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Proactive Control of the Production of Inflammatory Cytokines (Il 17, Il 1 ß) by Glycosylated Oligostilbenes i.e. Polydatin: Clinical Evidence in Dermatology

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It has long been proven that natural oligostilbenes such as resveratrol and its natural glycosylated precursor known as polydatin and/or piceid play a regulatory role in the production of pro-inflammatory cytokines such as IL17, IL6, IL1ß; previous publications have highlighted that these molecules also act on the genes that regulate the production of these molecules [1,2,16]. This property is accompanied by the more known antioxidant activity of stilbenoids and their ability to modulate the immune response to ROS and other pro-oxidant substances used in oncological therapies. [3,4]. In recent years, the oncological protocols were enriched with therapeutic aids related to the so-called "biological drugs" monoclonal antibodies to cell receptors such as EGFR which is often found expressed in many solid tumors (eg: colorectal, pancreas, lung, breast, genitourinary tract, glioblastomas, cervico-facial area) [5,6]. The inhibition of the function of this receptor determines a therapeutic potential capable of inhibiting the growth or progression of the tumors that express it [7,8].

Based on the structure and function of the EGFR, two different therapeutic strategies have recently been developed:

i. The first uses monoclonal antibodies that target the extracellular domain of the receptor, thus blocking the binding site with EGF with consequent inhibition of the processes of growth and progression of tumor cells [9].

ii. The second determines the blocking of EGFR activation using small molecules able to bind to the receptor tyrosine kinase, which is the enzyme responsible for the transduction of the post-receptor signal within the cell [10].

In the case of drugs that act as tyrosine kinase inhibitors, it has been seen that patients often experience an unpleasant collateral phenomenon affecting the epidermis that the appearance of inflammatory states, loss of tissue consistency and subsequent complications difficult to manage so much that they must consider the suspension of anticancer therapy when cortisone drugs and antibiotics for topical use do not lead to an improvement in the dermatological picture [11]. Recent research by our group has shown that polydatin, like resveratrol, is an inhibitor of the epidermal tyrosine kinase of the lung as reported in international patent EPO by Romano M C & Ravagnan G [12] that treatment with formulations for topical use improved the dermatological situation of patients treated with afatinib as suffering from lung cancer [13]. This trial evaluated the activity of polydatin, a well-tolerated natural extract, for the prophylaxis of skin toxicity during an afatinib-based treatment, avoiding the use of antibiotics. This molecule has a strong antioxidative and free-radical scavenger effect and would neutralize the cellular damage, responsible of the development of chronic diseases and ageing.

This first result has encouraged a further clinical experimentation in patients with different oncological pathology and treatment with biological drugs that generally create stressful situations of the epidermal tissue; in this evaluation we also wanted to verify whether the preventive treatment with the topical formulation before the oncological therapeutic treatment showed any difference compared to the concomitant treatment with the start of the use of the anticancer drug [14]. The results were satisfactory as can be seen from the summary of the published work in which it was demonstrated that our study showed a progressive clearing of the skin AEs secondary to different EGFRi therapies (cetuximab, panitumumab, afatinib, gefitinib, osimertinib) and an improved QoL post treatment with polydatin-based products. The topical treatment that was extremely safe and no side effects.

Other results submitted for publication by Ravagnan G & coll [15] show that polydatin can effectively prevent acute inflammatory response to crystals in the mouse model of CPP crystal-induced arthritis. As far as cytokine expression was concerned, mice in the therapeutic protocol showed reduced IL-1ß and CXCL1 mRNA levels when before treated for 48 h with polydatin and colchicine after CPP crystals injection. Serum levels of the same cytokines were also reduced, although without any significance.

This proactive protective action of polydatin in protecting the skin deserves to be reported both because its use has no contraindications but rather facilitates the administration of oncological drugs without the risk of possible interruptions of the therapeutic plan; also deserves further investigation on the mechanism of action also linked to role of beta defensins that are stimulated by the use of polydatin which intervenes, as it seems, on the control of the genetic regulation of interleukin synthesis, opening up new interesting fields of investigation both basic and clinical of natural glycosylated oligostilbenes [16].

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