

Reviewer 2 comments:

A review article by Marcinek et al. summarizes the possible effects of caffeine on blood platelets and the cardiovascular system through adenosine receptors. The article is well-written. Data are presented progressively, from describing the nature of caffeine and its general biological properties to the mechanisms by which caffeine exerts its effects on the cardiovascular system. The adenosine receptors were defined as key players in mediating caffeine effect on cells through inducing intracellular changes. However, this article still needs several improvements:

Our response:

We would like to thank the Reviewer 2 for a good opinion of our paper and for valuable comments. Our specific answers are listed below.

The methodology of the work is missing. The authors should explain the searched databases and the used keywords.

Thank you for this comment. In general, our paper is not a systematic review or meta-analysis. Therefore, we did not include a Methodology section in the first version of the manuscript. As the explanation, we have used PubMed, Scopus and Web of Science as the major databases for searching the scientific literature published prior to 31 March 2023. Additionally, we have used Google Scholar for retrieving more general data, such as reports, e.g. :

6. National Coffee Data Trends 2022. n.d., National Coffee Association. Available online: <https://www.ncausa.org/Newsroom/Coffee-consumption-hits-two-decade-high-2022-NCDT> (accessed 19/06/2024).

8. World Heart Report 2023: Confronting the World's Number One Killer. Geneva, Switzerland. World Heart Federation. 2023. Available online: <https://world-heart-federation.org/wp-content/uploads/World-Heart-Report-2023.pdf> (accessed 19/06/2024).

We used following keywords (or their synonyms) and their combinations: platelet(s), caffeine, adenosine, adenosine receptor(s), AR, coffee, cardiovascular, endothelium, antiplatelet therapy.

We have added the above information in the end of Introduction section in the corrected version of the manuscript.

Abbreviations should be consistent throughout the article. Whenever possible, write the full names followed by the abbreviations in parentheses. Lines 175, 285 should be corrected accordingly.

We have corrected the use of abbreviations in the new version of the manuscript.

Regarding the topic of this work, the use of caffeine as an adjuvant to plate inhibitors is well documented (PMID: 17892993). However, the efficacy of its standalone use is still doubtful. Coffee contains other phenolic compounds besides caffeine. Positive effect of these compounds on platelet inhibition has been suggested, as coffee drinking inhibited the aggregation of

platelets induced by several agonists, while caffeine alone failed to achieve similar effects. (PMID: 18439332)

In general, we agree with the above opinion. We would like to point out however, that the first cited paper (PMID: 17892993, Lev et al., Effect of caffeine on platelet inhibition by clopidogrel in healthy subjects and patients with coronary artery disease. Am Heart J. 2007 Oct;154(4):694.e1-7.) regards modulatory effects of caffeine on the action of well-known platelet drug clopidogrel which is the antagonist of P2Y₁₂ receptor. According to our knowledge, the effects of caffeine on the effectiveness of adenosine receptor agonists are not as widely described in the literature. Therefore, we made an attempt to fill this gap by writing our review. As regards the second cited paper (PMID: 18439332, Natella et al. Effect of coffee drinking on platelets: inhibition of aggregation and phenols incorporation. Br J Nutr. 2008 Dec;100(6):1276-82.), the inhibitory potential of phenolic compounds of plant origin on platelet function is a very broad topic. We are obviously aware that coffee also contains plant polyphenols that could affect platelet reactivity but we wanted to focus rather on caffeine itself not on coffee in our paper. Otherwise, the review would be too lengthy, in our opinion.

Diagrams summarizing the biological roles of caffeine on the cells of the cardiovascular system as well as the key playing factors (e.g., adenosine receptors, cAMP, etc.) will help to improve the readability of this work.

As suggested, we have added a novel Figure 2. The schematic illustration of modulating effects of caffeine on blood platelet function, in the amended version of the manuscript.

The concluding section, especially parts related to future directions, requires significant improvements.

We have significantly extended and modified the concluding remarks section, as suggested.