Systematic review of the potential role of cannabinoids as antiproliferative agents for urological cancers

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Abstract

Introduction: The palliative effects of cannabis sativa (marijuana), which include appetite stimulation, attenuation of nausea and emesis, and pain relief, are well known. The active components of cannabis sativa (cannabinoids) and their derivatives have received growing interest due to their diverse pharmacological activities, such as cell growth inhibition and tumour regression. The aim of this review is to look at the current evidence on the antiproliferative effects of cannabinoids in urological malignancies, including renal, prostate, bladder, and testicular cancers.

Methods: We conducted a systematic review of studies exploring the effect of cannabinoids on tumour activity, including all study types except expert opinions. A formal search was run on Medline database from 1946 to September 2016, along with a hand-search on PubMed for relevant studies.

Results: The search yielded a total of 93 studies from Medline and PubMed, of which 23 studies were included in the final analysis. To date, there are various in vitro studies elucidating the potential mechanism of action of cannabinoids for urological cancers, along with population-based studies specifically for testicular malignancies. To date, no clinical trials have been conducted for urological cancer patients.

Conclusions: These results demonstrate that the role of endocannabinoids for urological malignancies is an area of active research. Further research is required not only to evaluate the crosstalk between cancer signaling pathways and cannabinoids, but also large randomized clinical studies with urological patients need to be conducted before cannabinoids can be introduced as potential therapeutic options for urological neoplasms.

Introduction

Cannabinoids are a class of over 60 compounds derived from the plant cannabis sativa, as well as the synthetic or endogenous versions of these compounds.[1] The primary psychoactive component of the cannabis plant — Δ^9tetrahydrocannabinol, or THC — stimulates neural cannabinoid receptors, mimicking the action of endogenous cannabanoids (termed endocannabinoids).[2] Endocannabinoids exert important pharmacological and physiological actions by activating CB1 (brain type receptors) and CB2 (spleen type) receptors in mammals.[3] They mimic many of the effects of THC and activate both CB1 and CB2.[4] The endocannabinoid system (ECS) is widely distributed in mammalian tissues and regulates nervous, cardiovascular, digestive, reproductive, immune, and metabolic functions.[3]

Recent studies suggest that cannabinoids contribute to maintaining balance in cell proliferation and that targeting the ECS can affect growth of several different types of cancer, including gliomas, breast, colon, prostate, and hepatocellular carcinoma.[1,5-7] To date, there has only been one clinical trial looking at the antitumoural activity of cannabinoids on terminal human patients harbouring actively growing recurrent gliomas.[8] Hence, this review will outline the current evidence on the antiproliferative effects of endocannabinoids in the male genitourinary malignancies, including renal, prostate, bladder, and testicular cancers, and look to explore the possible role of future human clinical trials in the field.

Methods

Search strategy

We searched Medline database for relevant studies published in English from 1946 through September 30, 2016. The keywords used in the search were: "cannabinoids OR endocannabinoids OR cannabis" AND "prostatic neoplasms OR urinary bladder neoplasms OR testicular neoplasms OR ureteral neoplasms OR kidney neoplasms OR urethral neoplasms OR urological neoplasms." Furthermore, we did a hand-search of PubMed with keywords" "cannabinoids and prostate neoplasm," "cannabinoids and kidney neoplasm," "cannabinoids and bladder neoplasm," and "cannabinoids and testicular neoplasms."

Selection of studies

Identified studies were selected based on title and abstract screening by two independent authors. Full articles were

retrieved if a decision could not be made based on the abstracts. Disagreements were resolved by consensus and in rare cases by involving a third party.

Inclusion criteria

Articles were included if they met the following criteria: 1) in vitro studies that established a clear association between cannabinoid receptor activation or inactivation and subsequent effect on tumour activity; 2) in vivo studies that explored the effect on THC administration either locally or systemically on tumour activity and/or size; and 3) all study types were included except expert opinion pieces.

Data abstraction

Two authors independently reviewed each full-text article chosen after full-text screening to extract relevant data from the studies. Data abstraction focused on identifying the specific cannabinoid receptors expressed by oncogenic cells, binding of THC to those specific receptors, effect of THC on upregulation or down-regulation of cannabinoid receptor, and finally the that cannabinoid receptors have (if any) in antiproliferative activity.

Outcomes

The outcomes of interest were any objective evidence of anticarcinogenic or antiproliferative activity of cannabinoids in male urological malignancies either through in vitro or in vivo studies. The cancers of interest are renal, ureteric, bladder, prostate, and urethral neoplasms.

Results

Our search strategy resulted in the initial identification of 93 studies. Thirty-five duplicate studies were removed, leaving 58 unique studies. A further 18 studies were removed after title and abstract screening, excluding non-English articles, studies not addressing the research question, and expert opinion articles. Forty full-text articles were reviewed for eligibility for inclusion in the final analysis. Seventeen articles were excluded after full-text review, leaving 23 studies for final inclusion (Fig. 1).

Cannabinoids and renal cancer

A limited number of studies have assessed the presence cannabinoid receptors (CB1 and CB2) in renal neoplasms and even fewer have assessed the role, if any, of the ECS in carcinogenesis and cell proliferation of renal neoplasms. To date, Larrinaga et al demonstrated that renal tumour tissues expressed mRNA of CB1 receptor in the tubular system of adult kidneys.[9] Studies exploring the role of ECS in colorectal cancer have suggested that CB1 receptor loss can potentially enhance the proliferation ability of tumour cells due to lack of antitumoural effect of endocannabinoids.[10] Subsequently, Larrinaga et al went on hypothesize that since CB1 is highly expressed in proximal convoluted tubules of the nephron, a similar concept may apply to renal neoplasms, where CB1 down-regulation may play a role in increased proliferation renal tumours, specifically clear-cell renal cell carcinomas.[11] However, further research is needed to clarify the exact role and particular mechanisms exploring the ligands and receptors involved behind such a phenomenon.

Interestingly, another study exploring the activity of CB1 receptors in chromophobe and renal oncocytoma tissue lines found that they were expressed in similar levels to that of non-tumour tissues.[3] Often times it is difficult to histologically distinguish clear-cell renal cell carcinoma from chromophobe renal cell carcinoma and having the difference in the levels of CB1 receptor, i.e., down-regulated in clear-cell renal cell carcinoma while maintaining normal levels in chromophobe, could serve as an important diagnostic tool to differentiate between the two.[12]

Overall, the above studies have shown the presence of CB1 receptors in clear-cell renal cell carcinoma and chromophobe renal cell carcinoma, and in vitro experiments also point to the possible role of down-regulation of CB1 receptors in promoting clear-cell renal neoplasm cell proliferation. The receptors could not only play an important role in investigating treatment options, but could also be used for diagnostic purposes.

Cannabinoids and prostate cancer

In terms of urological malignancies, the highest amount of focus in the role of cannabinoids has been on prostate cancer. Various different biological mechinisms have been explored to explain the possiblity of the beneficial effect of cannabinoids of prostate. First, Orellana-Serradell et al postulated that by activation of apoptotic mechanisms, endocannabinoids could halt the growth of prostate cancer cells.[13] In their study, they used a commercial cell line and primary cultures derived from prostate cancer demonstarating the expression of CB1 and CB2 in those cell lines, which was more prominent in later stages of the disease. They also proved that treatment with endocannabinoids produced a dose-dependent cell growth inhibitory effect on all the different prostate cancer culture cells. Based on these results, they suggested that endocannabinoids may be a beneficial option for the treatment of prostate cancer that has become non-responsive to common therapies. Another study suggested that the anticancer activity of cannabinoids was linked to induction of phosphatases.[14] They demonstrated cannabinoids induced mRNA expression of

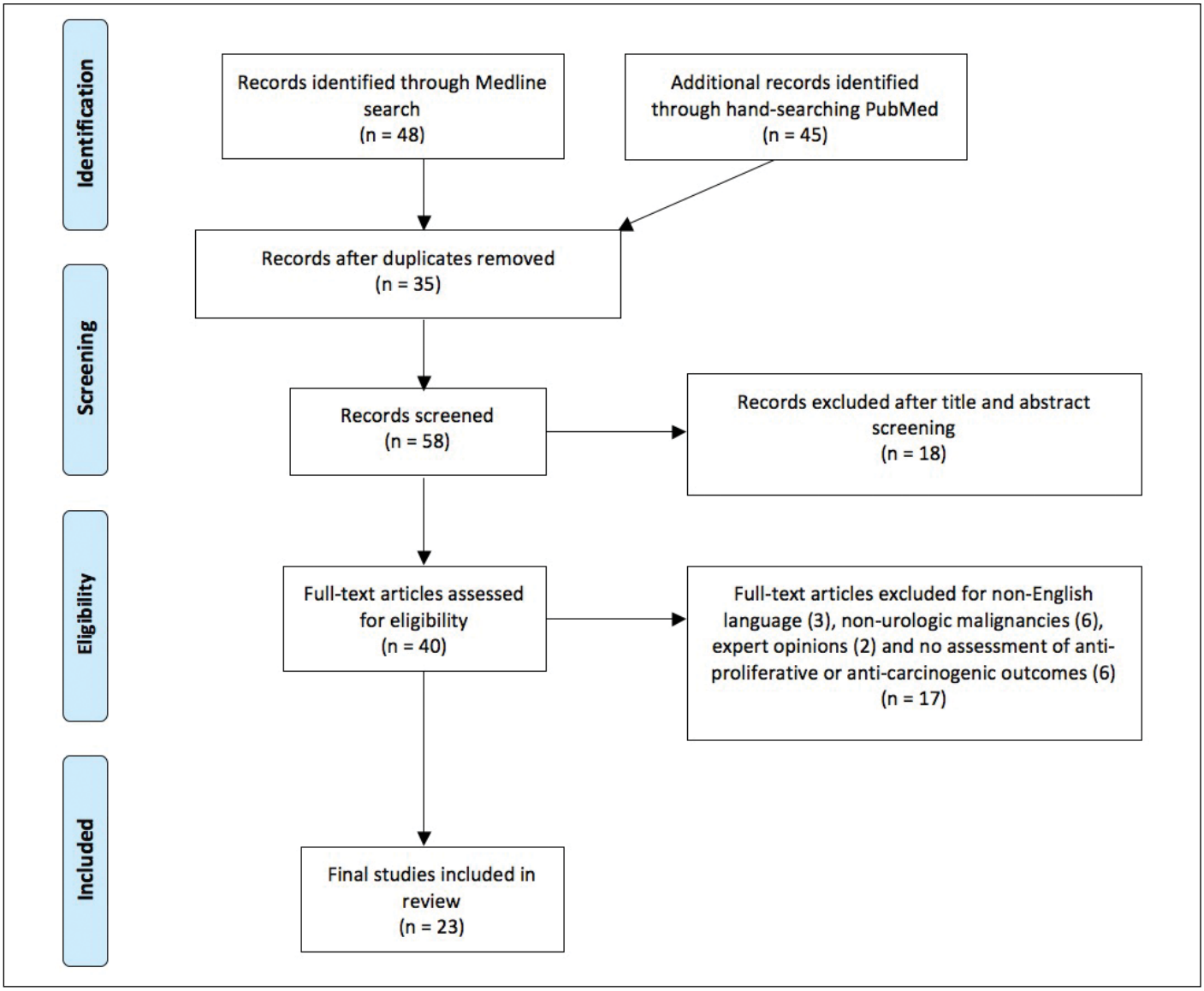

Fig. 1. Search strategy flowchart.

several phosphatases in prostate cancer cells and this was consistent with induction of phosphatases by other phytochemical anticancer drugs.

Olea-Herrero et al investigated the effect of the cannabinoid R(+)methanandamide in androgen-resistant prostate cancer cells and found a dose-dependent increase in the secretion of the cytokine IL-6.[15] Their study suggested that CB2 agonists may offer a novel approach in the treatment of prostate cancer by decreasing cancer epithelial cell proliferation. Chung et al used formalin-fixed, paraffin-embedded tissue samples from patients who were diagnosed with prostate cancer at a transurethral resection and probed whether the level of cannabinoid 1 receptor immunoreactivity (CB1IR) in prostate cancer tissues is associated with disease severity and outcome.[16] Ultimately, they found that high CB1IR immunoreactivity is associated with a more severe form of the disease at diagnosis and a poorer outcome. Lastly, Thors et al studied the expression of the endocannabinoid-metabolizing enzyme fatty acid amide hydrolase from patients diagnosed with prostate cancer.[17] In this study, the tumour epithelial fatty acid amide hydrolase was found to be associated with prostate cancer severity and outcome at mid-range, but not high CB1IR scores.

In summary, elucidating the exact intracellular pathways of the effect of cannabinoids on prostate cancer cells is still an area of active research that could have significant ramifications for treatment options in the future, especially for castrate-resisitant prostate cancers. Once plausible biological mechanisms are discovered, the next would step would be to move on to clinical trials to investigate whether or not there is any clinical utility for such treatment options.

Cannabinoids and bladder cancer

Our search yielded just one study exploring the role of cannabinoid receptors in the regulation of inflammation and proliferation of human bladder carcinoma cells.[18] There is an abundance of current literature pointing to the role of chronic inflammatory states in the development and progression of cancer, as well as the ability of tumour cells to metastasize. Furthermore, previous literature has shown that cancer cells can trigger release of inflammatory cells, such as cytokines and growth factors, that create a pro-inflammatory microenvironment often correlated to the highly invasive phenotype and metastatic potential of cancer.[19,20] Gasperi et al explored the effect N-arachidonoylethanolamine and 2-arachidonoylglycerol, the most biologically active endocannabinoids, on CB1 and CB2 receptors. The study demonstrated bladder cancer cell lines were regulated by activation of CB receptors where CB1 receptor activation played a more prominent role in proliferation and CB2 receptors were more effective in triggering the pro-inflammatory state.[18] Further research and more studies are required to understand the expression of these receptors in different stages of bladder cancers and also the varying effect of endocannabinoid ligands on the different CB1 and CB2 receptors.

Cannabinoids and testicular cancer

The data surrounding the link between endocannabinoids and testicular malignancies primarily comes from population-based studies exploring the risk of testicular cancer development among marijuana users. Daling et al conducted the initial case-control study reporting a 70% increased risk of non-seminoma and mixed histology testicular germ cell tumours among current marijuana (especially among users who started in adolescence) compared to matched controls (odds ratio [OR] 2.3; 95% confidence interval [CI] 1.3–4.0).[4] This initial data was further supported by a recent systematic review and meta-analysis conducted by Gurney et al, which included three case-control studies between 198 and 2015, including a total of 719 cases of testicular germ cell tumours along with 1419 controls.[2,21,22] This study further reinforced the findings of the 2009 case-control study suggesting that current cannabis use at least once weekly or for a long duration (>10 weeks) is associated with the development of testicular germ cell tumour (OR 1.62; 95% CI 1.13–2.31), with the strongest association for non-seminoma tumours.

While there are no studies specifically exploring the biological mechanism of action of the activity of endocannabinoids in testicular cancer, there are two main hypotheses in literature. The first hypothesis speculates that since endocannabinoids are degraded by fatty acid amid hydrolase while THC is mainly metabolized by cytochrome P_{450} enzymes with a half-life of four days in chronic marijuana users, the prolonged activation of CB1 and CB2 in marijuana users can disrupt the normal antitumour activity of the ECS.[4] The second hypothesis is related to the hypothalamus-pituitary-testicular axis. THC typically acts by activating the CB1 and CB2 receptor in the brain to induce a "high."[23] Cannabis has been shown to disrupt the hypothalamic-pituitary-testicular axis and prolonged exposure to cannabis with subsequent stimulation of cannabinoid receptors is thought to disrupt normal hormone regulation and cell proliferation in the testicles, which ultimately may contribute to testicular neoplasms.[2,23]

Additional studies of testicular germ cell tumours are needed to test these hypotheses, including molecular analyses of cannabinoid receptors and endocannabinoid signaling that may provide clues to specific biological mechanisms. If there is a role of the ECS in the development or proliferation of testicular germ cell tumours, it can be a potential target for therapeutic options in the future.

Conclusions and future prospects

Overall, this study explored the current state of literature investigating the role of cannabinoids as antiproliferative agents in urological tumours. With the ever-increasing and popular role of THC in palliative care, which includes inhibition of nausea and emesis associated with chemo or radiotherapy, appetite stimulation, pain relief, mood elevation, and relief from insomnia for oncology patient, clinicians are often confronted with questions from patients regarding the role of THC.[24] Aside from one clinical trial with end-stage glioblastoma multiforme patients, THC has not been studied clinically as a treatment for malignancy.[8] Unfortunately, there are many claims on the internet about the "curative" effects THC can have for cancer patients, where these articles often cite ongoing research articles. However, these articles and websites extrapolate in vitro study results and preclinical work into humans without any basis in fact.[25]

To date, no study has explored the evidence to answer queries from patients on the effects of THC on urological cancers. Hence, this review has elucidated the state of current evidence in various tumours, including renal, bladder, prostate, and testicular neoplasms. There is currently an abundance of literature, especially surrounding the biological mechanisms for prostate cancer; however, no human trials have been conducted. For renal, bladder, and testicular cancers, there is a mixture of in vitro literature along with population-based studies that can provide clues about the role of cannabinoids, but we are still ways away from understanding the therapeutic role of cannabinoids as antiproliferative and tumour-regression agents. However, there are several promising clinical trials currently registered at *http://ClinicalTrials.gov* pertaining to the role of cannabinoids for malignancies. A study organized by the Hadassah Medical Organization in Israel is looking to explore the

use of cannabinoids as single treatment in patients with solid tumours whose cancers are resistant to chemotherapy (NCT02255292). Another ongoing study is a phase 1/2 trial aimed at evaluating the combined effect of Sativex® (an oromucosal cannabis) and temozolomide in patients with recurrent glioblastoma multiforme (NCT01812603 and NCT01812616).[26]

In summary, although many studies have explored the in vitro mechanisms and population-based evidence for cannabinoids, there have been no clinical trials to date for urological patients. Currently, there is no conclusive evidence to support patient claims for starting on cannabinoid monotherapy for anticancer benefit when all other avenues for therapy have failed. Thus, further research is required not only to evaluate the crosstalk between cancer signaling pathways and the ECS, but also large randomized clinical studies with urological patients need to be conducted before cannabinoids can be introduced as potential therapeutic options for urological neoplasms.

Competing interests: Dr. Kapoor has been an advisor for Amgen, Astellas, GSK, Janssen, Pfizer, and Sanofi. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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