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A Review of Molecular Targets for In-Silico Validation of Pharmacological Activity

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ABSTRACT

Historically, the proof of safety and efficacy that corporations submit to regulatory bodies to support marketing authorisation requests for new medical products has been generated experimentally, either in vitro or in vivo. Recently, regulatory bodies have begun to receive and accept data acquired in silico, that is, through modelling and simulation. Before any technique, whether experimental or computational, may be deemed suitable for regulatory submission, it must first be regarded "qualified" by the regulatory agency. This entails evaluating the overall "credibility" of the approach in delivering specific evidence for a particular regulatory procedure. This research delineates numerous molecular targets employed to assess pharmacological potential using *in-silico* methodologies.

Key Words *In -silico* validation, Target Molecules & Pharmacological Activity

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INTRODUCTION

Modelling and simulation are conventional practices in several industrial sectors, serving to facilitate the design and mitigate risks associated with the assessment of safety and performance of new products. Computer modelling and simulation of people in both health and illness serve as a potent instrument in biomedical research, enhancing experimental and clinical studies through intricate mechanistic and systematic analyses that are unattainable by alternative methods. A substantial corpus of research in biomedicine has enhanced the legitimacy of modelling and simulation outside academic confines, with active engagement being observed in regulatory bodies and industry. Consequently, human in silico clinical trials are currently emerging as a significant paradigm in the advancement of medical therapeutics[1]. The phrase "*in-silico drug discovery*" refers to the methodology of finding and creating potential drug candidates via computational approaches. This concept employs supplementary molecular modelling tools with computer-aided drug design (CADD) techniques, including virtual ligand screening and profiling, in silico structure prediction, refinement, and optimisation. In-silico drug discovery has become a crucial element of

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modern pharmacological research since it reduces the time and resources required to identify and enhance therapeutic candidates[2]. To optimise the probability of identifying effective drug candidates, *in-silico* methods are often integrated with physical screening techniques[3]. Drug development significantly benefits from in-silico research for several reasons. They enhance the identification of promising drug candidates by streamlining the screening, design, and prediction of therapeutic efficacy of novel drugs[4]. Moreover, in-silico approaches facilitate toxicity prediction, allowing research teams to identify potentially detrimental impacts early in the development process, thereby conserving time and resources. Computational tools such as virtual ligand screening, molecular modelling, and docking-based virtual screening facilitate the identification of novel and promising compounds by predicting the binding modes of potential therapeutic candidates and analysing their interaction patterns. Furthermore, in-silico research enhances the flexibility and ethical integrity of early drug development by leveraging existing information to inform subsequent methodologies. Considering all factors, the benefits of in-silico drug discovery have led to the formation of a $8.3 billion annual business in 2022, and this trend is expected to persist[5].The basic in-silico approaches shown in fig.1.

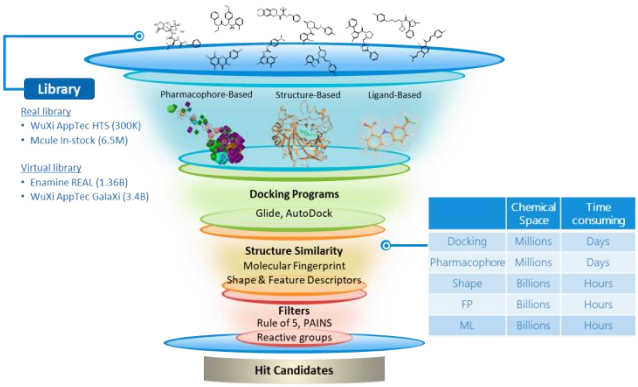

Figure 1 *In-Silico* drug designing approaches. Selection of Molecular target for screening of pharmacological potential

Anthelmintic Activity

Molecular docking of anthelmintic drug with β-tubulin to study the activity by drug-tubulin interaction is already proven by Grace basumatary etal;2020 because inhibition of β -tubulin of the helminths can severely affect their vital cellular functions such as mitosis, motility, and transport[6].

Anti-rheumatoid Activity

HK2 is highly upregulated in activated T cells and plays important roles in B cell lymphoma cell apoptosis. In human monocyte-derived DCs, Toll-like receptor (TLR)-4-dependent upregulation of glycolysis leads to enhanced HK2 activity involving p38-MAPK-dependent hypoxia inducible factor-1(HIF-1) accumulation. Besides, phosphoinositide-3-kinase (PI3K)/AKT pathways are involved in the phosphorylation of rate-limiting mitochondrial HK2. Janus kinase/Signal transducer and activators of transcription (JAK/STAT) signaling was also revealed to mediate glucose uptake and HK2 expression. Observation suggested that aberrant expression of HK2 may associate with pathological changes in RA by mediating related

signalling pathways. More surprisingly, HK2 antagonists, including ablation of glycolytic genes or treatment with 3-bromopyruvate, significantly relieved the severity of several arthritis models. Targeting a specific intracellular compartment of HK2 (i.e., nucleus, cytosol, or mitochondria) will provide a selective way to block the harmful effect of the enzyme in RA without affecting the glucose metabolism of normal cells. Therefore, HK2 is an attractive and selective target for the treatment of arthritis and is safer than global glucose metabolism inhibition[7].

GLS1, the enzyme responsible for the conversion of glutamine to glutamate, directly checks RAFLS proliferation, thereby mitigating the pathological intensity of the autoimmune disease, arthritis. Escalated levels of glutamate populate the synovial fluid of patients affected with RA. This directly associates with a raised level of IL-6. Hence, inhibition of these metabolic enzymes provides cell-specific, novel biological therapeutic targets for the development of novel compounds against RA[8] suggested by Flood S etal;2004.

Anti-diarrheal potential

Increased smooth muscle contraction (M3), gastric acid production from the parietal (oxyntic) cells of the stomach, and intestinal digesting enzyme release are all responses of the gut to muscarinic agonists. the effects of an antagonist on the oxyntic cell's M3 receptors when acting directly. Muscarinic antagonists block the M3 receptor-mediated contractions of the gastrointestinal tract brought on by Ach and other muscarinic agonists. However, they often aren't as efficient in reducing the contraction and motility that parasympathetic nerve stimulation causes. Irritable bowel syndrome (IBS), which is characterised by diarrhoea related to inflammation of the lower colon, including mild dysentery and diverticulitis. Existing drugs for the treatment of IBS, such as mebeverine, cimetropium and milverine have additional properties including Ca^{2+} channel blockade which contributes to their antispasmodic activity by Kenneth J etal;2001. There is therefore a need for selective M3 receptor antagonists for the treatment of gastrointestinal tract disorders[9].

Aphrodisiacs Activity

PDE5 is an enzyme found primarily in the smooth muscle of the corpus cavernosum that selectively cleaves and degrades cGMP to 5′-GMP. *PDE5* inhibitors are similar in structure to cGMP; they competitively bind to PDE5 and inhibit cGMP hydrolysis, thus enhancing the effects of NO. This increase in cGMP in the smooth muscle cells is responsible for prolonging an erection. *PDE-5* inhibitors lack a direct effect on corpus cavernosum smooth-muscle relaxation. Therefore, after administration, adequate sexual stimulation is necessary for an erection to occur[10].

Diuretic potential

Urea transporters have a significant impact on urine concentration (UTs). UT-A and UT-B are the names of the two UT subgroups. From a single gene, SLC14a2, six isoforms of the UT-A

subfamily—UT-A1 through UT-A6—are generated through alternative splicing and promoters. UT-A1 and UT-A3 are expressed in the renal inner medullary collecting duct, UT-A2 is detected in the thin descending limb, and UT-A4 mRNA is identified in the rat kidney medulla, despite the fact that endogenous expression of UT-A4 protein in the kidney has not been validated. The testes and colon, respectively, contain UT-A5 and UT-A6. The major locations of UT-B, which is encoded by the gene SLC14a1, are the descending vasa recta, the heart, colon, testis, bladder, brain, and erythrocytes. The ability of the kidney to concentrate urine can be decreased by selective UT inhibition, which also has the effect of producing a urea-selective diuretic without affecting the excretion of Na+, K+, or Cl. In order to limit urea recycling in the kidney and hence reduce the osmotic pressure gradient in the kidney, it is thought that UT inhibitors can have a diuretic effect[11].

Anti-androgenetic alopecia

5α-reducatase(SRD5As) enzyme is dihydronicotinamide adenine dinucleotide phosphate (NADPH)-dependent and play a significant role in steroidogenesis by catalysing 4-ene-3-keto steroids into more active 5α-reduced derivatives, including the reduction of testosterone (T) to dihydrotestosterone (DHT). Dihydrotestosterone (DHT), the most potent androgen hormone, is an important aetiologic factor of androgenetic alopecia (AGA), or hair loss. Steroid 5-alpha reductases (SRD5As) increase DHT production in the scalp hair follicles, resulting in hair thinning and hair loss. Even though synthetic SRD5A inhibitors (finasteride and dutasteride) are effective in treating AGA, they cause adverse effects[12].

Anti-pancreatitis activity

Several years of experimental studies have implicated nuclear factor-kappa B (NF-κB) activation as an early and central event in the progression of inflammation in AP. As per Jakkampudi A etal;2016 NF-κB, being a central molecule that links the initial acinar injury to systemic inflammation and perpetuate the inflammation[13].

Anti- SARS-CoV-2 Activity

SARS-CoV-2 helicase ***Nsp13*** has both ATPase and helicase activity, as it unwinds the RNA helices in an ATP-dependent manner. Remarkably, due to its high sequence conservation across the corona virus family, Nsp13 is considered an attractive target for the development of antiviral drugs. Also, it was shown that SARS-CoV-2 helicase Nsp13 can hydrolyze all types of NTPs including ATP to unwind the RNA helices. Therefore, the known ATP-binding site of the helicase Nsp13 is a promising target for effective inhibition. The outcome of investigation of docking analysis, chemical interactions, followed by the physicochemical based pharmacokinetic profiling has revealed that the flavonoid is executing its antiviral action *via* inhibiting SAR CoV Helicase thereby hindered the ATPase and helicase

activity, as it unwinds the RNA helices in an ATP-dependent pattern[14].

Mpro is an indispensable enzyme for viral replication and transcription. Coronaviruses possess the largest known RNA genomes with a length of about 30 kb.21 Their genomes consist of multiple open-reading frames (ORFs). Among them, two overlapping ORFs (ORF1a and ORF1ab) are translated into two large polyproteins, pp1a and pp1ab, via a −1 translation frameshift mechanism. Then, Mpro and papain-like protease (PLpro)22 cleave pp1a and pp1ab into 16 mature nonstructural proteins (NSPs).23 Mpro formed from NSP5 cleaves the two polyproteins at 11 recognition sites and creates NSP4 to NSP10 and NSP12 to NSP16 (NSP11 is the N terminal end of NSP12), while PLpro cleaves the other 3 sites to generate NSP1 to NSP3. Notably, NSP4 to NSP16 cleaved by Mpro contain many essential viral proteins, especially the RNA-dependent RNA polymerase (NSP12), RNA binding proteins (NSP9), helicase (NSP13), exoribonuclease (NSP14), and methyltransferase (NSP16).24,25 Therefore, effectively blocking Mpro could stop SARS-CoV-2 replication in human bodies and cure the disease. Second, according to the data from the global initiative on sharing all influenza data (GISAID), SARS-COV-2 Mpro is highly conserved. The mutation rate on its binding domain is lower than 0.001. Thus, mutations will not broadly impact the efficacy of SARS-CoV-2 Mpro inhibitors[15].

Anti-tuberculosis Potential

InhA catalyzes the discount of long-chain trans-2-enoyl-ACP with inside the type II fatty acid biosynthesis pathway of M. tuberculosis. Inhibition of InhA disrupts the biosynthesis of the mycolic acids which might be critical components of the mycobacterial cell wall. The final results of the existing research found out that the chosen molecule highly bounded with InhA thereby inhibiting the mycobacterial cell wall synthesis[16].

Cardioprotective potential

Modifications in cardiac energy metabolism significantly contribute to the elevated prevalence and severity of heart disease globally. These modifications may involve a reduction in ATP generation required to satisfy the heart's elevated energy demands, alongside detrimental shifts in the heart's energy substrate choice. Regarding this last issue, research indicates that a reduction in cardiac efficiency, resulting from an elevation in cardiac fatty acid oxidation and/or an increase in the uncoupling of glycolysis from glucose oxidation, detrimentally affects cardiac function and contributes to heart illness. Therapeutic techniques that regulate these metabolic pathways and enhance cardiac efficiency have advantageous outcomes in the context of heart disease. One method involves elevating cardiac malonyl CoA levels, a crucial inhibitor of mitochondrial fatty acid absorption. This encompasses the inhibition of malonyl CoA decarboxylase (MCD), leading to elevated cardiac malonyl CoA concentrations, reduced

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cardiac fatty acid oxidation rates, and enhanced cardiac efficiency[17].

Anti-depressant Activity

Nitric oxide is recognized for its substantial involvement in the pathophysiology of numerous bodily illnesses. Notwithstanding its brief half-life, nitric oxide is recognized for modulating different neurotransmitter systems in the body, suggesting its crucial involvement in the etiology of neurological illnesses. This "wonder" molecule frequently exhibits a "dual role" in many brain diseases. Evidence has demonstrated its significant significance in the etiology of severe depression. Nitric oxide regulates norepinephrine, serotonin, dopamine, and glutamate, the principal neurotransmitters implicated in the neurobiology of major depression. The nitric oxide modulatory effects of numerous new-generation antidepressants have been established. Nitric oxide is produced from l-arginine by the action of a NOS enzyme. NOS is a meticulously controlled enzyme including a heme domain that associates with the flavin mononucleotide (FMN)/flavin adenine dinucleotide (FAD) reductase enzyme, facilitating the transfer of electrons from nicotinamide adenine dinucleotide phosphate (NADPH) to the heme component.Three kinds of nitric oxide synthase (NOS) are recognized in mammals: nNOS (neuronal NOS; type I), iNOS (inducible NOS; type II), and eNOS (endothelial NOS; type III). All three isoforms of NOS are known to be expressed in various areas of the brain. Both nNOS and eNOS are constitutively expressed in the brain and are dependent on calcium/calmodulin. Nonetheless, research has demonstrated that these two isoforms of NOS may also be activated under specific stressful circumstances. Conversely, the expression of iNOS is meticulously regulated and is independent of calcium. nNOS is located in various regions of the brain linked to stress and depression, specifically the hippocampus, hypothalamus, dorsal raphe nucleus, and locus coeruleus. Numerous studies in the literature have revealed the critical function of nitric oxide in serious depression. These citations include:

- Plasma nitric oxide metabolites are significantly elevated in suicidal patients compared to nonsuicidal psychiatric patients and normal control subjects. Additionally, a clinical study indicates increased nitric oxide production in depressed patients, implying altered nitric oxide levels in individuals with major depression.
- Reducing the levels or inhibiting the generation of nitric oxide (by blocking NOS) in the brain can produce antidepressant-like effects, so suggesting the involvement of endogenous hippocampal nitric oxide in the pathophysiology of major depression[18].

Hepatoprotective Potential

In the family of cysteine-containing aspartate-specific proteases known as caspases, caspase-3 is one of the most significant apoptotic proteases. It can be triggered by the upstream initiator and operate on the particular substrate, causing morphological changes in the cells that eventually lead to apoptosis, as it is a

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downstream effector in the cascade reaction. The cytoplasmic form of caspase-3 normally exists as an inactive zymogen. A death complex is created when tumour necrosis factor (TNF) and Fas-associated death domain (FADD) join. This complex activates caspase-2, caspase-8, and other enzyme sources upstream before activating caspase-3 downstream through a process known as transactivation. Caspase-3 controls cell death by cleaving structural and regulatory proteins in the nucleus and cytoplasm. Caspase-3 inhibitors are a key focus of hepatoprotective medication research in the clinic[19].

Anti-Proliferative Potential

Polo-like kinase 1 (PLK1) is an essential protein in communicating cell-cycle progression and DNA damage. Overexpression of PLK1 has been validated as a marker for poor prognosis in many cancers. PLK1 knockdown decreases the survival of cancer cells. PLK1 is therefore an attractive target for anticancer treatments. Several inhibitors have been developed, and some have been clinically tested to show additive effects with conventional therapies. Upstream regulation of PLK1 involves multiple interactions of proteins such as FoxM1, E2F and p21. Other cancer-related proteins such as pRB and p53 also indirectly influence PLK1 expression. With the high mutation rates of these genes seen in cancers, they may be associated with PLK1 deregulation. This raises the question of whether PLK1 overexpression is a cause or a consequence of oncogenesis[20]. Polo-like kinase 1 (PLK1) is overexpressed near ubiquitously across all cancer types and dysregulation of this enzyme is closely tied to increased chromosomal instability and tumor heterogeneity. PLK1 is a mitotic kinase with a critical role in maintaining chromosomal integrity through its function in processes ranging from the mitotic checkpoint, centrosome biogenesis, bipolar spindle formation, chromosome segregation, DNA replication licensing, DNA damage repair, and cytokinesis as illustrated in fig.2. The relation between dysregulated PLK1 and chromosomal instability (CIN) makes it an attractive target for cancer therapy[21].

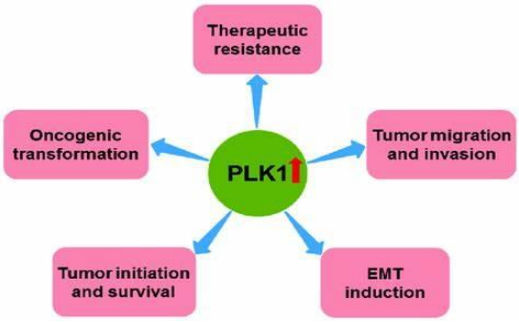

Figure 2 Role of PLK1 in cancer

Wound Healing Potential

Inflammation, matrix deposition, cell proliferation, tissue modelling, collagenation, and epithelialization are all components of the orderly and coordinated process of healing a wound as per 2012, Soni H et al[22-23]. It has been discovered that the glycogen synthase kinase-3 (GSK-3) protein, an important regulatory enzyme, is inhibited by the Wnt/b-catenin pathway, which promotes wound healing [24].

Anti-psoriatic arthritis Activity

Phosphodiesterase 4 (PDE4) is a principal phosphodiesterase found in immune cells (dendritic cells, T cells, macrophages, and

monocytes) and keratinocytes, and it catalyzes the hydrolysis of intracellular cyclic adenosine monophosphate (cAMP), a second messenger that mediates immunoregulatory effects. The synthesis of cAMP is modulated by hormonal activation of G-protein coupled receptors, which stimulate membrane-bound adenylyl cyclases to convert ATP into cAMP. PDE4 inhibitors are tiny compounds that target PDE4, resulting in elevated cytosolic cAMP levels, which then activate protein kinase A (PKA), exchange proteins 1/2 triggered by cAMP, and cyclic nucleotide-gated channels. PKA stimulates transcription factors such as cAMP-response element-binding protein (CREB), cAMP-responsive modulator (CREM), and ATF1 via phosphorylation, resulting in enhanced production of anti-inflammatory cytokines. The activation of these transcription factors results in the recruitment of coactivators CREB binding protein (CBP) or its homolog p300, which inhibits the proinflammatory transcription factor NF-κB by competing for these coactivators (CBP or p300). PDE4 modulates the production and signaling of essential cytokines implicated in the development of psoriasis[25].

Anti-fungal Potential

Fungal cell walls are essential for the viability, morphogenesis, and pathogenesis of fungi. Fungal cell walls are an attractive target for antifungal drug development because such a cellular structure is absent in human cells. Unlike the plant cell wall that is primarily made of cellulose (1,4-β-glucan), the fungal cell wall is composed mainly of 1,3-β-glucan, 1,6-β-glucan, chitin, and mannoproteins. Most approved and developing antifungal drugs that target the cell wall function by inhibiting GS [26].

Anti-obesity Activity

Reduced expression of NOX2 and NOX4 proteins and mRNA levels in 5/6Nx rats subjected to a high-fat diet. The reduction of ROS generation occurred in IMCD suspensions and mpkCCD cells. The inhibition of ROS generation caused by cholesterol in the kidney is likely due to the suppression of NOX protein expression and the enhancement of mitochondrial activity. Consequently, the inhibition of NOX2 and NOX4 may provide a viable therapeutic strategy for addressing obesity-related renal disorders[27].

Anti-diabetic Potential

Aldose reductase inhibitors are a category of pharmaceuticals that impede the degradation of glucose via the polyol pathway, potentially decelerating or reversing the advancement of neuropathy.Inhibiting aldose reductase to suppress glucose metabolism through the polyol route may prevent the aforementioned detrimental effects. Significant research over the past two decades has focused on evaluating the impact of aldose reductase inhibitors on human diabetic polyneuropathy[28].

Anti-microbial Activity

Current studies for the development of antibacterial drugs have focused on the aminoacyl-tRNA synthetase (AaRS) enzymes. By catalysing the creation of aminoacyl-tRNAs,

these enzymes serve crucial roles in protein biosynthesis (2). With this endeavor, natural plant Phenolics & flavonoids found in extracts of the plants known as, rosmarinic acid , chlorogenic acid rutin and quercetin has been identified as ligand and their aminoacyl-tRNA synthetase (AaRS) enzymes inhibitory activity has been checked *in-silico* with the help of docking approach[29].

Dihydrofolate reductase (DHFR): Finding new antifungals through the folate biosynthesis pathway is a promising yet unexplored avenue. Even the well-known and historically significant therapeutic target dihydrofolate reductase (DHFR) has not been proven to be an effective antifungal target. Here, we show that DHFR suppression prevents Candida albicans, a common human fungal infection, from growing[30].

Tetrahydrofolate (THF), when reduced, is a necessary cofactor for many cellular enzymes. It acts as a transporter for one-carbon (1C) units and facilitates their interconversion between different oxidation states. Along with many other significant metabolites, THF is necessary for the production of dTMP, purines, and methionine. Because they lack several of the enzymes needed to produce folate (FOL), mammals must obtain it through diet. For folic acid to enter cells and be transformed by dihydrofolate reductase (DHFR) into its active form, THF, a specific transport system is needed. Conversely, most prokaryotes and microbial eukaryotes must synthesis folic acid from scratch since they lack the transport systems present in humans. A great deal of success has been achieved in targeting the folate biosynthesis pathway in the creation of antibacterial, antiprotozoal, and anticancer medications.

Neurodegenerative diseases

For pharmacological intervention, the glutamatergic system continues to be a desirable chemical target. Potential treatment options for neurodegenerative diseases, epilepsy, schizophrenia, anxiety, and memory disorders include ligands acting on ionotropic glutamate receptors (iGluRs: NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isooxazolepropionic acid and kainate receptors) and metabotropic glutamate receptors (mGluRs). But only a small number of glutamate receptor ligands proved to be beneficial in therapeutic settings. Kainate receptor subfamily ligands appear to be particularly promising. Kainate receptors primarily mediate the mossy fibre long-term potentiation pathway, which is important in epileptogenesis and causing synaptic plasticity. Hence, kainate receptor antagonists have the potential to be both neuroprotective and anti-seizure medications[31].

5-HT1A: One of the serotonin receptors with the highest density in the brain is the 5-HT1A receptor. The primary biophysical consequence of serotonin binding to the 5-HT1A receptor is the activation of hyperpolarizing K+ channels, which is G-protein coupled. This receptor participates in a variety of additional chemical cascades, such as controlling phospholipase-C

activity, preventing cAMP from building up, and inhibiting decreasing calcium currents. Less serotonin is delivered into presynaptic neurons from the synapse when presynaptic serotonin transporters (5-HTT) are inhibited. As a result, the amount of serotonin in the synapse rises. The pre-synaptic autoreceptors on the soma of raphe neurons are where the increased serotonin first binds. Through hyperpolarization, this binding inhibits the firing of action potentials from these neurons, which results in a reduction in serotonin production[32].

Nitric oxide (NOS): It is well recognized that nitric oxide has a profound impact on the pathophysiology of numerous bodily illnesses. Nitric oxide is known to influence several neurotransmitter systems in the body despite having a very short half-life, and as a result, it is hypothesized to play a crucial role in the aetiology of neurological illnesses. It has frequently been discovered that this "wonder" molecule has a "dual role" in a variety of bodily neurological illnesses. Evidence has demonstrated that it has a significant role in the development of serious depression. Norepinephrine, serotonin, dopamine, and glutamate, the four main neurotransmitters involved in the neurobiology of major depression, are modulated by nitric oxide. Numerous new generations of antidepressants have been shown to modulate nitric oxide[33].

CREB1: CREB is a nuclear protein that is a member of the family of leucine zipper transcription factors. These proteins are expressed in various tissues and have a wide range of biological purposes. This family includes both repressor molecules like cAMP response element modulator (CREM) and inducible cAMP early repressor in addition to transcriptional activators like CREB and activating transcription factor (ATF) (ICER). To create the functional dimer, CREB has a basic leucine zipper motif that it can either homodimerize or heterodimerize with (to CREM or ATF). It also has a DNA-binding domain that allows it to recognise and bind to promoter cAMP response element (CRE) sequences. To mediate its activities, phosphorylation of a serine residue (S133) in its kinase-inducible domain is essential because it enables the recruitment of co-activator proteins and the start of transcription. CREB can be phosphorylated and then activated by a variety of upstream signalling cascades. The cAMP-protein kinase A (PKA) pathway is the primary route through which CREB is phosphorylated. The PKA cascade is a target for antidepressant medications and is known to be disturbed in animal models of depression[34].

MAO-B: In contrast, selective inhibition of MAO-B results in increased levels of DA in the Parkinsonian brain with partial depletion of DA-ergic neurons in SNpc and anti-Parkinsonian action. Selective inhibition of MAO-A leads to increased levels of neurotransmitter within noradrenergic (NA-ergic) and 5-HT-ergic neurons of the CNS[35].

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Various ligand and target receptor with reference to pharmacological activity was tabulated in table 1.

Concluding Remarks

Molecular docking has emerged as a crucial instrument in drug discovery. This study provides a concise overview of the existing molecular docking techniques, along with their evolution and uses in drug discovery. The identification of molecular targets can facilitate the development of novel medicines tailored to certain diseases. This review aimed to summarised the molecular targets for *in-silico* validation of pharmacological screening and disease treatment.The basic flowchart of molecular docking study showed in fig.3.

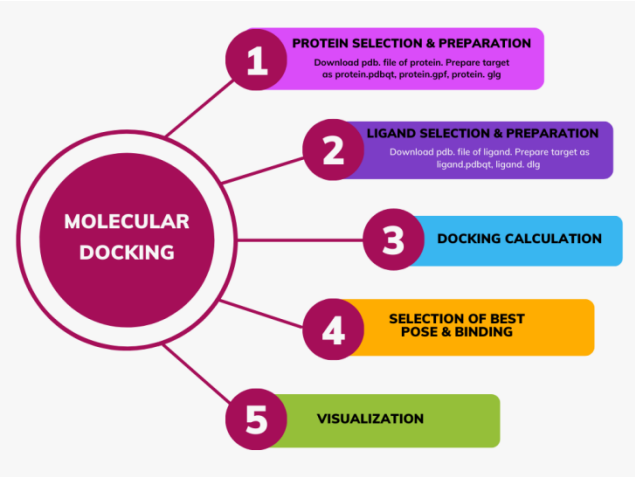

Figure 3 Flowchart of molecular docking study

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Table.1 Prior research conducted on molecular targets for pharmacological efficacy

Pharmacological Activity	Molecular target	Lead molecule
Anthelmintic	β-tubulin	betulin and karaounidiol[36]
Anti-arthritis	HK-2	quercetin and niazirinin[37]
Antidiarrheal	MUSCARINIC M3	quercetin, and quercetin-3-arabinoside[38]
Antioxidant	Heme oxygenase-1	quercetin, and rutin[39]
Aphrodisiac	PDE5	diosgenin, gitogenin, naringenin, and vitexin[40]
Diuretic	Urea transporters	A thienopyridine[41], CB-20
Diabetic Nephropathy	mTORC1	d-pinitol, gallic acid, ferulic acid, and syringic acid[42]
Anti-Alopecia	5-alpha reductase	apigenin, luteolin and taxifolin[43]
Pancreatitis Management	NF-KB	daidzein and genistein[44]
Anti- SARS-CoV Potential	*SARS-CoV-2 Nsp13* Helicase	Quercetin, Isorhametin, Rutin and Tamaraxiten[45]
Anti- Mycobacterium Tuberculosis	Enoyl-ACP-Reductase	baicalein, pectolinarin, myricetin, and hispidulin[46]
Cardioprotective	malonyl COA decarboxylase	apigenin and luteolin[47]
Antidepressant	NOS	alpha-pinene, limonene and carveol[48]
Hepatoprotective	CASPASE-3	chlorogenic acid and gallic acid[49]
Anti-arthritis	GLS-1 protein	quercetin, niazirinin [50]
Anticancer	mTOR1	Syringic acid[51]
Anti- SARS-CoV Potential	COVID -19 Main Protease	Silibin[52]
Anti- SARS-CoV Potential	COVID -19 Main Protease	Hydroxychloroquine [53]
Anti- SARS-CoV Potential	COVID -19 Main Protease	Rifampicin[54]
Antibacterial & Anti cancer activity	Dihydrofolate Reductase	Rutin [55]
Anti-atherosclerosis	High-density lipoprotein cholesterol	Genistein[56]
Anti-mycobacterial	PknB and DprE1	bisbenzylisoquinoline alkaloids 2-nortiliacorinine, tiliacorine and 13'-bromotiliacorinine[57]
Anti- SARS-CoV Potential	NFE2L2, PPARG, ESR1, ACE, IL6, and HMOX1	Chlorogenic acid [58]
Hepatic encephalopathy, hepatic coma urolithiasis, gastric and peptic ulcers, pyelonephritis management	Jack bean urease	diosmin, morin, chlorogenic acid, capsaicin and resveratrol[59]
Antiproliferative activity	KB2	chalcone (*E*)-1-(2-hydroxy-3,4,6-trimethoxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one derived[60]

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