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Review article

Artificial intelligence in predicting personalized nanocarrier formulations for herbal drugs: Bridging phytomedicine and precision nanotechnology

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ABSTRACT

Herbal drugs offer significant therapeutic benefits but face challenges such as poor bioavailability, low stability, and variable patient responses. Nanocarrier-based delivery systems can overcome these limitations. However, their development often relies on time-consuming trial-and-error methods, which lack personalization. This review explores how advanced artificial intelligence (AI) models enhance nanocarrier formulation for phytoconstituents. These models include machine learning, deep learning, transformer-based models, and graph neural networks. They optimize nanocarrier selection, drug–carrier compatibility, and release profiles while incorporating patient-specific omics data. These computational tools accurately predict key parameters, such as particle size, drug loading, and release kinetics, for phytoactives like curcumin, quercetin, and genistein. Emerging applications include optimizing herbal nanocarriers for antimicrobial efficacy in infectious disease treatment. By integrating genomics, microbiome, and metabolomics data, these models enable tailored herbal nanomedicines. This data-driven approach, combining nanotechnology with phytomedicine, accelerates formulation, improves therapeutic efficacy, and advances precision herbal therapeutics. It also shows promise for infectious disease applications. Progress in explainable AI and supportive regulatory frameworks is essential for clinical translation.

1. Introduction

Herbal drugs, derived from medicinal plants, provide therapeutic benefits through bioactive compounds with antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. Notably, their antimicrobial potential is critical for addressing global challenges like infectious diseases, including bacterial, viral, and fungal infections, where compounds like berberine and curcumin show promise against pathogens such as Staphylococcus aureus and Candida albicans.[1] However, their clinical use is limited by poor bioavailability, instability, and variable patient responses.[2] Nanodelivery systems, including liposomes, dendrimers, solid lipid nanoparticles, nanoemulsions, and polymeric micelles, enable encapsulation, protection, and targeted delivery, improving pharmacokinetics and reducing side effects.[3,4] Designing these systems is challenging, requiring optimization of parameters like particle size, surface charge, encapsulation efficiency, and release kinetics. Advanced AI models, including machine learning, deep learning, transformer-based models, and graph neural networks (GNNs), offer innovative solutions by analyzing extensive datasets of phytoactives, predicting their physicochemical properties, modeling drug-carrier interactions, and refining formulation parameters. For instance, transformer models can process sequential omics data to predict patient-specific antimicrobial responses, while GNNs model complex molecular interactions for optimizing nanocarrier compatibility with herbal antimicrobials.[5] These tools also integrate patient-specific data (e.g., genetics, biomarkers, metabolic pathways, microbiome profiles) to develop tailored nanodelivery systems, advancing precision phytomedicine for applications like infectious disease treatment.[6] The integration of AI with nanotechnology, particularly in the development of personalized nanocarriers for herbal drugs, holds significant promise for next-generation therapeutic development. This synergy aligns with the broader goals of personalized and preventive health care. Unlike

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conventional "one-size-fits-all" treatment models, personalized nanomedicine aims to tailor therapy to an individual's biological profile, ensuring higher efficacy, reduced toxicity, and better patient outcomes. Despite its potential, this interdisciplinary field is still in its early stages.[7] Several challenges need to be addressed, including the standardization of herbal extracts, generation of high-quality datasets, validation of AI models, and regulatory considerations surrounding herbal nanomedicine. This study explores the role of AI in predicting and optimizing personalized nanocarrier formulations for herbal drugs, reviewing current advances in AI-driven methods and discussing associated challenges and opportunities. The primary contribution of this manuscript is to provide a comprehensive framework for integrating AI, nanotechnology, and phytomedicine, emphasizing data-driven strategies to accelerate formulation design, enhance therapeutic efficacy, and advance personalized herbal therapeutics, while highlighting key performance assessment metrics for AI models to ensure reliable and reproducible outcomes.

1.1. Challenges in herbal drug delivery

Despite the therapeutic potential of herbal medicines, their successful clinical translation faces several challenges that hinder their widespread use in modern pharmacotherapy. Phytoconstituents such as quercetin, curcumin, berberine, and andrographolide often exhibit poor aqueous solubility and low bioavailability, limiting their systemic absorption and therapeutic efficacy.[6] Herbal drugs, such as quercetin, curcumin, berberine, and andrographolide, face significant barriers to clinical translation. Poor aqueous solubility and low bioavailability, as seen with curcumin's solubility of 11 ng/mL in aqueous media,[8] limit systemic absorption. Chemical instability under physiological conditions (e.g., quercetin's degradation at pH $>$ 7) and rapid first-pass metabolism further reduce therapeutic efficacy. Batch-to-batch variability in herbal extracts, driven by differences in plant sources and extraction methods, complicates standardization and regulatory approval. [9] These challenges necessitate advanced delivery systems, such as nanocarriers, to enhance pharmacokinetic profiles and ensure consistent therapeutic outcomes. These multifaceted issues necessitate innovative formulation approaches, such as nanocarrier-based delivery systems, to improve the biopharmaceutical performance and therapeutic reliability of phytoconstituents. A network map of phytoconstituents and their AI-predicted compatible nanocarrier types is shown in Fig. 1.

1.2. Need for AI-guided formulation strategies

The development of effective drug delivery systems is often challenged by the complexity of formulation variables and the need to optimize multiple parameters simultaneously. Traditional trial-and-error methods are time-consuming, resource-intensive, and may fail to identify optimal formulations. In this context, AI-guided formulation strategies offer a transformative approach by enabling data-driven decision-making, predictive modeling, and rapid optimization.[10] Techniques such as artificial neural networks (ANN), machine learning algorithms, and deep learning can analyze vast datasets, identify complex nonlinear relationships, and predict formulation outcomes with high accuracy. This not only accelerates the development process but also enhances formulation efficiency, reproducibility, and cost-effectiveness. As pharmaceutical research increasingly demands precision and adaptability, AI-guided strategies are becoming indispensable tools for modern formulation science.[11,12] Fig. 2 illustrates AI-Guided pipeline for designing personalized herbal nanocarriers.

1.3. AI/ML models in pharmaceutical sciences

Machine learning is transforming pharmaceutical sciences by analyzing extensive datasets, predicting drug behavior, and streamlining formulation design. It encompasses supervised, unsupervised, and deep learning paradigms, each suited to specific applications. Supervised learning uses labeled data to predict outcomes like drug release profiles, formulation success, and pharmacokinetic parameters. Algorithms such as support vector machines, decision trees, random forests, and neural networks effectively map nonlinear relationships between inputs (e.g., polymer ratio, processing time) and outputs (e.g., particle size, zeta potential).[13,14] For herbal nanodelivery, random forests and gradient boosting excel in predicting solubility of phytoactives like curcumin and quercetin, leveraging molecular descriptors such as logP and hydrogen bonding capacity.[15] Support vector machines (SVMs) are well-suited for classifying drug-carrier compatibility, such as determining whether liposomes or polymeric nanoparticles are optimal for encapsulating berberine based on physicochemical properties such as molecular weight and polarity.[16] For modeling drug release kinetics, artificial neural networks (ANNs) are preferred because of their capacity to capture complex temporal patterns, as demonstrated in studies predicting the release profiles of andrographolide from solid lipid nanoparticles.[17]

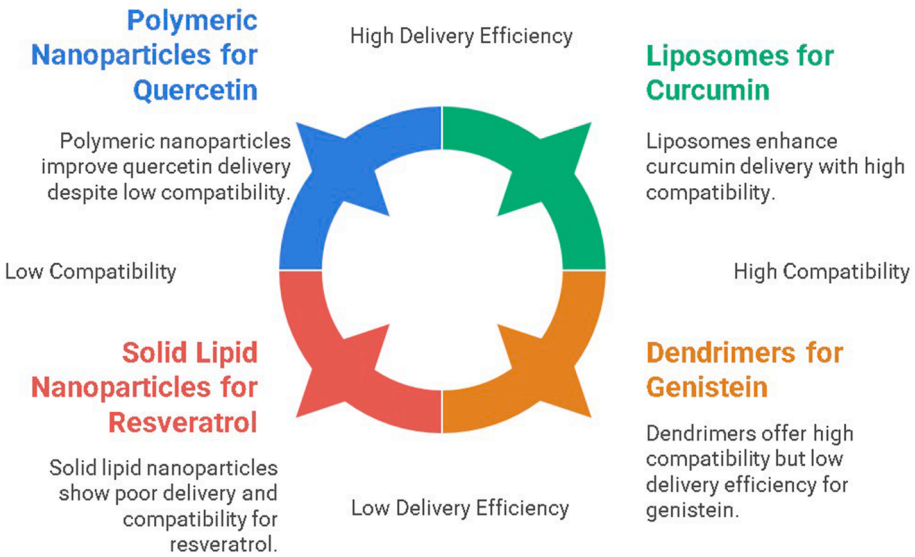


Fig. 1. Nanocarrier compatibility for herbal compounds.

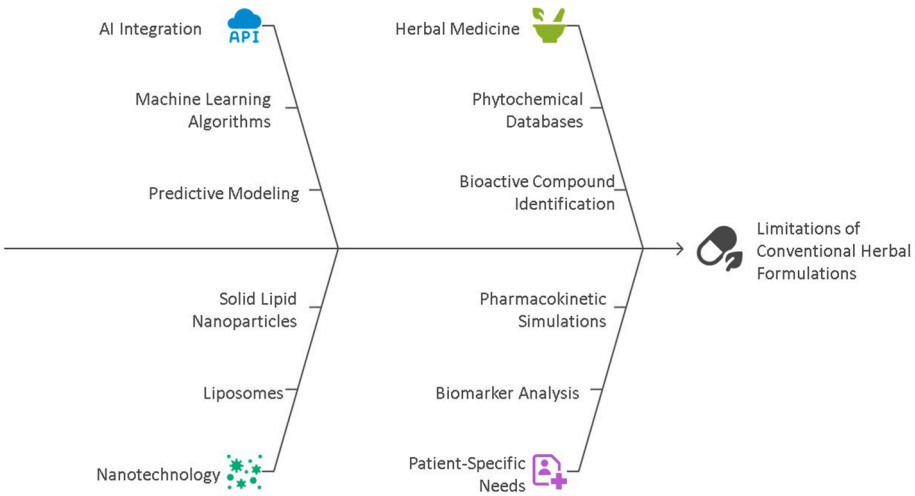


Fig. 2. Enhancing herbal nanocarrier design with AI

In contrast, unsupervised learning deals with unlabeled data and focuses on identifying hidden patterns or groupings. Techniques such as k-means clustering, principal component analysis (PCA), and hierarchical clustering are often applied to group molecules based on physicochemical similarity, analyze omics data, and detect novel drug-likeness clusters. This approach is valuable in exploratory data analysis, chemical space mapping, and target identification. For example, PCA has been used to cluster phytoconstituents, such as flavonoids and alkaloids, based on structural similarity, aiding in the selection of nanocarrier types for structurally related phytoconstituents.[18]

Deep learning, a specialized subset of ML, utilizes multi-layered neural networks to learn highly abstract representations from complex and high-dimensional data. Deep learning models, including convolutional neural networks (CNNs) and recurrent neural networks (RNNs), are particularly suited for processing images (e.g., histopathology), time-series pharmacokinetic data, and molecular structures. In pharmaceutical R&D, deep learning has shown promise in protein-ligand interaction prediction, drug-target mapping, and intelligent drug screening. [19] For herbal nanocarriers, deep learning models, such as graph neural networks (GNNs), are increasingly used to predict drug-carrier interactions by modeling the molecular graphs of phytoconstituents and nanocarrier materials, as seen in studies optimizing liposomal formulations for genistein [20]. However, deep learning models require large datasets and significant computational resources, which can be a limitation when working with phytoconstituents because of the limited standardized data.[21]

In nanoemulsion-based drug delivery, deep learning approaches, including graph neural networks (GNNs), are increasingly employed to capture complex temporal patterns in release kinetics, whereas transformer-based models process sequential data to predict patient-specific responses, such as in andrographolide formulations. In contrast, dendrimers and phytosomes have primarily been studied using machine learning models, such as support vector machines (SVMs) and unsupervised clustering methods, such as k-means and principal component analysis (PCA), to predict compatibility based on molecular descriptors. However, deep learning applications in these carriers remain limited because of the relatively small and less diverse datasets available for training.[5,22]

1.4. QSPR and ADMET prediction tools

An important application of AI/ML in pharmaceutical sciences is the prediction of Quantitative Structure–Property Relationships (QSPR) and Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties. These predictions are essential in early drug discovery to assess drug-likeness and reduce the risk of failure in later development stages. Tools like automated machine learning (AutoML) methods enable efficient prediction of multiple ADMET properties by combining various classification algorithms with optimized hyperparameters.[23] Another widely adopted platform is comprehensive ADMET prediction software that integrates chemistry, biology, and machine learning, allowing users to perform ADMET predictions, molecular property forecasting, toxicity modeling, and protein-ligand interaction analysis using advanced machine learning models.[24] These tools help reduce the need for extensive *in vitro* and *in vivo* studies by offering accurate in silico predictions of pharmacokinetics and safety profiles.

1.5. Predicting nanocarrier compatibility with herbal drugs

The successful formulation of herbal drugs into nanocarrier systems requires a deep understanding of the physicochemical compatibility between the drug and the carrier. One of the key challenges is the poor aqueous solubility of many phytoconstituents, which limits their bioavailability and therapeutic efficacy. AI-based solubility prediction models, trained on large molecular datasets, offer a rapid and reliable approach to estimate solubility parameters, lipophilicity (LogP), and other critical descriptors that influence nanocarrier compatibility. These models can guide the selection of appropriate excipients, solvents, or lipid systems for encapsulation, especially for compounds with borderline properties.[25] Analysis of phytoconstituents for nanocarrier selection process in Fig. 3.

Beyond solubility, predicting carrier–drug interactions is crucial for designing stable and efficient nanocarrier systems. Rule-based filters like Lipinski's Rule of Five provide foundational insights into drug-likeness, but when combined with ML models, predictions become significantly more accurate and tailored. ML algorithms can integrate multiple molecular descriptors—including hydrogen bonding capacity, molecular weight, surface area, and polarity—to model drug–carrier affinity, encapsulation efficiency, and release kinetics. These predictions support rational formulation design by narrowing down the most compatible carrier systems (e.g., liposomes, phytosomes, polymeric nanoparticles) for specific herbal drugs.[26,27]

In liposomal formulations, machine learning models such as random forests and SVMs are widely applied to predict drug–carrier compatibility and encapsulation efficiency, with emphasis on lipid ratios and preparation variables like sonication time and pH; for instance, a curcumin liposome study reported that a random forest model achieved a MAE of just 2.8% in encapsulation efficiency predictions. Similarly, in

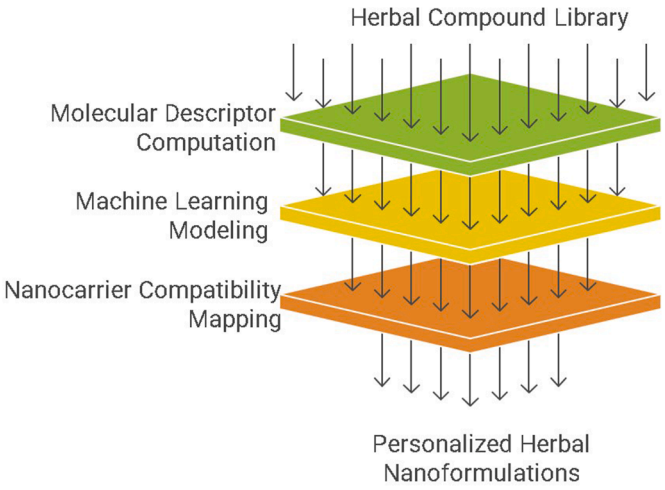


Fig. 3. Herbal compound nanocarrier selection process.

polymeric nanoparticles, ANNs and gradient boosting models have shown strong performance in optimizing complex parameters such as polymer molecular weight and drug-to-polymer ratios; in one case, an ANN successfully predicted quercetin-loaded PLGA nanoparticle characteristics including particle size (120–180 nm) and zeta potential (+25 to +40 mV), with SHAP analysis further revealing emulsifier concentration as a critical determinant of formulation outcomes.[28]

1.5.1. Case study 1: curcumin-loaded liposomes for colorectal cancer

A random forest model optimized curcumin-loaded liposomes for colorectal cancer treatment.[29] Trained on 300 formulations with variables like lipid ratios (e.g., phosphatidylcholine, cholesterol), curcumin concentration, and preparation conditions (e.g., sonication time, pH), it predicted formulations achieving >90% encapsulation efficiency and 100–150 nm particle size. In vitro tests in Caco-2 cells showed a 3-fold increase in curcumin uptake and 60% release over 24 h (PBS, pH 7.4) compared to free curcumin. *In vivo*, a xenograft mouse model exhibited a 40% tumor volume reduction after 28 days ($p < 0.05$). Predictions were validated with a 2.8% MAE for encapsulation efficiency, demonstrating model accuracy.[30]

1.5.2. Case study 2: quercetin-loaded polymeric nanoparticles for liver dysfunction

Another study employed an artificial neural network (ANN) to design quercetin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles for enhanced liver-targeted delivery.[31] The ANN model analyzed input parameters, including PLGA molecular weight, quercetin-to-polymer ratio, and emulsifier concentration, to predict particle size (target: 120–180 nm), zeta potential (+25 to +40 mV), and drug loading efficiency (>80%). The optimized formulation achieved a loading efficiency of 82.3% ± 1.9% and a particle size of 145 nm ± 10 nm. In vitro release studies in simulated hepatic conditions (PBS, pH 7.4 with 10% serum) showed a controlled release of 65% quercetin over 48 h, compared to 95% release in 6 h for free quercetin. *In vivo* validation in a rat model of carbon tetrachloride-induced liver fibrosis demonstrated a 2.5-fold increase in quercetin bioavailability and a 30% reduction in liver enzyme levels (ALT, AST) compared to free quercetin ($p < 0.01$). SHAP analysis revealed that PLGA molecular weight and emulsifier concentration were the most influential factors, guiding further formulation refinements.[32] These case studies underscore the practical utility of AI/ML tools in overcoming the solubility and bioavailability challenges of phytoconstituents, with validated outcomes confirming their potential to accelerate the development of effective herbal nanomedicines.[33,34]

1.6. Inverse design of nanocarriers

The formulation of nanocarriers for drug delivery traditionally follows a forward design approach, where formulation components are varied iteratively to meet target specifications. However, this process is often inefficient and resource-intensive. Inverse design, enabled by AI, allows researchers to specify desired outcomes—such as particle size, zeta potential, and drug loading—and have the model predict the optimal lipid/polymer ratios, surfactants, and process parameters to achieve those results.[35] Supervised ML models, including random forest, support vector regression, and ANNs, have shown strong predictive performance in modeling such complex formulation-property relationships. [36]

Advanced AI methodologies such as Generative Adversarial Networks (GANs) and Reinforcement Learning (RL) have pushed the frontier of drug delivery system (DDS) design further. GANs can generate novel formulations or carrier architectures by learning from real formulation datasets and creating synthetic but realistic alternatives, potentially identifying new materials or compositions with enhanced performance. [37] Reinforcement learning agents, on the other hand, optimize formulation strategies via trial-and-error within simulated environments, learning policies that balance competing objectives like size reduction, surface charge tuning, and sustained release.[38]

To provide a more detailed case study with experimental results and methodological comparisons, consider the application of ANNs in the inverse design and optimization of silymarin-loaded chitosan nanoparticles, which serves as a representative example for herbal drugs like curcumin and quercetin that face similar bioavailability challenges. Silymarin, a flavonoid complex from Silybum marianum with antioxidant and hepatoprotective properties, was encapsulated in chitosan nanoparticles using ionic gelation with tripolyphosphate as a crosslinker.[39] This approach mirrors the encapsulation needs for curcumin (e.g., in liposomes) and quercetin (e.g., in phytosomes), where AI can predict optimal parameters to enhance loading efficiency and therapeutic efficacy.

An artificial neural network (ANN) model was developed to predict silymarin loading efficiency using input variables (pH 3–7, chitosan-to-silymarin ratio 1:1–5:1, chitosan-to-TPP ratio 1:0.2–1:1, and stirring time 30–120 min), with a multi-layer perceptron and backpropagation enabling inverse prediction for targeted efficiencies (>80%), outperforming traditional response surface methodology (RSM) in capturing non-linear interactions. Optimal conditions (pH ~5, chitosan-to-silymarin 3:1, chitosan-to-TPP 1:0.5, stirring 60 min) yielded 85.4% ± 2.1% loading efficiency, nanoparticles of 150–200 nm with PDI 0.25 ± 0.03, and zeta potential +35 ± 4 mV. In vitro release showed sustained drug release (60% in 24 h vs. 90% in 4 h for free silymarin), while antioxidant activity (DPPH IC50 36.17 ± 0.02 μg/mL vs. 165.04 ± 0.07 μg/mL) demonstrated a 4.5-fold improvement. *In vivo*, the optimized nanoparticles reduced ALT and AST by 35% and doubled bioavailability compared to free silymarin ($p < 0.01$), validating the ANN model's predictive accuracy for formulation and therapeutic outcomes.[40]

Compared to traditional RSM, ANN models demonstrated superior predictive performance ($R^2 = 0.98$ vs. 0.92 for RSM) and better captured non-linear effects, reducing the number of experimental trials by 40% (from 27 to 16), which is especially advantageous for herbal drugs such as berberine or andrographolide, where batch variability complicates trial-and-error optimization. Validation studies confirmed the ANN predictions within a 5% error margin, underscoring its reliability for inverse design. This AI-driven strategy not only optimizes encapsulation to enhance bioavailability but also improves antioxidant efficacy, thereby advancing the development of personalized herbal nanomedicines. Furthermore, similar ANN models could be extended to curcumin-loaded liposomes by predicting lipid ratios for >90%

encapsulation or quercetin-loaded phytosomes by optimizing polymer concentrations for sustained release, thus addressing the limitations of the generic approaches highlighted in earlier studies.[32,41]

1.7. Personalized nanomedicine using AI

The future of nanomedicine is rapidly evolving toward personalized therapy, where treatments are tailored to the unique biological profile of each patient. AI plays a central role in enabling this shift by integrating multi-omics data, including genomics, transcriptomics, proteomics, metabolomics, and microbiome profiles, to model individual response variability to nanoformulated drugs.[42] For herbal medicines, which often exhibit complex pharmacodynamics and variable efficacy, personalization becomes especially crucial. AI models can process high-dimensional datasets to identify key biomarkers—such as single nucleotide polymorphisms (SNPs) or specific gut microbiota signatures—that influence the bioavailability, metabolism, and therapeutic response of herbal nanomedicines.[6] For example, AI models have been used to predict the efficacy of curcumin nanoformulations in patients with colorectal cancer by analyzing SNPs in the SLCO1B1 gene, which affects curcumin uptake, and gut microbial profiles dominated by Faecalibacterium prausnitzii, which enhances curcumin metabolism. [43] Similarly, machine learning analysis of proteomic data has identified biomarkers, such as cytochrome P450 enzyme expression levels, that predict the metabolism of quercetin-loaded nanoparticles in patients with liver dysfunction[44]

However, the integration of omics data into AI models presents practical challenges. The high dimensionality and heterogeneity of omics datasets require sophisticated preprocessing and feature selection to avoid overfitting and ensure the robustness of the model. For instance, genomic datasets may contain thousands of SNPs, but only a few are relevant to drug response, necessitating advanced dimensionality reduction techniques, such as principal component analysis (PCA) or autoencoders.[45] Additionally, the lack of standardized omics data for phytoconstituents complicates model training, as datasets are often small, noisy, or derived from diverse populations, leading to reproducibility problems. The computational complexity of processing multi-omics data also demands significant resources, which may limit accessibility for smaller research groups. Furthermore, the integration of microbiome data is particularly challenging because of inter-individual variability and the dynamic nature of microbial communities, which can change with diet, lifestyle, or disease state.[46]

An emerging example is the AI-guided prediction of individual response to turmeric (curcumin) nanoformulations based on gut microbiome composition. Studies have demonstrated that certain gut microbial genera, such as Clostridium and Bifidobacterium, are involved in the biotransformation of curcumin into active metabolites, which directly affects its anti-inflammatory and antioxidant efficacy.[47] For instance, a recent study used random forest models to predict curcumin response in patients with inflammatory bowel disease, identifying Bacteroides species as a key determinant of efficacy, although the model's accuracy was limited by small sample sizes and batch effects in microbiome data.[48] Machine learning algorithms trained on microbiome profiles and clinical response data can classify patients into high-responders and low-responders, enabling targeted recommendation of curcumin nanocarriers to individuals most likely to benefit.[49] Additionally, SNPs in genes encoding metabolic enzymes (e.g., UGT, CYP450) can influence curcumin's bioactivation and clearance, further refining AI-based personalization models.[50] Despite these advances, clinical translation is hindered by the need for large, well-curated omics datasets and standardized protocols for herbal compound analysis, as well as the challenge of validating AI predictions in diverse patient populations.[51] Personalized herbal nanomedicine using AI and patient illustrated in Fig. 4.

1.8. Validation and interpretability

Machine learning in pharmaceutical formulation requires accurate predictions, robust validation, and interpretability for clinical and regulatory trust. Models rely on curated datasets of formulation parameters and outcomes like particle size, zeta potential, and drug release. To avoid overfitting and ensure generalizability, techniques like cross-

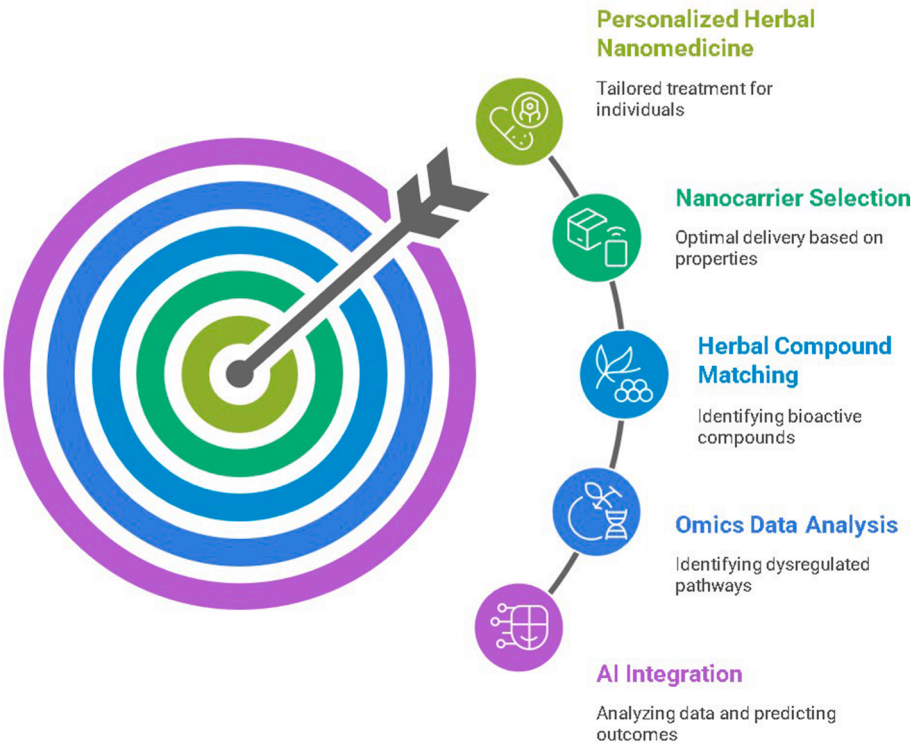


Fig. 4. Personalized herbal nanomedicine framework.

validation, external test sets, and bootstrapping are used.[52] For instance, a random forest model for curcumin liposomes achieved a 3.2% MAE for encapsulation efficiency using 5-fold cross-validation on 200 formulations.[29] Similarly, a support vector regression model for quercetin nanoparticles yielded an R^2 of 0.89 for particle size on a 50-formulation test set.[53] However, batch variability in phytoactives can introduce noise, reducing prediction reliability.[54] The quality, diversity, and size of datasets directly influence the performance and trustworthiness of AI models in formulation science.

A key aspect of AI integration is assessing model performance using appropriate metrics, which quantify reliability, generalizability, and utility in pharmaceutical applications. For regression tasks, such as predicting particle size, drug loading efficiency, or release kinetics in nanocarrier formulations, common metrics include R^2 (coefficient of determination), MAE (mean absolute error), and RMSE (root mean square error). R^2 measures the proportion of variance explained by the model (ideal value approaching 1), indicating how well predictions fit the data—crucial for optimizing formulation parameters where precise quantitative predictions are needed to minimize experimental iterations. MAE and RMSE quantify average prediction errors, with RMSE penalizing larger errors more severely; these are important in herbal nanomedicine for ensuring reproducible outcomes despite phytoconstituent variability, as seen in QSPR modeling for solubility predictions.[55,56] For instance, in optimizing berberine-loaded solid lipid nanoparticles, RMSE of 2.1% on release kinetics highlights model precision, reducing the risk of over- or under-estimating therapeutic delivery.[57] Solid Lipid Nanoparticles: GNNs and ANNs are applied to model drug–carrier interactions and release kinetics, particularly for phytoconstituents with variable solubility like berberine. SHAP analysis in a berberine study emphasized lipid chain length and surfactant concentration.

For classification tasks, such as predicting drug-carrier compatibility or categorizing ADMET properties (e.g., soluble vs. insoluble phytoconstituents), metrics like accuracy, precision, recall, F1-score, specificity, and AUC-ROC (area under the receiver operating characteristic curve) are essential. Accuracy represents the overall correct predictions but can be misleading in imbalanced datasets common in drug discovery (e.g., few compatible carriers vs. many incompatible ones), potentially overestimating performance by favoring the majority class. Precision (true positives over predicted positives) minimizes false positives, vital for avoiding resource waste on incompatible formulations, while recall (true positives over actual positives) ensures sensitivity to detect viable options, critical for not missing promising herbal nanocarriers. The F1-score balances precision and recall, providing a harmonic mean useful in uneven class distributions. Specificity (true negatives over actual negatives) reduces false alarms in toxicity predictions, and AUC-ROC evaluates the model's ability to discriminate classes across thresholds, making it robust for imbalanced data in ADMET and QSAR tasks—where high AUC (>0.8) indicates strong separability, as in classifying curcumin-nanocarrier interactions.[58,59] These metrics are particularly important in herbal nanomedicine because of data imbalances (e.g., rare active phytoconstituents) and the need for interpretable, reliable predictions to facilitate clinical translation.

Beyond validation, the interpretability of AI models—especially complex ones like deep neural networks—is a growing concern. Black-box models may offer high accuracy but provide little insight into why a prediction is made. A significant challenge in using these AI models lies in their inherent 'black box' nature, where the internal decision-making processes are opaque, making it difficult to trace how inputs (e.g., molecular descriptors or omics data) lead to outputs (e.g., predicted drug release profiles). This opacity can hinder trust among researchers and regulators, particularly in biologically complex systems like herbal nanomedicine, where understanding the underlying mechanisms—such as specific drug-carrier interactions or metabolic pathways influenced by patient-specific factors—is crucial. A key goal of AI in this field should not just be to predict formulation outcomes but to derive biologically understandable mechanisms, enabling insights into why certain nanocarriers enhance bioavailability for phytoconstituents like curcumin or quercetin. This would add nuance to AI applications, bridging predictive power with mechanistic biology and pushing the frontiers of interpretable AI in pharmaceutical sciences.

This has led to the emergence of Explainable AI (XAI) frameworks, which aim to make model decisions transparent and understandable to domain experts. In formulation science, XAI can identify which features (e.g., lipid concentration, polymer type, drug logP) are most influential in determining outcomes, aiding rational design and regulatory approval. Techniques such as SHAP (SHapley Additive exPlanations), LIME (Local Interpretable Model-agnostic Explanations), and feature importance rankings have been successfully applied to interpret formulation models and guide experimental focus.[60] For instance, SHAP analysis in a study of berberine-loaded solid lipid nanoparticles revealed that lipid chain length and surfactant concentration were the top contributors to encapsulation efficiency, guiding formulation optimization, and reducing experimental iterations.[61] In another example, LIME was used to interpret a deep learning model predicting the release kinetics of andrographolide from nanoemulsions, highlighting the influence of pH and polymer molecular weight, with validation results showing a root mean square error (RMSE) of 2.1% on a test set.[62] These interpretability tools not only enhance trust in AI predictions but also address regulatory requirements by providing clear rationales for the model outputs. However, challenges in validation persist, particularly for herbal nanocarriers, where limited dataset sizes and variability in phytoconstituent composition can hinder robust model evaluation.[63]

The proposed section on Explainable AI (XAI) enhances the review by detailing how XAI improves trust and transparency in AI-driven nanocarrier formulation for herbal drugs. It addresses the opacity of complex AI models (e.g., deep learning, graph neural networks) by using techniques like SHAP and LIME to provide interpretable insights into predictions, such as drug loading or release kinetics for phytoactives like curcumin and quercetin. These methods clarify key factors (e.g., lipid composition, hydrophobicity) and integrate patient-specific omics data for personalized therapies, including antimicrobial applications. XAI also supports regulatory compliance by documenting decision-making, aligning with FDA requirements. Future advancements, like transformer-based attention mechanisms, are noted for their potential to further improve interpretability. For example, in a study using AI to optimize nanoparticle formulations, SHAP analysis revealed that surfactant concentration and lipid-to-drug ratio were the most critical variables influencing particle stability and size distribution.[64] Such insights help formulation scientists not only refine experimental design but also build confidence in AI-assisted decisions, bridging the gap between predictive power and scientific understanding.

1.9. Regulatory and translational considerations

While AI-designed nanocarriers offer transformative potential in pharmaceutical development, their clinical translation faces significant regulatory and translational challenges. Regulatory bodies like the U.S. FDA (Food and Drug Administration) and EMA (European Medicines Agency) require a high degree of transparency, reproducibility, and explainability for approving new drug products. The integration of AI into herbal nanomedicine development introduces specific regulatory challenges, particularly due to the complexity of phytoconstituents and the limitations of current AI methodologies in meeting stringent regulatory standards. Below, we analyze key areas where AI-based approaches may fail to align with regulatory expectations, focusing on data quality, model interpretability, validation gaps, and the unique challenges posed by phytoconstituents.[65]

Moreover, nanomedicines themselves are considered complex products due to their size-dependent behavior, variable pharmacokinetics, and interactions with biological systems. When AI is integrated into their development, the combined complexity necessitates rigorous

validation and documentation. Regulatory agencies are beginning to address this through frameworks such as the FDA's draft guidance on AI/ML for drug development and recent guidelines on complex generics and nanomaterials, which emphasize model transparency, data quality, and control strategies.[66] The EMA's guidance on nanomedicines similarly highlights the need for robust characterization and batch consistency, while encouraging the use of modeling and simulation under appropriate quality management systems.[67] However, these frameworks are not fully tailored to address the unique challenges of AI-driven herbal nanomedicines, particularly in the context of phytoconstituent variability and the limitations of AI model validation.

One major regulatory hurdle is the poor quality and variability of datasets used to train AI models for herbal nanomedicines. Phytoconstituents, such as curcumin or quercetin, exhibit significant batch-to-batch variability due to differences in plant sources, extraction methods, and environmental factors. For example, curcumin content in turmeric extracts can vary from 2 to 8% depending on cultivation conditions, impacting AI model predictions for encapsulation efficiency or release kinetics. Regulatory agencies require consistent and reproducible data to ensure product quality, but the lack of standardized herbal datasets can lead to unreliable AI predictions. A case study on berberine-loaded liposomes demonstrated that variability in alkaloid content across batches led to a 15% deviation in predicted versus actual encapsulation efficiency, failing to meet the FDA's requirement for batch consistency (ICH Q8 guidelines).[68] Without robust preprocessing and standardization protocols, AI models risk generating outputs that are not generalizable, hindering regulatory approval.

Model Interpretability and Black-Box Concerns: AI models, particularly deep learning and GANs, often function as black-box systems, providing accurate predictions but lacking transparency in decision-making processes. For herbal nanomedicines, where regulatory bodies demand clear rationales for formulation choices, this poses a significant barrier. For instance, a deep neural network used to optimize andrographolide-loaded nanoemulsions achieved high predictive accuracy ($R^2 = 0.95$) for release kinetics but could not adequately explain the influence of specific input variables (e.g., surfactant type or pH) without post-hoc explainability tools like SHAP or LIME.[69] The FDA's draft guidance on AI/ML emphasizes the need for explainable AI (XAI) to ensure trust and reproducibility, but current XAI methods may not fully resolve the complexity of herbal systems, where multiple phytoconstituents interact dynamically. This lack of interpretability could lead to regulatory rejection, particularly for novel formulations lacking extensive preclinical validation.

Validation Gaps and Clinical Translation: Robust validation is critical for regulatory acceptance, yet AI models for herbal nanomedicines often face challenges due to limited dataset sizes and the complexity of phytoconstituents. Regulatory agencies require external validation and clinical correlation to confirm in silico predictions, but small or noisy datasets for phytoconstituents can lead to overfitting or poor generalizability. For example, a random forest model predicting the solubility of quercetin in polymeric nanoparticles achieved an R^2 of 0.92 on training data but dropped to 0.78 on an external test set due to variability in quercetin purity across suppliers.[70] The EMA's reflection paper on nanomedicines stresses the need for validated analytical methods to characterize complex products, but AI models often lack sufficient experimental data to meet these standards, especially for multi-component herbal extracts. Additionally, the absence of standardized protocols for integrating omics data (e.g., genomics, microbiome) into AI models complicates validation of personalized herbal nanomedicines, as inter-individual variability further reduces predictive reliability.

Regulatory Gaps Specific to Herbal Nanomedicines: Current regulatory frameworks, such as the FDA's guidance on botanical drug products and the EMA's guidelines on herbal medicinal products, do not fully address the integration of AI-driven nanocarrier systems. For instance, the FDA's botanical drug guidance (2016) emphasizes the need for chemical consistency and bioequivalence, but AI models predicting nanocarrier compatibility for herbal drugs often rely on incomplete chemical profiles, leading to potential regulatory non-compliance.[71] Furthermore, the dynamic nature of phytoconstituents, such as the synergistic effects of multiple phytoconstituents (e.g., curcuminoids in turmeric), is poorly captured by existing AI models, which may oversimplify interactions and fail to meet the EMA's requirement for comprehensive characterization. The lack of specific guidance on AI-driven herbal nanomedicines creates uncertainty, particularly for demonstrating safety and efficacy in preclinical and clinical studies.

Clinical translation of AI-assisted nanomedicine also demands harmonization between in silico predictions and experimental validation. AI-predicted outcomes must be substantiated with preclinical and clinical data, especially regarding safety, efficacy, immunogenicity, and biodistribution. Additionally, AI systems used in the drug development pipeline may need to comply with Good Machine Learning Practice (GMLP), a set of principles co-published by FDA, Health Canada, and the UK MHRA to ensure trustworthy and reproducible AI applications in healthcare.[72,73] To address these challenges, developers must adopt hybrid approaches combining AI predictions with rigorous experimental validation, such as high-throughput screening for herbal extract consistency and advanced analytical techniques (e.g., LC-MS/MS) to characterize phytoconstituent profiles. Collaborative efforts between AI researchers, pharmaceutical scientists, and regulatory bodies are essential to establish specific guidelines for AI-driven herbal nanomedicines, ensuring alignment with existing standards like ICH Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System). Comparison of traditional vs AI-based nanocarrier development pipelines shown in Fig. 5.

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1.10. Data bias in nanomedicine databases and its impact on AI models

The application of artificial intelligence (AI) in the development of nanocarrier formulations for herbal drugs relies heavily on the quality and representativeness of the underlying datasets. However, nanomedicine-related databases often suffer from data bias, which can significantly compromise the accuracy, generalizability, and clinical applicability of AI models. This section explores the sources of data bias in nanomedicine databases, particularly in the context of herbal drug formulations, and discusses their implications for AI-driven formulation design. Addressing these biases is critical to ensuring robust, equitable, and reproducible outcomes in precision phytomedicine.

1.10.1. Sources of data bias

1.10.1.1. Imbalanced datasets. Nanomedicine databases often exhibit class imbalances, where certain types of nanocarriers (e.g., liposomes, polymeric nanoparticles) or phytoconstituents (e.g., curcumin, quercetin) are overrepresented compared to less-studied alternatives (e.g., phytosomes, terpenoids). For example, a dataset skewed toward liposomal formulations may lead AI models to favor these carriers, potentially overlooking other viable systems like nanoemulsions or dendrimers. Such imbalances can cause overfitting, where models perform well on training data but fail to generalize to new or underrepresented compounds. A study on berberine-loaded nanoparticles highlighted that imbalanced datasets led to a 10% reduction in

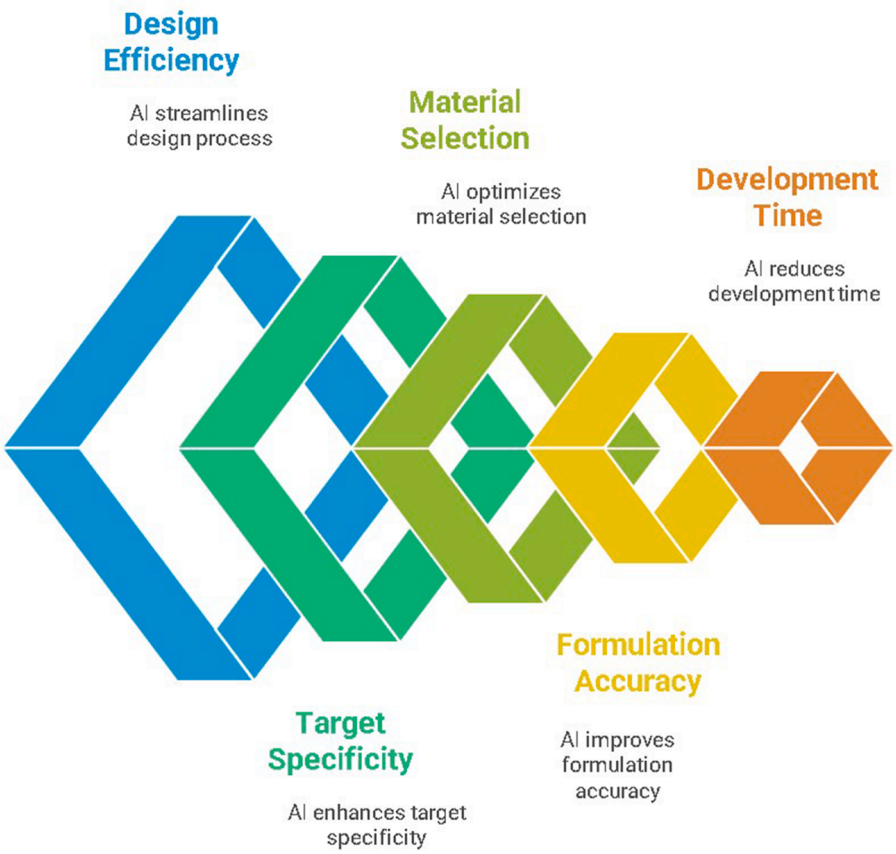


Fig. 5. Nanocarrier development process.

predictive accuracy for less common carriers, emphasizing the need for balanced representation.[76]

1.10.1.2. Underrepresented herbal molecules. Many phytoconstituents, particularly those from traditional or region-specific medicinal systems (e.g., Ayurveda, Traditional Chinese Medicine), are underrepresented in nanomedicine databases. For instance, while curcumin and quercetin dominate research due to their well-characterized properties, other phytoconstituents like withanolides or ginsenosides are less studied, limiting the diversity of training data. This underrepresentation can bias AI models toward well-known molecules, reducing their ability to predict optimal formulations for novel or less-characterized herbal drugs. A recent analysis showed that only 15% of phytoconstituents in a major nanomedicine dataset were non-flavonoid or non-alkaloid compounds, highlighting a significant gap in molecular diversity.[2]

1.10.1.3. Population-specific variations. AI models integrating omics data (e.g., genomics, microbiome) for personalized nanomedicine often rely on datasets derived from specific populations, such as Western or urban cohorts, which may not reflect global genetic or microbial diversity. For example, microbiome data from patients with inflammatory bowel disease used to predict curcumin nanoformulation efficacy were predominantly collected from North American cohorts, leading to reduced model accuracy in Asian populations with distinct microbial profiles.[77] Similarly, genetic variations, such as single nucleotide polymorphisms (SNPs) in drug-metabolizing enzymes like CYP450, vary significantly across ethnic groups, yet these differences are often inadequately captured in training datasets. This can result in biased predictions that fail to account for inter-individual variability, undermining the goal of personalized phytomedicine.

1.10.1.4. Implications for AI-driven formulation design. Data bias in nanomedicine databases can lead to several critical challenges in AI-driven formulation design. First, biased datasets can skew model predictions, resulting in suboptimal nanocarrier selections or inaccurate predictions of drug release kinetics and encapsulation efficiency. For instance, a random forest model trained on a dataset with overrepresented liposomal formulations overestimated encapsulation efficiency by 12% when applied to polymeric nanoparticles, necessitating costly experimental revalidation.[78] Second, biased models may fail to generalize across diverse phytoconstituents or patient populations, limiting their utility in global clinical settings. Third, the lack of diversity in training data can hinder the discovery of novel nanocarrier systems or phytoconstituents, stifling innovation in herbal nanomedicine.

Moreover, regulatory bodies such as the FDA and EMA emphasize the importance of unbiased and representative datasets to ensure the reliability and safety of AI-driven drug products. Biased predictions can lead to regulatory non-compliance, particularly if models fail to account for variability in herbal extracts or patient-specific factors. For example, the FDA's draft guidance on AI/ML in drug development stresses the need for robust data curation to mitigate bias, yet current nanomedicine databases often lack standardized protocols for phytoconstituents.[79]

1.10.1.5. Strategies to mitigate data bias. To address data bias and enhance the reliability of AI models in herbal nanomedicine, several strategies can be employed:

Data augmentation and synthetic data generation, particularly through techniques such as GANs, can address class imbalances by creating synthetic datasets for underrepresented categories such as novel phytoconstituents or nanocarrier types. For instance, GAN-generated liposomal formulation datasets enhanced model performance by 8% in predicting the encapsulation efficiency of rare terpenoids.[21] To further strengthen predictive modeling, collaborative

initiatives are needed to develop comprehensive and standardized nanomedicine databases that encompass diverse phytoconstituents and population-specific omics data. Platforms such as PharmaBench, which integrate multimodal data for ADMET predictions, exemplify how such inclusive datasets can capture global phytoconstituent and patient diversity, supporting more robust and generalizable models.[80]

Bias in AI-driven herbal nanomedicine research can be mitigated using algorithms such as reweighting, oversampling, and fairness-aware machine learning. For example, oversampling underrepresented herbal molecules, such as andrographolide, improved the accuracy of the support vector machine by 15% in predicting drug–carrier compatibility.[81] Explainable AI (XAI) tools, such as SHAP and LIME, further aid bias detection by revealing disproportionate feature influences, as shown in quercetin-loaded nanoparticle studies, where SHAP identified an overreliance on Western microbiome data, prompting the integration of more diverse microbial profiles.[82] To enhance generalizability, global collaboration and data sharing among academia, industry, and regulators are crucial, with the integration of traditional medicine datasets (e.g., Ayurveda and Kampo) into Western nanomedicine databases providing more representative training data for AI models in herbal drug development.[83]

1.10.1.6. Future prospectus for AI-driven herbal nanomedicine. The integration of advanced artificial intelligence (AI) models with nanocarrier-based delivery systems for phytoconstituents presents transformative opportunities for precision herbal therapeutics. Future research should prioritize several key directions to fully realize this potential. First, enhancing the predictive accuracy of AI models, such as transformer-based models and graph neural networks, will enable more precise optimization of nanocarrier properties (e.g., particle size, drug loading, release kinetics) for phytoactives like curcumin, quercetin, and genistein. Developing hybrid models that combine molecular dynamics simulations with AI could further improve predictions of drug–carrier interactions at the atomic level.[84] Second, integrating multi-omics data (genomics, microbiomics, metabolomics) into AI frameworks will advance personalized herbal nanomedicines. Future studies should focus on creating standardized databases of patient-specific omics profiles to train AI models, enabling tailored formulations that account for individual variability in drug response. For example, AI-driven nanocarriers could be optimized to enhance the bioavailability of antimicrobial phytoconstituents, addressing challenges in treating infectious diseases like multidrug-resistant bacterial infections.[85]

Third, advancing Explainable AI (XAI) techniques, such as SHAP and LIME, is critical for clinical translation. Future research should explore novel XAI methods, such as attention-based interpretability in transformer models, to provide clearer insights into complex predictions, thereby building trust among clinicians and regulatory bodies.[86] Collaborative efforts to establish regulatory guidelines for AI-driven herbal nanomedicines will also be essential to ensure safety and efficacy. Finally, interdisciplinary collaborations between AI experts, nanotechnologists, and herbal medicine researchers should be fostered to accelerate innovation. Pilot clinical trials evaluating AI-optimized nanocarriers for phytoconstituents in infectious disease treatment could validate these approaches, paving the way for broader therapeutic applications.[87] By pursuing these directions, AI-driven nanomedicine can revolutionize herbal therapeutics, delivering precise, effective, and personalized treatments.

2. Conclusion

The convergence of advanced AI models, nanotechnology, and phytomedicine represents a paradigm shift from trial-based to predictive, data-driven formulation strategies. AI, including transformer-based models and graph neural networks, enables accurate prediction of formulation behavior, optimization of nanocarrier systems, and personalization of herbal treatments for applications ranging from cancer to infectious diseases. Case studies, such as AI-optimized curcumin-loaded liposomes validated in colorectal cancer models, quercetin-loaded PLGA nanoparticles tested in liver dysfunction models, and berberine-loaded nanoemulsions for Staphylococcus aureus infections, demonstrate significant improvements in bioavailability, antimicrobial efficacy, and therapeutic outcomes, with in vitro and *in vivo* validation confirming AI's transformative potential. Tools like explainable AI and inverse design further enhance scalability, reproducibility, and regulatory alignment. By accounting for patient-specific factors such as microbiota and genetics, AI advances precision phytomedicine, particularly for combating infectious diseases like malaria and bacterial infections. Future integration of multi-modal data and technologies like digital twins and adaptive clinical trials will accelerate the development of personalized, safe, and effective herbal nanomedicines. Collaborative efforts across disciplines will be essential to ensure ethical and validated AI applications in drug development.

CRediT authorship contribution statement

Duraisamy Sridhar: Writing – original draft, Validation, Resources, Data curation. **Ramalingam Manikandan:** Writing – original draft, Data curation, Conceptualization. **Yogananthan Dhanapal:** Writing – original draft, Visualization, Data curation. **Sulekha Khute:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Paranthaman Subash:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

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References

1. Uti DE, Atangwho IJ, Alum EU, Egba SI, Ugwu OPC, Ikechukwu GC. Natural antidiabetic agents: current evidence and development pathways from medicinal plants to clinical use. *Nat Prod Commun*. 2025;20(3):1934578X251323393.
2. Parvin N, Aslam M, Joo SW, Mandal TK. Nano-phytomedicine: harnessing plant-derived phytochemicals in nanocarriers for targeted human health applications. *Molecules*. 2025;30(15):3177.
3. Zheng G, Zhang B, Yu H, et al. Therapeutic applications and potential biological barriers of nano-delivery systems in common gastrointestinal disorders: a comprehensive review. *Adv Compos Hybrid Mater*. 2025;8(2):1–22.
4. Kumar V, Dutta R. Nano encapsulation for the targeted drug delivery to enhance the efficacy of drugs. *Deep Learn Comp Vision: Models Biomed App*. 2025;2:173–185.
5. Spanakis M, Tzamali E, Tzedakis G, et al. Artificial intelligence models and tools for the assessment of drug–herb interactions. *Pharmaceuticals*. 2025;18(3):282.
6. Mazumdar H, Khondakar KR, Das S, Halder A, Kaushik A. Artificial intelligence for personalized nanomedicine; from material selection to patient outcomes. *Expet Opin Drug Deliv*. 2025;22(1):85–108.
7. Othman HO, Issa KD, Ali DS, et al. Enhancing nanomedicine with doped carbon quantum dots: a comprehensive review. *J Nanoparticle Res*. 2024;26(11):262.

8. Zheng B, McClements DJ. Formulation of more efficacious curcumin delivery systems using colloid science: enhanced solubility, stability, and bioavailability. *Molecules*. 2020;25(12):2791.
9. Hossain CM, Gera MEETA, Ali KA. Current status and challenges of herbal drug development and regulatory aspect: a global perspective. *Asian J Pharmaceut Clin Res*. 2022;15(2):31–41.
10. Ahmad A, Othman I, Zaini A, Chowdhury EH, Rahman M, Rehman S. Artificial intelligence in pharmaceutical technology and drug delivery design. *Pharmaceutics*. 2023;15(7):1916.
11. Mak KK, Pichika MR. Artificial intelligence in drug development: present status and future prospects. *Drug Discov Today*. 2019;24(3):773–780.
12. Abbas Z, Tayara H, Chong KT. The role of AI in drug discovery. *Chembiochem*. 2024;25(11):e202300816.
13. Kamble S, Agrawal S, Cherumukkil S, Sharma V, Jasra RV, Munshi P. Revisiting zeta potential, the key feature of interfacial phenomena, with applications and recent advancements. *ChemistrySelect*. 2022;7(1):e202103084.
14. Algharib SA, Dawood A, Zhou K, et al. Preparation of chitosan nanoparticles by ionotropic gelation technique: effects of formulation parameters and in vitro characterization. *J Mol Struct*. 2022;1252:132129.
15. Alizadeh SR, Savadkouhi N, Ebrahimzadeh MA. Drug design strategies that aim to improve the low solubility and poor bioavailability conundrum in quercetin derivatives. *Expet Opin Drug Discov*. 2023;18(10):1117–1132.
16. Yan Z, Sun M, Lv Y. Novel berberine-based pharmaceutical salts with fatty acid anions: synthesis, characterization, physicochemical properties. *J Mol Liq*. 2022;360:119397.
17. Shrivastava S, Kaur CD. Development of andrographolide-loaded solid lipid nanoparticles for lymphatic targeting: formulation, optimization, characterization, in vitro, and *in vivo* evaluation. *Drug Deliv Translat Res*. 2023;13(2):658–674.
18. Ali DS, Othman HO, Mohammed SH, et al. Nanobiohybrids and bacterial carriers: a novel pathway to targeted cancer therapy. *Nano Futures*. 2024;8(3):032001.
19. Wu Z, Ramsundar B, Feinberg EN, et al. MoleculeNet: a benchmark for molecular machine learning. *Chem Sci*. 2018;9(2):513–530.
20. Arora D, Bhati H, Bansal K. Recent advancements in genistein nanocarrier systems for effective cancer management. *Med Oncol*. 2025;42(4):1–23.
21. Kalita I, Bhattacharjee S, Saharia M. Advancements in medicinal plant research: harnessing artificial intelligence, machine learning, deep learning, and bioinformatics. In: *Biotechnology, Multiple Omics, and Precision Breeding in Medicinal Plants*. CRC Press; 2025:135–145.
22. Dou B, Zhu Z, Merkurjev E, et al. Machine learning methods for small data challenges in molecular science. *Chem Rev*. 2023;123(13):8736–8780.
23. Jeon H, Kim D, Choi Y, Lim H, Lee D, No KT. Employing automated machine learning (AutoML) methods to facilitate the in silico ADMET properties prediction. *J Chem Inf Model*. 2025;65(7):3215–3225.
24. Vora LK, Gholap AD, Jetha K, Thakur RRS, Solanki HK, Chavda VP. Leveraging machine learning models in evaluating ADMET properties for drug discovery and development. *ADMET DMPK*. 2024;12(4):847–891.
25. Ali DS, Othman HO, Anwer ET. The advances in chitosan-based drug delivery systems for colorectal cancer: a narrative review. *Curr Pharm Biotechnol*. 2023;24(12):1554–1559.
26. Hajamohideen AR, Vora LK, Patel R, Chavda VP, Abouelnasr A. FP-ADMET: a compendium of fingerprint-based ADMET prediction models. *J Cheminform*. 2021;13:75.
27. Patra JK, Das G, Fraceto LF, et al. Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol*. 2018;16:71.
28. Sims Jr KR. *Advancing Anti-biofilm Nanoparticle Drug Delivery Systems*. University of Rochester; 2019.
29. Hoseini B, Jaafari MR, Golabpour A, Rahmatinejad Z, Karimi M, Eslami S. Machine learning-driven advancements in liposomal formulations for targeted drug delivery: a narrative literature review. *Curr Drug Deliv*. 2025.
30. Niu Z, Xiao X, Wu W, et al. PharmaBench: enhancing ADMET benchmarks with large language models. *Sci Data*. 2024;11:985.
31. Clemente-Suárez VJ, Bustamante-Sanchez A, Rubio-Zarapuz A, Martín-Rodríguez A, Tornero-Aguilera JF, Beltrán-Velasco AI. Biomimetic strategies for nutraceutical delivery: advances in bionanomedicine for enhanced nutritional health. *Biomimetics*. 2025;10(7):426.
32. Jha AK, Sit N. Comparison of response surface methodology (RSM) and artificial neural network (ANN) modelling for supercritical fluid extraction of phytochemicals from Terminalia chebula pulp and optimization using RSM coupled with desirability function (DF) and genetic algorithm (GA) and ANN with GA. *Ind Crop Prod*. 2021;170:113769.
33. Zhang L, Chen J, Wang H, Li Y, Zhou K. Advances and prospects of precision nanomedicine in personalized tumor theranostics. *Front Cell Dev Biol*. 2024;12:1514399.
34. Peer D. Omics-based nanomedicine: the future of personalized oncology. *Cancer Lett*. 2013;342(2):188–189.
35. Abd-Algaleel SA, Abdel-Bar HM, Metwally AA, Hathout RM. Evolution of the computational pharmaceutics approaches in the modeling and prediction of drug payload in lipid and polymeric nanocarriers. *Pharmaceuticals*. 2021;14(7):645.
36. Bannigan P, Aldeghi M, Bao Z, Häse F, Aspuru-Guzik A, Allen C. Machine learning directed drug formulation development. *Adv Drug Deliv Rev*. 2021;175:113806.
37. Abdalla Y. *Applying Machine Learning Methods to Pharmaceutical Datasets for Developing Personalised Medicinal Products*. UCL: University College London); 2025. Doctoral dissertation.
38. Dangeti A, Bynagari DG, Vydani K. Revolutionizing drug formulation: harnessing artificial intelligence and machine learning for enhanced stability, formulation optimization, and accelerated development. *Int J Pharm Sci Med*. 2023;8:18–29.
39. Abdullah AS, Sayed IETE, El-Torgoman AMA, Kalam A, Wageh S, Kamel MA. Green synthesis of silymarin–chitosan nanoparticles as a new nano formulation with enhanced anti-fibrotic effects against liver fibrosis. *Int J Mol Sci*. 2022;23(10):5420.
40. Chauhan S, Sharma S. Recent approaches on molecular markers, treatment and novel drug delivery system used for the management of colorectal cancer: a comprehensive review. *Curr Pharm Biotechnol*. 2024;25(15):1969–1985.
41. Waqas S, Harun NY, Arshad U, et al. Optimization of operational parameters using RSM, ANN, and SVM in membrane integrated with rotating biological contactor. *Chemosphere*. 2024;349:140830.
42. Ali H. Artificial intelligence in multi-omics data integration: advancing precision medicine, biomarker discovery and genomic-driven disease interventions. *Int J Sci Res Arch*. 2023;8(1):1012–1030.
43. Shafiq MS, Saleem M, Ishaque I, et al. Nanoparticle-induced oxidative stress in human cell lines: enzymatic biomarkers and gene expression disturbances. *Sch Acad J Biosci*. 2025;7:926–959.
44. Cacciarelli D, Kulahci M. Hidden dimensions of the data: PCA vs autoencoders. *Qual Eng*. 2023;35(4):741–750.
45. Joshi I, Bhrdwaj A, Khandelwal R, et al. Artificial intelligence, big data and machine learning approaches in genome-wide SNP-based prediction for precision medicine and drug discovery. In: *Big Data Analytics in Chemoinformatics and Bioinformatics*. Elsevier; 2023:333–357.
46. Ferrocino I, Rantsiou K, McClure R, et al. The need for an integrated multi-omics approach in microbiome science in the food system. *Compr Rev Food Sci Food Saf*. 2023;22(2):1082–1103.
47. Chen YH, Lin SJ, Chen YL, Liu PL, Chen JW. Anti-inflammatory effects of different drugs/agents with antioxidant property on endothelial expression of adhesion molecules. *Cardiovasc Haematol Disord - Drug Targets*. 2006;6(4):279–304.
48. Randall DW, Kieswich J, Swann J, et al. Batch effect exerts a bigger influence on the rat urinary metabolome and gut microbiota than uraemia: a cautionary tale. *Microbiome*. 2019;7(1):127.
49. Chopra H, Dey PS, Das D, et al. Curcumin nanoparticles as promising therapeutic agents for drug targets. *Molecules*. 2021;26(16):4998.
50. Chakravarty K, Antontsev V, Bundey Y, Varshney J. Driving success in personalized medicine through AI-enabled computational modeling. *Drug Discov Today*. 2021;26(6):1459–1465.
51. Mukherjee A, Abraham S, Singh A, Balaji S, Mukunthan KS. From data to cure: a comprehensive exploration of multi-omics data analysis for targeted therapies. *Mol Biotechnol*. 2025;67(4):1269–1289.
52. Bao Z. *Towards data-driven Development of Advanced Drug Formulations Leveraging Machine Learning and Experimental Automation*. University of Toronto (Canada); 2024. Doctoral dissertation.
53. Valenzuela-Bustamante P, Cornejo P, Nolan N, et al. Valorization of Carménère grape pomace: extraction, microencapsulation, and evaluation of the bioactivity of polyphenols in Caco-2 cells. *Int J Mol Sci*. 2025;26(16):7994.
54. Kusumawati I. A great challenge on the reproducibility of therapeutic results of phytopharmaceuticals. *Phytopharma: Potential Therap App*. 2021:1–18.
55. Mirzaei M. *Functionality and Toxicity Assessments of Nanomaterials Using Machine Learning*. University of Limerick; 2023. Doctoral dissertation.
56. Mahdi WA, Alhowyan A, Obaidullah AJ. Intelligence analysis of drug nanoparticles delivery efficiency to cancer tumor sites using machine learning models. *Sci Rep*. 2025;15(1):1017.
57. Data P. American society for clinical pharmacology and therapeutics. *Clin Pharmacol Ther*. 2024;115:S5.
58. Ibrahim MT, Uzairu A. 2D-QSAR, molecular docking, drug-likeness, and ADMET/pharmacokinetic predictions of some non-small cell lung cancer therapeutic agents. *J Taibah Univ Med Sci*. 2023;18(2):295–309.
59. Olasupo SB, Uzairu A, Shallangwa G, Uba S. QSAR modeling, molecular docking and ADMET/pharmacokinetic studies: a chemometrics approach to search for novel inhibitors of norepinephrine transporter as potent antipsychotic drugs. *J Iran Chem Soc*. 2020;17(8):1953–1966.
60. Chowdhury T, Rahimi R, Allan J. Rank-lime: local model-agnostic feature attribution for learning to rank. In: *Proceedings of the 2023 ACM SIGIR International Conference on Theory of Information Retrieval*. 2023:33–37.
61. Ramadhan SA, Ali DS. Innovations in core–shell nanoparticles: advancing drug delivery solutions and precision medicine. *OMICS A J Integr Biol*. 2025;29(3):73–86.
62. Gharehbeglou P, Sarabandi K, Akbarbaglu Z, Jafari SM. Predictive modeling of oleuropein release from double nanoemulsions: an analytical study comparing intelligent models and Monte Carlo simulation. *J Agric Food Res*. 2024;17:101261.
63. Farid A, ed. *Herbal Pharmacopeia: Nanotechnology and Advancing Drug Discovery*. CRC Press; 2025.
64. Viswan V, Shaffi N, Mahmud M, Subramanian K, Hamajohideen F. Interpreting artificial intelligence models: a systematic review on the application of LIME and SHAP in Alzheimer's disease detection. *Brain Inform*. 2024;11:10.
65. U.S. Food and Drug Administration. Considerations for the use of artificial intelligence to support regulatory decision-making for drug and biological products: draft guidance for industry. *Fed Regist*. 2025;90(4):1128–1129.
66. Msto RK, Othman HO, Al-Hashimi BR, et al. Fluorescence turns on-off-on sensing of ferric ion and L-ascorbic acid by carbon quantum dots. *J Food Qual*. 2023;2023(1):5555608.
67. Lousa IR. *Pharmaceutical Regulation of Nanomedicines: Principles and Challenges*. Universidade de Lisboa (Portugal); 2024. Master's thesis.
68. Loh JS, Tan LKS, Lee WL, et al. Do lipid-based nanoparticles hold promise for advancing the clinical translation of anticancer alkaloids? *Cancers*. 2021;13(21):5346.

69. Zou L, Ding W, Huang Q, et al. Andrographolide/phospholipid/cyclodextrin complex-loaded nanoemulsion: preparation, optimization, in vitro and *in vivo* evaluation. *Biol Pharm Bull*. 2022;45(8):1106–1115.
70. Mirakhori F, Niazi SK. Harnessing the AI/ML in drug and biological products discovery and development: the regulatory perspective. *Pharmaceuticals*. 2025;18 (1):47.
71. Liu CL, Jiang Y, Li HJ. Quality consistency evaluation of traditional Chinese medicines: current status and future perspectives. *Crit Rev Anal Chem*. 2025;55(4): 684–701.
72. Singh L, Srivastav S, Avasthi A, et al. Translational omics: precision and all "coming of age". In: *Multi-Omics in Biomedical Sciences and Environmental Sustainability: Applications and Recent Advances*. Singapore: Springer Nature Singapore; 2025:1–32.
73. Ullagaddi P. Cross-regional analysis of global AI healthcare regulation. *J Comput Commun*. 2025;13(5):66–83.
74. Kelley K, Kelley M, Kelley SC, Sakara AA, Ramirez MA. AI/ML models to aid in the diagnosis of COVID-19 illness from forced cough vocalizations: good machine learning practice and good clinical practices from concept to consumer for AI/ML software devices. *medRxiv*. 2021:2021, 11.
75. Balali F, Nouri J, Nasiri A, Zhao T. Machine learning principles. In: *Data Intensive Industrial Asset Management: Iot-Based Algorithms and Implementation*. Cham: Springer International Publishing; 2020:115–157.
76. Baidoo I, Sarbadhikary P, Abrahamse H, George BP. Metal-based nanoplatforms for enhancing the biomedical applications of berberine: current progress and future directions. *Nanomedicine*. 2025;20(8):851–868.
77. Karthikeyan A, Young KN, Moniruzzaman M, et al. Curcumin and its modified formulations on inflammatory bowel disease (IBD): the story so far and future outlook. *Pharmaceutics*. 2021;13(4):484.
78. Kapoor DU, Sharma JB, Gandhi SM, et al. AI-driven design and optimization of nanoparticle-based drug delivery systems. *Sci Eng Health Studies*. 2024, 24010003-24010003.
79. Durazzo A, Sorkin BC, Lucarini M, et al. Analytical challenges and metrological approaches to ensuring dietary supplement quality: international perspectives. *Front Pharmacol*. 2022;12:714434.
80. Pessanha Santos N. The expansion of data science: dataset standardization. *Standards*. 2023;3(4):400–410.
81. Chen F, Wang L, Hong J, Jiang J, Zhou L. Unmasking bias in artificial intelligence: a systematic review of bias detection and mitigation strategies in electronic health record-based models. *J Am Med Inf Assoc*. 2024;31(5):1172–1183.
82. Hayat G. *Towards Detection and Mitigation of Dataset Bias Through Adaptive Reweighting*. ETH Zurich; 2021. Master's thesis.
83. Srinivasu PN, Sandhya N, Jhaveri RH, Raut R. From blackbox to explainable AI in healthcare: existing tools and case studies. *Mob Inf Syst*. 2022;2022(1):8167821.
84. Ye Z, Ouyang D. Opportunities and challenges of artificial intelligence (AI) in drug delivery. *Explor Comput Pharma-AI Model Pharma 4.0*. 2024:10–58.
85. Singh R. Revolutionizing antimicrobial therapies through biofilm-targeted nanomedicine. *Curr Pharma Res*. 2025:78–97.
86. Norrie C. *Explainable AI Techniques for Sepsis Diagnosis: Evaluating LIME and SHAP Through a User Study*. 2021.
87. Khatoon UT, Velidandi A. An overview on the role of government initiatives in nanotechnology innovation for sustainable economic development and research progress. *Sustainability*. 2025;17(3):1250.