NEW PERSPECTIVES OF THE *IN VITRO* THERAPEUTIC ACTIVITY OF OLEOCANTHAL AGAINST LEISHMANIASIS

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Extra virgin olive oil (EVOO) is the cornerstone and the main source of fat in the Mediterranean diet (MD). Phenolic compounds of EVOO, and in particular secoiridoids, are secondary metabolites that have attracted research attention because of their beneficial impact on human health [1]. This study describes the most recent findings on the anti-microbial properties of the secoiridoid oleocanthal (OLEO), focusing on an *in vitro* model of leishmaniasis, a vector-borne disease with a worldwide distribution and a wide spectrum of clinical manifestations, caused by obligatory intracellular parasites. The available chemotherapeutic approaches have numerous disadvantages, such as high cost, relapses, toxicity and drug resistance. Thus, the development of new therapeutics is focused on new compounds contained in the MD, and on combination therapies. To this end, we assessed the leishmanicidal activity of OLEO, either alone or in combination with miltefosine, a standard anti-leishmanial chemotherapeutic drug, against viscerotropic *L. infantum* and dermotropic *L. major* extracellular promastigotes and intracellular amastigotes. The half-maximal inhibitory and cytotoxic concentrations (IC_{50} and CC_{50} values) of OLEO were estimated using the resazurin cell viability assay. OLEO inhibited the viability of promastigotes and amastigotes in a concentration-dependent manner for both *Leishmania* strains. In addition, the *in vitro* combinatorial effect of OLEO with miltefosine was determined, for the first time, using the modified isobologram approach, against *L. infantum* and *L. major* promastigotes and amastigotes and the relevant isobolograms revealed synergism and antagonism, respectively. Furthermore, the intracellular production of microbicidal ROS was enhanced in *Leishmania* promastigotes treated with drug combinations compared to miltefosine-treated parasites. Overall, our findings provide evidence that OLEO, either alone or in combination with currently used chemotherapeutic agent, is a promising anti-leishmanial molecule against both viscerotropic and dermotropic *Leishmania* strains.

References

[1] Romani Annalisa, Francesca Ieri, Silvia Urciuoli, Annalisa Noce, Giulia Marrone, Chiara Nediani, and Roberta Bernini. 2019. “Health Effects of Phenolic Compounds Found in Extra-Virgin Olive Oil, by-Products, and Leaf of Olea Europaea L.” *Nutrients* 11:1776

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