GAVIN POTENZA

DRUG DEVELOPMENT

The treasure chest

Pharmaceutical research into the chemicals found in cannabis has so far supplied only one licensed medicine. But scientists think there could be hundreds more.

BY BRIAN OWENS

The annual meeting of the International Cannabinoid Research Society (ICRS) is a highly unusual scientific conference. It has been closed to all media since its inception 25 years ago, lending an air of mystery to the gathering of researchers who study the unique chemicals found in cannabis.

In a relaxation of the organization's long-standing policy, ICRS permitted *Nature* reporters to attend this year's conference, which was hosted by Acadia University in the tiny Canadian town of Wolfville, Nova Scotia. The tight-knit group of researchers are bound together by onerous government restrictions on their subject, and by their sufferance of lingering suspicions from other scientists that they are a bunch of hippies trying to get an illicit drug legalized.

"The status of cannabis as an illegal substance makes it difficult for some people to take it seriously," concedes Mark Ware, a pain specialist at McGill University in Montreal, Canada, who focuses on the analgesic properties of cannabis.

But cannabis researchers are working hard to shed that image. On the whole they are not interested in the effects of smoking the plant. Their domain is the pharmacological study of the hundreds of chemical compounds in cannabis to determine how they could be developed into licensed pharmaceutical drugs to treat dozens of different conditions — while avoiding or minimizing the psychoactive effects. And they are slowly beginning to move these compounds from the laboratory to the clinic. "Stripped right down to the pure pharmacology, it's easy to make the case for cannabis as a medicine," says Ware.

TWO GREEN PATHS

Phytocannabinoids — a collection of more than 100 related chemical compounds found in cannabis — are the subject of most interest. The primary, but not the only, targets for these compounds are the body's endocannabinoid receptors CB_1 and CB_2 (see 'A personable system'). Hence researchers have two avenues by which they can exploit the medicinal effects of cannabinoids. One strategy is to target the endocannabinoid receptors directly, by designing drugs that will activate or suppress them. The other is to harness the effects of the phytocannabinoids and turn these compounds into drugs.

The first approach has already resulted in one high-profile failure. In 2006, the European Medicines Agency approved a small-molecule anti-obesity drug called rimonabant (Acomplia) that suppressed appetite by blocking the CB_1 receptor. But, just two years later, it was withdrawn over safety concerns: people taking rimonabant had double the risk of developing

➲ NATURE.COM
For more on the endocannabinoid system see:
go.nature.com/tudro5

psychiatric disorders, including depression and suicidal thoughts.

Despite this high-profile flop, Ware remains optimistic about targeting the cannabinoid receptors. "It continues to be a valid approach," he says. "But it will be a number of years before we'll see any new drugs emerge."

The second approach — deriving drugs from the plant's phytocannabinoids — offers a plethora of possibilities. Although researchers have identified more than 100 compounds, for decades pharmaceutical research started and ended with cannabis's main psychoactive chemical tetrahydrocannabinol (THC; see page S2). There were a few studies into cannabidiol (CBD) as a treatment for epilepsy in the 1980s — led by chemist Raphael Mechoulam at The Hebrew University of Jerusalem who first discovered THC in the 1960s[1] (see page S12). But with the focus on THC and the widespread illegality of cannabis, this research was overlooked. It is only in the past few years that interest in CBD, as well as in other cannabinoids such as cannabigerol, cannabichromene and a THC variant called tetrahydrocannabivarin (THCV), has bloomed. "We've just scratched the surface," says Jahan Marcu, director of research and development at the California-based company Green Standard Diagnostics, which helps labs purify and test cannabinoids. "There is lots of potential to explore other compounds that have great therapeutic indications."

"It will be a number of years before we see any new drugs emerge"

MARK J. WINTER/SPL

REVERSE DRUG DISCOVERY

Much of the research on the therapeutic benefits of cannabinoids started with anecdotal reports from people smoking cannabis to self-medicate for a range of ailments. Patients' experiences were captured and used to inform pharmaceutical drug development. This method, which Ware calls "reverse drug discovery", harks back to the way in which some of the most important drugs were found. The seventeenth-century observation that indigenous people in South America used the bark of the cinchona plant to treat malaria, for example, led to the discovery of quinine and the development of the first antimalarial drugs.

The approach has already led to the creation of synthetic phytocannabinoids. Dronabinol, for example, is a synthetic version of THC that is used to treat appetite loss in people with AIDS, and to relieve nausea associated with chemotherapy. Similarly, nabilone is used for nausea in patients undergoing chemotherapy.

So far, however, there is only one medication based on natural phytocannabinoids: a mouth spray called Sativex (nabiximols), made by GW Pharmaceuticals, based in London, which is approved in 27 countries to treat spasticity associated with multiple sclerosis. Nabiximols is a whole-plant extract refined to contain about equal levels of THC and CBD. "Both THC and CBD have different pharmacologies that are complementary, in efficacy and safety," says Stephen Wright, chief medical officer at GW Pharmaceuticals.

The company's drugs are made from plants bred to have specific concentrations of the desired phytocannabinoids, says Wright. Cuttings are then taken from a mother plant to ensure each generation retains the same characteristics. "Once we have bred the plants that meet our needs," he says, "we can control the chemical phenotype by fixing the genotype." Such consistency is essential if a company is to derive a pharmaceutical product that meets tough regulatory standards.

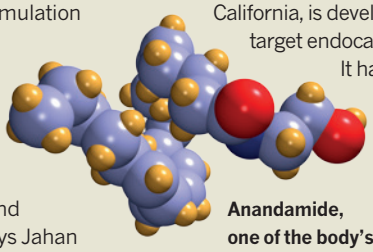
In addition to seeking approval for further uses of nabiximols — the drug is currently in phase III trials for cancer pain — GW is also exploring other cannabinoid agents. A CBD-based drug called Epidiolex (cannabidiol) is in phase III trials for two rare forms of epilepsy. And several other drugs are in phase II trials: THC and CBD to treat glioma brain cancer, THCV for type 2 diabetes and CBD for schizophrenia.

The results reported at the ICRS meeting reveal a vast array of further opportunities that are much earlier in the drug-development pipeline. Researchers presented data on the potential of phytocannabinoids to treat

A PERSONABLE SYSTEM

Endocannabinoids are everywhere

The body's endocannabinoid system is the pathway by which tetrahydrocannabinol (THC) exerts its psychoactive effects, and is the target for many of the plant's other cannabinoids. It is intrinsic to a number of different processes, including appetite, memory, alertness, pain, inflammation and bone health, and stimulation of the endocannabinoid system is associated with the protection of healthy cells. "The endocannabinoid system helps us eat, sleep, relax, forget and protect our neurons," says Jahan Marcu, director of research and development at California-based Green Standard Diagnostics.



Anandamide, one of the body's cannabinoids

Endocannabinoid receptors are spread throughout the body, and are believed to be more numerous than those of any other receptor system. Indeed, the fact that the endocannabinoid system is so widespread, and plays a part in so many different brain functions, could explain why the compounds found in cannabis seem to have no end of medical uses. Researchers have identified two main receptors so far: CB_1 and CB_2. CB_1 is found predominantly in the nervous system, but also in connective tissues, gonads, glands and organs; CB_2 is mainly found in the immune system.

The endocannabinoid receptors did not evolve just so that people could enjoy the effects of cannabis. The body produces its own cannabinoids: endocannabinoids, which are neuromodulators, meaning that instead of affecting just one neuron across a synapse, they diffuse throughout the nervous system and affect multiple neurons (dopamine is another example of a neuromodulator). The two best understood endocannabinoids are anandamide, found primarily in the brain, and 2-arachidonoyl glycerol (2-AG), found mainly in the rest of the body.

Abide Therapeutics, based in San Diego, California, is developing treatments that target endocannabinoid levels directly. It has developed a drug that increases natural levels of 2-AG in the brain by inhibiting monoacylglycerol lipase, a protein that breaks it down. Abide began enrolling participants in a phase I safety study in Belgium in July 2015.

The drug could potentially be used to treat neuropathic pain, neuroinflammation and even neurodegenerative diseases such as Alzheimer's. "Modulating endocannabinoids in neurological diseases has real breakthrough potential," says Abide president Alan Ezekowitz.

Raphael Mechoulam, a chemist at The Hebrew University of Jerusalem and the researcher who first identified THC, suspects that the endocannabinoid system is more than just a set of receptors. With crucial roles in processes such as memory, emotional response, learning and so on — he speculates that endocannabinoids are key to shaping people's personalities[6]. "The body makes more than 150 endocannabinoid-like compounds — but why?" he says. "Is this one of the reasons individuals are different? Perhaps the different ratios of these compounds is part of what causes differences in personalities." **B. O.**

GW PHARMACEUTICALS

At GW Pharmaceuticals' growing facility, cannabis clones are grown to ensure chemical consistency.

conditions such as acute and chronic pain, kidney disorders, Alzheimer's disease, opioid and nicotine dependence and post-traumatic stress disorder. "Cannabis is a bit like a treasure chest of compounds," says Roger Pertwee, a pharmacologist at the University of Aberdeen, UK, who has been studying cannabinoids since the late 1960s.

"Stripped down to the pure pharmacology, it's easy to make the case for cannabis as a medicine."

And it is not just cannabinoids in the chest. Cannabis also contains another class of compounds known as terpenes, which give the plant its characteristic smell (they are also found in cannabis's close relative, hops). Some terpenes have been found to have anti-inflammatory, antibacterial, anti-anxiety or analgesic properties, says Ware. Various combinations of cannabinoids and terpenes could provide diverse therapeutic results, perhaps accounting for why people claim to experience different symptomatic relief from smoking certain strains (see page S4). "Whether [those effects] are therapeutically meaningful is unknown," Ware says.

Such combined interaction has been reported in the endocannabinoid system, as the 'entourage effect'. The body releases other chemicals at the same time as endocannabinoids, creating a stronger effect than that achieved with endocannabinoids alone. Many researchers think there is an equivalent entourage effect for phytocannabinoids. Pertwee gives THC and CBD as an example. THC acts through the CB_1 receptor as a painkiller, calming overexcited neurons, whereas CBD provides anti-inflammatory effects through other routes. He also suggests that terpenes might modify the effects of phytocannabinoids. Ethan Russo, medical director of Phytecs, Los Angeles, California, is studying this phenomenon. Russo's team is looking into whether combinations of complementary cannabinoids and other compounds, including terpenes, might work better than a single purified chemical[2].

There is still a long way to go before most of the prospective cannabis-based drugs make it into the medicine cabinet. The work presented at the ICRS meeting was almost entirely in animal models, with only a handful of clinical trials underway. "There have been lots of preclinical discoveries," says Pertwee. "Now we have to see whether they are hype or genuinely good ideas."

PRECISION MEDICINE

One of the big concerns about developing drugs from phytocannabinoids is whether it is possible to isolate the desired effects. THC, for example, is a potent painkiller, but comes with unwanted psychoactive side effects such as difficulty with recall. Peter McCormick, a pharmacologist at the University of East Anglia in Norwich, UK, may have found a way around that. He and his colleagues found that in mice that lacked a particular serotonin receptor THC still had painkilling effects, but did not impair memory.

THC targets the CB_1 receptor. And it turns out that the receptor missing in McCormick's mice, 5-HT_{2A}, also interacts with CB_1. When the team used a small peptide molecule to impede the 5-HT_{2A} and CB_1 interaction in normal mice, the same effect was seen[3]. He suggests that this could be a way to target the effects of cannabinoids more precisely. "It seems we can separate out the 'good' from the 'bad' effects of THC."

But even non-psychoactive phytocannabinoids that target CB_1 or CB_2 receptors can have unwanted side effects. "The endocannabinoid system is so ubiquitous, you can't target just one physiological process," says Ware. "It's hard to come up with clean drugs."

So researchers are looking for a way to modulate the effect of drugs that target this system. Endocannabinoid receptors have two binding sites: the main pocket and a secondary one — known as an allosteric site. A molecule that binds to an allosteric site changes the shape of the main receptor — altering the intensity of the effect of any molecule bound there[4]. Allosteric compounds, whether found in the body, in cannabis or elsewhere, could be used to fine-tune the effects of phytocannabinoid drugs, reducing unwanted side effects. Pertwee says that researchers have managed to identify a few allosteric endocannabinoids, but it is not known whether cannabis itself contains any. "We're now screening hundreds of compounds looking for good allosteric modulators," says Pertwee.

The other challenges facing cannabinoid research, however, are less tractable. Government restrictions on cannabis keep the field small, and make it difficult to get high-quality research materials, says Marcu. GW, for example, is the only reliable source of cannabigerol (which has shown promise as an antidepressant[5]), creating a bottleneck for research, he says.

And, despite the fact that researchers are working with purified phytocannabinoids, most of which have no psychoactive effects, they are still subject to the same restrictive regulations. This makes sending even small amounts of phytocannabinoids between labs in the United States all but impossible, says Marcu. And it means only a few pharmaceutical companies are willing to take the work forward into clinical trials.

Research is becoming easier as cannabis-based drugs, many of which contain no THC, become more accepted in mainstream medicine. But progress is still not fast enough for Mechoulam. "We knew 30 years ago that CBD lowered seizures for epilepsy, and it's the only thing that helps some kids," he says. Now 84, he has little patience left for the legal obstacles. "It's ridiculous," he says. "We're talking about the health of children here." ■

Brian Owens *is a freelance science writer based in St. Stephen, New Brunswick.*

1. Gaoni, Y. & Mechoulam, R. *J. Am. Chem. Soc.* **86,** 1646–1647 (1964).
2. Russo, E. *Br. J. Pharmacol.* **163,** 1344–1364 (2011).
3. Viñals, X. *et al. PLoS Biol.* **13,** e1002194 (2015).
4. Price, M. R. *et al. Mol. Pharmacol.* **68,** 1484–1495 (2005).
5. Musty, R. E. & Deyo, R. A. *Proc. Symp. Int. Cannabinoid Res. Soc.* 32 (ICRS, 2006).
6. Mechoulam, R. & Parker, L. A. *Annu. Rev. Psychol.* **64,** 21–47 (2013).