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Evaluation of the effect of deacetyl-tanghinin on cardiac activity

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Abstract

Desacetyl-tanghinin is a cardiac glycoside isolated from *Tanghinia venenifera* Poir. (Apocynaceae). The present study aimed to evaluate its effects on cardiac activity using the Langendorff retroperfusion technique on an experimentally failing isolated frog heart. The compound was introduced into the perfusion system, and its effects on cardiac output, contractile force, heart rate, and diastolic filling time were assessed. Its influence on cardiac electrical activity was also investigated by recording the electrocardiogram (ECG) using lead II.

The results showed that, at concentrations ranging from 1×10^{-5} to 7.96×10^{-5} M, desacetyl-tanghinin increased the cardiac output from 27 ± 0.577 mL/min to 83.4 ± 1.154 mL/min, force of contraction from baseline to 177.15 ± 1.01 %, with a pD_2 value of 5.336. The same concentration range decreased heart rate from 55 ± 0.06 to 28.99 beats/min, while it increased diastolic duration from 0.05 ± 0.02 to 0.153 ± 0.005 s ($p < 0.05$). These findings indicate a positive inotropic and lusitropic effect associated with a negative chronotropic effect.

The ECG recording shows atrioventricular block at 2.89 ± 0.17 mg/kg, extrasystoles at 3.41 ± 0.148 mg/kg, ventricular fibrillation at 5 ± 0.24 mg/kg, and cardiac arrest at 6.85 ± 0.37 mg/kg.

These results demonstrate that desacetyl-tanghinin increases heart output of failing isolated frog heart, exhibits positive inotropic and lusitropic, and negative chronotropic effects, which are characteristic pharmacological properties of cardiotonic glycosides.

Keywords: Cardiotonic; Desacetyl-Tanghinin; Electrocardiogram; Positive Inotrope

1. Introduction

Cardiac glycosides are clinically prescribed to manage chronic heart failure and cardiac arrhythmias due to their potent positive inotropic and negative chronotropic effects. These compounds are widely distributed in the plant kingdom, particularly in the Apocynaceae family, including *Strophanthus spp*. and *Tanghinia venenifera*, and in the Plantaginaceae (formerly Scrophulariaceae), notably *Digitalis spp*., which are classical sources of cardenolides such as digoxin, digitoxin, and ouabain. Other plant families, including Oleaceae (*Nerium oleander*) and Asclepiadaceae (*Asclepias spp*.), also contain cardenolides, while certain Crassulaceae species, such as *Kalanchoe spp*., contain bufadienolides. In addition, bufadienolides are found in the animal kingdom, for instance in *Bufo gargarizans* (bufalin, cinobufagin) and *Bufo marinus* (marinobufagenin). These natural sources have historically served as the basis for therapeutic agents, underscoring the pharmacological significance of cardiac glycosides [1]. They are known for their positive inotropic and

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negative chronotropic effects by inhibiting the membrane Na^+/K^+ ATPase of cardiomyocytes. This leads to an accumulation of intracellular sodium, which activates L-type calcium channels, thereby increasing intracellular calcium levels. By binding to ryanodine receptors of the sarcoplasmic reticulum, these calcium ions trigger the release of calcium from these stores, further raising cytoplasmic calcium concentration and consequently enhancing cardiac muscle contraction (positive inotropic effect) [2]. Concurrently, cardiac glycosides enhance the heart's sensitivity to vagal stimulation, slowing the firing of the sinoatrial node and conduction through the atrioventricular node, which results in a reduced heart rate (negative chronotropic effect). Combined with their positive inotropic action, these effects improve cardiac efficiency by producing stronger contractions at a slower rate, thereby enhancing cardiac output - a mechanism particularly beneficial in the management of heart failure [3].

Research on cardiotonic glycosides remains highly relevant due to the ongoing prevalence of heart failure and cardiac arrhythmias, conditions that continue to pose significant clinical challenges worldwide. Heart failure affects tens of millions of people globally, with the number of cases more than doubling from approximately 25 million to over 55 million between 1990 and 2021, making it a leading contributor to morbidity and healthcare burden [4]. Cardiac arrhythmias are also widespread, with atrial fibrillation alone affecting an estimated 33.5 million individuals worldwide and lifetime risk rising with age [5]. Despite the availability of modern therapies, glycosides such as digoxin retain therapeutic value. Furthermore, numerous plant and animal sources of cardiac glycosides remain underexplored, offering opportunities to discover novel compounds with enhanced efficacy or reduced toxicity.

Previous studies realized in our lab have shown cardiotonic activity of tanghinin and acetyl-tanghinin isolated from *Tanghinia venenifera* Poir. (Apocynaceae) [6], Building on these findings, we hypothesized that desacetyl-tanghinin may also exhibit cardiotonic activity.

2. Materials and methods

2.1. Animal of experimentations

In vitro experiments were conducted on isolated hearts of frog (*Hoplobatrachus tigerinus*) weighing between 80 and 150 g. The animals were purchased from the Analakely market (Antananarivo, Madagascar). Prior to experimentation, they were acclimated for 5 days in the animal house of the Laboratory of General Pharmacology, Pharmacokinetics, and Cosmetology (LPGPC), Faculty of Sciences, University of Antananarivo, under a 12 h light / 12 h dark cycle. They were fed with crickets and had free access to water.

In vivo experiments were performed on male and female guinea pigs aged 8-10 months and weighing 300-400 g. The animals were maintained under a 12 h light / 12 h dark cycle in the same laboratory animal house, fed with grass, and had free access to water.

2.2. Preparation and setup of the isolated heart

To isolate the heart, the frogs were decerebrated and despinalized using a mounted needle. They were then placed in the dorsal decubitus position, and a thoracotomy was performed, the pericardium was removed. The heart was carefully excised and placed in a Petri dish containing Ringer's physiological solution, at room temperature (Table 1).

Table 1 Composition of 1 litre of Ringer's physiological solution [7]

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

The isolated heart was mounted in a 15 ml organ bath aerated with air. Both ends were fixed with S-shaped silver holder. The lower end was anchored to the bottom of the organ bath, while the upper end was connected to an isometric transducer using an inextensible cotton thread. The transducer was linked to a Harvard oscillograph to record the contractions.

2.3. Evaluation of the effect of desacetyl-tanghinin on cardiac output

To evaluate its effect on cardiac output, a modified Langendorff method was used. Ringer solution was perfused through the sinus venosus to permit delivery of oxygenated Ringer solution. The isolated frog heart was rendered experimentally insufficient by allowing it to contract for an extended period. Subsequently, the compound was injected into the sinus

venosus at concentrations ranging from 10^{-5} to 7.96 x 10^{-5} M. Minimum of 5 min was allowed between the addition of samples. The perfusate coming out through thoracic aorta was collected in a container and its volume was measured [8].

2.4. Evaluation of the effect of desacetyl-tanghinin on cardiac activity

To assess the effect of desacetyl-tanghinin on cardiac activity, the heart was experimentally rendered failing. For this purpose, the organ was mounted in the organ bath. The lower end was anchored to the bottom of the bath, while the upper end was connected to an isometric transducer using an inextensible cotton thread. The transducer was linked to a Harvard oscillograph to record the contractions. The isolated organ was allowed to contract until a maximal reduction of its contractile force. Once the heart had been rendered experimentally insufficient, the effects desacetyl-tanghinin on contraction force, heart rate, and filling time were evaluated by adding it to the organ bath in a cumulative manner from 1×10^{-5} M to achieve increasing concentrations.

Its effect on cardiac contraction was expressed as the increase in contraction amplitude compared with that of the impaired heart. While, heart rate, expressed in beats per minute, was determined by counting the number of contractions recorded within one minute. Filling time was determined by measuring the duration of diastole [9].

2.5. Effect of desacetyl-tanghinin on cardiac nervous system

To investigate the effect of desacetyl-tanghinin on the cardiac nervous system, an electrocardiogram (ECG) was recorded using lead II. Prior to the experiment, animals were fasted for 18 h. They were anesthetized with benzodiazepam (1,5 mg/kg, intramuscular injection) and placed in the dorsal decubitus position. One jugular vein was catheterized using a silicone cannula connected to a syringe pump (Harvard) containing desacetyl-tanghinin at a concentration of 1 mg/mL. The perfusion rate was set at 0.12 mL/min. Electrodes were attached to each forelimb of the animal, while another electrode was placed on the left hind limb to obtain the lead II ECG recording [10].

2.6. Results and data analysis

All results are expressed as means ± sem (Standard Error of the Mean). The One-Way Analysis of Variance (ANOVA) test was used, followed by Student's t-test with the software Microsoft Office LTSC Excel 2021, to compare batch means with each other. Differences between two means were considered statistically significant at $p < 0.05$.

3. Results

3.1. Effect of desacetyl-tanghinin on cardiac output

Perfusion of desacetyl-tanghinin increases the cardiac output of the experimentally impaired isolated heart. Moreover, the increase is concentration dependent. In the absence of the compound, normal cardiac output was 27 ± 0.577 mL/min, whereas in the presence of desacetyl-tanghinin, it reached 83.4 ± 1.154 mL/min at a concentration of 7.96×10^{-5} M ($p < 0.05$) (Figure 1). These results indicate that, desacetyl-tanghinin improves cardiac output of the failing isolated heart. However, in its presence at a concentration beyond 9.95×10^{-5} M, the cardiac output decreases.

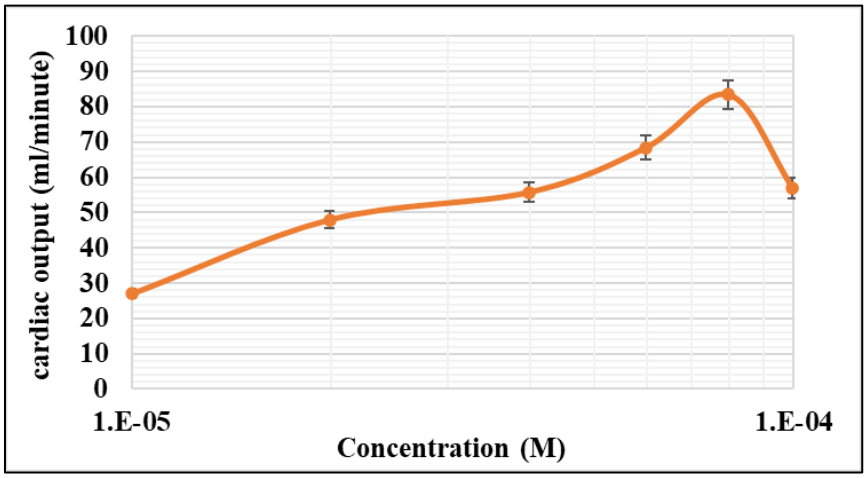

Figure 1 Variation of cardiac output of the experimentally impaired isolated frog heart in the presence of desacetyl-tanghinin perfused according to Langendorff method ($\bar{x} \pm \bar{\sigma}$; n = 10; $p < 0.05$)

3.2. Effect of desacetyl-tanghinin on cardiac contraction force

Addition of the compound in the organ bath, in a cumulative manner, induces a concentration-dependent increase of the contraction amplitude of the isolated frog heart. The initial contraction amplitude of the impaired isolated heart is considered as 0 %, whereas in the presence of desacetyl-tanghinin, it reaches an increase of 177.15 ± 1.01 % at concentrations ranging from 1×10^{-5} to 7.96×10^{-5} M, with a pD_2 value of 5.336 ($p < 0.05$) (Figure 2). These results demonstrate that desacetyl-tanghinin enhances cardiac contraction force, indicating its positive inotropic effect. At concentration higher than 9.95×10^{-5} M, the contraction amplitude decreases.

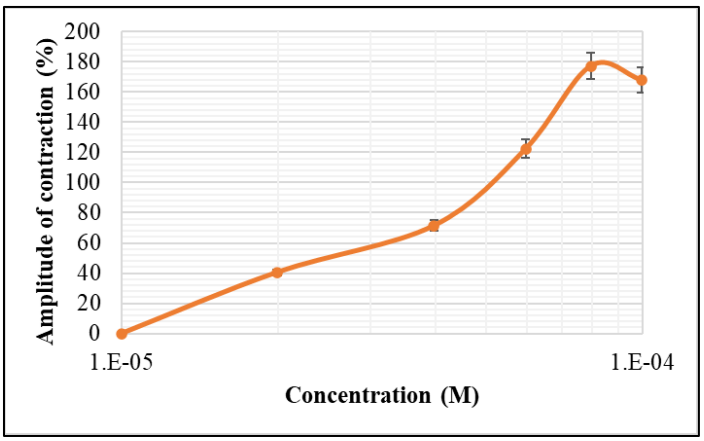

Figure 2 Contraction amplitude of the experimentally impaired isolated frog heart in the presence of desacetyl-tanghinin, added cumulatively in the organ bath ($\bar{x} \pm \bar{\sigma}$; n = 10; $p < 0.05$)

3.3. Effect of desacetyl-tanghinin on heart rate

Injection of desacetyl-tanghinin in the organ bath decreases the heart rate of the isolated frog heart in a concentration-dependent manner. The heart rate of the impaired isolated frog heart is 55 ± 0.06 beats/min, whereas in the presence of desacetyl-tanghinin, it decreases up to 28.99 ± 0.28 beats/min at concentrations ranging from 1×10^{-5} to 7.96×10^{-5} M ($p < 0.05$) (Figure 3). These results indicate that desacetyl-tanghinin slows the heart rate, demonstrating a negative chronotropic effect. At a higher concentration from 9.95×10^{-5} M, the compound increases the heart rate.

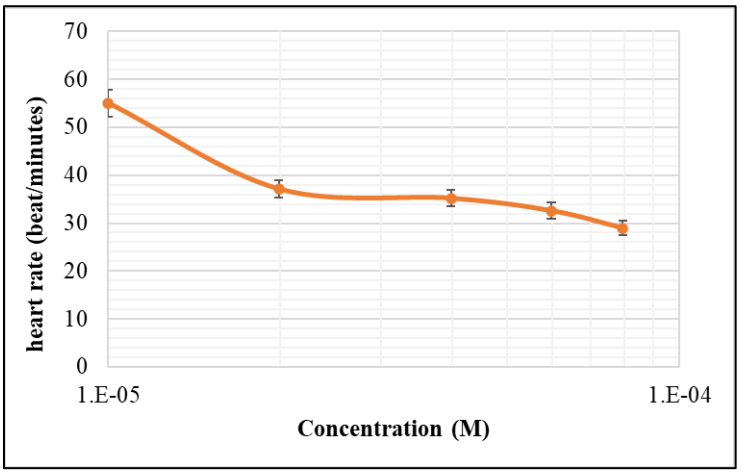

Figure 3 Beating frequency of the experimentally impaired isolated frog heart in the presence of desacetyl-tanghinin, added cumulatively in the organ bath ($\bar{x} \pm \bar{\sigma}$; n = 10; $p < 0.05$)

3.4. Effect of desacetyl-tanghinin on filling time

Injection of desacetyl-tanghinin in the organ bath increases the diastolic duration of the isolated heart, in a concentration-dependent manner. Diastolic duration of the impaired isolated heart is 0.05 ± 0.02 mL/sec, whereas in the presence of desacetyl-tanghinin, it reaches up to 0.153 ± 0.05 mL/sec at concentrations ranging from 1×10^{-5} to 7.96×10^{-5} M ($p < 0.05$) (Figure 4). These results demonstrate that desacetyl-tanghinin prolongs diastole, increasing

the filling time and indicating its positive lusitropic effect. At concentrations higher than 9.95×10^{-5} M, the diastolic duration decreases.

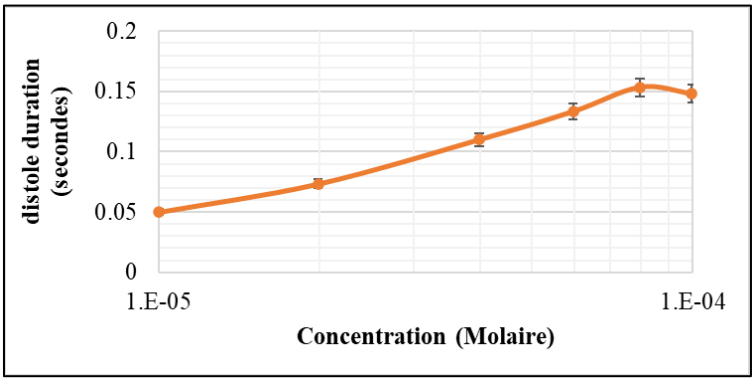

Figure 4 Diastolic duration of the experimentally impaired isolated frog heart in the presence of desacetyl-tanghinin, added cumulatively in the organ bath ($\bar{x} \pm \bar{\sigma}$; n = 10; p < 0.05)

3.5. Effect of desacetyl-tanghinin on cardiac nervous system

Desacetyl-tanghinin perfused at 4 mg/h induces cardiac rhythm disturbances, beginning with bradycardia at a dose of 1.59 ± 0.11 mg/kg. Then, at a dose of 3.14 ± 0.14 mg/kg, an atrioventricular block appears, characterized by two successive P waves without a corresponding QRS complex. From a dose of 3.41 ± 0.148 mg/kg, ventricular extrasystoles, and T-wave inversion are observed. Then, starting at 5± 0.24 mg/kg, ventricular fibrillation occurs, followed by cardiac arrest at a dose of 6.85± 0.37 mg/kg (p < 0.05) (Figure 5a-e).

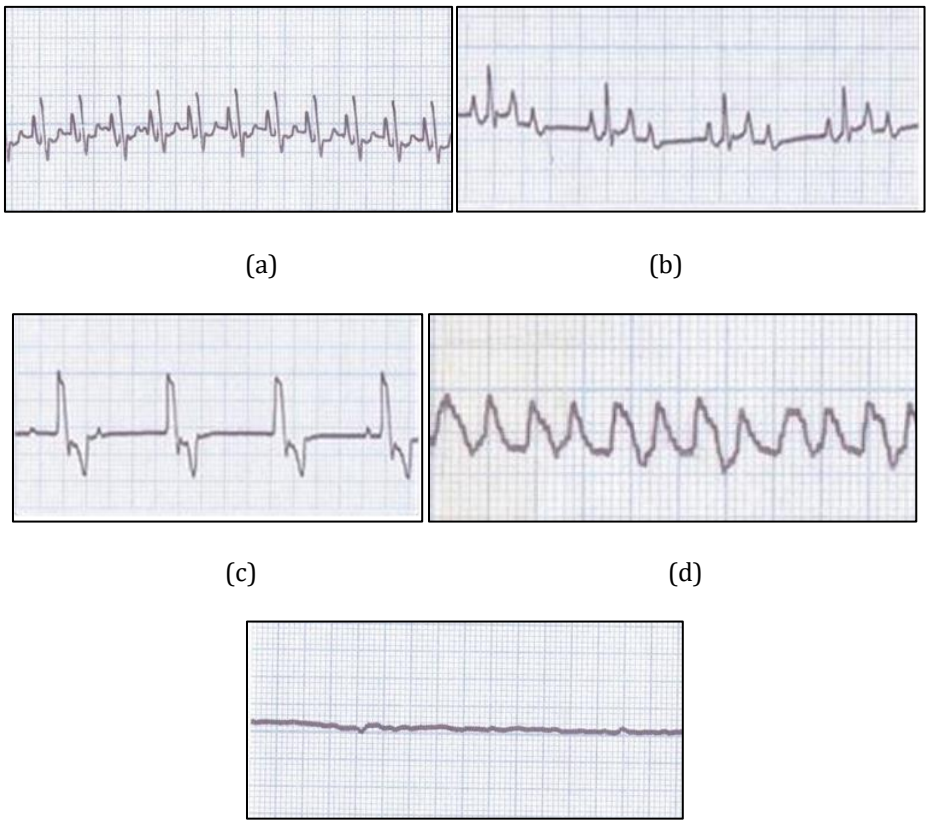

Figure 5 ECG recorded in lead II from an anesthetized guinea pig during desacetyl-tanghinin perfusion at 4 mg/h. (a: normal ECG; b: atrioventricular block at dose 3.14 ± 0.14 mg/kg; c: ventricular extra systole ant T wave inversion at dose 3.41 ± 0.148 mg/kg; d: ventricular fibrillation at dose 5 mg/kg; e: cardiac arrest at dose 6.85 mg/kg)

4. Discussion

Desacetyl-tanghinin, a cardiac glycoside isolated from *Tanghinia venenifera* (Apocynaceae), belongs to a class of compounds well known for their cardiotonic properties and clinical use in heart failure, where contraction strength is reduced and ventricular ejection is compromised [11]. In this study, the effects of desacetyl-tanghinin were evaluated *in vivo* focusing on ECG, and *in vitro* on experimentally impaired frog hearts, focusing on cardiac output, contraction force, heart rate, and filling time.

Our results demonstrate a concentration-dependent increase in cardiac output, with maximal enhancement observed at 7.96×10^{-5} M. This effect is mediated by a combination of positive inotropy and negative chronotropy. The increased contraction force enhances cardiac output, while the associated slowing of heart rate prolongs diastolic filling time, allowing greater ventricular preload and stroke volume. These findings are consistent with previous observations on neriifolin in guinea pig cardiac muscle and are characteristic of cardiac glycosides [9]. This inotropic effect likely arises from inhibition of the Na^+/K^+-ATPase pump in cardiomyocytes, leading to intracellular sodium accumulation, reduced Na^+/Ca^{2+} exchange, and increased intracellular calcium. Elevated calcium levels activate troponin C, increasing actin–myosin cross-bridge formation and cardiac contraction [12, 13, 14].

The negative chronotropic effect observed at lower doses prolongs diastole and enhances ventricular filling, optimizing cardiac efficiency while minimizing myocardial energy expenditure-particularly beneficial in impaired hearts [15].

ECG recordings in anesthetized guinea pigs corroborated these findings: low doses induced bradycardia, medium doses caused atrioventricular (AV) block indicative of slowed AV nodal conduction, and higher doses produced premature ventricular contractions and T-wave inversions, reflecting potential arrhythmogenicity [16]. These electrophysiological changes illustrate the dose-dependent interplay between contractile and electrical cardiac effects of desacetyl-tanghinin.

Comparisons with related compounds from the same plant, tanghinin and acetyl-tanghinin, show similar inotropic effects on isolated guinea pig papillary muscles, although these compounds exhibit higher efficacy and toxicity than desacetyl-tanghinin [6]. Notably, at high concentrations *in vitro*, desacetyl-tanghinin reduced cardiac output and contraction force, shortened diastolic duration, decreased filling time, and paradoxically increased heart rate, effects that may correspond to ventricular fibrillation on ECG. These toxic manifestations likely result from excessive ionic modulation or myocardial overstimulation, consistent with the narrow therapeutic window typical of cardiac glycosides [17].

5. Conclusion

Overall, these results demonstrate that desacetyl-tanghinin exerts coordinated, dose-dependent effects on the heart: at moderate concentrations, it enhances contractility and filling while reducing heart rate, whereas at high concentrations, its effects become deleterious, reducing efficiency and promoting arrhythmias. The combination of positive inotropy, negative chronotropy, and prolonged diastole reflects a classical glycoside-like profile, supporting its potential use in experimental models of heart failure while emphasizing the narrow margin between therapeutic and toxic doses.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

Statement of ethical approval

Care and use of the animals were approved by the bioethics committee of the Sciences Faculty, University of Antananarivo, Madagascar, registered as CEA/FS-UA/ Registre n° 11/2024.

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