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Commentary

Extracts from *Nicotiana glauca* as a therapeutic strategy against rhabdomyosarcoma

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Rhabdomyosarcoma (RMS) is a type of soft tissue sarcoma, which commonly appears in the head, neck, genitourinary region and extremities [1]. RMS is believed to originate due to alterations in the growth and activity of immature precursor muscle cells, preventing their differentiation into skeletal muscle cells and thus acquiring malignant potential [2]. Among soft tissue sarcomas, it is the most common in children and adolescents, being rare in adults [3]. According to the 2020 World Health Organization classification, there are different types of RMS: embryonal, alveolar, pleomorphic, and spindle cell/sclerosing rhabdomyosarcoma, with embryonal rhabdomyosarcoma being the most common subtype [4]. The survival rate of children with RMS has improved, however this is not the case for children diagnosed with metastatic or recurrent RMS [5,6]. For this reason, it is necessary to search for therapeutic strategies that can attack RMS cells as well as stop their growth and invasion capacity.

Phytochemicals are known to have anticancer effects, which are associated with the inhibition of mitosis, the induction of apoptosis, and protection against damage caused by free radicals [7,8]. These effects are largely explained by the role of phytochemicals as modulators of cellular signaling pathways [9]. Currently, several phytochemicals are part of cancer therapies, such as vinca alkaloids, taxane diterpenoids, camptothecin derivatives, and epipodophyllotoxin [10]. For example, vinca alkaloids bind to β-tubulin, inhibiting microtubule polymerization, affecting cell motility and shape, and leading to the death of malignant cells. Vinblastine and vincristine are the two alkaloids used in clinical oncology for almost 50 years [11].

Our group studied the health benefits of *Nicotiana glauca (N.g.),* a plant belonging to the Solanaceae family that is widely distributed in Argentina. This family has a large number of species of medicinal value that have demonstrated analgesic, antineoplastic, hypoglycemic, antimicrobial or antiparasitic properties [12].

We have previously found that liposoluble extract from *N.g.* induces cell death by apoptosis in the murine myoblast cell line C2C12 [13]. Since the origin of RMS arises from alterations in muscle cell differentiation and RMS has a differentiation state comparable to that of early myoblasts [14], the aim of our work entitled *"The extract of Nicotiana glauca induces apoptosis in rhabdomyosarcoma cells"*, was to study the effect of *N.g.* lipid extract on embryonal rhabdomyosarcoma cell line (RD).

In addition, the participation and subcellular localization of key proteins related to programmed cell death, cell invasion and metastasis were investigated.

Rhabdomyosarcoma, like other types of cancer, usually presents evasion of apoptosis, which could explain its resistance to chemotherapy [15]. Our research group demonstrated that the lipid extract from *N.g.* induced apoptosis in RD cell line. Changes were observed in nuclear morphology and mitochondrial distribution, caspase 3 cleavage and its nuclear translocation, key events during apoptosis [16].

Of relevance, we verified that the extracts from *N.g.* also decreased the proliferation and, potentially, migration of RD cells, mechanisms related to the invasion and metastasis of tumor cells [16].

Based on these findings, our research group deepened its studies in search the molecular bases of these results.

As we mentioned before, RMS arises from the deregulation of the differentiation process in precursor cells of myogenesis. This fact highlights the importance of studying molecular pathways related to embryonal development, since any alteration in them could be the cause of the pathogenesis and progression of this sarcoma during the postnatal stage. The Notch and wnt/β-catenin pathways are important for defining cell fate and tissue and organ differentiation, as well as for stem cell maintenance and tissue homeostasis [17].

The wnt/β-catenin pathway is important since its deregulation has been associated with different types of cancer [18]. When this pathway is active, phosphorylation and consequent proteasomal degradation of β-catenin are inhibited, leading to its cytoplasmic accumulation and subsequent nuclear translocation, activating the transcription of genes related to cell growth, and proliferation. β-catenin may also act by regulating genes that activate the epithelial-mesenchymal transition, a key event in the transformation to a tumor cell phenotype [19]. In the absence of ligands that activate this pathway, β-catenin is degraded and remains at low concentrations at the cytoplasm [20]. Activation of this pathway appears in most cases of colorectal cancer, where genetic mutations lead to the loss of β-catenin degradation and its consequent accumulation inside the nucleus [21]. There is evidence that activation of wnt/β-catenin signaling also participates in pancreatic, ovarian, prostate, breast and hepatocellular cancer, so nuclear β-catenin can be considered as a tumor marker [18].

Wnt/β-catenin signaling is also related to apoptotic cell death. It has been seen that cells that stably express one of the ligands that activate the wnt/β-catenin pathway, present resistance to apoptosis during chemotherapy by inhibiting the release of cytochrome c and the activation of caspase 9, essential steps in this type of cell death [22].

Our study demonstrated the activation of this pathway under basal conditions in RD cell line, observing the exclusively nuclear localization of the β-catenin protein [16]. This behavior is typical of some tumor and tumor cell lines like RD, since in non-tumor C2C12 cells, the location of β-catenin was merely cytoplasmic. Notably, in RD cells, treatment with the lipid extract from *N.g.* greatly decreased nuclear localization of β-catenin and increased the cytosolic one. These changes in subcellular localization were observed by immunocytochemical and western blot assays [16]. As a therapeutic strategy, the science tries to discover inhibitory molecules of the wnt/β-catenin pathway in order to allow the proteasomal degradation of β-catenin [23]. Although in this study we did not demonstrate β-catenin degradation, we only observed that *N.g.* extract treatment induced, in RD cell line, a non-tumor behavior with changes in the subcellular localization of β-catenin protein and, therefore a decreasing capacity for cell proliferation and malignant transformation, making them more susceptible to apoptosis induction.

Another important pathway in RMS is the Notch pathway, which acts during embryonal development in different tissues regulating cell fate, including skeletal muscle, inhibiting differentiation in precursor cells of myogenesis [24,25]. When this pathway is activated, the Notch transmembrane receptor undergoes proteolytic cleavages from which the intracellular domain is released into the cytoplasm, a previous step to enter into the nucleus, allowing the regulation of the expression of certain genes that are under its control [26]. This molecular pathway is constitutively activated in RMS and has been associated with their metastatic phenotype. In addition, it has been shown that in RMS, Notch regulates cell adhesion, migration and invasion [27]. In our work, we demonstrated by immunocytochemistry techniques, employing a specific antibody against the intracellular fragment of the Notch 1 receptor, that treatment of RD cell line with the lipid extract of *N.g.* was capable of reducing cleavage and nuclear translocation of the intracellular fragment of the Notch 1 receptor, suggesting once again the potential of the extract to decreases the aggressive phenotype [16].

The Notch and wnt/β-catenin pathways are evolutionarily conserved and play a crucial role in myogenesis. Wnt/β-catenin signaling regulates different points of myogenesis, such as proliferation, myoblast fusion and maintenance [28]. As already mentioned, Notch signaling participates in the choice of cell fate in myogenesis, it has been seen that the positive regulation of this pathway promotes the proliferation of myoblasts and prevents their differentiation into myotubes [29,30]. The interaction of both pathways has been demonstrated in cancer cells, where Notch activation allows then the activation of the wnt/β-catenin pathway as it happens, for example, in chronic lymphocytic leukemia [31].

We highlight the importance of downregulating both pathways since, they act in the gene expression of proteins related to the invasiveness and metastasis of RMS, in addition to being key in the regulation of differentiation of myogenic progenitor cells.

N.g. extracts, as it seems not only induced cell death in RD cells but also reduced the aggressive and metastatic characteristics of this tumor type.

Although alternatives are being studied that aim to inhibit the pathways related to tumor aggressiveness, there is no information regarding whether a particular compound can act by repressing both the Notch and wnt/β-catenin pathways.

N.g. extracts were able to decrease the activation of both pathways, maybe as a consequence of its apoptotic effect, so the study's future goal is to identify and characterize the specific molecules within the extracts responsible for these effects, with the aim of developing novel therapeutic strategies, particularly those that trigger cell differentiation to counteract uncontrolled growth and malignancy of these cells.

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