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**RESEARCH ARTICLE**

# ANTILEUKEMIC POTENTIALS OF *GARCINOL*: AN *INSILCO STUDY*

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**ABSTRACT**

Computational assessment of the binding interactions of drugs is essential for enhancing the discovery of new drugs. In this perspective approved drugs for Leukemia Imantinib and Tretinoin and Garcinol a bioactive component of *Garcinia indica* was docked into inhibitor binding cavity of Nuclear Factor kappa B receptor and Tyrosine kinase receptor to understand their mode of binding interactions *in silico*. Lamarckian genetic algorithm methodology was employed for docking simulations using AutoDock 4.2 program. The results signify that Garcinol has significant free energy of binding which is close to that of the reference standards Imantinib and Tretinoin. These molecular docking studies in our view will contribute for further development of plant derived anti-leukemic drugs.



## INTRODUCTION

Bioactivity-guided isolation methods have led to discoveries of important anticancer agents of plant origin viz., Taxol from *Taxus brevifolia* (Wani *et al*., 1971), Camptothecin from *Camptotheca acuminate* (Wall *et al*., 1966), Vinblastine and vincristine, from *Catharanthus roseus* (Ngan *et al*., 2001; Dhamodharan *et al*., 1995), Epipodophyllotoxin active anti-tumor agent from the roots of *Podophyllum* species (Stahelin, 1973), Homoharringtonine from *Cephalotaxus harringtonia* var. *Drupacea* (Kantarjian *et al*., 1996; Cragg *et al*., 2005), and Elliptinium a derivative of ellipticine from *Bleekeria vitensis* (Cragg *et al*., 2005). So anticipating that plants can provide potential bioactive compounds for the development of new leads to combat cancer disease, *Insilco* approach is beneficial; as Bioinformatics is essential for enhancing the discovery of new drugs (Simon, 2005).

Garcinol, with a molecular weight of 602, is the active constituent of *Garcinia indica*, which is crystallized out as yellow needles (1.5%) from the hexane extract of the fruit rind (Subhash *et al*., 2009). *G. indica* (Family: Clusiaceae; Genus: Garcinia) grows extensively on the western coast of India and is known by various names, Bindin, Biran, Bhirand, Bhinda, Katambi, Panarpuli, Ratamba or Amsool, has many culinary, pharmaceutical and industrial uses (Subhash *et al*., 2009). The plant has got many medicinal activities like cardiotonic, cooling, emollient, demulcent; improve peristalsis, anthelmentic and antitumour (Khatib *et al*., 2010) antioxidant as well as hepatoprotectivity ($Amol_a$ *et al*., 2011), both antifungal and antibacterial properties (Varalakshmi *et al*., 2010) ulcer protective effect ($Amol_b$ *et al*., 2010). The major chemical constituents of the fruit extract include citric acid, hydroxycitric acid (HCA), hydroxycitric acid lactone, and oxalic acid in addition to the benzophenone derivatives, garcinol and its isomer isogarcinol (Subhash *et al*., 2009). Garcinol shows strong antioxidant activity since it contains both phenolic hydroxyl groups as well as a β-diketone moiety (Pan *et al*., 2001). Various studies have also validated the anticancer potentials of Garcinol (Subhash *et al*., 2009). Hence the present molecular docking study was undertaken to predict the preferred orientation and binding affinity, of lead molecule Garcinol against Leukemia target receptors Nuclear Factor kappa B (NFkB) and Tyrosine kinase. Results were compared with approved drugs for Leukemia viz., Imantinib and Tretinoin.

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## MATERIALS AND METHODS

### Selection Of Target Proteins

**NFkB Receptor:** Nuclear transcription factor NFkB, plays a key role in oncogenesis induced by Human T-cell Leukemia Virus-I (HTLV-I) (Mori *et al*., 1999). NFkB can be activated by HTLV-I encoded tax and is constitutively activated in all adult T-cell leukemia cells (ATL) (Mori *et al*., 1999). Constitutively activated NFkB appears to be the molecular basis for aberrant growth and cytokine gene expression observed in ATL. Therefore, NFkB inhibitors may provide new therapeutic modalities for HTLV-I infections and ATL (Takeo *et al*., 2005). Crystal structure of NFkB protein was downloaded from Protein Data Bank (PDB Id: 1VKX) (Chen *et al*., 1998).

**Tyrosine kinase Receptor:** Tyrosine kinases are important mediators of the signaling cascade, determining key roles in diverse biological processes like growth, differentiation, metabolism and apoptosis in response to external and internal stimuli. Recent advances have implicated the role of tyrosine kinases in the pathophysiology of cancer (Manash and Anup

2004). The role of tyrosine kinases in cancer molecular pathogenesis is immense and recently kinases have come in vogue as potential anticancer drug targets (Manash and Anup 2004). As the activity of the c-Kit receptor protein-tyrosine kinase is tightly regulated in normal cells, whereas deregulated c-Kit kinase activity is implicated in the pathogenesis of human cancers, it was selected for molecular docking studies and crystal structure was downloaded from Protein Data Bank (PDB Id: 1T46) (Mol *et al*., 2004).

### Ligand Preparation

The structures of approved drugs for Leukemia, Imantinib (Drug bank Id: DB00619) and Tretinoin (Drug bank Id: DB00755) were downloaded from drug bank (Knox *et al*., 2011). These ligands were converted into protein data bank format using Open Babel software (Noel *et al* 2011). 3D structure of Garcinol was drawn in chem sketch 3D software of ACD LABS.

### Docking Target Receptors With Garcinol Using Auto Dock

The Graphical User Interface program Auto-Dock Tools was used for docking studies (Michel F Sanner, 1999). Polar hydrogens were added and non polar hydrogens were merged into the receptor PDB file. The grid box size was set at 62, 62 and 62 A° (x, y, and z) to include all the amino acid residues that are present in the active site of rigid macromolecules. Auto Grid 4.2 Program was used to produce grid maps. The spacing between grid points was 0.375 angstroms. The Lamarckian Genetic Algorithm (LGA) was chosen search for the best conformers. During the docking process, a maximum of 10 conformers was considered. The population size was set to 150 and the individuals were initialized randomly. Maximum number of energy evaluation was set to 250000, maximum number of generations 27000, maximum number of top individual that automatically survived set to 1, mutation rate of 0.02, crossover rate of 0.8, Step sizes were 0.2 Å for translations, 50.0° for quaternion and 50.0° for torsions. Cluster tolerance 2.0Aº, external grid energy 1000.0, max initial energy 0.0, max number of retries 10000 and 10 LGA runs were performed (Archana *et al*., 2010). Auto dock results were analyzed to study the interactions and the binding energy of the docked structure.

## RESULTS AND DISCUSSION

### Molecular interactions of Ligands and NFkB receptor

Garcinol cluster rank 1 with lowest binding energy -5.46 kcal/mol had 02 hydrogen bond interactions at residues lysine 200 and lysine 507. Hydrogen bond distance between the donor and acceptor atoms was found to be 1.754 and 1.881 respectively. Imantinib cluster rank 1 with lowest binding energy -5.99 kcal/mol had 02 hydrogen bond interactions at residues lysine 105 and aspargine 167. Hydrogen bond distance between the donor and acceptor atoms was found to be 2.17 and 1.741 respectively. Tretinoin cluster rank 1 with lowest binding energy -7.36 kcal/mol had 3 hydrogen bond interactions at residues lysine 200 and glysine 229. Hydrogen bond distance between the donor and acceptor atoms was found to be 2.012 and 1.748 respectively.

**Table 1: Molecular interactions of Ligands and NFkB receptor**

| Ligand | Binding Energy | H-Bonds formed | H-bond donor | H-bond acceptor |
|---|---|---|---|---|
| Garcinol | -5.46 | 02 | 1VKX:A:LYS200:HZ3<br>1VKX:A:LYS507:HZ3 | Garcinol::LIG1:O<br>Garcinol::LIG1:O |
| Imantinib | -5.16 | 02 | Imantinib::LIG1:H<br>1VKX:A:LYS105:HN | 1VKX:A:ASP167:OD2<br>Imantinib::LIG1:N |
| Tretinoin | -7.36 | 02 | 1VKX:A:LYS200:HZ1<br>1VKX:A:GLN229:HE22 | Tretinoin::LIG1:O<br>Tretinoin::LIG1:O |

### Molecular interactions of Ligands and Tyrosine kinase Receptor

Garcinol cluster rank 1 with lowest binding energy -6.2 kcal/mol had 3 hydrogen bond interactions at residues aspargine 183, alanine 133 and aspargine 184. Hydrogen bond distance between the donor and acceptor atoms was found to be 2.019, 1.31 and 2.074 respectively. Imantinib cluster rank 1 with lowest binding energy -5.99 kcal/mol had no hydrogen bond interactions indicating weak bonding between the receptor and ligand. Tretinoin cluster rank 1 with lowest binding energy -6.03 kcal/mol had no hydrogen bond interactions indicating weak bonding between the receptor and ligand.

**Table 2: Molecular interactions of Ligands and Tyrosine kinase Receptor**

| Ligand | Binding Energy | H-Bonds formed | H-bond donor | H-bond acceptor |
|---|---|---|---|---|
| Garcinol | -6.2 | 03 | Garcinol:LIG1:H<br>1T46:A:ALA33:HN<br>Garcinol:LIG1:H | 1T46:A:ASN183:O<br>Garcinol:LIG1:O<br>1T46:A:ASP184:OD1 |
| Imantinib | -5.99 | 00 | -- | -- |
| Tretinoin | -6.03 | 00 | -- | -- |

It was found that Garcinol has significant free energy of binding which is close to that of the reference standards Imantinib and Tretinoin. To analyze binding mode of protein ligand complexes, their structures were viewed in detail utilizing ADT. The binding mode of Garcinol, Imantinib and Tretinoin is shown in Figure 1. From these docking studies, it was predicted that Garcinol fits within the active site of NFkB and Tyrosine kinase Receptors and significant binding interactions have been noticed. Further *invitro* and *invivo* studies will help to validate anti-leukemic potentials of Garcinol.

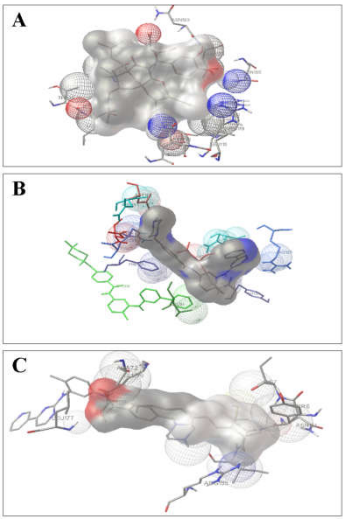


**Figure 1**: **The binding mode of A-Garcinol, B-Imantinib and C-Tretinoin and their interactions with the receptor Tyrosine kinase**

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