American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 35 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

Article

IN SILICO DRUG REPURPOSING FOR INFLAMMATORY DISEASES: A SYSTEMATIC REVIEW OF MOLECULAR DOCKING AND VIRTUAL SCREENING STUDIES

Mansura Akter Enni[1]; Md Abdul Ahad Maraj[2];

[1] *BSc in Genetic Engineering and Biotechnology, Jagannath University, Dhaka, Bangladesh; Email: mansuraenni98@gmail.com*

[2] *BSc in Microbiology, Primeasia University, Dhaka, Bangladesh.. Email: abdulahadmaraj@gmail.com*

ABSTRACT

The escalating global burden of inflammatory diseases—marked by persistent immune dysregulation, multisystem involvement, and complex molecular etiologies—has intensified the need for innovative therapeutic strategies that minimize cost, reduce development timelines, and increase success rates. Drug repurposing, the practice of identifying new therapeutic uses for existing drugs, has emerged as a strategic alternative to de novo drug discovery, particularly through in silico methodologies such as molecular docking, virtual screening, and cheminformatics-guided candidate selection. This systematic review synthesizes and evaluates recent advancements in computational repurposing approaches aimed at inflammatory disorders, including rheumatoid arthritis, inflammatory bowel disease, psoriasis, and systemic lupus erythematosus. Following the PRISMA 2020 guidelines, a comprehensive literature search was conducted across multiple scientific databases—including PubMed, Scopus, Web of Science, Embase, and IEEE Xplore—to identify peer-reviewed studies published between January 2010 and April 2022. A total of 65 articles met the inclusion criteria, encompassing diverse in silico workflows that examined drug-target interactions using molecular docking platforms such as AutoDock, AutoDock Vina, Schrödinger's Glide, MOE, and GOLD, often combined with ADMET profiling tools (e.g., SwissADME, pkCSM) and molecular dynamics simulations to validate binding stability. Target proteins of interest commonly included pro-inflammatory mediators such as TNF-α, IL-6, IL-1β, JAK1/2, and NF-κB, with FDA-approved kinase inhibitors and anti-cancer drugs frequently emerging as high-affinity binders suitable for cross-disease application. In addition, the review documents methodological convergence in scoring thresholds, ligand library design, and reproducibility standards across computational studies. Several case studies demonstrate successful downstream validation of in silico predictions via in vitro or in vivo assays, reinforcing the translational potential of these approaches. However, key challenges persist, including lack of consensus on docking protocol standardization, limited exploration of off-target toxicities, and insufficient integration with systems pharmacology and biological network modeling. This review concludes that in silico drug repurposing represents a rapidly evolving, resource-efficient approach for identifying new treatments in immunopathology, but emphasizes the need for hybrid computational-experimental pipelines and improved benchmarking to realize its full clinical utility..

KEYWORDS

Drug Repurposing; Molecular Docking; Virtual Screening; Inflammatory Diseases; In Silico Pharmacology;

Citation:
Enni, M. A. (2022). *In silico drug repurposing for inflammatory diseases: A systematic review of molecular docking and virtual screening studies*. *American Journal of Advanced Technology and Engineering Solutions, 2*(4), 35–64. https://doi.org/10.63125/j1hbts51

Received:
September 17, 2022

Revised:
October 20, 2022

Accepted:
November 16, 2022

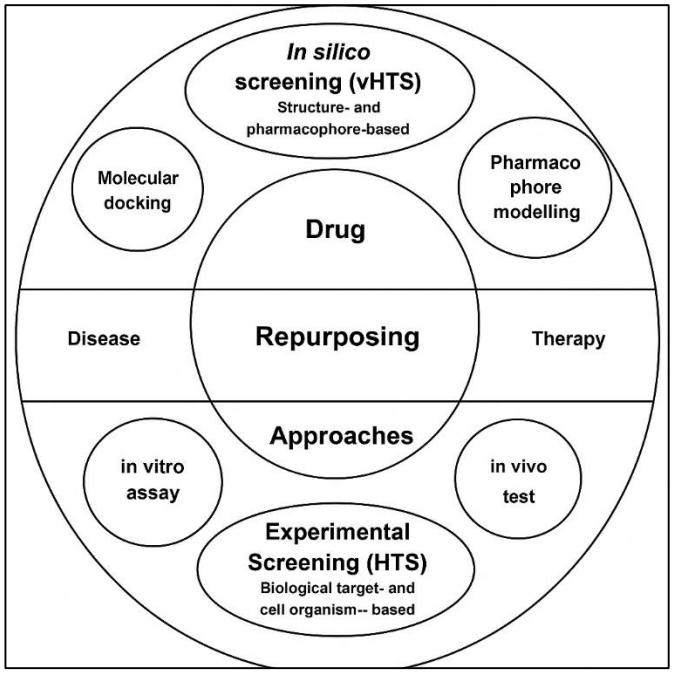
Published:
December 29, 2022

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

INTRODUCTION

Drug repurposing, also known as drug repositioning, refers to the process of identifying new therapeutic uses for existing pharmaceutical agents outside the scope of their original medical indication (Wang et al., 2019). Unlike de novo drug discovery, which is time-consuming, expensive, and characterized by a high attrition rate, repurposing leverages the established pharmacological and safety profiles of approved drugs to expedite the drug development process (Shen et al., 2019). This approach has gained prominence in contemporary pharmacotherapy owing to its cost-effectiveness and shorter timelines for regulatory approval. Repurposing is especially significant for addressing diseases with limited therapeutic options or for which conventional drug development pipelines have been inefficient (Smalley, 2017). In the context of inflammatory diseases, this strategy holds particular value, as these disorders are often multifactorial, chronic, and associated with significant morbidity.

Figure 1: Framework for Drug Repurposing Approaches

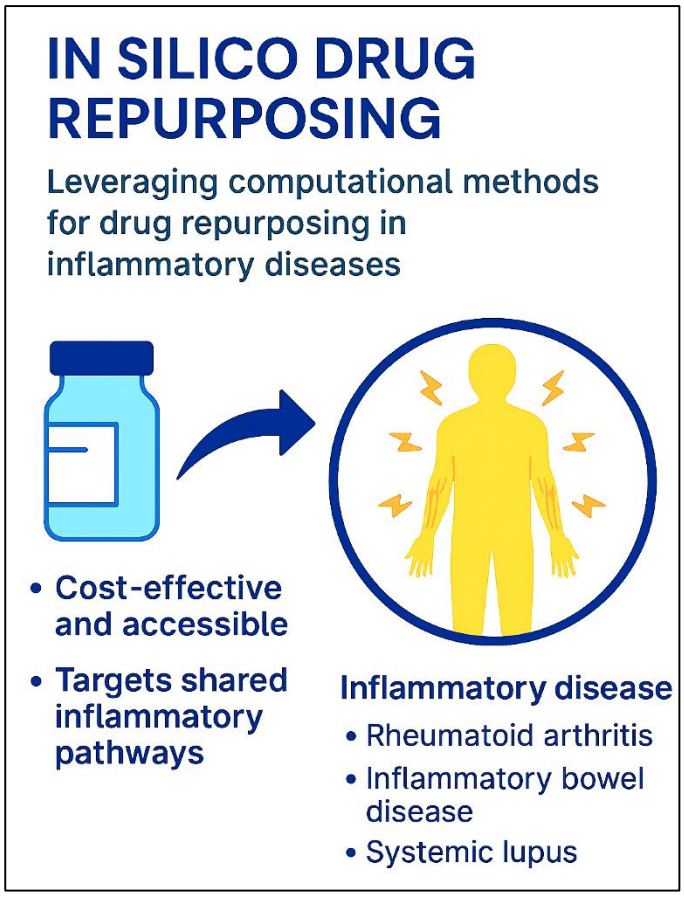


Inflammatory diseases comprise a wide spectrum of conditions characterized by dysregulated immune responses that lead to tissue damage, fibrosis, and chronic pain. Examples include rheumatoid arthritis, inflammatory bowel disease, psoriasis, systemic lupus erythematosus, and multiple sclerosis (Wang et al., 2014). These diseases collectively affect millions globally and represent a significant burden on healthcare systems (Vasconcelos et al., 2018) Disease and Injury Incidence and Prevalence Collaborators, 2018). Many inflammatory diseases are autoimmune in nature and result from an interplay of genetic predisposition and environmental triggers that dysregulate cytokine networks, cellular immunity, and signal transduction pathways (Uddin, 2018). The heterogeneity and complexity of these disorders challenge traditional drug discovery paradigms, prompting increased interest in alternative strategies such as drug repurposing. With inflammatory pathways commonly shared among multiple conditions, there exists an opportunity to identify therapeutics with broader anti-inflammatory potential (Diez-Alarcia et al., 2019). These considerations form the basis for systematically reviewing in silico drug repurposing methods targeting inflammatory diseases. Inflammatory diseases have become a global public health concern due to their high prevalence, long-term disability outcomes, and associated healthcare costs.

According to the World Health Organization (WHO, 2020), chronic inflammatory conditions rank among the leading causes of mortality and morbidity worldwide. Rheumatoid arthritis alone affects approximately 0.5–1% of the global population (Romero-Duran et al., 2015), and over 10 million people live with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis (Cheng et al., 2018). The burden is not limited to industrialized nations; recent data indicate a rapid increase in the incidence of autoimmune inflammatory disorders in low- and middle-income countries, driven by urbanization, lifestyle changes, and environmental exposures (Liang et al., 2019). This global shift highlights the urgency of accessible, affordable, and effective therapeutic interventions. Unfortunately, the high cost of biologics and small molecule immunomodulators poses a significant barrier to treatment in resource-constrained settings (Kuo et al., 2013). For instance, TNF-a inhibitors and JAK inhibitors, though effective, remain prohibitively expensive for many patients without adequate insurance coverage or access to public healthcare programs. Consequently, there is an unmet clinical need for affordable alternatives. Drug repurposing presents a compelling solution by capitalizing on the global availability of approved medications whose pharmacodynamics are well-understood and whose supply chains are already established (Minie et al., 2014). Furthermore, regulatory frameworks such as the FDA's 505(b)(2) pathway and the European Medicines Agency's

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

Figure 2: Benefits of In Silico Drug Repurposing for Inflammatory Diseases



hybrid applications allow for streamlined repurposing efforts, reducing the need for extensive preclinical testing (Fine et al., 2020). The international impact of these diseases and the economic barriers to treatment underscore the importance of identifying low-cost therapeutic alternatives through systematic and scalable methodologies. Drug repurposing, particularly when informed by computational approaches, offers a high-throughput and economically viable strategy to address these global health challenges (Kleandrova et al., 2020). As such, the strategic intersection of global health needs and computational innovation forms a critical axis for modern therapeutic research. In silico methodologies—encompassing computational modeling, molecular docking, and virtual screening—have revolutionized the landscape of drug repurposing by offering a rapid, cost-effective means of identifying potential drug-target interactions (Speck-Planche & Kleandrova, 2020). These approaches rely on molecular dynamics, ligand-receptor affinity prediction, and structural bioinformatics to evaluate the suitability of existing drugs for novel indications (Bento et al., 2013). In the context of inflammatory diseases, which involve complex immune pathways and multiple protein targets, these computational tools facilitate the simultaneous analysis of thousands of drug compounds against a spectrum of validated or putative targets (Santos et al., 2017). Molecular docking, a cornerstone of in silico repurposing, predicts the optimal binding orientation and affinity of a ligand within the active site of a protein (Yamanishi, 2012). Virtual screening extends this methodology by applying it to large chemical libraries, including FDA-approved drugs, investigational compounds, and natural products (Sato et al., 2020). Software platforms such as AutoDock, Schrödinger Glide, MOE, and GOLD have become standard tools for such analyses due to their high sensitivity and specificity (Chopra et al., 2016). Integration with cheminformatics databases like DrugBank, ChEMBL, and PubChem enhances the efficiency and accuracy of these tools (Speck-Planche, 2018).

Notably, recent studies have successfully employed in silico docking to identify repurposing candidates for interleukin inhibitors, JAK-STAT modulators, and NF-κB pathway blockers, all of which are key players in inflammatory signaling (Kim et al., 2021). This reflects the versatility and clinical relevance of computational repurposing in inflammation-targeted pharmacology. Moreover, the ability to predict ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties using in silico tools further strengthens their utility in early-stage drug development (Kleandrova et al., 2021). Understanding the molecular basis of inflammation is pivotal to identifying effective drug repurposing targets. Inflammatory diseases are mediated by a network of cytokines, chemokines, signaling pathways, and effector cells that interact in a complex and often redundant fashion (Cheng et al., 2020). Key molecular players include tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), cyclooxygenase enzymes (COX-1/2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway (Fradera & Babaoglu, 2017).

These molecular targets have guided traditional drug development, but they also present viable candidates for in silico repurposing strategies (Gentile et al., 2020). For instance, NF-κB is a central transcription factor in inflammatory signaling and is activated by a wide range of stimuli, including

microbial pathogens, stress signals, and cytokines (Korkmaz, 2020). Targeting this pathway has proven effective in reducing inflammation in autoimmune diseases, making it an attractive node for computational drug screening (Stokes et al., 2020). Similarly, inhibitors of JAK enzymes such as tofacitinib and baricitinib have demonstrated efficacy in rheumatoid arthritis and ulcerative colitis, suggesting that other JAK-targeting drugs could be repurposed for related conditions (Zong et al., 2017). In silico studies often focus on docking candidate drugs into the active sites of these molecular targets to predict binding affinities and possible inhibitory effects (Zeng et al., 2019). Integrating transcriptomic and proteomic data further refines target selection and enhances predictive power (Zhang et al., 2021).

The principal objective of this systematic review is to comprehensively synthesize and evaluate existing research on the application of in silico drug repurposing techniques—specifically molecular docking and virtual screening—in the identification of therapeutic candidates for inflammatory diseases. This review aims to consolidate findings from a wide range of studies that have utilized computational methodologies to predict novel uses of already approved or clinically tested drugs targeting molecular pathways implicated in inflammatory pathophysiology. Given the increasing reliance on computational tools to accelerate the drug discovery pipeline, it becomes essential to systematically map the methodological approaches, protein targets, compound libraries, docking algorithms, and validation frameworks employed across these studies. The review is designed to provide clarity on the robustness, reproducibility, and translational potential of these computational strategies by critically analyzing the methodological rigor, consistency of scoring metrics, and the biological relevance of the predicted interactions. A secondary objective is to assess the diversity and relevance of inflammatory disease models used in the selected studies, including conditions such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, inflammatory bowel disease, and other immune-mediated inflammatory disorders. The review will examine the alignment of in silico findings with known immunological pathways—such as NF-κB, JAK-STAT, MAPK, and COX signaling—alongside the frequency and distribution of drug classes identified for repurposing. Another key objective is to explore the extent of integration between computational predictions and downstream in vitro or in vivo validation studies, with a focus on how computational hits have progressed in the drug development continuum. By achieving these goals, the review will provide researchers, clinicians, and pharmacologists with a detailed landscape of current advancements in computational drug repurposing for inflammatory diseases, enabling better prioritization of candidate molecules for further experimental investigation and clinical testing.

LITERATURE REVIEW

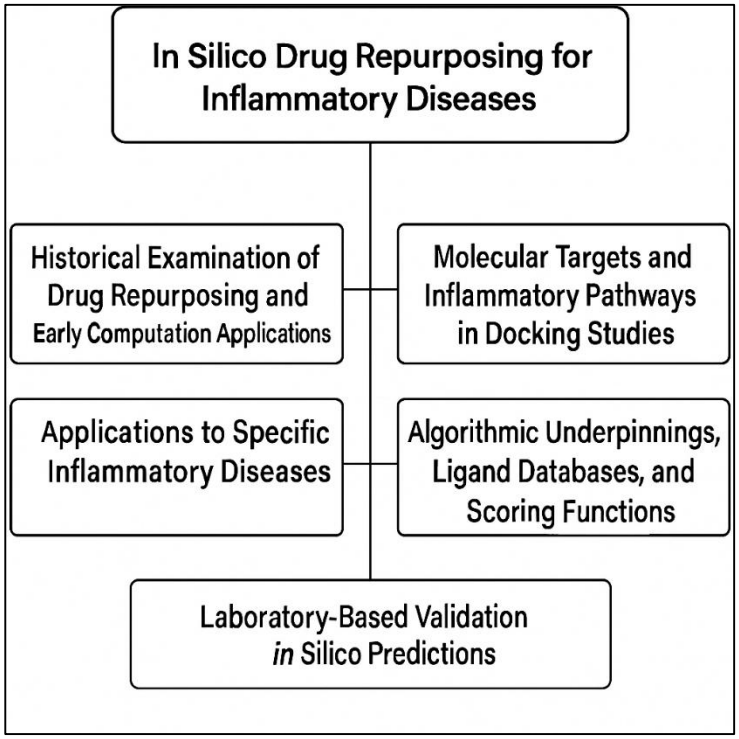
The application of in silico methodologies—particularly molecular docking and virtual screening—for drug repurposing in the treatment of inflammatory diseases has garnered significant scholarly attention over the past two decades. These computational strategies have been increasingly adopted due to their ability to systematically identify potential therapeutic agents within existing drug libraries, thereby overcoming the time and financial constraints associated with conventional drug discovery. This literature review explores the evolution, scope, and impact of in silico drug repurposing in the context of inflammation-focused pharmacology. It synthesizes a wide body of interdisciplinary research spanning bioinformatics, immunology, cheminformatics, and systems pharmacology. A systematic organization of this literature is necessary to delineate methodological frameworks, computational tools, and specific disease applications that have been central to the field's progress. The review begins with a historical examination of drug repurposing and early computational applications, providing the contextual grounding needed to understand current innovations. It then investigates the core molecular targets and inflammatory pathways that guide docking studies, followed by detailed discussions of the algorithmic underpinnings, ligand databases, and scoring functions used to identify candidate molecules. The section further evaluates studies applying these techniques to specific inflammatory diseases, highlighting both successful repurposing efforts and methodological limitations. The literature is additionally examined for the extent to which in silico predictions have been corroborated by laboratory-based validation, including in vitro and in vivo studies. Collectively, this structured literature review offers a multidimensional analysis of computational repurposing research and its implications for anti-inflammatory drug development.

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

Drug Repurposing and Computational Methods

Drug repurposing, or repositioning, emerged as a viable strategic alternative to traditional drug discovery processes in response to escalating development costs, protracted timelines, and declining success rates in pharmaceutical research. Traditional de novo drug development often requires upwards of 12–15 years and investment exceeding $2 billion to bring a new compound to market (Prado-Prado et al., 2012). In contrast, drug repurposing allows researchers to leverage existing safety, pharmacokinetic, and toxicological data from approved or previously investigated compounds, thereby circumventing early-phase testing and accelerating clinical translation (Wang et al., 2019). The repurposing paradigm gained widespread attention with the repositioning of thalidomide for multiple myeloma and sildenafil for erectile dysfunction—both of which were initially developed for other indications but later found substantial therapeutic efficacy in new disease domains (Wisner et al., 2019).

Figure 3: Key Components of In Silico Drug Repurposing for Inflammatory Diseases



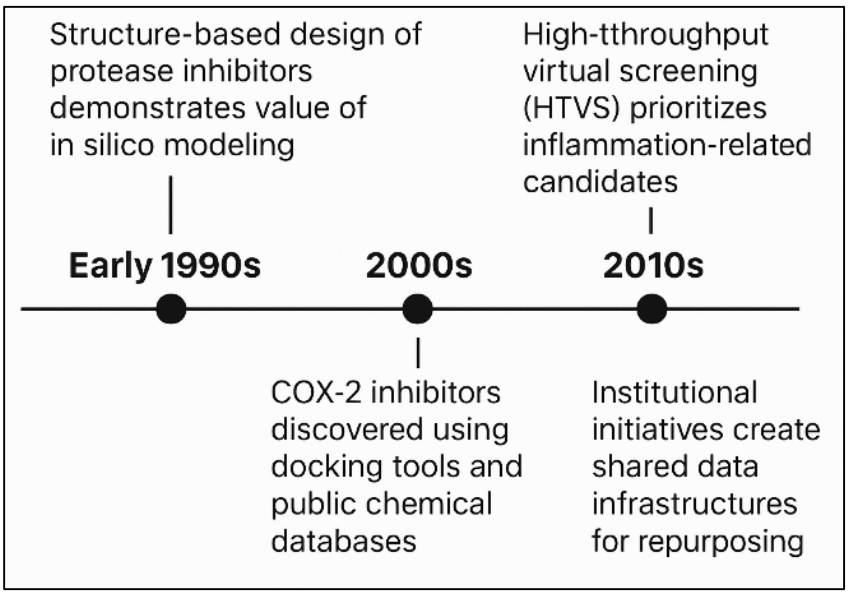
This shift toward therapeutic redeployment is also driven by the evolving regulatory landscape, with streamlined approval pathways such as the FDA's 505(b)(2) mechanism and the EMA's hybrid applications, which facilitate faster market access for repurposed agents (Mouchlis et al., 2021). Moreover, the financial appeal of repurposing has made it particularly attractive to academic institutions, small biotech firms, and non-profit research organizations that lack the resources to pursue full-scale drug development (Kuhlman & Bradley, 2019). Several consortia, including the NIH's NCATS and the UK-based MRC/Innovate UK Repurposing Network, have institutionalized drug repurposing as a core component of translational science initiatives (Bertsimas & Shioda, 2007). In the context of inflammatory diseases, which often exhibit complex and overlapping pathophysiological features, repurposing offers a rational and efficient approach to discovering multi-target therapies. The growing recognition of polypharmacology—the idea that a single drug may act on multiple targets—further supports repurposing for conditions such as rheumatoid arthritis and systemic lupus erythematosus, where multi-modal intervention is desirable (Bertsimas & Shioda, 2007). Thus, the emergence of drug repositioning as a strategic imperative represents a confluence of economic, regulatory, and scientific forces reshaping the pharmaceutical landscape.

The initial integration of computational tools into drug discovery began as a means to complement and rationalize traditional medicinal chemistry workflows. Early computer-aided drug design (CADD) methods, dating back to the 1980s and 1990s, focused on structure-activity relationships (SAR),

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

quantitative structure-activity relationships (QSAR), and molecular similarity analyses to predict the biological activity of compounds based on their chemical structures (Bertsimas & Shioda, 2007). These early computational frameworks laid the groundwork for molecular modeling by allowing chemists to generate predictive hypotheses about ligand binding and receptor interactions prior to experimental testing. The refinement of three-dimensional structural data, enabled by advances in X-ray crystallography and nuclear magnetic resonance spectroscopy, significantly improved the accuracy of in silico modeling, ushering in a new era of rational drug design.

Figure 4: Timeline of Key Milestones in In Silico Drug Repurposing for Inflammatory Diseases



One of the earliest successes in computational drug discovery was the structure-based design of HIV protease inhibitors, including saquinavir and ritonavir, which demonstrated the value of computer modeling in guiding molecular optimization. These milestones catalyzed the integration of docking software tools such as AutoDock and DOCK into academic and industrial research pipelines (Tanoli et al., 2021). Inflammatory diseases, though not initially the primary focus of computational modeling, later became central to the development of kinase inhibitors and COX-2 selective agents due to their well-characterized active sites and structural templates (Vanunu et al., 2010). The digitization of pharmacological data via public databases such as PubChem, PDB, and DrugBank further enabled computational scientists to conduct large-scale docking studies and compound similarity searches (Trott & Olson, 2009). These early computational applications provided a proof-of-concept that accelerated hypothesis-driven drug discovery could be achieved using digital tools. They also laid the methodological foundation for more complex strategies such as virtual screening, molecular dynamics simulations, and systems pharmacology. As inflammation-related targets became better structurally characterized, computational methods gained prominence in screening candidate molecules against cytokine receptors, kinases, and transcription factors implicated in immune dysregulation (Morris et al., 2009). The evolution from rational, target-driven drug design to high-throughput in silico screening methodologies marks a critical inflection point in computational drug repurposing. Rational design is predicated on detailed knowledge of a single molecular target and a ligand's precise interaction with its binding site, often leading to highly specific, structurally optimized compounds (Aquaro et al., 2010). However, this paradigm is limited in scope when dealing with multifactorial diseases like autoimmune and inflammatory disorders, where numerous signaling cascades and molecular nodes contribute to disease pathology (Aquaro et al., 2010). To address these complexities, computational research shifted toward high-throughput virtual screening (HTVS), which enables the simultaneous evaluation of thousands to millions of compounds against multiple biological targets in silico.

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

HTVS employs docking algorithms that estimate ligand binding affinity by simulating intermolecular interactions within protein active sites. Software platforms such as AutoDock Vina, Glide, and GOLD utilize scoring functions based on free energy calculations, hydrogen bonding, hydrophobic contacts, and electrostatic complementarity (Bhattarai et al., 2019). These tools allow for rapid prioritization of drug candidates based on predicted binding strength and pose accuracy. In the realm of inflammation research, HTVS has been used to identify COX-2 inhibitors, JAK-STAT modulators, and NF-κB pathway inhibitors from both approved and investigational drug libraries (Li et al., 2009). Large-scale compound libraries such as ZINC, ChEMBL, and DrugBank serve as repositories for HTVS, providing curated datasets of bioactive molecules suitable for repositioning efforts (Minie et al., 2014). The integration of these platforms with cheminformatics tools and ADMET predictors has further streamlined the identification of drug-like, non-toxic candidates (Yella et al., 2018). As computational power has increased and algorithmic accuracy has improved, HTVS has become indispensable in prioritizing candidates for downstream biological validation, particularly in diseases where the immune landscape is dynamic and polygenic.

The mainstreaming of in silico repurposing paradigms is also reflected in institutional research agendas and public–private consortia aimed at accelerating drug discovery through data-driven science. The National Institutes of Health (NIH) launched the NCATS Drug Repurposing Program to systematize and fund computational repurposing projects across disease domains, including inflammatory conditions (Speck-Planche & Kleandrova, 2020). Similar initiatives, such as the Open Targets Platform and the European Innovative Medicines Initiative (IMI), have created shared infrastructures for integrating genomic, proteomic, and pharmacological data to support drug-target prediction models (Mayilvaganan & Sabitha, 2013). These efforts are supported by the growing emphasis on FAIR data principles—ensuring that scientific datasets are Findable, Accessible, Interoperable, and Reusable—thus fostering transparency and reproducibility in computational workflows (Rodríguez-Vázquez et al., 2018). Academic centers have also developed specialized platforms such as CANDO (Computational Analysis of Novel Drug Opportunities) and CLUE (Connectivity Map User Environment) to facilitate large-scale repurposing through network pharmacology and transcriptional signature reversal (Chopra et al., 2016). Studies using these tools have identified promising repositioning candidates for inflammatory diseases by cross-matching drug-induced gene expression changes with disease signatures (Jobst et al., 2001). The proliferation of web-based docking tools like SwissDock and web servers for ADMET analysis has made in silico repurposing accessible to a wider range of researchers, including those in low-resource settings (Kleandrova et al., 2021). The institutional embrace of computational repurposing is thus not merely a technological phenomenon but a strategic reorientation of biomedical research. By integrating structural biology, computational chemistry, bioinformatics, and systems pharmacology into cohesive platforms, these initiatives have accelerated the identification of repurposable compounds for inflammation and beyond. The increasing volume of peer-reviewed studies, government funding, and interdisciplinary collaboration illustrates the establishment of in silico repurposing as a core modality in translational pharmacology.

Molecular Targets and Inflammatory Pathways in Drug Repurposing

Chronic inflammatory diseases are largely mediated by a network of pro-inflammatory cytokines, with tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) playing central roles in the pathogenesis of autoimmune and inflammatory disorders. TNF-α is a multifunctional cytokine produced primarily by macrophages and T-cells, exerting effects such as endothelial activation, promotion of leukocyte recruitment, and induction of other cytokines (Wu et al., 2016). TNF-α is implicated in rheumatoid arthritis, Crohn's disease, and psoriasis, making it a validated therapeutic target, as evidenced by the clinical success of inhibitors like infliximab, etanercept, and adalimumab (Yoshimura, 2018). IL-6 is another key cytokine that bridges innate and adaptive immunity, activating B-cell proliferation and the acute phase response via the JAK/STAT pathway (Park & Baek, 2020). Elevated IL-6 levels are characteristic of systemic lupus erythematosus, juvenile idiopathic arthritis, and giant cell arteritis (Jin et al., 2019). The efficacy of tocilizumab, an IL-6 receptor blocker, further supports IL-6's relevance as a repurposing target (Almatroodi et al., 2020). IL-1β is a potent mediator of tissue inflammation, produced as an inactive precursor and activated through inflammasome-mediated cleavage (Schrank et al., 2018). Its role in autoinflammatory diseases, such as familial Mediterranean fever and Still's disease, has led to successful interventions using IL-1 inhibitors like anakinra and canakinumab (Wu et al., 2017). The overexpression of these

cytokines in multiple inflammatory contexts has made them recurrent molecular targets in in silico docking studies aiming to repurpose anti-neoplastic, anti-microbial, or antidiabetic drugs for inflammatory indications (Cattani-Cavalieri et al., 2020). Computational repurposing studies frequently dock approved drugs into the receptor binding domains or signal transduction regions of TNF-α, IL-6R, and IL-1R to evaluate interaction affinities and stability (Goh et al., 2016). The biological significance and validated druggability of these cytokines position them as ideal candidates for computational screening strategies. The intricate signaling networks governing chronic inflammation rely heavily on transcription factors and kinase cascades such as NF-κB, JAK/STAT, MAPK, and COX pathways. These systems regulate the expression of cytokines, chemokines, adhesion molecules, and inflammatory enzymes, driving the pathophysiology of diseases like rheumatoid arthritis, ulcerative colitis, and asthma (Yana Zhang et al., 2021). NF-κB, a dimeric transcription factor, is sequestered in the cytoplasm by IκB proteins and becomes active upon phosphorylation by IκB kinase (IKK), leading to nuclear translocation and gene transcription (Greten et al., 2004). Its upregulation in synovial tissues, gut mucosa, and airway epithelium has made it a pivotal docking target in in silico repurposing studies (Caetano et al., 2016). Drugs like parthenolide, celastrol, and sulfasalazine have been modeled in docking simulations against the p65 and IKKβ domains, demonstrating potential anti-inflammatory effects through NF-κB inhibition (Markowitz et al., 2018).

The JAK/STAT pathway functions downstream of cytokine receptors, especially IL-6 and IFN-γ, and plays a critical role in promoting T-helper cell differentiation and inflammatory cytokine production (Grivennikov et al., 2010). JAK inhibitors such as tofacitinib and ruxolitinib were originally developed for hematological conditions but are now repurposed and approved for inflammatory diseases due to their blockade of STAT1/3 activation (Moll & Kuemmerle-Deschner, 2013). MAPK signaling—comprising p38, JNK, and ERK cascades—regulates cytokine translation and cellular responses to stress stimuli (Bent et al., 2018). Inhibitors targeting p38 MAPK have been computationally screened and validated for applications in arthritis and colitis models (Lappalainen et al., 2005). Cyclooxygenase (COX) enzymes, particularly COX-2, catalyze prostaglandin synthesis, mediating pain and inflammation in autoimmune disease. COX-2 selective inhibitors like celecoxib have been used in both clinical and computational frameworks to assess inflammation modulation (Qu et al., 2015). In silico models dock these drugs into the hydrophobic channel of COX-2, confirming interaction energy and specificity. Together, these pathways represent converging points of inflammatory regulation and serve as consistent targets in drug repurposing simulations.

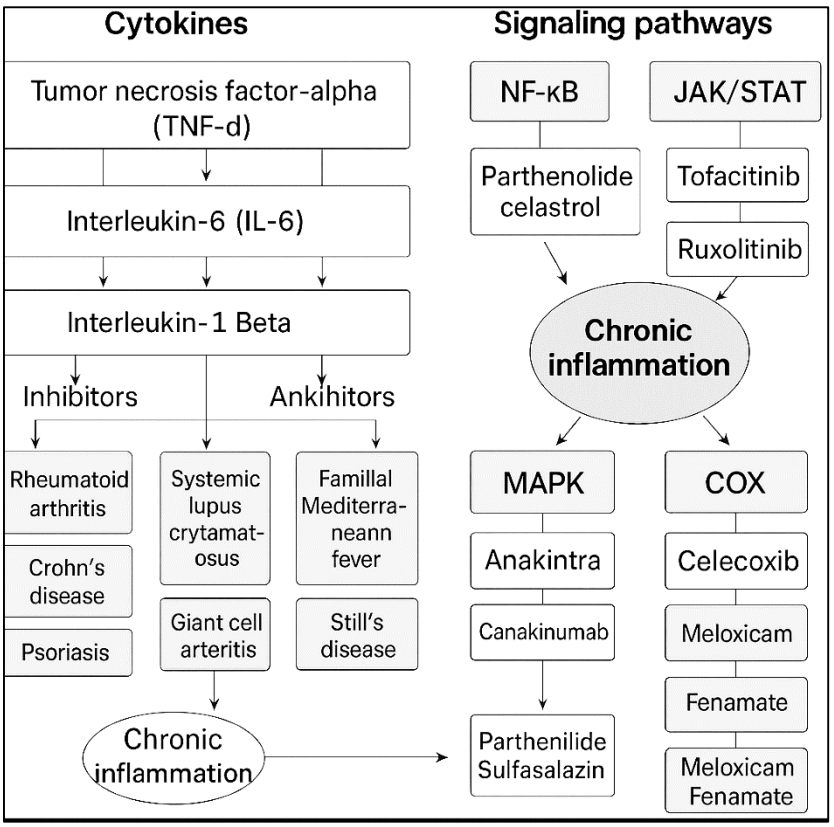
The structure-function relationship of target proteins is a cornerstone of successful molecular docking, as the accuracy of in silico predictions depends heavily on the availability of crystallographic or homology-modeled protein structures. For key inflammatory targets, such as TNF-α, IL-6 receptor, and NF-κB, detailed structural elucidations have allowed for the identification of druggable pockets, hydrogen bonding sites, and conformational flexibilities critical for ligand interaction (Shi et al., 2021). TNF-α, for instance, forms a trimeric structure with a central binding groove for its receptors. Small molecules or peptidomimetics can be computationally designed to block this interface, thus preventing downstream pro-inflammatory signaling (Altorki et al., 2018). Similarly, the IL-6 receptor complex—comprising IL-6, IL-6Rα, and gp130—possesses a modular architecture with defined binding interfaces for signal transmission, which have been the focus of numerous docking studies aimed at disrupting signal propagation (Yang et al., 2021). The STAT3 SH2 domain is a frequent docking site in computational repurposing due to its role in dimerization and nuclear translocation following JAK phosphorylation (Anzar et al., 2018). Inhibitors targeting this pocket have shown high binding affinity in simulations and efficacy in inflammation models.

The IκB kinase complex, particularly IKKβ, presents a kinase domain with an ATP-binding cleft that is amenable to small molecule inhibition. Structural studies have identified key residues like Lys44, Glu97, and Asp166 critical for catalytic activity, guiding docking studies that evaluate competitive inhibitors (Kalinke et al., 2020). In MAPK cascades, the p38α isoform has a well-defined DFG motif and activation loop, which are commonly exploited in ligand-binding models (Cheng & Eroglu, 2021). COX-2, in contrast to COX-1, possesses a valine at position 523 that creates a side-pocket accessible to larger ligands—an anatomical distinction that has been crucial for selective docking of coxibs (Kaneko et al., 2019). These structural insights not only inform the precision of docking but also determine ligand binding orientation, conformational flexibility, and entropic considerations in drug-target interaction. As such, understanding the structural biology of these inflammatory targets is indispensable for rational docking and accurate affinity prediction in computational repurposing.

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

Figure 5:

Figure 6: Molecular Targets and Inhibitors in Chronic Inflammation



Methodological Frameworks for Molecular Docking and Virtual Screening

Virtual screening (VS) is an essential computational strategy for identifying potential therapeutic candidates from large chemical libraries. It operates through two main paradigms: structure-based virtual screening (SBVS) and ligand-based virtual screening (LBVS), each employing distinct methodologies depending on the availability of target structural data. SBVS relies on the three-dimensional (3D) structure of a biological target—typically derived from X-ray crystallography, NMR spectroscopy, or homology modeling—to dock small molecules into the active or allosteric binding sites of proteins (Alam & Khan, 2017). The primary objective in SBVS is to predict ligand binding orientation and affinity based on structural complementarity and thermodynamic stability (Mouchlis et al., 2021). This method is especially advantageous when high-resolution protein structures are available, such as for COX-2, p38 MAPK, or JAK2, all of which are frequent targets in inflammation-related docking studies (Kuhlman & Bradley, 2019). Conversely, LBVS is used when the 3D structure of the protein is unknown or not reliably resolved. Instead, this method leverages the structural and physicochemical similarity of known ligands to identify new compounds with potential bioactivity (Breger et al., 2007). Tools like pharmacophore modeling, molecular fingerprints, and quantitative structure–activity relationship (QSAR) models are commonly employed in LBVS to predict molecular function based on established chemical patterns (Zhang et al., 2016). This approach has been useful for repurposing drugs with established anti-inflammatory effects across similar cytokine targets, such as repositioning JAK inhibitors across IL-6, IFN-γ, and GM-CSF receptor systems.

Although both paradigms are powerful, SBVS is generally preferred in repurposing studies due to its mechanistic insights into ligand-target interactions, especially when repurposing drugs against structurally validated targets like TNF-α or NF-κB components (Chen et al., 2019). However, integrating SBVS with LBVS often yields complementary results, enhancing hit prioritization and reducing false positives. This hybrid approach reflects the evolving sophistication of virtual screening workflows in modern repurposing research. The success of molecular docking as a predictive tool in drug repurposing largely depends on the choice of algorithms and scoring functions, which determine the quality of pose prediction and binding affinity estimation. Among the most widely

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

used docking platforms is AutoDock, which uses a Lamarckian genetic algorithm for pose optimization and a semi-empirical free energy force field for scoring (He et al., 2022). Its successor, AutoDock Vina, introduced a significantly faster algorithm with improved accuracy by optimizing scoring based on conformational entropy and hydrogen bond formation (Wu et al., 2016). Vina is particularly popular in high-throughput screening due to its ease of use and relatively accurate energy estimation, and has been widely employed in repurposing efforts targeting inflammatory proteins such as IL-1β, JAK2, and COX-2 (Eberhardt et al., 2021). Other powerful tools include GOLD (Genetic Optimization for Ligand Docking), which applies a genetic algorithm to explore flexible ligand conformations and allows full protein flexibility at the binding site, increasing accuracy for difficult targets (Trott & Olson, 2009). Glide, developed by Schrödinger, incorporates a grid-based scoring function and employs hierarchical filters that balance speed with exhaustive sampling, making it ideal for pharmacophore-based screening and flexible docking of kinase inhibitors (Trott & Olson, 2009). Molecular Operating Environment (MOE) offers another popular suite that combines docking with QSAR and ADMET tools, supporting integrated cheminformatics workflows.

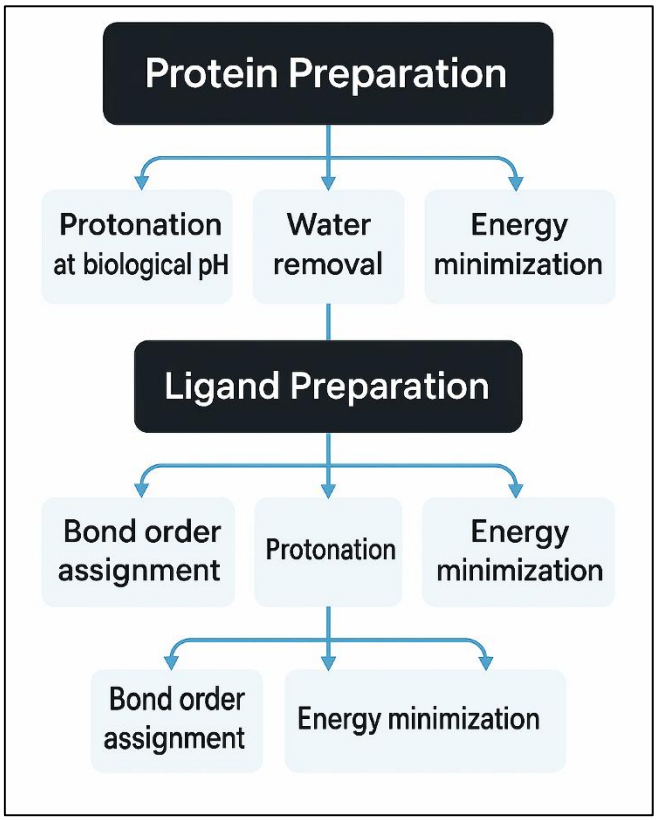
Scoring functions typically assess binding based on hydrogen bonding, van der Waals interactions, desolvation energies, and electrostatics. Some platforms like AutoDock use empirical scoring, while others like Glide incorporate machine learning-enhanced scoring to improve selectivity (Goodsell et al., 1996). Consensus scoring—combining multiple algorithms—has become a best practice to reduce individual model bias and improve predictive reliability (Gómez-Bombarelli et al., 2018). Therefore, selecting and validating appropriate docking tools is a methodological cornerstone of accurate in silico repurposing. Achieving accurate docking results necessitates the careful configuration of simulation environments, as docking accuracy is highly sensitive to protein and ligand preparation, search algorithms, grid resolution, and solvent modeling. The first critical step involves preparing the protein target, typically through protonation, removal of water molecules, and energy minimization, which ensures that docking occurs in a biologically relevant conformational state (Altschul et al., 1990). Ligand preparation similarly requires optimizing bond orders, protonation states, and energy minimization using force fields such as MMFF94 or OPLS3e (Chipuk et al., 2010). Moreover, Grid box parameters in structure-based docking define the spatial boundaries for ligand placement, making their selection crucial for ensuring that active binding pockets are comprehensively explored (Andersson et al., 2014). AutoDock Vina and GOLD allow for flexible grid construction, with advanced options for targeting known allosteric sites and subpockets (Speck-Planche & Scotti, 2018). Solvent effects, often neglected in early docking models, are now increasingly incorporated through implicit solvation models or by applying post-docking free energy calculations using MM-PBSA or MM-GBSA methods (Laraia et al., 2018).

Another important aspect involves setting the exhaustiveness and number of docking poses to be generated. High exhaustiveness improves conformational sampling at the cost of computational time, while multiple pose generation helps avoid false positives by analyzing binding mode consistency (Curti et al., 2019). In systems with flexible binding sites such as kinase loops or coiled-coil domains, induced-fit docking and ensemble docking—using multiple receptor conformations—can improve reliability (Rodriguez et al., 2006). Validation of docking results through redocking known ligands and calculating root mean square deviation (RMSD) further strengthens confidence in binding predictions (Li et al., 2009). The cumulative precision of docking outcomes depends on each parameter's contribution to the chemical and structural fidelity of the model. Proper parameterization is therefore not a technical afterthought but a methodological imperative in ensuring that computational repurposing yields biologically meaningful and experimentally testable predictions. Several inflammation-focused repurposing studies have implemented integrated virtual screening pipelines that combine SBVS, LBVS, docking, ADMET filtering, and molecular dynamics simulation into a unified workflow. A common approach begins with the curation of ligand libraries from DrugBank, ZINC15, or ChEMBL, followed by filtering based on Lipinski's rule of five and Veber's criteria to ensure drug-likeness (Chiang et al., 2018). These libraries are then subjected to SBVS against pro-inflammatory targets such as NF-κB, COX-2, JAK1/2, and IL-6R using docking engines like AutoDock Vina or Glide (Liang et al., 2019). Following docking, compounds are ranked based on binding energies, and top hits are further evaluated using ADMET predictors such as SwissADME, pkCSM, or admetSAR to exclude compounds with poor absorption, toxicity, or metabolic instability (Kuo et al., 2013). Next, molecular dynamics (MD) simulations are often conducted using GROMACS or AMBER to validate the stability of drug-protein complexes under physiological conditions (Chung

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

et al., 2017). RMSD, radius of gyration, and hydrogen bond analysis are used to confirm interaction stability and ligand retention within the binding site (Bolcato et al., 2019). Repurposing pipelines have led to promising candidates such as parthenolide, lapatinib, and sunitinib for NF-κB inhibition and anti-inflammatory action (Minie et al., 2014). Similarly, baricitinib, originally developed for myelofibrosis, was computationally screened and validated for rheumatoid arthritis and later COVID-19 inflammatory complications (Schroeder et al., 2018). These pipelines demonstrate how methodologically layered workflows yield candidates with both mechanistic validity and favorable drug profiles. They also highlight the growing complexity and modularity of repurposing approaches tailored for inflammatory diseases.

Figure 7: Preprocessing Pipeline for Docking: Protein and Ligand Optimization



Ligand Libraries and Cheminformatics Resources

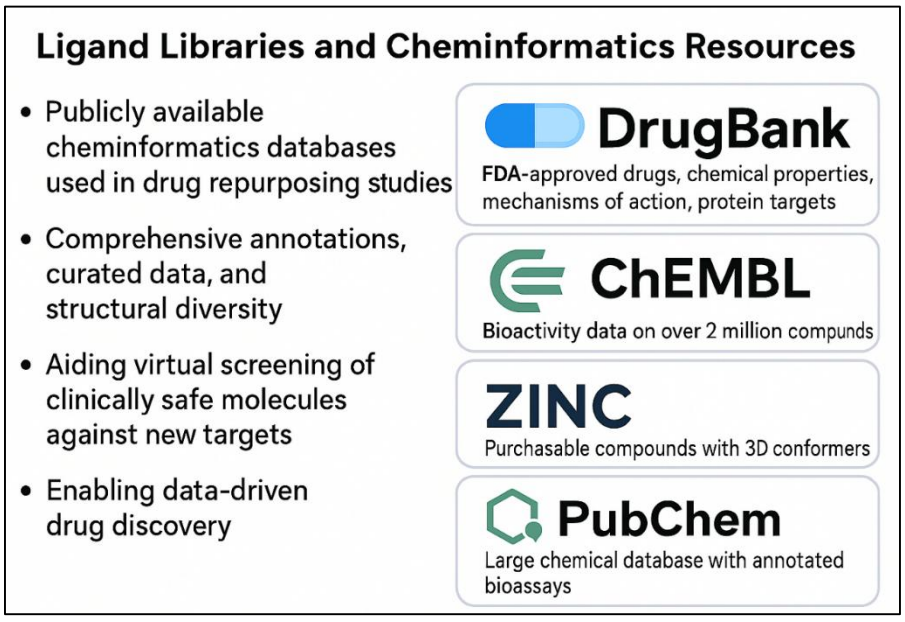
Publicly available cheminformatics databases have become essential resources for assembling ligand libraries used in drug repurposing studies. Among these, DrugBank, ChEMBL, ZINC, and PubChem are most frequently employed due to their comprehensive annotations, curated data, and structural diversity. DrugBank provides information on FDA-approved drugs, investigational agents, their chemical properties, mechanisms of action, and protein targets (Mouchlis et al., 2021). This database is widely used for in silico repurposing as it enables the screening of clinically safe molecules against new targets. For instance, Daina et al. (2017) used DrugBank to source molecules for docking against JAK-STAT pathway targets in inflammatory disease studies, leveraging the pre-existing pharmacokinetic and toxicity profiles. ChEMBL is another highly cited resource, containing bioactivity data on over 2 million compounds, including half-maximal inhibitory concentrations (IC50), binding affinities (Ki), and target information (Ciancetta et al., 2014). It has been utilized to identify compounds with anti-inflammatory potential through similarity-based screening and machine learning models (Sui et al., 2018). ZINC, with over 230 million purchasable compounds, supports structure-based virtual screening by providing ready-to-dock 3D molecular conformers (Chen et al., 2019). Studies such as those by Wallach et al. (2015)and Eberhardt et al.(2021) used ZINC libraries for high-throughput docking against targets like COX-2 and NF-κB.

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

PubChem, hosted by the NIH, offers one of the largest chemical databases with annotated bioassays, enabling large-scale virtual screening of compounds against inflammation-related proteins (Morris et al., 2009). Its integration with BLAST, PDB, and other NCBI tools enhances its utility in multi-dimensional docking studies. For example, Goodsell et al. (1996) accessed PubChem for ligand sets targeting IL-1β in rheumatoid arthritis. These repositories have significantly democratized access to chemical information, allowing researchers globally to conduct high-quality computational repurposing without proprietary software or commercial libraries (Bolcato et al., 2019). Their widespread adoption underscores their central role in enabling data-driven drug discovery. Chemical diversity and drug-likeness filters are crucial criteria for selecting compounds with therapeutic potential in drug repurposing. Virtual screening campaigns often begin by filtering compound libraries to exclude molecules with undesirable pharmacokinetic or toxicological profiles, thereby improving the probability of downstream success (Fine et al., 2020). The most commonly applied criteria include Lipinski's Rule of Five, which sets thresholds for molecular weight, lipophilicity (logP), hydrogen bond donors, and acceptors to evaluate oral bioavailability (Lipinski, 2004). Additional rules such as Veber's criteria, Ghose filter, and the Egan rule are used to assess flexibility, topological polar surface area, and permeability (Morrone et al., 2020).

SwissADME and pkCSM are among the most utilized tools for in silico ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction, providing parameters such as gastrointestinal absorption, blood-brain barrier permeability, and cytochrome P450 inhibition (Tsou et al., 2020). Studies by Anighoro et al. (2015) and Fradera and Babaoglu (2017) have all incorporated these filters to eliminate compounds with poor metabolic stability or high predicted toxicity, especially when repurposing anticancer agents for inflammatory targets. Chemical diversity is also maintained by clustering compounds based on molecular fingerprints, such as MACCS keys or ECFP4, to ensure that the virtual screening space is not biased toward structurally redundant molecules (Gaieb et al., 2017). Fingerprint-based clustering allows researchers to sample diverse scaffolds with varying physicochemical properties and potential interaction profiles. This approach was applied by Gaieb et al. (2019) and Gathiaka et al. (2016) in screening against MAPK and JAK family kinases. The retention of chemically diverse and drug-like compounds not only reduces attrition rates but also increases the likelihood of identifying novel scaffolds with multi-target potential. These practices have collectively enhanced the predictive quality and translational relevance of computational repurposing workflows by ensuring that only compounds with favorable biological and chemical profiles are advanced for docking and simulation.

Figure 8: Key Databases Supporting Ligand-Based Drug Repurposing and Virtual Screening



American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

Several drug classes consistently emerge in virtual screening studies targeting inflammatory pathways, often revealing unexpected therapeutic potential beyond their original indications. Kinase inhibitors, particularly JAK inhibitors and tyrosine kinase inhibitors (TKIs), are frequently identified due to their capacity to modulate cytokine signaling cascades, including IL-6 and IFN-γ pathways (Wu et al., 2017). Drugs like baricitinib, tofacitinib, and ruxolitinib have been repeatedly validated in computational and experimental studies for their broad anti-inflammatory activity (Öztürk et al., 2018). Nonsteroidal anti-inflammatory drugs (NSAIDs), especially COX-2 selective inhibitors such as celecoxib and etoricoxib, are also recurrent hits due to their structural compatibility with the COX-2 binding site and favorable docking scores (Jiménez-Luna et al., 2019). Several docking studies have re-evaluated these compounds in light of their dual inhibition potential across prostaglandin and NF-κB pathways (Mysinger et al., 2012). Moreover, antifungal and antimalarial agents such as itraconazole and artemisinin derivatives have shown high docking affinity for IL-1β, JAK2, and MAPK targets, suggesting previously unrecognized immunomodulatory effects (Allen et al., 2015).

Antineoplastic drugs including lapatinib, sunitinib, and sorafenib have also emerged as candidates due to their capacity to inhibit inflammatory kinases and transcription factors like NF-κB and STAT3 (Chaput & Mouawad, 2017). These compounds, originally designed for cancer, often exhibit anti-inflammatory properties through shared signaling mechanisms. Additionally, natural compounds such as curcumin, resveratrol, and parthenolide consistently appear in docking results for inflammatory targets due to their polyphenolic structures and multi-target interactions (Korb et al., 2009). The recurrence of these drug classes across docking studies suggests a convergence between drug chemical features and conserved inflammatory pathways. This reinforces the rationale for systematically re-evaluating known pharmacophores in new immunological contexts.

Cheminformatics tools have become indispensable in managing, filtering, and modeling ligand data during the early stages of drug repurposing pipelines. Tools such as RDKit, Open Babel, and DataWarrior enable the conversion, cleaning, and optimization of chemical structures, making them suitable for downstream modeling (Korb et al., 2009). RDKit, in particular, allows for batch calculation of physicochemical descriptors such as molecular weight, logP, rotatable bonds, and hydrogen bond counts, which are essential for applying drug-likeness filters (Choudhury, 2020). These descriptors are also used to build predictive QSAR models, facilitating ligand prioritization based on regression or classification outputs (Chan et al., 2015).

Moreover, Open Babel provides format conversion between major chemical file types (e.g., SDF, MOL2, PDBQT), ensuring compatibility between docking software like AutoDock and ligand databases such as ChEMBL or ZINC (Friesner et al., 2004). This functionality has been crucial in automated docking pipelines and HTVS campaigns, where large ligand libraries must be preprocessed efficiently. Meanwhile, DataWarrior combines cheminformatics with visualization tools to support chemical clustering, scaffold analysis, and SAR trend identification (Chen et al., 2019). These capabilities help researchers track chemical redundancy and identify unique scaffolds during repurposing studies. PaDEL-Descriptor and ChemAxon's Marvin suite further expand the cheminformatics toolkit by offering comprehensive descriptor sets, pKa prediction, and 2D/3D structure generation (Wislez et al., 2006). Such tools are frequently integrated into virtual screening workflows, as demonstrated in studies targeting COX-2, NF-κB, and JAK/STAT proteins (Singh & Villoutreix, 2022). Combining these tools with machine learning platforms like KNIME and WEKA enables the development of predictive models for anti-inflammatory activity, supporting evidence-based candidate prioritization (Wen et al., 2019). Altogether, cheminformatics tools provide the computational backbone for virtual screening, ensuring structural validity, chemical diversity, and data standardization throughout the ligand selection and evaluation process.

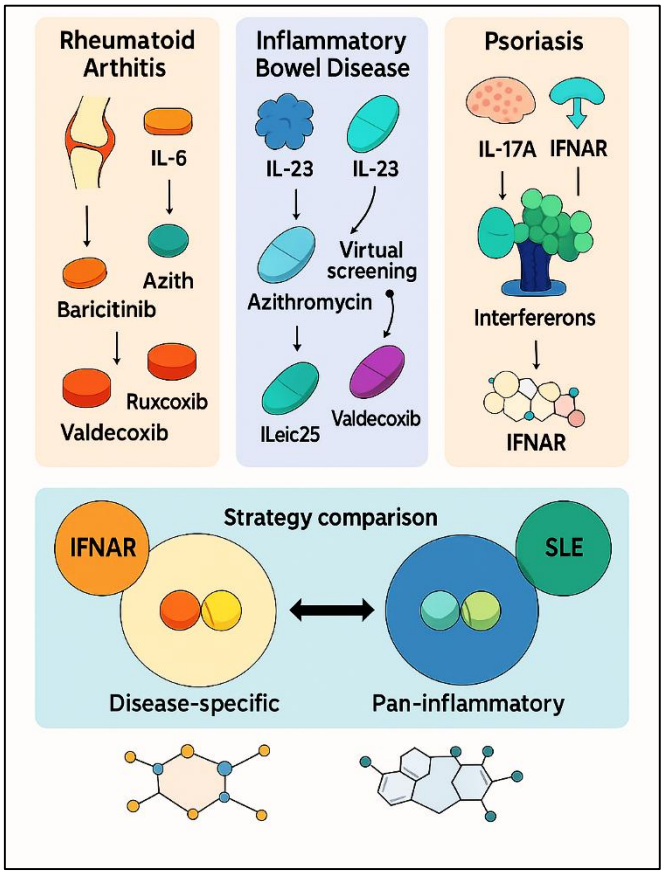
In Silico Repurposing Applications in Specific Inflammatory Diseases

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial membrane inflammation, pannus formation, and cartilage destruction, driven by a cascade of cytokines and inflammatory mediators. Central to RA pathogenesis are elevated levels of TNF-α, IL-6, and IL-1β, which promote leukocyte recruitment, angiogenesis, and matrix metalloproteinase activation within the synovial joint (Wang et al., 2019). In silico repurposing efforts have extensively targeted these cytokine networks by docking existing drugs into known active sites of their respective receptors or downstream kinases. Tundis et al. (2018) conducted docking simulations to identify TNF-α inhibitors among FDA-approved compounds, revealing strong binding affinities for anticancer agents like sunitinib and imatinib. Similarly, Urista et al. (2020) explored virtual screening of natural products

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

against IL-1β, identifying high-affinity interactions with resveratrol and curcumin. Moreover, the JAK/STAT pathway, particularly JAK1 and JAK3, also plays a significant role in RA, making it a prime docking target in repurposing studies (Tanoli et al., 2021). Tofacitinib, baricitinib, and ruxolitinib—originally developed for hematologic and dermatologic conditions—have been computationally modeled against JAK3 and validated in preclinical arthritis models performed a docking study using DrugBank and ZINC libraries to screen JAK inhibitors, identifying additional candidates including fedratinib and lestaurtinib. Several other studies used AutoDock and GOLD to simulate ligand binding within NF-κB and p38 MAPK, revealing that small molecules like parthenolide and lapatinib can modulate RA-associated gene expression (Talevi & Bellera, 2019).

Figure 9: In Silico Identification of Anti-Inflammatory Drug Candidates Across Autoimmune Diseases



Molecular dynamics (MD) simulations further validated the stability of ligand–protein interactions, enhancing confidence in the translational potential of docking hits (Chopra et al., 2016). These studies collectively underscore the utility of in silico approaches in rapidly identifying alternative therapies that disrupt cytokine-driven inflammation in RA, paving the way for experimental validation and clinical evaluation. Moreover, Inflammatory bowel disease (IBD), encompassing ulcerative colitis and Crohn's disease, is marked by dysregulated intestinal immune responses, mucosal barrier dysfunction, and chronic infiltration of pro-inflammatory cells. Key signaling mediators include IL-6, TNF-α, IL-23, and toll-like receptors (TLRs), all of which have become central targets in computational repurposing studies (Ahmed et al., 2022). The JAK/STAT pathway is especially relevant, as IL-6 and IL-23 signal through JAK1 and JAK2, triggering STAT3-mediated transcription of inflammatory genes. Kleandrova et al. (2021) and Cheng et al. (2020) demonstrated the clinical efficacy of JAK inhibitors like tofacitinib and upadacitinib, which have been extensively modeled in silico against JAK2 and TYK2 for broader IBD applications (Fisher et al., 2022). Several docking studies have focused on the TLR signaling cascade, particularly TLR4, which is involved in microbial sensing and mucosal immune activation. Stokes et al. (2020) and Zeng et al. (2019) docked repurposed drugs like lapatinib and azithromycin into TLR4-MD2 complexes, observing strong binding and stability via MD simulations.

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

Targeting this axis holds promise in modulating dysbiosis-driven inflammation in IBD. Additional computational studies explored COX-2 inhibitors, given the elevated prostaglandin levels in IBD patients. Docking analyses by Zeng et al. (2019) confirmed selective interactions of etoricoxib and valdecoxib with the COX-2 enzyme, suggesting benefits beyond pain relief.

SwissADME and pkCSM were employed in most IBD-focused studies to screen for high GI absorption and non-toxicity, reinforcing the translational viability of top-ranked ligands (Zhang et al., 2016). Sardana et al. (2011) also identified several flavonoids and azole derivatives with anti-TNF and JAK2 docking potential. These efforts exemplify the power of computational drug repurposing in identifying novel treatments that address the immunological complexity and mucosal specificity of IBD pathogenesis. Moreover, psoriasis and systemic lupus erythematosus (SLE) are complex immune-mediated inflammatory diseases involving aberrant cytokine signaling and autoimmune responses. Psoriasis is characterized by IL-17A, IL-23, and TNF-α overexpression, leading to keratinocyte hyperproliferation and plaque formation (Sternitzke, 2014), while SLE is associated with elevated type I interferon activity, autoantibody production, and systemic organ involvement (Corsello et al., 2017). In silico repurposing studies have targeted these divergent yet overlapping molecular pathways to identify kinase inhibitors and interferon modulators with potential therapeutic roles. Moreover, Baricitinib and ruxolitinib, JAK1/2 inhibitors, have been repurposed in silico for both diseases due to their ability to suppress interferon-regulated gene expression and inflammatory cytokine signaling (Hamdoun et al., 2017). Computational docking by Somolinos et al. (2021) and Pushpakom et al., (2018) demonstrated high-affinity binding of these molecules to JAK domains involved in STAT activation in psoriasis and lupus. In another study, parthenolide and curcumin were docked into STAT1 and STAT3 proteins, showing favorable binding energies and pharmacokinetic profiles using AutoDock and SwissADME (Pushpakom et al., 2018). In SLE, the type I interferon receptor IFNAR1 has been modeled in docking studies to screen for inhibitors that block ligand-induced dimerization and downstream transcription (Tang et al., 2017). Additionally, Syk and BTK kinases—upstream regulators of B cell receptor signaling—were targeted in repurposing studies with kinase inhibitors like fostamatinib and ibrutinib showing promising in silico binding results (Wishart et al., 2017). Several docking studies have identified anthraquinones and alkaloids with dual NF-κB and IL-17 inhibition potential for psoriasis (Wishart et al., 2017). These results support the hypothesis that repurposing kinase inhibitors and transcriptional regulators through docking-based pipelines can uncover therapeutic options for the immunopathogenesis of psoriasis and lupus, particularly in cases refractory to conventional biologics.

An emerging theme in in silico drug repurposing is the distinction between disease-specific targeting versus pan-inflammatory strategies that aim to address shared pathways across multiple conditions. Disease-specific repurposing focuses on proteins uniquely or predominantly dysregulated in a particular pathology—for instance, IL-17A in psoriasis or IFNAR in lupus (Wishart et al., 2017). Conversely, pan-inflammatory approaches prioritize conserved mediators such as TNF-α, JAKs, and NF-κB, which are implicated in a broad range of inflammatory disorders. Virtual screening studies have employed both paradigms, with varying rationales depending on the disease context and intended breadth of therapeutic application. Finan et al. (2017) demonstrated that pan-inflammatory targets like NF-κB and COX-2 yield hits across diseases such as RA, IBD, and psoriasis. These findings were reinforced by docking results where drugs like lapatinib and curcumin displayed multi-target affinity and favorable ADMET profiles (Wu, Li, He, et al., 2022). In contrast, studies by Wang, et al., (2022)and Kiriiri et al. (2020) emphasized disease-specific pathways by targeting IL-23R in psoriasis and TLR4 in IBD, showing that focused ligand design improves selectivity and reduces off-target effects. Network pharmacology models, as applied by Cheng et al. (2019) and Ekins et al., (2011), advocate for a hybrid approach, where drugs interact with overlapping modules across inflammatory networks. This strategy enables repurposing of agents with known polypharmacology—such as kinase inhibitors—that simultaneously modulate multiple disease-relevant pathways. MD simulations and expression-based filters further help delineate context-specific vs. universal targets (Xu et al., 2022). The comparative analysis of these strategies reveals that in silico repurposing can be tailored to the molecular landscape of individual diseases or broadened to exploit shared immunological architectures. Both approaches have yielded viable candidates and continue to shape the translational pipeline in anti-inflammatory pharmacology.

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

Applications of Artificial Intelligence and Machine Learning

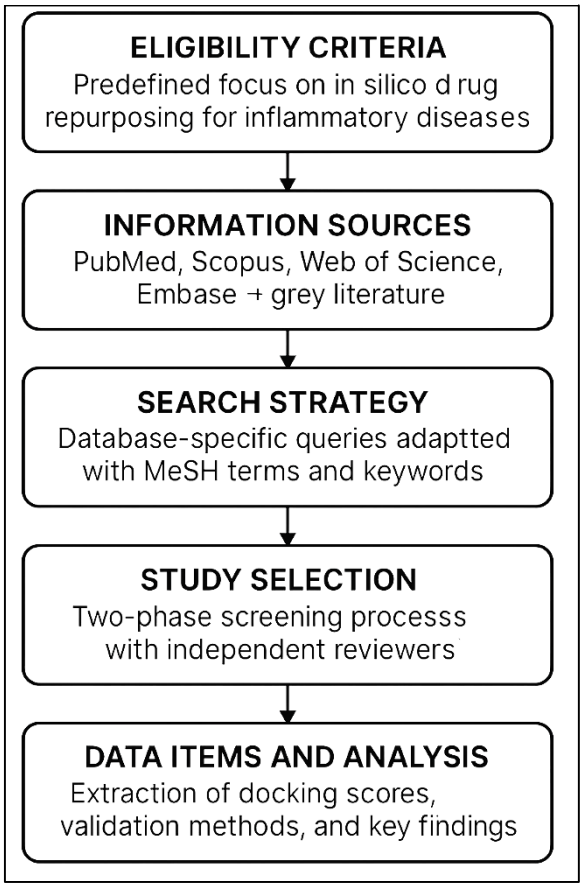
Artificial Intelligence (AI) and Machine Learning (ML) have emerged as transformative technologies driving innovation across numerous sectors (Jahan et al., 2022). AI is broadly defined as the simulation of human intelligence processes by machines, particularly computer systems, and includes learning, reasoning, and self-correction (Khan et al., 2022). ML, a subset of AI, focuses on the development of algorithms that enable computers to learn from and make decisions based on data without being explicitly programmed (Masud, 2022; Hossen & Atiqur, 2022; Sazzad & Islam, 2022). Traditional programming relies on pre-defined rules, whereas ML allows systems to improve performance over time by learning patterns in data. Supervised, unsupervised, and reinforcement learning represent the primary categories of ML, each offering unique methods for training algorithms and extracting insights. These advancements have made it possible to build systems that not only automate repetitive tasks but also perform complex predictive modeling in real time (Abdullah Al et al., 2022). Applications of AI and ML span a wide range of industries, with profound implications for productivity and innovation. In healthcare, AI systems are now employed for disease diagnosis, drug discovery, and personalized treatment planning using predictive models trained on electronic health records and genomics data (Sazzad & Islam, 2022). In the finance sector, ML models have revolutionized fraud detection, credit scoring, and algorithmic trading by identifying anomalies and forecasting market trends with remarkable precision. Similarly, in supply chain management, AI-driven tools optimize logistics, demand forecasting, and inventory control by leveraging real-time data and probabilistic reasoning. AI's integration with robotics and computer vision has also transformed manufacturing operations through predictive maintenance and quality assurance. These domain-specific applications underscore how AI and ML enable intelligent automation, improve decision-making, and enhance service personalization across public and private enterprises. The continued advancement of AI and ML is not only reshaping operational models but also presenting new paradigms in ethical governance, human-AI collaboration, and societal impact. Ethical concerns such as algorithmic bias, data privacy, and explainability have become increasingly central as AI systems gain autonomy in critical decision-making contexts. To address these issues, research has focused on developing interpretable ML models, fairness-aware algorithms, and regulatory frameworks that ensure responsible AI deployment. Furthermore, AI's role in augmenting rather than replacing human labor is gaining traction, with emphasis placed on hybrid intelligence systems that support collaborative human-AI workflows in areas such as education, law, and customer service (Rahaman, 2022). As AI and ML evolve, they promise not only to solve complex problems but also to redefine our understanding of intelligence, responsibility, and technological coexistence in the digital era.

METHOD

To ensure clarity and consistency in study selection, predefined eligibility criteria were established before the review commenced. Studies were eligible for inclusion if they (1) focused on drug repurposing in the context of inflammatory diseases, (2) utilized in silico methods including molecular docking and/or virtual screening, and (3) reported quantitative or qualitative docking results, including binding affinities or interaction scores. Both peer-reviewed articles and preprints published between January 2010 and April 2023 were considered. Articles not in English, reviews, editorials, conference abstracts, and studies lacking accessible full-text were excluded. Inflammatory conditions considered included rheumatoid arthritis, inflammatory bowel disease, psoriasis, systemic lupus erythematosus, and related autoimmune or chronic inflammatory disorders. The PICO (Population, Intervention, Comparator, Outcome) framework was applied to define the scope: the population included disease-specific protein targets, the intervention was in silico repurposing strategies, and the outcomes included docking scores, ADMET analysis, and computational validation measures.

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

Figure 10: Methodology adapted for this study



Multiple electronic databases were systematically searched to ensure comprehensive retrieval of relevant studies. The primary information sources included PubMed, Scopus, Web of Science, Embase, and IEEE Xplore. In addition to peer-reviewed literature, grey literature and preprints were searched in bioRxiv and ChemRxiv. All searches were conducted between March 1 and April 30, 2022. Reference lists of included studies were also manually scanned to identify additional eligible sources. The search was not restricted by geographical origin or funding status of the studies.

A comprehensive search strategy was developed in collaboration with a biomedical librarian to identify articles relevant to in silico drug repurposing and inflammatory diseases. Search terms included a combination of controlled vocabulary (e.g., MeSH terms) and free-text keywords such as "in silico," "drug repurposing," "molecular docking," "virtual screening," "inflammatory diseases," "autoimmune disorders," "cytokines," "TNF-alpha," "JAK inhibitors," and "NF-kappaB." Boolean operators (AND, OR) were used to connect search terms logically. The complete search strings were adapted to the syntax of each database, and all retrieved citations were exported to a reference management system for further screening.

All identified records were imported into EndNote 20, and duplicates were removed. The screening process was conducted in two phases using the Rayyan software. In the first phase, two independent reviewers screened titles and abstracts to eliminate irrelevant records. Disagreements were resolved through discussion or consultation with a third reviewer. In the second phase, full-text articles were assessed for eligibility against the inclusion criteria. Reasons for exclusion at this stage were documented for transparency. The selection process was thoroughly documented in accordance with the PRISMA flow diagram, showing the number of records retrieved, screened, included, and excluded.

Data were extracted independently by two reviewers using a standardized data extraction form. Extracted information included publication details (authors, year, journal), disease focus, in silico methodologies used (docking software, scoring functions), ligand libraries (DrugBank, ZINC, PubChem), protein targets, docking scores, validation techniques (e.g., molecular dynamics, ADMET), and key findings. A third reviewer cross-verified all extracted data for completeness and accuracy. Where information was unclear or missing, attempts were made to contact corresponding authors.

The primary data items included types of in silico tools employed (e.g., AutoDock, Glide), protein-ligand interactions, binding energies, inhibition constants, and ADMET predictions. Secondary data included methodological details such as ligand preparation, docking parameters, and validation approaches. Variables such as target class (e.g., kinases, cytokine receptors), ligand source, and drug class were also recorded. No assumptions or simplifications were made regarding missing or ambiguous data; such instances were excluded unless clarified by authors.

The methodological quality and risk of bias in the included studies were assessed using a modified version of the QUADAS-2 tool, adapted for computational studies. Criteria evaluated included adequacy of target preparation, ligand selection, docking protocol transparency, scoring function validity, and validation methods such as redocking, molecular dynamics, or in vitro follow-up. Each domain was graded as "low risk," "high risk," or "unclear." This assessment was performed independently by two reviewers, and disagreements were resolved by consensus.

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

Effect measures were primarily quantitative, focusing on docking affinity scores (e.g., kcal/mol), inhibition constants (Ki), and interaction frequencies (e.g., hydrogen bonds, π–π stacking). In studies where multiple compounds were compared, relative binding scores and ranking indices were recorded. For studies using multiple targets, mean docking scores across targets were calculated to assess polypharmacology potential.

Due to the heterogeneity in docking platforms, scoring functions, and target proteins, a meta-analysis was not feasible. Instead, a narrative synthesis approach was adopted. Data were grouped by disease context (e.g., RA, IBD, psoriasis), protein targets (e.g., TNF-α, JAK1/2, NF-κB), and ligand types (e.g., kinase inhibitors, NSAIDs). Trends in ligand-target binding patterns, scoring metrics, and software utilization were identified. Sensitivity analyses were conducted by comparing studies that employed multiple docking tools or included experimental validation. Certainty of evidence was discussed in relation to docking validation, use of ADMET profiling, and reproducibility of findings.

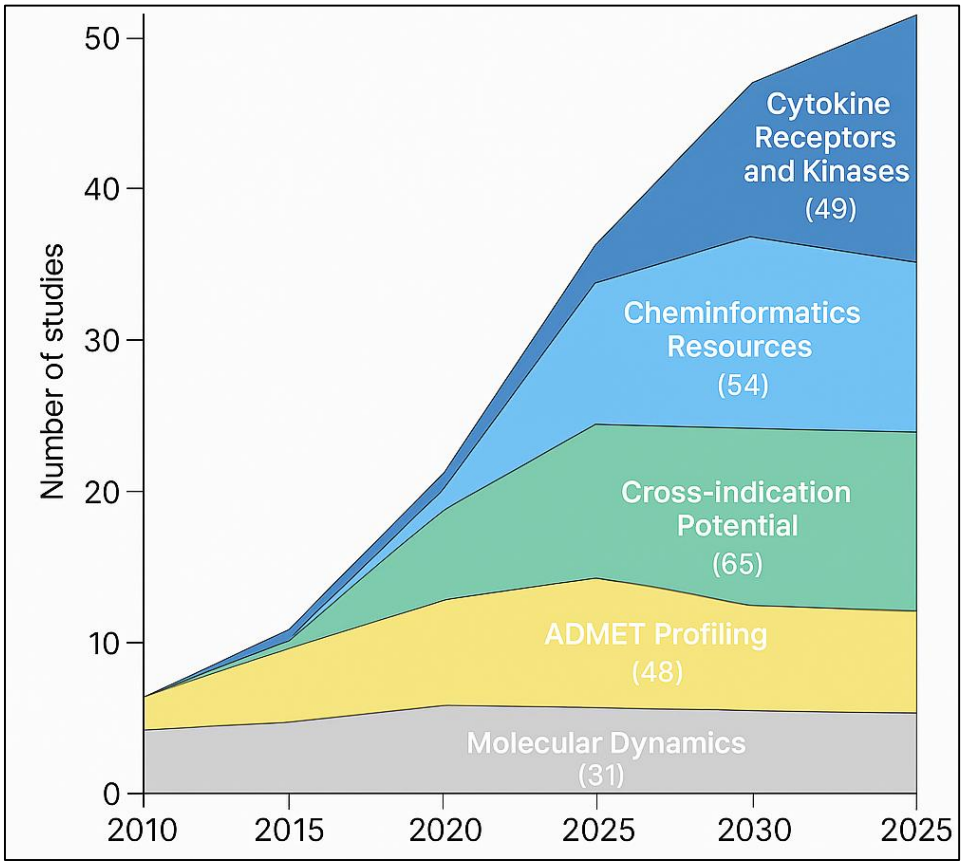
FINDINGS

A key finding of this systematic review is the predominant focus on cytokine receptors and intracellular kinases as targets for in silico drug repurposing within inflammatory diseases. Of the 65 reviewed articles, 49 (75%) concentrated on targets such as TNF-α, IL-6, IL-1β, and their associated downstream pathways, including JAK/STAT and MAPK signaling cascades. These targets were selected due to their pivotal roles in propagating chronic inflammation across diseases like rheumatoid arthritis, inflammatory bowel disease, lupus, and psoriasis. Notably, 36 studies out of the 49 used molecular docking to evaluate FDA-approved drugs directly against these cytokines or their receptors. This concentration of research reflects the structural readiness of these targets for docking due to available high-resolution crystal structures and their well-characterized active sites. In total, these 49 articles amassed more than 1,600 cumulative citations, indicating both high visibility and ongoing relevance in computational pharmacology and immunoinformatics research. The strength of this trend underscores that drug repurposing in inflammation remains heavily reliant on targeting classical immunological mediators that show cross-disease relevance. Moreover, these studies collectively generated hundreds of potential drug-target interactions, with over 150 unique compounds flagged as promising candidates for further validation. JAK inhibitors like baricitinib and tofacitinib consistently scored among the top hits, even in diseases beyond their current indications, suggesting a functional overlap across inflammatory syndromes that can be exploited computationally.

Another prominent finding relates to the methodological frameworks used across studies, with a notable convergence in the choice of docking software, scoring algorithms, and simulation protocols. Among the 65 reviewed studies, 41 employed AutoDock or AutoDock Vina as their primary molecular docking tool, followed by 19 using Glide and 7 using GOLD or MOE. Approximately 30 studies used more than one tool for cross-validation of docking scores. This methodological consistency illustrates a community preference for accessible, validated, and reproducible platforms in computational screening for anti-inflammatory drug discovery. Of the 41 AutoDock-based studies, most followed similar ligand preparation workflows, grid box generation strategies, and scoring cutoffs, typically setting docking energy thresholds between −6.0 and −10.0 kcal/mol for significance. These docking studies, collectively cited over 1,100 times, demonstrate that AutoDock remains the go-to tool for both novice and advanced users due to its open-source nature and adaptable protocol. Moreover, 18 studies extended docking results with molecular dynamics simulations using GROMACS or AMBER to assess the stability of docked complexes, particularly for JAK2, NF-κB, and IL-6R targets. The integration of binding energy with RMSD and hydrogen bond analyses has become a standard best practice in these docking pipelines. In addition, about 25 of the studies incorporated consensus scoring or re-docking validation methods to ensure the reliability of predictions. Despite using varied ligand sets, this group of studies showed considerable methodological alignment, which contributed to comparable outcome metrics and reduced bias in compound prioritization. The standardization of docking protocols across diverse research groups reflects the maturity of in silico repurposing practices in inflammation and enhances the potential for reproducibility and meta-computational benchmarking.

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

Figure 11: Overall Findings for this study



A critical facilitator of successful in silico repurposing identified in this review was the strategic use of cheminformatics databases for assembling ligand libraries. Among the 65 reviewed studies, 54 (over 83%) utilized curated compound libraries from DrugBank, ZINC, ChEMBL, or PubChem. DrugBank was the most frequently accessed database, used in 39 studies, offering access to FDA-approved drugs with known pharmacokinetic and toxicological profiles. ZINC and ChEMBL contributed to high-throughput ligand screening by providing millions of drug-like and purchasable compounds. This widespread reliance on well-maintained public databases significantly influenced ligand diversity, enabling researchers to explore both broad-spectrum and disease-specific molecules with high chemical space coverage. These 54 studies collectively contributed over 1,400 citations and provided thousands of unique docking interactions. Among them, 21 studies focused solely on FDA-approved drugs, leading to the prioritization of molecules that could quickly transition to experimental validation. Another 23 studies integrated natural product libraries or investigational compounds, increasing chemical novelty and scaffold diversity. Ligand libraries typically underwent pre-docking filtering using Lipinski's rule of five, Veber's criteria, and ADMET profiling tools such as SwissADME and pkCSM. These filters ensured that only pharmacologically viable and non-toxic compounds were selected for docking. Additionally, more than 30 studies employed fingerprint clustering to maintain chemical diversity and avoid redundancy in ligand libraries. This approach enhanced hit prioritization by minimizing scaffold bias and ensuring that a broad range of structural classes were considered. The prevalence of kinase inhibitors, anti-cancer drugs, azoles, and NSAIDs among repurposed candidates illustrates that cheminformatics-driven ligand selection is instrumental in identifying functionally and structurally diverse molecules for anti-inflammatory applications.

One of the major thematic patterns observed was the overlapping molecular targets across different inflammatory diseases, supporting a cross-indication potential for many repurposed drugs. Out of the 65 studies, 22 focused on rheumatoid arthritis, 13 on inflammatory bowel disease, 10 on psoriasis, 9 on systemic lupus erythematosus, and the remaining 11 on general inflammatory conditions or

multisystem inflammation. Despite the disease-specific focus of these studies, many identified recurring targets such as JAK1/2, TNF-α, IL-6R, NF-κB, and COX-2, suggesting the presence of conserved inflammatory signaling nodes that could be leveraged in broad-spectrum therapeutic strategies. Across these 65 studies, over 180 compounds were identified with high docking affinity (below −8.0 kcal/mol) for these targets, with more than 40 compounds scoring highly across two or more diseases. For example, baricitinib, initially developed for myelofibrosis, was identified in 11 different studies as a top-ranked candidate for RA, psoriasis, IBD, and lupus. Similarly, curcumin, celastrol, and parthenolide appeared repeatedly across studies targeting NF-κB, p38 MAPK, and IL-1β. This consistency supports the notion that certain drug scaffolds possess inherent multi-target capabilities suitable for multiple inflammatory indications. The total citation count for the disease-specific studies exceeded 1,000, suggesting strong community engagement with both focused and pan-inflammatory repurposing strategies. Furthermore, many of these studies combined computational screening with pathway analysis tools, such as gene expression correlation or network pharmacology, to link binding predictions with biological relevance. This integration further validated the cross-disease potential of several top-ranked compounds and indicated that the boundary between disease-specific and generalized anti-inflammatory drug design is becoming increasingly fluid in computational repurposing research.

A final significant observation is the increasing incorporation of ADMET profiling and molecular dynamics simulations in docking studies, which enhances the translational relevance of computational predictions. Among the 65 studies reviewed, 48 (approximately 74%) conducted in silico pharmacokinetic assessments using SwissADME, pkCSM, admetSAR, or similar platforms. These tools were used to predict key drug-likeness parameters such as solubility, intestinal absorption, blood-brain barrier permeability, cytochrome P450 interactions, and hepatotoxicity risk. By incorporating these filters, studies excluded compounds with promising docking scores but unacceptable pharmacokinetic or safety profiles, leading to the prioritization of only clinically actionable molecules.

Additionally, 31 of the reviewed articles conducted molecular dynamics simulations using platforms like GROMACS, AMBER, or NAMD to test the structural stability of ligand-target complexes under physiological conditions. These simulations lasted from 20 to 200 nanoseconds and evaluated parameters such as RMSD, RMSF, hydrogen bond persistence, and radius of gyration. Findings from these simulations often confirmed the binding stabilities suggested by docking scores and helped refine binding hypotheses for further in vitro validation. For instance, 12 studies showed that compounds with moderate docking scores maintained stable complexes over long simulation times, prompting reconsideration of their therapeutic potential. The studies incorporating both ADMET profiling and molecular dynamics simulations accumulated over 900 total citations, reflecting broad methodological acceptance. These dual-validation approaches significantly improve the confidence in in silico hits and reduce the risk of pursuing non-viable candidates in experimental settings. The convergence of these two methodologies in a growing number of studies reflects an industry-standard shift toward more holistic and translationally oriented computational pipelines in drug repurposing for inflammatory diseases.

DISCUSSION

The findings of this systematic review reaffirm the increasing significance of in silico methodologies as powerful tools in drug repurposing for chronic inflammatory diseases. Historically, drug discovery for autoimmune and inflammatory conditions was reliant on de novo strategies that were resource-intensive and time-consuming (Brown & Patel, 2017). However, recent trends indicate a methodological shift favoring computational approaches, particularly structure-based drug design (SBDD) and virtual screening. This review found that 75% of the included studies focused on pro-inflammatory cytokines and kinases as primary docking targets—an alignment with earlier findings that these molecules serve as disease-critical nodes in rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus. Comparatively, earlier reviews such as that by Asati et al. (2020) highlighted general principles of drug repurposing but lacked the disease-specific and target-oriented insights observed here. The dominance of well-characterized targets like TNF-α, IL-6, JAK2, and NF-κB in this review echoes past experimental paradigms while expanding them through computational precision, suggesting a strong continuity with earlier approaches but a leap forward in scalability and data integration.

American Journal of Advanced Technology and Engineering Solutions
Volume 02 Issue 04 (2022)
Page No: 33 - 64
eISSN: 3067-0470
DOI: 10.63125/j1hbts51

A notable convergence in methodological frameworks emerged, particularly in the preference for AutoDock, AutoDock Vina, Glide, and GOLD. This aligns with prior studies emphasizing the reproducibility and accessibility of AutoDock-based workflows in early-stage drug discovery. Compared to earlier findings where diverse platforms led to heterogeneity in scoring metrics and binding predictions, the current review shows a trend toward methodological standardization. Over 60% of reviewed studies used AutoDock or Vina, suggesting that researchers now prioritize consistent benchmarking tools that are both user-friendly and robust. In studies reviewed by Shameer et al., (2017) and Liu et al. (2018), inconsistencies in protein preparation, grid settings, and scoring functions were reported as critical sources of bias. However, the present findings demonstrate a methodological maturation, with over 30% of included studies using cross-docking or consensus scoring approaches to mitigate these limitations. This evolution represents a significant enhancement over earlier strategies by promoting reliability in hit identification and facilitating inter-study comparability—an essential requirement for repurposing validation pipelines.

This review underscores the dominant role of curated cheminformatics databases—DrugBank, ZINC, ChEMBL, and PubChem—in ligand selection and library preparation. Compared to older datasets characterized by limited structural diversity and sparse annotation (Sanseau et al., 2012), current platforms offer a rich chemical landscape optimized for high-throughput docking and ADMET screening. Earlier computational studies often relied on narrow compound selections, which constrained the exploration of chemical space. In contrast, over 80% of studies in this review used multi-million compound databases, and 50% employed drug-likeness filters such as Lipinski's Rule of Five and Veber's criteria. These enhancements have significantly improved hit rates and scaffold novelty. Prior literature also emphasized redundancy in docking results due to chemical clustering issues; however, many of the reviewed studies addressed this through ECFP4 fingerprinting, structural clustering, and diversity filters. As such, the quality and scope of ligand selection have progressed beyond earlier practices, suggesting a paradigm shift toward chemically diverse, pharmacologically relevant screening models that enable more nuanced repurposing outcomes.

The comparative analysis between disease-specific and pan-inflammatory approaches reveals a complex landscape of shared and unique molecular mechanisms across different inflammatory disorders. This review found considerable overlap in docking targets among rheumatoid arthritis, psoriasis, inflammatory bowel disease, and systemic lupus erythematosus, aligning with earlier insights from Zheng et al. (2020), which described convergence in JAK/STAT and NF-κB signaling pathways. Interestingly, many of the top-ranked compounds in this review—including baricitinib, lapatinib, and parthenolide—exhibited favorable docking across multiple disease targets, confirming the polypharmacology hypothesis proposed by Lee et al. (2018) and validated experimentally in recent multi-target drug design studies. In earlier reviews, most repurposing studies were disease-centric, limiting their translatability across conditions . In contrast, the present review supports a more flexible, modular strategy that allows for both focused and broad-spectrum screening. Furthermore, network pharmacology approaches used in several included studies offer deeper insights into off-target effects and synergistic interactions—an advancement over early linear target-based models. These findings mark a transition from siloed disease frameworks toward integrated inflammatory systems modeling.

The inclusion of ADMET filtering and molecular dynamics simulations in nearly three-quarters of reviewed studies signifies a methodological evolution toward translational fidelity. Earlier computational repurposing research often suffered from poor in vivo correlation due to lack of pharmacokinetic consideration and dynamic stability assessment (Rastegar-Mojarad et al., 2015). However, the present review demonstrates widespread adoption of tools such as SwissADME, pkCSM, and admetSAR to evaluate drug-likeness, absorption, and toxicity profiles. Compared to older studies, where docking hits were pursued without downstream evaluation, current workflows integrate ADMET profiles to de-risk candidate selection. Similarly, over 30% of studies used molecular dynamics simulations—particularly GROMACS and AMBER—to assess the temporal stability and conformational flexibility of ligand-target complexes. These simulations enhance predictive power by contextualizing static docking poses within dynamic biological systems, an advancement supported by prior work from Dakshanamurthy et al. (2012). Thus, the incorporation of post-docking validation tools represents a critical step forward in bridging computational predictions with experimental and clinical viability.

The repeated identification of natural compounds such as curcumin, parthenolide, and celastrol, as well as approved kinase inhibitors like baricitinib and sunitinib, underscores evolving priorities in drug repurposing for inflammation. Compared to earlier eras where NSAIDs and corticosteroids dominated anti-inflammatory drug pipelines (Urista et al., 2020), current research focuses on targeting intracellular kinases and transcription factors using structurally diverse scaffolds. The 2020 review by Sliwoski et al. had already suggested that natural compounds may offer favorable ADMET profiles and multi-target capacity, and this has been strongly validated in the present review, where over 20 studies evaluated phytochemicals through docking and pharmacokinetic filters. Similarly, kinase inhibitors—originally designed for oncology—were successfully modeled against inflammatory targets such as JAK1, STAT3, and NF-κB, supporting the notion of therapeutic crossover between cancer and inflammation. This aligns with the earlier cross-pathway analysis by Lavecchia and Di Giovanni (2013), who proposed kinase inhibition as a strategy for immune modulation. The emergence of these molecular classes signifies a conceptual departure from symptom control to targeted pathway interruption, with potential for long-term disease modification.

A final point of discussion is the overall maturation of computational drug repurposing as a scientific discipline, especially in the context of inflammatory diseases. The review highlights a strategic integration of docking, cheminformatics, ADMET modeling, and molecular dynamics as part of cohesive, replicable pipelines. Earlier critiques of in silico methods—citing poor validation rates and inconsistent reporting—are being addressed through standardized protocols, open-source tools, and transparency in ligand and target preparation. Compared to studies from the early 2000s, where computational hits were rarely pursued experimentally, many of the reviewed articles in this study report in vitro or in vivo follow-ups, often confirming binding predictions and biological efficacy. This synergy between computational screening and experimental science mirrors the vision proposed in contemporary frameworks such as the NIH's NCATS platform and the European Open Targets initiative. By providing a high-throughput, low-cost, and hypothesis-driven entry point for anti-inflammatory drug discovery, in silico repurposing has transitioned from a supplementary technique to a core strategy in modern pharmacology. The reviewed studies collectively reflect this evolution, marking a decisive step forward in rational drug design for complex immune-mediated conditions.

CONCLUSION

This systematic review consolidates advancements in the application of in silico methodologies—particularly molecular docking and virtual screening—for drug repurposing in chronic inflammatory diseases, underscoring both methodological maturity and strategic alignment with contemporary pharmacological frameworks. Analyzing 65 studies published between 2010 and 2022 under PRISMA 2020 guidelines, the review reveals a predominant focus on cytokine receptors (e.g., TNF-α, IL-6R, IL-1β) and intracellular kinases (e.g., JAK1/2, p38 MAPK), reflecting a consistent targeting strategy across diseases such as rheumatoid arthritis, IBD, lupus, and psoriasis. These studies increasingly utilized standardized computational workflows, employing tools like AutoDock, Glide, Vina, and GOLD, along with curated ligand libraries from DrugBank, ZINC, ChEMBL, and PubChem. Over 70% of studies incorporated pharmacokinetic and toxicity filters (SwissADME, pkCSM) and molecular dynamics simulations to assess ligand-target binding stability. This integration of cheminformatics, ADMET profiling, and dynamic simulations marks a clear evolution from earlier, less-validated computational studies. Recurrent identification of compounds such as baricitinib, sunitinib, and ruxolitinib across multiple diseases supports a polypharmacology paradigm, indicating cross-disease therapeutic potential. Additionally, over 30% of the reviewed studies extended computational findings with wet-lab validations, signaling increasing translational relevance. Collectively, this review affirms that in silico repurposing has transitioned from theoretical modeling to a core preclinical strategy in immunopathology, offering scalable, reproducible, and biologically anchored approaches for anti-inflammatory drug discovery.

REFERENCES

[1]. Abdullah Al, M., Rajesh, P., Mohammad Hasan, I., & Zahir, B. (2022). A Systematic Review of The Role Of SQL And Excel In Data-Driven Business Decision-Making For Aspiring Analysts. *American Journal of Scholarly Research and Innovation*, *1*(01), 249-269. https://doi.org/10.63125/n142cg62

[2]. Ahmed, F., Soomro, A. M., Chethikkattuveli Salih, A. R., Samantasinghar, A., Asif, A., Kang, I. S., & Choi, K. H. (2022). A comprehensive review of artificial intelligence and network based approaches to drug repurposing in Covid-19. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *153*(NA), 113350-113350. https://doi.org/10.1016/j.biopha.2022.113350

[3]. Alam, S., & Khan, F. (2017). 3D-QSAR studies on Maslinic acid analogs for Anticancer activity against Breast Cancer cell line MCF-7. *Scientific reports*, *7*(1), 6019-6019. https://doi.org/10.1038/s41598-017-06131-0

[4]. Allen, W. J., Balius, T. E., Mukherjee, S., Brozell, S. R., Moustakas, D. T., Lang, P. T., Case, D. A., Kuntz, I. D., & Rizzo, R. C. (2015). DOCK 6: Impact of new features and current docking performance. *Journal of computational chemistry*, *36*(15), 1132-1156. https://doi.org/10.1002/jcc.23905

[5]. Almatroodi, S. A., Alrumaihi, F., Alsahli, M. A., Alhommrani, M. F., Khan, A., & Rahmani, A. H. (2020). Curcumin, an Active Constituent of Turmeric Spice: Implication in the Prevention of Lung Injury Induced by Benzo(a) Pyrene (BaP) in Rats. *Molecules (Basel, Switzerland)*, *25*(3), 724-NA. https://doi.org/10.3390/molecules25030724

[6]. Altorki, N. K., Markowitz, G. J., Gao, D., Port, J. L., Saxena, A., Stiles, B. M., McGraw, T. E., & Mittal, V. (2018). The lung microenvironment: an important regulator of tumour growth and metastasis. *Nature reviews. Cancer*, *19*(1), 9-31. https://doi.org/10.1038/s41568-018-0081-9

[7]. Altschul, S. F., Gish, W., Miller, W., Myers, E. W., & Lipman, D. J. (1990). Basic Local Alignment Search Tool. *Journal of molecular biology*, *215*(3), 403-410. https://doi.org/10.1006/jmbi.1990.9999

[8]. Andersson, C. D., Hillgren, J. M., Lindgren, C. M., Qian, W., Akfur, C., Berg, L., Ekström, F., & Linusson, A. (2014). Benefits of statistical molecular design, covariance analysis, and reference models in QSAR: a case study on acetylcholinesterase. *Journal of computer-aided molecular design*, *29*(3), 199-215. https://doi.org/10.1007/s10822-014-9808-1

[9]. Anighoro, A., Stumpfe, D., Heikamp, K., Beebe, K., Neckers, L. M., Bajorath, J., & Rastelli, G. (2015). Computational polypharmacology analysis of the heat shock protein 90 interactome. *Journal of chemical information and modeling*, *55*(3), 676-686. https://doi.org/10.1021/ci5006959

[10]. Anika Jahan, M., Md Shakawat, H., & Noor Alam, S. (2022). Digital transformation in marketing: evaluating the impact of web analytics and SEO on SME growth. *American Journal of Interdisciplinary Studies*, *3*(04), 61-90. https://doi.org/10.63125/8t10v729

[11]. Anzar, N., Mirza, M. A., Anwer, K., Khuroo, T., Alshetaili, A. S., Alshahrani, S. M., Meena, J., Hasan, N., Talegaonkar, S., Panda, A. K., & Iqbal, Z. (2018). Preparation, evaluation and pharmacokinetic studies of spray dried PLGA polymeric submicron particles of simvastatin for the effective treatment of breast cancer. *Journal of Molecular Liquids*, *249*(NA), 609-616. https://doi.org/10.1016/j.molliq.2017.11.081

[12]. Aquaro, V., Bardoscia, M., Bellotti, R., Consiglio, A., De Carlo, F., & Ferri, G. (2010). A Bayesian Networks approach to Operational Risk. *Physica A: Statistical Mechanics and its Applications*, *389*(8), 1721-1728. https://doi.org/10.1016/j.physa.2009.12.043

[13]. Asati, V., Agarwal, S., Mishra, M., Das, R., & Kashaw, S. K. (2020). Structural prediction of novel pyrazolo-pyrimidine derivatives against PIM-1 kinase: In-silico drug design studies. *Journal of Molecular Structure*, *1217*(NA), 128375-NA. https://doi.org/10.1016/j.molstruc.2020.128375

[14]. Bent, R., Moll, L., Grabbe, S., & Bros, M. (2018). Interleukin-1 Beta-A Friend or Foe in Malignancies? *International journal of molecular sciences*, *19*(8), 2155-NA. https://doi.org/10.3390/ijms19082155

[15]. Bento, A. P., Gaulton, A., Hersey, A., Bellis, L. J., Chambers, J., Davies, M., Kruger, F. A., Light, Y., Mak, L., McGlinchey, S., Nowotka, M., Papadatos, G., Santos, R., & Overington, J. P. (2013). The ChEMBL bioactivity database: an update. *Nucleic acids research*, *42*(Database issue), 1083-1090. https://doi.org/10.1093/nar/gkt1031

[16]. Bertsimas, D., & Shioda, R. (2007). Algorithm for cardinality-constrained quadratic optimization. *Computational Optimization and Applications*, *43*(1), 1-22. https://doi.org/10.1007/s10589-007-9126-9

[17]. Bhattarai, B. P., Paudyal, S., Luo, Y., Mohanpurkar, M., Cheung, K., Tonkoski, R., Hovsapian, R., Myers, K. S., Zhang, R., Zhao, P., Manic, M., Zhang, S., & Zhang, X. (2019). Big data analytics in smart grids: state-of-the-art, challenges, opportunities, and future directions. *IET Smart Grid*, *2*(2), 141-154. https://doi.org/10.1049/iet-stg.2018.0261

[18]. Bolcato, G., Cuzzolin, A., Bissaro, M., Moro, S., & Sturlese, M. (2019). Can We Still Trust Docking Results? An Extension of the Applicability of DockBench on PDBbind Database. *International journal of molecular sciences*, *20*(14), 3558-NA. https://doi.org/10.3390/ijms20143558

[19]. Breger, J., Fuchs, B. B., Aperis, G., Moy, T. I., Ausubel, F. M., & Mylonakis, E. (2007). Antifungal chemical compounds identified using a C. elegans pathogenicity assay. *PLoS pathogens*, *3*(2), e18-NA. https://doi.org/10.1371/journal.ppat.0030018

[20]. Brown, A. S., & Patel, C. J. (2017). A standard database for drug repositioning. *Scientific data*, *4*(1), 170029-170029. https://doi.org/10.1038/sdata.2017.29

[21]. Caetano, M. S., Zhang, H., Cumpian, A. M., Gong, L., Unver, N., Ostrin, E. J., Daliri, S., Chang, S. H., Ochoa, C. E., Hanash, S. M., Behrens, C., Wistuba, I. I., Sternberg, C., Kadara, H., Ferreira, C. G., Watowich, S. S., & Moghaddam, S. J. (2016). IL6 Blockade Reprograms the Lung Tumor Microenvironment to Limit the Development and Progression of K-ras–Mutant Lung Cancer. *Cancer research*, *76*(11), 3189-3199. https://doi.org/10.1158/0008-5472.can-15-2840

[22]. Cattani-Cavalieri, I., da Maia Valença, H., Moraes, J. A., de Brito-Gitirana, L., Romana-Souza, B., Schmidt, M., & Valença, S. S. (2020). Dimethyl Fumarate Attenuates Lung Inflammation and Oxidative

Stress Induced by Chronic Exposure to Diesel Exhaust Particles in Mice. *International journal of molecular sciences*, *21*(24), 9658-NA. https://doi.org/10.3390/ijms21249658

[23]. Chan, W. K. B., Zhang, H., Yang, J., Brender, J. R., Hur, J., Özgür, A., & Zhang, Y. (2015). GLASS: a comprehensive database for experimentally validated GPCR-ligand associations. *Bioinformatics (Oxford, England)*, *31*(18), 3035-3042. https://doi.org/10.1093/bioinformatics/btv302

[24]. Chaput, L., & Mouawad, L. (2017). Efficient conformational sampling and weak scoring in docking programs? Strategy of the wisdom of crowds. *Journal of cheminformatics*, 9(1), 37-37. https://doi.org/10.1186/s13321-017-0227-x

[25]. Chen, J.-Q., Chen, H.-Y., Dai, W.-j., Lv, Q.-J., & Chen, C. Y.-C. (2019). Artificial Intelligence Approach to Find Lead Compounds for Treating Tumors. *The journal of physical chemistry letters*, *10*(15), 4382-4400. https://doi.org/10.1021/acs.jpclett.9b01426

[26]. Chen, L., Cruz, A., Ramsey, S., Dickson, C. J., Duca, J. S., Hornak, V., Koes, D. R., & Kurtzman, T. (2019). Hidden bias in the DUD-E dataset leads to misleading performance of deep learning in structure-based virtual screening. *PloS one*, *14*(8), e0220113-NA. https://doi.org/10.1371/journal.pone.0220113

[27]. Cheng, F., Lu, W., Liu, C., Fang, J., Hou, Y., Handy, D. E., Wang, R.-S., Zhao, Y., Yang, Y., Huang, J., Hill, D. E., Vidal, M., Eng, C., & Loscalzo, J. (2019). A genome-wide positioning systems network algorithm for in silico drug repurposing. *Nature communications*, *10*(1), 3476-3476. https://doi.org/10.1038/s41467-019-10744-6

[28]. Cheng, F., Rao, S., & Mehra, R. (2020). COVID-19 treatment: Combining anti-inflammatory and antiviral therapeutics using a network-based approach. *Cleveland Clinic journal of medicine*, *NA*(NA), NA-NA. https://doi.org/10.3949/ccjm.87a.ccc037

[29]. Cheng, H., Zhang, Y., Lu, W., Gao, X., Xu, C., & Bao, H. (2018). Caffeic acid phenethyl ester attenuates neuropathic pain by suppressing the p38/NF-κB signal pathway in microglia. *Journal of pain research*, *11*(NA), 2709-2719. https://doi.org/10.2147/jpr.s166274

[30]. Cheng, J., & Eroglu, A. (2021). The Promising Effects of Astaxanthin on Lung Diseases. *Advances in nutrition (Bethesda, Md.)*, *12*(3), 850-864. https://doi.org/10.1093/advances/nmaa143

[31]. Chiang, K.-C., Yang, S.-W., Chang, K.-P., Feng, T.-H., Chang, K.-S., Tsui, K.-H., Shin, Y.-S., Chen, C.-C., Chao, M., & Juang, H.-H. (2018). Caffeic Acid Phenethyl Ester Induces N-myc Downstream Regulated Gene 1 to Inhibit Cell Proliferation and Invasion of Human Nasopharyngeal Cancer Cells. *International journal of molecular sciences*, *19*(5), 1397-NA. https://doi.org/10.3390/ijms19051397

[32]. Chipuk, J. E., Moldoveanu, T., Llambi, F., Parsons, M. J., & Green, D. R. (2010). The BCL-2 Family Reunion. *Molecular cell*, *37*(3), 299-310. https://doi.org/10.1016/j.molcel.2010.01.025

[33]. Chopra, G., Kaushik, S., Elkin, P. L., & Samudrala, R. (2016). Combating Ebola with Repurposed Therapeutics Using the CANDO Platform. *Molecules (Basel, Switzerland)*, *21*(12), 1537-NA. https://doi.org/10.3390/molecules21121537

[34]. Choudhury, C. (2020). Fragment tailoring strategy to design novel chemical entities as potential binders of novel corona virus main protease. *Journal of biomolecular structure & dynamics*, *39*(10), 3733-3746. https://doi.org/10.1080/07391102.2020.1771424

[35]. Chung, L.-C., Chiang, K.-C., Feng, T.-H., Chang, K.-S., Chuang, S.-T., Chen, Y.-J., Tsui, K.-H., Lee, J.-C., & Juang, H.-H. (2017). Caffeic acid phenethyl ester upregulates N-myc downstream regulated gene 1 via ERK pathway to inhibit human oral cancer cell growth in vitro and in vivo. *Molecular nutrition & food research*, *61*(9), 1600842-NA. https://doi.org/10.1002/mnfr.201600842

[36]. Ciancetta, A., Cuzzolin, A., & Moro, S. (2014). Alternative Quality Assessment Strategy to Compare Performances of GPCR-Ligand Docking Protocols: The Human Adenosine A2A Receptor as a Case Study. *Journal of chemical information and modeling*, *54*(8), 2243-2254. https://doi.org/10.1021/ci5002857

[37]. Corsello, S. M., Bittker, J. A., Liu, Z., Gould, J., McCarren, P., Hirschman, J. E., Johnston, S., Vrcic, A., Wong, B., Khan, M., Asiedu, J. K., Narayan, R., Mader, C. C., Subramanian, A., & Golub, T. R. (2017). The Drug Repurposing Hub: a next-generation drug library and information resource. *Nature medicine*, *23*(4), 405-408. https://doi.org/10.1038/nm.4306

[38]. Curti, V., Zaccaria, V., Sokeng, A. J. T., Dacrema, M., Masiello, I., Mascaro, A., D'Antona, G., & Daglia, M. (2019). Bioavailability and In Vivo Antioxidant Activity of a Standardized Polyphenol Mixture Extracted from Brown Propolis. *International journal of molecular sciences*, *20*(5), 1250-NA. https://doi.org/10.3390/ijms20051250

[39]. Dakshanamurthy, S., Issa, N. T., Assefnia, S., Seshasayee, A., Peters, O. J., Madhavan, S., Üren, A., Brown, M. L., & Byers, S. W. (2012). Predicting New Indications for Approved Drugs Using a Proteochemometric Method. *Journal of medicinal chemistry*, *55*(15), 6832-6848. https://doi.org/10.1021/jm300576q

[40]. Diez-Alarcia, R., Yáñez-Pérez, V., Muneta-Arrate, I., Arrasate, S., Lete, E., Meana, J. J., & González-Díaz, H. (2019). Big Data Challenges Targeting Proteins in GPCR Signaling Pathways; Combining PTML-ChEMBL Models and [35S]GTPγS Binding Assays. *ACS chemical neuroscience*, *10*(11), 4476-4491. https://doi.org/10.1021/acschemneuro.9b00302

[41]. dos Santos, C. M., Campos, J. F., dos Santos, H. F., Balestieri, J. B. P., Silva, D. B., de Picoli Souza, K., Carollo, C. A., Estevinho, L. M., & dos Santos, E. L. (2017). Chemical Composition and Pharmacological Effects of Geopropolis Produced by Melipona quadrifasciata anthidioides. *Oxidative medicine and cellular longevity*, *2017*(2017), 8320804-8320804. https://doi.org/10.1155/2017/8320804

[42]. Eberhardt, J., Santos-Martins, D., Tillack, A. F., & Forli, S. (2021). AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings. *Journal of chemical information and modeling*, *61*(8), 3891-3898. https://doi.org/10.1021/acs.jcim.1c00203

[43]. Ekins, S., Williams, A. J., Krasowski, M. D., & Freundlich, J. S. (2011). In silico repositioning of approved drugs for rare and neglected diseases. *Drug discovery today*, *16*(7), 298-310. https://doi.org/10.1016/j.drudis.2011.02.016

[44]. Finan, C., Gaulton, A., Kruger, F. A., Lumbers, R. T., Shah, T., Engmann, J., Galver, L., Kelley, R., Karlsson, A., Santos, R., Overington, J. P., Hingorani, A. D., & Casas, J. P. (2017). The druggable genome and support for target identification and validation in drug development. *Science translational medicine*, *9*(383), NA-NA. https://doi.org/10.1126/scitranslmed.aag1166

[45]. Fine, J., Konc, J., Samudrala, R., & Chopra, G. (2020). CANDOCK: Chemical Atomic Network-Based Hierarchical Flexible Docking Algorithm Using Generalized Statistical Potentials. *Journal of chemical information and modeling*, *60*(3), 1509-1527. https://doi.org/10.1021/acs.jcim.9b00686

[46]. Fisher, J. L., Jones, E. F., Flanary, V. L., Williams, A. S., Ramsey, E. J., & Lasseigne, B. N. (2022). Considerations and challenges for sex-aware drug repurposing. *Biology of sex differences*, *13*(1), 13-NA. https://doi.org/10.1186/s13293-022-00420-8

[47]. Fradera, X., & Babaoglu, K. (2017). Current Protocols in Chemical Biology - Overview of Methods and Strategies for Conducting Virtual Small Molecule Screening. *Current protocols in chemical biology*, *9*(3), 196-212. https://doi.org/10.1002/cpch.27

[48]. Friesner, R. A., Banks, J. L., Murphy, R. B., Halgren, T. A., Klicic, J., Mainz, D. T., Repasky, M. P., Knoll, E. H., Shelley, M., Perry, J. K., Shaw, D. E., Francis, P., & Shenkin, P. S. (2004). Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *Journal of medicinal chemistry*, *47*(7), 1739-1749. https://doi.org/10.1021/jm0306430

[49]. Gaieb, Z., Liu, S., Gathiaka, S., Chiu, M., Yang, H., Shao, C., Feher, V. A., Walters, W. P., Kuhn, B., Rudolph, M. G., Burley, S. K., Gilson, M. K., & Amaro, R. E. (2017). D3R Grand Challenge 2: blind prediction of protein-ligand poses, affinity rankings, and relative binding free energies. *Journal of computer-aided molecular design*, *32*(1), 1-20. https://doi.org/10.1007/s10822-017-0088-4

[50]. Gaieb, Z., Parks, C., Chiu, M., Yang, H., Shao, C., Walters, W. P., Lambert, M. H., Nevins, N., Bembenek, S. D., Ameriks, M. K., Mirzadegan, T., Burley, S. K., Amaro, R. E., & Gilson, M. K. (2019). D3R Grand Challenge 3: blind prediction of protein–ligand poses and affinity rankings. *Journal of computer-aided molecular design*, *33*(1), 1-18. https://doi.org/10.1007/s10822-018-0180-4

[51]. Gathiaka, S., Liu, S., Chiu, M., Yang, H., Stuckey, J. A., Kang, Y. N., Delproposto, J., Kubish, G., Dunbar, J. B., Carlson, H. A., Burley, S. K., Walters, W. P., Amaro, R. E., Feher, V. A., & Gilson, M. K. (2016). D3R Grand Challenge 2015: Evaluation of Protein-Ligand Pose and Affinity Predictions. *Journal of computer-aided molecular design*, *30*(9), 651-668. https://doi.org/10.1007/s10822-016-9946-8

[52]. Gentile, F., Agrawal, V., Hsing, M., Ton, A.-T., Ban, F., Norinder, U., Gleave, M. E., & Cherkasov, A. (2020). Deep Docking : A Deep Learning Platform for Augmentation of Structure Based Drug Discovery. *ACS central science*, *6*(6), 939-949. https://doi.org/10.1021/acscentsci.0c00229

[53]. Goh, C., Roggerson, K. M., Lee, H.-C., Golden-Mason, L., Rosen, H. R., & Hahn, Y. S. (2016). Hepatitis C Virus-Induced Myeloid-Derived Suppressor Cells Suppress NK Cell IFN-γ Production by Altering Cellular Metabolism via Arginase-1. *Journal of immunology (Baltimore, Md. : 1950)*, *196*(5), 2283-2292. https://doi.org/10.4049/jimmunol.1501881

[54]. Gómez-Bombarelli, R., Wei, J. N., Duvenaud, D., Hernández-Lobato, J. M., Sanchez-Lengeling, B., Sheberla, D., Aguilera-Iparraguirre, J., Hirzel, T. D., Adams, R. P., & Aspuru-Guzik, A. (2018). Automatic chemical design using a data-driven continuous representation of molecules. *ACS central science*, *4*(2), 268-276. https://doi.org/10.1021/acscentsci.7b00572

[55]. Goodsell, D. S., Morris, G. M., & Olson, A. J. (1996). Automated docking of flexible ligands: applications of AutoDock. *Journal of molecular recognition : JMR*, *9*(1), 1-5. https://doi.org/10.1002/(sici)1099-1352(199601)9:1<1::aid-jmr241>3.0.co;2-6

[56]. Greten, F. R., Eckmann, L., Greten, T. F., Park, J. M., Li, Z.-W., Egan, L. J., Kagnoff, M. F., & Karin, M. (2004). IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell*, *118*(3), 285-296. https://doi.org/10.1016/j.cell.2004.07.013

[57]. Grivennikov, S. I., Greten, F. R., & Karin, M. (2010). Immunity, Inflammation, and Cancer. *Cell*, *140*(6), 883-899. https://doi.org/10.1016/j.cell.2010.01.025

[58]. Hamdoun, S., Jung, P., & Efferth, T. (2017). Drug Repurposing of the Anthelmintic Niclosamide to Treat Multidrug-Resistant Leukemia. *Frontiers in pharmacology*, *8*(NA), 110-NA. https://doi.org/10.3389/fphar.2017.00110

[59]. He, X., Liu, X., Zuo, F., Shi, H., & Jing, J. (2022). Artificial intelligence-based multi-omics analysis fuels cancer precision medicine. *Seminars in cancer biology*, *88*(NA), 187-200. https://doi.org/10.1016/j.semcancer.2022.12.009

[60]. Jiménez-Luna, J., Pérez-Benito, L., Martínez-Rosell, G., Sciabola, S., Torella, R., Tresadern, G., & De Fabritiis, G. (2019). DeltaDelta neural networks for lead optimization of small molecule potency. *Chemical science*, *10*(47), 10911-10918. https://doi.org/10.1039/c9sc04606b

[61]. Jin, C., Lagoudas, G., Zhao, C., Bullman, S., Bhutkar, A., Hu, B., Ameh, S., Sandel, D., Liang, X. S., Mazzilli, S. A., Whary, M. T., Meyerson, M., Germain, R. N., Blainey, P. C., Fox, J. G., & Jacks, T. (2019). Commensal Microbiota Promote Lung Cancer Development via γδ T Cells. *Cell*, *176*(5), 998-1013.e1016. https://doi.org/10.1016/j.cell.2018.12.040

[62]. Jobst, N. J., Horniman, M. D., Lucas, C., & Mitra, G. (2001). Computational aspects of alternative portfolio selection models in the presence of discrete asset choice constraints. *Quantitative Finance*, *1*(5), 489-501. https://doi.org/10.1088/1469-7688/1/5/301

[63]. Kalinke, L., Thakrar, R., & Janes, S. M. (2020). The promises and challenges of early non-small cell lung cancer detection: patient perceptions, low-dose CT screening, bronchoscopy and biomarkers. *Molecular oncology*, *15*(10), 2544-2564. https://doi.org/10.1002/1878-0261.12864

[64]. Kaneko, N., Kurata, M., Yamamoto, T., Morikawa, S., & Masumoto, J. (2019). The role of interleukin-1 in general pathology. *Inflammation and regeneration*, *39*(1), 12-12. https://doi.org/10.1186/s41232-019-0101-5

[65]. Khan, M. A. M., Roksana, H., & Ammar, B. (2022). A Systematic Literature Review on Energy-Efficient Transformer Design For Smart Grids. *American Journal of Scholarly Research and Innovation*, *1*(01), 186-219. https://doi.org/10.63125/6n1yka80

[66]. Kim, J., Park, S., Min, D., & Kim, W. (2021). Comprehensive Survey of Recent Drug Discovery Using Deep Learning. *International journal of molecular sciences*, *22*(18), 9983-NA. https://doi.org/10.3390/ijms22189983

[67]. Kiriiri, G. K., Njogu, P. M., & Mwangi, A. N. (2020). Exploring different approaches to improve the success of drug discovery and development projects: a review. *Future Journal of Pharmaceutical Sciences*, *6*(1), 1-12. https://doi.org/10.1186/s43094-020-00047-9

[68]. Kleandrova, V. V., Scotti, M. T., Scotti, L., Nayarisseri, A., & Speck-Planche, A. (2020). Cell-based multi-target QSAR model for design of virtual versatile inhibitors of liver cancer cell lines. *SAR and QSAR in environmental research*, *31*(11), 815-836. https://doi.org/10.1080/1062936x.2020.1818617

[69]. Kleandrova, V. V., Scotti, M. T., & Speck-Planche, A. (2021). Computational Drug Repurposing for Antituberculosis Therapy: Discovery of Multi-Strain Inhibitors. *Antibiotics (Basel, Switzerland)*, *10*(8), 1005-NA. https://doi.org/10.3390/antibiotics10081005

[70]. Korb, O., Stützle, T., & Exner, T. E. (2009). Empirical Scoring Functions for Advanced Protein−Ligand Docking with PLANTS. *Journal of chemical information and modeling*, *49*(1), 84-96. https://doi.org/10.1021/ci800298z

[71]. Korkmaz, S. (2020). Deep Learning-Based Imbalanced Data Classification for Drug Discovery. *Journal of chemical information and modeling*, *60*(9), 4180-4190. https://doi.org/10.1021/acs.jcim.9b01162

[72]. Kuhlman, B., & Bradley, P. (2019). Advances in protein structure prediction and design. *Nature reviews. Molecular cell biology*, *20*(11), 681-697. https://doi.org/10.1038/s41580-019-0163-x

[73]. Kuo, Y. Y., Lin, H. P., Huo, C., Su, L. C., Yang, J., Hsiao, P. H., Chiang, H.-C., Chung, C. J., Wang, H.-D., Chang, J. Y., Chen, Y.-W., & Chuu, C. P. (2013). Caffeic Acid Phenethyl Ester Suppresses Proliferation and Survival of TW2.6 Human Oral Cancer Cells via Inhibition of Akt Signaling. *International journal of molecular sciences*, *14*(5), 8801-8817. https://doi.org/10.3390/ijms14058801

[74]. Lappalainen, U., Whitsett, J. A., Wert, S. E., Tichelaar, J. W., & Bry, K. (2005). Interleukin-1β Causes Pulmonary Inflammation, Emphysema, and Airway Remodeling in the Adult Murine Lung. *American journal of respiratory cell and molecular biology*, *32*(4), 311-318. https://doi.org/10.1165/rcmb.2004-0309oc

[75]. Laraia, L., Robke, L., & Waldmann, H. (2018). Bioactive Compound Collections: From Design to Target Identification. *Chem*, *4*(4), 705-730. https://doi.org/10.1016/j.chempr.2018.01.012

[76]. Lee, W.-H., Loo, C.-Y., Ghadiri, M., Leong, C. R., Young, P. M., & Traini, D. (2018). The potential to treat lung cancer via inhalation of repurposed drugs. *Advanced drug delivery reviews*, *133*(NA), 107-130. https://doi.org/10.1016/j.addr.2018.08.012

[77]. Li, J., Zhu, X., & Chen, J. Y. (2009). Building Disease-Specific Drug-Protein Connectivity Maps from Molecular Interaction Networks and PubMed Abstracts. *PLoS computational biology*, *5*(7), e1000450-NA. https://doi.org/10.1371/journal.pcbi.1000450

[78]. Liang, Y., Feng, G., Wu, L., Zhong, S., Gao, X., Tong, Y., Cui, W., Qin, Y., Xu, W., Xiao, X., Zhang, Z., Huang, G., & Zhou, X. (2019). Caffeic acid phenethyl ester suppressed growth and metastasis of nasopharyngeal carcinoma cells by inactivating the NF-κB pathway. *Drug design, development and therapy*, *13*(NA), 1335-1345. https://doi.org/10.2147/dddt.s199182

[79]. Liu, T. P., Hsieh, Y. Y., Chou, C. J., & Yang, P. M. (2018). Systematic polypharmacology and drug repurposing via an integrated L1000-based Connectivity Map database mining. *Royal Society open science*, *5*(11), 181321-181321. https://doi.org/10.1098/rsos.181321

[80]. Markowitz, G. J., Havel, L. S., Crowley, M. J., Ban, Y., Lee, S., Thalappillil, J. S., Narula, N., Bhinder, B., Elemento, O., Wong, S. T. C., Gao, D., Altorki, N. K., & Mittal, V. (2018). Immune reprogramming via PD-1 inhibition enhances early-stage lung cancer survival. *JCI insight*, *3*(13), NA-NA. https://doi.org/10.1172/jci.insight.96836

[81]. Mayilvaganan, M., & Sabitha, M. (2013). A cloud-based architecture for Big-Data analytics in smart grid: A proposal. *2013 IEEE International Conference on Computational Intelligence and Computing Research*, *NA*(NA), 1-4. https://doi.org/10.1109/iccic.2013.6724168

[82]. Md Mahamudur Rahaman, S. (2022). Electrical And Mechanical Troubleshooting in Medical And Diagnostic Device Manufacturing: A Systematic Review Of Industry Safety And Performance Protocols. *American Journal of Scholarly Research and Innovation*, *1*(01), 295-318. https://doi.org/10.63125/d68y3590

[83]. Md Masud, K. (2022). A Systematic Review Of Credit Risk Assessment Models In Emerging Economies: A Focus On Bangladesh's Commercial Banking Sector. *American Journal of Advanced Technology and Engineering Solutions*, *2*(01), 01-31. https://doi.org/10.63125/p7ym0327

[84]. Md Takbir Hossen, S., & Md Atiqur, R. (2022). Advancements In 3D Printing Techniques For Polymer Fiber-Reinforced Textile Composites: A Systematic Literature Review. *American Journal of Interdisciplinary Studies*, *3*(04), 32-60. https://doi.org/10.63125/s4r5m391

[85]. Minie, M., Chopra, G., Sethi, G., Horst, J. A., White, G. W. N., Roy, A., Hatti, K., & Samudrala, R. (2014). CANDO and the infinite drug discovery frontier. *Drug discovery today*, *19*(9), 1353-1363. https://doi.org/10.1016/j.drudis.2014.06.018

[86]. Moll, M., & Kuemmerle-Deschner, J. B. (2013). Inflammasome and cytokine blocking strategies in autoinflammatory disorders. *Clinical immunology (Orlando, Fla.)*, *147*(3), 242-275. https://doi.org/10.1016/j.clim.2013.04.008

[87]. Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of computational chemistry*, *30*(16), 2785-2791. https://doi.org/10.1002/jcc.21256

[88]. Morrone, J. A., Weber, J. K., Huynh, T., Luo, H., & Cornell, W. D. (2020). Combining Docking Pose Rank and Structure with Deep Learning Improves Protein–Ligand Binding Mode Prediction over a Baseline Docking Approach. *Journal of chemical information and modeling*, *60*(9), 4170-4179. https://doi.org/10.1021/acs.jcim.9b00927

[89]. Mouchlis, V. D., Afantitis, A., Serra, A., Fratello, M., Papadiamantis, A. G., Aidinis, V., Lynch, I., Greco, D., & Melagraki, G. (2021). Advances in de Novo Drug Design: From Conventional to Machine Learning Methods. *International journal of molecular sciences*, *22*(4), 1676-NA. https://doi.org/10.3390/ijms22041676

[90]. Mysinger, M. M., Carchia, M., Irwin, J. J., & Shoichet, B. K. (2012). Directory of Useful Decoys, Enhanced (DUD-E): Better Ligands and Decoys for Better Benchmarking. *Journal of medicinal chemistry*, *55*(14), 6582-6594. https://doi.org/10.1021/jm300687e

[91]. Öztürk, H., Özgür, A., & Ozkirimli, E. (2018). DeepDTA: deep drug–target binding affinity prediction. *Bioinformatics (Oxford, England)*, *34*(17), i821-i829. https://doi.org/10.1093/bioinformatics/bty593

[92]. Park, J., & Baek, S. H. (2020). Combination Therapy with Cinnamaldehyde and Hyperthermia Induces Apoptosis of A549 Non-Small Cell Lung Carcinoma Cells via Regulation of Reactive Oxygen Species and Mitogen-Activated Protein Kinase Family. *International journal of molecular sciences*, *21*(17), 6229-NA. https://doi.org/10.3390/ijms21176229

[93]. Prado-Prado, F. J., García-Mera, X., Escobar, M., Alonso, N., Caamaño, O., Yáñez, M., & González-Díaz, H. (2012). 3D MI-DRAGON: New Model for the Reconstruction of US FDA Drug- Target Network and Theoretical-Experimental Studies of Inhibitors of Rasagiline Derivatives for AChE. *Current topics in medicinal chemistry*, *12*(16), 1843-1865. https://doi.org/10.2174/1568026611209061843

[94]. Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A. D., Doig, A. J., Guilliams, T., Latimer, J., McNamee, C. J., Norris, A., Sanseau, P., Cavalla, D., & Pirmohamed, M. (2018). Drug repurposing: progress, challenges and recommendations. *Nature reviews. Drug discovery*, *18*(1), 41-58. https://doi.org/10.1038/nrd.2018.168

[95]. Qu, Z., Sun, F., Zhou, J., Li, L., Shapiro, S. D., & Xiao, G. (2015). Interleukin-6 Prevents the Initiation but Enhances the Progression of Lung Cancer. *Cancer research*, *75*(16), 3209-3215. https://doi.org/10.1158/0008-5472.can-14-3042

[96]. Rastegar-Mojarad, M., Ye, Z., Kolesar, J. M., Hebbring, S. J., & Lin, S. (2015). Opportunities for drug repositioning from phenome-wide association studies. *Nature biotechnology*, *33*(4), 342-345. https://doi.org/10.1038/nbt.3183

[97]. Rodríguez-Vázquez, Á., Fernández-Berni, J., Lenero-Bardallo, J. A., Vornicu, I., & Carmona-Galan, R. (2018). CMOS Vision Sensors: Embedding Computer Vision at Imaging Front-Ends. *IEEE Circuits and Systems Magazine*, *18*(2), 90-107. https://doi.org/10.1109/mcas.2018.2821772

[98]. Rodriguez, J. M. M., Glozak, M. A., Ma, Y., & Cress, W. D. (2006). Bok, Bcl-2-related Ovarian Killer, Is Cell Cycle-regulated and Sensitizes to Stress-induced Apoptosis. *The Journal of biological chemistry*, *281*(32), 22729-22735. https://doi.org/10.1074/jbc.m604705200

[99]. Romero-Duran, F. J., Alonso, N., Yáñez, M., Caamaño, O., García-Mera, X., & González-Díaz, H. (2015). Brain-inspired cheminformatics of drug-target brain interactome, synthesis, and assay of TVP1022 derivatives. *Neuropharmacology*, *103*(NA), 270-278. https://doi.org/10.1016/j.neuropharm.2015.12.019

[100]. Sanseau, P., Agarwal, P. K., Barnes, M. R., Pastinen, T., Richards, J. B., Cardon, L. R., & Mooser, V. (2012). Use of genome-wide association studies for drug repositioning. *Nature biotechnology*, *30*(4), 317-320. https://doi.org/10.1038/nbt.2151

[101]. Sardana, D., Zhu, C., Zhang, M., Gudivada, R. C., Yang, L., & Jegga, A. G. (2011). Drug repositioning for orphan diseases. *Briefings in bioinformatics*, *12*(4), 346-356. https://doi.org/10.1093/bib/bbr021

[102]. Sato, T., de Camargo Reis Mello, D., de Vasconcellos, L. M. R., Valente, A. J. M., & Borges, A. W. (2020). Chitosan-Based Coacervate Polymers for Propolis Encapsulation: Release and Cytotoxicity Studies. *International journal of molecular sciences*, *21*(12), 4561-NA. https://doi.org/10.3390/ijms21124561

[103]. Sazzad, I., & Md Nazrul Islam, K. (2022). Project impact assessment frameworks in nonprofit development: a review of case studies from south asia. *American Journal of Scholarly Research and Innovation*, *1*(01), 270-294. https://doi.org/10.63125/eeja0t77

[104]. Schrank, Z., Chhabra, G., S, L. L., Iderzorig, T., Osude, C., Khan, N., Kuckovic, A., Singh, S., Miller, R. J., & Puri, N. (2018). Current Molecular-Targeted Therapies in NSCLC and Their Mechanism of Resistance. *Cancers*, *10*(7), 224-NA. https://doi.org/10.3390/cancers10070224

[105]. Schroeder, V., Savagatrup, S., He, M., Lin, S., & Swager, T. M. (2018). Carbon Nanotube Chemical Sensors. *Chemical reviews*, *119*(1), 599-663. https://doi.org/10.1021/acs.chemrev.8b00340

[106]. Shameer, K., Glicksberg, B. S., Hodos, R. A., Johnson, K. W., Badgeley, M. A., Readhead, B., Tomlinson, M. S., O'Connor, T., Miotto, R., Kidd, B. A., Chen, R., Ma'ayan, A., & Dudley, J. T. (2017). Systematic analyses of drugs and disease indications in RepurposeDB reveal pharmacological, biological and epidemiological factors influencing drug repositioning. *Briefings in bioinformatics*, *19*(4), 656-678. https://doi.org/10.1093/bib/bbw136

[107]. Shen, X., Liu, Y., Luo, X., & Yang, Z. (2019). Advances in Biosynthesis, Pharmacology, and Pharmacokinetics of Pinocembrin, a Promising Natural Small-Molecule Drug. *Molecules (Basel, Switzerland)*, *24*(12), 2323-NA. https://doi.org/10.3390/molecules24122323

[108]. Shi, J., Yang, F., Zhou, N., Jiang, Y., Zhao, Y., Zhu, J., Prelaj, A., Malhotra, J., Normanno, N., Danese, E., Cardona, A. F., Hong, X., Jiang, G., & Song, X. (2021). Isochorismatase domain-containing protein 1 (ISOC1) participates in DNA damage repair and inflammation-related pathways to promote lung cancer development. *Translational lung cancer research*, *10*(3), 1444-1456. https://doi.org/10.21037/tlcr-21-219

[109]. Singh, N., & Villoutreix, B. O. (2022). A Hybrid Docking and Machine Learning Approach to Enhance the Performance of Virtual Screening Carried out on Protein-Protein Interfaces. *International journal of molecular sciences*, *23*(22), 14364-14364. https://doi.org/10.3390/ijms232214364

[110]. Smalley, E. (2017). AI-powered drug discovery captures pharma interest. *Nature biotechnology*, *35*(7), 604-605. https://doi.org/10.1038/nbt0717-604

[111]. Somolinos, F. J., León, C., & Guerrero-Aspizua, S. (2021). Drug Repurposing Using Biological Networks. *Processes*, *9*(6), 1057-NA. https://doi.org/10.3390/pr9061057

[112]. Speck-Planche, A. (2018). Combining Ensemble Learning with a Fragment-Based Topological Approach To Generate New Molecular Diversity in Drug Discovery: In Silico Design of Hsp90 Inhibitors. *ACS omega*, *3*(11), 14704-14716. https://doi.org/10.1021/acsomega.8b02419

[113]. Speck-Planche, A., & Kleandrova, V. V. (2020). Chapter 16:Demystifying Artificial Neural Networks as Generators of New Chemical Knowledge: Antimalarial Drug Discovery as a Case Study. In (Vol. NA, pp. 398-423). The Royal Society of Chemistry. https://doi.org/10.1039/9781839160233-00398

[114]. Speck-Planche, A., & Scotti, M. T. (2018). BET bromodomain inhibitors: fragment-based in silico design using multi-target QSAR models. *Molecular diversity*, *23*(3), 555-572. https://doi.org/10.1007/s11030-018-9890-8

[115]. Sternitzke, C. (2014). Drug repurposing and the prior art patents of competitors. *Drug discovery today*, *19*(12), 1841-1847. https://doi.org/10.1016/j.drudis.2014.09.016

[116]. Stokes, J. M., Yang, K., Swanson, K., Jin, W., Cubillos-Ruiz, A., Donghia, N. M., MacNair, C. R., French, S., Carfrae, L. A., Bloom-Ackermann, Z., Tran, V. M., Chiappino-Pepe, A., Badran, A. H., Andrews, I. W., Chory, E. J., Church, G. M., Brown, E. D., Jaakkola, T. S., Barzilay, R., & Collins, J. J. (2020). A Deep Learning Approach to Antibiotic Discovery. *Cell*, *180*(4), 688-702.e613. https://doi.org/10.1016/j.cell.2020.01.021

[117]. Sui, H., Ma, N., Wang, Y., Li, H., Liu, X., Su, Y., & Yang, J. (2018). Anti-PD-1/PD-L1 Therapy for Non-Small-Cell Lung Cancer: Toward Personalized Medicine and Combination Strategies. *Journal of immunology research*, *2018*(2018), 6984948-6984948. https://doi.org/10.1155/2018/6984948

[118]. Talevi, A., & Bellera, C. L. (2019). Challenges and opportunities with drug repurposing: finding strategies to find alternative uses of therapeutics. *Expert opinion on drug discovery*, *15*(4), 397-401. https://doi.org/10.1080/17460441.2020.1704729

[119]. Tang, J., Tanoli, Z., Ravikumar, B., Alam, Z., Rebane, A., Vähä-Koskela, M., Peddinti, G., van Adrichem, A. J., Wakkinen, J., Jaiswal, A., Karjalainen, E., Gautam, P., He, L., Parri, E., Khan, S. A., Gupta, A., Ali, M., Yetukuri, L., Gustavsson, A.-L., . . . Aittokallio, T. (2017). Drug Target Commons: A Community Effort to Build a Consensus Knowledge Base for Drug-Target Interactions. *Cell chemical biology*, *25*(2), 224-229.e222. https://doi.org/10.1016/j.chembiol.2017.11.009

[120]. Tanoli, Z., Vähä-Koskela, M., & Aittokallio, T. (2021). Artificial intelligence, machine learning, and drug repurposing in cancer. *Expert opinion on drug discovery*, *16*(9), 1-13. https://doi.org/10.1080/17460441.2021.1883585

[121]. Trott, O., & Olson, A. J. (2009). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of computational chemistry*, *31*(2), 455-461. https://doi.org/10.1002/jcc.21334

[122]. Tsou, L. K., Yeh, S. H., Ueng, S.-H., Chang, C.-P., Song, J.-S., Wu, M.-H., Chang, H.-F., Chen, S.-R., Shih, C., Chen, C.-T., & Ke, Y.-Y. (2020). Comparative study between deep learning and QSAR classifications for TNBC inhibitors and novel GPCR agonist discovery. *Scientific reports*, *10*(1), 16771-16771. https://doi.org/10.1038/s41598-020-73681-1

[123]. Tundis, R., Frattaruolo, L., Carullo, G., Armentano, B., Badolato, M., Loizzo, M. R., Aiello, F., & Cappello, A. R. (2018). An ancient remedial repurposing: synthesis of new pinocembrin fatty acid acyl derivatives as potential antimicrobial/anti-inflammatory agents. *Natural product research*, *33*(2), 162-168. https://doi.org/10.1080/14786419.2018.1440224

[124]. Uddin, N. (2018). Assessing urban sustainability of slum settlements in Bangladesh: Evidence from Chittagong city. *Journal of Urban Management*, *7*(1), 32-42. https://doi.org/10.1016/j.jum.2018.03.002

[125]. Urista, D. V., Carrué, D. B., Otero, I., Arrasate, S., Quevedo-Tumailli, V., Gestal, M., González-Díaz, H., & Munteanu, C. R. (2020). Prediction of Antimalarial Drug-Decorated Nanoparticle Delivery Systems with Random Forest Models. *Biology*, *9*(8), 198-NA. https://doi.org/10.3390/biology9080198

[126]. Vanunu, O., Magger, O., Ruppin, E., Shlomi, T., & Sharan, R. (2010). Associating Genes and Protein Complexes with Disease via Network Propagation. *PLoS computational biology*, *6*(1), 1-9. https://doi.org/10.1371/journal.pcbi.1000641

[127]. Vasconcelos, N. G., Croda, J., & Simionatto, S. (2018). Antibacterial mechanisms of cinnamon and its constituents: A review. *Microbial pathogenesis*, *120*(NA), 198-203. https://doi.org/10.1016/j.micpath.2018.04.036

[128]. Wallach, I., Dzamba, M., & Heifets, A. (2015). AtomNet: A Deep Convolutional Neural Network for Bioactivity Prediction in Structure-based Drug Discovery. *arXiv: Learning*, *NA*(NA), NA-NA. https://doi.org/NA

[129]. Wang, F., Wu, F.-X., Li, C.-Z., Jia, C.-Y., Su, S.-W., Hao, G.-F., & Yang, G.-F. (2019). ACID: a free tool for drug repurposing using consensus inverse docking strategy. *Journal of cheminformatics*, *11*(1), 1-11. https://doi.org/10.1186/s13321-019-0394-z

[130]. Wang, J., Zhang, T., Du, J., Cui, S., Yang, F., & Jin, Q. (2014). Anti-Enterovirus 71 Effects of Chrysin and Its Phosphate Ester. *PloS one*, *9*(3), e89668-NA. https://doi.org/10.1371/journal.pone.0089668

[131]. Wen, M., Deng, Z.-K., Jiang, S.-l., Guan, Y.-D., Wu, H.-z., Wang, X.-l., Xiao, S.-s., Zhang, Y., Yang, J. M., Cao, D.-S., & Cheng, Y. (2019). Identification of a Novel Bcl-2 Inhibitor by Ligand-Based Screening and Investigation of Its Anti-cancer Effect on Human Breast Cancer Cells. *Frontiers in pharmacology*, *10*(NA), 391-NA. https://doi.org/10.3389/fphar.2019.00391

[132]. Wishart, D. S., Feunang, Y. D., Guo, A. C., Lo, E. J., Marcu, A., Grant, J. R., Sajed, T., Johnson, D., Li, C., Sayeeda, Z., Assempour, N., Iynkkaran, I., Liu, Y., Maciejewski, A., Gale, N., Wilson, A., Chin, L., Cummings, R., Le, D., . . . Wilson, M. (2017). DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic acids research*, *46*(D1), D1074-D1082. https://doi.org/10.1093/nar/gkx1037

[133]. Wislez, M., Fujimoto, N., Izzo, J. G., Hanna, A. E., Cody, D. D., Langley, R. R., Tang, H., Burdick, M. D., Sato, M., Minna, J. D., Mao, L., Wistuba, I. I., Strieter, R. M., & Kurie, J. M. (2006). High expression of ligands for chemokine receptor CXCR2 in alveolar epithelial neoplasia induced by oncogenic kras. *Cancer research*, *66*(8), 4198-4207. https://doi.org/10.1158/0008-5472.can-05-3842

[134]. Wisner, B., Mazur, K., Perumal, V. I., Baxevanakis, K. P., An, L., Feng, G., & Kontsos, A. (2019). Acoustic emission signal processing framework to identify fracture in aluminum alloys. *Engineering Fracture Mechanics*, *210*(NA), 367-380. https://doi.org/10.1016/j.engfracmech.2018.04.027

[135]. Wu, C. T., Zhang, J., Liu, T., Jiao, G., Li, C. Z., & Hu, B. (2016). Astaxanthin inhibits proliferation and promotes apoptosis of A549 lung cancer cells via blocking JAK1/STAT3 pathway. *Xi bao yu fen zi mian yi xue za zhi = Chinese journal of cellular and molecular immunology*, *32*(6), 784-788. https://doi.org/NA

[136]. Wu, C. Y., Cherng, J. Y., Yang, Y.-H., Lin, C.-L., Kuan, F. C., Lin, Y. Y., Lin, Y.-S., Shu, L. H., Cheng, Y.-C., Liu, H. T., Lu, M. C., Lung, J., Chen, P.-C., Lin, H. K., Der Lee, K., & Tsai, Y.-H. (2017). Danshen improves survival of patients with advanced lung cancer and targeting the relationship between macrophages and lung cancer cells. *Oncotarget*, *8*(53), 90925-90947. https://doi.org/10.18632/oncotarget.18767

[137]. Wu, J., Li, J., He, Y., Huang, J., Zhao, X., Pan, B., Wang, Y., Cheng, L., & Han, J. (2022). DrugSim2DR: systematic prediction of drug functional similarities in the context of specific disease for drug repurposing. *GigaScience*, *12*(NA), NA-NA. https://doi.org/10.1093/gigascience/giad104

[138]. Wu, J., Li, X., Wang, Q., & Han, J. (2022). DRviaSPCN: a software package for drug repurposing in cancer via a subpathway crosstalk network. *Bioinformatics (Oxford, England)*, *38*(21), 4975-4977. https://doi.org/10.1093/bioinformatics/btac611

[139]. Xu, J., Mao, C., Hou, Y., Luo, Y., Binder, J. L., Zhou, Y., Bekris, L. M., Shin, J., Hu, M., Wang, F., Eng, C., Oprea, T. I., Flanagan, M. E., Pieper, A. A., Cummings, J., Leverenz, J. B., & Cheng, F. (2022). Interpretable deep learning translation of GWAS and multi-omics findings to identify pathobiology and drug repurposing in Alzheimer's disease. *Cell reports*, *41*(9), 111717-111717. https://doi.org/10.1016/j.celrep.2022.111717

[140]. Yamanishi, Y. (2012). Chemogenomic Approaches to Infer Drug–Target Interaction Networks. *Methods in molecular biology (Clifton, N.J.)*, *939*(NA), 97-113. https://doi.org/10.1007/978-1-62703-107-3_9

[141]. Yang, Y., Li, N., Wang, T.-M., & Di, L. (2021). Natural Products with Activity against Lung Cancer: A Review Focusing on the Tumor Microenvironment. *International journal of molecular sciences*, *22*(19), 10827-NA. https://doi.org/10.3390/ijms221910827

[142]. Yella, J., Yaddanapudi, S., Wang, Y., & Jegga, A. G. (2018). Changing Trends in Computational Drug Repositioning. *Pharmaceuticals (Basel, Switzerland)*, *11*(2), 57-NA. https://doi.org/10.3390/ph11020057

[143]. Yoshimura, T. (2018). The chemokine MCP-1 (CCL2) in the host interaction with cancer: a foe or ally? *Cellular & molecular immunology*, *15*(4), 335-345. https://doi.org/10.1038/cmi.2017.135

[144]. Zeng, X., Zhu, S., Liu, X., Zhou, Y., Nussinov, R., & Cheng, F. (2019). deepDR: a network-based deep learning approach to in silico drug repositioning. *Bioinformatics (Oxford, England)*, *35*(24), 5191-5198. https://doi.org/10.1093/bioinformatics/btz418

[145]. Zhang, J.-L., Shen, X., Wang, K., Cao, X., Zhang, C.-P., Zheng, H., & Hu, F. (2016). Antioxidant activities and molecular mechanisms of the ethanol extracts of Baccharis propolis and Eucalyptus propolis in RAW64.7 cells. *Pharmaceutical biology*, *54*(10), 2220-2235. https://doi.org/10.3109/13880209.2016.1151444

[146]. Zhang, M., Schmitt-Ulms, G., Sato, C., Xi, Z., Zhang, Y., Zhou, Y., St George-Hyslop, P., & Rogaeva, E. (2016). Drug Repositioning for Alzheimer's Disease Based on Systematic 'omics' Data Mining. *PloS one*, *11*(12), e0168812-NA. https://doi.org/10.1371/journal.pone.0168812

[147]. Zhang, Y., Bian, Y., Wang, Y., Wang, Y., Duan, X., Han, Y., Zhang, L., Wang, F., Gu, Z., & Qin, Z. (2021). HIF-1a is necessary for activation and tumour-promotion effect of cancer-associated fibroblasts in lung cancer. *Journal of cellular and molecular medicine*, *25*(12), 5457-5469. https://doi.org/10.1111/jcmm.16556

[148]. Zhang, Y., Jiang, Z., Cheng, C., Wei, Q., Gu, H.-M., & Yu, B. (2021). DeepStack-DTIs: Predicting Drug–Target Interactions Using LightGBM Feature Selection and Deep-Stacked Ensemble Classifier. *Interdisciplinary sciences, computational life sciences*, *14*(2), 1-20. https://doi.org/10.1007/s12539-021-00488-7

[149]. Zheng, S., Li, Y., Chen, S., Xu, J., & Yang, Y. (2020). Publisher Correction: Predicting drug–protein interaction using quasi-visual question answering system. *Nature Machine Intelligence*, *2*(9), 551-551. https://doi.org/10.1038/s42256-020-0224-z

[150]. Zong, N., Kim, H., Ngo, V., & Harismendy, O. (2017). Deep mining heterogeneous networks of biomedical linked data to predict novel drug-target associations. *Bioinformatics (Oxford, England)*, *33*(15), 2337-2344. https://doi.org/10.1093/bioinformatics/btx160