufacturing variability may not improve net benefit. Updated distribution analyses support reporting full organ distributions, time points and recovery methods rather than repeating a single universal tumour-delivery percentage.[46],[47]

10.3 Generalisability beyond the five candidates

Although the review is bounded, the framework generalises to other natural products. A plant name should be replaced by a product definition; an in-vitro concentration by an exposure and active-moiety hypothesis; a carrier descriptor by a QTPP and control strategy; and a broad “anticancer” claim by an indication and estimand. Complex botanicals require more, not less, analytical and clinical discipline because multiple constituents, batch variability and uncertain active moieties increase the number of ways in which evidence can fail to transfer.

10.4 Research priorities

The most valuable next studies are not additional unlinked cell experiments. Priorities are sponsor-independent replication of positive clinical signals; product-specific interaction studies; exposure-response analyses that distinguish parent, metabolites and formulation fractions; clinically feasible route and dose comparisons; repeated-batch and stability data; comparative pharmacokinetics and biodistribution against free active and empty carrier; and randomised trials with prespecified patient-relevant endpoints. Registered supportive-care trials, including the ongoing nanoemulsion-curcumin study for aromatase-inhibitor arthralgia, should report complete product characterisation, adherence and harms when completed.

Research teams should prospectively define a translational stopping rule. If a product cannot be manufactured consistently, does not achieve interpretable exposure, reduces the exposure of essential anticancer therapy, produces organ or carrier toxicity, or fails a clinically meaningful endpoint, the appropriate result is discontinuation or redesign rather than continued mechanistic publication. Negative and null studies are especially valuable

when product identity, exposure and endpoint conduct are sufficiently rigorous to identify where the development chain failed.

11. LIMITATIONS

This review is bounded and critical rather than exhaustive. PubMed/MEDLINE was the principal bibliographic database; Embase, Scopus and Web of Science were not independently rerun for this revision. Study selection and extraction were not performed in duplicate, and no formal Cochrane RoB 2, ROBINS-I, SYRCLE or GRADE panel was completed. The preclinical table is purposive and illustrates translational barriers rather than estimating the prevalence of study features. Some product, funding and sponsor-role details require confirmation from complete articles and supplementary files. These limitations preclude claims of comprehensive systematic-review certainty.

Evidence also changes over time. The 2025 curcumin chemotherapy trial and fatty-liver trial are recent and should be reappraised as correspondence, corrections and replication emerge. ClinicalTrials.gov records can change after the search date. Regulatory classification varies by jurisdiction, and this review primarily uses FDA and ICH concepts as internationally recognisable development frameworks. Finally, absence of direct evidence is not proof of no effect; it means that routine clinical claims are not justified.

12. CONCLUSION

Candidate phytochemical and botanical products in breast cancer occupy different and generally early stages of development. Human formulation studies can demonstrate exposure enhancement; interaction and safety studies show that increased exposure can also be harmful; and preclinical carriers can establish technical feasibility. None of these findings alone establishes recurrence, survival or routine supportive-care benefit. Translation requires a defined product and indication, candidate-specific QTPP and control strategy, validated active-moiety and interaction assessment, clinically relevant nonclinical studies, and randomised clinical proof with transparent harms. At present, no reviewed product should replace standard therapy or be promoted for breast-cancer control outside a properly governed clinical study.

DECLARATIONS

Author contributions (CRediT taxonomy)

Ishani Thakur: Conceptualisation, methodology, investigation, data curation and writing-original draft. Monika Sharma: Visualisation and writing-review and editing. Deepak Singla: Clinical interpretation, visualisation and writing-review and editing. Shalini Singh: Supervision, validation and writing-review and editing. All authors reviewed and approved the final manuscript.

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