4.3 = *ONOPORDUM ILLYRICUM* L.: NEW ANTI-HIV-1 AGENTS FROM AN EDIBLE MEDITERRANEAN PLANT

CINZIA SANNA[1], MAURO BALLERO[1], ENZO TRAMONTANO[2], ANDREA MAXIA[1], ALFREDO MACCIONI[1], ARIANNA MARENGO[1], ORAZIO TAGLIALATELA-SCAFATI[3], ANGELA CORONA[2], FRANCESCA ESPOSITO[2]
[1]Department of Live and Environment Sciences, University of Cagliari, Via Sant'Ignazio 13, 09123 Cagliari, Italy; [2]Department of Live and Environment Sciences, University of Cagliari, Cittadella Universitaria di Monserrato SS554, 09042 Monserrato (Cagliari), Italy; [3]Department of Pharmacy, University of Naples, Via D. Montesano 49, Naples, Italy

Onopordum illyricum L. is a wild plant belonging to Compositae family spread in the Mediterranean region, in Portugal and Albania (1). It's very common in Sardinia where its young scapes and capitula are eaten raw in salad as side dishes (2), representing a food of good nutritional value. In the traditional medicine a decoction or tea of the whole plant is used as a digestive and to treat cough and biliary diseases (2); the flowering tops are used as a febrifuge for the treatment of malarial fever and for washing exanthematic skin (3).
Within a project aiming to find new agents inhibiting the replication of human immunodeficiency virus type 1 (HIV-1) from the Sardinian flora, the ethanolic extract and the ethyl acetate, n-hexane, butanol and water fractions obtained from aerial parts of *O. illyricum* have been assayed on the HIV-1 reverse transcriptase (RT) associated ribonuclease H (RNase-H) activity, a multifunctional viral enzyme that is still a good target because, at the moment, in the antiretroviral therapy are not present drugs that target this function. Since the human immunodeficiency virus (HIV) has been established to be the etiological agent of the acquired immunodeficiency syndrome (AIDS) (4,5), an originally unpredicted number of drugs have been approved for the treatment of the HIV infected patients (6). The management of this disease, however, is still complex and worrisome due to problems such as monitoring of therapy efficacy, chronic administration drug toxicity, poor tolerability, drug resistance development or therapy adjustment after treatment failures (7). For all these reasons the search for new inhibitors with novel mechanism of action and effective on HIV drug-resistant strains is still a worldwide health care issue (8,9).
In this work the ethanolic extract obtained from aerial parts of *O. illyricum* have been tested on the HIV-1 RT associated RNase-H function on *in vitro* biochemical assay and it showed an IC_{50} value of 8.84 ± 0.53 µg/mL. Given that relevant and selective activity relates to IC_{50} values below 100 µg/ml for extracts and below 25 µM for pure compounds (10), *O. illyricum* extract have showed a significant antiviral activity. The extract was fractionated and the butanolic fraction was the most active one, with a similar inhibition value to the total extract (IC_{50} = 8.97 ± 0.13 µg/mL). Previous studies reported for this plant the presence of fatty acids, sesquiterpene lactones, triterpenes, polyphenols and caffeoylquinic acid derivatives (11,12,13). According to them, luteolin, apigenin, hispidulin, arctin, 1,5-dicaffeoylquinic acid, onopordopicrin, deoxyonopordopicrin were isolated from the butanolic fraction and their inhibitory effect was evaluated on RNase-H activity. In particular, luteolin, apigenin, arctin, and, deoxyonopordopicrin inhibited the HIV-1 RNase-H function with IC_{50} values between 56 and 70 µg/mL. Differently, onopordopicrin showed an IC_{50} value of 16 µg/mL. The most active compounds, hispidulin and 1,5-dicaffeoylquinic acid, inhibited the HIV-1 RNase-H activity with IC_{50} values of 8,68 and 3,66 µg/mL, respectively. We have identified new natural derivatives that are able to inhibit the HIV-1 RNase H activity.

1) T.G. Tutin, V.H. Heywood, N.A. Burges, D.M. Moore, D.H. Valentine, S.M. Walters, D.A. Webb (1976) Flora Europaea, 4, 247, Cambridge University Press.
2) A.D. Atzei (2003) Le piante nella tradizione popolare della Sardegna. Carlo Delfino Editore
3) M. Ballero, A. Bruni, G. Sacchetti, F. Poli (1997) Acta Phytoterapeutica, 1, 23-29.
4) F. Barré-Sinoussi, J.C. Chermann, F. Rey, M.T. Nugeyre, S. Chamaret, J. Gruest, C. Dauguet, C. Axler-Blin, F. Vézinet- Brun, C. Rouzioux, W. Rozenbaum, L. Montagnier (1983) Science, 220, 868–871.
5) S. Broder, R.C. Gallo (1984) N. Engl. J. Med, 311, 1292–1297.
6) Y. Mehellou & E. De Clercq (2010) J Med Chem, 53, 521–538.
7) A.M.N. Tsibris, M.S. Hirsch (2010) J. Virol. 2010, 84, 5458-5464.
8) F. Esposito, A. Corona, E. Tramontano (2012) Mol Biol Int, 2012,586401
9) F. Esposito, A. Corona, L. Zinzula, T. Kharlamova, E. Tramontano (2012) Chemotherapy, 58, 299–307.
10) P. Cos, A.J. Vlietinick, D. Vanden Berghe, L. Maes (2006) J Ethnopharmacol, 106, 290-302.
11) L. Verotta, L. Belvisi, V. Bertacche, M.C. Loi (2008) NPC, 3, 2037-2042.
12) A. Braca, N. De Tommasi, I. Morelli, C. Pizza (1999) J Nat Prod, 62, 1371-1375.