Cannabinoid Application Overview (Part 1) March 5 2017 - Zagreb, Croatia

I am very happy to be affiliated with the group that Jason Bowman represents and I am pleased that the government of Zimbabwe, is behaving in such a progressive manner towards the many beneficial uses of the cannabis hemp plant. This amazing gift from nature will not only solve most of our medical issues, it will also provide mankind with a much more sensible and sustainable existence. Therefore I am truly looking forward to seeing this project take place and I would like to thank the government of Zimbabwe, for allowing us the opportunity to work with them, in making this world a better place for us all.

Highest Regards

Rick Simpson

CANNABIS HISTORY: From Traditional Practices to Modern Medicine

Cannabis and its extracts have been used by countless generations over the centuries to treat and cure many conditions from pain and inflammation to blindness. African, Asian, Persian, Arabic and Hebrew texts, for example, all document a long and vast history of topical and internal use. It is indicated for glaucoma, inflammation, pityriasis rosea and lichen planus, for example, by using the fresh juice as a wash along with extracts. Texts also cite various cannabis treatments for vitiligo and leprosy, and state that cannabis leaves used as a hair rinse even stimulated hair growth. In Africa, The Ebers Papyrus, dating to Amenhotep I (circa 1546–1526 BC), found in the Valley of the Kings contain 877 remedies which includes a prescription for cannabis to treat inflammation.[1] Other 11th and 12th centuries texts prescribed cannabis leaf juices to cure abscesses and an "oily wax" made from cannabis extracts applied to tumors. Cannabis extracts were also indicated as effective painkillers, and for soothing neurological pain. In 1839 British surgeon W.B. O'Shaughnessy, who learned of its medicinal properties while working in India, introduced cannabis to Western Medicine. Cannabis extracts and infusions became widely promoted for reported analgesic, sedative, anti-inflammatory, antispasmodic, and anticonvulsant effects.[2]

MATERIA MEDICA: From 1839 to Present

The 1844 review of Dr. Neligan's book, published in The Lancet (Vol. 1 pp 99-101), refers to the work as a full, yet concise, account of the present state of materia medica. Dr. Neligan confirmed O'Shaughnessy's findings and concludes that cannabis preparations chiefly employed in the treatment of neuralgic and painful afflictions proved mostly very beneficial. "Thus, they have been given in tetanus, hydrophobia, infantile convulsions, sciatica, chorea, neuralgic pains, and chronic rheumatism; they have been also used to subdue sleeplessness or disturbed rest". Both the book and review conclude that the trials made with cannabis extract "…[I]n the diseases above enumerated, suggest that cannabis may be often used with benefit as a substitute for opium, in cases or which that drug is unsuited from idiosyncrasy or any other cause; and also that it does often succeed in abating, sometimes in completely removing pain, where this agent totally fails us."[3] More recent studies confirm topical and oral administration of cannabinoids results in analgesic effects in models of inflammatory and neuropathic pain especially for the control of breakthrough pain.[4]

In 2001, Rick Simpson re-discovered the healing properties of cannabis when he used it to help to treat a head injury. Then, in 2003, Rick used cannabis extracts to heal his own skin cancer. He began to teach the public how to heal themselves of countless conditions which now have come to include cancer, HIV/AIDS, skin disorders, glaucoma, and many others. Rick began to write and lecture extensively on the subject. Also in 2003, Dr. Manuel Guzmán published research which confirmed that cannabinoids "…[H]ave been shown to inhibit the growth of tumour cells in culture and animal models by modulating key cell-signalling pathways." A chemotherapeutic potential for plant-derived and endogenous cannabinoids in CRC therapy was reviewed in 2005 and published by Patsos, HA et al. (See Table 1 next page)[5]. Unlike chemotherapy treatments, cannabis is non-toxic and effective.

Table 1 | **Plant-derived and endogenous cannabinoids have potent anti-neoplastic properties**

A number of cannabinoid compounds have antitumoural action in different tumour types, via induction of apoptosis, cell cycle arrest or inhibition of angiogenesis and metastasis. Adapted with permission from Nature Publishing Group (http://www.nature.com/) from [2]. AEA, arachidonoyl ethanolamide (anandamide); 2-AG, 2-arachidonoyl glycerol; CB cannabinoid; Met-F-AEA, 2 methyl-arachidonyl-2′-fluoro-ethylamide; THC, tetrahydrocannabinol; VEGF, vascular endothelial growth factor.

Tumour type	Experimental system	Cannabinoid	Effect	Mechanism
Lung carcinoma	*In vivo* (mouse) *In vitro*	THC	Tumour size decreased: cell growth inhibition	Not determined
Glioma	*In vitro* *In vivo* (mouse, rat, human)	THC, WIN-55,212-2, JWH-133, cannabidiol, AEA	Tumour size decreased: apoptosis, reduced angiogenesis: blocked VEGF pathway	CB_1 & CB_2
Thyroid epithelioma	*In vivo* (mouse) *In vitro*	Met-F-AEA	Decreased tumour size: cell cycle arrest	CB_1
Lymphoma/leukaemia	*In vivo* (mouse) *In vitro*	THC, AEA, HU-210, JWH-015	Decreased tumour size: apoptosis	CB_2
Breast carcinoma	*In vitro*	AEA	Cell-cycle arrest	CB_1
Prostate carcinoma	*In vitro*	AEA, THC	Apoptosis	CB_1 (?)
Neuroblastoma	*In vitro*	AEA, THC	Apoptosis	VR1
Colorectal carcinoma	*In vitro*	AEA, 2-AG	Growth inhibition	CB_1

Source: The Molecular Biology of Colorectal Cancer (2005) pg. 713

CURRENT CANNABINOID APPLICATIONS OVERVIEW PART 1: Mastocytosis, Glaucoma and Colon Cancer

Mastocytosis is a group of rare disorders of both children and adults caused by the presence of too many mast cells (mastocytes) and CD34+ mast cell precursors in a person's body. The most common cutaneous mastocytosis is **urticaria pigmentosa (UP)**. Systemic mastocytosis involves the internal organs, usually in addition to involving the skin. Mast cells collect in various tissues and can affect organs such as the liver, spleen, lymph nodes, and bone marrow. Other types of mast cell disease include mast cell leukemia, and mast cell sarcoma. While currently, no official cure for mastocytosis exists, it is known that cannabinoid treatment can alleviate symptoms effectively. In rare cases in which mastocytosis is cancerous or associated with a blood disorder, the patient may also be effectively treated with cannabinoids because the distribution of cannabinoid receptors 1 (CB1) and 2 (CB2) on sensory nerve fibers and adnexal structures in human skin and connective tissues is well-known.[6]

Colon Cancers treated with cannabinoids may be abated and killed via apoptosis (programmed mutating cell death). In addition, gliomas, leukemias, melanomas and other cancer cell types also cease dividing and die. Findings confirm that activation of the autophagy-mediated cell death pathway occurs upstream of apoptosis in cannabinoid antitumoral action.[7]

Glaucoma treated with cannabinoids is also a well-studied traditional practice because cannabinoids reduce ocular pressure. In 2002, Tomi Järvinen et al. published a study which found: "…[S]ome cannabinoids may ameliorate optic neuronal damage through suppression of *N*-methyl-D-aspartate receptor hyperexcitability, stimulation of neural microcirculation, and the suppression of both apoptosis and damaging free radical reactions, among other mechanisms."[8] In 2004, Tomida et al. published a more extensive review which concluded: "Other possible applications of cannabinoids in ophthalmology could be explored. Age related macular degeneration (AMD) is the leading cause of blindness in the United Kingdom. Perhaps the potent antioxidant properties of the cannabinoids may be beneficial in AMD, offering a possible alternative to established antioxidant supplements. Cannabinoids have been shown to inhibit angiogenesis, leading to a decrease in the expression of proangiogenic factors such as VEGF Evidence suggests that VEGF plays a major part in the development of choroidal neovascularisation in AMD, and clinical trials using anti-VEGF therapies are being conducted. The CB2 receptors are also under intense investigation for their possible immunomodulatory effects. The anti-inflammatory properties of CB2 receptor agonists might also prove to be of therapeutic relevance in different forms of inflammatory eye disease."[9]

CANNABIS TREATMENT POTENTIAL IN ZIMBABWE

Each of these conditions can be treated with cannabis extracts. We recommend considering Pigmentosa treatment trials start as topical ONLY with any extract we can readily produce with what is now available in Zimbabwe. As our medicinal Indica genetics are available for internal extracts, all patients can take the oral doses and most likely successfully mitigate, if not fully address their issues. While there may be some local landraces suitable for oral ingestion, we can not know this with any certainty until we have more information. In any event, Rick Simpson has agreed to allow GreenEarth to bring his Indica genetics to Zimbabwe and commence growing immediately, so that within a few months, we can be sure to have extracts with the curing qualities patients require for internal ingestion pursuant to Rick's proven protocol.

NOTE: Extracts produced from Sativa landraces may overly stimulate patients rather than sedate them, thus complicating ingestion versus topical because while Sativa topical applications can be somewhat effective, they do not have the strong sedative effects found in medicinal Indica varieties. A careful distinction must be made.

HOW CANNABIS EXTRACTS WORK

Cannabinoid receptors mediate the psychopharmacological action of cannabis extracts. The endocannabinoid system regulates numerous cellular and physiological processes through the activation of these receptors targeted by endogenously produced endocannabinoids. Receptors are localised in the central and peripheral nervous system as well as on cells of the immune system, and elsewhere. CB1 and CB2 immunoreactivity has been observed in cutaneous nerve fiber bundles, mast cells, macrophages, epidermal keratinocytes, and the epithelial cells of hair follicles, sebocytes and eccrine sweat glands. In epidermal keratinocytes, hair follicle and sebaceous glands, CB1 and CB2 have been found to be distributed in a complementary fashion. Double-immunostaining with an anti-CGRP antibody suggests the presence of cannabinoid receptors on small afferent peptidergic nerves.[10]

The abundant distribution of cannabinoid receptors on skin nerve fibers and mast cells provides implications for an anti-inflammatory, anti-nociceptive action of cannabinoid receptor agonists which confirms historic therapeutic trials. The CB2 receptor helps expand stem cells by promoting fat burning. In addition, the CB1 receptor promotes electron transport driven ATP production that also produces free radicals. Efficient energy production allows for the differentiation of the cells so they can become what they are replacing. U.S. Patent No. US6630507B1 "Cannabinoids as antioxidants and neuroprotectants" details these mechanisms and claims that: "The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV..."[11]

In summary, it is known that cannabinoid receptor activation induces apoptosis through tumor necrosis factor by way of mediated ceramide de novo synthesis in colon cancer cells. We also know that phytocannabinoids such as Δ9-THC and cannabidiol exert chemopreventive effects in vivo and reduce cell proliferation through multiple mechanisms including apoptosis.[12]

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