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Cannabis-related pharmaceutical drugs

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Abstract: Despite the surge in the research of cannabis chemistry and its biological and medical activity, only a few cannabis-based pharmaceutical-grade drugs have been developed and marketed to date. Not many of these drugs are Food and Drug Administration (FDA)-approved and some are still going through regulation processes. Active compounds including cannabinergic compounds (i.e., molecules targeted to modulate the endocannabinoid system) or analogs of phytocannabinoids (cannabinoids produced by the plant) may be developed into single-molecule drugs. However, since in many cases treatment with whole plant extract is preferred over treatment with a single purified molecule, some more recently developed cannabis-derived drugs contain several molecules. Different combinations of active plant ingredients (API) from cannabis with proven synergy may be identified and developed as drugs to treat different medical conditions. However, possible negative effects between cannabis compounds should also be considered, as well as the effect of the cannabis treatment on the endocannabinoid system. FDA registration of single, few or multiple molecules as drugs is a challenging process and certain considerations that should be reviewed in this process, including issues of drug-drug interactions, are also discussed here.

Keywords: cannabis, cannabinergic, drug, FDA-approved, medical conditions, pharmaceutical-grade, phytocannabinoid

1. Introduction

1.1 Basic cannabis chemotaxonomy

To date, only a few cannabis-based pharmaceutical grade medicines have been developed and marketed. A review of the market reveals that registered cannabis-based drugs follow the common, rather dated, dichotomous chemo-variation approach to *Cannabis sativa*, where only the relative contents of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are considered. Under this rather simplistic chemotaxonomy cannabis strains are divided into three main chemovars based on the relative amounts of the two predominant phytocannabinoids (i.e., cannabinoids produced by the plant)—chemovar I with high levels of THC, the intermediate chemovar II strains with equal relative amounts of THC:CBD, and chemovar III strains producing relative high amounts of CBD [1]. The basic cannabis chemotaxonomy gave grounds to the first drugs that are FDA registered, discussed below.

1.2 Cannabinergic compounds

Any molecule that modulates the endocannabinoid system, regardless of its chemical structure or pharmacological activity is termed "cannabinergic" [2]. The endocannabinoid system includes the cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), their endogenous endocannabinoids ligands (N-arachidonoylethanolamine [anandamide] and 2-arachidonoylglycerol [2-AG]), and the endocannabinoid metabolism enzymes [3]. Therefore, the cannabinergic group of compounds includes CB1 or CB2 receptor ligands or blockers, substrates or inhibitors of fatty acid

amide hydrolase, and the endocannabinoid transporters. Studies of structure–activity relationships between endocannabinoid receptors and many synthesized cannabinergic compounds (e.g., phytocannabinoid analogues and derivatives) have been performed, along with the determination of cannabinergic biological activities and pharmacokinetic properties [4-6]. Cannabinergic compounds are considered as targets for the development of novel medications, e.g., for pain management [5,7] or as anti-inflammatory therapeutics [8].

2. Chronology of the cannabis-based drugs development

2.1 Drugs of one molecule

2.1.1 Cannabis-'inspired' drugs

Using a synthetic compound over the purified phytocannabinoid reflects the desire to brand a drug as a non-plant material, yet "inspired" by plant compounds. The first registered drug Marinol®, contains high amounts of dronabinol, the synthetic equivalent of THC (**Table 1**). Marinol was registered and clinically tested for appetite stimulation and antiemetic. The antiemetic efficacy of Marinol was greatest in patients receiving cytotoxic therapy for Hodgkin's and non-Hodgkin's lymphomas.

2.1.2 Cannabis-derived drugs

The second drug registered Epidiolex® contains high amounts of plant-derived CBD (**Table 1**). Epidiolex, in development since 2002, was the first cannabis-derived drug approved by the U.S. Food and Drug Administration (FDA) in 2018. The FDA granted approval of Epidiolex for the treatment of two rare and severe types of epilepsy – Dravet syndrome and Lennox-Gastaut [9,10]. Other one-molecule drugs, inspired by- or based on- cannabis were approved for treatment of different medical conditions including cancer-related pain relief, appetite stimulation and nausea and vomiting associated with cancer chemotherapy (**Table 1**). Recently FDA approved Epidiolex for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients one year of age and older [11].

Table 1. Cannabis- inspired or based medicines available today and their pharmaceutical status.

Drug name	indication	basic formulation	clinical studies	proved efficacy	key limiting toxicity	recommended dosage	drug-drug interactions reported	approval	Reference
Drugs of one molecule									
MARINOL® by GW pharmaceuticals	Appetite stimulation; antiemetic associated with cancer chemotherapy	Dronabinol (synthetic THC)	yes	yes	100 mg/day or 30 mg/kg	Appetite stimulation: 2.5 mg twice daily; Antiemetic: 5 mg 3-4 times daily		FDA	[12]
EPIDIOLEX® by GW pharmaceuticals	Lennox-Gastaut syndrome and Dravet syndrome in patients	Plant derived CBD	yes	yes	20mg/kg/day	5-20 mg/kg/day	CYP1A2, CYP2B6 Substrates, uridine 5' diphospho-glucuronosyltransferase 1A9	FDA	[13]

							(UGT1A9) and UGT2B7. CYP2C8 and CYP2C9 substrates		
SYNDROS® by Benuvia Therapeutics Inc	Anorexia; nausea and vomiting associated with cancer chemotherapy	Dronabinol (synthetic THC)	yes	yes	25 mg/day	4.2 mg/day	Neuropsychiatric Adverse Reactions; Hemodynamic Instability	FDA	[14]
CESAMET® by Valeant Pharma Int	nausea and vomiting induced by cancer chemotherapy	Nabilone (synthetic THC)	yes			2 mg/day	diazepam 5 mg; sodium secobarbital 100 mg; alcohol (absolute) 45 mL; codeine 65 mg	FDA	[15]
INM-755 cream by Inmed pharma	skin diseases and wounds Epidermolysis Bullosa	Bacteria *E. coli* fermentation derived of one rare CBN (Cannabinol)	yes Phase 1-2 ongoing	no		Two strengths of INM-755 cream are currently tested			[16]
Drugs of combinatoric formulations									
SATIVEX® Oromucosal Spray by GW pharmaceuticals	pain relief	Plant-derived CBD:THC and terpenes	yes	yes	90 mg/day	5-60 mg/day	reversible inhibitor of CYP3A4, 1A2, 2B6, 2C9 and 2C19	EU, Cana-da	[17]

2.2 Drugs of combinatoric formulations

Sativex, a GW pharmaceuticals drug designated for pain relief with relative equal amounts of both THC and CBD, and some terpenes (**Table 1**) marked the updated notion of the power of plant-derived drugs based on the synergistic effect of different components. Sativex was targeted for the treatment of moderate to severe spasticity related with multiple sclerosis (MS). This is specifically in patients who have not responded sufficiently to other anti-spasticity medication. The results of a pivotal phase 3 trial suggest a successful Sativex therapy for this indication [18]. In addition, Sativex was shown to be effective for the treatment of other medical conditions. For example, treatment with Sativex was demonstrated to markedly improve the frequency and severity of motor and vocal tics post-treatment in treatment-resistant Tourette syndrome patients [19]. Sativex is not yet approved by the FDA but it is registered for commercial distribution in Europe and Canada.

3. Taking advantage of the 'entourage effect'

For many centuries, plants and plant extracts were used for therapeutic treatments as phytomedicines for a vast variety of symptoms and medical conditions [20]. Phytomedicines are based on the medical activity of active compounds present in plants. As detailed above, the idea behind drug development based on phytomedicines, like that of Marinol of GW pharmaceuticals for example, was to obtain the most abundant active compounds present in cannabis inflorescence and to mimic its activity using purified compounds administered in known dosages. However, in many cases the biological effect of the whole plant extract shows preferred activity over treatment with a single purified molecule. This enhancement of activity detected in phytomedicines was designated as the 'entourage' effect [21]. Indeed, often, different components present in plants` extracts promote the activity of the lead active compound(s) [22].

One major difficulty with the entourage effect of traditional medicines is that the mechanism of action is unresolved. In fact, traditional medicines in general and phytomedicines in particular assume this 'entourage' as a concept or philosophy of therapy and in many cases strive to achieve it using a single plant extract or some mixture of multiple plants. Some of the effects of compounds present in a given herbal preparation may be enhanced due to the cumulative activity of its constituents. In many other cases the enhancement of activity by the combination of compounds may be at a synergistic level, as paired combinations of compounds exert effects that are more than the sum of their separate effects [23]. Synergy may be based on enhanced bioavailability and ease of transport of active compounds across barriers such as cell or organelle membranes, or enhanced protection of an active molecule from degradation by enzymes [24]. Synergy may also result from the activation of more than one signaling pathway in the host cells, leading to an increased response [25].

The 'entourage effect' as the enhanced activity of combinations of phytocannabinoids was first recognized by Mechoulam and Ben-Shabat [26]. We suggested that the ‘entourage effect’ was one of the main motivations and considerations in the domestication of cannabis [27]. Synergy in cannabis was lately demonstrated between phytocannabinoids [28-29] and further between phytocannabinoids and terpenes [30]. Moreover, insight into the synergy between cannabis compounds was provided both at the level of chemical composition and respective biological activity [29, 31]. The identified synergistic interactions between cannabis molecules might be the 'entourage effect' reported for cannabis preparations, as synergistic effects activate new biological pathways not activated by each of the components alone [29, 31]. However, the incomplete understanding (for now) of the mechanism behind this 'entourage effect' makes it difficult for pharmaceutical procedures for drug development and approval (discussed below).

Therefore, we suggest that selection of combinations of highly active plant ingredients (API) from cannabis may open opportunities for new drug development to treat various medical conditions [27]. Identifying the APIs and their specific compositions within a plant extract, then manufacturing a pure and quantifiable composition, may lead to pharmaceutical drugs inspired by- or based on- only the beneficial compounds in cannabis for a certain medical condition. Importantly, these might be targeted to specific mechanisms involved with various diseases [27,29,32].

4. Other 'entourage' considerations

4.1 The ‘parasitage effect’

While the overwhelming richness of compounds in cannabis strains can enhance activity, they can also depress activity. Besides the APIs for the treatment of a given condition, whole extracts also contain other compounds which do not contribute to the desired biological or clinical effect. Moreover, in cases where activity is improved by selecting the most active fractions and eliminating parts of the whole extract, there is a general implication that there might also be negative molecular interactions. Indeed, it was found that the removal of either antagonistic or non-active compounds lowered the required concentrations of APIs [29]. We call this phenomenon the ‘parasitage effect’: in physics, the term ‘parasitage’ describes destructive interference resulting from the interaction of coherent waves (for example) coming from the same source [33]. We use this term here to describe

the contra-'entourage effect', a phenomenon in which certain co-produced compounds interfere with each other to diminish a chemo-biologic effect, instead of correlate to enhance it.

The 'parasitage effect' of negative molecular interactions might result from the blockage of API activated pathways. Cannabinoids are targeting multiple receptors (e.g., CB1, CB2, transient receptor potential vanilloid receptor 1 [TRPV1], [34]). Hence, antagonistic interference with API receptor binding might provide evidence for existence of the parasitage effect as well. Yet, specific negative interactions between cannabis compounds should still be demonstrated and the mechanism explored.

4.2 Interaction between endocannabinoids and cannabinoids (synthetic or plant-derived)

For any cannabis-inspired or cannabis-based drug formulated from one or multiple molecules, its effect on the endocannabinoid system should be considered. THC and its propyl analogue tetrahydrocannabivarin (THCV) are capable of binding with high affinity to CB1 and CB2 receptors [34]. In addition, some of the phytocannabinoids affect (activate/inhibit) receptors and enzymes associated with the endocannabinoid system, which may suggest that at least part of the phytocannabinoid mode of action involves modulation of endocannabinoid activity [35,36]. For example, CBD inhibited AEA uptake in an *in vitro* study [37]. Also, CBD *in vivo* treatment of the nude mouse xenograft model increased the activity of the main anandamide-degrading enzyme, fatty acid amide hydrolase (FAAH) while decreased anandamide content in tumor samples [38]. However, the relevance of the interactions between phytocannabinoids and the endocannabinoid system to according to clinical use needs to be further studied.

5. Drug-Drug interactions

A change in a drug's effect on the body when the drug is taken together with other drugs, such as common drug-drug interactions (DDIs) should be considered more broadly since DDI may modulate efficacy versus toxicity. Most commonly, DDI results in adverse drug events, which may be caused from changes in pharmaceutical, pharmacokinetic, or pharmacodynamic properties.

The interactions between plant-derived products and synthetic drugs (herein: 'drugs') are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions. The studies of drug-drug, food-drug, and particularly plant-derived drug-drug interactions and of genetic factors affecting pharmacokinetics and pharmacodynamics are expected to improve drug safety and to enable personalized drug therapy. Attention is needed for interactions between plant-derived products and synthetic drugs (or naturally occurring chemicals) with a narrow therapeutic index (i.e., a narrow range of doses that confer effectivity without unacceptable adverse effects). However to date, well-designed clinical studies evaluating herbal supplement-drug interactions are limited and sometimes inconclusive [39].

On the other hand, there are numerous *in-vitro* and *in-vivo* studies indicating that phytocannabinoid metabolism is mostly performed by the Cytochrome P450 (CYP) isoenzymes. For example, CBD is metabolized by CYP 3A4, 2C19 and to a lesser extent by CYP 2c8, 2C9, 1A2, 2C8, 2B6, and 2E1 [40,41]. This metabolism via CYP enzymes may create an inhibition or enhancement of these enzymes activity and thereby, affect the metabolism of various drugs and cause different DDIs outcomes. In a case report, a threefold increase in tacrolimus levels was detected following the addition of CBD due to CYP3A4/5 inhibition. CBD also inhibits CYP2C19 and thereby leads to threefold increase in levels of the active metabolite of clobazam [42]. Interactions with other drugs metabolized by these isoenzymes should be anticipated.

In addition, CBD is a potent inhibitor of CYP2D6 [43]. CYP2D6 metabolizes many antidepressants, so CBD may increase serum concentrations of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone) [44]. Vice versa, any drug presenting an inhibiting or inducing effect on one of these enzymes may change CBD pharmacodynamics, and thus affect CBD levels [45]. These effects should be considered in the risk-benefit assessment of CBD therapy and patients and consumers made aware of potential safety hazards of CBD use. Also, some CYP isoform activity is crucial for the

endocannabinoid system. Cardiac CYP2J2 for example, which is inhibited by several phytocannabinoids, results in reduced metabolism of endogenous cardio-protective cannabinoids, like anandamide [46].

Overall, although further research on DDIs of CBD is needed, CBD may have serious interactions with drugs. It can affect levels of other drugs, its own level can be increased or decreased by other medications and additive effects of CBD can occur with other drugs (e.g, in the case of painkiller drugs).

6. Registration Drugs: one molecule or combinatoric formulations

There is a significant interest in the development of therapies and other consumer products derived from cannabis and its components, including CBD. Registering one, few or multiple molecules as drugs is a challenging task. Despite the synergistic effect of plant extracts over single compounds, traditional medicines based on whole plants, herbal extracts or mixtures are not recognized as certified drugs as they are non-registerable. Registerable drugs are based on known amounts of pure compounds, which can be synthesized and recombined and thus registered as formulated medicines. As opposed to that, chemical compositions of plant extracts are highly complex with up to hundreds different components. Thus, their exact combination is not reproducible by plant growth according to the Good Manufacturing Practices (GMP). Therefore, identifying the active compounds in order to either purify or synthesize the determined active ingredients into accurate and reproducible drugs is the focus of pharmaceutical companies.

Obviously, patients should have confidence in the drug's uniformity, equal strength and consistent delivery that support appropriate dosing needed for treating patients with complex and serious conditions, and this also applies to 'combination products'. To that purpose, the FDA issued a guidance for GMP requirements for combination products [47], to codify the availability and quality of drugs, biologics, devices, and combination products that consistently meet applicable requirements and specifications both as combination products or as a single drug. Reasons for rejection combination products could include pharmacokinetics and/or pharmacodynamic interactions between the combined constituents, the effects of additional manufacturing steps, or other differences arising from this combination.

An FDA guideline was also issued on the regulation of cannabis and cannabis-derived products, including CBD. The FDA stated that it recognizes the potential opportunities that cannabis or cannabis-derived compounds may offer and acknowledges the significance of these possibilities. However, it is aware of some companies are marketing cannabis-derived compounds in violation of the Federal Food, Drug and Cosmetic Act (FD&C Act) and this marketing may put the health and safety of consumers at risk [48].

The drug review and approval process generally contain several defined steps. In **Table 2** is a brief summary of the Canadian Drug Review and Approval Process in accordance with the Food and Drugs Act (FDA), the Food and Drug Regulations (FDR), the related policies and Health Canada guidelines, which is similar in any other country [49]. Canada is the first G20 country to legalize recreational cannabis on a national scale, for both recreational and medicinal purposes. Consequently, several biotech and big pharmaceutical companies have officially entered the Canadian cannabis industry to facilitate cannabis legalization and regulation over other countries. The general drug review and approval process steps below (**Table 2**), however, are similar across the diverse regulatory agencies.

Table 2. The general drug review and approval process steps

Stage	Activities
1. Initial drug research	Discovering and identifying various chemical, biological substances or other products on the way towards developing a drug; testing for activity, efficacy, toxicity and ultimately, gathering preliminary information on its effectiveness and safety. If the results are promising,

	researchers will proceed to the next stage of development.
2. Pre-clinical studies	Administration of the drug to selected species of animals (*in vivo*) or cells (*in vitro*). The drug must be shown to cause no serious harm (toxicity) at the doses required to have an effect either in a single compound or in DDIs. If results from these initial studies are promising and further tests show acceptable safety levels and clear or potential efficacy, then the next step would be to submit a Clinical Trial Application.
3. Clinical trials	The results of clinical trials conducted in humans are key components of the review process by the regulatory agency. The purpose of a trial is to gather clinical information about a drug's effectiveness, safety, determine best dosing/usage in humans, evaluate any adverse drug reactions, DDIs and compare results to already existing treatments for the same disease or condition or, to placebo when no treatment already exists for the aimed pathology (when ethically possible). The information gathered from these trials are then included in the dossiers to be reviewed by the relevant agencies.
4. Drug approval process	If results of all the preclinical studies and the clinical trials show that a drug's potential therapeutic benefit outweighs its risks (side effects, toxicity, etc.), and the chemistry and manufacturing dossier is complete, then the sponsor may decide to file a New Drug Submission (NDS) with the appropriate regulatory agency in order to be granted authorization to sell the drug in the country.
5. After-approval	The regulatory agency requires a sponsor to ensure that the use of its drug is done under the terms of its market authorization. In addition, Life Cycle Management activities (post-approval submissions, for new indications, new dosage forms, new strengths, manufacturing changes, etc.) are required to ensure the maintenance of the product license with its related improvements. In summary, sponsors need to ensure its continued compliance with the Food and Drug Regulations while their products are on the market. On the other hand, the regulatory agency monitors drug information and adverse drug reaction reporting, conducts market surveillance, investigates complaints and manages recalls if necessary, amongst other things.
6. Additional regulations	There are also more processes and regulations to follow and consider, before, during or after the review process, and before that drug is officially marketed, distributed and sold in a country. Topics such as licensing,

	warehousing, wholesale distribution rules and the Drug Establishment License (DEL), regulations around distribution to consumers, regulations around the marketing and advertising activities, provincial requirements, health insurance funding rules, among others.

7. Conclusions

Cannabis-based therapy is a powerful and promising tool as it takes advantage of an existing receptors system to affect multiple and different body systems and biological processes. However, as this sensitive and balanced system of endocannabinoids serves other endogenous molecules and is also associated with drug metabolism, Cannabis based therapy should be carefully examined and applied.

As illustrated in **Figure 1**, Cannabis-inspired drugs may be developed as synthetic cannabinoids or their derivatives. Cannabinergic-drugs may also be developed to specifically attenuate components of the endocannabinoid system (e.g., endocannabinoid receptors). Cannabis-based drugs may be composed of one phytomolecule or as a combinatory formulation of APIs from the plant. Activity of API combinations may be enhanced by employing the 'entourage and avoiding the 'parasitage' effects. In any case, interaction(s) between endocannabinoids and cannabinoids (synthetic or plant-derived) or cannabinergic compounds should be examined, steps for drug review should be taken and approval process be followed.

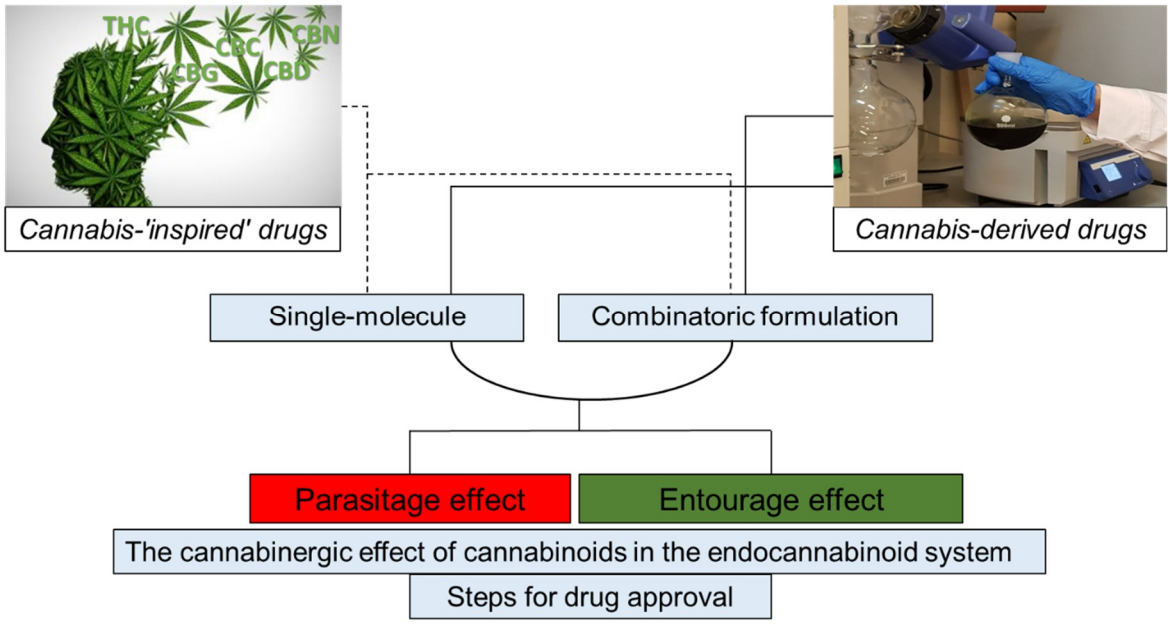

Figure 1. Illustration of concepts associated with the development of cannabis-related pharmaceutical drugs. Cannabis-inspired drugs, cannabinergic-drugs or cannabis-based drugs are to be developed while interaction(s) between phytocannabinoids or synthetic cannabinoids and the endocannabinoid system should be examined. Drug review and approval process steps should be taken.

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