Global Journal of
Pharmacy & Pharmaceutical Sciences
ISSN: 2573-2250

Juniper Publishers
key to the Researchers

Review Article
Volume 9 Issue 5 - June 2022
DOI: 10.19080/GJPPS.2022.09.555772

Glob J Pharmaceu Sci

Preclinical Studies with Digitalis Lanata: A Bibliographic Review

Garcia Metz Soraya Katine[1]*, Carvalho Alex Aparecido de[1], Antunes Da Silva Carina Fabricia[1], Moraes Elton de[1], Kaefer Fernanda[1], Dias Maxwell Maximiano[1], Lopes Ricardo Letycia[2] and Pires Galan Vanessa[2]

[1]*Pharmacy Student, Uniamérica, College Biopark, Brazil*

[2]*Guiding Professors Biopark Faculty, Brazil*

Submission: June 02, 2022; **Published:** June 23, 2022

***Corresponding author:** Garcia Metz Soraya Katine, Pharmacy Student, Uniamérica, College Biopark, Toledo, Brazil

Abstract

Popular knowledge has always served as a guide for scientific medical study. For over 200 years, the plant known as foxglove has contributed to the treatment of cardiac pathologies. This plant contains more than 80 cardenolide compounds, with digitalis glycosides being the main ones. Even with unquestionable benefits, its use has always been surrounded by care due to its high toxicity, even at low concentrations, requiring researchers to carry out preclinical studies to prove safe doses. In this sense, the present work aims to carry out a bibliographical review in order to compile works that present pre-clinical studies using the active principal digoxin, seeking to understand the procedures carried out by the researchers and the results obtained in their studies. This is a literature review article whose research was carried out in August 2021 and covered the areas of botany, pharmacognosy, biology and pharmaceutical sciences. Databases such as SciELO, PubMed and Academic Google were used, which provided more than 28,000 works. After passing the inclusion and exclusion criteria, four articles were selected, summarized, and compared. Of these, two studies presented the assessment of digoxin in cardiac pathologies, with results confirming the dosages and treatment times previously stipulated for the drug. The other two selected works present new perspectives for the use of drugs already available on the market containing digoxin for the treatment of visceral leishmaniasis and for fighting inflammation in the liver and cancer, respectively. Thus, the highlighted works demonstrate that the use of animal models to carry out tests with digoxin helps in studies to prove the drug's safety and efficacy in cardiac pathologies. On the other hand, they also significantly contribute to the medical profession, patients, and the pharmaceutical industry by increasing the possibility of treating other already known pathologies, with a focus on improving existing treatments.

Keywords: Digoxin; Digitalis glycosides; Heart diseases; Pharmaceutical industry; Drug safety

Introduction

One of the oldest traditions of humanity is the use of some plants to cure and prevent diseases Veiga Junior et al. [1]. This popular knowledge, over time, is becoming study material as a valuable source of active natural components, which can generate the discovery of new drug molecules Argenta et al. [2]. In the Renaissance period, there was an increase in interest in medicinal plants, with publications in the English language, which perpetuated for approximately 400 years. The reports present prescriptions made by many doctors, relating the plants used and including the species Digitalis purpurea Costa [3]. Digitalis is among the most important plant drugs for the treatment of congestive heart failure. The class encompasses Digitalis purpurea L. (digitoxin) and Digitalis lanata E. (digitoxin, digoxin, lanatoside C and deacetyl-lanatoside C=deslanoside) Simões [4]. At the beginning of its medicinal use, the species used for the extraction of digoxin was D. purpurea, but due to its high toxicity even at low concentrations, the substance began to be extracted from D. lanata which is less toxic and promotes the same therapeutic effects Silva [5]. D lanata is responsible for 90% of the production of cardioactive heterosides Simões [4]. The plant D. lanata is popularly known as yellow-flowered digitalis and belongs to the Scrophulariaceae family. It is found in the Mediterranean basin and central Europe and comprises about 20 species Bruneton [6]. The D. lanata plant has more than 80 cardenolide compounds, with digitalis glycosides being the main constituents [7,8]. Chemically, digoxin extracted from the plant Deladeira - D. Lanata, has its molecule composed of a sugar and a cardenolide, molecular formula C41 H64 O14 and molecular mass 780.95 g/mol Edwards [9]. The digoxin molecule can be seen in Figure 1.

Andrade [10] describes that the extraction of primary cardiotonic glycosides is performed with fresh plants or by submitting the plants to an enzymatic inactivation process so

that the sugar molecules that integrate them are conserved. For the elimination of secondary cardiotonic glycosides, the drying process is performed. According to the author, a hydroalcoholic solution, such as 50% or 70% ethanol at high temperatures, should be used. Then, the macromolecules of the extract must be precipitated. For this, lead acetate can be used and separated using a medium polarity solvent, such as chloroform. Finally, with the acidification of the hydroalcoholic solution, hydrolysis is carried out, thus obtaining only the aglycones of the compound. In this context, desiccated leaves are used, which may contain a content greater than 1% of cardiotonic heterosides, mainly lanatosides A, B, C and D. Bruneton [6]. D. lanata, currently commercialized in Brazil, is the industrial source of digoxin and lanatosides C. Both are used in the treatment of congestive heart failure. The composition of digoxin as a raw material for the manufacture of medicines is characterized by odorless white crystals that are insoluble in water or ether, slightly soluble in alcohol and freely soluble in pyridine. As drugs, digoxin is supplied as tablets in dosages of 125 µg (0.125 mg) or 250 µg (0.25 mg), as capsules in dosages of 100 µg (0.1 mg) or 200 µg (0.2 mg), as elixir at 50 µg/mL (0.05 mg/mL), or for intravenous injection as a sterile solution in ampoules of 2 mL at 250 µg (0.25 mg) per mL or 100 µg (0.1 mg) per mL Edwards [9]. In the body, digoxin acts in several ways, and the action of cardenolides is based on the inhibition of Na+/K+-ATPase ions, involved in the sodium/potassium pump mechanism dependent on these ions and their relationship with myocardial cells [9,11]. Digitalis glycosides produce positive ionotropic effects and are often used for the treatment of heart failure. Increased intracellular calcium (Ca++) causes ionotropic action forming the basis for arrhythmias related to digitalis intoxication Horto Didático [8]. In addition, it also acts on the sympathetic nerve promoting an increase in vagal tone (vagomimetic effect), thus contributing to the treatment of heart failure. These results are also beneficial for the control of supraventricular arrhythmias Edwards [9]. In general, the plant is used in cardiac treatment, but it has also had activity cited as anti-inflammatory, antitumor, antioxidant, anti-aging, among others [8,12,13]. Due to the diverse possibilities of treatment, before the introduction of a drug on the market, it is necessary to conduct pre-clinical studies involving animals in order to obtain data that demonstrate the effects, limits and safety conditions of the drug being studied Brasil [14]. In this context, the present work aims to carry out a literature review in order to compile studies performed with digoxin in animals, seeking to understand the procedures performed by the researchers and the results obtained in their studies.

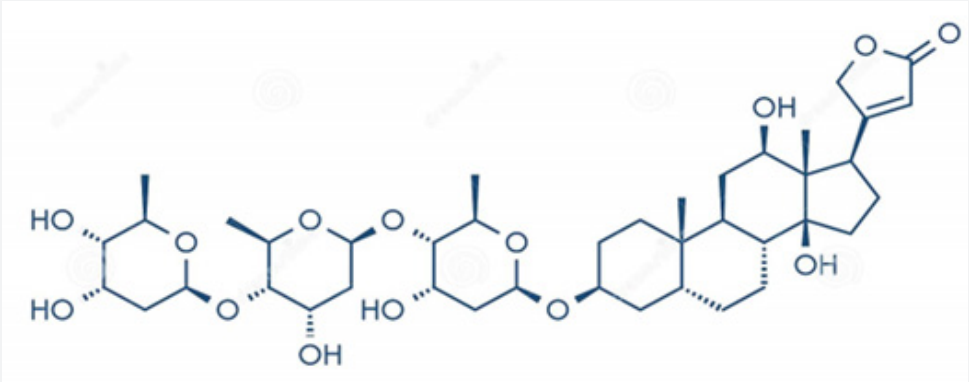

Figure 1: Digoxin molecule.

Materials and Methodology

This is a literature review, carried out in August 2021. The search for theoretical material took place in the SciELO, PubMed and Google Scholar databases, using the descriptors: "digitalis lanata", "digoxina", "digoxina ratos". From this search, more than 28,000 results were found, which were submitted to the selection criteria. Research was also carried out on websites of Universities and scientific research institutions, in addition to books and journals in the field of botany and pharmacognosy. As inclusion criteria, studies were selected that presented studies with cardioactive heterosides and pre-clinical trials involving the drug digoxin and animals, both for cardiac pathologies and investigations into new treatments. Then, as exclusion criteria, studies that presented association with other drugs and did not detail the concentrations of digoxin used were chosen. The selected works were read in full, summarized and their findings detailed in the present work.

Development

Digoxin is the best-known molecule and has been used for more than two centuries in the treatment of heart failure (HF). However, its effectiveness has been questioned due to its short therapeutic margin Botelho [15]. In order to present the main data of each selected work, Table 1 was prepared with the summary of each experience. Source: Self elaboration (2021).

How to cite this article: Garcia M S K, Carvalho A A d, Antunes D S C F, Moraes E d, Kaefer F, et al. Preclinical Studies with Digitalis Lanata: A Bibliographic Review. Glob J Pharmaceu Sci. 2022; 9(5): 555772. DOI: 10.19080/GJPPS.2022.09.555772

Table 1: Comparison of selected articles.

	Neves et al. [16]	Botelho [15]	Freitas et al. [7]	Teijeiro et al. [17]
Objective	To evaluate the effects of digoxin on the cardiac morphology of rats in high-intensity physical training (IAT)	To investigate cardiorenal electromechanical and structural changes after prolonged administration of oleandrin	To evaluate the antileishmanial activity of cardenolide derivatives	To demonstrate that the interleukin-17A (IL-17A) axis can be an efficient anti-obesity strategy
Species Used	Rats of the species Wistar (Rattus novergicus albinus)	Rats of the species Wistar (Rattus novergicus albinus)	Mice of the species BALB/c	Mice of the species C57BL/6
Technical Features	48 male rats, Age: two months; Feeding: commercial feed, 12-hour lighting relay	12 male rats, Age: five to six weeks, Starting weight: 137g, ood: food ad libitum and water	female mice, Age: eight weeks	Adult male mice, Food: various types of diet, 12-hour lighting relay
Drug Used	Digoxin	Digoxin and Heparin	Digitoxigenin and β-acetyl-digitoxin, extracted from the methanolic extract of D. lanata leaves	Digoxin
Tests	Determination of blood lactate concentration, anatomical data, nutritional profile and histological analysis	Electrocardiogram, blood collection and heart fragments	Analyzes of biochemical dosage, CRP, parasite load and liver function in spleen, liver and lymph node tissues	Body weight assessment, Determination of weight loss efficiency, Body mass composition, Behavioral tests, Metabolic activity, Blood parameters, Tests relating to metabolic components

Neves et al. [16] grouped the animals into groups of four individuals, having conducted their study as follows:

a) Control (C): application of saline solution

b) Trained (T): application of saline solution; physical adaptation for 7 days on a treadmill with a speed of 10 m/min lasting 15 minutes per day. Then, they underwent maximum effort, where saline solution was reapplied 30 and 60 days after the beginning of the training.

c) Digoxin (DIGO): administration of 30.0 μg.kg-1 of digoxin once a day for 75 days

d) Trained plus digoxin (TDIGO): administration of 30.0 μg.kg-1 of digoxin once a day for 75 days, physical adaptation for 7 days on a treadmill with a speed of 10 m/min lasting 15 minutes per day. Then, they underwent maximal effort, where digoxin was reapplied 30 and 60 days after the start of training.

The proposed training rules aimed to enable actions to benefit cardiac function and hypertrophy. As a conclusion of the study Neves et al. [16] emphasize that even using doses above those recommended, the levels of creatinine, TGO, TGP and total proteins remained stable in the animals. They also cite that digoxin alone or associated with IAT has not been shown to harm the kidneys or liver of the animals but favored cardiomyocyte hypertrophy in sedentary and/or trained rats. On the other hand, Botelho [15] separated the animals into three groups with four rats and carried out their study for 21 days, applying the drugs subcutaneously.

a) Group control: NaCl 0,9%.

b) Group DIG 50: administration of 50 μg/kg of digoxin.

c) Group DIG 100: application of 100 μg/kg of digoxin.

Clinical evaluation was performed daily by the author based on the normal behavior of the species. Sensitivity at the application site and possible signs of heart failure were evaluated. The treatment was conducted with digoxin, and in the same period three animals from each group received heparin. The results of the work of Botelho [15] pointed out that the group of rats that received a higher dose of digoxin, after the seventh application, showed a small sensitivity at the application site. However, the researchers pointed out that there were no clinical changes in the rats and no symptoms of adverse reactions due to intoxication were observed. There was also no arrhythmia during the three weeks of study, and it can be concluded that the doses administered, and the time used were sufficient to induce cardiac alterations without altering the autonomic modulation in the animals.

How to cite this article: Garcia M S K, Carvalho A A d, Antunes D S C F, Moraes E d, Kaefer F, et al. Preclinical Studies with Digitalis Lanata: A Bibliographic Review. Glob J Pharmaceu Sci. 2022; 9(5): 555772. DOI: 10.19080/GJPPS.2022.09.555772

Both studies were initiated with the purpose of evaluating cardiac pathologies, having as results the confirmation of the dosages and treatment times previously stipulated for the drug. In contrast, Freitas [7] sought improvements in the treatment of visceral leishmaniasis since the drugs used in the treatment are highly toxic, painful to administer and/or therapeutic failure, in addition to their high cost. The animals were infected by the subcutaneous route by L. Infantum and after 60 days the treatment was started. Each drug was applied once a day every other day for 10 days. The author concluded that Digitoxigenin and β-acetyl-digitoxin showed selective action against L. infantum both in their free form and when incorporated into a delivery system composed of micelles, thus demonstrating that they are effective in the treatment of visceral leishmaniasis. The study published by Teijeiro et al. [17], carried out monitoring of obese mice, where at first the initial objective was to fight inflammation in the liver and check possible treatments for cancer, but they observed a loss of up to 40% of weight in them during the study period, of 8 months. These overweight mice were treated with digoxin and, even while maintaining a high-fat diet, were cured of metabolic disorders often linked to obesity, a major inflammatory disease. These authors concluded that digoxin could be used for the treatment of obesity, for a short period, until they managed to stabilize the weight reduction and, later, adhere to a healthier diet. In addition, they emphasize that their findings proved that Digoxin improves insulin sensitivity and/or hypercholesterolemia, contributing to the aforementioned treatment. Works such as those carried out by [7,17] present new perspectives for the use of drugs already available on the market, contributing significantly to the pharmaceutical industry [18] and patients by increasing the possibility of treatment for already known pathologies.

Final Consideration

From the bibliographic survey it was possible to perceive the importance of carrying out pre-clinical studies with the use of animals. This type of study contributes both to confirm the recommended dosage, duration of treatment and drug safety, as well as to evaluate the use of the drug in new treatments, since animal models represent the real capacity of physiological simulation.

References

1. Veiga Junior Valdir F, Aparecida MMM, Angelo CP (2005) Plantas medicinais: cura segura? In: Epartamento de Química, Universidade Federal do Rio Grande do Norte, Campus Universitário.
2. Crestanello AS, Crestanello AL, Rogério GS, Schneider CV (2011) Plantas medicinais: cultura popular versus ciência. Vivências: Revista Eletrônica de Extensão da URI 7: 51-60.
3. Batista CF (1999) da Digitalis e Hidropsia: do empirismo do séc. XVI à indústria farmacêutica do séc. XX. Ribeirão Preto-SP, Material didático da Faculdade de Ciências Farmacêuticas da Universidade de São Paulo.
4. Maria SC (2017) Farmacognosia: Do Produto Natural ao Medicamento (Portuguese Edition) Kindle Edition, Portugal.
5. Silva J (2012) Contribuição para o estudo molecular e morfológico de espécies do gênero Digitalis L. no período de. Tese (Mestrado em Medicamentos a Base de Plantas) - Universidade de Lisboa, Faculdade de Farmácia Departamento de Ciências Farmacológicas, Lisboa, Portugal.
6. Bruneton J (2009) Pharmacognosie. Phytochimie. Plantes médicinales. Paris: Lavoisier, France.
7. Simões FC (2021) Avaliação da atividade Antileishmanial de Cardenolídeos para uso no tratamento da Leishmaniose Visceral. Universidade Federal de Minas Gerais.
8. (2020) Horto Didático de Plantas Medicinais Do HU/CCS. Dedaleira ou digital. UFSC.
9. Joel NE (2009) Chapter 189 - Digoxin, Small Animal Critical Care Medicine, Elsevier, pp. 805-806.
10. Andrade (2014) Milene Aparecida. Glicosídeos cardiotônicos. Compostos bioativos vegetais. Palmas.
11. Amir A (2019) The sodium pump and digitalis drugs: Dogmas and fallacies. Pharmacology Research & Perspectives 7(4): e00505.
12. Marije S (2013) Glicosídeos cardíacos na terapia do câncer: das investigações pré-clínicas aos ensaios clínicos. Novos medicamentos em investigação 31(4): 1087-1094.
13. Jagielska Joanna (2009) A digitoxina produz propriedades anti-inflamatórias e vasoprotetoras em células endoteliais: implicações terapêuticas para o tratamento da aterosclerose? Atherosclerosis 206(2): 390-396.
14. Brasil (2017) Ministério da Saúde. Agência Nacional de Vigilância Sanitária - ANVISA. Nota da Anvisa sobre o uso de animais em estudos pré-clínicos.
15. Botelho AFM (2018) Efeitos dos glicosídeos cardioativos (digoxina, ouabaína e oleandrina) na fisiologia cardiorrenal em ratos wistar hígidos. Tese (Doutorando em Ciência animal) - Universidade federal de Minas Gerais Escola de Veterinária. Belo Horizonte, pp. 36-43.
16. Neves Claodete Hasselstrom, Aguiar Andreo Fernando, Aguiar Danilo Henrique, Leopoldo André Soares (2016) Digoxina e verapamil induzem hipertrofia em cardiomiócitos de ratos sedentários e/ou treinados. Revista Brasileira de Medicina do Esporte 22: 399-402.
17. Teixeira A, Garrido A, Ferre A, Perna C, Djouder N (2021) Inhibition of the IL-17A axis in adipocytes suppresses diet-induced obesity and metabolic disorders in mice. Nat Metab 3(4): 496-512.
18. (2021) Molécula de fármaco da insuficiência cardíaca digoxina. extraído da planta foxglove digital lanata skeletal formula Disponível RABIA.

How to cite this article: Garcia M S K, Carvalho A A d, Antunes D S C F, Moraes E d, Kaefer F, et al. Preclinical Studies with Digitalis Lanata: A Bibliographic Review. Glob J Pharmaceu Sci. 2022; 9(5): 555772. DOI: 10.19080/GJPPS.2022.09.555772

DOI: 10.19080/GJPPS.2022.09.555772

How to cite this article: Garcia M S K, Carvalho A A d, Antunes D S C F, Moraes E d, Kaefer F, et al. Preclinical Studies with Digitalis Lanata: A Bibliographic Review. Glob J Pharmaceu Sci. 2022; 9(5): 555772. DOI: 10.19080/GJPPS.2022.09.555772