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Comparative study of the effects of acetyl-tanghinin, tanghinin, and deacetyl tanghinin isolated from *Tanghinia venenifera* Poir. (Apocynaceae) on cardiac activity

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Abstract

This study aimed to compare the relationship between chemical structures and pharmacological activities of three cardiac glycosides isolated from *Tanghinia venenifera* (Apocynaceae): acetyl-tanghinin, tanghinin, and deacetyl-tanghinin, by evaluating their effects on myocardial contractility, heart rate, transmembrane permeability, and binding affinity toward Na^+/K^+-ATPase. Experiments were performed using an experimentally impaired isolated frog heart, complemented by transmembrane diffusion assays and in silico molecular docking analyses.

All three compounds exhibited positive inotropic and negative chronotropic effects. Acetyl-tanghinin showed the greatest inotropic activity (221.23 ± 0.90 %), followed by tanghinin (197.01 ± 1.18 %) and deacetyl-tanghinin (177.15 ± 1.01 %) ($p < 0.05$). They also decreased respectively the heart rate from 55 ± 0.06 beats/min to 27 ± 0.05 beats/min, 28.51 ± 2.1 beats/min and 28.99 beats/min ($p < 0.05$). Membrane permeation studies demonstrated that increasing the number of acetyl groups enhanced lipophilicity and facilitated transmembrane diffusion, thereby improving intracellular availability. Molecular docking revealed that deacetyl-tanghinin displayed the strongest binding affinity for Na^+/K^+-ATPase because of its higher polarity, although this greater affinity did not translate into superior pharmacological efficacy because of its low transmembrane diffusion.

These findings indicate that the cardiotonic activity of these glycosides is governed by a balance between lipophilicity, membrane permeability, and receptor binding affinity. Structural acetylation plays a critical role in optimizing biological activity by promoting transmembrane diffusion while maintaining interaction with the molecular target. Overall, this study highlights the importance of subtle structural modifications in determining their pharmacological properties and provides valuable insights for the rational design of cardiotonic agents with improved therapeutic potential

Keywords: Acetyl-tanghinin; Cardiotonic; Deacetyl-tanghinin; Tanghinin

1. Introduction

Tanghinia venenifera belongs to the Apocynaceae family, which is well known for its richness in cardiotonic glycosides [1]. Historically, this plant was used as an ordeal poison during the reign of Queen Ranavalona III in Madagascar [2]. Studies have demonstrated its cardiotoxic activity, attributed to the presence of cardiac glycosides [3].

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In 1990, Nataranja and colleagues investigated the cardiotonic activity of extracts obtained from *Tanghinia venenifera* seed kernels [2, 3]. In parallel, Randimbivololona and co-workers (1990) examined the cardiotonic effects of seed kernels extract from this plant and have isolated tanghinin and acetyl-tanghinin, both belonging to the class of cardiac glycosides [4]. More recently, Razanadrabenafindra and colleagues, working in the same laboratory as Randimbivololona, extended these investigations and demonstrated the cardiotonic activity of hydroalcoholic extracts from the leaves of *Tanghinia venenifera* [5]. In addition, they also explored the effects of deacetyl-tanghinin on cardiac activity [6].

Tanghinin, acetyl-tanghinin and deacetyl-tanghinin share the common structural backbone of cardiac glycosides but differ in the presence and position of glucose substituents at R_1 and R_2 (Figure 1).

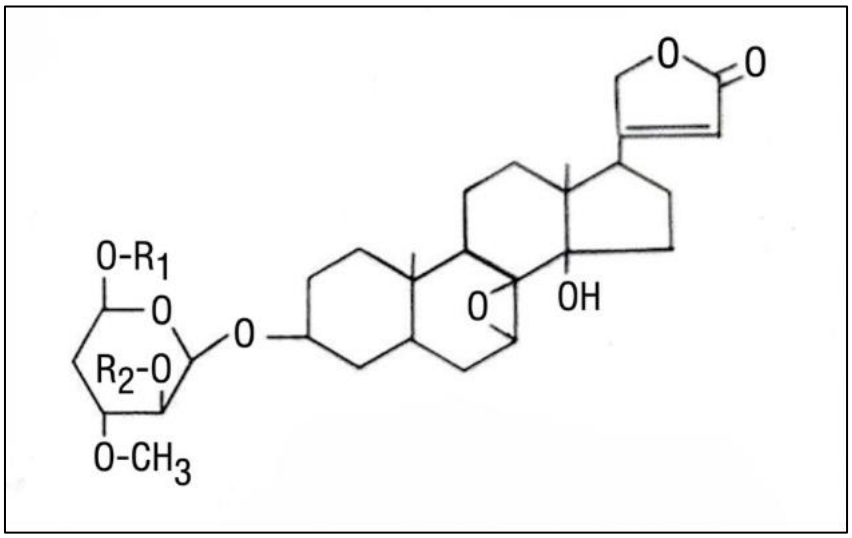

Figure 1 Basic structure of the three molecules isolated from *Tanghinia venenifera*

Tanghinin: R_1= H R_2= acetyl

Acetyl – tanghinin: R_1= acetyl R_2= acetyl

Deacetyl – tanghinin: R_1= H R_2= H

Since these three molecules share the same core structure, the aim of this study was to investigate the quantitative structure-activity relationship (QSAR) underlying their cardiotonic effects on an experimentally induced failing isolated frog heart. To achieve this objective, their effects on contractile force and heart rate, as well as their transmembrane transport, were evaluated and compared. Finally, preliminary *in silico* studies were conducted to explain their affinity for the Na^+/K^+-ATPase enzyme.

2. Materials and Methods

2.1. Experimental animals

Frogs of the species *Hoplobatrachus tigerinus*, weighing between 150 and 160 g, were used in this study. They were purchased from a local market and subsequently acclimatized for 10 days prior to experimentation in the animal house of the Laboratory of General Pharmacology, Pharmacokinetics and Cosmetology (LPGPC), Faculty of Sciences, University of Antananarivo. The animals were maintained under a 12 h light/12 h dark cycle, fed with insects, and had free access to water.

2.2. Preparation of isolated heart and experimental setup

In order isolate the heart, the frog was decerebrated and the spinal cord was destroyed, then placed in the supine position on a dissection board. A thoracotomy was performed, and the pericardium was removed [7]. The heart was then excised and placed in a Petri dish containing Ringer's solution at room temperature (Table 1).

The ventricular tip and thoracic aorta heart were secured using a S-shaped silver hook. The hook at ventricular tip was fixed to the bottom of the organ bath, containing 15 mL Ringer's solution and aerated with a system (KOKO©), at room temperature, while the second hook was connected to an isometric sensor via an inextensible cotton thread under a base tension of 1 g. This sensor was linked to an isometric transducer connected to a Harvard® oscillograph, equipped with a writing stylus that recorded contraction amplitude on millimetre paper.

Table 1 Composition of Ringer's solution (1 g/L) [8]

NaCl (g)	KCl (g)	$CaCl_2$ (g)	Dextrose (g)	$NaHCO_3$ (g)	H_2O (g)
6	0.14	0.12	1	0.2	1000

2.3. Evaluation of the activity on cardiac function

The cardiac activity of the three molecules was evaluated using an experimentally induced failing isolated heart which was prepared by reducing myocardial contractile force. Heart failure was induced by leaving it to contract for a long time. During this period, the bath was renewed every 15 minutes. Once the organ showed signs of failure, acetyl-tanghinin and tanghinin were injected cumulatively into the organ bath at concentrations ranging from 1.95×10^{-6} M until maximal contraction amplitude while from 1,99 x 10-5 M for deacetyl - tanghinin. Their contractile forces and heart rates were recorded and analysed [9].

2.4. Evaluation of transmembrane transport

To study the transmembrane transport kinetics of the three compounds, epithelial transmembrane diffusion was assessed using the Franz cell method. For this purpose, frog skin was isolated and cleaned with ethanol, then placed between the donor and receptor compartments. The prepared solution was subsequently added to the donor compartment. Transmembrane diffusion was evaluated by collecting samples from the receptor compartment at 15, 30, 45, 60, 120, 180, 240, 300, and 320 minutes. Three drops of Kedde's reagent were added to each collected sample to detect the presence of cardiac glycosides. The samples were then analysed using a spectrophotometer (PHOTOMETER MODEL© 721) at a visible wavelength of 580 nm to measure absorbance [10, 11].

2.5. *In silico* evaluation of the affinity of the three molecules

To complement the *in vitro* findings, an *in silico* bioinformatics approach was conducted to provide an exploratory insight into the potential mechanism of action of the three compounds toward Na^+/K^+-ATPase. The three-dimensional structure of Na^+/K^+-ATPase (PDB ID: 3A3Y) [12], was retrieved from the RCSB- Protein Data Bank (https://www.rcsb.org/) [13]. The protein structure was prepared by removing water molecules and heteroatoms, followed by the addition of polar hydrogen atoms and appropriate charge assignment, using BIOVIA Discovery Studio [14]. The chemical structures of the three ligands were obtained from the PubChem database [15]. Molecular docking simulations were performed using PyRx v0.8.0.0 [16], employing the AutoDock Vina scoring function [17]. The docking grid was defined to cover the reported active site of Na^+/K^+-ATPase [18], and same parameters were applied for all ligands to ensure comparability of results. The best docking poses were selected based on the lowest binding energy values (Kcal/mol). Protein–ligand interactions were subsequently analysed using BIOVIA Discovery Studio [14], focusing on hydrogen bonds, hydrophobic interactions, and key amino acid residues involved in ligand binding.

2.6. Expression and analysis of results

The results were expressed as mean values with standard errors ($\bar{x} \pm \bar{\sigma}$). The means were compared using Student's t-test with Microsoft Office LTSC Excel 2016 software. Differences between two means were considered statistically significant for $p < 0.05$.

3. Results

3.1. Effect of the three molecules on contractile force

Administered cumulatively in the bath containing the failed isolated frog heart, the three compounds increased the contraction amplitude in a concentration-dependent manner. Initially, the contraction amplitude was considered to 0. Acetyl-tanghinin and tanghinin at the same concentration of 1.36×10^{-5} M, show respectively a maximum increase of 221.23 ± 0.90 % and 197.01 ± 1.18 %, while deacetyl-tanghinin at a concentration of 7.96×10^{-5} M induces an

increase of 177.15 ± 1.01 % ($p < 0.05$) and pD_2 values of 5.336, 5.218 and 4.696 respectively (Figure 2). These results demonstrate that all three compounds enhance cardiac contractile force, indicating a positive inotropic effect. Thus, acetyl-tanghinin exhibited higher activity than tanghinin and deacetyl-tanghinin. However, at concentrations above 1.55×10^{-5} M, the opposite effect was observed: both acetylated compounds reduce contraction amplitude. The same phenomenon was observed for deacetyl-tanghinin but only at concentration above 9.95×10^{-5} M.

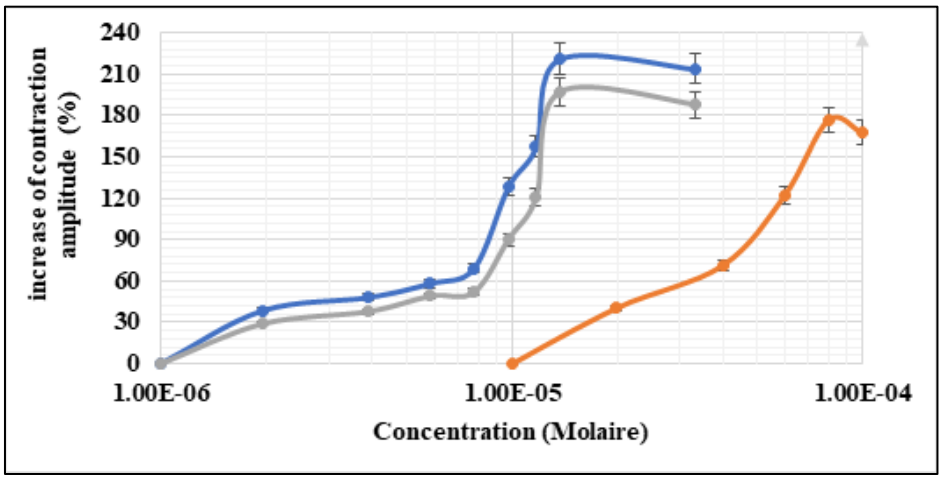

Figure 2 Variation of the increase in contraction amplitude of the experimentally induced failing isolated frog heart in the presence of acetyl-tanghinin ( ), tanghinin ( ), and deacetyl-tanghinin ( ), administered cumulatively in the organ bath ($\bar{x} \pm \bar{\sigma}$; $n = 10$; $p < 0.05$)

3.2. Effect of the three molecules on heart rate

The three compounds decreased the heart rate of the isolated frog heart with concentration-dependent and cumulative manner. Without treatment, the normal heart rate was 55 ± 0.06 beats/min. After injection in the bath of acetyl-tanghinin, this value decreased to 27 ± 0.05 beats/min compared with 28.51 ± 2.1 beats/min for tanghinin at the same concentration of 1.36 × 10-5 M. In the presence of deacetyl-tanghinin at 7.96 × 10-5 M, the heart rate was 28.99 ± 0.28 beats/min ($p < 0.05$) (Figure 3). These results indicate that all three compounds slow the heart rate, demonstrating a negative chronotropic effect.

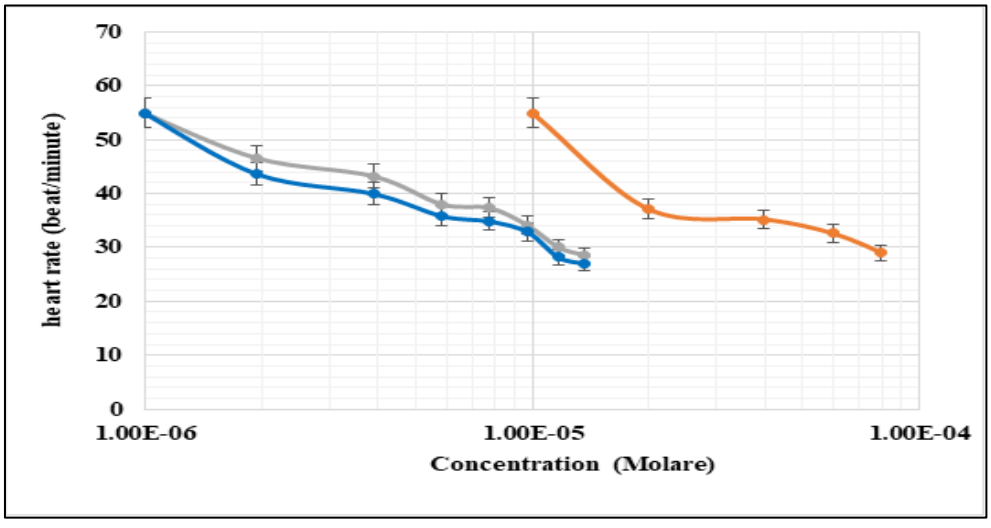

Figure 3 Variation in the beating frequency of the experimentally induced failing isolated frog heart in the presence of tanghinin ( ), acetyl-tanghinin ( ), and deacetyl-tanghinin ( ), administered cumulatively in the organ bath ($\bar{x} \pm \bar{\sigma}$; $n = 10$; $p < 0.05$)

3.3. Kinetics of transmembrane transport of the three molecules

The three compounds crossed the membrane over time according to their absorption kinetics. For acetyl-tanghinin, the absorbance measured with Kedde's reagent was 1.073 ± 0.020, compared with 1.020 ± 0.001 for tanghinin and 0.903 ± 0.011 for deacetyl-tanghinin (Figure 4). The shape of the curves shows a similar variation in absorbance for all molecules tested with slightly lower values for the deacetyl derivative meaning that it was less permeable than the two others acetylated molecules.

These results suggest that the presence or absence of the acetyl group has a significant influence on molecular permeability and consequently on solubility.

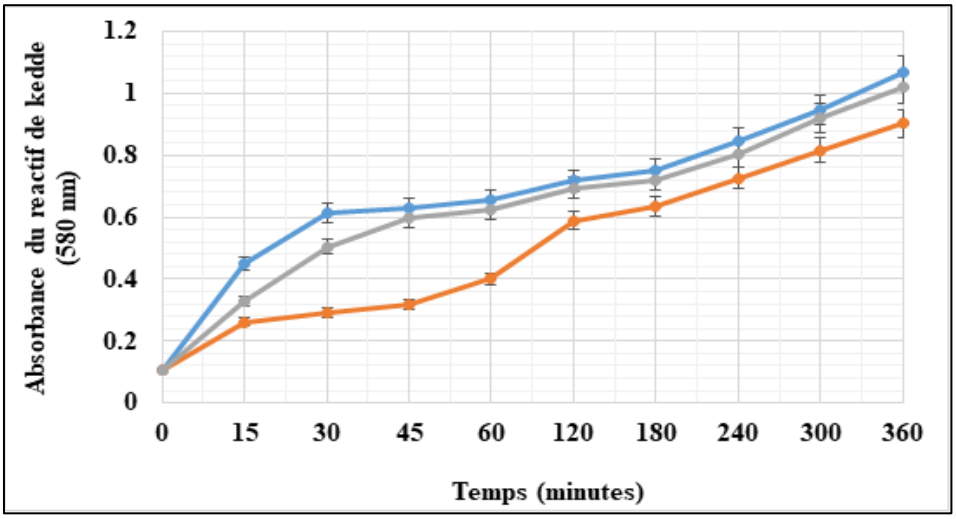

Figure 4 Variation in Kedde's reagent absorbance of acetyl-tanghinin ( ), tanghinin ( ), and deacetyl-tanghinin ( ) during membrane permeation ($\bar{x} \pm \bar{\sigma}$; n = 10; $p < 0.05$)

3.4. Affinity of the three molecules on ATPase site *in silico*

The *in-silico* study performed on acetyl-tanghinin, tanghinin, and deacetyl-tanghinin shows strong negative binding energy for all molecules indicating that they have a great affinity for the receptor, particularly the deacetyl-tanghinin with the higher value of −9.4 kcal/mol. Generally, the greater a molecule's affinity for a ligand, the stronger its interaction with it. However, according to the results in Table 2, the number of hydrogen bonds in deacetyl-tanghinin (which has no acetyl group in its structure), which is 4, is lower than that of tanghinin (with one acetyl group), which is 6, and that of acetyl-tanghinin (with two acetyl groups), which is 8. This further confirms the key role of acetyl groups in the cardiovascular activity of the latter two molecules.

Table 2 *In silico* docking results and physicochemical properties of deacetyl-tanghinin, tanghinin, and acetyl-tanghinin

Parameters	Deacetyl-tanghinin	Tanghinin	Acetyl-tanghinin
Binding energy (kcal/mol)	-9.4	-8.8	-8.6
Hydrogen bond number	4	6	8
RMSD (Å)	0.0	0.0	0.0
Relative polarity	High	Moderate	Low
log P (Lipophilicity)	1.2 (low)	1.8 (moderate)	2.3 (high)
Molecular weight (g/mol)	548,7	590,7	632,7

On the other hand, the various amino acid interactions, including van der Waals forces, carbon–hydrogen bonds, conventional hydrogen bonds, π-donor hydrogen bonds, Π-σ interactions, and alkyl interactions, play a role in binding and stabilizing the ligands at the Na^+/K^+-ATPase receptor (Figure 5) (Table 3).

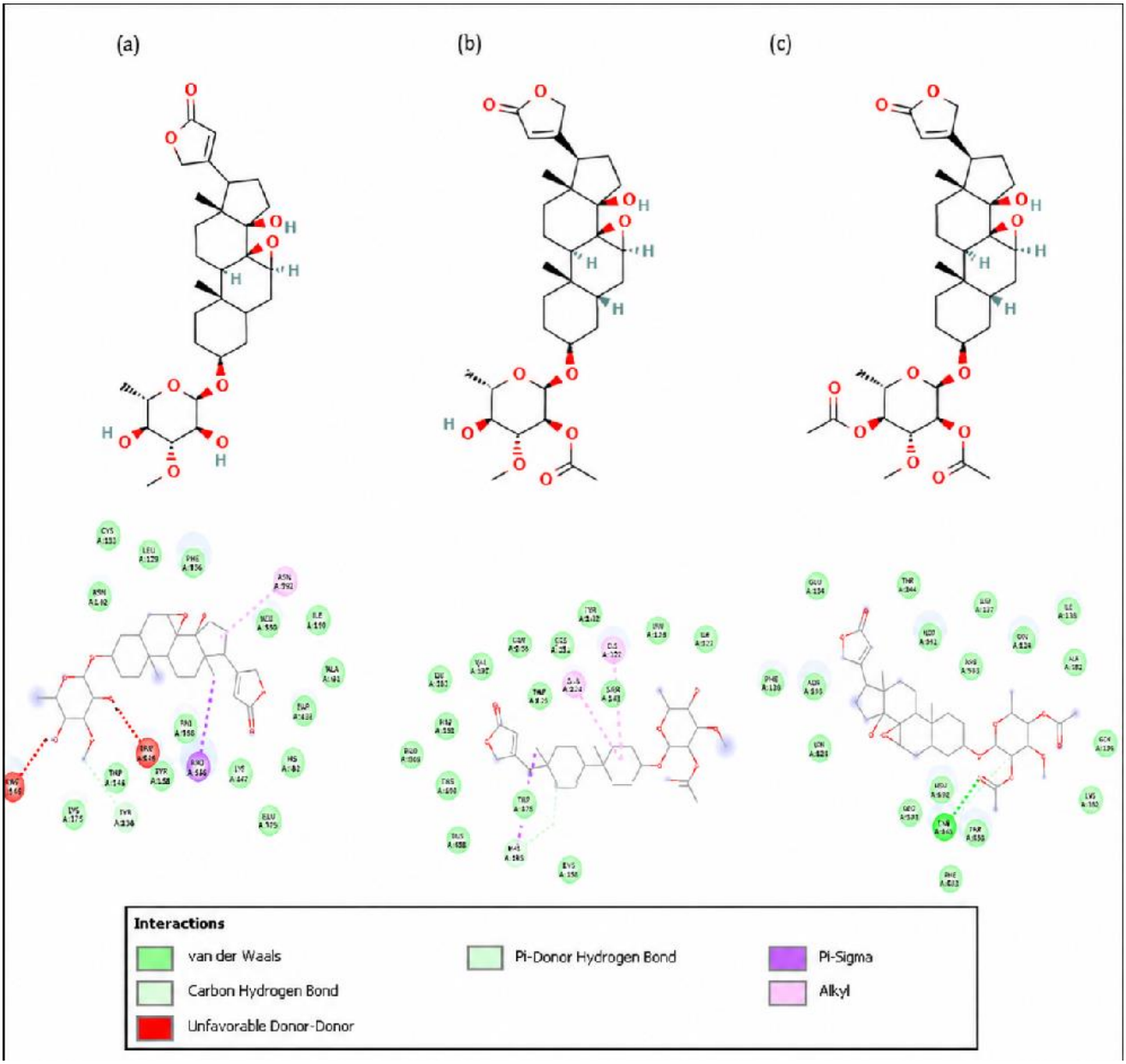

Figure 5 Visual representation of the analysis of the binding interactions of deacetyl-tanghinin (a), tanghinin (b), and acetyl-tanghinin (c) at the Na^+/K^+ ATPase receptor

Table 3 The different interactions involved in the interaction between Na^+/K^+ ATPase receptor and the ligands

Interactions	Deacetyl-tanghinin	Tangihinin	Acetyl-tanghinin
Van der Waals	CYS A: 111, ASN A: 129, LEU A: 132, THR A: 804, GLY A: 326, ILE A: 807, GLU A: 786, ALA A: 330, ILE A: 787, LEU A: 791, ILE A: 327, LEU A: 800, ASP A: 126, PHE A: 916, LYS A: 912	PHE A: 323, GLY A: 326, VAL A: 329, ILE A: 807, GLU A: 786, ALA A: 330, ILE A: 787, ILE A: 327, LEU A: 800, THR A: 804, CYS A: 111, LEU A: 132, ASN A: 129, LEU A: 113, ILE A: 117, GLN A: 118	LYS A: 912, ARG A: 893, GLU A: 124, TRP A: 894, ASP A: 891, LEU A: 132, PHE A: 793, CYS A: 111, ILE A: 322, ILE A: 325, LEU A: 110, GLY A: 326, ILE A: 328
Carbon hydrogen bond	TYR A: 908	-	ARG A: 893, ASP A: 891, CYS A: 111, ILE A: 322,

			GLY A: 326, LEU A: 800, PHE A: 790, THR A: 804
Conventional hydrogen bond	THR A: 804	-	THR A: 804
Pi donor hydrogen bond	-	PHE A: 790, ILEU A: 322, ALA A: 114, GLN A: 118, LEU A: 113	-
Pi sigma	PHE A: 790	PHE A: 790	-
Alkyl	VAL A:329	ALA A:114, ILE A: 322	-

Furthermore, their log P values, ranging from 1 to 3, and their molecular weights are highly conducive to their permeability, as they are neither too polar nor too non-polar, with smaller molecular weights (< 500 a.m.u) and can easily cross cell membranes. This explains their activity.

However, when comparing their structures, it is observed that as the number of acetyl groups increases, their mass increases and their polarity decreases.

4. Discussion

Tanghinin, acetyl-tanghinin, and deacetyl-tanghinin share the characteristic steroidal core of cardiac glycosides. This strongly suggests that they all have a similar primary mechanism involving inhibition of the Na^+/K^+-ATPase. Despite this common structural backbone, the presence or absence of acetyl groups at R_1 and R_2 and their positioning significantly modulate their physicochemical properties, particularly polarity.

The introduction of acetyl groups increases lipophilicity, as reflected by high log P value of acetyl-tanghinin (2.3) compared to tanghinin (1.8) and deacetyl-tanghinin (1.2). This parameter is a critical determinant of passive transmembrane diffusion as described by the classical Overton's rule, whereby more lipophilic compounds exhibit enhanced permeability across biological membranes [18]. This explains the faster transmembrane diffusion of acetyl-tanghinin compared to the two more polar derivatives. Conversely, the high polarity of deacetyl-tanghinin likely limits its membrane permeability, thereby reducing its intracellular availability. According to Lipinski's rule, which is used to estimate the oral bioavailability of a compound based on its two-dimensional structure (molecular weight ≤ 500, log P < 5, hydrogen bond donors ≤ 5; hydrogen bond acceptors ≤ 10), the three molecules exhibit good absorption and good permeability and therefore good bioavailability, the three molecules exhibit good absorption and good permeability and therefore good bioavailability.

These differences in membrane permeability are clearly reflected into the observed pharmacological responses. Acetyl-tanghinin produces a more pronounced positive inotropic effect, which can be attributed to its enhanced ability to cross the cell membrane and rapidly reach intracellular targets within cardiomyocytes. Its strong activity reflects more the quantity that reaches the receptor than the quality of its binding to it. This is why, *in silico* docking studies reveal an inverse relationship between polarity and binding energy. Deacetyl-tanghinin, the most polar compound, shows the highest binding affinity (−9.4 kcal/mol), followed by tanghinin (−8.8 kcal/mol) and acetyl-tanghinin (−8.6 kcal/mol). This suggests that polar compounds may form stronger hydrogen bonds and electrostatic interactions within the Na^+/K^+-ATPase binding site, consistent with previous studies highlighting the importance of hydrogen binding in ligand–receptor interactions [19].

But their number does not strictly correlate with binding energy. Acetyl-tanghinin forms a greater number of hydrogen bond interactions (8) compared to tanghinin (6) and deacetyl-tanghinin (4), indicating enhanced stabilization within the binding site. This suggests that not only the strength but also the spatial distribution and multiplicity of interactions contribute to overall binding stability [20].

However, at elevated concentrations, all three compounds lead to a decrease in contraction amplitude. This effect may reflect excessive inhibition of the Na^+/K^+-ATPase, resulting in intracellular calcium overload and subsequent impairment of contractile function, a phenomenon widely described for cardiac glycosides [21].

All three compounds also induce a negative chronotropic effect, suggesting an influence on cardiac conduction, potentially mediated by their electrophysiological actions. The greater activity of acetyl-tanghinin in this regard further supports the role of lipophilicity in facilitating rapid access to cardiac sites.

Taken together, these findings emphasise the importance of striking a balance between lipophilicity and polarity. Greater lipophilicity enhances membrane permeability and bioavailability, while higher polarity improves binding affinity at the receptor level. The overall pharmacological activity thus reflects a compromise between these opposing factors.

From a structure–activity relationship (SAR) perspective, acetylation appears to be a key to optimizing biological activity through structural modification. The presence of acetyl groups increases lipophilicity, promotes transmembrane diffusion and increases the number of stabilizing interactions within the receptor site. This results in superior inotropic and chronotropic effects despite slightly lower binding affinity. In contrast, deacetylation increases polarity and receptor affinity but limits membrane permeability, ultimately reducing pharmacological efficacy [22].

5. Conclusion

This study demonstrates that tanghinin, acetyl-tanghinin, and deacetyl-tanghinin, three cardiac glycosides differing only in the number of acetyl groups, exert potent positive inotropic and negative chronotropic effects. Although they share the same steroidal scaffold, variations in acetylation markedly influence their physicochemical properties and cardiotonic efficacy. Acetyl-tanghinin exhibited the greatest pharmacological activity, likely due to its optimal balance between lipophilicity, membrane permeability, and receptor interaction, despite displaying a lower predicted Na^+/K^+-ATPase binding affinity than deacetyl-tanghinin. In contrast, deacetyl-tanghinin showed the strongest predicted receptor binding but weaker biological activity, indicating that receptor affinity alone is insufficient to determine cardiotonic efficacy. These findings highlight that the biological activity of *Tanghinia venenifera* cardiac glycosides results from an interplay among structural acetylation, molecular polarity, membrane transport, and receptor binding. They provide new insights into the structure–activity relationships of these natural compounds and identify acetylation as a key structural determinant of cardiotonic activity.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

Prior to the start of the experiments, ethical approval for animal use was obtained from the Ethics Committee of the Faculty of Science, University of Antananarivo, under approval register CEA/FS-UA/Registre n°13/2025.

References

[1] Hollman A. Plants and cardiac glycosides. British Heart Journal. 1985; 54: 258 - 261.

[2] Andriananja M O. Contribution to the study of the two cardiotonic varieties of tanghin in Madagascar: *Tanghinia venenifera* (Apocynaceae) and *Menabea venenata* (Asclepiadaceae). Bulletin of the Malagasy Academy. 1986; 60/10: 113 - 116.

[3] Natarajan R, Rakotoarivelo J, Bost J. Cardiotonic activity of total extracts of *Tanghinia venenifera.* Therapie. 1968; 23(1): 39 - 49.

[4] Randimbivololona F, Rakotomanga N. inotropic effets of Tanghinin and Acetyl-tanghinin on guinea-pig isolated papillary muscle. International Archives of Pharmacodynamics and Therapy. 1990; 307: 83 - 91.

[5] Razanadrabenafindra R, Razafimahazoro S D, Ratovonarindra K, Quansah N, Vestalys Ramanandraibe V, Randrianavony P. Evaluation of the effect of the hydroalcoholic extract of *Tanghinia venenifera Poir.* (Apocynaceae) leaves on cardiac activity. World Journal of Biology Pharmacy and Health Sciences. 2026; 25(03): 20 - 26.

[6] Razanadrabenafindra R, Vestalys Ramanandraibe V, Razafimahazoro S D, Ratovonarindra K, Quansah N, Randrianavony P. Evaluation of the effect of deacetyl-tanghinin on cardiac activity. GSC Biological and Pharmaceutical Sciences. 2026; 34(03), 128 - 134.

[7] Etou Ossibi A W, Elion Itou R. D G, Morabanza C J, Nsonde Ntandou G F, Ouamba J M, Abena A A. Effect of the Hydroethanolic Extract of *Lippia multifora Moldenke* on the Isolated Toad Heart. International Journal of Biological and Chemical Sciences, 2016; 10(6): 2617 - 2636.

[8] Kitchen I. Textbook of *in vitro* practical pharmacology. 1st ed. Oxford: Blackwell Scientific; 1984. p. 5 - 6.

[9] Randrianavony P. Effect of neriifolin on the cardiac muscle of the *in vitro* guinea-pig. [Ph.D. dissertation]. Antananarivo (Madagascar): Faculty of Science, University of Antananarivo; 1993.

[10] Ng S, Rouse J, Sanderson D, Eccleston G. A comparative study of transmembrane diffusion and permeation of ibuprofen across synthetic membranes using franz diffusion cells. Pharmaceutics. 2010; 2: 209 - 223.

[11] Fong H H H S, Tin-Wa M, Farnsworth N R. Pratical manuel for phytochemical screening. Revue Collège of Pharmacy, University of Illinos (CHICAGO). 1977; 275 - 277.

[12] Patela N C, Kumarb P S, Modic M K, Sonia N M, Modia R N, Pandyaa A H. Cardiotonic steroids as potential Naþ/Kþ-ATPase inhibitors– a computational study. Journal of receptors and signal transduction. 2019; 39(3): 226 - 234.

[13] Berman H M, Kleywegt G J, Nakamura H, Markley J L. The future of the Protein Data Bank. Biopolymers. 2013; 99(3): 218 - 222.

[14] Biovia, Dassault Systèmes, Discovery Studio Visualizer, Release 2017, San Diego: DassaultSystèmes,2017. Available from https://www.3ds.com/fr/products/biovia/discovery-studio/visualization.

[15] Kim S., Thiessen P A, Bolton E E, Chen J, Fu G, Gindulyte, A, Han L, He J, He S, Shoemaker B A, Wang J, Yu B, Zhang J, Bryant S H. PubChem Substance and Compound databases. Nucleic Acids Research. 2016; 44(1): 1202 - 1213.

[16] Dallakyan S, Olson A. Small-molecule library screening by docking with PyRx. Methods in Molecular Biology. 2015; 1263: 243 - 250.

[17] Trott O., Olson A J. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal Computational Chemistry. (2010); 31(2): 455 - 461.

[18] Ogawa H, Shinoda T, Cornelius F, Toyoshima C. Crystal structure of the sodium-potassium pump (Na^+, K^+-ATPase) with bound potassium and ouabain. Proceedings of the national academy of sciences of the United States of America. (2009); 106(33): 13742 - 13747.

[19] Lipinski C A, Lombardo F, Dominy B W, Feeney P J Experimental and computational approaches to estimate solubility and permeability in drug discovery. Advanced Drug Delivery Reviews. 2001; 46(1-3): 3 - 26.

[20] Kitchen D B, Decornez, H, Furr J R, Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nature Reviews Drug Discovery. 2004; 3(11): 935 - 949.

[21] Chen D, Oezguen N, Urvil P, Ferguson C, Dann M S, Savidge C T. Regulation of protein-ligand binding affinity by hydrogen bond pairing. Science Advances. 2016; 1 - 16.

[22] Eisner D A, Caldwell J L, Kistamás K, Trafford A W. Calcium and excitation–contraction coupling in the heart. Circulation Research. 2009; 104(6): 673 - 683.

[23] Ditzinger F, Price D J, Ilie A R, Köhl N J, Kuentz M. Lipophilicity and hydrophobicity considerations in bio-enabling oral formulations approaches. Journal of Pharmacy and Pharmacology. 2019; 71(4): 464 - 482.

[24] Ginex T, Vázquez J, Gibert E, Herrero E, Luque F J. Lipophilicity in drug design: an overview of lipophilicity descriptors in 3D-QSAR studies. Future Medicinal Chemistry. 2019; 11(10): 1177 - 1193.