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Editorial

Repositioning Cannabinoids in Recent Drug Discovery and it's Manifestation in Cancer Therapy

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Humankind has cherished an extensive and complex relationship with cannabinoids - complex terpenophenolic compounds that are most widely known for their psychoactive effects - since time immemorial. While it traces its humble origins as a measure of pain relief in ancient civilizations, in recent times, *Cannabis sativa* has enjoyed notoriety unknown to any other cryptogram. However, modern research has witnessed a shift towards the medicinal applications of the compounds as a whole, regardless of its origin. It is ironic that the researchers that aimed at proving the risks associated with marijuana at the onset of the twentieth century, actually stumbled upon the conspicuous reverse facts. A two-year chronic administration of high Tetrahydrocannabinol (THC) doses unveil a striking reduction in the spontaneous onset of hormone-dependent tumor in breast-cancer study [1]. Cannabinoids bind and activate Gαi protein coupled receptors, CB1 (central receptor) and CB2 (peripheral receptor) which induce psychotropic, hallucinogenic and addictive effects [2]. While CB1 receptors are ubiquitous, they are concentrated in the central nervous system where their neuromodulatory and immunomodulatory effects are largely anticipated [3]. CB2 receptors are common in the enriched area of B lymphocytes [4]. Some studies also unveil interactions with a third receptor known as transient receptor potential vanilloid type 1 (TRPV1). The endocannabinoid system comprising of its receptors and ligands is a promising field of study in therapeutic research, mainly because of the reported analgesic, immunosuppressive, anti-inflammatory, antiemetic, appetite-stimulant, and tumor-growth inhibiting effects [5]. Common examples include Anandamide, a compound primarily utilized for its apoptotic potential in treatment of breast cancer (blocks G1 - S phase transition and regulates Raf- 1/ERK/MAP pathway) [6] and Δ^9-tetrahydrocannabinol (Δ^9-THC), a highly active component extracted from the trichomes of *Cannabis sativa* plant, which is known for its application in attenuated catalepsy [7].

Cancer is a medical condition that needs no introduction but in its barebones is uncontrolled proliferation of cells which may infiltrate other tissues causing severe damage to the organ systems [8]. Current investigation on the disease focuses on its regulatory pathways and characteristic properties of drug-resistance, therefore, targeting these cancer cells by disrupting their cell cycle or introducing DNA damage which may eliminate the rogue cells, is the biotechnological approach to combat it. Not only have cannabinoids that have been approved for clinical usage in certain countries counteract the common side effects of chemotherapy or radiotherapy such as pain, insomnia, loss of appetite, nausea and emesis but they also show promise in causing selective apoptosis of cancer cells [9]. CB1/2 receptors are equally responsible for cell proliferation, invasion, motility, apoptosis and adhesion of cancer cells both *in vivo* and *in vitro* and largely known to influence fat metabolism, neuromodulation, inflammation, cardiovascular, reproductive and respiratory functions in the body [10]. To do so, the ligands cause the modulation of Ca^{2+} and K^+ channels that regulate c-AMP levels in most tissues and models. CB1/2 receptors also regulate members of mitogen activated protein kinase family (MAPKs), extracellular regulated kinase-1 and -2 (ERK12), p38 and c-Jun N terminal kinase (JNK) [11]. Apoptosis is also induced through activation of caspases dependent and independent pathways in cancer cells [8]. There is however the question of the addictive and psychoactive effects of medicinal marijuana and as a result their synthetic counterparts are largely being studied in therapeutic domains. CP55940, a highly potent *in vivo*, non-classical cannabinoid is

well known for its antineoplastic and selective nature [12]. Several key processes play a role in supporting the proliferation and sustained invasion of cancer cells during the disease progression. Therefore, the age-old tactic of rendering the enemy incapacitated by severing its ties to life can be employed to effectively deal with the disease. This is where cannabinoids become a pivotal player in the biology of cancer. For instance, lipid metabolism is a crucial pathway in cancer biochemistry as illustrated by the fact that high ceramide levels in the endoplasmic reticulum of cells that may result due to either an increase in the membrane's sphingomyelin hydrolysis or ceramide de novo synthesis could induce stress which triggers cell death in human glioma and pancreatic adenocarcinoma [13-15]. Cannabinoids, by increasing this synthesized ceramide content can trigger a very specific programmed cell death - Autophagy, a fundamental 'clean-up' process of the cell and is a cytoprotective mechanism that also confers a direct link with cannabinoids [16,17]. These compounds induce autophagy in diverse cell lines and it is observed that pharmacologic or genetic inhibition of this process prevents cannabinoid anti-tumor activity in major animal models, underscoring the importance of autophagy for cannabinoid's antineoplastic activities [18,19]. Another way to disrupt cancer cell growth is by inhibiting the synthesis of the growth factors involved. Cannabinoids are known to block the activation of VEGF pathway (vascular endothelial growth factor), which induces neo-vascularization and angiogenesis. Both the ligand (VEGF) and its receptors (VEGFR1 and VEGFR2) are strongly attenuated in skin carcinoma [20], glioma [21] and thyroid carcinoma [22], following cannabinoid treatment. Furthermore, cannabinoid receptor activation in vascular endothelial cells abrogates proliferation and migration by causing apoptosis [23]. Through targeting tumor immunogenicity, another important auxiliary mechanism of cancer cells can be dealt with: THC treatment of immunocompetent mice has demonstrated a shift in the cytokine profile [24] (from Th1 to Th2) which has induced mobilization of myeloid-derived suppressor cells. It is important to note that cannabinoids strengthen the immune surveillance of already immune-competent cells and in general are shown to lower the overall immunity of organisms [25]. Senescence of cancer cells is emerging as a novel approach to combating tumor growth rather than the more direct approach of apoptosis [27], due to recent reports of anastasis, a deadly cellular process that is exploited by tumor cells after they exhibit near-death morphology by various anti-cancer treatments [26]. While there do exist preliminary reports of senolytic activity from cannabinoids, astronger, more viable link between the two needs to be established as a potential target for cancer therapy [32]. As the mechanisms involving the endocannabinoid system is essentially a monotherapy, the potential of cannabinoid-combination therapies becomes highly selective and non-toxic, two properties which are highly desirable and important [29]. The emergence of combinational therapies has begun putting cannabinoids at their core, not only because of their recognized palliative effects but also their anti-tumor properties [28]. In the following example of THC and temozolomide co-administration, strong antitumor action is reported in glioma xenografts and temozolomide-resistant tumors. It is also remarkable that zero toxicity is reported in this study conducted on mice [30]. Another reported success is the application of gemcitabine and various cannabinoid agonists that synergistically reduces the viability of pancreatic cancer cells [31]. However, the most jarring addictive effects of this class of drugs cannot be ignored and current research is being aimed at purifying various cannabinoids and analyzing the degree of their psychoactive effects to minimize the side effects of cannabinoids. The most promising of these are synthetic cannabinoids, which may also undergo further downstream regulation to increase quality and decrease harmful effects associated. The use of predictive biomarkers to demarcate the sensitivity of various tumors to cannabinoid-based therapies must therefore include the activation of growth factors, modulation of cell signaling pathways and antitumor properties.

In conclusion, the stigma associated with cannabinoids in cancer therapy must give way to a realization of its potential benefits in combating the disease while at the same time, eliminating the threat of addiction and an overall negative impact on the patient's mental health. There is an imperative need to reinforce modern cancer therapy by use of natural compounds which pose little threat to human life when compared to their chemical counterparts.

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