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5-Nitroindazole Against Lung Cancer: A multitargeted in-silico Molecular Docking Study †

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Abstract: Abstract: Lung Cancer has taken over all cancers in terms of diagnosis and mortality worldwide, which is why it is on the World Health Organisation's (WHO) priority list. As per the data reported by the WHO, cancer has caused 10 million death each year, and lung cancer alone caused 1.80 mil-lion deaths in 2020. Also, the FDA has approved almost 100 drugs against lung cancer, but it is not curable as most drugs target a single protein or block a single pathway. In this study, we screened the Drug Bank library against three major proteins- Ribosomal protein S6 kinase alpha-6, Cyclic-dependent protein kinase-2, and Insulin-like growth factor-1 of lung cancer- and identified the com-pound 5-Nitroindazole as a multitargeted inhibitor that potentially can treat lung cancer. For the screening, we deployed multisampling algorithms such as HTVS, SP and XP, followed by the MM\GBSA calculation, and the study was extended to molecular fingerprinting analysis and AD-MET calculations to understand the complex behaviour. The docking scores against the proteins 6G77, 1AQ1 and 1K3A were -6.884 Kcal/mol, -7.515 Kcal/mol and -6.754 Kcal/mol, respectively, considered in a good scoring category. Also, the compound has shown all the values satisfying the ADMET criteria, and the fingerprint analysis has shown wide similarities. The best feature of the proposed drug candidate is that it simultaneously targets multiple proteins of lung cancer, the chance of developing resistance is relatively less, and it drastically can reduce the burden of the pharma industry. However, Molecular Dynamics Simulation and experimental validation is needed.

Keywords: Lung Cancer; Molecular Docking; 5-Nitroindazole; Molecular Fingerprints

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1. Introduction

Lung carcinoma (LC) is the leading cause of illness and death globally among lung diseases, and it begins as a primary metastatic tumour in the lung and subsequently spreads to other body regions [1, 2]. Small-cell lung cancer, also known as SCLC and non-small cell lung cancer that is NSCLC, is the most diagnosed type of LC. Most lung cancer statistics include SCLC and NSCLC, and the SCLC account for around 10% to 15% of all lung malignancies [3, 4]. The hallmark signs of LC include weight loss, breathing difficulty, bloody coughing, and chest discomfort. LC is now the fourth most significant cause of hospitalisation in people with respiratory diseases, while NSCLC is the primary cause of LC-associated death (up to 85 per cent of LC) (NS-CLC). Genetic and epigenetic alterations in the cellular DNA led LC to form [5, 6]. The extensive molecular dissection of NSCLC has recognised the groundwork for developing new small therapeutic compounds that target mutations in the EGFR, K-Ras, ALK, c-MET, B-Raf, LKB1, and NKX2-1 genes, all of which are important in disease progression [7, 8]. Among these LC genes, activating mutations in the EGFR gene are seen in 10-40% of NSCLC patients [7, 9]. The

EGFR gene encodes a transmembrane epidermal growth factor receptor protein that, when activated (by ligand interaction), transmits signals necessary for migration, cellular proliferation, differentiation and survival [10]. Tobacco smoking, hereditary factors, food and obesity, and environmental variables such as air pollution have all been associated with LC's aetiology [11, 12]. Lung cancers are widely classed as SCLC and NSCLC; the latter accounts for 85 per cent of all cases, with adenocarcinoma accounting for 40 per cent of NSCLCs. The most effective strategy to treat NSCLC adenocarcinoma is to target the epidermal growth factor receptor (EGFR) [13, 14]. The most prevalent EGFR-targeting medicines are Erlotinib, Gefitinib, and Afatinib. Among the challenges medicinal chemists addressed was identifying polymorphism-related kinase inhibitors, one of the critical targets for EGFR tyrosine kinase inhibitors [15]. The use of EGFR therapy to address NSCLC with the mutational resistance of T790M is a critical treatment requirement. Hyperexpresion of the EGFR tyrosine kinase has been identified as the most prevalent reason behind the NSCLCs, which mainly afflict cigarette smokers and are gender-specific to females. Osimertinib and Afatinib are second and third-generation NSCLC treatment drugs [16–18]. The first-generation reversible NSCLC treatment drugs, in particular, were developed to handle EGFRL858R mutations. Second-generation irreversible NSCLC treatment drugs targeted EGFRT790M mutations [19, 20]. Third-generation irreversible NSCLC therapeutic drugs were also developed to treat EGFRT790M/L790M double mutations.

In lung cancer, there are huge lists of reported proteins and genes, and a few biomarkers have been used extensively, and this is true in various cases to design the drug and the reason behind the resistance development. The PDB ID 6G77 entitled RSK4 N-terminal Kinase Domain has been used for various drug repurposing as it is a promoter for drug resistance and metastasis that can be an excellent option to treat as the target [21]. PDB ID 1AQ1 is Human Cyclin-Dependent Kinase-2 that participates in the DNA replication processes and cell division in all eukaryotes, including humans. CDK2 forms complexes with cyclin E in the G and G/S phases of the cell cycle [22]. In comparison, the PDBID 1K3A is an insulin-like growth factor-1 receptor kinase that participates in the therapeutic interventions managed by autophosphorylation within three sites of the kinase activation loop [23]. On the other hand, the fast growth of computational biology or bioinformatics has created a fantastic chance for designing Nobel molecules with features to remove the resistance to EGFR-specified sensitivity. Computational techniques for predicting drug candidates for the resistance to developed mutational and creating resistance-evading medications have proved highly reliable. The molecular modelling approach is molecular docking, which is used to investigate the interaction between the 3D structures of a ligand and a receptor and how the ligand binds firmly in the active region of the receptor. It also helps with the virtual screening of a chemical library during the pre-clinical stage of drug development. When there are numerous compounds to examine and access to physical samples is limited, the evaluation of absorption, distribution, metabolism, and excretion (ADME) in drug development is included early in the discovery phase [24-29].

In this study, we have identified three important protein targets of lung cancer, screened the drug bank against each, and identified the potential drug candidate 5-Nitroindazole as a multitargeted inhibitor against lung cancer proteins. Further, we extended our analysis for the ADMET and fingerprinting, and after getting satisfactory results, we proposed the molecular dynamics simulation in water for at least 100ns in the NVT ensemble and analysed the trajectories for each of the complexes.

2. Methods

We have downloaded the drug library from Drug Bank, proteins from PDB, and docked. The study extended to multiple directions to explore the drug candidate's suitability. The same has been plotted in figure 1 to understand the methods easily. Further, the detailed methods are as follows-

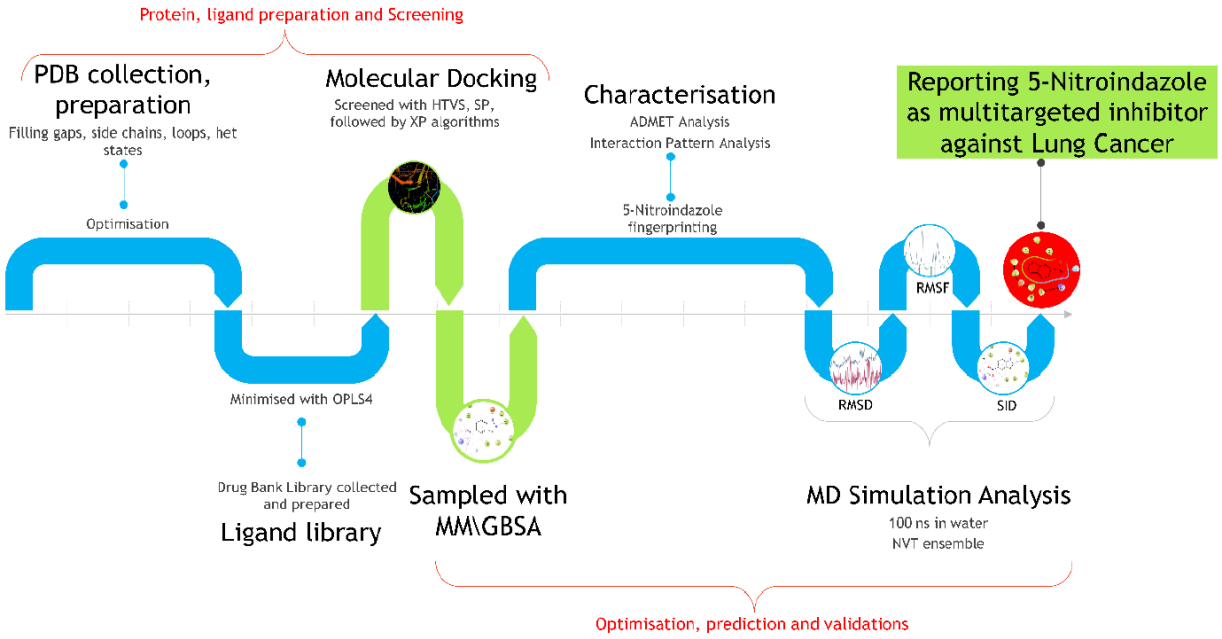

Figure 1. Showing the workflow of the complete study; graphical abstract showing the methods to identify the 5-Nitroindazole as a multitargeted inhibitor against lung cancer.

2.1. *Protein preparation*

We mined various through various literature and identified the protein targets responsible for an essential role in the case of lung cancer development. We extensively reviewed the literature to validate the selected target proteins and identified three proteins that have a significant role in lung cancer development. The identified proteins were RSK4 N-terminal Kinase Domain, Human Cyclin-Dependent Kinase-2, insulin-like growth factor-1 receptor kinase that further was downloaded from the https://www.rcsb.org/ database and their PDBID were- 6G77, 1AQ1, and 1K3A, and imported into the workspace of Schrödinger Maestro for preparation using the Protein Preparation Wizard [21-23, 30, 31]. PDBID: 6G77 has two chains, A and B also present solvent and other metals/ions. After preparation, only chain A for misidentified delete chain B, solvent and other metals/ions. In PDBID: 1AQ1 and 1K3A have only chain A and solvents. We deleted solvent from the protein during preparation and kept only chain A for the subsequent study. We maintained the same parameters for all proteins throughout the preparation process, and we chose the preprocess workspace structure tab to assign bonds using the CCD tool. Added H-atoms, created zero-order and disulfide bonds, converted selenomethionines to methionines, filled in missing side chains, filled in loops using Prime, and generated het states using Epik at pH 7.0 to +/- 2.0 [30, 32, 33]. We also refined our structure using crystal symmetry and optimised and removed water energy. Further, each PDB structure was minimised with the OPLS4 force field [34].

2.2. *Ligand library collection and preparation:*

The Drug Bank database provides an interactive platform to access information about the drug as well the structures of the compounds. That is the main reason behind taking the complete database of the Drug Bank to access its information for our studies. We downloaded the entire ligand library from https://go.drugbank.com/, which contains 14,940 compounds, many of which are licensed biologic medications, some of which are nutraceuticals, and some were experimental drugs updated in January 2022 with version 5.1.9 [35]. We have used the LigPrep tool in Maestro for preparation. The OPLS4 forcefield was used to minimise the ligands, and the size was restricted to not more than 500 atoms

to filter the compounds not fitting into the good drug candidate category [34, 36].Tautomers and stereoisomers were created with the given chiral carbon, computations were limited to not more than 32 per ligand, and the complete process produced a sum of 1,55,888 ligands that were further used for molecular docking.

2.3. Glide grid generation and Multitargeted Molecular Docking:

An integral and crucial part of the docking procedure is generating grids on the active site. The active site of the proteins was calculated with the help of the SiteMap tool with predefined algorithms to predict the protein's active site [30]. The PDBIDs: 6G77, 1AQ1, and 1K3A were individually selected and entered into the grid box to fit on the active site and performed the griding sets. Further, molecular docking was performed with the help of Maestro's 'Virtual Screening Workflow' (VSW) tool that offers ligand-target docking-based screening with multiple sampling algorithms at once [30, 37]. The ligand library was filtered using QikProp and Lipinski's Rule to meet the requirements for Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) characteristics [38]. Additionally, Epik state penalties for docking were generated [32]. Further, to reduce the computational cost, we performed the High-Throughput Virtual Screening (HTVS), Standard-precision (SP), and Extra precision (XP) and passed only the top 5% of the data to the next level of screening. Additionally, we have filtered out best poses with the help of Molecular mechanics with generalised born and surface area solvation (MM/GBSA). In order to further manual filtering, the calculated data was sorted to determine which compound or complex had the highest likelihood of binding to each of the chosen protein targets [33].

2.4. ADMET and Interaction Fingerprinting analysis:

The molecular level of the information regarding the ADMET properties of the compounds was generated using the QikProp tool, which provides an extensive calculation and various features [30, 38]. We selected the 5-Nitroindazole compound from the workspace, kept it for the calculations, and compared it with the standard values. Further, we have also performed and analysed the interaction fingerprints of the protein ligands. The interaction fingerprints tool was used to analyse the patterns, and the protein-ligand complexes were used for this study. All the proteins had different sequences, so we aligned them and generated the fingerprints. We have selected any in the bonding types, coloured the main plot against the docking score and exported only the interacting residues to find the better pattern. Further, the data were taken into the main plot for pattern, residue interaction count and ligand interactions for proper understanding.

3. Results and Discussion

3.1. Interaction Analysis:

The multisampling algorithms-based screening has led us to identify the multitargeted potential of 5-Nitroindazole. We have analysed its bonding configurations with the help of the ligand interaction diagram tool to get with bond and residue types. The 5- Nitroindazole with Ribosomal protein S6 kinase alpha-6 (6G77) showed a docking score of –6.88 Kcal/mol and MM/GBSA score of –30.17 Kcal/mol (Table 1) interaction with four hydrogen bonding by LYS105, THR215. Both residues individually interact with the O atom, ASP153 with the NH atom and LEU155 with the N atom of the ligand (Figure 2A). Interaction of 5-Nitroindazole with Cyclic-dependent protein kinase 2 (1AQ1) shows a docking score of -7.51 Kcal/mol and MM/GBSA score of -30.34 Kcal/mol while interacting with two hydrogen bonds among LEU83 with N atom, GLU81 with NH atom and pication interact by PHE80 with N+ atom of the ligand (Figure 2B). 5-Nitroindazole interacts with Insulin-like growth factor 1 (1K3A) and has shown a docking sore of –6.75 Kcal/mol and MM/GBSA score of –23.22 Kcal/mol by two hydrogen bonding among

GLU1050, MET1052 with NH atom and with N atom also form a salt bridge by LYS1003 with O atom of the ligand (Figure 2C). The complete ligand interaction diagram has led us to identify the best bonding residues with different types, such as hydrogen bonds, pi-cations and many more. Also, we have identified the coverage in the main pocket of the proteins. The identified compound is compact in the protein's pocket and has shown broad interaction types such as hydrogen bonding, pi-cation, and many more, making the structure much more substantial and stable during the treatment or even at the validation level. This interaction has also predicted that the molecular dynamics simulation might have fewer deviations and fluctuations.

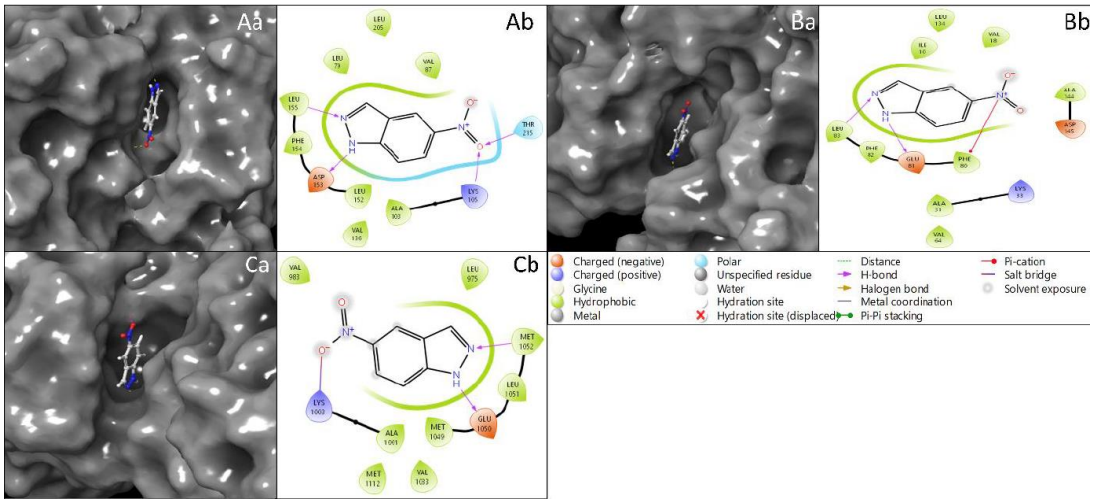

Figure 2. Showing the 3-D and 2-D diagram of the protein-ligand interactions. The 3-D representation of (Aa) 6G77, Ba) 1AQ1, (Ca) 1K3A are shown, while the 2-D representation of (Ab) 6G77, (Bb)1AQ1, (Cb) 1K3A and the legend is shown for proper interpretations of the bonds, and residues.

Table 1. Showing the docking score (Kcal/mol) and MM\GBSA (kcal/mol) score and other vital calculations against each protein and 5-Nitroindazole compound.

S No.	PDB ID	Compound Name	Docking Score	MM\GBSA	Prime Hbond	Prime vdW
1	6G77	5-Nitroindazole	-6.884	-30.17	-153	-1376.02
2	1AQ1	5-Nitroindazole	-6.884	-30.34	-143.6	-1319.21
3	1K3A	5-Nitroindazole	-6.884	-23.22	-165.96	-1319.54

3.2. ADMET and interaction pattern Identification

The ADMET analysis has revealed that the identified compound 5-Nitroindazole can be a better multitargeted therapeutic, and its higher doses can be administered to make it more efficient for cancer cells. The compound is also inactive for the CNS, which boosts the level of understanding of how this compound cannot harm other brain and nervous systems. The compound has a molecular weight of 163.135, considered among the optimised ones, and the compound has no amines, amidines, acids, or amides. Also, the compound's SASA is 336.065, FOSA is 0, FISA is 165.954, PISA is 170.11 WPSA is 0. There is also one donor and two acceptor hydrogen bond capacity to stabilise the compound with the protein targets. The complete ADMET analysis has revealed that 5-Nitroindazole can be one of the prominent compounds to treat lung cancer, and its multitargeted approach can also accept and will show a boosted performance to cure lung cancer. The pattern analysis has revealed that the compound is widely interacting with an identified and expected pattern. LEU79, VAL87, ALA103, LYS105, VAL136, LEU152, LEY152, ASP153, PHE154, PHE154, LEU155, LEU205, and THR215 are the interacting residues with 5-nitroindazole. The coloured main plot shows the interaction patterns against the position of

the amino acids of 6G77. 1AQ1 and 1K3A proteins, while the left plot shows the count of ligand interactions. Most of the interactions were found in the initial sequences of the proteins and the residues after 152 positions. The pattern analysis has shown that the compound 5-nitroindazole has enough potential to bind multiple targets, and its higher doses might block multiple targets together and can lead to the shrinking of the lung cancer cells. The compound's H-bond acceptor and donor capacity make it unique and boost its stability with multiple protein targets.

Table 2. Showing the ADMET properties of 5-Nitroindazole calculated with the QikProp tool against the standard values.

Descriptors	Standard Values	5-Nitroindazole	Descriptors	Standard Values	5-Nitroindazole
#stars	0 – 5	0	QPlogS	−6.5 – 0.5	-1.73
#amine	0 – 1	0	CIQPlogS	−6.5 – 0.5	-2.244
#amidine	0	0	QPlogHERG	concern below −5	-3.457
#acid	0 – 1	0	QPPCaco	<25 poor, >500 great	264.335
#amide	0 – 1	0	QPlogBB	−3.0 – 1.2	-0.773
#rotor	0 – 15	1	QPPMDCK	<25 poor, >500 great	117.427
#rtvFG	0 – 2	0	QPlogKp	−8.0 – −1.0	-3.883
CNS	−2 (inactive), +2 (active)	-1	IP(eV)	7.9 – 10.5	9.544
mol MW	130.0 – 725.0	163.135	EA(eV)	−0.9 – 1.7	1.223
dipole	1.0 – 12.5	6.586	#metab	1 – 8	1
SASA	300.0 – 1000.0	336.065	QPlogKhsa	−1.5 – 1.5	-0.375
FOSA	0.0 – 750.0	0	HumanOralAbsorption	N/A	3
FISA	7.0 – 330.0	165.954	PercentHumanOralAbsorption	>80% is high, <25% is poor	77.139
PISA	0.0 – 450.0	170.11	SAfluorine	0.0 – 100.0	0
WPSA	0.0 – 175.0	0	SAamideO	0.0 – 35.0	0
volume	500.0 – 2000.0	520.507	PSA	7.0 – 200.0	75.765
donorHB	0.0 – 6.0	1	#NandO	2 – 15	5
acceptHB	2.0 – 20.0	2	RuleOfFive	maximum is 4	0
dip^2/V	0.0 – 0.13	0.083336	RuleOfThree	maximum is 3	0
ACxDN^.5/SA	0.0 – 0.05	0.0059512	#ringatoms	N/A	9
glob	0.75 – 0.95	0.931165	#in34	N/A	0
QPpolrz	13.0 – 70.0	15.659	#in56	N/A	9
QPlogPC16	4.0 – 18.0	5.814	#noncon	N/A	0
QPlogPoct	8.0 – 35.0	8.667	#nonHatm	N/A	12
QPlogPw	4.0 – 45.0	6.028	Jm	N/A	0.577
QPlogPo/w	−2.0 – 6.5	1.168			

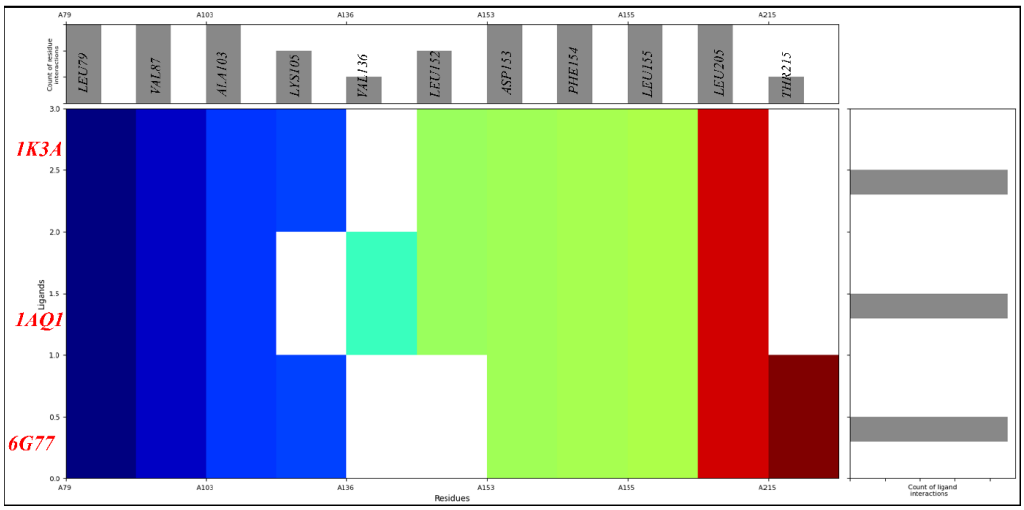

Figure 3. Showing the interaction patterns of 5-Nitroindazole against the considered proteins 6G77,. 1AQ1 and 1K3A and coloured with blue to red to understand the position of the residue from N to C terminal.

4. . Conclusion:

The food and drug administration has approved almost 100 drugs against SCLC and NSCLC, which are being used actively. However, this is unfortunate; despite so much expenditure, the world frequently faces the drug resistance problem and needs a new drug. This study includes multisampling algorithms based on screening, ADMET analysis, interaction pattern analysis and MD simulation for 100ns in the SPC water medium. In this study, we have identified 5-Nitroindazole as a multitargeted inhibitor against lung cancer, validated with computational methods, and proven as a prominent candidate with less chance to develop resistance or it might take a more extended period. It can be experimentally validated and used for the welfare of humankind. This study also set an example of how to proceed with multitargeted drug designing or repurposing to cure any prevalent disease and developing resistance.

5. . Declarations:

Ethical Responsibilities: Since this study is entirely in-silico, ethical obligations are not **a**pplicable because they do not directly involve humans or other organisms.

Consent for publication: Both authors agree to submit the manuscript in the conference proceeding.

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Competing and conflict of interest: The authors declare no potential competing or conflict of interest.

Author Contributions: Conceptualisation, Data collection/curation, analysis, writing and extensive editing of the first draft, SA; Computational resources, reviewing and editing, supervision, KR.

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