Exploration of phytochemicals for inhibition of monoamine oxidase-A induced cancer using molecular docking studies

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Abstract: Monoamine oxidase A (MAO-A), an enzyme found on outer mitochondrial membrane, catalyzes the oxidative deamination of biogenic amines. Recently, it has been studied that MAO-A have a role in the cancer progression by elevating the generation of Reactive oxygen species (ROS) and by promoting epithelial to mesenchymal transition (EMT) through activation of Vascular endothelial growth factor (VEGF) and its co-receptor neuropilin-1. In this study, an attempt has been made to identify new lead candidates for inhibiting the MAO-A induced initiation and progression of cancer by using molecular docking method. For this purpose, 967 phyto-chemicals from African medicinal plants (AfroDb) were docked gainst the MAO-A (PDB ID: 2Z5X) using Molegro Virtual Docker (MVD) software. MVD calculates the binding energies of target enzyme and ligands at lowest energy conformations by using the piecewise linear potential (PLP) scoring functions. Evaluation of docking studies suggests that compounds Quercetin (ZINC03869685), Apigenin (ZINC03871576), Luteolin (ZINC18185774), [(2R,3S,4R,5S) 3,4,5 trihydroxytetrahydropyran-2-yl]methyl (ZINC14422042) and Scutellarein (ZINC05842416) are docked with highest MVD score -104.412 kcal/mol, -100.189 kcal/mol, -98.5797 kcal/mol, -98.1878 kcal/mol, -97.5296 kcal/mol respectively, therefore, can effectively inhibit MAO-A enzyme and can serve a role as potential lead compounds for developing new drugs for the suppression of cancer.

Keywords: Molegro virtual docker, cancer, monoamine oxidase-A, African medicinal plants.

INTRODUCTION

Monoamine Oxidase (MAO) (EC 1.4.3.4), a flavoenzyme, catalyzes the oxidative deamination of biogenic amines like serotonin, dopamine, tyramine and norepinephrine into their corresponding aldehydes (Edmondson *et al*., 2007). It exists in two isoforms namely Monoamine Oxidase A (MAO-A) and Monoamine Oxidase B (MAO-B) (Rybaczyk *et al*., 2008). Both are present in the outer mitochondrial membrane of almost all the tissues as intrinsic proteins (Youdim *et al*., 2006).

These two isoenzymes have different distributions, substrate preferences, inhibitor specificities and biological functions. MAO-A oxidizes epinephrine, serotonin and norepinephrine and clorgyline is the irreversible inhibitor of this enzyme. Monoamine Oxidase-B oxidizes benzylamine and phenylethylamine and is irreversibly inhibited by deprenyl and pargyline (Youdim *et al*., 2006). Whereas, dopamine and tyramine serves as a substrate for both the two isoforms. There as 527 and 520 amino acid residues in MAO-A & MAO-B respectively and have 70% sequence similarity.

As Monoamine oxidase (MAO) is involved in the regulation and degradation of neurotransmitters, therefore MAO abnormality has been associated with various neurological and psychological diseases, emotional disorders such as depression, Parkinson disease and Alzheimer disease (Bortolato *et al*., 2008).

Recent studies has also shown involvement of MAO, specially MAO-A, in different cancer cell progression including prostate cancer, colorectal cancer, hepatocellular carcinoma and lung cancer (Liu *et al*., 2018; Lin *et al*., 2017) as MAO-A-mediated production of reactive oxygen species (ROS) may result in DNA damage and oxidative injury of cells and may cause tumor initiation and progression. Reported studies suggest that tumors from patients with aggressive cancer show increased levels of MAO-A (Wu *et al*., 2014), thus, the use of MAO-A inhibitors could be a potential therapy for the neuro-endocrine tumors and can be used as future anti-cancer drugs (Lin *et al*., 2017).

MAO-A contains a single cavity that is substrate binding cavity (Edmondson *et al*., 2009) of volume ~550 $Å^3$, the residues Ile180, Asn181, Phe208, Ile335 surrounds this cavity. The amino acids Gln215, Tyr444, Ile180 and Tyr407 in MAO-A binding site plays a crucial role in orienting and stabilizing substrate or inhibitor binding (Binda *et al.,* 2003).

Computer-aided drug design (CADD) is used in combination with *in vitro* lab techniques to identify new drug targets and to design putative drugs for both known and new targets. It can also generate a structure-activity

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relationship (SAR) in between the drug candidate and the target protein, that is then used to assist the drug designing process, thus, reduces the time and expenses (Yu and MacKerell, 2017). The two types of computer-aided drug design (CADD) methods are i) structure-based drug design (SBDD) and ii) ligand-based drug design (LBDD) (Yu and MacKerell, 2017). During this study, SBDD method have been used that particularly uses the 3D structure of macromolecule, identify the binding site and predict the binding mode and interactions in between the ligand and the macromolecule that are important for their biological activity (Surabhi and Singh 2018). Ligand-based methods uses the pharmacophore searching and similarity and/or fingerprint searching, whereas, structure based methods commonly uses molecular docking to search large databases of chemical compounds for possible drug candidates (Lyne, 2002).

Molecular docking is now a days commonly used in computer aided drug design as it can predict the preferred binding orientation of a ligand within the active site of a protein of known three-dimensional structure (Ruyck *et al*., 2016) thus, can predict the strength of binding between the ligand and the protein (Sledz and Caflisch, 2018). The docked compounds are then ranked through a scoring function (Wang *et al*., 2018). This docking method of virtual screening has been successfully used to discover hits for many biological targets (Meng *et al*., 2011).

In the present study, chemical constituents from African medicinal plants from AfroDb were screened against the MAO-A for identification of potential inhibitors of this enzyme by using the molecular docking studies.

MATERIALS AND METHODS

During this study, in order to search for inhibitors for the enzyme MAO-A, virtual screening of phytochemicals from African Medicinal plants have been performed using molecular docking method. For this purpose, three dimensional structures of both protein and the small molecules were required.

Protein preparation

Three dimensional structure of MAO-A was retrieved from Protein Data Bank (PDB) which is a database of 3D structures of biological macromolecules (DNA, RNA & Protein) (Berman *et al.,* 2000). In PDB, five crystal strcutures for MAO-A were available. The structure of MAO-A bound with Harmine (PDB ID 2Z5X) was selected for this study (Son *et al*., 2008). This structure has been resolved by X-ray crystallography at resolution 2.2 Å.

In order to perform the docking studies, Molegro Virtual Docker (MVD) software (Thomsen and Christensen, 2006) have been used. At first, the 3D structure of the protein MAO-A in complex with Harmine (PDB ID: 2Z5X) was downloaded from PDB and imported to the MVD work space. Imported protein was then prepared by assigning the missing bonds, hydrogens, and charges. During docking studies, at first, cavities (potential binding sites) were detected in the protein through guided evolution algorithm (Storn and Price, 1997) and a constraint of 10Å in radius was set up in order to limit the search space around the active site i.e. cavity where Harmine was bound.

Ligand preparation

During this study, AfroDb, a database of phytochemicals from African Medicinal plants (Ntie-Kang *et al*., 2013) , a subset of ZINC database, was used. This AfroDB contains approximately 1000 compounds from natural products from across the African continent. These compounds are known to have activities against a number of tropical diseases such as hypertension and cancer (Ntie-Kang *et al*., 2013). All the 967 ligands from this database were downloaded in mol2 format, these structures were then imported to the MVD workspace and optimized for docking studies.

Docking simulations

Once the protein and all the ligands were prepared, docking simulations were started. Water molecules and cofactors were also included while performing the docking. The MVD software docked each ligand in to the binding site of MAO-A. During this studies, ten docking runs were conducted and 10 docking solutions were obatined (poses) for each ligand and ranked them in order of increasing energies of the interaction. The pose with lowest energy was selected, as the lowest the energy, the better is the conformation, along with that hydrogen interactions that are formed in between the compound and amino acids of the active site were also analyzed for the top scores poses.

For predicting the binding pose of a ligand (drug candidate), MVD evaluate ligand conformations and estimate energy of interaction between each conformation and the protein by using the scoring function that is derived from piecewise linear potential (PLP) that was initially introduced by Gehlhaar *et al.,* 1995 and afterward continued by Yang and Chen, 2004.

RESULTS

During this study, novel MAO-A inhibitors from natural sources were searched using the docking method, as reported studies has shown that natural compounds are rich source of potential anticancer lead structures. A set of 967 compounds form AfroDb, a database of chemical compounds from African medicinal plants, were docked into the MAO-A active site using the MVD software in order to identify their binding affinity. The docking

results of top 25 compounds are presented in table 1, including the docking score, hydrogen bond energy and amino acids involved in the hydrogen bond interaction. Binding mode of top two docking hits (quercetin and apigenin) within the active of MAO-A are presented in fig. 2a and 2b respectively.

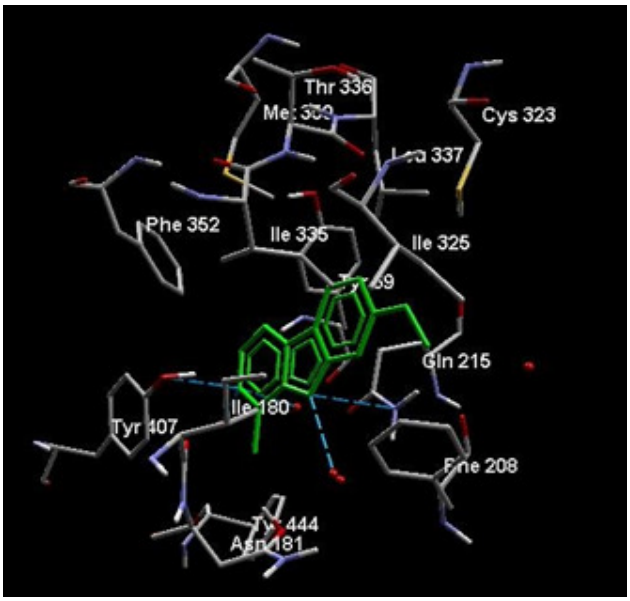


Fig. 1: Binding of Harmine (in green color) within the active site of MAO-A (PDB ID 2Z5X)

The three dimensional structure of MAO-A (PDB ID: 2Z5X) that has Harmine as a ligand have been used in this research work. Earlier studies shows that Tyr407, Tyr444, Gln215 and Ile180 are crucial for the activity of MAO-A (Son *et al*., 2008). Harmine (HRM) acts as a reversible inhibitor, binding of MAO-A with Harmine shows that it forms hydrogen bond interactions with amino acid residues Gln215 and Tyr407 (fig. 1), the two amino acids vital for the activity of the enzyme (Son *et al*., 2008).

During the docking studies, 349 out of 967compounds docked well within the active site of the MAO-A with the negative interaction energy. It is observed that the top hits, with highest docking scores, obtained during this study, established strong hydrogen bond interactions with the amino acids that have a key role in the catalytic activity of the enzyme i.e. Tyr444, Tyr407, Gln215 and Ile180 (fig. 1).

During this study, the compound ZINC03869685 (Quercetin), a flavanoid, displayed the highest docking score, -104.412 Kcal/mol and forms hydrogen bond interactions with Gln215, Tyr444 and Asn181 (fig. 2a), as discussed earlier, the interactions with Gln215 and Tyr444 play a crucial role in the activity of MAO- A isozyme.

Other phyto-chemicals from the African medicinal plants, among the top five hits during this study, ZINC03871576 (Apigenin), ZINC18185774 (Luteolin), ZINC14422042 ([(2R,3S,4R,5S) 3,4,5 trihydroxytetrahy dropyran-2-yl]methyl) and ZINC05842416 (Scutellarein) are docked with high MVD score -100.189 kcal/mol, -98.5797 kcal/mol, -98.1878 kcal/mol, -97.5296 kcal/mol respectively (table 1). Apigenin, Luteolin and Scutellarein are also falvanoids and the docking simulations predicted that they exhibits higher binding affinity towards MAO-A and forms hydrogen bonding with amino acids Tyr444, Gln215, Cys323 and Asn181 within the active site of MAO-A (table 1), apart from this, Luteolin also formed linkage with Phe208 and Ile180.

Reported docking studies predict that these compounds can serve as possible lead molecules for the inhibition of Monoamine Oxidase A and could be the possible drug candiates for the treatment of cancer.

DISCUSSION

MAO-A, an outer membrane-bound, mitochondrial enzyme that is involved in the degradation of monoamine neurotransmitters and produces hydrogen peroxide (H_2O_2) as a by-product during the reaction (Youdim *et al*., 2006). Although, the main function of MAO-A is as a neurotransmitter regulator, but recently its role in tumorigenesis has been also identified and this oncogenic role of MAO-A is through increasing the oxidative stress within the cell. Reported studies have shown that over-expression of MAO-A promotes tumor growth (Wu *et al*., 2014; Gordon *et al*., 2014). Interestingly, inhibition of MAO-A by the drugs administered for neurological diseases, also inhibits the tumor growth and metastasis in mice (Wu *et al*., 2014).

These studies indicate that MAO-A could be one of the target for treating the various types of tumours. It is further supported by the recent studies where drugs that are used to regulate the serotonin uptake have also shown to minimize the risk of colon cancer in man (Rybaczyk *et al*., 2008). As most of the currently used chemotherapeutics are associated with toxicity, therefore, development of new anti-cancer agents is still in demand.

According to various reported studies, long-term use of vegetables and fruits rich diet reduces the chances of many chronic diseases including cancer (Xiao *et al*. 2011). Natural dietary agents have cancer chemo-preventive role that can suppress or prevent the progression of cancer (Benetou *et al*., 2015) therefore, compounds from natural sources could serve as potential candidates for treatment and prevention of cancer.

During this study, computer-aided docking experiments were carried out on human MAO-A crystal structure (PDB ID: 2Z5X) and photochemicals from African plants have been screened against the MAO-A using the MVD software.

Table 1: Docking results of top 25 hits with MVD score, Hydrogen bond energy and amino acids involved in interaction

S. No.	Ligands	MVD Score (Kcal/mol)	Hydrogen Bond energy	Interacting amino acids
1	ZINC03869685	-104.412	-4.13884	Gln215, Tyr444, Asn18, Cys323
2	ZINC03871576	-100.189	-2.90407	Tyr444, Gln215, Asn181, Cys323
3	ZINC18185774	-98.5797	-5.42146	Gln215, Phe208, Asn181, Tyr444, Cys323, Ile180
4	ZINC14422042	-98.1878	-6.49807	Tyr444, Tyr407, Asn181, Phe208, Thr336
5	ZINC05842416	-97.5296	-3.02891	Tyr444, Gln215, Asn181, Cys323
6	ZINC00001785	-97.1289	-2.69596	Tyr444, Gln215, Asn181
7	ZINC00119983	-95.9549	-3.84406	Tyr444, Gln215, Asn181
8	ZINC95486352	-95.8004	-5.06276	Tyr444, Phe208, Thr336, Asn181
9	ZINC95486352	-95.6573	-4.87732	Phe208, Thr336, Tyr444, Asn181
10	ZINC95486265	-95.2813	-4.93287	Tyr444, Phe208, Thr336, Asn181
11	ZINC95486137	-94.2787	-1.2236	Tyr444, Phe208
12	ZINC00119988	-93.9969	-3.983	Tyr444, Gln215, Asn181, Ile180
13	ZINC14649032	-92.8318	-3.27566	Tyr407, Gln215, Asn181, Thr336
14	ZINC95486297	-92.7077	-2.5	Asn181, Tyr444
15	ZINC95486297	-92.1209	-2.5	Tyr444, Asn181
16	ZINC01721693	-90.7853	-2.5	Tyr444, Gln215
17	ZINC02386253	-89.2219	-1.02472	Tyr444
18	ZINC95486009	-89.1814	-0.0689898	Tyr444
19	ZINC95486293	-89.1372	-2.5	Asn181, Tyr444
20	ZINC05765089	-88.5733	-2.19655	Tyr444, Gln215, Phe208, Thr336
21	ZINC00035526	-88.2881	-3.8994	Tyr444, Tyr407, Gln215, Thr336
22	ZINC95486168	-88.259	-7.61334	Tyr407, Gln215, Ile180, Thr336, Phe208
23	ZINC28456059	-87.2454	-5	Tyr444, Asn181
24	ZINC01663628	-87.0169	-5.07006	Ile180, Tyr407
25	ZINC95485902	-86.7082	-5	Tyr444, Asn181, Phe208

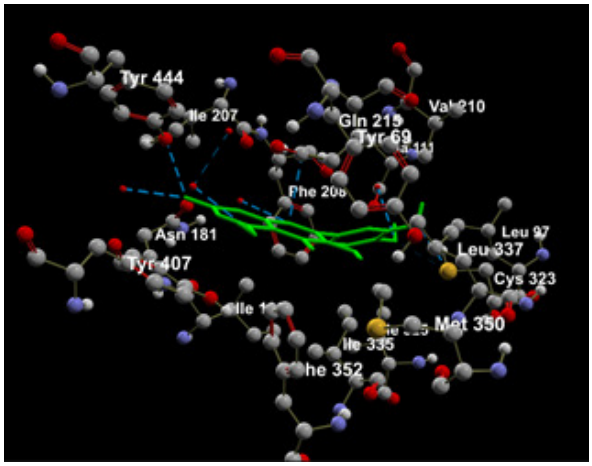
The top hits obtained during the studies (Quercetin, Apigenin Luteolin Scutellarein), mostly flavonoid in nature, were docked well within the active site of the MAO-A and successfully formed the hydrogen bond interactions that are crucial for its catalytic activity. Flavonoids, polyphenolic secondary plant metabolites, possess broad-spectrum pharmacological activities such as antibacterial, antiviral, antioxidant, anti-allergic, and anti-inflammatory, including their potential role as anti-cancer agents (Panche *et al*., 2016).

These flavonoids interact in between different types of genes and enzymes and play a major role for prevention against cancer, therefore, they are beneficial for health and considered as chemopreventive or therapeutic agents against cancer (Ravishankar *et al*., 2013).

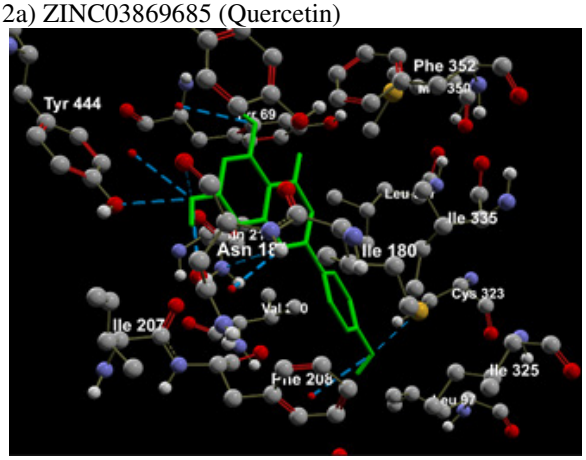
Quercetin, 3,5,7,3′,4′-Pentahydroxyflavone, is among the best predicted hits during this study with highest docking score of -104.412 Kcal/mol against the MAO-A. It has diverse biological effects, it inhibits various enzymes that are linked to cell proliferation and signal transduction pathways (Brito 2015). Also, quercetin has reported inhibitory activity against the growth of various malignant cancers such as leukemia, breast, hepatic, ovarian, colorectal, gastric and endometrial cancers (Tao *et al*., 2015; Lan *et al*., 2017). Previous experimental studies also show potent inhibitory activity of quercetin towards MAO-A with IC_{50} value in micro-molar range (Larit *et al*., 2018; Dhiman *et al*., 2019).

The other compounds predicted during this study to be active against the enzyme MAO-A are also reported to have anti-inflammatory and anticancer activity. Apigenin, 5,7,4′-trihydroxyflavone, also a flavonoid, have reported anti-cancer activity (Meng *et al*., 2017; Bo and Zaho, 2017) whereas, Luteolin (5,7,3′,4′-tetrahydroxyflavone), is also reported to have anti-inflammatory, chemo preventive, chemotherapeutic function (Jiang *et al*., 2018; Wang *et al*., 2017).

Scutellarein has also been reported to inhibit cancer cell metastasis and demonstrated significant anticancer activity in human colon cancer cell lines and has role in the treatment of cancer (Ni *et al*., 2018; Chan *et al.,* 2019). But still further *in vitro* and *in vivo* studies are required to explore the role of these flavanoids as inhibitors of MAO-A, therefore, as potential cancer therapeutics.



2a) ZINC03869685 (Quercetin)



2b) ZINC03871576 (Apigenin)

Fig. 2: Docking of a) Quercetin b) Apigenin within the active site of MAO-A.(Docked ligands are presented in green color and hydrogen bonding with blue dashed line).

CONCLUSION

The main aim of the present study is to investigate the MAO-A inhibition potential of the compounds from African Medicinal plants and to find out the hits with high inhibition potential that can be used for the prevention/treatment of cancer by using the structure based drug designing approach.

During this study, Quercetin, Apigenin, Luteolin, [(2R,3S,4R,5S) 3,4,5 trihydroxytetrahydropyran-2-yl]methyl) and Scutellarein are predicted to be most potent inhibitors of MAO-A as they exhibited the highet docking score and mode of binding of these compounds is also compatible with binding site of MAO-A. Therefore, these compounds may serve as potential therapeutic leads in the development of clinically effective MAO-A inhibitors. Further, lead optimization and preclinical and clinical investigations on the above compounds are necessary to develop potential drug entity for the treatment of cancer.

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