

Review of: "Saponins and their synergistic antibacterial activity with traditional antibiotics against *Staphylococcus aureus* and *Escherichia coli*: Review"

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Potential competing interests: No potential competing interests to declare.

Overall this review article is interesting and highlights the antimicrobial significance of Saponins with respect to synergism with antibiotics.

As this review article is explaining the antimicrobial action and synergism of saponin it needs to give some explanation of how saponins effect or block bacterial efflux pumps? Possibly saponins can also disrupt the outer membrane of gram-negative bacterial calls, please review the literature and add any relevant information.

It would help the reader if you added figure(s) or diagram(s) to help explain the different mechanisms by which saponins work.

As biofilm formation is an important way for bacteria to become tolerant to antibiotics, a section of the antibiofilm activity of saponins should be included. Please review this literature. Here are some examples, but there are probably many other papers to include:

- a. Tatli Cankaya II, Somuncuoglu EI. Potential and Prophylactic Use of Plants Containing Saponin-Type Compounds as Antibiofilm Agents against Respiratory Tract Infections. Evid Based Complement Alternat Med. 2021 Jul 23;2021:6814215. doi: 10.1155/2021/6814215. PMID: 34349828; PMCID: PMC8328696.
- b. Shang F, Wang H, Xue T. Anti-Biofilm Effect of Tea Saponin on a *Streptococcus agalactiae* Strain Isolated from Bovine Mastitis. Animals (Basel). 2020 Sep 22;10(9):1713. doi: 10.3390/ani10091713. PMID: 32971787; PMCID: PMC7552639.
- c. *J. Nat. Prod.* 2019, 82, 6, 1487–1495 Publication Date: June 4, 2019 <https://doi.org/10.1021/acs.jnatprod.8b00970>

And some studies describing synergistic antibiofilm action of saponins such as:

Wei MP, Yu H, Guo YH, Cheng YL, Xie YF, Yao WR. Synergistic combination of Sapindoside A and B: A novel antibiofilm agent against *Cutibacterium acnes*. Microbiol Res. 2022 Jan;254:126912. doi: 10.1016/j.micres.2021.126912. Epub 2021 Nov 1. PMID: 34742105.

With respect to biofilm inhibition, the authors should discuss the mechanism of inhibition of quorum sensing by saponins

for example:

- a. Asfour HZ. Anti-Quorum Sensing Natural Compounds. J Microsc Ultrastruct. 2018 Jan-Mar;6(1):1-10. doi: 10.4103/JMAU.JMAU_10_18. PMID: 30023261; PMCID: PMC6014249.
- b. Paluch E, Rewak-Soroczyńska J, Jędrusik I, Mazurkiewicz E, Jermakow K. Prevention of biofilm formation by quorum quenching. Appl Microbiol Biotechnol. 2020 Mar;104(5):1871-1881. doi: 10.1007/s00253-020-10349-w. Epub 2020 Jan 11. PMID: 31927762; PMCID: PMC7007913.
- c. Bouyahya, Abdelhakim, et al. "Medicinal plant products targeting quorum sensing for combating bacterial infections." *Asian Pacific journal of tropical medicine* 10.8 (2017): 729-743.

Figure 1. States “Synergy of plants with antibiotics against bacteria, measured in fractional inhibitory concentration index (FICI)”. Is it really plants, or should it be saponins as those are the plants products the review is concerned about. Please add some structures of different saponins that have been shown to produce synergism with antibiotics.

The references need updating **to include more recent ones**

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The information from the European Center for Disease Prevention and Control that “estimated that in 2007 around 400,000 infections and 25,000 deaths were caused by a few common bacteria that had developed resistance to most antibiotics[4]” is very old and needs updating.

The information in the following paragraph should be supplemented with data for antimicrobial activity described

“Thus, the antimicrobial activity of saponins against food-borne bacteria has been studied extensively.

In this context, Dong et al investigated the antimicrobial activity of saponins found in *Chenopodium quinoa*. The investigators managed to extract and purify six different compounds, and they tested the antimicrobial activity of each of these compounds against six types of food-borne bacteria. The results of their experiment indicated that all of the compounds exhibited antimicrobial activity against *S. aureus*, *S. epidermidis*, and *B. cereus*. The antimicrobial activity was also shown to be correlated with the concentration of the respective saponin. Furthermore, the investigators were able to show that the mechanism of action for the antibacterial effect of the saponins consisted of disruption of the bacterial cell wall and cell membrane, with the consequent release of cellular contents [33].”

Please avoid repetitions of statement throughout the manuscript in some instances the authors can merge these sections and give relevant information with brief explanations.

