Trakya University Journal of Natural Sciences, 26(2), 135–142, 2025
DOI: 10.23902/trkjnat.524243354
www.tujns.org

Research Article

In silico analysis of molecular docking between nicotine and *GSTP1* gene in oral squamous cell carcinoma

Shashanka Thowdanahalli Munipapanna[1], Prabhudas Nelaturi[2]*

[1]*Chikkamagaluru Institute of Medical Sciences, Department of Biochemistry, Karnataka, India*
[2]*Saveetha University, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Department of Anatomy, Unit of Molecular Biology, Tamil Nadu, India*

Cite this article as: Munipapanna, S. T., & Nelaturi, P. (2025). *In silico* analysis of molecular docking between nicotine and *GSTP1* gene in oral squamous cell carcinoma. *Trakya University Journal of Natural Sciences, 26*(2), 135–142. https://doi.org/10.23902/trkjnat.524243354

Abstract

Oral squamous cell carcinoma (OSCC) is a predominant cancer strongly associated with risk factors like use of tobacco, viral infections, and genetic predispositions. Genetic risk factors often involve polymorphisms in genes that are critical for various biological pathways. Glutathione S-transferase pi 1 (*GSTP1*) is a gene involved in detoxifying oral carcinogens and the Ile105Val variant of *GSTP1* is associated with increased risk of cancer development including OSCC. Understanding the interaction between *GSTP1* and carcinogens such as nicotine offers valuable insights into OSCC progression. The study employed *in silico* screening with molecular docking technique in order to explore the binding affinity between nicotine and *GSTP1*. Methods included the use of canonical SMILES from PubChem for drug-likeness and pharmacokinetic assessments. Alongside toxicity evaluation through ToxiM platform, docking analysis revealed a strong binding affinity of -7.1 kcal/mol score. The interaction was stabilized by a Pi–sigma bond with TYR109 at 3.579 Å and Pi–alkyl bonds with PHE9, ARG14, and ILE105. These findings emphasize the crucial role of *GSTP1*, particularly the Ile105Val variant, in progression of OSCC. The study highlighted the involvement of *GSTP1* in carcinogen detoxification and contribute to a better understanding of OSCC's biochemical pathways.

Özet

Oral skuamöz hücreli karsinom (OSHK), tütün kullanımı, viral enfeksiyonlar ve genetik yatkınlıklar gibi risk faktörleriyle güçlü ilişkilide olan baskın bir kanser tipidir. Genetik risk faktörleri arasında genellikle çeşitli biyolojik yolaklar için kritik olan gen polimorfizmleri yer almaktadır. Glutatyon S-transferaz pi 1 (*GSTP1*), oral kanserojenlerin detoksifikasyonunda rol oynayan bir gendir ve *GSTP1*'in Ile105Val varyantı, OSHK dahil olmak üzere kanser gelişimi riskinin artmasıyla ilişkilidir. *GSTP1* ile nikotin gibi kanserojenler arasındaki etkileşimin anlaşılması, OSHK ilerlemesi konusunda değerli bilgiler sunmaktadır. Bu çalışmada, nikotin ve *GSTP1* arasındaki bağlanma afinitesini keşfetmek için moleküler yerleştirme tekniğiyle *in silico* tarama kullanılmıştır. İlaç benzerliği ve farmakokinetik değerlendirmeler için PubChem'den kanonik SMILES kullanılmıştır. ToxiM platformu aracılığıyla yapılan toksisite değerlendirmesinin yanı sıra, yerleştirme analizi -7,1 kcal/mol puanlık güçlü bir bağlanma afinitesi ortaya koymuştur. Etkileşim, 3,579 Å'da TYR109 ile bir Pi–sigma bağı ve PHE9, ARG14 ve ILE105 ile Pi-alkil bağları ile stabilize edilmiştir. Bu bulgular, GSTP1'in, özellikle Ile105Val varyantının OSHK ilerlemesindeki kritik rolünü vurgular niteliktedir. Sonuçlar, *GSTP1*'in kanserojen detoksifikasyonuna katılımını vurgulamış ve OSHK'nın biyokimyasal yollarının daha iyi anlaşılmasına katkıda bulunmuştur.

Keywords: toxicity prediction, cancer genetics, tobacco, gene-environment interactions, computational biology

Edited by: *Melike Sapmaz Metin*

***Corresponding Author:** Nelaturi Prabhudas, **E-mail:** prabhudasn.smc@saveetha.com*
***ORCID iDs of the authors:** STM. 0009-0003-7428-4202, PN. 0000-0002-0390-3235*

Received: 24 January 2025, **Accepted:** 10 June 2025, **Epub:** 11 July 2025, **Published:** 15 October 2025

Introduction

Oral squamous cell carcinoma (OSCC) is recognized as the thirteenth most predominant cancer in the world, accounting for approximately 15% of all cancer cases. Despite advances in medical science, the prognosis for OSCC remains challenging, with less than 60% of patients surviving beyond five years (Tan et al., 2023). OSCC affects the buccal mucosa followed by other oral sites, such as the alveolar surface, hard palate, anterior two-third of tongue and floor of mouth. The development of OSCC is strongly associated with several risk factors, including tobacco use, infection of human papillomavirus (HPV), and genetic predispositions (Ramalingam et al., 2023). Genetic risk factors often involve polymorphisms in genes that are critical for various biological pathways. These pathways include carcinogen detoxification, DNA repair, cell cycle regulation, extracellular matrix stability, immune response, and inflammation (Kay et al., 2019). The gene glutathione S-transferase pi 1 (*GSTP1*) plays crucial role as an enzyme essential for the detoxification of carcinogens, particularly in the oral mucosa. It controls cancer by forming conjugation between harmful substances with glutathione, which is a major cellular antioxidant. Elevated expression of *GSTP1* is frequently observed in OSCC and is associated in resistance to chemotherapy. Conversely, decreased *GSTP1* expression is associated with increased DNA damage when exposed to carcinogens (Schnekenburger et al., 2014).

The gene *GSTP1* is located on chromosome 11q13.2 and encodes for the *GSTP1* enzyme, a key player in detoxifying carcinogens in the oral mucosa. Genetic variations within the *GSTP1* gene, particularly single nucleotide polymorphisms (SNPs), can significantly impact its enzymatic activity and increases the risk of the developing cancer. The selected three variants, Arg187Trp (rs11549), Ala114Val (rs1138272), and lle105Val (rs1695), of the *GSTP1* gene were revealed to be linked to cancer susceptibility, clinical relevance, and roles in carcinogen detoxification. The lle105Val variant, which has been extensively studied is strongly associated with an increased risk of tobacco-related cancers and is known to reduce enzymatic actions. Although the Ala114Val polymorphism is less clearly linked to cancer risk, it is important due to its potential to alter ligand binding affinity and destabilize protein structure. The Arg187Trp variant was prioritized for its predicted harmful effect on protein function which may impair detoxification and the management of oxidative stress. One of the most studied SNPs in this gene is Ile105Val (c.313A>G; rs1695) (Mandal & Mittal, 2020). Polymorphism results in a replacement of isoleucine (Ile) with valine (Val) at codon 105, notably reducing the enzyme activity of approximately 21.8% of its normal function. The Ile105Val variant of *GSTP1* is associated with an increased risk of various cancers, including those of the head and neck, thyroid, breast, lung, stomach, liver, and prostate (Parl, 2005). The reduction in *GSTP1* activity caused by this polymorphism impair the ability of the enzyme thereby affect the detoxification of carcinogens. Accumulation of carcinogens can intensify cancer susceptibility in individuals carrying the Ile105Val (c.313A>G; rs1695) variant (Arja et al., 2014; Mandal & Mittal, 2020).

The present study aimed to investigate the binding interaction between nicotine and *GSTP1* through molecular docking analysis, with particular focus on the Ile105Val polymorphism. Previous studies have highlighted the association between *GSTP1* variants and increased OSCC risk, with evidence showing that the Ile105Val variant is linked to higher oral cancer susceptibility and altered detoxification capacity (Koh et al., 2011). Several investigations have emphasized the clinical relevance of *GSTP1* polymorphisms in carcinogenesis and their contribution to impaired detoxification of carcinogens such as areca-nut metabolites. Previous studies have demonstrated a significant association between *GSTP1* polymorphisms, particularly the Ile105Val variant, and cancer susceptibility, including OSCC (Li et al., 2013; Marshall et al., 2000). The Ile105Val substitution is known to alter GSTP1 enzymatic activity, leading to reduced detoxification efficiency and increased vulnerability to carcinogenic compounds (Mandal & Mittal, 2020). Numerous investigations have reported correlations between this polymorphism and OSCC risk, underscoring its involvement in oxidative stress modulation and xenobiotic metabolism (Yadav et al., 2020; Pandith et al., 2013; Sharma et al., 2014; Akkus & Kucuk Kurtulgan, 2025). Despite these findings, the mechanistic details of how nicotine interacts with *GSTP1* and its variants remain insufficiently characterized. This study addresses this gap by integrating molecular docking analysis to explore how nicotine binding may impair *GSTP1* function, offering new insights into potential role in OSCC pathogenesis.

Materials and Methods

Structure Retrieval

The Protein Data Bank (PDB) coordinates for the structural domain (17GS; UniProtID: P09211) of *GSTP1* was obtained from the PDB database. Nicotine compound (PubChemCID: 89594) (Figure 1), including L-nicotine (BS; ID: 349993228), were retrieved from the PubChem database.

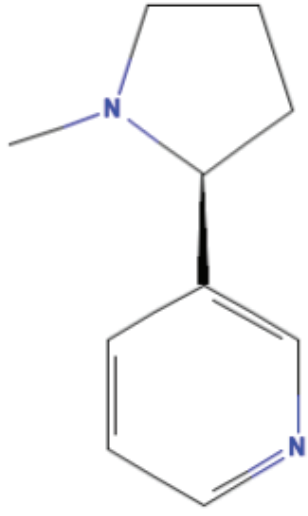

Figure 1. Nicotine PubChem Compound ID (CID: 89594).

Ligand Preparation

Ligands were prepared via Chimera software version 1.15, and protein preparation was performed via AutoDock Vina version 1.5.7. Energy minimization for both proteins and ligands was conducted via the YASARA minimization server. Water molecules and heteroatoms were removed, polar hydrogens were added, and nonpolar hydrogens were merged. Kollman and Gasteiger charges were added. Ligands, initially downloaded in SDF format from PubChem, were converted to PDB format via Open Babel. Ligand charges were neutralized, and Gasteiger charges were applied. Default torsion settings were retained.

Molecular Docking

Molecular docking was carried out via AutoDock Vina (SwissDock). Initial blind docking was followed by precision docking. The grid spacing was set to 1 Å, and the grid box was manually adjusted to include all active-site residues of the receptor. The grid box dimensions were set at X = 30, Y = 30, and Z = 30 and centered at X = 21.289, Y = 5.227, and Z = 21.348 for the 17GS protein. Docking was performed in triplicate, and exhaustiveness was adjusted to optimize the docking process. Docking experiments were also conducted via InstaDock for additional validation. For visualization of the protein–ligand interactions, Discovery Studio was utilized. Modifications to both proteins and ligands, including the addition of hydrogen atoms, removal of water molecules, and substitution of amino acids, were performed via Discovery Studio. AutoDock Tools version 1.5.6, was employed to explore the binding modes of the inhibitory compounds on the *GSTP1* enzyme (17GS). The protein and ligand files were saved in pdbqt format following preparation, and the grid box parameters were carefully set to cover the entire target enzyme. Binding interactions were analysed via PyMol for 3D visualization.

Visualization of Docking Poses

PyMol was used to visualize and analyse the docked poses and protein structures, as well as to render figures. Two–dimensional protein–ligand interactions were generated via LigPlot+ (version 2.2.5) and Discovery Studio Visualize. Cartoons of the protein–ligand interactions were produced to illustrate the docking results.

Validation Using the Database of Useful Decoys: Enhanced (DUDE. E)

To assess the docking method and minimize false positives, decoys with similar physical properties to the reference ligand were generated via DUDE. E database (http://decoys.docking.org). These decoys were compared with five target proteins available on the server.

ADMET Predictions

Pharmacokinetic properties, including absorption, distribution, metabolism, excretion, and toxicity (ADMET), were predicted via SwissADME. Canonical SMILES from PubChem was used to calculate drug-likeness and pharmacokinetic profiles.

Toxicity Prediction

Toxicity predictions were performed via ToxiM software. The PDB or SDF files of the desired compounds or their PubChem compound ID numbers were input into ToxiM to assess toxicity via various descriptors, fingerprints, and hybrid models.

Results

Selection and Preparation of Ligands

Eight flavonoid ligand compounds were selected for molecular docking analysis. These ligands were obtained in SDF format, and their 2D structures were retrieved from the PubChem database (Figure 1). The sole ligand specifically mentioned in this work is nicotine, found by PubChem Compound ID (CID: 89594). Although the section on methods notes that eight flavonoid ligands were chosen for molecular docking analysis, their names, IDs, or chemical structures were neither mentioned nor recorded in the results. The SDF files were converted to PDB format via Discovery Studio software to facilitate further analysis. The selected ligands, particularly nicotine, interact effectively with *GSTP1* with one ligand, 17GS, which strongly binds at the 105th position of the gene. Nicotine compounds were then analysed via the SWISS-ADME database for toxicity prediction, which revealed high permeability and significant absorption in human intestinal and lung tissues, suggesting enhanced bioavailability. Twenty nicotine derivatives docked against a target protein are shown in the image as a ribbon structure with their binding poses and docking scores. The docking scores of selected nicotine derivatives ranging from -6.4 to -7.6 kcal/mol indicate different levels of binding affinity, and each ligand is displayed in its predicted binding conformation. The strongest binding was notably shown by ligands 15 (-7.6 kcal/mol), 20 (-7.5 kcal/mol), and 8 (-7.5 kcal/mol), indicating a high potential for interaction with the protein's active site. The nicotine derivatives of ligands' moieties are aromatic and heterocyclic, which is consistent with scaffolds that resemble nicotine compounds, like pyridine and pyrrolidine rings (Figure 2).

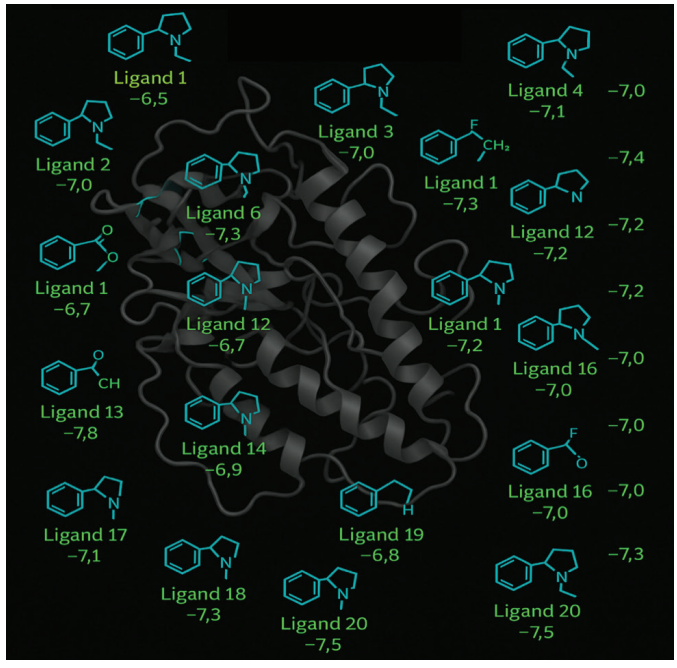

Figure 2. Schematic representation of binding poses and docking scores of nicotine derivatives (varies ligands) with the target *GSTP1*.

Molecular Docking Studies

The study primarily focused on the molecular docking of nicotine with *GSTP1* and its variants was the main focus of the study, which reported different docking scores and binding modes for each. With the wild-type *GSTP1*, nicotine showed a docking score of -7.1 kcal/mol. It interacted with TYR109 via a Pi–sigma bond and with PHE9, ARG14, and ILE105 via Pi–alkyl interactions. With a docking score of -9.8 kcal/mol, the Arg187Trp variant showed the highest binding affinity among the variants. It formed Pi–Pi stacking interactions with TRP104 and hydrogen bonds with GLU68, SER75, and CYS101. The Ile105Val variant had the lowest binding score of -4.5 kcal/mol with little effect from interactions, whereas the Ala114Val variant had a moderate binding score of -7.2 kcal/mol and interacted with CYS101 and SER108 through hydrogen bonds. The study focused on the in-depth examination of nicotine's interactions with *GSTP1* and its missense variants, rather than providing specific docking results for the eight flavonoid ligands that were initially mentioned.

Molecular docking between nicotine and *GSTP1* revealed a strong interaction with docking score of -7.1 kcal/mol, indicating a stable binding affinity (Table 1). The interaction of nicotine with specific amino acids, including TYR109, PHE9, ARG14, and ILE105, occurs primarily through hydrophobic interactions. TYR109 formed a Pi–sigma interaction at a short distance of 3.579 Å, contributing to the stability of the complex (Figure 3). PHE9 and ARG14 exhibited Pi–alkyl interactions with nicotine at distances of 5.138 Å and 5.252 Å, respectively, whereas ILE105 formed a Pi–alkyl interaction at 5.210 Å (Figure 4). These hydrophobic interactions suggest that nicotine stabilizes its binding within the GSTP1 enzyme, potentially affecting its detoxification function.

The *GSTP1* gene has role in detoxifying harmful compounds by making conjugation of glutathione with various substances. The strong binding of nicotine to *GSTP1* could modulate or inhibit the activity of the enzyme, affecting its detoxification role. This stable interaction suggest that nicotine may interfere with the function of *GSTP1* with possible implications for nicotine metabolism and toxicity. However, further studies are required to explore the specific effects of this binding on *GSTP1* activity.

Molecular Modelling of *GSTP1* Variants

In this study, molecular modelling was used to assess the impact of three *GSTP1* missense variants (Ile105Val, Ala114Val, and Arg187Trp) on the risk of oral squamous cell carcinoma. Molecular docking simulations focused on the binding interactions between *GSTP1* and its substrates to predict functional disruptions caused by these variants. Three clinically significant missense variations in the *GSTP1* gene -Arg187Trp (rs115494), Ala114Val (rs1138272),

Table 1. Screening of nicotine against the protein target *GSTP1*.

GSTP1 type	Docking score (kcal/mol)	Key interactions	Binding affinity
Wild-type	-7.1	Pi–sigma bond with TYR109; Pi–alkyl with PHE9, ARG14, ILE105	Moderate
Arg187Trp	-9.8	Hydrogen bonds with GLU68, SER75, CYS101; Pi–Pi stacking with TRP104	Strongest
Ala114Val	-7.2	Hydrogen bonds with CYS101, SER108	Moderate
Ile105Val	-4.5	Minimal interaction impact	Weakest

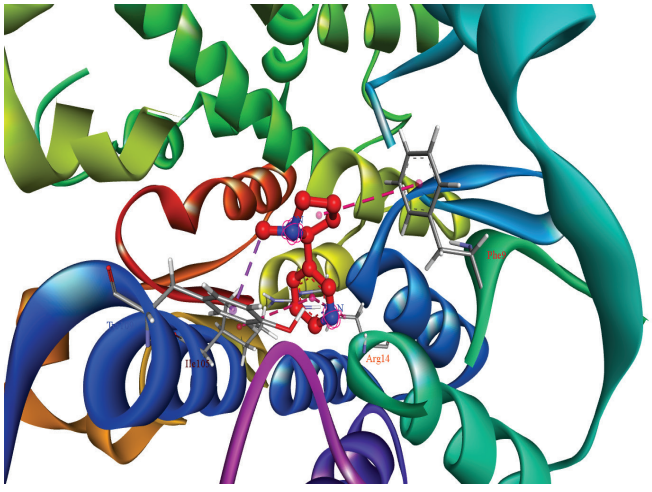

Figure 3. Structure of the treated protein target of the nicotine compound.

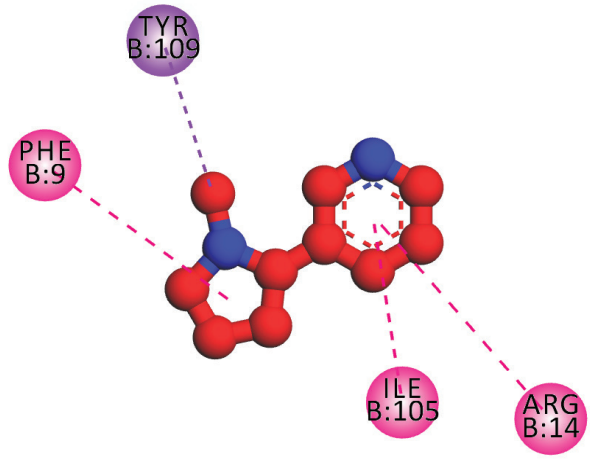

Figure 4. 2D interaction view of nicotine with target of the *GSTP1* gene's SNPs positions.

and Ile105Val (rs1695)- are the focus of the study. The genetic variations were selected because of their functional significance in carcinogen detoxification and their associations with cancer risk. Ile105Val was added because of its proven impact on detoxification effectiveness. Its association with decreased enzymatic activity and a higher risk of tobacco-related cancers, such as bladder, lung, and OSCC, has also been thoroughly studied. Because of its ability to generate ligand interactions that change protein structure, the Ala114Val variant was found to have a weaker association with the risk of oral cancer. Since it was expected that Arg187Trp would have a detrimental effect on protein function, detoxification, and the control of oxidative stress, it was given top priority because of its likely substantial functional effect. Bioinformatic docking studies were used to determine the genetic implications of these variations on *GSTP1*'s interaction with nicotine and their possible significance in the pathophysiology of OSCC. In South Asian groups, the allele frequencies were 0.31, 0.06, and 0.01 (Figure 5).

The Arg187Trp variant showed the highest docking score (-9.8 kcal/mol) that indicates a significant alteration in binding affinity and protein function. It forms strong hydrogen bonds with critical residues such as Glu68, Ser75, and Cys101 and pi–pi stacking interaction with Trp104. Findings suggest a compromised detoxification function, particularly in individuals exposed to carcinogens such as tobacco. The Ala114Val variant with a docking score of -7.2 kcal/mol, also showed significant interactions with Cys101 and Ser108, indicating moderate functional disruption. Conversely, the Ile105Val variant had a weaker docking score (-4.5 kcal/mol) and showed minimal impact on binding, aligning with its lower association with OSCC risk (Figure 6). The observed changes in docking scores for the Ala114Val and Arg187Trp variants imply the presence of possible allosteric effects, despite the fact that Ala114 and Arg187 are not found within the identified nicotine-binding pocket of *GSTP1*. By indirectly altering the structural and physicochemical properties of the ligand-binding site on a gene, missense mutations that arise far from the active binding pocket it may affect a protein's overall conformation, flexibility, and dynamic properties. The differences in expected binding affinities observed in the docking study of this particular gene in the Arg187Trp and Ala114Val variants could be explained by such allosteric effects.

Overall, these findings indicate that the Arg187Trp and Ala114Val variants are likely to impair the detoxification capacity of *GSTP1*, particularly in the context of carcinogen exposure. This reduced detoxification efficiency may lead to increased oxidative stress and DNA damage, contributing to the development of OSCC.

Discussion

Cancer is a major health risk associated with chewing tobacco, focusing specifically on its impact which differ from other smokeless tobacco products that cause seven disease outcomes examined about six i.e. esophageal cancer, lip and oral cavity cancer, laryngeal cancer, nasopharyngeal cancer, other pharyngeal cancers, and stroke have been found but less evidence related to tobacco use (Gil et al., 2024). This study conducted on the molecular interaction between nicotine and *GSTP1*, alongside three clinically relevant *GSTP1* variants of Ile105Val (rs1695),

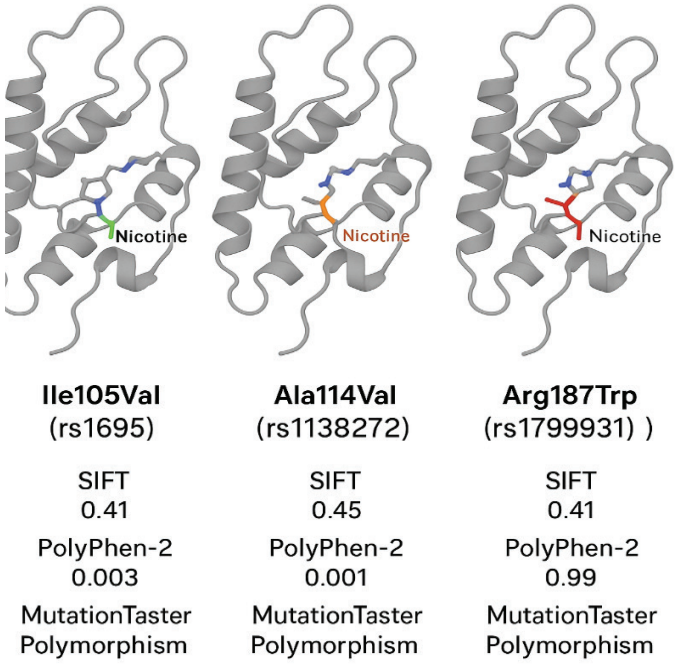

Figure 5. Molecular structural impact the Ile105Val, Ala114Val, and Arg187Trp variants with allele frequencies.

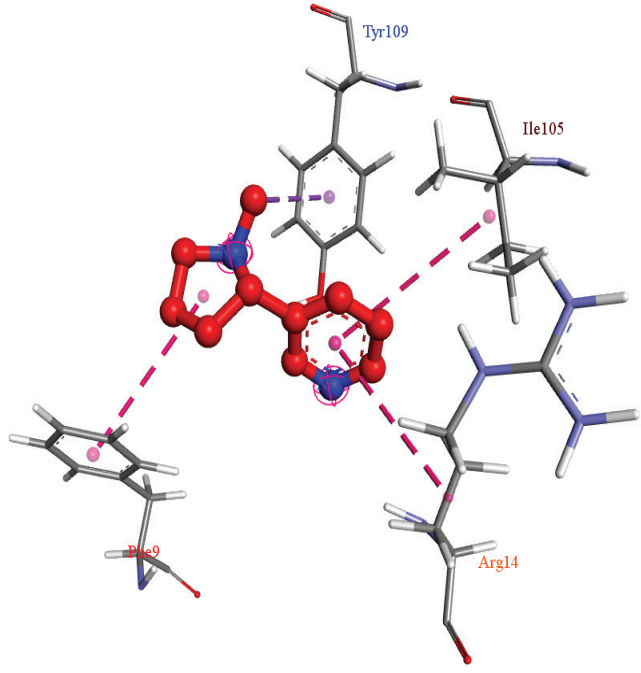

Figure 6. 3D interaction view of nicotine with target of interest 105 SNPs position in the *GSTP1* gene.

Ala114Val (rs1138272) and Arg187Trp (rs11549467) using *in silico* docking and modelling techniques. *GSTP1* plays an essential role in detoxifying electrophilic compounds, including those derived from tobacco and polymorphisms in this gene have been shown to influence cancer susceptibility (Awad et al., 2024; Vasconcelos & Gilbert, 2018). Docking analysis revealed that nicotine binds moderately to the wild-type *GSTP1* with a docking score of -7.1 kal/mol. This interaction was primarily stabilized by Pi–sigma and Pi–alkyl interactions involving TYR109, PHE9, ARG14 and ILE105 suggesting that nicotine could potentially occupy the enzyme's active site influencing its detoxification capacity. Menthol, a common flavour additive found to increase airflow sensation while it impairs respiratory reflex, enhancing lung exposure to harmful substances in both cigarettes and e-cigarettes (Kaur et al., 2018).

Among the studied variants the Arg187Trp mutation showed the highest binding affinity for nicotine (-9.8 kcal/mol) forming multiple hydrogen bonds and Pi–Pi stacking interactions with surrounding residues, including GLU68, SER75, CYS101 and TRP104. Although Arg187 is distant from the active site, this variant likely induces conformational changes that enhance ligand binding it a phenomenon consistent with allosteric modulation mechanism previously reported for GST enzymes. These findings emphasize the long-term effects of early nicotine exposure on genetic regulation (Blaskovic et al., 2022). The Ala114Val variant exhibited a moderate docking score of -7.2 kcal/mal, with hydrogen bonding observed CYS101 and SER108. Though not directly within the binding pocket Ala114 may subtly influence protein flexibility and the orientation of nearby residues, potentially affecting ligand accommodation. The process coupled with the regulation of growth factors, may contribute to cancer progression by promoting tumor growth (Barr et al., 2007). *GST* gene polymorphisms modify the effect of maternal smoking on offspring DNA methylation, showing sec-specific differences at certain CpG sites (Kheirkhah Rahimabad et al., 2023).

A study provided insights into nicotine metabolism, revealing a complex relationship between nicotine transport, protein expression, glycometabolism, and nitrogen metabolism with implications in various biochemical pathways (Mo et al., 2021). Another aspect of the study examined the Ile105Val SNP in the *GSTP1* gene in relation to OSCC in an Indian population. However, further investigation into additional *GSTP1* polymorphisms, such as Ala114Val and Arg187Trp revealed stronger associations with OSCC, suggested that other functional SNPs may play more critical role in disease pathogenicity. The *GSTP1* Ile105Val polymorphism (rs1695) is a genetic variation in the *GSTP1* gene that lead to an amino acid substitution from isoleucine (Ile) to valine (Val) at position 105 (Li et al., 2013). The Val105 variant has been associated with increased susceptibility to several cancers, including lung, breast, and oral cancers, particularly in individuals exposed to environmental toxins such as tobacco smoke (Marshall et al., 2000; Yadav et al., 2020). Due to its role in cancer risk, the *GSTP1* Ile105Val SNP is widely studied in cancer predisposition. Docking analysis can assess nicotine's binding to *GSTP1*, offering insight into how this interaction may affect the enzyme's detoxification function (Pandith et al., 2013). The consumption of tobaco major constituent of nicotine, the primary addictive component of tobacco, binds to nicotinic acetylcholine receptors (nAChRs), specifically the α7-nAChR subtype expressed in OSCC cells. This cellular intigrety will be stimulates intracellular signalling cascades, notably the PI3K/AKT pathway, which leads to increased production of synuclein gamma, a protein associated to cancer formation. Interestingly, the carcinogenic features connected to nicotine-induced expression are diminished when the AKT pathway or α7-nAChR is suppressed. Additionally, nicotine and its metabolites–particularly NNN and NNK–act as agonists on nAChRs, increasing the invasion, proliferation, and spread of oral cancer cells (Shen et al., 2024). The relative functional relevance of the Ile105Val, Ala114Val, and Arg187Trp variations of *GSTP1* may be better binding affinities and interaction residues based on our molecular docking research. The docking findings demonstrated a consistent binding energy of -7.1 kcal/mol between nicotine and the wild-type *GSTP1* protein, indicating that nicotine may impair *GSTP1*'s detoxifying function and promote carcinogen buildup. With the greatest binding affinity of -9.8 kcal/mol of the variations studied, Arg187Trp indicated a strong potential to interfere with detoxification operations. As previously reported, the Ile105Val variant, on the other hand, displayed a reduced binding affinity of -4.5 kcal/mol, suggesting its very minor influence on *GSTP1* enzymatic activity (Akkus & Kucuk Kurtulgan, 2025). The Ile105Val variant displayed the weakest binding affinity (-4.5 kcal/mol), likely due to steric alteration within the active site. Substituting isoleucine with valine slightly reduces the side chain volume, possibly disrupting the stability of ligand binding. This finding is consistent with experimental evidence indicating reduced enzymatic activity and substrate binding for the Ile105Val variant (Hollman et al., 2016). Interestingly, even though Ala114Val and Arg187Trp are situated outside the active binding region in our model, discrepancies in their docking scores suggest the potential of allosteric effects that might have an indirect influence on ligand interactions. Collectively, these findings suggest that *GSTP1* variants particularly Arg187Trp and Ala114Val may alter nicotine binding stability and potentially compromise detoxification efficiency with implications for tobacco-related cancer susceptibility. The study findings explore the function of the *GSTP1* Ile105Val (rs1695) and other functionally significant SNPs in the glutathione S-transferase family, connecting them to differences in detoxification ability and cancer susceptibility, specifically OSCC (Sharma et al., 2014). The mechanistic understanding of nicotine-related carcinogenesis by highlighting the interactions between nicotine and *GSTP1* may impair enzymatic function through docking analysis and proteomic insights. With significant ramifications for public health and tailored cancer prevention strategies, the work integrates epidemiological, toxicological, and molecular genetic evidence to enhance our understanding of tobacco-related disease risk.

Conclusion

OSCC poses significant public health challenges as its development is influenced by various genetic and environmental factors. The *GSTP1* enzyme, particularly its Ile105Val (rs1695) polymorphism, plays a crucial role in the detoxification of carcinogens and has been linked to cancer susceptibility. Understanding the interaction between nicotine and *GSTP1* through docking analysis could shed light on the biochemical mechanisms underlying cancer risk and provide valuable information for developing targeted interventions. By integrating molecular modelling, docking analysis, and proteomic data, the findings demonstrate how nicotine's interaction with variant *GSTP1* enzymes may impair detoxification capacity, contributing to carcinogenesis. The findings also underscore the broader impact of functionally significant SNPs within the *GSTP1* family on individual variability in cancer risk. These results have important public health implications, supporting the development of personalized prevention strategies and advancing our understanding of the molecular underpinnings of tobacco-related diseases.

Ethics

Ethics Committee Approval: Since the article does not contain any studies with human or animal subject, its approval to the ethics committee was not required.

Data Sharing Statement: All data are available within the study.

Footnotes

Author Contributions: Conceptualization: S.T.M., and P.N.; Design/methodology: S.T.M., and P.N.; Execution/investigation: S.T.M.; Resources/materials: S.T.M.; Data acquisition: S.T.M.; Data analysis/interpretation: S.T.M., and P.N.; Writing – original draft: S.T.M., and P.N.; Writing – review & editing/critical revision: S.T.M., and P.N.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: No external funding acquired.

References

Akkus, N., & Kucuk Kurtulgan, H. (2025). Glutathione S-transferase polymorphisms and their role in recurrent pregnancy loss: A genetic risk assessment. *Turkish Journal of Obstetrics and Gynecology, 22*(1), 19-25. https://doi.org/10.4274/tjod.galenos.2025.57609

Arja, C., Ravuri, R. R., Pulamaghatta, V. N., Surapaneni, K. M., Raya, P., Adimoolam, C., & Kanala, K. R. (2014). Genetic determinants of chronic obstructive pulmonary disease in South Indian male smokers. *PLoS One, 9*(2), e89957. https://doi.org/10.1371/journal.pone.0089957

Awad, A. A., Itumalla, R., Gaidhane, A. M., Khatib, M. N., Ballal, S., Bansal, P., Srivastava, M., Arora, I., Kumar, M., Sinha, A., Pant, K., Serhan, H. A., & Shabil, M. (2024). Association of electronic cigarette use and suicidal behaviors: a systematic review and meta-analysis. *BMC Psychiatry, 24*(1), 608. https://doi.org/10.1186/s12888-024-06012-7

Barr, J., Sharma, C. S., Sarkar, S., Wise, K., Dong, L., Periyakaruppan, A., & Ramesh, G. T. (2007). Nicotine induces oxidative stress and activates nuclear transcription factor kappa B in rat mesencephalic cells. *Molecular and Cellular Biochemistry, 297*(1-2), 93-99. https://doi.org/10.1007/s11010-006-9333-1

Blaskovic, S., Donati, Y., Ruchonnet-Metrailler, I., Avila, Y., Schittny, D., Schlepütz, C. M., Schittny, J. C., & Barazzone-Argiroffo, C. (2022). Early life exposure to nicotine modifies lung gene response after elastase-induced emphysema. *Respiratory Research, 23*(1), 44. https://doi.org/10.1186/s12931-022-01956-4

Gil, G. F., Anderson, J. A., Aravkin, A., Bhangdia, K., Carr, S., Dai, X., Flor, L. S., Hay, S. I., Malloy, M. J., McLaughlin, S. A., Mullany, E. C., Murray, C. J. L., O'Connell, E. M., Okereke, C., Sorensen, R. J. D., Whisnant, J., Zheng, P., & Gakidou, E. (2024). Health effects associated with chewing tobacco: a Burden of Proof study. *Nature Communications, 15*(1), 1082. https://doi.org/10.1038/s41467-024-45074-9

Hollman, A. L., Tchounwou, P. B., & Huang, H.C. (2016). The Association between Gene-Environment Interactions and Diseases Involving the Human GST Superfamily with SNP Variants. *International Journal of Environmental Research and Public Health, 13*(4), 379. https://www.mdpi.com/1660-4601/13/4/379

Kaur, G., Muthumalage, T., & Rahman, I. (2018). Mechanisms of toxicity and biomarkers of flavoring and flavor enhancing chemicals in emerging tobacco and non-tobacco products. *Toxicology Letters, 288*, 143-155. https://doi.org/10.1016/j.toxlet.2018.02.025

Kay, J., Thadhani, E., Samson, L., & Engelward, B. (2019). Inflammation-induced DNA damage, mutations and cancer. *DNA Repair (Amst), 83*, 102673. https://doi.org/10.1016/j.dnarep.2019.102673

Kheirkhah Rahimabad, P., Jones, A. D., Zhang, H., Chen, S., Jiang, Y., Ewart, S., Holloway, J. W., Arshad, H., Eslamimehr, S., Bruce, R., & Karmaus, W. (2023). Polymorphisms in Glutathione S-Transferase (GST) Genes Modify the Effect of Exposure to Maternal Smoking Metabolites in Pregnancy and Offspring DNA Methylation. *Genes, 14*(8), 1644. https://doi.org/10.3390/genes14081644

Koh, W. P., Nelson, H. H., Yuan, J. M., Van den Berg, D., Jin, A., Wang, R., & Yu, M. C. (2011). Glutathione S-transferase (GST) gene polymorphisms, cigarette smoking and colorectal cancer risk among Chinese in Singapore. *Carcinogenesis, 32*(10), 1507-1511. https://doi.org/10.1093/carcin/bgr175

Li, W., Chen, J., & Liu, C. (2013). Glutathione S-transferase P1 Ile105Val polymorphism and oral cancer risk: a meta-analysis. *International Journal of Medical Sciences, 10*(4), 392-398. https://doi.org/10.7150/ijms.5770

Mandal, R. K., & Mittal, R. D. (2020). Glutathione S-Transferase P1 313 (A > G) Ile105Val Polymorphism Contributes to Cancer Susceptibility in Indian Population: a meta-analysis of 39 Case-Control Studies. *Indian Journal of Clinical Biochemistry, 35*(1), 8-19. https://doi.org/10.1007/s12291-018-0787-1

Marshall, S. E., Bordea, C., Haldar, N. A., Mullighan, C. G., Wojnarowska, F., Morris, P. J., & Welsh, K. I. (2000). Glutathione S-transferase polymorphisms and skin cancer after renal transplantation. *Kidney International, 58*(5), 2186-2193. https://doi.org/https://doi.org/10.1111/j.1523-1755.2000.00392.x

Mo, Z., Pu, Y., Zhou, J., Tian, Z., Teng, J., Chen, Q., Duan, L., & Liu, R. (2021). Effect of the over-dominant expression of proteins on nicotine heterosis via proteomic analysis. *Scientific Reports, 11*(1), 21063. https://doi.org/10.1038/s41598-021-00614-x

Pandith, A. A., Lateef, A., Shahnawaz, S., Hussain, A., Malla, T. M., Azad, N., Shehjar, F., Salim, M., & Shah, Z. A. (2013). GSTP1 gene Ile105Val polymorphism causes an elevated risk for bladder carcinogenesis in smokers. *Asian Pacific Journal of Cancer Prevention, 14*(11), 6375-6378. https://doi.org/10.7314/apjcp.2013.14.11.6375

Parl, F. F. (2005). Glutathione S-transferase genotypes and cancer risk. *Cancer Letters, 221*(2), 123-129. https://doi.org/https://doi.org/10.1016/j.canlet.2004.06.016

Ramalingam, K., Krishnan, M., Ramani, P., & Muthukrishnan, A. (2023). Quality of life assessment with european organisation for research and treatment of cancer questionnaire (head and neck module 43) and its clinicopathological correlation among patients treated for oral squamous cell carcinoma: an exploratory study. *Cureus, 15*(2), e34650. https://doi.org/10.7759/cureus.34650

Schnekenburger, M., Karius, T., & Diederich, M. (2014). Regulation of epigenetic traits of the glutathione S-transferase P1 gene: from detoxification toward cancer prevention and diagnosis. *Frontiers in Pharmacology, 5*, 170. https://doi.org/10.3389/fphar.2014.00170

Sharma, A., Pandey, A., Sharma, S., Chatterjee, I., Mehrotra, R., Sehgal, A., & Sharma, J. K. (2014). Genetic polymorphism of glutathione S-transferase P1 (GSTP1) in Delhi population and comparison with other global populations. *Meta Gene, 2*, 134-142. https://doi.org/10.1016/j.mgene.2013.12.003

Shen, Y., Huang, Q., Yuan, X., Gong, H., Xu, C., Du, H., Hsueh, C.-Y., & Zhou, L. (2024). Nicotine-induced activation of cholinergic receptor nicotinic alpha 5 subunit mediates the malignant behaviours of laryngeal squamous epithelial cells by interacting with RABL6. *Cell Death Discovery, 10*(1), 286. https://doi.org/10.1038/s41420-024-02051-x

Tan, Y., Wang, Z., Xu, M., Li, B., Huang, Z., Qin, S., Nice, E. C., Tang, J., & Huang, C. (2023). Oral squamous cell carcinomas: state of the field and emerging directions. *International Journal of Oral Science, 15*(1), 44. https://doi.org/10.1038/s41368-023-00249-w

Vasconcelos, V., & Gilbert, H. (2018). Smokers' knowledge and perception of electronic cigarettes (e-cigarettes): a qualitative study of non-quitting smokers in a North London general practice. *Primary Health Care Research & Development, 20*, e38. https://doi.org/10.1017/s1463423618000439

Yadav, P., Banerjee, A., Boruah, N., Singh, C. S., Chatterjee, P., Mukherjee, S., Dakhar, H., Nongrum, H. B., Bhattacharjee, A., & Chatterjee, A. (2020). Glutathione S-transferasesP1 AA (105Ile) allele increases oral cancer risk, interacts strongly with c-Jun kinase and weakly detoxifies areca-nut metabolites. *Scientific Reports, 10*(1), 6032. https://doi.org/10.1038/s41598-020-63034-3