Research Article **Open Access**

Therapeutic utilization of tetrodotoxin for treating carcinomas: a comparative molecular docking and dosage adjustment study

Anna Grigoryan[1,2], Hamlet Karayan[3], Samvel Bagdasaryan[4], Tatevik Evadzhyan[5], Peri Ghukasyan[1], Marina Melkumyan[6], Bella Babayan[4]

[1]Russian-Armenian University (RAU), 123 Hovsep Emin St, 0051 Yerevan, Republic of Armenia (RA); [2]"Agrobiotechnology Scientific Center", Branch of ANAU (Armenian National Agrarian University) Foundation, 1 Isi le Mulino St., 1101 Ejmiatsin, RA; [3]The University of Edinburgh, Old College, South Bridge, Edinburgh EH8 9YL, United Kingdom; [4]Yerevan State University (YSU), Research Institute of Biology, 1 Alex Manoogian, 0025 Yerevan, RA; [5] Astghik Medical Center, Aram Str. 82/84, 43, 0065 Yerevan, RA; [6] Scientific and Production Center (SPC) "Armbiotechnology", National Academy of Sciences of Republic of Armenia (NAS RA), 14 Gyurjyan Str., 0056 Yerevan, RA;

***Corresponding author:** Anna Grigoryan, PhD, Senior Researcher, Head of Chair, RAU, 123 Hovsep Emin St, 0051 Yerevan, RA; "Agrobiotechnology SC", Branch of ANAU Foundation, 1 Isi le Mulino St., 1101 Ejmiatsin, RA.

Submission Date: September 23rd, 2025; **Acceptance Date:** October 19th, 2025; **Publication Date:** October 22nd, 2025

Please cite this article as: Grigoryan A., Karayan H., Bagdasaryan S., Evadzhyan T., Ghukasyan P., Melkumyan M., Babayan B. Therapeutic Utilization of Tetrodotoxin for Treating Carcinomas: A Comparative Molecular Docking and Dosage Adjustment Study. *Bioactive Compounds in Health and* Disease 2025; 8(10): 422 – 431. DOI: https://doi.org/10.31989/bchd.8i10.1788

ABSTRACT

Background: Cancer metastasis is facilitated by voltage-gated sodium channels (VGSCs) through the extracellular matrix (ECM) degradation. VGSCs play a pivotal role in cancer invasion during its epithelial-mesenchymal transition; hence, decreasing treatability. Tetrodotoxin (TTX) is a potent, selective neurotoxin that blocks VGSCs, particularly Nav1.7, which is overexpressed in carcinomas, especially type II endometrial and ductal carcinomas. TTX is found mainly in puffer fish (Fugu) and other marine and terrestrial animals used in traditional Japanese cuisine. TTX carries the potential for therapeutic applications; however, it's limited by a high toxicity and narrow therapeutic index (NTI), requiring precise dosage control for medicinal use [38]. Thus, TTX appropriate adjustment could give novel anti-metastatic agent, while maintaining a non-toxic concentration for human, what is very important. Limited insights exist on TTX's toxicology and therapeutic potential.

Objective: This study employed a multifaceted approach to evaluate the therapeutic potential of TTX in inhibiting carcinoma metastasis while ensuring concentrations remain within non-toxic levels for humans. Due to the hazardous nature of TTX, Carbamazepine (CBZ), an anticonvulsant known to block Nav1.7, was selected as a

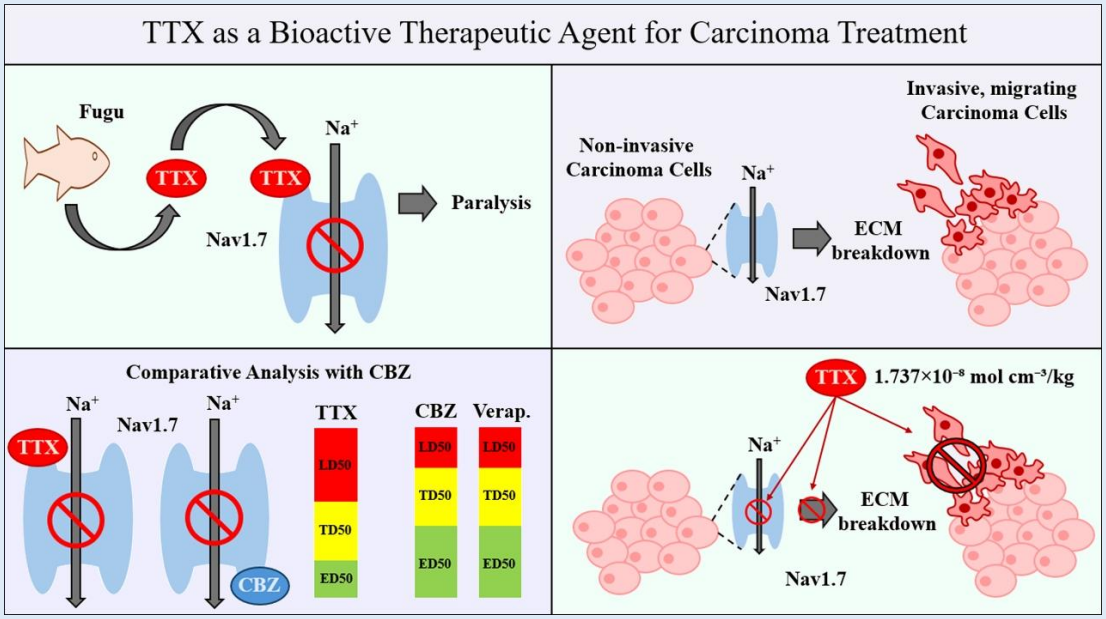
reference compound. CBZ's established pharmacokinetic profile and lower toxicity allowed for safer experimental handling and provided a comparative baseline for TTX's efficacy. Since collecting volumetric data on CBZ, according to Mohr's method, was unfeasible due to its fully molecular composition, Verapamil was introduced as a similar channel-blocking drug in chloride salt form.

Methods: Verapamil chloride was used for precipitation titration to estimate CBZ's effective (ED_{50}), toxic (TD_{50}), and lethal (LD_{50}) doses. This was done by using the ED_{50} of Verapamil and transcribing it to CBZ, as they have very similar TI. Similar tactics were carried out for the determination of the ED_{50} of TTX in concentration form, yielding its therapeutic dose. TI of TTX was calculated. Molecular Docking analysis of both CBZ and TTX's interaction with Nav1.7, independently 5 times using 20 starting conformations for each compound, with the virtual box size not exceeding 27,000 Å.

Results: *In silico* analysis showed that TTX binds to Nav1.7 within a pocket, demonstrating lower affinity but greater efficacy due to site-specific interactions, while CBZ binds on a more exposed level with less efficacy. Volumetric dosage-adjustment analysis indicated that, while TTX has NTI ≈ 1.6, careful administration could allow localized carcinoma treatment at 1.737×10^{-8} mol cm^{-3}/kg. The findings support the hypothesis that TTX, in controlled dosage-adjustment and targeted delivery, could inhibit carcinoma metastasis.

Conclusion: TTX has the potential to inhibit the invasion of carcinoma cells, especially those of ductal and type II endometrial carcinomas, by selectively blocking Nav1.7. Careful dosage control and targeted drug delivery systems (which would vary with the stage of the cancer's development) are necessary to minimize systemic toxicity. Further research is required to practically develop safe administration methods to enhance TTX's therapeutic viability, with *in vivo* methodologies.

Keywords: Cancer, tetrodotoxin (TTX), voltage-gated sodium channels (VGSCs), carbamazepine (CBZ), novel anti-metastatic agent, verapamil, bioactive, functional food.



INTRODUCTION

Neurotoxins are chemicals that interfere with the nervous system functionality. They can either inhibit the electrochemical cascade of an action potential or neurotransmitter actions [1,2]. Tetrodotoxin (TTX) is a particularly fascinating and highly lethal neurotoxin, originally found in the ovary and liver of puffer fish (Fugu, *Tetraodon* genus or *Takifugu rubripes,* traditionally used in Japanese sashimi), which functions according to the former, by binding to voltage-gated sodium channels (VGSC) and inhibiting Na^+ flow. TTX pharmacology has been studied extensively in Japan, as Fugu is regarded as one of the most delicious fish among the Japanese [3-5]. TTX is a bioactive compound capable of paralytic harm; however, its ability to halt the functionality of a significant transport channel can have medical implications, particularly for carcinoma treatments [6-8].

Carcinomas are cancerous tumors that arise from epithelial tissues and can be generalized (metastatic) or localized depending on the stage. VGSCs play a determining role in the metastasis of carcinomas, leading to cancer advancement [9,10]. Persistent Na currents, pH modulation, and Na^+/Ca^{2+} exchange drive the degradation of the extracellular matrix (ECM) and epithelial-mesenchymal transition, leading to the cancer fluidity increasing its metastatic potential [11-12]. Particularly, VGSC types Nav1.7 and Nav1.5 were found to contribute most. Type II endometrial cancer and ductal carcinoma are some of the carcinomas that possess the most VGSC activity and can be expected to be most responsive if mitigated with TTX [13-15]. It binds to the specific binding site at the outer pore region, also known as the selectivity filter of Nav1.7, similar to other TTX-sensitive VGSCs [16]. Once TTX is bound, the channel's morphology and the binding affinity halt practically all Na^+ flow, which would show promising anti-metastatic activity at pre-metastatic carcinomas. Nav1.7 concentrations have been shown to be spatially localized near invadopodia, where they enhance the activity of membrane-type matrix metalloproteinases (MT-MMPs) that degrade the extracellular matrix (ECM), leading to metastasis [17]. Blocked Nav1.7 VGSCs would reduce MMP activity near the invadopodia and preserve the ECM for longer [17].

This study aims to investigate whether TTX, a highly potent blocker from the potential functional food Fugu, can be adjusted and used as a bioactive therapeutic compound for carcinoma treatment [14, 15]. To accomplish this, comparative approaches will be carried out with the reference compound Carbamazepine (CBZ), an already medically established VGSC blocker, prescribed as an anticonvulsant. CBZ acts as a VGSC modulator and inhibits its pathological hyperactivity by binding to α-subunit of VGSC, specifically at a binding pocket formed by the external pore loop and the pore-lining part of domain IV [16]. CBZ and TTX differ greatly in their binding sites and mechanisms; however, CBZ intake at higher toxic dosages can resemble TTX toxicity, as both produce central nervous system (CNS) depression, though TTX toxicity results in absolute paralysis rather than only CNS depression [17]. Hence, it can be assumed that CBZ at high dosages is a TTX mimicking compound and the necessary dosage adjustments of CBZ can be referred to TTX [18-19]. The outcome will provide administrative volumetric dosage data for TTX, as handling a substance as potent as TTX requires administering appropriate concentrations to avoid instant adverse effects, while allowing the toxin sufficient chemical space to target the carcinoma cells [18-20].

Hence, it's hypothesized that TTX, if adjusted appropriately according to CBZ's adjustments, could be utilized effectively in blocking Nav1.7 in carcinoma cells to preserve ECM and halt invasion, while not posing the neurological harm. The contrary null hypothesis would state that TTX's toxic dosage adjustment, according to CBZ's adjustment, doesn't mean that the neurotoxin can be used in cancer treatment. To execute volumetric dosage adjustments, effective, toxic, and lethal half dosages of TTX and CBZ should be present. An effective dosage for TTX would be considered any dose that has not historically caused toxicity when ingested by a

human. TTX has been briefly studied and even tested as a pain killer at 5 µg/kg b.i.d. Thus, the human organism can somewhat tolerate and survive taking a maximum of 5µg/kg at once; hence for this study, this data will be estimated as the TTX effective dosage (ED_{50}). In case of higher doses, TTX intake would induce neurotoxicity, partial paralysis, numbness, and shutting down of organ systems, up to its lethal dosage terminating the lives of half of the affected individuals: LD_{50}=1500 µg for humans (21.4 µg/kg). Non-lethal but somewhat irreversible toxicity is estimated at TD_{50}=8 µg/kg (table 1) [21, 22].

Table 1. Dosage and compatibility characteristics of TTX, CBZ and Verapamil (70 kg considered average human weight).

TTX dosage values (in µg/kg)		**CBZ Overdose values (in mg/kg) some cases**		**Important Values for Verapamil and CBZ compatibility (in mg/kg)**	
				ED_{50}(Verap.)	2.86
ED50 (TTX)	5	ED50 (CBZ)	4.8	TD_{50}(Verap.)	11.4
TD50 (TTX)	8	TD50 (CBZ)	21	TI (Verap.)	3.99
LD50 (TTX)	21.4	LD50 (CBZ)	343	TI (CBZ)	4.38

The ED_{50} and TD_{50} values remain estimations, as there are ethical drawbacks to properly testing them. CBZ as a pharmaceutical becomes toxic and even lethal through overdose [23-25]. Due to CBZ's molecular composition, it wouldn't be possible to conduct volumetric analysis on it using precipitation titration methodologies, as a result Verapamil, which is another channel blocking agent, possessing a chloride salt form was introduced. Verapamil was a compatible match as it has a very similar TI (TD_{50}, ED_{50}) to CBZ [26-28].

This study will incorporate *in silico* and volumetric analyses to establish the safe volumetric dose of TTX and to examine TTX and CBZ binding to Nav1.7 in support of the feasibility that TTX can be used as an antimetastatic agent. The approaches answering the question would contribute to current knowledge of TTX and CBZ, potentially introducing a novel therapeutic agent in oncology. The main quality of this treatment would be halting carcinoma invasion rather than destroying the existing cancerous tissue.

METHODS:

For volumetric data, precipitation titration was carried out, according to Mohr's method, which is used to determine the concentration of chloride, bromide or cyanide ions in a solution. It involves chromate ions (K_2CrO_4) as the indicator and $AgNO_3$ 0.1 M solution as the titrant [29]. The measurements were carried out three times. Molecular docking (AutoDock Vina software and Molecular Graphics Laboratory tools) was applied to assess the potential of TTX's utilization as a pharmaceutical. The interactions of TTX and CBZ as organic ligands with Nav1.7 (with application of Protein Data Bank data of Nav1.7) is a channel protein were studied independently 5 times using 20 starting conformations for each compound, with the virtual box size not exceeding 27,000 Å**.** The affinity and the amino acids (AA) of binding sites were estimated for 11 probable conformations.

RESULTS:

Verapamil's ED_{50} was measured as 7.3 mL.

$$v\left(AgNO_3(aq)\right) = v(Verap.); n(Ag^+) = n(Verap.) = 0.0073\ mol$$

$$[Verap.] = 0.0000104 mol\ cm^{-3}/kg\ or\ Verap.(ED50) \approx CBZ(ED50) = 0.0073\ mol/kg$$

Hence, the concentration of CBZ at its ED_{50} is 0.0000104 mol cm^{-3}/kg. TD_{50} and LD_{50} values can be established through the TI values:

$$CBZ(TD50) = TI(CBZ) \times ED50(CBZ) = 0.0000456 mol\ cm^{-3}/kg; CBZ(LD50) = 0.000743 mol\ cm^{-3}/kg$$

The therapeutic window, ranging from ED_{50} to TD_{50} is 0.0000352, which is not a very high value, narrowing the therapeutic range of CBZ (Figure 2). This brings forth the matter of secondary responses. Secondary responses of an administered drug are more intensive with a lower TI. Hence, TTX, being a potent toxin, is supposed to have a even lower TI. TTX's dosages should be in concentration values therefore in mol cm^{-3}/kg. If administered, its concentration plays a significant role in its pharmacokinetic pathways, and TTX's concentration would be assumed through CBZ's:

$$LD50(TTX) = 0.0214mg/kg;$$

$$LD50(CBZ) = 343mg/kg;$$

$$[LD50(CBZ)] = 0.000743mol\ cm^{-3}/kg$$

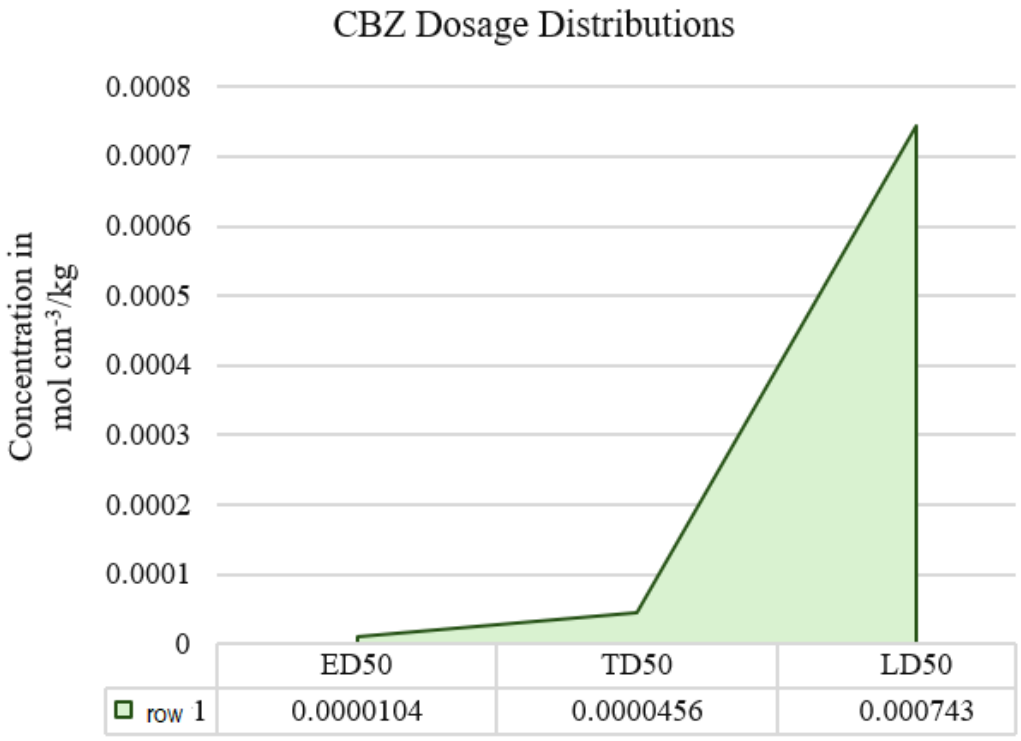


Figure 2. Dosage distribution of CBZ showing its ED_{50}, TD_{50} and LD_{50} in mol cm^{-3}/kg.

After settling the LD_{50} concentration value, theoretical foundations should be considered to proceed with the dosage adjustments. Logically, the TI of TTX should be smaller than that of CBZ. The comparative therapeutic window expression would be the following. As TTX has been studied previously to have some therapeutic potential, its TI should exceed 1.

$$[LD50(TTX)] = \frac{[LD50(CBZ)]LD50(TTX)}{LD50(CBZ)}$$

$$= 4.579 \times 10^{-8} mol\ cm^{-3}/kg$$

$$TI(TTX) < 4.38;\ TD50(TTX) - ED50(TTX) < TD50(CBZ) - ED50(CBZ);\ 1 < TI(TTX) < 4.38$$

Considering how selective and potent TTX is, it would be classified as an agent with NTI (very small difference between the effective and the toxic doses), meaning that its TI should be lower than 2 [30-32]. It belongs somewhere within the abovementioned range. For further calculations, the mean of the range will be considered TTX's TI, which is 1.5. The TI of 1.5 is very near the TI calculated from the estimated ED_{50} and TD_{50} values of TTX, which is 1.6; hence, those values can be considered valid for the study and be converted into mol cm^{-3}/kg (figure 3).

$$1 < TI(TTX) < 2;\ [ED50(TTX)] = 1.083 \times 10^{-8} mol\ cm^{-3}/kg;\ [TD50(TTX)] = 1.737 \times 10^{-8} mol\ cm^{-3}/kg$$

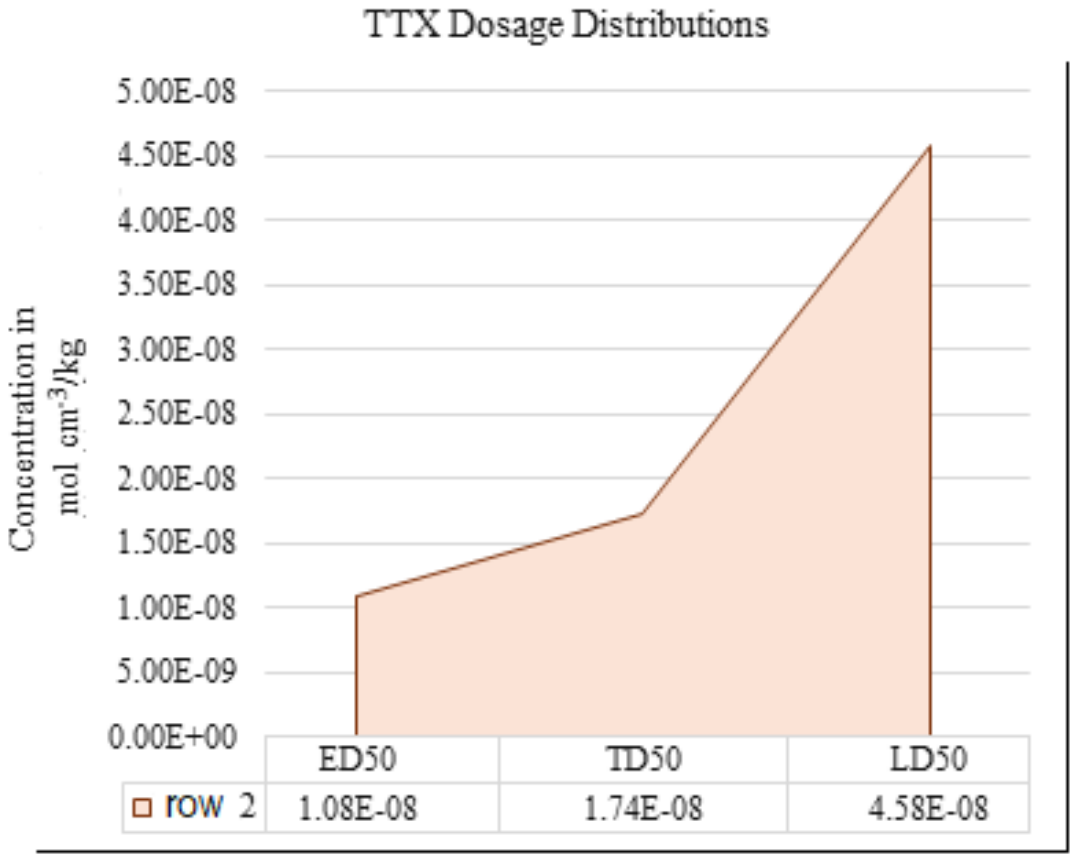


Figure 3. Dosage distribution of TTX showing its ED_{50}, TD_{50} and LD_{50} in mol cm^{-3}/kg.

The gradual increase in Figure 2 compared to the drastic increase in Figure 3, shows that TTX is a more toxic compound. TTX's therapeutic window would be:

$$1.083 \times 10^{-8} mol \frac{cm^{-3}}{kg} \rightarrow$$

$$1.737 \times 10^{-8} mol\ cm^{-3}/kg \ \ ranging\ 0.654\times 10^{-8}$$

If TTX is to be considered bioactive from a functional food source, to be utilized as a therapeutic agent based on the adjustments of CBZ, it would have to have up to 1.737×10^{-8} mol cm^{-3}/kg concentration in the sample that would be administered (upper boundary of therapeutic window). To back up the feasibility of the occurrence and the validity of the comparison, biological insights from the docking analysis would be needed. The binding sites of TTX and CBZ on Nav1,7, with their respective affinities, are presented in Table 2 and Figure 4.

Table 2. Molecular docking of TTX and CBZ interactions with Nav.1.7 (at T=309.75K).

Ligand	Amino acids of binding Site	Affinity (ΔG)	K
TTX	Arg356, Tyr362, Asn365, Arg922, Glu927, Ile929, Glu930, Lys1406, Gly1407, Ile1410, Ser1697, Ala1698, Gly1699, Asp1701, Gly1702	-8.0kJ/mol	1.003
CBZ	Cys1328, Thr1404, Leu1449, Phe1452, Ile1453, Trp1700, Val1741, Ile1744, Ile1745, Phe1748, Leu1749, Val1752	-8.9kJ/mol	1.004

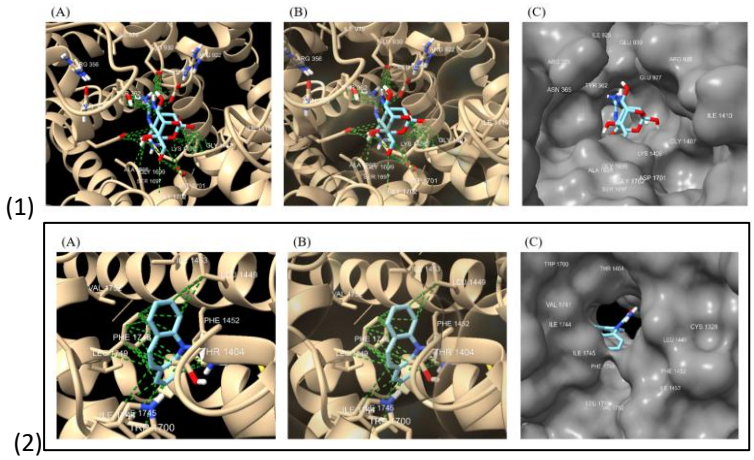


Figure 4. Molecular Docking of TTX (1) and CBZ (2). *I:* A – ligand in a ribbon diagram of Nav1.7; B – ligand with an indicated surface; C – space-filling model (closest to Nav1.7's actual physical shape); *II:* A – ligand with Nav1.7; B – ligand at the binding site in a ribbon diagram with an indicated surface; C – the space-filling model.

Figure 5. TTX and CBZ binding sites on Nav1.7: pattern of AA's in each binding sight for each ligand.

DISCUSSION:

Higher formation constant (K) values indicate higher affinity. TTX is a highly selective and potent poison, so it's theorized to have either a high affinity or a more impactful efficacy. Considering that a much less selective ligand, CBZ, has a higher K value, the toxicity of TTX lies in its efficacy. To address this, the properties of the binding sites should be evaluated [33-36]. Firstly, the configuration of each binding site should be determined. The docking provided the AAs the ligand is bound to and their number in the polypeptide chain of Nav1.7. If the number of the AAs varies by a large difference, that means the ligand is in a deeper pocket of Nav1.7, hence it is more likely to have more impactful efficacy than a ligand that binds to a shallower pocket of the protein. According to the presented data, CBZ is bound to 12 AAs in Nav1.7, ranging near the 1400s and 1700s; TTX is bound to 16 AAs in Nav1.7, more than CBZ, involving much more variety in numbers of the AAs, hence indicating its position in a pocketed section of Nav1.7, with potentially more impactful efficacy and high selectiveness due to its morphological specificity [37,38]. The morphological properties can be visually observed further (Figure 5). The deep-pocketed binding and efficacy of TTX show that it has the potential to selectively attach to the Nav1.7 VGSCs of a carcinoma and terminally block them to impede the epithelial-mesenchymal transition of the tissue and stop metastasis, if administered at the correct dosage within its established therapeutic window [39].

Practical Applications: TTX's administration to the cancer would have to involve no intravenous administration, considering it would be more bioavailable with greater secondary effects. At stage 0, its interventions are not highly necessary, as less risk-bearing options are available. At stages I and II, as the ECM starts degrading, it can be administered locally, at the lower end to the median of its therapeutic window, through direct injections to the epithelial tissue near the site [40].

Thus, TTX-based novel anti-metastatic agents could be potentially elaborated in future. At stage III, it can be administered at the higher end of its therapeutic window, to the local lymph vessels that would flow towards the carcinoma, to minimize its spread to the organism and maximize its influence on the cancer. Little can TTX do at stage IV of cancer, as it has already fully metastasized. Through these applications, TTX would be a bioactive compound, making fugu a functional food from which it originates [41].

CONCLUSION:

TTX can be adjusted according to the dosage adjustments of CBZ and potentially act as a bioactive therapeutic agent, sourced from fugu, which can subsequently be considered a functional food. It is important to note that the adjustments should account for the molarities of the substances rather than their masses, as this reflects how they are administered in clinical practice. Concentration plays a key role in determining how the drug reaches its target, what kind of secondary responses are to be expected, and its overall bioavailability. Hence, the significance of the volumetric analysis, where the ED50 of Verapamil was a model for CBZ's. The results, combined with sources, showed the effective, toxic, lethal half-dosage molarities of CBZ. TTX was assumed to be an NTI compound, and its TI was estimated accordingly. Building on TTX's known LD50, adjustments were made according to CBZ's and the therapeutic window was finalized with an upper boundary of 1.737×10^{-8} mol cm^{-3}/kg. *In silico* molecular docking analysis was then conducted to estimate the affinity and efficacy of the TTX-Nav1.7 complex and back up the dosage adjustment. Once again, a key element was comparative analysis with the CBZ-Nav1.7 complex. TTX exhibited lower affinity towards Nav1.7 than CBZ. Hence, its potency had to lie in its efficacy, which was proven to be impactful, due to the morphology of its binding site, and the binding site's variety in AA placement. The conclusions proved TTX's selectiveness, and its utilization for therapeutic uses was justified if administered correctly, at the appropriate dosage and stage of a carcinoma's development. As Nav1.7 is TTX-vulnerable, and TTX is selective towards Nav1.7, if delivered appropriately, TTX is supposed to halt the degradation of the ECM of the carcinoma and stop its development. However, the existing tissue is expected to remain intact as it was before the administration of TTX. Thus, the null hypothesis was rejected, and the hypothesis was confirmed.

Abbreviations: AA, Amino Acid; b.i.d., *Bis in die* (twice daily); CBZ, Carbamazepine; CNS, Central Nervous System; ECM, Extracellular Matrix; ED_{50}, Median Effective Dose; LD_{50}, Median Lethal Dose; MT-MMP, Membrane type Matrix Metalloproteinase; NTI, Narrow Therapeutic Index; TD_{50}, Median Toxic Dose; TTX, Tetrodotoxin; VGSC, Voltage-Gated Na Channel.

Competing interests: The authors of the paper had no competing interests

AUTHORS' CONTRIBUTIONS:

All authors contributed to this research.

REFERENCES:

1. Bucciarelli GM, Lechner M, Fontes A, Kats LB, Eisthen HL, Shaffer HB. From Poison to Promise: The Evolution of Tetrodotoxin and Its Potential as a Therapeutic. *Toxins.* 2021;13:517.
DOI: https://doi.org/10.3390/toxins13080517
2. Narahashi T. Tetrodotoxin – A brief history. *Proc Jpn Acad Ser B Phys Biol Sci.* 2008;84(5):147–154.
DOI: https://doi.org/10.2183/pjab.84.147

3. Jal S, Khora SS. An overview on the origin and production of tetrodotoxin, a potent neurotoxin. *J. Appl. Microb.* 2015;119(4):907-916. DOI: https://doi.org/10.1111/jam.12896
4. Zhang H, Hou J, Zhu Y, Wu B, Ren J, Sun Z, Liu X. Comparative Analysis of Intestinal Microbiota Between Tetrodotoxin-Containing and Tetrodotoxin-Free Takifugu rubripes. *Mar. Drugs.* 2025;23:140. DOI: https://doi.org/10.3390/md23040140
5. Ho CW, Chen PY, Liao YT, Cheng YF, Tsou HH, Liu TY, Liang KH. Uncovering the microbiome landscape in sashimi delicacies. *Sci Rep.* 2024;14(1):5454. DOI: https://doi.org/10.1038/s41598-024-55938-1
6. Varini C, Manganelli M, Scardala S, Antonelli P, Losasso C, Testai E. An Update of Tetrodotoxins Toxicity and Risk Assessment Associated to Contaminated Seafood Consumption in Europe: A Systematic Review. *Toxins.* 2025;17:76. DOI: https://doi.org/10.3390/toxins17020076
7. Katikou P, Gokbulut C, Kosker AR, Campàs M, Ozogul F. An Updated Review of Tetrodotoxin and Its Peculiarities. *Mar. Drugs.* 2022;20:47. DOI: https://doi.org/10.3390/md20010047
8. Nissl B, Mülbaier M, Grisoni F, Trauner D, Bermúdez M, Dialer C. The Chemistry and Biology of the Tetrodotoxin Natural Product Family. *ChemRxiv.* 2025;64(35):e202502404. DOI: https://doi.org/10.26434/chemrxiv-2025-vt7tq
9. Khonthun C, Khoothiam K, Chumphukam O, Thongboontho R, Oonlao P, Nuntaboon P, Phromnoi K, Screening and characterization of antioxidant, anti-aging, and anti-microbial activity of herbal extracts in Northern Thailand. *FFHD*. 2023;13(2):52-68, DOI: https://www.doi.org/10.31989/ffhd.v13i2.1070
10. Narahashi T. Pharmacology of Tetrodotoxin. *J.of Toxicology: Toxin Reviews*. 2001;20(1):67-84. DOI: https://doi.org/10.1081/txr-100102537
11. W-C Hsieh, C-W Yang, Y-S Haung, T-W Chao, T-F Tsai, I-J Su. Chemoprevention of HBV-related hepatocellular carcinomaby the combined product of resveratrol and silymarinin transgenic mice. *FFHD* 2013;3(9):341-352. DOI: https://doi.org/10.31989/ffhd.v3i9.41
12. Haffani YZ, Torkhani M, Halim NB, Chrigui S, Mami NB, Boudhrioua N, Safra I, Darmou D. oleuropein exhibits anticancer effects by inducing apoptosis and inhibiting cell motility in MCF7 and MDA-MB231 cancer cells. *FFHD,* 2025;15(3):162-175. DOI: https://doi.org/10.31989/ffhd.v15i3.1577
13. Lago J, Rodríguez LP, Blanco L, Vieites JM, Cabado AG. Tetrodotoxin, an Extremely Potent Marine Neurotoxin: Distribution, Toxicity, Origin and Therapeutical Uses. *Mar. Drugs.* 2015;13:6384-6406. DOI: https://doi.org/10.3390/md13106384
14. Huerta MA, de la Nava J, Artacho-Cordón A, Nieto FR. Efficacy and Security of Tetrodotoxin in the Treatment of Cancer-Related Pain: Systematic Review and Meta-Analysis. *Mar Drugs.* 2023;21(5):316. DOI: https://doi.org/10.3390/md21050316
15. Teibo JO, Ayinde KS, Olaoba OT, Adelusi TI, Teibo TKA, Bamikunle MV, Jimoh YA. Functional foods' bioactive components and their chemoprevention mechanism in cervical, breast and liver cancers: A systematic review. *FFHD.* 2021;11(11):559-585. DOI: https://www.doi.org/10.31989/ffhd.v11i11.818
16. González-Cano R, Ruiz-Cantero MC, Santos-Caballero M, Gómez-Navas C, Tejada MA, Nieto FR. Tetrodotoxin, a Potential Drug for Neuropathic and Cancer Pain Relief. *Toxins.* 2021;13:483-499. DOI: https://doi.org/10.3390/toxins13070483
17. Davis C. E., Davis P. F., Gubler D. A. Epigenetic Effects of Four Nutraceutical Products on Human Liver Cells. *FFHD* 2025;15(1):50-67. DOI: https://doi.org/10.31989/ffhd.v15i1.1524
18. Liu H, Weng J, Huang CLH, Jackson AP. Voltage-gated sodium channels in cancers. *Biomarker Research.* 2024, 12(1). DOI: https://doi.org/10.1186/s40364-024-00620-x
19. Liu J, Tan H, Yang W, Yao S, Hong L. The voltage-gated sodium channel $Na_v1.7$ associated with endometrial cancer. *J. of Cancer.* 2019;10(20):4954-4960. DOI: https://doi.org/10.7150/jca.31544
20. Mi Sha W, Liu S. Tetrodotoxin and the state-of-the-art progress of its associated analytical methods. *Front. Microbiol.* 2024;15:6-14. DOI: https://doi.org/10.3389/fmicb.2024.1413741
21. Zhang X, Qiao K, Cui R, Xu M, Cai S, Huang Q, Liu Z. Tetrodotoxin: The State-of-the-Art Progress in Characterization, Detection, Biosynthesis, and Transport Enrichment. *Mar. Drugs.* 2024;22:531-548. DOI: https://doi.org/10.3390/md22120531
22. Tsukamoto T, Chiba Y, Wakamori M. Differential binding of tetrodotoxin and its derivatives to voltage-sensitive sodium channel subtypes (Na v 1.1 to Na v 1.7). *British J of Pharmacology*. 2017;174(21):3881-3892. DOI: https://doi.org/10.1111/bph.13985
23. Pukkanasut P, Jaskula-Sztul R, Gomora JC, Velu SE. Therapeutic targeting of voltage-gated sodium channel NaV1.7 for cancer metastasis. *Frontiers in Pharmacology*. 2024;15:11-28. DOI: https://doi.org/10.3389/fphar.2024.1416705
24. Burton E, Ward A, Tamlin L, El-Masri S, Goh R, Ghaoui R, Bacchi S. Tetrodotoxin toxicity: an increasing threat. *Pract Neurol.* 2025;25(4):377-379. DOI: https://doi.org/10.1136/pn-2024-004368

25. Chen P, Wang J, Zhang S. Total syntheses of Tetrodotoxin and 9-epiTetrodotoxin. *Nat Commun.* 2024;15:679-687. DOI: https://doi.org/10.1038/s41467-024-45037-0
26. David B. Konrad et al. A concise synthesis of tetrodotoxin. *Science.* 2022; 377:411-415. DOI: https://doi.org/10.1126/science.abn0571
27. Gallego MDC, García MA. Acute Carbamazepine Intoxication. *Neurol Int.* 2022;14(3):614-618. DOI: https://doi.org/10.3390/neurolint14030049
28. Srilakshmi P, Prathana SGM. "Carbamazepine Induced Ataxia: A Case Report in Pediatrics". *J. of Clin. and Pharm. Research,* 2022;2(2):27-29, DOI: https://doi.org/10.61427/jcpr.v2.i2.2022.58
29. Madejska A, Michalski M, Osek J. Marine tetrodotoxin as a risk for human health. *J of Vet. Research.* 2019;63(4):579-586. DOI: https://doi.org/10.2478/jvetres-2019-0060
30. Schmidt S, Schmitz-Buhl M. Signs and symptoms of carbamazepine overdose. *J. of Neurology.* 1995;242(3):169-173. DOI: https://doi.org/10.1007/BF00936891
31. Wang L, Wang Y, Zhang RY, Wang Y, Liang W, Li TG. Management of acute carbamazepine poisoning: A narrative review. *World J Psychiatry*. 2023;19;13(11):816-830. DOI: https://doi.org/10.5498/wjp.v13.i11.816
32. Karaman K, Türkdoğan KA, Çanakçı SE. Which is the best in carbamazepine overdose. Clin. Case. Rep. 2017;5(10):1612-1615. DOI: https://doi.org/10.1002/ccr3.1118
33. Mattila J, Mäntylä R, Taskinen J, Männistö P. Pharmacokinetics of sustained-release verapamil after a single administration and at steady state. *EU J. of Drug Metabol. and Pharmacokinetics.* 1985;10(2):133-138. DOI: https://doi.org/10.1007/bf03189707
34. Kumagai S, Sambe T, Shibata K, Mizukami T, Goibuchi S. Comparative Analysis of Verapamil Pharmacokinetics: Evaluating the Impact of Simple Suspension and Crushing Administration Methods. *J. Clin. Med. 2024*;13(19):5969. DOI: https://doi.org/10.3390/jcm13195969
35. Atemnkeng F, Shabani J, Chen L, Gala B, Ramalho J, Diaz K, Nfonoyim J. A Fatal Case of Massive Verapamil Overdose: An Overview of the Treatment Options. *J Med Cases.* 2021;12(9):373-376. DOI: https://doi.org/10.14740/jmc3763
36. Charpentier C, Flandrois M, Labombarda F, Maragnes P, Jokic M, Villedieu F. Intoxication aigüe au vérapamil: attention à l'effet retard. *Arch Pediatr.* 2014;21(12):1344-7. DOI: https://doi.org/10.1016/j.arcped.2014.09.013
37. Belcher R, Macdonald AMG, Parry E. On Mohr's method for the determination of chlorides. *Anal. Chim. Acta.* 1957;16:524-529. DOI: https://doi.org/10.1016/s0003-2670(00)89979-1
38. Bialer M, Levy RH, Perucca E. Does Carbamazepine Have a Narrow Therapeutic Plasma Concentration Range. *Therapeutic Drug Monitoring*. 1998;20(1):56-59. DOI: https://doi.org/10.1097/00007691-199802000-00010
39. Sadohara R, Martirosyan D. Functional Food Center's vision on functional foods definition and science in comparison to FDA's health claim authorization and Japan's Foods for Specified Health Uses. *FFHD* 2020;10(11):465-481. DOI: https://www.doi.org/10.31989/ffhd.v10i11.753
40. Ali H, Rasool S, Saidu MB, Germán P, Szebeni GJ, Szabó E, Rédei D, Hohmann J, Zupkó I. Characterization of the Antiproliferative and Antimetastatic Properties of *C. pauciflorus* Meroterpenoid Centrapalus Coumarin F. *Int J Mol Sci.* 2025;26(10):4489. DOI: https://doi.org/10.3390/ijms26104489
41. Yesayan AH, Chetta M, Babayan BG, Yesayan TA, Esoyan SS. Sevoyan GG. The epigenetic impact of daily diet food choices on human health and chronic diseases. *FFHD* 2024;14(10). DOI: https://doi.org/10.31989/ffhd.v14i10.1464