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In Silico Approach For Detection Of The Effect Of *UGT1A1* Polymorphisms On Telmisartan Response

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Abstract: Hypertension is a cardiovascular disease that manifests itself with a continuous increase in systemic arterial blood pressure and can lead to serious complications over time. It is estimated that 37% of hypertensive patients receive treatment and one-third of them are under control. Telmisartan is an angiotensin receptor blocker used in the treatment of hypertension. Uridine 5'-diphospho-glucuronyltransferase 1 (UGT1A1) gene encodes the Uridine 5'-diphospho-glucuronyltransferase (UGT) enzyme and metabolizes the telmisartan. Single nucleotide polymorphisms cause amino acid, protein structure, and function to change. These changes affect the drug response and therapy. Polymorphisms of the UGT1A1 gene (rs4148323, rs28934877) cause telmisartan resistance. In this study, the SWISS-MODEL database and Chimera 1.15 ver. Programs were used to create homology models. The HOPE database was used to calculate the damage of mutation on protein structure and show the mutation effects on protein. The HDock server was used to demonstrate interactions between telmisartan and wild-type protein and, mutant type protein. It was detected that the mutant residue of *UGT1A1* (rs4148323) is located in an important domain for protein activity. Mutation might disturb the protein function. rs28934877 is likely damaging to the protein. These mutations cause the loss of interactions and affect the drug response. By docking analysis, Telmisartan drug interactions were shown between wild and mutant types protein Possible drug conformation is designed for the effective treatment of patients carrying the common mutation.

Keywords: Telmisartan; docking; Single nucleotide polymorphism (SNP); hypertension; *UGT1A1; in silico*

1 Introduction

Hypertension is the third leading cause of death in the world and causes 12,8% of adult deaths (https://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en). It is estimated that 9,4 million individuals die because of hypertension and complication related to hypertension (http://www.who.int/). It has been shown by the World Health Organization data that 45% of deaths due to heart diseases and 51% due to stroke in developing countries are caused by hypertension (Kılıc et al. 2016). Moreover WHO predicts that the prevalence of hypertension will reach 29,2%, and the number of patients with hypertension will be 1.56 billion worldwide in 2025 (WHO 2015 http://www.who.int/ Accessed: 14.08.2022).

Hypertension is defined as the high pressure exerted by the blood in the blood vessels against the vessel wall. If this high blood pressure continues for a long time, this causes damage to the vessel. If a person measures diastolic blood pressure higher than 90 mmHg and systolic blood pressure higher than 140 mmHg in three different measurements, this will be enough to define hypertension (Martinez-Quinones et al. 2018).

Many risk factors may cause the development of hypertension in a person. The risk of hypertension increases with advancing age (Huang et al. 2018). Family stories may also affect the development of hypertension risk. Being overweight, do not perform physical activity, or smoking tobacco are also considered risk factors for the development of hypertension (Papathanasiou et al. 2015). Molecular genetic studies show that hypertension is an inherited disease. Genetic and environmental factors are responsible for the development of hypertension (Ding et al. 2018).

There are pharmacological and nonpharmacological approaches to hypertension therapy. Telmisartan is a pharmacological approach for the hypertension therapy. It is a nonpeptide molecule. Its molecular weight is 514.63. It has a pH between three and nine and is soluble in strong bases (Sweetman, 2007). Telmisartan is an angiotensin receptor

blocker used in the treatment of hypertension (Sharpe et al. 2001). It is well absorbed in the gastrointestinal tract. It is highly bound to plasma proteins. Telmisartan competes with angiotensin and antagonizes the binding of angiotensin to the receptor and thus its effects in the therapeutic concentration range. It has a longer-lasting effect because it more effectively suppresses Angiotensin-2, which is present in the blood and increases blood pressure in the body (Sweetman, 2007). Telmisartan relaxes blood vessels. Telmisartan has been used in the treatment of hypertension since the early 2000s.

Uridine 5'-diphospho-glucuronyltransferase (UDP-5'-diphospho glucuronyltransferase, UGT) is a phase II drug metabolizing enzyme. It catalyzes the glucuronidation of compounds ,and it transfers glucuronic acid from UDP-glucuronic acid to substrates (Dutton, 1980). The uridine 5'-diphospho-glucuronyltransferase 1 (*UGT1A1*) gene encodes the UGT enzyme. The *UGT1A1* gene contains 5 exons and is located on 2q37 (Ritter et al. 1992). The *UGT1A1* gene encodes the UGT enzyme and performs a chemical reaction called glucuronidation, preventing the accumulation of toxic waste in our bodies. Some genetic variations in *UGT1A1* reduce the enzymatic activity of UGT, which impairs the body's ability to detox and causes toxic substances to accumulate in the body. *UGT1A1* is one of the primary genetic variants responsible for reduced detox ability. UGT enzyme metabolizes the telmisartan in the body (Yamada et al. 2011). Glucuronidation of telmisartan was shown in Figure 1.

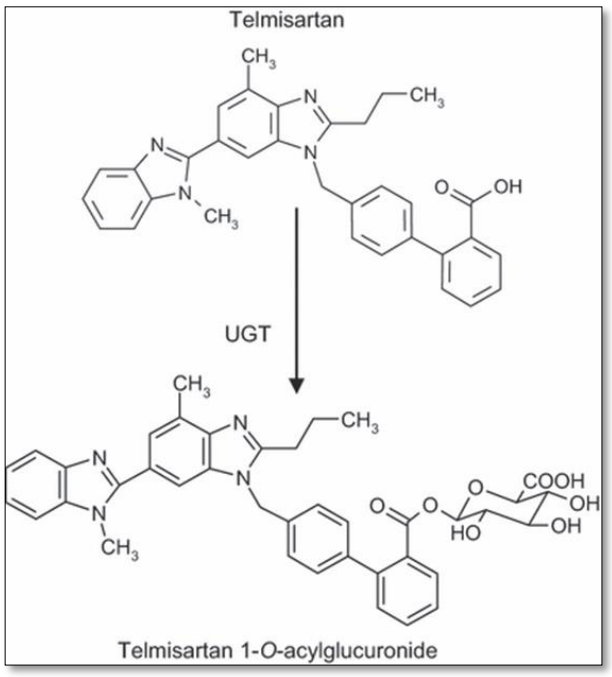

Fig 1. Glucuronidation of telmisartan (Ebner et al. 2012).

Lu Huang et al. found that genetic polymorphisms of *UGT1A1* (rs4148323) were effective on blood pressure and plasma telmisartan concentration in patients with hypertension (Huang et al. 2019). In the studies, it was determined that the rs28934877, rs34993780 mutation in the UGT1A1 gene plays an effective role in the development of hypertension, heart failure, and cardiac disorders, and increases the risk of developing heart failure and hypertension (Di et al. 2009; Zhang et al. 2012; Maruo et al. 2000). Studies on the subject show that mutations in the *UGT1A1* gene play a role in the development of hypertension (Bosma et al. 2003; Schewertner et al. 2008).

2 Materials and Method

2.1 Homology Modeling Databases

The Genebank database of the National Center for Biotechnology Information, USA, NCBI was used to detect pathogenic SNPs of the *UGT1A1* gene (https://www.ncbi.nlm.nih.gov/ Access date: 20.08.2022). Two SNPs (rs4148323, rs28934877) were selected to relate hypertension and Telmisartan response on the database. Genebank database of the National Center for Biotechnology Information, USA, NCBI serves the FASTA format of an amino acid sequence of the UGT1A1 gene (https://www.ncbi.nlm.nih.gov/ Access date: 20.08.2022). The amino acid sequence of wild type and mutant types were shown in Table 1.

Table 1. The amino acid sequence of wild-type and mutant types (https://www.ncbi.nlm.nih.gov/ Access date: 20.08.2022).

UGT1A1

MAVESQGGRPLVLGLLLCVLGPVVSHAGKILLIPVDG
SHWLSMLGAIQQLQQRGHEIVVLAPDASLYIRDGAFY
TLKTYPVPFQREDVKESFVSLGHNVFENDSFLQRVIK
TYKKIKKDSAMLLSGCSHLLHNKELMASLAESSFDV
MLTDPFLPCSPIVAQYLSLPTVFFLHALPCSLEFEATQ
CPNPFSYVPRPLSSHSDHMTFLQRVKNMLIAFSQNFL
CDVVYSPYATLASEFLQREVTVQDLLSSASVWLFRSD
FVKDYPRPIMPNMVFVGGINCLHQNPLSQEFEAYINA
SGEHGIVVFSLGSMVSEIPEKKAMAIADALGKIPQTVL
WRYTGTRPSNLANNTILVKWLPQNDLLGHPMTRAFIT
HAGSHGVYESICNGVPMVMMPLFGDQMDNAKRMET
KGAGVTLNVLEMTSEDLENALKAVINDKSYKENIMR
LSSLHKDRPVEPLDLAVFWVEFVMRHKGAPHLRPAA
HDLTWYQYHSLDVIGFLLAVVLTVAFITFKCCAYGYR
KCLGKKGRVKKAHKSKTH

rs4148323

MAVESQGGRPLVLGLLLCVLGPVVSHAGKILLIPVDG
SHWLSMLGAIQQLQQRGHEIVVLAPDASLYIRD**R**AFY
TLKTYPVPFQREDVKESFVSLGHNVFENDSFLQRVIK
TYKKIKKDSAMLLSGCSHLLHNKELMASLAESSFDV
MLTDPFLPCSPIVAQYLSLPTVFFLHALPCSLEFEATQ
CPNPFSYVPRPLSSHSDHMTFLQRVKNMLIAFSQNFL
CDVVYSPYATLASEFLQREVTVQDLLSSASVWLFRSD
FVKDYPRPIMPNMVFVGGINCLHQNPLSQEFEAYINA
SGEHGIVVFSLGSMVSEIPEKKAMAIADALGKIPQTVL
WRYTGTRPSNLANNTILVKWLPQNDLLGHPMTRAFIT
HAGSHGVYESICNGVPMVMMPLFGDQMDNAKRMET
KGAGVTLNVLEMTSEDLENALKAVINDKSYKENIMR
LSSLHKDRPVEPLDLAVFWVEFVMRHKGAPHLRPAA
HDLTWYQYHSLDVIGFLLAVVLTVAFITFKCCAYGYR

KCLGKKGRVKKAHKSKTH

rs28934877

MAVESQGGRPLVLGLLLCVLGPVVSHAGKILLIPVDG
SHWLSMLGAIQQLQQRGHEIVVLAPDASLYIRDGAFY
TLKTYPVPFQREDVKESFVSLGHNVFENDSFLQRVIK
TYKKIKKDSAMLLSGCSHLLHNKELMASLAESSFDV
MLTDPFLPCSPIVAQYLSLPTVFFLHALPCSLEFEATQ
CPNPFSYVPRPLSSHSDHMTFLQRVKNMLIAFSQNFL
CDVVYSPYATLASEFLQREVTVQDLLSSASVWLFRSD
FVKDYPRPIMPNMVFVGGINCLHQNPLSQEFEAYINA
SGEHGIVVFSLGSMVSEIPEKKAMAIADALGKIPQTVL
WRYTGTRPSNLANNTILVKWLPQNDLLGHPMTRAFIT
HAGSHGVYESICNGVPMVMMPLFGDQMDDAKRMET
KGAGVTLNVLEMTSEDLENALKAVINDKSYKENIMR
LSSLHKDRPVEPLDLAVFWVEFVMRHKGAPHLRPAA
HDLTWYQYHSLDVIGFLLAVVLTVAFITFKCCAYGYR
KCLGKKGRVKKAHKSKTH

SWISS-MODEL was used to create homology modeling of *UGT1A1* (wild type, rs4148323, and rs28934877) (Waterhouse et al. 2018). Three-dimensional models were examined with the UCSF Chimera program, which is a visualization tool (Pettersen et al. 2004). The UCSF Chimera program was used to visualize the wild and mutant (rs4148323, and rs28934877) protein structures.

2.2. Bioinformatic Analysis Of Homology Models

HOPE was used for the detection of the structural effect of the mutation. HOPE shows the mutation effects, and calculates the probable damage of mutation on the protein structure. In this study, it was shown that UGT1A1 mutation affects protein structure by the HOPE database (Venselaar et al. 2010).

2.3. Molecular Docking Study

The docking method predicts the interactions between the conformation and orientation of the ligand structure and a target binding site. Docking studies are the most important methods for drug discovery. In drug resistance studies, docking has an important role to understand the interactions between drugs and the target region. As a result, new therapies can be developed by the docking method for drug resistance in patients. Three-dimensional (3D) structures are obtained for docking studies. Docking programs are used to obtain these 3D structures. In drug discovery studies, the HDock server is usually used (Yan et al. 2017). HDock uses a genetic algorithm. Genetic algorithms transfer the energy and geometry information of a newly formed conformation of the molecule to the next conformation and thus they are obtained optimal conformations. In this study, the HDock server was used for the molecular docking study of *UGT1A1* and telmisartan. (Yan et al. 2017).

3 Results

The amino acid sequence format which is used as a basis in bioinformatics studies was created based on the NCBI-P33261 accession number sequence.

SWISS-MODEL was used to obtain three-dimensional (3D) structures and homology modeling was performed by the Swiss-Model database and the Chimera program. UGT1A1 wild and rs4148323 and rs28934877 overlapping structures were shown in Figure 1 and Figure 2.

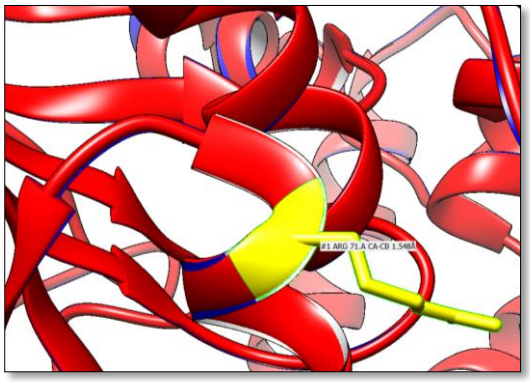

Fig 1. The ribbon structure of UGT1A1 wild-type and rs4148323 overlapping (Pettersen et al., 2004).

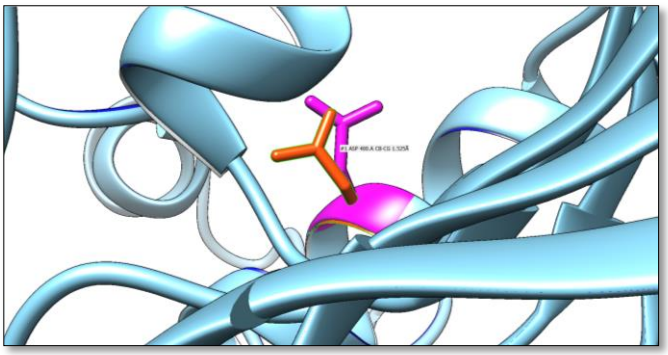

Fig 2. The ribbon structure of UGT1A1 wild-type and rs28934877 overlapping (orange is the wild type and purple is the mutant type amino acid) (Pettersen et al., 2004).

Schematic structures of the wild (left) and the mutant (right) amino acids for rs4148323 were shown in Figure 3.

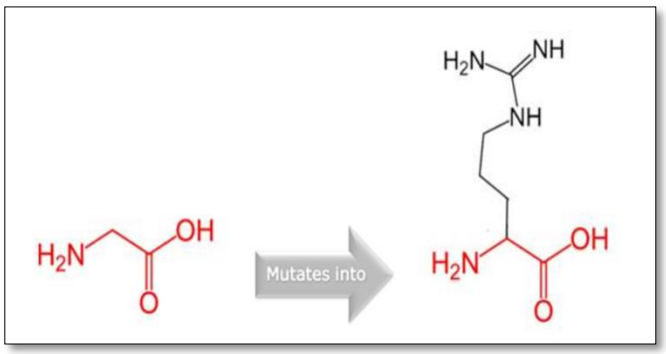

Fig 3. Schematic structures of the wild (left) and the mutant (right) amino acid (rs4148323) (Venselaar et al., 2010).

The wild-type residue is glycine and changes to Arginine at position 71 in the mutant type (rs4148323). While the wild-type residue charge had a NEUTRAL charge, the mutant residue charge was POSITIVE. It was detected that the wild-type residue was more hydrophobic than the mutant residue. Glycine is a wild-type residue and the most flexible residue. Flexibility plays an important role in protein function. Mutation of this glycine can abolish this function. These

results showed that the mutation is deleterious. The mutated residue is located in an important region for the protein's

main activity. Mutated residue might disturb the protein's main function (BMC Bioinformatics, 2010)

Schematic structures of the wild (left) and the mutant (right) amino acids for rs28934877 were shown in Figure 4.

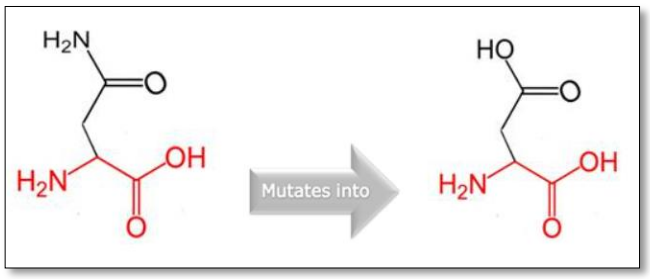

Fig 4. Schematic structures of the wild (left) and the mutant (right) amino acid (rs28934877) (Venselaar et al., 2010).

In rs28934877, the Asparagine amino acid was changed to an Aspartic acid at position 400. While the wild-type residue had a NEUTRAL charge, the mutant residue charge was NEGATIVE. It was detected that this mutation is probably damaging to the protein.

Amino acid changing was demonstrated in Figures 5 and 6 for rs4148323 and rs28934877.

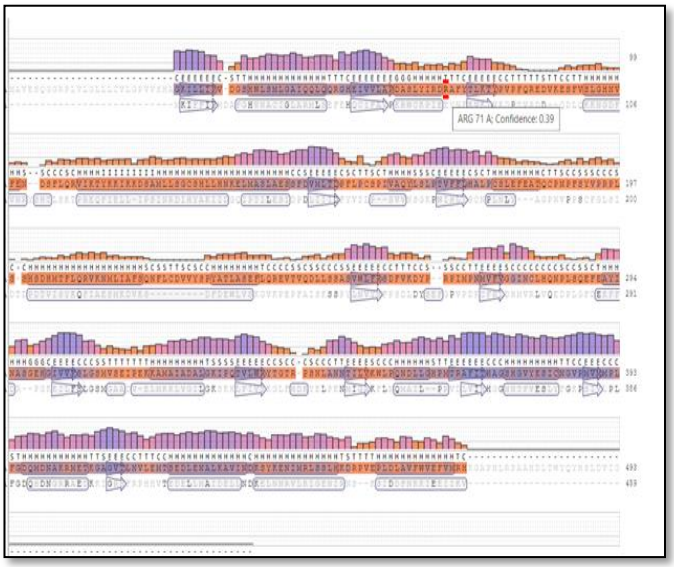

Fig 5. rs4148323 amino acid sequence and amino acid change (Pettersen et al. 2004)

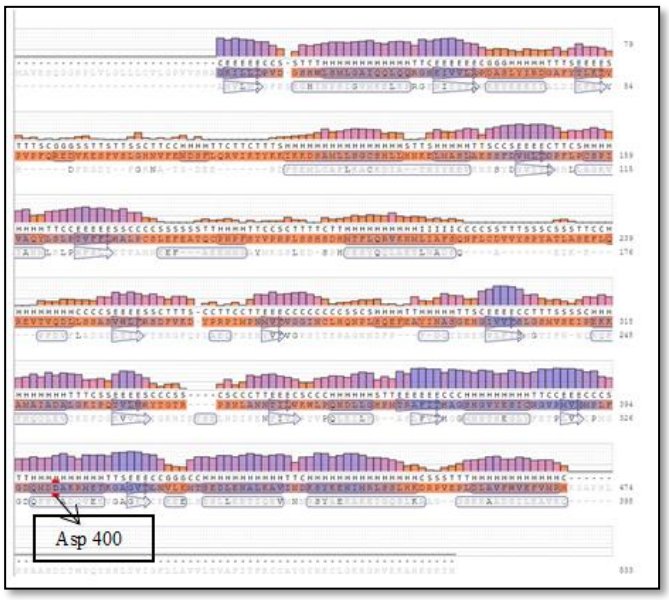

Fig 6. rs28934877 amino acid sequence and amino acid change (Pettersen et al. 2004)

HDock server and BIOVA Discovery Studio were used for the molecular docking study between telmisartan and UGT1A1. HDock and BIOVA Discovery Studio is used Bioinformatics-based methods to predict the structure and generate interactions (Yan Y. et al., 2017; https://3ds.com/productsservices/biovia/products).
Telmisartan docking results were shown in Figure 7-9.

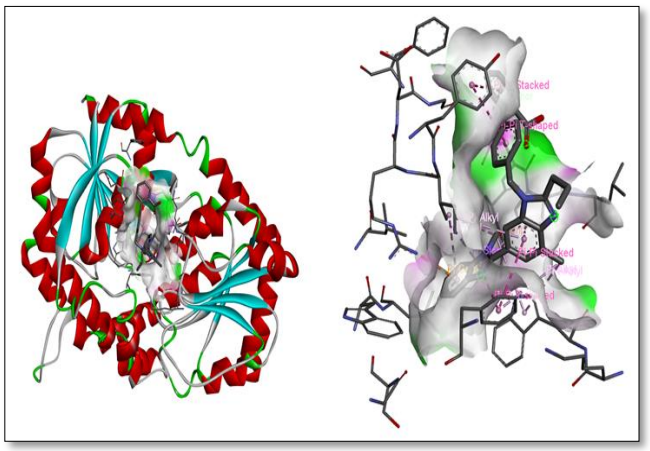

Fig 7. Visualization of the UGT1A1 (wild) complex and telmisartan docking via BIOVIA Discovery Studio (https://3ds.com/productsservices/biovia/products).

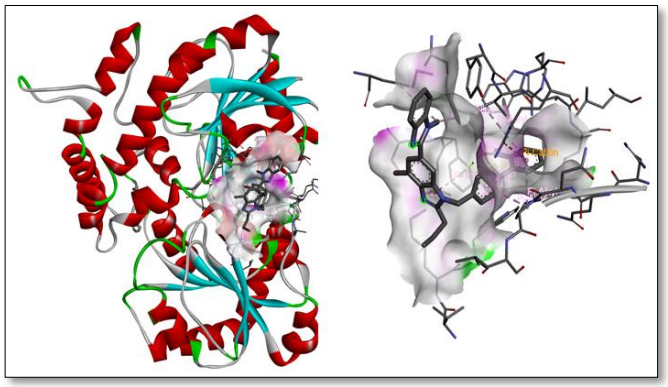

Fig 8. Visualization of the rs4148323 complex and telmisartan docking via BIOVIA Discovery Studio (https://3ds.com/productsservices/biovia/products).

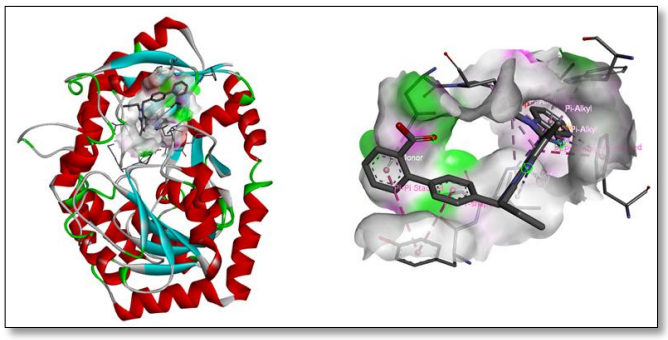

Fig 9. Visualization of the rs28934877 complex and telmisartan docking via BIOVIA Discovery Studio (https://3ds.com/productsservices/biovia/products).

4 Discussion

Telmisartan is a blocker of angiotensin II receptor . It is widely used in the treatment of hypertension in the clinic. Telmisartan is metabolised by UGTs (Shin HJ. et al., 2015). Variations of UGTs cause changes in protein structure. Because of this situation, it is thought that these changes affect drug interactions. Structural and confirmational changes caused by variations in the receptor can damage the function of the protein. Thus receptor-drug interactions may be impaired. Patients treated with drugs may show unresponsiveness to the drug due to damage caused by mutations. As a result, drug resistance may develop in patients.

In a study, Huang L. et al. detected that UGT1A1 mutations affected the bioavailability of telmisartan (Huang L. et al., 2019). UGT1A1 encodes the UGT enzyme, which is responsible for metabolizing the drug in the body. Mutations in UGT1A1 affect the coding and production of the enzyme. As a result, the metabolism of the drug also negatively affects this process. Pei Q. et al. also found that UGT1A1 variations affect the pharmacokinetics of telmisartan in Chinese patients (Pei Q. et al., 2017). Shin HJ. Et al. pointed out that Telmisartan pharmacokinetics affected the *UGT1A1* variations in Korean patients. In this study, it was determined that UGT1A1 (rs4148323, rs28934877) variations damage the structure and function of the protein. This may affect the bioavailability and pharmacokinetics of the drug.

In this study, it was observed that the UGT1A1 mutations (rs4148323, rs28934877) are related to telmisartan responsiveness, and these mutations might cause telmisartan resistance. Interactions between telmisartan and wild-type protein and mutant proteins were shown by docking analysis.

5 Conclusion

In this study, it was detected that UGT1A1 (rs4148323, rs28934877) mutations are deleterious. The mutated residue is located in an important domain for protein activity. It was detected that rs4148323 might disturb this function might disturb protein function. rs28934877 is probably damaging to the protein. Protein damage might affect the development of telmisartan resistance in hypertension patients might reduce drug response and complicate the treatment.

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Authors' contributions: Concept – G.K.K; Design, Supervision, Funding, Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review, Writing, Critical Review

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