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Targeting CDK2 in Lung Cancer: *In-Silico* exploration of natural compounds derived from *Moringa Oleifera*

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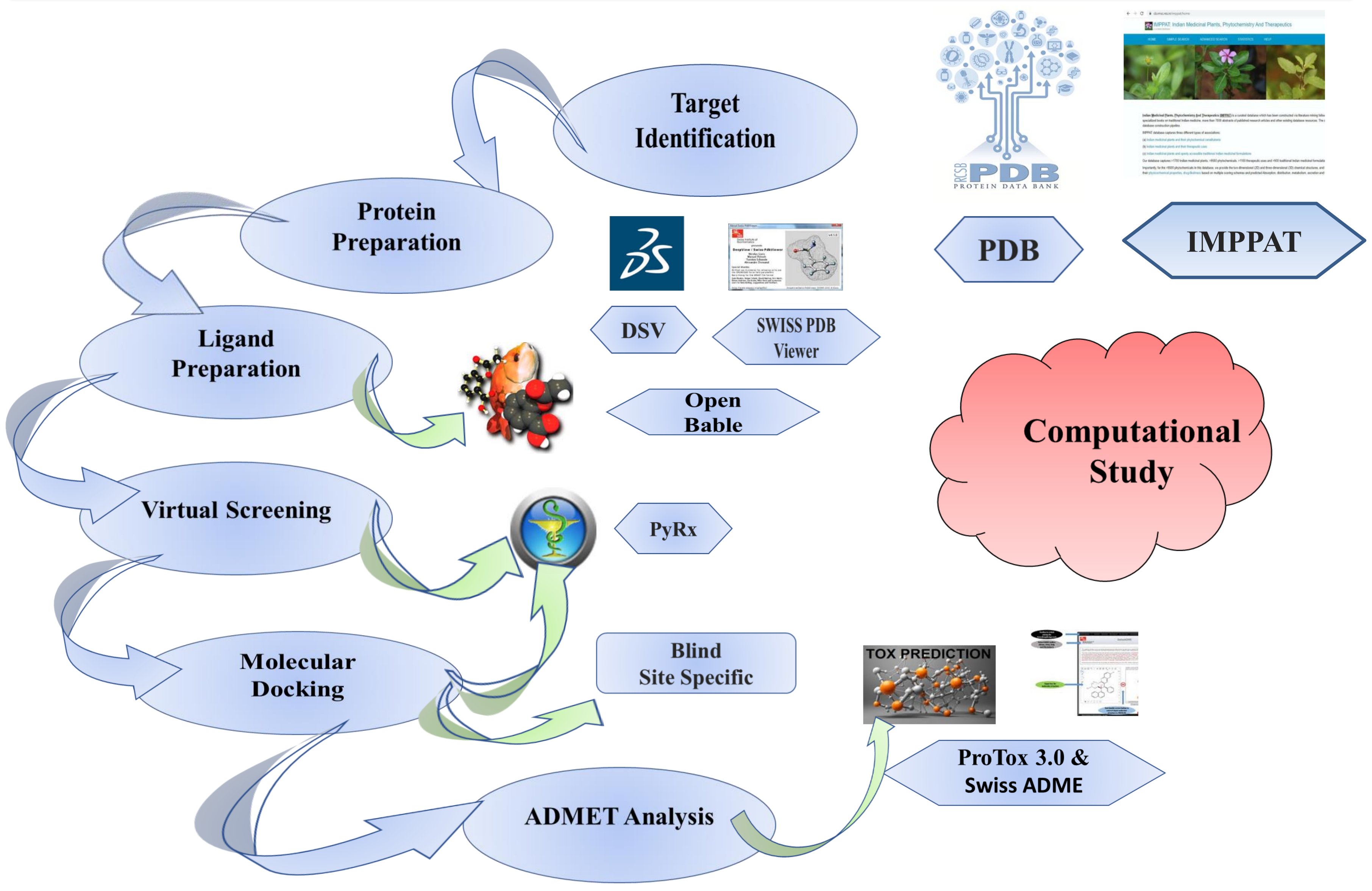
INTRODUCTION & AIM

One of the main causes of cancer-related mortality globally, lung cancer claims the lives of more than a million people each year. Non-small cell lung cancer accounts for around 80% of cases. The success rate of conventional cancer therapies, including radiation, chemotherapy, and surgery, is poor. Therefore, creating new medications is essential to halting the spread of lung cancer [1, 2]. Because protein kinases play a crucial role in controlling a variety of cellular signal transduction pathways, targeting them has emerged as one of the most popular and successful cancer therapy strategies. Numerous essential physiological functions, such as transcription, metabolism, apoptosis, differentiation, cell proliferation, and survival, are regulated by these kinases. Protein kinases support both healthy cellular activity and the pathological processes linked to cancer by regulating these vital activities [3]. A potential treatment option for CDK2-dependent malignancies is the creation of novel CDK2 inhibitors [4]. Herbal therapy is a very effective alternative to Western medicine in the battle against cancer. Herbal medicine has evolved into a safe, non-toxic, and reasonably accessible source of cancer-curing compounds. The purpose of this study is to offer a suggestion for the usage of natural substances, which are often found in the Indian subcontinent region [5]. Moringa oleifera is one such important medicinal plant that is used in all traditional medical systems[6]. Due to the plant's numerous uses, numerous studies were conducted to separate bioactive chemicals from different plant portions [7]. Because of their low cost, herbal plants, sometimes referred to as phytomedicine, are still widely used and trusted as an alternative in the medical sector [8]. As an anti-inflammatory, antioxidant, anticancer, antidiabetic, and cardioprotective agent, M. oleifera has a wide range of therapeutic uses. It has hepatoprotective and renoprotective properties in addition to antibacterial action. In light of this, the current study was created to find potential natural compounds from M. oleifera that target CDK2 by virtually screening a chemical database in order to further lung cancer treatment approaches.

METHOD



RESULTS & DISCUSSION

In the assessment of the potential utility of drug molecules within the body, the ADME properties of adsorption, metabolism, distribution, and excretion are considered crucial parameters. During the ADME experiments, the widely recognized Lipinski's Rule of Five was employed as a key factor in identifying the most suitable compounds. Table summarizes the drug-like characteristics of the top 6 performing ligands. After careful evaluation, the compound niazirinin was selected as the most promising candidate for further study of its molecular interactions. For analyzing ADME properties SwissADME and PKCSM virtual tools were used. For toxicity analysis protox-3 was used.

Table: ADME properties of most promising ligand

Ligand	Lipinski rule	GI absorbtion	Water solubility (log mol/l)	BBB Permeant	Lipophilicity Log P_{ow}
Beta-Sitostenone	Yes; 1 violation: MLOGP>4.15	Low	1.31e-07 mol/l	No	5.00
Delta7-Avenasterol	Yes; 1 violation: MLOGP>4.15	Low	1.49e-06 mol/l	No	5.12
28-Isoavenasterol acetate	Yes; 1 violation: MLOGP>4.15	Low	9.35e-08 mol/l	No	4.96
N,alpha-L-rhamnopyranosyl vincosamide	No; 3 violations	Low	5.22e+00 mol/l	No	2.95
Niazirinin	Yes; 0 violation	High	1.27e-02 mol/l	No	2.25
Pterygospermin	Yes; 0 violation	High	5.89e-06 mol/l	No	3.45

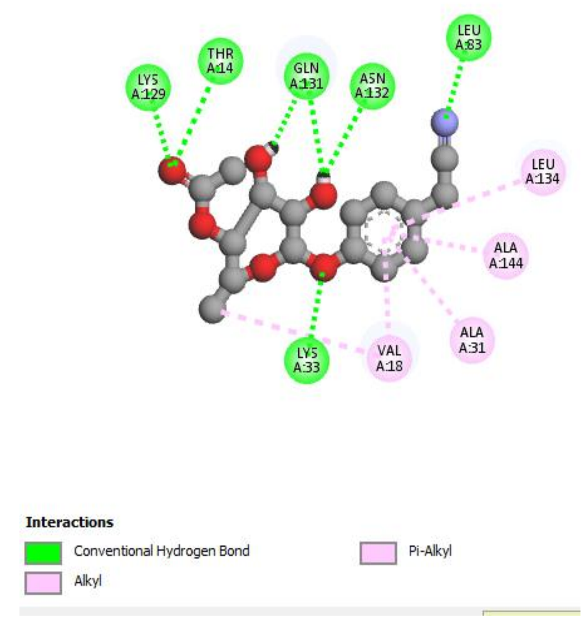


Fig 1. A 2D representation of key interactions Complex

*In-silico s*creening of 191 bioactive compounds from *M. oleifera* identified niazirinin as a potential CDK2 inhibitor, with a binding free energy of -8.1 kJ/mol. Molecular docking analysis revealed key interactions, including **hydrogen bonds** with THR14 (2.41 Å), LYS33 (2.02 Å) LEU83 (2.04 Å), LYS129 (2.08 Å), GLN131 (2.04 Å, 2.01 Å), ASN132 (2.50 Å), and **hydrophobic interactions** with VAL18 (4.57 Å, 4.53 Å) and Ala31 (4.84 Å). Additionally, **ADMET** (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis demonstrated that Niazirinin possesses favorable pharmacokinetic properties, including high gastrointestinal absorption, optimal blood-brain barrier permeability, and minimal toxicity risks. These findings suggest that *M. oleifera* could serve as a promising source of natural therapeutics for lung cancer, warranting further ***in vitro*** and ***in vivo*** validation

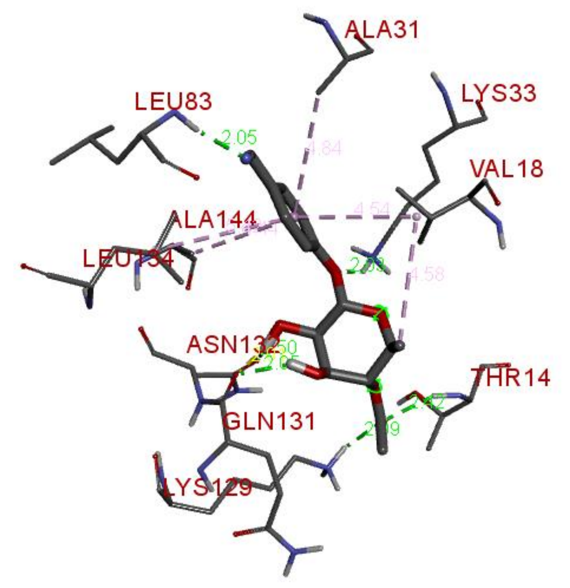


Fig 2. A 3D view of the binding of Protein-Ligand Complex

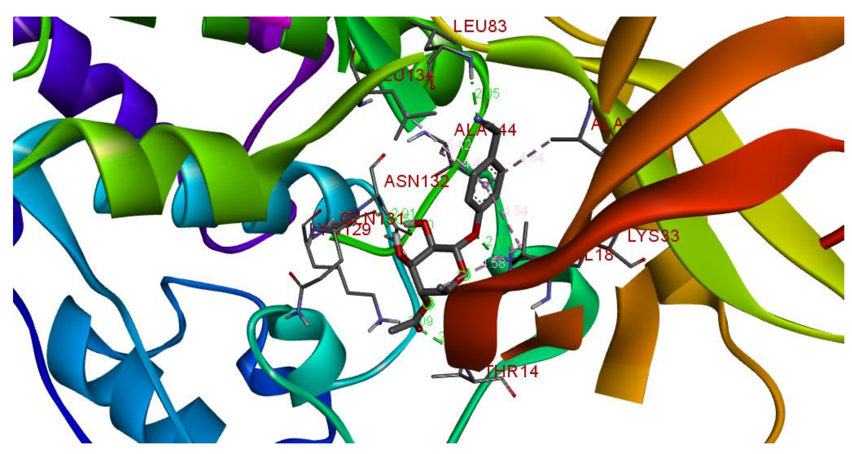


Fig 3. A close-up of binding sites Protein-Ligand Complex

CONCLUSION

Niazirinin is identified as the most potent inhibitor with a binding affinity of -8.1 kJ/mol. It has high gastrointestinal absorption and favorable pharmacokinetics. It is non cyto-toxic and non-carcinogenic. It forms 6 conventional hydrogen bonds, 3 Pi-alkyl interactions and one alkyl bond with CD2. So, Niazirinin is a promising candidate for lung cancer with Strong binding affinity, favorable ADMET profile, and safety.

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