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Research Article

Molecular docking studies of different phytochemicals obtained from medicinal Plants of Uttarakhand region for identification of potential inhibitors against mucormycosis causing fungal species

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Abstract
Mucormycosis is an insidious fungal infection caused by members of Mucorales and zygomycotic species. During the last few years, mucormycosis has become the third most common invasive fungal infection in patients with haematological malignancies and organ transplantations. The incidence of mucormycosis is particularly high in patients with immunocompromised health. It has been reported that CotH receptor proteins have a potential role in binding *Rhizopus species* with the host cells. Further, CotH1, CotH2, and CotH3 are the spore-coating protein of mucormycosis, which are mostly responsible for the invasion of host cells and causing diseases. The present study aimed to predict the structure of CotH1, CotH2, and CotH3 receptors in *Rhizpous delemar* using homology modelling on SWISS Server and validated the model based on GMQE and QMEAN scores followed by analysis of the predicted model on Ramachandran plot. Further, molecular docking studies of the predominant 46 phytochemicals found in the medicinal plants of Uttarakhand region, India were done against these three receptors. Autodock vina results have shown that the binding energy value of Curcumin was -8.5 Kcal/mol against CotH1, and the binding energy value of Allosecurinin was -7.6 Kcal/mol against CotH2 and binding energy value of Isoquercetin was -7.7 Kcal/mol against CotH3. Evaluation of the ADMET parameters has shown the high efficacy of these compounds. The present Insilico study suggests that Curcumin, Allosecurinine, and Isoquercetin are effective lead molecules against the receptors CotH1, CotH2, and CotH3 in the mucormycosis caused by fungal species *R. delemar.*

Keywords: Allosecurinine , CotH, Curcumin, Docking, Homology Modelling, Isoquercetin, Mucormycosis, Pharmacokinetics, *Rhizopus delemar*

INTRODUCTION

Mucormycosis is a major infectious disease caused by fungal species, mainly Rhizopus. Filamentous molds commonly cause this type of infection. The infection occurs through inoculation of the spores in the wounds, consumption of contaminated food, or inhalation of the spores. Globally, the incidence of mucormycosis ranges from 0.005 to 1.7 cases per million population, with a greater overall prevalence rate in developing countries (Skiada *et al.,* 2020; Chander *et al.,* 2018). A recent study in 2019–2020 reported that India has the highest rate of this fungal infection worldwide (Prakash *et al.*, 2019). Further, In India, the second wave of COVID-19 caused a tremendous spike in the cases of Mucormycosis infection. Furthermore, the rapid speed of spread of mucormycosis can be devastating. Even a 12-hour delay in diagnosis can be fatal and 50% of cases of mucormycosis have historically been diagnosed only after death (Skiada *et al*., 2011; García-Carnero *et al*., 2022) which makes the situation more alarming. 70% of the cases of mucormycosis are known to be reported from Rhizopus species (Roden *et al*.,2005; Ibrahim *et al*., 2012).

The application of steroids during COVID infection is made in critical cases to reduce inflammation of the lungs in order to save the life of the patients, but a major drawback is that these steroids decrease the immunity of the patients and elevate the level of the sugar in normal as well as diabetic individuals. Reduced immunity and enhanced glucose levels trigger the case of mucormycosis in covid patients (Spellberg *et al.*, 2005). The development of vaccination is emerging as a mandatory requirement to combat the spreading of infection (Deutsch *et al.,* 2019). Vaccine development is time-consuming and costly, but there are different methods that can be used to decrease the time span and cost of vaccine development. One such type of method is bioinformatics approach for vaccine development. The screening of the epitopes by the silico method has been widely used to predict the *Rhizopus delemar* immunogenicity (Biswas *et al.,* 2022).

Mucormycosis infection is life-threatening, with a low rate of success in its treatment. Currently available medical treatments include debridement surgical antifungal therapy (Ribes *et al*., 2000). A critical review of the data shows that the mortality rates in this infection range from 40% to 100% in patients with pre-existing medical conditions like persistent neutropenia, Diabetes mellitus type 2 or invasion of the cerebral portion (Ibrahim *et al*.,2005; Spellberg *et al.,*2009). The survivor of patients from infection typically depends on the disfigurement from the surgical interventions (Kauffman , 2004).

The new treatment and invention therapies are urgently required. Although the weakened immune system of patients, e.g. due to organ transplantation and hematological malignancy (Spellberg *et al*.,2005; Neblett *et al*., 2012), malnourishment or prematurity (Petrikkos *et al*.,2012) increases the risk of hyperglycemia, mucormycosis, diabetic ketoacidosis(DKA) and the other acidosis forms uniquely in the patients making them more susceptible for the mucormycosis (Artis *et al*., 2012).The different predisposing factors for mucormycosis are the types of characteristics for the propensity to invade vasculature resulting in blood vessels and tissue subsequent necrosis (Wächtler *et al*., 2012).

Efficacy of various medicinal plants has been studied against the causative fungus of mucormycosis. Antifungal activity of the Ethanolic leaf extracts of *plants Ziziphus mauritiana Catharanthus roseus, Lantana camara, Nerium indicum, Sida cordifolia* were studied against the fungus Mucor circinelloides using the disc diffusion assay.Results of this investigative study showed that ethanolic leaf extracts of C. roseus had high antimycotic activity against *M. circinelloides* while *Z. mauritiana*'s leaf extracts exhibited minimum antifungal activity against *M. circinelloides* (Bhadauria *et al*.,2011; Renu *et al.,*2022).

As plant extracts and plant products (phytochemicals) are known to show good antimicrobial activity against bacterial and fungal infections, this research has been conducted taking into account,the major medicinal plants found in Uttarakhand region and investigating the role of the phytochemicals extracted from these plants against Cot H receptors of Rhizopus delegar species using Insilico strategy. Cot H has been known to be involved in fungal pathogenesis and enhance the invasion of host cells during mucormycosis infection (Ashraf *et al*.,2012; Gebremariam *et al.,* 2014). It has been investigated that mucormycosis-causing fungal pathogenic strains bind to glucose-regulated protein 78 (GRP78) on the endothelial receptors. Enhanced expressions of GRP78 result in accelerated fungal invasion and damage of endothelial cells in a receptor-dependent manner . Finally, DKA mice express more GRP78 in the target organs than normal mice and are protected from mucormycosis when given anti-GRP78 Abs . Researchers have demonstrated that spore coat protein homolog (CotH) cell surface proteins, mainly CotH3, are the promiscuous ligands of Mucorales that strengthen and mediate the attachment to GRP78 during the interaction of Mucorales with the host cell and this interaction of GRP78 with CotH receptors promotes invasion of the host cells. Further, experiments on mice have shown that CotH is a promising target for the development of immunological therapeutics against mucormycosis. (Liu *et al,* 2010).

Due to the known role of Cot H receptors, structure prediction and molecular docking studies of the phytochemicals obtained from medicinal plants of the Uttarakhand region was made against these receptors.

MATERIALS AND METHODS

Methodology

Prediction of the target protein structure using homology modelling:

As the structure of the three target proteins, CotH1, CotH2 and CotH3 , considered for this research investigation were not available in the RCSB database, 3D model structure was constructed for these receptors using SWISS-MODEL SERVER (Waterhouse *et al*.,2018; Bienert *et al.,*2017; Guex *et al*.,2009). Sequence of template proteins showing identity and similarity of more than 90% was used to build the model. The Swiss-Model template library search utilized the algorithms of the BLAST and HHblits to identify templates and generate target template alignments. Out of fifty templates generated, the best four templates were selected on the basis of GMQE value (Higher GMQE value) and query coverage percentage. Build model tool was further used for generating the model after template target alignment, loop modelling and side chain evaluation. Various structural models which were generated after model building were evaluated on the basis of GMQE score and QMEAN score (Studer *et al.,* 2020; Bertoni *et al*.,2017). QMEAN score is the most important factor for choosing the best model. If the QMEAN value is 0, then it is considered the best value, QMEAN score below -4 is considered the worst value, and the subsequent model built at this score is considered inaccurate. For prediction of the structure of CotH1, Model 1, 5jd9.1.A template was considered as the best among the four template models on the basis of the GMQE, QMEAN and Sequence Identity scores i.e. 0.43, -3.52 and 24.71%, respectively and this model was taken for structure assessment by clicking Structure assessment.

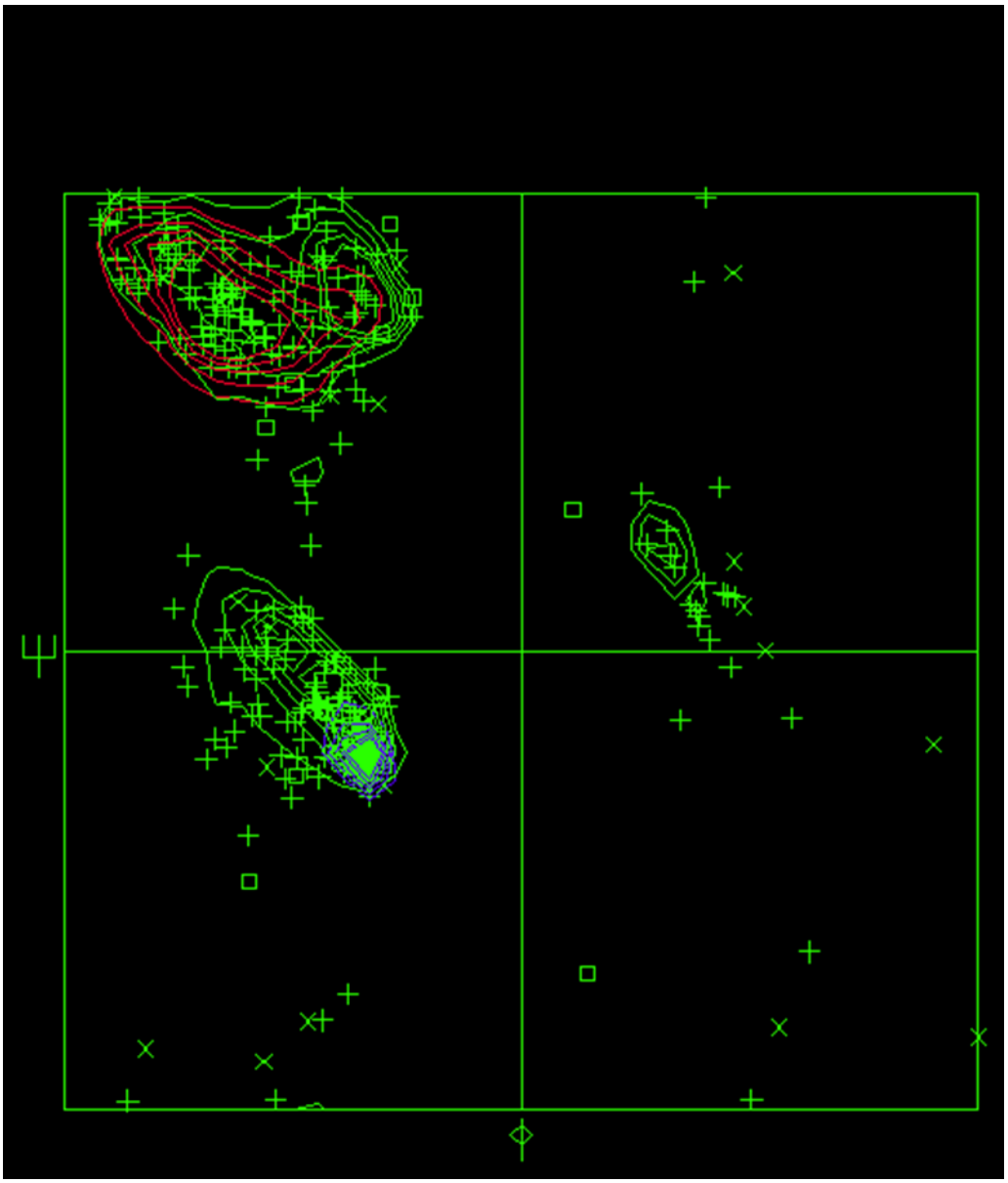


Fig 1 A. *Ramachandran Plot of CotH1 receptor protein*

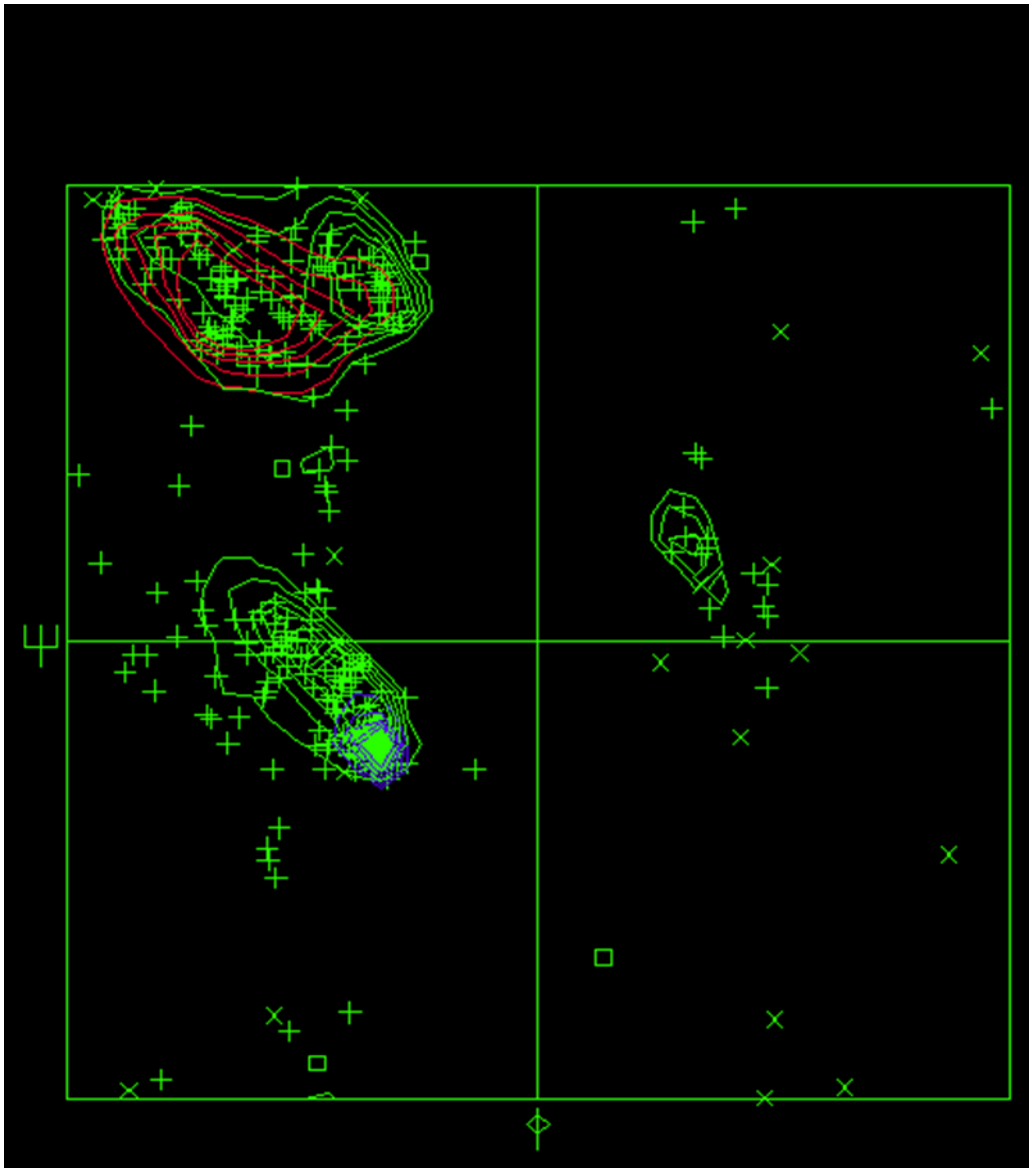


Fig. 1 B. *Ramachandran plot of CotH2 receptor protein*

Similarly, for building model of CotH2, Model 1, i.e. 5jd9.1.A template was considered the best among the four templates on the basis of the GMQE, QMEAN and Sequence Identity scores, i.e. 0.44, -3.09 and 28.68%, respectively and for CotH3, respectively, Model 1, i.e. 5jd9.1.A template was considered the best among the four templates on the basis of the GMQE, QMEAN and Sequence Identity scores, i.e. 0.42, -3.48 and 26.68%, respectively. After assessment of the stability of the structural models on the Ramachandran, plot structures were saved in PDB format.

Phytochemicals (ligands) selected against coth receptors

Forty-six phytochemicals which were extracted from various medicinal plants found in maximum numbers in the Uttarakhand region, were selected for this study. Phenolics, alkaloids and phytochemicals obtained from medicinal plants- *croton tricolor, Rauwolfia, Physostigma, Nux vomica, Aloe barbadensis Mill., Andrographis paniculate , Allium salivum , Eugenia caryophyllata ,Curcuma longa, Datura metel L. and Emblica officinalis Piper species like Piper dennisii, Piper fimbrilalum, Piper glabralum, Piper grande Vahl, Ergot* were considered for this investigation. Chemical structure of these 46 phytochemicals were downloaded in sdf format from pubchem database (Kim *et al.*, 2019). The properties of these molecules, as per Lipinski's rule (Lipinski, 2004) of 5 were observed to assess their drug likeliness. SWISS ADME software was used to assess the ADMET parameters and drug likeliness of selected phytochemicals.

Molecular docking studies of selected phytochemicals

All the 3 receptors were processed and prepared for molecular docking using Biovia Discovery software version 2020 (BIOVIA, 2020). Water molecules and het-

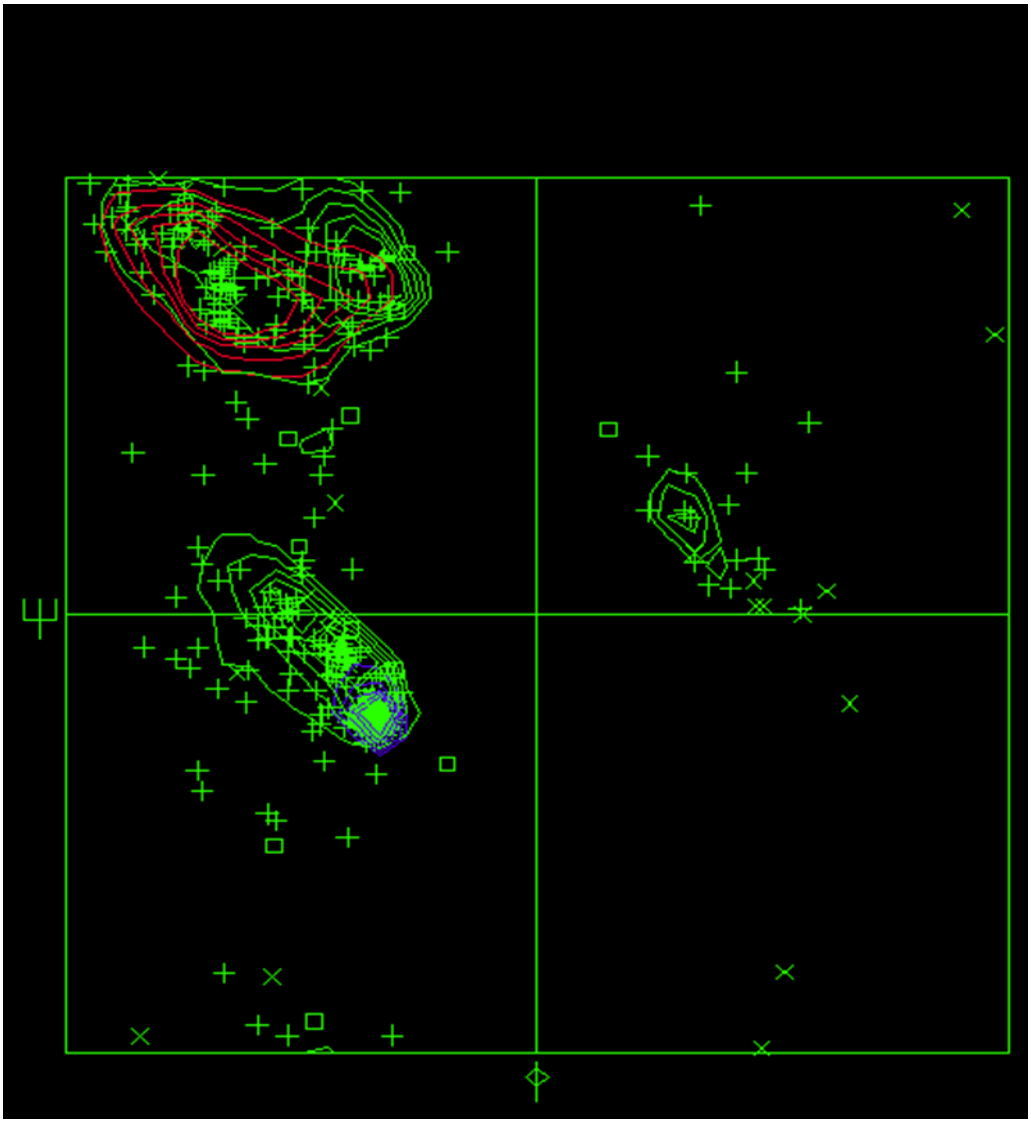


Fig. 1 C. *Ramachandran plot of CotH3 receptor protein*

eroatoms were removed followed by addition of polar hydrogen and Kollman charges. PyRx software (Morris *et al*.,2009; Dallakyan *et al.,* 2015) was used for the preparation of all 46 phytochemicals as ligands, followed by molecular docking. Nine conformers of each phytochemical were generated and molecular docking conformer with minimum free energy and maximum binding affinity along with upper and lower bound RMSD in the range of zero were selected for further study.

Analysis of the admet properties

SWISS ADME tool (Daina *et al.,*2017) was applied for the calculation of various pharmacokinetic and pharmacodynamic properties of these 46 phytochemicals including molecular formula, molecular weight, number of heavier atoms, number of aromatic atoms, fractions CSP3, number rotatable bonds, number H-bond acceptors, number of H-bond donors, molar refractivity, TPSA, Lipophilicity properties like ILOGP, XLOGP3, WLOGP, water solubility properties, drug-likeness properties, synthetic accessibility etc. Furthermore, the probability of the compounds being an irritant, mutagenic agent, or tumorigenic agent, and their reproductive effectivity in nature was determined using OSIRIS software (Sander, 2001) obtained from the organic chemistry portal.

RESULTS

Mucormycosis angioinvasion relies on the interaction of CotH proteins. Structure prediction results for CotH proteins were observed as follows:

Structure prediction results for coth1, coth2 and coth3

Ligands/phytochemicals selected for docking

46 Phytochemicals which are obtained from medicinal plants of the Uttarakhand region and have been used in this study are reported in Table 4. Medicinal plants con-

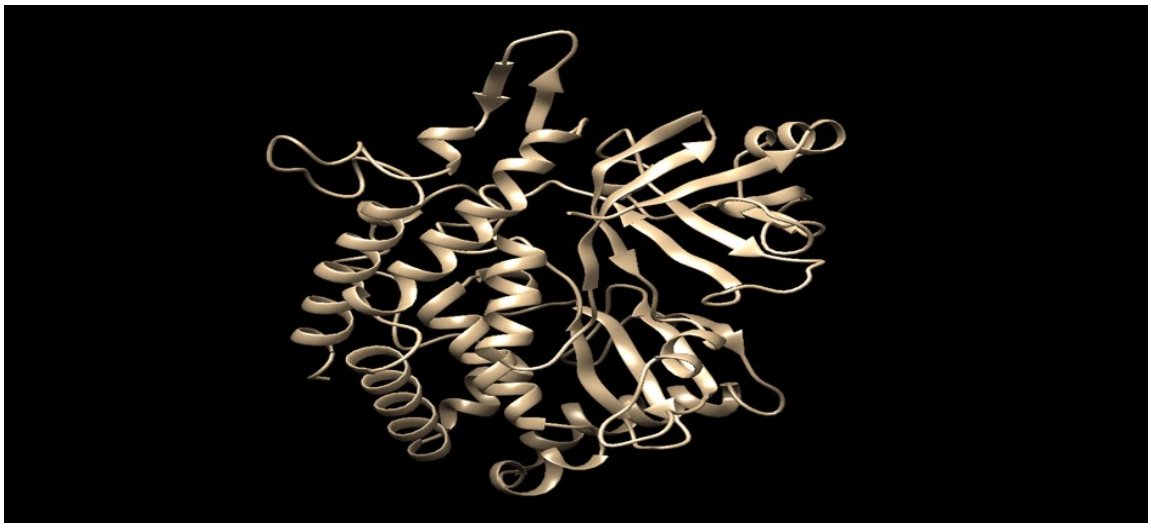


Fig. 2. *CotH1 Chimera structure*

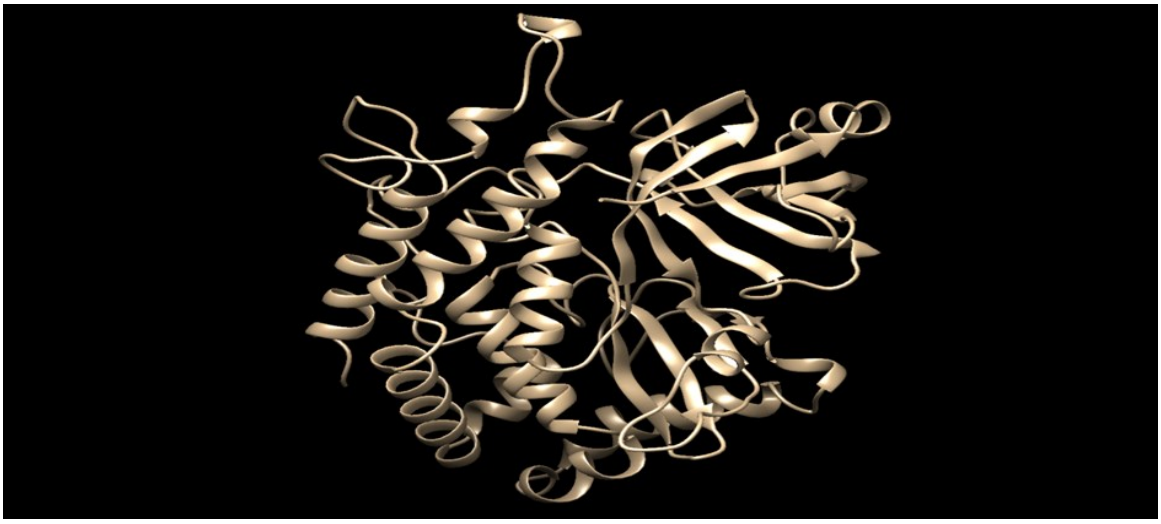


Fig. 3. *CotH2 Chimera structure*

Table 1. CotH1 Model score

Models	GMQE Score	QMEAN Score	Seq. Identity
Model 1 (5jd9.1.A)	0.43	-3.52	24.71%
Model 2 (6ne9.1.A)	0.04	-0.18	28.30%
Model 3 (6rzo.1.B)	0.03	-0.14	24.53%
Model 4 (6as3.1.B)	0.02	-0.40	15.56%

Table 2. CotH2 Model score

Models	GMQE Score	QMEAN Score	Seq. Identity
Model 1 (5jd9.1.A)	0.44	-3.09	28.68%
Model 2 (6as3.1.B)	0.02	-0.69	13.33%
Model 3 (6arz.1.A)	0.02	-0.97	13.33%
Model 3 (6as4.1.A)	0.02	-0.90	13.34%

Table 3. CotH3 Model score

Models	GMQE Score	QMEAN Score	Seq. Identity
Model 1 (5jd9.1.A)	0.42	-3.48	26.68%
Model 2 (2bhu.1.A)	0.04	-1.15	26.42%
Model 3 (6ne9.1.A)	0.03	-2.04	20.75%
Model 3 (6rzo.1.A)	0.03	-1.85	18.18%

Table 4. Phytochemicals with CID number

Phytochemical name	CID
Epiglobulol	11858788
Alpha-bisabolol	10586
Alpha-trans-bergamotene	86608
Beta-caryophyllene	5281515
Turmerone	558221
Beta-atlantone	181580
Zingiberone	31211
Eugenol	3314
Di-2-propenyl trisulphide	16315
Di-2-propenyl disulphide	16590
Catechin	9064
Luteolin	5280445
Quercetin	5280343
Gallic acid	370
Baicalein	5281605
Wogonin	5281703
Ferulic acid	445858
Caffeic acid	689043
Curcumin	969516
Isoquercetin	5280804
Phenanthridine	9189
Cycleanine	121313
Cocroline	21579624
Berberine	2353
Eupolauridine	72486
Allosecurinine	267769
Alpha-Thujene	6451618
Sabinene	18818
6-methyl-5-hepten-2-one	9862
Alpha-phellandrene	7460
Alpha-terpinene	7462
p-Cimene	7463
Limonene	22311
Beta-phellandrene	11142
(Z)-Beta-ocimene	5320250
(E)-Beta-ocimene	5281553
Alpha-pinene	6654
Camphene	6616
Beta-pinene	14896
Myrcene	31253
p-Cymene	7463
Limonene	22311
1,8-Cineole	2758
Y-Terpinene	7461
Linalool	6549
Thymol	6989

sidered for this study are *Croton tricolor, Curcuma Longa, Eugenia caryophyllata, Allium salivum, Emblica officinalis, Ergot, Rauwolfia, Physostigma, Nux vomica,* Piper species like *Piper dennisii, Piper fimbrilalum, Piper glabralum* and *Thymus vulgaris*(Clara *et al*. 2017; de Lira *et al.* 2012)

Molecular docking results

The 3D structures of targets structure of CotH 1,2 and 3 were prepared by removing water molecules and unnecessary chemical complexes, adding required charges, polar hydrogen, and missing side chains using the Biovia Discover Studio (version 2021) .Molecular docking studies were performed using PyRx software whereby 46 phytochemicals listed in Table 4 were docked against 3 CotH receptors.

Phenolics and alkaloids obtained from medicinal plants exhibited binding affinity in the range -5.5 Kcal/mol to -9 Kcal/mol. The highest affinity of binding was obtained for phenolics obtained from Thymus vulgaris and it was -9 Kcal/mol against the CotH2 receptor of *R.delemar.* The lowest affinity value of -5.3 Kcal/mol was obtained for the alkaloid obtained from Piper species against CotH1 receptor.

Admet results obtained for phytochemicals

The pharmacokinetic parameters included values of Molar refractivity, TPSA, Lipophilicity, Water solubility, Drug likeness score, Lipinski's score, Lead likeness, Synthetic accessibility for the best ligands predicted against CotH1, CotH2 and CotH3 are shown in Figs. 5 , 6 and 7 respectively.

DISCUSSION

Molecular docking results obtained from Autodock Vina indicated that Curcumin has the best binding affinity towards CotH1, Allosecurinin has the best binding affinity towards CotH2 and Isoquercetin has the best binding affinity towards CotH3. The binding energy value of Curcumin was obtained as -8.5 Kcal/mol against CotH1, and the binding energy value of Allosecurinin was obtained as -7.6 Kcal/mol against CotH2 and the binding energy value of Isoquercetin was obtained as -7.7 Kcal/mol against CotH3. These three phytochemicals showed most stable binding towards the CotH receptors which led to further investigation of their pharmacokinetic parameters using SWISS ADME tool and OSIRIS property explorer.

The antifungal activity of various phytochemicals against the RNA-dependent RNA polymerase (RdRp) protein was studied by applying computational approaches. Analysis of values of the binding affinity showed that Dregamine (-11.1 kcal/mol), Alantolactone (-9.5), Isoalantolactone (-9.5) and Solasodine (-9.5) exhibited the lowest energy value, indicating a strong

Table 5. Molecular docking results of phytochemicals against CotH1 protein of *Rhizopus delemar*

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
CotH1_5281605_uff_E=241.95	-8.4	0	0
CotH1_5281605_uff_E=241.95	-8.3	6.308	3.922
CotH1_5281605_uff_E=241.95	-7.5	6.326	3.983
CotH1_5281605_uff_E=241.95	-7.5	36.404	34.952
CotH1_5281605_uff_E=241.95	-7.4	6.085	3.896
CotH1_5281605_uff_E=241.95	-6.8	48.882	46.743
CotH1_5281605_uff_E=241.95	-6.5	36.369	35.066
CotH1_5281605_uff_E=241.95	-6.5	48.748	47.511
CotH1_5281605_uff_E=241.95	-6.4	35.826	34.044
CotH1_689043_uff_E=98.60	-6.4	0	0
CotH1_689043_uff_E=98.60	-6.1	5.417	4.089
CotH1_689043_uff_E=98.60	-5.8	7.571	5.308
CotH1_689043_uff_E=98.60	-5.7	5.688	4.172
CotH1_689043_uff_E=98.60	-5.7	1.978	1.145
CotH1_689043_uff_E=98.60	-5.5	35.005	34.245
CotH1_689043_uff_E=98.60	-5.5	9.602	6.348
CotH1_689043_uff_E=98.60	-5.4	46.419	45.384
CotH1_689043_uff_E=98.60	-5.3	6.711	2.84
CotH1_9064_uff_E=204.84	-8.4	0	0
CotH1_9064_uff_E=204.84	-7.8	2.518	1.914
CotH1_9064_uff_E=204.84	-7.6	35.948	34.054
CotH1_9064_uff_E=204.84	-7.3	6.807	4.128
CotH1_9064_uff_E=204.84	-7.2	6.511	4.555
CotH1_9064_uff_E=204.84	-7.1	36.068	34.681
CotH1_9064_uff_E=204.84	-7.1	7.125	4.391
CotH1_9064_uff_E=204.84	-7	13.549	10.251
CotH1_9064_uff_E=204.84	-6.9	23.178	20.876
CotH1_969516_uff_E=272.07	-8.5	0	0
CotH1_969516_uff_E=272.07	-7.4	46.735	45.046
CotH1_969516_uff_E=272.07	-7.1	47.919	46.051
CotH1_969516_uff_E=272.07	-7	6.625	3.308
CotH1_969516_uff_E=272.07	-6.8	27.212	21.51
CotH1_969516_uff_E=272.07	-6.8	48.455	46.199
CotH1_969516_uff_E=272.07	-6.7	8.958	5.039
CotH1_969516_uff_E=272.07	-6.6	23.152	17.352
CotH1_969516_uff_E=272.07	-6.5	27.447	21.794
CotH1_445858_uff_E=177.42	-6.1	0	0
CotH1_445858_uff_E=177.42	-6.1	5.759	3.682
CotH1_445858_uff_E=177.42	-5.9	36.167	35.222
CotH1_445858_uff_E=177.42	-5.9	2.456	1.256
CotH1_445858_uff_E=177.42	-5.6	24.046	21.932
CotH1_445858_uff_E=177.42	-5.4	47.321	45.772
CotH1_445858_uff_E=177.42	-5.1	47.004	46.308
CotH1_445858_uff_E=177.42	-5.1	5.066	3.27
CotH1_445858_uff_E=177.42	-5	36.468	35.355

Contd….

Table 5. Contd….

CotH1_370_uff_E=77.82	-5.7	0	0
CotH1_370_uff_E=77.82	-5.6	2.545	0.431
CotH1_370_uff_E=77.82	-5.5	4.014	1.076
CotH1_370_uff_E=77.82	-5.5	4.552	0.881
CotH1_370_uff_E=77.82	-5.5	36.925	35.662
CotH1_370_uff_E=77.82	-5.5	36.905	35.644
CotH1_370_uff_E=77.82	-5.5	36.791	35.791
CotH1_370_uff_E=77.82	-5.4	2.96	1.681
CotH1_370_uff_E=77.82	-5.4	36.723	35.549
CotH1_5280804_uff_E=610.61	-7.5	0	0
CotH1_5280804_uff_E=610.61	-7.3	21.598	18.614
CotH1_5280804_uff_E=610.61	-7.1	30.482	28.215
CotH1_5280804_uff_E=610.61	-7.1	29.613	27.002
CotH1_5280804_uff_E=610.61	-7	5.602	2.321
CotH1_5280804_uff_E=610.61	-6.9	22.119	18.882
CotH1_5280804_uff_E=610.61	-6.9	21.686	18.128
CotH1_5280804_uff_E=610.61	-6.9	39.641	36.19
CotH1_5280804_uff_E=610.61	-6.8	21.472	17.157
CotH1_5280445_uff_E=242.10	-8.1	0	0
CotH1_5280445_uff_E=242.10	-7.5	6.691	4.147
CotH1_5280445_uff_E=242.10	-7.1	36.106	35.009
CotH1_5280445_uff_E=242.10	-7.1	6.81	4.858
CotH1_5280445_uff_E=242.10	-7	35.984	34.969
CotH1_5280445_uff_E=242.10	-6.9	7.139	4.682
CotH1_5280445_uff_E=242.10	-6.8	48.115	46.383
CotH1_5280445_uff_E=242.10	-6.8	35.395	34.231
CotH1_5280445_uff_E=242.10	-6.7	47.406	45.962
CotH1_5280343_uff_E=380.43	-7.8	0	0
CotH1_5280343_uff_E=380.43	-7.4	5.725	3.864
CotH1_5280343_uff_E=380.43	-7.3	36.265	34.263
CotH1_5280343_uff_E=380.43	-7.2	6.672	3.23
CotH1_5280343_uff_E=380.43	-7.1	36.568	34.98
CotH1_5280343_uff_E=380.43	-7	6.51	3.996
CotH1_5280343_uff_E=380.43	-6.9	35.699	34.989
CotH1_5280343_uff_E=380.43	-6.7	7.312	3.25
CotH1_5280343_uff_E=380.43	-6.7	36.542	34.66
CotH1_5281703_uff_E=315.73	-8.3	0	0
CotH1_5281703_uff_E=315.73	-7.5	6.352	2.95
CotH1_5281703_uff_E=315.73	-7.3	5.812	2.815
CotH1_5281703_uff_E=315.73	-6.8	6.19	3.543
CotH1_5281703_uff_E=315.73	-6.4	6.441	2.259
CotH1_5281703_uff_E=315.73	-6.4	35.217	34.094
CotH1_5281703_uff_E=315.73	-6.4	49.326	46.838
CotH1_5281703_uff_E=315.73	-6.3	50.407	48.309
CotH1_5281703_uff_E=315.73	-6.2	25.622	22.653

Table 6. Molecular Docking results of Phytochemicals against CotH2 protein of *Rhizopus delemar*

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
CotH2_267769_uff_E=541.50	-7.6	0	0
CotH2_267769_uff_E=541.50	-6.8	18.791	17.352
CotH2_267769_uff_E=541.50	-6.5	4.163	2.632
CotH2_267769_uff_E=541.50	-6.4	18.112	17.001
CotH2_267769_uff_E=541.50	-6.4	18.018	16.975
CotH2_267769_uff_E=541.50	-6.3	18.118	16.725
CotH2_267769_uff_E=541.50	-6	24.647	23.326
CotH2_267769_uff_E=541.50	-5.9	38.179	36.399
CotH2_267769_uff_E=541.50	-5.8	26.055	23.624
CotH2_2353_uff_E=579.86	-7.4	0	0
CotH2_2353_uff_E=579.86	-7.2	21.335	19.414
CotH2_2353_uff_E=579.86	-7.1	7.739	2.379
CotH2_2353_uff_E=579.86	-6.8	28.781	25.007
CotH2_2353_uff_E=579.86	-6.8	2.666	2.12
CotH2_2353_uff_E=579.86	-6.7	21.669	19.647
CotH2_2353_uff_E=579.86	-6.6	33.222	30.595
CotH2_2353_uff_E=579.86	-6.6	19.815	17.693
CotH2_2353_uff_E=579.86	-6.4	6.687	3.831
CotH2_21579624_uff_E=827.46	-9	0	0
CotH2_21579624_uff_E=827.46	-8.4	40.247	37.639
CotH2_21579624_uff_E=827.46	-8.1	6.735	1.834
CotH2_21579624_uff_E=827.46	-8.1	7.431	2.499
CotH2_21579624_uff_E=827.46	-7.9	7.5	2.746
CotH2_21579624_uff_E=827.46	-7.9	38.228	34.282
CotH2_21579624_uff_E=827.46	-7.9	8.506	3.809
CotH2_21579624_uff_E=827.46	-7.9	36.956	33.507
CotH2_21579624_uff_E=827.46	-7.8	6.622	2.303
CotH2_121313_uff_E=1058.49	-7.7	0	0
CotH2_121313_uff_E=1058.49	-7.6	20.905	15.74
CotH2_121313_uff_E=1058.49	-7.6	20.042	15.758
CotH2_121313_uff_E=1058.49	-7.2	9.426	2.814
CotH2_121313_uff_E=1058.49	-7.2	3.982	2.603
CotH2_121313_uff_E=1058.49	-6.9	8.902	5.959
CotH2_121313_uff_E=1058.49	-6.8	17.639	13.794
CotH2_121313_uff_E=1058.49	-6.8	26.746	22.412
CotH2_121313_uff_E=1058.49	-6.8	19.841	13.816
CotH2_72486_uff_E=405.19	-7	0	0
CotH2_72486_uff_E=405.19	-7	2.949	0.196
CotH2_72486_uff_E=405.19	-6.7	17.567	16.85
CotH2_72486_uff_E=405.19	-6.7	17.292	15.694
CotH2_72486_uff_E=405.19	-6.5	4.492	1.901
CotH2_72486_uff_E=405.19	-6.5	4.156	1.895
CotH2_72486_uff_E=405.19	-6.5	18.05	17.014
CotH2_72486_uff_E=405.19	-6.3	18.232	17.35
CotH2_72486_uff_E=405.19	-6.3	26.268	23.697
CotH2_9189_uff_E=156.77	-7.4	0	0
CotH2_9189_uff_E=156.77	-7.3	4.403	0.521
CotH2_9189_uff_E=156.77	-6.5	16.633	15.087
CotH2_9189_uff_E=156.77	-6.3	17.102	15.545
CotH2_9189_uff_E=156.77	-6.2	18.069	16.791
CotH2_9189_uff_E=156.77	-6.1	17.282	16.488
CotH2_9189_uff_E=156.77	-6.1	42.045	40.094
CotH2_9189_uff_E=156.77	-6.1	42.218	40.086
CotH2_9189_uff_E=156.77	-6.1	4.728	1.552

Table 7. Molecular Docking results of Phytochemicals against CotH3 protein of *Rhizopus delemar*

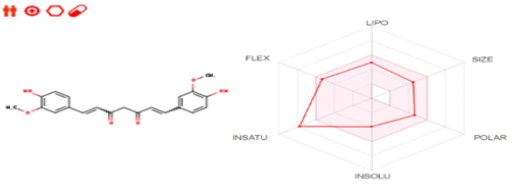
Ligand	Binding Affinity	rmsd/ub	rmsd/lb
CotH3_5281605_uff_E=241.95	-7.4	0	0
CotH3_5281605_uff_E=241.95	-7.3	14.772	12.385
CotH3_5281605_uff_E=241.95	-7.1	38.381	35.573
CotH3_5281605_uff_E=241.95	-6.9	16.594	14.98
CotH3_5281605_uff_E=241.95	-6.9	2.073	1.713
CotH3_5281605_uff_E=241.95	-6.9	6.496	1.948
CotH3_5281605_uff_E=241.95	-6.8	16.989	15.142
CotH3_5281605_uff_E=241.95	-6.8	40.659	39.425
CotH3_5281605_uff_E=241.95	-6.8	24.793	22.928
CotH3_689043_uff_E=98.60	-5.7	0	0
CotH3_689043_uff_E=98.60	-5.6	13.11	10.923
CotH3_689043_uff_E=98.60	-5.4	10.929	9.366
CotH3_689043_uff_E=98.60	-5.4	5.448	2.819
CotH3_689043_uff_E=98.60	-5.3	6.011	1.395
CotH3_689043_uff_E=98.60	-5.3	11.833	9.779
CotH3_689043_uff_E=98.60	-5.3	11.764	9.253
CotH3_689043_uff_E=98.60	-5.2	4.627	3.419
CotH3_689043_uff_E=98.60	-5.1	37.283	35.325
CotH3_9064_uff_E=204.84	-7.5	0	0
CotH3_9064_uff_E=204.84	-7.3	6.854	1.883
CotH3_9064_uff_E=204.84	-7.1	16.28	13.501
CotH3_9064_uff_E=204.84	-7.1	6.659	1.423
CotH3_9064_uff_E=204.84	-6.9	14.412	10.252
CotH3_9064_uff_E=204.84	-6.9	17.521	13.85
CotH3_9064_uff_E=204.84	-6.5	13.775	10.291
CotH3_9064_uff_E=204.84	-6.3	31.881	29.552
CotH3_9064_uff_E=204.84	-6.2	30.453	28.049
CotH3_969516_uff_E=272.07	-7	0	0
CotH3_969516_uff_E=272.07	-6.9	11.221	1.138
CotH3_969516_uff_E=272.07	-6.6	8.713	4.194
CotH3_969516_uff_E=272.07	-6.4	11.841	6.801
CotH3_969516_uff_E=272.07	-6.3	9.348	5.219
CotH3_969516_uff_E=272.07	-6.3	9.932	4.552
CotH3_969516_uff_E=272.07	-6.3	41.279	37.544
CotH3_969516_uff_E=272.07	-6.3	9.549	5.484
CotH3_969516_uff_E=272.07	-6.2	29.014	26.733
CotH3_445858_uff_E=177.42	-6.9	0	0
CotH3_445858_uff_E=177.42	-5.4	28.062	25.877
CotH3_445858_uff_E=177.42	-5.3	32.857	31.203
CotH3_445858_uff_E=177.42	-5.2	32.854	31.714
CotH3_445858_uff_E=177.42	-5.1	26.394	25.185
CotH3_445858_uff_E=177.42	-5.1	33.366	31.392
CotH3_445858_uff_E=177.42	-5.1	33.205	31.243
CotH3_445858_uff_E=177.42	-5	33.071	31.815
CotH3_445858_uff_E=177.42	-5	18.87	18.227

Contd….

Table 7. Contd…..

CotH3_370_uff_E=77.82	-6.2	0	0
CotH3_370_uff_E=77.82	-6	4.088	1.156
CotH3_370_uff_E=77.82	-5.9	4.764	1.334
CotH3_370_uff_E=77.82	-5.8	33.258	32.31
CotH3_370_uff_E=77.82	-5.8	33.264	32.352
CotH3_370_uff_E=77.82	-5.5	21.432	20.536
CotH3_370_uff_E=77.82	-5.5	2.566	1.019
CotH3_370_uff_E=77.82	-5.5	32.716	31.66
CotH3_370_uff_E=77.82	-5.5	32.618	31.645
CotH3_5280804_uff_E=610.61	-7.7	0	0
CotH3_5280804_uff_E=610.61	-7.4	2.424	1.275
CotH3_5280804_uff_E=610.61	-7.2	6.534	2.305
CotH3_5280804_uff_E=610.61	-7.1	32.635	29.17
CotH3_5280804_uff_E=610.61	-7	6.454	2.5
CotH3_5280804_uff_E=610.61	-7	17.839	12.556
CotH3_5280804_uff_E=610.61	-6.9	31.672	27.693
CotH3_5280804_uff_E=610.61	-6.8	25.739	20.989
CotH3_5280804_uff_E=610.61	-6.8	24.673	19.826
CotH3_5280445_uff_E=242.10	-7.2	0	0
CotH3_5280445_uff_E=242.10	-7.2	6.904	1.628
CotH3_5280445_uff_E=242.10	-7.1	17.067	13.625
CotH3_5280445_uff_E=242.10	-7.1	15.574	12.88
CotH3_5280445_uff_E=242.10	-7	14.838	12.119
CotH3_5280445_uff_E=242.10	-6.9	40.805	38.908
CotH3_5280445_uff_E=242.10	-6.8	12.998	9.811
CotH3_5280445_uff_E=242.10	-6.8	14.518	10.933
CotH3_5280445_uff_E=242.10	-6.7	2.542	1.683
CotH3_5280343_uff_E=380.43	-7.6	0	0
CotH3_5280343_uff_E=380.43	-7.3	17.549	13.525
CotH3_5280343_uff_E=380.43	-7.2	13.762	10.63
CotH3_5280343_uff_E=380.43	-7.1	7.16	2.48
CotH3_5280343_uff_E=380.43	-7	6.723	1.464
CotH3_5280343_uff_E=380.43	-7	14.041	9.913
CotH3_5280343_uff_E=380.43	-6.9	14.959	11.959
CotH3_5280343_uff_E=380.43	-6.8	3.549	2.627
CotH3_5280343_uff_E=380.43	-6.8	13.832	10.131
CotH3_5281703_uff_E=315.73	-6.8	0	0
CotH3_5281703_uff_E=315.73	-6.8	3.49	2.606
CotH3_5281703_uff_E=315.73	-6.8	30.998	30.285
CotH3_5281703_uff_E=315.73	-6.6	29.144	27.138
CotH3_5281703_uff_E=315.73	-6.5	27.119	25.887
CotH3_5281703_uff_E=315.73	-6.5	3.343	1.216
CotH3_5281703_uff_E=315.73	-6.4	29.94	27.715
CotH3_5281703_uff_E=315.73	-6.4	41.12	38.926
CotH3_5281703_uff_E=315.73	-6.3	24.103	22.189

Curcumin



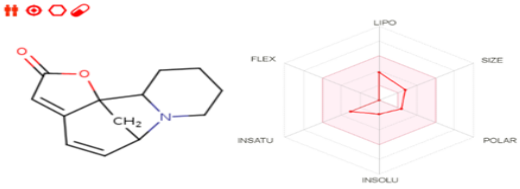
SMILES COc1cc(C=CC(=O)CC(=O)C=Cc2ccc(c(c2)OC)O)ccc1O

Physicochemical Properties	
Formula	C21H20O6
Molecular weight	368.38 g/mol
Num. heavy atoms	27
Num. arom. heavy atoms	12
Fraction Csp3	0.14
Num. rotatable bonds	8
Num. H-bond acceptors	6
Num. H-bond donors	2
Molar Refractivity	102.80
TPSA	93.06 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.27
Log $P_{o/w}$ (XLOGP3)	3.20
Log $P_{o/w}$ (WLOGP)	3.15
Log $P_{o/w}$ (MLOGP)	1.47
Log $P_{o/w}$ (SILICOS-IT)	4.04
Consensus Log $P_{o/w}$	3.03

Water Solubility	
Log *S* (ESOL)	-3.94
Solubility	4.22e-02 mg/ml ; 1.15e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.83
Solubility	5.50e-03 mg/ml ; 1.49e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-4.45
Solubility	1.31e-02 mg/ml ; 3.56e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.28 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: beta_keto_anhydride, michael_acceptor_1
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	2.97

Fig. 5. *Swiss ADME results of Curcumin*

Allosecurinin



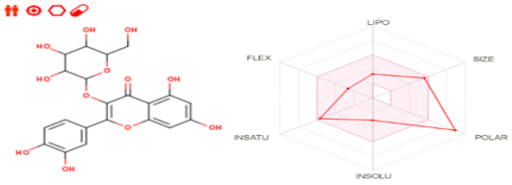
SMILES O=C1C=C2C3(O1)CC(C=C2)N1C3CCCC1

Physicochemical Properties	
Formula	C13H15NO2
Molecular weight	217.26 g/mol
Num. heavy atoms	16
Num. arom. heavy atoms	0
Fraction Csp3	0.62
Num. rotatable bonds	0
Num. H-bond acceptors	3
Num. H-bond donors	0
Molar Refractivity	63.33
TPSA	29.54 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.37
Log $P_{o/w}$ (XLOGP3)	1.10
Log $P_{o/w}$ (WLOGP)	1.02
Log $P_{o/w}$ (MLOGP)	1.95
Log $P_{o/w}$ (SILICOS-IT)	1.35
Consensus Log $P_{o/w}$	1.56

Water Solubility	
Log *S* (ESOL)	-1.88
Solubility	2.86e+00 mg/ml ; 1.32e-02 mol/l
Class	Very soluble
Log *S* (Ali)	-1.31
Solubility	1.06e+01 mg/ml ; 4.86e-02 mol/l
Class	Very soluble
Log *S* (SILICOS-IT)	-1.26
Solubility	1.19e+01 mg/ml ; 5.47e-02 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.84 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: MW<250
Synthetic accessibility	4.83

Fig 6. *Swiss ADME results of Allosecurinin*

Isoquercetin



SMILES OCC1OC(Oc2c(oc3c(c2=O)c(O)cc(c3)O)c2ccc(c(c2)O)O)C(C(C1O)O)O

Physicochemical Properties	
Formula	C21H20O12
Molecular weight	464.38 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	16
Fraction Csp3	0.29
Num. rotatable bonds	4
Num. H-bond acceptors	12
Num. H-bond donors	8
Molar Refractivity	110.16
TPSA	210.51 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.11
Log $P_{o/w}$ (XLOGP3)	0.36
Log $P_{o/w}$ (WLOGP)	-0.54
Log $P_{o/w}$ (MLOGP)	-2.59
Log $P_{o/w}$ (SILICOS-IT)	-0.59
Consensus Log $P_{o/w}$	-0.25

Water Solubility	
Log *S* (ESOL)	-3.04
Solubility	4.23e-01 mg/ml ; 9.10e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.35
Solubility	2.10e-02 mg/ml ; 4.51e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-1.51
Solubility	1.43e+01 mg/ml ; 3.08e-02 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.88 cm/s
Druglikeness	
Lipinski	No; 2 violations: NorO>10, NHorOH>5
Ghose	No; 1 violation: WLOGP<-0.4
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 3 violations: TPSA>150, H-acc>10, H-don>5
Bioavailability Score	0.17
Medicinal Chemistry	
PAINS	1 alert: catechol_A
Brenk	1 alert: catechol
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	5.32

Fig. 7. *Swiss ADME results of Isoquercetin*

binding affinity towards RdRp protein (Vikas Jha *et al.*, 2022).

Another in silico study was conducted to study the efficacy of phytochemicals obtained from *Allium sativum* against mucormycosis fungus using Biovia discovery software which indicated that garlic phytochemicals and Z-ajoene could be good medicine for black fungi. Binding affinity value of -5.07 Kcal/mol was obtained for Z-ajoene against 1,3-beta-glucan synthase enzyme of mucormycosis fungus (Sharma *et al.*, 2021).

In order to identify potential inhibitors of mucormycosis, 158 antifungal phytochemicals were screened using molecular docking against glucoamylase enzyme of Rhizopus oryzae. Majority of the compounds showed lower binding energy values than Isomaltotriose (-6.4 kcal/mol). Computational studies also revealed the strongest binding affinity of the screened phytochemicals was Dioscin (-9.4 kcal/mol).

(Hamaamin *et al.,* 2022).

Curcumin (Chemical formula: C21H20O6) has a molecular weight of 368.38 g/mol. It has 27 heavy atoms, possesses 6 Hydrogen bond acceptors, 2 Hydrogen bond donors, 8 rotatable bonds, Molar refractivity value of 102.80 and TPSA score of 93.06A, which shows its score on a bit higher side as ideal TPSA value of a drug molecule should be less than 83.00 A. Lipophilicity value of Curcumin was obtained as ILOGP: 3.27, XLOGP3: 3.20, WLOGP: 3.15, along with water solubility value of 4.22e-02 mg/ml; 1.15e-04 mol/l which shows high efficacy of Curcumin to be dissolved in bloodstream. Positive Drug likeness and Lipinski score were seen for Curcumin and no pain alerts are associated with it.

Allosecurinine (Chemical formula: C13H15NO2) has a molecular weight of 217.26 g/mol. It has 16 heavy atoms, possesses 3 Hydrogen bond acceptors, 0 Hydrogen bond donors, 0 rotatable bonds, Molar refractivity value of 63.33, Synthetic accessibility value of 4.83 and TPSA score of 29.54A which shows that it has good accessible surface area. Lipophilicity value of Curcumin was obtained as ILOGP: 2.37, XLOGP3: 1.10, WLOGP: 1.02, and water solubility value of 2.86e+00 mg/ml; 1.32-02 mol/l, which shows high efficacy of Allosecurinine to be dissolved in bloodstream. Positive Drug likeness and Lipinski score were seen for Allosecurinine and no pain alerts are associated with it.

Isoquercetin (Chemical formula: C21H20O12) has molecular weight of 464.32 g/mol. It has 33 heavy atoms, possesses 12 Hydrogen bond acceptors, 8 Hydrogen bond donors, 4 rotatable bonds, Molar refractivity value of 110.16, Synthetic accessibility value of 4.83 and TPSA score of 210.51 A which shows that it has good accessible surface area. Lipophilicity value of Curcumin was obtained as ILOGP: 2.11, XLOGP3: 0.36, WLOGP: -0.54 along with water solubility value of 4.23 -01 mg/ml; 9.10 e-04 mol/l and a negative Lipinski's score as molecular weight of Isoquercetin is on bit higher side. As per the cut off, molecular weight should be not be more than 350 g/mol and also number of hydrogen bond acceptors should not be more than 10, but Isoquercetin possesses 12 Hydrogen bond acceptor. There are pain alerts associated with this molecule but the rest parameters are in optimum range. Binding affinity of Isoquercetin which is -7.7 Kcal/mol against Cot H3, shows it as a potential lead molecule against Cot H3 receptor.

Conclusion

The analysis of the present study shows that these 3phytochemicals- Curcumin, Allosecurinine, and Isoquercetin are potential lead molecules against the receptors CotH1, CotH2, and CotH3 in the mucormycosis-causing fungal species, *Rhizopus delemar* as they possess high binding affinity against Cot receptors and analogues of these compounds can be further tested against CotH receptors. Structural models built for Cot receptors using homology modelling have stable and favourable regions per Ramachandran Plot analysis. All the alpha helices, beta sheets and turns were in favourable phi psi angle regions. Autodock vina results have shown that the binding energy value of Curcumin was -8.5 Kcal/mol against CotH1, and the binding energy value of Allosecurinin was -7.6 Kcal/mol against CotH2 and the binding energy value of Isoquercetin was -7.7 Kcal/mol against CotH3. Evaluation of the ADMET parameters has shown that these compounds possess good likeliness as drug molecules and have no mutagenicity or associated toxicity as irritants. Further, *in vitro* and *in vivo* experiments can be performed to check the efficacy of these phytochemicals Curcumin, Allosecurinine, and Isoquercetin, against *R. delemar* species to determine the potential efficacy. The present research serves as a blueprint for further investigation and development of therapeutics against life-threatening mucormycosis infection.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Artis, W. M., Fountain, J. A., Delcher, H. K. & Jones, H. E. (2012). A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability. *Diabetes,* 31(12), 1109–1114. https://doi.org/10.2337/diacare.31.12.1109
2. Ashraf S. Ibrahim, Brad Spellberg, Thomas J. Walsh & Dimitrios P. Kontoyiannis. (2012) Pathogenesis of Mucormycosis, *Clinical Infectious Diseases*, Volume 54, Pages S16–S22, https://doi.org/10.1093/cid/cir865
3. Bertoni, M., Kiefer, F., Biasini, M., Bordoli, L. & Schwede,

T.(2017). Modeling protein quaternary structure of homo- and hetero-oligomers beyond binary interactions by homology. *Scientific Reports* 7 . https://doi.org/10.1038/s41598-017-09654-8

4. Bhadauria S & P. Kumar. (2011).In vitro antimycotic activity of some medicinal plants against human pathogenic dermatophytes *Indian journal of fundamental and Applied Life Sciences*, vol. 1, pp. 2231–6345.
5. Bienert, S., Waterhouse, A., de Beer, T.A.P., Tauriello, G., Studer, G., Bordoli, L. & Schwede, T.(2017). The SWISS-MODEL Repository - new features and functionality. *Nucleic Acids Res*. 45, D313-D319. https://doi.org/10.1093/nar/gkw1132
6. Biswas, S. & Hasija, Y. (2022).Mucormycosis Vaccine Design using Bioinformatic Tools. *Lecture Notes in Electrical Engineering* .[DOI: 10.1007/978-981-16-9885-9_21]
7. BIOVIA, Dassault Systèmes, *BIOVIA Workbook, Release* (2020). *BIOVIA Pipeline Pilot, Release 2020, San Diego*
8. Chander, J., Kaur, M., Singla, N., Punia, R. P.S., Singhal, S. K., Attri, A.K., Alastruey-Izquierdo, A., Stchigel, A. M., Cano-Lira, J. F. & Guarro, J. (2018). Mucormycosis: Battle with the Deadly Enemy over a Five-Year Period in India. *J. Fungi (Basel)*. 6;4(2):46. doi: 10.3390/jof4020046
9. Clara Baldin, Ashraf S. Ibrahim (2017). Molecular mechanisms of mucormycosis-The bitter and the sweet. *PLOS*. 13(8).
10. Dallakyan, Sargis & Olson, Arthur mall (2015)Molecule Library Screening by Docking with PyRx. *Methods in molecular biology (*Clifton, N.J.), 1263. 243-250. https://doi.org/10.1007/978-1-4939-2269-7_19.
11. Daina, A., Michielin, O. & Zoete, V. (2017).SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep.* 7**,** 42717. https://doi.org/10.1038/srep42717
12. Deutsch, Peter George, Joshua Whittaker & Shashi Prasad (2019). Invasive and non-invasive fungal rhinosinusitis—a review and update of the evidence. *Medicina* 55.7: 319.
13. de Lira Mota, K. S., de Oliveira Pereira F, de Oliveira, W. A., Lima, I. O. & de Oliveira Lima E. (2012)Antifungal activity of Thymus vulgaris L. essential oil and its constituent phytochemicals against *Rhizopus oryzae*: interaction with ergosterol. *Molecules*.17(12):14418-33. doi: 10.3390/molecules171214418
14. García-Carnero L.C. & Mora-Montes H. M.(2022). Mucormycosis and COVID-19-Associated Mucormycosis: Insights of a Deadly but Neglected Mycosis. *J Fungi (Basel)*. ;8(5):445. doi: 10.3390/jof8050445.
15. Gebremariam, T., Liu, M, Luo, G., Bruno, V., Phan, Q. T. & Waring, A. J. Edwards J. E. Jr, Filler, S.G., Yeaman, M.R. & Ibrahim, A. S. (2014). CotH3 mediates fungal invasion of host cells during mucormycosis. *J Clin Invest*.Jan;124(1):237-50. doi: 10.1172/JCI71349
16. Guex, N., Peitsch, M.C. & Schwede, T.(2009). Automated comparative protein structure modeling with SWISS-MODEL and Swiss-PdbViewer: A historical perspective. *Electrophoresis* 30, S162-S173 . https://doi.org/10.1002/elps.200900140
17. Hamaamin Hussen N, Hameed Hasan A, Jamalis J, Shakya S, Chander S, Kharkwal H, Murugesan S, Ajit Bastikar V, Pyarelal Gupta P.(2022). Potential inhibitory activity of phytoconstituents against black fungus: *In silico* ADMET, molecular docking and MD simulation studies. *Comput Toxicol*. ,24:100247. doi: 10.1016/j.comtox.2022.100247.
18. Ibrahim, A. S., Spellberg, B., Avanessian, V., Fu, Y. & Edwards, J. E., Jr (2005). Rhizopus oryzae adheres to, is phagocytosed by, and damages endothelial cells in vitro. *Infection and immunity*, 73(2), 778–783. https://doi.org/10.1128/IAI.73.2.778-783.2005
19. Ibrahim, A. S., Spellberg, B., Walsh, T. J., & Kontoyiannis, D. P. (2012). Pathogenesis of mucormycosis. Clinical infectious diseases : an official publication of the *Infectious Diseases Society of America*, 54 Suppl 1(Suppl 1), S16–S22. https://doi.org/10.1093/cid/cir865
20. Kauffman, C. A. (2004). Zygomycosis: reemergence of an old pathogen. Clinical infectious diseases : an official publication of *the Infectious Diseases Society of America*, 39 (4), 588–590. https://doi.org/10.1086/422729
21. Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., Li, Q., Shoemaker, B. A., Thiessen, P. A., Yu, B., Zaslavsky, L., Zhang, J. & Bolton, E. E.(2019). PubChem in 2021: new data content and improved web interfaces. *Nucleic Acids Res.*, ,*49*(D1), D1388–D1395. https://doi.org/10.1093/nar/gkaa971
22. Lipinski, Christopher A. (2004).Lead- and drug-like compounds: the rule-of-five revolution. Drug Discov. Today Technol. 1, 337-341. *Drug Discovery Today: Technologies***.**,1. 337-341. https://doi.org/10.1016/j.ddtec.2004.11.007.
23. Liu M, et al. (2010) The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. *J Clin Invest.*, **120**(6):1914–1924. doi: 10.1172/JCI42164
24. 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. *J. Computational Chemistry* **2009**, **16**: 2785-91. doi: 10.1002/jcc.21256
25. Neblett Fanfair, R., Benedict, K., Bos, J., Bennett, S. D., Lo, Y. C., Adebanjo, T., Etienne, K., Deak, E., Derado, G., Shieh, W. J., Drew, C., Zaki, S., Sugerman, D., Gade, L., Thompson, E. H., Sutton, D. A., Engelthaler, D. M., Schupp, J. M., Brandt, M. E., Harris, J. R., …& Park, B. J. (2012). Necrotizing cutaneous mucormycosis after a tornado in Joplin, Missouri, in 2011. *The New England Journal of Medicine,* 367(23), 2214–2225. https://doi.org/10.1056/NEJMoa1204781
26. Prakash H, Chakrabarti A (2019).Global Epidemiology of Mucormycosis. *Journal of Fungi*. 5(1):26. https://doi.org/10.3390/jof5010026
27. Petrikkos, G., Skiada, A., Lortholary, O., Roilides, E., Walsh, T. J. & Kontoyiannis, D. P. (2012). Epidemiology and clinical manifestations of mucormycosis. Clinical infectious diseases : an official publication of *the Infectious Diseases Society of America*, 54 Suppl 1, S23–S34. https://doi.org/10.1093/cid/cir866
28. Ribes, J. A., Vanover-Sams, C. L. & Baker, D. J. (2000). Zygomycetes in human disease. *Clinical Microbiology Reviews*, 13(2), 236–301. https://doi.org/10.1128/CMR.13.2.236.
29. Renu Jangid, Tahira Begum (2022). Antimycotic activity of some medicinal plants against *Mucor circinelloides*. *Bio-*

med Research International, 22, 1-5, https://doi.org/10.1155/2022/3523920.

30. Roden, M. M., Zaoutis, T. E., Buchanan, W. L., Knudsen, T. A., Sarkisova, T. A., Schaufele, R. L., Sein, M., Sein, T., Chiou, C. C., Chu, J. H., Kontoyiannis, D. P. & Walsh, T. J. (2005). Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clinical infectious diseases : an official publication of *the Infectious Diseases Society of America,* 41(5), 634–653. https://doi.org/10.1086/432579
31. Sander, T. (2001). OSIRIS Property Explorer. *Organic Chemistry Portal*.
32. Sharma, S., Sharma, A., Gupta, U. (2021). Molecular Docking studies on the Antifungal activity of Allium sativum (Garlic) against Mucormycosis (black fungus) by BIOVIA discovery studio visualizer 21.1.0.0. *Ann Antivir Antiretrovir* 5(1): 028-032. DOI: https://dx.doi.org/10.17352/aaa.000013
33. Spellberg, B., Edwards Jr, J. & Ibrahim, A. (2005). Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clinical microbiology reviews*, *18* (3), 556-569. https://doi.org/10.1128/CMR.18.3.556-569.2005
34. Skiada A, Pavleas I, Drogari-Apiranthitou M.(2020). Epidemiology and Diagnosis of Mucormycosis: An update. *Journal of Fungi*, 6(4),265. https://doi.org/10.3390/jof6040265
35. Skiada, A, L. Pagano, A. Groll, S. Zimmerli, B. Dupont, K. Lagrou, C. Lass-Florl, E. Bouza, N. Klimko, P. Gaustad, M. Richardson, P. Hamal, M. Akova, J.F. Meis, J.-L. Rodriguez-Tudela, E. Roilides, A. & Mitrousia-Ziouva, G. Petrikkos (2011).Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007,*Clinical Microbiology and Infection,* Volume 17 (12)Pages 1859-1867,https://doi.org/10.1111/j.1469-0691.2010.03456.x.
36. Spellberg, B., Walsh, T. J., Kontoyiannis, D. P., Edwards, J., Jr. & Ibrahim, A. S. (2009). Recent advances in the management of mucormycosis: from bench to bedside. *Clinical Infectious Diseases,* 48(12), 1743–1751. https://doi.org/10.1086/599105
37. Spellberg, B., Edwards, J., Jr., & Ibrahim, A. (2005). Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clinical Microbiology Reviews,* 18(3), 556–569. https://doi.org/10.1128/CMR.18.3.556-569.2005
38. Studer, G., Rempfer, C., Waterhouse, A.M., Gumienny, G., Haas, J. & Schwede, T. (2020). Q MEAND is Co - distance constraints applied on model quality estimation. *Bioinformatics* 36, 1765-1771 https://doi.org/10.1093/bioinformatics/btz828
39. Vikas Jha, Bhakti Madaye, Esha Gupta, Shreya Thube, Sankalp Kasbe, Darpan Kaur Matharoo, Piya Shah, Mafiz Shaikh & Arpita Marick. (2022). Molecular Docking Studies of Phytochemicals Against RNA-dependent RNA Polymerase of Mucormycosis, *Journal of Diseases and Medicinal Plants*. 8 (2), 34-40. doi: 10.11648/j.jdmp.20220802.13
40. Wächtler, B., Citiulo, F., Jablonowski, N., Förster, S., Dalle, F., Schaller, M., Wilson, D. & Hube, B. (2012). *Candida albicans*-epithelial interactions: dissecting the roles of active penetration, induced endocytosis and host factors on the infection process. *PloS one*, 7(5), e36952. https://doi.org/10.1371/journal.pone.0036952
41. 41) Waterhouse, A., Bertoni, M., Bienert, S., Studer, G., Tauriello, G., Gumienny, R., Heer, F.T., de Beer, T.A.P., Rempfer, C., Bordoli, L., Lepore, R. & Schwede, T. (2018) SWISS-MODEL: homology modelling of protein structures and complexes. *Nucleic Acids Res.* 46(W1), W296-W303 https://doi.org/10.1093/nar/gky427