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Research Article

Molecular docking studies of gloriosa superba for anti cancer and anti tuberculosis

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ABSTRACT

Gloriosa superba is a medicinal plant generally found in western parts of Tamilnadu and kerala in India. Gloriosa superba having the medicinal property of anticancer, antibacterial, antifungal, anti Tuberculosis and mutagenic activities. In these studies, we are going to analysis the anti-cancer and anti-tuberculosis property of Gloriosa superba by using molecular docking studies. Cancer is a major cause of death and the number of new cases, as well as the number of individuals living with cancer, is expanding continuously. Cervical cancer is one of the most common cancers among women worldwide. Tuberculosis is a common and often deadly infectious disease caused by mycobacteria, usually Mycobacterium tuberculosis in humans. Tuberculosis usually attacks the lungs but can also affect other parts of the body. The phytochemicals of Gloriosa superba are analysed and optimized with the Arguslab to investigate the interactions between the target compounds and the amino acid residues of the E7 and DAHP. All the compound has shown binding pose between from – 3.25 to -7.95 and -7.95 into -11.40 out of ten compounds. Chrysophanic acid with E7 protein and Colchicine with DAHP protein show best ligand energy -9.52049 and -7.47679Kcal/mol with 1 and 3 hydrogen bond of distance is 2.3 and 2.2,2.9 and 3.2 respectively.

Keywords: Gloriosa superba, Docking, Cervical cancer and Tuberculosis, Argus lab, E7, DAHP

INTRODUCTION

Gloriosa superba derives its name Gloriosa from the word “Glorious”, which means handsome and superba from the word “superb “Means splendid or majestic kind. This plant has been a source of medicine right from the ancient time. This plant in Liliaceae family. The taxonomic Description of this plant is Erect perennial, tuberous, scandent or climbing herbs; grasp with tendrils formed at the tip of the leaves. Ingestion of Gloriosa superba tubers causes severe and potentially fatal toxic effects. It is very tolerant of nutrient-poor soils. Gloriosa Superba is generally found in western parts of Tamilnadu and Kerela India.[1] The methanolic, aqueous and petroleum ether extracts of the root tubers of Gloriosa superb having antibacterial, antifungal and mutagenic activities. The tubers of G. superba were found to possess mutagenic properties by Ames Salmonella mutagenicity test due to the presence of the colchicines. The tuberous roots are useful in curing inflammation, ulcers, scrofula, bleeding piles, white discharge, skin diseases, leprosy, indigestion, helminthiasis, snake bites, baldness, intermittent fever and debility. The tubers contain colchicines, benzoic and salicylic acid, sterols and resinous substances- colchicines, 3-demethyl colchicine, 1,2-didemethyl colchicine, 2,3-didemethyl colchicine, N-formyl, N-deacetyl colchicines, colchicocide, gloriosine, tannins and superbine. [2].

Tuberculosis is presently regarded as the most dangerous infective diseases worldwide. And it is one of the leading causes of death due to a single infectious pathogen. Approximately one-third of the world’s population has been infected with the causative pathogens *Mycobacterium tuberculosis* (M.TB). Eight billion people fall sick with TB every year and globally it accounts for almost three deaths annually(3) M. tuberculosis is a host pathogen which cannot survive outside the environment. The treatment of TB remains unsatisfactory. The resurgence of this disease has primarily been due to the emergence of drug resistant tubercle, especially to the most effective drug, isoniazid and rifampicin(4) Every year, more

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than 8 million people develop an active form of the disease, which subsequently claims the lives of nearly 2 million. This translates to over 4,900 deaths per day, and more than 95% of these are in developing countries(5) In 2002, the WHO estimated that if the worldwide spread of tuberculosis was left unchecked, then the disease would be responsible for approximately 36 million more deaths by the year 2020. Despite the current global situation, anti-tubercular drugs have remained largely unchanged over the last four decades(6) Moreover the emergence of TB has also been accompanied by the appearance of Single-Drug-Resistant (SDR) and Multi-Drug-Resistant (MDR) is particularly alarming(7)

It has been shown that the shikimate biosynthetic pathway of Mt, where the 3-deoxy-d-arabinoheptulosonate-7-phosphate (DAHP) is converted to chorismate, is essential for the synthesis of all aromatic amino acids, folic acid and ubiquinone [8]. The Shikimate pathway is an attractive target for herbicides and antimicrobial agents because it is essential in microbes and plants but absent in animals. The 3-deoxy-D-arabino-heptulosonate 7-phosphatesynthase (DAHPS) is the first enzyme of this pathway, which is involved in the condensation of phosphoenolpyruvate (PEP) and D-erythrose 4-phosphate (E4P) to produce 3-deoxy-D-arabino-heptulosonate7-phosphate (DAHP). shikimate 3-phosphotransferase catalyzes the fifth chemical reaction of shikimate pathway. This metabolic route is responsible for the production of chorismate, a precursor of aromatic amino acids. This especially interesting enzymatic step is indispensable for the survival of the etiological agent of tuberculosis and not found in animals. Therefore the enzyme ATP: shikimate 3-phosphotransferase has been classified as a target for chemotherapeutic development of antitubercular drugs.(9) Cancer is a major cause of death and the number of new cases, as well as the number of individuals living with cancer, is expanding continuously. Cervical cancer is one of the most common cancers among women worldwide, Its mortality exemplifies health inequity, as its rates are higher in low & middle income countries [10]. The human papilloma virus (HPV) is the main causative agent for cervical cancer. The viral DNA from specific group of HPV can be detected in 90% of all cervical cancer[11]. Cervical cancer risk seems to be influenced by other variables too, like smoking and immunodeficiency. Infection with other sexually transmitted viruses seems to act as a cofactor in the development of cervical cancer (12). Cervical cancer is caused by infection of high-risk human papillomavirus (HPVs). Two high risk types of HPVs, HPV16 and HPV18 are the causative agent for virtually over 95% of cervical cancer cases [13].The persistent expression of HPV16 E6 and E7 oncoproteins has been shown to be necessary to transform primary human keratinocytes *in vitro* [14]. Oncoprotein E6 is essential for oncogenesis induced by (HPV). The structure of HPV16- E6 C-terminal domain reveals a zinc binding fold. A model of full-length E6 is proposed and analyzed in the context of HPV evolution. E6 appears as a chameleon protein combining a conserved structural scaffold with highly variable surfaces participating in generic or specialized HPV functions. The E6 proteins from high-risk HPV types bind to p53 in conjunction with aubiquitin-ligase known as E6-AP or ubiquitin protein ligase. The ubiquitination of p53 that occurs as a result of complex formation targets this protein for proteasome- mediated degradation, and significantly reduces the half-life of p53. The decrease in p53 levels brought about by E6 is thought to be important for viral replication; An analysis of a small number of cervical tumours and normal controls has suggested that the presence of the p53-R72 allele can be a risk factor in HPV-induced cancer [14].

MATERIALS AND METHODS

Swiss Prot Database: Swiss-Prot is a manually curated biological database of protein sequences. Swiss-Prot strives to provide reliable protein sequences associated with a high level of annotation, a minimal level of redundancy and high level of integration with other databases.

Active site prediction: After obtaining the final model, the possible binding sites of short neurotoxin were searched using Computed Atlas of Surface Topography of Proteins (CASTp). These include pockets located on protein surfaces and voids buried in the interior of proteins. CASTp includes a graphical user interface, flexible interactive visualization, as well as on-the-fly calculation for user uploaded structures [17]

Docking: Docking the inhibitors against the active site of the E7 and Dahp Docking is a computational technique that samples conformations of small molecules in protein binding sites; scoring functions are used to assess which of these conformations best complements the protein binding site[18]. The inhibitor and target protein was geometrically optimized and docked using docking engine Argus Dock.

RESULTS AND DISCUSSION

Molecular modeling (docking) study was carried out for compound like from

2demethylcolchicine,3-desmethylcolchicine, Benzoic acid, choline, chrysophanic acid, Colchicines, Glorisol, salicyclic acid, Sitosterol and Stigmasterol from Gloriosa superba (1A-13) fig 1(A,B,C,D ,E,F,G,H,,I, and J) for Cervical cancer and Tuberculosis .

The target protein and inhibitors were geometrically optimized. Given the three-dimensional structure of a target receptor molecule usually a protein; chemical compounds having potential affinity toward site are designed rationally, with the aid of computational methods. Detailed bioinformatics analysis offers a convenient methodology for efficient insilico preliminary analysis of possible function of new drug.

All the Ten inhibitors were docked against active site of the target proteins using Argus lab which gives an insight into the binding modes for the various inhibitors. Out of 10 inhibitors analyzed i.e. 2demethylcolchicine,3-desmethylcolchicine,

Benzoic acid, choline, chrysophanic acid, Colchicines, Glorisol, salicyclic acid, Sitosterol and Stigmasterol has showed higher binding energy of 11.85 Kcal/mol against the target protein. The binding energy of all the inhibitors was shown in Table 1. Figure 4 represents the docked complex of the inhibitors to that of the target protein.

The Table 2 describes the molecular properties of E7 and DAHP protein in chrysophanic acid and Colchicine (Table 2). Chrysophanic acid and Colchicine is a small sized molecule with a molecular weight of 254.2375 g/mol and 399.437 g/mol Respectively. It has two hydrogen bond donors and four hydrogen bond acceptors with two rotatable bond. The chrysophanic acid and Colchicine compound has the LogP value of 3.5 and 1 .Thereby it satisfies all the criteria of Lipinski's rule of five (Christopher et al., 1997).

2-demethylcolchicine

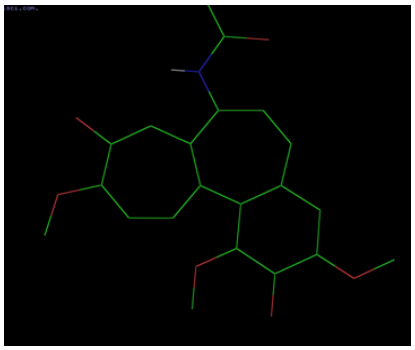


fig.1A

3desmethylcolchicine

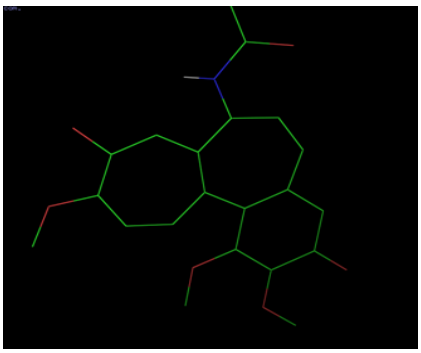


fig.1B

cholin

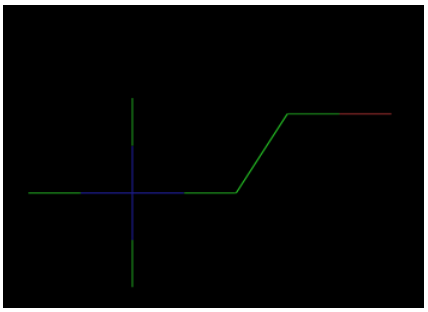


fig.1C

benzoic acid

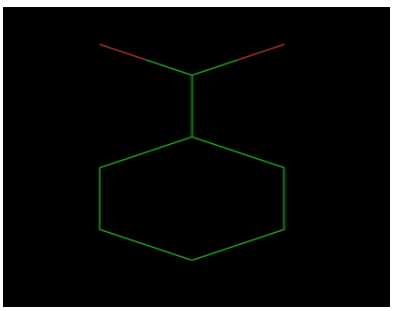


fig.1D

chrysophanic acid

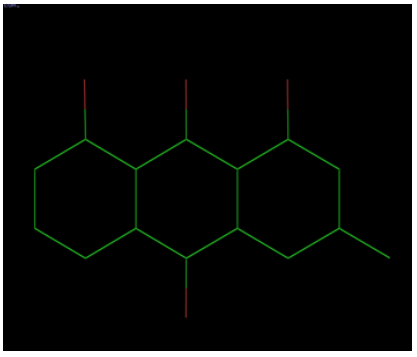


fig.1E

Colchicines

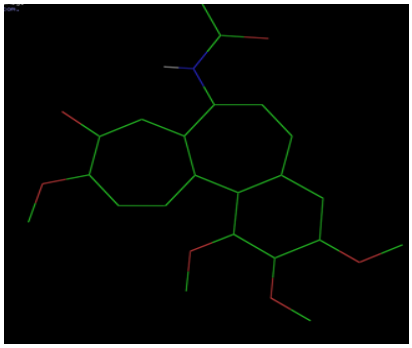


fig.1F

Glorisol

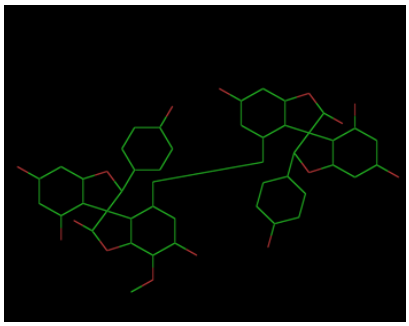


fig.1G

salicyclic acid

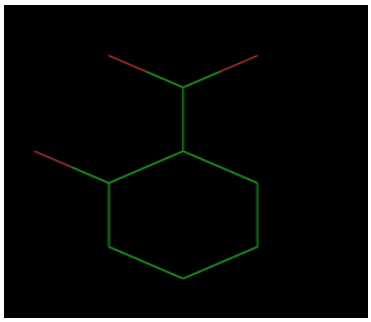


fig.1H

Sitosterol

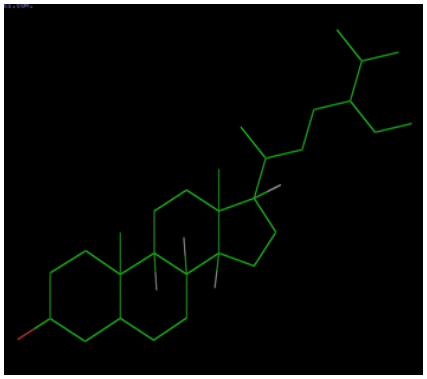


fig.1I

Stigmasterol

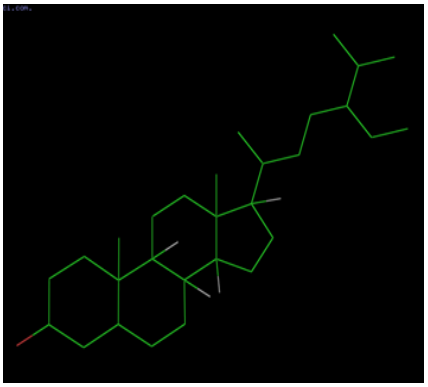
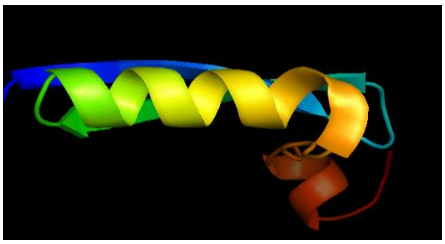


fig.1J

Figure 3 shows the structure E7 and DAHP.



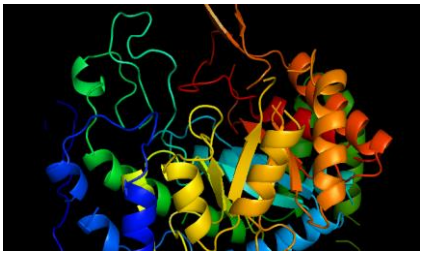


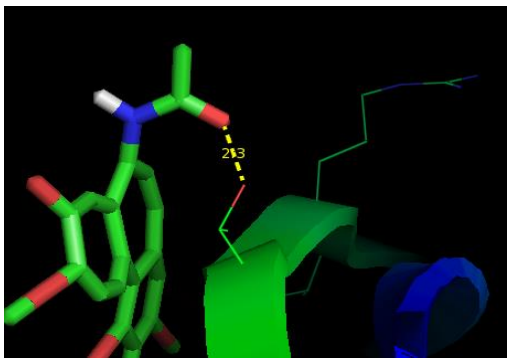
Table 1A: It shows the Docking results of GLORIOSA SUPERBA derived compounds against E7 protein

Compound Name	Binding energy value(kcal/mol)	No.of Hydrogen bond
2-Demethylcol chicine	-3.24947	Nil
3-Desmethylcol chicine	-5.6538	1
Benzoic acid	-7.95201	Nil
Choline	-3.63147	2
Chrysophanic acid	-9.52049	1
Colchicine	-5.56013	Nil
Glorisol	Nil	Nil
Salicyclic acid	-7.35178	Nil
Sitosterol	-6.86571	Nil
Stigmasterol	-5.40686	Nil

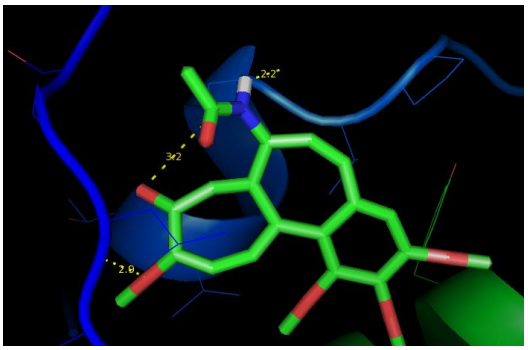
Table 1B: It shows the Docking results of GLORIOSA SUPERBA derived compounds against DAHP protein

s.no	Compound Name	Binding energy value(kcal/mol)	No.of Hydrogen bond
1	2-Demethylcolchicine	**-7.95243**	**2**
2	3-Desmethylcolchicine	**-8.32373**	**2**
3	Benzoic acid	**-8.78842**	**3**
4	Choline	**-3.73865**	**7**
5	Chrysophanic acid	**-8.86378**	**Nill**
6	Colchicine	**-7.47679**	**7**
7	Glorisol	**Nill**	**Nill**
8	Salicyclic acid	**-8.22659**	**2**
9	Sitosterol	**-11.4016**	**Nill**
10	Stigmastero	**-11.8419**	**Nill**

Docking complex of E7 and DAHP protein



E7 protein with chrysophanic acid



DAHP protein with Colchicine

Fig. 4: Represents the Docked Complex of the Inhibitors to that of the Target Protein.

Table 2A: Molecular property of chrysophanic acid

S.no	PROPERTY	VALUE
1	Molecular formula	C15H10O4
2	Formula weight	254.2375 [g/mol]
3	A logp	3.5
4	No. of hydrogen acceptors	4
5	No. of hydrogen donors	2
6	Density	481-74-3
7	Monoisotopic mass	254.057907

Table 2B: Molecular property of Colchicines

S.no	PROPERTY	VALUE
1	Molecular formula	$C_{22}H_{25}NO_6$
2	Formula weight	399.437
3	A logp	1
4	No. of hydrogen acceptors	6
5	No. of hydrogen donors	1
6	Density	106
7	Monoisotopic mass	399.168188

CONCLUSIONS

The present study indicates that analysis the property herbal plant Gloriosa superba can be used in the treatment of cervical cancer and tuberclousis which shows a strong binding affinity towards E7 and DAHP protein. This brings a strong focus towards these plant that, when administered during the treatment of cancer and tuberclousis may block E7 & DAHP. Gloriosa superba showed the highest affinity towards E7 and DAHP compared to other compounds. This creates a strong hypothesis that the effects of complex formation by E7 and DAHP and Gloriosa superba contribute towards combating against Cancer and Tuberculosis. Hence, Gloriosa superba may become a prospective target for inhibition of cancer and Tuberculosis and may unlock a strong initiative in developing novel ligand which is specified towards it. Hence the compound specified in this work can undergo certain specification to improve its drug properties and could act as a best drug for cancer and Tuberculosis. The mechanism of action of Gloriosa superba inhibit the activity of E7 and DAHP that is involved Causing tumor and Tuberculosis hence Glorsia superba having both property of anti cancer and anti Tuberculosis.

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