Psychotropics:
A scientific, regulatory, and public view on the medicinal use of cannabinoids and psilocybin

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Abstract

Research on psychotropics is gaining more popularity worldwide and support from drug regulatory agencies, which recognise the unmet medical needs of certain patient communities, such as patients with mental disorders and patients with cancer who experience depression. Cannabinoids and psilocybin have shown promising results in preclinical studies and clinical trials, but the current clinical evidence is scarce, and the regulatory requirements are strict due to high potential for drug abuse. The US FDA has recently released a draft, non-binding guidance on clinical trials with psychedelics. Europe is currently falling behind the US and Canada in terms of regulating psychotropic substances. The article provides a general introduction on conducting clinical trials with psychotropics and the regulatory requirements (as of October 2023) when submitting marketing authorisation application. In the near future, as more data becomes available, research on psychotropics will definitely shape the European regulatory landscape.

Psychotropics are popular again

Drug development is a risky but rewarding endeavour.[1] About 90 percent of clinical drug development fails in the Phase I stage. But when a drug is approved, patients benefit: it can improve their quality of life or can turn a terminal prognosis into a chronic disease. This is especially true for cancer treatment. The projections calculated using current real-world data on cancer show that by 2040, 28 million people will be affected by the disease worldwide, and the investment in cancer research has been growing steadily every year with a slight plateau during the coronavirus disease 2019 (COVID-19) pandemic.[2,3] Effective cancer treatment can cure the disease or at least improve a patient's overall survival and quality of life.[4] But often, patients develop depression and are at a higher risk of suicide, and therefore are prescribed strong antidepressants to help them cope with their symptoms.[5] Patients are often given strong opioids to manage pain, but long-term usage leads to increased tolerance or resistance making opioids ineffective.[6]

A similar scenario is seen in patients with mental disorders. It can take time for the medicine to take effect and to find the correct dosage, and some side effects can have a major impact on a patient's quality of life (such as weight gain, sexual dysfunction, dizziness, or suicidal thoughts).[7,8] Especially severe forms of mental disorders, such as post-traumatic stress disorder and major depressive disorder, are challenging to treat.[9]

Consequently, new research on psychotropics has created a fresh field of opportunities: the development of new biotechnological methodology (cell culture) to meet the research objectives of the pharma industry and clinical research laboratories. If effective, psychotropics can be used to treat neurological diseases, especially in patients with breakthrough depression (recurring depression) or patients with terminal cancer.[10]

This article explores the scientific, regulatory, and public positions on potential medicinal use of cannabinoids (cannabidiol and tetrahydrocannabinol) in pain and depression, and psilocybin's potential to improve patients' wellbeing. It also provides an update on the status of the biotechnological methodologies (cell culture) that could be used to produce the mentioned substances, and latest recommenda-

Abbreviations

CBC	Cannabichromine
CBD	Cannabidiol
CBDA	Cannabidiolic acid
CBG	Cannabigerol
CBGA	Cannabigerolic acid
CBN	Cannabinol
CMC	Chemistry, Manufacturing, and Controls
CRISPR-Cas9	CRISPR-Associated protein 9
EFPIA	European Federation of Pharmaceutical Industries and Associations
MDMA	3,4-methylenedioxy-methamphetamine (also known as ecstasy or molly)
NHS	National Health Service
THC	Tetrahydrocannabinol
THCB	Tetrahydrocannabutol
THCA	Tetrahydrocannabinolic acid
THCAS	Tetrahydrocannabinolic acid synthase
THCV	Tetrahydrocannabivarin

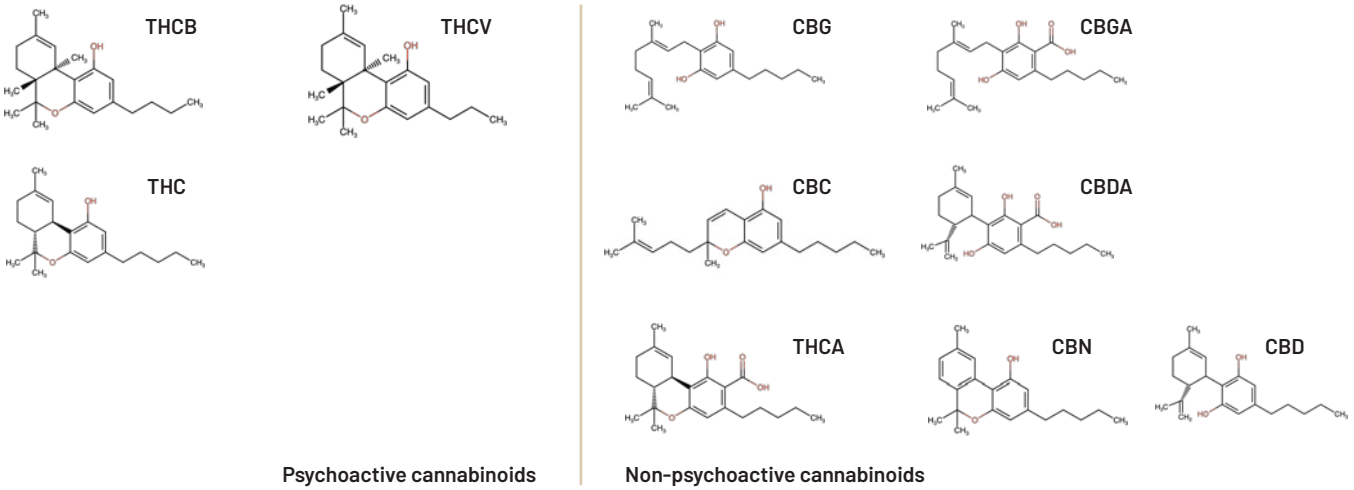

Figure 1. Chemical formulas of various cannabinoid molecules

Abbreviations: CBC, cannabichromine; CBD, cannabidiol; CBDA, cannabidiolic acid; CBG, cannabigerol; CBGA, cannabigerolic acid; CBN, cannabinol; THC, tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; THCB, tetrahydrocannabutol; THCV, tetrahydrocannabivarin;

tions (as of October 2023) published by the regulatory agencies on preparing documentation when conducting clinical trials and submitting marketing authorisation application.

Biotechnological production: The best way to ensure high-quality medicine for patients, or just innovation start-up hype? A scientific perspective

Biotechnology is defined as "the technique of using microorganisms, such as bacteria, to perform chemical processing, such as waste recycling, or to produce other materials, such as beer and wine, cheese, antibiotics, and (using genetic engineering) hormones, vaccines, etc".[11] Increased interest and investment into psychotropics means a higher demand on the market. While traditional manufacturing using chemical synthesis and extraction work well, albeit with minor downsides (impurities, racemate mixture, highly expensive purification), biotechnologists are still looking for innovative and efficient ways to maximise the production of psychotropics using the cellular metabolism pathways of various hosts.

Cannabis – a natural producer of psychotropic and non-psychotropic substances

Cannabis sativa L. is the sixth most important crop in the US.[12] Besides recreational and medicinal uses, the plant can be used for production of clothing and nutrition products

Photo: Indorgo Canada

Figure 2.* Cannabis *buds that produce CBD

Photo: Thomas Elliott

Figure 3. Glandular trichomes in* Cannabis sativa *L.

Table 1. List of cannabis-derived medicinal products

Brand name	Active compound(s)	Authorised in countries	Indication	Route of administration
Epidyolex®	CBD	EU (not available in every country), US (named Epidiolex®)	Lennox-Gastaut syndrome, Dravet syndrome, adjunctive therapy of seizures associated with tuberous sclerosis complex	Oral
Marinol® (dronabinol)	(-)-trans-delta-9-tetrahydrocannabinol isolated from the plant	EU (not available in every country), US, Australia	Cancer treatment, AIDS, multiple sclerosis	Oral
Cesamet® (nabilone)	synthetic (-)-trans-delta-9-tetrahydrocannabinol	EU (not available in every country), US, Australia	Cancer treatment	Oral
Sativex® (Nabiximols)	Cannabis herbal preparation (extract of cannabis)(oil) THC and CBD	EU (not available in every country)	Multiple sclerosis	Oral

(seed oil, protein powders, etc.). Cannabinoids, the major group of compounds present in the plant, show various health benefits (anti-cancer, painkilling, muscle and nerve relaxing) and some of them exhibit psychoactive characteristics.[13,14] The well-known cannabinoids are the psychotropic Δ^9-tetrahydrocannabinol (Δ^9-THC, isolated in 1964) and the non-psychotropic cannabidiol (CBD, isolated in 1940).[15] Other cannabinoids are cannabidiolic acid (CBDA), cannabigerol (CBG), cannabinol (CBN), cannabichromene (CBC), and the derivatives of tetrahydrocannabinolic acid (Δ^9-THCB, Δ^9-THCV, Δ^8-THC). Current research confirms that only THC, THCV, and THCB have psychotropic characteristics.[16] (Figure 1) THC and CBD have the same "relative" (precursor substance), cannabigerolic acid (CGBA), which is produced in the glandural trichomes. Glandural trichomes are hair-like growths that secrete various secondary metabolites; they are found on the leaves, stems, and flowers of the plant.[17,18] The highest CBD concentration is found in the glandural trichomes of the cannabis flowers, which are used for CBD isolation at the industrial scale (Figures 2 and 3).

Latest in vitro and animal studies have shown that CBD has anti-anxiety, anti-nausea, anti-arthritic, anti-inflammatory, and immunomodulatory properties. Interestingly, preclinical studies have shown that CBD can work synergistically with anti-cancer agents and improve their efficacy.[19] Toxicity studies on CBD have shown that it is generally well tolerated, except in very high doses.[20] On the contrary, the THC interferes with the regulation of cancer development, promoting cancer and inflammation. There is a high risk of abuse in chronic therapy, and animal studies have shown high mortality and reproductive atrophy and hyperplasia.[21–24]

A recent systematic review on worldwide clinical trials with cannabis for therapeutic purposes reported that most of the clinical trials were performed in the US, Brazil, Australia, Netherlands, Israel, Switzerland, and the UK.[25] The EU clinical trials register lists 73 clinical trials involving cannabis (as of October 2023) and 17 of them test the efficacy of CBD against pain (as of October 2023).[26,27] The most common indications are: cannabis use disorder, effects of THC and its toxicity, cancer, multiple sclerosis, pain, and fibromyalgia. Clinical Trial Information System (CTIS) lists six clinical trials with cannabis.[28]

ClinicalTrials.gov lists many interventional clinical trials using cannabis; the most common indications are depression, marijuana abuse, pain, cannabis dependence, and multiple sclerosis.[29] Currently, there are four medicinal products authorised for the European market (Table 1). One of the products is Sativex, developed by Jazz pharmaceuticals (GW pharmaceuticals). Sativex® is an herbal preparation in the form of an oral mucosal spray containing a standardised cannabis extract, nabiximols. The extract contains 27 mg/mL THC and 25 mg/mL CBD.[30] Several safety studies with Sativex® have been conducted, especially for pain management in patients with cancer.[30] Latest studies did not show that Sativex® is superior to placebo.[31–33]

Cannabinoids can be produced by direct extraction from plants, by chemical synthesis, or using microbial cells (fermentation). The most common way to produce CBD in the industrial setting is to grow *Cannabis sativa* either in greenhouses or outdoors and to chemically extract CBD and THC from the plants.[34] In recent years, the CRISPR-Cas9 gene editing technique has enabled the industry to produce plants that are more resistant to climatic hazards and diseases, that yield more cannabinoids, and that produce more or less of specific metabolites.[35]

The industry claims that the main benefit of the traditional isolation is the co-isolation of other compounds (terpenes, flavonoids) in very low concentration, which could be responsible for improving the therapeutic effect (also called "entourage effect").[36,37] The entourage effect is defined as a synergistic cooperation of compounds in *Cannabis sativa* that increases its efficacy. However, the regulatory and public data available on the entourage effect are scarce.

Chemical synthesis of cannabinoids is less efficient than the traditional method.[38] So, a novel approach for cannabinoids synthesis was developed in 2019: microbial fermentation.[39] Microbial fermentation enables production of a

single compound in a single-cell organism such as yeast, bacteria, or algae.[34] Luo et al. introduced cannabis genes into yeast (*Saccharomyces cerevisiae*), giving it the ability to metabolise sugars into CBGA (the precursor of THC and CBD). The CBGA yield, however, was low (milligram and microgram scale).[40] Lange et al. were able to produce the enzyme Δ^9-tetrahydrocannabinolic acid synthase (THCAS) using yeast (*Pichia pastoris*).[41] THCAS catalyses the production of THCA from CBGA, THCA is the precursor substance of THC.[41] THC production has also been tested in other organisms, such as *E.coli*, *S. cerevisiae,* and *K. phaffii*.[34,42] The attempts to biosynthesise cannabinoids in algae chloroplasts are still in the early start-up business stage as the method has proven to be very expensive; algae has thick cell walls which require complex and expensive techniques to break them.[34]

Favero et al. published a list of patents (filed as of 2014) for cannabinoid biosynthesis using microbial fermentation.[34] The latest patents (from 2020 to October 2023) use yeast or bacteria to produce cannabinoids via the geranyl pyrophosphate pathway by introducing various *Cannabis sativa* genes or enzymes.[34] Two companies in the USA patented cannabinoid synthesis in microalgae.[34] Available information shows that production of cannabinoids using biotechnological methodology is still in its infancy (Figure 4).

Cannabinoids can be produced by direct extraction from plant, by chemical synthesis, or using microbial cells (fermentation).

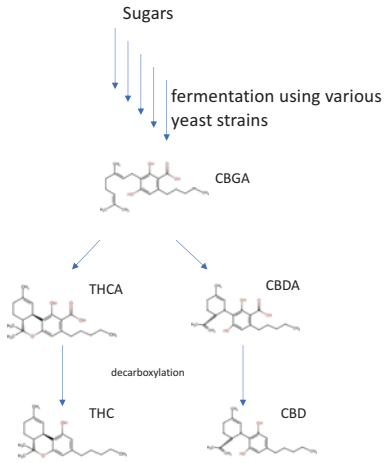

Figure 4. Favero et al., demonstrated a biochemical method to synthesise THC and CBD from sugars.

Sugars are fermented using various yeast strains to produce CBGA and subsequently using various chemical techniques to yield pure THC and CBD. The method is still in its infancy.

Abbreviations: CBD, cannabidiol; CBDA, cannabidiolic acid; CBGA, cannabigerolic acid; THC, tetrahydrocannabinol; THCA, tetrahydrocannabidiolic acid.

Psilocybin – the magic in magic mushrooms

Psilocybin is a natural psychoactive tryptamine isolated from magic mushrooms (most common genus is Psilocybe).[43–45] First industrial isolation of psilocybin was done by A. Hofmann from the Mexican mushroom *Psilicybe mexicana* Heim (Figures 5 and 6).[46]

Synthetic psilocybin was first marketed in the 1960s by Sandoz under the brand name Indocybin®.[44] Initially marketed for clinical research, it was abused as a recreational drug, which led to research being put on hold for 30 years.[47] Clinical trials have shown that psilocybin in small doses can help people achieve mystical experience (altered state of consciousness).[48] Only high doses of psilocybin showed a potential to treat depressive state and negative attitude in patients with advanced cancer, which was confirmed by the patients and their observers. The treatment increased the overall wellbeing of the patients.[49] However, a clinical study performed by Griffiths et al. confirmed that higher dosage led to increased recurrence of adverse effects (headaches, nausea, dizziness, anxiety).[49] The reporting of higher anxiety, albeit by a small number of patients, is common in almost every clinical trial on psilocybin.[48,50] There have been two *Nature* articles on patients with post-traumatic stress disorder treated with psychotropics that reported overall life quality improvement since their treatment.[51,52] Currently there are no authorised psilocybin products on the market, but 11 clinical trials are ongoing (according to EMA Executive Director Emer Cooke).[53] Australia has approved psilocybin for medicinal use in psychiatric patients in 2023.[10]

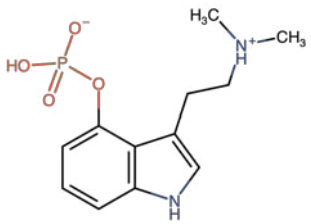

Figure 5. Chemical structure of psilocybin

Psilocybin can be isolated from magic mushrooms, produced via microbial fermentation (using procaryotic or eucaryotic hosts), or chemically synthesised from hydroxyindole.[45,54] Flower et al. were able to synthesise psilocybin (approximately 30 mg/L) and 13 derivates of psilocybin using genetically modified *E. coli* in a small-scale using tryptamine.[45] This de novo synthesis is a novel approach that was only tested at a microscale and should be analysed for suitability for industry-scale production.[45] Current limitations for microbial fermentation are the optimisation of the methods for higher yield production, purification, and up-scaling.

Current regulatory guidance: a friend or a foe?

Cannabis

With the US and Canada pioneering cannabis legalisation[55] and the rising therapeutic demand for cannabis products and derivatives in Europe, the pressure to regulate cannabis products in Europe is on the rise. The EMA has published a guidance document on cannabis-derived medicinal products.[56] According to the guidance, there shall be no difference in marketing cannabis-derived medicinal products, as the Marketing Authorisation Holders (MAHs) should comply with the definition of a medicinal product (Article 1(2) of Directive 2001/83/EC).

Photo Marco Allegretti (@attimi.komorebi)

Figure 6. Magic mushrooms close-up

Medicinal products are submitted in the form of a dossier (Common Technical Document, CTD) and the applicant must include the results of pre-clinical research and clinical trials. If the active substance falls under well-established use (known use for more than 10 years in the EU), the applicant can submit scientific literature, which should demonstrate safety and efficacy of the new medicinal product (Article 10a of Directive 2001/83/EC).[57] There are also exceptions for herbal medicinal products. If they have been used for more than 30 years (at least 15 years in the EU) and are intended for use without medical surveillance and aren't administered by injection, then the Traditional Herbal Medicinal Products Directive (Directive 2004/24/EC and Directive 2001/83/EC (Article 16a)) applies.[57] On the contrary, if the requirements for herbal medicinal products are not fulfilled (not well-established use under Article 10a or traditional use under Article 16a(1)), then the application must comply with the general requirements of the Marketing Authorisation Application (they fall under the definition of medicinal products).[57] Furthermore, in October 2022, the European pharmacopoeia (Ph. Eur.) published monographs on *Cannabis flos* (flowers) and extracts from cannabis, which will be published in January 2024 in the Ph. Eur. Supplement 11.5 and will take effect as of July 2024.[58,59]

At the moment, the European Federation of Pharmaceutical Industries and Associations (EFPIA) does not have a position statement on cannabis-derived products and psilocybin, but they acknowledge the importance of the psychotropics, which was published in the EFPIA pipeline innovation review (dated August 2022).[60,61] The US FDA has not approved any medicine containing cannabis, but has authorised cannabis-derived substance (CBD in Epidiolex®/Epidyolex®) and synthetic cannabis substances (dronabinol in Marinol and Syndros and nabolone in Cesamet®).[62] The US FDA is supporting cannabis-derived medicine only if the benefits greatly outweigh the risks.[62]

Psychotropic substances

Psychotropic substances are regulated globally and at the EU level. To prevent drug abuse, the UN has classified these substances into four schedules, which can be found in the Annex of the 1971 UN Convention on Psychotropic Substances.[63] The EU system regulated the drug precursors following specifications listed in the Regulation (EC) No. 111/205 and 273/2004.[63,64] Furthermore, plant extracts can be used in a clinical trial but have to comply with the general requirements defined in the Ph. Eur., national pharmacopoeias, and the EMA guidance documents.[65] However, every country can further tighten the requirements.[65]

Cannabis-derived medicinal products have the same conditions as every marketing authorisation application; the therapeutic benefits must outweigh the potential risks.

As for the development of psychotropic substances, the EMA has not published any guidelines regarding clinical trial development and marketing authorisation. Cannabis-derived medicinal products have the same conditions as every Marketing Authorisation Application; the therapeutic benefits must outweigh the potential risks.[56] However, the EMA and the US FDA published various general guideline documents on conducting clinical trials with psychotropic substances.[66] In August 2023, the US FDA published a draft guideline on developing psychedelics. It is focused on conducting clinical trials, data collection, and patient safety. In general, the applicant must provide sufficient CMC data (which are an important part of the CTD), and the application varies depending on the substance origin (i.e. from plant material, algae, etc.).[67,68] EMA indirectly followed the US FDA steps and published a draft guidance on conducting clinical trials for major depressive disorder in September 2023.[69] The draft guideline also concentrates on psychotropics – psilocybin, LSD, DMT and mecaline – and acknowledges major challenges in clinical trials (placebo, comparator, expectancy and unblinding, dosing, maintenance of effect, safety and psychotherapy).[69] It is recommended to seek scientific advice prior to conducting clinical trials, due to complexity and safety of psychotropics (concerning side effects).[69]

In March 2023, EMA Executive Director Emer Cooke wrote a letter in which she confirmed that the EMA wants to focus on promoting the development of psychedelics for unmet medical needs, especially for mental health conditions, as the risk profile seems to be low.[70] In Europe, the research on psychotropics is still very restricted, in comparison to Canada, the US, and Australia. As of July 2023, Australia allows the prescription of psilocybin and MDMA (ecstasy) as medicine.[10]

The public view on psychotropics

According to Wikipedia, some countries in Europe have legalised medicinal and scientific cannabis use while recreational use is only tolerated.[71] For example, in Germany, according to a draft document published in September, possession of 25 grams of cannabis and cultivating up to three plants for individual purposes are allowed.[72,73]

Recreational use is very restricted in Netherlands; it is tolerated only in licensed coffeeshops.[74] They can only sell small quantity of cannabis (less than five grams and no more than five plants) to residents of Netherlands.[75] Legalised medicinal use of cannabis is a very different story: it is allowed in most of the EU countries (with slight differences in regulatory requirements), UK, and other countries.[71]

Travelling with psychotropics may be challenging but still possible, depending on the country's requirements. Most of the restrictions are published on the International Narcotics Control Board website[76] with a disclaimer that it is advised to contact the embassy or consulate of the corresponding country before travelling.[77] Magic mushrooms are generally considered illegal for cultivation, sale, transport, and possession, except in a few countries (such as Netherlands and Austria).

Many health associations have published their position statements on cannabis, and they vary. The American Psychiatric Association doesn't see any benefit in treating psychiatric disorders with cannabis, and it opposes the use of cannabis in children, adolescents, and young adults up to the age of 25.[78] The American Nurses Society regards cannabis beneficial only for patients who really need it and if the treatment has been proved to be effective.[79] The UK's National Health Service published a guidance for prescribing cannabis-derived products; it does not recommend medicinal use for chronic pain unless for clinical trial purposes.[80] Globally, traditional medicine is getting more recognition; the WHO is striving to incorporate traditional medicine into conventional healthcare and deliver more evidence-based data. The topic was discussed in August 2023, in India, at the First WHO Traditional Medicine Global Summit.[81]

What does the future hold for psychotropics?

Psychotropic drugs have shown promising results in treating symptoms of mental health disorders and pain management, and their potential to improve patients' wellbeing should not be neglected. However, as Spiderman said, "with great power comes great responsibility". The main challenges in using psychotropics as therapy are managing their side effects,[82] carefully considering the patient population, and regulating the environment in which they are used (hospital, doctor's office, etc.). Patient safety is the highest priority and can be ensured by establishing regulatory guidances, risk mitigations, and worldwide regulations to prevent drug abuse that occurred during the 1960s. The US Centers for Disease Control and Prevention reported that cannabis-induced disorder is most common in people who use cannabis during youth or adolescencxe and use it frequently.[83,84] With so much contradictory scientific data, regulatory agencies (especially in Europe) are delaying in publishing mandatory guidances on conducting research with psychoactive substances and their marketing authorisation. According to the US FDA Director of Psychiatry Tiffany Farchione, psilocybin is still an investigational product.[10] Nevertheless, the regulatory agencies acknowledge the unmet medical needs and are working towards finding solutions for it.

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The opinions expressed in this article are the author's own and not necessarily shared by her employer or EMWA.

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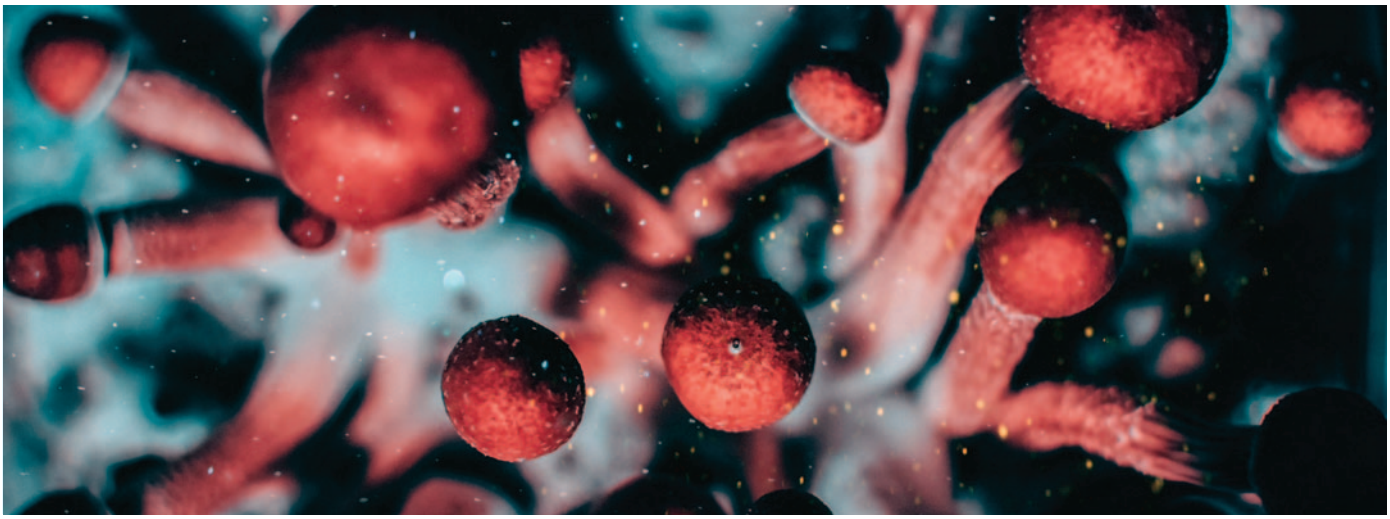

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