STRUCTURAL ANALYSIS OF BURKHOLDERIA PSEUDOMALLEI (MELIOIDOSIS) RECEPTOR AND FINDING NOVEL DRUG LEADS FOR THE RECEPTOR

Rehan Khan*, Jimema Paul, Preenon Bagchi

Institute of Biosciences and Technology, MGM University, Chht.

Sambhajinagar, India

khanrehan9395@gmail.com

Abstract. Melioidosis or Whitmore's disease is caused by Burkholderia pseudomallei infection in humans. Burkholderia pseudomallei is the self-propelling bacteria that zooms around using its trusty flagellum, measuring a mere 2-5 micrometers in length and 0.4-0.8 micrometers in diameter. A human infection caused by Burkholderia pseudomallei is called melioidosis, which is also known as Whitmore's disease. People and animals who have direct contact with soil or water that is contaminated with the bacterium B. pseudomallei can develop melioidosis. Treating melioidosis requires two stages: a strong initial phase of intravenous medication to combat the infection followed by a secondary phase to prevent any potential recurrence of the disease. Its mortality is 20 to 50% even with treatment. There are several major challenges facing vaccine research, including the limited efficacy of the vaccines in animal models, the difficulty in determining which method is most appropriate for administering vaccines to humans, and establishing human trials in endemic regions due to logistical and financial concerns. The methodology followed was, the FASTA/FASTQ sequence of the genes-receptors of the above disease were retrieved from SRA database to galaxy and the sequence quality was checked using FASTQC tool. Further, we modelled the 3D structure of the FASTA protein sequence using modeller. The best model was selected using Ramachandran plot. Phytocompounds from medicinal plants is considered Tragia involucrate, Cynanchum acidum, Aegle marmelos, Adhatoda vasica, Andrographis paniculata as considered as novel drug leads is retrieved from PUBCHEM database. The phytocompounds are checked for drug-like properties using molinspiration software. The compounds having no violations was considered for further docking studies. The phytocompounds - Caffeic acid, Anthracenedione, Vasicine, Xanthotoxol having least docking score & most interactions is considered as the drug lead for melioidosis. Further receptor ligand binding assay studies will be done to establish the compounds as drug for the above disease.

Keywords: Melioidosis, Burkholderia pseudomallei, Whitmore's disease, Bioinformatics, Docking, Phytocompound

1 Introduction

Melioidosis, which is also called Whitmore's disease, is a bacterial infection caused by Burkholderia pseudomallei that affects humans. Throughout the world, this particular bacterium is widespread, but is especially prevalent in Thailand, Northern Australia and South Asia.

R. Somashekhar et al. (eds.), *Proceedings of the International Conference on Advances in Nano-Neuro-Bio-Quantum (ICAN 2023)*,
Advances in Intelligent Systems Research 69,
https://doi.org/10.2991/978-94-6463-294-1_8

Although it is mainly a soil-dwelling bacteria, a study performed by Apinya Pumpuang and others showed that Burkholderia pseudomallei survived in distilled water for 16 years, demonstrating that it is capable of living in water if a specific environment is provided [1]. It is noteworthy that the bacteria have been shown to be resilient to a variety of harsh conditions, despite nutritional deficiencies, extreme temperatures, and high pH levels. Melioidosis is a disease that is more commonly found in humans and certain domesticated animals like goats, pigs, sheep, and cattle. These animals are more prone to contract the infection. It happens less frequently in other animals, but is possible for them to get infected and causes the disease melioidosis [2]. Burkholderia pseudomallei has a length of 2- 5 μm and a diameter of 0.4-0.8 μm with flagellum capable of self-propulsion. A wide range of artificial nutrient environments can be used to grow bacteria, especially those containing betaine and arginine, which gives the bacteria an edge. The bacteria that cause the disease are spread by direct contact either with contaminated water and soil containing these bacteria. Despite treatment, it has a mortality rate of 20 to 50%.

1.1 Causes

People and animals who have direct contact with soil or water that is contaminated with the bacterium B. pseudomallei can develop melioidosis. The most common ways of direct contact include:

- breathing in contaminated dust or water droplets.
- drinking contaminated water that hasn't been chlorinated. touching contaminated soil with the hands or feet, especially if there are small cuts in the skin. The transmission of this infection from one person to another is extremely rare, and it is also unlikely to be spread by insects.
- the bacteria can live for years in contaminated soil and water

1.2 Genes involved

1) bimA
2) bicA

1.3 How the genes cause the disease

1) bimA

The study proposed by Burtnick and Brett states, B. pseudomallei bimA gene (annotated as bpss1492 in the reference K96243 genome) is encoded on the second smaller chromosome within an operon of several co-regulated genes, including genes encoding the VirAG two component system required for regulation of the virulence associated T6SS of B. pseudomallei [3], [4].

The Study by Lu Q., Xu. et al., [4] focused on characterization of the role of native BimC protein in a virulent B. pseudomallei strain. Shrinon V., et al. says that, the constructed and characterized a B. pseudomallei ΔbimC deletion mutant and determined its role in B. pseudomallei intracellular survival and virulence [4], [5].

2) bicA

Chen Y, et al., says that, BicA acts as a chaperone to control the expression of the T3SS-3 translocon and effector, as well as associated regulatory genes. The BsaN/BicA complex, by altering gene expression, likely contributes significantly to the adaptation and intracellular survival of B. pseudomallei within host cells [6], [7].

The study proposed by Joshua K, et al., states, malA-M gene cluster (BP1026B_II0328-II0340)

encodes a polyketide synthase-derived cytotoxic siderophore termed malleilactone [8]. Biggins JB et al., proposed that, B. thailandensis strains harboring mutations in the mal gene cluster are less virulent in the Caenorhabditis elegans nematode and the Dictyostelium discoideum co-culture models of infection, suggesting that malleilactone is a Burkholderia virulence determinant [9].

A. Objectives

The objective is to study a comprehensive approach for identifying potential drug leads from traditional medicinal plants for the treatment of Melioidosis, combining computational tools and analyses for a systematic study.

B. Abbreviations

a. BLAST : Basic Local Alignment Search Tool

b. FASTA : Fast All

c. FASTQ : Fast Quality

d. NCBI : National Center for Biotechnology Information

e. SRA : Sequence Read Archive

f. Et al. : and others

g. HTS : High Throughput Screening

h. FASTQC : Fast Quality Control

i. SMILES : Simplied Molecular Input Line Entry System

2. Materials and Methodology

The step-by-step methodology outlines the systematic approach taken to identify potential drug leads from traditional medicinal plants for Melioidosis treatment, involving various computational tools and analyses.

1. Data Retrieval:

Retrieve the gene receptor sequences associated with Burkholderia pseudomallei (Melioidosis) from the NCBI database (as shown in Table 1).

2. 3D Structure Modeling:

Employ Modeller software to create 3D structural models of the retrieved gene receptor sequences.

Utilize five template proteins to generate multiple models for each receptor sequence.

Evaluate the quality of models using the Ramachandran Plot analysis.

Select the most accurate and reliable models based on Ramachandran Plot results as the final 3D structures.

3. Identification of Therapeutic Candidates:

Explore traditional medicinal plants known for potential therapeutic effects against the target disease (Melioidosis).

Extract the Simplified Molecular Input Line Entry System (SMILES) notation for the phytochemicals from the PUBCHEM database.

4. Lipinski's Rule of Five Analysis:

   Employ Molinspiration software to assess the phytocompounds' compliance with Lipinski's Rule of Five, a guideline for drug-likeness.

   Evaluate parameters including molecular weight, hydrogen bond donors, hydrogen bond acceptors, lipophilicity (logP), and polar surface area.

5. Selection of Potential Drug Leads:

   Identify phytochemicals that satisfy Lipinski's Rule of Five criteria without any violations.

   Consider these compounds as potential drug leads with favorable drug-likeness properties.

6. Receptor-Ligand Docking Studies:

   Utilize a molecular docking server to perform receptor-ligand docking simulations.

   Analyze the interactions between the selected phytocompounds and the modeled gene receptor structures.

   Assess binding affinity using docking scores that quantify the strength of the interaction.

7. Interaction and Binding Analysis:

   Examine the docking results to determine the number and type of interactions established between the phytocompounds and receptor structures.

   Consider factors such as hydrogen bonding, hydrophobic interactions, and electrostatic interactions.

8. Selection of Lead Compounds:

   Evaluate the docking scores and interaction profiles of the phytocompounds with the receptor structures.

   Identify the compounds that exhibit the highest docking scores and favorable interactions as potential lead compounds.

9. Confirmation of Drug Leads:

   Shortlist the best-performing compounds based on docking scores, interactions, and binding properties.

   Validate the drug leads through additional analyses, such as energy minimization and molecular dynamics simulations, to assess stability and reliability.

10. Conclusion of Drug Lead Candidates:

    Conclude by identifying the most promising phytocompounds as potential drug lead candidates for Melioidosis treatment, considering their favorable structural interactions and compliance with drug-likeness criteria.

Gene receptor	Accession number	Homologous templates
BICA	CP000753.1	5NLAA 7W5WJ 4TRRA
BIMA	OU342711.1	6T7DA

Table 1: Accession number of the gene receptor with their homologous templates.

3. Results

3.1 Modelling

The best model was selected using Ramachandran Plot (Table 2).

The gene receptors in Table 1 were modelled using modeller. The modeller generated 5 models.

Table 2(a): Ramachandran Plot analysis of BIMA

Statistics	**# res in phipsi core**	**# res in phipsi allowed**	**# res in phipsi generous**	**# res in phipsi outside**	
BIMA.B99990001	56%	24%	10%	7%	
BIMA.B99990002	57.3%	24.7%	10%	8%	**Selected**
BIMA.B99990003	54%	24%	11%	9%	
BIMA.B99990004	53%	25%	11%	9%	
BIMA.B99990005	56%	22%	9%	11%	

Table 2(b): Ramachandran Plot analysis of BICA

Statistics	**# res in phipsi core**	**# res in phipsi allowed**	**# res in phipsi generous**	**# res in phipsi outside**	
BICA.B99990001	75.8%	16.7%	4.5%	3.0%	
BICA.B99990002	75.9%	17.3%	4.2%	2.6%	
BICA.B99990003	78.4%	15.2%	4.7%	1.8%	**Selected**
BICA.B99990004	77.4%	15.7%	4.0%	2.9%	
BICA.B99990005	78.4%	14.5%	4.2%	2.9%	

3.2 Phytocompounds and Their Smiles Using Pubchem

Scientific Name	***Tragia involucrata***
Phytocompound	**SMILES**
Stigmasterol	CC[C@H](/C=C/[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C)C(C)C
Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Rutin	C[C@H]1[C@@H]([C@H]([C@H]([C@@H](O1)OC[C@@H]2[C@H]([C@@H]([C@H]([C@@H](O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O [11]
Ar- Tumerone	CC1=CC=C(C=C1)C(C)CC(=O)C=C(C)C
Anthracenedione	C1=CC=C2C=C3C(=CC2=C1)C=CC(=O)C3=O
1,8-dihydroxy-3-methyl	CC1=CC(=C2C(=C1C3=C(C(=C(C=C3O)OC)C(=O)C)O)CC4=C(C2=O)C(=CC=C4)O)O

Scientific Name	***Cynanchum acidum***
Phytocompound	**SMILES**
Raoulic acid	CC(=CCC1CC(CCC2(C(CCC1=C)CC2C(=C)C)C)C(=C)C(=O)O)C
Cynandione A	CC(=O)C1=C(C(=C(C=C1)O)C2=C(C=CC(=C2C(=O)C)O)O)O
Succinic Acid	C(CC(=O)O)C(=O)O
Benzene	C1=CC=CC=C1 [10]
Caffeic acid	C1=CC(=C(C=C1/C=C/C(=O)O)O)O [10]
Chlorogenic acid	C1[C@H]([C@H]([C@@H](C[C@@]1(C(=O)O)O)OC(=O)/C=C/C2=CC(=C(C=C2)O)O)O)O [11]
3,4 Dicaffeoylquinic acid	C1[C@H]([C@H]([C@@H](C[C@@]1(C(=O)O)O)OC(=O)/C=C/C2=CC(=C(C=C2)O)O)OC(=O)/C=C/C3=CC(=C(C=C3)O)O)O

Scientific Name	***Aegle marmelos***
Phytocompound	**SMILES**
Marmesin	CC(C)([C@@H]1CC2=C(O1)C=C3C(=C2)C=CC(=O)O3)O
Rutin	C[C@H]1[C@@H]([C@H]([C@H]([C@@H](O1)OC[C@@H]2[C@H]([C@@H]([C@H]([C@@H](O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O [11]
Xanthotoxol	C1=CC(=O)OC2=C(C3=C(C=CO3)C=C21)O
Coumarin	C1=CC=C2C(=C1)C=CC(=O)O2

Scientific Name	***Tragia involucrata***
Phytocompound	**SMILES**
Stigmasterol	CC[C@H](/C=C/[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C)C(C)C
Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Rutin	C[C@H]1[C@@H]([C@H]([C@H]([C@@H](O1)OC[C@@H]2[C@H]([C@@H]([C@H]([C@@H](O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O [11]
Ar- Tumerone	CC1=CC=C(C=C1)C(C)CC(=O)C=C(C)C
Anthracenedione	C1=CC=C2C=C3C(=CC2=C1)C=CC(=O)C3=O
1,8-dihydroxy-3-methyl	CC1=CC(=C2C(=C1C3=C(C(=C(C=C3O)OC)C(=O)C)O)CC4=C(C2=O)C(=CC=C4)O)O
Aegeline	COC1=CC=C(C=C1)C(CNC(=O)/C=C/C2=CC=CC=C2)O
Imperatorin	CC(=CCOC1=C2C(=CC3=C1OC=C3)C=CC(=O)O2)C
Caffeic acid	C1=CC(=C(C=C1/C=C/C(=O)O)O)O
Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O

Scientific Name	***Adhatoda vasica***
Phytocompound	**SMILES**
Vasicine	C1CN2CC3=CC=CC=C3N=C2[C@H]1O
Quinazoline	C1=CC=C2C(=C1)C=NC=N2
Bromhexine	CN(CC1=C(C(=CC(=C1)Br)Br)N)C2CCCCC2
Vasicinone (www.cheminfo.org)	C1CN2C(=NC3=CC=CC=C3C2=O)[C@H]1O
Vasicinol	C1CN2CC3=C(C=CC(=C3)O)N=C2[C@H]1O

Scientific Name	***Andrographis paniculata***
Phytocompound	**SMILES**
Paniculidine A	CC(CCC1=CNC2=CC=CC=C21)C(=O)OC
Paniculidine B	C[C@H](CCC1=CN(C2=CC=CC=C21)OC)CO
Panicolin	COC1=C(C2=C(C(=C1)O)C(=O)C=C(O2)C3=CC=CC=C3O)OC
Neoandrographolide	C[C@]1(CCC[C@@]2([C@@H]1CCC(=C)[C@H]2CCC3=CCOC3=O)C)CO[C@H]4[C@@H]([C@H]([C@@H]([C@H](O4)CO)O)O)O

14-Deoxy-11-oxoandrographolide	C[C@@]12CC[C@H]([C@@]([C@H]1CCC(=C)[C@H]2C(=O)CC3=CCOC3=O)(C)CO)O
5-Hydroxy-7,8,2,3-tetramethoxyflavone	COC1C(=O)C2=C(C(=C(C=C2O)OC)OC)OC1(C3=CC=CC=C3)OC

3.3 Ramachandran Plot

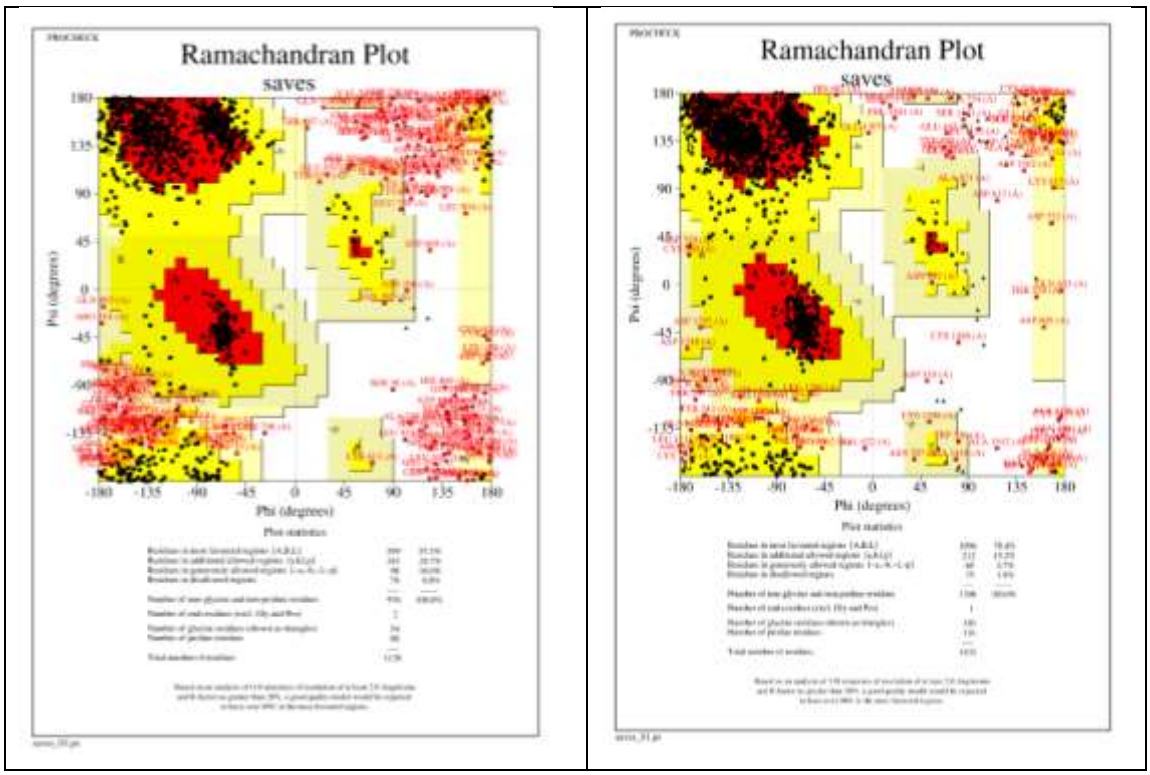


Fig 1. Ramachandran Plot of best model of BIMA and BICA receptor

3.4 Calculating ADME Properties of Phytocompounds Using Molinspiration

Table 4. The compounds having nvioloation 0 are considered for docking studies using the selected models in Table 4 (Table 5, 6).

3.5 Protein- Ligand Docking

This code takes a medical text in English about diabetes as input, and identifies disease-related features using part-of-speech tagging and regular expressions. It then uses the translate package to translate these features to any other languages and prints them out. The output of this code is a list of disease-related features and their translations to other languages.

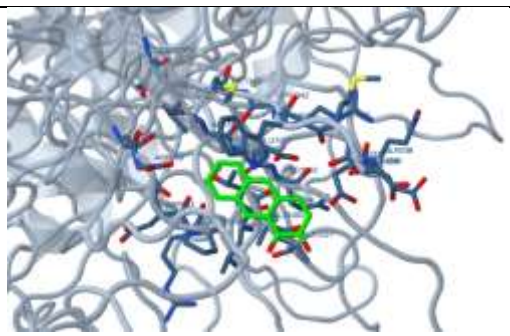
Phytocompounds	Docking score	No. of interaction	Docking (Yes/No)
1,8-dihydroxy-3-methyl	-5.37kcal/mol	31	Yes
5-Hydroxy-7,8,2,3-tetramethoxyflavone	-4.65kcal/mol	21	Yes

Phytocompounds	miLogP	TPSA	natoms	MW	nON	nOHNH	nrotb	volume	nviolations
Stigmasterol	7.87	20.23	30	412.70	1	1	5	450.33	1
Quercetin	1.68	131.35	22	302.24	7	5	1	240.08	0
Rutin	-1.06	269.43	43	610.52	16	10	3	496.07	6
Ar- Tumerone	4.48	17.07	16	216.32	1	0	4	230.32	0
Anthracenedione	2.83	34.14	16	208.22	2	0	0	182.58	0
1,8-dihydroxy-3-methyl	4.80	124.29	31	420.42	7	4	3	361.53	0
Raoulic acid	7.30	37.30	27	370.58	2	1	5	396.23	1
Cynandione A	2.57	115.05	22	302.28	6	4	3	258.61	0
Succinic Acid	-0.66	74.60	8	118.09	4	2	3	100.24	0
Benzene	1.94	0.00	6	78.11	0	0	0	84.04	0
Caffeic acid	0.94	77.75	13	180.16	4	3	2	154.50	0
Chlorogenic acid	-0.45	164.74	25	354.31	9	6	5	296.27	1
3,4 Dicaffeoylquinic acid	1.21	211.28	37	516.46	12	7	9	431.08	3
Marmesin	2.18	59.67	18	246.26	4	1	1	218.00	0
Xanthotoxol	2.00	63.58	15	202.16	4	1	1	162.16	0
Coumarin	2.01	30.21	11	146.15	2	0	0	128.59	0
Aegeline	2.64	58.56	22	297.35	4	2	6	281.45	0
Imperatorin	3.95	52.59	20	270.28	4	0	3	240.47	0
Vasicine	1.04	35.83	14	188.23	3	1	0	173.66	0
Quinazoline	1.54	25.78	10	130.15	2	0	0	119.72	0
Bromhexine	4.60	29.26	18	376.14	2	2	3	267.25	0
Vasicinone	0.48	55.12	15	202.21	4	1	0	175.84	0
Vasicinol	0.53	56.06	15	204.23	4	2	0	181.67	0
Paniculidine A	3.39	42.10	17	231.29	3	1	5	224.54	0
Peniculidine B	2.93	34.40	17	233.31	3	1	5	230.76	0
Panicolin	3.00	89.14	23	314.29	6	2	3	267.12	0
Neoandrographolide	1.17	125.69	34	480.60	8	4	7	454.37	0
14-Deoxy-11-oxoandrographolide	0.62	83.83	25	348.44	5	2	4	332.47	0
5-Hydroxy-7,8,2,3-tetramethoxyflavone	2.66	83.47	26	360.36	7	1	5	316.11	0

14-Deoxy-11-oxoandrographolide	-5.57kcal/mol	24	Yes
Aegeline	-5.53kcal/mol	28	Yes
Anthracenedione	-5.67 kcal/mol	27	Yes
Ar-Tumerone	-5.40kcal/mol	21	Yes
Benzene	-3.63kcal/mol	24	Yes
Bromhexine	-4.84 kcal/mol	23	Yes
Caffeic acid	-4.70kcal/mol	28	Yes
Coumarin	-4.78kcal/mol	15	Yes
Cynandione A	-4.43kcal/mol	19	Yes
Imperatorin	-5.81kcal/mol	18	Yes

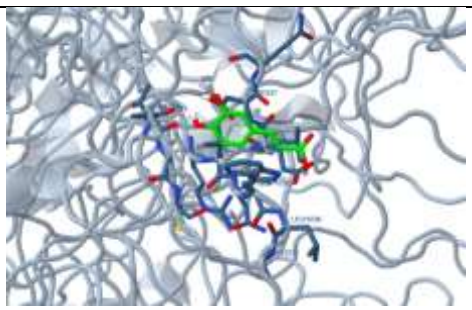
Marmesin	-5.22kcal/mol	15	Yes
Neoandrographolide	-5.17kcal/mol	22	Yes
Panicolin	-5.58kcal.mol	33	Yes
Paniculidine A	-5.17kcal/mol	19	Yes
Paniculidine B	-5.23kcal/mol	28	Yes
Quercetin	-4.67kcal/mol	15	Yes
Quinazoline	-2.88kcal.mol	12	Yes
Succinic Acid	-3.13kcal/mol	13	Yes
Vasicine	-3.76kcal/mol	19	Yes
Vasicinol	-3.88kcal/mol	27	Yes
Vasicinone	-3.67kcal/mol	24	Yes
Xanthotoxol	-4.70kcal/mol	20	Yes

Table 5(a): Docking Results of BICA



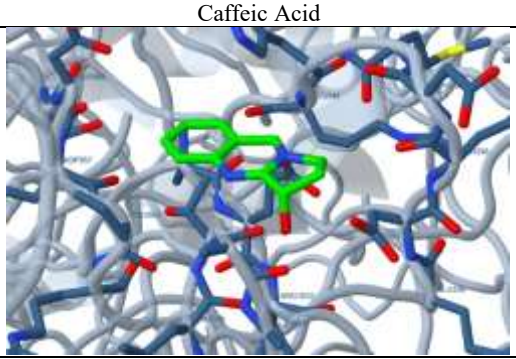
Anthracenedione

Anthracenedione docking interacting amino acids



Caffeic Acid

Caffeic Acid docking interacting amino acids



Vasicine

Vasicine docking interacting amino acids

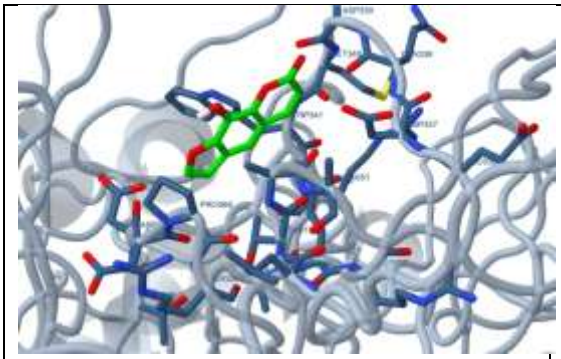
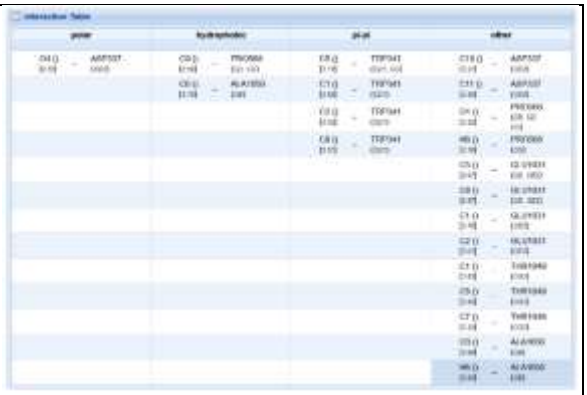
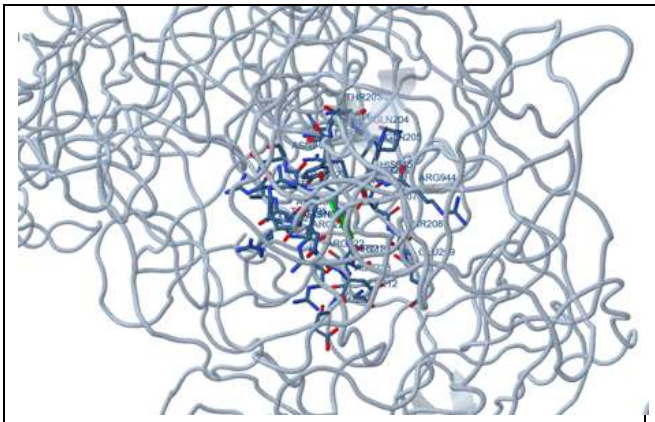
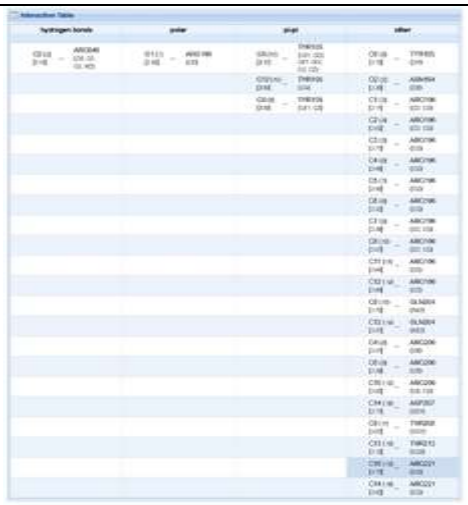
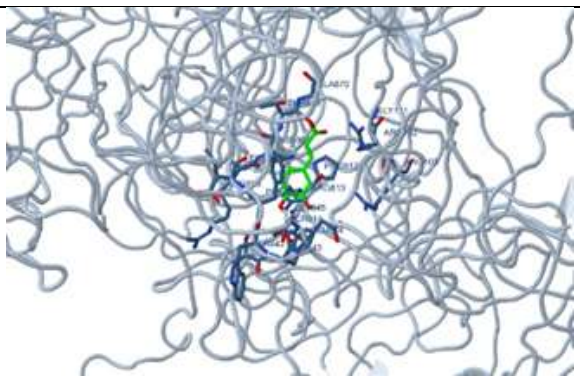
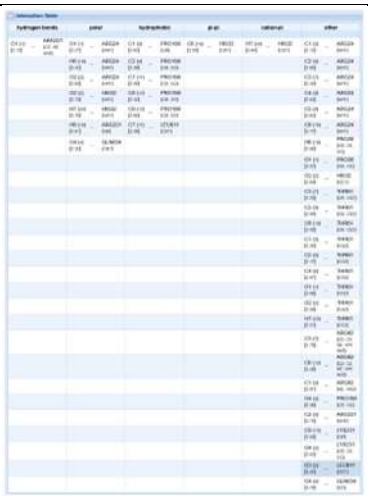
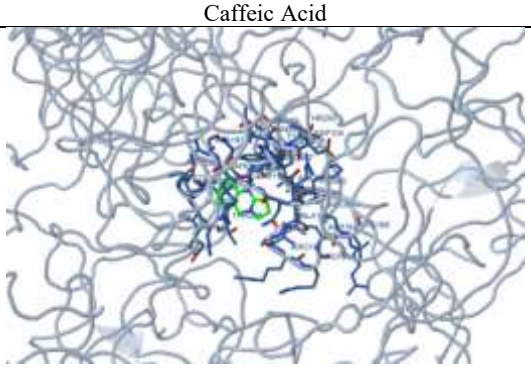
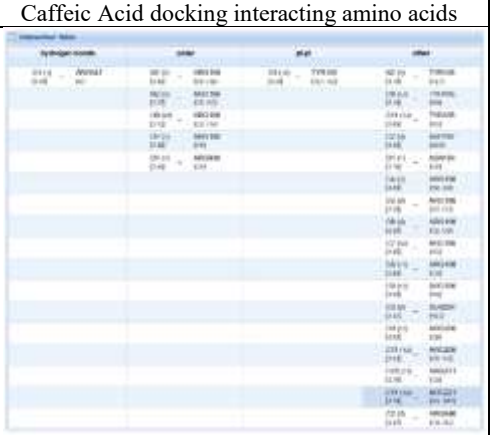
	
Xanthotoxol	Xanthotoxol docking interacting amino acids

Table 5(b): Docking Results of BICA

Phytocompounds	**Docking score**	**No. of interaction**	**Docking (Yes/No)**
1,8-dihydroxy-3-methyl	+155.18kcal/mol	63	No
5-Hydroxy-7,8,2,3-tetramethoxyflavone	+27.90kcal/mol	57	No
14-Deoxy-11-oxoandrographolide	+7.58kcal/mol	47	No
Aegeline	+18.86kcal/mol	73	No
Anthracenedione	-5.03kcal/mol	27	Yes
Ar-Tumerone	+2.44kcal/mol	36	No
Benzene	-3.44kcal/mol	12	Yes
Bromhexine	+4.38kcal/mol	52	No
Caffeic acid	-3.41kcal/mol	43	Yes
Coumarin	-4.22kcal/mol	15	Yes
Cynandione A	+46.46kcal/mol	69	No
Imperatorin	+20.68kcal/mol	40	No
Marmesin	+8.17kcal/mol	49	No
Neoandrographolide	+156.49kcal/mol	99	No
Panicolin	+21.62kcal.mol	66	No
Paniculidine A	-0.41kcal/mol	48	Yes
Paniculidine B	+0.27kcal/mol	42	No
Quercetin	-4.38kcal/mol	15	Yes
Quinazoline	-3.76kcal.mol	21	Yes
Succinic Acid	-1.33kcal/mol	13	Yes
Vasicine	-3.02kcal/mol	24	Yes
Vasicinol	-0.52kcal/mol	19	Yes
Vasicinone	-3.82kcal/mol	19	Yes
Xanthotoxol	-4.36kcal/mol	26	Yes

Table 6(a): Docking Results of BIMA

	
Anthracenedione	Anthracenedione docking interacting amino acids
	
Caffeic Acid	Caffeic Acid docking interacting amino acids
	
Vasicine	Vasicine docking interacting amino acids

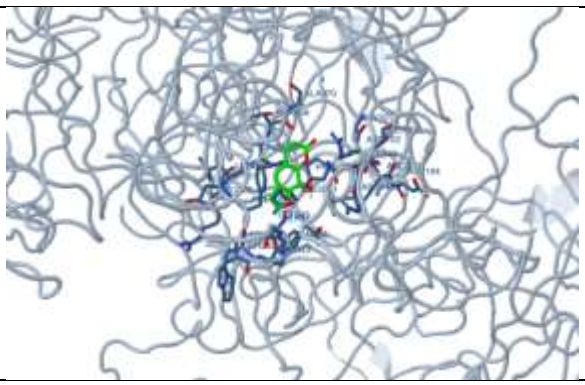
	
Xanthotoxol	Xanthotoxol docking interacting amino acids

Table 6(b): Docking Results of BIMA

4. Discussion

The analysis of docking results has unveiled valuable insights into the potential interactions between the selected phytocompounds, namely Caffeic acid, Anthracenedione, Vasicine, and Xanthotoxol, and the receptors bimA and bicA in the context of treating Melioidosis. Docking scores, along with the number of interactions observed, provide critical information about the strength and nature of binding between the compounds and receptors, shedding light on their potential as drug candidates for this challenging disease.

1) Caffeic acid, a well-known phenolic compound found in various plant sources, has demonstrated its binding affinity towards both bimA and bicA receptors. The calculated docking score of -3.41 kcal/mol with bimA indicates a reasonably strong interaction, while the 43 interactions observed suggest a complex binding mode. Similarly, the docking score of -4.70 kcal/mol with bicA suggests a more favorable binding, supported by the 28 interactions. These docking scores, coupled with the substantial number of interactions, highlight the potential of Caffeic acid to establish robust binding interactions with both receptors, indicating its potential as a multifaceted drug candidate.

2) Anthracenedione, a compound with known antimicrobial properties, has exhibited remarkable binding characteristics as well. The docking score of -5.03 kcal/mol with bimA and the corresponding 27 interactions underscore its strong potential for binding to this receptor. Equally noteworthy is the docking score of -5.67 kcal/mol with bicA, along with 27 interactions, suggesting a highly stable binding configuration. Anthracenedione's consistently strong binding scores and interactions with both receptors signify its potential as a potent therapeutic agent against Melioidosis.

3) Vasicine, a prominent alkaloid with diverse pharmacological activities, has also exhibited promising binding results. The docking score of -3.02 kcal/mol with bimA, accompanied by 24 interactions, indicates a significant potential for binding. Similarly, its docking score of -3.76 kcal/mol with bicA, along with 19 interactions, reflects a notable binding capability. Although the binding scores are slightly less potent compared to some other compounds, Vasicine's consistent interactions with both receptors warrant further investigation to assess its overall effectiveness.

4) Xanthotoxol, a compound known for its anti-inflammatory and antibacterial properties, has likewise demonstrated favorable docking outcomes. With a docking score of -4.36 kcal/mol and 26 interactions with bimA, as well as a docking score of -4.70 kcal/mol and 20 interactions with bicA, Xanthotoxol showcases robust binding potential for both receptors. These results imply that Xanthotoxol could be a compelling candidate for drug development in the fight against Melioidosis.

The extensive analysis of docking scores and interactions has provided a comprehensive understanding of the potential of Caffeic acid, Anthracenedione, Vasicine, and Xanthotoxol as drug leads for Melioidosis. Their ability to interact favorably with both bimA and bicA receptors indicates a multifaceted approach that could target various aspects of the disease. These findings lay the groundwork for further experimental

validations, including receptor-ligand binding assays and subsequent stages of drug development, to confirm the efficacy of these compounds as novel therapeutic options for Melioidosis.

5. Conclusion

The phytocompounds Caffeic acid, Anthracenedione, Vasicine, Xanthotoxol with receptors bicA, bimA has yielded intriguing results that hold promise for the potential development of novel drug leads for the treatment of Melioidosis. The docking simulations conducted in this study have highlighted the ability of these compounds to bind effectively with both the bicA and bimA receptors, indicating a potential for therapeutic relevance in combating the disease. Hence, these compounds can be considered as novel drug leads for the Melioidosis. Further receptor ligand binding assay can be done to prove its efficacy as drug for the disease. The findings underscore the importance of advancing research to validate the predicted interactions through receptor-ligand binding assays and subsequent stages of drug development. The collective efforts in understanding the molecular basis of these interactions hold promise for addressing the urgent need for improved therapeutic options against Melioidosis.

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