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Potential Indirect Effects of Energy Drink Components on the Human Body Mediated by Genetically Determined Structural and Functional Alterations of the Taurine Transporter (TauT)

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ABSTRACT

Energy drink consumption has been rising steadily across the globe. Taurine is among the most common bioactive components found in these beverages. Its entry into cells depends on several metabolic transport systems, and the taurine transporter (TauT), encoded by the SLC6A6 gene, is one of the main ones. Because TauT helps keep intracellular taurine levels stable, it is essential for many physiological processes.

This study set out to examine how taurine, as well as genetically determined structural and functional changes in the taurine transporter (TauT), affect the human body. Deleterious single-nucleotide polymorphisms (SNPs) in TauT were first identified. Homology modeling was then carried out to predict the three-dimensional conformation of both the native and amino acid-substituted variants and to assess their possible physiological effects.

Of the variants identified, p.Ala78Glu was chosen for structural analysis and homology modeling. Three-dimensional models of the native and mutant TauTproteins were built, after which molecular docking with taurine was performed using SwissDock.

The docking analysis showed that the amino acid substitution changed the predicted binding orientation of taurine within the TauT transporter. When compared with the native TauT–taurine complex, the mutant complex formed three additional hydrogen bonds.

INTRODUCTION

Background and significance of the study

The consumption of energy drinks (EDs) has been steadily increasing worldwide. Modern society operates in a 24-hour environment in which work and other activities frequently extend beyond conventional daytime hours. As a result, energy drinks have gained widespread popularity across all age groups owing to their perceived psychostimulatory properties. These beverages are commonly believed to enhance alertness, improve reaction time, and promote overall well-being.

Under conditions of increasing occupational and academic demands, individuals often seek to extend their productive working hours, leading to a growing demand for energy drinks. Consequently, the consumption of psychostimulatory substances continues to rise. One of the most widely used bioactive ingredients in energy drinks is taurine. The transport of taurine into cells is mediated by several metabolic transport systems. One of the principal mechanisms involves the taurine transporter (TauT), a sodium- and chloride-dependent membrane transporter encoded by the SLC6A6 gene. TauT plays a crucial role in maintaining intracellular taurine homeostasis and is therefore essential for numerous physiological processes.

The objective of the present study was to investigate the effects of taurine and genetically determined structural and functional alterations of the taurine transporter (TauT) on the human body.

To achieve this objective, the following research tasks were established:

1. To identify deleterious single-nucleotide polymorphisms (SNPs) of the TauT protein reported in the scientific literature and publicly available biological databases.
2. To perform homology modeling of the TauT protein in order to predict its three-dimensional conformation in both the native and amino acid-substituted variants.
3. To analyze the identified structural alterations of the TauT protein and evaluate their potential effects on human physiological systems.

RESEARCH METHODOLOGY

An analysis of the most widely consumed energy drinks (EDs) in the CIS countries, including Red Bull, Monster Energy, Burn, and Adrenaline Rush, demonstrated that their principal ingredients are caffeine, taurine, glucose, sucrose, and B-group vitamins. Among these components, caffeine and taurine are primarily responsible for the stimulatory effects of energy drinks.

Caffeine (1,3,7-trimethylxanthine) is naturally present in coffee, tea, and chocolate, which represent the major dietary sources of this compound. These products are readily accessible across virtually all

socioeconomic groups. Caffeine acts as a non-selective antagonist of adenosine receptors in the central nervous system. Its primary pharmacological effect is psychostimulation, accompanied by additional effects on the respiratory, muscular, and cardiovascular systems [1].

Taurine (2-aminoethanesulfonic acid) is a conditionally non-essential amino acid that is primarily obtained through dietary sources, including tuna, turkey (dark meat), and chicken. Despite the limited evidence regarding its effects on human and animal health, taurine is widely used as a dietary supplement and a common ingredient in energy drinks. Experimental and clinical studies indicate that taurine participates in bile acid conjugation, contributes to the regulation of arterial blood pressure, and exhibits antioxidant as well as anti-inflammatory properties [2].

The psychostimulatory properties of both caffeine and taurine were first recognized during the nineteenth century. However, taurine has received considerably less attention than caffeine because of its comparatively weaker stimulatory effects. Nevertheless, taurine possesses numerous non-stimulatory physiological functions that remain insufficiently investigated.

The consumption of energy drinks has been associated with several adverse health effects, including hypotension, supraventricular tachycardia, anxiety, and vomiting [3]. These adverse events are generally attributed to caffeine intoxication; however, the combined presence of taurine, glucose, and sucrose may potentiate these effects through additive or synergistic interactions, thereby increasing both their severity and clinical manifestation.

MECHANISM OF TAURINE TRANSPORT INTO THE CELL AND ITS PHYSIOLOGICAL FUNCTIONS

Taurine performs a wide range of physiological functions, including bile acid conjugation, osmoregulation, antioxidant defense, neuronal development, and membrane stabilization**.** These physiological processes are regulated by the enzymes involved in taurine biosynthesis—cysteine dioxygenase (CDO) and cysteine sulfinic acid decarboxylase (CSAD)—as well as by the taurine transporter (TauT). In addition, taurine plays an essential role in cellular energy metabolism**,** skeletal muscle function**,** cardiac function**,** hepatic metabolism**,** and adipose tissue physiology**.**

The taurine transporter (TauT), encoded by the SLC6A6 gene, is considered the principal mechanism responsible for taurine uptake into cells. TauT is a high-affinity, low-capacity**,** sodium- and chloride-dependent membrane transporter belonging to the solute carrier family 6 (SLC6)**.** It is localized within the plasma membrane and mediates the active transport of taurine across the cell membrane. Structurally, TauT consists of 12 hydrophobic transmembrane (TM) helices, with both the N-terminal and C-terminal domains exposed to the cytoplasmic compartment. Sodium (Na^+) and chloride (Cl^-) ions are essential for taurine transport, as they bind to the extracellular region adjacent to the N-terminal portion of the transporter, thereby facilitating substrate translocation [4]. According to the study Homology

Modelling of the Taurine Transporter, TauT operates through the alternating-access mechanism, which incorporates structural features characteristic of the rocker-switch, elevator, and gated-pore transport mechanisms.

The alternating-access mechanism (Figure 2) represents a fundamental model describing the function of membrane transport proteins. According to this model, conformational changes in the transporter alternately expose the substrate-binding site to either side of the membrane, thereby enabling substrate translocation while preventing the formation of a continuous transmembrane pore [5]. The rocker-switch mechanism, which is characteristic of the major facilitator superfamily (MFS) of transporters, is believed to operate according to the alternating-access principle [6]. In this mechanism, the substrate-binding site remains relatively fixed within the membrane, whereas coordinated conformational changes of the protein alternately expose the binding site to either the extracellular or intracellular environment [7]. At any given time, one side of the transporter remains open while the opposite side is closed, thereby preventing unrestricted diffusion across the membrane.

The elevator mechanism involves the movement of a transport domain containing the substrate-binding site relative to a structurally stable scaffold domain. During the transport cycle, the transport domain undergoes a vertical displacement approximately perpendicular to the membrane plane, thereby carrying the substrate-binding site across the membrane through coordinated conformational rearrangements of the protein. These structural transitions provide alternating access to the substrate-binding site from either side of the membrane. In TauT, transmembrane helices TM1, TM2, TM6, and TM7 (Figure 3) undergo the principal conformational movements during the transport cycle, whereas the remaining transmembrane helices constitute a relatively rigid structural scaffold. As a result of these coordinated conformational changes, taurine is transported into the cell, where it participates in cellular energy metabolism and supports the normal physiological functions of multiple human tissues (Figure 1).

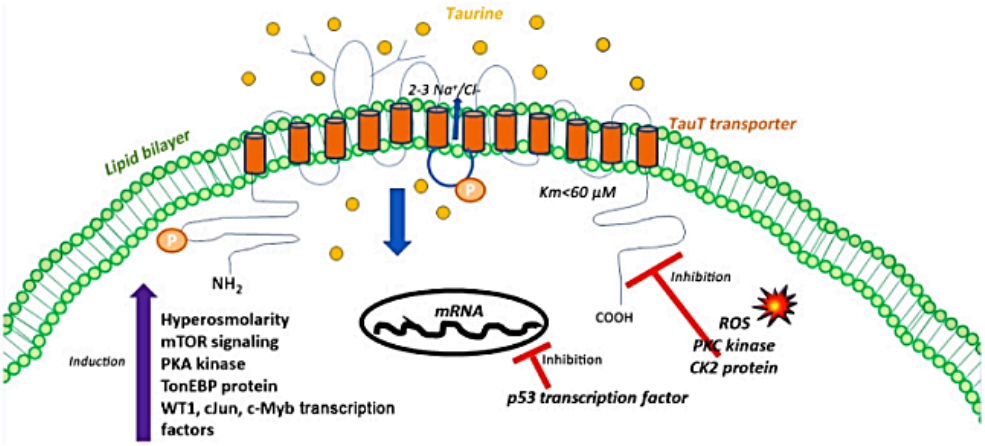


Figure 1 - General Mechanism of Taurine–Cell Interaction [8]

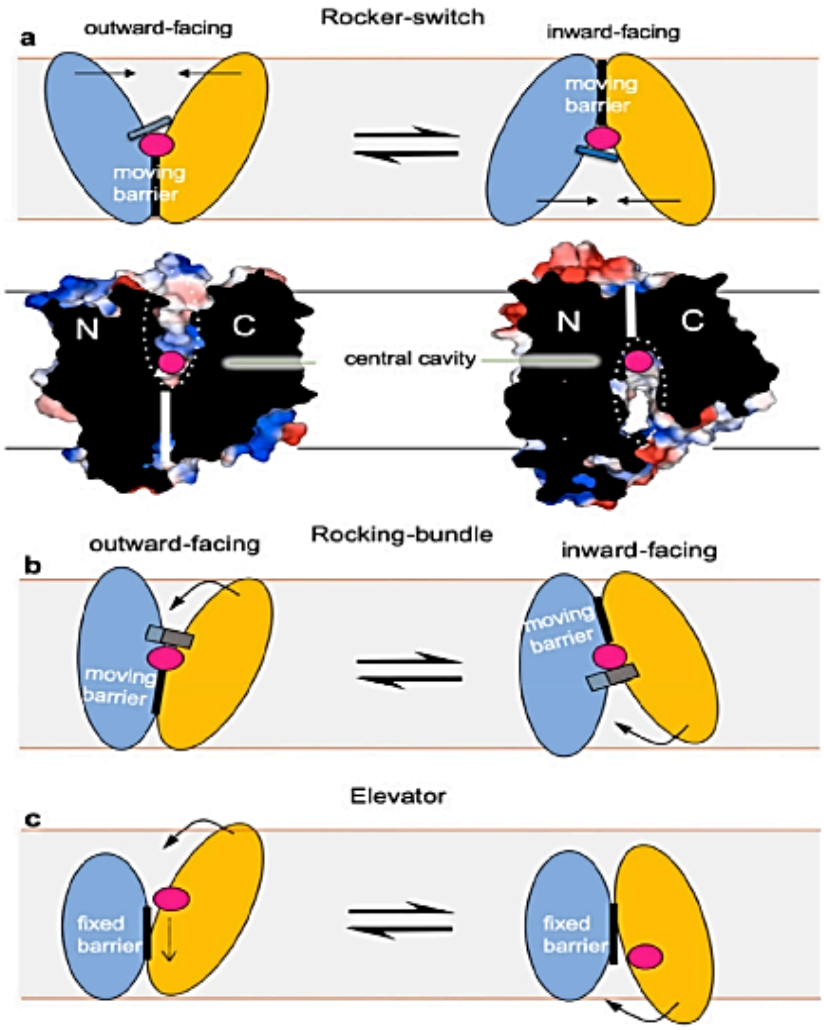


Figure 2 - Schematic Representation of the Alternating-Access Transport Mechanism [9]

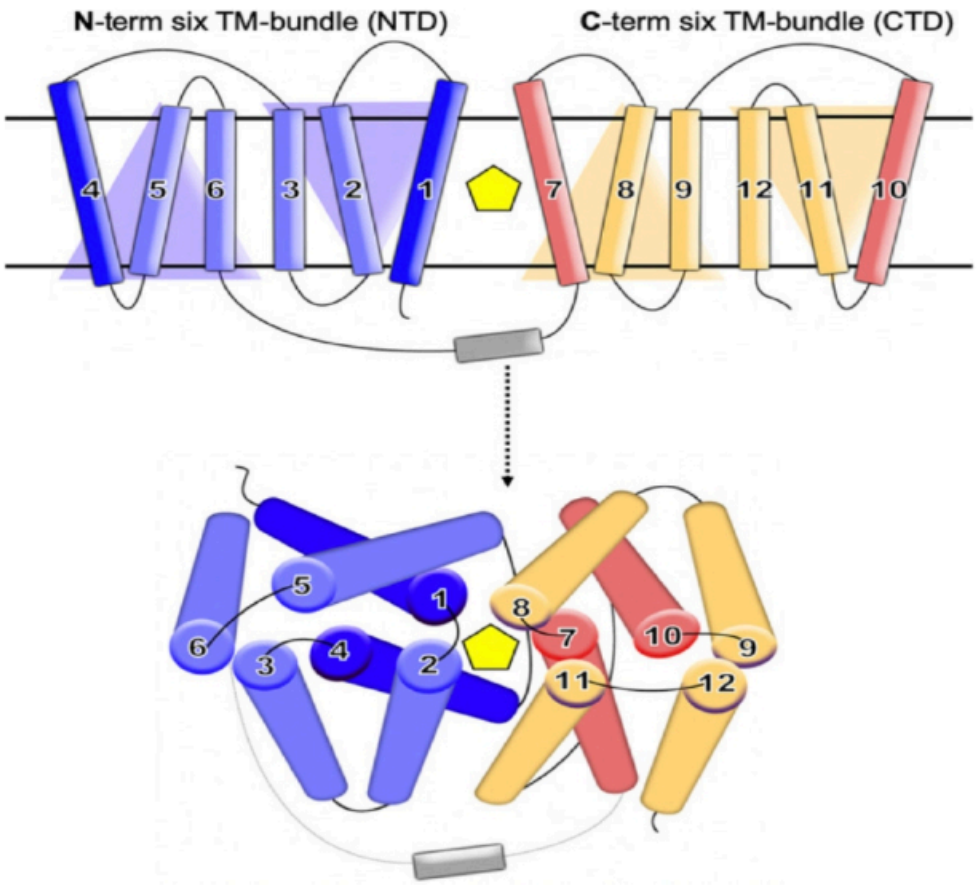


Figure 3 - Interactions Between the Transmembrane Helices of the

Taurine Transporter (TauT) [9]

CHARACTERIZATION OF KNOWN SINGLE-NUCLEOTIDE POLYMORPHISMS OF THE TAURINE TRANSPORTER (TauT)

Approximately 80 single-nucleotide polymorphisms (SNPs) have been identified in the taurine transporter (TauT). Among these variants, only two have been reported to possess potential clinical significance. The first polymorphism involves a cytosine-to-adenine (C>A) nucleotide substitution at position 233, resulting in the replacement of alanine with glutamic acid at amino acid position 78 (p.Ala78Glu). The second polymorphism is characterized by a glycine-to-valine substitution at amino acid position 399

(p.Gly399Val). According to the study Taurine Treatment of Retinal Degeneration and Cardiomyopathy in a Consanguineous Family with SLC6A6 Taurine Transporter Deficiency, the p.Gly399Val variant is not considered to pose a significant pathogenic risk to humans. Consequently, the p.Ala78Glu variant was selected for the structural analysis and homology modeling performed in the present study.

The nucleotide sequence of the sodium- and chloride-dependent taurine transporter (SLC6A6) corresponding to nucleotides 0–240 is presented in Appendix A.

GAGAGCTGCCTGCTCAGACAACAGACACGCGAGGTCAGGAAGAAGCCGCTTATA
AATTACCGCTTCCTTC
GCGCCGCCGCCAACGCCGAGCCCCGAGGACCGCAAGCCCAGAGGACAAGCTGC
GCCAAGAGGGAGTGCGG
AGCGTTCACCCAGCGGGTCAGAGAGCGAGCGGGCAGGCAGCCCCCGGCCGGCG
GAACCCGGCACAGCCGA GCAGAGCGCGGGCGGCGCCGCCGCCACCCC
GCAGAGCGCGGGCGGCGCCGCCGCCACCCC

Nucleotide sequence of the sodium- and chloride-dependent taurine transporter (SLC6A6) (Nucleotides 0–240) (Appendix B):

GAGAGCTGCCTGCTCAGACAACAGACACGCGAGGTCAGGAAGAAGCCGCTTATA
AATTACCGCTTCCTTC
GCGCCGCCGCCAACGCCGAGCCCCGAGGACCGCAAGCCCAGAGGACAAGCTGC
GCCAAGAGGGAGTGCGG
AGCGTTCACCCAGCGGGTCAGAGAGCGAGCGGGCAGGCAGCCCCCGGCCGGCG
GAACCCGGCACAGCCGA GCAGAGCGCGGGCGGCGCCGCAGCCACCCC
Cytosine-to-adenine (C>A) substitution at nucleotide position 233.

Amino Acid Sequence of the Sodium- and Chloride-Dependent Taurine Transporter (SLC6A6):

1 MATKEKLQCL KDFHKDILKP SPGKSPGTRP EDEAEGKPPQ REKWSSKIDF VLSVAGGFVG

61 LGNVWRFPYL CYKNGGGAFL IPYFIFLFGS GLPVFFLEII IGQYTSEGGI TCWEKICPLF

121 SGIGYASVVI VSLLNVYYIV ILAWATYYLF QSFQKELPWA HCNHSWNTPH CMEDTMRKNK

181 SVWITISSTN FTSPVIEFWE RNVLSLSPGI DHPGSLKWDL ALCLLLVWLV CFFCIWKGVR

241 STGKVVYFTA TFPFAMLLVL LVRGLTLPGA GAGIKFYLYP DITRLEDPQV WIDAGTQIFF

301 SYAICLGAMT SLGSYNKYKY NSYRDCMLLG CLNSGTSFVS GFAIFSILGF MAQEQGVDIA

361 DVAESGPGLA FIAYPKAVTM MPLPTFWSIL FFIMLLLLGL DSQFVEVEGQ ITSLVDLYPS

421 FLRKGYRREI FIAFVCSISY LLGLTMVTEG GMYVFQLFDY YAASGVCLLW VAFFECFVIA

481 WIYGGDNLYD GIEDMIGYRP GPWMKYSWAV ITPVLCVGCF IFSLVKYVPL TYNKTYVYPN

541 WAIGLGWSLA LSSMLCVPLV IVIRLCQTEG PFLVRVKYLL TPREPNRWAV EREGATPYNS

601 RTVMNGALVK PTHIIVETMM

The nucleotide substitution resulted in an amino acid substitution within the TauT protein sequence. Specifically, alanine was replaced by glutamic acid at amino acid position 78 (p.Ala78Glu).

1 MATKEKLQCL KDFHKDILKP SPGKSPGTRP EDEAEGKPPQ REKWSSKIDF VLSVAGGFVG

61 LGNVWRFPYL CYKNGGGEFL IPYFIFLFGS GLPVFFLEII IGQYTSEGGI TCWEKICPLF

121 SGIGYASVVI VSLLNVYYIV ILAWATYYLF QSFQKELPWA HCNHSWNTPH CMEDTMRKNK

181 SVWITISSTN FTSPVIEFWE RNVLSLSPGI DHPGSLKWDL ALCLLLVWLV CFFCIWKGVR

241 STGKVVYFTA TFPFAMLLVL LVRGLTLPGA GAGIKFYLYP DITRLEDPQV WIDAGTQIFF

301 SYAICLGAMT SLGSYNKYKY NSYRDCMLLG CLNSGTSFVS GFAIFSILGF MAQEQGVDIA

361 DVAESGPGLA FIAYPKAVTM MPLPTFWSIL FFIMLLLLGL DSQFVEVEGQ ITSLVDLYPS

421 FLRKGYRREI FIAFVCSISY LLGLTMVTEG GMYVFQLFDY YAASGVCLLW VAFFECFVIA

481 WIYGGDNLYD GIEDMIGYRP GPWMKYSWAV ITPVLCVGCF IFSLVKYVPL TYNKTYVYPN

541 WAIGLGWSLA LSSMLCVPLV IVIRLCQTEG PFLVRVKYLL TPREPNRWAV EREGATPYNS

601 RTVMNGALVK PTHIIVETMM

HOMOLOGY MODELING OF THE THREE-DIMENSIONAL STRUCTURE OF THE TAURINE TRANSPORTER (TauT)

The three-dimensional (3D) structure of the TauT protein was predicted using the homology modeling approach implemented through the SWISS-MODEL web server, developed by the Biozentrum, University of Basel.

The construction of a homology model involves four principal stages [10–14]:

1. Selection of an appropriate template protein exhibiting the highest sequence similarity to the target protein and possessing an experimentally determined three-dimensional structure.
2. Sequence alignment between the target protein and the selected template.
3. Construction of the three-dimensional model of the target protein by maximizing the use of structurally resolved regions of the template protein.
4. Assessment of the quality and reliability of the generated structural model.

The amino acid sequence of the native TauT protein was submitted to the SWISS-MODEL server. The server automatically identified the most suitable structural template for model generation. The selected template corresponded to the Canis lupus familiaris taurine transporter, exhibiting 94.68% sequence identity with the human TauT protein. Based on this template, a three-dimensional structural model of the human TauT protein was generated (Figure 4).

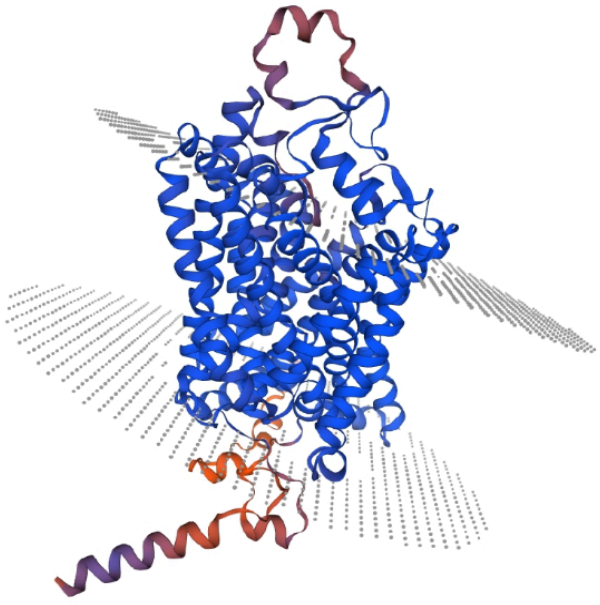


Figure 4 - Homology model of the native taurine transporter (TauT)

In the absence of experimentally resolved three-dimensional structures of both the native and mutant TauT proteins, homology modeling was also performed for the amino acid-substituted variant to evaluate the potential structural consequences of the identified mutation (Figure 5).

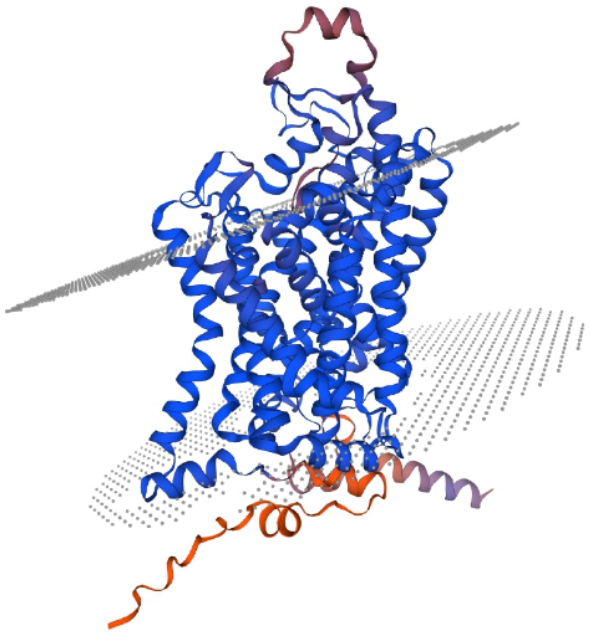


Figure 5 - Homology model of the mutant taurine transporter (TauT)

MOLECULAR DOCKING OF THE NATIVE AND MUTANT TauT PROTEINS WITH TAURINE

Molecular docking is a computational molecular modeling technique used to predict the most energetically favorable and stable binding conformation of a ligand within the binding site of a receptor.

Molecular docking was performed using the SwissDock web server [15–17]. The first stage involved selecting appropriate protein structures for docking. In the present study, the three-dimensional structures generated by homology modeling (described in the section Homology Modeling of the

Three-Dimensional Structure of the Taurine Transporter (TauT)*)* were used. Both the native and mutant TauT protein models served as receptor structures. The protein models were uploaded to the SwissDock server in Protein Data Bank (.pdb) format.

The second stage consisted of ligand selection. SwissDock provides access to an extensive ligand library, from which taurine was selected as the ligand for all docking simulations.

Following submission of the receptor and ligand structures, SwissDock generated 256 potential protein–ligand binding poses. These docking solutions were ranked according to their predicted binding properties, including van der Waals interactions, electrostatic interactions, and surface complementarity between the receptor and the ligand. Among the generated docking solutions, the most stable binding pose, characterized by the lowest predicted binding energy, was selected for subsequent structural analysis. The selection was based on the docking score (estimated binding free energy), which is calculated according to the following equation:

$$\triangle G_{bind} = \triangle G_{solvent} + \triangle G_{conf} + \triangle G_{int} + \triangle G_{rot} + \triangle G_{t/t} + \triangle G_{vib}$$

The docking score is composed of several energy terms, including the solvation energy**,** conformational energy**,** Gibbs free energy**,** internal rotational energy**,** the free energy associated with ligand–receptor complex formation, and the free energy contribution arising from changes in vibrational modes**.** A lower (more negative) docking energy indicates a more stable protein–ligand complex and, consequently, a higher probability of favorable binding between the ligand and the receptor (Table 1).

Accordingly, the docking simulation of the native TauT protein with taurine yielded the following results (Table 1).

Table 1 - Molecular docking results for the native TauT protein–taurine complex

S	Cluster	Rank	FullFitness Score	Estimated ΔG (kcal/mol)	Hydrogen Bonds	Hydrogen Bonds with Atom 1	Hydrogen Bonds with Atom 2
V	0	1	-1967.008	-6.836275	2	2	2
V	0	0	-1967.0259	-6.833913	2	2	2
V	0	2	-1966.9617	-6.8326545	2	2	2
V	17	0	-1963.7046	-6.729894	2	2	2
V	17	1	-1963.7046	-6.729994	2	2	2
V	17	2	-1963.2661	-6.6785107	2	2	2
V	17	3	-1963.2661	-6.6785107	2	2	2

The selected docking pose (Figure 6) exhibited the lowest estimated binding free energy (ΔG) and formed two hydrogen bonds between the ligand and the receptor. These results indicate that this protein–ligand complex represents the most stable binding conformation among the predicted docking poses and is therefore the most probable binding mode of taurine to the TauT transporter.

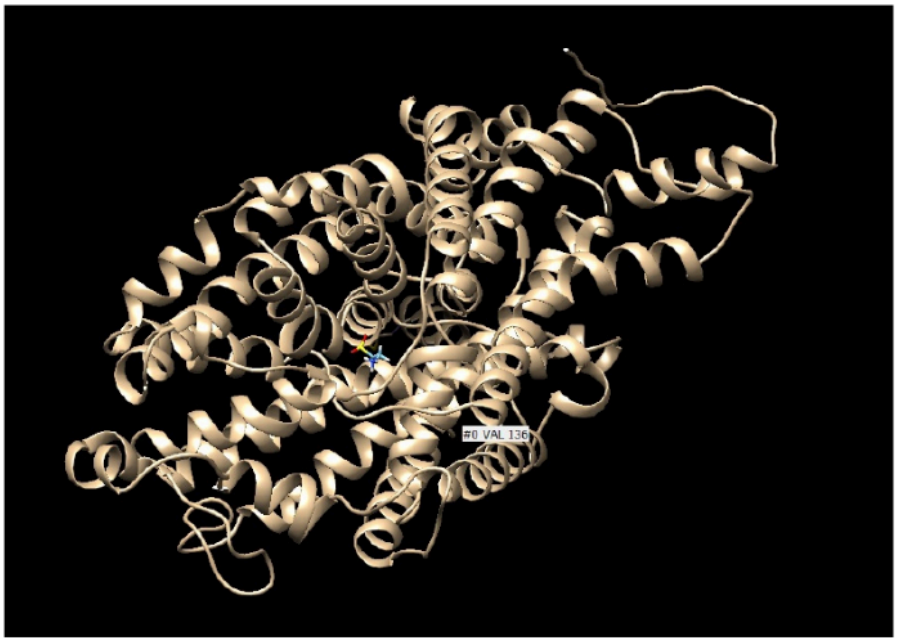


Figure 6 - Molecular docking model of the native TauT–Taurine Complex

The docking simulation of the mutant TauT protein with taurine yielded the following results (Table 2).
Table 2. Molecular Docking Results for the Mutant TauT Protein–Taurine Complex

S	Cluster	Rank	FullFitness Score	Estimated ΔG (kcal/mol)	Hydrogen Bonds	Hydrogen Bonds with Atom 1	Hydrogen Bonds with Atom 2
V	18	2	-1803.0355	-6.9833374	5	4	5
V	0	0	-1808.3804	-6.8538103	5	4	5
V	0	1	-1807.8798	-6.8187914	5	4	5
V	18	1	-1803.4124	-6.7428894	5	5	4
V	0	2	-1806.6475	-6.7200685	5	4	5
V	18	0	-1803.9282	-6.6565433	3	3	3
V	2	1	-1807.0935	-6.58193	2	2	2

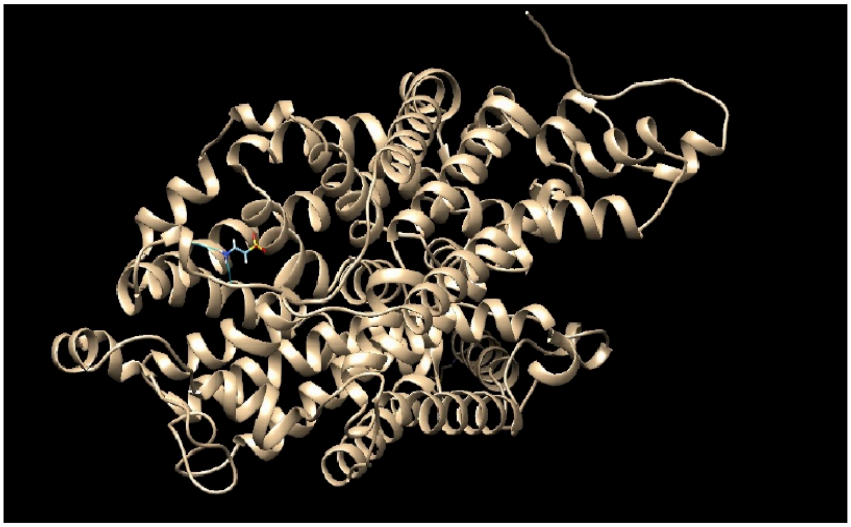


Figure 7 - Molecular docking model of the mutant TauT–Taurine Complex

The molecular docking analysis demonstrated that the amino acid substitution altered the predicted binding orientation of taurine within the TauT transporter (Figure 7). This observation is further supported by the formation of additional hydrogen bonds in the mutant protein–ligand complex. The orientation of taurine within the transporter is likely to be functionally important because TauT operates as a transmembrane protein embedded in the plasma membrane.

POTENTIAL CONSEQUENCES OF ENERGY DRINK CONSUMPTION IN INDIVIDUALS CARRYING A MUTANT TauT VARIANT

Some individuals may carry a mutant variant of the TauT transporter without being aware of its presence. Although taurine is classified as a conditionally non-essential amino acid, it plays a critical role in numerous physiological processes essential for normal cellular function. The mutant TauT variant investigated in the present study is characterized by the substitution of alanine with glutamic acid at amino acid position 78 (p.Ala78Glu). Taurine acts as a potent organic osmolyte. Elevated extracellular taurine concentrations may promote the movement of water out of cells. Activation of the RAS begins with the secretion of renin by the kidneys, which cleaves angiotensinogen to produce angiotensin I. Under the action of angiotensin-converting enzyme (ACE), angiotensin I is subsequently converted into angiotensin II. Angiotensin II induces vasoconstriction, thereby increasing systemic arterial blood

pressure. In individuals with pre-existing cardiovascular disorders, including chronic heart failure or congenital heart disease, such an increase in arterial blood pressure may elevate the risk of severe cardiovascular complications and, in extreme cases, may contribute to fatal outcomes (Figure 8).

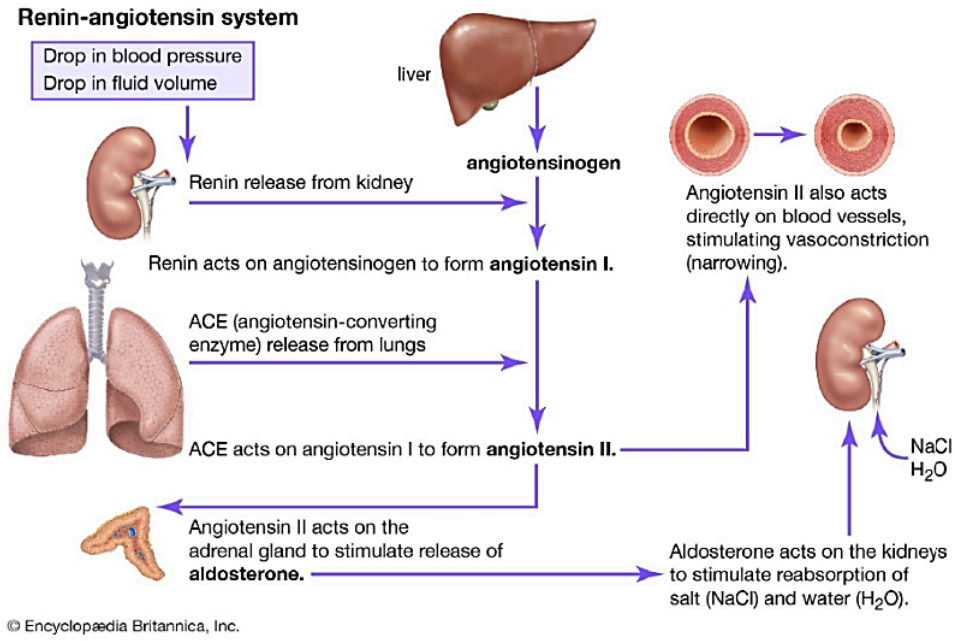


Figure 8 - Schematic representation of the Renin–Angiotensin System (RAS) [18]

Taurine is the end product of the metabolism of sulfur-containing amino acids (Figure 9). Sulfur-containing amino acids include methionine, cysteine, homocysteine, and cystine. Alterations in taurine homeostasis may influence the metabolism of sulfur-containing amino acids and may be associated with elevated homocysteine concentrations. Elevated plasma homocysteine is recognized as an independent risk factor for endothelial dysfunction and cardiovascular disease, as it promotes toxic injury to the vascular endothelium and increases the risk of cardiovascular complications.

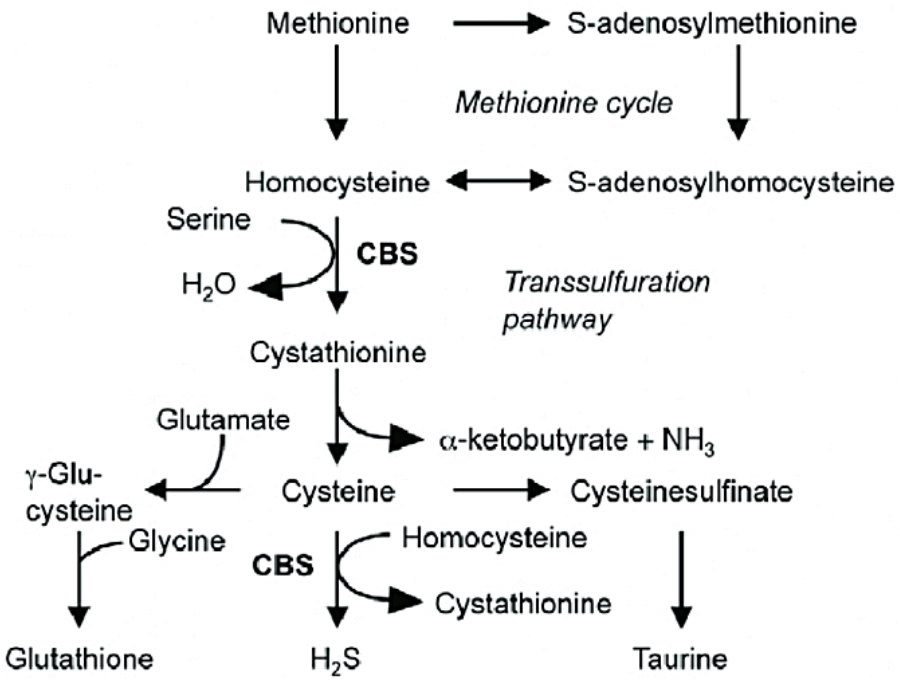


Figure 9 - Metabolism of sulfur-containing amino acids [19]

CONCLUSION

In the present study, the nucleotide and amino acid alterations in the taurine transporter (TauT) were analyzed. In addition, homology modeling of both the native and mutant TauT proteins was performed, followed by molecular docking analyses to evaluate the potential effects of the identified amino acid substitution on taurine binding.

The objectives of the study were successfully accomplished:

1. A clinically relevant single-nucleotide polymorphism resulting in the p.Ala78Glu amino acid substitution was identified through a comprehensive review of the scientific literature and publicly available genetic databases.
2. Homology modeling and molecular docking of the native TauT protein were successfully performed to characterize its structural features and predicted interaction with taurine.

3. Homology modeling and molecular docking of the mutant TauT protein carrying the p.Ala78Glu substitution were successfully performed to evaluate the structural and functional consequences of the mutation.
4. The potential physiological consequences of the mutant TauT variant for human health were also analyzed.

The study was based on evidence obtained from peer-reviewed publications indexed in PubMed, genetic and genomic databases maintained by the National Center for Biotechnology Information (NCBI), and other scientific literature relevant to the research topic.

The findings of this study may provide a theoretical basis for future investigations of the taurine transporter, contribute to the development of recombinant therapeutic strategies targeting TauT dysfunction, and support the expansion of relevant biological and genetic databases.

BIOINFORMATICS TOOLS AND DATABASES (In Silico)

- SwissDock (molecular docking): http://www.swissdock.ch/
- SWISS-MODEL (homology modeling): https://swissmodel.expasy.org/
- NCBI ClinVar (SLC6A6 variant database): https://www.ncbi.nlm.nih.gov/clinvar/RCV001449581/
- NCBI Nucleotide Database (reference nucleotide sequence NM_003043.6): https://www.ncbi.nlm.nih.gov/nuccore/NM_003043.6?report=graph&search=NM_003043.6%3Ac.233C%3EA
- UniProt Knowledgebase (UniProtKB) (TauT protein sequence, accession P31641): https://www.uniprot.org/uniprotkb/P31641/entry#sequences
- NCBI Protein Database (reference protein sequence NP_003034.2): https://www.ncbi.nlm.nih.gov/protein/NP_003034.2?report=genbank&log$=prottop&blast_rank=2&RID=9X71NXKK016

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Appendix 1

GAGAGCTGCCTGCTCAGACAACAGACACGCGAGGTCAGGAAGAAGCCGCTTATA
AATTACCGCTTCCTTC
GCGCCGCCGCCAACGCCGAGCCCCGAGGACCGCAAGCCCAGAGGACAAGCTGC
GCCAAGAGGGAGTGCGG
AGCGTTCACCCAGCGGGTCAGAGAGCGAGCGGGCAGGCAGCCCCCGGCCGGCG
GAACCCGGCACAGCCGA
GCAGAGCGCGGGCGGCGCCGCCGCCACCCC
AGATCCAGAACCAGAACCACAGCCCTTCTGAGGAGCTCCCAAACAAAGCAAGGA
GATGGCCACC
AAGGAGAAGCTGCAGTGTCTGAAAGATTTCCACAAGGACATCCTGAAGCCCTCA
CCAGGGAAGAGCCCAG
GCACGCGGCCTGAGGACGAGGCTGAGGGAAAACCTCCGCAGAGGGAGAAGTGG
TCTAGCAAGATCGACTT
TGTGCTCTCTGTGGCTGGCGGCTTCGTGGGCTTGGGCAACGTCTGGCGCTTCCCG
TACCTCTGCTACAAG
AATGGTGGAGGTGCGTTTCTCATACCGTATTTTATTTTCCTGTTTGGGAGCGGCCTG
CCTGTGTTTTTCT
TGGAGATCATCATAGGCCAGTACACCTCTGAAGGGGGCATCACCTGCTGGGAAAA
GATCTGCCCCTTGTT
CTCTGGTATCGGCTATGCCTCCGTTGTAATTGTGTCCCTCCTGAATGTCTACTACAT
CGTCATCCTGGCC
TGGGCCACATACTACCTGTTCCAGTCCTTCCAGAAGGAGCTGCCCTGGGCACACT
GCAACCACAGCTGGA

Appendix 2

GAGAGCTGCCTGCTCAGACAACAGACACGCGAGGTCAGGAAGAAGCCGCTTATA
AATTACCGCTTCCTTC
GCGCCGCCGCCAACGCCGAGCCCCGAGGACCGCAAGCCCAGAGGACAAGCTGC
GCCAAGAGGGAGTGCGG
AGCGTTCACCCAGCGGGTCAGAGAGCGAGCGGGCAGGCAGCCCCCGGCCGGCG
GAACCCGGCACAGCCGA
GCAGAGCGCGGGCGGCGCCGCAGCCACCCCAGATCCAGAACCAGAACCACAGCC
CTTCTGAGGAGCTCCC
AAACAAAGCAAGGAGATGGCCACCAAGGAGAAGCTGCAGTGTCTGAAAGATTTC
CACAAGGACATCCTGA
AGCCCTCACCAGGGAAGAGCCCAGGCACGCGGCCTGAGGACGAGGCTGAGGGA
AAACCTCCGCAGAGGGA
GAAGTGGTCTAGCAAGATCGACTTTGTGCTCTCTGTGGCTGGCGGCTTCGTGGGC
TTGGGCAACGTCTGG

CGCTTCCCGTACCTCTGCTACAAGAATGGTGGAGGTGCGTTTCTCATACCGTATTTT
ATTTTCCTGTTTG
GGAGCGGCCTGCCTGTGTTTTTCTTGGAGATCATCATAGGCCAGTACACCTCTGAA
GGGGGCATCACCTG
CTGGGAAAAGATCTGCCCCTTGTTCTCTGGTATCGGCTATGCCTCCGTTGTAATTGT
GTCCCTCCTGAAT
GTCTACTACATCGTCATCCTGGCCTGGGCCACATACTACCTGTTCCAGTCCTTCCAG
AAGGAGCTGCCCT
GGGCACACTGCAACCACAGCTGGAACACACCTCACTGCATGGAGGACACCATGC
GCAAGAACAAGAGTGT
CTGGATCACCATCAGCTCCACCAACTTCACCTCCCCTGTCATCGAGTTCTGGGAGC
GCAACGTGCTGAGC
TTGTCCCCTGGAATCGACCACCCAGGCTCTCTGAAATGGGACCTCGCTCTCTGCCT
TCTTTTAGTCTGGC TAGTGTGTTTCTTCTGCATCTGGAAGGGCGTCAGGTCCACTGGGAAG