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Next-Gen Pharmaceutics: Merging CRISPR, Artificial Intelligence, and Green Chemistry for Smart Drug Delivery

Next-Gen Pharmaceutics with CRISPR, AI & Green Chemistry

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ABSTRACT

Conventional pharmaceutical development faces significant challenges, including poor drug targeting, lengthy development timelines, and environmental concerns associated with chemical synthesis. Recent advances in biotechnology and digital science, however, offer transformative solutions to these issues. This review examines the convergence of CRISPR gene-editing, artificial intelligence (AI), and green nanotechnology—collectively termed the CRAGE framework—as a multidisciplinary strategy for achieving smarter, more sustainable, and patient-specific drug delivery systems. A comprehensive literature review was conducted using PubMed, Scopus, and Web of Science, focusing on peer-reviewed studies published between 2010 and 2025, with an emphasis on case studies, clinical progress, and technological integration among CRISPR, AI, and green nanoparticle synthesis. Findings indicate that CRISPR enables highly specific gene-level interventions, AI supports predictive modeling, formulation design, and toxicity assessment, and green nanotechnology offers eco-friendly carriers with excellent biocompatibility and controlled release properties. The synergistic application of these technologies effectively addresses the limitations of conventional drug delivery approaches and lays the foundation for next-generation pharmaceutics. Integrating CRISPR, AI, and green chemistry represents a paradigm shift in pharmaceutical sciences, enhancing precision, sustainability, and therapeutic efficacy while promoting the development of targeted, environmentally benign, and personalized drug delivery platforms.

Keywords: *CRISPR, Artificial Intelligence, Green Nanotechnology, Smart Drug Delivery, Personalized Medicine, Sustainable Pharmaceutics, Targeted Therapy*

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Introduction:

The pharmaceutical landscape is undergoing a profound transformation, fueled by the convergence of biological, computational, and eco-conscious technologies. Despite substantial progress in drug discovery and delivery, many therapeutic agents still suffer from poor bioavailability, off-target effects, and complex manufacturing processes[1]. Moreover, growing concerns over environmental sustainability and the need for personalized medicine demand a paradigm shift in how drugs are designed, developed, and delivered[2].

To address these challenges, three disruptive technologies-CRISPR-based gene editing, artificial intelligence (AI), and green nanotechnology—have emerged at the forefront of pharmaceutical innovation. Each

offers distinct advantages: CRISPR enables precise genetic modulation at the molecular level, AI accelerates data-driven drug design and optimization, and green chemistry facilitates eco-friendly nanoparticle synthesis with reduced toxicity and enhanced biocompatibility[3][4][5].

When integrated, these platforms create a powerful framework referred to as CRAGE-an acronym representing CRISPR, AI, and Green Engineering[6]. This convergence offers unprecedented opportunities to develop next-generation drug delivery systems that are target-specific, customizable, and environmentally sustainable[7]. CRAGE-based approaches are paving the way for personalized therapeutics in areas such as cancer, genetic disorders, antimicrobial resistance, and rare diseases[8].

This review aims to provide a comprehensive overview of each pillar of the CRAGE framework, detailing their mechanisms, recent advances, and applications in smart drug delivery. It further explores how their integration is reshaping pharmaceutical research and accelerating clinical translation[9]. By analyzing current trends, limitations, and future directions, this article underscores the transformative potential of CRAGE technologies in building a smarter, safer, and more sustainable future for global healthcare and time line illustrated in figure 1[10].

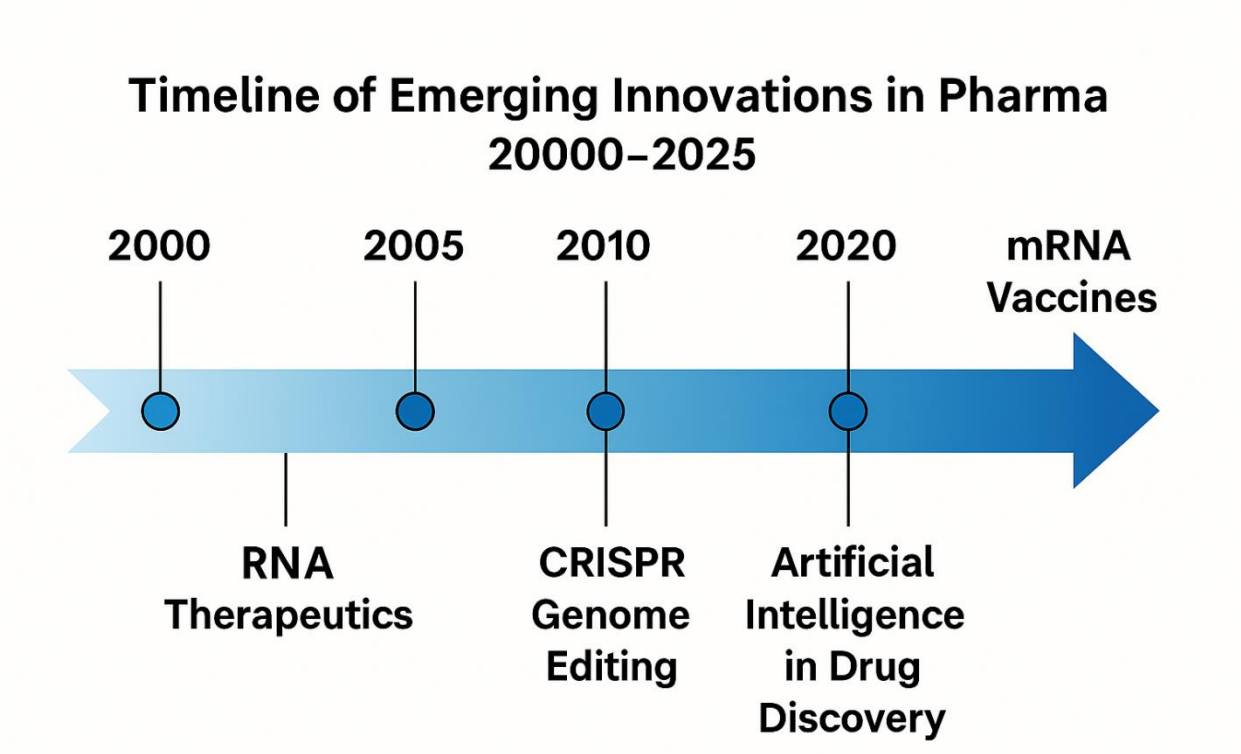

Figure 1: *Timeline of Emerging Innovations in Pharma (2000–2025)*

2. CRISPR Technology in Pharmaceutics[11]

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) has transformed the field of gene-based therapeutics. The ability to edit individual genomic locations with high precision and programmable control through the CRISPR/Cas systems, particularly the popular CRISPR-Cas9, provides unprecedented control over gene function. At first, a defensive mechanism of the bacteria, but now, it is used to fix genetic mutations, suppress genes associated with diseases, and add therapeutic changes [12].

CRISPR technology is also being studied as a means to improve the efficacy of drugs and as a means of modelling disease, in addition to the curative gene therapy applications in the field of pharmaceuticals. CRISPR is, for instance, employed to create patient-specific disease models for more precise drug screening and development. Moreover, it is now undergoing clinical trials to correct mutations involved in monogenic disorders like sickle cell anemia, Duchenne muscular dystrophy and hereditary blindness, where it has been proven to be safe and feasible[13].

A promising approach is the combination of CRISPR and sophisticated delivery mechanisms. Viral vectors, green-synthesized carriers and even lipid nanoparticles (LNPs) are being engineered to carry CRISPR efficiently in vivo [14]. The carriers can shield the CRISPR components from degradation and deliver them specifically to certain cells or tissues. These formulations have been used with success against cancers, liver diseases and hematological diseases [15].

Although the power of CRISPR is transformative, it does come with its drawbacks. Other issues of active research and debate involve off-target editing, immune responses, delivery considerations and ethical concerns. Still, ongoing progress in the design of the CRISPR, including base editing and prime editing, is helping to solve many of these problems [16].

The use of CRISPR in future pharmaceutics is expected to evolve from curative to personalized, on-demand therapeutics delivered via table 1 and mechanism in figure 2 as it increasingly gets integrated with AI-based modelling and green platforms for delivery[17].

Table 1. Selected CRISPR-Based Therapies in Development

Disease/Application	Target Gene/Mechanism	Delivery System	Development Stage	References
Sickle Cell Disease	BCL11A suppression	Electroporation + LNPs	Phase 1/2 Trial	[18]
Leber Congenital Amaurosis	CEP290 correction	AAV vector	Phase 1 Trial	[19]

Transthyretin Amyloidosis	TTR knockout	LNP-mediated IV delivery	Preclinical	[20][21]
Cancer Immunotherapy	PD-1 gene knockout	Ex vivo T-cell editing	Clinical	[22]
Beta Thalassemia	HBB correction	Electroporation	Phase 2	[23]

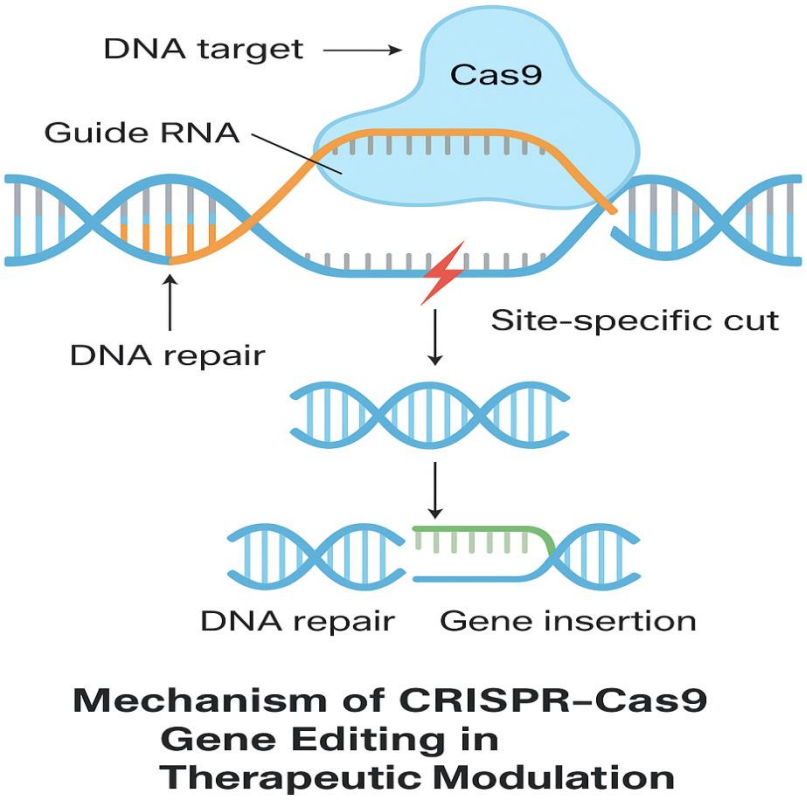

Figure 2. Mechanism of CRISPR-Cas9 Gene Editing in Therapeutic Modulation

3. Artificial Intelligence in Pharmaceutical Sciences

Artificial Intelligence (AI) is redefining pharmaceutical innovation by enhancing the accuracy, speed, and efficiency of drug discovery, development, and delivery[24]. AI, particularly machine learning (ML) and deep learning (DL) algorithms, enables the analysis of complex biological datasets and the prediction of molecular behavior, thus significantly shortening the drug development cycle and reducing associated costs[25].

In early-stage drug discovery, AI facilitates the identification of novel therapeutic targets and potential drug candidates through virtual screening and de novo molecule generation. Models such as DeepChem, AtomNet, and AlphaFold2 have demonstrated the ability to predict protein-ligand interactions, 3D protein structures, and optimal pharmacophores with exceptional accuracy. This computational insight helps avoid trial-and-error approaches traditionally associated with formulation and optimization processes[26][27].

Beyond discovery, AI is also transforming pharmaceutical formulation by optimizing parameters such as particle size, stability, drug release kinetics, and excipient compatibility.

Data-driven tools can predict solubility, permeability, and shelf-life based on chemical structures and formulation conditions. Such predictive capabilities are invaluable when designing nanoformulations, transdermal systems, or oral controlled-release platforms[28][29].

In clinical development, AI algorithms support patient stratification, dosage prediction, and real-time monitoring during clinical trials. Digital twins—virtual representations of patients—are being developed to simulate drug responses and enhance personalized medicine[30]. Moreover, AI is being utilized for pharmacovigilance by identifying adverse drug reactions through post-market surveillance using big data from electronic health records and social media[31].

The convergence of AI with CRISPR and green nanotechnology further enables precision design and real-time optimization of complex drug delivery systems. For example, AI can predict the best gRNA sequences in CRISPR editing or model the most stable green-synthesized nanoparticles for site-specific targeting and growth with discovery illustrated in figure 3 and figure 4[32].

Despite its advantages, AI's adoption faces challenges including data quality, model transparency, regulatory acceptance, and the need for interdisciplinary collaboration. Nonetheless, the ongoing advancements in explainable AI (XAI) and regulatory frameworks signal a promising future for AI-driven pharmaceutical systems and tools given in table 2[33].

Table 2. AI Tools in Pharmaceutical Sciences and Their Applications

AI Tool/Platform	Primary Function	Application Area	Notable Advantage	References
AlphaFold2	Protein structure prediction	Target identification	High 3D accuracy	[34]
DeepChem	Drug property modeling	Virtual screening	Open-source integration	[35]
IBM Watson	Text mining & data analysis	Drug repurposing	NLP-based synthesis	[36]
AtomNet	Molecular docking	Lead optimization	Deep learning scoring	[37]
DeepTox	Toxicity prediction	Safety assessment	In silico ADMET screening	[38]

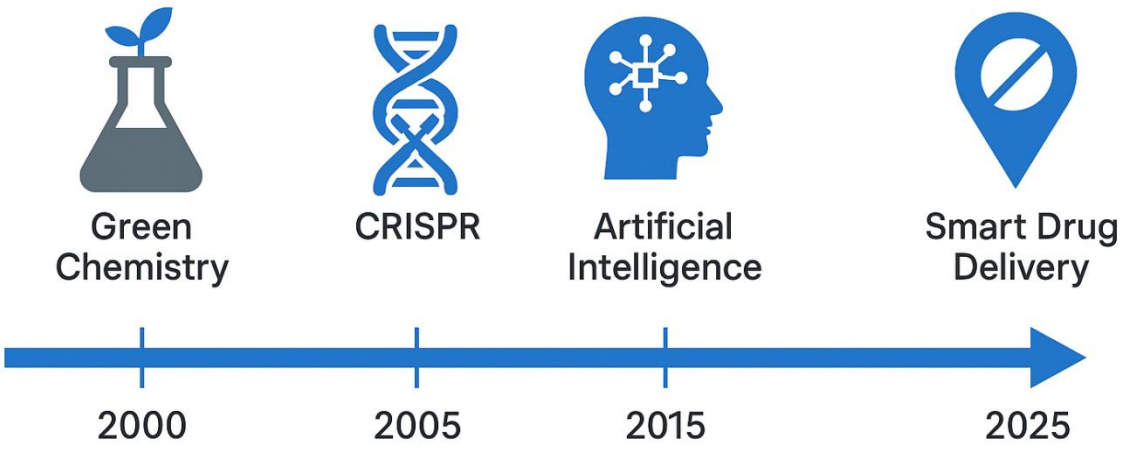

Figure 3: *Growth of AI-based Drug Development (2000–2025)*

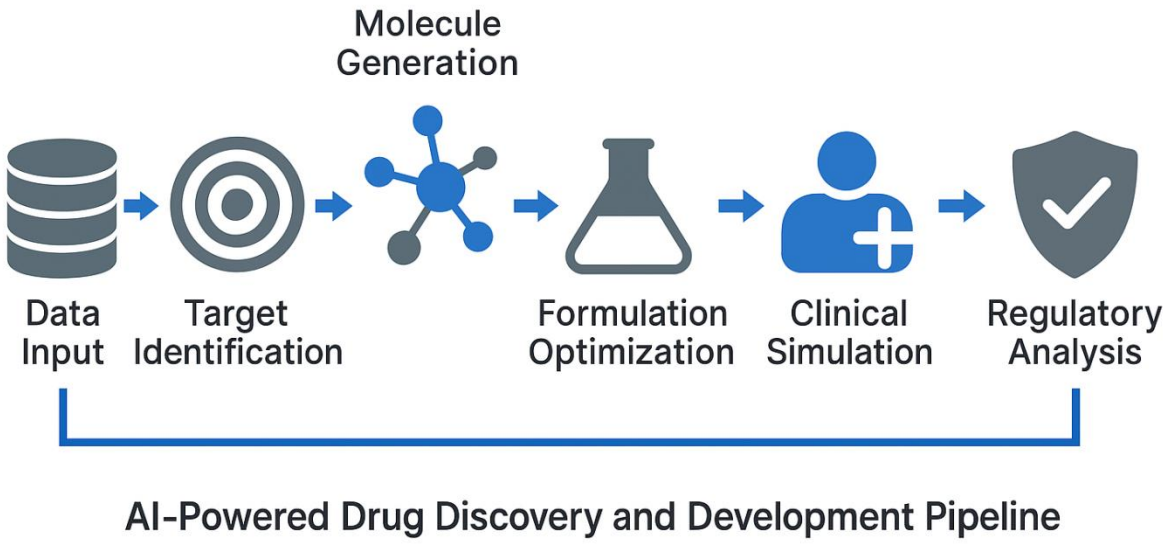

Figure 4. Workflow: AI-Powered Drug Discovery and Development Pipeline

4. Green Nanotechnology in Drug Delivery

4.1 Introduction to Green Nanotechnology

Green nanotechnology integrates the principles of green chemistry with nanoscience to create biocompatible, eco-friendly, and functionally efficient drug delivery systems[39]. This approach addresses key limitations of conventional nanoparticle synthesis, such as toxic solvents, harsh reaction conditions, and poor biodegradability[40]. By leveraging natural reducing and stabilizing agents from plant extracts, microorganisms, and biodegradable polymers, green nanotechnology enables sustainable production of nanoparticles with enhanced pharmacological profiles[41].

4.2 Principles and Advantages[42][43]

The core principles of green nanotechnology include:

- Use of non-toxic solvents (e.g., water, ethanol)
- Employment of renewable biological sources (e.g., neem, aloe vera, turmeric)

- Energy-efficient synthesis at room temperature or mild conditions
- Generation of biodegradable and non-immunogenic nanocarriers

These eco-conscious nanostructures not only minimize environmental burden but also offer advantages such as improved solubility, targeted delivery, prolonged circulation time, and reduced systemic toxicity[44].

4.3 Phytochemical-Mediated Synthesis of Nanoparticles[45]

Phytochemicals such as flavonoids, terpenoids, phenolics, alkaloids, and saponins serve as natural reducing, capping, and stabilizing agents. They facilitate the formation of nanoparticles by reducing metal ions (e.g., Ag^{+}, Au^{3+}, Zn^{2+}) and preventing aggregation. The resulting particles exhibit controlled morphology, stability, and therapeutic functionality and also given in table 3 and shown in figure 5[46].

4.4 Case Studies and Applications

Several plant-based nanoparticle systems have demonstrated efficacy in delivering anticancer, antimicrobial, and anti-inflammatory agents. For example:

- **Neem (Azadirachta indica):** Synthesizes silver nanoparticles with potent antimicrobial activity[47].
- **Aloe vera:** Mediates zinc oxide nanoparticle formation for wound healing[48].
- **Turmeric (Curcuma longa):** Produces gold nanoparticles with enhanced biocompatibility and antioxidant potential[49].

These platforms are being explored for oral, topical, and parenteral delivery routes, especially in diseases requiring sustained and localized release.

Table 3. Examples of Green-Synthesized Nanoparticles for Drug Delivery

Plant Source	Nanoparticle Type	Active Phytochemicals	Biomedical Application	References
Neem	AgNPs	Azadirachtin, flavonoids	Antibacterial, wound healing	[50]
Aloe vera	ZnONPs	Anthraquinones, tannins	Antimicrobial, dermatological	[51]
Green Tea	AuNPs	Catechins, polyphenols	Antioxidant, anticancer	[52]
Ginger	AgNPs	Gingerol, shogaol	Anti-inflammatory, oral hygiene	[53]
Turmeric	AuNPs, CuONPs	Curcumin, demethoxycurcumin	Antioxidant, anticancer	[54]

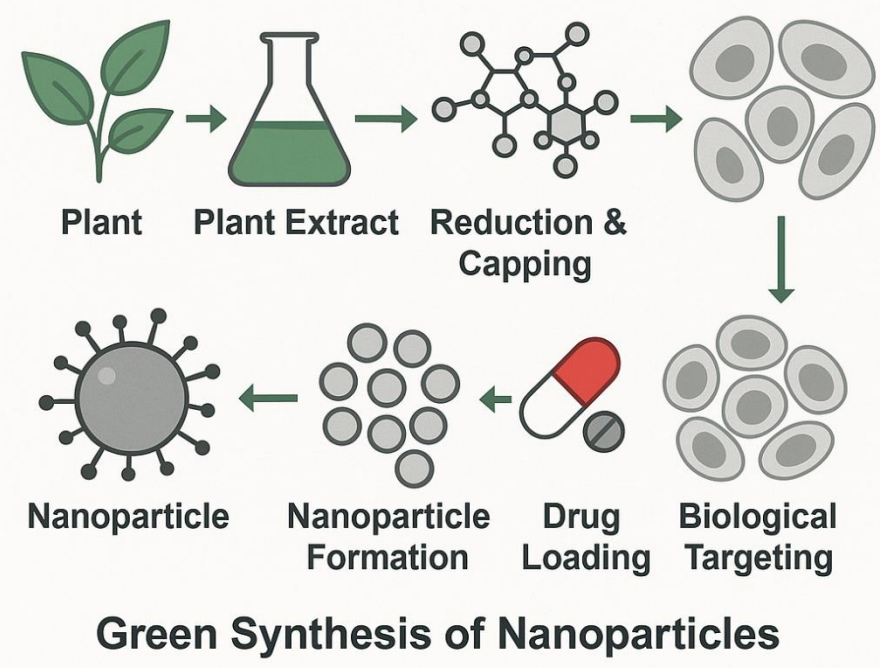

Figure 5. Schematic Representation of Green Synthesis of Nanoparticles

(A diagram showing: Plant extract → phytochemicals → reduction & capping → nanoparticle formation → drug loading → biological targeting)

4.5 Integration with CRISPR and AI

Green-synthesized nanoparticles emerge as biocompatible carriers for CRISPR-Cas components, improving systemic stability and targeted delivery. AI-driven formulation design is being used to predict ideal green synthesis conditions, phytochemical ratios, and biological outcomes—making green nanotechnology an essential link in the CRAGE triad[55][56].

5. The CRAGE Framework: Convergence of CRISPR, AI, and Green Nanotechnology

The integration of CRISPR gene-editing, artificial intelligence, and green nanotechnology—collectively termed the CRAGE framework—marks a transformative paradigm in pharmaceutical sciences. This triad leverages the precision of genome editing, the predictive power of machine learning, and the sustainability of green chemistry to design smart drug delivery systems that are safer, faster, and personalized[57][58].

5.1 Conceptual Synergy

Each CRAGE component contributes uniquely:

- **CRISPR** allows for highly targeted gene modifications, offering a curative approach to monogenic and acquired diseases[59].
- **AI** facilitates intelligent drug design, prediction of gRNA efficacy, nanoparticle behavior, and patient-specific treatment regimens[60].

- **Green Nanotechnology** provides eco-friendly carriers for CRISPR payloads and conventional drugs, enhancing delivery efficiency and reducing toxicity[43].

Together, these elements form a closed-loop innovation cycle where AI designs, green nanotech delivers, and CRISPR corrects.

5.2 Smart Drug Delivery via CRAGE

In CRAGE-integrated platforms, AI models first predict optimal drug-nanocarrier configurations and therapeutic targets. Green-synthesized nanoparticles are then engineered as delivery vehicles for CRISPR-Cas constructs or small-molecule drugs. Once delivered, CRISPR enables gene-level corrections or modulations, leading to highly personalized and effective outcomes given in table 4 and illustrated in figure 6 [61][62].

Applications include:

- CRISPR delivery using green-synthesized lipid or polymer nanoparticles in cancer and liver diseases[63].
- AI optimization of CRISPR gRNA design for maximum on-target specificity[64].
- Formulation of phytochemical-stabilized nanocarriers for co-delivery of gene-editing tools and therapeutic agents[65].

5.3 Case Studies

1. **Targeted Gene Editing in Cancer**: AI-assisted design of Cas9 gRNA and biodegradable turmeric-derived AuNPs for in vivo CRISPR delivery to tumor cells[66].
2. **CRISPR-Loaded Green Nanocarriers**: Neem-extract synthesized AgNPs used for delivering CRISPR plasmids in bacterial infection models[67].
3. **AI-Guided Smart Formulations**: Use of reinforcement learning to model drug release from green polymeric nanoparticles tailored to individual pharmacokinetic profiles[68].

Table 4. Representative CRAGE-Based Innovations

Technology Integration	Application Area	Outcome	Status	References
AI + CRISPR	Gene mutation correction	Enhanced gRNA accuracy	Preclinical	[69]
CRISPR + Green Nanoparticles	Cancer immunotherapy	Targeted tumor gene silencing	Preclinical	[70]
AI + Green Nanocarriers	Oral nanoformulation	Optimized release profile	Clinical Trials	[71]
CRAGE (All 3 Combined)	Antimicrobial resistance	Gene knockout + drug delivery	Lab-scale Proof	[72]

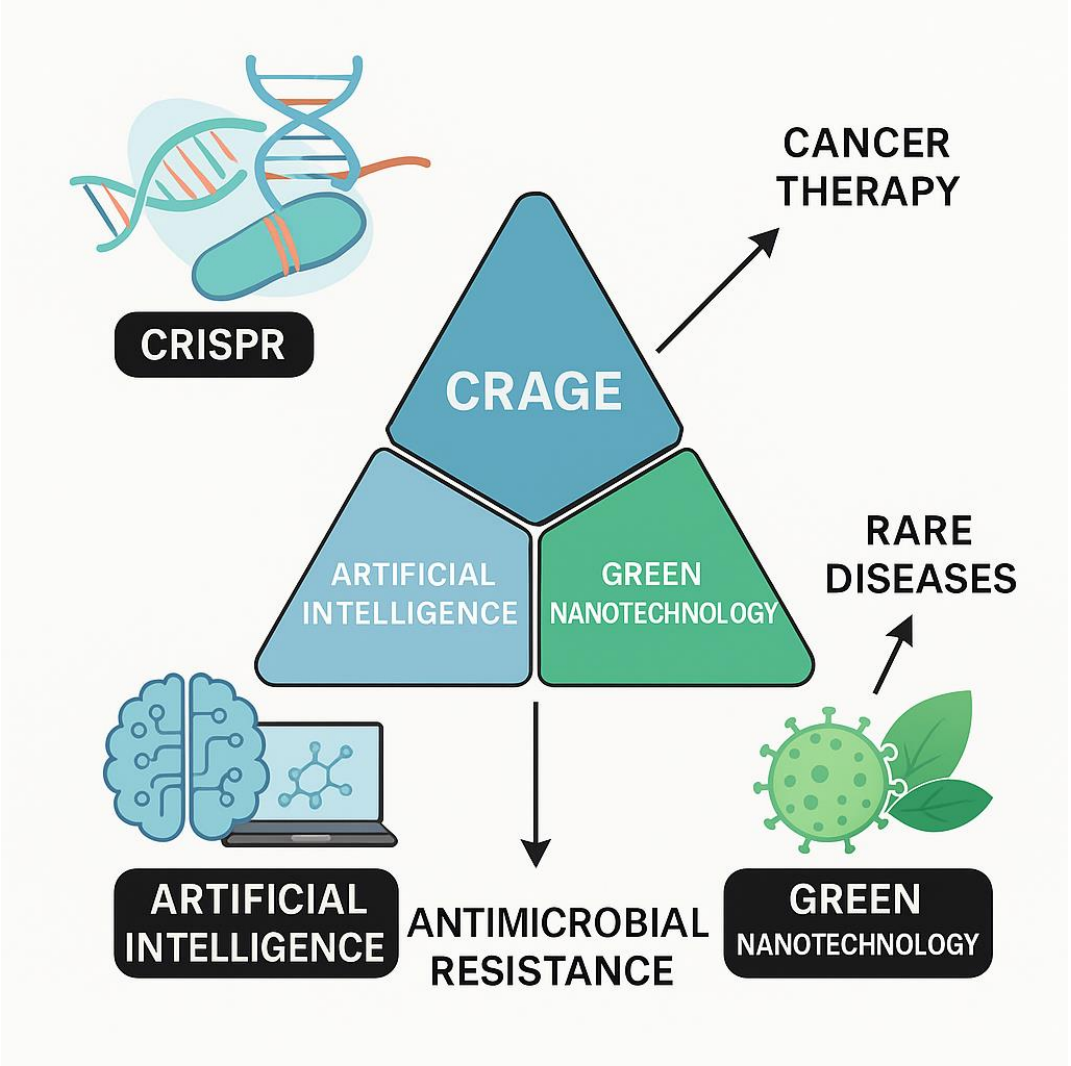

Figure 6. CRAGE Framework – Integrative Model for Smart Drug Delivery.

5.4 Clinical Implications and Opportunities

The CRAGE approach offers solutions for:

- **Personalized therapies** based on genomic and metabolic profiles
- **Eco-conscious pharmaceutical design** reducing ecological burden
- **Faster clinical translation** via in silico trials and low-toxicity delivery platforms

As regulatory bodies begin to recognize the safety and efficacy of such integrated systems, CRAGE is anticipated to drive next-generation therapeutic platforms into clinical and commercial reality[73][74].

6. Regulatory and Clinical Translation of CRAGE Technologies

The translation of innovative drug delivery systems from bench to bedside requires more than scientific efficacy—it mandates compliance with robust regulatory frameworks, clinical safety evaluations, and ethical scrutiny. The CRAGE model**,** which integrates CRISPR, AI, and green nanotechnology, introduces unique regulatory challenges as well as opportunities to reshape current paradigms in pharmaceutical development[72].

6.1 Regulatory Landscape: CRISPR, AI & Green Nanotech

- **CRISPR-Based Therapeutics**:

Regulatory agencies like the FDA and EMA have acknowledged the transformative potential of gene-editing therapies. The FDA's **Cellular & Gene Therapy** division requires investigational new drug (IND) applications to demonstrate not only efficacy but also gene-editing specificity, off-target minimization, and vector safety.
Example: The approval of clinical trials for CTX001 (for β-thalassemia and sickle cell anemia) marked a milestone in CRISPR regulation given in table 5[75].

- **AI in Drug Development**:

The FDA's Digital Health Center of Excellence now offers guidance on AI/ML-based medical software, especially in adaptive learning models. Explainability (XAI), validation datasets, and real-time auditing are core requirements for clinical AI platforms.
Challenge: Regulatory lag due to the dynamic nature of AI models[76].

- **Green Nanoparticles**:

Although green synthesis is still emerging, nanoparticles are subject to nanotoxicology assessment under EMA's and FDA's nanomedicine guidelines. Biodegradability, interaction with immune cells, and eco-safety are key evaluation points[77].

6.2 Clinical Trials and CRAGE Integration

The integration of CRAGE technologies in clinical settings is underway through:

- First-in-human CRISPR therapies
- AI-based virtual trials and patient stratification tools
- Green nanoformulations tested in Phase I–II studies for oral and topical delivery

Hybrid protocols combining in silico simulations (AI), gene modulation (CRISPR), and green nanoformulations are being proposed to fast-track ethical approval and reduce trial cost Illustrated in figure 7[78].

Table 5. Regulatory Guidelines Across CRAGE Components

Technology	Regulatory Body	Key Guidelines	Current Status
CRISPR	FDA, EMA	INDs, off-target risk, long-term monitoring	Clinical trial approved
AI	FDA (CDRH), EU AI Act	Explainability, dataset bias, reproducibility	Under evaluation
Green Nanotech	EMA, ISO 10993-22	Biodegradability, nanotoxicity, sustainability	Preclinical to early trials

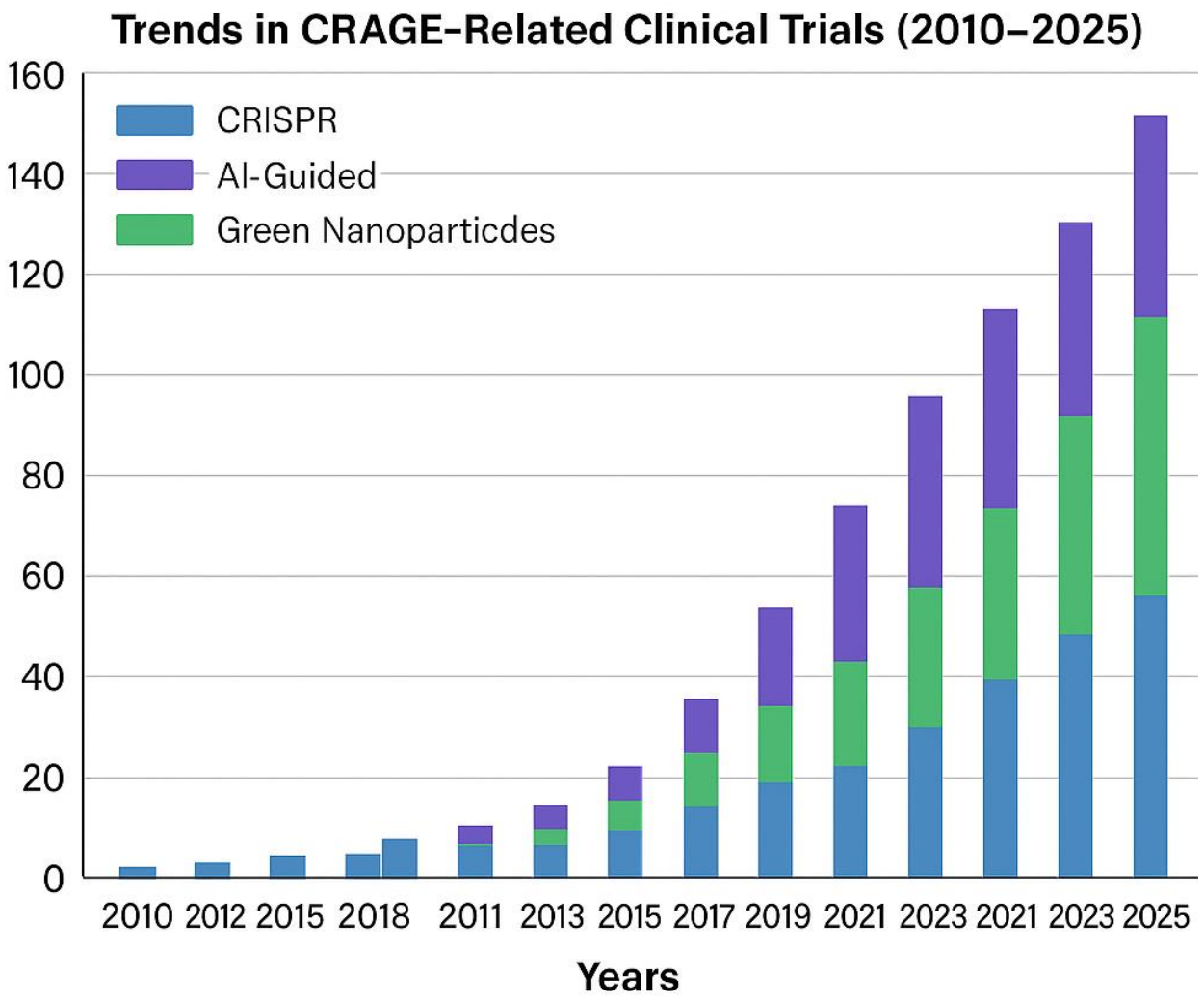

Figure 7. Trends in CRAGE-Related Clinical Trials (2010–2025)

6.3 Ethical and Legal Considerations

CRAGE technologies, especially CRISPR and AI, bring complex ethical implications:

- Germline editing concerns
- Algorithmic bias in clinical decision-making
- Intellectual property disputes involving green bioresources and AI algorithms

Transparent data governance, international harmonization of ethical norms, and cross-border clinical trial standards are urgently needed to support CRAGE deployment in real-world settings[79].

7. Challenges and Future Directions in CRAGE-Based Drug Delivery

While the CRAGE framework (CRISPR, AI, and Green Nanotechnology) offers unprecedented opportunities for precision, personalization, and sustainability in pharmaceutics, several hurdles must be addressed to ensure effective translation into clinical and industrial applications Shown in figure 8

7.1 Current Challenges

a) Integration Complexity

Each component of CRAGE operates within a distinct scientific and regulatory paradigm. Coordinating these technologies into a unified, functional delivery system demands interdisciplinary collaboration and harmonized protocols, which remain underdeveloped in many settings.

b) Standardization and Scalability

Green synthesis protocols vary significantly based on plant species, geographical origin, and extraction methods. Similarly, CRISPR editing efficiency and AI model reproducibility are often dependent on experimental design and data quality. Lack of standardization limits reproducibility and scalability in industrial production.

c) Regulatory Lag

While individually recognized, combined CRAGE technologies often fall outside the purview of existing guidelines. This slows down clinical trial approvals and market entry. AI's adaptive algorithms, for instance, challenge traditional validation models, while green nanoparticles raise unresolved questions in nanotoxicology.

d) Ethical and Data Governance Issues

CRISPR raises concerns over germline modification and long-term genetic consequences. AI models, if trained on biased or incomplete datasets, may lead to erroneous or discriminatory treatment recommendations. Furthermore, access to biogenic materials in green nanotech raises intellectual property and biopiracy concerns.

7.2 Future Directions

a) Modular CRAGE Platforms

Developing modular and programmable drug delivery systems that can be easily tailored by swapping out gene targets, AI models, or nanoparticle compositions will help streamline regulatory approval and manufacturing.

b) Explainable and Transparent AI (XAI)

Investing in transparent, interpretable AI models will not only improve trust but also aid in regulatory clearance. Models that can justify predictions will become essential for personalized therapies and CRISPR design tools.

c) Sustainable and Ethical Frameworks

Global harmonization of ethical norms, especially in genetic interventions and access to natural resources, must be a priority. Integrating One Health and Circular Economy principles in green nanotech development can align pharmaceutics with UN SDGs (Sustainable Development Goals).

d) Funding and Policy Support

Governments and regulatory agencies must establish innovation sandboxes and public–private consortia to fast-track CRAGE innovations. Dedicated funding for interdisciplinary research will be critical to bridge gaps in formulation, delivery, and clinical validation.

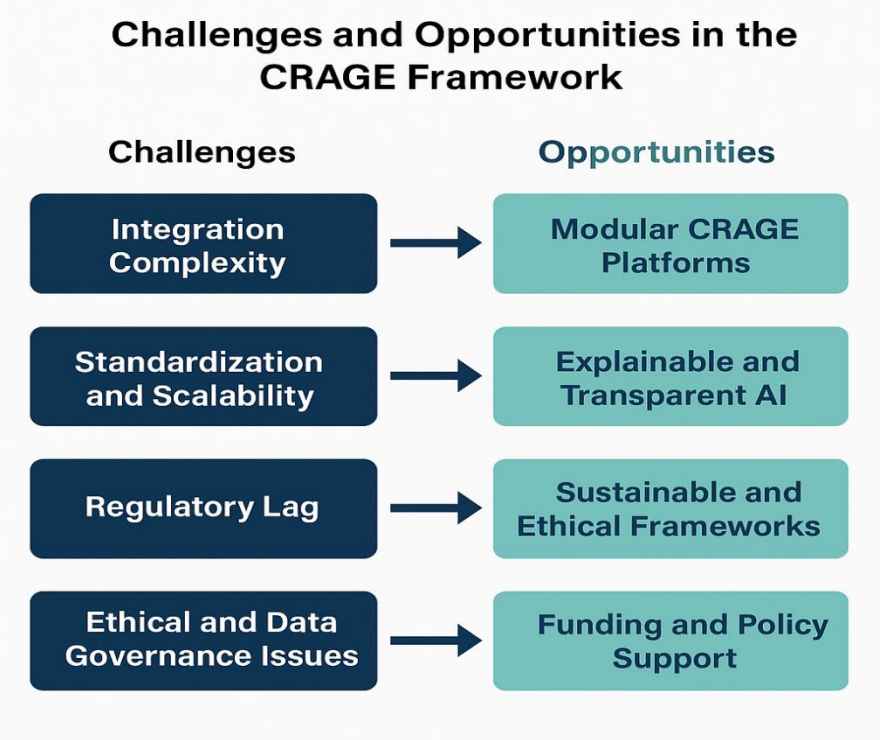

Figure 8. Challenges and Opportunities in the CRAGE Framework.

8. Conclusion and Summary

The convergence of CRISPR gene-editing**,** artificial intelligence**,** and green nanotechnology—represented by the CRAGE framework—heralds a new era in pharmaceutical sciences. This integrated approach transcends the limitations of traditional drug discovery and delivery, enabling precise genetic interventions, intelligent formulation design, and environmentally sustainable therapeutic solutions.

CRISPR offers unparalleled specificity for gene targeting, paving the way for curative treatments for genetic and acquired diseases. AI empowers researchers with predictive analytics, modeling tools, and adaptive systems that accelerate drug development while reducing cost and error. Meanwhile, green nanotechnology ensures the creation of biocompatible and eco-friendly drug carriers that minimize systemic toxicity and support sustainable practices.

Together, these technologies provide a holistic platform for next-generation pharmaceutics-one that is smarter, safer, and more personalized. The CRAGE model shows immense promise across therapeutic domains such as cancer immunotherapy, infectious disease control, rare genetic disorders, and precision medicine.

Despite these advances, several challenges persist, including regulatory ambiguities, ethical concerns, and the need for technological standardization. Addressing these through international cooperation, transparent AI frameworks, and ethical governance will be critical to fully realize CRAGE's potential.

In conclusion, CRAGE technologies are not isolated advancements but complementary pillars of a unified pharmaceutical revolution. With continued interdisciplinary collaboration, investment, and policy support, the vision of intelligent, targeted, and sustainable medicine can transition from laboratory research to global clinical practice—benefiting both patients and the planet.

Acknowledgments

Conflict of interests

The authors declare no conflicts of interest.

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Data availability

All data referenced and analyzed in this review were derived from previously published literature and are publicly available in the cited journals, databases, and repositories. No original datasets were generated in this study.

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