

# The Webscout

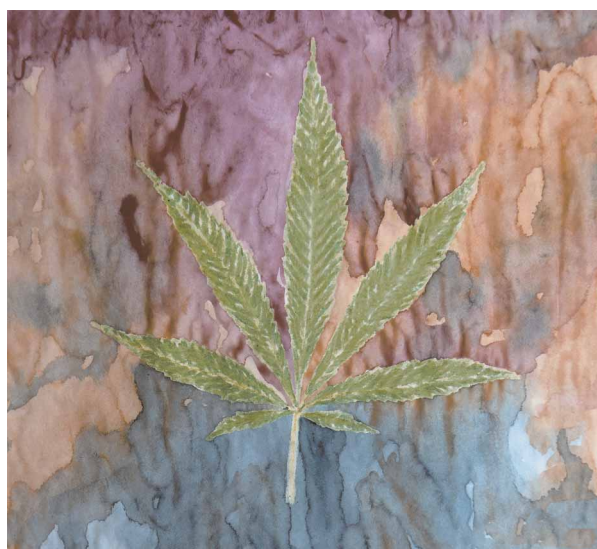
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## Cannabinoids in oncology: more than a palliative

Usually you have chemotherapeutics and biologicals in mind when you are talking about oncology. Would you have thought of cannabinoids? I don't think so but for decades, cannabinoids have been known to exert palliative effects in cancer patients including appetite stimulation and pain relief.<sup>1,2</sup>  $\Delta^9$ -Tetrahydrocannabinol (Unimed Pharmaceuticals, THC, Marinol<sup>®</sup>) and its synthetic analogue nabilone (Valeant Pharmaceuticals International, Cesamet<sup>®</sup>) are approved for the treatment of chemotherapy-induced nausea and emesis. Sativex<sup>®</sup> (Unimed Pharmaceuticals), a mucosal spray containing cannabis extract, licensed for multiple sclerosis spasticity, is currently under development for cancer pain (Phase III stage). In Canada, Sativex<sup>®</sup> has already been approved as an adjunctive analgesic treatment in adult patients with advanced cancer. And apart from the established use in palliative care, you might be astonished to hear that cannabinoids are regarded as possible anti-tumour agents with a low-toxicity profile.

However, firstly we need to step back a little. What are cannabinoids? The hemp plant *Cannabis sativa* produces approximately 60 unique



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compounds known as cannabinoids, of which THC is the most studied owing to its high potency and abundance. THC is mainly responsible for the desired effects in the recreational use of cannabis and marijuana. Cannabinoids exert a wide array of effects within the central nervous system (CNS) as well as in the periphery such as immune, cardiovascular, digestive, reproductive, and ocular functions. Most of these effects are mediated via two cannabinoid-specific receptors, CB<sub>1</sub> and CB<sub>2</sub>. The CB<sub>1</sub> receptor is particularly abundant in the CNS, whereas the CB<sub>2</sub> receptor is predominantly expressed by peripheral immune cells. The most important endogenous ligands on these receptors are anandamide and 2-arachidonylglycerol, which together with the respective receptors and specific processes of synthesis, uptake and degradation constitute the endogenous cannabinoid system. As the isolation of anandamide and 2-arachidonylglycerol, further endocannabinoids have been identified like noladin ether and virodhamine, the latter having been identified as the first endogenously occurring CB<sub>1</sub> receptor antagonist.<sup>3</sup>

Cannabinoids might directly inhibit cancer growth via complex mechanisms. Actually, the anti-proliferative properties of cannabis compounds were first reported 30 years ago by Munson *et al.*,<sup>4</sup> who showed that THC inhibits lung adenocarcinoma cell growth *in vitro* and after oral administration in mice. Although these observations were promising, further studies in this area were not carried out until the late 1990s. Various cannabinoids, including plant-derived, synthetic, and endocannabinoids have now been shown to block cancer cell proliferation and to induce apoptosis of cancer cells both *in vitro*<sup>5,6</sup> and *in vivo*.<sup>7,8</sup> Cannabinoids also possess promising anti-angiogenic, anti-invasive, and anti-metastatic potential. This is, for example, associated with a reduced expression of vascular endothelial growth factor<sup>9</sup> and other pro-angiogenic cytokines as well as modulation of expression of matrix metalloproteinases and their inhibitors. Matrix metalloproteinases are proteolytic enzymes that allow tissue breakdown and remodeling during angiogenesis and metastasis.<sup>10-12</sup>

The endocannabinoid system is activated in several cancer tissues and malignant cells, and *in vivo* and *in vitro* studies indicated that this upregulation might be involved in the tonical control of tumour growth.<sup>13</sup> Endocannabinoids possess anti-tumourigenic potential via inhibition of proliferation,<sup>14</sup> induction of apoptosis,<sup>15</sup> and inhibition of angiogenesis.<sup>16</sup> Manipulation of the endogenous cannabinoid system may represent a means to combat tumour development. Table 1 gives an overview of findings regarding cannabinoid-based cancer therapy.

Despite promising evidence from *in vitro* and *in vivo* studies, clinical data are still very rare. The first study could not prove a benefit of cannabinoid treatment in glioma patients, but at least provides the basis for further clinical investigation.<sup>17</sup> Clinicaltrials.gov reveals no further cannabinoid studies in cancer apart from palliative use. Limitations for cannabinoids and endocannabinoids as cancer therapeutics may be their psychotropic activity and modulation of the immune response, which will need to be circumvented.

The following websites will give you a comprehensive picture of the possibilities of the use of cannabinoids in medicine in general and specifically as an anti-tumour treatment:

- <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697681/?tool=pubmed>
- <http://pharmrev.aspetjournals.org/content/58/3/389.long>

These are reviews on CB receptor agonists as therapeutic options by Pertwee,<sup>19</sup> one of the leading working groups in cannabinoid research, and Pacher *et al.*<sup>3</sup>

- <http://jpet.aspetjournals.org/content/332/2/336.long>
- <http://herb.com/guzman.pdf><sup>18</sup>

Further reading on the anti-tumourigenic properties of cannabinoids for those of you who want to gain deeper mechanistic insights.

- <http://cancer.about.com/od/chemotherapysideeffects/a/Marinol.htm>

Dronabinol is another name used for THC and it is the active ingredient of Marinol<sup>®</sup>. Whether medical marijuana or Marinol<sup>®</sup> is the better choice is a matter of debate. Here you can find a collection of articles around this debate. However, a clear answer is still outstanding.

- <http://www.gwpharm.com/Sativex.aspx>

Sativex<sup>®</sup> is a quite interesting medication. On the one hand, because of its route of administration (i.e. mucosal spray), on the other hand because of its active ingredient, which is an extract of cannabis that is standardized for the content of THC and cannabidiol. The manufacturer's website on Sativex<sup>®</sup> offers a lot of information around this special product and the development of it.

- <http://www.cannabis-med.org/index.php?lng=en>

The use of cannabis, its ingredients or derivatives is not only a medical question, it is to a great extent a

Table 1: Applications, mechanisms, and pros and cons of cannabimimetics in cancer therapy

	CB <sub>1</sub> agonists/activators	CB <sub>2</sub> agonists/activators	Endocannabinoids	Endocannabinoid analogs
Possible application	Mammary, prostate, thyroid, cervical and colon carcinoma, neuroblastoma, glioma, lung cancer	Cervical carcinoma, glioma, lung cancer	Mammary, prostate, and thyroid carcinoma	Glioma, cervical carcinoma
Mechanisms	Inhibition of mitogen-induced stimulation of the G <sub>0</sub> /G <sub>1</sub> -S phase of cell cycle - inhibition of metastasis, cancer cell invasion, migration, angiogenesis	Apoptosis, inhibition of cancer cell invasion	Inhibition of mitogen-induced stimulation of the G <sub>0</sub> /G <sub>1</sub> -S phase of cell cycle	Apoptosis receptor independent
Advantages	Little or no toxicity, little or no suppression of the immune system	No psychotropic effects, little or no toxicity	Little or no toxicity	Metabolically stable
Disadvantages	Psychotropic effects, possible dependence	Interference with the immune response	Little efficacy due to metabolic instability	Toxicity not yet assessed

Adapted and updated from<sup>20</sup> and<sup>21</sup>.

political one. It is restricted in its use by the narcotic laws and therefore the use of medicinal cannabis and its components are closely connected to a debate about legalization of the use of cannabis. The International Association of Cannabis in Medicines fights for the medical use of cannabis, and it is indeed a fight, with law and politics, as you can read from their website. Apart from these aspects, the website is a great source for up-to-date information on what is going on in the world of cannabis research.

<http://www.youtube.com/watch?v=8Md2WNqqxTQ&feature=fvst>

Medical Cannabis explained... If you prefer listening and watching instead of reading, here you go! This video covers the medical aspects and also provides a short excursion on the political aspects and the history of cannabis use.

If you have any further questions or you have any other comments or suggestions, please email me.

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## Communication needs of cancer patients

Cancer patients have a need to access easily understandable information about the disease, treatments, side effects, and outcomes as quickly as possible. This article reviews the many facets of the special and changing communication requirements of oncology patients and provides some relevant ULRs.

Why the need for secondary resources, you might ask. Aren't these patients getting the information they need from their doctors? Some are not, and there are several possible explanations for this. Research has shown that while some patients are willing to trust in their physician's knowledge and therefore are unlikely to seek out extra information, others are reluctant to take up too much of a doctor's time, aware of the limited time they then have for other patients.<sup>1,2</sup> If cancer patients do not get the answers they want from their doctor's surgery, the Internet is an obvious port of call but the information they find there might not be easily understandable. One study, for example, found that 'information regarding breast cancer prevention obtained from the National Cancer Institute's web site is written at far too high of a level'.<sup>3</sup>

A study conducted among 269 cancer patients in the UK in the mid-1990s found that 79% of them wanted as much information as possible.<sup>4</sup> However, particularly in the case of cancer, all issues stemming from an accurately conveyed and understood diagnosis may be difficult to correctly identify, particularly as some doctors do not reveal the actual diagnosis to the patient – 'in many cases even when the patient asked to be told the truth'.<sup>5</sup> An online survey of cancer patients conducted in Israel in November 2011 found that 35% defined the information they received from their doctors about their disease and possible treatments as insufficient, 28% regarded it as incomplete, and 21% said it was unclear.<sup>6</sup>

In the UK, the NHS Cancer Plan (2000)<sup>7</sup> sets out the importance of cancer patients having access to high-quality, accurate information, whereas in the US, the National Comprehensive Cancer Network (NCCN), which provides clinical practice guidelines for physicians, has recently created patient-friendly versions to provide state of the art cancer treatment information in easy-to-understand language. The rationale is to help patients with cancer speak with their treating oncologist about their best treatment options (see box).

It is also important to realize that cancer patients are not a homogeneous group. Research has shown that their information needs are fluid, liable to change as their disease progresses. Various studies have found that patients at certain times during their treatment avoided potentially negative information as part of a coping mechanism.<sup>1,8</sup>

With better prevention, early diagnostics, and ever-improving treatments, more patients survive and new issues concerning them have surfaced, making the survivor another important stakeholder in the field of cancer communication.

Originally the term 'cancer survivor' referred to family members who had lost a loved one to the disease. However, by the 1960s physicians began to refer to 'cancer survivors' as those who had survived 5 years past their diagnosis or treatment, when the risk of a recurrent cancer had diminished substantially. These days there are still differing views as to what constitutes a survivor, but the National Coalition for Cancer Survivorship and the NCI Office of Cancer Survivorship consider a person to be a cancer survivor from the time of cancer diagnosis through the balance of his or her life.<sup>9</sup>

The rise in survivor rates reflects big strides in cancer detection and treatment and the effect of an aging population. For example, nearly 12 million people in the USA, almost four times as many as 40 years ago, are survivors.<sup>10</sup> In the UK, there are over 2 million survivors, predicted to rise to 4 million by 2030.<sup>11</sup>

As you can imagine, there has also been an accompanying rise in the number of survivor narratives available (see box, for an example). These survivors, like many patients are usually well informed and particularly motivated to transmit the knowledge they gained during their treatment to fellow patients. For example, some 70% claim they would volunteer to assist in survivorship activities.<sup>12</sup>

This patient group is now very visible on most information sites. The website of the American Society of Clinical Oncology (ASCO) even has its own section dedicated to survivors (see box). Survivors' quest for information and involvement in oncology issues may not lessen once treatment for cancer has ended because many of them face a lifetime of side effects caused by their treatments. In one study of over 1000 survivors, 53% of respondents reported secondary health problems and 49% that non-medical cancer-related needs were unmet.<sup>11</sup>

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## A selection of websites relevant for cancer patients

Website of the American Society of Clinical Oncology (ASCO):  
<http://www.asco.org/>

ASCO's website for patients/section for survivors:  
[www.cancer.net/www.cancer.net/patient/Survivorship/](http://www.cancer.net/www.cancer.net/patient/Survivorship/)

National Cancer Institute (NCI):  
[www.cancer.gov/cancertopics](http://www.cancer.gov/cancertopics)

National Comprehensive Cancer Network (NCCN) Guidelines for Patients™:  
[www.nccn.org/patients/default.asp](http://www.nccn.org/patients/default.asp).

A medical education website for oncology clinicians:  
<http://www.researchtopractice.com/>

Free individualized survivor care plan:  
<http://www.oncolink.com/oncolife/>

An example of a survivor narrative:  
<http://www.nccn.com/component/content/article/67/848-elizabeth-edwards-and-sam-donaldson-discuss-cancer.html>

A cancer survivor networking/dating site:  
<http://www.cancermatch.com/>