4.2 = *HYPERICUM SCRUGLII*, A SPECIES ENDEMIC TO SARDINIA AS A SOURCE OF POTENTIAL HIV-1 INTEGRASE INHIBITORS

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Earlier research on the development of effective anti-human immunodeficiency virus type 1 (HIV-1) agents has been focused on inhibitors of the critical viral enzymes, reverse transcriptase (RT) and protease (PR), but there is an urgent need to develop new and more effective therapeutics and the drug targets have been extended to include HIV-1 integrase (IN) inhibitors (1,2). IN is the enzyme responsible for integration of viral provirus into the human genome, a critical event for HIV permanent infection that is then irreversible (3). Till date, there are only three integrase inhibitors approved by US-FDA and resistance to them is known (4,5). Thus, the search for new integrase inhibitors with novel mechanism of action and effective on HIV drug-resistant strains is still a worldwide health care issue (6,7).

Hence, in our ongoing research of bioactive natural products inhibiting the replication of HIV-1 from the Sardinian endemic flora, some compounds obtained from aerial parts of *Hypericum scruglii* Bacch., Brullo et Salmeri have been assayed to evaluate their HIV-1 IN inhibition ability.

Hypericum scruglii is a perennial herb belonging to Hypericaceae family, endemic and exclusive of Sardinia (Italy), where it grows generally linked to calcareous substrates (8). For a long time the Sardinian populations of this species have been identified as *Hypericum tomentosum* L., but a detailed analysis of living material reported that they differ from typical specimens of *H. tomentosum* respect to the shape and size of leaves, floral structures and capsules (9).

The lyophilized aerial parts of *H. scruglii* was extracted using a H_2O/MeOH (1:1) solution. The obtained extract was purified by column chromatography (SiO_2, Sephadex LH-20, RP, C8 and C18) and six compounds (3-Geranyl-1-(2'-methylbutanoyl)phloroglucinol, 3-Geranyl-1-(2'-methylpropanoyl)phloroglucinol, 1,3,5-benzentriol 2-[(2S,3R)-3-(3,4-dihydroxylphenyl)-2,3-dihydroxylpropyl], 3-(13-hydroxygeranyl)-1-(2'-methylbutanoyl)phloroglucinol, 3,4-dihydroxybenzoic acid and quercitrin) were isolated. All compounds were further purified by HPLC and their structures were established on the basis of physical and spectroscopic analysis. The 3-(13-hydroxygeranyl)-1-(2'-methylbutanoyl)phloroglucinol is reported for the first time.

All isolated compounds have been tested for their ability to inhibit the HIV-1 IN strand-transfer catalytic activity in Homogeneous Time Resolved Fluorescence assay (10). Five of them showed a significant inhibition activity with IC_{50} values between 1.58 and 13 µg/mL; only 3,4-dihydroxybenzoic acid was found to be inactive. In particular, the most active compound, quercitrin, inhibited the HIV-1 IN catalytic activity with IC_{50} value of 1.58 ± 0.16 µg/mL.

In our research on novel HIV-1 enzyme inhibitors, we report compounds that display strong inhibition against HIV-1 IN and that could be used for further drug development.

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