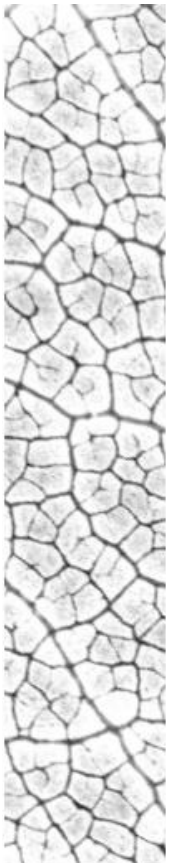

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Molecular docking and analysis of MEP2 protein in Candida albicans membrane

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Abstract
MEP2 is an important protein for the transportation of ammonium from outside to inner cell for metabolisms and nutrition in Candida albicans. The drug design technique is the best tool to obstruction important mechanism of pathogenic organisms. MEP2 contain identical chain (A and B) which make a crystal structure of protein. Molecular docking of the MEP2 protein has been done by using COACH-D web tool and analyzing the structure by CASTp tool. The results showed that there are three ligands which can be used as inhibitors for MEP2 protein activity, these ligands are NME, XE and NH3 can act and conjugated in many pockets within protein structure.

Keywords: MEP2 protein, Molecular Docking, Candida albicans

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INTRODUCTION

Many fungi in the world are classified as pathogens, especially the yeast candida, it infected a broad spectrum of organism by many mechanism, the scientist tried to designed a medicine for stopped and inhibition the pathogenies by targeted one of the many essentials protein such as membrane protein (Van Den Berg et al., 2016 & Nabati et al., 2020).

The microorganisms have the ability to transport nutrient from outside the cell membrane and throw it to inside the cell by using such enzymes system which have a huge role for metabolism of any nutrient entered (Dabas & Morschhäuser, 2007 & Soleimani et al., 2020).

The most important nutrient supplement for any microorganisms is nitrogen, the source of nitrogen in most environment is ammonium, there are three types of ammonium transporter protein, MEP1, MEP2 and MEP3, the most important one is MEP2 comparing with the rest. The absence of all MEP genes in any yeast strain prevent them to grow on agar medium when the source of nitrogen is NH4 below 5mM in the medium. Each MEP alone able to make strain survive under limited nitrogen source condition, there are a high correlation between nitrogen level and gene transcription; in limited nitrogen sources and low concentration, the transcription will increase and become very active to ease of access the nitrogen supplement. MEP2 consider as sensor for ammonium deficiency in growth medium, its induced fungi to forming pseudohypha as results of limitation of ammonium sources. A crystal structure of Candida alibicans transporter protein (MEP2) is 5AF1, the major role of this protein is inducing Candida albicance yeast to switch to filamentous shape by forming pseudohypha for growth which is responsible of fungal pathogenicity. The biggest difference between 5AF1 (MEP2) and other known transporter of ammonium are being located on the intercellular position of the cell membrane (Brito et al., 2020 & Nabati., 2020).

MATERIALS AND METHODS

Protein MEP2 shape and structure

To study the structure and shape of the protein the CASTp 3:0 (Computed Atlas od Surface Topography of protein) web tool was used (Tian et al., 2018).

Non-Homologous Target Gene

For any drug design, must be there are no side effect, this mean the gene target in pathogens must not homologous with human genes. PBIT (Pipline Builder for Identification of Target) web tool were used to identification of drug targets for human infection disease) (Shende et al., 2017)

Protein Pocket finding

Protein pocket is a cavity in the interior or on surface of protein, it is representing a suitable place for ligand binding to prevent the protein for activity. CASTp were used to find out the pocket in MEP2 protein structure (Rizvi et al., 2013).

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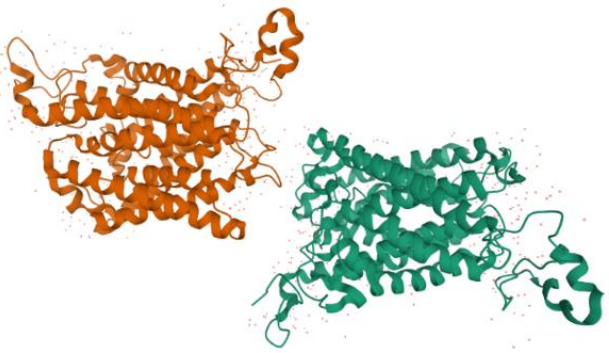

Fig. 1. 3D structure of MEP2 protein

```
Query  : 5AF1.A
Subject: 5AF1.B
Query=
        (451 letters)
>
         Length = 451

 Score =  912 bits (2356), Expect = 0.0
 Identities = 435/451 (96%), Positives = 435/451 (96%)

Query: 1   GQFTGTGTGGDVFKVDLNEQFDRADMVWIGTASVLVWIMIPGVGLLYSGISRKKHXXXXX 60
           GQFTGTGTGGDVFKVDLNEQFDRADMVWIGTASVLVWIMIPGVGLLYSGISRKKH
Sbjct: 1   GQFTGTGTGGDVFKVDLNEQFDRADMVWIGTASVLVWIMIPGVGLLYSGISRKKHALSLM 60
Query: 61  XXXXXXXXXXXFQWFWWGYSLVFAHNGSVFLGTLQNFCLKDVLGAPSIVKTVPDILFCLY 120
           FQWFWWGYSLVFAHNGSVFLGTLQNFCLKDVLGAPSIVKTVPDILFCLY
Sbjct: 61  WAALMAACVAAFQWFWWGYSLVFAHNGSVFLGTLQNFCLKDVLGAPSIVKTVPDILFCLY 120
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           QGMFAAVTAILMAGAGCERARLGPMMVFLFIWLTVVYCPIAYWTWGGNGWLVSLGALDFA
Sbjct: 121 QGMFAAVTAILMAGAGCERARLGPMMVFLFIWLTVVYCPIAYWTWGGNGWLVSLGALDFA 180
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Query: 421 LGTDLAQIGEYAYYADDDPETNPYVLEPIRS 451
           LGTDLAQIGEYAYYADDDPETNPYVLEPIRS
Sbjct: 421 LGTDLAQIGEYAYYADDDPETNPYVLEPIRS 451
```

Fig. 2. Similarity between two MEP2 protein chains

Non-homology analysis against human proteome

Number of input sequence/s:1

Criteria for non-homologous proteins: E-value > 0.005 or % sequence identity < 50

	Query name	No. of hits	BLAST report
☑	SAF1:A|PDBID|CHAIN|SEQUENCE	13	Download

1 of the 1 input sequences are non-homologous (highlighted in blue) **based on input BLAST parameters.**

Fig. 3. None-homologous of MEP2 in human proteome

Protein Docking

To predict sufficient ligand to form complex with a protein; COACH-D, a protein docking algorithms web tool was used to find protein ligands and amino acids residue (Stank et al., 2016).

RESULTS AND DISCUSSION

Protein structure: The *Cnadida albicans* MEP2 protein consist from two chain; chain A and chain B, they are very identical in sequences and play an important role for the protein activity, **Fig. 1**.

The two chains appear to be identical in 96%, **Fig. 2**.

This two chain appear to be like a two wing for the protein and offer many pocket for ligand activity.

Drug target: for any medicine design the most important thing that the medicine doesn't have any side

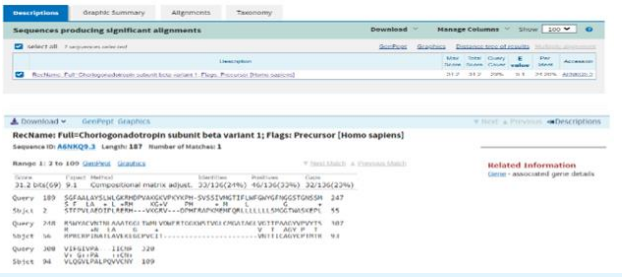
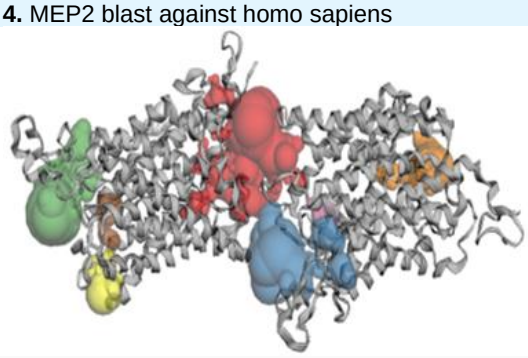


Fig. 4. MEP2 blast against homo sapiens



Configure the visualization of pockets

Show	Pocket ID	Area (SA)	Volume (SA)	Negative Volume Color	Representation Style
✓	1	1491.032	1943.333	Red	Cartoon
✓	2	976.782	1184.363	Blue	Cartoon
✓	3	659.080	723.902	Green	Cartoon
✓	4	385.212	286.755	Orange	Cartoon
✓	5	137.299	85.867	Yellow	Cartoon
✓	6	138.977	51.493	Brown	Cartoon
✓	7	101.106	41.542	Pink	Cartoon
✓	8	52.665	22.785	White	Cartoon

Fig. 5. Pockets in MEP2 protein

effect on human; the non-homologous, the MEP2 protein was blast against homo sapiens and analysis for non-homology against human proteome by using PBIT and NCBI blast (Khalil, 2020). The results showed that there is none- homologous (24% identity) and this make the medicine safe to use for human and effect on pathogens only but no the host, **Figs. 3** and **4**.

MEP2 protein pocket: There are many sites in protein chain that make a good position for ligand binding which is called pockets, to find out this pockets, **Fig. 5**.

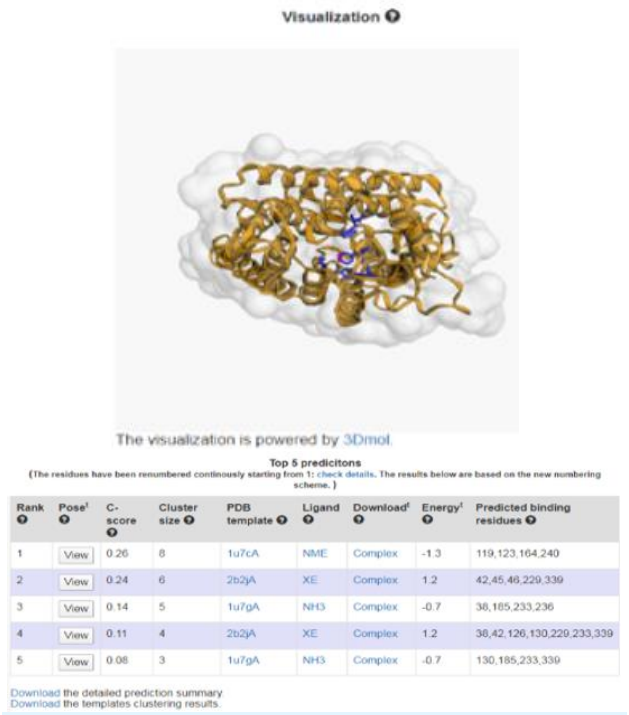


Fig. 6. Docking Results

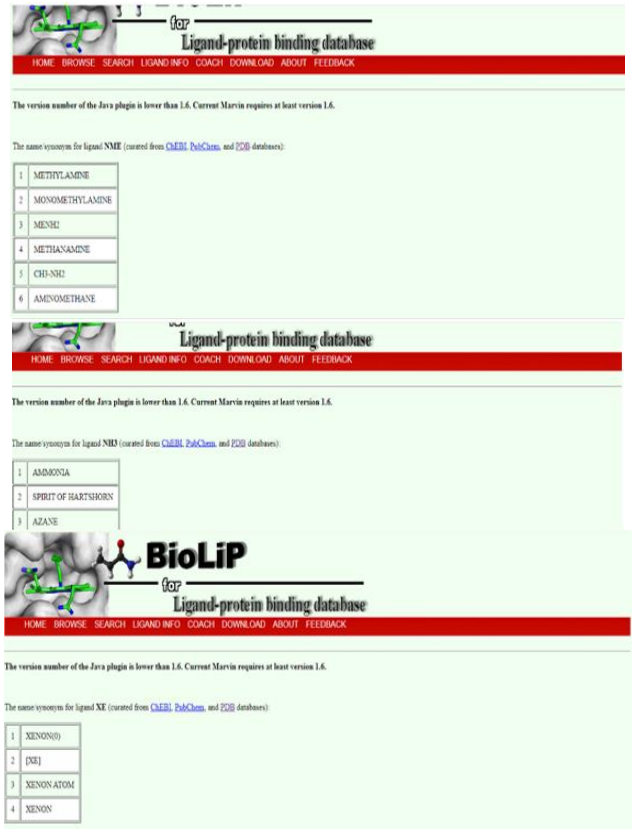


Fig. 7. MEP2 protein ligands

The pockets represent the area which the ligand binding with the protein and play an important role for drugs design, and any new pocket identified in target protein may be a critical choice for any target inhibition. The MEP2 protein have eight pocket in its structure, **Fig. 5**. Each pockets have a special colour by using ClusTp tool.

Table 1. Amino Acid residues

PocID	Chain	SeqID	AA	Atom	PocID	Chain	SeqID	AA	Atom	PocID	Chain	SeqID	AA	Atom
1	A	6	THR	O	1	A	111	VAL	CA	8	A	39	TRP	CD1
1	A	7	GLY	CA	1	A	111	VAL	CG1	8	A	39	TRP	NE1
1	A	7	GLY	O	1	A	111	VAL	CG2	8	A	42	ILE	CD1
1	A	8	THR	CA	1	A	112	LYS	N	8	A	69	ALA	CA
1	A	8	THR	CB	1	A	112	LYS	CB	8	A	69	ALA	O
1	A	8	THR	CG2	1	A	112	LYS	CG	8	A	69	ALA	CB
1	A	9	GLY	N	1	A	112	LYS	CD	8	A	72	ALA	C
1	A	9	GLY	CA	1	A	112	LYS	CE	8	A	72	ALA	O
1	A	9	GLY	O	1	A	112	LYS	NZ	8	A	72	ALA	CB
1	A	31	ILE	CG2	1	A	113	THR	N	8	A	73	ALA	N
1	A	31	ILE	CD1	1	A	113	THR	OG1	8	A	73	ALA	CA
1	A	81	TYR	CE2	1	A	113	THR	CG2	8	A	73	ALA	CB
1	A	81	TYR	OH	1	A	114	VAL	CG2	8	A	76	TRP	CB
1	A	84	VAL	O	1	A	116	ASP	CB	8	A	76	TRP	CD1
1	A	85	PHE	CA	1	A	116	ASP	CG	8	A	120	CYS	O
1	A	85	PHE	O	1	A	116	ASP	OD2	8	A	121	LEU	CA
1	A	85	PHE	CE1	1	A	119	PHE	CD1	8	A	121	LEU	O

Protein docking: The docking results showed there are three ligands in five positions; MNE, NH3 and XE these ligands and their synonyms as shown in **Fig. 6**.

The Ligands have an important role in forming a complex on target protein and changing its activity. The first ligand is methylamine (MNE) which is wildly used as antifungal medicine against pathogenic yeast like Candida, it's chemical formula is CH3NH2 and occurred in many vegetable and some foods. The second ligand is Ammonia (NH3), it's play as a substance that sometimes replaces water to surrounding metal ion to make complex in aquas phase. The third ligand is Xenon (XE), it's a Nobel gas which is act as ligand with many metal. Many groups of ligand containing in their structure bonds of Xenon-nitrogen, one of the many compound which play as ligand are FXe[N(SO2F)2] and the ligand Xe[N(SO2F)2]2, **Fig. 7** (Saberi Fathi & Tuszynski, 2014).

Amino acid residues: Amino acid is a compound which consists of carbon substitute by carboxylic acid, as a result of protein docking the ligand conjugate with protein in protein pockets, 884 amino acids lose one or more of these components and become amino acid residue. These amino acid are listed in **Table 1** (Jing & Feng, 2015).

CONCLUSION

The MEP2 protein is a very important protein for microorganism's activity and any disruption in its activity leading to inhibit the organisms and limited its activity.

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