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Abstract

From the search for CHIKV inhibitors to the discovery of a potent anti-HIV infection agent

LITAUDON Marc

Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France.

Abstract:

As part of an ongoing program aiming at the discovery of novel inhibitors of chikungunya virus (CHIKV) replication from tropical plants, we discovered by chance that daphnane-type diterpenoids isolated from Trigonostemon cherrieri, a critically endangered endemic Euphorbiaceae from New Caledonia, exhibited significant and selective antiviral activity. This result was the starting point for the phytochemical and biological investigation of other Euphorbiaceae species originating from different tropical and Mediterranean regions leading to the characterization of several bioactive tigliane-type diterpenoids, some of which possessing extremely potent and selective anti-CHIKV properties. To further explore the structure-activity relationships of such diterpenoids, the anti-CHIKV and anti-HIV activities of about 40 tiglianes isolated from different Euphorbiaceae species or commercially available were evaluated. Surprisingly, the results showed that there was a strong correlation between both activities, suggesting that the anti-CHIKV activity of the diterpene esters might result from their ability to modulate the activity of protein kinase C isozymes as is the case for their anti-HIV activity. Among the most interesting compounds, a 4b-deoxyphorbol ester (4b-dPE, figure below) isolated from Euphorbia amygdaloides was found to have a 20-100 times more potent anti-HIV activity than prostratin, which had raised considerable interest in early 2000s owing to a potential clinical application. Further, it has been shown that 4b-dPE reactivates HIV-1 from latency and could potentially contribute to decrease the viral reservoir, downregulates the expression of the HIV-1 receptors CD4, CCR5 and CXCR4, and that combination of 4b-dPE with various antiretroviral drugs showed a consistent synergistic effect, suggesting that 4b-dPE represents a new lead compound for the treatment of HIV-1 latency in combination with antiretroviral drugs.

Biography:

Marc Litaudon has completed his PhD in 1991 from University Paris-Sud, France and Postdoctoral Studies from University of Canterbury (New Zealand). In 1994 he served in New Caledonia as the Head of "Laboratory of Medicinal Plants" (CNRS). In 2001, he joined the ICSN and since has led its phytochemical laboratory and the management and scientific development of the "ICSN Extracts Library". He was appointed deputy director of ICSN in 2020. He has published more than 200 papers in reputed journals and has been serving as an editorial board member of "Phytochemistry" and "Plants".

Recent Publications:

1. Litaudon M, et al Anal Chem, 2019.
2. Litaudon M, et al Fitoterapia, 2020.
3. Litaudon M, et al J Anal Methods Chem, 2019.
4. Litaudon M, et al Nat Prod Res, 2019.
5. Litaudon M, et al J Biol Chem, 2020.
6. Litaudon M, et al Bioorg Med Chem Lett, 2020.

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