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A Review on Approaches of Drug Design

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ABSTRACT:

Drug configuration is a significant stage in the disclosure and improvement of new helpful specialists. Effective drugs have been developed in a variety of ways, each with advantages and disadvantages. Traditional, computational, fragment-based, and hybrid approaches to drug design are all covered in detail in this review. We talk about the standards, applications, and difficulties related with each methodology, featuring their effect on the medication revelation process. Structure-based drug design, ligand-based drug design, high-throughput screening, molecular dynamics simulations, quantum mechanics, machine learning, fragment-based drug design, and hybrid strategies are among the topics we focus on. We also look into personalized medicine, artificial intelligence, deep learning, nanotechnology, and new horizons in drug design. This survey expects to give an important asset to specialists, drug industry experts, and understudies keen on drug plan and revelation. We hope to inspire creative solutions to the complex problems drug design faces by highlighting the field's current state and future directions. (1)

KEYWORD: Drug design, structure-based design, ligand-based design, fragment-based design, computational approaches, hybrid approaches, artificial intelligence, personalized medicine.

1. INTRODUCTION:

Drug configuration is a multidisciplinary field that assumes a vital part in the disclosure and improvement of new restorative specialists. The creation of safe, effective, and selective drugs that target specific biological mechanisms with the intention of enhancing patient outcomes and quality of life is the primary objective of drug design. Drug design has been approached in a variety of ways over time, each with advantages and disadvantages. The medication configuration process includes a profound comprehension of the intricate communications between little particles and natural frameworks. Researchers are now able to explore new chemical space, predict biological activity, and optimize pharmacokinetics and pharmacodynamics thanks to advances in computational power, structural biology, and artificial intelligence. This survey plans to give a thorough outline of the methodologies utilized in drug configuration, featuring their standards, applications, and difficulties. Computational methods, fragment-based strategies, and hybrid strategies will all be discussed in addition to conventional strategies like structure-based and ligand-based design. We will also investigate upcoming technologies and trends like deep learning, personalized medicine, and artificial intelligence. (10,11)

Fig No: 1 Drug Design Devolopment

2. APPROACHES OF DRUG DESIGN:

The approaches to drug design that can be included in the review:

A. Traditional Approaches

1. Structure-Based Drug Design (SBDD)
2. Ligand-Based Drug Design (LBDD)
3. High-Throughput Screening (HTS)
4. Lead-Based Drug Design

B. Computational Approaches

1. Molecular Dynamics Simulations (MDS)
2. Quantum Mechanics (QM)
3. Molecular Docking
4. Machine Learning (ML)
5. Deep Learning (DL)

C. Fragment-Based Approaches

1. Fragment-Based Drug Design (FBDD)
2. Fragment-Based Lead Discovery (FBLD)
3. Fragment-Based Optimization

D. Hybrid Approaches

1. Structure-Based Ligand Design (SBLD)
2. Multi-Disciplinary Optimization (MDO)
3. Integrative Computational and Experimental Approach.

E. Rational Drug Design Approach

1. Target-Based Drug Design
2. Ligand-Based Drug Design
3. Structure-Based Drug Design.

F. New Frontiers

1 Artificial Intelligence (AI) in Drug Design

2 Deep Learning (DL) for Predictive Models

3 Nanotechnology-Based Drug Delivery

4 Personalized Medicine and Precision Drug Design

5 Fragment-Based Drug Design with AI.

G. Other Approaches

1 Pharmacophore-Based Drug Design

2 QSAR-Based Drug Design

3 Molecular Similarity-Based Drug Design

4 Bio-isostere-Based Drug Design.

2.1) STRUCTURE -BASED DRUG DESIGN: (SBDD)

Definition: SBDD is a drug design approach that utilizes the three-dimensional structure of a target protein to design and optimize small molecule ligands.

Principle: SBDD involves understanding the molecular interactions between the target protein and potential ligands, guiding the design of compounds that bind specifically and effectively.

Steps:

1. Protein structure determination (X-ray crystallography, NMR)
2. Target identification and validation
3. Ligand design and optimization
4. Molecular docking and simulation
5. Lead compound identification and refinement

Techniques:

1. Molecular dynamics simulations
2. Docking algorithms (e.g., Auto Dock, GOLD)
3. Scoring functions (e.g., MM-PBSA, MM-GBSA)
4. Virtual screening
5. Fragment-based design

Advantages:

1. Rational design approach
2. Improved binding affinity and specificity
3. Reduced toxicity and side effects
4. Enhanced lead optimization

Success Stories:

1. HIV protease inhibitors
2. Kinase inhibitors (e.g., Gleevec)
3. Anti-inflammatory drugs (e.g., COX-2 inhibitors)

Software Tools:

1. Auto Dock
2. GOLD
3. MOE
4. Discovery Studio
5. Schrödinger. (2)

2.2) LIGAND-BASED DRUG DESIGN (LBDD)

Definition: LBDD is a drug design approach that focuses on small molecule ligands, utilizing their chemical and structural properties to design new compounds.

Principle: LBDD involves analyzing known ligands and their interactions with target proteins, guiding the design of novel compounds with optimized binding affinity and specificity.

Steps:

1. Ligand selection and analysis
2. Pharmacophore modeling
3. Quantitative Structure-Activity Relationship (QSAR) analysis
4. Molecular similarity analysis

5. Lead compound identification and refinement

Techniques:

1. Pharmacophore modeling (e.g., PHASE, MOE)

2. QSAR analysis (e.g., CoMFA, CoMSIA)

3. Molecular similarity analysis (e.g., fingerprint-based methods)

4. Virtual screening

5. Library design and screening

Advantages:

1. Rapid identification of lead compounds

2. Improved binding affinity and specificity

3. Reduced toxicity and side effects

4. Enhanced lead optimization

Success Stories:

1. HIV reverse transcriptase inhibitors

2. Protease inhibitors (e.g., ritonavir)

3. Anti-inflammatory drugs (e.g., celecoxib)

Software Tools:

1. PHASE

2. MOE

3. Discovery Studio

4. Schrödinger

5. PyMOL (3)

2.3) FRAGMENT-BASED DRUG DESIGN (FBDD)

Definition: FBDD is a drug design approach that involves breaking down small molecules into smaller fragments, screening these fragments for binding affinity, and combining them to form lead compounds.

Principle: FBDD exploits the concept of molecular recognition, where small fragments bind specifically to target proteins, guiding the design of optimized lead compounds.

Steps:

1. Fragment library design and synthesis

2. Fragment screening (e.g., NMR, SPR)

3. Hit identification and validation

4. Fragment linking and merging

5. Lead compound optimization

Techniques:

1. Fragment-based screening (FBS)

2. Nuclear Magnetic Resonance (NMR) spectroscopy

3. Surface Plasmon Resonance (SPR)

4. X-ray crystallography

5. Computational fragment-based design

Advantages:

1. Efficient exploration of chemical space
2. Improved binding affinity and specificity
3. Reduced molecular weight and complexity
4. Enhanced lead optimization

Success Stories:

1. Protease inhibitors (e.g., Boceprevir)
2. Kinase inhibitors (e.g., Lapatinib)
3. Anti-inflammatory drugs (e.g., Tofacitinib)

Software Tools:

1. FBDD Suite
2. Fragment-Based Design Tool (FBDT)
3. MOE
4. Discovery Studio
5. Schrödinger. (4)

2.4) HIGH-THROUGHPUT SCREENING (HTS)

Definition: HTS is a drug discovery approach that utilizes automated testing of large libraries of compounds to identify potential lead compounds.

Principle: HTS involves rapid and efficient screening of compounds against a specific biological target, enabling identification of hits and subsequent optimization.

Steps:

1. Compound library preparation
2. Assay development and optimization
3. Screening (e.g., enzymatic, cellular, or biochemical assays)
4. Hit identification and validation
5. Lead compound optimization.

Techniques:

1. Automated liquid handling
2. Microplate assays (e.g., 96-well, 384-well)
3. High-content screening (HCS)
4. Flow cytometry
5. Label-free detection (e.g., surface plasmon resonance)

Advantages:

1. Rapid identification of potential leads
2. Efficient screening of large compound libraries
3. Reduced costs and increased productivity
4. Improved accuracy and reproducibility

Success Stories:

1. HIV protease inhibitors

2. Cancer therapeutics (e.g., kinase inhibitors)

3. Anti-inflammatory drugs (e.g., COX-2 inhibitors)

Software Tools:

1. Accelrys HTS software

2. Biovia HTS software

3. Genedata HTS software

4. IDBS HTS software

5. Tecan HTS software.

2.5) COMPUTER-AIDED DRUG DESIGN (CADD)

Definition: CADD is a computational approach to drug design that utilizes computer simulations, algorithms, and models to predict and optimize the behavior of molecules.

Principle: CADD integrates computational methods with experimental data to design and optimize lead compounds.

Applications:

1. Structure-based design

2. Ligand-based design

3. Fragment-based design

4. High-throughput virtual screening

5. Molecular dynamics simulations

Techniques:

1. Molecular modeling

2. Molecular docking

3. Scoring functions

4. Pharmacophore modeling

5. QSAR analysis

Advantages:

1. Rapid identification of potential leads

2. Improved binding affinity and specificity

3. Reduced toxicity and side effects

4. Enhanced lead optimization

Success Stories:

1. HIV protease inhibitors

2. Cancer therapeutics (e.g., kinase inhibitors)

3. Anti-inflammatory drugs (e.g., COX-2 inhibitors)

Software Tools:

1. Schrödinger

2. MOE

3. Discovery Studio

4. Auto Dock

5. GROMACS.

2.6) RATIONAL DRUG DESIGN (RDD)

Definition: RDD is a drug design approach that utilizes a systematic and logical process to design and optimize lead compounds.

Principle: RDD integrates computational and experimental methods to understand the molecular interactions between the target protein and potential ligands.

Applications:

1. Structure-based design

2. Ligand-based design

3. Fragment-based design

4. High-throughput virtual screening

Techniques:

1. Molecular modeling

2. Molecular docking

3. Scoring functions

4. Pharmacophore modeling

5. QSAR analysis

Advantages:

1. Improved binding affinity and specificity

2. Reduced toxicity and side effects

3. Enhanced lead optimization

4. Increased efficiency

Success Stories:

1. HIV protease inhibitors

2. Cancer therapeutics (e.g., kinase inhibitors)

3. Anti-inflammatory drugs (e.g., COX-2 inhibitors)

Software Tools:

1. Schrödinger

2. MOE

3. Discovery Studio

4. Auto Dock

5. GROMACS.

2.7) HYBRID APPROACH

Definition: A hybrid approach combines multiple drug design methods to leverage their strengths and overcome individual limitations.

Applications:

1. Structure-based and ligand-based design

2. Fragment-based and high-throughput screening

3. Computational and experimental methods

4. Machine learning and molecular modeling

Techniques:

1. Integrative computational and experimental approach
2. Multi-disciplinary optimization
3. Consensus scoring
4. Hybrid docking and scoring

Advantages:

1. Improved accuracy and reliability
2. Enhanced lead discovery and optimization
3. Increased efficiency and productivity
4. Better understanding of molecular interactions

Success Stories:

1. HIV protease inhibitors
2. Cancer therapeutics (e.g., kinase inhibitors)
3. Anti-inflammatory drugs (e.g., COX-2 inhibitors)

Software Tools:

1. Schrödinger
2. MOE
3. Discovery Studio
4. Auto Dock
5. GROMACS.

3. RECENT ADVANCES:

Recent advances in drug design approaches have transformed the way medications are discovered and developed.

Computer-Aided Drug Design

One significant advancement is the use of computer-aided drug design, which employs computational models and simulations to predict the efficacy and safety of potential drugs [1]. This approach enables researchers to screen large libraries of compounds and identify promising candidates more efficiently**.**

Structure-Based Drug Design

Structure-based drug design is another critical approach, where the three-dimensional structure of a biological target is used to design drugs that bind specifically to it [1]. This method has led to the development of highly effective medications, such as HIV protease inhibitors and cancer therapeutics.

Ligand-Based Drug Design

Ligand-based drug design involves designing drugs based on the knowledge of other molecules that bind to the same biological target [1]. This approach uses pharmacophore modeling and quantitative structure-activity relationships (QSAR) to predict the activity of new compounds**.**

Hybrid Approach

A hybrid approach combining multiple drug design methods has also gained popularity This integrated approach leverages the strengths of individual methods to overcome their limitations and improve the accuracy of predictions.

Machine Learning and Artificial Intelligence

The application of machine learning and artificial intelligence in drug design has opened up new avenues for discovery [1]. These technologies enable the analysis of large datasets, identification of patterns, and prediction of drug efficacy and safety.

mRNA-Based Therapies

mRNA-based therapies have emerged as a promising area in drug design [1]. These therapies involve using messenger RNA to convey genetic information into cells, enabling the production of specific proteins to treat diseases.

These advances in drug design have significantly improved the efficiency and effectiveness of the drug discovery process, leading to the development of innovative treatments for various diseases. (15 ,16,17)

3.1) ARTIFICIAL INTELLIGENCE (AI) IN DRUG DESIGN

AI has transformed the drug design process by enabling rapid analysis of vast amounts of data, identifying patterns, and predicting optimal compounds.

Applications:

1. Predictive modeling
2. Molecular simulation
3. Virtual screening
4. Lead optimization
5. Target identification

Techniques:

1. Machine learning (ML)
2. Deep learning (DL)
3. Natural language processing (NLP)
4. Generative models
5. Reinforcement learning

Advantages:

1. Improved accuracy and efficiency
2. Enhanced lead discovery and optimization
3. Reduced costs and time
4. Personalized medicine

Success Stories:

1. Atomwise's AI-designed compounds for Ebola
2. DeepMind's AlphaFold for protein structure prediction
3. Insilico Medicine's AI-generated compounds for cancer

Software Tools:

1. DeepChem
2. RDKit
3. OpenEye
4. Schrödinger
5. IBM Watson. (6)

3.2) DEEP LEARNING IN DRUG DESIGN

DL has revolutionized drug discovery by enabling rapid analysis of vast amounts of data, identifying patterns, and predicting optimal compounds.

Applications:

1. Structure-based drug design
2. Ligand-based drug design
3. De novo design

4. Lead optimization

5. Toxicity prediction

6. Pharmacokinetics prediction

DL Architectures:

1. Convolutional Neural Networks (CNN)

2. Recurrent Neural Networks (RNN)

3. Generative Adversarial Networks (GAN)

4. Autoencoders

5. Transformers

Advantages:

1. Improved accuracy and efficiency

2. Enhanced lead discovery and optimization

3. Reduced costs and time

4. Personalized medicine

Success Stories:

1. Atomwise's AI-designed compounds for Ebola

2. DeepMind's AlphaFold for protein structure prediction

3. Insilico Medicine's AI-generated compounds for cancer.

Software Tools:

1. DeepChem

2. RDKit

3. OpenEye

4. Schrödinger

5. IBM Watson. (7)

3.3) VIRTUAL SCREENING IN DRUG DESIGN

VS is a computational method for identifying potential lead compounds by screening large libraries of molecules against a specific biological target.

Applications:

1. Lead discovery

2. Lead optimization

3. Target identification

4. Toxicity prediction

5. Pharmacokinetics prediction

VS Techniques:

1. Molecular docking

2. Molecular dynamics simulations

3. Quantum mechanics calculations

4. Pharmacophore modeling

5. Machine learning-based screening

Advantages:

1. Reduced costs and time
2. Increased efficiency
3. Improved accuracy
4. Enhanced lead discovery and optimization

Success Stories:

1. Identification of novel inhibitors for HIV protease
2. Discovery of anti-cancer compounds
3. Development of anti-inflammatory agents

Software Tools:

1. AutoDock
2. Glide
3. GOLD
4. MOE
5. Schrödinger.

3.4) MOLECULAR DYNAMICS IN DRUG DESIGN

MD simulations investigate the dynamic behavior of molecules, providing insights into protein-ligand interactions, protein flexibility, and ligand binding.

Applications:

1. Protein-ligand binding affinity prediction
2. Protein flexibility and conformational analysis
3. Ligand binding site identification
4. Drug resistance mechanism investigation
5. Protein-protein interaction studies

MD Techniques

1. Classical MD
2. Quantum MD
3. Hybrid QM/MM MD
4. Coarse-grained MD
5. Enhanced sampling methods (e.g., umbrella sampling)

Advantages:

1. Detailed understanding of protein-ligand interactions
2. Improved prediction of binding affinities
3. Identification of cryptic binding sites
4. Investigation of protein flexibility and dynamics

Success Stories:

1. Identification of novel binding sites for G-protein coupled receptors
2. Investigation of HIV protease inhibitor resistance
3. Design of potent inhibitors for kinase targets

Software Tools:

1. GROMACS
2. AMBER
3. CHARMM
4. NAMD
5. Desmond.

4. CHALLENGES

4.1) TARGET VALIDATION CHALLENGES IN DRUG DESIGN

Target validation is a critical step in drug discovery, ensuring that the selected target is relevant to the disease and modulating it will produce the desired therapeutic effect.

Challenges:

1. Limited understanding of disease biology
2. Complexity of protein-protein interactions
3. Off-target effects
4. Validation of novel targets
5. Translation from preclinical to clinical settings

Target Validation Strategies:

1. Genetic validation (e.g., knockout/knockdown studies)
2. Pharmacological validation (e.g., tool compounds)
3. Biochemical validation (e.g., enzyme assays)
4. Cellular validation (e.g., cell-based assays)
5. In vivo validation (e.g., animal models)

Approaches to Overcome Challenges:

1. Integrative genomics and proteomics
2. CRISPR/Cas9 gene editing
3. RNA interference (RNAi)
4. High-throughput screening (HTS)
5. Computational modeling and simulation

Technologies for Target Validation:

1. Next-generation sequencing (NGS)
2. Mass spectrometry (MS)
3. Protein crystallography
4. Biacore (surface plasmon resonance)
5. Flow cytometry

Case Studies:

1. Target validation for Alzheimer's disease
2. Validation of cancer targets (e.g., BRAF, EGFR)
3. Target validation for infectious diseases (e.g., HIV, TB)

4.2) LEAD OPTIMIZATION CHALLENGES IN DRUG DESIGN

Lead optimization is a critical stage in drug discovery, refining hits from high-throughput screening to identify potent, selective, and safe lead compounds.

Challenges:

1. Balancing potency, selectivity, and pharmacokinetics
2. Managing molecular weight, lipophilicity, and solubility
3. Optimizing metabolic stability and bioavailability
4. Minimizing off-target effects and toxicity
5. Addressing pharmacokinetic-pharmacodynamic relationships

Lead Optimization Strategies:

1. Structure-based design
2. Fragment-based design
3. Ligand-based design
4. High-throughput screening (HTS)
5. Computational modeling and simulation

Approaches to Overcome Challenges:

1. Integrating in vitro and in vivo data
2. Using predictive models (e.g., QSAR, PBPK)
3. Employing design of experiments (DoE)
4. Leveraging machine learning and artificial intelligence
5. Collaborative multidisciplinary teams

Technologies for Lead Optimization:

1. X-ray crystallography
2. Nuclear magnetic resonance (NMR)
3. Mass spectrometry (MS)
4. High-performance liquid chromatography (HPLC)
5. Bioanalytical assays

Case Studies:

1. Optimization of HIV protease inhibitors
2. Development of anti-cancer agents (e.g., kinase inhibitors)
3. Optimization of anti-inflammatory compounds.

4.3) TOXICITY PREDICTION CHALLENGES IN DRUG DESIGN

Toxicity prediction is crucial in drug discovery to identify potential safety issues early on.

Challenges:

1. Complexity of biological systems
2. Limited understanding of toxicity mechanisms
3. Data quality and availability
4. Prediction model accuracy
5. Integrating multiple toxicity endpoints

Toxicity Prediction Strategies:

1. In silico models (e.g., QSAR, machine learning)
2. In vitro assays (e.g., cellular, biochemical)
3. In vivo studies (e.g., animal models)
4. Hybrid approaches (combining multiple methods)

Approaches to Overcome Challenges:

1. Integrating multiple data sources
2. Developing more accurate prediction models
3. Using 3D cellular models
4. Incorporating pharmacokinetic and pharmacodynamic data
5. Collaborative efforts (industry, academia, regulatory agencies)

Technologies for Toxicity Prediction:

1. High-throughput screening (HTS)
2. High-content screening (HCS)
3. Omics technologies (genomics, proteomics, metabolomics)
4. Computational modeling and simulation
5. Artificial intelligence and machine learning

Case Studies:

1. Prediction of liver toxicity for NSAIDs
2. Identification of cardiotoxic compounds
3. Development of safer kinase inhibitors.

4.4) RESISTANCE DEVELOPMENT CHALLENGES IN DRUG DESIGN

Resistance development is a major obstacle in drug discovery, limiting treatment efficacy.

Challenges:

1. Genetic mutations in target proteins
2. Increased efflux pump expression
3. Modified metabolic pathways
4. Horizontal gene transfer
5. Epigenetic modifications

Resistance Development Mechanisms:

1. Spontaneous mutations
2. Selection pressure
3. Gene amplification
4. Epigenetic regulation
5. Horizontal gene transfer

Approaches to Overcome Challenges:

1. Targeting multiple pathways
2. Designing resistance-proof compounds

3. Combination therapies

4. Optimizing dosing regimens

5. Monitoring resistance development

Technologies for Resistance Prediction:

1. Computational modeling

2. Machine learning

3. High-throughput screening

4. Next-generation sequencing

5. CRISPR/Cas9 gene editing

Case Studies:

1. Antibiotic resistance in bacteria

2. HIV resistance to antiretroviral therapy

3. Cancer resistance to chemotherapy. (18, 19, 20)

5. FUTURE DIRECTION OF PERSONALIZED MEDICINE IN DRUG DESIGN

5.1) Personalized Medicine

Personalized medicine aims to tailor treatments to individual patients based on genetic, environmental, and lifestyle factors.

Future Directions:

1. Precision medicine initiatives

2. Genomic medicine advancements

3. Artificial intelligence (AI) integration

4. Machine learning (ML) applications

5. Point-of-care diagnostics development

Opportunities:

1. Improved treatment outcomes

2. Reduced adverse reactions

3. Enhanced patient satisfaction

4. Increased efficiency

5. New business models.

5.2) FUTURE DIRECTION OF PRECISION MEDICINE IN DRUG DESIGN

Precision medicine aims to tailor treatments to individual patients based on genetic, environmental, and lifestyle factors.

Future Directions:

1. Integrative genomics and epigenomics

2. Artificial intelligence (AI) and machine learning (ML) applications

3. Single-cell analysis and spatialomics

4. Liquid biopsies and circulating biomarkers

5. Gene editing (CRISPR/Cas9) and gene therapy

Opportunities:

1. Improved treatment outcomes and patient survival
2. Reduced adverse reactions and toxicity
3. Enhanced patient satisfaction and quality of life
4. Increased efficiency and reduced healthcare costs
5. New business models and partnerships. (9)

5.3) MULTI-TARGET THERAPIES AIM TO SIMULTANEOUSLY MODULATE MULTIPLE BIOLOGICAL TARGETS, IMPROVING ***TREATMENT EFFICACY.***

Future Directions:

1. Poly-pharmacology and network pharmacology
2. Combination therapies and synergy
3. Precision medicine and personalized therapies
4. Epigenetic and gene regulation modulation
5. Immunotherapy and cancer vaccines

Opportunities:

1. Improved treatment outcomes and patient survival
2. Reduced resistance and relapse
3. Enhanced patient satisfaction and quality of life
4. Increased efficiency and reduced healthcare costs
5. New business models and partnerships. (5)

5.4) NATURAL PRODUCTS HAVE BEEN A RICH SOURCE OF INSPIRATION FOR DRUG DISCOVERY.

Future Directions:

1. Integrated approaches combining natural product chemistry and synthetic biology
2. Exploration of uncharted chemical space through natural product-inspired libraries
3. Structure-based design and fragment-based approaches
4. Computational modeling and machine learning applications
5. Biotechnology-enabled natural product production

Opportunities:

1. Novel mechanism of action discovery
2. Improved treatment outcomes and patient survival
3. Enhanced patient satisfaction and quality of life
4. Increased efficiency and reduced healthcare costs
5. New business models and partnerships. (8)

6. CONCLUSION:

Drug design has evolved significantly over the years, integrating advances in computational power, structural biology, and chemical biology. Various approaches, including structure-based design, ligand-based design, fragment-based design, and multitarget therapies, have been developed to improve efficacy, selectivity, and safety.

The integration of artificial intelligence, machine learning, and deep learning has revolutionized drug design, enabling rapid identification of potential leads and optimization of compounds.

Natural product-inspired design and precision medicine approaches have also shown promise in addressing unmet medical needs.

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