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Molecular Docking Studies of Derivatives of *Majorana hortensis* Leaves against Anti Apoptotic Targets

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Abstract : Objective: Cancer is one of the most devastating disease and development of anticancer drugs or targets is of paramount importance in the field of biomedicine. Methods: *Majorana hortensis* leaves were subjected phytochemical analysis and piperitol from saponin fraction and terpinene 4-ol and trans sabinene hydrate from terpene fraction showed significant anticancer properties. Hence the above 3 ligands were targeted against the apoptotic targets (Trail, Bax, Bcl2, MDM2, Bak). The study was carried out using Schrodinger (GLIDE) software and the results were documented based on glide score, glide energy, pose number, good contacts, confirmation, and H bonding. Results: Results showed that piperitol possessed good docking capacity with all 5 targets. However, for Terpene 4-ol docking was not seen with MDM2 and Bak proteins. For trans-sabinene hydrate, docking did not appear in Bax, MDM2 and Bak. Conclusion: This proved that piperitol was most potent for anticancer therapy with respect to molecular docking studies.
Keywords : piperitol, terpene 4–ol, trans-sabinene hydrate, docking, anti apoptotic proteins.

Introduction:

Cancer was identified as one of the most devastating diseases of the 20th century and was found to be spreading with increasing incidence towards 21st century. It is a group of disease characterized by uncontrolled cell-division leading to abnormal growth of the tissue [1]. Excessive cell division and evasion of cell death is characteristic features of the cancer. Plethora of literature explains the importance of targeting apoptotic pathway in cancer therapy by small molecular compounds[2]. The desirable feature of apoptosis or cell death is inhibited by a class of anti-apoptotic proteins. The anti-apoptotic family of Bcl-2 genes and proteins are over expressed in the tumor progression[3].The treatment strategies led to side effects of synthetic drugs which pressed the need for plant derived drugs.

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Plant based products are in the rise which contribute towards the anticancer properties. It is the new approach to clinical chemistry for the optimization of screening and testing by means of the observation on particular compound [4]. The need of biological screening and chemical synthesis has increased in order to obtain the early information of absorption, distribution, metabolism, excretion, and toxicity data[5].This information allows researchers to understand and characterize many physiological processes based on interactions between proteins or between proteins and small molecules (ligands),as the case of the drug-target binding [6].This paved way for the docking techniques. The docking process is the virtual simulation of the energetic interaction betweenthe ligand and the target, including the prediction of the best ligand conformation and orientation within the binding site[7].The development of new anticancer drugs proves to be a very elaborate, costly and time-consuming process. CADDis becoming increasingly important, with less investment in technology, resources, and time.Given the 3D structure of a target molecule, chemical compounds may have a potentially higher affinity for their target when are designed rationally with the aid of computational methods. In recent years, several cases of successful applications of structure-based drug design have been reported[8]. The main objective of molecular docking is to attain ligand-receptor complex with optimized conformation and with the intention of possessing less binding free energy. The net predicted binding free energy (ΔGbind) is revealed in terms of various parameters, hydrogenbond (ΔGhbond), electrostatic (ΔGelec), total internal energy (ΔGtotal) and unbound system's energy (ΔGunb). Therefore, the predicted binding free energy (ΔGbind) provides additional clues about the nature of various kinds of interactions leading to the molecular docking [9].

Materials and Methods:

In order to understand the nature of interactions of these ligands, we carried out molecular docking between all compounds. The molecular docking studies were performed using glide (Maestro, 2013) module with default docking parameter settings, the docking scores summarized in tables below. Table 1 shows he interactions of piperitol with 5 target proteins (TRAIL, Bac, BAX, Bcl-2 and MDM2). Table 2 shows the profile of terpene 4-ol with the same 5 anti apoptotic protein targets as above. Table 3 depicts the interactions of trans-sabenine 4 –ol with the same 5 anti apoptotic protein targets. The interaction profile of all docked poses was generated for the interaction analysis of ligand with proteins.The docking program GLIDE was used to perform the interaction between piperitol, teripinol-4-ol and trans-sabinene hydrate. Success of molecular docking depends on how the ligand binds to the defined binding siteof a protein. The parameters considered are glide score, glide energy, pose number, good contacts, confirmation changes and H bonds.

Results and Discussion

Glide Score and energy:

The glide score was highest in piperitol binding with target Bax which showed a glide score of -4.8 and corresponding glide score of -22.9 which was the highest followed by TRAIL, Bak, MDM2 and Bcl-2 (Table 1).Terpene-4-ol did not exhibit any glide score or energy for MDM2 and Bak (Table 2).Trans-sabinene hydrate possessed values only for 2 target proteins namely TRAIL and Bax (Table 3). Glide performs a complete systematic search of the conformational, orientation and positional space of the docked ligand[10]. Even when binding conformations are correctly predicted, the calculations eventually do not turn out correct unless we are able to differentiate correct poses from incorrect ones, and if 'true' ligands cannot be identified. Hence, the scoring functions and scheme is of fundamental importance [11].

Table 1. Glidesp docking of the ligand piperitol with the Target proteins

S.No.	Docking Parameters (Piperitol)	Target Proteins				
		Trail	**Bcl2**	**Bax**	**MDM2**	**Bak**
1.	Glide Score	-4.430	-3.822	-4.876	-3.972	-4.129
2.	Glide Energy	-17.236	-17.00	-22.918	-19.513	-19.33
3.	Pose number	79	55	96	360	167
4.	Good Contacts	105	134	173	179	138
5.	Conformation number	5	1	3	3	3
6.	H-bonds	2	1	1	1	1

Pose number:

The pose selection is very important as the docking scores are dependent on these. The prediction of correct ligand pose or orientation is one of the most important things in ranking of new chemical entity (NCEs). This depends on how well computational docking program predict the binding pocket. This can be done by comparison of the crystal structure pose to the docked pose [12]. The maximum pose number was seen for piperitol with MDM2 target protein (Table 1); however no pose number was derived with the other 2 bioactive molecules namely terpeine-4-ol and trans-sabinene hydrate (Table 2 and Table 3).

Table 2.Glide sp docking of the ligand terpinene-4-ol with the Target proteins

S.No	Docking Parameters (terpinene-4-ol)	Target Proteins				
		Trail	Bcl2	Bax	MDM2	Bak
1.	Glide Score	-5.03	-3.87	-3.71	---	---
2.	Glide Energy	-17.83	-17.24	-18.50	---	---
3.	Pose number	242	300	258	---	---
4.	Good Contacts	121	139	153	---	---
5.	Conformation number	1	1	1	---	---
6.	H-bonds	1	2	0	---	---

Table 3.Glide sp docking of the ligand trans-sabinene hydrate with the target proteins

S.No.	Docking Parameters (trans sabinene hydrate)	Target Proteins				
		Trail	Bcl2	Bax	MDM2	Bak
1.	Glide Score	-3.87	---	-3.87	---	---
2.	Glide Energy	-17.24	---	-17.24	---	---
3.	Pose number	300	---	300	---	---
4.	Good Contacts	139	---	139	---	---
5.	Conformation number	1	---	1	---	---
6.	H-bonds	2	---	2	---	---

Good contacts:

For piperitol, the number of good contacts was essentially good number ranging from 179 with MDM2, 173 with Bax, 138 for Bac, 134 for Bcl-2 wih the lowest with TRAIL (Table 1). However, with terpene 4-ol contacts were nil with MDM2 and Bac (Table 2). Similarly, with trans-sabiene 4-ol there were only 139 contacts for TRAIL and Bax and no other contacts with the rest of the 3 targets (Table 3). This indicated that piperitol was more likely to be considered as a better bioactive compound compared to the other two.

Conformational Changes:

Current protein–protein docking methods are often successful if experimentally determined partner proteins undergo little conformational changes upon binding [13]. Molecular docking forecasts an optimized conformation and relative orientation for both the protein and ligand molecule [14]. Conformation changes were seen highest in TRAIL with 5 followed by other 3 target proteins Bac, Bax and MDM2 with regard to piperitol (Table 1). With terpene4-ol the conformational changes was 1 and that was also present in the case of only TRAIL, Bax and Bcl-2 (Table 2). However for the third bioactive compound, trans-sabinene hydrate conformational changes was observed in 2 targets with a score of 1 for both TRAIL and Bax (Table 3). This indicated that piperitol was a better compound compared to the other two.

H bond:

The hydrogen bonding was noted for each of the target proteins with the 3 bioactive compounds. The greater the number of bonds the better was the affinity of the interaction between the ligand and receptor. It was observed from the above experiment that H bonding was strongest with TRAIL (2 H bonds) in the case of piperitol followed by 1 bond in the case of piperitol with Bcl, Bak, MDM2 and Bax (Table 1). However, in the case of terpeine 4-ol there were 2 H bonds and 1 bond each with TRAIL alone. No bonds were formed with the rest of targets (Table 2). With regard to transsabinene hydrate, 2 H bonds were formed for TRAIL and Bax proteins and not with the other protein targets (Table 3). These results are in accordance with the work done [15] who used natural pyridoacridines as anticancer agents and proved using molecular docking. Molecular interactions involving H-bonds between protein and ligands were deduced based on dock score functions. Bcl-2 and gossypol derivative 3k complex has shown better interaction among Bcl-2family members. Top ranked hydrazide-hydrazone gossypol derivatives against each anti-apoptotic target were further probed for ADME properties [16].

Conclusion:

Piperitol is having a greater affinity towards binding with all the anti apoptotic proteins namely Trail, Bcl2, Bax, MDM2 and Bak compared to terpeine-4-ol and trans-sabiene hydrate which shows the former to be the active compound to be used for further studies.

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