

AI-Enabled Green Manufacturing of Hepatoprotective Herbal Medicines: Sustainable Approaches to Phytochemical Extraction and Standardization

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Abstract

Liver disorders continue to be a significant worldwide health concern, and hepatoprotective herbal medicines derived from plants such as *Silybum marianum*, *Curcuma longa*, *Andrographis paniculata*, and *Phyllanthus* species continue to occupy a central role in their management. However, standard extraction and standardization workflows are often solvent-intensive, energy-demanding, and poorly replicable, making tension with modern sustainability and regulatory expectations. This review synthesizes new literature on the convergence of artificial intelligence (AI) and green chemistry in the manufacture of hepatoprotective phytopharmaceuticals. We inspect green extraction platforms: supercritical CO₂ extraction, ultrasound- and microwave-assisted extraction, and natural deep eutectic solvents, alongside AI/machine-learning instruments comprising artificial neural networks, response surface methodology hybrids, genetic and particle-swarm algorithms, and chemometric fingerprinting for quality control. Comparative resource-use trends, green chemistry metrics, and representative case studies (silymarin, curcuminoids, customary Chinese medicine quality markers) are presented through tables and schematic figures. The review concludes that AI-guided process optimization can significantly improve extraction productivity, batch consistency, and environmental performance, while highlighting persistent problems in scale-up, data standardization, and regulatory validation that must be addressed for extensive and prevalent industrial adoption.

Keywords

Artificial intelligence, Green extraction, Hepatoprotective agents, Machine learning, Phytochemical standardization, Sustainable manufacturing, Silymarin, Deep eutectic solvents.

1. Introduction

Hepatic disorders comprising non-alcoholic fatty liver disease (NAFLD), viral hepatitis, alcoholic liver disease, and drug-induced liver injury represent a substantial and growing worldwide disease burden, with cirrhosis solely approximated to cause over a million deaths annually [11]. In the absence of curative pharmacotherapy for numerous persistent liver conditions, herbal hepatoprotectants have kept clinical and commercial relevance for decades, with silymarin from milk thistle representing one of the most thoroughly analyzed examples [9,10,13]

The transition of these botanicals from customary remedies into uniform and consistent pharmaceutical-grade products depends critically on two interlinked operations: (i) the productive, particular, and environmentally responsible extraction of active phytoconstituents, and (ii) strong and durable analytical standardization that guarantees batch-to-batch consistency. Conventional techniques for both activities Soxhlet extraction with hazardous organic solvents, single-marker quantification, and trial-and-error process development are increasingly examined as incompatible with green chemistry principles and modern quality-by-design frameworks [5,15,20]

Over the past decade, two independent but complementary changes have reshaped this landscape. First, green extraction technologies such as supercritical fluid extraction (SFE), ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and designer solvents such as ionic liquids and natural deep eutectic solvents (NADES) have matured into industrially feasible options to standard solvent extraction [15,16,19,21]. Second, artificial intelligence and machine learning instruments- artificial neural networks (ANN), genetic algorithms (GA), particle swarm optimization (PSO), and chemometric classifiers have been increasingly applied to optimize extraction parameters, predict results, and automate quality control decision-making [2,4,6,7,8]

This review combines these two streams specifically in the setting of hepatoprotective herbal medicines, offering an organized synthesis of green extraction platforms, AI-driven process optimization, AI-enabled standardization and fingerprinting, and the sustainability metrics used to benchmark ‘greenness’ across the production pipeline. Representative tables, a conceptual framework diagram, and schematic charts are used throughout to unify trends reported across the primary literature.

2. Hepatoprotective Herbal Medicines: Scope and Rationale

A relatively small number of botanical genera account for the majority of clinically and commercially notable hepatoprotective phytopharmaceuticals. Table 1 summarizes representative plants, their primary marker phytoconstituents, and reported processes of hepatoprotection

Despite robust preclinical support, clinical translation of these agents is often limited by poor aqueous solubility, variable raw-material quality, and, most relevant to this review, conflicting and contradictory, environmentally

Table 1: Representative hepatoprotective herbal plants and their principal marker phytoconstituents [9,10,11,12,13,18]

Plant Source	Key Marker Phytoconstituent(s)	Reported Mechanism(s) of Hepatoprotection	Refs.
<i>Silybum marianum</i> (milk thistle)	Silybin, silydianin, silychristin, isosilybin (collectively silymarin)	Antioxidant, anti-lipid peroxidative, membrane-stabilizing, antifibrotic, immunomodulatory	9-13
<i>Curcuma longa</i> (turmeric)	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	Antioxidant, anti-inflammatory, modulation of NF- κ B signalling	18
<i>Andrographis paniculata</i>	Andrographolide	Antioxidant, hepatocyte membrane protection, anti-inflammatory	12
<i>Phyllanthus</i> species	Phyllanthin, hypophyllanthin, lignans	Antiviral (anti-HBV), antioxidant, hepatocyte regeneration support	12
<i>Glycyrrhiza glabra</i> (licorice)	Glycyrrhizin, glycyrrhetic acid	Anti-inflammatory, membrane-stabilizing	12
<i>Picrorhiza kurroa</i>	Picroliv (picroside/kutkoside complex)	Antioxidant, choleretic, immunomodulatory	12

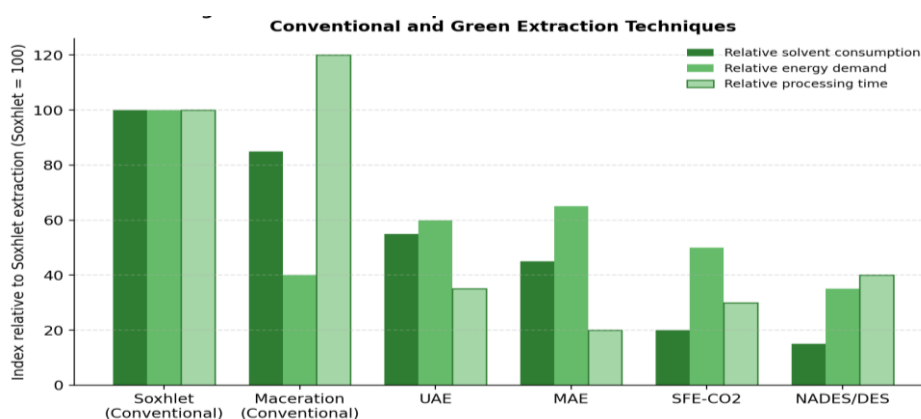
burdensome extraction and standardization practices that undermine reproducibility across batches and manufacturers.

3. Green Extraction Technologies for Hepatoprotective Phytochemicals

Conventional extraction (Soxhlet, prolonged maceration, reflux) commonly relies on huge and massive volumes of hazardous organic solvents, high thermal input, and long processing times, all of which increase the environmental footprint and risk degrading thermolabile hepatoprotective constituents [15,20]. Green extraction technologies address these limitations through process intensification and solvent replacement. Table 2 compares the important and significant techniques.

Table 2: Comparative overview of green extraction technologies applied to hepatoprotective phytochemicals. [15,20]

Technique	Operating Principle	Key Green Attributes	Typical Limitations
Ultrasound-assisted extraction (UAE)	Acoustic cavitation disrupts plant cell walls, enhancing solvent penetration	Reduced solvent volume and time; ambient-to-moderate temperature	Scale-up heterogeneity; probe/bath design sensitivity
Microwave-assisted extraction (MAE)	Selective dielectric heating of polar solvent/matrix	Short extraction times; lower energy input than Soxhlet	Risk of localized overheating of thermolabile actives
Supercritical CO ₂ extraction (SFE-CO ₂)	CO ₂ above its critical point acts as a tunable, non-toxic solvent	Non-toxic, recyclable solvent; solvent-residue-free extract	High capital cost; limited polarity range without co-solvents
Natural deep eutectic solvents (NADES) / DES	Hydrogen-bond donor-acceptor mixtures (e.g., betaine-glycerol, sugar-organic acid)	Biodegradable, low-toxicity, tunable polarity, negligible vapor pressure	Higher viscosity; nascent regulatory/pharmacopoeial guidance
Pressurized liquid / subcritical water extraction	Water or solvent held liquid above boiling point under pressure	Water as primary solvent; fast; closed-loop solvent recovery	High-pressure equipment requirements

**Figure 1: Synthesis of resource-use trends reported across green-extraction literature.**[16,17]

As illustrated in Figure, green techniques generally decrease solvent consumption and, with the exception of specific DES systems requiring longer contact times, furthermore lower processing time relative to Soxhlet

extraction. NADES and SFE-CO₂, in specific and precise, have been highlighted for their compatibility with heat-sensitive flavonolignans and curcuminoids relevant to hepatoprotective formulations [16,17,19,21]

4. Artificial Intelligence and Machine Learning in Extraction Process Optimization

Design of Experiments (DoE) approaches such as response surface methodology (RSM) have long supported extraction optimization. Still, AI/ML strategies increasingly outperform or complement RSM by capturing non-linear parameter interactions. Artificial neural networks (ANN), frequently linked with genetic algorithms (ANN-GA) or particle swarm optimization (ANN-PSO), have been used to model connections between extraction variables (time, temperature, solvent ratio, power) and outputs such as total phenolic content, flavonoid yield, and antioxidant activity [4,6,7,8]. Comparative studies report that ANN-GA hybrids can surpass RSM in both predictive accuracy and the antioxidant/phenolic results of optimized extracts [8]

4.1 Representative AI/ML Techniques

Table 3: AI/ML techniques are applied across the green extraction and standardization pipeline.[4-8]

AI/ML Technique	Typical Role in the Pipeline	Example Application
Artificial Neural Network (ANN)	Non-linear surrogate model of extraction-yield relationships	Predicting phenolic/flavonoid yield from ultrasound parameters
Response Surface Methodology (RSM, statistical baseline)	Quadratic regression-based optimization; benchmark for ML comparison	Microwave-assisted pigment extraction optimization
Genetic Algorithm (GA) / Particle Swarm Optimization (PSO)	Global optimization of ANN-predicted response surfaces	Identifying optimal time-temperature-solvent ratio combinations
Partial Least Squares Discriminant Analysis (PLS-DA) / SVM	Classification and marker-compound correlation with bioactivity	Linking chromatographic fingerprints to pharmacological effect
Convolutional Neural Network (CNN) with NIRS	Real-time, non-destructive batch quality monitoring	In-line monitoring across production batches

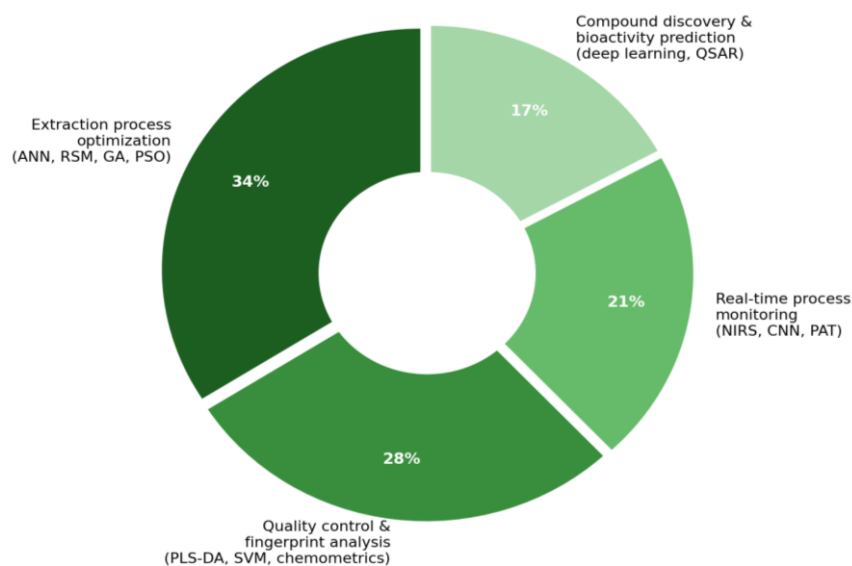


Figure 2: Schematic distribution based on the relative emphasis of AI/ML.[4,6]

5. AI-Enabled Standardization and Quality Control

Standardization of herbal hepatoprotectants has historically relied on single-marker quantification (for instance, total silymarin information by HPLC), which inadequately captures the multi-component nature of therapeutic activity. Chromatographic fingerprinting (HPLC, HPTLC, UPLC-QTOF, GC-MS) combined with chemometric analysis is now viewed as a more holistic approach, endorsed by WHO and important and significant pharmacopoeias for authentication and adulteration detection [22,23]. AI/ML techniques extend this further: spectrum-effect modelling applying techniques such as grey relational analysis, partial least-squares regression, and CNN-BiLSTM architectures has been used to correlate chemical fingerprints directly with pharmacological activity, facilitating identification of quality markers (Q-markers) instead of arbitrary reference compounds [24,27]

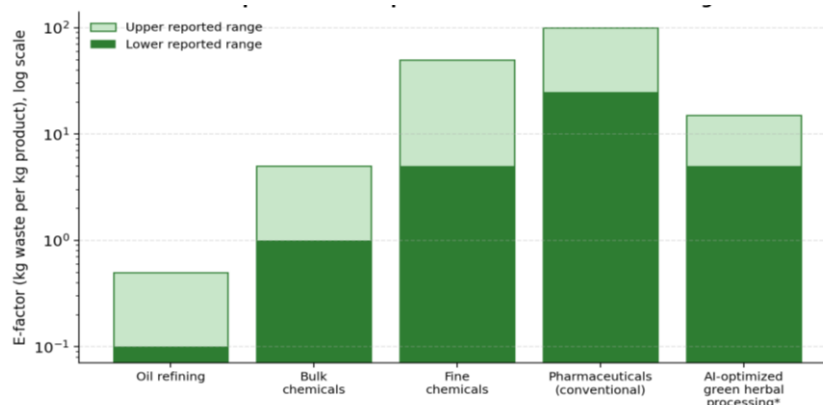
Metabolomics-driven standardization, integrating NMR, LC-MS, and GC-MS profiling with PCA and PLS-DA, further supports authentication and batch consistency while accommodating the natural variability of botanical raw materials [25]. Non-destructive, real-time tracking: for illustration, CNN-based near-infrared spectroscopy (NIRS) systems confirmed across dozens of production batches; illustrates the industrial scalability of AI-enabled quality control [27]

6. Sustainability Metrics and the Green Manufacturing Framework

Quantifying the environmental performance of extraction and standardization procedures necessitates standardized green chemistry metrics. The E-factor (kilograms of waste per kilogram of product) and process mass intensity (PMI) persist as the most broadly used mass-based indicators, while life cycle assessment (LCA) offers a more complete and thorough cradle-to-grave evaluation of global warming potential, water application, and ecotoxicity [28,29,32,33]. Table 4 summarizes the main metrics.

Table 4: Principal green chemistry and sustainability metrics applicable to herbal medicine manufacturing. [28,29]

Metric	Definition	Relevance to Herbal Manufacturing
E-factor	kg waste generated / kg product	Benchmarks solvent and raw-material waste across extraction routes
Process Mass Intensity (PMI)	Total mass input/mass of product	Captures full material burden, including water and auxiliary reagents
Atom Economy	MW of desired product/sum of MW of all reactants	Less directly applicable to extraction, more relevant to derivatization steps
Life Cycle Assessment (LCA)	Cradle-to-grave environmental impact across defined categories (ISO 14040)	Evaluates energy source, solvent recovery, and end-of-life waste treatment
Relative Process Greenness (RPG) / iGAL 2.0	Composite index benchmarking PMI, E-factor, yield, and convergence	Enables cross-process comparison during green process selection

**Figure 3: Projected range for AI-optimized green extraction of herbal activities. [32,33]**

The pharmaceutical sector has historically reported among the highest and preminent E-factors of any chemical sector segment, indicating multi-step synthesis, purification, and quality-control overhead [32]. AI-guided extraction optimization, by minimizing solvent volumes, cutting energy-intensive heating/cooling cycles, and minimizing off-specification batches through predictive quality control, is placed as a lever to narrow this gap for herbal phytopharmaceutical processing, though strong and durable process-specific LCA data for AI-optimized green herbal production persist limited in the present and existing literature [2,33,34]

7. Representative Case Studies

7.1 Silymarin from *Silybum marianum*

Silymarin extraction has been investigated employing phytosome and micellar delivery systems to address bioavailability limitations, alongside emerging green extraction protocols; ongoing pharmacokinetic and delivery-focused clinical studies (for example, the LipoMicel micellar formulation) show active industrial interest in reformulating silymarin production for enhanced and upgraded consistency and bioavailability [13]

7.2 Curcuminoids from *Curcuma longa*

Supercritical CO₂ extraction of turmeric has accomplished high curcuminoid recovery (up to approximately 90%) within markedly shorter extraction times than standard solvent extraction when operated at elevated pressure, with ultrasound- or microwave-assisted hybridization further enhancing mass transfer [18]

7.3 AI-Driven Q-Marker Identification in Traditional Chinese Medicine

A recorded case integrating multi-wavelength HPLC fingerprinting with bioassay data and CNN-BiLSTM spectrum-effect modelling successfully identified essential bioactive compounds and enabled non-destructive, real-time quality control confirmed across 72 production batches, demonstrating a pragmatic framework applicable to hepatoprotective botanical standardization [27]

8. Challenges and Future Perspectives

- Data shortage and heterogeneity: AI/ML models need huge, uniform datasets that is frequently inaccessible for less-studied hepatoprotective species, constraining generalizability.
- Scale-up gap: Many green extraction and AI-optimization studies are conducted at laboratory scale; pilot- and industrial-scale validation, along with matched LCA data, remains comparatively scarce.
- Regulatory harmonization: Pharmacopoeial approval of NADES/DES-based extracts and AI-derived quality markers is still developing across important and significant regulatory jurisdictions.
- Model interpretability: ‘Black-box’ deep learning models used for spectrum-effect correlation need explainability frameworks to obtain regulatory and clinical trust.
- Techno-economic viability: High capital costs of SFE-CO₂ and advanced analytical/AI systems may restrict adoption by small and mid-sized herbal manufacturers.

Future work should prioritise open, uniform and consistent extraction and fingerprinting datasets, integration of LCA directly into AI optimisation-neutral functions (multi-objective optimization balancing yield, bioactivity, and environmental impact), and cooperative regulatory science to officially confirm AI-derived Q-markers alongside standard pharmacopoeial standards.

9. Conclusion

The convergence of green extraction technologies and artificial intelligence provides a coherent pathway toward more sustainable, replicable production of hepatoprotective herbal medicines. Green solvent systems reduce the environmental strain of phytochemical separation, while AI/ML instruments enhance process productivity, permit

multi-parameter optimization beyond the reach of classical design-of-experiments methods, and support holistic, activity-linked standardization. Realizing the total and whole advantage of this convergence at industrial scale will need sustained investment in data systems, pilot-scale validation, and regulatory science customized to AI-enabled green pharmaceutical production.

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