



Protein Corona Effects Belong in the Design Loop for Nanocarried Phytochemicals Because Biological Identity Can Override the Intended Nanoparticle Surface

Aisha Bello^{1*}, Zainab Sule¹, Ibrahim Musa², Grace Adeyemi³, Ahmed Youssef⁴

¹Department of Protein Corona and Nanocarrier Design, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria.

²Department of Biological Identity of Nanocarried Phytochemicals, Faculty of Pharmacy, University of Ilorin, Ilorin, Nigeria.

³Department of Nanoparticle Surface and Biological Override, Faculty of Pharmaceutical Sciences, Federal University of Agriculture Abeokuta, Abeokuta, Nigeria.

⁴Department of Nanocarrier Design Loop Integration, Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan.

ABSTRACT

Nanocarriers are commonly designed and characterized as manufactured objects, yet their biologically encountered surfaces can differ substantially from those measured before administration. Adsorption and exchange of proteins and other biomolecules generate an acquired corona that can alter receptor accessibility, cellular uptake, immune recognition, biodistribution, colloidal behavior, and cargo exposure. This problem is particularly important for nanocarried phytochemicals because the payload may itself influence interfacial chemistry, particle stability, release, and the biomolecular environment encountered along the administration route. This article develops an original mechanistic framework in which protein-corona formation is treated as a formulation variable within, rather than after, nanocarrier optimization. The framework distinguishes manufactured surface identity, acquired biological identity, dynamic corona state, functional biological consequences, and translationally validated identity. It further separates relatively persistent from rapidly exchanging corona components and treats ligand accessibility, uptake, biodistribution, immune recognition, and cargo release as context-dependent consequences rather than deterministic outputs of nominal surface engineering. Evidence from nanomedicine, gastrointestinal nanocarriers, corona-modulation studies, and dynamic corona characterization supports the underlying distinctions, while the proposed integration remains a design hypothesis requiring prospective validation. A corona-aware design loop should therefore characterize the nanoparticle before biological exposure, during relevant biofluid transformation, and after acquisition of the surface state responsible for the intended biological interaction. The framework does not imply that corona composition alone predicts therapeutic performance, nor that in-vitro corona measurements automatically reproduce in-vivo nanoparticle identity.

Key Words: Protein corona, Biological identity, Phytochemicals, Nanocarriers, Surface remodeling, Nano-bio interface

eIJPPR 2026; 16(4):109-118

HOW TO CITE THIS ARTICLE: Bello A, Sule Z, Musa I, Adeyemi G, Youssef A. Protein Corona Effects Belong in the Design Loop for Nanocarried Phytochemicals Because Biological Identity Can Override the Intended Nanoparticle Surface. Int J Pharm Phytopharmacol Res. 2026;16(4):109-18. <https://doi.org/10.51847/B0QTxjXbmc>

INTRODUCTION

Nanocarrier development conventionally begins with controllable attributes: particle size, morphology, surface charge, hydrophilicity, coating density, ligand

presentation, payload loading, and release characteristics. These measurements describe a manufactured nanoparticle, but biological exposure adds another surface-engineering event that occurs outside the formulation

Corresponding author: Aisha Bello

Address: Department of Protein Corona and Nanocarrier Design, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria.

E-mail: ✉aisha.bello@ui.edu.ng

Received: 08 May 2026; **Revised:** 05 August 2026; **Accepted:** 11 August 2026

This is an **open access** journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.



laboratory. Endogenous biomolecules adsorb onto nanomedicines and can alter how their surfaces are recognized by cells, receptors, and clearance systems. Contemporary analysis of biomolecular coronas therefore supports a distinction between the material originally produced and the interface that biological systems actually encounter [1].

The consequence is not simply a layer of adventitious protein. Recent work with lipid nanoparticles shows that corona formation can alter tissue localization, cellular internalization, and functional cargo delivery, demonstrating that a nanocarrier retaining its manufactured core may nevertheless acquire a substantially different functional identity after contact with biological fluids [2]. These observations challenge a formulation logic in which surface chemistry is optimized once and then assumed to remain biologically readable.

For phytochemical delivery, the problem has an additional dimension. Polyphenols and other plant-derived molecules can be interfacially active, may reside partly within or near a carrier surface, and may encounter changing protein, enzyme, lipid, mucus, electrolyte, and pH environments before reaching the intended tissue. The relevant design object is consequently not only the particle placed into a vial or dosage form but the evolving particle–cargo–biomolecule assembly that exists at the site of biological interaction.

The mechanistic proposition developed here is therefore corona-aware rather than corona-deterministic. Protein-corona evidence should enter the formulation design loop because acquired biological identity can override, conceal, complement, or redirect intended surface functions. Corona composition, however, is not treated as a sufficient predictor of efficacy: biological outcome also depends on exchange kinetics, molecular accessibility, exposure route,

target-cell context, cargo state, and the correspondence between experimental corona models and the in-vivo environment.

Intended surface identity versus acquired biological identity

A useful starting distinction is between intended surface identity and acquired biological identity. Intended identity comprises the surface properties deliberately created during formulation: chemistry, charge, hydrophobicity, coatings, ligands, geometry, and the interfacial consequences of cargo loading. Acquired identity emerges after the particle encounters biological media. In-vivo analysis of PEGylated gold nanostructures showed that particle size and shape influenced both the amount and composition of adsorbed proteins after circulation, directly demonstrating that the manufactured material conditions—but does not uniquely specify—the subsequent corona [3]. Surface engineering can also deliberately influence this transition. Glycosylated nanovesicles have been used to regulate corona formation and thereby modify biological interactions, illustrating that biological identity is not necessarily an uncontrollable nuisance; it can become an engineering target when an experimentally demonstrated surface–corona relationship exists [4]. What should not follow is the stronger assumption that one engineered corona state will persist across biological compartments.

The framework proposed here therefore separates five identities or interpretive states rather than treating “nanoparticle identity” as a single fixed construct. Their distinctions are summarized in **Table 1**.

Table 1 should be read as a boundary matrix: it distinguishes what each nanoparticle-identity construct describes from the stronger biological inference that the same construct cannot, by itself, support.

Table 1. Proposed construct boundaries for surface identity across the biological life of a phytochemical nanocarrier

Identity construct	Defined by	Primary question answered	Inference permitted	Inference not justified alone
Manufactured identity	Material, size, shape, charge, coating, ligand display, cargo state	What particle was formulated?	Reproducibility of starting formulation	Biological receptor accessibility
Initial acquired identity	Biomolecules recruited at first relevant biofluid exposure	What surface first confronts the biological environment?	Early nano–bio interface description	Persistence across compartments
Dynamic corona identity	Retained and exchanging biomolecular populations over time	How does the interface evolve?	Time- and medium-conditioned surface state	One permanent corona composition
Functional biological identity	Accessible motifs and interactions governing uptake, immune recognition, transport, or release	What biological interactions can the remodeled surface support?	Context-specific functional interpretation	Therapeutic efficacy from composition alone
Translationally qualified identity	Surface state demonstrated under exposure conditions relevant to intended use	Does the measured identity remain relevant beyond the test system?	Bounded formulation–biology linkage	Universal in-vivo prediction

Note: The five-state organization is a proposed mechanistic synthesis. The states are analytical distinctions rather than experimentally validated universal stages, and a nanocarrier may occupy overlapping or rapidly changing states.

This distinction also clarifies why corona measurements should feed back into formulation rather than merely appear in late-stage characterization. A ligand can remain chemically attached yet become sterically inaccessible; a hydrophilic coating can reduce some interactions without eliminating selective protein recruitment; and two particles

with similar manufactured size can acquire different biological interfaces. **Figure 1** integrates these relationships and makes explicit that biological identity is generated by interactions among surface design, cargo, biological context, corona dynamics, and downstream recognition rather than by a one-directional coating event.

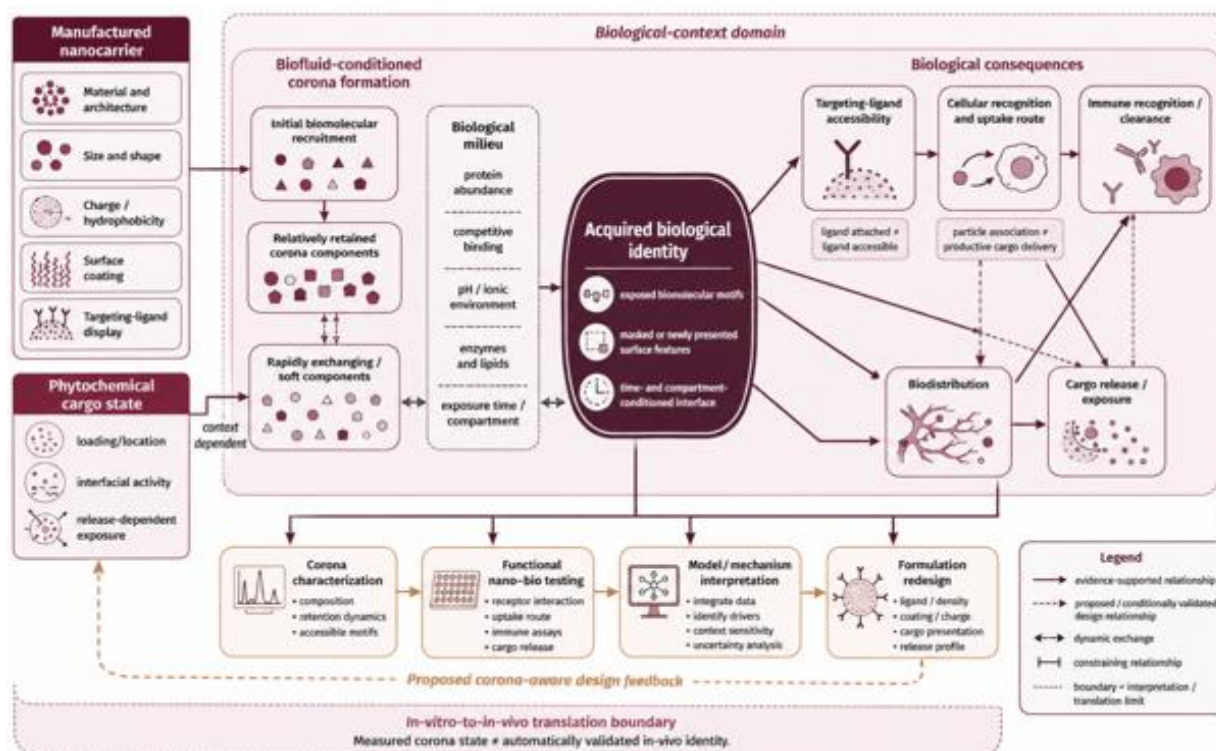


Figure 1. Biological surface rewriting as a corona-aware design framework for nanocarried phytochemicals

Formation of the protein corona

Corona formation begins when a nanoparticle surface enters a biological medium containing molecules capable of adsorption. The resulting composition cannot be represented adequately by a simple “protein present/protein absent” variable because adsorption is selective and depends on both the physicochemical surface and the competing molecular environment. Protein nanoparticle studies demonstrate that charge and hydrophobicity can produce distinct corona profiles, reinforcing the principle that the starting surface acts as a selective interaction field rather than an inert substrate [5]. The biological medium supplies the other half of the system. Engineered-corona studies emphasize that the proteins available, their relative concentrations, adsorption affinities, conformational responses, and competition for interfacial space can reshape the resulting nanoparticle surface [6]. Consequently, identical manufactured particles should not automatically be expected to acquire identical identities in plasma, gastrointestinal fluid, mucus-associated environments, inflammatory states, or other distinct biological compartments.

For formulation science, the relevant variable is therefore not merely “corona formation” but corona formation under a specified material–medium–time condition. This qualification matters because measurements made after a single incubation condition collapse several mechanistically separable factors: recruitment, displacement, conformational rearrangement, loss of weakly associated components, and artifacts introduced during isolation.

The framework therefore treats formation as a conditional state transition rather than an instantaneous conversion from bare to coated particle. The manufactured surface constrains the interaction possibilities; the biological environment supplies competing biomolecules; and time determines which part of that interaction history remains experimentally visible. This interpretation establishes the basis for separating relatively persistent and dynamically exchanging components.

Hard, soft, and dynamically exchanging corona components

The language of “hard” and “soft” corona is useful only when treated as an operational description of interaction persistence, not as evidence for two perfectly discrete biological shells. In-vivo work on complement adsorption has shown that corona-associated proteins can undergo dynamic exchange after nanoparticles enter the circulation, demonstrating that apparently associated proteins need not represent a permanent surface state [7].

Direct in-situ analysis further shows why weakly associated material should not be treated as experimental noise by default. Methods capable of examining the soft corona without relying entirely on conventional separation have revealed dynamically associated populations that contribute to the nanoparticle interface but may be lost during washing and isolation [8]. Real-time single-particle measurements likewise demonstrate that corona assembly can be followed as a kinetic process in serum rather than inferred only from an endpoint proteomic inventory [9].

These observations require three distinctions. First, residence time is not equivalent to functional importance: a rapidly exchanging component may still influence the interface during a biologically relevant encounter. Second, protein abundance in an isolated corona does not by itself establish receptor engagement, immune function, or transport consequence. Third, an experimentally recovered “hard corona” is partly method-dependent because sample processing selects which interactions survive analysis.

The proposed framework therefore represents corona identity as a distribution of interaction persistence and accessibility over time. Relatively retained proteins, exchanging proteins, and transiently encountered biomolecules may contribute differently to biological recognition. Characterization should consequently match the mechanistic question: compositional proteomics when identity is sought, kinetic or in-situ methods when exchange is central, and functional testing when the claim concerns uptake, targeting, clearance, or cargo delivery.

Phytochemical cargo can influence corona formation

For nanocarried phytochemicals, cargo should not automatically be treated as mechanistically invisible behind the carrier surface. A gastrointestinal study of epigallocatechin gallate delivery showed that a digestive-enzyme corona formed around resistant-starch nanoparticles and altered EGCG release, directly connecting biological adsorption with phytochemical exposure from the carrier [10]. The significance is bidirectional: biological molecules can modify carrier behavior, while cargo localization and release can change the interface available during that process.

Evidence that small molecules can deliberately modulate corona composition provides a complementary mechanistic premise. Small-molecule surface modulation

has been used to alter protein recruitment in nanoparticle-based plasma proteome profiling, showing that low-molecular-weight chemical functionality can reshape the adsorbed protein landscape [11]. This does not establish that every encapsulated phytochemical will alter its corona, particularly when cargo remains fully shielded within a carrier core. It does establish that the chemical environment presented at the nano–bio interface can matter.

Quercetin-containing edible protein nanoparticles provide still closer cargo-specific evidence: protein-corona formation altered physicochemical and functional behavior of the quercetin carrier system [12]. These observations justify incorporating cargo state into corona-aware formulation reasoning, but not treating “phytochemical” as a single predictive descriptor.

The proposed design implication is therefore conditional. Cargo identity becomes corona-relevant when loading changes surface chemistry, architecture, charge, hydrophobicity, protein conformation, colloidal stability, or release sufficiently to alter the exposed nano–bio interface. Experiments should test that dependency directly by comparing matched unloaded and loaded carriers under the same biological conditions rather than attributing every corona difference to the phytochemical itself.

Corona-controlled cellular uptake and biodistribution

Acquired corona identity can change not only how much nanoparticle material associates with cells but also how cells internalize it. Controlled experiments have shown that altering corona composition can change the cellular internalization mechanisms used for nanoparticles [13]. This is mechanistically more informative than reporting uptake magnitude alone because distinct entry routes can produce different intracellular trafficking and cargo-delivery consequences.

Corona effects can also interact directly with an engineered targeting system. In enterocyte models, mucus-derived protein coronas on transferrin-functionalized nanoparticles acted as both facilitators and barriers to transcellular transport, illustrating that biological remodeling need not simply “mask targeting”; it can condition ligand function in a more context-specific manner [14]. A nominally identical ligand-bearing particle can therefore behave differently depending on the corona assembled before receptor encounter.

In-vivo delivery studies provide another warning against reducing corona biology to nonspecific fouling. Rational organization of lipid nanoparticles, nucleic-acid cargo, and corona interactions has been used to create stealth bionanoarchitectures with altered in-vivo delivery behavior [15]. Such evidence supports the possibility that corona effects may sometimes be harnessed rather than

merely minimized, while remaining formulation- and context-dependent.

Three boundaries follow. Cell association is not equivalent to productive internalization; internalization is not equivalent to cytosolic or target-site cargo delivery; and altered biodistribution is not equivalent to therapeutic benefit. The proposed framework therefore places corona-conditioned uptake and biodistribution downstream of biological identity but upstream of pharmacological interpretation. For phytochemical nanocarriers, this distinction is essential: increased particle uptake is meaningful only when the phytochemical remains available in the required molecular state, reaches the relevant intracellular or tissue compartment, and produces an independently demonstrated pharmacological effect.

Targeting ligands under biological surface remodeling

Ligand conjugation establishes an intended recognition mechanism, but it does not establish that the same ligand remains sterically available after biological exposure. Corona-associated proteins can shield ligands, change their orientation relative to the particle surface, introduce competing receptor-binding motifs, or create new interactions that dominate over the engineered ligand. Conversely, selected endogenous proteins may be

exploited as biologically functional surface elements rather than regarded exclusively as contaminants. This duality underlies the view that the protein corona can be either detrimental or useful depending on the desired delivery mechanism [16].

Artificial-corona strategies extend that premise by deliberately recruiting or installing biologically recognizable proteins to direct nanoparticle interactions [17]. The relevant comparison is therefore not “targeted versus untargeted nanoparticle” at manufacture, but nominal targeting versus biologically accessible targeting after surface remodeling. Across uptake, mucus-conditioned transport, and engineered-corona studies, biological surface composition can act as an active determinant of nanoparticle recognition rather than a passive coating [13, 14, 17].

A ligand-bearing carrier should consequently be interrogated at several functional levels: chemical retention of the ligand, accessibility after corona acquisition, receptor-dependent binding, internalization route, and successful delivery of biologically available cargo. Failure at any one level cannot be inferred from another. The distinctions needed to avoid this conflation are summarized in **Table 2**.

Table 2. Distinguishing nominal ligand display from corona-remodeled targeting function

Targeting level	What is established	What biological remodeling can change	Appropriate interpretation
Ligand conjugation	Ligand remains chemically attached	Surface exposure and orientation	Manufactured targeting potential
Ligand accessibility	Recognition motif remains exposed	Steric masking or competitive adsorption	Corona-conditioned availability
Receptor recognition	Accessible surface engages a receptor	New corona-derived binding motifs	Context-specific recognition
Cellular entry	Particle is internalized	Entry pathway and intracellular routing	Uptake mechanism, not cargo action
Functional delivery	Cargo reaches a relevant compartment in active form	Trafficking, release, degradation	Delivery consequence
Translational targeting	Function persists under relevant biological conditions	Compartment, disease, species, host variation	Qualified rather than universal targeting

Note: The hierarchy is a proposed analytical distinction. Progression between levels is not assumed to be inevitable.

Figure 2 makes this point operational: ligand display begins the targeting hypothesis, whereas corona remodeling determines which recognition opportunities

remain biologically available and which competing routes emerge.

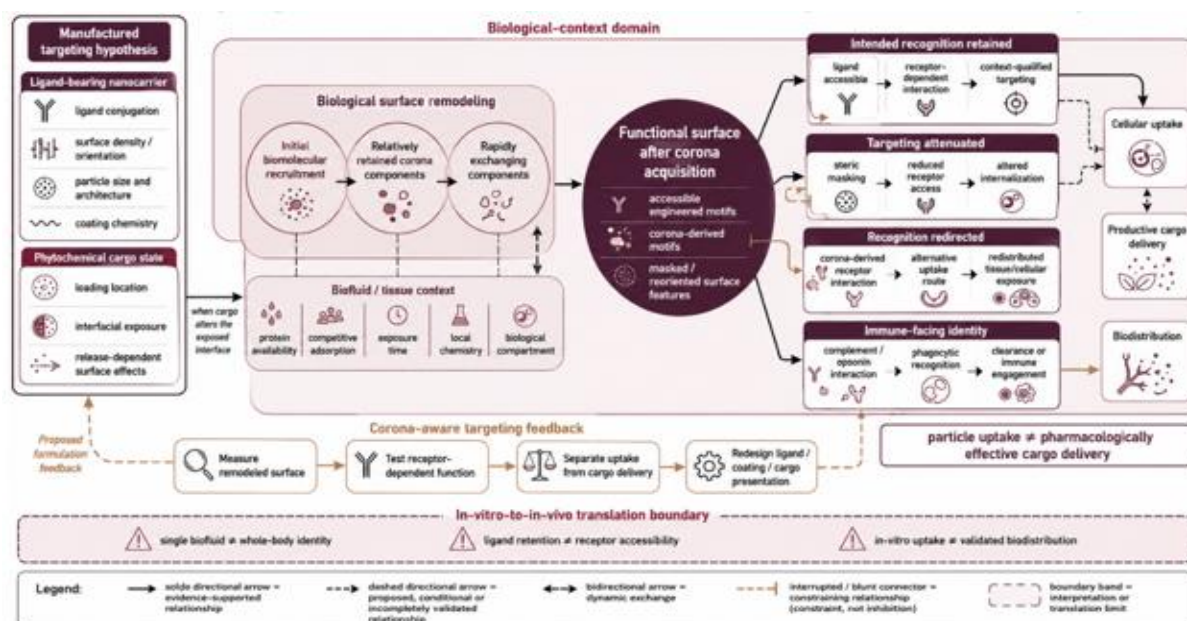


Figure 2. Targeting becomes a context-qualified state after biological surface remodeling

Immune recognition and clearance

The acquired surface also determines what the immune system can recognize. This interaction should not be reduced to a binary “stealth versus opsonized” classification. Specific surface modifications of iron oxide nanoparticles have been shown to provoke complement-dependent innate and adaptive antileukaemia immune responses, demonstrating that corona-associated immune interactions can become biologically active rather than merely accelerating nonspecific disposal [18].

Host state can further change that interaction. Inflammatory disease progression has been reported to reshape biomolecular-corona-mediated immune activation profiles [19]. Thus, a corona characterized in healthy pooled plasma may not preserve the same composition or immune consequence in a diseased host. For phytochemical nanocarriers, whose intended applications frequently involve inflammatory or metabolically altered tissues, disease context should therefore be treated as an experimental variable rather than an incidental source of noise.

The mechanistic boundary is important: complement deposition, cytokine changes, phagocyte association and shortened circulation are not interchangeable endpoints. Each interrogates a different step between biological identity and systemic disposition. Corona-aware development should specify which immune interaction is being measured and whether that interaction is intended, tolerated, or formulation-limiting.

A corona-aware nanocarrier design loop

A useful design loop begins before biological testing. The manufactured formulation establishes an initial hypothesis

about the interface; biological exposure then tests whether that hypothesis survives surface rewriting. In SORT lipid nanoparticles, quaternary-ammonium lipid structure and the associated protein corona jointly influenced lung-specific mRNA delivery, providing direct evidence that formulation composition and acquired biological identity can interact in organ-level delivery behavior [20]. Oral nanoparticle work similarly shows that surface hydrophobicity and rigidity can condition corona formation and treatment-related biological behavior in the gastrointestinal environment [21].

The proposed corona-aware design loop therefore contains four iterative questions: What surface was manufactured? What biological identity was acquired under the intended exposure condition? Which acquired features were functionally responsible for recognition, uptake, clearance or delivery? Which controllable formulation variables should be changed in response?

This formulation logic rejects two shortcuts. First, a favorable corona composition should not be optimized as an endpoint detached from biological function. Second, an unfavorable in-vitro corona should not automatically eliminate a formulation without testing whether the identified proteins are accessible, persistent and causally relevant to the downstream phenotype. Corona measurements become valuable when they reduce uncertainty in a formulation decision.

Predicting corona composition from material and biological context

Predictive modeling offers a route from descriptive corona catalogues toward testable biological-identity hypotheses. Machine learning has predicted functional corona

composition and associated cellular recognition using nanoparticle descriptors, showing that material-to-corona and corona-to-cell relationships can be treated computationally [22]. More recent modeling has extended prediction toward the relative abundance of multiple corona proteins [23], while AI-based work on DNA nanostructures illustrates how composition prediction can be adapted to structurally specialized nanosystems [24]. The data problem remains central. PROTCROWN provides a curated resource intended to organize protein-corona observations and facilitate analysis of protein-nanoparticle interactions [25]. Cross-system meta-analysis coupled with machine learning further demonstrates the possibility of extracting recurrent predictors across nanoparticle and biological-media datasets [26]. These developments support predictive modeling, but they do not establish a universal biological-identity model. For nanocarried phytochemicals, the proposed representation should therefore include more than nominal carrier class. Candidate inputs include particle size, architecture, charge, hydrophobicity, rigidity, coating chemistry, ligand display, cargo-associated changes in the accessible interface, biofluid composition, exposure time

and host context. Outputs should also remain separated: protein abundance, functional motif exposure, cellular recognition and biodistribution are different prediction tasks. Model performance on one should not be interpreted as validation of another.

Feeding corona evidence back into formulation optimization

Corona evidence becomes actionable only when analytical outputs can be compared reliably across formulation iterations. Harmonized proteomic processing has been shown to reduce cross-facility analytical variation in nanoparticle-corona studies [27]. This requirement converts standardization from a reporting issue into a design-loop requirement: if the measured corona changes because the workflow changes, an apparent formulation improvement may be analytical rather than biological. The proposed feedback loop therefore links each modifiable formulation variable to a defined corona observation and a defined functional test. **Table 3** organizes these dimensions without assuming that every carrier requires optimization of every corona property.

Table 3. Proposed dimensions of a corona-aware formulation feedback loop

Design dimension	Evidence returned to formulation	Decision use	Failure signal requiring investigation
Surface chemistry	Recruitment and accessibility pattern	Refine coating or ligand presentation	Intended motif becomes biologically obscured
Cargo state	Cargo-dependent interfacial change	Adjust loading or localization	Loaded and unloaded carriers acquire divergent identity
Biological exposure	Context-specific corona state	Select relevant test medium and timing	Corona changes across compartments
Corona dynamics	Retention and exchange behavior	Choose characterization timescale	Endpoint analysis misses transient interactions
Functional interaction	Uptake, receptor use, immune recognition	Prioritize biologically meaningful surface states	Composition changes without functional consequence
Translation	Persistence across increasingly relevant models	Decide whether prediction can be transferred	In-vitro identity fails outside the original system

Note: This matrix is a proposed formulation-decision framework, not a validated optimization algorithm.

When in vitro corona models fail to represent in vivo identity

A central failure mode is to treat an isolated corona preparation as if it were the intact biological interface. Corona characterization itself can be altered by differences in processing, mass-spectrometry workflows, and contamination or fusion involving other biological particles [27-29]. Improved mass-spectrometry protocols therefore address reproducibility of corona measurement [28], while recent work shows that protein aggregates, extracellular vesicles and lipoprotein fusion can complicate interpretation of ionizable-lipid-nanoparticle corona analyses [29]. Even analytically correct measurements may remain biologically incomplete. Diluted serum, static incubation,

one exposure time and aggressive washing can suppress exchange processes or remove weakly associated components that existed during the actual cell encounter. Conversely, proteins detected after isolation may not remain accessible in vivo. A compositional match is therefore stronger evidence than a compositional mismatch only when sampling, exposure history and analytical recovery are themselves comparable.

The proposed validation sequence is consequently context preserving: characterize without biological exposure, characterize under controlled relevant biofluids, test the functional consequence of the remodeled surface, and then determine whether the same relationship persists in increasingly realistic biological systems. The purpose is not to reproduce every in-vivo molecular event, but to

identify where a simpler model ceases to support the intended mechanistic claim.

Translational boundaries and validation priorities

Host biology can rewrite the corona beyond what formulation descriptors alone predict. Gut microbiota have been shown to regulate lipid-nanoparticle corona formation, biodistribution and cellular uptake, providing a direct example of a host-level variable altering acquired identity [30]. Disease progression, gastrointestinal particle–environment interactions and microbiota status therefore illustrate different forms of biological context dependence [19, 21, 30]. These findings argue against assuming that a corona signature obtained in one host condition represents a transferable formulation property.

The wider protein-corona literature likewise positions biological identity as a concept extending across nanomedicine and other nano–bio contexts, while emphasizing substantial dependence on material and environmental conditions [31]. Translation should therefore proceed by validating the relationship of interest, not merely reproducing a protein list.

For a phytochemical carrier intended for oral, systemic or tissue-localized delivery, priorities differ. Oral systems should preserve digestive, mucus, microbial and epithelial context; systemic systems require attention to complement, circulation, organ distribution and disease-altered plasma; tissue-directed systems require evidence that accessible targeting or corona-derived motifs persist at the relevant site.

Table 4 makes the corresponding boundaries explicit.

Table 4. Mechanisms that can break the link between measured corona and translational biological identity

Boundary mechanism	Why interpretation can fail	Minimum validation priority	Claim that should remain withheld
Biofluid mismatch	Available biomolecules differ from intended exposure	Test relevant biological medium	One universal corona composition
Time and compartment change	Exchange continues after initial exposure	Sample relevant temporal states	Permanent biological identity
Isolation artefact	Washing can remove weak associations	Compare complementary methods	Isolated fraction equals intact interface
Biological-particle interference	Aggregates, vesicles or lipoproteins can confound analysis	Control co-isolation and fusion	Every detected protein was directly surface bound
Host or disease variation	Immune, metabolic and microbial environments differ	Validate relevant host states	Healthy-model corona transfers unchanged
Functional-endpoint mismatch	Composition does not establish receptor use or delivery	Couple composition to functional assays	Protein abundance alone predicts efficacy
Model-domain shift	Predictive models depend on represented materials and media	External and prospective testing	Universal prediction beyond training domain

Note: The boundary structure is a proposed validation framework. It identifies conditions that can weaken inference; it does not specify universal acceptance thresholds.

Taken together, these priorities place corona analysis between material characterization and translational interpretation. A development program becomes corona-aware not when it measures the largest possible protein panel, but when it can show which aspects of acquired identity matter for the intended delivery mechanism, where those relationships persist, and where they fail.

CONCLUSION

A nanocarrier is manufactured with one surface but encounters biology through an acquired and evolving interface. For phytochemical delivery, this distinction is especially consequential because surface architecture, cargo state, biological milieu, corona dynamics and host context can converge before the intended cellular or pharmacological interaction occurs.

The framework proposed here places that transformation inside the formulation design loop. It separates intended surface identity from acquired biological identity;

composition from accessibility; persistent from exchanging corona components; particle uptake from productive cargo delivery; and in-vitro characterization from translational validation. These separations prevent corona biology from becoming either an unexplained source of formulation failure or an overinterpreted biomarker of success.

Corona-aware design does not require eliminating protein adsorption or reproducing an invariant corona. It requires identifying which remodeled surface state is relevant to the intended function, determining how controllable formulation variables influence that state, and testing whether the resulting formulation–corona–function relationship survives increasingly realistic biological contexts. The development target is therefore not merely a stable manufactured nanoparticle, but a biological nanoparticle whose relevant identity has been explicitly interrogated.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

REFERENCES

- [1] Salvati A. The biomolecular corona of nanomedicines: Effects on nanomedicine outcomes and emerging opportunities. *Curr Opin Biotechnol.* 2024;87:103101. doi:10.1016/j.copbio.2024.103101
- [2] Voke E, Huang Y, Santini C, Dilliard SA, Wang M, Song X, et al. Protein corona formed on lipid nanoparticles compromises delivery efficiency of mRNA cargo. *Nat Commun.* 2025;16(1):8699. doi:10.1038/s41467-025-63726-2
- [3] García-Álvarez R, Hadjidemetriou M, Sánchez-Iglesias A, Liz-Marzán LM, Kostarelos K. In vivo formation of protein corona on gold nanoparticles. The effect of their size and shape. *Nanoscale.* 2018;10(3):1256-64. doi:10.1039/C7NR08322J
- [4] Miao Y, Li L, Wang Y, Wang J, Zhou Y, Guo L, et al. Regulating protein corona on nanovesicles by glycosylated polyhydroxy polymer modification for efficient drug delivery. *Nat Commun.* 2024;15(1):1159. doi:10.1038/s41467-024-45254-7
- [5] Pustulka SM, Ling K, Pish SL, Champion JA. Protein nanoparticle charge and hydrophobicity govern protein corona and macrophage uptake. *ACS Appl Mater Interfaces.* 2020;12(43):48284-95. doi:10.1021/acsami.0c12341
- [6] Marques C, Borchard G, Jordan O. Unveiling the challenges of engineered protein corona from the proteins' perspective. *Int J Pharm.* 2024;654:123987. doi:10.1016/j.ijpharm.2024.123987
- [7] Chen F, Wang G, Griffin JJ, Brennenman B, Banda NK, Holers VM, et al. Complement proteins bind to nanoparticle protein corona and undergo dynamic exchange in vivo. *Nat Nanotechnol.* 2017;12(4):387-93. doi:10.1038/nnano.2016.269
- [8] Baimanov D, Wang J, Zhang J, Liu K, Cong Y, Shi X, et al. In situ analysis of nanoparticle soft corona and dynamic evolution. *Nat Commun.* 2022;13(1):5389. doi:10.1038/s41467-022-33044-y
- [9] Dolci M, Wang Y, Nooteboom SW, Soto Rodriguez PED, Sánchez S, Albertazzi L, et al. Real-time optical tracking of protein corona formation on single nanoparticles in serum. *ACS Nano.* 2023;17(20):20167-78. doi:10.1021/acsnano.3c05872
- [10] Wang S, Duan Z, Zheng L, Yang Y, Zheng X, Xiao D, et al. Digestive enzyme corona formed in simulated gastrointestinal tract and its impact on EGCG release from banana resistant starch nanoparticles. *Food Hydrocoll.* 2024;146:109267. doi:10.1016/j.foodhyd.2023.109267
- [11] Ashkarran AA, Gharibi H, Sadeghi SA, Modaresi SM, Wang Q, Lin TJ, et al. Small molecule modulation of protein corona for deep plasma proteome profiling. *Nat Commun.* 2024;15(1):9621. doi:10.1038/s41467-024-53966-z
- [12] Wu YR, Zhou Q, Li J, Wang W, Zhou YB, Liu K. The formation of protein coronas and its effect on the quercetin-edible dock protein nanoparticles. *Food Hydrocoll.* 2024;157:110432. doi:10.1016/j.foodhyd.2024.110432
- [13] Francia V, Yang K, Deville S, Reker-Smit C, Nelissen I, Salvati A. Corona composition can affect the mechanisms cells use to internalize nanoparticles. *ACS Nano.* 2019;13(10):11107-21. doi:10.1021/acsnano.9b03824
- [14] Yang D, Feng Y, Yuan Y, Zhang L, Zhou Y, Midgley AC, et al. Protein coronas derived from mucus act as both spear and shield to regulate transferrin functionalized nanoparticle transcellular transport in enterocytes. *ACS Nano.* 2024;18(10):7455-72. doi:10.1021/acsnano.3c11315
- [15] Renzi S, Digiacoimo L, Pozzi D, Quagliarini E, Vulpis E, Giuli MV, et al. Structuring lipid nanoparticles, DNA, and protein corona into stealth bionanoarchitectures for in vivo gene delivery. *Nat Commun.* 2024;15(1):9119. doi:10.1038/s41467-024-53569-8
- [16] Kim W, Ly NK, He Y, Li Y, Yuan Z, Yeo Y. Protein corona: Friend or foe? Co-opting serum proteins for nanoparticle delivery. *Adv Drug Deliv Rev.* 2023;192:114635. doi:10.1016/j.addr.2022.114635
- [17] Caracciolo G. Artificial protein coronas: Directing nanoparticles to targets. *Trends Pharmacol Sci.* 2024;45(7):602-13. doi:10.1016/j.tips.2024.05.003
- [18] Li Y, Wu W, Liu Q, Wu Q, Ren P, Xi X, et al. Specific surface-modified iron oxide nanoparticles trigger complement-dependent innate and adaptive antileukaemia immunity. *Nat Commun.* 2024;15(1):10400. doi:10.1038/s41467-024-54810-0
- [19] Shaw JR, Caprio N, Truong N, Weldemariam M, Tran A, Pilli N, et al. Inflammatory disease progression shapes nanoparticle biomolecular corona-mediated immune activation profiles. *Nat Commun.* 2025;16(1):924. doi:10.1038/s41467-025-56210-4
- [20] Dilliard SA, Sun Y, Brown MO, Sung YC, Chatterjee S, Farbiak L, et al. The interplay of quaternary ammonium lipid structure and protein corona on lung-specific mRNA delivery by selective organ targeting (SORT) nanoparticles. *J Control Release.* 2023;361:361-72. doi:10.1016/j.jconrel.2023.07.058

- [21] Wu J, Ni M, Xing L, Wang Y, Liu X, Zheng Y, et al. Surface hydrophobicity and rigidity determines protein corona on orally delivered nanoparticles treating colitis. *Nat Commun.* 2026;17(1):2497. doi:10.1038/s41467-026-70453-9
- [22] Ban Z, Yuan P, Yu F, Peng T, Zhou Q, Hu X. Machine learning predicts the functional composition of the protein corona and the cellular recognition of nanoparticles. *Proc Natl Acad Sci U S A.* 2020;117(19):10492-9. doi:10.1073/pnas.1919755117
- [23] Fu X, Yang C, Su Y, Liu C, Qiu H, Yu Y, et al. Machine learning enables comprehensive prediction of the relative protein abundance of multiple proteins on the protein corona. *Research (Wash D C).* 2024;7:0487. doi:10.34133/research.0487
- [24] Huzar J, Coreas R, Landry MP, Tikhomirov G. AI-based prediction of protein corona composition on DNA nanostructures. *ACS Nano.* 2025;19(4):4333-45. doi:10.1021/acsnano.4c12259
- [25] Su Y, Fu X, Wei L, Zhang Z, Zou Q, Cui F. PROTCROWN: A manually curated resource of protein corona data for unlocking the potential of protein-nanoparticle interactions. *Nano Lett.* 2025;25(5):1739-44. doi:10.1021/acs.nanolett.4c05955
- [26] Canchola A, Li K, Chen K, Borboa-Pimentel A, Chou C, Dela Rama R, et al. Meta-analysis and machine learning prediction of protein corona composition across nanoparticle systems in biological media. *ACS Nano.* 2025;19(43):37633-50. doi:10.1021/acsnano.5c08608
- [27] Gharibi H, Ashkarran AA, Jafari M, Voke E, Landry MP, Saei AA, et al. A uniform data processing pipeline enables harmonized nanoparticle protein corona analysis across proteomics core facilities. *Nat Commun.* 2024;15(1):342. doi:10.1038/s41467-023-44678-x
- [28] Tang H, Wang J, Mahmoudi M. Improving accuracy and reproducibility of mass spectrometry characterization of protein coronas on nanoparticles. *Nat Protoc.* 2025;20(11):3057-63. doi:10.1038/s41596-025-01204-1
- [29] Borhan B, Murray AM, Saei AA, Ghaffari B, Jackson JE, Mohammed N, et al. Influence of protein aggregates, extracellular vesicles, and lipoprotein fusion on ionizable lipid nanoparticles protein corona analysis. *Nat Commun.* 2026;17(1):5261. doi:10.1038/s41467-026-74240-4
- [30] Khetan R, Donnellan L, Collins K, Kamath S, Ariaee A, Rajapaksha W, et al. The gut microbiota regulates the protein corona formation, biodistribution, and cellular uptake of lipid nanoparticles. *J Control Release.* 2026;395:114995. doi:10.1016/j.jconrel.2026.114995
- [31] Mahmoudi M, Landry MP, Moore A, Coreas R. The protein corona from nanomedicine to environmental science. *Nat Rev Mater.* 2023;8(7):422-38. doi:10.1038/s41578-023-00552-2