AI-Driven Reverse Pharmacology & Accelerated Drug Repurposing Using Ancient Indian Manuscripts – A Comprehensive Review

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Abstract

This paper presents a comprehensive literature review on AI-driven drug repurposing, contrasting traditional pharmacological methods with advanced AI-based approaches to elucidate their respective strengths and limitations. It systematically explores key computational techniques—such as network pharmacology, molecular docking, and deep learning—and their role in identifying drug-target interactions and predicting novel therapeutic indications. Special emphasis is placed on the digitalization and AI validation of traditional medical knowledge, particularly reverse pharmacology's "bedside-to-bench" paradigm, which transforms historical clinical narratives into testable hypotheses. Through analysis of prominent case studies, the paper highlights both the transformative potential of AI integration in accelerating drug repurposing and the persistent challenges related to data heterogeneity and regulatory complexities. The vision of this review is to establish a holistic framework that synergizes computational innovations with ancestral wisdom, positioning AI-driven reverse pharmacology as a paradigm shift with the capacity to revolutionize drug discovery and therapeutic innovation. The mission is to provide critical insights and guide future research toward overcoming existing barriers, thereby enhancing the effectiveness and scope of medication repurposing strategies.

Keywords: Drug Repurposing, Reverse Pharmacology, Artificial Intelligence (AI), Ayurveda, Ancient Indian Manuscripts

1. Introduction to AI-Driven Reverse Pharmacology

1. 1 Definition and Scope of Reverse Pharmacology

Reverse pharmacology constitutes a transdisciplinary scientific approach that integrates documented clinical and experiential data from traditional knowledge systems into actionable leads for drug development.[1] Unlike conventional forward pharmacology, which encounters high failure rates and escalating costs despite advances in genomics and high-throughput screening, reverse pharmacology initiates with documented clinical observations and experiential data derived from traditional knowledge systems.[1] This methodology holds particular significance in relation to ancient Indian manuscripts, which encompass a vast repository of traditional medical knowledge yet to be fully explored and incorporated into contemporary pharmacological practices.

1.2 Importance of Drug Repurposing

Drug repurposing, also referred to as drug repositioning or reprofiling, represents an innovative strategy that leverages existing pharmaceuticals for new therapeutic indications, thereby offering the potential to reduce development costs and accelerate timelines.[3] The significance of drug repurposing is profound, as it expedites the availability of treatments while mitigating the financial burdens and protracted processes associated with de novo drug development. The application of AI technologies enhances the efficiency of drug

repurposing initiatives by employing machine learning algorithms to analyze extensive datasets and identify prospective therapeutic candidates from historical texts.

1.3 Role of AI in Pharmacology

The convergence of artificial intelligence (AI) and pharmacology presents a transformative opportunity within drug discovery, particularly through the framework of reverse pharmacology. Structured datasets derived from ancient manuscripts and traditional medicinal texts serve as foundational inputs by extracting recorded indications, formulations, preparation methods, and ethnobotanical contexts to generate candidate leads and repurposing hypotheses. Ethnomedical knowledge provides clinically observed signals that inform subsequent computational screening and validation processes.[2] Traditional Indian medical systems, such as Ayurveda and Siddha, offer a rich repository of herbal remedies and healing practices whose relevance to modern pharmacology lies in their potential to inform and guide contemporary drug development. Nevertheless, integrating AI into reverse pharmacology introduces challenges related to data quality, ethical considerations, and bridging the divide between traditional knowledge and scientific validation.

1.4. AI in Drug Repurposing and Reverse Pharmacology

Within the domains of drug repurposing and reverse pharmacology, artificial intelligence and computational methodologies are employed to predict bio-interactions between compounds and potential target proteins, substantially reducing the time and cost associated with traditional drug development. These methodologies are particularly efficacious for ancient Indian medicine (Ayurveda), as they can elucidate the complexities of traditional formulations by identifying bioactive compounds and correlating them with specific biochemical pathways.

1.4.1 AI Tools in Drug Repurposing and Reverse Pharmacology

AI tools applied within these fields encompass a spectrum from classical machine learning to advanced deep learning architectures and network-based models:

- **Machine Learning (ML) Models:** Conventional algorithms such as Random Forest (RF), Support Vector Machines (SVM), and Naive Bayes (NB) are utilized for predictive modeling, ranking molecular descriptors, and identifying putative drug-disease interactions.[16]
- **Deep Learning (DL) Architectures:** Deep Neural Networks (DNNs) and Deep Belief Networks (DBNs) analyze high-dimensional data to uncover latent structures and establish relationships across multiple targets simultaneously. Convolutional Neural Networks (CNNs) facilitate structure-based screening by capturing specific features from three-dimensional voxel representations of ligands and receptors.[16] Recurrent Neural Networks (RNNs) process sequential data, such as SMILES strings (chemical notations), to predict physicochemical properties or generate novel molecular structures.[16]
- **Network Pharmacology Tools:** Software such as Cytoscape, Pajek, and GUESS enable visualization and analysis of protein–compound/disease–gene networks to elucidate synergistic effects inherent in multi-component herbal therapies.[14]
- **Generative Models:** Variational Autoencoders (VAEs) and Generative Adversarial Networks (GANs) are employed to design new ligands that preserve the scaffolds of extant drugs or natural products while optimizing desired pharmacological properties.[18]
- **Virtual Screening (VS):** Both structure-based and ligand-based VS methodologies utilize computational algorithms to screen extensive libraries of approved drugs and natural products against specific disease targets.[19]

1.5 AI in the Repurposing of Ancient Indian Medicine

AI facilitates the repurposing of Ayurvedic medicine by bridging the gap between traditional holistic wisdom and modern scientific validation through several mechanisms:

- Elucidation of Complex Formulations: AI tools critically assist in identifying bioactive compounds within Ayurvedic plants and associating them with therapeutic effects, thereby supporting the development of novel products and optimization of dosage regimens.[2]

- Herb Identification and Quality Control: Deep learning models trained on botanical images (leaves, roots, stems) enable real-time differentiation of closely related herbs, reducing human error and mitigating adulteration risks in manufacturing processes.[2]
- Analysis of Ancient Texts: Analytical algorithms process extensive textual corpora from Ayurvedic literature and research articles to extract valuable information regarding traditional uses and pharmacological characteristics of various herbs.[14]
- Integration with Reverse Pharmacology (RP): RP inverts the conventional "laboratory-to-clinic" paradigm into a "clinic-to-laboratories" trajectory, commencing with documented human clinical experiences from Ayurveda.[14] AI expedites this process by predicting molecular mechanisms of action for traditional formulations through reverse engineering based on network data.[2,14]
- Multi-Target Therapeutic Strategies: Given that many complex diseases arise from dysregulation of entire biological networks, AI and network pharmacology facilitate the investigation of multi-target therapeutics, thereby reflecting the holistic, multi-ingredient approach characteristic of Ayurvedic treatment modalities.[14]

Table 1 : Selected successful drug repurposing examples and the repurposing approach employed

Drug name	Original indication	New indication	Date of approval	Repurposing approach used	Comments on outcome of repurposing
Zidovudine	Cancer	HIV/AIDS	1987	In vitro screening of compound libraries	Zidovudine was the first anti-HIV drug to be approved by the FDA
Minoxidil	Hypertension	Hair loss	1988	Retrospective clinical analysis (identification of hair growth as an adverse effect)	Global sales for minoxidil were US$860 million in 2016
Sildenafil	Angina	Erectile dysfunction	1998	Retrospective clinical analysis	Marketed as Viagra, sildenafil became the leading product in the erectile dysfunction drug market, with global sales in 2012 of $2.05 billion
Thalidomide	Morning sickness	Erythema nodosum leprosum and multiple myeloma	1998 and 2006	Off-label usage and pharmacological analysis	Thalidomide derivatives have achieved substantial clinical and commercial success in multiple myeloma
Celecoxib	Pain and inflammation	Familial adenomatous polyps	2000	Pharmacological analysis	The total revenue from Celebrex (Pfizer) at the end of 2014 was $2.69 billion
Atomoxetine	Parkinson disease	ADHD	2002	Pharmacological analysis	Strattera (Eli Lilly) recorded global sales of $855 million in 2016

Duloxetine	Depression	SUI	2004	Pharmacological analysis	Approved by the EMA for SUI. The application was withdrawn in the US. Duloxetine is approved for the treatment of depression and chronic pain in the US
Rituximab	Various cancers	Rheumatoid arthritis	2006	Retrospective clinical analysis (remission of coexisting rheumatoid arthritis in patients with non-Hodgkin lymphoma treated with rituximab)	Global sales of rituximab topped $7 billion in 2015
Raloxifene	Osteoporosis	Breast cancer	2007	Retrospective clinical analysis	Approved by the FDA for invasive breast cancer. Worldwide sales of $237 million in 2015
Fingolimod	Transplant rejection	MS	2010	Pharmacological and structural analysis	First oral disease-modifying therapy to be approved for MS. Global sales for fingolimod (Gilenya) reached $3.1 billion in 2017
Dapoxetine	Analgesia and depression	Premature ejaculation	2012	Pharmacological analysis	Approved in the UK and a number of European countries; still awaiting approval in the US. Peak sales are projected to reach $750 million
Topiramate	Epilepsy	Obesity	2012	Pharmacological analysis	Qsymia (Vivus) contains topiramate in combination with phentermine
Ketoconazole	Fungal infections	Cushing syndrome	2014	Pharmacological analysis	Approved by the EMA for Cushing syndrome in adults and adolescents above the age of 12 years
Aspirin	Analgesia	Colorectal cancer	2015	Retrospective clinical and pharmacological analysis	US Preventive Services Task Force released draft recommendations in September 2015 regarding the use of

					aspirin to help prevent cardiovascular disease and colorectal cancer

2. Drug Repurposing

Drug repurposing, also known as drug repositioning, reprofiling, or re-tasking, refers to the process of identifying novel therapeutic applications for medications that are already approved, discontinued, or shelved. Instead of developing new chemical entities from the ground up, researchers seek existing compounds that can treat conditions other than those for which they were originally developed. Repurposing can identify new compounds based on observed phenotypic benefits without explicitly defining the mechanism of action. These findings can be directly tested in preclinical animal models and may progress rapidly to phase 2 clinical trials.

2.1 Types of Drug Repurposing

2.1.1 Based on Pharmacological Mechanism

- **On-target repurposing:** This occurs when a drug's known pharmacological mechanism is applied to a new disease indication while acting on its original specific target. Typically, this involves administering an approved drug at comparable or lower doses to modulate the same biological pathway in a different patient population.[5,6]
- **Off-target repurposing:** This involves identifying new therapeutic indications based on the drug's interactions with novel targets distinct from the original ones. It requires examining chemical structures to detect effects mediated via previously unrecognized pharmacological mechanisms. This approach may necessitate comprehensive clinical development similar to that for new chemical entities, especially if different dosages or tissue compartments are involved.[5,6]

2.1.2 Based on Methodological Approach

- **Experimental (activity-based) approaches:** These methods involve physical screening of compounds using assays, including target- and cell-based screening. While they reduce false positives and facilitate hit confirmation, they are labor-intensive and require access to physical drug libraries.[4,7]
- **Computational (in-silico) approaches:** Data-driven strategies utilizing diverse data types (e.g., gene expression, chemical structure, genotypes) to generate repurposing hypotheses. These approaches save time and resources by eliminating the need for physical compounds but may yield higher false-positive rates during screening.[6,7]

2.1.3 Based on Strategic Focus

Drug-oriented (drug-centric): Focuses on discovering new applications for existing drugs, often leveraging chemical structure, side effect profiles, and phenotypic screening data.

- **Target-oriented (target-centered):** Concentrates on specific proteins or biomarkers, linking them to potential drugs or diseases, frequently employing high-throughput screening or molecular docking.
- **Disease-oriented (disease-centered):** Seeks effective therapeutics for particular diseases using phenotypic information or omics data (genomics, proteomics) to identify relevant drugs.[4,6]

2.1.4 Based on Discovery Mode

- **Accidental:** New indications are discovered serendipitously, often through observation of unexpected side effects during treatment of other conditions.[4,6]
- **Systematic:** Involves methodical, high-throughput searches for new uses of existing drugs, typically utilizing advanced data analytics and extensive databases.[5]

2.2 Approaches to Drug Repurposing

Drug repurposing expedites drug development and reduces costs compared to de novo discovery, traditionally relying on observation and experimental validation rather than solely predictive computational models.[10]

2.2.1 Clinical Observation and Serendipity

Historically, repurposing has been opportunistic, arising when unexpected therapeutic benefits or side effects are noted during clinical use or post-marketing surveillance. Physicians and researchers identify pharmacological effects in patients (bedside observations) unrelated to the original indication.[4,7,27]

Examples:

- *Sildenafil (Viagra):* Initially developed for angina and hypertension, repurposed for erectile dysfunction after retrospective clinical data analysis revealed efficacy.[7]
- *Thalidomide:* Originally marketed for morning sickness (later withdrawn due to teratogenicity), found effective for erythema nodosum leprosum and multiple myeloma.[7,27]
- *Minoxidil:* Developed for hypertension, repurposed for hair loss after hair growth was observed as a side effect.[1,7]
- *Bupropion:* Initially prescribed as an antidepressant, later repurposed for smoking cessation.[7]

2.2.2 Literature-Based Repurposing

This method involves systematic mining of scientific literature, clinical trial databases, and patents to uncover novel drug-disease relationships by leveraging extensive biological and pharmaceutical knowledge stored in unstructured text or curated databases.[29,30]

- **Text Mining:** Algorithms extract semantic relationships (e.g., drug-gene or gene-disease associations) from abstracts in repositories such as PubMed and MEDLINE to reveal indirect connections. Machine learning methods based on word embeddings have identified repurposing candidates for diseases like psoriasis.[30,31]
- **Knowledge Graphs:** Large-scale biomedical knowledge graphs (e.g., Drug Repurposing Knowledge Graph, DRKG) integrate medications, diseases, and biological processes. Deep learning models utilize these graphs to recommend candidate drugs.[32]
- **Bibliometrics:** Large-scale analyses of chemical–disease relationships in literature reveal that over 60% of drugs have been investigated for multiple diseases.[27]

2.3 Experimental Screening Approaches

Experimental methods involve physical evaluation of compound libraries in biological assays, subdivided into target-based and phenotypic screening.[33]

- **In Vitro Screening:**
    a. *Phenotypic Screening:* Tests compounds in cellular disease models to observe biological effects (e.g., cancer cell death) without prior knowledge of molecular targets; historically effective for first-in-class drug discovery.
    b. *High-Throughput Screening (HTS):* Automated testing of large compound libraries against biological targets or phenotypes in multi-well formats.[4,10,33]
    c. *Cell-Based Assays:* Techniques like the PRISM assay enable rapid drug sensitivity testing across pooled barcoded cancer cell lines.[34]
    d. *Stem Cell Models:* Disease-specific models derived from patient-induced pluripotent stem cells (iPSCs).[28]
    e. *Binding Assays:* Methods such as affinity chromatography, mass spectrometry, and Cellular Thermal Shift Assays (CETSA) identify direct drug-protein interactions.[6,10]
- **In Vivo Models:**
  Used to validate efficacy and safety of repurposing candidates in whole organisms following in vitro screening.[4,6]
    a. *Whole-Organism Screening:* Small model organisms enable high-throughput phenotypic screening.[4]
    b. *Zebrafish:* Genetically tractable and permeable to small molecules; used to screen FDA-approved drugs for leukemia and tobacco dependence behaviors.[10,7]

c. *Mammalian Models:* Mice, ferrets, and non-human primates assess pharmacokinetics and pathogenesis. For example, transgenic mice expressing human ACE2 were essential for testing repurposed drugs against SARS-CoV-2.[35]

Limitations: Animal models may not fully recapitulate human disease pathophysiology, and safety profiles may not translate entirely to humans.[35]

2.4 Approved Drugs and Repurposing

Approved drugs are prime candidates for repurposing due to their established clinical development history and marketed status, with well-characterized safety, tolerability, and pharmacokinetic profiles.[4,7]

- **Advantages:** Reduced risk of failure due to known safety; shortened development timelines by 3–12 years; potential to bypass early-phase safety trials.
- **Methodology:** Employs on-target strategies (same target, new indication) or off-target strategies (new targets).
- **Challenges:** Intellectual property barriers due to weak patent protection for new uses; off-label generic use reducing commercial incentives; possible requirement for new Phase I trials if dosage differs.[5,7]

2.5 Natural Products and Traditional Medicines Repurposing

Bioactive compounds from plants and traditional remedies, with centuries of medical use, are investigated for new indications, especially in oncology and infectious diseases.

- **Potential:** Natural products have extensive safety and biological activity records, serving as templates for novel drug design via synthetic analogs or prodrugs.
- **Challenges:** Dosage for new indications may differ substantially from traditional uses, complicating repurposing.[8,9]

Ayurvedic Herbs and Formulations[11,14,17,20,21,22,24]

Table 2 : Ayurvedic formulations

Herb/ Formulation	Description	Therapeutic Uses	Bioactive Compounds	Mechanism of Action
Ashwagandha (Withania somnifera)	Known as "Indian Winter Cherry"; symbolizes strength and virility.	Treats stress, insomnia, neurodegenerative diseases, fatigue; classified as Rasayana (rejuvenator).	Steroidal lactones (Withanolides), especially Withaferin A.	Targets tumor proteasome; inhibits NF-κB activation via NEMO/IKK complex; induces apoptosis in cancer cells.
Guduchi / Giloy (Tinospora cordifolia)	Climbing shrub called "Amrita" (imperishable) in Ayurveda and Gilu in Unani medicine.	Immunomodulator, antipyretic, blood purifier; used for tuberculosis, leprosy, and COVID-19 regulation.	Tinosporin, tinosporide, cordifolide, diterpenoid lactones.	Stimulates macrophages; promotes NF-κB translocation; boosts immune response; potential SARS-CoV-2 spike protein modulation.

Turmeric (Curcuma longa) / Curcumin	Golden spice with centuries of medicinal use.	Anti-inflammatory, antioxidant, anti-cancer.	Curcumin.	Suppresses proteasome activity in colon cancer cells; inhibits telomerase (hTERT), Wnt/β-catenin, Hippo/YAP pathways; regulates NF-κB; inhibits COX-2.
Rauwolfia serpentina (Indian Snakeroot)	Medicinal plant studied by Sen and Bose in 1931.	Antihypertensive, tranquilizer; originally used for insanity.	Reserpine alkaloid.	Example of reverse pharmacology; clinical observation led to modern drug development.
Guggul (Commiphora mukul)	Used for cholesterol lowering.	Cholesterol reduction.	E- and Z-guggulsterone.	Antagonizes bile acid receptor FXR; inhibits FXR-mediated suppression of cholesterol 7α-hydroxylase (CYP7A1); promotes cholesterol conversion to bile acids and excretion; antioxidant effects; potential mild thyroid stimulation.
Mucuna pruriens	A tropical, annual climbing shrub (velvet bean)	Parkinson's disease.	Natural source of L-DOPA.	Provides L-DOPA for dopaminergic therapy.
Brahmi (Bacopa monnieri)	Bacopa monnieri is a non-aromatic herb.	Memory enhancer, neuroprotective.	Bacosides.	Cognitive enhancement; potential Alzheimer's disease therapy.
Tulsi (Ocimum sanctum)	"Holy Basil".	Antimicrobial, immunomodulatory, anti-asthmatic, antiviral.	Eugenol, ursolic acid, rosmarinic acid.	Regulates stress hormones; reduces oxidative stress; inhibits COX-2; modulates gene expression (NF-κB, Nrf2); detoxification; broad antimicrobial effects.
Pippali (Piper longum)	Long pepper; Rasayana in Atharvaveda.	Respiratory diseases, anti-inflammatory.	Piperine.	Suppresses cerebral ischemia-induced inflammation by inhibiting COX-2 and NF-κB; enhances bioavailability of other drugs.
Shirisa (Albizia lebbek)	Known as the Woman's tongue tree, is a large deciduous tree in the *Fabaceae* family	Anti-allergic, antihistamine, respiratory disorders.	Lebbeckoside C, and Lebbekanin (A-H)	Stabilizes mast cells; reduces pro-inflammatory cytokines (IL-6, TNF-α).
Haritaki (Terminalia chebula)	"King of Medicine" in Tibet; part of Triphala.	Cytoprotective, immunomodulatory; digestive and cardiovascular diseases.	tannins (32–34%), gallic acid, ellagic acid, chebulic acid, and chebulinic acid	Act as antioxidants, anti-inflammatory, and antimicrobial agents. Its mechanism of action involves modulating signaling pathways (like NF-κB), inducing apoptosis in cancer cells, and enhancing gastrointestinal motility.

Amra (Mangifera indica / Mango)	Known as Indian Hog Plum or *Spondias pinnata*) is a small, tangy tropical fruit popular in South and Southeast Asia	Immunomodulatory, antiviral.	Mangiferin, quercetin, gallic acid.	Mangiferin modulates immune response; exhibits anti-dementia effects.
Triphala	Polyherbal formulation: Terminalia chebula, Terminalia bellerica, Phyllanthus emblica.	Anti-cancer, anti-inflammatory, digestive health.	Polyphenols (gallic acid, ellagic acid, chebulinic acid, chebulagic acid).	Scavenges free radicals; reduces lipid peroxidation; modulates gut microbiota (increases Bifidobacteria); induces apoptosis in cancer cells.

3. Drug Repurposing Using Ancient Manuscripts

3.1 Application of Modern Computational Methods

Modern computational techniques applied to historical medical texts constitute a subset of reverse pharmacology, progressing from "bedside" (clinical observations recorded in ancient literature) to "bench-side" (laboratory validation) to develop standardized medications.[25]

3.2 Importance of Traditional Medical Knowledge

Ancient medical systems such as Ayurveda and Traditional Chinese Medicine (TCM) represent invaluable repositories of clinical insights accumulated over millennia. This experiential wisdom offers strategic advantages for drug repurposing:[9,25]

- **Established Safety:** Long-term human use provides better-understood safety profiles, allowing researchers to bypass initial safety screenings.[9,25]
- **Reduced Development Costs and Time:** Integration of traditional knowledge can reduce drug development timelines from 12–15 years to approximately 5 years at significantly lower cost.[26,35]
- **Synergy and Polypharmacology:** Traditional multi-ingredient formulations provide a systems biology approach suited to treating complex, multi-target diseases.[9,26]

3.3 Digitization of Ancient Texts

Physical manuscripts are being digitized to enable systematic analysis of traditional knowledge.[39]

- **Traditional Knowledge Digital Library (TKDL):** Established in India to protect and catalog traditional knowledge, preventing misappropriation and assisting patent offices in prior art verification.[26]
- **Decision Support Systems:** Projects like Ayusoft convert classical Ayurvedic literature into digital formats, creating comprehensive knowledge bases for scientific validation and dissemination.[26,36]

3.4 Text Mining and Semantic Analysis of Manuscripts

Advanced AI and machine learning methods extract structured data from unstructured ancient texts.

- **Semantic Analysis:** Automated medical knowledge graphs are generated through semantic analysis, linking clinical conditions to specific herbal remedies.[12]
- **Pattern Recognition:** Machine learning interprets complex plant pharmacology across extensive datasets to predict bioactivities and herb-drug synergisms.[37]
- **Automated Prescription Generation:** Deep learning techniques such as Convolutional Neural Networks (CNNs) identify correlations between patient features (e.g., facial characteristics) and traditional prescriptions.[12]

3.5 Mapping Traditional Disease Concepts to Modern Diseases

Translating archaic disease descriptions into contemporary pathological terms is essential for identifying viable treatment targets.

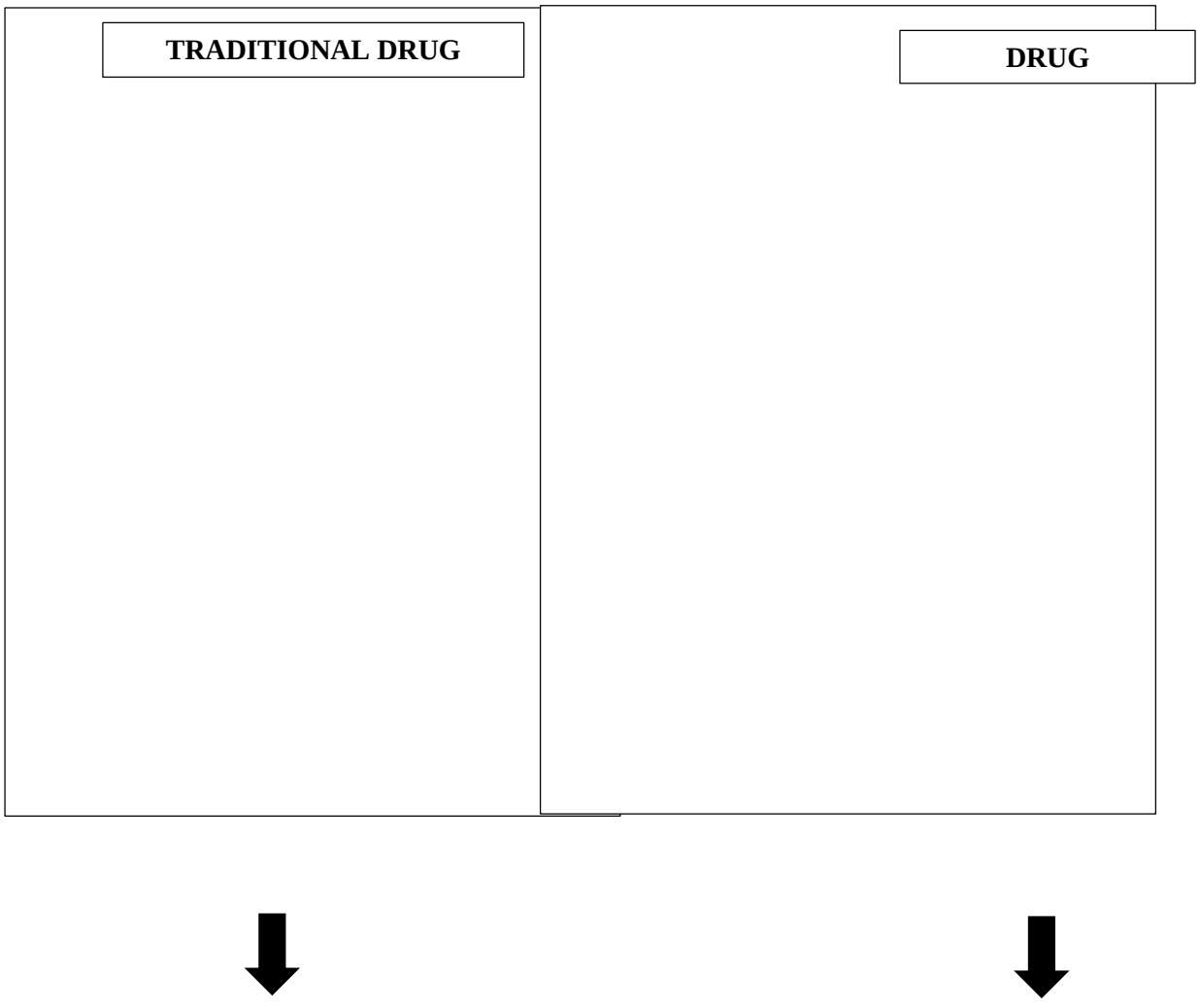
- **Clinical Correlation:** For instance, the Korean herbal remedy Sochehwan (SCH), traditionally a digestant, was repurposed for alcoholic steatohepatitis upon discovering its modulation of Cytochrome P450 2E1 expression.[38]
- **Ayurvedic Principles:** Concepts such as Vyadhiksamatwa (immunity) correlate with modern immunological markers, enabling investigation of herbs like Withania somnifera (Ashwagandha) for neurological and stress-related immune conditions.[23]
- **Mechanism Elucidation:** Traditional drug attributes (rasa, guna, virya) are analyzed to understand their biochemical effects on modern drug targets.[25]

3.6 Network Pharmacology of Herbal Formulations

Given the polypharmacological nature of herbal medicines, network pharmacology provides a framework to elucidate mechanisms.

- **Reverse Docking:** Computationally screens for protein targets binding specific herbal compounds such as Acteoside, Quercetin, and Epigallocatechin gallate (EGCG), aiding mechanism of action identification.[13]
- **Network-Based Predictions:** Tools like SAveRUNNER and network propagation assess interactions between herbal targets and disease-associated proteins within the human interactome.[39,40]
- **In Silico Screening:** Network pharmacology has identified traditional Chinese medicine (TCM) prescriptions, including Licorice and Scutellaria, as potential COVID-19 therapies targeting viral proteins and human ACE2 receptors.[12,38]

Figure no. 1 Difference between traditional drug discovery and drug repurposing



5 Stages :

1. Discovery and preclinical
2. Safety review
3. Clinical research
4. FDA review
5. FDA post-market safety monitoring

- Generally, more time consuming
- High investment or cost
- More risk of failure
- Clinical efficacy and safety profile should be evaluated

4 Stages :

1. Compound identification
2. Compound acquisition
3. Development
4. FDA post-market safety monitoring

- Less time consuming
- Lesser investment compared to traditional drug discovery
- Less risk of failure
- Clinical efficacy and safety profiles already exist

Figure 1: Difference between traditional drug discovery and drug repurposing

4. Sources of Drug Repurposing Candidates

Here some common data resources are given in table no. 3,4 and 5.

Table 3 : Drug Database[7]

Name of the Database	Description	Link
PubChem (Bolton et al., 2008)	Biological activity of >60 million unique compounds	http://pubchem.ncbi.nlm.nih.gov/
ChEMBL (Gaulton et al., 2012)	Curated database with compound activity against target genes	https://www.ebi.ac.uk/chembl
LINCS (Vidović et al., 2014)	Follow-up project to CMap; L1000-based expression profiles of drug-treated cancer cell lines	http://lincscloud.org/
ProjectAchilles (Cowley et al., 2014)	Cancer cell line RNAi screen to identify genes relevant to cell survival	https://portals.broadinstitute.org/achilles
CMap (Connectivity Map) (Lamb et al., 2006)	Expression profiles of drug-treated cancer cell lines	http://www.broadinstitute.org/cmap
CTRP (Basu et al., 2013; Seashore-Ludlow et al., 2015; Rees et al., 2016)	Screening of 860 cancer cell lines for sensitivity to 480 drugs and probes; comparison with mutation, expression, and CNV data	http://www.broadinstitute.org/ctrp.v2.2
ImmPort (Bhattacharya et al., 2014)	Portal containing 222 studies with ~37k subjects; includes ELISA, ELISPOT, and flow cytometry data	https://immport.niaid.nih.gov/

PharmGKB (Hewett, 2002)	Expert-curated gene–drug genotype–phenotype connections, dosing guidelines, and drug labels	https://www.pharmgkb.org/
e-Drug3D (Pihan et al., 2012)	Mirrors US pharmacopoeia of small drugs; 1,822 molecular structures	http://cheminfo.ipmc.cnrs.fr/MOLDB/index.html
DailyMed	Catalogue of drug listings and drug label information	https://dailymed.nlm.nih.gov/dailymed/
Comparative Toxicogenomics Database (CTD) (Mattingly et al., 2006; Pihan et al., 2012)	~1.5 M chemical–gene, ~2 M chemical–disease, and ~20 M gene–disease interactions	http://ctdbase.org/

Table 4 :Disease Database[7]

Type	**Name**	**Description**	**Link**
Multi-omic level	TCGA (The Cancer Genome Atlas Research Network et al., 2013)	Clinical and multi-omic data of 33 different tumor types	http://tcga-data.nci.nih.gov
	ICGC (International Cancer Genome Consortium et al., 2010)	Genomic, transcriptomic and epigenomic data from ±25,000 tumours	http://icgc.org/
	CCLE (Barretina et al., 2012)	Cancer cell line database of gene expression arrays, CNVs, mutations, and IC50s	http://software.broadinstitute.org/software/cprg/
Genomic	dbGaP (Mailman et al., 2007)	Database of genotype and sequence data with phenotype information	http://www.ncbi.nlm.nih.gov/gap
	DisGeNET (Piñero et al., 2015)	Curated database with text-mining derived	http://www.disgenet.org/web/DisGeNET/menu

		associations to generate human gene–disease associations	
	dbSNP (Sherry, 2001)	Database for SNPs, DIPs and STRs for human and model organisms	http://www.ncbi.nlm.nih.gov/snp
	dbVar (Lappalainen et al., 2013)	Database of human genome structural variations including CNVs	http://www.ncbi.nlm.nih.gov/dbvar
	1000 Genomes Project (1000 Genomes Project Consortium et al., 2015)	Large resource of human variation and genotype (2,504 samples)	http://www.1000genomes.org/
	COSMIC (Forbes et al., 2014)	Cancer-focused database with expert curation based on literature and systematic screening data	http://cancer.sanger.ac.uk/cosmic
Transcriptomic	GTEx (Lonsdale et al., 2013)	Connects genotype with tissue-specific expression levels for comprehensive human eQTLs	http://www.gtexportal.org/
	GEO (Barrett et al., 2013)	Raw and processed transcriptomic data from microarrays, RNA-Seq and	http://www.ncbi.nlm.nih.gov/geo

		other platforms	
	ArrayExpress (Kolesnikov et al., 2015)	Raw and processed transcriptomic data	https://www.ebi.ac.uk/arrayexpress
	Allen Brain Atlas (Allen Institute for Brain Science, 2017)	Expression data from human and mouse brain compartments	http://www.brain-map.org/
Proteomic	Human Proteome Map (Kim et al., 2014)	LC–MS/MS proteomics of multiple organs/tissues	http://www.humanproteomemap.org/
	STRING-DB (von Mering et al., 2005)	Known and predicted protein–protein interaction database including >9 million proteins	http://string-db.org/
Epigenetic	ENCODE (The ENCODE Project Consortium, 2004)	Annotation of human genome function using TF ChIP-Seq and RNA-Seq	https://genome.ucsc.edu/ENCODE/
	Roadmap Epigenomics (Bernstein et al., 2010)	Epigenetic data including ChIP-Seq and DNA methylation from many cell types and tissues	http://www.roadmapepigenomics.org/
	PsychENCODE (PsychENCODE Consortium et al., 2015)	Epigenetic data from psychiatric disease and healthy brains, focused on non-coding genome	https://www.synapse.org/#!Synapse:syn4921369/wiki/235539

Table 5 : Omics analytical tools[7]

Tool Name	Description	Link
ksRepo (Brown et al., 2016)	Integrates gene expression and drug datasets from different platforms	https://github.com/adam-sam-brown/ksRepo
GoPredict (Louhimo et al., 2016)	Gene ontology–based drug prioritization for breast and ovarian cancer	http://csblcanges.fimm.fi/GOPredict/
PREDICT (Gottlieb et al., 2011)	Drug–drug and disease–disease relatedness	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3159979/
RE:fine Drugs (Moosavinasab et al., 2016)	Interactive portal linking 916 drugs, 567 genes and 1,770 diseases using GWAS and PheWAS	https://drug-repurposing.nationwidechildrens.org/search
RANKS (Valentini et al., 2016)	Graph-based node label ranking; applicable to drug repurposing	https://cran.r-project.org/web/packages/RANKS/index.html
COGENA (Jia et al., 2016)	Gene co-expression analysis with repositioning-oriented enrichment analysis	https://github.com/zhilongjia/cogena
DR.PRODIS (Zhou et al., 2015)	Tests user input molecule against pre-computed target libraries	http://cssb.biology.gatech.edu/repurpose
GIFT (Zu et al., 2015)	Infers chemogenomic features from drug chemical substructures	http://bioinfo.au.tsinghua.edu.cn/software/GIFT/
NFFinder (Setoain et al., 2015)	Searches gene expression profiles to identify conditions similar to or opposite a query	http://nffinder.cnb.csic.es/
PROMISCUOUS (von Eichborn et al., 2011)	Searchable database of protein–protein and drug–protein connections	http://bioinformatics.charite.de/promiscuous/
MANTRA (Iorio et al., 2010)	Uses network theory and non-parametric statistics of expression data to identify alternative mechanisms of action	http://mantra.tigem.it/

DSigDB (Yoo et al., 2015)	GSEA-formatted gene sets of drug binding data, CMap data, kinase signatures and computational drug–gene interaction predictions	http://tanlab.ucdenver.edu/DSigDB/DSigDBv1.0/

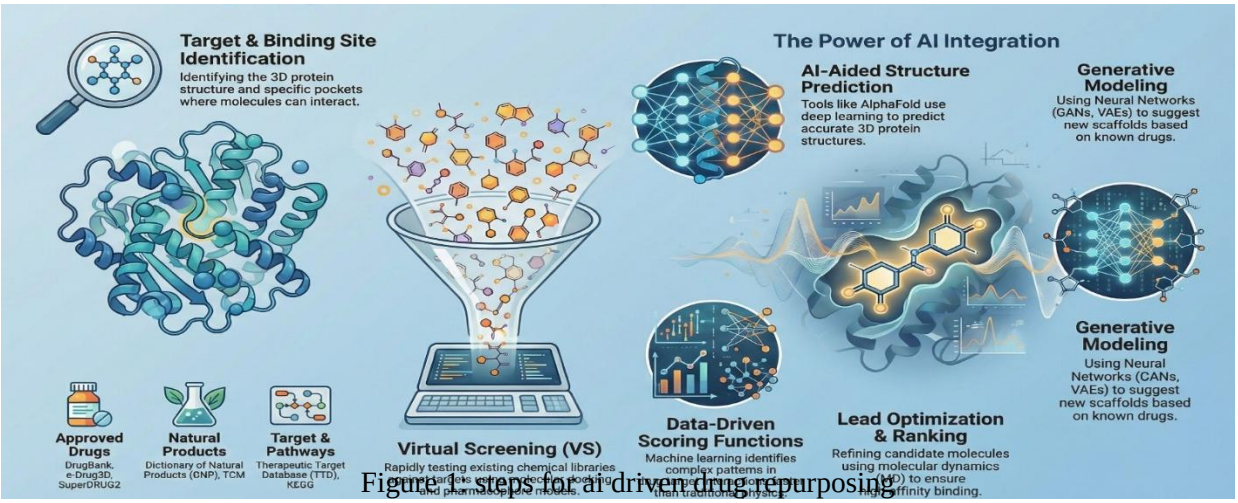
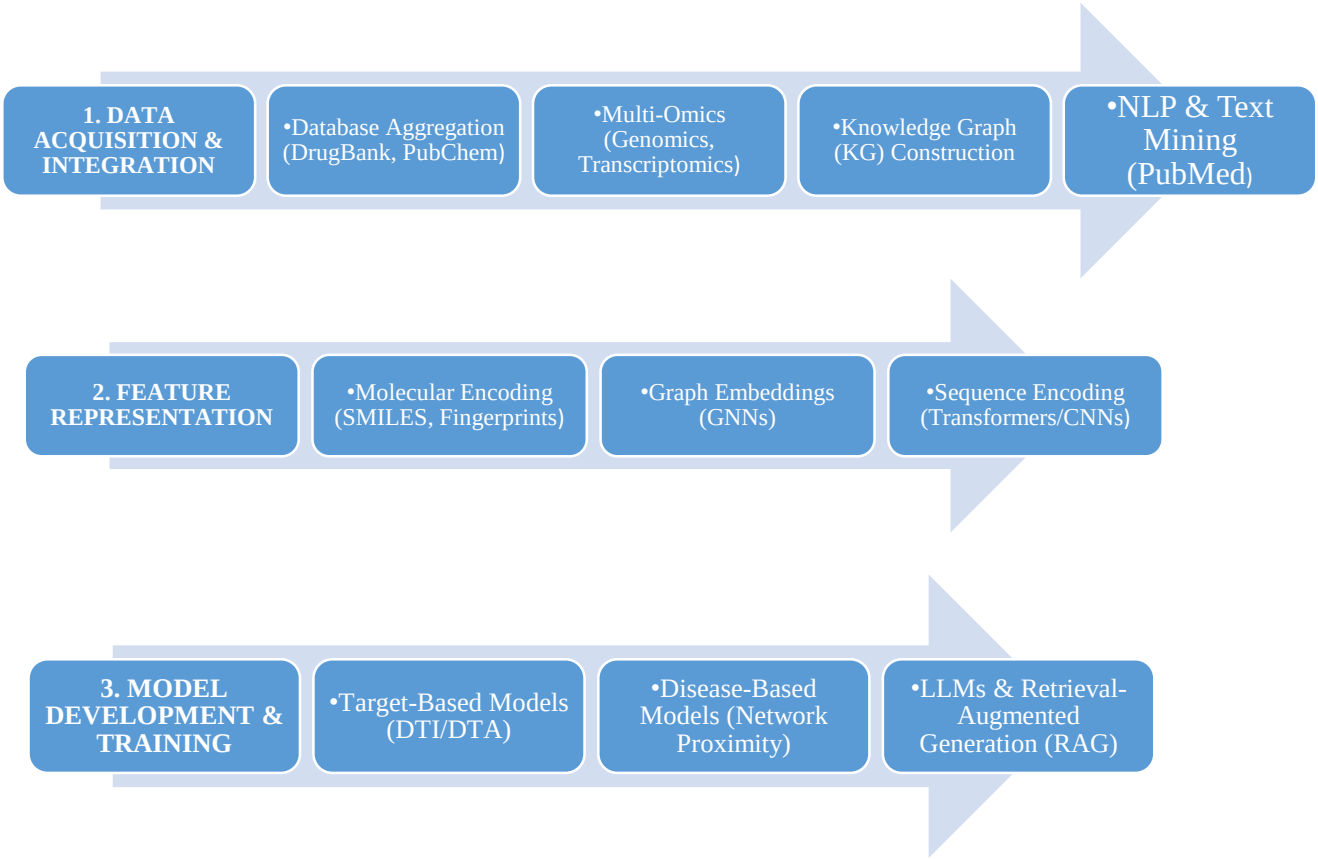
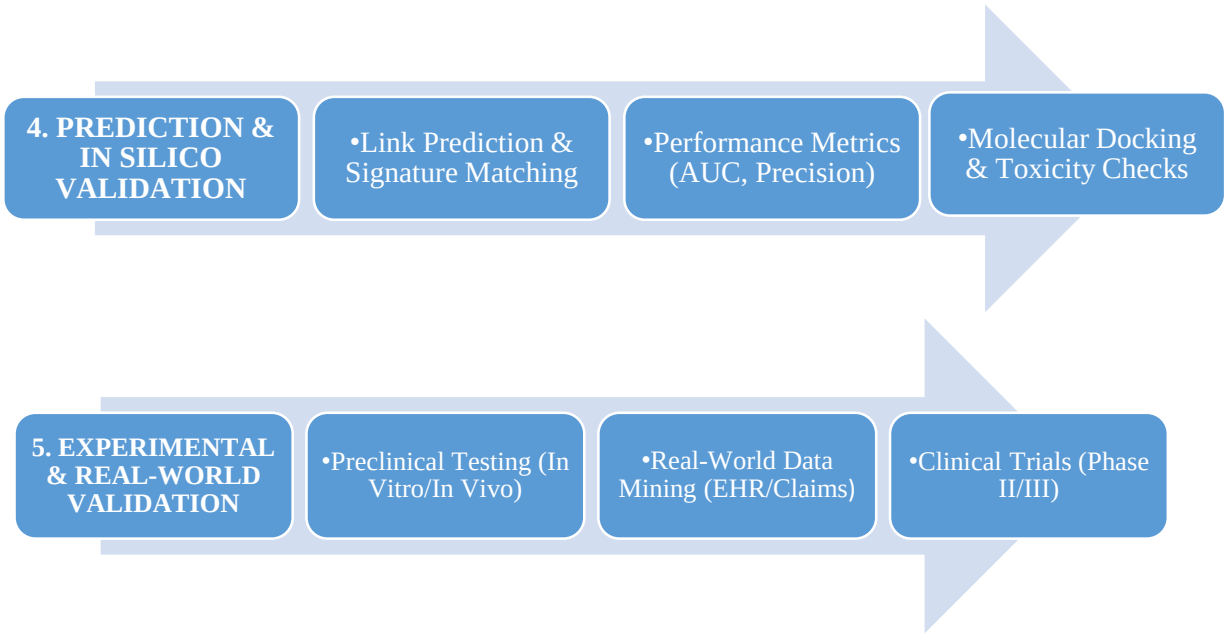


Figure 1. steps for ai driven drug repurposing

7. Process of drug repurposing :





5. Case Studies:

5.1 Drug repurposing in breast cancer:

Breast cancer (BC) is a well-known cancer that arises from the glandular milk duct epithelial cells or breast lobules primary cause of death worldwide. Several medication classes are used in the treatment of cancer. Alkylating substances such as cyclophosphamide and Thiotepa harm DNA, preventing gene expression and cell proliferation. Cyclophosphamide, which functions as an immunomodulator at lower dosages and an alkylating agent at larger doses, presents challenges due to its dual reaction; hence, careful dosage considerations are required.[41]

5.1.2 Anti-Alcoholic Drug Sensitization of Drug-Resistant BC Cells:

Aldehyde dehydrogenase primarily targets anti-alcoholic medications. Disulfiram (DSF) is a copper-binding protein that acts as a copper ionophore. It was first utilized as an anti-alcohol medication in clinical settings to treat alcoholism. Because of this characteristic, DSF can produce reactive oxygen species (ROS) that cause copper-mediated oxidative stress. DSF has recently been used as an adjuvant in the treatment of solid tumors, including BC.[42]

5.1.3 BC Cell Sensitization to Anthelmintic Medications:

The benzimidazole-based anthelmintic drugs flubendazole, mebendazole, and albendazole are known to cause cell death in both mammalian and parasitic cells. This process targets microtubule systems by preventing the uptake and transport of glucose. In therapeutic trials, they have been repurposed for anticancer activity. By triggering caspase 3 activity, ABZ and MBZ caused apoptosis in HT29 colon cancer cells as well as MCF-7 and MDA-MB 231 BC cells.[42]

5.2 Success stories in Dravyaguna research:

5.2.1 Nimba (Azadirachta indica A. Juss.):

Bioactive substances found in nimba leaves and preparations include as flavonoids (like quercetin) and limonoids (like azadirachtin, nimbolide). The strong antioxidant and free radical scavenging properties of nimba are attributed to these phytoconstituents.11 Interestingly, nimbolide and azadirachtin both show strong, dose-

dependent antioxidant activity, frequently surpassing that of common antioxidants like ascorbic acid. Nimba also has the potential to reduce inflammation. The growing anti-cancer potential of nimba is very intriguing. Neem extracts have been shown to affect a number of molecular targets, including tumor suppression, angiogenic factors (VEGF), apoptotic regulators (Bcl-2 family members), and sor genes (p53, PTEN).[43]

5.2.2 Haridra (Curcuma longa L.):

Turmeric (Haridra) is a common anti-inflammatory and Rakta-shodhaka (blood cleanser) in Ayurvedic medicine. Curcumin is a key topic of current research because to its strong anti-inflammatory and antioxidant properties. It regulates important molecular pathways including COX-2, NF-κB, and other cytokines that are required for long-term inflammatory actions. Haridra possesses anti-inflammatory, anti-cancer, neuroprotective, anti-diabetic, hepatoprotective, and gastroprotective properties. Preclinical research has demonstrated that turmeric improves liver detoxification enzymes, prevents chemically caused ulcers, and stops cancer cells from growing in vitro.[43] Curcumin inhibits cell proliferation in MDA-MB-231 cells by downregulating AKT expression, demonstrating strong anticancer effects. Curcumin also inhibits the mTORC1 pathway, which is essential for cell survival, proliferation, and angiogenesis.[44]

5.2.3 Ashwagandha (Withania somnifera L. Dunal):

It has previously been administered to enhance immunity, endurance, sexual health, and resilience to aging and stress. Ashwagandha roots include a variety of alkaloids and steroidal lactones called withanolides, as well as other bioactive metabolites including saponins. Its adaptogenic, antioxidant, anti-inflammatory, and immunomodulatory qualities are mostly caused by these constituents. Analysis further emphasizes its broad pharmacological spectrum, which includes analgesic, sedative, anxiolytic, anti-stress, and cognitive-enhancing properties. Clinical trials further support ashwagandha's therapeutic potential for mental health. Participants who took ashwagandha had much lower anxiety and depression levels than those who got a placebo, according to randomized controlled studies.[43]

5.3 Repurposed drugs from phytochemical's origin:

Compared to manufactured medications, phytochemical-derived drugs offer additional advantages. By integrating fruits in our normal diet, we can limit about 20% of cancers, including stomach, pancreatic, colon, and cervical cancers. Flavonoids, alkaloids, phenols, antioxidants, vitamins, terpenoids, and sesquiterpenes are abundant in phytochemicals. [44]

5.3.1 Artemisinin:

Chinese medicine has long utilized artemisinin, a sesquiterpene lactone derived from the Artemisia annua plant, as an antimalarial medication to treat fever and chills. This medication is safe, well-tolerated, and has minimal toxicity when used to treat cancer. [44]

5.3.2 Ginkgo biloba:

Because of its antiangiogenic properties and inhibition of carcinogen-related activities, ginkgo biloba leaf extract has anticancer properties. By blocking topoisomerase-II, causing DNA fragmentation, and inducing G2/M cell cycle arrest, the isoflavone compound genistein exhibits antineoplastic action.[44]

5.3.3 Resveratrol:

A phytoalexin called resveratrol inhibits the activation of NF-κB caused by tumor necrosis factor, hence regulating the development of tumors. Grapes contain resveratrol, which has potent anti-inflammatory and antioxidant

qualities. When paired with quercetin, resveratrol inhibits the growth of cancer cells and encourages their demise.[44]

5.3.4 Hypericin:

An anthraquinone derivative called hypericin works as an anticancer agent by stopping carcinogens' genotoxic effects. The anthraquinone derivative hypericin, which comes from Hypericum perforatum, alters the extracellular signal-regulated kinase (ERK1/2) cascade. Its potential as an anticancer drug is further enhanced by its partial inhibition of the STAT-1 and NF-κB signaling pathways.[44]

5.3.5 Reserpine:

Reserpine, an alkaloid derived from the roots of Rauwolfia serpentina (Indian snakeroot), is a significant drug discovery accomplishment accomplished using reverse pharmacology, a process that validates traditional clinical observations using scientific means. In 1931, Indian scientists Gananath Sen and Kartick Chandra Bose demonstrated the drug's antihypertensive and tranquilizing effects, based on its traditional use for diseases such as "insanity" and hypertension. Following a critical 1949 study by Rustom Jal Vakil on its use in essential hypertension, Ciba-Geigy commercialized reserpine as the first antipsychotic and antihypertensive drug worldwide. Furthermore, the discovery of its distinct side effects, which included depression and extrapyramidal symptoms, proved to be a watershed moment in the creation of new antidepressants and Parkinson's disease medications.[28]

6. Challenges And Limitations Of AI Drug Repurposing:

AI is a potent tool that can enhance and speed up current drug discovery procedures rather than taking their place. It can be difficult to smoothly incorporate AI into the drug discovery process, though [45]. The accuracy and comprehensiveness of the underlying data are critical to the success of drug repurposing algorithms. Simultaneously, modern scientific rigor demands controlled clinical trials, validated extracts, and reproducible pharmacological data. Traditional doctors and biomedical scientists must actively communicate and respect one another in order to bridge these paradigms.[43]

Limited experimental data, gaps in clinical records, or omissions in biological databases can all result in incomplete data, which is defined by missing or inadequate information. Incomplete data can result in models that are unable to accurately depict biological processes, which can lead to subpar predictive performance.[46]The prevalence of missing data varies significantly between data sources; some crucial variables have absence rates higher than 25%, which may jeopardize the accuracy of model training and predictions.[47]

First of all, one of the most important principles in AI training is described by the phrase, “garbage in, garbage out”, which means that the quality of input data defines the outcome, and any kind of bias could be associated with poor results. For example, the accuracy of the training process is impacted by training datasets that are frequently noisy and biased toward positive findings, while negative data is scarce.[48] Some pharmaceutical companies are less likely than others to release their chemical libraries (such as failed drugs) to branch out the potential applications of their compound collections (or could prove extremely selective at choosing partners). This could pose a fundamental barrier to drug repurposing prospects if a potential repurposed indication falls outside the organization's core disease area, even though a shelved drug could be viewed as idle capital or a missed or postposed opportunity.[49]

Real-world drug discovery workflows are particularly hampered by the "black box" nature of complex Deep Learning (DL) models, which makes it difficult to conduct thorough validation and efficient troubleshooting.(53) Some AI models, especially sophisticated deep learning algorithms, have opaque internal workings. These models use complex calculations that are hard for people to comprehend to arrive at their conclusions. Drug discovery is hampered by this lack of interpretability.(48) The lack of transparency is a challenge in drug development, where trust from researchers, clinicians, and regulatory bodies is important.[51]

Additionally, it is vital to maintain the integrity of traditional knowledge, including the subtleties of administration and preparation as described in classical texts.[43] Traditional methods rely heavily on human expertise and intuition, whereas AI operates using data and algorithms. Researchers must establish effective communication channels between AI and human experts to ensure that both approaches are used optimally.[45] The zero-shot drug repurposing problem requires AI models to find new drug-disease relationships without any prior examples, either because there is no effective treatment or because the original indication of the drug under investigation and the new indication are irrelevant.[48]

Because biological datasets come from a variety of experimental platforms, patient populations, and methodological approaches that could introduce systematic biases and confounding factors, data heterogeneity is a persistent challenge.[47] The heterogeneity and challenges posed by large-scale drug databases make it difficult to apply drug repurposing algorithms efficiently. Incomplete data can lead to biased and inaccurate models, whereas imbalanced samples can skew predictions and reduce the model's sensitivity to rare but significant patterns.[46]

Another important point is the challenge of validating DL models for drug development. A good model should be tested thoroughly for its accuracy, reproducibility, and, most importantly, its generalizability over different datasets and experimental conditions.[51] The biological understanding and therapeutic priorities may change significantly during the several years that can pass between computational predictions and experimental validation.[47]

Inequality in results accessibility, caused by complex methods, specialized teams, and high-performance computing infrastructure frequently required for effective AI utilization, can result in a 'digital divide' within the drug discovery landscape.[50] In addition to GPUs and TPUs, which are largely out of reach for many research institutions and startups, efficient computing infrastructure is required to train complex models on large datasets. Additionally, because drug development uses a lot of energy, these DLs are not environmentally friendly.(51) Another obstacle to adoption may be the requirement for specialized staff.[52]

Ethical concerns about using AI in healthcare, such as algorithmic bias and fairness, must be addressed. [52] One major obstacle to widespread adoption is the creation of user-friendly interfaces that display intricate algorithmic outputs in formats that are pertinent to clinical settings.[47] Different regulatory agencies, such as the FDA, require evidence of model performance, validation, and comprehensive documentation. The lack of a standard DL model assessment protocol complicates the regulatory approval process.[51] Certain legal issues may make it more difficult to patent a novel medical use and/or to enforce patent rights, which would reduce the incentives for repurposing drugs.[49] All of these points summarize the ethical concerns raised by the use of AI, emphasizing the need for more careful and precise data handling procedures. Furthermore, the field is limited by the lack of a comprehensive regulatory framework.[48]

7. Future Perspectives On AI Driven Drug Repurposing:

The demonstrated benefits of AI in drug discovery, such as speed, efficiency, and cost-effectiveness, indicate that its use will likely grow. [53] Pharmaceutical companies are investing in AI because the future is here. There may be a larger race to develop a drug than ever before, using AI.[54] A significant opportunity exists at the intersection of AI and personalized medicine, where AI can quickly and efficiently analyze massive amounts of biomedical data. Machine learning and deep learning models excel at processing large datasets containing genetic, proteomic, metabolomic, and clinical data.[46]

The next generation of AI models in pathogen biology will look beyond genomic datasets and adopt a multimodal approach. This will entail combining protein structures, metabolic pathways, host-pathogen interaction networks, and high-resolution electron microscopy images.[45] Another study addressed the urgent need for antibiotic resistance solutions through novel approaches that investigate the therapeutic potential of natural products and their synthetic derivatives. These efforts reflect a broader shift in thinking, with drug repurposing serving as a comprehensive strategy to address global health concerns.[55]

The combination of artificial intelligence and other emerging technologies, such as quantum computing, synthetic biology, and nanotechnology, opens up previously unimaginable opportunities for therapeutic innovation.

Quantum algorithms may allow for the optimization of molecular conformations and drug-target interactions on scales that are currently computationally intractable. Synthetic biology approaches can generate novel therapeutic targets and delivery mechanisms based on AI-driven insights. Nanotechnology platforms can address blood-brain barrier issues, which currently limit therapeutic options for neurodegenerative diseases.[47]

Nonetheless, the reverse pharmacology approach has greatly expanded Dravyaguna's scope from traditional herbal classification to a globally relevant, interdisciplinary research field. It emphasizes Ayurveda's potential as a source of credible, evidence-based therapeutics for the twenty-first century, in addition to its cultural heritage.[43]

These GANs and VAEs, which extract patterns from massive datasets of molecular attributes and structures, are algorithms capable of designing new drugs with effective pharmacodynamic and pharmacokinetic profiles. Deep learning models outperform conventional methods in predicting the potential toxicity of novel therapeutic candidates. DL models can identify potential safety issues early in the medication development process.[51]

Systems medicine/network pharmacology provides an integrative perspective on previous (and seemingly opposing) paradigms in drug discovery: phenotypic-oriented and target-oriented, or 'rational' drug discovery. Network and metabolic control analysis can be useful tools for developing multi-target therapeutics or selecting a synergistic drug combination.[49]

Physicians could gain insight into the mechanisms of repurposing predictions by using interpretable AI models, thereby increasing trust and adoption in daily clinical practice. Meanwhile, the development of a comprehensive regulatory framework would improve the design of clinical trials based on AI-generated predictions. As a result, repurposed drugs could be evaluated faster, providing patients with earlier access to safe and effective therapeutic options.[48]

By addressing data quality and privacy concerns, improving computational methodologies, and collaborating closely with regulatory bodies, the field can use AI to unlock new therapeutic opportunities and deliver benefits to patients faster than ever before. The road ahead will require a collaborative effort from all stakeholders to ensure that AI serves as a catalyst for progress in drug repositioning.[56]

Collaborative initiatives like Open Targets, the COVID Moonshot Project, and the LINCS (Library of Integrated Network-Based Cellular Signatures) program make tools, data, and AI models more accessible to everyone, accelerating innovation through global collaboration.[57]

8. Discussion and Conclusion :

The intersection of artificial intelligence and reverse pharmacology holds immense promise for transforming drug discovery, especially by tapping into the vast repository of traditional Indian manuscripts and medicinal systems like Ayurveda, Siddha, and Unani. Reverse pharmacology begins with clinical observations and experiential data from traditional medicine practices, circumventing the high failure rates, exorbitant costs, and prolonged timelines characteristic of conventional drug development. With AI-driven methodologies, researchers analyze historical texts to extract indications, formulations, and ethnobotanical knowledge, translating ancient wisdom into modern therapeutic leads. AI tools such as machine learning algorithms—including random forests, support vector machines, neural networks, and deep architectures—are employed to predict drug-target interactions, unravel compound efficacies, and identify bioactive molecules from herbal sources. Network pharmacology visualizes how multi-component herbal formulations interact with complex biological networks, embodying principles of holistic medicine, and enabling multi-target therapeutic strategies suitable for multifactorial diseases. Significantly, AI accelerates the identification of natural compounds like curcumin, withanolides from Ashwagandha, resveratrol, and ginseng derivatives, validating their efficacy through computational docking, molecular dynamics, and simulations against contemporary disease targets such as SARS-CoV-2 proteins, cancer pathways, and metabolic disorders. In addition to natural products, approved drugs are repurposed for new indications, leveraging existing safety, pharmacokinetic, and clinical data to cut development time drastically, even enabling rapid deployment during health crises. Traditional formulations like Guggul, Guduchi, Haridra, and Tulsi are being digitally cataloged and analyzed using machine learning, semantic text mining, and knowledge graph techniques, which facilitate the mapping of archaic disease concepts onto modern pathology, thereby

uncovering new therapeutic applications. Computational approaches—such as molecular docking, target prediction algorithms, and integrated bioinformatics databases like DrugBank, ChEMBL, and the Therapeutic Target Database—aid in virtual screening and hypothesis generation for drug repositioning. Case studies include the repurposing of drugs like disulfiram and albendazole for cancer, anti-inflammatory effects of turmeric, and the anti-cancer properties of artemisinin, with validation through in vitro and in vivo models. However, challenges persist, including data incompleteness, quality issues, interpretability of deep learning models, ethical concerns, regulatory hurdles, and the need for standardized validation protocols. The opaque nature of complex AI algorithms, data heterogeneity, bias, and the energy-intensive demands of deep learning infrastructure hinder adoption. Furthermore, integrating traditional regulatory frameworks with AI-driven discoveries necessitates clear guidelines for model validation, transparency, and reproducibility. The future of AI in reverse pharmacology is optimistic, with avenues like multimodal data integration encompassing genomics, metabolomics, proteomics, and imaging, and the incorporation of innovative technologies such as quantum computing, synthetic biology, and nanotechnology. These advancements promise to enhance personalized medicine, discover novel therapeutic targets, and develop synergistic multi-drug regimens. Emphasizing interdisciplinarity, collaborations among AI researchers, pharmacologists, traditional medicine practitioners, and regulators are crucial to translating computational insights into clinical realities efficiently. Initiatives like the Knowledge Digital Library (TKDL), Open Targets, and global efforts to share data and AI models exemplify the collective movement towards harnessing AI's potential in drug repurposing rooted in traditional knowledge systems. The continued evolution of interpretability, regulatory clarity, ethical data handling, and environmental sustainability will determine how effectively this promising nexus between ancient wisdom and cutting-edge technology can advance global health outcomes. Embracing these innovations offers a pathway to faster, safer, and more affordable therapeutics, bridging cultural knowledge with modern science to meet pressing health challenges and expand the therapeutic arsenal beyond conventional limits.

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