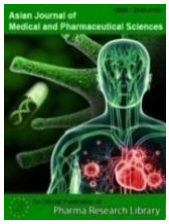

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A Review on Integrating Green Synthesis with Molecular Docking for Novel Drug Discovery

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A B S T R A C T

The integration of green synthesis and molecular docking represents a transformative paradigm in sustainable drug discovery. Green synthesis offers an environmentally friendly route for producing bioactive compounds and nanoparticles using renewable resources, non-toxic solvents, and energy efficient processes, thereby minimizing ecological impact and improving biocompatibility. Concurrently, molecular docking provides a computational framework to predict and optimize ligand–target interactions, accelerating lead identification and reducing experimental costs. The convergence of these two methodologies creates a synergistic workflow where green synthesized phytochemicals or nanoparticles are computationally screened for target specificity, enabling rational drug design with enhanced efficacy and reduced toxicity. This review outlines the principles and advantages of green synthesis and molecular docking, discusses case studies involving green-synthesized metal nanoparticles (ZnO, CuO, Ag, Au and Fe_2O_3) and their in-silico validation, and highlights applications across anticancer, antimicrobial, antiviral, neuroprotective, cardiovascular, and nanoparticle-based drug delivery systems. Key challenges such as standardization of green synthesis, docking accuracy, and translation from in silico to in vivo models are critically analyzed. Future perspectives emphasize the integration of artificial intelligence, machine learning, and omics technologies to enhance predictive precision, scalability, and sustainability. Collectively, this eco-computational framework paves the way for next-generation pharmaceutical innovation that aligns therapeutic advancement with environmental responsibility.

Keywords: Green synthesis, Molecular docking, Sustainable drug discovery, Computational aided drug design

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C O N T E N T S

1. Introduction

Drug discovery is a long, costly, and complex process, often taking over a decade and billions of dollars to bring a new drug to market. Conventional synthesis involves hazardous solvents, toxic reagents, and energy-intensive methods, posing significant environmental and safety concerns. Moreover, drug development is challenged by

high attrition rates due to inefficacy or toxicity during clinical trials (1). The growing emphasis on sustainability and green technologies highlights the urgent need for eco-friendly drug development strategies. Green synthesis reduces environmental hazards by utilizing benign solvents, renewable feedstocks, and energy-efficient processes. Parallelly, molecular docking accelerates the early stages of drug design by predicting interactions between biomolecules and ligands computationally (2).

The integration of green synthesis with molecular docking offers a synergistic strategy that combines eco-friendly synthesis with computational efficiency. This dual approach is transforming modern drug discovery by facilitating the design of safer, more effective, and environmentally sustainable therapeutic agents. By merging sustainable synthesis methods with advanced computational modelling, it enables the development of drug candidates with enhanced efficacy, reduced toxicity, minimized ecological impact (3,4).

2. Green Synthesis in Drug Development

2.1. Concept of green synthesis: Green synthesis emphasizes the design and production of chemical compounds through processes that minimize hazardous reagents, energy consumption, and waste generation (5). Within drug discovery, this includes the use of green solvents, renewable feedstocks, and novel catalytic systems, thereby reducing the pharmaceutical sector's environmental footprint. Importantly, such methods not only support sustainability but also improve biocompatibility, making them highly relevant for therapeutic applications (6).

2.2. The importance of green chemistry:

- Human and ecosystem health: By reducing exposure to hazardous chemicals (in synthesis, intermediates, solvents), there are fewer risks to workers, local communities, and downstream ecosystems.
- Innovation in pharmaceuticals: In drug synthesis, green chemistry principles lead to safer synthetic routes, less hazardous solvents, process intensification (continuous flow, one-pot and multicomponent reactions), and often reduce the environmental footprint of active pharmaceutical ingredient (API) production (7).
- Economic benefits: Greener processes often reduce costs by minimizing waste disposal, using cheaper or less toxic reagents, lowering energy consumption, and improving yields (8).
- Regulatory compliance and social licence: As environmental regulations become stricter and public awareness grows, industries that adopt green chemistry can gain competitive advantage and public acceptance (9).

2.3. Advantages of Green synthesis over conventional synthesis methods: Green synthesis offers several advantages compared to conventional chemical synthesis approaches.

- It employs eco-friendly solvents such as water and ethanol, eliminating the need for hazardous organic solvents that pose risks to human health and the environment.
- It reduces energy consumption by utilizing mild reaction conditions, including ambient temperature and pressure, thereby making the process more sustainable (10).
- Green synthesis frequently employs plant extracts, microorganisms, or other natural reducing and stabilizing agents, which are renewable, biodegradable, and cost-effective.
- This reduces the generation of toxic by-products and enhances biocompatibility, making the synthesized products safer for biomedical applications (11).
- Green synthesis is scalable, economically viable, and aligns with the principles of green chemistry, which emphasize waste minimization, atom economy, and the use of renewable feedstocks.

Overall, green synthesis provides an eco-conscious and sustainable alternative to conventional methods, ensuring environmental safety and improved pharmacological potential.

2.4. Principles of Green Chemistry in pharmaceutical applications:

Fig1: Principles of green chemistry

- Prevention – design processes that avoid waste generation rather than treating waste afterward.
- Atom economy – maximize incorporation of all raw materials into the final drug molecule.
- Less hazardous synthesis – use methods that minimize toxicity to humans and the environment.
- Designing safer chemicals – create compounds that are effective yet degrade into non-toxic products.
- Safer solvents and auxiliaries – replace hazardous solvents with green alternatives like water, ethanol, or supercritical CO_2 .
- Energy efficiency – conduct reactions at ambient temperature and pressure when possible.
- Use of renewable feedstocks – derive raw materials from renewable biological sources instead of petroleum-based ones.
- Reduce derivatives – minimize unnecessary derivatization (protecting/deprotecting steps).
- Catalysis – employ catalysts (enzymes, metal nanoparticles, etc.) over stoichiometric reagents.

- Design for degradation – ensure final products degrade into harmless substances after therapeutic action
- Real-time analysis for pollution prevention – integrate monitoring tools to avoid hazardous byproducts.
- Inherently safer chemistry – design processes that reduce the risk of accidents such as explosions or releases.
- Incorporating these principles into pharmaceutical synthesis ensures that drug discovery aligns with both therapeutic efficacy and environmental stewardship (12,13).

3. Molecular Docking in Drug Design

3.1. Basics of molecular docking:

Molecular docking is a computational method that predicts the orientation and affinity of a ligand binding to a target protein or nucleic acid, providing insights into drug–target interactions (14). It involves a search algorithm, which explores ligand conformations within the binding site, and a scoring function, which estimates binding energies based on hydrogen bonding, hydrophobic, electrostatic, and van der Waals interactions (15). Common approaches include stochastic, genetic, and systematic search methods that balance accuracy with efficiency (16,17).

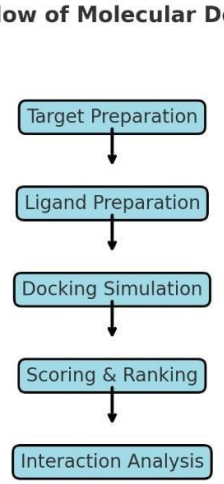

Fig 2: Molecular docking work flow

As a core tool in computer-aided drug design (CADD), docking enables rapid, low-cost screening of large compound libraries compared to experimental methods (18,19). In green synthesis, it complements eco-friendly drug discovery by evaluating the bioactive potential of phytochemicals and green-synthesized nanoparticles (20).

3.2. Role in virtual screening and lead optimization:

3.2.1. Molecular Docking in Virtual Screening:

Virtual screening (VS) employs molecular docking to evaluate the binding affinity between ligands and target proteins, thereby prioritizing compounds for experimental validation. This computational approach significantly reduces both the time and cost associated with traditional high-throughput screening methods. By simulating ligand–receptor interactions, docking identifies potential hits that can be further optimized. Recent advancements in docking algorithms, such as AutoDock, Glide, and Vina, have improved the accuracy and efficiency of these predictions (21,22).

3.2.2. Lead Optimization through Molecular Docking:

Once potential hits are identified, molecular docking facilitates lead optimization by providing detailed insights into ligand–receptor interactions at the atomic level. This information guides the structural modification of lead compounds to enhance binding affinity, selectivity, and pharmacokinetic properties. Techniques such as fragment-based docking and covalent docking have been employed to strengthen interactions between ligands and their targets (23).

3.3. Advantages of Molecular Docking in Drug Design:

- **High-throughput virtual screening:** Docking enables the rapid screening of extensive compound libraries to identify potential drug candidates, thus reducing the time and cost associated with experimental screening.
- **Structural insight into binding interactions:** It provides detailed information about ligand–receptor interactions, including hydrogen bonding, hydrophobic contacts, and electrostatic interactions, facilitating the understanding of structure–activity relationships.
- **Rational lead optimization:** Docking assists medicinal chemists in optimizing lead compounds by predicting how structural modifications influence binding affinity and selectivity (24).
- **Integration with computational tools:** It can be combined with molecular dynamics simulations, QSAR modeling, pharmacophore mapping, and machine learning approaches to enhance predictive performance and design efficiency (25).
- **Cost-effective and accessible:** The availability of open-source software and structural databases makes molecular docking a cost-effective and widely accessible approach for both academic and industrial researchers.
- **Versatility in application:** Docking supports various applications such as drug repurposing, polypharmacology studies, and the identification of off-target effects, thereby broadening its role in modern drug discovery (26).

4. Integrating Green Synthesis with Molecular Docking

4.1. Workflow of combining both approaches:

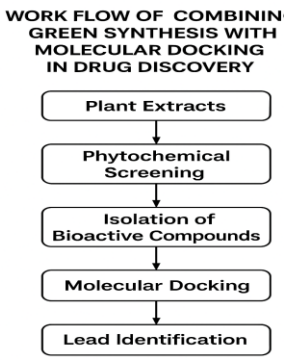

Fig 3: Work flow of combining green synthesis with molecular docking in drug discovery

The integration of green synthesis and molecular docking represents a holistic strategy that bridges eco-friendly material fabrication with computational drug design. The workflow typically begins with the green synthesis of bioactive compounds or nanoparticles using plant, microbial, or algal extracts as reducing and capping agents (27). These biosynthesized entities are then characterized physicochemically and evaluated for biological potential. Parallelly, molecular docking is employed to predict the binding interactions of phytoconstituents or nanoparticle-ligand complexes with disease-specific targets such as enzymes, receptors, or nucleic acids (28). The resulting docking data guide the optimization of synthesis parameters—such as surface functionalization or ligand loading—to enhance target affinity and pharmacodynamic properties. Finally, in vitro or in vivo validation confirms the predicted activity, completing a sustainable, iterative discovery cycle (29).

4.2. Case studies/examples:

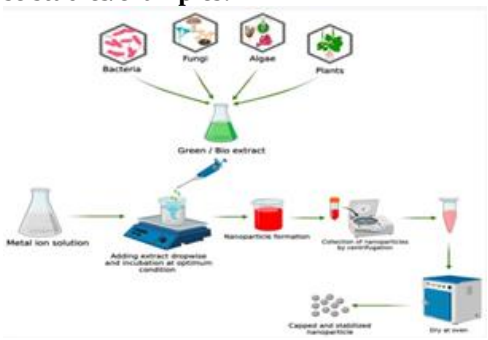

Fig 4: The schematic diagram shows the biosynthesis of nano particles

4.2.1. Zinc Oxide Nanoparticles:

According to Sabir, Arshad, and Chaudhari (30,31), these NPs have a variety of uses in the food additive, cosmetics, rubber, antimicrobial agents, and photocatalysts industries. With a binding energy of −2.93 kcal/mol, zinc oxide nanoparticles utilizing *Cymbopogon citratus* extract demonstrated a good binding relationship between ZnO and DNA gyrase subunit B (32).

4.2.2. Copper Oxide Nanoparticles:

Kocabas and colleagues used *Phragmites australis* leaf extract for the synthesis of copper oxide nanoparticles. They carried out *in silico* molecular docking against the active binding sites of dihydropteroate synthase, thymidylate kinase, and *Staphylococcus aureus* FtsZ, with docking scores of −9.067, −8.048, and −7.349 kcal/mol, respectively (33).

4.2.3. Silver Nanoparticles:

Banerjee et al. synthesized silver nanoparticles in a different work using fruit extract from *Phyllanthus acidus*. The produced nanoparticles had an inhibitory effect on the inflammatory protein NFκβ, according to an *in silico* molecular docking analysis, with docking scores of −6.9 and −6.5 Kcal/mol (34).

4.2.4. Gold Nanoparticles:

According to Al-Radadi, gold nanoparticles containing *Commiphora myrrh* exhibited a stronger negative docking score (−3.976 Kcal/mol) when compared to the VEGFR-2 domain (35).

4.2.5. Iron Oxide Nanoparticles:

Yasmin Abo-zeid and colleagues used docking studies to examine the interaction of iron oxide nanoparticles (IONPs) (Fe2O3 and Fe3O4) with the spike protein receptor binding domain (S1-RBD) of SARS-CoV-2. The glycoproteins E1 and E2 of the hepatitis C virus (HCV) were also subjected to a comparable docking investigation. These investigations demonstrated the effective interactions between Fe2O3 and Fe3O4 and the SARS-CoV-2 S1-RBD, as well as the HCV glycoproteins E1 and E2 (36).

4.3. Synergistic advantages (cost-effectiveness, eco-safety, target specificity):

- Cost-effectiveness arises from the use of natural precursors and the reduction of synthetic complexity, eliminating expensive reagents and minimizing waste (37).
- Eco-safety is achieved through solvent-free or water-based reactions, biocompatible capping agents, and reduced hazardous by-products, aligning with the principles of green chemistry.
- Target specificity improves through docking-guided screening, which enables rational selection of ligands or nanoparticle conjugates with high binding affinity and selectivity toward molecular targets (38).
- This integrative framework thus combines sustainability, computational precision, and therapeutic efficacy, paving the way for next-generation drug discovery platforms that are both environmentally responsible and scientifically robust (39).

5. Applications in Drug Discovery

5.1. Anticancer agents:

The integration of green synthesis and molecular docking has opened new avenues for identifying and optimizing eco-friendly anticancer therapeutics. Phytochemically synthesized metal nanoparticles, particularly gold, silver, and zinc oxide nanoparticles, have demonstrated potent cytotoxic effects against cancer cell lines through mechanisms involving reactive oxygen species (ROS) generation, mitochondrial dysfunction, and apoptosis induction. Molecular docking assists in elucidating the interaction of phytoconstituents or nanoparticle-bound ligands with cancer-related targets such as topoisomerases, kinases, and caspases, thereby guiding rational drug design (40). For instance, green-synthesized gold nanoparticles conjugated with quercetin showed enhanced binding affinity toward the Bcl-2 family proteins, improving apoptotic potential compared with free compound (41). The combination of eco-friendly nanomaterials and docking-guided target prediction therefore represents a sustainable route to anticancer drug discovery.

5.2. Antimicrobial/antiviral compounds:

Green-synthesized nanoparticles, bioactive phytochemicals have exhibited broad-spectrum antimicrobial and antiviral activities due to their ability to disrupt microbial membranes, inhibit enzyme systems, and interfere with viral replication (42,43). Silver and copper nanoparticles synthesized using plant extracts have shown potent

inhibitory effects against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*. Molecular docking complements these findings by predicting the binding affinity of bioactive compounds or nanoparticle surface ligands to microbial and viral targets such as DNA gyrase, dihydrofolate reductase, and SARS-CoV-2 main protease (44). For example, docking-based screening of phytochemicals from *Azadirachta indica* identified several potential inhibitors of SARS-CoV-2 Mpro, validated through subsequent in vitro assays. Thus, integrating docking studies with green synthetic approaches facilitates the rapid identification of safe, sustainable antimicrobial and antiviral candidates.

5.3. Neuroprotective and cardiovascular therapeutics:

Green-synthesized compounds and nanoparticles are increasingly being explored for neuroprotective and cardioprotective applications. Phytochemical-based nanoparticles possess antioxidant and anti-inflammatory properties that mitigate oxidative stress and neuronal damage associated with neurodegenerative diseases such as Alzheimer's and Parkinson's. Docking analyses of flavonoids, alkaloids, and terpenoids derived from green sources have revealed promising interactions with acetylcholinesterase, monoamine oxidase, and amyloid-β targets (45,46). Similarly, plant-derived metallic nanoparticles have shown potential in cardiovascular therapy through modulation of nitric oxide pathways and inhibition of angiotensin-converting enzyme (ACE) (47). Docking-guided predictions of bioactive phytoconstituents with cardiovascular targets such as β-adrenergic and calcium channel receptors aid in the rational selection of cardioprotective candidates synthesized via green routes (48).

5.4. Nanoparticle-based drug delivery systems:

Green-synthesized nanoparticles have emerged as efficient and biocompatible drug delivery systems, enabling targeted, controlled, and sustained drug release. Using plant or microbial extracts as reducing and capping agents enhances nanoparticle stability while minimizing toxicity. Such nanoparticles can be functionalized with therapeutic ligands, antibodies, or targeting moieties predicted via molecular docking to interact selectively with disease-specific receptors (49). For example, docking-guided conjugation of curcumin or doxorubicin onto green-synthesized gold nanoparticles improved their affinity for cancer cell surface markers, enhancing cellular uptake and therapeutic efficacy (50). Biopolymer-coated nanoparticles derived from natural sources also exhibit pH-responsive or enzyme-triggered drug release properties, which can be optimized using computational modeling (51). This synergy of green synthesis and docking paves the way for intelligent, sustainable, and precision-oriented drug delivery systems.

6. Challenges and Limitations

6.1. Standardization issues in green synthesis:

Although green synthesis has emerged as a sustainable alternative to conventional chemical methods, the lack of standardized protocols remains a major limitation. Parameters such as precursor concentration, plant or microbial extract composition, reaction temperature, and pH significantly influence nanoparticle morphology and bioactivity, leading to inconsistencies across studies. The variability in phytochemical profiles due to seasonal, geographical, and extraction differences further complicates reproducibility. Moreover, insufficient mechanistic understanding of bioreduction and stabilization processes restricts precise control over particle size and distribution (52). Establishing globally accepted standard operating procedures (SOPs) and analytical validation criteria is therefore essential to ensure reproducible and scalable green synthesis suitable for pharmaceutical applications (53).

6.2. Docking accuracy and validation concerns:

Molecular docking, while highly efficient, is inherently limited by the accuracy of its scoring functions and the quality of structural input data. Most docking algorithms simplify protein flexibility and solvent effects, leading to false positives or inaccurate binding affinity predictions (54). The absence of universally validated scoring functions and the dependence on static crystal structures hinder realistic simulation of dynamic biological environments (55). Furthermore, discrepancies among different docking software and scoring algorithms result in variable outcomes for the same ligand–target pair (56). Rigorous post-docking validation—through molecular dynamics simulations, free energy calculations, or experimental verification—is essential to improve reliability and reduce prediction errors (57). The integration of AI-based refinement models holds promise, but these approaches still require extensive benchmarking and transparency in training datasets.

6.3. Translational barriers from *in silico to In-vivo / In-vitro*: A major challenge in integrating green synthesis with molecular docking lies in translating computational predictions into experimentally validated outcomes. Docking results may not always correlate with in vitro or in vivo pharmacological activity due to factors such as poor bioavailability, metabolic instability, or off-target effects (58). The biological behavior of green-synthesized nanoparticles, including their absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles, remains underexplored and varies with synthesis conditions. Moreover, differences in biological models, experimental protocols, and assay sensitivity can lead to inconsistent validation results (59). Bridging this gap requires interdisciplinary collaboration, combining computational modeling with robust biological testing and pharmacokinetic evaluation to ensure translational fidelity from virtual screening to real-world efficacy (60).

7. Future Perspectives

The future of sustainable drug discovery lies in integrating molecular docking, green synthesis, and artificial intelligence (AI). Machine learning algorithms enhance docking accuracy, predict binding affinities, and design novel bioactive scaffolds consistent with green chemistry principles (61) Coupling docking with omics technologies such as genomics and metabolomics enables comprehensive insights into target identification, drug–target interactions, improving safety and efficacy (62). Sustainable scale-up of green synthesis through biocatalysis, continuous-flow methods, and digital simulation ensures environmentally

friendly and reproducible production (63). Evolving regulatory frameworks incorporating green chemistry metrics and standardized computational methods will further promote transparent and eco-compliant drug development (64). Together, these advancements mark a shift toward efficient, sustainable, precision-driven pharmaceutical innovation.

8. Conclusion

The convergence of green synthesis and molecular docking represents a transformative approach in modern drug discovery, combining environmental sustainability with computational precision. Green synthesis enables the eco-friendly production of bioactive compounds and nanoparticles using renewable resources and minimal hazardous reagents, while molecular docking provides a computational framework for predicting ligand–target interactions and optimizing lead molecules. Integrating these methodologies bridges sustainable chemistry with rational drug design, promoting the development of therapeutics that are both potent and environmentally benign. This integration aligns with green chemistry principles by reducing waste, enhancing biocompatibility, and improving economic scalability. Looking ahead, advances in AI-driven docking, machine learning-assisted phytochemical screening, and automated green synthesis platforms will further enhance the precision and sustainability of drug development. Establishing standardized protocols, comprehensive phytochemical databases, and robust validation models will be crucial to ensure reproducibility and translational impact, paving the way for a new era of sustainable, cost-effective, and ethically responsible pharmaceutical innovation.

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

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