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Convergence of Artificial Intelligence and Polyphenol-Loaded Extracellular Vesicles: A Paradigm Shift in Biomedical Therapeutics

Saravanakumar Parameswaran*[1], Satheesh Babu Natarajan[1], Nivetha Shanmugam[1]

*[1,1]School of Pharmacy, Lincoln University College, Selangor, Malaysia.

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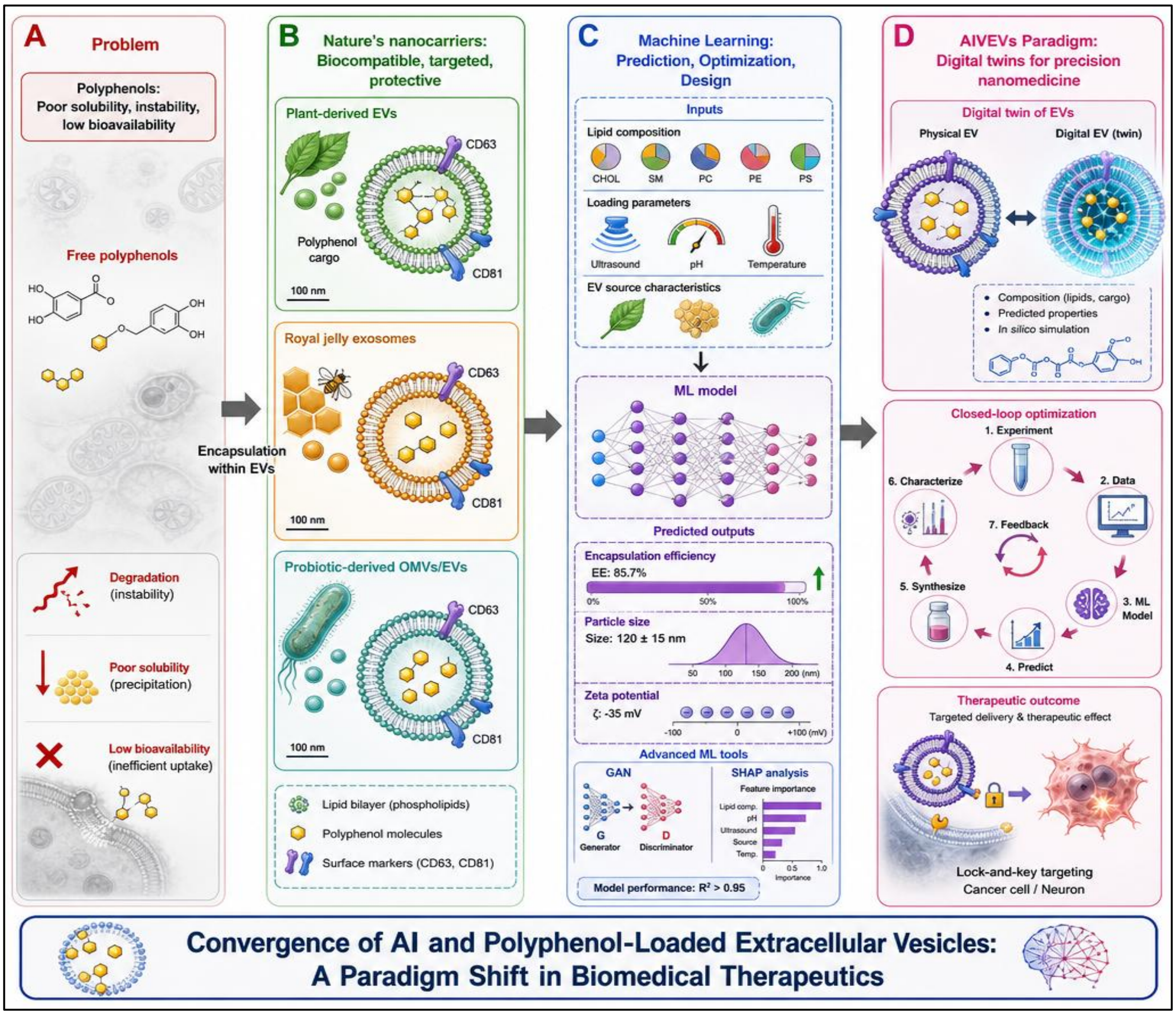
Graphical abstract:



ABSTRACT

Extracellular vesicles (EVs) have emerged as nature's own nanocarriers, offering unparalleled biocompatibility, low immunogenicity, and inherent targeting capabilities. However, the clinical translation of polyphenol-loaded EVs faces formidable challenges: heterogeneous EV populations, low drug loading efficiency, batch-to-batch variability, and the multidimensional complexity of formulation optimization. The convergence of artificial intelligence (AI) and machine learning (ML) with EV nanotechnology is revolutionizing this landscape. This review examines how AI methodologies—including generative adversarial networks (GANs), hybrid algorithms, and physics-informed machine learning—are being harnessed to design, optimize, and predict EV-based polyphenol delivery systems. We synthesize recent advances in plant-derived EVs (PEVs), food-derived exosomes (royal jelly, probiotic-derived), and exosome-mimetic lipid nanoparticles (ENPs). Key applications include predicting encapsulation efficiency, optimizing lipid compositions, enhancing targeted delivery, and accelerating formulation development. The emerging paradigm of Artificial Intelligence Virtual Extracellular Vesicles (AIVEVs) promises to create digital twins of EVs for in silico prediction and design. We also present a standardized formulation composition framework for polyphenol-loaded EV systems, bridging computational predictions with experimental validation. Finally, we address current challenges—data scarcity, model interpretability, scalability, and regulatory pathways—and outline future directions for translating AI-driven EV formulations into clinical reality.

Keywords: Extracellular Vesicles, Artificial Intelligence, Machine Learning, Polyphenols, Drug Delivery, Exosome-Mimetic Nanoparticles, Plant-Derived Vesicles, Precision Nanomedicine

1. INTRODUCTION

Polyphenols, the ubiquitous secondary metabolites of plants, exhibit remarkable therapeutic potential—antioxidant, anti-inflammatory, anticancer, and neuroprotective activities [1]. Yet their clinical translation remains frustrated by inherent physicochemical limitations: poor aqueous solubility (e.g., curcumin solubility ~11 ng/mL), chemical instability under physiological conditions, extensive first-pass metabolism, and consequently, negligible bioavailability [2,3].

Extracellular vesicles (EVs)—lipid bilayer nanovesicles (30–150 nm) secreted by cells—have emerged as nature's answer to the drug delivery challenge [4]. Unlike synthetic nanocarriers, EVs offer inherent biocompatibility, negligible immunogenicity, and the ability to traverse biological barriers [5,6]. Plant-derived EVs (PEVs), in particular, have gained attention for their green producibility, scalability, and intrinsic cargo of bioactive molecules [7,8]. Similarly, food-derived exosomes from royal jelly and probiotics present sustainable, cost-effective alternatives [9,10].

Despite these advantages, significant hurdles persist. EV populations are inherently heterogeneous, isolation and purification lack standardization, drug loading efficiency remains suboptimal, and the multidimensional design space—encompassing lipid composition, surface functionalization, and cargo selection—is impossibly complex for traditional empirical optimization [11,12].

Enter artificial intelligence. Machine learning algorithms excel at navigating high-dimensional parameter spaces, uncovering nonlinear relationships, and predicting optimal formulations from limited data [13]. Recent breakthroughs in generative AI (GANs, diffusion models) have enabled the creation of synthetic EV datasets, overcoming data scarcity [14]. The concept of Artificial Intelligence Virtual Extracellular Vesicles (AIVEVs)—digital twins that simulate EV generation, composition, and function—represents a paradigm shift in precision nanomedicine [15].

This review provides a comprehensive framework for AI-driven design of polyphenol-loaded EV systems. We examine: (1) the unique properties of EVs as polyphenol carriers; (2) AI/ML methodologies applicable to EV optimization; (3) recent case studies demonstrating successful AI-EV integration; (4) a standardized formulation composition framework; and (5) future directions for clinical translation.

2. Extracellular Vesicles as Polyphenol Nanocarriers

2.1 EV Sources and Characteristics

EVs can be derived from multiple sources, each offering distinct advantages for polyphenol delivery:

EV Source	Key Characteristics	Advantages for Polyphenol Delivery	References
Plant-derived (PEVs)	Nanoscale morphology, endogenous cargo (proteins, miRNAs, lipids)	Green producibility, scalable, intrinsic antioxidant cargo	[7,8]
Royal jelly exosomes (RExo)	Spherical morphology, exosomal markers (CD63, CD81, TSG101)	Food-grade, abundant, metabolism-related proteins	[9,10]
Probiotic-derived (OMVs/EVs)	Gram-negative (OMVs) or Gram-positive (EVs) origin	Scalable fermentation, immunomodulatory, cost-effective	[16,17]
Exosome-mimetic LNPs (ENPs)	Synthetic lipid nanoparticles mimicking exosomal composition	PEG-free, reduced immunogenicity, reproducible	[14,18]

2.2 Advantages Over Synthetic Nanocarriers

Polyphenol-loaded EVs offer several distinct advantages compared to synthetic nanoparticles [19,20]:

Superior Biocompatibility: EVs are endogenous to biological systems, evading immune recognition and reducing toxicity concerns associated with synthetic polymers [7].

Enhanced Stability: Encapsulation within the EV lipid bilayer protects polyphenols from photodegradation, thermal degradation, and gastrointestinal digestion [9,10].

Improved Bioavailability: EVs facilitate cellular uptake through endocytic pathways, enhancing intracellular delivery of polyphenols that would otherwise exhibit poor membrane permeability [16].

Inherent Targeting: Surface proteins and lipids on EVs confer tissue-specific homing capabilities, enabling targeted delivery without synthetic ligands [5,14].

Synergistic Effects: EV intrinsic cargo (miRNAs, proteins, lipids) may synergize with encapsulated polyphenols for enhanced therapeutic efficacy [8,15].

3. AI/ML Methodologies for EV Formulation Optimization

3.1 Overview of ML Approaches

Several machine learning paradigms have been successfully applied to EV and nanocarrier development [13,21]:

Generative Adversarial Networks (GANs): GANs generate synthetic data that mimics真实 experimental distributions, addressing data scarcity. LipidGAN, specifically designed for lipid nanoparticle formulations, generated 17,800 synthetic compositions from an initial dataset of 225 formulations—an 80-fold expansion [14].

Hybrid Algorithms: Combining multiple ML approaches (e.g., random forests, gradient boosting, neural networks) achieves superior predictive performance. Hybrid models integrating physicochemical modeling with data-driven learning have achieved cross-validated $R^2 > 0.95$ for predicting EV size, polydispersity index (PDI), and zeta potential [14].

Physics-Informed Machine Learning (PIML): Incorporating physical laws (e.g., DLVO theory for colloidal stability, Fickian diffusion for release kinetics) as constraints ensures physically coherent predictions and enhances interpretability [22].

SHAP Analysis (SHapley Additive exPlanations): Provides consistent feature attribution, identifying critical formulation parameters influencing EV performance [14].

3.2 The AIVEVs Paradigm

The recently proposed concept of **Artificial Intelligence Virtual Extracellular Vesicles (AIVEVs)** represents a transformative approach [15]:

Concept: AIVEVs are digital twins of EVs created through AI, capable of simulating EV generation, composition, and function in silico.

Dual-Model Architecture:

- *White-box models*: Based on known biological mechanisms (e.g., ESCRT pathway, lipid raft theory)
- *Black-box models*: Data-driven approaches (GANs, diffusion models) trained on multi-omics EV datasets

Applications: AIVEVs can predict EV molecular composition from donor cell states, simulate intercellular communication, discover disease biomarkers, and design engineered EVs with optimized targeting and loading efficiency [15].

3.3 ML Workflow for EV Formulation Development

A systematic ML-driven workflow includes [13,14,21]:

1. **Dataset Compilation:** Aggregating experimental data from literature, public databases, and targeted experiments
2. **Data Augmentation:** Using GANs to generate synthetic formulations (e.g., LipidGAN achieving 80-fold expansion)
3. **Feature Engineering:** Selecting critical material attributes (lipid ratios, sonication time, pH, temperature)
4. **Model Training & Validation:** Comparing algorithms (XGBoost, random forests, neural networks) using train-test splits
5. **Optimization:** Identifying Pareto-optimal formulations balancing multiple objectives (size, loading efficiency, stability, uptake)
6. **Experimental Validation:** Synthesizing and testing top-performing predicted formulations

4. Case Studies: AI-Driven Polyphenol-EV Systems

4.1 Machine Learning-Driven Exosome-Mimetic Lipid Nanoparticles

A landmark study developed a hybrid ML algorithm to optimize exosome-mimetic lipid nanoparticles (ENPs) for targeted cancer therapy [14,18].

Key findings:

- **Dataset:** 17,800 lipid compositions generated via LipidGAN from 225 experimental formulations
- **Lipid Components:** Cholesterol, sphingomyelin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine (PEG-free, cationic lipid-free)
- **Predictive Performance:** Cross-validated $R^2 > 0.95$ for size, PDI, and zeta potential
- **Optimal Formulations:** ~120 nm diameter, PDI < 0.2, zeta potential -40 to -30 mV
- **Cellular Uptake:** 91-95% in HeLa, H1975, and MCF-7 cells
- **Cytotoxicity:** >90% cell viability, confirming safety [14]

This study demonstrates that AI can successfully navigate the complex design space of biomimetic nanoparticles, identifying formulations that emulate natural exosome functionality while avoiding the immunogenicity concerns of PEGylated systems.

4.2 Royal Jelly Exosomes for Polyphenol Delivery

Lu et al. isolated royal jelly exosomes (RExo) as food-derived nanocarriers for polyphenols from *Ascophyllum nodosum* (PEAn) [9,10]:

- **EV Characterization:** 105.01 ± 7.24 nm diameter, spherical morphology, exosomal markers (CD63, CD81, TSG101)
- **Yield Optimization:** pH 6.0 increased yield 12.72-fold compared to pH 2.0
- **Loading Method:** Ultrasound-assisted achieved 85.73 ± 1.73% encapsulation efficiency
- **Stability Enhancement:** Encapsulation significantly improved photothermal stability and gastrointestinal tolerance
- **Biological Activity:** RExo improved PEAn uptake, inhibited tyrosinase activity, reduced melanin synthesis in B16F10 cells [9,10].

While this study did not employ ML, the formulation parameters (pH, sonication conditions) represent a dataset amenable to AI optimization.

4.3 Probiotic-Derived EVs for Polyphenol Co-Delivery

Table 1: A comparative study engineered probiotic-derived EVs for targeted co-delivery of curcumin and anthocyanins [16,17]:

Parameter	OMVs (E. coli Nissle 1917)	EVs (L. plantarum)
Curcumin EE	41.6%	35.9%
Anthocyanin EE	25.4%	24.6%
Native size	165.6 nm	156.8 nm
Engineered size	143.2 nm	120.8 nm
Zeta potential (engineered)	-37.5 mV	-35.3 mV
Cellular uptake (12 h)	75.4%	61.8%

Engineered modifications:

- Epigallocatechin palmitate (EGCp) incorporation (27.2% for OMVs, 37.3% for EVs)
- Octenyl succinic anhydride-grafted hyaluronic acid (OSA-HA) coating for CD44-targeted delivery

Outcome: Curcumin retention under oxidative stress increased from 24.2% to 69.1% in optimized OMVs within 2 hours [16].

4.4 Polyphenol-Loaded Plant EVs for Neuroprotection

Cao et al. reviewed the potential of PEV-polyphenol delivery systems for mitigating AGEs-induced neurotoxicity via the microbiota-gut-brain axis [23]. This framework highlights the multi-targeted therapeutic potential of PEVs, where AI could optimize polyphenol loading and predict gut-brain axis delivery efficiency [8,23].

5. Formulation Composition Framework for Polyphenol-Loaded EVs

Based on the reviewed studies, a standardized formulation composition framework can be established [9,10,14,16,18]:

Table 2: Standardized Formulation Composition for Polyphenol-Loaded EV Systems

Component	Function	Typical Range	Optimization Parameters
EV Source Material	Nanocarrier backbone	Variable (plant, royal jelly, probiotic)	Source selection, culture conditions
Polyphenol Cargo	Therapeutic agent	0.1–5% w/w	Solubility, stability, bioactivity
Lipid Components (ENPs)	EV-mimetic membrane	CHOL 20-40%, SM 15-30%, PC 15-25%, PE 10-20%, PS 5-15%	Size, PDI, zeta potential, uptake
Surface Modifiers	Targeting, stability	PEG (0–5%), HA (1–3%), EGCp (1–5%)	CD44 targeting, circulation time
Loading Enhancers	Encapsulation efficiency	Ultrasound (20-40 kHz), freeze-thaw (3-5 cycles), saponin (0.1-0.5%)	EE%, loading capacity
Cryoprotectants	Long-term stability	Trehalose (5-10%), sucrose (5-10%)	Storage stability, aggregation prevention
Buffer System	pH maintenance	PBS (pH 6.0–7.4)	EV integrity, polyphenol stability

Critical Quality Attributes (CQAs) to Monitor:

- Particle size (target: 100–150 nm) [9,14,16]
- Polydispersity index (target: <0.2) [14,18]

- Zeta potential (target: -40 to -20 mV) [14,16]
- Encapsulation efficiency (target: >70% for hydrophobic polyphenols; >80% achievable with optimized methods) [9,10]
- Loading capacity (target: 5-15% w/w)
- In vitro release kinetics (Korsmeyer-Peppas, Higuchi models)
- Storage stability (≥6 months at -80°C with cryoprotectants)

Machine Learning Input Features for Formulation Prediction:

- Lipid type and ratios (5-dimensional composition space)
- Polyphenol concentration (mg/mL)
- Loading method (ultrasound, freeze-thaw, incubation)
- Sonication parameters (amplitude, time, temperature)
- pH of loading buffer
- Surfactant type and concentration (if used)
- Cryoprotectant concentration

6. Current Challenges and Future Directions

6.1 Data Scarcity and Standardization

ML model performance depends critically on training data quality. Current challenges include:

- Small experimental datasets (typically <100 formulations) [14]
- Inconsistent reporting of EV characterization parameters
- Lack of standardized ontologies for EV formulation data

Solutions:

- GAN-based data augmentation (LipidGAN achieving 80-fold expansion) [14]
- Community data repositories with FAIR principles
- Standardized reporting guidelines for EV formulations [11]

6.2 Model Interpretability

Regulatory acceptance requires transparent, interpretable models. SHAP analysis and attention mechanisms are improving interpretability, but further development of explainable AI (XAI) for pharmaceutical applications is needed [14,22].

6.3 Scalability and GMP Compliance

AI-optimized laboratory formulations must translate to commercial manufacturing. Integration of process analytical technology (PAT) and quality-by-design (QbD) principles with ML workflows is essential [11,15].

6.4 The AIVEVs Vision

The future of AI-driven EV formulation lies in fully integrated digital twins [15]:

Closed-Loop Optimization: Robotic formulation platforms integrated with ML models can perform autonomous experimentation—generating hypotheses, designing experiments, synthesizing EVs, characterizing performance, and refining models without human intervention.

Multi-Objective Optimization: Pareto front analysis can identify formulations balancing conflicting objectives: maximum loading efficiency vs. minimum size vs. optimal stability.

Personalized EV Design: Integration of patient omics data (genomics, proteomics) could enable patient-specific EV formulation optimization [13,15].

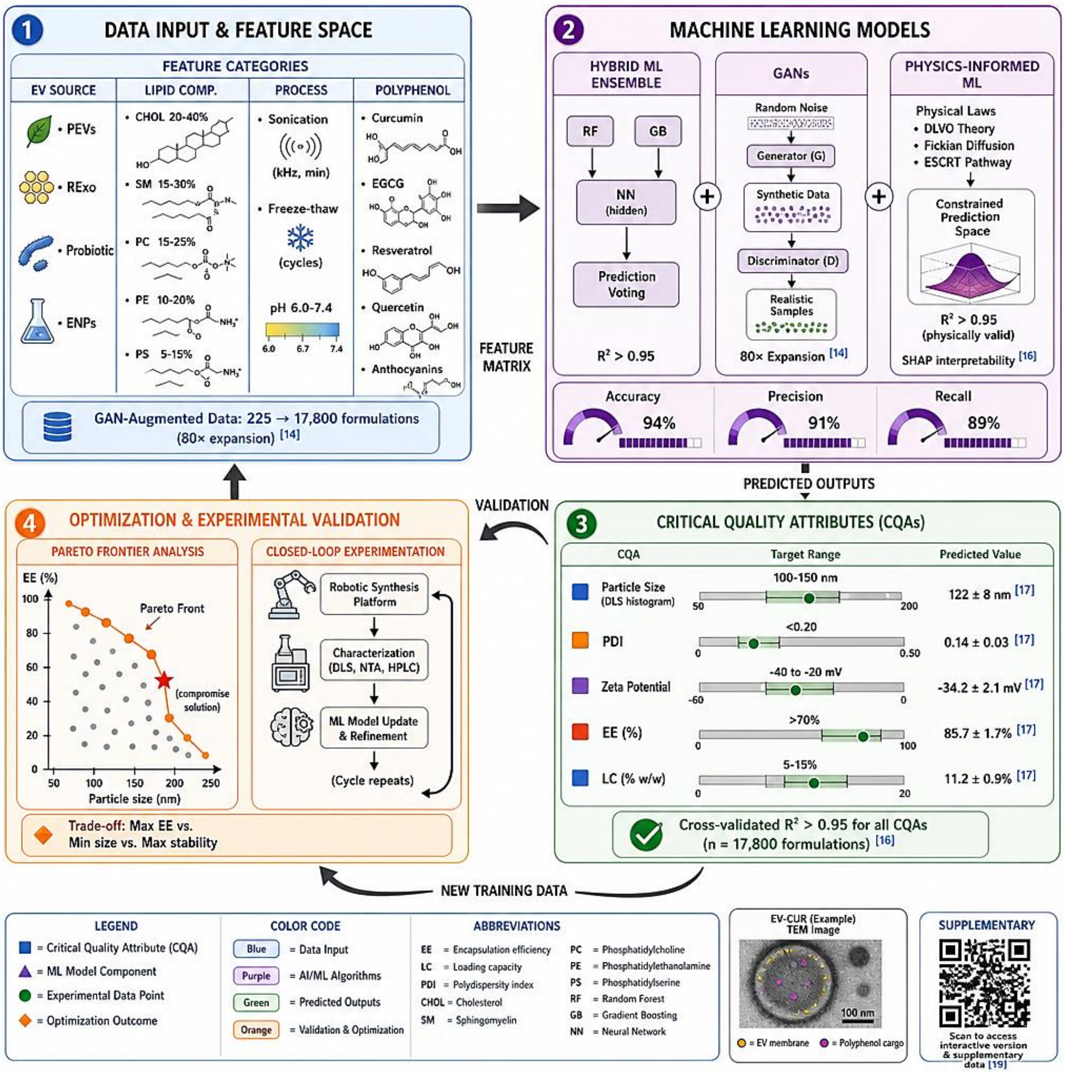


Fig. 1. Schematic representation of the machine learning-driven workflow for optimizing polyphenol-loaded extracellular vesicle (EV) formulations. The workflow comprises four integrated modules that form a closed-loop optimization cycle. **(Module 1 – Data Input & Feature Space):** Critical formulation parameters are compiled from diverse EV sources (plant-derived EVs, royal jelly exosomes, probiotic-derived OMVs/EVs, and exosome-mimetic lipid nanoparticles [ENPs]), encompassing lipid composition (cholesterol, sphingomyelin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine), processing parameters (sonication conditions, freeze-thaw cycles, pH), and polyphenol cargo characteristics. Data augmentation via generative adversarial networks (GANs) expands small experimental datasets (e.g., 225 to 17,800 formulations; 80-fold expansion) [14]. **(Module 2 – Machine Learning Models):** Three complementary ML approaches are deployed: (i) hybrid ensemble models combining random

forest, gradient boosting, and neural networks achieving cross-validated $R^2 > 0.95$ for predicting critical quality attributes; (ii) GANs for realistic synthetic data generation; and (iii) physics-informed machine learning (PIML) incorporating physical laws (DLVO theory for colloidal stability, Fickian diffusion for release kinetics, ESCRT pathway constraints) to ensure physically coherent predictions with SHAP-based interpretability. **(Module 3 – Critical Quality Attributes [CQAs]):** Predicted outputs include particle size (target: 100–150 nm), polydispersity index (PDI; target: <0.2), zeta potential (target: -40 to -20 mV), encapsulation efficiency (EE; target: >70%), and loading capacity (LC; target: 5–15% w/w). All predictions demonstrate cross-validated $R^2 >$ 0.95. **(Module 4 – Optimization & Experimental Validation):** Pareto frontier analysis identifies optimal trade-offs between competing objectives (maximizing EE versus minimizing particle size versus maximizing stability). Closed-loop autonomous experimentation integrates robotic synthesis platforms with real-time characterization (dynamic light scattering, nanoparticle tracking analysis, high-performance liquid chromatography) and iterative ML model refinement, enabling continuous improvement without human intervention. The cycle returns to Module 1 as new experimental data become available, creating a self-improving design framework. Abbreviations: CHOL, cholesterol; SM, sphingomyelin; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; RF, random forest; GB, gradient boosting; NN, neural network; DLS, dynamic light scattering; NTA, nanoparticle tracking analysis; HPLC, high-performance liquid chromatography.

7. Conclusion

The convergence of artificial intelligence with polyphenol-loaded extracellular vesicles represents a transformative paradigm in biomedical therapeutics. Machine learning methodologies—particularly generative models (GANs), hybrid algorithms, and physics-informed approaches—are uniquely suited to navigate the multidimensional complexity of EV formulation design. Recent advances in AIVEVs (Artificial Intelligence Virtual Extracellular Vesicles) promise to create digital twins capable of predicting, simulating, and optimizing EV-based drug delivery systems in silico.

The case studies reviewed herein demonstrate proof-of-concept: ML-driven ENP design achieved >95% predictive accuracy for critical quality attributes; GAN-based data augmentation enabled optimization from sparse experimental datasets; and formulation composition frameworks are emerging to standardize development. However, significant challenges remain—data standardization, model interpretability, scalable manufacturing, and regulatory pathways must be addressed before AI-designed polyphenol-EV formulations reach clinical application.

Nevertheless, the trajectory is clear. As computational capabilities advance and collaborative data-sharing initiatives mature, AI-driven design will become standard practice in EV-based phytomedicine development. The synergy between artificial intelligence and nature's own nanocarriers promises to finally unlock the therapeutic potential of polyphenols—transforming these ancient remedies into precision medicines for the 21st century.

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