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In-Silico Antifungal Drug Discovery for Mucormycosis Targeting β- Glucan Synthase

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ABSTRACT

Mucormycosis or Black fungus is an infectious disease caused by a group of fungi involving *Rhizopus, Mucor, Absidia, and Cunninghamella.* The discovery of new and more potent anti-fungal drugs was prompted by the advent of multi-drug resistance invasive fungus strains. The enzyme glucan synthase is essential for the production of cell walls. As a result, 1,3 β-glucan synthase was chosen as a possible therapeutic target and docked with inhibitors to see how they interacted. Molecular docking study revealed that nearly all of the phytochemicals bind strongly to the target's active sites, with binding affinities ranging from (-6.1 to -12.0 kcal/mol), indicating that their actions are related. Lupinisolone A and Cubebin have the highest binding affinity (-12.0 and -10.6 kcal/mol, respectively), forming hydrophobic interactions and hydrogen bonds with receptor protein amino acid residues. Drug likeliness profiles by assaying absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies provided guidelines and mechanistic scope for identification of top dock scored phytochemicals as a potent anti-fungal drug. Therefore, Lupinisolone A from *L. albus* may represent a potential herbal treatment to act as an anti-fungal drug.

Keywords: Drug discovery, Molecular docking, Mucormycosis, Black fungus, Plants-derived phytochemicals, Glucan synthase

1. INTRODUCTION

The prevalence of invasive fungal infections is increasing with an enormous rate causing major challenges to healthcare professionals (Jain *et al.* 2010). There could be multiple possible reasons for leading risk factors for invasive fungal infection ie., the use of intensive chemotherapy, diseases like HIV which cause immunosuppression, and immunosuppressive drugs (Garber 2001, Ravikant et al. 2015).

Mucormycosis or black fungus is a type of fungal infection which is infrequent and invasive in nature, Mucor mould, which is widely found in soil, plants, manure, and decaying fruits and vegetables, are the major cause of this invasive fungal disease. Mucormycosis is also known as "Black fungus" and "Zygomycosis", Because the human immune system can eradicate big organisms, these invasive fungal infections are uncommon. The prevalent causative agents of mucormycosis in human populations are associated with 2

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orders, i.e., Mucorales and Entomophthorales. The 4 genera which are most closely related to disease in human individuals are *Rhizopus, Mucor, Absidia, and Cunninghamella*, within the order of Mucorales (Riley *et al.* 2016). The Entomophthorales includes 2 genera, Conidiobolus and Basidiobolus. Among all the agents of mucormycosis, *Rhizopus oryzae* was found to be the most active that it causes approximately 70% of all cases. An increase in mucormycosis cases is believed to be due to immunocompromised therapy, with the advances in modern medicine. Medication of angio invasive fungal disease is quite complex because the cellular and molecular mechanisms of eukaryotic pathogens are similar to the human host, which restricts the use of therapeutic options with high fatality (Ramalingam *et al.* 2019, Roden *et al.* 2005).

Aspergillus and *Candida* are being found as the main fungal pathogens or co-infection in people with COVID-19. In recent, most of the cases of mucormycosis in the human population with COVID-19 have been reported with an increasing number of cases worldwide, in particular from India (Singh *et al.* 2021). As the second wave of COVID-19 moves through India, mucormycosis is has been seen with an alarming increase in numbers. According to the data provided by the Union health minister of India, India has reported 45,432 cases of mucormycosis as of July 15. 84.4% of individual patients had a history of Covid-19. 77.6% of them are rhinocerebral in nature, 34.3% are Cutaneous, and 3% are Pulmonary (Dutta, 2021).

For the cure of mucormycosis-infected individuals, Amphotericin-B and Isavuconazole alone or in combination with other antifungal agents are being used (Sipsas *et al.* 2018). Due to the limitation of therapeutic options and antifungal drugs, there is significant demand for novel drug targets. With the evolution in technologies using computational approaches and biomedical science at hand, we hope that in the future we can make a better natural drug against Mucormycosis. *In-silico* molecular docking, a research work that has shown a lot of promise in terms of screening multiple pharmacological candidates quickly, efficiently, and affordably. There is an alarming necessity for the development of novel therapeutic drugs against mucormycosis (Calderone *et al.* 2014).

Plant-derived phytochemicals possess potential therapeutic benefits in the case of a variety of antifungal infections (Sadeghi-Nejad *et al.* 2017). And there have been several studies done where numerous compounds have been identified to show antifungal activity. This work aimed to perform an in-silico study to find potent possible candidate molecules that can be used as a drug against mucormycosis. (Duraipandiyan *et al.* 2011).

Based on a recent study, our selected target receptor 1,3-β-glucan synthase protein molecule was retrieved from Protein Data Bank (PDB) which is a database for the 3D molecular structure submitted by biological and biochemical scientists from around the world is freely accessible on the web-server via the Worldwide Website Protein Data Bank. 1,3-β-glucan synthase is a glucosyl transferring enzyme essential for the synthesis of β-glucan in fungal species having a structural role in the formation of the cell. 1,3-β-glucan synthase can be a probable target for designing antifungal drugs because no structure like this enzyme exists in our body (Sharma *et al.* 2021).

2. MATERIALS AND METHODS

Preparation of target protein and ligand molecules

The 3-D structure of the receptor protein, 1,3-β-glucan synthase protein with PDB ID: 4M80 was considered and retrieved from RCSB-PDB (Protein Data Bank) which is a 3D molecular structure crystallographic database submitted by biological and biochemical scientists from around the world is freely accessible on the web browser via the Worldwide Website Protein Data Bank. Structural optimization of the receptor protein was done using Chimera software (Pettersen *et al.* 2004). The protein molecule was saved in pdbqt format after the existing water molecules were removed and polar hydrogen molecules were added. Docking investigations were conducted using this produced receptor protein. Prediction of active sites in the 3D protein receptor was done by the CASTp server for identifying and measuring cavities (Binkowski *et al.* 2003).

Several phytochemicals with antifungal properties are present in medicinal plants like *Acalypha indica, Azadirachta indica, Cinnamomum camphora, Datura metal, Lupinus albus, Piper longum, Rubia cardifolia,* and others. Total 561 phytochemical compounds from 51 different plants (Table 1) having antifungal activities were retrieved in a PDB file from the IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) website for Indian Medicinal Plants (https://cb.imsc.res.in/imppat/home). (Mohanraj *et al. 2018*)

PyRx software was used to optimize the ligands' structural properties (energy minimization and protonation) (Dallakyan *et al.* 2015). The Open Babble GUI was used to convert the ligand's PDB format to PDBQT format before doing the molecular docking study. For molecular docking, these synthesized ligands were used.

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Table 1: List of medicinal plants from which phytochemical compounds are retrieved for docking analysis

1.	*Acalypha indica*	**2.**	*Eupatorium cannabinum*
3.	*Achyranthus bidentate*	**4.**	*Gloriosa superba*
5.	*Acorus calamus*	**6.**	*Hydnocarpus laurifolia*
7.	*Aegle marmelos*	**8.**	*Juniperus communis*
9.	*Albizzia procera*	**10.**	*Lupinus albus*
11.	*Alpinia galangal*	**12.**	*Ocimum basilicum*
13.	*Ananus cosmos*	**14.**	*Ocimum gratissimum*
15.	*Aquilegia vulgaris*	**16.**	*Piper chaba*
17.	*Aristolochia indica*	**18.**	*Piper longum*
19.	*Asclepias curassavica*	**20.**	*Piper nigrum*
21.	*Atlantia monophylla*	**22.**	*Punica granatum*
23.	*Azadirachta indica*	**24.**	*Ricinus communis*
25.	*Bauhinia tomentosa*	**26.**	*Rubia cordifolia*
27.	*Blumea balsamifera*	**28.**	*Rubia tinctorum*
29.	*Caesalpinia pulcherrima*	**30.**	*Solanum tuberosum*
31.	*Capsicum frutesens*	**32.**	*Sphaeranthus indicus*
33.	*Cassia fistula*	**34.**	*Teucrium polium*
35.	*Cinnamomum camphora*	**36.**	*Thymus vulgaris*
37.	*Cinnamomum tamla*	**38.**	*Tinospora cordifolia*
39.	*Cinnamomum verum*	**40.**	*Trachyspermum ammi*
41.	*Curcuma longa*	**42.**	*Trigonella foenum-graecum*
43.	*Datura metal*	**44.**	*Vitex negundo*
45.	*Diospyros ebenum*	**46.**	*Zingiber officinale*
47.	*Ecballium elaterium*	**48.**	*Ziziphus oenoplia*
49.	*Eletteria cardamomum*	**50.**	*Zygophyllum simplex*
51.	*Embelia ribes*		

Molecular Docking

Docking (Figure-1) is an essential step in the computational approach for drug discovery and designing. To perform docking (receptor based approach) both the receptor protein and the ligands have to be in pdbqt format. Docking analysis was done by using PyRx (Dallakyan *et al.* 2015). In our study, the protein that we choose has a significant role in the synthesis of β-glucan in fungi which have a structural role in the formation of the cell and has shown to be potential for an antiviral drug target. At the end of the docking, an output file is generated that shows the binding affinity of the ligand.

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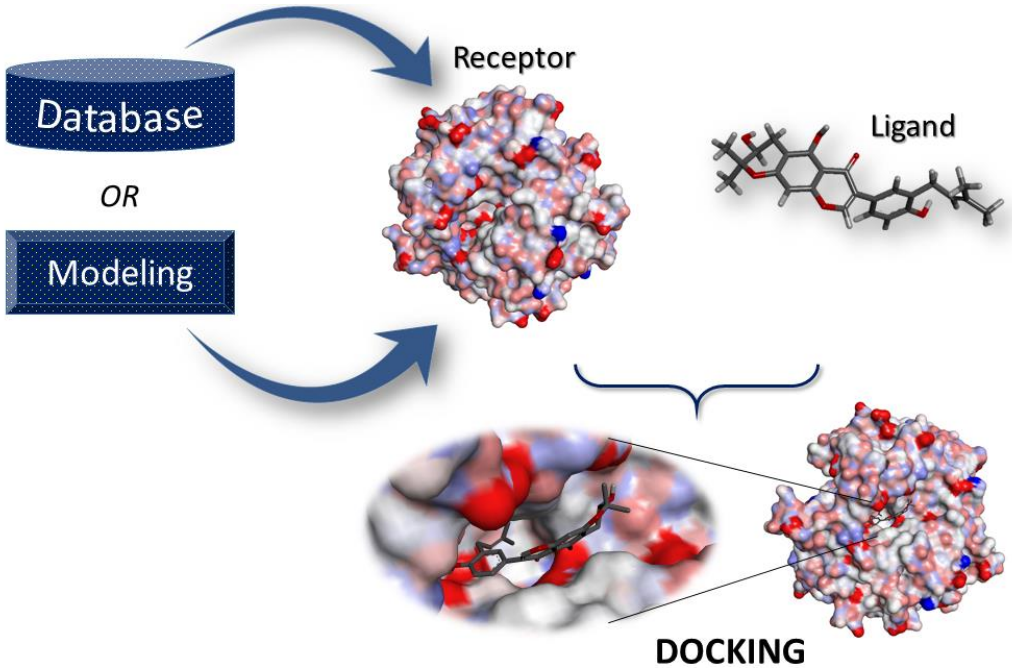

Figure 1: Flow chart of molecular docking

ADME properties (Absorption, Distribution, Metabolism, Excretion)

The canonical smiles format of each phytochemical and ligands were derived from PubChem and uploaded to the Swiss ADME website (http://www.swissadme.ch/) for the evaluation of ADME properties, drug-likeness nature, pharmacokinetic properties, and medicinal chemistry friendliness of one or multiple small molecules to support drug discovery. Boiled-EGG representation was also considered for predicting the passive diffusion of the ligands through gastrointestinal absorption and blood-brain barrier permeation (Daina *et al*. 2017). All the selected 561 ligand molecules were checked and confirmed for the drug-likeness property.

3. RESULTS AND DISCUSSION

This protein 1,3 beta-glucan synthase protein was downloaded in the 3D PDB format (Figure-2) which was then converted to PDBQT format where all the water molecules were removed and if any ligand is bound to the originally downloaded protein molecule even those were to be removed. While preparing the protein molecule in BIOVIA DISCOVERY STUDIO binding site was edited by generating a sphere. The attributes of the sphere were noted as the XYZ (4.3862, 64.7461, 9.6908) value with exhaustiveness 8. These values were needed for docking the protein and the ligand molecules.

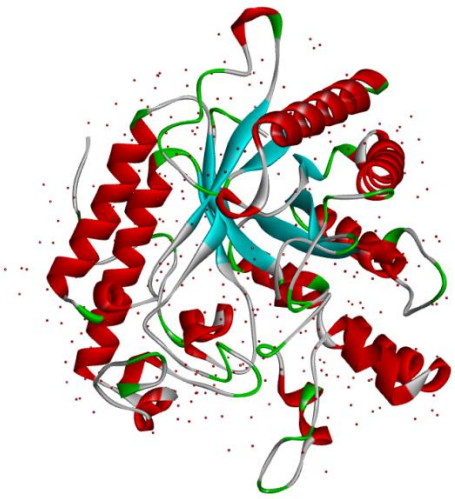

Figure 2: The 3D structure of the receptor protein, 1,3 beta-glucan synthase protein

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561 ligand molecules were docked with the protein and among them, 20 ligands showing the best interaction with the protein molecule were chosen. These 20 ligands namely Lupinisolone A (-12.0), Cubebin (-10.6), Lupinisoflavone L (-10.6), Lupinalbin C (-10.5), Gamma-Terpinenes (-10.3), Atolaphyllidine (-10.2), Lupinisoflavone E (-10.2), Seocalcitol (-10.2), Haemanthamines (-10.1), Aurantiamide (-10.1), Atalaphylline (-10.1), Lignans machilin F (-10.1), Daturataturin A aglycone (-10.0), Lupilutin (-10.0), Parvisoflavone B (-10.0), Daturametelin D (-9.9), DITERPENE II (-9.8), Paroxetine (-9.7), Physcion (-9.7), and Berberine (-9.6) showed the highest binding affinities as compared to the other molecules (Table 2).

Pharmacokinetics of ligand is studied by applying Lipinski's rule of five, thus, determining absorption, distribution, metabolism & excretion of a drug. After the virtual screening, ligands with the best binding affinities were subjected to check for their drug-likeness where some of the ligands did not show any likeness for the drug but all the other remaining compounds showed drug-likeness. The compounds that showed drug-likeness as well as those that did not show drug-likeness were docked against the protein.

Table 2: Swiss-ADME analysis of selected compounds showing Lipinski's rule violations and Boiled egg presentations

Phytochemical compounds	PubChem ID	Molecular Weight	Lipinski's Rule Violations	GI Absorption	BBB permeation	Binding energy
Lupinisolone A	CID:14237665	422.48 g/mol	0	High	No	-12.0
Cubebin	CID:117443	356.37 g/mol	0	High	Yes	-10.6
Lupinisoflavone L	CID:14728997	436.46 g/mol	0	High	No	-10.6
Lupinalbin C	CID:14309762	368.34 g/mol	0	High	No	-10.5
AC1N75QA (Gamma-Terpinenes)	CID:4272093	348.83 g/mol	1	High	Yes	-10.3
Atolaphyllidine	CID:5479542	309.32 g/mol	0	High	No	-10.2
Lupinisoflavone E	CID:93373-44-5	438.48 g/mol	0	High	No	-10.2
Seocalcitol	CID:5288149	454.70 g/mol	1	High	No	-10.2
AC1L4PUZ (Haemanthamines)	CID:118701104	470.61 g/mol	0	High	No	-10.1
Aurantiamide	CID:185904	402.49 g/mol	0	High	Yes	-10.1
Atalaphylline	CID:442887	379.46 g/mol	0	High	No	-10.1
Lignans machilin F	CID:13844301	342.39 g/mol	0	High	Yes	-10.1
Daturataturin A aglycone	CID:91885231	454.61 g/mol	0	High	No	-10.0
Lupilutin	CASID:104691-85-2	370.36 g/mol	0	High	No	-10.0

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Parvisoflavone B	CID:14550385	352.34 g/mol	0	High	No	-10.0
Daturametelin D	CID:101588714	468.63 g/mol	0	High	Yes	-9.9
DITERPENE II (LACTONE)	CID:339816	346.42 g/mol	0	High	Yes	-9.8
Paroxetine	CID:43815	329.37 g/mol	0	High	Yes	-9.7
Physcion	CID:10639	284.27 g/mol	0	High	No	-9.7
Berberine	CID:2353	336.37 g/mol	0	High	Yes	-9.6

The highest binding affinity was shown by Lupinisolone A, a phytochemical from *L. albus*, which also expressed drug-likeness, and for a boiled egg, it showed high gastrointestinal absorption but it could not cross BBB (blood-brain barrier) permeability. Another phytochemical Cubebin from *Piper cubeba* and *Piper nigrum* showed very good binding affinity, expressed drug-likeness, and for a boiled egg, it showed high gastrointestinal absorption and BBB (blood-brain barrier) permeability was also yes. This suggests that Cubebin and Lupinisolone A both can be used as a potent drug for mucormycosis. Not all compounds expressing high binding affinity showed boiled egg presentation. For a drug molecule, the gastrointestinal (GI) absorption should be high, so some of these molecules showed high GI absorption but could not cross BBB permeability. The remaining ligands also showed binding against the protein molecule whether they showed drug-likeness or not. Few molecules did not show drug-likeness and yet bonded well with high binding affinity. Most of the phytochemicals chosen showed an affinity for the protein molecule.

In this study, phytochemicals of *L. albus* were found to be the most potent candidate, among the 45 phytochemicals of *L. albus* most of them show high GI absorption with BBB permeability (Table 3). Some molecules that did not show BBB permeability, those molecules can be modified further and used as drugs.

Table 3: Swiss-ADME analysis of phytochemicals from *Lupinus albus* showing Lipinski's rule violations and Boiled egg presentations with binding energy

Lupinus albus						
Phytochemical compound	**PubChem ID**	**Molecular Weight**	**Lipinski's Rule Violation**	**GI Absorption**	**BBB permeation**	**Binding energy**
Lupinol A	CID:101608758	438.48 g/mol	0	High	No	-9.5
13-Hydroxymultiflorine	CID:85280874	264.37 g/mol	0	High	Yes	-8.3
2'-Hydroxygenistein	CID:5282074	286.24 g/mol	0	High	No	-8.5
2'-Hydroxyisolupalbigenin	CID:14237659	422.48 g/mol	0	Low	No	-9.4
Albine	CID:442936	232.33 g/mol	0	High	Yes	-7.8
Alpinumisoflavone	CID:5490139	336.34 g/mol	0	High	No	-9.7
Angustifoline	CID:442939	234.34 g/mol	0	High	Yes	-8.4
Angustone A	CID:15664151	422.48 g/mol	0	Low	No	-9.3
Angustone B	CID:5481235	420.46 g/mol	0	High	No	-9.7
Genisteine	CID:15939859	234.39 g/mol	0	Low	Yes	-7.8
Licoisoflavone B	CID:5481234	352.34 g/mol	0	High	No	-9.9
Lupalbigenin	CID:10001388	406.48 g/mol	0	High	No	-9.7
Lupanine	CID:119201	248.37 g/mol	0	High	Yes	-7.7
Lupilutin	CASID:104691-85-2	370.36 g/mol	0	High	No	-10
Lupinalbin A	CID:5324349	284.22 g/mol	0	High	No	-9
Lupinalbin B	CID:14309761	352.34 g/mol	0	High	No	-9.6
Lupinalbin C	CID:14309762	368.34 g/mol	0	High	No	-10.5

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Lupinalbin D	CID:44260099	352.34 g/mol	0	High	No	-9.6
Lupinalbin E	CID:44260097	368.34 g/mol	0	High	No	-9.8
Lupinalbin F	CID:44260100	420.46 g/mol	0	Low	No	-9.8
Lupinalbin G	CASID:128718-50-3	368.34 g/mol	0	High	No	-9.1
Lupinisoflavone A	CID:5319901	352.34 g/mol	0	High	No	-9
Lupinisoflavone B	CID:632835	370.36 g/mol	0	High	No	-8.3
Lupinisoflavone C	CID:44257284	354.36 g/mol	0	High	No	-9.9
Lupinisoflavone E	CASID:93373-44-5	438.48 g/mol	0	High	No	-10.2
Lupinisoflavone F	CASID:93373-43-4	454.48 g/mol	0	High	No	-8.6
Lupinisoflavone G	CID:14237661	422.48 g/mol	0	High	No	-9
Lupinisoflavone H	CID:14237662	438.48 g/mol	0	High	No	-9.5
Lupinisoflavone I	CID:14237663	438.48 g/mol	0	High	No	-9.7
Lupinisoflavone J	CID:14237664	438.48 g/mol	0	High	No	-4.1
Lupinisoflavone K	CID:14728996	436.46 g/mol	0	High	No	-9.2
Lupinisoflavone L	CID:14728997	436.46 g/mol	0	High	No	-10.6
Lupinisoflavone M	CID:14728998	456.49 g/mol	0	Low	No	-9.9
Lupinisoflavone N	CID:14728999	472.49 g/mol	1	Low	No	-9.9
Lupinisol A	CID:14237668	422.48 g/mol	0	High	No	-9.5
Lupinisol B	CID:14237669	438.48 g/mol	0	Low	No	-9.2
Lupinisol C	CID:14237670	438.48 g/mol	0	Low	No	-9.3
Lupinisolone A	CID:14237665	422.48 g/mol	0	High	No	-12.0
Lupinisolone B	CID:14237666	438.48 g/mol	0	High	No	-9.5
Lupinisolone C	CID:14237667	438.48 g/mol	0	High	No	-6.1
Lupisoflavone	CID:101602348	368.39 g/mol	0	High	No	-9.2
Multiflorine	CID:6918763	246.35 g/mol	0	High	Yes	-8.1
Parvisoflavone B	CID:14550385	352.34 g/mol	0	High	No	-10
SCHEMBL7152319	CID:88101068	342.30 g/mol	2	Low	No	-6.6
Sophoraisoflavone A	CID:10383349	352.34 g/mol	0	High	No	-9.7

The top 20 phytochemicals among 561 phytocompounds and phytochemicals from *L. Albus* were chosen for docking analysis, and the molecules were then docked to the protein's active site. All of the ligands have different binding affinities in terms of (Kcal/mol). Table 2 and Table 3 describe the different properties and binding affinities of the docked complexes, with a synopsis of the top 20 Phytochemicals and the phytochemicals of *L. Albus* binding affinity scores derived by AutoDock Vina in terms of kcal/mol. The higher the binding affinity between the receptor, the higher the energy score, and Lupinisolone A had the highest binding affinity of all the examined substances.

The docked complex of 1,3-β-glucan synthase is shown in Figure 3. With the maximum binding affinity of -12.0 Kcal/mol, this docked conformation of Lupinisolone A with 1,3-β-glucan synthase was found using PyRx (AutoDock Vina).

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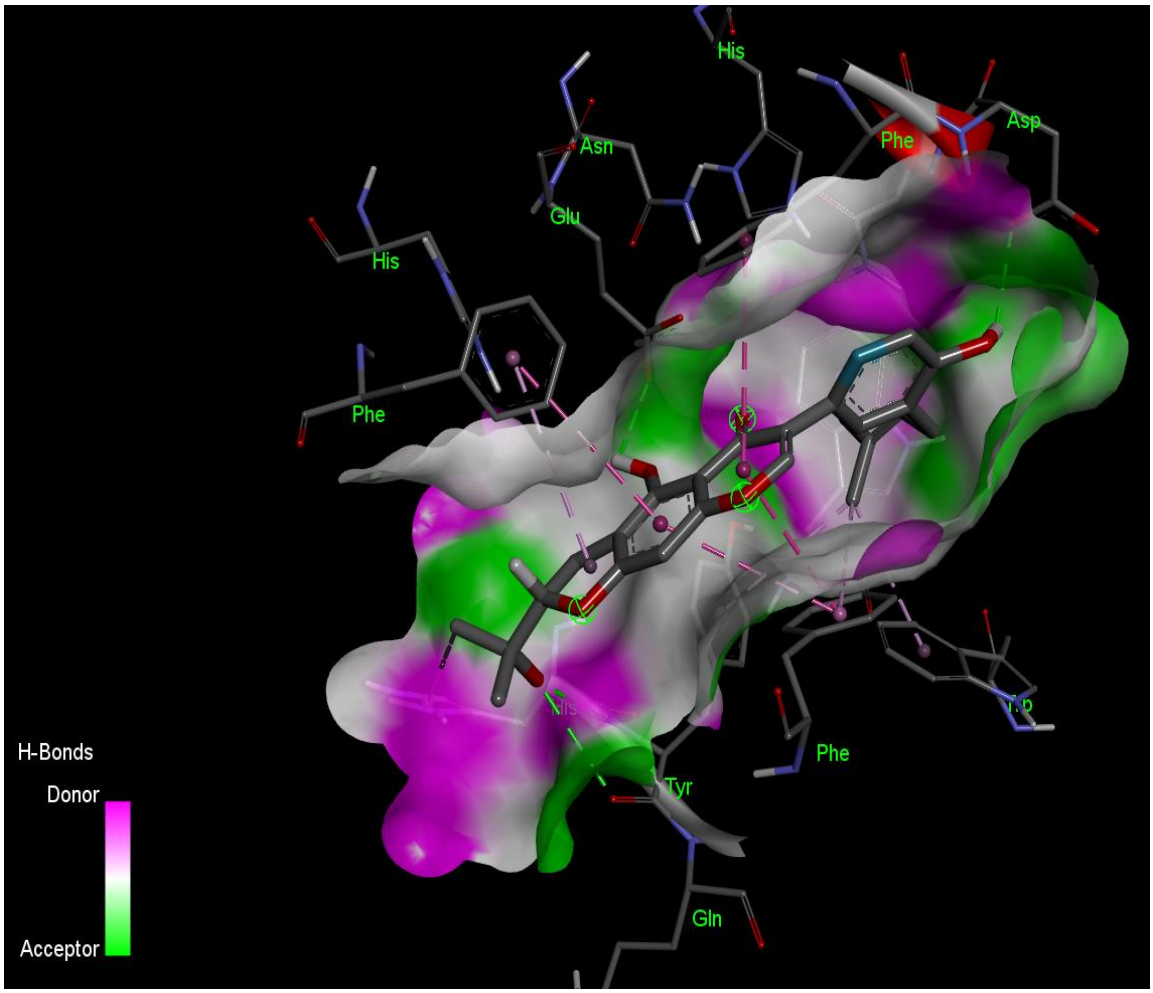

Figure 3: A docked complex of 1,3-β-glucan synthase with Lupinisolone A showing H-bond interaction.

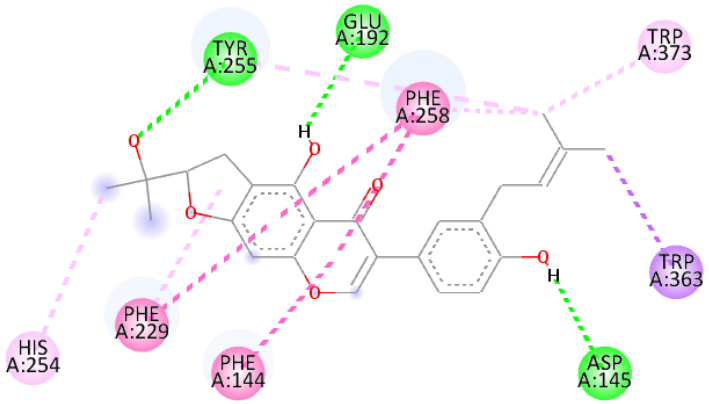

Figure 4 (a): Interaction plot between Lupinisolone A and 1,3-β-glucan synthase protein

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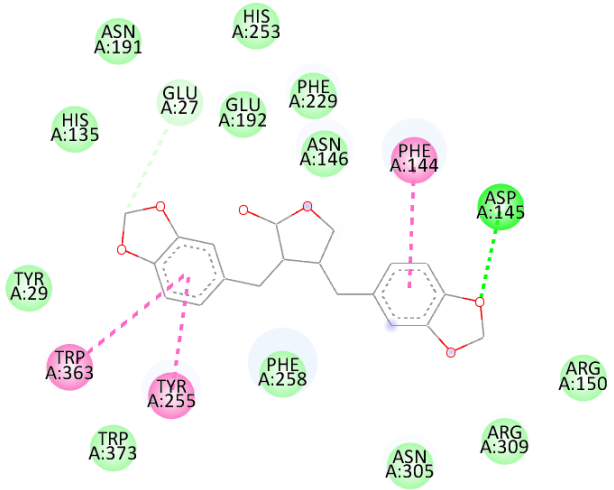

Figure 4 (b): Interaction plot between Lupinisolone A and 1,3-β-glucan synthase protein

The interaction plot of the 1,3-β-glucan synthase protein and top 2 predicted phytochemical is shown in Figure 4 (a) & (b), which was visualized using the Discovery studio visualizer and the interacting amino acid residues are represented in **Table 4**. It represents numerous residues that relate to distinct forms of interactions between phytocompounds and the 1,3-β-glucan synthase protein.

Table 4.4: Interactions between ligands and a target protein's amino acid residues

Phytochemical compounds	PubChem ID	Binding energy	Amino Acids
Lupinisolone A	CID:14237665	-12.0	PHE144, ASP145, ASN146,GLU192, PHE229, HIS254, TYR255, PHE258, TRP363, TRP373
Cubebin	CID:117443	-10.6	GLU27, PHE144, ASP145, TYR255, TRP363

4. CONCLUSION

A potential inhibitor protein was selected and docked against 561 ligands using Autodock Vina incorporated in Pyrx software. With our computational approach, we found some potential anti-fungal compounds that inhibit the 1,3 beta-glucan synthase of Mucormycosis. This study suggests that Cubebin and Lupinisolone A both can be used as a potent drug for mucormycosis. This would bring an end to the persistent health risk imposed by fungal infections. In conclusion, we can say that the computational project performed can be treated as a guide for experimental work on the 1,3-β-glucan synthase and antifungal drug design.

Ethical approval

Not applicable.

Funding:

This study has not received any external funding.

Conflict of Interest:

The authors declare that there are no conflicts of interests.

Data and materials availability:

All data associated with this study are present in the paper.

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