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COMMENTARY

Towards the use of non-psychoactive cannabinoids for prostate cancer

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The palliative effects of *Cannabis sativa* (marijuana), and its putative main active ingredient, Δ^9-tetrahydrocannabinol (THC), which include appetite stimulation, attenuation of nausea and emesis associated with chemo- or radiotherapy, pain relief, mood elevation, and relief from insomnia in cancer patients, are well-known. Because of the adverse psychoactive effects of THC, numerous recent preclinical studies have been focused on investigating other non-psychoactive constituents of *C. sativa*, such as cannabidiol, for potential therapeutic use. In this issue of the *British Journal of Pharmacology*, De Petrocellis and colleagues present comprehensive evidence that plant-derived cannabinoids, especially cannabidiol, are potent inhibitors of prostate carcinoma viability *in vitro*. They also showed that the extract was active *in vivo*, either alone or when administered with drugs commonly used to treat prostate cancer (the anti-mitotic chemotherapeutic drug docetaxel (Taxotere) or the anti-androgen bicalutamide (Casodex)) and explored the potential mechanisms behind these antineoplastic effects.

LINKED ARTICLE
This article is a commentary on De Petrocellis *et al.*, pp. 79–102 of this issue. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2012.02027.x

Abbreviations

LNCaP cells, androgen-sensitive human prostate adenocarcinoma cells derived from the left supraclavicular lymph node metastasis; THC, Δ^9-tetrahydrocannabinol; TRP channels, transient receptor potential cation channels; TRPM8, transient receptor potential cation channel subfamily M member 8

Prostate cancer is the most common malignancy among men of all races and is one of the leading causes of cancer death in this population (Schroder, 2010). Although significant advances have been made in the early screening and treatment of prostate cancer by various pharmacological, surgical and radiotherapy approaches during the past decade, the traditional approach of radical treatment may often lead to severe adverse consequences and decreased quality of life.

The palliative effects of *Cannabis sativa* (marijuana) and its putative main active ingredient, the Δ^9-tetrahydrocannabinol (THC), which include inhibition of nausea and emesis associated with chemo- or radiotherapy, appetite stimulation, pain relief, mood elevation and relief from insomnia in cancer patients, have been well recognized for centuries (Pacher *et al.*, 2006). Synthetic THC (Marinol, Dronabinol) and its derivative nabilone (Cesamet), as well as plant-derived extracts containing controlled amounts of THC and other plant-derived cannabinoids (Sativex), have been approved in several countries to control nausea in cancer patients undergoing chemotherapy, to stimulate appetite and/or to attenuate cancer-related pain (Pacher *et al.*, 2006; Velasco *et al.*, 2012).

In addition to the therapeutic effects outlined above, THC, synthetic cannabinoid ligands and endocannabinoids or endocannabinoid-like substances have all been shown to induce cell death and to inhibit proliferation and/or migration of several murine and/or human cancer cell lines, as well as inhibiting the growth of certain types of tumours or

tumour cell xenografts *in vivo* (Guindon and Hohmann, 2011; Velasco *et al.*, 2012), including prostate cancer (Diaz-Laviada, 2011). Accumulating evidence indicates that a functional endocannabinoid system exists in normal prostate tissue, which is dysregulated in prostate cancer (Diaz-Laviada, 2011). Furthermore, overexpression of several components of the endocannabinoid system appears to correlate with the prostate cancer grade and progression (Diaz-Laviada, 2011).

Because the clinical use of THC is limited by adverse psychoactive effects, numerous non-psychoactive constituents of *C. sativa*, particularly cannabidiol, have been extensively investigated in preclinical models of inflammation (Izzo *et al.*, 2009; Russo, 2011) and cancer (Guindon and Hohmann, 2011; Massi *et al.*, 2012) recently. Most of these preclinical studies emphasize the extensive therapeutic potential of cannabidiol in various types of inflammatory diseases (Izzo *et al.*, 2009) and cancers (Massi *et al.*, 2012).

In this very interesting paper, the authors (De Petrocellis *et al.*, 2012) describe the results of a very comprehensive study carried out with non-psychoactive cannabinoids on prostate carcinoma cells. The authors first screened 12 plant cannabinoids, including THC, and cannabinoid-enriched extracts from the strains of *Cannabis* selected to produce most of the corresponding compounds. They have done so in four different androgen receptor-dependent and -independent cell lines, and used normal culturing conditions, as well as conditions of serum deprivation. They presented novel data that plant-derived cannabinoids, and cannabidiol in particular, are potent inhibitor of prostate carcinoma viability under conditions of serum deprivation; whereas the extracts are more efficacious under normal culturing conditions. Next, the authors investigated if one of the most potent cannabinoid-enriched extracts *in vitro* was also efficacious *in vivo*, following systemic administration, in xenograft models obtained by using two of the four cell lines used *in vitro*. They reported that the extract is also active *in vivo*, either alone or when administered with the anti-androgen bicalutamide (Casodex) or a potent anti-mitotic chemotherapeutic drug docetaxel (Taxotere), which are often used to treat prostate cancer. Finally, the authors investigated, in all four prostate carcinoma cell lines, the cellular and molecular mechanism of action of cannabidiol and other two pure cannabinoids. They reported that these compounds act mostly by inducing apoptosis via activation of intracellular intrinsic pathways, which only partially involves antagonism of transient receptor potential cation channel subfamily M member 8 (TRPM8) and/or androgen receptor down-regulation (and only in certain cancer cell lines). This pro-apoptotic effect in cancer cells was independent of cannabinoid receptors or other TRP channels and, in the case of cannabidiol, was accompanied by intracellular calcium elevation and/or reactive oxygen species formation, depending on the cell line. Finally, the authors also showed that cannabidiol is more efficacious in inducing apoptosis in LNCaP cells that were partially differentiated into neuroendocrine-like cells, an *in vitro* model of invasive and untreatable prostate carcinoma.

Taken together, the results in this paper represent a considerable experimental effort and provide a wealth of important information on how plant-derived, non-psychoactive, cannabinoids can induce apoptosis in prostate carcinoma cells through a variety of mechanisms. The *in vivo* data, obtained in xenograft models, suggest that these compounds, and cannabidiol in particular, should be further tested against this type of cancer. This finding, coupled with recent evidence suggesting that cannabidiol inhibits angiogenesis (Solinas *et al.*, 2012) and various key pro-inflammatory pathways (e.g. NF-κB, COX-2 and inducible NOS) (Mukhopadhyay *et al.*, 2011) implicated in growth and progression of various malignancies, and also attenuates the tissue injury caused by a widely used chemotherapeutic drug cisplatin (Pan *et al.*, 2009), is particularly encouraging from a therapeutic point of view.

The results described in this paper also supplement previous evidence that THC can counteract prostate carcinoma *in vitro* and *in vivo* via activation of cannabinoid CB_1 and CB_2 receptors (Sarfaraz *et al.*, 2005; 2008) and are therefore important in view of the recent use and marketing of Sativex (1:1, THC : cannabidiol preparation) for the treatment of neuropathic pain and spasticity in patients with multiple sclerosis, and coupled with previous reports (Sarfaraz *et al.*, 2005; 2008; Diaz-Laviada, 2011) provide a strong rationale for clinical testing of cannabidiol and Sativex (the toxicology of which have been widely investigated in humans) (Izzo *et al.*, 2009) against prostate carcinoma.

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Conflict of interest

Author declares no conflicts of interest to disclose.

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