Effect of Lichen Secondary Metabolites on Human Prostate Cancer Cells

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Prostate cancer is one of the most common forms of cancer in men and continues to be a problem in the developed world (Jemalet al., 2011). Conventional therapy to eradicate tumour cells, e.g. surgery, chemotherapy, radiotherapy and hormonal treatments, has resulted in prolonged survival and cure in some patients. However, relapse and metastases occur frequently and in general are unresponsive to conventional therapy. In normal prostate tissue, androgens regulate the growth and differentiation of epithelial cells. In early stages of prostate cancer, proliferation is increased by androgens and can be kept in check by various therapies aimed at either decreasing circulating androgens or by blocking the androgen receptor using antagonists. However, in advanced stages of prostate cancer, growth and development typically become refractory to androgen effects and cells continue to grow unchecked. Aggressive treatment of patients with combination chemotherapy usually results in severe side-effects and is rarely curative. Therefore, new therapeutic approaches are needed with the objective of overcoming tumour cell resistance and reducing drug-mediated toxicity. In this regard, many nutritive and non nutritive phytochemicals with diversified biological properties have shown promising responses for the prevention and/or intervention of prostate cancer (Russo et al., 2012). Lichens and their metabolites have long been used by humans. Throughout the ages lichen extracts have been used for various purposes, in particular as dyes, perfumes and for various remedies in folk medicine since ancient Egyptian times. Chemical studies on the secondary metabolites present in lichens have led to the isolation of many new substances, which by today number over 800. These compounds, which comprise aliphatic, cycloaliphatic, aromatic, and terpenic compounds, are unique with respect to those of higher plants and show interesting biological and pharmacological activities. Several well characterized depsidones and depsides exhibit anti-inflammatory, analgesic, antipyretic, antibacterial, antifungal and anticancer properties (Russo et al., 2012). With the aim of identifying novel agents with antigrowth and pro-apoptotic activity on prostate cancer cells, in the present study, we evaluated the effect of two lichen secondary metabolites the depside gyrophoric acid and the depsidone physodic acid on cell growth and death in androgen-sensitive (LNCaP) and androgen-insensitive (DU-145) human prostate cancer cells. The cell viability was measured using MTT assay. LDH release, a marker of membrane breakdown, was also measured. For the detection of apoptosis, the evaluation of DNA fragmentation and caspase-3 activity assay were employed. The expression of Bcl-2, Bax, NOS2 and Hsp70 proteins was detected by western blot analysis. Generation of reactive oxygen species was measured by using a fluorescent probe. The results obtained show that depsides gyrophoric, after 72 h of treatment, inhibited the growth of prostate cancer cells only at more high concentration (50 uM). Whereas the depsidone physodic acid showed a dose–response relationship in the range of 6.25–50 uM concentrations in LNCaP and DU-145 cells, activating an apoptotic process. The novel finding, in the present study, is that apoptosis induced by physodic acid appears to be mediated, at least in part, via the inhibition of Hsp70 expression, that may be correlated with a modulation of redox-sensitive mechanisms. The results reported here confirm the promising biological properties of depsidone compounds (Russo et al., 2012), and may offer a further impulse to the development of analogues with more potent efficacy against prostate cancer cells.

Jemal et al. (2011) *CA Cancer J Clin.* 61, 69-90.
Russo et al. (2012) *Chem Biol Interact.* 195, 1-10.