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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 81658

Title: New uses for an old remedy: digoxin as a potential treatment for steatohepatitis and other disorders

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06360124
Position: Peer Reviewer
Academic degree: PhD
Professional title: Assistant Professor
Reviewer's Country/Territory: Iran
Author's Country/Territory: United States

Manuscript submission date: 2022-11-19

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-11-19 08:14

Reviewer performed review: 2022-11-23 18:00

Review time: 4 Days and 9 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This manuscript provides A Review on "New uses for an old remedy: digoxin as a potential treatment for steatohepatitis and other disorders" has been considered. The writing and organize of the manuscript need to improve. There are also some issues in structure and scientific writing, need to be noted: 1. Review papers must provide a comprehensive critical review of recent developments in a specific area or theme that is within the journal's scope and not only a list of published studies. 2. Reviews are expected to have an extensive literature review followed by an indepth and critical analysis of the state of the art, and identify challenges for future research. 3. It is better to cite more original studies. 4. The content of the selected original articles used in this review should be prepared in the form of a table. 5. It would be helpful to add explanations in more detail about therapeutic results of digoxin and discuss subsequent pathological and also therapeutic outcomes in every research. therefore, in order to make the article more informative, each therapeutic case of digoxin should be accompanied by their biochemical, histological, and molecular outcomes at least included in the table. 6. In text: When "CGs", "RORγt", "IL", ... were first written, their full names were not mentioned and direct abbreviations were written in the text. 7.

Unfortunately, the manuscript has revealed some grammatical and typographical problems that needs to be addressed. So, the English language of manuscript should carefully check and edit. 8. The authors should add related references to the results using the table. 9. It would be nice to add more recent articles in references.

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Peer-review model: Single blind

Reviewer's code: 03441022
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Associate Professor
Reviewer's Country/Territory: Poland
Author's Country/Territory: United States

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Reviewer accepted review: 2022-11-27 08:10

Reviewer performed review: 2022-12-02 08:08

Review time: 4 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Jamshed et al. present a review article suggesting the use of cardenolide, digoxin as a potential drug in the treatment of steatohepatitis characterized by inflammation of the liver with concurrent fat accumulation. The article reads well, but often one has the impression of superficial treatment of some aspects of the topic. This also applies to the omission of some citations, which is astonishing in some cases. 1. Digoxin in a Nutshell: an overview of 200 years. Line 78-84. The authors should cite the following papers: [Am. J. Cardiol., 65 (1990), pp. 10E-16E. doi: 10.1016/0002-9149(90)90245-v]; [Prog. Cardiovasc. Dis., 21 (1978), pp. 141-158. doi: 10.1016/0033-0620(78)90020-8]; [J. Am. Coll. Cardiol., 5 (1985), pp. 16A-21A. doi: 10.1016/s0735-1097(85)80459-9]. 2. Digoxin in steatohepatitis section. It has been recently reported that lack of hepatic glucose-6 phosphatase results in liver damage [Mol Metab. 2021 Jan;43:101108.doi: 10.1016/j.molmet.2020.101108]. This gene is directly regulated by the RORgamma isoform of the RORC gene. Karas et al. showed that at non-toxic concentrations digoxin and other cardiac glycosides are agonists of this receptor [Front Pharmacol. 2019 Jan 7;9:1460. doi: 10.3389/fphar.2018.01460]; [Toxicol Lett. 2018 Oct 1;295:314-324. doi: 10.1016/j.toxlet.2018.07.002] being able to upregulate G6PC expression and thus might improve liver cell functions. 3. Digoxin in obesity and metabolic disorders. The authors mentioned RORgammaT and IL17A, however, they did not cite the first identification of digoxin as an inverse agonist of this receptor [Nature. 2011 Apr 28;472(7344):486-90. doi: 10.1038/nature09978.]! This is not ok in my opinion. The authors should put more attention the fact that digoxin is considered as an endogenous cardiac glycoside and a modulator of many nuclear receptors' activity Please see and cite: [Biomed

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Pharmacother. 2020 Jul;127:110106. doi: 10.1016/j.biopha.2020]. 4. Digoxin in cancer. The authors should definitively read and cite [Biomed. Pharmacother., 84 (2016), pp. 1036-1041 doi: 10.1016/j.biopha.2016.10.030]. As Th17 cells are promising in adoptive therapy [Blood 112, 362–373. doi: 10.1182/blood-2007-11-120998]; [Immunotherapy 2, 21–24. doi: 10.2217/imt.09.83] digoxin was suggested to be an effective compound that could improve the Th17 phenotype [Front Pharmacol. 2019 Jan 7;9:1460. doi: 10.3389/fphar.2018.01460]. 5. Digoxin in viral infection. In line 336, the authors claim "Digoxin inhibits coronavirus and other viruses [46]". What does it mean? Which coronavirus (there are many) and what it inhibits? Replication, infectivity, entry? The authors should also write on which concentrations of digoxin show its antiviral activity and how it is related to the toxicity of this drug. 6. In general, the authors avoid indicating digoxin concentrations when describing various studies, which is crucial to whether digoxin can be considered a drug for a given condition at all. Please correct it. 7.

Why in the last paragraph the authors do not cite relevant articles? This is completely incomprehensible. In this paragraph, the authors should focus on the rationale for the use of digoxin having in mind that this drug exerts high toxicity and is dangerous to patients. Lines 430-433 - statements like that require relevant citations and based on the [Front Pharmacol. 2019 Jan 7;9:1460. doi: 10.3389/fphar.2018.01460.] there are not fully true. 8. Lines 426-430 "At relatively high concentrations, digoxin and other cardiac glycosides inhibit the Na-K ATPase pump, leading to accumulation of sodium ions in the cytosol that drives an influx of calcium into the heart, increasing contractility. At lower doses, digoxin induces the Na-K ATPase to act as a receptor that can modulate a variety of pathways." Please include these concentrations and cite relevant articles. 9. Figure 1. The authors should improve the figure. First, please include the structure of digoxin, include names of the reactive oxygen species, etc. Include also the figure showing other digoxin activities. 10. Table 1. Please include digoxin doses

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that are planned to be examined in the clinical trials. Minor concerns 1. Line 431. Replace RORt with RORγT.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

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Peer-review model: Single blind

Reviewer's code: 03441022

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Poland

Author's Country/Territory: United States

Manuscript submission date: 2022-11-19

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2023-01-20 08:21

Reviewer performed review: 2023-01-20 08:50

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors improved the manuscript significantly however, they made a substantial error: "More recently, Karas et al. reported opposing findings with cardiac glycosides activating RORγT in HepG2 cells (…) RORγ is broadly expressed so in HepG2 this isoform is present, and Th17 express exclusively RORγT, thus the authors should correct this sentence accordingly: "More recently, Karas et al. reported opposing findings with cardiac glycosides activating RORγ in HepG2 cells and RORγT in Th17 lymphocytes" And further: "RORγ directly regulates glucose-6 phosphatase (G6Pase) and a number of genes involved in glucose regulation and insulin sensitivity **. G6Pase facilitates glucose-6 phosphate (G6P) hydrolysis into inorganic phosphate and free glucose [50-52], with suppression of hepatic G6Pase resulting in accumulation of G6P and metabolic reprogramming involving increased carbohydrate response element binding protein (ChREBP) activity and gene expression that lead to hepatic steatosis [53-56]. Digoxin-mediated activation of RORγ upregulates G6Pase, resulting in improved glucose homeostasis and decreased NAFLD phenotype"