Promoting cannabis products to pharmaceutical drugs

1. Introduction

In recent years, medicines based on Cannabis sativa L., including herbal cannabis (marijuana) products, have become increasingly available to patients in many countries. However, scientific evidence of the medical activities of these herbal products and their targeted bioavailability to patients in many countries.

2. Promoting cannabis products: precise content of compounds

Any individual Cannabis sativa variety contains hundreds of different secondary metabolites (Aizpurua-Olaizola et al., 2016), including a plethora of identified and categorized phytocannabinoids (Hanuš et al., 2016). Moreover, new studies show that the beneficial activity of cannabis cannot be attributed to a single compound (Russo, 2011; Blasco-Benito et al., 2018; Nallathambi et al., 2018). Besides cannabinoids, hundreds of other secondary metabolites, such as terpenoids, sterols and flavonoids, are produced by cannabis inflorescences (De Meijer, 2014). Some of these volatile and semi-volatile compounds account for the typical aroma of cannabis, and perhaps for part of its biological activity (Singh and Sharma, 2015).

As a result, patients are being treated with cannabis products that are not well defined, and suffer from a lack of efficacy or reproducibility, probably due to uncharacterized changes in the unknown compositions of active compounds. To overcome this difficulty, Cannabis sativa used for medical treatment should be better defined for their precise content of phytocannabinoids, terpenoids, and perhaps additional plant secondary metabolites.

3. Promoting cannabis products: identification of synergistic interactions

Significant synergistic effects, popularly termed “entourage”, have been reported for whole cannabis extract versus the activity of its individual compounds in cells and animal models (Russo, 2011; Blasco-Benito et al., 2018; Nallathambi et al., 2018). Recently, synergistic combinations of cannabinoids and terpenes have been found with increased cytotoxic activity against colorectal cancer (CRC) cell lines (Nallathambi et al., 2018). Synergistic interactions may occur between different cannabinoids (i.e., “intra-entourage”) (Berman et al., 2018), or between cannabinoids and terpenes (i.e., “inter-entourage”) (Nallathambi et al., 2018). Hence, cannabis preparations should be optimized to contain mixtures of these Cannabis sativa-derived compounds and/or whole extract with compositions showing the greatest synergistic activity.

4. Promoting cannabis products: identification of mode of action

4.1. Cannabinoid receptors and signaling in cells induced by specific ligands

Another way to improve a given Cannabis sativa preparation is by revealing its mode of action. THC, synthetic compounds and endocannabinoids have been suggested to activate G-protein-coupled cannabinoid receptor 1 (CB1). Another identified and isolated endocannabinoid receptor is cannabinoid receptor 2 (CB2) (Pertwee et al., 2010). These receptors mediate the synaptic and cellular effects of endocannabinoids in various cells and tissues (Maccarrone et al., 2015). Recent evidence suggests that agonists that bind to the endocannabinoid receptors...
demonstrate functional selectivity, activating or inhibiting CB$_1$ and CB$_2$ downstream signaling pathways via both canonical and non-canonical signaling pathways (Priestley et al., 2017). Therefore, there is a relatively substantial amount of knowledge on the signal transduction following CB receptor activation by specific ligands.

4.2. Signaling in cells in response to C. sativa whole extract

In contrast to the knowledge on ligand-activated signal transduction via CB receptors, almost nothing is known about the induced or repressed signaling in cells, tissues and organs by cannabis whole extract. This lack of knowledge on its mode of action may be due to the complexity of the whole extract as compared to a pure, single compound; complexity that derived from the array of cannabinoids in C. sativa whole extract being accompanied by an abundance of terpenoids.

Numerous studies suggest that terpenoids have therapeutic properties and affect cytokine levels and enzymatic activity (de Santana Souza et al., 2014). Little is known about the mode of action of terpenoids in terms of upstream signaling pathways (e.g., receptor and intracellular activation), and this should be further studied in relation to drug development from plant material. C. sativa included. This complexity, leading to the synergistic interactions reported between cannabis-derived compounds, may originate from the activation of more than one signaling pathway to affect a certain condition.

To monitor intra- and inter-entourage effects, we recently made an initial effort to better understand the signaling pathways which are synergistically induced by certain mixtures of phytocannabinoids and terpenoids that are active against CRC cell lines. CRC cells were treated with individual and combined fractions of C. sativa chemotype I extract. RNA profiling identified more than 2000 differentially expressed genes that were affected by treatment with the synergistic combination but not when treated with the individual fractions (Nallathambi et al., 2018). Among the activated signaling pathway components related to the differentially expressed genes were the secreted Wnt glycoproteins that are involved in cell–cell communication, and tumor suppressor PS3 transcription factor. These pathways and others are involved in cell-cycle arrest and apoptosis; they are often disregulated in CRC patients and are a desired target for anticancer drugs (Cheng et al., 2018). Their attenuation by certain synergistic mixtures of cannabis-derived compounds suggests that certain compositions may target specific biological pathways in cells to affect cell death, and may prove to be a new mode of action for cannabis anticancer therapy compared to individual compounds (Nallathambi et al., 2018). However, more examples should be studied, and in particular proven in vivo in humans, to assess their mode of action. This is discussed in the following.

5. Steps required to promote the quality of cannabis products

The steps required to promote the quality of herbal or synthetic cannabis products to that of a pharmaceutical drug are illustrated in Fig. 1. First, when a treatment with C. sativa extract is sought, a comprehensive chemical profile of the given variety used should be generated and fully reported (De Meijer, 2014). Second, appropriate synergistic mixtures of cannabis compounds should be determined for use in medical treatments and as a basis for breeding and designation of new C. sativa strains. These new strains will produce the proper combinations of compounds, be characterized by a full chemical profile and be labeled for a specific medical use (i.e., a given activity or disease). Third, the compounds can be purified from cannabis plants or synthesized. The compounds may be used to mimic the designated activity of the compositions defined as biologically active. Fourth, characterization of the biological pathways affected in human cells and tissues and specific targeting of these biological pathways by cannabis products may lead to drug innovation. This should be supported by data resources such as the Therapeutic Targets Database, which covers the association of most target and drug entries to the corresponding pathway and includes a pathway-interaction database supporting drug discovery and design (Yang et al., 2015).

However, cannabis-based drug development will lead to new pharmaceutical products only if the new drug effectively targets a specific receptor in a cell, without showing any relevant toxicity. In comparison to other drugs used for the treatment of some medical conditions (e.g., epilepsy and psychotic disorders), CBD often has a better side-effect profile and comparable or superior efficacy (Russo, 2019). However, some important pharmacological and toxicological parameters have yet to be studied, particularly for cannabis compounds other than the most studied CBD and THC. In addition, more clinical trials with a greater number of participants and longer chronic cannabis compound administration are needed for the individual cannabis compounds and synergistic mixtures (Hillard and Grotenhermen, 2017).

This process involves specific preclinical development and testing, followed by trials in humans to determine the efficacy of the drug under cost-effective conditions. Therefore, preclinical development strategies such as the crucial in vitro to in vivo extrapolation (IVIVE) of cell assays and animal in vivo to human in vivo extrapolations are needed to identify the most promising individual cannabis compounds or mixtures of compounds for activity in humans. Accordingly, plasma exposure showing efficacy but no toxicity in animals is routinely considered to calculate the first-in-human (FIH) dose projections that will give the same plasma exposure assuming similar mechanisms of action in each species. This should be followed by clinical trials to determine whether the newly identified individual cannabis compounds or their combinations will show a sufficient safety margin at the expected therapeutic doses.

More importantly, we suggest that the goal of finding proper synergistic mixtures of active cannabis compounds is key; hence, these studies should also be designed around this goal. In particular, drug–drug interactions (DDI), which are a common cause of adverse reactions and efficacy, must be investigated among the C. sativa molecules; synergistic efficacy responses may then result in a lower dosage in humans. However, the large number of compound mixtures that can be generated, even from small compound collections, all but negates the feasibility of exhaustive experimental testing in vivo or in humans. The ability to predict the behavior of compound combinations in in vitro biological systems, whittling down the number of combinations to be tested, is therefore crucial. Moreover, to facilitate drug design, high-throughput screening by in vitro facilities such as in vitro cell assays based on individual versus mixtures of cannabis compounds should be compared for efficacy and toxicity concerns.

Furthermore, the corresponding active concentration determined in these in vitro assays could be challenged by using in silico molecular structure-based pharmacokinetics/pharmacodynamics (PKPD) modeling, including the DDI effect, to reproduce the active concentration of each individual cannabis compound present in the mixtures under in vivo conditions. These may serve as primary tools for early-stage drug discovery to facilitate the identification of promising candidates (synergistic mixtures) based on their potential efficacy and plasma kinetics in vivo, to be further studied from more specific IVIVEs, animal studies and clinical trials. Overall, the absorption, distribution, metabolism and elimination versus toxicity (ADME/Tox) should be characterized for each newly identified active compound or mixture followed by an estimation of the expected therapeutic doses (The Drug Development Process. US Food and Drug Administration https://www.fda.gov/forpatients/approvals/drugs/; Bulusu et al., 2016; Poulin, 2016), including integrative structure-pharmacokinetic-pharmacodynamic modeling (Vlot et al., 2018).

6. Conclusions

Despite the high availability of C. sativa herbal products and their wide beneficial use in medicine, they remain mostly uncharacterized. With the worldwide progress in approval of cannabis for medicinal use the current approach of “botanical drug” needs to be changed. Medical cannabis product development should include safety and efficacy considerations as those used for a fully defined pharmaceutical product. Drug development of cannabis-based products should follow accepted
drug development and design schemes; however, the importance of the synergistic interactions between the different cannabis compounds must be taken into consideration. Cannabis medicalization has become part of many governmental policies worldwide. Establishing common and reasonable grounds for cannabis medical use by promoting the quality and therapeutic activity of herbal or synthetic cannabis products to a pharma grade is essential.

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References


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