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Mini Review

Cannabinoids and Cancer-What's Next?

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Abstract

The study of the anti-cancer activity of marijuana derivatives is currently focusing on two cannabinoids: THC and CBD. They show good *in-vitro* and *in-vivo* activity against many types of cancer cells, but their psychoactive properties (THC) and low bioavailability make them difficult to use as a cancer treatment. The development of a new technology to isolate cannabinoid acids THCA and CBDA opens new directions in the search for anticancer drugs based on their derivatives with good anti-tumor activity, better bioavailability, and a lack of psychoactive properties.

Keywords: Cannabinoids; Cancer; THC; CBD; THCA; CBDA

Abbreviations: THCA: Tetrahydrocannabinolic Acid; CBDA: Cannabidiolic Acid

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The ever-growing interest in cannabinoids as potential anti-cancer drugs has led to many studies investigating their activity on several types of cancers both *in-vitro* and *in-vivo* [1,2]. Most studies have focused on characterizing the activity of the two main and most available cannabinoids: THC and CBD. Both cannabinoids have been shown to decrease proliferation and induce apoptosis of some types of cancer cells. One potential mechanism of their action may be mediated by specific binding to the cannabinoid G-protein coupled receptors CB1 and CB2. Numerous studies have confirmed that cancer cells express these receptors in significantly higher amounts than normal cells and that the concentration of receptors on the cell surface largely determines the severity of the disease [3]. Therefore, the use of cannabinoids in pancreatic cancer therapy is often beneficial, particularly when combined with other anti-cancer drugs such as nab-paclitaxel and gemcitabine [4]. Exposure to these cannabinoids can however also yield ambiguous results. The presence of up to 1μM of THC reported in the blood of marijuana smokers results in the progression of some types of head and neck squamous cell carcinomas [5]. A similar action of THC has been reported in SF126 glioblastoma cells, but in U87MG cells THC does not exhibit such an effect at 1μM concentrations and below [6]. Another important property of these cannabinoids is their effect on the immune system, specifically the suppression of cancer-causing cytokines such as IL-6 and cyclooxygenases [7]. In some instances, however cannabinoid use has a negative effect on cancer treatments particularly when combined with modern immunomodulatory anticancer drugs [8]. Since the use of these cannabinoids, and CBD, is now gaining momentum, not only as a potential "cure for all diseases" but also as an additive in various creams and foods, the issue of their bioavailability has come to the fore. In the process of a more in-depth study of the pharmacokinetic parameters of these compounds, their low bioavailability when taken orally gives rise to an insurmountable problem especially because of the requirement for high blood concentration of the drugs. The bioavailability of THC taken orally is reported to be 4-12%, inhalation (smoking marijuana) increases bioavailability to 25-35% [9]. The bioavailability of oral CBD is only 13-19% in humans, and it is mainly eliminated in feces.

Research on the medicinal use of THC, and CBD, has most recently focused on the derivatives of these compounds which yield prodrugs with significantly higher bioavailability [10]. The main problem with this approach is the difficulty of determining whether

these substances break down to the original drug or act as a new drug. Addressing this issue will require significant expenditure to synthesize the derivatives as well as to evaluate their efficacy in preclinical and clinical studies. Other synthetic modifications of THC and CBD, in particular the reduction or oxidation of the double C-C bonds, lead to a loss of activity. The only example of a successful modification of the CBD is oxidation of the phenol ring to a quinone HU-331, which inhibited the human topoisomerase IIα, a known anticancer drug target [11]. Using extracts from different cannabis hybrids, as well as changing extraction methods and solvents, are also not viable options to obtain anticancer medicines due to variability in the composition of the starting cannabinoids and the presence of a large amount of trace impurities as well as the potential risk of copurifying chemicals used to protect the plant crop.

All these results lead us to consider the main products of the cannabis plant- tetrahydrocannabinolic (THCA) and cannibidiolic (CBDA) acids - as the basis for new anti-cancer drugs. Intensive research on these compounds in recent years has not only provided supportive evidence for their anti-inflammatory and anticancer activity, but, more importantly, the absence of any psychoactive properties. This is consistent with the fact that they bind to CB1 and CB2 cannabinoid receptors: THCA binds to CB1R at the concentration range of 630nM to 3μM and to CB2R from 1.3nM to 10μM. The large THCA concentration range for binding to CB1R may be indicative of a partial THCA decarboxylation event which forms THC during the course of the experiment, as THC has a significantly higher affinity for the CB1R. CBDA has been shown to bind to CB1R at >10000nM but has very good CB2R affinity (4.9-77nM) [12,13]. Another important feature of cannabinoid acids compared to THC and CBD is their high bioavailability. A preliminary study comparing the oral bioavailability of cannabinolic acids with THC, CBD and their metabolites showed that THCA and CBDA concentrations in blood are more than 10 times higher than for THC and CBD and reach a maximum one hour after ingestion. Comparison of half-life data of these acids in the body showed the significant advantage of THCA compared to CBDA and other things being equal, makes THCA particularly useful as a potential drug [14].

Initially biological studies of these acids focused on their in vitro and in vivo anti-inflammatory activity. These studies established the ability of THCA and CBDA to suppress the proinflammatory cytokines COX-1 and COX-2, IL-2, IL-8 as well as others [15]. THCA, unlike THC, was able to inhibit the expression of tumor necrosis factor alpha (TNF-a) in a dose dependent manner [16,17]. Anticancer studies have shown poor CBDA activity against CEM and HL60 leukemia and human prostate LNCaP cells [18]. In contrast CBDA has been shown to inhibit cell migration and to decrease the c-fos protooncogene expression and cyclooxygenase-2 (COX-2) in the highly aggressive MDA-MB-231 breast cancer cell line [19]. THCA also inhibits the growth of some types of breast cancer (IC50 of 9.8μM in MCF-7 and 18.2μM in MDA-MB-231) and prostate cancer cell lines (IC50 of 25μM in DU-145) [20]. Although there is currently an explosive expansion of cannabinolic acid research, these compounds tend to spontaneously decarboxylate and there is currently no inexpensive and effective method to isolate them from plants. Cannabinolic acid decarboxylation is influenced by the phenolic OH-groups in the ortho- and para-positions, which correlate with the greater tendency of THCA to decarboxylate compared to CBDA [21]. The isolation problem was recently successfully resolved by using extraction technology based on ion-exchange resins [22] which gave good yields and sufficient purity for the compounds to be used as starting materials in organic synthesis [23].

The presence of a carboxyl group in the cannabinoid acid molecules opens up a truly “Klondike” opportunity to obtain different derivatives and study their biological activity. This was initially shown as part of a patent [23] describing the synthesis and biological activity of some of the amide, hydrazide and other derivatives of THCA and CBDA. In vitro anticancer screening on some types of cancer cells such as T47D (breast), U251, U87MG (brain), A549 (lung), PC-3 (prostate), TE-6 (esophagus), Caco-2, HT-29 (colon), OPM-2, U266 (myeloma), SK-HEP-1 (liver), PANC-1, AsPC-1 (pancreas) allowed to identify several compounds with activity at the 1.3-10μM level. Two THCA derivatives, ALAM027 and ALAM108, have been shown to suppress tumor growth to a level that is comparable to that of established anticancer drugs such as gemcitabine and paclitaxel, in vivo, in the human PANC-1 pancreatic tumor xenograft model (Figure 1) [24]. It should be noted that these compounds were administered orally as oil-based solutions, as opposed to via injection as is the case for many of the established cancer drugs.

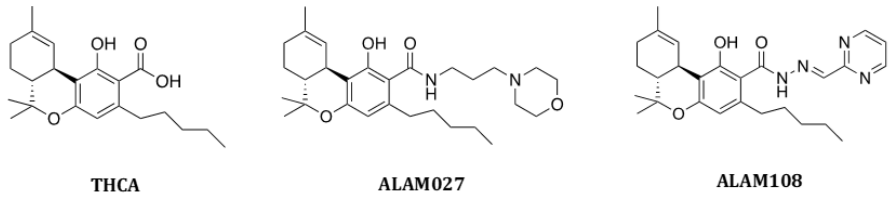

Figure 1: Chemical structures of THCA, ALAM027 and ALAM108.

Conclusion

Potential mechanisms for the anticancer and cytotoxic activity of ALAM027 and ALAM108 may involve their ability to initiate expression of the proinflammatory cytokine THF-alpha in LPS induced PBMCs [23].

The use of cannabinoid acids as starting compounds for the synthesis of novel derivatives can be considered as the next significant stage in the evolution of cannabinoid anticancer research.

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