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# Identification Of Novel Ligands For Leukemia

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***ABSTRACT***

***Leukemia is malignancy of any cellular element in the blood or bone marrow. There are several researches finding on identification of candidate genes involved in the leukemia. In this work the genes involved in leukemia are identified and their 3d structure were generated using homology modeling. Phytocompounds as novel drug candidate for leukemia were established using computer aided drug design studies.***

***Key words: Leukemia, BLAST, Protein modelling, Screening, Drug designing, Docking, ADME.***

## I. INTRODUCTION

Leukemia is a type of cancer that starts within blood forming tissue like bone marrow and produces large number of abnormal blood. A person having leukemia suffers from abnormal production of blood cells. Leukemia symptoms include bleeding, bruising problems with an increased risk of infections; these symptoms occur because lack of normal blood cells. Chemotherapy, radiation therapy and targets therapy can be used to treat/heal leukemia. Leukemia causes the production of excessive amounts of white bloods cells thus weakening the immune system. Leukemia cells often look different from normal white blood cells and hence they do not function properly [1, 2, 3].

Leukemia is divided in two ways, one way is by how quickly the disease develops and degrades, other way is by type of blood cell. Leukemia is both acute and chronic. In acute leukemia case the blood cells usually remain very immature and cannot perform their normal functions wherein in chronic leukemia blood cells are present but in general these cells are mature enough to carry out most of their normal functions. Leukemia starts in either of the two main types of white blood. Leukemia affects lymphoid cells, it is called lymphocytic leukemia, while myeloid cell are seen affected and the disease is called myelogenous leukemia [1, 2].

Scientists are making excellent progress in understanding how changes in a person's DNA causes normal bone marrow cells to develop into

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leukemia cells. A great and knowledgeable understanding of the genes (including certain regions of the DNA) involved in certain translocations often occur in all providing inslight into why these cells become abnormal. Doctors are looking in to learning how to use these changes to help them determines a person's outlook and whether they should receive more or less intensive treatment [2, 3, 4].

## II. METHODOLOGY

**Identification of gene for leukemia:**

Amino acid sequences of the gene responsible for were retrieved from GenBank their accession numbers have been noted (Table 1).

Table 1: Amino acids' Genbank accession number with homologous templates.

| Receptor | Accession Number | Template 1 | Template 2 | Template 3 |
|---|---|---|---|---|
| BLK | P51451.3 | 2PLO_A | 2ZM1_A | 3KXZ_A |
| CCNA1 | AAH36346.1 | 2G9X_B | 3DOG_B | 3BHT_B |

**Homology Modelling:**

For structure modelling templates for the protein has been selected using BLAST and retrieved from protein data bank. Homologous sequences were retrieved from protein data bank using BLAST. Homology modelling of the receptor is done using the templates for the receptor in the given table. Templates were retrieved from Protein Data Bank (Table 1). The models were verified using Ramachandran plot.

**Virtual Screening**

The above receptors were virtually screened with the phyto-compounds Beta vulgaris, tannin, indoxyl-5-ketogluconate, Luteolin, trifolin, gartanine, lapachol, alliin, podpphyllotoxin and phenolic.

## III. RESULTS AND DISCUSSION

**Homology Modelling**

The 3d structures of the above receptor were modeled using modeler software using multiple templates. The models were verified using Ramachandran Plot and the best models were selected for virtual screening (Table 2).

Table 2: Rampage Ramachandran Plot results.

| **Genes** | **Number of residues in favoured region** | **Number of residues in allowed region** | **Number of residues in outlier region** | |
|---|---|---|---|---|
| BLK1 | 464 (92.2%) | 26 (5.2%) | 13 (2.6%) | |
| BLK2 | 468 (93.0%) | 24 (4.8%) | 11 (2.2%) | |
| BLK3 | 465 (92.4%) | 30 (6.0%) | 8 (1.6%) | |
| BLK4 | 455 (90.5%) | 30 (6.0%) | 18 (3.6%) | |
| **BLK5** | **469 (93.2%)** | **26 (5.2%)** | **8 (1.6%)** | **selected** |
| CCNA1-1 | 427 (92.4%) | 25 (5.4%) | 10 (2.2%) | |
| **CCNA1-2** | **436 (94.4%)** | **18 (3.9%)** | **8 (1.7%)** | **selected** |
| CCNA1 | 430 | 22 | 10 | |

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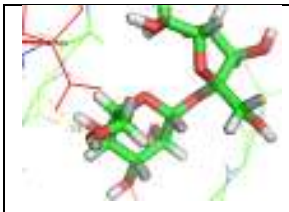
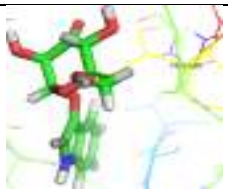
| | | | | |
|---|---|---|---|---|
| -3 | (93.1%) | (4.8%) | (2.2%) | |
| CCNA1 -4 | 430 (93.1%) | 22 (4.8%) | 10 (2.2%) | |
| CCNA1 -5 | 424 (91.8%) | 26 (5.6%) | 12 (2.6%) | |

**Virtual screening**

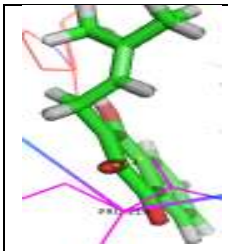
As per virtual screening results it is seen that BLK receptor interacts with Beta vulgaris with a docking score of -1.976651e+002kcal/mol and interacts with the receptor at PRO-505. Also, BLK receptor interacts with Gartanine with a docking score of -3.272773e+002kcal/mol and interacts with the receptor at GLY-318. Also, BLK receptor interacts with indoxyl-5-ketogluconate with a docking score of -2.272719e+002kcal/mol and interacts with receptor at PRO-505. Again, BLK receptor interacts with lapachol with a docking score of -2.110463e+002kcal/mol and interacts with the receptor at PRO-219. Again, BLK receptor interacts with tannin with a docking score of -3.217989e+002kcal/mol and interacts with the receptor at PHE-160, LEU-162.



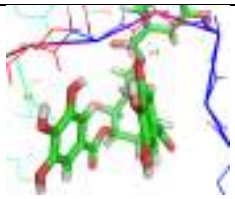
Interaction of BLK receptor with Beta vulgaris



Interactive of BLK receptor with indoxyl-5-ketogluconate



Interaction of BLK receptor with Lapachol



Interaction of BLK receptor with Tannin

Fig. 1: Interaction results of BLK receptor protein

CCNA1 receptor interacts with Alliin with a docking score of -1.649425e+002kcal/mol and interacts with the receptor at GLU-374, SER-371 given in the above table 6.6. CCNA1 receptor interacts with Beta vulgaris with a docking score of -2.260138e+002kcal/mol and interacts with the receptor at LEU-422, VAL-419. CCNA1 receptor interacts with Gartanine with a docking score of -2.845848e+002kcal/mol and interacts with the receptor at LYS-365.CCNA1 receptor interacts with indoxyl-5-ketogluconate with a docking score of -2.280598e+002kcal/mol and interacts with the receptor at GLU-374, ALA-368, and THR-343. CCNA1 receptor interacts with Luteolin with a docking score of -2.297661e+002kcal/mol and interacts with the receptor at TYR-381. CCNA1 receptor interacts with phenolic with a docking score of -2.216560e+002 kcal/mol and interacts with the receptor at LEU-348. CCNA1 receptor interacts with podpphyllotoxin with a docking score of -2.538618e+002kcal/mol and interacts with the receptor at ARG-359, LYS-448. CCNA1 receptor interacts with tannin with a docking score of -3.112596e+002 kcal/mol and interacts with the receptor at ARG-359. CCNA1 receptor interacts with Trifolin with a docking score of -2.803408e+002kcal/mol and interacts with the

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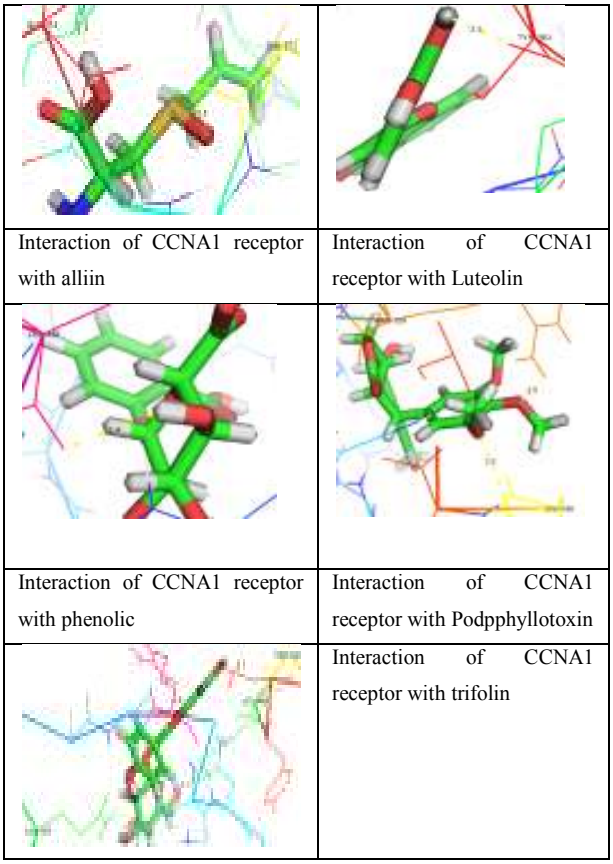
receptor at ARG-359, GLN-354, SER-447 and LYS-448.



Interaction of CCNA1 receptor with alliin

Interaction of CCNA1 receptor with Luteolin

Interaction of CCNA1 receptor with phenolic

Interaction of CCNA1 receptor with Podpphyllotoxin

Interaction of CCNA1 receptor with trifolin

Fig. 2: Interaction results of CCNA1 receptor protein

**ADME studies**

It is that beta vulgaris is having 2 violations as per molinpiration's ADME predictions and hence it cannot be used as drug candidate. Again tannin is showing 3 violations and hence it also cannot be used as drug candidate. Indoxyl-5-ketogluconate shows no violations and hence it can be safely used as drug candidate. Luteolin shows no violations and hence it also cannot be used as drug candidate. Trifolin is showing 2 violations and hence it also cannot be used as drug candidate. Gartanine is showing 1 violation and hence it also cannot be used as drug candidate. Lapachol shows no violations and hence it can be safely used as drug candidate. Phenolic shows no violations and hence it can be safely used as drug candidate. Alliin shows no violations and hence it can be safely used as drug candidate. Podpphyllotoxin shows no violations and hence it can be safely used as drug candidate (Table 3).

Table 3: ADME results

| **Compound name** | **Molinspiration log p** | **Molecular polar surface area TPSA** | **Number of non hydrogen atoms** | **Molecular weight** | **Number of hydrogen bond acceptors (O and N Atoms)** | **Number of hydrogen bond donors (OH and NH groups)** | **Number of rotatable bonds** | **Volume** | **Number of rule of 5 violations** |
|---|---|---|---|---|---|---|---|---|---|
| Beta vulgaris | -3.745 | 189.526 | 23.0 | 342.297 | 11 | 8 | 5 | 283.578 | 2 |
| Tannin | 0.643 | 310.6 | 45.0 | 636.4 | 18 | 11 | 10 | 49 | 3 |

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| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 57 | | 71 | | | | 8.044 | |
| indoxyl-5-ketogluconate | -0.8 | 112.014 | 21.0 | 293.275 | 7 | 4 | 3 | 247.298 | 0 |
| Luteolin | 1.974 | 111.123 | 21.0 | 286.239 | 6 | 4 | 1 | 232.066 | 0 |
| Trifolin | 0.125 | 190.275 | 32.0 | 448.38 | 11 | 7 | 4 | 364.188 | 2 |
| Gartanine | 6.068 | 111.123 | 29.0 | 396.439 | 6 | 4 | 4 | 359.331 | 1 |
| Lapachol | 3.16 | 54.37 | 18.0 | 242.274 | 3 | 1 | 2 | 223.944 | 0 |
| Alliin | -3.393 | 80.393 | 11.0 | 177.225 | 4 | 3 | 5 | 154.764 | 0 |
| Podophyllotoxin | 1.317 | 92.703 | 30.0 | 414.41 | 8 | 1 | 4 | 354. | 0 |
| Phenolic | -0.507 | 153.75 | 22.0 | 314.246 | 9 | 5 | 4 | 253.366 | 0 |

## CONCLUSION

Based on virtual screening and ADME screening it is seen that indoxyl-5-ketogluconate and Luteolin is selected as novel drug leads for treating leukemia. Since indoxyl-5-ketogluconate and Luteolin had good docking score and interactions with leukemia receptors and fulfills all criteria under ADME, hence they can be successfully used as drugs for treating leukemia.

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