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Identification of Novel Natural Products with Immunomodulatory Activity

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IMMUNE SYSTEM AND NATURAL PRODUCTS

Dysfunctions of the immune system may lead to different life-threatening diseases. Despite a plethora of available pharmacological tools, novel therapeutic approaches showing high efficacy, but minimal side effects are needed for the treatment of immune-related diseases[1],[2]. Natural products represent a promising source for new therapeutic agents and, in the last 20 years, the research on natural products has increased significantly.

AIM OF THE PROJECT

The main aim of this project is the identification of natural products with immunomodulatory function on human T cells.

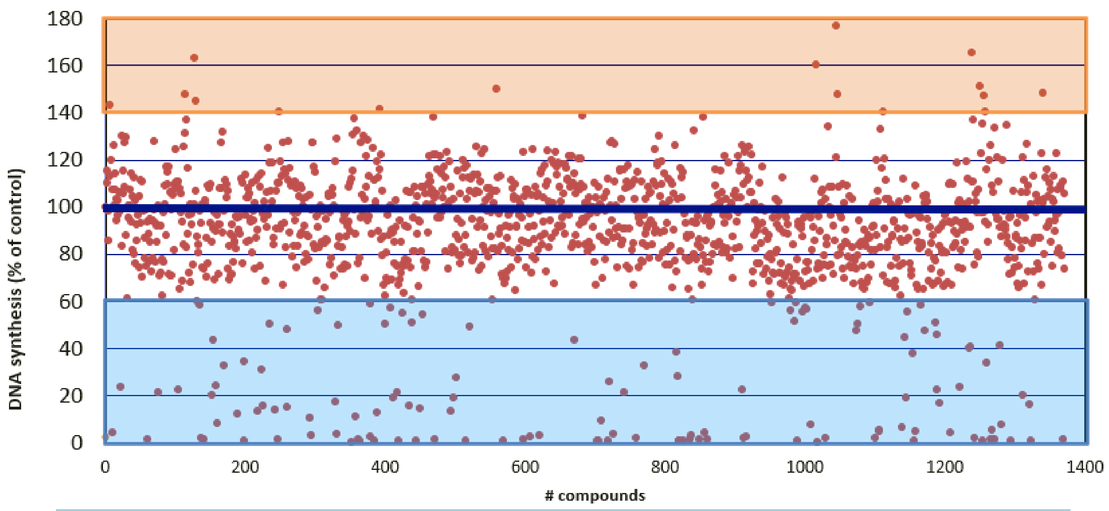

Fig. 1 Screening of a natural products library.

RESULTS

The immunomodulatory effect of 1369 compounds of plant, microorganism, and animal origin was tested using peripheral blood mononuclear cells (PBMCs) stimulated with the mitogen PHA (**Fig. 1**). We found 22 immunostimulatory compounds (A) and 127 immunosuppressive compounds (B).

A. Immunostimulatory Compounds

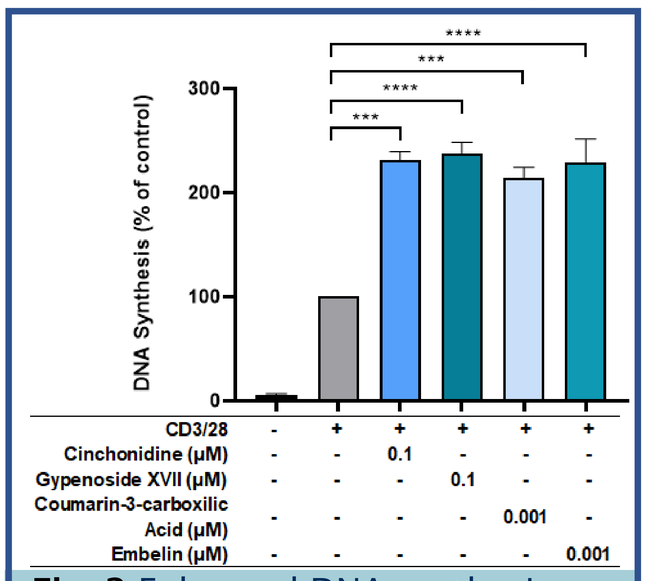

Fig. 2 Enhanced DNA synthesis upon treatment with the selected compounds.

The effect on the proliferation of purified peripheral blood T cells of 22 selected immuno-stimulatory compounds was further evaluated.

From the tested 22 compounds, we selected four substances (Cinchinodine, Gypenoside XVII, Coumarin-3-carboxylic acid and Embelin) that significantly increase DNA synthesis of T cells stimulated with CD3/28 (**Fig. 2**).

To further evaluate the effects of immunostimulatory compounds on T-cell activation, we analyzed the expression levels of the activation markers CD69 and CD25 (**Table 1**).

	DNA Synthesis	CD69	CD25
Control	100%	100%	100%
Coumarin-3-carboxylic Acid	230%	NS	NS
Cinchonidine	240%	NS	155%
Embelin	210%	122%	160%
Gypenoside XVII	220%	NS	166%

Table 1. Summary of the effects of the selected immunostimulatory compounds on the proliferation and the expression of the activation markers CD69 and CD25.

B. Immunosuppressive Compounds

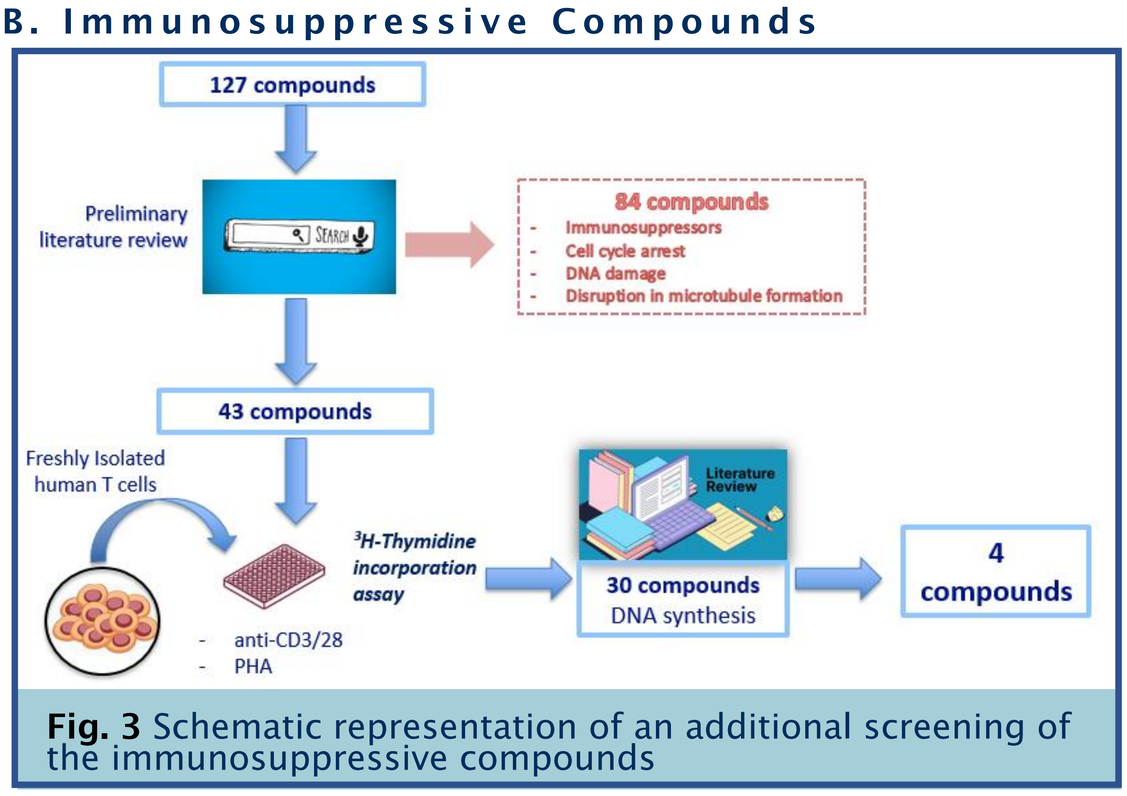

Fig. 3 Schematic representation of an additional screening of the immunosuppressive compounds

From the initial 127 immunosuppressive compounds identified in the initial screening (**Fig.1**), 4 compounds were selected according to the strategy depicted in **Fig. 3**.

As shown in **Fig. 4**, the select compounds show a strong inhibition of T-cell proliferation upon CD3/28 stimulation.

The effects of the compounds were further investigated upon PMA/Ionomycin stimulation.

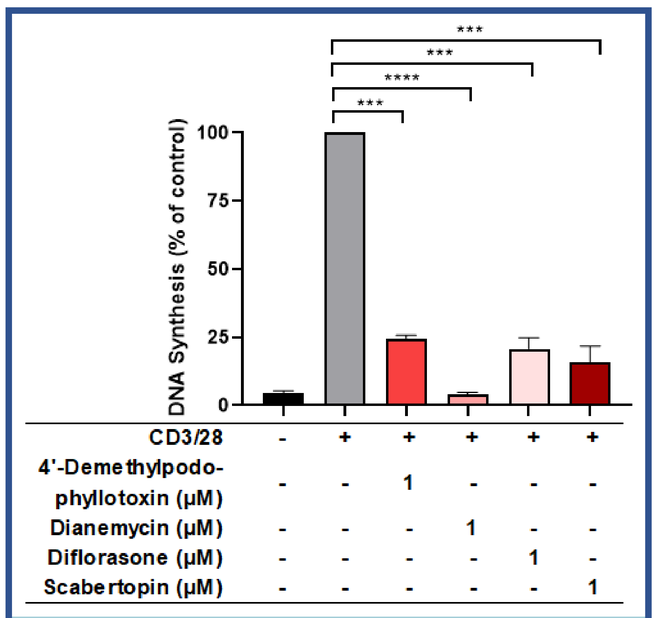

Fig. 4 Inhibition of DNA synthesis upon treatment with the selected compounds.

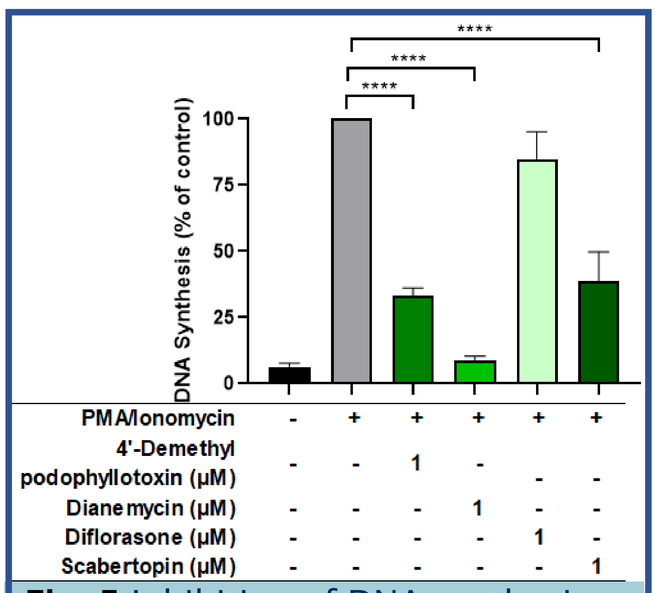

Fig. 5 Inhibition of DNA synthesis upon treatment with the selected compounds.

Interestingly, Diflorasone only inhibits proliferation when T cells are stimulated with CD3/28, but not with PMA+Iono, see **Fig. 4** and **Fig. 5**. These data suggest that Diflorasone acts upstream of PLCγ in the regulation of TCR signaling.

Diflorasone is a glucocorticoid representing a novel potential drug for the treatment of human diseases.

CONCLUSIONS

We have identified 4 novel potent immunostimulatory compounds (Cinchinodine, Gypenoside XVII, Coumarin-3-carboxylic acid and Embelin) and 4 potent immunosuppressive compounds (4'-Demethylpodophyllotoxin, Dianemycin, Diflorasone and Scabertopin) on T-cell proliferation *in vitro*.

BIBLIOGRAFY

1. Ok, Lee and Shin. Immune Network. 2019, 19(6), e37.
2. Splunter Mv, et al. PLOS ONE. 2019, 14(12): e0225825.

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