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Can Formulation Rescue Orally Limited Phytochemicals? A Systematic Review of Bioavailability Gains, Exposure Evidence, and Translation Across Delivery Technologies

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ABSTRACT

Many phytochemicals combine pharmacological interest with low or variable oral systemic exposure arising from poor aqueous solubility, dissolution limitations, gastrointestinal instability, permeability constraints, efflux, and extensive presystemic metabolism. Formulation technologies are frequently presented as solutions, yet improvement in formulation performance is not equivalent to demonstrated improvement in systemic exposure, and exposure enhancement does not itself establish therapeutic benefit. A systematic-review framework was used to evaluate oral formulation studies according to measured pharmacokinetic exposure, formulation technology, comparator, analyte definition, evidence level, and translational setting. Human randomized or crossover pharmacokinetic evidence and preclinical oral pharmacokinetic studies were considered separately. Dissolution or permeability improvement without corresponding systemic-exposure evidence was not treated as proof of bioavailability rescue. Owing to substantial heterogeneity in compounds, formulations, doses, analytes, species, and comparators, synthesis was qualitative rather than quantitatively pooled. Repeated within-study increases in systemic exposure were reported across lipidic, self-emulsifying, nanoparticulate, supersaturating, cyclodextrin-based, gastroretentive, and hybrid delivery systems. Apparent gains were nevertheless conditional on compound properties, analytical definition, comparator selection, physiological setting, and evidence level. Human evidence was substantially narrower than the preclinical formulation literature, and analytically different definitions of circulating phytochemical materially affected interpretation. Formulation can rescue oral exposure for selected phytochemicals under defined conditions, but no delivery technology can presently be regarded as a universal solution. Translation requires evidence connecting formulation mechanism to rigorously defined systemic exposure and, separately, to pharmacodynamic or clinical relevance.

Keywords: Phytochemicals, Oral bioavailability, Pharmacokinetics, Drug delivery, Nanoformulation, Systemic exposure

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Introduction

Poor oral bioavailability is a recurring development problem for phytochemicals, but it does not arise from one universal mechanism. Limited aqueous solubility, slow dissolution, precipitation, gastrointestinal instability, low permeability, intestinal efflux, presystemic metabolism, and host-dependent biotransformation may contribute in different combinations. Contemporary formulation approaches can alter one or more of these barriers, while

human bioavailability remains dependent on the chemical entity, formulation, analytical definition, and biological context [1–3].

Curcumin illustrates both the opportunity and the interpretive difficulty. Numerous formulations have been designed to increase apparent solubility, dispersion, gastrointestinal availability, or systemic exposure, and many studies report improvements relative to conventional preparations. However, the curcumin literature remains heterogeneous in formulation composition, dose, comparator, measured analytes, and downstream outcomes. Increased formulation performance or circulating exposure cannot therefore be treated automatically as evidence of therapeutic effectiveness [4].

The same problem extends beyond curcumin. Human resveratrol pharmacokinetic data show substantial variability across oral studies, emphasizing that an orally administered phytochemical cannot be assigned a single context-free bioavailability value [5]. Formulation effects interact with dosing conditions, metabolism, sampling, and the analytical species used to represent exposure.

Analytical definition is particularly consequential. Measurements of unconjugated parent compound, circulating metabolites, total analyte after enzymatic deconjugation, or composite curcuminoid pools do not describe the same pharmacokinetic quantity. A recent critical reappraisal of enhanced-bioavailability curcumin formulations emphasized that apparent magnitude can depend strongly on what is measured and how comparisons are constructed [6]. Accordingly, this review uses formulation rescue in a deliberately narrow sense: a formulation-associated improvement in directly measured oral systemic exposure relative to a defined comparator. Improved dissolution, cellular transport, or biological activity without pharmacokinetic exposure evidence is not treated as equivalent proof of rescue.

Review objectives and outcomes

The primary objective was to determine what the available literature can establish about formulation-mediated improvement in systemic exposure to orally administered phytochemicals. Priority was given to pharmacokinetic endpoints such as area under the concentration-time curve, maximum observed concentration, and relative or absolute oral bioavailability where reported. Formulation characteristics were interpreted as possible explanations for an exposure difference rather than substitutes for exposure measurement [1].

A second objective was to compare represented delivery technologies without constructing an unsupported league table. Reported fold improvements across different compounds, doses, species, comparators, sampling schedules, and analytical definitions are not inherently commensurable. Particular attention was therefore given to whether exposure represented parent compound, free analyte, conjugated or deconjugated material, metabolites, or composite chemical measurements [6].

The third objective was translational: to distinguish physicochemical or mechanistic formulation success from animal pharmacokinetic success and from human pharmacokinetic evidence. The review therefore proposes a conditional interpretation in which stronger claims require alignment among the formulation problem being addressed, an appropriate comparator, a defined systemic-exposure endpoint, and an evidence level compatible with the intended translational conclusion.

Materials and Methods

The review was structured using PRISMA 2020 reporting principles [7]. Eligible evidence concerned oral delivery of phytochemicals or closely related plant-derived small molecules and included direct comparative systemic pharmacokinetic evaluation or evidence directly relevant to interpretation of such evaluation. Studies reporting only dissolution, solubility, permeability, cellular uptake, or pharmacodynamic activity without systemic-exposure measurement were not treated as direct evidence of oral bioavailability rescue.

Candidate literature was identified through iterative combinations of compound, formulation, oral delivery, bioavailability, pharmacokinetic, exposure, nanoparticle, lipid, self-emulsifying, micellar, supersaturation, solid-dispersion, cyclodextrin, and related terms. Article identity and DOI information were checked during evidence curation. No prospective review registration was available for this review.

For each direct study, extraction focused on phytochemical identity, formulation technology, comparator, species or human population, dosing context, exposure analyte, pharmacokinetic endpoint, reported mechanistic evidence, and translational level. Randomized and crossover human evidence was interpreted using design-appropriate risk-of-bias principles rather than assuming certainty from randomization alone [8]. Preclinical evidence was

interpreted with explicit attention to methodological and translational limitations specific to animal and in-vitro research [9].

Substantial heterogeneity in formulation chemistry, analyte definition, dose, species, physiological condition, and comparator precluded a defensible common quantitative estimand. Consequently, reported pharmacokinetic changes were synthesized qualitatively, with greater interpretive weight placed on internally controlled comparisons than on cross-study numerical ranking.

Study selection and evidence characteristics

The final evidence set contained both human direct pharmacokinetic comparisons and a broader range of preclinical formulation studies. Human evidence was particularly valuable because it directly tested whether a formulation altered systemic exposure in the intended species, but even these studies remained product- and context-specific.

A water-soluble curcumin formulation produced higher measured systemic exposure than a conventional curcumin tablet within a human comparison [10]. The result supports formulation-dependent exposure but does not establish that all water-soluble systems are superior or that greater exposure improves clinical outcomes.

Randomized crossover evidence similarly showed enhanced flavonolignan exposure from a micellar silymarin formulation [11]. This supports the capacity of micellization to modify systemic delivery in that product context but should not be converted into a platform-wide effect estimate.

A multi-phytochemical micellar formulation containing chrysin, quercetin, and rutin illustrates an additional attribution problem. Its crossover pharmacokinetic evaluation showed formulation-associated changes in measured constituent exposure [12], but a multicomponent product cannot automatically reveal which ingredient, excipient interaction, or formulation mechanism generated the observed pharmacokinetic behavior.

Resveratrol provides another direct human example. Two oral formulations produced different pharmacokinetic profiles in healthy fasting subjects under a crossover design [13]. Such evidence is directly relevant to exposure but remains bounded by the tested products, fasting state, dose, and population.

Preclinical studies represented a substantially broader set of delivery architectures. They provide valuable evidence that specific biopharmaceutical barriers can be altered, but animal fold improvements are not human effect estimates. Across both human and preclinical studies, meaningful interpretation therefore required knowledge of the comparator, measured analyte, and biological context.

The verified candidate-level evidence audit is summarized in **Figure 1**. Because raw database-identification, deduplication, screening, retrieval, and reason-specific exclusion counts were not reproducibly available, unavailable PRISMA counts were not reconstructed or back-calculated. **Figure 1** therefore reports only the verified candidate-level evidence-selection structure.

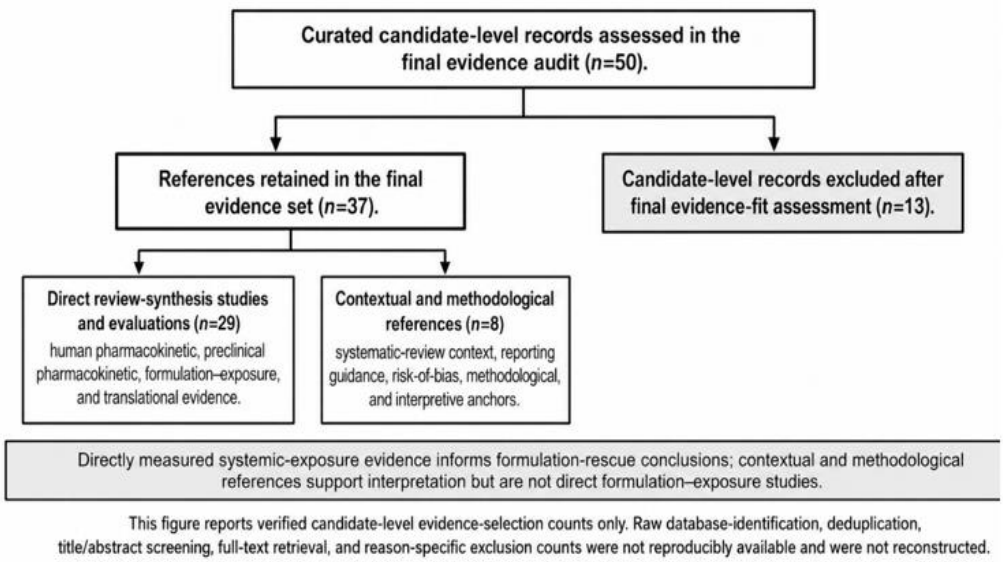

Figure 1. Verified candidate-level evidence-selection flow for the phytochemical oral-bioavailability review

Table 1. Evidence characteristics governing interpretation of oral formulation rescue

Evidence stratum	Representative context	What the evidence can establish	Principal interpretation boundary
Human single-ingredient comparative pharmacokinetics	Curcumin, silymarin, resveratrol formulations	Within-study formulation-dependent systemic exposure	Product, dose, analytical method, fasting state, and population remain specific
Human multi-ingredient pharmacokinetics	Micellar combinations of several phytochemicals	Exposure behavior of the administered combination and measured constituents	Individual ingredient or mechanism cannot automatically be isolated
Preclinical oral pharmacokinetics	Lipidic, particulate, supersaturating, and residence-modifying systems	Exposure improvement within the tested species and comparator design	Animal magnitude is not a human effect estimate
Mechanistic formulation evidence	Solubilization, precipitation control, transport, or efflux modification	Plausible contributors to a pharmacokinetic difference when specifically examined	Mechanism should not be inferred from exposure enhancement alone
Analytical-definition evidence	Parent, total, conjugated, metabolite, or composite measurements	The chemical species to which an exposure claim applies	Unlike analyte definitions should not be directly pooled or ranked

Note: These evidence strata are a proposed interpretive organization rather than a validated evidence hierarchy.

Formulation strategies represented in the literature

Recent primary studies illustrate mechanistically distinct strategies, including phospholipid-complex nanosuspension, supersaturation, and self-nanoemulsification, each evaluated using in-vivo oral pharmacokinetics [14–16]. Their coexistence is important because orally limited phytochemicals do not necessarily share the same dominant barrier, and different formulations may succeed for different reasons.

A luteolin-loaded PLA shape-memory gastroretentive system represents residence-time engineering rather than a conventional solubility-only intervention [17]. Prolonging gastric or upper-intestinal residence may increase opportunities for dissolution or absorption when the compound and absorption window are compatible, but the principle should not be generalized to compounds with different gastrointestinal behavior.

Polymeric nanoparticles provide another approach. Puerarin-loaded PLGA nanoparticles increased oral exposure in rats relative to the study comparator [18]. Cubic liquid-crystal nanoparticles likewise increased puerarin blood bioavailability and distribution in a preclinical model [19]. The associated pharmacological findings remain separate from the evidence that exposure changed.

Self-microemulsifying systems were represented across chemically distinct phytochemicals. A berberine hydrochloride self-microemulsifying drug delivery system increased pharmacokinetic exposure relative to a commercial-tablet comparator in rats [20]. Such systems may improve dispersion and apparent solubilization, but exposure enhancement does not by itself distinguish these effects from excipient-mediated transport or metabolic influences.

Hybrid delivery systems combine mechanisms. Cationic curcumin nanocrystal-loaded liposomes increased oral bioavailability relative to crude material in vivo [21]. Chitosan/lecithin nanoparticles similarly improved curcumin bioavailability in a preclinical comparison [22]. These studies demonstrate technological feasibility but do not establish a fixed nanoparticle effect size.

Supersaturation provides a different design logic: instead of only increasing equilibrium solubility, the formulation seeks to maintain a transiently high dissolved concentration while suppressing precipitation. Cyclodextrin-supported oxyberberine nanoaggregates produced a marked relative-bioavailability increase in the reported animal experiment [23]. The magnitude is informative within that study but is not a human estimate or a formulation-class effect.

Conversion of lipidic systems into solid dosage forms may address handling or stability while preserving self-emulsifying behavior. A solid self-nanoemulsifying drug delivery system of rhein improved biopharmaceutical performance and systemic exposure in the reported preclinical evaluation [24]. Such results support further translation but do not establish long-term stability, manufacturing scalability, or human exposure.

Liposomes remain represented in recent work as well. Bisdemethoxycurcumin liposomes increased oral pharmacokinetic exposure in a preclinical comparison [25]. Associated anti-fibrotic activity cannot be attributed solely to the pharmacokinetic difference without a design that directly tests exposure-mediated causality.

Mechanistic studies can make formulation interpretation more informative. A luteolin self-microemulsifying formulation provided evidence that P-glycoprotein efflux inhibition contributed to enhanced oral exposure [26]. Importantly, transporter modulation should be interpreted as contributory rather than exclusive because solubilization, dispersion, and other excipient effects may operate simultaneously.

Physiological state also modifies apparent formulation performance. A β-cyclodextrin metal-organic framework increased luteolin bioavailability in both healthy and acetaminophen-injured rats, but the reported magnitude differed between physiological states [27]. The exposure gain therefore cannot be treated as an invariant property of the carrier.

Collectively, these studies support a mechanistically plural model. Formulation rescue is a property of the compound–formulation–comparator–physiology combination, not of a technology name in isolation.

Effects on bioavailability and systemic exposure

The strongest interpretation of "rescue" comes from within-study pharmacokinetic comparisons. In a human comparison of several innovative curcumin formulations, relative oral exposure differed markedly among products [28]. The conclusion is narrower than a technology ranking: formulation can materially alter human exposure, but the observed magnitude remains dependent on the tested products, doses, and analytical approach.

Exposure success is also separable from pharmacodynamic success. In a double-blind randomized active-controlled crossover trial, micellar curcumin increased systemic exposure without producing a corresponding pattern across selected short-term inflammatory and PCSK-9 measurements that would justify treating pharmacokinetic enhancement as established therapeutic benefit [29]. A formulation can therefore solve an exposure problem while leaving the biological significance of the additional exposure unresolved.

A separate human crossover study demonstrated formulation-dependent single-dose curcuminoid pharmacokinetics [30]. Together with analytical reassessment of the field, this reinforces that "higher bioavailability" is not a self-interpreting metric. Parent curcumin, conjugated species, metabolites, and total analyte after hydrolysis can produce different apparent pharmacokinetic narratives.

Across preclinical studies, favorable exposure changes were frequent but cross-study magnitude remained difficult to interpret. Systems differed in compound, excipients, dose, species, comparator, analytical method, and physiological state. Accordingly, a large numerical improvement in one animal model should not outrank a smaller but analytically rigorous human comparison simply because the fold value is larger.

Comparison across delivery technologies

Direct ranking of formulation classes is not supported because delivery technology is confounded with compound identity, comparator, dose, and evidence level. Human evidence should generally carry greater translational weight than animal-only effect magnitude while still remaining context-specific. A randomized double-blind crossover study in healthy fasting subjects showed higher curcumin exposure from the tested novel formulation than from its turmeric-extract comparator [31]. This is strong evidence for that comparison, not proof that the formulation is universally superior under fed, chronic, or clinical-use conditions.

Biorelevant in-vitro methods may strengthen technology evaluation when validated against human pharmacokinetics. A biphasic dissolution method reproduced the relative ordering of human curcumin formulation bioavailability within the evaluated product set [32]. This is an important translational bridge because it tests whether a formulation-relevant laboratory measurement predicts actual human exposure rather than merely demonstrating improved dissolution. However, it does not establish a universal in-vitro–in-vivo relationship across phytochemicals.

Preclinical Bio-SNEDDS work with apigenin provides another direct demonstration that self-emulsifying systems can improve solubility and oral bioavailability [33]. Together with newer apigenin evidence, it supports technological capability, but it does not establish a human exposure advantage.

The appropriate comparison is therefore conditional rather than ordinal. Technologies should be assessed according to whether they address a plausible limiting process, whether the exposure endpoint is direct and analytically defined, whether the comparator is meaningful, whether the formulation is physically stable, and whether validation has progressed from animal models to humans.

Table 2. Cross-technology interpretation matrix for oral phytochemical exposure rescue

Technology family	Principal formulation role represented	Exposure evidence represented	Main translation boundary
Self-emulsifying or micellar systems	Solubilization, dispersion, sometimes transporter modulation	Human and preclinical	Product/excipient specificity; exposure does not establish efficacy
Lipid, phospholipid, or vesicular carriers	Solubilization, partitioning, colloidal presentation	Predominantly preclinical with selected human comparisons	Species, composition, and analyte dependence
Polymeric or biopolymer nanoparticles	Encapsulation and altered intestinal presentation	Preclinical	Animal gains cannot be converted directly to human effects
Supersaturating and solid-state systems	Maintain dissolved concentration and suppress precipitation	Preclinical; some translational dissolution evidence	Supersaturation stability and transfer remain compound-specific
Gastroretentive systems	Modify gastrointestinal residence	Preclinical	Benefit depends on absorption site and gastrointestinal physiology
Cyclodextrin or framework carriers	Inclusion, dissolution enhancement, multicomponent delivery	Preclinical	Physiological state and carrier-specific effects
Hybrid systems	Combine particulate, lipidic, mucoadhesive, or other mechanisms	Preclinical	Mechanistic attribution becomes difficult

Note: This matrix is a proposed qualitative synthesis and is not a performance ranking.

Translation from preclinical to human evidence

Optimization does not itself establish translation. Multivariate and central-composite optimization of curcumin-loaded solid self-nanoemulsifying drug delivery systems improved dissolution and bioavailability in a preclinical setting [34]. This demonstrates that formulation variables can be systematically tuned within a design space, but it does not establish human pharmacokinetics, manufacturing readiness, or therapeutic benefit.

The persistence of the preclinical-to-human gap is visible in earlier self-nanoemulsifying work. Myricetin formulation development produced improved oral delivery in in-vitro and animal evaluations [35]. The study remains informative because it demonstrates direct preclinical exposure rescue, yet accumulation of animal successes does not convert them into human evidence.

Human pharmacokinetic evidence introduces a further requirement: exposure must eventually be related to biological consequences. Curcumin pharmacokinetics have been linked experimentally with downstream antioxidant and epigenetic gene-expression measurements using pharmacokinetic/pharmacodynamic modeling in healthy volunteers [36]. This illustrates a higher evidential layer than exposure alone while remaining distinct from clinical efficacy.

Solid-state strategies face the same translational boundary. A third-generation lyophilized resveratrol solid dispersion improved oral bioavailability in a preclinical evaluation [37]. This supports solid dispersion as a plausible formulation solution but does not establish human exposure gain.

Human crossover studies nevertheless demonstrate repeatedly that curcumin systemic exposure can be formulation-dependent [6,10,28]. What remains comparatively sparse is systematic replication across chemically diverse phytochemicals using common analytical definitions and direct linkage between exposure and meaningful pharmacodynamic outcomes.

The evidence synthesized above suggests that formulation rescue is best understood as a sequence of conditional evidential transitions rather than as a binary property of a formulation. **Figure 2** integrates these transitions from the initial oral limitation through direct exposure evidence, human confirmation, and eventual exposure–response interpretation.

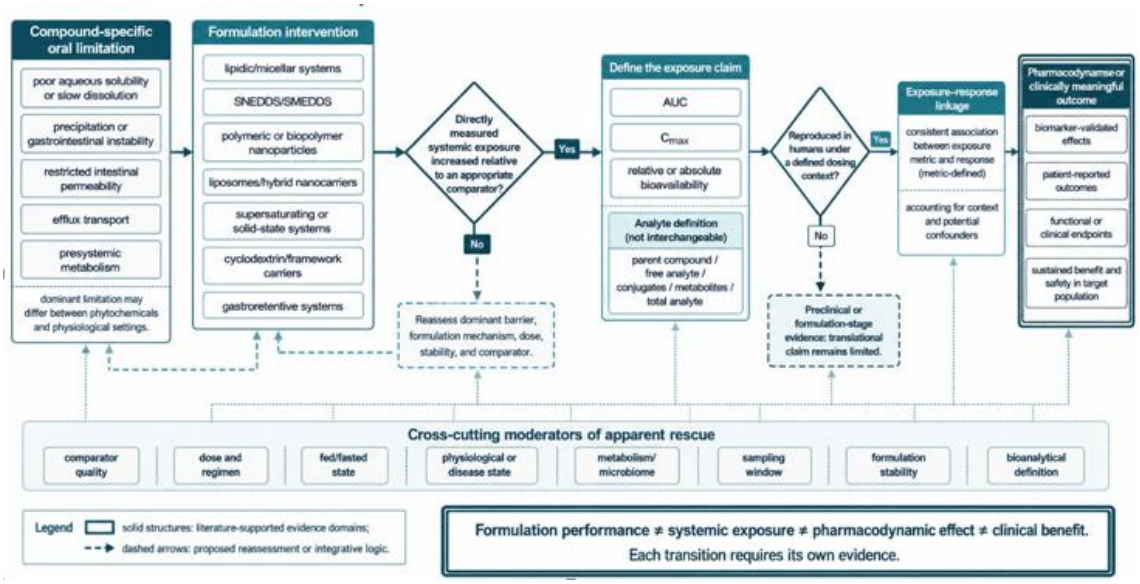

Figure 2. From formulation-mediated exposure rescue to translational relevance: a conditional evidence architecture

Results and Discussion

The review supports a qualified answer to the central question: formulation can rescue measured oral exposure for selected phytochemicals, but rescue is conditional rather than platform-intrinsic.

Three dimensions determine the strength of a rescue claim. First, the formulation should address a plausible limiting process. Second, exposure should be measured using a chemically explicit analytical definition. Third, the evidence level should match the translational claim being made. Curcumin demonstrates why the second requirement is indispensable: different analytical definitions can materially alter the apparent magnitude and interpretation of enhanced bioavailability [6].

Mechanistic evidence strengthens interpretation but should not be overextended. The luteolin self-microemulsifying study indicates that P-glycoprotein inhibition can contribute to exposure gain [26]. That does not mean transporter inhibition is the sole mechanism. Formulations commonly change several parameters simultaneously, including solubilization, colloidal state, gastrointestinal residence, permeability, and metabolism.

Outcome separation is equally important. The micellar curcumin crossover study demonstrates that increased systemic exposure need not generate a concordant short-term biomarker response [29]. Consequently, pharmacokinetic success cannot substitute for evidence of pharmacodynamic or therapeutic value.

Validated translational methods may help bridge the gap. The curcumin biphasic dissolution study showed that an appropriately designed in-vitro method could reproduce relative human formulation performance within a defined product set [32]. This suggests that formulation development would benefit from moving away from generic dissolution enhancement toward validated, compound-specific predictors of human exposure.

The diversity of successful experimental technologies also argues against interpreting the field as a competition among carrier labels. A self-emulsifying system, supersaturating formulation, nanoparticle, phospholipid complex, cyclodextrin carrier, or gastroretentive device may each be rational when aligned with the relevant limitation. The more informative question is not which technology is universally best, but whether the intervention changes the process that limits exposure for the particular phytochemical under the intended physiological conditions.

This distinction is especially important when large relative-bioavailability increases are reported. Fold enhancement depends on the denominator. A poorly performing comparator can generate an impressive relative value even when absolute exposure remains modest. Conversely, a comparatively smaller increase against a strong optimized comparator may represent a more informative development result. Cross-study fold improvements should therefore not be interpreted without examining comparator identity, dose equivalence, analyte definition, and pharmacokinetic sampling.

Analytical treatment creates another potential source of overstatement. For compounds that undergo extensive conjugation or metabolism, parent compound concentration and total analyte after enzymatic hydrolysis answer different biological questions. Combining them under the general label "bioavailability" can obscure whether formulation increased exposure to the pharmacologically relevant species or merely altered the measured pool. Future studies should report analytical processing explicitly and avoid presenting parent and total-analyte exposure as interchangeable outcomes.

Physiological context should also be incorporated into formulation evaluation. Differences between healthy and disease-associated gastrointestinal or metabolic states may affect dissolution, transporter activity, intestinal permeability, hepatic extraction, and metabolite formation. The luteolin framework study showing different apparent gains across physiological states illustrates why an exposure enhancement cannot be assumed to remain constant across populations [27].

The evidence further suggests that formulation-development success should be evaluated by a hierarchy of increasingly stringent questions. The first question is whether the intervention changes a relevant physicochemical or transport property. The second is whether this produces directly measured systemic exposure. The third is whether the exposure change is reproducible in humans. The fourth is whether the additional exposure changes target engagement, pharmacodynamic response, or another meaningful biological endpoint. The fifth is whether those changes ultimately alter clinical outcomes. Skipping levels in this sequence produces claims that are stronger than the evidence supporting them.

Future studies should therefore prioritize comparability rather than maximal reported fold gain. Useful designs include molar-equivalent head-to-head dosing, shared validated bioanalytical methods, explicit separation of free parent, conjugates, and metabolites, fed/fasted comparisons where relevant, independent batch replication, stability testing, and predefined pharmacokinetic endpoints.

Negative findings should also be considered informative. Improved dissolution without increased systemic exposure suggests that another barrier, such as permeability or metabolism, remains dominant. Increased systemic exposure without pharmacodynamic change may indicate that the wrong circulating species, tissue compartment, exposure window, or biological endpoint is being emphasized. A formulation that does not increase systemic exposure may still be valuable for local gastrointestinal pharmacology, but that would represent a different therapeutic objective and should not be described as systemic bioavailability rescue.

Evidence limitations and heterogeneity

The principal limitation of the evidence base is heterogeneity at nearly every level relevant to bioavailability. Human polyphenol exposure varies with host and metabolic factors [3], while analytical treatment can substantially change the apparent meaning of an exposure difference [6]. Dose, sampling duration, fasting status, comparator choice, metabolite formation, formulation composition, and assay processing further limit direct comparison.

For this reason, cross-study fold gains were not quantitatively pooled. The absence of pooling should not be interpreted as evidence that formulation effects are small. Rather, the available numerical effects often represent different estimands.

The evidence is also uneven in translational maturity. A substantial portion of technology diversity is supported primarily by animal pharmacokinetics, while direct human evidence is concentrated in a smaller number of compounds. Physiological state may itself alter apparent formulation performance, as demonstrated by the different luteolin responses observed in healthy and injured animals [27].

Even human crossover studies remain bounded by their experimental setting. A fasting comparison cannot automatically predict chronic administration, fed exposure, disease populations, or therapeutic response [31]. Consequently, the evidence base is stronger for the proposition that formulation can alter systemic exposure than for claims regarding the general superiority of particular technologies.

Mechanistic attribution remains another challenge. Complex delivery systems can modify several processes simultaneously. Without targeted perturbation, an exposure increase cannot be assigned uniquely to solubilization, transport modulation, intestinal residence, metabolic inhibition, or another pathway.

The evidence set also includes a concentration of curcumin studies. Curcumin is useful as a model of formulation-sensitive oral exposure, but replication within one compound cannot establish equivalent formulation behavior across structurally and metabolically distinct phytochemicals. More comparative human work is required for flavonoids, stilbenes, alkaloids, and other poorly exposed natural products.

Finally, raw database-identification and screening counts required for a complete numerical PRISMA flow diagram were not reproducibly available in the verified evidence record. They were therefore not reconstructed. **Figure 1** reports only auditable candidate-level evidence-selection counts. This preserves the distinction between a verified evidence audit and a retrospectively manufactured search-flow history.

Conclusion

Oral formulation can increase systemic exposure to selected phytochemicals, and the reviewed literature provides direct human and preclinical examples across multiple delivery strategies. The central finding, however, is not that one platform has solved phytochemical bioavailability. Apparent rescue is conditional on the compound, formulation, comparator, physiological setting, measured analyte, and evidence level.

A useful interpretation separates three questions. First, does the formulation correct a relevant biopharmaceutical limitation? Second, does that correction produce a reproducible increase in a clearly defined systemic-exposure endpoint? Third, does the exposure change translate into a pharmacodynamic or clinically meaningful effect? Evidence for an earlier question cannot substitute for evidence at a later one.

This review therefore proposes a conditional rather than technology-ranking framework. Stronger future evidence will require harmonized bioanalysis, meaningful head-to-head comparators, explicit parent/metabolite definitions, human pharmacokinetic replication, physiologically relevant dosing conditions, validated biorelevant methods, formulation-stability evidence, and exposure–response linkage.

Formulation should ultimately be viewed as a conditional rescue strategy rather than a universal solution. Large pharmacokinetic gains can justify further development, but they should not be interpreted as proof of therapeutic effectiveness or broad translational readiness until the complete evidential chain has been established.

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