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In silico assessment of chronic toxicity of a combination drug namely 'Olmesartan medoxomil and Hydrochlorothiazide', marketed in Bangladesh

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Abstract

Background: Nowadays combination therapy has become more popular due to their additional effect, synergistic effect and antagonistic effect. Any of these can influence the treatment profile. Combination therapy is used to treat some chronic diseases like diabetes, hypertension, cancer etc. But recently India has banned some fixed dose drug combinations due to their increased chances of adverse drug effects and drug interactions. So it is the time to take a look on the present drug combinations available in Bangladesh. An in silico study may provide important information about their probable toxicities. Drugs available in the combination may deposit slowly in the body and may lead to toxicities. Here an antihypertensive drug combination 'Olmesartan medoxomil and Hydrochlorothiazide' had been studied.

Results: Olmesartan medoxomil and Hydrochlorothiazide have not been found to comply any similar protein to interact with each other, thus no possible chance of additional toxicity of the combination in case of long term use.

Conclusions: At first, using PubChem the ligand was searched for a canonical SMILE. By inputting the canonical SMILE in Protox, a basic information about toxicities was predicted. From Swiss Target Prediction, target proteins responsible for both efficacy and toxicity were identified. These protein structures were downloaded from Protein Data Bank and edited with Flare. Undesired amino acid, ligand–ligand complex, fatty acid, and water molecules were removed by PyMOL. Structurally modified proteins and ligands were inputted in Swiss PDB viewer for energy minimization. Energy minimization is a very important step because unfavorable bond length, bond strength and torsion angle between protein and ligand may interfere with docking procedure. Then docking between Olmesartan medoxomil (ligand) and the proteins responsible for efficacy and toxicity was performed by PyRx. Vina binding affinity provided the value of binding strength between the ligand and the proteins, which determines how strong the bond is. The more negative the vina binding affinity, the stronger the bond. Discovery studio software was used to visualize the docking complexes. Same steps were followed for Hydrochlorothiazide to identify proteins responsible for desired and undesired effects, but no toxic effect was found from protox.

Keywords: Combination therapy, Molecular docking, In silico method, Vina binding affinity

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Background

Combination therapy, also known as polytherapy indicates the use of two or more therapeutic agents for treating a disease condition with the moto to provide better

treatment [1]. 'Polypharmacy' is a related term, that also means using multiple drugs whether for treating the same or separate medical conditions. The term 'Polymedicine' is also used for the similar meaning. It is believed that the combined drugs may show additional or synergistic effect to treat the disease better than any of those drugs could alone do. A combination therapy shows its effect by three mechanisms. Those are synergism, additive effect and antagonism. Among them synergism is the most desired effect, where the combined effect of the drugs is higher than their individual effects [2]. When the combined effect is the simple sum of the individual effects of those drugs, the condition is known as additive effect [2]. Finally, antagonism means the condition when the combined effect is less potent than the sum of individual potency of each drugs, that has been predicted. Combinations are now popular because of some reasons like with different mechanism of actions the drugs show the similar effect to treat the disease, drug resistance can be minimized and cost minimization. Another important fact is that when drugs are given in combination they are given in decreased dose, so toxicity of each drug decreases [2]. There are some disadvantages of combination therapy like in fixed dose combinations the dose is inflexible and their conflicting pharmacokinetics. Another one is that If two drugs interact with the same protein, by binding with which each of the drugs or their active metabolites show toxicity, then the combination may cause a great harm to the patients [2]. And if the combination is given for long term use, then these factors should be considered. India has banned 344 FDCs including the combination 'Olmesartan + Hydrochlorothiazide + Clorthalidone' because of toxicity observed, that is sudden reduction in blood pressure which leads to hypotension [3]. 'Olmesartan medoxomil + Hydrochlorothiazide' is a very popular combination that is available in Bangladesh. Not only in Bangladesh, this combination is highly used all over the world for treating hypertension. As 'Olmesartan medoxomil + Hydrochlorothiazide' combination is close to 'Olmesartan + Hydrochlorothiazide + chlorthalidone' combination, it had been considered for predicting toxicity.

Olmesartan medoxomil is a nonpeptide angiotensin receptor blocker (ARB), which selectively and competitively inhibits type I angiotensin II receptor without affecting other receptors of the cardiovascular system. The type I angiotensin receptor is responsible for vasoconstriction and elevation of blood pressure. Olmesartan medoxomil is a prodrug that is rapidly converted to Olmesartan inside the body [4]. Olmesartan is a highly protein bound drug that has a low volume of distribution [4]. Hydrochlorothiazide belongs to a class of drugs known diuretics or water pills. Though the actual mechanism of

action is not known yet, it is found to make more urine and inhibits the reabsorption of Na and Chloride in the distal tubules causing increased excretion of Na and water, Potassium and Hydrogen ions. So blood volume decreases and results in reduction of blood pressure [5].

Computer Aided Drug Design (CADD) is a computational technique that aims to make a link between information technology and chemistry [6]. New drug molecules can be designed, analyzed, developed by using this technology. CADD can be of two types [6]:

1. Structure based drug design (SBDD)
2. Ligand based drug design (LBDD)

Molecular docking is a tool in CADD that is used to predict the binding mode between a ligand and a target protein. The binding between a ligand and a protein is docked and is generally used in structure based drug design (SBDD) to predict both strength and type of signal produced [7, 8]. Docking also provides information about binding affinity of the ligand to the protein, protein bound conformation and free energies of binding for small molecule ligands (drugs) to macromolecular targets (proteins) [8]. For virtual screening and understanding the function of the target, single docking experiments are useful. But in case of identifying new inhibitors for the purpose of drug development, a large number of compounds are docked and ranked [8].

Methods

Molecular docking is used to determine the binding characteristics between a ligand and a protein [8]. A large number of tools are available for this purpose but in this study only a few of those was used. Several websites and softwares are included in this process. These all are used step by step and the list is given bellow:

PubChem (https://pubchem.ncbi.nlm.nih.gov/), Protox (http://tox.charite.de/protox_II/), Swiss target prediction (http://www.swisstargetprediction.ch/), RCSB Protein Data Bank (https://www.rcsb.org/), Flare, PyMol, Swiss PDB, PyRx.

Here the combination 'Olmesartan medoxomil & Hydrochlorothiazide' had been considered. Two drugs could not be taken at a time, so the same procedures were separately followed for both drugs one by one. First, the drug 'Olmesartan medoxomil' had been considered. From PubChem the structure of Olmesartan medoxomil had been searched and the 'Canonical SMILES' had been copied [9, 10]. That is:

> CCCC1=NC(=C(N1CC2=CC=C(C=C2)
> C3=CC=CC=C3C4=NNN=N4)C(=O)
> OCC5=C(OC(=O)O5)C)C(C)(C)O

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The SMILES had been pasted in Protox [11]. From protox, informations about probable toxicities that might be showed by the drug had been obtained. It had been seen that the drug has active immunotoxicity (probability 0.96) [11]. After that Swiss Target Prediction had been used [12]. By pasting that canonical SMILES in the search option, the names of the proteins with which the drug might interact and the probabilities of those bindings had been observed [12]. A long list containing about 68 proteins had been obtained. Some of these proteins are responsible for the drug's desired effect. By binding with these proteins 'Olmesartan medoxomil' shows its hypertension lowering effect. But simultaneously the drug also binds with some other proteins in the system, that may not show any beneficial effect that enhances its' quality and acceptability as an antihypertensive drug. Among these proteins two proteins had been considered for docking purpose using Autodock Vina [13]. Those two proteins are:

I. Tyrosine-protein kinase JAK2
II. Angiotensin II receptor

From Protox it had been known that the drug might show immunotoxicity. After searching about the proteins with which the drug binds and might cause immunotoxicity had been identified then cleaned and saved properly. Those are:

1. Caspase-8
2. COX-2
3. ADAM-17
4. Complement Factor-D
5. Endothelin receptor ET-B
6. Caspase-3

The 3D structures of these proteins had been downloaded from Protein Data Bank with resolution of 2–2.5 Å [14]. But those raw structures cannot be used for docking purpose. These structures not only consist of the desired protein portions but also some unnecessary spaces, amino acids, fatty acids, water molecules, other side molecules. So before using these for docking these unnecessary portions should be cleaned. This can be done by using PyMol software [15]. Sometimes while downloading any protein structure from the Protein Data Bank, the exact protein structure is not found. Rather the protein may be found in a complex form with other ligand that is not of our interest or protein–protein complex may also be found. In those cases, the software named Flare is used to edit the protein–ligand complex or protein–protein complex. The unnecessary ligand portion or protein chain

is cut down from the desired protein portion. After doing all these processes a cleaned form of the desired protein is saved for further use. The cleaned protein structures had been opened in swiss PDB and energy minimization had been done so that the docking can be done properly [16]. Energy minimization is done to reduce the potential energy of the protein and ligand. The bond lengths and bond strengths inside the protein makes the protein and ligand unstable. So energy minimization is done prior to docking to get the optimal binding of the desired ligand with the desired protein [17]. As docking cannot be done in both cases when the protein's or ligand's size is either too big or too small. In maximum cases ligands are of small size, that's why energy minimization is not done in case of ligands. So in most of the cases energy minimization is done only for the proteins to make them stable [17]. These energy-minimized proteins had been saved for the next docking purpose. After preparing all target proteins and ligand, pyRx software had been used for the docking purpose [18]. Each protein had been docked with the ligand (Olmesartan medoxomil) and the result had been observed and interpreted properly (Figs. 1, 2, 3, 4, 5, 6).

All the procedures that had been followed for Olmesartan medoxomil, once again those had been used step by step for Hydrochlorothiazide to determine the target proteins, by binding with which of them Hydrochlorothiazide shows intended effect and with which it shows toxicity. But no toxicity profile was found in case of Hydrochlorothiazide [11].
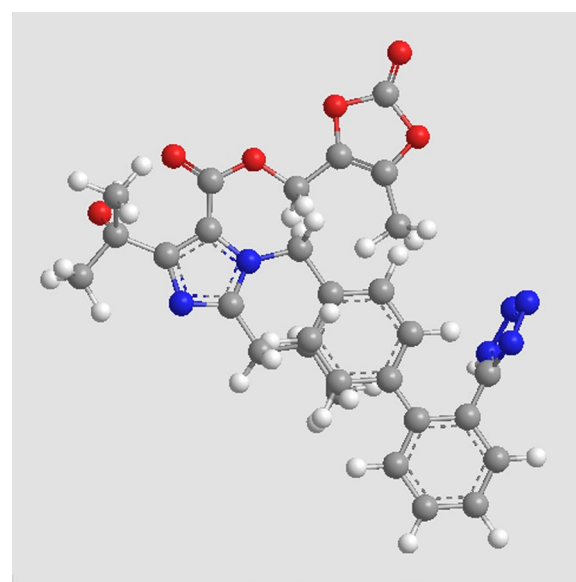
Fig. 1 Structure of Olmesartan medoxomil
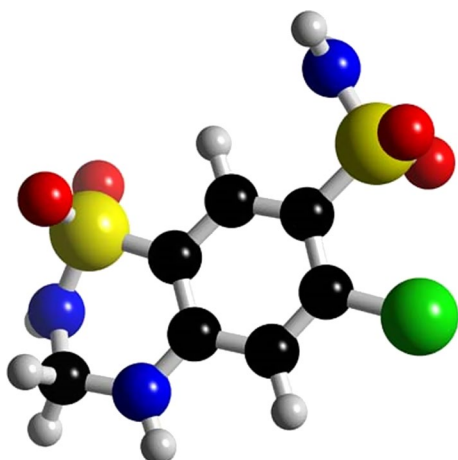
Fig. 2 Structure of Hydrochlorothiazide

Result

The goal of molecular docking is to understand and predict molecular recognition, finding likely binding modes both structurally and energetically, predicting binding affinity. For predicting toxicity of a combination drug, firstly each drug molecule needs to be considered separately and their basic characteristics should be known like volume, mass, H bond donor, H bond acceptor, Log P (Table 1; Figs. 7, 8, 9, 10 and 11).

Efficacy profiling of Olmesartan medoxomil

Among the proteins that been identified for being responsible for showing intended effect of Olmesartan medoxomil after binding to it, two proteins had been docked with Olmesartan medoxomil for knowing the binding affinity. The software named autodock vina in PyRx had been used for this purpose.

Autodock vina in PyRx- Python prescription 0.8, is a virtual screening software for computational drug discovery that can be used to screen libraries of compounds against potential drug targeted [19]. Pyrx enables medicinal chemists to run virtual screening from any platform and helps users in every step of this process- from data preparation to job submission and analysis of the results.

| Original author	Warren Lyford DeLano
Developer	Schrödinger, Inc
Initial release	2000; 20 years ago
Stable release	2.3.2/17 May 2019; 11 months ago
Written in	C, C++, Python
Operating system	Cross-platform: macOS, Unix, Linux, Windows
Platform	IA-32, x86-64
Available in	English
Type	Molecular modelling
License	Python
Website	pymol.org/

Toxicity Model Report

| Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.50
Toxicity end points	Carcinogenicity	carcino	Inactive	0.59
Toxicity end points	Immunotoxicity	immuno	Active	0.96
Toxicity end points	Mutagenicity	mutagen	Inactive	0.58
Toxicity end points	Cytotoxicity	cyto	Inactive	0.66
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.88
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.93
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.95
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.94
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.94
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.82
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.93
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.98

Fig. 3 Basic idea about toxicity of Olmesartan medoxomil from Protox

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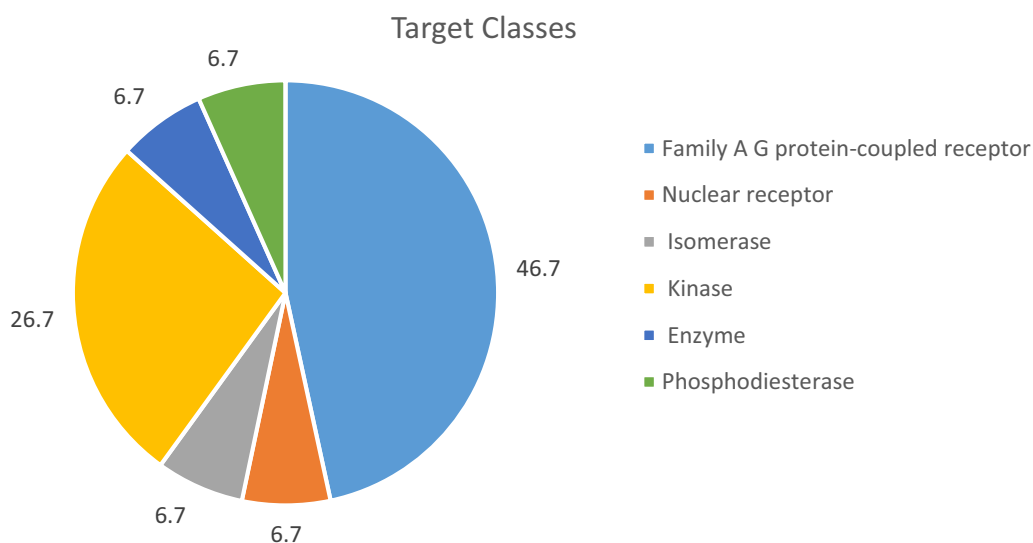
Fig. 4 A pie chart representing the target classes of enzymes with which Olmesartan medoxomil interact
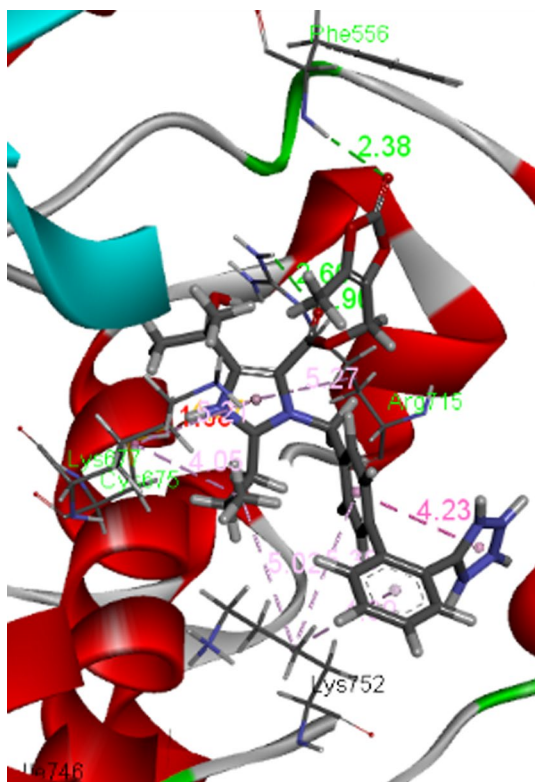
Fig. 5 Docking of Tyrosin protein kinase JAK2 and Olmesartan medoxomil
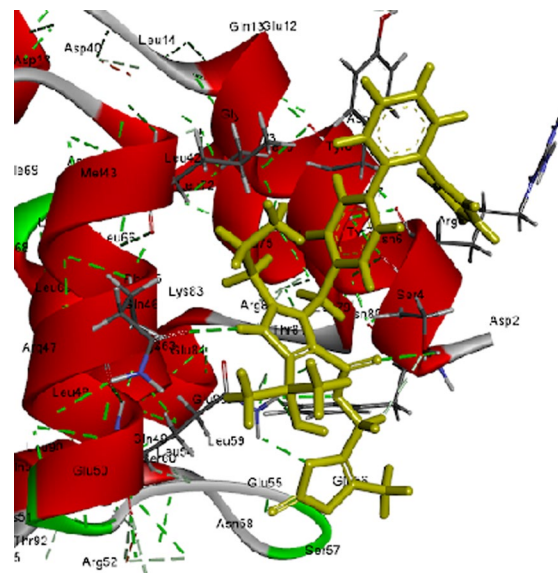
Fig. 6 Various bonds of Tyrosine-protein kinase JAK2 with different amino acids

Toxicity profiling of Olmesartan medoxomil

Caspase-8 and COX-2 are two proteins, binding with which Olmesartan medoxomil shows immunotoxicity. Using Autodock Vina, docking of Olmesartan medoxomil (ligand) had been done with both Caspase-8 and COX-2 (proteins). The amino acid sequence of Caspase-8 and the specific amino acids with which Olmesartan medoxomil can bind, had been identified from PyMol (Tables 3, 4).

Tyrosine-protein kinase JAK2

See Table 2.

Table 1 Molecular characteristics of Olmesartan medoxomil and Hydrochlorothiazide

Compound	Volume (cm³)	Mass (amu)	H bond donor	H bond acceptor	Log P
Olmesartan medoxomil	403.5 ± 7.0	558.2	4	7	5.23
Hydrochlorothiazide	175.8 ± 3.0	297.7	2	10	− 0.07

Volume, mass, H bond donor, H bond acceptor, Log P are some basic characteristics of these drugs


Fig. 7 Docking of Caspase-8 and Olmesartan medoxomil

Fig. 8 Various bonds of caspase 8 with different amino acids
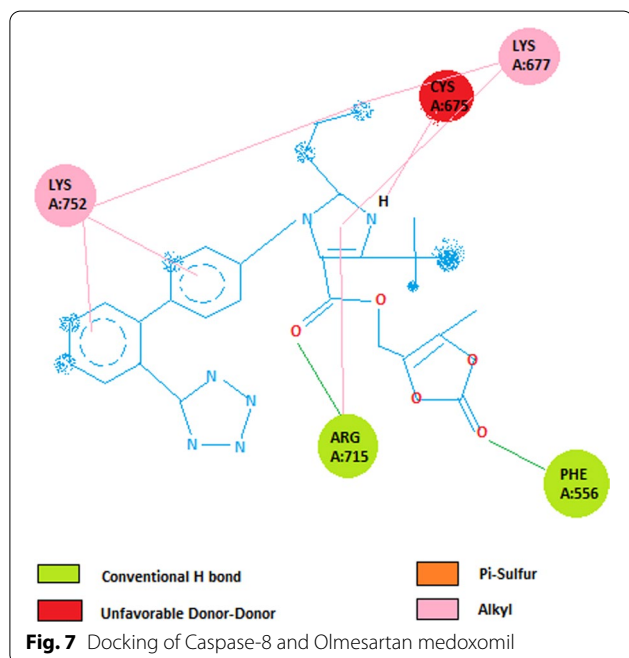
Amino acid sequence of Caspase-8

DFSRNLYDIGEQLDSEDLASLKFL**SLDY**IPQRKQEPIK-
DALMLFQRLQEKRMLEESNLSFLKELLFRINRLDLLI-
TYLNTRKEEMERELQTPGRAQISAYRVMLYQISEEVS-
RSELRSFKFLLQEEISKCKLDDDMNLLDIFIEMKR-
VILGEGKLDILKRVCAQINKSLLKIINDYEE

(Bold marked amino acids represent that Olmesartan medoxomil interacts with these amino acids.) (Tables 5, 6).

Amino acid sequence of COX-2

GAPTPVNPCCYYPCQ**HQ**GICVRF**GLD**RYQCDC-
TRTGYSG**PN**CTIPGLWTWLRNSLRPSPSFTHFLLTH-
GRWFWEFVNATFIREMLMRLMRLVLTVRSNLIP-
SPPTYNSAHDYISWESFSNVSYYTRILPSVPKDCPT-
PMGTKGKKQLPDAQLLARRFLLRRKFIPDPQGTN-
LMFAFFAQHFTHQFFKTSGKMGPGFTKALGHG-
VDLGHIYGDNLERQYQLRLFKFGKLKYQVLDGE-
MYPPSVEEAPVLMHYPRGIPPQSQMAVGQEVF-
GLLPGLMLYATLWLREHNRVCDLLKAEHPTWGD-
EQLFQTTRLILIGETIKIVIEEYVQQLSGYFLQLKFD-

Fig. 9 Docking of COX-2 and Olmesartan medoxomil

Fig. 10 Various bonds of COX2 with different amino acids
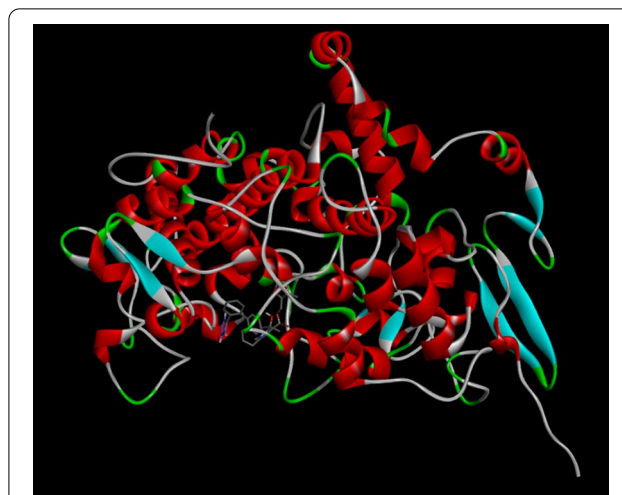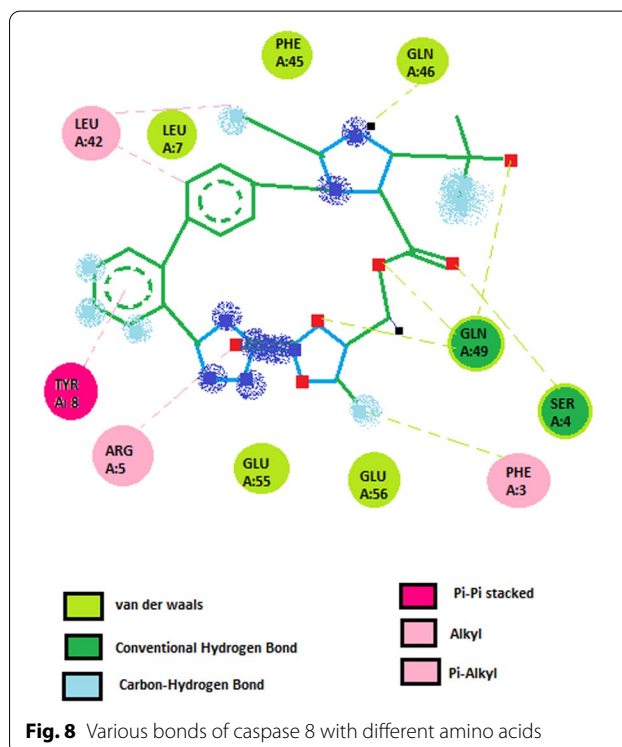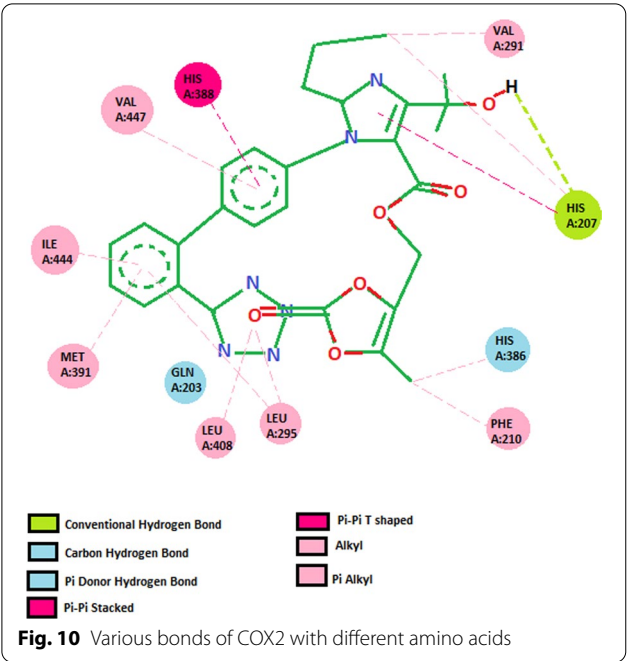
PELLFGVQFQYRNRIAMEFNHLYHWHPLMPDS-
FKVGSQEYSYEQFLFNTSMLVDYGVEALVDAFSR-
QIAGRIGGGRNMDHHILHVAVDVIRESREMRLQP-
FNEYRKRFGMKPYTSFQELVGEKEMAAELEELYG-
DIDALEFYPGLLLEKCHPNSIFGESMIEIGAPFSLK-
GLLGNPICSPEYWKPSTFGGEVGFNIVKTATLKKLV-
CLNTKTCPYVSFRVPD

(Bold marked amino acids represent that Olmesartan medoxomil interacts with these amino acids.)

Comparison
See Table 7.

Discussion
Docking, an in silico method, provides a basic idea about a drug's interaction to proteins. Caspase-8 and COX-2 are two proteins, binding with which Olmesartan medoxomil shows immunotoxicity. Using Autodock Vina, docking of Olmesartan medoxomil (ligand) had been done with both Caspase-8 and COX-2 (proteins). The amino acid sequence of Caspase-8 and the specific amino acids with which Olmesartan medoxomil can bind, had been identified from PyMol. The energy which is released by bond formation and/or during interaction of the ligand and protein is termed in form of binding energy. For a favourable reaction, the free energy is negative. The binding of the ligand and protein becomes better if the binding energy is less in magnitude. In Autodock Vina, binding energy has been used to find out the ligand that shows stable complex interaction with protein (e.g. enzyme) [22]. And, the ligand-receptor complex will be more stable if it has more negative value or lower binding affinity. After docking of Olmesartan medoxomil with Caspase-8 and COX-2, in between Caspase-8 and COX-2, Olmesartan medoxomil had been found to have lesser binding energy with COX-2. That means, Olmesartan medoxomil binds more strongly with COX-2 than Caspase-8, and

| Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.92
Toxicity end points	Carcinogenicity	carcino	Inactive	0.86
Toxicity end points	Immunotoxicity	immuno	Inactive	0.94
Toxicity end points	Mutagenicity	mutagen	Inactive	0.96
Toxicity end points	Cytotoxicity	cyto	Inactive	0.69
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	1.0
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.99
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.99
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.99
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.99
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	1.0

Fig. 11 Toxicity prediction of Hydrochlorothiazide from Protox

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Table 2 2D and 3D structure of docked Olmesartan medoxomil and Tyrosine-protein kinase JAK2 receptor

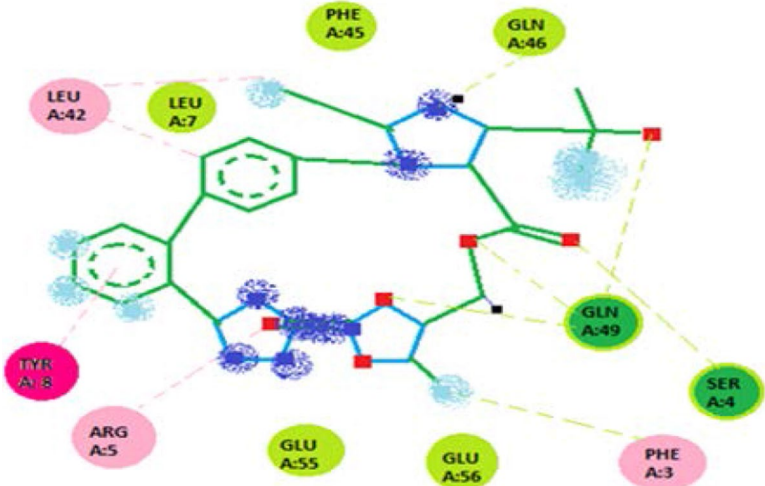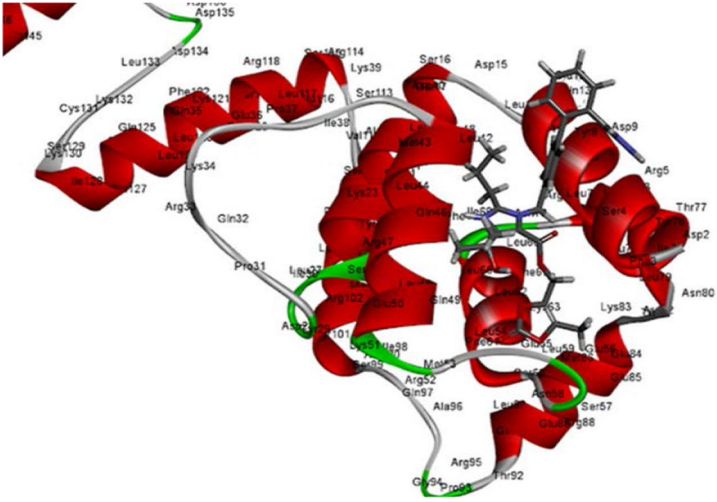| Docking of Tyrosine-protein kinase JAK2 receptor with Olmesartan medoxomil	
Vina Binding Affinity	− 8.5
rmsd/ub and rmsd/lb	Both are 0
2D structure	
3D structure	
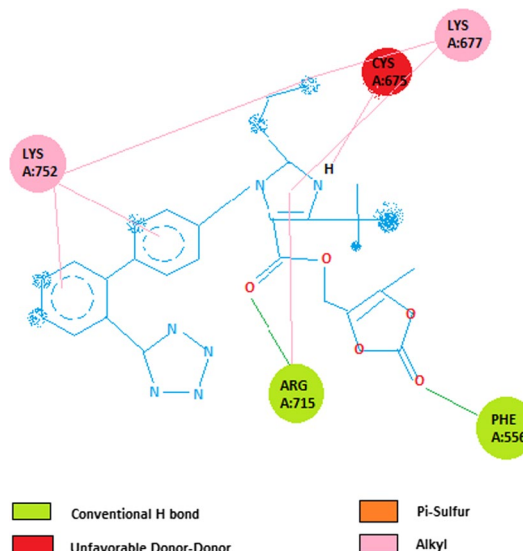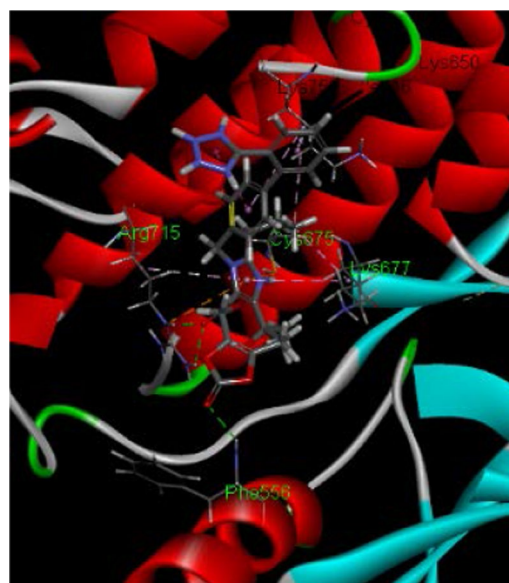
Vina binding affinity is − 8.5

shows immunotoxicity. But Hydrochlorothiazide had not been found to have any toxicity from Protox, so no docking had been done with any protein. Again from Swiss Target Prediction, the name of proteins had been found with which Hydrochlorothiazide interacts. It had been seen that there is no common protein with which both Olmesartan medoxomil and Hydrochlorothiazide interact. The toxicity of the combination 'Olmesartan medoxomil & Hydrochlorothiazide' is the combined toxic effect of Olmesartan medoxomil and Hydrochlorothiazide. As Hydrochlorothiazide had not been found to have any toxicity and common protein with which Olmesartan medoxomil interacts, the ultimate toxicity of the combination is the toxicity that is possessed by Olmesartan medoxomil. So this combination had been considered not to have any additional toxicity except that had been found in case of Olmesartan Medoxomil alone.

Table 3 2D and 3D structure of docked Olmesartan medoxomil and Caspase-8

Docking of Caspase-8 with Olmesartan medoxomil	
Vina binding affinity	− 7.1
rmsd/ub and rmsd/lb	0.533
2D structure	

3D structure	

Vina binding affinity is − 7.1 and RMSD value is 0.533 [20, 21]

Table 4 Docking of Caspase-8 with Olmesartan medoxomil

| Sl No	Type of amino acid	Full name	Hydrophobicity	pKa	Avg. isotopic displacement
1	Serine	A:Ser26	− 0.8		48.166
2	Leucine	A:Leu27	3.8		51.52
3	Aspartic acid	A:Asp28	− 3.5	3.9	52.136
4	Tyrocine	A:Tyr29	− 1.3	10	63.487

Conclusion

Proteins are responsible for any functions in the body, either beneficial or deleterious. Drugs also show their effects by binding with relevant receptor proteins. Activation of one protein may influence the action of another protein. That's why polypharmacy or

Table 5 2D and 3D structure of docked Olmesartan medoxomil and COX-2

Docking of COX-2 with Olmesartan medoxomil	
Vina binding affinity	− 8.3
rmsd/ub and rmsd/lb	0.472
2D structure	
3D structure	
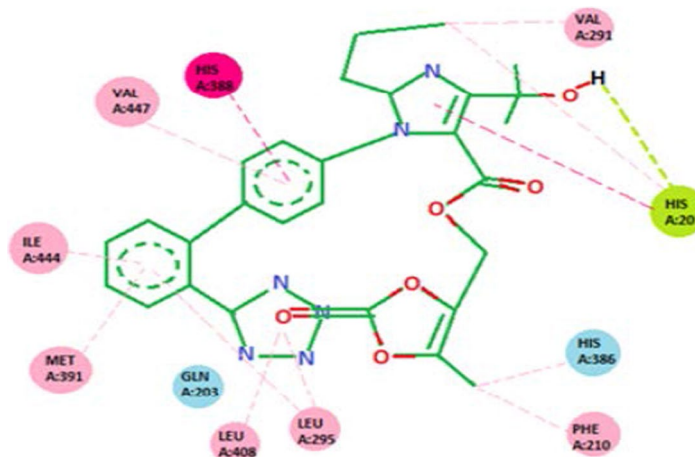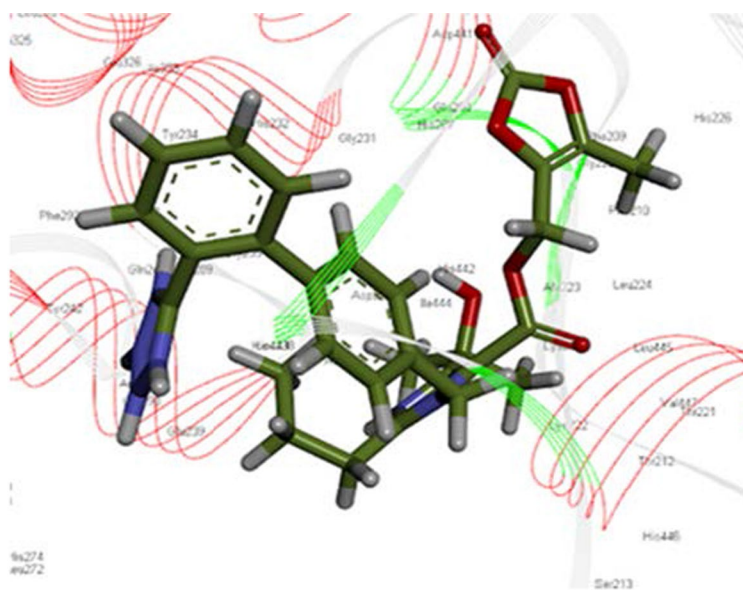
Vina binding affinity is − 8.3, and RMSD value is 0.472 [20, 21]

combination therapy needs special consideration, as two or more drug works inside the body at the same time. A computer based system can help deciding either a drug combination is safe or not by providing data based knowledge about it. Here we studied about a well-used drug combination 'Olmesartan medoxomil and Hydrochlorothiazide'. It had been found that Olmesartan medoxomil binds with about 68 proteins, and Hydrochlorothiazide binds with about 13 proteins. But there is not a single protein in common with which both of these drugs are interacting. Again we had seen that

Olmesartan medoxomil might show immunotoxicity by interacting with 6 proteins, it had been possible to dock the drug with 2 of those proteins. But hydrochlorothiazide had been found to be a safe drug, as Protox did not show any toxicity prediction. So, it can be said that the combination 'Olmesartan medoxomil & Hydrochlorothiazide' is safe. If chronically used Olmesartan medoxomil may show immunotoxicity, but hydrochlorothiazide is not anyhow responsible in promoting this toxicity. If Olmesartan medoxomil is given alone chronically as a drug, it may also show immunotoxicity in the

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Table 6 Docking of COX-2 and Olmesartan medoxomil

Sl No	Type of amino acid	Full name	Hydrophobicity	PKa	Avg. isotopic displacement
1	Histidine	A:His43	− 3.2	6	94.488
2	Glutamine	A:Gln44	− 3.5		86.792
3	Glycine	A:Gly51	− 0.4		93.47
4	Leucine	A:Leu52	3.8		95.75
5	Aspartic acid	A:Asp53	− 3.5	3.9	90.929
6	Threonine	A:Thr60	− 0.7		88.487
7	Arginine	A:Arg61	− 4.5	12	87.718
8	Proline	A:Prp67	− 1.6		89.393
9	Asparagine	A:Asn68	− 3.5		98.224

Table 7 Comparison between efficacy profiling and toxicity profiling of Olmesartan medoxomil

Drug-1			Drug-2		
Olmesartan medoxomil			Hydrochlorothiazide		
Protein	Group	Vina binding affinity	Protein	Group	Free energy
Tyrosine protein kinase JAK2 receptor	Efficacy	− 8.5	Carbonic amhydrases	Efficacy	N/A
Caspase-8	Toxicity	− 7.1	Glutamate receptor ionotropic, AMPA 1, AMPA 2	Efficacy	N/A
COX-2	Toxicity	− 8.3			

patients. But the combination 'Olmesartan medoxomil & Hydrochlorothiazide' shows better effect in reducing blood pressure than only 'Olmesartan medoxomil'. So using the combination will be preferable for hypertension patients, as the combination had not been found to produce any additional toxicity. Rather, using this combination increases the antihypertensive effect by working synergistically.

Abbreviations
FDC: Fixed dose combination; ARB: Angiotensin receptor blocker; CADD: Computer aided drug design; SBDD: Structure based drug design; LBDD: Ligand based drug design; PDB: Protein Data Bank; RMSD: Root mean square deviation; COX: Cyclooxygenase.

Authors' contributions
The idea of performing this research and designing of methodology came from MSR and SKK. All authors contributed equally to perform the analysis and to collect experimental data under the supervision of SKK. Data analysis was conducted by MSR and RT. The draft manuscript was prepared by MSR with the assistance of SKK, BKS and RT. SKK critically reviewed the manuscript. All authors read and approved the final manuscript.

Availability of data and materials
The datasets used and/or analyzed during the study are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests to conduct the study.

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