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MAPPING OF NATURAL KAPOSI SARCOMA INHIBITOR USING NETWORK BIOLOGY APPROACH

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ABSTRACT

Identification of protein-ligand interaction networks on a proteome scale is crucial to address a wide range of biological problems such as correlating molecular functions to physiological processes and designing safe and efficient therapeutics. In this study we have developed a novel computational strategy to identify ligand binding profiles of proteins across gene families and applied it to predicting protein functions, elucidating molecular mechanisms of drug adverse effects, and repositioning safe pharmaceuticals to treat different diseases The resultant network is then extrapolated to proteomics level to sort out the genes only expressed in the specific cancer types. The network is statistically analyzed and represented by the graphical interpretation to encounter the hub nodes. The objective of developing a biological networking is for the evaluation and validation of cancer drugs and their targets. In the field of cancer biology, the drug and their targets holds a role of paramount importance. With the work conducted here it shows the study of relation between drug target networks. Kaposi's sarcoma (KS) is a systemic disease which can present with cutaneous lesions with or without internal involvement. Genes belonging to the group of proto-oncogenes and tumor suppressors are best targeted for cancer studies. Biological networks like gene regulatory networks, protein interaction network is usually created to simplify the studies. In the present study, 26 proteins as receptor were selected for the study; all the receptors were responsible for the cause of Kaposi's sarcoma. Also, 121 natural anti-Kaposi Sarcoma compounds were selected from different sources the natural components were the best component for blocking of abnormal activity.

INTRODUCTION: Kaposi's sarcoma (KS) was originally described by Moritz Kaposi (KA-po-she), a Hungarian dermatologist practicing at the University of Vienna in 1872. Classic KS as originally described was a relatively indolent disease affecting elderly men from the Mediterranean region, or of Eastern European descent [1]. Endemic KS was described later in young African people, mainly from sub-Saharan Africa, as a more aggressive disease which infiltrated the skin extensively, especially on the lower limbs [2].

In Europe and North America KSHV is transmitted through saliva. Thus, kissing is a theoretical risk factor for transmission although transmission between heterosexuals appears to be rare [3].

Higher rates of transmission among gay and bisexual men has been attributed to "deep kissing" sexual partners with KSHV [4].

Mechanism of the Disease: KSHV is transmissible during organ transplantation and to a lesser extent through blood transfusion. Kaposi's sarcoma (KS) is an angio-proliferative disease characterized by proliferation of spindle- shaped cells predominantly of endothelial cell origin, neoangiogenesis, inflammatory cell infiltration, and edema [5].

Relationship to AIDS: With the rise of the AIDS epidemic, KS, as initially one of the most common AIDS symptoms, was researched more intensively in hopes that it might reveal the cause of AIDS. The disease was erroneously referred to as the "AIDS rash". In 2007, San Francisco doctors reported a Kaposi's sarcoma cluster among gay men [6].

Signaling pathway for the Disease: Kaposi's sarcoma-associated herpesvirus (KSHV) has been implicated in Kaposi's sarcoma, as well as in primary effusion lymphoma and multicentric Castleman's disease.

Signaling pathways changes that may responsible for this type of cancer including the K1 protein of KSHV has been shown to induce cellular transformation and focus formation and to deregulate B-lymphocyte signaling pathways by functionally mimicking the activated B-cell receptor complex [7] (**Fig. 1**).

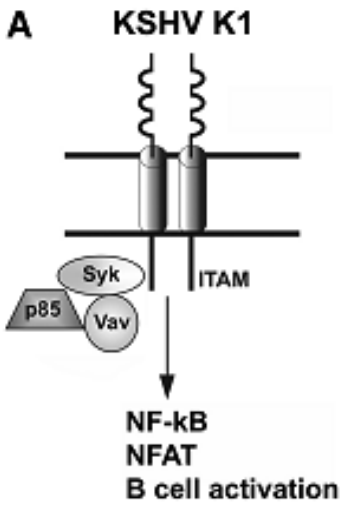

FIG.1. THE KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS (KSHV) K1 AND K15 SIGNALING PROTEINS

(A) A schematic diagram of the KSHV K1 protein. The K1 protein has an extracellular domain, transmembrane domain, and a cytoplasmic tail. The cytoplasmic tail contains an immunoreceptor tyrosine-based activation motif (ITAM).

MATERIALS AND METHODS:

A. **Data mining, Target & Lead Identification:** The Kaposi's sarcoma specific natural Inhibitors were annotated from a wide range of publishers and databases like Wiley, Blackwell Synergy, Medline, Pubchem, Ingenta Connect, Chemfinder, Drug Bank etc. The protein complex structures were collected from various online databases. The complex protein and the small molecules were collected from various sources and these were subjected to multi-receptor docking analysis using AutoDock Vina., after the protein and ligand docking the matrix has been created for the scores obtained. From the score the target and the lead were identified.

B. **Binding Site Analysis:** Identification and evaluation of surface binding-pockets and occluded cavities are initial steps in protein structure-based drug design. Characterizing the active site's shape as well as the distribution of surrounding residues plays an important role for a variety of applications such as automated ligand docking or *in situ* modeling. After the multi receptor docking step, the protein and the Kaposi's inhibitor was subjected to binding site analysis in Q site Finder [8, 9] (**Fig. 2**).

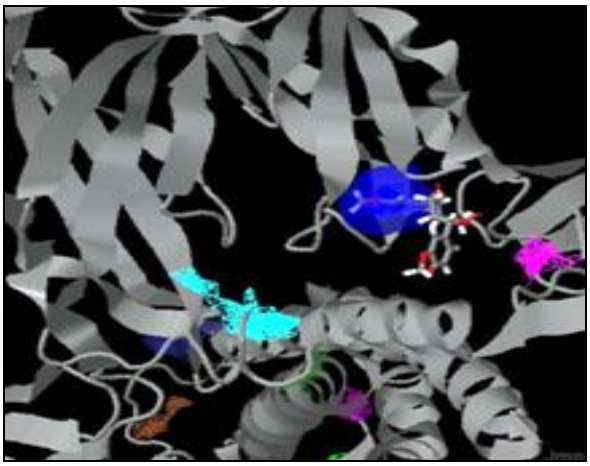

FIG 2: BINDING SITE ANALYIS OF THE INHIBITOR AND THE KS TARGET

C. **Network Analysis:** With the help of the Docking Score and the Protein ID collected from the AutoDock, the network was predicted using VisAnt, an open source tool for drawing the network. The network was highly interacted with the Kaposi 's sarcoma inhibitors. The more highly interacted protein and ligand were considered as the hub node for the study [10, 11, 12, 13].

D. **Hub node Analysis:** Our next objective was to analyze the interconnections among the hubs. We postulated that the hubs were linked in a hub network that was connected via a core of 'super hubs'. But since the super hubs were very less in number. The hub count was more in number, that is virtually the interaction between the receptor and the inhibitor was more consistent.LANA-1 and GLTSCR2/PICT-1 were the two highest interacted proteins among the 26 targets studied [14] (**Fig. 3**).

E. **Ranking:** Once a set of proteins are derived from the hub nodes, their consequent top ten molecules were ranked and the natural molecules were subjected for study (**Fig. 4**) [15, 16].

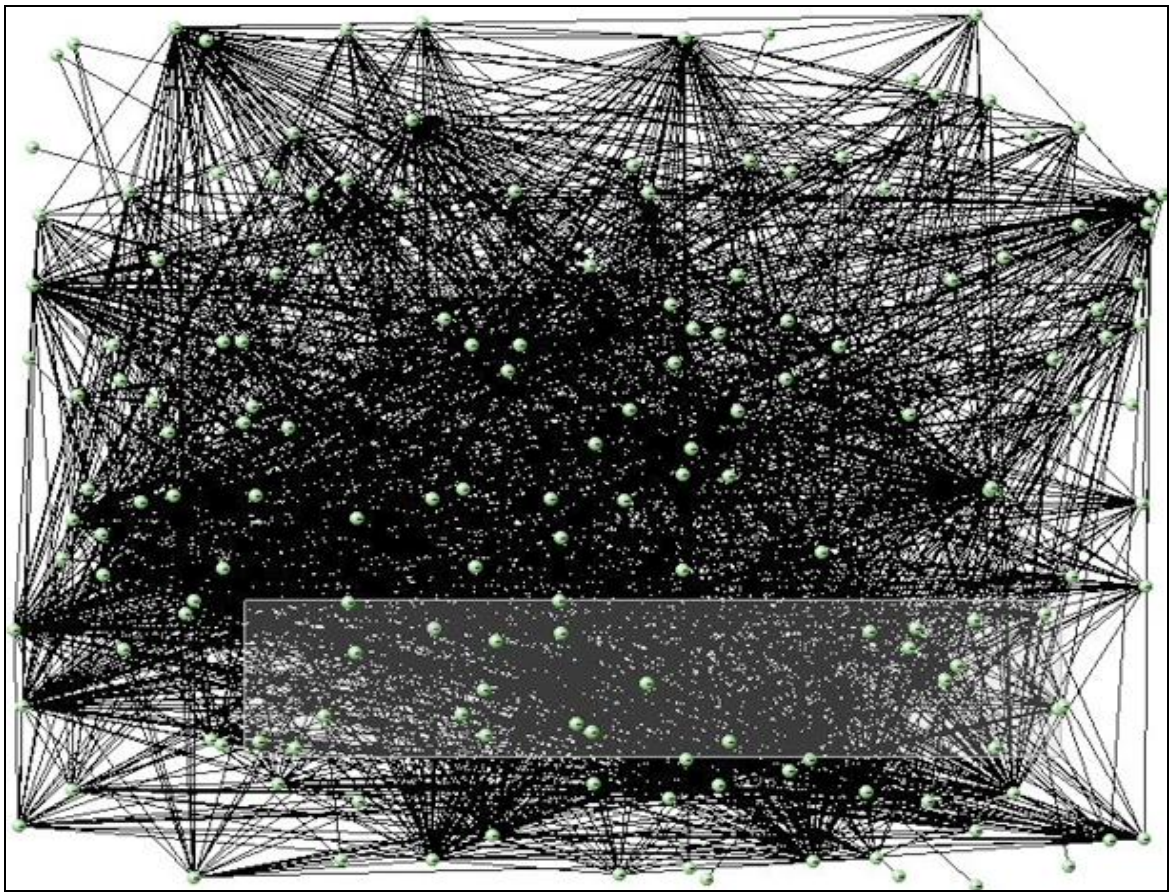

FIG. 3: HUB NODE ANALYSIS *VIZ* INTERACTION BETWEEN INHIBITORS AND TARGET

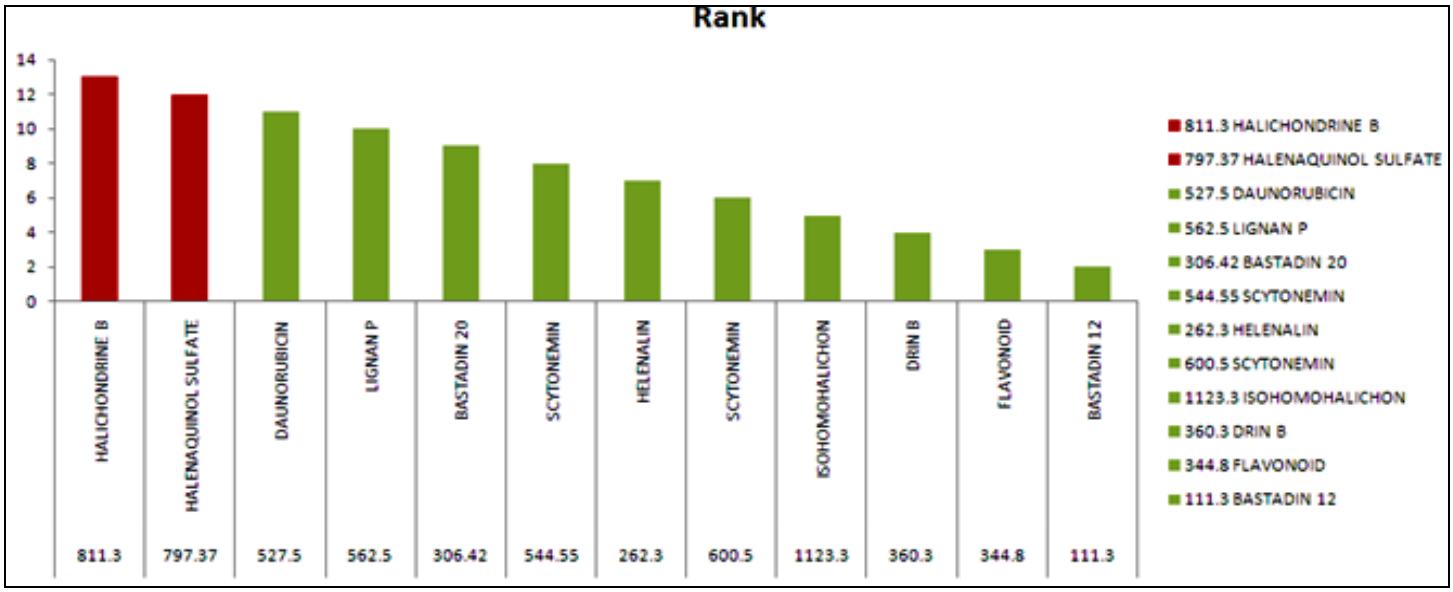

FIG. 4: RANKING ORDER OF THE LEAD *HALICHONDRINE B AND HALENAQUINOL SULFATE*

F. **Statistical Analysis:**

a. The two sets (X, Y) of ligands and the target receptors respectively are taken and using their mean docking score, the VisAnt and the highest degree of interaction was found to be LANA-1 and GLTSCR2/PICT-1.

b. Linear regression is an approach to modeling the relationship between a scalar variable Y and one or more variables denoted X. In linear regression, data are modeled using linear functions, and unknown model parameters are estimated from the data. Such models are called linear models. In the Linear Regression Model Dock score Vs TPSA were plotted against each other in that two specific molecules *viz Halichondrine B And Halenaquinol Sulfate* shows more plotted towards the regression line **Fig. 5** [17, 18, 19].

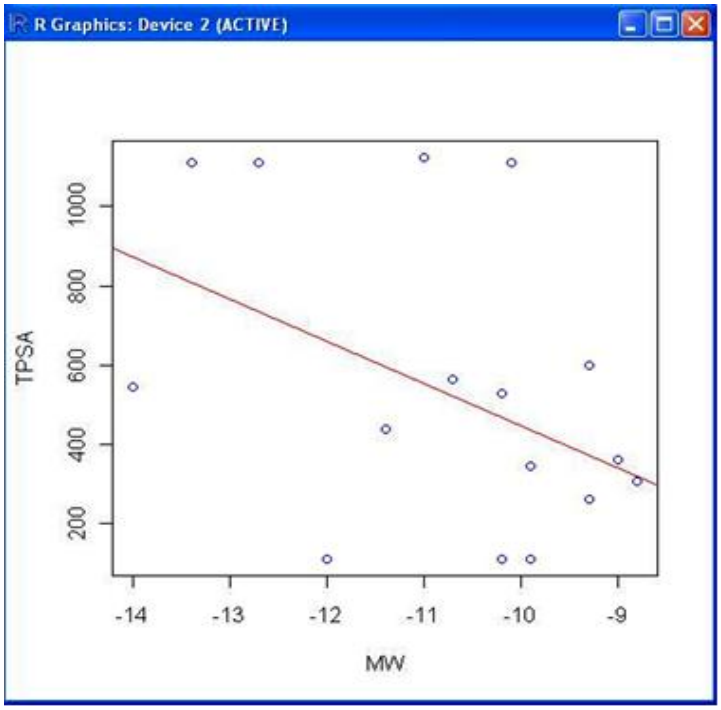

FIG. 5: LINEAR REGRESSION OF THE DATA SET

RESULTS: From the network analysis, the highest interaction was found to be the LANA-1 and GLTSCR2/PICT-1.and the highest interaction was found to be with the Kaposi's sarcoma inhibitor *Halichondrine B* [20, 21, 22, 23] *and Halenaquinol Sulfate* [24, 25], found in marine sponge *Halichondria okadai and Xestospongia sapra*.

DISCUSSION: From the network analysis, here by concludes that the molecule *Halichondrine B and Halenaquinol Sulfate*, has highest potency to bind with the Kaposi's sarcoma. The binding site analysis between the Kaposi's sarcoma proteins and the inhibitor shows the impact of binding regions. After the multi receptor docking analysis the Dock score of *Halichondrine B and Halenaquinol Sulfate* shows the maximum interaction when compared to other natural Kaposi's sarcoma inhibitor. Thus, *Halichondrine B and Halenaquinol Sulfate* inhibitor found in marine sponges could be a lead molecule for the treatment of Kaposi's sarcoma.

CONCLUSION: Our study further confirms that *in- silico* drug screening is an effective alternative for identification of lead compounds. Several natural lead compounds were identified and tested using molecular docking for their effectiveness against Kaposi's Sarcoma Cancer. *Halichondrine B and Halenaquinol Sulfate* was identified to be effective inhibitors that had the ability to bind to LANA-1 and GLTSCR2/PICT-1. Their binding energies were also found to be lower than Finasteride. Our results contribute to understanding the mechanisms to explain previous experimental observations and may provide a lead into anticancer research.

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