PUBLISHED ON 29TH FEB 2012

VIRTUAL SCREENING OF WILD ETHNOMEDICINAL PLANT *EUPHORBIA HIRTA* L. AS ANTI-HIV, ANTI-MALARIAL, ANTI-CANCER AND ANTI-TB PROPERTIES

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ABSTRACT:

For a long period of time in history, plants have been valuable and indispensable sources of natural products for the health of human beings and they have a great potential for producing new drugs. Even today ethnic groups and local people who live near to the forests use plant products to cure several diseases. Tropical and sub-tropical areas of the world are bestowed with abundant flora and herbs which have untapped properties, such as antimicrobial, antiviral and antifungal. According to the World Health Organization, plants are a source of compounds that have the ability to combat disease, antimicrobial, antiviral and antifungal activities. In addition to this, medicinal plants have been used for centuries as remedies for human ailments and diseases because they contain components of therapeutic value. Also they are less toxic to humans and environmental friendly due to fewer pollutants produced in production and have minimal health hazards. *Euphorbia hirta* L. it is wild ethnomedicinal plant is used by the tribes and local people of North Gujarat area as local medicine and proven pre-clinically for anti-inflammation, asthma, wound healing and diarrhea. It has antioxidant activity also. In present work an attempt has been carried out to evaluate anti-HIV, anti-malarial, anti-cancer and anti-TB action of such species. Medicinal plants containing natural and its synthesize chemical compound belonging to two research targets (Mitogen-activated protein kinase for cancer and Thymidine monophosphate kinase for TB) and two successful targets (HIV protease for HIV and Enoyl-ACP reductase for malaria). Beside that ligand library compounds were also examined for druglikeness. Molecular docking studies were carried out with docking programmed.

KEY WORDS: *Virtual screening, Wild ethnomedicinal plant, Euphorbia hirta* L., *ANTI-HIV, Anti-Malarial, Anti-Cancer, Anti-Tb Properties.*

INTRODUCTION:

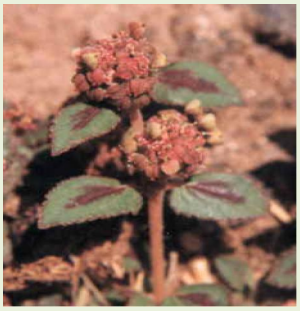
Recent years have witnessed that there is a revival of interest in drug discovery from medicinal plants for the maintenance of human health in all parts of the world. The worldwide use of natural products including medicinal plants has become more and more important in primary health care especially in developing and developed countries. Many pharmacognostical and pharmacological investigations are carried out to identify new drugs or to find new lead structures for the development of novel therapeutic agents for the treatment of human diseases such as AIDS, cancer and many other infectious diseases [Newman *et.al.* 1981–2002].

Human immunodeficiency virus (HIV) is a retrovirus that can leads to acquired immunodeficiency syndrome (AIDS), a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections. Previous names for the virus include human T-lymphotropic virus-III (HTLV III), lymphadenopathy-associated virus (LAV), and AIDS-associated retrovirus (ARV) [Rick Sowadsky et.al. 2006, Coffin et.al. 1986]. There is currently no vaccine or permanent cure for HIV or AIDS. The only known method of prevention is avoiding exposure to the virus. However, an antiretroviral treatment, known as post-exposure prophylaxis, is believed to reduce the risk of infection if begun directly after exposure. Current treatment for HIV infection consists of highly active antiretroviral therapy or HAART. [Fan *et.al.* 2005]

Several drugs are used for the treatment of malaria like chloroqinine and proguadine which are used as common chemotherapy. Over 90% of all malaria cases occur in Africa, and most are caused by *Plasmodium falciparum*. Compared to HIV and cancer less attention has been paid in this filed with reference to computer aided drug discovery approach towards the development of novel anti malaria drug candidate. Recently development *in silico* antibacterial drug development includes search of novel inhibitor and comparative modeling development of novel technology.

About one third of the world's population has latent tuberculosis, caused by *Mycobacterium tuberculosis* infection. From this pool, roughly 9 million cases of active tuberculosis emerge annually, resulting in 23 million deaths. The majority new cases occur in the most populated nations, India and China but the highest rates of disease are seen in sub-Saharan Africa, the Indonesian and Philippine archipelagos, Afghanistan, Bolivia, and Peru. Rifampicin and Isoniazid are the main drugs used today as standard anti tuberculosis therapy. *Tubercle bacilli* undergo random chromosomal mutations that have made them resistant to every drug used to

treat tuberculosis. The challenge of managing multidrug resistant tuberculosis is complex and creates the need the new drug candidate to fight the battle against *Tubercle bacilli*. Literature indicates the vast exploration of virtual screening based approach in anti-tuberculosis drug discovery field [Gopalakrishnan *et.al.* 2005, Kantardjieff *et.al.* 2004, Singh *et.al.* 2007, Srivastava *et.al.* 2007]



Euphorbia hirta L. is belongs to family Euphorbiaceae, commonly known as 'Rati *Dudheli'* is an annual 10-30cm tall, slender hairy herb. Leaves 1-4.2 x 0.5-2cm, elliptic or ovate-oblong, hairy. Cyathium inflorescences small, greenish-yellow, numerous, in dense, axillary, clustered cymes. Capsule hairy, 3-lobed. Seeds reddish-brown, ovoid-trigonous and rugose. It is abundant in waste places along the roadsides and open grasslands. It bears flowers and fruits throughout the year. Such species is native to India and Australia [Rastogi *et.al.* 2002].

This wild ethnomedicinal plant is used by the tribes and local people of North Gujarat forest area as local medicine in various ways. Fresh plant is crushed with black pepper and mixed in to water. This mixture is taken to remove kidney stones. Fresh root pieces are kept in ear cavities of a patient, who is suffering from malaria. Roots are crushed with cow milk and given to the child to ease bowel movements. Leaf juice is mixed with sugar and taken as well as the paste of young twigs is plastered to cure piles. Young flowering shoots are crushed with sesame oil, warmed and applied on of rheumatic swellings. Leaf paste is applied on eczema. Latex is used as a stain in making permanant tattoos by local people. Traditionally, it is used in treatment of gastrointestinal disorders, bronchial and respiratory diseases, kidney stones, diabetes and in conjunctivitis. It also exhibits anti-pyretic, analgesic, anti-bacterial, anxiolytic, anthelmintic, anti-fertility, anti-spasmodic, anti-fungal, and anti-inflammatory activities [Sood *et.al.* 2005, Elizabeth *et.al.* 2002]. It has been reported that this species contains alkaloids, saponins, flavonoids, tannins, phenolic acids and amino acids [Hore et.al. 2006]. It also contain Galloylquinic acid, Phorbol acid, leucocyanidol, quercitol, camphol, quercetin, chlorophenolic acid, shikimic acid chemical compound. [Rastogi *et.al.*1979]

MATERIAL AND METHODS:

Forest areas and villages of research area were frequently visited, to collect the information about the forest wealth and uses of wild plant species were noted. Village wise men, experienced informants, elderly people, head man of the hamlets, tribal medicine men, were contacted and by repeated queries data was gathered. This is the original and ancient knowledge, which was not documented systematically earlier but from last few decades

several ethnobotanical workers have been worked on this subject. Screening of these ethnomedicinal species and select interested plants for further study.

More than 240 natural and synthesize chemical compound were selected for PubChem compound database for creation of ligand library.

Expert system for calculation of druglikeness score based on qualifies scoring was used as described by Smitha *et. al.* (2006) from on line server molinspiration. (www.molinspiration.com)

Various successful and research target were selected from literature survey and 3D protein structure of target was downloaded from the protein data bank.

Targets were analyzed for active site details and hydrogen was added for docking. Docking was done by using GOLD 3.2 software. Scoring was done by gold score and chem score method. Conesus scoring was done by collative score from Gold docking program.

Consensus scoring of the both docking programmed was done to find out the best lead among all the hit included in the study.

RESULT AND DISCUSSION:

1. More than 240 natural and synthesize chemical compound were included in study. Initial filtering of the entire compound for the Lipinski rule of five and toxicity, and mutagenicity lead set of 3 compounds which used in the further study.
2. Virtual screening of filtered 3 compounds was done against PDB structure of two research targets (Mitogen-activated protein kinase for cancer [3ORN] and Thymidine monophosphate kinase for TB [1G3U]) and two successful targets (HIV protease for HIV [1AID] and Enoyl-ACP reductase for malaria [1NHG]). [Table 1]
3. For the first research target 3ORN maximum gold score was observed for ligand CID_7057976 followed by ligand CID_8742 and ligand CID_1094. While, maximum chem score was observed for ligand CID_8742 followed by ligand CID_7057976 and ligand CID_1094. [Fig 1]
4. In case of second research 1G3U target included in study best gold score was for Ligand CID_1094 followed by ligand CID_7057976, ligand CID_8742; whereas best Chem score was Ligand CID_7057976 found best followed by ligand CID_8742 and ligand CID_1094. [Fig 2]
5. The successful target 1AID was scored best gold score for ligand CID_1094 followed by ligand CID_8742 and ligand CID_7057976.While, maximum chem score was observed for Ligand CID_8742 followed by ligand CID_7057976 and ligand CID_1094. [Fig 3]

6. The second successful target 1NHG was found to have best gold score for ligand CID_7057976 followed by ligand CID_8742 and ligand CID_1094. Whereas best Chem score was ligand CID_7057976 found best followed by ligand CID_8742 and ligand CID_1094. [Fig 4]
7. In the second step to compile the result of two docking programmed were compiled to gather with consensus scoring method. On performing the consensus scoring for target 3ORN ligand CID_7057976 found best followed by ligand CID_8742, ligand CID_1094. For target 1G3U ligand CID_7057976 was best scored followed by ligand CID_8742and ligand CID_1094.
8. The ligand CID_8742 was best scored for target 1AID followed by ligand CID_7057976, ligand CID_1094. For target 1NHG ligand CID_7057976 was found best followed by ligand CID_8742and ligand CID_1094.
9. The best scored ligand CID_7057976 was selected for further study.

CONCLUSION:

Best score and efficient binding of the ligand (3R,4S,5R)-3,4,5-trihydroxycyclohex-1-ene-1-carboxylate with two research target Mitogen-activated protein kinase, Thymidine monophosphate kinase and two successful target HIV protease, Enoyl-ACP reductase from the ligand library included in study.

The result indicates ligand CID_7057976 as best from library for further study. The synthesize chemical compound having best score comparison to the natural chemical compound present in the *Euphorbia hirta* L. wild medicinal plant.

ACKNOWLEDGEMENTS:

Authors are very much thankful to all the informators of study area for sharing their knowledge. The work has been inspired and encouraged by the faculty members of Department of Botany, Science College, Talod and Microbiology Department, Nootan Science College, Visnagar.

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Table-1: Receptors structure included in study

Disease	Target name	Target type	PDB ID
Cancer	Mitogen-activated protein kinase	Research target	3ORN
HIV	HIV protease	Successful target	1AID
Malaria	Enoyl-ACP reductase	Successful target	1NHG
TB	Thymidine monophosphate kinase	Research target	1G3U

Table-2: Workflow diagram

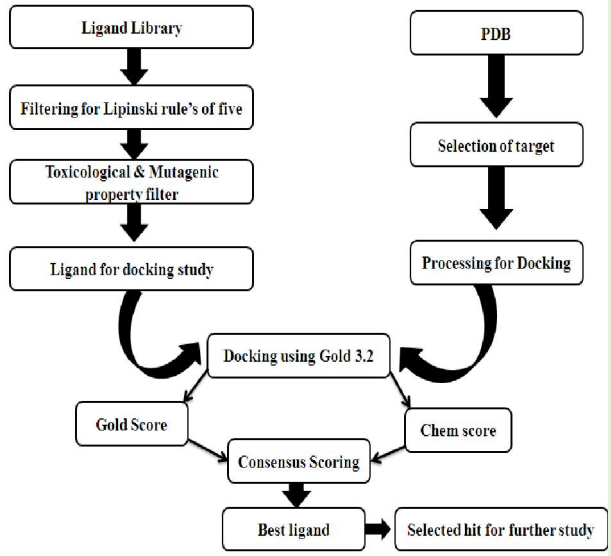

Fig.-1: Docking score of Mitogen-activated protein kinase (3ORN)

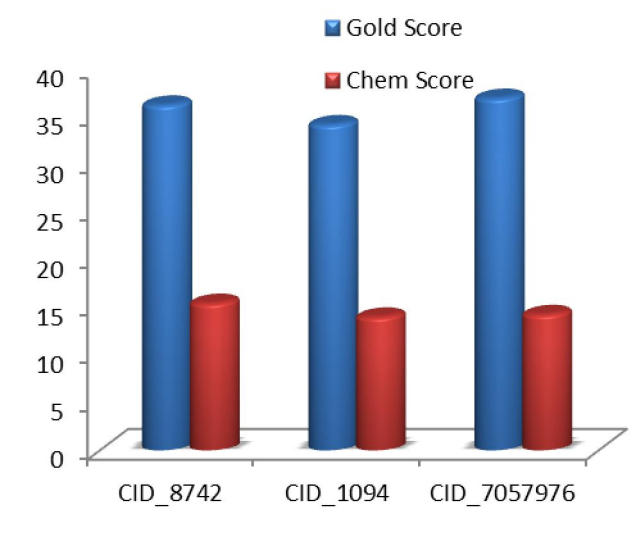

Fig.-2: Docking score of Thymidine monophosphate kinase (1G3U)

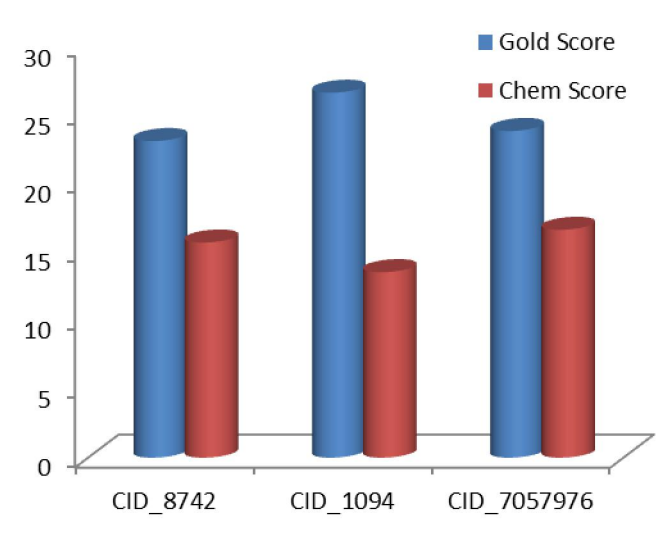

Fig.-3: Docking score of HIV protease (1AID)

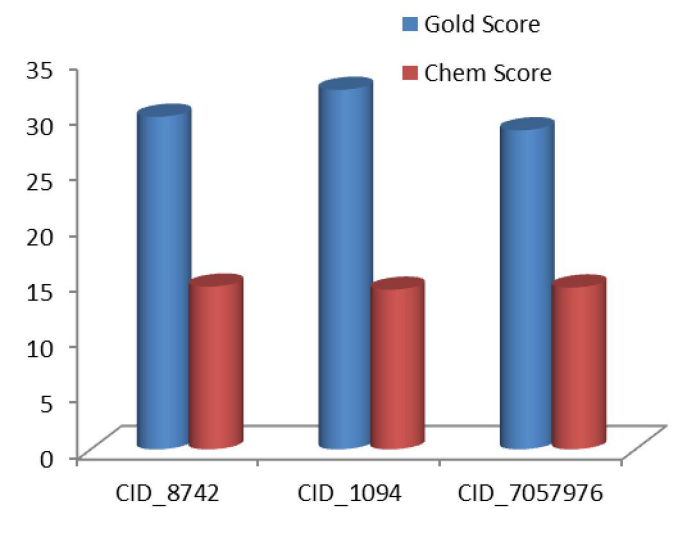

Fig.-4: Docking score of Enoyl-ACP reductase (1NHG)