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REVIEW ARTICLE

Cannabis and anticancer drugs: societal usage and expected pharmacological interactions – a review

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ABSTRACT

Cannabis is a plant that has been used for centuries to relieve a wide range of symptoms. Since the 1960s, interest in medical research into this plant has grown steadily. Already very popular for recreational use, a growing number of consumers not accustomed to using cannabis for psychoactive purposes have begun to use it as an alternative or complement to mainstream pharmaceutical medicines. The principal unsubstantiated or 'social' uses of cannabis are based mainly on data that is at best controversial, but usually not scientifically proven. The aim of this review was to identify the scientific basis and reasons that lead patients with cancer to consume cannabis, and also to identify whether there is a risk of interaction between cannabis and anticancer medicines through drug transporters (P-glycoprotein and other ATP-binding cassette superfamily members) Cytochromes P450 (3A, 1A, 2B, 2C, 2D families…) and glucuronyl transferases.

INTRODUCTION

Cancer is a major cause of death throughout the world, the source of 8.2 million deaths in 2012. In France, 355 500 new cases were diagnosed in 2012 [1]. The number of cancer cases per year is expected to increase from 14 million in 2012 to 22 million over the next two decades [1,2]. Therapeutic strategy depends on many factors, the principal ones being the histological type of the tumour, its location, the patient's history, the level of invasion, etc. Against this background, chemotherapy is a key element of treatment, and if it cannot be carried out optimally in terms of the dose administered and frequency of courses, the outlook for the patient may be poor.

Treatment of cancer requires intensive, aggressive chemotherapy, and the attack on healthy cells and tissues can cause many side effects.

The principal acute toxicities expected during chemotherapy courses are haematological, digestive (nausea, vomiting, diarrhoea, mucositis), pain (nociceptive and neuropathic), alopecia and constant fatigue.

As well as these nonspecific toxicities, some molecules cause exposure to specific chronic toxicities: cardiac (anthracyclines), bladder toxicity (alkylants), neurotoxicity (Periwinkle alkaloids, cisplatin), renal toxicity (methotrexate, platinum salts).

Poor tolerance of side effects is one of the major causes of patient nonadherence to cytotoxic chemotherapy protocols, but also of 'de-intensification' of courses by increased spacing of the courses or reduction in the doses.

There are many therapies designed for treatment of these major adverse effects. In some cases, the toxicities are so stressful that the patients turn to alternative treatments. Cannabis forms part of those 'alternative'

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treatments whose consumption for therapeutic purposes (which we differentiate from recreational) seems to be receiving a new boost.

The use of cannabis for medical purposes is nothing new.

Pen Ts'ao Ching, the Chinese Pharmacopoeia drawn up from oral traditions dating back to 2700 B.C., evokes the medical use of cannabis [3]. It indicates the use of cannabis seeds for rheumatic pain, constipation, female reproduction disorders and malaria.

In India, the plant was already being used in 1000 B.C. for its numerous therapeutic functions: analgesic (neuralgia, headache, toothache), anticonvulsant (epilepsy, tetanus, rabies), hypnotic, tranquilliser (anxiety, mania, hysteria), anaesthesic, anti-inflammatory (rheumatism and other inflammatory pathologies), antibiotic (topical use for cutaneous infections, Erysipelas, tuberculosis), antiparasitic (nematodes), antispasmodic (colic, diarrhoea, rabies, tetanus), appetite stimulant, diuretic, aphrodisiac or anaphrodisiac, antitussive and expectorant (bronchitis, asthma) [3–6].

According to a survey by the French Drug and Drug Addiction Monitoring Organisation (OFDT), regular consumers of cannabis without any particular illness evoke soporific, soothing, relaxing effects enabling detachment and a shift of focus in difficult situations (e.g. fear of death) [7].

Likewise, in blogs and forums such as *Psychoactive* or *thctalk*, patients with multiple sclerosis or AIDS extol the virtues of cannabis, in particular for relieving their pain (thctalk.com/cannabis-forum). In these same blogs, some discussions include testimonies claiming the efficacy of cannabis in particular for cancer pathologies. By way of example, here is a testimony taken from the discussion forum *thctalk:*

> "Now sadly her daughter who is about 10 has cancer is really sick, lost her hair and is having chemo so they got permission to give her cannabis oil in capsules, it's really helping her!"

> "I saw a programme about a man who had a son with severe epilepsy and nothing they had tried would stop him fitting Then he tried cannabis oil and the little fella perked right up, had no fits and generally had a much better quality of life."

This use of cannabis to relieve the adverse effects of anticancer chemotherapy is not recent. In 1975, Stephen Sallan and his team published the first study aimed at evaluating the anti-emetic potential of cannabis during anticancer chemotherapy [8]. As the author explains, this first study in humans has its roots in the stories of some of his patients.

In this review, we wanted to produce a summary of two important issues concerning the treatment of side effects of cytotoxic chemotherapy:

- Is there any clinical evidence of the therapeutic potential of cannabis which supports the use of cannabis during anticancer chemotherapy?
- Should we be concerned about interactions, if cannabis or its derivatives are consumed during anticancer chemotherapy?

Literature retrieval was accessed through PubMed, social media, blog and user forums using the terms cannabis, cannabinol, cannabidiol, anticancer drugs, herbal–drug interaction, Cytochrome P450, UGT (uridine 5′-diphospho-glucuronosyltransferase), and P-glycoprotein. Relevant original research articles and review articles were evaluated. Articles were selected if they were published in English or French and focused on any of the keywords or appeared to have substantial content addressing the drug interactions.

The bibliographical summary we propose is a report broken down into four parts. The first will recall generalities on cannabis, the second discusses the different ABC transporters liable to be modulated by cannabis compounds, the third, according to the same principle, will cover the modulation of Cytochrome P450, and it will conclude with a summary of the results obtained.

CANNABIS AND CANNABINOIDS

Cannabis is the most widely consumed drug in the world, between 125 and 203 million people made use of it worldwide in 2009, that is an annual rate of prevalence comprised between 2.8 and 4.5%, and France is the leading consumer in Europe [9,10]. In parallel, new medicines containing molecules derived from cannabis have been put on the market, some of them advertising the improvement of certain adverse effects caused by chemotherapy and the relief of some kinds of cancer pain [10,11]. These different potentially beneficial effects may lead to personal consumption of cannabis or the prescription of these new medicines during the use of anticancer chemotherapy. We therefore raise the question of the risk of interaction, in particular pharmacokinetic, between the natural constituents of cannabis and anticancer treatments.

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Principal active substances and method of consumption

Cultivated hemp, also called *Cannabis*, grows in the wild state in numerous regions of the globe and can be cultivated in very varied environments. Different varieties exist, but the species consumed are often the same: *Cannabis sativa*, *Cannabis indica* and hybrids. Depending on crop conditions, the part of the plant consumed, or even the way in which it is consumed, the quality and quantity of psychoactive molecules, vary enormously. The plant contains more than 421 different chemical compounds, including 60 cannabinoids, and when it is smoked more than 2000 compounds are produced by pyrolysis [12–14]. Among the many cannabinoids, three main ones stand out as follows:

- *Δ9-tetrahydrocannabinol = THC = Dronabinol:* This is the principal psychoactive substance contained in the plant. Four stereoisomers exist, but only the *trans*-isomer is present in the natural form. Two related substances, Δ9-tetrahydrocannabinol-2-oic acid and Δ9-tetrahydrocannabinol-4-oic acid (THCA), are also present in cannabis, sometimes in large quantities. When it is smoked, THCA is partially converted into THC.
- *Cannabidiol (CBD):* acts as an antagonist (CB1) and is present at a higher concentration in the resin than in the natural plant matter. It does not possess any psychotropic property.
- *Cannabinol (CBN):* cannabinoid derived from the oxidation of THC. It is mainly found in old samples of cannabis [15].

The way in which cannabis is consumed depends on the form used, so the three principal forms are the following:

- *'Grass':* mixture of flower tops and dried leaves reduced to powder. Pure smoke (pipes) or mixed with tobacco in cigarette paper (most usual method of consumption in France).
- *Resin (or 'Shit', 'Hashish'):* brown or yellow powder obtained by beating and sieving of the dried leaves and flower tops, which are then compressed in the form of bars. It can be smoked mixed with tobacco or consumed with food (mixed into pastries, e.g.). In this form, cannabis is frequently blended with other products (henna, shoe polish, paraffin, pollen, medicines, earth, excrements, ether, etc.).
- *Oil:* brownish-green to blackish viscous liquid. For example, it can be derived from the extraction of the resin using 90° alcohol followed by exposure to the sun to evaporate the alcohol. The liquid obtained is solidified by heating to make the product marketable.

Authorized product and medicinal cannabis

For the past 20 years, the idea of using cannabis for therapy has become increasingly popular (*Table* I). Whereas some countries have long remained sceptical, fearing ambiguity over the illegal use of cannabis, others have invested in research programmes. We can therefore cite different countries such as the United States, Canada, Austria, Finland, Germany, Israel, Portugal and Spain, which have authorized and regulated the marketing of cannabis for therapeutic purposes. In 2017, four specialities based on synthetic or extract cannabinoids were available on the world market: Marinol®, Cesamet®, Sativex® and Epidiolex®.

As well as these pharmaceutical products, some countries have authorized the sale in pharmacies of natural forms of cannabis, known as medicinal cannabis, the production of which depends on public operators. The Netherlands, Spain, Italy, Finland and some states of the United States such as California have authorized the marketing of medicinal cannabis. The indications are wide-ranging and it is subject to medical prescription, provided that all other medicines intended to relieve the patient's discomfort have been ineffective. There are five such products, with different THC ± CBD content: Bedrocan®, Bedrobinol®, Bediol®, Bedica® and Bedrolite.

In some countries such as the Netherlands, the medicinal cannabis programme (*The Dutch Medicinal Cannabis Program*) advises patients to consume medicinal cannabis using a spray or in infusion. The spray helps to heat the plant until the active principles are volatilized and transferred to a balloon. The balloon swells with vapours and once full the patient inhales the vapours. This method of consumption has the advantage of not burning the plant and hence of limiting the carcinogenic risk of combustion products.

Pharmacology of natural cannabinoids

The research into the effects of cannabinoids is relatively recent. It was only with the discovery in 1988 of a first receptor which seemed to be dedicated to cannabinoids that the assumption of an endogenous system appeared [16–18]. It took only 4 years for the first endogenous ligand to be discovered, this was anandamide [19]; 3 years later, 2-Arachidonoylglycerol was added to the list [20]. Thus, less than 20 years ago, the system of endogenous cannabinoids

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Table I Authorized product and medicinal cannabis.

Origine	Brand name (form)	Active substance (dose)	Indication/usage
Synthetic THC	Marinol® (Capsule)	Dronabinol (2.5–10 mg)	Anorexia (AIDS), anticancer drug induced nausea and vomiting
Synthetic derivative of THC	Cesamet® (Capsule)	Nabilone (1 mg)	Anticancer drug induced nausea and vomiting
Natural extract of cloned phenotype	Sativex® (Mouth spray)	Nabiximols (2.7 mg of THC/2.5 mg of CBD)	Neuropathic pain (multiple sclerosis)
Natural extract of CBD	Epidiolex® (liquid solution)	CBD 100 mg/mL	Resistant epilepsy syndromes (Dravet syndrome and Lennox Gastaud syndrome)
Cannabis sativa	Bedrocan® (Cannabis flos)	THC/CDB 22%/<1%	Various indication (chronic pain, nausea, vomiting, anorexia, Gilles de la Tourette syndrome
Cannabis sativa	Bedrobinol® (Cannabis flos)	THC/CDB 13.5%/<1%	
Cannabis sativa	Bediol® (granulate)	THC/CDB 6.5%/8%	
Cannabis indica	Bedica® (granulate)	THC/CDB 14%/<1%	
Cannabis sativa	Bedrolite® (granulate)	THC/CDB <1%/9%	Refractory forms of epilepsy

or endocannabinoids was discovered. Since then, the impact of that system at physiological and behavioural level has been studied constantly [21–27].

Endogenous receptors

To date, two cannabinoid receptors have been identified: CB1 and CB2. These are seven transmembrane domain receptors coupled with an inhibitory Gi/o protein, negatively regulating adenylate cyclase. Stimulation of CB1 and CB2 induces a cascade of phosphorylation, which causes the activation of the MAP-kinase pathway. CB1 can also be coupled with an ion channel via this same Go/i protein which positively regulates the type A potassium channels and negatively the type N and P/Q calcium channels and type D potassium channels [28,29].

The CB1 receptors are mainly situated in the central nervous system and a few other locations such as the colon, liver, adipose tissue, pancreas and muscle, including the heart. They are the most widely expressed endocannabinoid receptors in the body. The CB2 receptors have a more limited distribution, being found principally in the cells of the immune system (macrophages, lymphocytes, polynuclear neutrophils, monocytes) and the immune cells of the central nervous system (microglial cells) [26]. The activation of the CB1 receptors may also inhibit the type 5-HT3 ion channels [30,31].

Side by side with these two receptors, KO mice for CB1 and CB2 have helped to reveal a response to anandamide, mediated by a member of another family of receptors, the type 1 transient receptor potential vanilloid ion channels (TRPV1). These are cation channels, present in the sensory neurons of the skin, heart, blood vessels and lungs. Their activation provokes the release of neuropeptides (substance P) which produce effects such as pain, tachycardia, vasodilation and bronchoconstriction [32,33].

Endogenous ligands

The endogenous cannabinoids or endocannabinoids are present in the central nervous system and in some peripheral tissues (*Figure* 1). Endogenous cannabinoids are the source of a retrograde signal that inhibits the release of the neurotransmitters by the cannabinoids. At present, five compounds produced by the brain and presenting an affinity with the endogenous cannabinoid receptors have been identified as follows: anandamide, 2-Arachidonoylglycerol, noladine, virodhamine and *N*-arachidonoyl dopamine. The common point between these ligands is that they suppress the sensation of pain [29–33].

Exogenous ligands

Tetrahydrocannabinol, the principal psychoactive compound present in cannabis, is a CB1 and CB2 receptor agonist. The other active substance of cannabis, cannabidiol (CBD) also acts on the CB1 and CB2 receptors but not much at the central nervous system level (*Figure* 1). It is also a TRPV1 receptor agonist [34]. The first studies concerning the use of CBD alone, not associated with THC, are in progress. Only the results of the phase I trials (set out in detail in the next chapter) are available [35–37].

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Only few studies analyse the other active principles of cannabis, as THC and CBD are the most abundant molecules of the plant and the most active.

Pharmacokinetics

In this chapter, we will only investigate the molecules responsible for a pharmacological effect, and consequently the most concentrated molecules, THC, cannabidiol (CBD) and cannabinol (CBN).

Method of administration or consumption

Inhalation is the method most commonly used by cannabis users. When a cannabis cigarette is consumed, the peak of THC concentration is attained in less than 10 min (T_{max}). A study using cannabis cigarettes containing standardized levels of THC, 16 or 34 mg, shows that the plasmatic concentrations of THC are detectable from the first inhalation. Maximum concentrations (C_{max}) are attained after 9 min and are respectively 84 ng/mL (range: from 50 to 129 ng/mL) and 162 ng/mL (range: from 76 to 267 ng/mL) [15]. Bioavailability is very variable from one subject to another. It depends both on physiological parameters such as respiratory capacity, but also on the inhalation dynamic: number, duration and spacing of inhalations. Another important parameter is the type of consumption, while in the occasional smoker bioavailability is in the order of 10–14%, it may reach 23 or 27% in regular consumers [38–40]. According to a study conducted more than 40 years ago, the use of a pipe increases THC bioavailability to 45% [37].

After oral administration, circulating concentrations of THC are lower and subject to greater variability than those found by inhaled administration. The C_{max} varies from 4 to 11 ng/mL, and the T_{max} is attained 1–5 h after ingestion of 20 mg of THC mixed with a biscuit [38]. The bioavailability of THC, measured between 4 and 20%, demonstrates that variability, which depends on several parameters such as speed of absorption, gastric pH, but also the galenic form of the THC. It seems in fact that the solubilization of THC in an oily vehicle such as cannabis oil improves its bioavailability [39]. For this reason, dronabinol, marketed under the name of Marinol®, is formulated in sesame oil and packaged in capsule form, which makes it possible to increase bioavailability by reducing degradation in the stomach and encouraging its systemic uptake. The use of oral administration also provides exposure to a non-negligible first pass effect in the liver, resulting in low bioavailability of THC, through hepatic transformation into active (11-OH-THC) and inactive metabolites. Furthermore, an enterohepatic recirculation can be observed, which causes a second peak of concentration, weaker than the first one but leading to more extended effects [40].

Sublingual administration only relates to medicines such as Sativex®. It helps avoid the first pass effect in the liver; other channels (rectal, transcutaneous) are also being explored for the administration of molecules derived from *cannabis.*

Cannabidiol is a cannabinoid present in the natural state in *Cannabis sativa.* Although nonpsychoactive, it is thought to present pharmacological, analgesic, neuroprotective, sedative, antipsychotic, anti-emetic, antispasmodic and anti-inflammatory properties. It is also thought to be implicated in the reduction in side effects of THC: such as anxiety and psychotic states [41–44]. After inhalation of a cannabis cigarette containing 2 mg of CBD, the T_{max} is attained in 15–30 min with a C_{max} comprised at around 2 ng/mL [45]. Recent phase I trials indicate that doses of 300–600 mg of CBD, orally administered, seem to be well tolerated while at the same time exposing volunteers to concentrations far higher than those measured after consumption of plant (AUC, T_{max} and C_{max}) [46,47].

Cannabinol is present in non-negligible quantities, similar to CBD, in products consumed by users. However, there is very little research on it. Its bioavailability after inhalation is in the order of 40% with great interindividual variability (8–77%). It is also practically exempt from any psychoactive effect, estimated to be 10 times lower than that of THC [48].

Distribution

The volume of distribution of THC in the organism is from 4 to 14 L/kg; its strong tissue fixation is responsible for a rapid decrease in blood concentrations. The THC penetrates rapidly in the highly vascularized tissues of the lungs, kidneys, heart and liver. In animals, in particular pigs, studies on THC distribution show that less than 1% of the dose administered is found at brain level [49–51]. Due to its lipophilia, cannabinoids can be detected in biopsies of adipose tissues 4 weeks after the last consumption of cannabis. The distribution of phytocannabinoids does not appear to depend on any specific transportation process.

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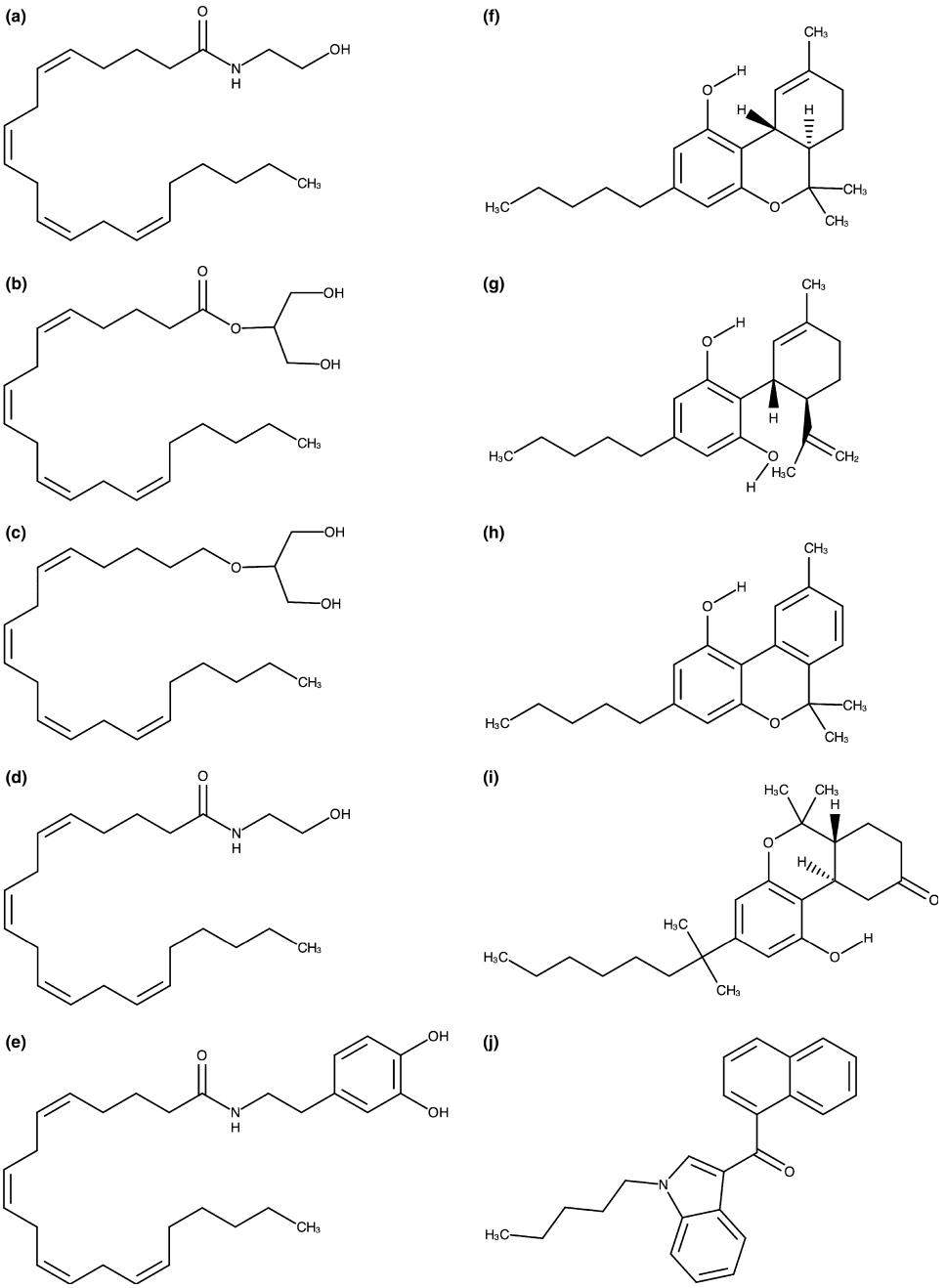

Figure 1 Chemical structure of the main endogenous (left panel) and exogenous cannabinoids (right panel). (a) Anandamide, (b) 2-Arachidonoylglycerol, (c) noladine, (d) virodhamine, (e) *N*-arachidonoyl dopamine, (f) THC, (g) cannabidiol, (h) cannabinol, (i) nabilone, (j) JWH018 'Spice' component.

Metabolism and elimination

Around 80–90% of THC is eliminated in 5 days. This consists mainly of compounds, which are hydroxylated or carboxylated, then glucuronidated. The principal enzymes implicated are the Cytochromes P450 3A4, 2C9 and 2C19 and the UGTs 1A7, 1A8, 1A9 and 2B7 (cf. *Figure* 1, *Figure* 2 and *Table* II). It is estimated that 65% are excreted through the bile duct and 20% through the kidneys. Conjugated metabolites are mostly found in the urine (*Figure* 3). The existence of an enterohepatic cycle and renal reabsorption translates into prolonged psychoactive effects, which may

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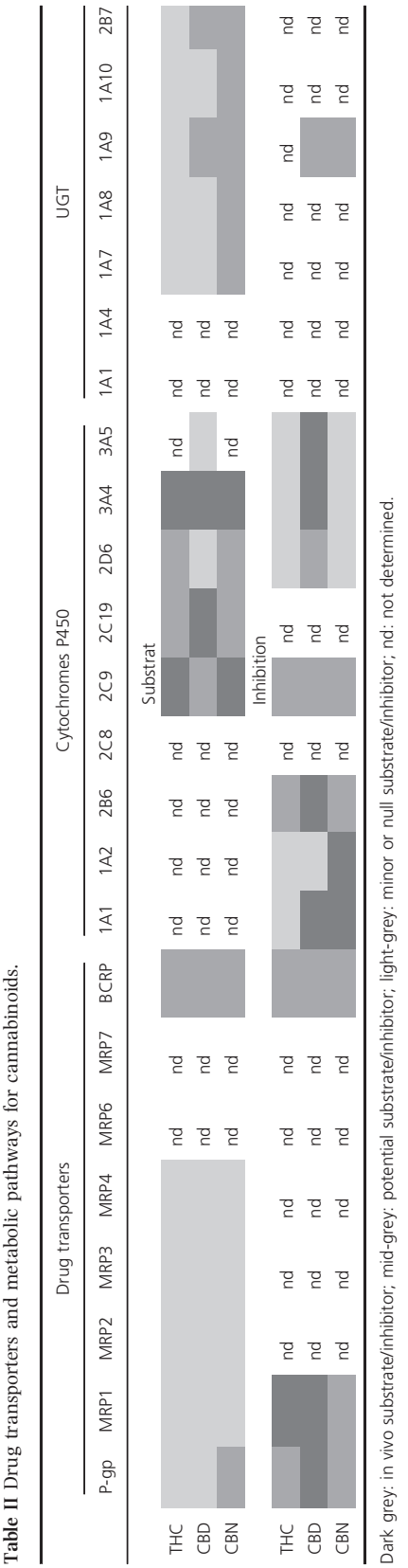
Table II Drug transporters and metabolic pathways for cannabinoids.



persist in the case of an isolated intake for 45–150 min after consumption has ceased [52–56]. CBD and CBN may be directly glucuronidated [57].

Concentration–effect relationship

Some studies have compared the increase in THC blood concentrations over time and the psychotropic effects experienced by subjects after consumption of cigarettes containing 9 mg of THC (standard cigarettes as defined in the United States by the National Institute of Drug Abuse). The results show that the psychotropic effects obtained after the isolated consumption of a joint containing 9 mg of THC persist for a period of around 2 h, whereas the concentration of THC in the blood is rapidly very low, in the order of ng/mL after 2 h. The extent of the effects seems to be dependent on the dose and on the maximum blood concentration observed [58–60].

In regular consumers, it would appear that the subjective effects of inhaled cannabis vary very little depending on the dose [61]. According to the same study, only the cardiovascular effects and craving appear to be dose-dependent.

A study published in 2014 by a Dutch team shows that the cannabis with the greatest concentration of THC (69 mg per cigarette) leads to a 8 h sedation after consumption, almost six times higher than that of placebo [62,63].

Nevertheless, the tendency in the last 2–3 decades has been an increase in THC content of the products consumed. So if the most recent studies have endeavoured to adhere to this reality of consumption, the older studies lose their relevance, thus explaining sometimes divergent results.

Thus, the psychoactive 'power' of cannabis-based products will depend on the content of psychoactive molecules as well as the method of consumption. The tendency in the last few years has been towards a global increase in average THC content of products available on the market. Two American studies, which analysed cannabis preparations seized between 1980–1997 and 1993–2008 in the United States, show a growing increase in THC concentrations over that period. In the first study, the average THC concentrations in the samples seized on the American market were 3.9% for inflorescences and 4.6% for cannabis resin [48]. In the second study, these concentrations reach 4.5 ± 3.1% and 14.1 ± 15.7%, respectively [64]. The European data of the European Monitoring Center of Drug and Drug Addiction (EMCDDA) are comparable

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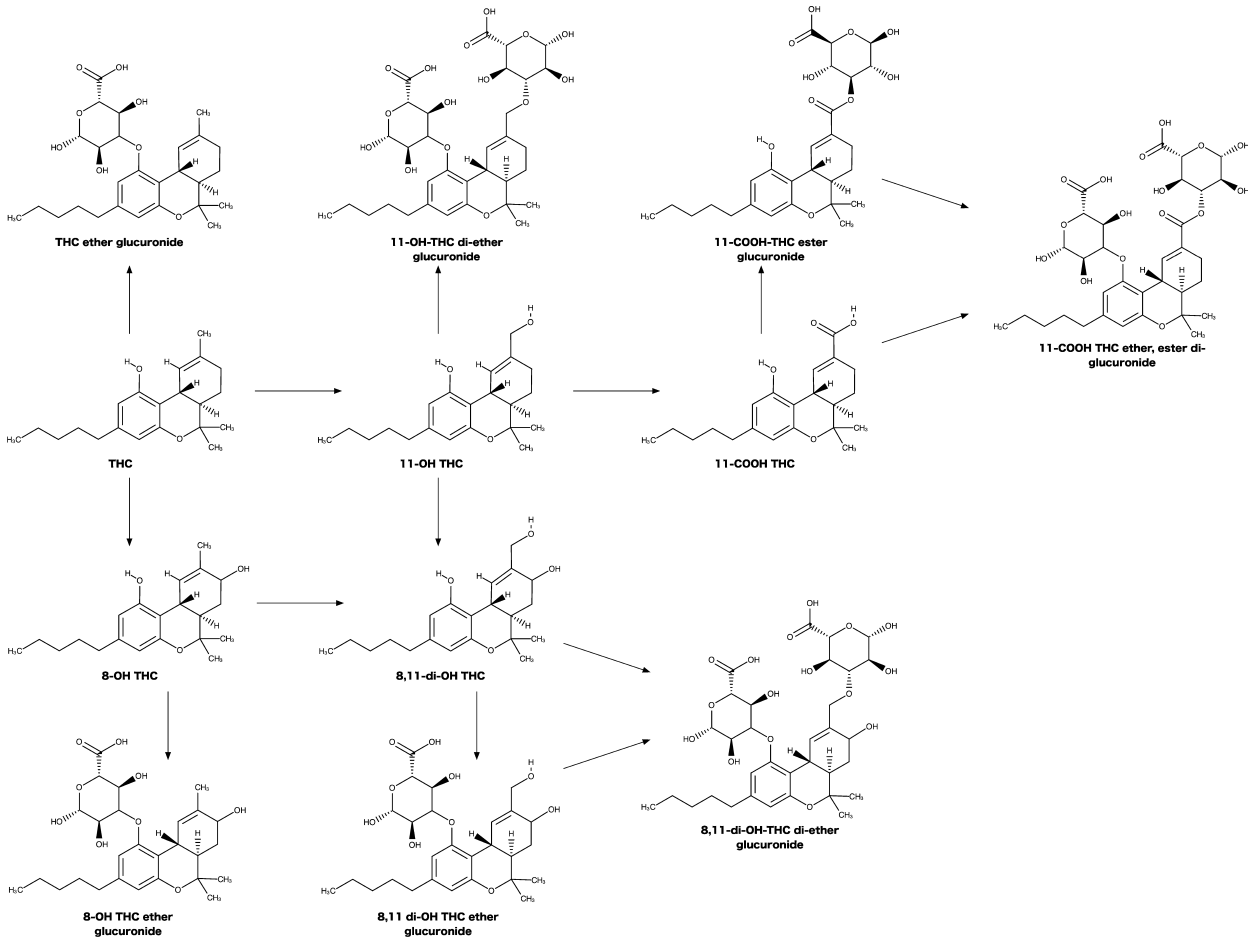

Figure 2 THC metabolic pathway.

to average THC content of 1–12% for the resin and 1–16.5% for cannabis grass (including sinsemilla, literally 'without seeds'; these are nonfertilized mature female flowers) [65]. However, the THC concentration and hence the 'power' of the psychoactive effect vary strongly from one place of production to another, so the data obtained by the different authorities should be used with caution.

The manner of consumption is also a source of variability of the psychoactive 'power' of cannabis, depending on whether the cannabis is smoked in the form of a 'joint' or through a water pipe (hookah, 'bong'), ingested together with food or drunk after infusion in hot water. It therefore appears difficult to evaluate in real life the exposure that a 'joint', herbal tea or water pipe will engender, or even the qualitative composition of the substances introduced in the organism. The data concerning THC concentrations vary greatly, from 10% on average for grass and resin to 30% for oil [66–68].

SOCIAL USAGE OF CANNABIS IN CANCER

As we stated in the previous chapter, the cannabinoids used in clinics currently have restricted indications and are not available everywhere. Associations between patients with cancer, support groups, discussion forums, etc. are bursting with information concerning the very wide-ranging uses of cannabis for medical purposes [69]. On what scientific *substratum* are these sometimes fanciful, sometimes rational allegations attributed to cannabis-based?

In this chapter, we will investigate the scientific validity of the principal uses or principal 'profane' or

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unsubstantiated uses that may be made of cannabis in cancerous pathologies.

Orexigen effect

Following the studies that evaluated the potential of THC for stimulating the appetite in patients with AIDS, several teams investigated this effect in the population of patients with cancer. While dronabinol obtained a marketing authorization for patients with AIDS, the effect of cannabis on appetite in patients with cancer appears to have divided researchers. Some studies concluded that there is some efficacy of THC in improving taste and by extension appetite in patients at an advanced stage of cancer [67], others find no significant differences in terms of quality of life and appetite between the administration of THC, a cannabis extract or a placebo [68]. In 2002, the study of Jatoi et al. did not show any superiority of dronabinol compared to megestrol acetate, nor the synergy of their combination on patients' anorexia [70]. Thus, to date, there is no proof that stimulation of appetite in patients with cancer is as effective as in people with AIDS [71].

Analgesic effect

A meta-analysis published in 2001 analysed trials comparing the efficacy of a cannabinoid with an analgesic or a placebo in patients with acute post-operative pain, chronic pain or cancer pain [11]. In trials on chemo-induced pain, at a dose of 5–20 mg by oral administration, THC showed an analgesic effect superior to the placebo. The THC showed a dose/toxicity ratio with at 20 mg a very strong sedation in 100% of patients but well tolerated à 10 mg of THC. At 10 mg, THC was better tolerated, but the frequency of the adverse effects was still higher than with 60 or 120 mg of codeine.

A recently published pilot study sought to find out whether the use of nabiximols in mouth spray form could be useful for treating the neuropathic pain associated with some types of chemotherapy [72]. This study, comprising 16 patients, was unable to confirm the superiority of cannabis extract compared to placebo. However, the authors emphasize that five patients responded very well and that for them the improvement in pain was significant. Another study tested the effect of cannabis inhalation using a pipe on neuropathic pain. The authors concluded that the inhalation of 25 mg of cannabis grass at 9.4% of THC three times a day for 5 days reduced the intensity of the pain while being well tolerated [73].

Although not convincing, these studies shed light on great variability in the response to cannabinoids. Larger trials should make it possible to identify the characteristics of responsive or nonresponsive patients. To date, six clinical trials have evaluated the effect of nabiximols (Sativex®) on pain associated with cancer (source clinicaltrials.gov consulted on 6 December 2017).

Antitumour effect

Since the first preclinical study that evoked the anticancer effect of cannabinoids, many teams have investigated the implication of the endocannabinoid system in tumour pathologies. While the signalling cascades activated by the endocannabinoid system are becoming increasingly well known, the consequences are multiple, complex, redundant and still poorly understood. Conflicting effects have been reported depending on the tumour model studied and the combinations of molecules evaluated. The data on which there is consensus relate to the implication of this system in the regulation of cellular proliferation, apoptosis and to a lesser degree, tumour dissemination [26,74–77]. The principal pathways implicated are the MAPK pathway (activation), the PI3-kinase pathway (inhibition) and the ceramide pathway [18,19]. While there are many in vitro studies, no clinical study has specifically studied the antitumour effect of cannabinoids. However, three articles are worth mentioning. In 2006, there was a phase I pilot study to test intratumour injection of THC in nine patients with glioblastoma in the ultimate stage of the disease [78]. The authors concluded that the treatment was well tolerated and that the patient's survival was not modified by the treatment. In 2011, an article reported the history of spontaneous regressions of astrocytoma in two teenagers who were regular consumers of cannabis. The authors based themselves solely on the coincidence of time between the consumption of cannabis and the tumour regression [79]. In 2013, Canadian authors reported the case of a child aged 14 hospitalized for palliative care for a recurrence of acute lymphoblastic leukaemia for whom different cannabis preparations appeared to have a dose-dependent effect on the number of circulating blasts [80]. Preclinical and clinical studies will be necessary to define the antitumour power of cannabinoids.

Nevertheless, the 'antitumour effect' is very anecdotal, and controlled studies are missing to prove the benefits of cannabis or cannabinoids to fight or controlling cancer.

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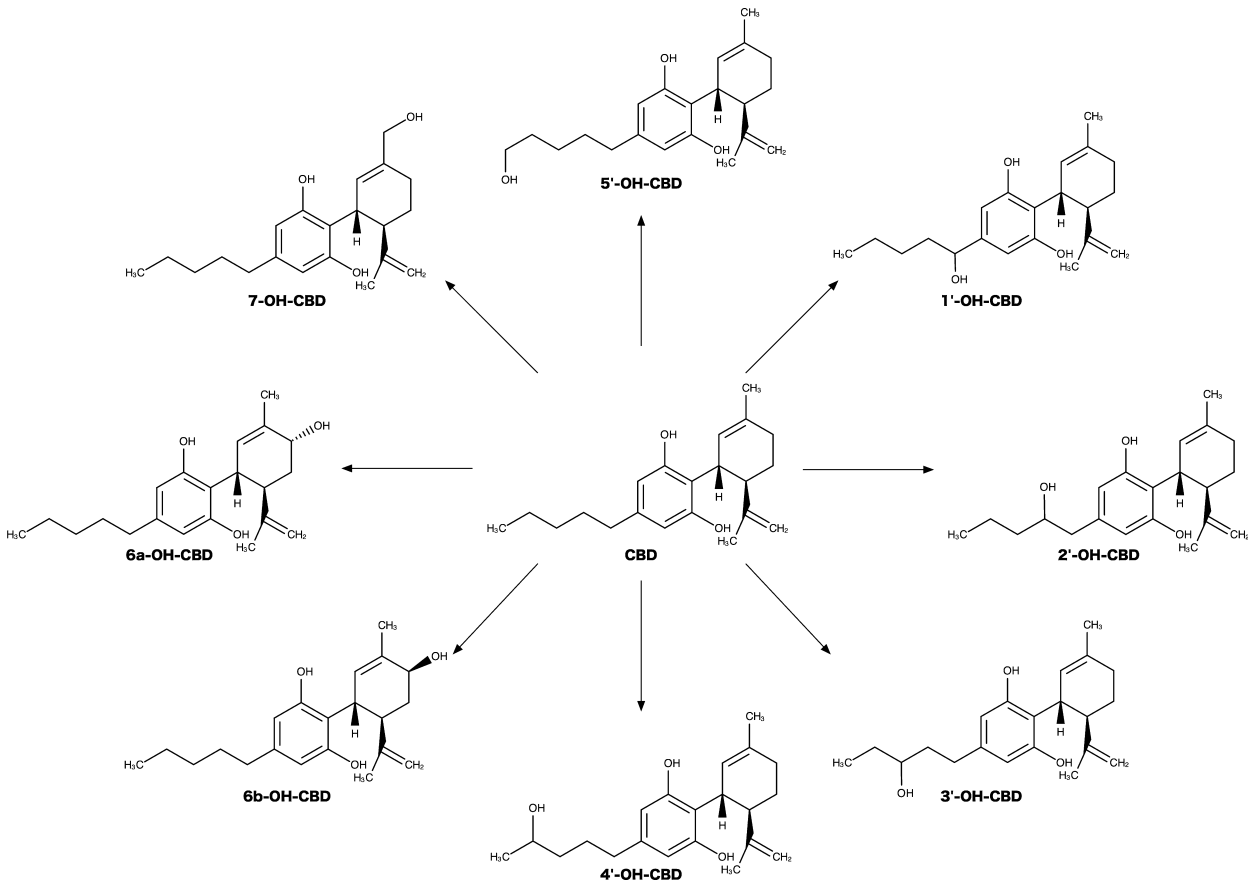

Figure 3 Cannabidiol metabolic pathway.

Anxiolytic effect

Many discussion forums extol the effects of cannabis for reducing stress and promoting the well-being of patients with cancer. Could patients with cancer derive benefit from that effect, via an improvement in their psychological state?

A prospective study conducted on patients with lung cancer at an advanced stage shows that depression and anxiety are associated with survival reduced by 14–7 months [81]. Patients in a good state of mental health adhered better to their treatment. In 2011, Indian researchers showed a significant correlation between depression and response to a neo-adjuvant therapy [82].

For the time being, no study has shown an anxiolytic effect of natural or synthetic cannabinoids. In the 70s and 80s, clinical trials investigated the anxiolytic potential of cannabinoids. The results in healthy volunteers were highly contrasting or even contradictory. According to some authors, an anxiolysis is obtained, whereas for others, the anxiogenic effect is dominant, and more recent studies are no clearer [83–86]. It would seem that low doses of CB_1 receptor agonists are anxiolytic, whereas excessive stimulation appears to give rise to opposite effects. Furthermore, the quantity of CBD in the products consumed could explain the major psychoactive effects of 'Spice' (synthetic marijuana) compared to THC [87–89]. This lead could explain the discordant results of the studies mentioned above.

Effects on sleep and fatigue

The first animal studies regarding the effects of cannabinoids on the regulation of sleep/wake cycles date back to the 1970s. CBD seems to be particularly implicated, but the results are contradictory. Some studies indicate a reduction in sleep time and a positive effect on vigilance [90–92]. Other teams report an improvement in sleep in insomniac patients [93]. Most of the recent studies only investigated indirectly (secondary objectives) the improvement of sleep disorders

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associated with different pathologies. Although they have yet to be confirmed, the results seem to conflate towards an improvement in the difficulty patients had in falling asleep [51,94–100].

A survey published in 2014 indicates that fatigue and somnolence are the most frequent adverse effects when medicinal cannabis is used in patients with cancer [101].

Effect on the gastrointestinal system: chemo-induced diarrhoea and inflammation of the digestive tract

Some anticancer chemotherapies induce profuse dose-limiting diarrhoea (irinotecan, 5-fluorouracil, bortezomib). Some studies have investigated the effect of cannabinoids on intestinal motility. It would seem that THC reduces faecal mass and diminishes intestinal transit. Moreover, THC inhibits the intestinal contractions induced by cholinergic transmission [102]. However, no clinical trial has evaluated this effect on chemo-induced diarrhoea. The only clinical studies concerning the antidiarrhoea potential of cannabinoids concern irritable bowel syndrome. The results are divided, showing a better response in patients who are carriers of a certain polymorphism of the CB1 receptors when they are treated with dronabinol [103–105]. Furthermore, many patients suffering from inflammatory pathologies of the intestine, Crohn's disease, for example, report relief when they smoke marijuana and many in vitro studies demonstrate the gastric protection potential of endocannabinoids [106]. To date, no study has investigated the effects of cannabinoids on chemo-induced diarrhoea.

Effect on the gastrointestinal system: chemo-induced nausea and vomiting

The role of cannabinoids in the treatment of chemo-induced nausea and vomiting (CINV) is not new and has been studied since the 1970s [107]. Indeed, the use of cannabinoids for the treatment of CINV is approved by regulatory administration, although the efficacy and safety of botanical marijuana have not been as thoroughly studied as has synthetic cannabinoids [108]. As mentioned previously, dronabibol and nabilone are two synthetics cannabinoids authorized to treat severe nausea and vomiting induced by anticancer treatment in patient who do not respond to conventional anti-emetic treatments. In 2017, Pergolizzi et al. published a systematic review concerning usage of cannabinoids for conventional anti-emetic treatments prophylaxis [109]. All studies suggested that cannabinoids conferred a benefit in CINV prophylaxis compared to either placebo, but this difference did not achieve statistical significance in all studies when cannabinoids were compared to active comparator drugs [12,110]. Because of methodological limitations of the early 1980s–2000s clinical trials, further research reflecting current chemotherapy regimens and newer anti-emetic drugs is likely to modify these conclusions [107].

Actual consensus is to recommend cannabinoids only as third-line treatment in the management of CINV. Because safe and effective anti-emetics are available, cannabinoids cannot be recommended as first- or second-line therapy for CINV [111]. Moreover, due to the lack of randomized controlled trials data and safety concerns, herbal cannabis cannot be recommended for CINV [112,113].

Studies in real-life situations

Real uses of cannabis

It is difficult to evaluate the proportion of patients who use medicinal cannabis. Indeed, there exist individual parameters such as underlying pathologies, the profile of response to previous treatments, and social parameters such as the illicit nature of cannabis in many European countries which make epidemiological studies difficult.

However, the conclusions of a 2004 Spanish study made it possible to draw the real profile of consumer patients and estimate the anticipated benefits and secondary effects linked to cannabis intake for symptomatic relief. This study was carried out with 2200 patients belonging to thirty patient associations. Only 6% acknowledged using cannabis for therapeutic purposes. Almost half were suffering from cancer, with the other pathologies each representing less than 10% of the patients (AIDS, multiple sclerosis, etc.). Surprisingly, the typical consumer patient was a 45-year-old woman, using cannabis for a short period (3 months–1 year), mainly smoked (69%), but also ingested (23%) or infused (16%). In 63% of cases, it was on their own initiative, and in 13% on a doctor's advice. The beneficial effects, for almost half of the patients, were a hypnotic effect (56%), an improvement in nausea (47%), pain (46%) and appetite (46%). The secondary effects were dry mouth in almost half of the patients, a change in their emotional state, memory impairment and ocular irritation [114].

Furthermore, in the Netherlands, an analysis of prescriptions associated with the purchase of cannabis on

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sale in pharmacies showed that half of the cannabis consumers also took analgesics. Only 2.7% took anticancer medicines and 0.9% antiretrovirals. However, the authors expressed some reservations as to their analysis as the patients could go to several pharmacies or even to 'Coffee Shops'. The result of these studies shows that the use of cannabis by patients with cancer remains anecdotal although areas of bias alter the reliability of the analysis [115].

Limitations of use

The adverse effects of cannabinoids in the short term (somnolence, vertigo, dizziness, feeling of drunkenness) and in the long term (anxiety, social problems, development of psychoses) limit their use and prompt some countries to not prohibit them [116]. Furthermore, cannabis-related treatments are effective vs. placebo but are not always compared to reference treatments.

New concerns over toxicity are emerging from recent literature: cardiac toxicity, hyperemesis syndrome and the controversial link between cannabis and testicular cancer.

Cannabinoid hyperemesis syndrome is a variant of cyclical vomiting syndrome in a context of chronic cannabis usage (daily usage for several years) [117–119].

A link between cannabis consumption and testicular cancer has been stated. Several studies reinforce this view [120–122]. In a case–control study conducted on 163 young men with testicular cancer and 292 control men, the men who had smoked cannabis presented twice as much risk of developing a form of testicular cancer with a poor prognosis compared to those who had not smoked any [112]. Several studies reinforce this view [12,111,112]. Nevertheless, in 2017, a Swedish epidemiologic study included near 50 000 men from 1970 to 2011 found no relationships between lifetime 'ever' cannabis use and the development of testicular cancer and only heavy cannabis users were associated with a higher incidence of testicular cancer [123].

Cardiac toxicity was another example of troubles caused by cannabis. There are more and more reports in the literature of cardiac complications or cardiac deaths associated with the consumption of cannabis [124–126]. According to a French study, 1.8% of complications attributed to cannabis, declared between 2006 and 2010, were of a cardiovascular nature, with a 25% mortality rate [127]. A review of the literature published in 2015 lists cases of acute coronary syndrome, sudden death, paroxysmal atrial fibrillation, stroke, cardiomyopathy and myopericarditis [128]. One study showed that variability of heart rate was increased in cannabis smokers [116], while other studies reveal that the consumption of cannabis or synthetic cannabis ('Spice') may increase the risk of myocardial infarction [117,118]. On the other hand, an animal study appears to be in favour of the cardioprotective effect of cannabidiol in mice treated with doxorubicin [129]. It would probably be wise to the cautious in cases of pre-existing heart failure or treatment with cardiotoxic chemotherapy such as anthracyclines.

RISKS OF PHARMACOKINETIC INTERACTIONS BETWEEN CANNABINOIDS AND ANTICANCER DRUGS

Membrane transporters

Membrane transporters are implicated in the homoeostasis of numerous endogenous substances (lipids, carbohydrates, hormones, amino acids, etc.); some also play an important role in the pharmacokinetics of many medicines (absorption, bioavailability, tissular distribution, cellular distribution, efflux, elimination).

There are two large superfamilies' of transporters: the members of the ABC superfamily (ATP-binding cassette) which are membrane transporters of ATP-dependent efflux and the SLC superfamilies' (SoLute carrier) which are exchangers (uniport, symport or antiport). Generally speaking, the SLCs allow medicines to penetrate the cell, whereas the ABCs help them leave the cells. In this chapter, we will look at studies that report on interactions of a pharmacokinetic kind during concomitant administration of an anticancer treatment and consumption of natural cannabis. Very few studies have investigated the pharmacokinetic interactions between the natural constituents of cannabis and these transporters.

Recent data in animals suggest that cannabinoids may be substrates of P-gp [130,131]. In vitro, cannabinoids bind to many members of the ABC transporter family, including BCRP and P-gp (*Table* II) [131–136].

Glycoprotein P

P-gp is an efflux pump coded by the MDR1/ABCB1 gene and implicated in the efflux of a wide variety of substrates (*Table* III). It is naturally present within many healthy tissues such as the intestinal epithelium,

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Table III Metabolism and transport drug database of main anticancer agent.

	Drug transporters								Cytochromes P450									UGT						
	P-gp	MRP1	MRP2	MRP3	MRP4	MRP6	MRP7	BCRP	1A1	1A2	2B6	2C8	2C9	2C19	2D6	3A4	3A5	1A1	1A4	1A7	1A8	1A9	1A10	2B7
Antimetabolites																								
Cladribine	nd	nd	nd	nd		nd	nd		nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Methotrexate						nd	nd		nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Alkylating agents																								
Cyclophosphamid	nd		nd	nd	nd	nd	nd		nd	nd		nd			nd		nd	nd	nd	nd	nd	nd	nd	nd
Dacarbazine	nd	nd	nd	nd	nd	nd	nd	nd			nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Ifosfamine	nd		nd	nd	nd	nd	nd		nd	nd		nd			nd			nd	nd	nd	nd	nd	nd	nd
Thiotepa	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd
Cisplatin	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Taxans																								
Docetaxel		nd		nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd			nd	nd	nd	nd	nd	nd	nd
Paclitaxel		nd		nd	nd	nd		nd	nd	nd	nd		nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd
Vinca-alcaloides																								
Vinblastine				nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd
Vincristine					nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd			nd	nd	nd	nd	nd	nd	nd
Vinorelbine		nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd
Topoisomerase I/II inhibitors																								
Irinotecan				nd		nd	nd		nd	nd	nd	nd	nd	nd	nd				nd	nd	nd		nd	nd
Topotecan		nd	nd	nd		nd	nd		nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd
Etoposide					nd			nd	nd	nd	nd	nd	nd	nd	nd				nd	nd	nd	nd	nd	nd
Hormonal therapies																								
Tamoxifene		nd	nd	nd	nd	nd	nd	nd				nd		nd					nd	nd				
Anastrozole	nd	nd	nd	nd	nd	nd	nd	nd	nd		nd		nd	nd	nd			nd		nd	nd	nd	nd	nd
Letrozole	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd
Flutamine	nd	nd	nd	nd	nd	nd	nd	nd			nd	nd	nd	nd	nd	nd	nd			nd	nd	nd	nd	nd
Tyrosine Kinase inhibitors																								
Gefitinib		nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd			nd	nd	nd	nd	nd	nd	nd	nd
Imatinib		nd	nd	nd	nd	nd	nd		nd		nd	nd						nd	nd	nd	nd	nd	nd	nd
Sorafenib		nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd		nd	nd
Erlotinib		nd	nd	nd	nd	nd	nd			nd	nd		nd	nd	nd				nd	nd	nd	nd	nd	nd
Lapatinib		nd	nd	nd	nd	nd	nd		nd	nd	nd		nd		nd			nd	nd	nd	nd	nd	nd	nd
Nilotinib		nd	nd	nd	nd	nd	nd		nd	nd	nd		nd	nd	nd		nd		nd	nd	nd	nd	nd	nd
Dasatinib		nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd
Ponatinib		nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd
Sunitinib		nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd
Pazopanib		nd	nd	nd	nd	nd	nd		nd		nd		nd	nd	nd		nd		nd	nd	nd	nd	nd	nd
Vemurafenib		nd	nd	nd	nd	nd	nd		nd		nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd

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Table III. Continued

	Drug transporters								Cytochromes P450								UGT						
	P-gp	MRP1	MRP2	MRP3	MRP4	MRP6	MRP7	BCRP	1A1	1A2	2B6	2C8	2C9	2C19	2D6	3A4	3A5	1A1	1A4	1A7	1A8	1A9	1A10	2B7
Crizotinib	nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd			nd	nd	nd	nd	nd	nd	nd
Intercalants																								
Mitoxantrone			nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Daunorubicine			nd	nd	nd				nd	nd	nd	nd	nd	nd	nd		nd	nd	nd	nd	nd	nd	nd	nd
Doxorubicine				nd	nd		nd		nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Idarubicine		nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd

Dark grey: major pathway; light-grey: minor pathway; nd: not determined.

the hepatocytes, the renal tubules and the blood–brain barrier and is implicated in many pharmacokinetic processes. It plays a fundamental role in the protection and detoxification of the organism against many endogenous and exogenous substances by preventing them from passing through the natural barriers of the organism and stopping their accumulation [137,138]. It was initially discovered at the membrane level of some tumour cells, thus giving them a phenotype resistance vis-à-vis some anticancer drugs [139].

Action of cannabinoids on P-gp – possible interactions: No clinical study has specifically studied the risk of interaction between cannabinoids and anticancer agents. However, chronic and acute exposure to natural cannabinoids shows, in vitro, the existence of interactions between P-gp and THC, THC-COOH, CBD and CBN [133,136,140]. Cannabinoids could have different effects depending on the duration of exposure. Chronic exposure reducing the expression of P-gp [133,136,141] [or] brief exposure increasing the transcript expression of P-gp [142]. The inhibitory effect of CBD is thought to be more significant than that of THC, probably due to the fact of their different affinities for the CB1, CB2 and TRPV1 receptors [141,142]. However, the concentrations tested in these studies are higher than the concentrations usually measured in cannabis smokers.

Breast cancer resistance protein – BCRP

The BCRP transporter is coded by the MXR/ABCG2 gene (mitoxantrone resistance-associated gene). BCRP is strongly expressed at the level of the liver, intestines, colon, blood–brain barrier and placenta. It intervenes in the absorption of medicines and their excretion via the bile. In addition, it may be overexpressed by tumour cells (breast, colon, stomach) thereby conferring phenotypic resistance to those tumours in the event of treatment by means of BCRP substrate medicines (*Table* III).

Action of cannabinoids on BCRP – possible interactions: In 2007, a team investigated the possible interactions of Δ^9-THC, CBD and CBN with the transporter ABCG2. This study showed that in vitro, these three cannabinoids are capable of inhibiting the efflux of mitoxantrone and topotecan [132] (*Table* II). The mechanism implicated appears to be a direct interaction between the pump and the cannabinoids. These results are confirmed by other studies, in particular an ex vivo study carried out on samples of human placenta [140,143]. However, the impact of cannabinoids on the modulation of BCRP gene expression is not clear, as the studies are contradictory [132,141,143].

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Breast cancer resistance protein – MRP

The transporters of the MRP family are coded by the ABCC gene. MRP1 is mainly expressed at the level of the kidney, lungs, skeletal muscle and hematopoietic cells. Like P-gp and BCRP, the transporters of the MRP family participate in the transport of many anticancer molecules [144] (*Table* III).

Action of cannabinoids on MRP1: A team from Sydney University tested in vitro the action of THC, CBD and CBN on the MRP1 transporter. The intracellular accumulation of several substrates of MRP1, including vincristine, was increased by the three cannabinoids tested with a more marked effect for CBD [134]. Moreover, a study by Wittgen et al. indicates that some molecules capable of interacting with the CB1 receptors could also modulate the expression of the MRP1, MRP2, MRP3 and MRP4 transporters [145] (*Table* II).

All the experiments carried out in vitro on the transporters are merely avenues of discussion, as only clinical studies will be able to confirm potential modifications in the pharmacokinetics of anticancer drugs. The experimental methods used in these cited studies are far beyond the concentrations observed in man under the usual conditions of use of cannabis.

Cytochrome P450

Cytochromes P450 (CYP450) are enzymatic systems strongly implicated in the biotransformation of medicines for their metabolism or activation. The CYP450 belong to the 3A family and are responsible for the metabolism of more than 50% of medicines. CYP2D6 metabolizes 25–30% of medicines. The other cytochromes implicated being 1A1, 1A2, 1B1, 2B6, 2C9 and 2C19. The principal cytochromes implicated in the metabolism of anticancer drugs are indicated in *Table* III.

Cytochrome P450 3A4/5

This family of cytochromes is implicated in the metabolism of more than 50% of medicines marketed. The two principal isoforms are CYP3A4 and CYP3A5 (CYP3A7, a foetal variant expressed by almost 8% of the Caucasian population, will not be discussed). The expression of isoform 3A5 is subject to a genetic polymorphism that determines its expression in binary format. In the Caucasian population, only 8–15% of individuals, as opposed to almost 45% of Africans, express this variant [146]. Many anticancer drugs are metabolized by Cytochromes 3A4/5 (*Table* III).

Action of cannabinoids on CYP450 3A: The inhibitory effect of THC, CBD and CBN on the CYP3A was studied by a Japanese team [147]. In vitro, these three derivatives inhibit the activity of CYP450 3A, with CBD presenting a far more marked inhibitory power. The mechanism implicated seems to be a competitive inhibition, with an inhibition constant measured for CBD of 1 μM for 3A4 and 0.195 μM for 3A5 [14,48,148]. These inhibitory concentrations are compatible with the concentrations measured in the blood circulation of the regular consumer of inhaled cannabis (Stout & Cimino 2013). A 2002 publication reports on a myocardial infarction attributed to an interaction between cannabis and sildenafil (Viagra®) in a young man [149].

CYP 2D6

Of all the hepatic cytochromes, CYP2D6 is the most 'efficient'; its expression is relatively minor in the liver but it metabolizes a large number of xenobiotics, 25–30% of which are medicines used in man [150]. Of all the cytochromes implicated in the metabolism of medicines, CYP2D6 is indisputably the most polymorphic [151] and the activity of the proteins derived from these allelic variants may be classed in four levels: slow, intermediary, rapid and ultrarapid [152]. Contrary to other hepatic cytochromes, its expression does not depend on environmental agents and is not inducible either by tobacco or alcohol or by natural or artificial steroids. On the other hand, some medicines are capable of inhibiting it, thereby provoking sometimes serious medicinal interactions [153,154]. Finally, few anticancer drugs are metabolized by Cytochrome 2D6, but some interactions have major consequences. The polymorphisms or interactions responsible for the reduced activity of CYP2D6 are responsible for the lower efficacy of tamoxifen. In fact, tamoxifen is a prodrug which requires a functional CYP2D6 to be activated in active metabolites [155]. Some studies have shown that the concomitant intake of CYP2D6 inhibitors diminishes tamoxifen concentrations by 50% [156]. Some epidemiological studies also show similar results [156–160].

Action of cannabinoids on cyp450 2D6: In 2011, a Japanese team investigated the effects of THC, CBD and CBN on the catalytic activity of CYP2D6 [161]. Of all the compounds tested, CBD is, in vitro, the most powerful inhibitor of CYP2D6. The inhibition constants measured for CBD are of the same order as that of fluoxetin. However, as the authors mention in the

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discussion, the concentrations of CBD found in the blood after consumption of cannabis are lower than those necessary to engender a significant inhibition of Cytochrome 2D6 from the clinical consequences.

CYP2C9

Cytochrome 2C9 represents about 18% of the cytochromes in the liver. It is implicated in the metabolism of many medicines [162]. The anticancer drugs metabolized by 2C9 are indicated in *Table* III.

Action of cannabinoids on cyp450 2C9: A Japanese team evaluated in vitro the effect of THC, CBD and CBN on the activity of CYP2C9 [163]. The three cannabinoids tested inhibit the activity of CYP2C9 with effects comparable to the known inhibitors. Unlike THC and CBN, CBD has an inhibitory effect that appears to vary according to the substrate used. Furthermore, exposure to THC would appear to depend on the genetic polymorphisms of CYP2C9, as carriers of the CYP2C9*3/*3 variant present THC exposure three times higher than carriers of the CYP2C9*1/*1 variant [164].

Other cytochromes: 1A1, 1A2, 1B1, 2B6 and 2C8

Cannabis derivatives are also capable of inhibiting Cytochromes P450 1A1, 1A2 1B1, 2B6 and 2C8 implicated in the metabolism of some anticancer drugs are listed in *Table* III. CYP2C8 was only discovered very recently [165]. It intervenes in the metabolism of 5% of medicines, but it is of increasing interest as it appears to have a redundant role with CYP3A4. The structural analogies of the catalytic site of these two cytochromes explain their common substrates [166]. CBD seems to present the highest inhibitory power; however, no in vivo study supports the relevance of these experimental results [56,167,168].

Glucuronidation

As indicated in *Table* III, many anticancer agents are also UGT substrates. Glucuronidation makes it possible to increase hydro-solubility and facilitates the urinary elimination of medication. These enzymes are mainly expressed at hepatic level. Just as for cytochromes, they are classed according to their gene sequence, which makes it possible to distinguish two families, UGT1 and UGT2, and three subfamilies, UGT1A, UGT2A and UGT2B, with many members [169].

Among the anticancer agents, irinotecan, flutamide and etoposide require this glucuronidation phase. For SN-38 (active metabolite of irinotecan), this phase is preponderant and regulates its elimination. Recent studies have thus shown that any modification of the activity of UGT1A1, whether of genetic origin or otherwise, determines the balance between clinical efficacy and tolerance [170–173]. However, the data of the literature are not easy to find, and while the existence of glucuronidated metabolites is known, the UGTs responsible are not always identified.

Action of cannabinoids on UGTs

In vitro, some cannabinoids are capable of inhibiting certain members of the family of UGTs, underpinning potential interactions with anticancer drugs (*Table* II). Recent experiments in vitro indicate that CBD may be an inhibitor of UGT1A9 and 2B7 and CBN may inhibit UGT1A7, 1A8, 1A9 and activate UGT2B7 [53,57,174,175]. To date, no trial has studied the clinical impact of these possible interactions.

Clinical studies

An exhaustive search of the bibliographic data has produced only one study which evaluated the impact of medicinal cannabis tea, Bedrocan®, on the kinetics of docetaxel and irinotecan [176]. This cross-over study does not show any influence of cannabis administered in this form on patients' exposure to docetaxel, irinotecan, SN-38 and SN-38-glucuronide. These results cannot, however, be extrapolated to the more generally used methods of administration.

CONCLUSION

More and more patients with cancer are consuming cannabis (natural or synthetic) either on medical prescription within the framework of a precise indication (but variable from one country to another) or by 'social' incentives.

Marketing authorizations for synthetic derivatives of cannabis or extracts, isolated from standardized plants, used in precise medical indications, are sowing confusion: both among those who are against and those who are for cannabis, whether in the medical and scientific community or in society in general.

Some discussion forums express the mistrust of the synthetic forms of THC, deemed too 'chemical'. Others think that these cannabinoids are less effective than the plant form, and denounce 'the interests of the big pharmaceutical laboratories which seek to profit by the emergence of therapeutic cannabis and sell these molecules at a very high price'.

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The use of cannabis as a complement for supportive care of patients with cancer is nothing new and seems to be a reasonable alternative. However, at a pharmacological level, many unknowns persist, in particular as regards medicines with a risk of interactions, particularly interactions between cannabinoids and anticancer molecules. Of all the cannabinoids, CBD appears to be a promising molecule, which is the focus of many hopes, but it is also the natural cannabinoid with the greatest risk of interactions (*Table* II). In spite of an exhaustive search, very little data concerning the risk of interaction between cannabinoids and medicines are available [176]. As shown in *Table* III, with the exception of P-gp, all pharmacokinetic interactions concern inhibitions of transport or metabolism.

It is important for healthcare professionals to be able, without difficulty, to know whether cannabinoids, whatever their origin, can be used or should be formally rejected. While the use of cannabis as a complement for supportive care of patients with cancer seems reasonable, clinical studies aimed at determining the interactions are necessary. Even though this review is focused on pharmacokinetic interactions between cannabinoids and anticancer drugs, it also highlights the lack of data concerning the efficacy and safety of cannabinoids in patients with cancer. Further studies are warranted to explore the potential interactions but also to assess their efficacy and safety in the many situations in which patients are already using them.

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ABBREVIATIONS

ABC – ATP-binding cassette
AUC – area under the curve
BCRP – breast cancer resistance protein
CBD – cannabidiol
CBN – cannabinol
CINV – chemo-induced nausea and vomiting
C_{max} – maximum concentration
MAPK – mitogen-activated protein kinases
MDR – multidrug resistance
MRP – multidrug resistance-associated protein
MXR/ABCG2 – mitoxantrone resistance-associated gene
OFDT – Observatoire français des drogues et des toxicomanies
PI3K – phosphoinositide 3-kinase
SLC – SoLute carrier
THCA – Δ9-tetrahydrocannabinol-4-oic acid
THC – tetrahydrocannabinol
T_{max} – time of the peak of concentration
TRPV1 – type 1 transient receptor potential vanilloid ion channels
UGT – uridine 5′-diphospho-glucuronosyltransferase

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