

The work of Marija Kosić, entitled Drug Repositioning in Doxorubicin-Induced Cardiotoxicity Protection, is an interesting review on drug repositioning and potential new therapies in doxorubicin-induced cardiotoxicity (DIC). However, the main text—particularly the section on physiopathology—requires restructuring, as several mini-paragraphs appear in the main text. In spite, it would be valuable to include in the figure the mechanisms associated with cardiotoxicity, integrating other agents described in the article, such as minocycline and fibrates. Furthermore, the review would benefit from a more detailed discussion of **the role of epigenetic changes** induced by doxorubicin, as well as an expanded section addressing **fibrosis and inflammation** as key contributors to DIC.

Thank you for your suggestion. The text has been restructured as you suggested. Minocyclin and fibrates have been included in Figure 2. The role of epigenetic changes induced by doxorubicine has been added on page 6 (lines 27-43) and page 7 (lines 1-7) as well as an expanded section addressing fibrosis and inflammation as contributors to DIC on page 5 (lines 25-44) and page 6 (lines 1-4).

It is also recommended to reconsider the idea that cardiotoxicity may be secondary to effects on cell types beyond cardiomyocytes, such as fibroblasts (Patricelli, C., Lehmann, P., Oxford, J.T. et al. Doxorubicin-induced modulation of TGF- β signaling cascade in mouse fibroblasts: insights into cardiotoxicity mechanisms. *Sci Rep* 13, 18944, 2023. <https://doi.org/10.1038/s41598-023-46216-7>; Levick SP, Soto-Pantoja DR, Bi J, Hundley WG, Widiapradja A, Manteufel EJ, Bradshaw TW, Meléndez GC. Doxorubicin-Induced Myocardial Fibrosis Involves the Neurokinin-1 Receptor and Direct Effects on Cardiac Fibroblasts. *Heart Lung Circ.* 2019;28(10):1598–1605. doi: 10.1016/j.hlc.2018.08.003).

The section about the role of fibroblasts and other cellular targets in DIC has been added on page 7 (lines 9-34). We include proposed references on page 5 (line 30) and page 6 (line 4).

Although the authors attempt to provide a broad analysis of potential strategies to reduce cardiotoxicity, including titration and pharmacogenomics, this approach somewhat distracts from the initial objectives of the review.

We agree; however, reviewers 1 and 3 requested expanded sections on pharmacokinetics (page 8 lines 22-33) and epigenetics (page 6 lines 27-43 and page 7 lines 1-7). We hope we found a reasonable measure to meet all suggestions.

The section on paroxetine, in particular, should be restructured to maintain neutrality and the expected third-person academic style. In addition, the authors should further highlight their own previous contributions to the field.

Regarding paroxetine, it is important to note that treatment in patients with heart failure did not significantly reduce 28-day all-cause mortality (Xu H, Meng L, Long H, Shi Y, Liu Y, Wang L, Liu D. Paroxetine and Mortality in Heart Failure: A Retrospective Cohort Study. *Front Cardiovasc Med.* 2022. doi: 10.3389/fcvm.2021.794584). The discussion should also address the potential for cardiotoxicity, as observed in other species. For example, paroxetine has been shown to induce cardiotoxic effects in zebrafish larvae, where inflammation was proposed as a potential mechanism of cardiac dysfunction (Zhu Y, Song F, Gu J, Wu L, Wu W, Ji G. Paroxetine induced larva zebrafish cardiotoxicity through inflammation response. *Ecotoxicol Environ Saf.* 2023 Jul 15;260:115096. doi: 10.1016/j.ecoenv.2023). Additionally, paroxetine has been reported to slow conduction and reduce excitability in cardiac cells (Plijer, I.S.; Verkerk, A.O.; Wilders, R. The Antidepressant Paroxetine Reduces the Cardiac Sodium Current. *Int. J. Mol. Sci.* 2023, 24, 1904. <https://doi.org/10.3390/ijms24031904>). These are also relevant evidence that should be discussed in the section.

Thank you for this observation. The section on paroxetine is restructured to maintain neutrality and a third-person academic style. We added a paragraph on cardiovascular risks, embryotoxicity, and environmental concerns, and we included all the suggested publications. See page 20 (lines 10-38) and page 21 (lines 12-16).

Moreover, the discussion should be expanded to cover evidence suggesting that paroxetine may modulate fibrotic, inflammatory, and angiogenesis-related pathways in post-myocardial infarction models (Alonazi AS, Almodawah S, Aldigi R, Bin Dayel A, Alamin M, Almotairi AR, El-Tohamy MF, Alharbi H, Ali R, Alshammari TK, Alrasheed NM. Potential cardioprotective effect of paroxetine against ventricular remodeling in an animal model of myocardial infarction: a comparative study. BMC Pharmacol Toxicol. 2024;25(1):99. doi: 10.1186/s40360-024-00824-9).

Effects of paroxetine on inflammation, fibrosis, and angiogenesis, including the suggested reference, are added on page 20 (lines 39-44) and page 21 (lines 1-12).

Finally, the inclusion of **a summary table** would be helpful to allow readers to easily identify the main beneficial outcomes of the pharmacological treatments discussed.

Thank you for suggesting. A summary table on repurposed drugs has been added (Page 19).