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Letter to the Editor

Comments on "Quercetin and Nano Quercetin: Cytotoxicity, Antileishmanial and Antimicrobial Activities against Resistance Strains: Insights and Future Directions"

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Dear Editor-in-Chief

I have read the original article by Hanif and colleagues (1). The authors investigated the *in vitro* antileishmanial and antibacterial effects of quercetin and its niosomal nanoformulation against resistant clinical strains of bacteria and *Leishmania infantum*. Their finding that nano-quercetin exhibited superior activity compared to free quercetin, with negligible cytotoxicity on L929 fibroblast cells, is both promising and timely, given the rising global burden of drug-resistant infections (2,3).

The study is particularly valuable because it addresses two critical public health challenges: the emergence of antimicrobial resistance and the limited therapeutic options for leishmaniasis. By demonstrating that a natural flavonoid, when encapsulated in a niosome based nanocarrier, can achieve enhanced efficacy, the authors provide a strong rationale for further development of plant derived compounds as alternative therapeutics (4).

One of the most notable findings is the concentration and time dependent leishmanicidal activity of nano-quercetin against both promastigote and amastigote stages of *L. infantum*, with IC50 values as low as 20.4 µg/ml after 48 hours. Importantly, nano-quercetin showed activity comparable to standard drugs such as glucantime and miltefosine, without statistically significant differences. These results align with previous reports highlighting the potential of quercetin against protozoan parasites (5). However, the authors did not investigate the underlying

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mechanisms of action, such as induction of apoptosis, reactive oxygen species generation, or inhibition of parasite specific enzymes. Future studies employing flow cytometry or molecular docking would help elucidate these pathways (6).

From a bacteriological perspective, the study confirms that Gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Campylobacter jejuni*) are less susceptible to quercetin than Gram positive strains (*Staphylococcus aureus*, *Bacillus cereus*, *Listeria monocytogenes*). The authors attribute this difference to the outer membrane barrier of Gram negative bacteria, which is a reasonable explanation. Nevertheless, the study did not assess whether nano-quercetin alters membrane permeability or inhibits efflux pumps—mechanisms that could be elucidated via transmission electron microscopy or ethidium bromide accumulation assays (7).

Another strength of the study is the cytotoxicity assessment on normal mouse fibroblast cells (L929), where both quercetin and nano-quercetin showed over 93% viability at 800 µg/ml. This indicates a favorable safety profile. However, the authors did not calculate the selectivity index (SI) for all tested concentrations, although the methodology mentioned it. Reporting SI values would allow readers to better compare the therapeutic window of nano-quercetin versus conventional drugs (8). Additionally, the study was conducted entirely *in vitro*; *in vivo* validation using animal models (e.g., *L. infantum* infected BALB/c mice) is necessary to assess pharmacokinetics, tissue distribution, and long-term safety before clinical translation (9).

From a public health perspective, this research has several important implications. First, it underscores the potential of nanoformulated natural products as cost effective and accessible alternatives to conventional antimicrobials, particularly in low-resource settings where leishmaniasis and bacterial infections are endemic (10). Second, the lack of toxicity even at high concentrations supports the feasibility of developing oral or topical formulations. Third, the study highlights the need for further research into combination therapies for instance, using nano-quercetin alongside subtherapeutic doses of standard drugs to reduce toxicity and overcome resistance.

However, the study has certain limitations that should be acknowledged. The characterization of nano-quercetin was limited to size and morphology (70–150 nm, spherical). Additional parameters such as encapsulation efficiency, zeta potential, polydispersity index, and in vitro release profile would provide a more complete picture of the formulation's stability and performance. Moreover, the authors did not specify whether the nanoformulation was tested for long-term storage stability or batch to batch reproducibility, which are critical for translational development.

Furthermore, the statistical analysis, while appropriate, was based on relatively small sample sizes. The non-significant differences between nano-quercetin and positive controls (e.g., $P = 0.072$ and 0.063) should be interpreted with caution, as these may reflect insufficient power rather than true equivalence.

In conclusion, Hanif and colleagues have made a valuable contribution to the field of natural product-based antimicrobials by demonstrating that nanoencapsulation enhances the activity of quercetin against drug-resistant bacteria and *Leishmania* parasites, with excellent safety *in vitro*. To build upon these findings, future research should focus on mechanistic studies, *in vivo* efficacy models, and comprehensive physicochemical characterization of the nanoformulation. If these steps are successfully completed, nano-quercetin could emerge as a promising candidate for the treatment of parasitic and bacterial diseases, especially in the era of rising antimicrobial resistance.

Conflict of Interest

The author declares no conflict of interest.

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