Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 18 March 2026
Revised 26 April 2026
Accepted 20 May 2026

Natural Resources for Human Health 2026, Vol. 6 (3): 636–644

KEYWORDS:
multidrug resistance; P-glycoprotein; ABC transporters; phytochemicals; chemosensitisation; PI3K/AKT; NF-κB; nanomedicine

Reversing Multidrug Resistance in Cancer Using Phytochemicals: Targeting Efflux Pumps and Survival Pathways

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ABSTRACT: Multidrug resistance (MDR) is the principal cause of chemotherapy failure and is implicated in over 90% of deaths from advanced cancer. Its best-characterised driver is the overexpression of ATP-binding-cassette (ABC) efflux transporters—P-glycoprotein (P-gp/ABCB1), multidrug-resistance-associated protein 1 (MRP1/ABCC1) and breast cancer resistance protein (BCRP/ABCG2)—which actively extrude structurally diverse anticancer drugs and thereby lower their intracellular concentration. This transporter-mediated efflux acts in concert with dysregulated pro-survival and anti-apoptotic signalling (PI3K/AKT/mTOR, NF-κB, MAPK and Wnt/β-catenin), which both up-regulates the transporters and enables evasion of drug-induced apoptosis. Three generations of synthetic efflux-pump inhibitors have largely failed in the clinic because of intrinsic toxicity, poor selectivity and unfavourable pharmacokinetics. Phytochemicals—curcumin, resveratrol, quercetin, EGCG, tetrandrine, taxifolin, capsaicin, piperine and related natural products—have consequently emerged as a promising "fourth generation" of MDR reversers.

This review synthesises their dual mechanism of action: direct functional inhibition and transcriptional down-regulation of ABC transporters on the one hand, and suppression of the survival pathways that sustain the resistant, apoptosis-evading phenotype on the other. Compiled data show reversal folds of roughly 3–15 relative to chemotherapy alone, two- to threefold increases in intracellular drug accumulation, and strong synergy in

combination indices. Because most phytochemicals suffer from low aqueous solubility and poor systemic bioavailability, nanocarrier co-delivery systems—which additionally provide tumour targeting and reduce exposure of healthy P-gp-expressing tissues—are examined as the key translational enabler. The review concludes that phytochemicals, deployed within rationally engineered co-delivery platforms and combination regimens, represent a credible and comparatively non-toxic strategy for reversing cancer MDR, while highlighting the standardisation, pharmacokinetic and clinical-validation gaps that remain.

1. INTRODUCTION

Chemotherapy remains a cornerstone of systemic cancer treatment, yet its long-term success is repeatedly undermined by the emergence of multidrug resistance (MDR)—the phenomenon whereby tumour cells become simultaneously insensitive to a broad range of structurally and mechanistically unrelated cytotoxic agents. [1,2] MDR may be intrinsic (present before treatment) or acquired (selected for during therapy), and once established it is the dominant reason that initially responsive tumours relapse; resistance is implicated in more than 90% of deaths in patients with advanced malignancy. [2,3] Overcoming it is therefore among the most consequential unmet needs in oncology.

Although MDR is multifactorial—encompassing reduced drug uptake, altered drug targets, enhanced DNA repair and cell-cycle checkpoint adaptation—the single most important and best-defined mechanism is the increased efflux of drugs by ATP-binding-cassette (ABC) transporters overexpressed at the plasma membrane. [1,3,4] These transporters use the energy of ATP hydrolysis to pump chemotherapeutics out of the cell, keeping intracellular concentrations below the cytotoxic threshold. Critically, transporter overexpression does not occur in isolation: it is driven and reinforced by aberrant pro-survival and anti-apoptotic signalling, so that the resistant cell both expels the drug and resists the apoptosis that any residual drug would trigger. [2,5] Effective reversal of MDR therefore benefits from a strategy that targets both arms of the phenotype simultaneously.

Pharmacological efforts to inhibit efflux pumps have produced three successive generations of synthetic modulators, from verapamil and cyclosporine A to the third-generation agents tariquidar, elacridar and zosuquidar. Despite high in-vitro potency, these have largely failed in clinical trials, chiefly because inhibiting P-gp—which is also expressed in the intestine, liver, kidney and blood–brain barrier—produces unacceptable toxicity and pharmacokinetic interactions, compounded by poor selectivity and low serum stability. [3,6,7] Against this backdrop, phytochemicals have attracted intense interest as a safer "fourth generation" of MDR reversers: they inhibit efflux pumps, they modulate the survival pathways that sustain resistance, and they do so with comparatively benign toxicity profiles. [1,4,8] This review examines how phytochemicals reverse cancer MDR through the dual targeting of efflux transporters and survival pathways, and how nanotechnology is being used to overcome their principal limitation—poor bioavailability. Figure 1 summarises the conceptual strategy.

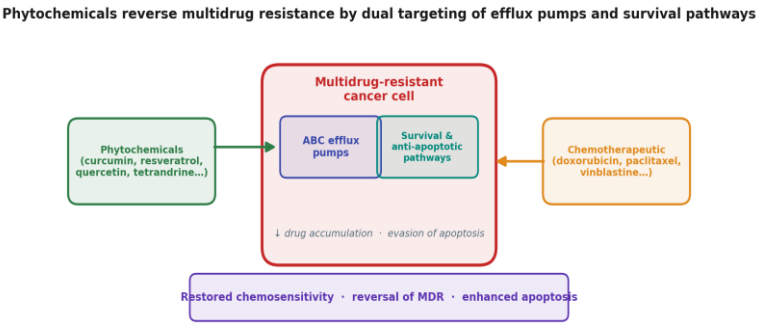

Figure 1. The dual-targeting rationale. Multidrug-resistant cancer cells combine ATP-driven drug efflux with dysregulated survival and anti-apoptotic signalling. Phytochemicals act on both arms—blocking efflux pumps to restore intracellular drug levels and suppressing survival pathways to re-enable apoptosis—thereby resensitising the cell to co-administered chemotherapeutics.

2. ABC EFFLUX TRANSPORTERS AND THE MDR PHENOTYPE

The human ABC superfamily comprises 48 transporters, of which three are principally responsible for clinical MDR (Table 1). P-glycoprotein (P-gp), the 170-kDa product of the *ABCB1* (*MDR1*) gene, is the best characterised: its two transmembrane domains recognise a remarkably broad range of hydrophobic substrates while its two nucleotide-binding domains bind and hydrolyse ATP to power extrusion. [9,10] MRP1 (*ABCC1*) transports glutathione and other organic-anion conjugates in addition to native drugs, and BCRP (*ABCG2*) is a half-transporter that functions as a homodimer and confers resistance to camptothecins, mitoxantrone and tyrosine-kinase inhibitors. [4,9] Their overexpression is regulated by the same survival pathways discussed in Section 4, tying efflux and signalling into a single, self-reinforcing resistance programme. Figure 2 depicts the membrane mechanism and the modes by which phytochemicals interfere with it.

Transporter	Gene	Size / structure	Representative drug substrates	Notes
P-glycoprotein (P-gp)	ABCB1 / MDR1	170 kDa; 2 TMD + 2 NBD	Doxorubicin, paclitaxel, vinblastine, etoposide	Most studied; broad substrate range
MRP1	ABCC1	190 kDa; 3 MSD	Vincristine, methotrexate, GSH conjugates	Effluxes anionic/conjugated drugs
BCRP	ABCG2	72 kDa half-transporter	Mitoxantrone, topotecan, SN-38, TKIs	Functions as homodimer
ABCB5	*ABCB5*	P-gp homologue	Doxorubicin, taxanes	Melanoma / stem-cell marker

Table 1. The principal ABC efflux transporters implicated in cancer multidrug resistance, their genes, structural features and representative drug substrates. Overlapping but distinct substrate specificities mean tumours frequently co-express more than one.

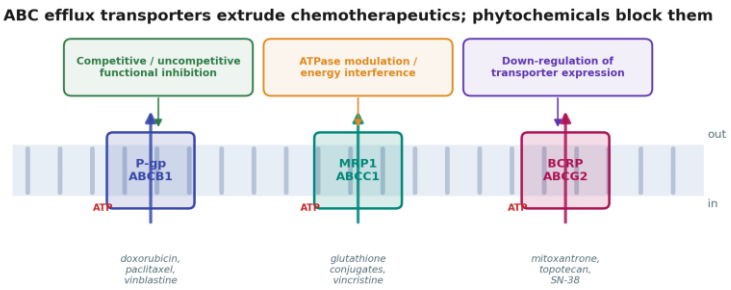

Figure 2. Membrane mechanism of ABC-transporter-mediated efflux and phytochemical inhibition. P-gp, MRP1 and BCRP extrude their respective drug substrates using ATP hydrolysis. Phytochemicals reverse this through three broad modes: competitive or uncompetitive functional inhibition of transport, interference with ATPase activity, and transcriptional down-regulation of transporter expression.

3. WHY SYNTHETIC EFFLUX-PUMP INHIBITORS HAVE FAILED

The pharmacological history of MDR reversal is instructive (Table 2). First-generation inhibitors such as verapamil and cyclosporine A were repurposed drugs with low affinity for P-gp, requiring doses that produced cardiovascular and immunosuppressive toxicity. Second-generation analogues (valspodar/PSC833, dexverapamil) improved potency but caused severe pharmacokinetic interactions, unpredictably raising plasma levels of the co-administered cytotoxic. Third-generation

agents (tariquidar, elacridar, zosuquidar) were rationally designed for high potency and selectivity, yet still bind non-specifically to P-gp in the blood–brain barrier and gastrointestinal tract, causing toxicity, and several failed to improve outcomes in randomised trials. [3,6,7] The recurring lesson is that potent, indiscriminate inhibition of a transporter with essential physiological roles is intrinsically hazardous. Phytochemicals—often described as a fourth generation—offer a different profile: generally lower potency but markedly lower toxicity, multi-target action, and amenability to tumour-targeted delivery. [4,8]

Generation	Representative agents	Key feature	Clinical outcome
First	Verapamil, cyclosporine A	Repurposed; low affinity	Dose-limiting cardiac / immune toxicity
Second	Valspodar (PSC833), dexverapamil	Higher potency	Severe PK interactions; trials disappointing
Third	Tariquidar, elacridar, zosuquidar	Potent, selective by design	BBB/GI toxicity; largely failed in trials
Fourth (natural)	Curcumin, resveratrol, quercetin, tetrandrine	Multi-target; low toxicity	Promising; limited by bioavailability

Table 2. Four generations of efflux-pump modulators. Synthetic first- to third-generation inhibitors combined high potency with unacceptable toxicity or pharmacokinetic liabilities; phytochemical "fourth-generation" modulators trade some potency for a substantially improved safety and multi-target profile.

4. PHYTOCHEMICAL INHIBITION OF EFFLUX PUMPS

Phytochemicals reverse transporter-mediated resistance through the three complementary modes shown in Figure 2. Many—including curcumin, quercetin, EGCG and the alkaloid tetrandrine—directly inhibit P-gp transport function, competing with or allosterically hindering substrate handling; taxifolin, for example, has been shown to act as an uncompetitive inhibitor of P-gp-mediated efflux while also lowering *ABCB1* expression. [8,11] A structure–activity principle recurs across studies: the hydrophobicity of a phytochemical, rather than its antioxidant capacity, governs its P-gp-inhibitory potency—lipophilic compounds such as carnosic acid and ursolic acid are active, whereas hydrophilic analogues such as rosmarinic acid and glycosylated flavonoids are not. [12] Beyond direct inhibition, resveratrol and quercetin transcriptionally down-regulate *MDR1*/P-gp expression, and several agents modulate transporter ATPase activity, starving the pump of energy. [13,14] Table 3 maps representative phytochemicals to their transporter and pathway targets.

Phytochemical	Plant source	Primary target(s)	Mechanism of reversal
Curcumin	Curcuma longa	P-gp, MRP1, BCRP	Functional inhibition; ↓ expression; mitochondrial pro-apoptotic
Resveratrol	Grape, berries	P-gp / MDR1	↓ MDR1 transcription; NF-κB & p38 MAPK suppression
Quercetin	Onion, apple, tea	P-gp; PI3K/AKT	↓ P-gp via PI3K/AKT/P-gp cascade; pro-apoptotic
EGCG	Green tea	P-gp, MRP1	Functional inhibition; membrane effects
Tetrandrine	Stephania tetrandra	P-gp	Potent functional inhibition; ROS induction
Taxifolin	Larch, citrus	P-gp / ABCB1	Uncompetitive inhibition; ↓ ABCB1 expression

Phytochemical	Plant source	Primary target(s)	Mechanism of reversal
Capsaicin	Capsicum spp.	P-gp	Efflux inhibition; ↑ drug accumulation
Piperine	Piper nigrum	P-gp; metabolism	Efflux inhibition; ↓ CYP/UGT metabolism (bioenhancer)

Table 3. Representative MDR-reversing phytochemicals, their botanical sources and their transporter and signalling targets. Many act simultaneously on efflux and survival pathways, the basis of their dual mechanism.

4.1 Chemosensitising potency

The practical measure of a reverser is the reversal fold—the ratio of the chemotherapeutic's IC_{50} in resistant cells alone to its IC_{50} in the presence of the modulator. Figure 3 compiles representative reversal folds against doxorubicin or paclitaxel in P-gp-overexpressing lines. Values typically range from about 3 to 15, with the bisbenzylisoquinoline alkaloid tetrandrine and curcumin among the most potent, and several agents matching or exceeding the first-generation reference verapamil at non-toxic concentrations. [8,14,15] The corresponding restoration of intracellular drug levels is direct: co-treatment with phytochemicals increases intracellular accumulation of doxorubicin two- to threefold as efflux is blocked (Figure 5).

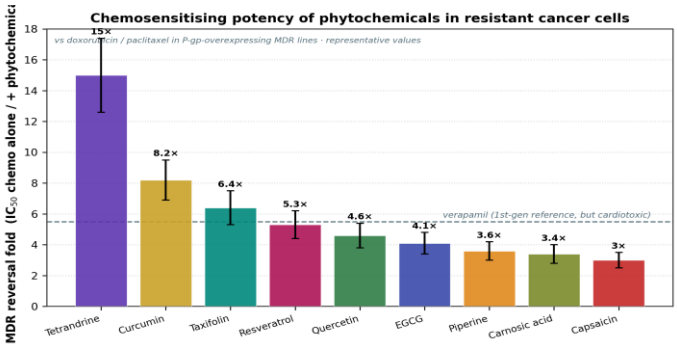

Figure 3. Chemosensitising potency of representative phytochemicals, expressed as MDR reversal fold (IC_{50} of the chemotherapeutic alone divided by IC_{50} in the presence of the phytochemical) in P-gp-overexpressing resistant cell lines. The dashed line marks the approximate activity of the first-generation reference verapamil, which is limited clinically by cardiotoxicity. Values are representative figures compiled from the cited literature.

5. TARGETING SURVIVAL AND ANTI-APOPTOTIC PATHWAYS

Efflux inhibition alone is often insufficient, because resistant cells are additionally wired to survive. Several signalling axes—PI3K/AKT/mTOR, NF-κB, the MAPK cascades (p38 and ERK) and Wnt/β-catenin—are constitutively activated in MDR tumours, where they perform a dual function: up-regulating ABC-transporter expression and simultaneously suppressing apoptosis by inducing anti-apoptotic effectors such as Bcl-2 and survivin, promoting epithelial–mesenchymal transition and sustaining cancer-stem-cell traits. [5,16] Figure 4 maps this network and the points at which phytochemicals intervene. Quercetin, for instance, reverses oxaliplatin resistance in gastric cancer by inhibiting the PI3K/AKT/P-gp cascade, thereby lowering P-gp and restoring apoptosis, and resveratrol suppresses P-gp-mediated resistance in osteosarcoma cells by blocking NF-κB and p38 MAPK activation. [13,17] Curcumin acts more distally, converging on the mitochondria to dissipate the membrane potential, deplete ATP and release cytochrome *c*, triggering the caspase-9/caspase-3 cascade and re-enabling apoptosis in resistant cells. [18]

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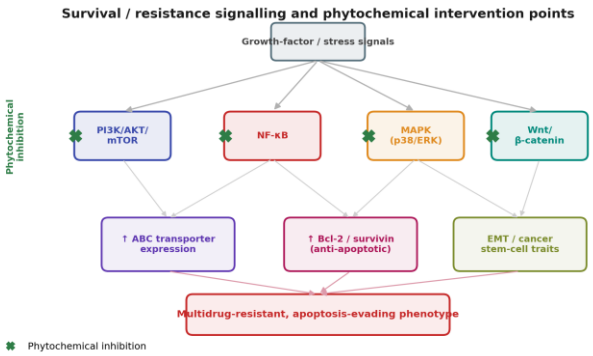

Figure 4. Survival/resistance signalling network and phytochemical intervention points. Growth-factor and stress signals activate PI3K/AKT/mTOR, NF-κB, MAPK and Wnt/β-catenin, which up-regulate ABC transporters and anti-apoptotic effectors and drive EMT and stem-cell traits, producing a resistant, apoptosis-evading phenotype. Phytochemicals (X) inhibit these nodes, coupling efflux reversal to restored apoptosis.

Pathway	Role in MDR	Anti-apoptotic / resistance output	Phytochemical modulators
PI3K/AKT/mTOR	↑ transporter expression; survival	↑ Bcl-2; ↓ pro-apoptotic BAX	Quercetin, curcumin, resveratrol
NF-κB	↑ MDR1; inflammation-linked survival	↑ survivin, Bcl-xL	Resveratrol, curcumin, EGCG
MAPK (p38 / ERK)	Stress-adaptive transporter induction	Apoptosis threshold ↑	Resveratrol, curcumin
Wnt/β-catenin	Stemness; BCRP regulation	EMT; drug tolerance	Curcumin, quercetin, silibinin

Table 4. Survival and resistance signalling pathways in cancer MDR, their contribution to the resistant phenotype, and phytochemicals reported to inhibit them. The overlap of modulators across pathways reflects the pleiotropic, multi-target nature of phytochemical action.

6. CHEMOSENSITISATION AND SYNERGY

The dual mechanism translates into pronounced chemosensitisation. Figure 5 illustrates the two quantitative signatures: a steep fall in the chemotherapeutic's IC_{50} in resistant cells when a phytochemical is co-administered—approaching the sensitivity of parental cells—and a two- to threefold increase in intracellular drug accumulation as efflux is suppressed. [15,18,19] Because phytochemicals attack resistance through several non-overlapping mechanisms, their combinations with cytotoxic drugs are frequently synergistic rather than merely additive, with combination indices below unity and fractional effects that exceed the sum of the parts. [14,15] This synergy is the pharmacological basis for using phytochemicals as adjuvants: it permits equal or greater tumour kill at a lower dose of the cytotoxic agent, narrowing the therapeutic-index problem that limits conventional chemotherapy.

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eISSN: 2583-1194

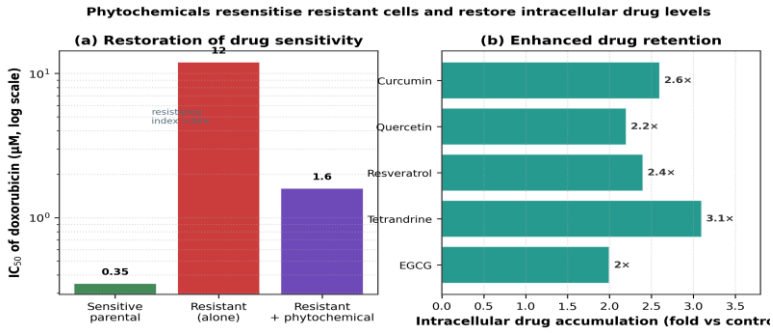

Figure 5. Chemosensitisation by phytochemicals. (a) The IC_{50} of doxorubicin, greatly elevated in resistant cells relative to parental cells (a resistance index of the order of tens-fold), falls sharply when a phytochemical modulator is co-administered. (b) Representative fold increases in intracellular drug accumulation produced by efflux-blocking phytochemicals. Values are representative figures compiled from the cited studies.

7. OVERCOMING BIOAVAILABILITY: NANOCARRIER CO-DELIVERY

The dominant obstacle to clinical translation of phytochemical MDR reversers is pharmacokinetic. Most of the leading actives—curcumin above all—have poor aqueous solubility, chemical instability and low, erratic systemic bioavailability, so that concentrations shown to reverse MDR in vitro are rarely achievable in plasma with oral or free-drug dosing. [20,21] Nanocarrier co-delivery addresses this on several fronts at once: it solubilises and stabilises the phytochemical, co-encapsulates it with the cytotoxic partner so that both reach the tumour together and in a controlled ratio, exploits the enhanced-permeability-and-retention effect (and, with surface ligands, active targeting) to concentrate the payload in tumour tissue, and—importantly—limits exposure of healthy P-gp-expressing tissues, mitigating the very toxicity that sank the synthetic inhibitors. [20,21,22] Diverse platforms have been used, including polymeric and lipid nanoparticles, liposomes, mesoporous silica and clay-based nanomaterials (Table 5). Curcumin-based systems are especially well developed: the polymeric NanoDoxCurc formulation overcame doxorubicin resistance across several tumour models in vivo while reducing anthracycline cardiotoxicity, and curcumin–paclitaxel and tetrandrine–paclitaxel co-delivery nanoparticles have restored sensitivity in resistant breast and ovarian cancer cells. [20,21,22]

Nanocarrier	Phytochemical + drug	Model	Reported outcome
Polymeric nanoparticle (NanoDoxCurc)	Curcumin + doxorubicin	Myeloma, leukaemia, prostate, ovarian	Overcame DOX resistance in vivo; ↓ cardiotoxicity
Lipid / lipid-polymer nanoparticle	Curcumin + paclitaxel	MCF-7/ADR breast cancer	Targeted delivery; enhanced cytotoxicity
iRGD lipid-polymer hybrid	Tetrandrine + paclitaxel	A2780/PTX ovarian cancer	↑ ROS, apoptosis; P-gp inhibition
Mesoporous silica nanoparticle	Curcumin + cisplatin prodrug	MDR carcinoma	Synergistic chemo-/photodynamic effect
Halloysite–hectorite clay	Curcumin + doxorubicin	MCF-7R (2D & 3D)	↑ DOX accumulation; MDR reversal

Table 5. Representative nanocarrier systems for co-delivery of phytochemicals with chemotherapeutics to overcome MDR. Co-encapsulation stabilises the phytochemical, enables tumour targeting, and reduces exposure of healthy tissues—addressing both the bioavailability and toxicity barriers.

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Figure 6 places these strategies in comparative perspective. It contrasts synthetic first- and third-generation inhibitors with free and nanocarrier-delivered phytochemicals across the criteria that determine clinical viability. Free phytochemicals excel on tolerability and multi-target action but are penalised by bioavailability; the nanocarrier-delivered form recovers that deficit while retaining the safety advantage, producing the most balanced overall profile.

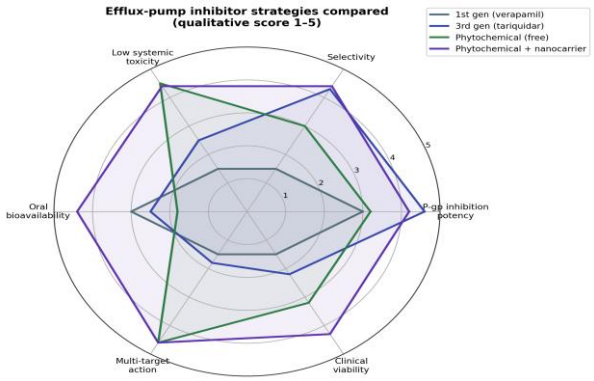

Figure 6. Comparative profile of efflux-pump inhibitor strategies across six clinically relevant criteria (1 = weak, 5 = strong). Synthetic inhibitors (verapamil, tariquidar) combine potency and selectivity with poor tolerability; free phytochemicals are well tolerated and multi-target but poorly bioavailable; nanocarrier-delivered phytochemicals recover bioavailability and targeting while preserving safety, giving the most balanced translational profile.

8. CHALLENGES AND FUTURE PERSPECTIVES

Several obstacles must be resolved before phytochemical MDR reversal reaches the clinic. Pharmacokinetics and standardisation: beyond bioavailability, natural-product preparations vary in purity and composition, and reversal data are reported with heterogeneous cell lines, doses and endpoints, impeding comparison; standardised, well-characterised actives and harmonised assays are needed. Selectivity and safety at scale: although phytochemicals are comparatively benign, potent efflux inhibition can still raise the toxicity of co-administered cytotoxics by increasing their accumulation in normal tissues—precisely why tumour-targeted nanodelivery is central rather than optional. Clinical validation: the great majority of evidence is preclinical, and rigorously designed trials with pharmacodynamic biomarkers of transporter and pathway engagement are largely lacking. Systems complexity: tumours co-express multiple transporters and rewire survival signalling under pressure, so single-agent, single-target reversal is likely to be evaded; rational multi-target combinations and adaptive regimens are required. [1,4,8,20] Promising directions include structure-guided optimisation and semisynthetic derivatisation of lead phytochemicals to raise potency and drug-likeness, stimulus-responsive and ligand-targeted nanocarriers for precise co-delivery, and computational (molecular-docking and machine-learning) screening to prioritise combinations before experimental testing. [8,10]

9. CONCLUSION

Multidrug resistance is sustained by a self-reinforcing partnership between ABC-transporter-mediated drug efflux and dysregulated survival signalling, and durable reversal therefore requires attacking both. Phytochemicals are distinctively suited to this task: acting through multiple, non-overlapping mechanisms, they inhibit and down-regulate P-gp, MRP1 and BCRP while simultaneously suppressing the PI3K/AKT, NF-κB, MAPK and Wnt pathways that up-regulate those transporters and block apoptosis. In preclinical models they achieve reversal folds of roughly 3–15, restore intracellular drug accumulation two- to threefold, and synergise with standard cytotoxics—all with a toxicity profile far more favourable than the synthetic inhibitors that failed clinically. Their Achilles' heel is bioavailability, and the decisive advance has been nanocarrier co-delivery, which stabilises the actives, co-targets tumour tissue and spares healthy organs. The evidence supports a clear strategic conclusion: phytochemicals should be developed not as free-drug replacements for synthetic modulators but as rationally optimised, tumour-targeted co-delivery adjuvants within multi-target combination regimens. Realising their promise now depends on standardised actives, biomarker-guided clinical trials and continued innovation in targeted delivery.

Declarations

Funding: No external funding was received for this work.

Conflicts of interest: The authors declare no conflict of interest.

Author contributions: Conceptualisation, A.O.; investigation and writing—original draft, A.O. and A.T.; visualisation, A.T.; writing—review and editing, A.T.; supervision, A.O. All authors approved the final manuscript.

Data availability: No new primary data were generated; all data discussed are available in the cited references.

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