Section: Research Paper

Personalized remedies for oral lichen planus

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Abstract:

The deaths due to Oral Cancer can at least be prevented theoretically. The key is to identify potential malignant lesions and prevent them from turning into oral cancer using personalized medicine, the application of pharmacogenomics to individual clinical management. Personalized medicine is rapidly impacting how medicines are discovered and tailored to individual ailments for maximum benefit. This study includes molecular docking studies of natural compounds targeting oral lichen planus which is a potentially malignant lesion. Molecular docking process involves different binding modes of ligands with the active site of the target receptor protein using the docking software Autodock4.2. Out of Ten selected compounds, it has been observed that the compounds namely Fritillebin B and Bidebiline E showed most negative binding energies against "The structure of tumor necrosis factor-alpha at 2.6 angstroms resolution. Implications for receptor binding" (1TNF) of Homo sapiens. The docking results provided better insight into the development of new drugs for oral lichen planus.

Keywords: Oral cancer, oral lichen planus, Molecular Docking, Autodock4.2

Introduction:

Well-established or known risk factors for oral cancer include tobacco, betel/areca nut, alcohol, and high-risk oncogenic human papillomavirus (HPV) 16/18. However, only 5-10% of people with high-risk lifestyles develop oral cancer.[1] This can be explained by individual genomic variations expressed as single nucleotide polymorphisms (SNPs) that affect susceptibility to oral cancer.[2] It is estimated that there are about 11 million SNPs in the human population, averaging one every 1,300 base pairs.[3] Using the foundational knowledge provided by the Human Genome Project, the discovery of specific disease-causing genetic alterations has increased dramatically.[4] Most of the human diseases, with few exceptions like physical injuries, are associated with mutations (i.e, alterations) in DNA structure and function. These disorders include approximately 4,000 inheritable disorders that result from changes in single gene.[5]

SNPs are of particular interest in studying cancer susceptibility and cancer protection. SNPs in genes involved in carcinogen metabolism, DNA repair, cell cycle control, extracellular matrix alterations, and folic acid metabolism may be associated with increased susceptibility to oral cancer, and susceptibility varies by ethnic group. These genetic alterations may also

accelerate the transformation of oral potentially malignant disorders (OPMD) into malignancies. Therefore, catching at the OPMD stage itself may help reduce the oral cancer burden. Suggestive markers of increased susceptibility for Oculopharyngeal muscular dystrophy risk based on significant associations worldwide. [6]

In the recent past, proof had emerged indicating that a considerable part of variability in drug response is genetically determined, with age, nutrition, fitness status, environmental exposure, epigenetic elements and concurrent remedy playing vital contributory roles. These observations of fairly variable drug response, which started out within side the early 1950s, caused the delivery of a brand new medical area bobbing up from the confluence of genetics, biochemistry, and pharmacology called pharmacogenetics. Pharmacogenomics is the study of an individual`s genetic inheritance influences the body's reaction to drugs.[7] Pharmacogenomics had facilitated greater powerful drugs with decreased toxicity, determination of suitable drug dosages, the manufacturing of better or healthier vaccines and most significantly the idea of the concept of personalized medicine (PM).[8] Also, personalized most cancers remedy includes an entire biochemical characterization of the tumor using multi-dimensional analyses for a variety of biological endpoints, which results in a calculated selection on the best remedy, thus, resulting in substantially stepped forward Overall Response (ORR) and Overall Survival (OS) rates.[9] In precision drug for most cancers, remedies can be as a result matched to the genetic abnormalities of the tumour – modifications in the DNA code. These DNA abnormalities in a patient`s tumour may be detected through genetic testing or through DNA sequencing.[10]

Oral lichen planus

Oral lichen planus (OLP) is a chronic disease in which the immune system plays a major role[11]. Since OLP is an immune-related disorder, stress, anxiety, and other immune-related factors can contribute to the disease[12]. The disease predominantly affects women and affects 2-5 percent of the common population. Its beginning potential is also in four to five decade of life[13]. The exact aetiology of OLP has not been discovered and is associated with various triggers such as mechanical, electrochemical, traumatic and psychological, stress, malnutrition, infectious, overwork, mucosal irritants and allergies, endocrine disorders. It is mainly considered as a multifactorial process. Salivary gland disorders, genetic susceptibility and immune disorders[14-16].

Diagnosis of OLP is usually made by clinical and histological examination. However, for classic lesions, diagnosis can be made based on clinical presence alone[17]. Moreover, there is a spectrum of oral lichenoid lesions (OLL) that can confound differential diagnosis. For example, systemic medications such as non-steroidal anti-inflammatory drugs, certain anti-hypertensives, and oral hypoglycemic agents may contribute to the development of oral lichen-lichenoid reaction (OLR)[18-19]. Restorative materials such as amalgam, gold, and nickel may also be associated with local OLR in many patients. It is worth noting that some skin diseases may show some lichenoid features clinically or histologically.[20]

The treatment of this condition becomes more important as it is also considered as one of the OPMDs. The various treatments available are using of various immunomodulators and anti-oxidants either topically and/or systemically. Till now in the literature there is no satisfactory treatment is available for curing the condition and sometimes these medications have to be used for much longer periods to avoid symptoms, malignant transformation and recurrence, though they have considerable side effects. In this scenario the evidence based effective natural compounds can give better results in various conditions.

The goal of molecular docking is to predict the conformation of the ligand within the target (receptor) binding site[21] and estimate the affinity of this particular interaction. Most scoring functions take into account the size, flexibility, internal conformational energy, and atomic positions of the ligand.[22] Alternatively, molecular docking can be used integratively to achieve goals beyond the prediction of protein-ligand binding modes. Ligand docking helps computationally design or redesign binding pockets by altering ligand-protein interactions. In this method, the binding pocket of a known target is used as a scaffold. Ligands are docked into binding pockets of defined proteins of interest and the combined energy values are used to identify promising pockets created by protein design programs[23].

Methodology:

Molecular docking studies:

Molecular docking studies were performed to investigate the binding mode of selected compounds against the proteins of Lichen planus and Oral submucous Fibrosis using molecular docking program AutoDock4.2.[24] For molecular docking studies with AutoDock 4.2, all the selected natural ligands were downloaded from NCBIpubchem database[25] and for computational studies, the geometry of all the downloaded compounds were optimized (Figure 1A) using sybyl6.7 software[26] by using Gasteiger-Huckel charges after that, it was used for molecular docking.. The prepared natural ligand molecules were used as input files for AutoDock 4.2 in the next step. There are a lot of protein crystal structures available in the RCSB (a protein structure databank (https://www.rcsb.org/); thus, to check the binding accuracy, we docked different natural compounds against the selected protein. The crystal structures with accession number 1TNF (The structure of tumour necrosis factor-alpha at 2.6 angstroms resolution. Implications for receptor binding)[27] was reported to be obtained through the X-ray diffraction method with 2.6 Å resolution. Initially, the protein and ligands were prepared individually for docking. For docking simulations Autodock 4.2 was used. Autodock 4.2 uses Lamarckian genetic algorithm. Default parameters were applied for docking and the protein was set as rigid and ligand as flexible. The active site was identified by using PDBSUM. X,Y,Z coordinates were set and used a grid of 60, 60, 60. Grid spacing of 0.375 Å and for the calculation of the energetic map distance-dependent dielectric constant were used. After completion of the docking the results were analysed and selected best pose. In silico measurements were carried out using Autodock4.2 and visualized using Ligplot+.[28]

Results and Discussion:

Obtained binding energies and hydrogen bond interactions of selected compounds i.e., Fritillebin B, Bidebilin E, Quercetin, Curcumin, Quercetin, Naringenin, Naringin, Clobetasol propionate, Triamcinolone and Tritinoin from the molecular docking, whereas the docked conformation of Fritillebin B in the active sites of *1TNF* is presented in Figure 1 respectively.

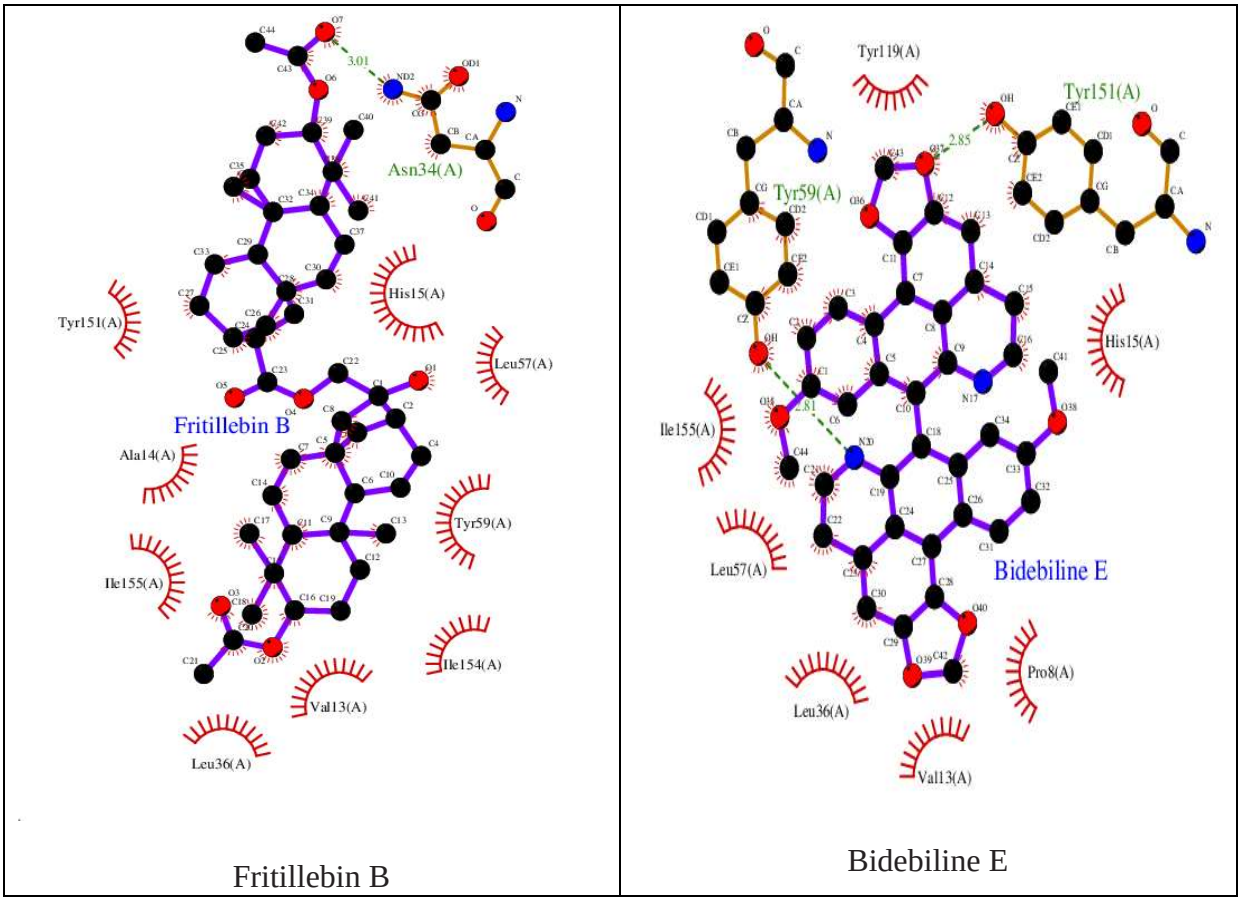
To validate the accuracy of AutoDock 4.2 as an appropriate docking tool for the present purpose, the co-crystallized ligands (natural molecules with 1TNF) were docked within "The structure of tumour necrosis factor-alpha at 2.6 angstroms resolution. Implications for receptor binding". In principle, the scoring function used will succeed when the optimal docking conformation of the ligand resembles the native ligand bound in the experimental crystal structure. According to the method of validation cited in the literature, the successful scoring function is the one in which the RMSD of the best docked conformation is ≤2.0 Å from the experimental one.

Compound Fritillebin B exhibited most negative binding energy with "The structure of tumour necrosis factor-alpha at 2.6 angstroms resolution. Implications for receptor binding".

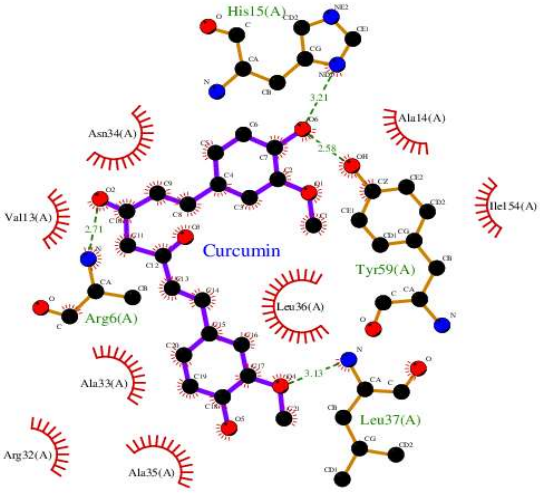
The compound Fritillebin B exhibited most negative binding energy of –7.65 kcal/mol with interacting Asn34. Quercetin showed six interactions with Arg31, Arg32, Ala33, Asn34, Ala35(2), having binding energy of -5.87 kcal/mol. All the other compounds also exhibited excellent most negative binding energies with the selected protein. All the protein interactions, binding energies are shown in table 1 and interacting poses are shown in figure 1.

Compound number	Binding energy ΔG (kcal/mol)	Dissociation constant (kl)	Interacting amino acids
Fritillebin B	-7.65	2.47	Asn34
Bidebiline E	-7.45	3.44	Tyr59, Tyr151
Curcumin	-6.34	22.51 µM	Arg6, Lys11, His15, Tyr59
Quercetin	-5.87	49.56	Arg31, Arg32, Ala33, Asn34, Ala35(2)
Naringenin	-5.64	74.03	Leu37
Naringin	-5.42	106.28	Arg6, Pro8, Ala35
Resveratrol	-5.13	173.11	Arg32, Ala33, Asn39
Clobetasol propionate	-6.09	34.32 µM	Arg6, Ala33, Arg31, Ala35, Leu37
Triamcinolone	-5.78	58.37 µM	Arg6, Arg32, Ala33, Ala35, Leu379(2)
Tritinoin	-5.44	103.07 µM	Asn34

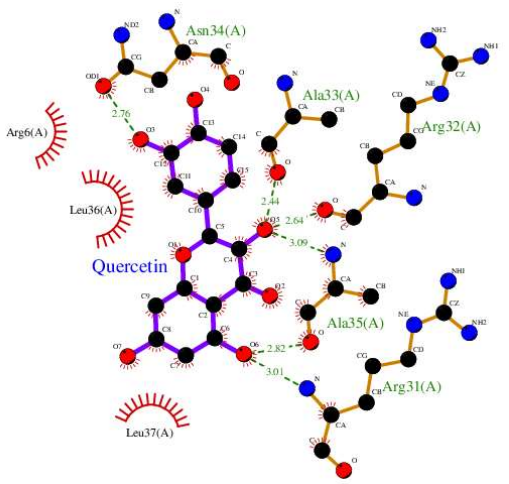
Table 1: Compounds with binding energy and interacting amino acids



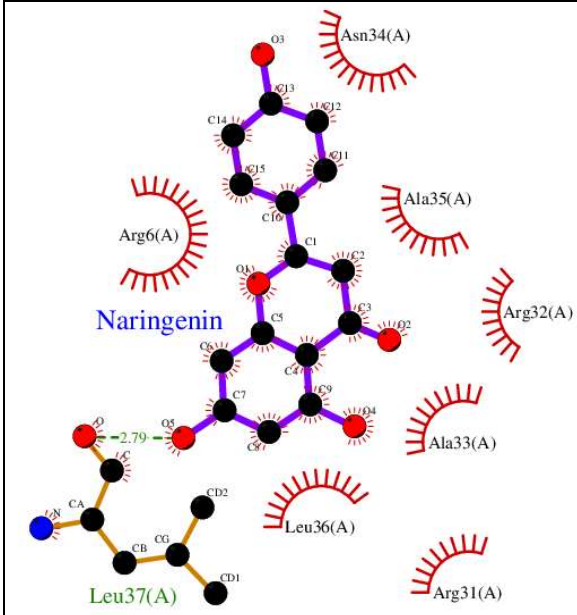
Fritillebin B Bidebiline E



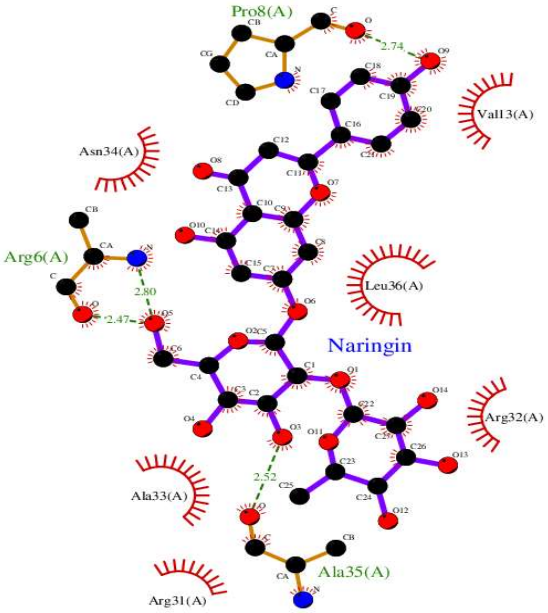
Curcumin



Quercetin



Naringenin



Naringin

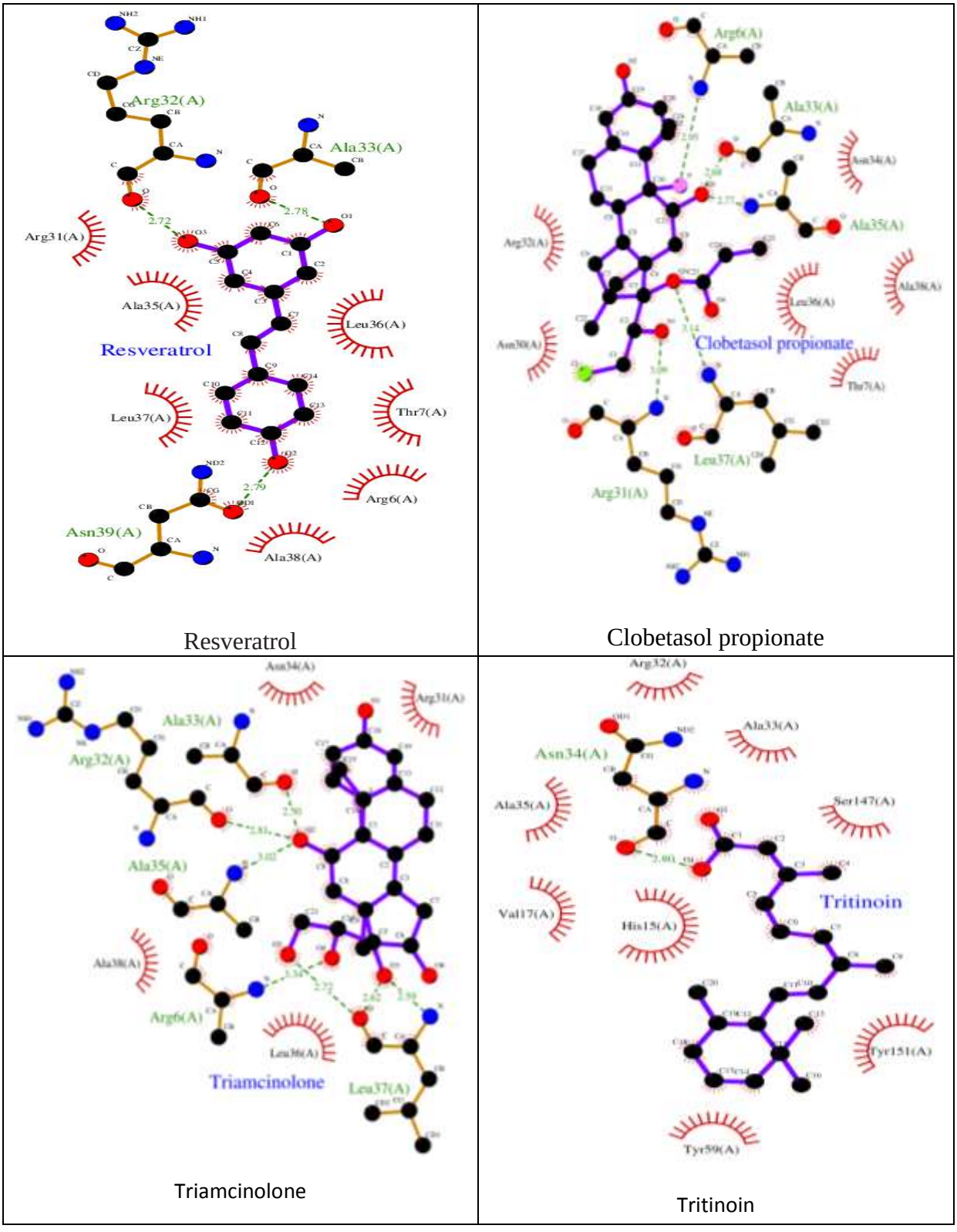


Figure 1: Protein-ligand interacting poses of all the selected compounds

Conclusion:

Fritillebin B is a potential drug candidate to be considered in the development of anticancer agents to combat the oral lichen planus. This study provides an insight into the design and prediction of potential modes of interaction and the binding affinities of seven natural

compounds and three known drugs. *Fritillebin B* had the most negative binding energy value among the other molecules. Experimental studies needed to further validate the target protein.

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