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BRUNCH

# PLANT PHARMA

Researchers in Singapore are looking to turn the therapeutic compounds in cannabinoids into legitimate medicine

**BY MARISSA LEE**

YEW Wen Shan, a 44-year-old enzymologist at the National University of Singapore, has been working on ways to extract the medicine out of marijuana. And Singapore's National Research Foundation (NRF) has thrown its weight behind the project, a move that at first glance might seem startling - given the country's zero-tolerance drug laws - but is in fact quite astute. Associate Professor Yew's research in the field will seed the ground for synthetic drugs that offer the therapeutic effects of cannabis, without their mind-altering impact and minus the illegalities. He and his team of scientists here are looking for novel ways to biosynthesise cannabinoids – the chemical compounds found in the cannabis plant – without the need to grow the cannabis plant. >>>

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**With the global market in medical marijuana** growing to new highs, research in this direction certainly looks both medically and economically viable. Worldwide spending on medical marijuana will hit US$19.1 billion by 2027, according to a report from Arcview Market Research this month.

North America will lead the way. Marijuana is legal for medical purposes in Canada, and in 29 states in America. As of Jan 1, 2018, Denmark has also allowed the use of medical cannabis for patients suffering from certain illnesses, joining Austria, the Czech Republic, Finland, Germany, Italy, Portugal, Poland and Spain as European Union members that now authorise the use of marijuana as a medicine.

Announced in January, Singapore's cannabinoid programme is one part of a broader S$25 million investment meant to deepen the country's capabilities in synthetic biology. Over five years, the NRF will invest S$25 million in a Synthetic Biology Research and Development Programme.

"Research into cannabinoids is a niche area that Singapore can compete globally in," the NRF says. Work here will also target diseases that are relevant to Singapore, such as neurodegenerative diseases (for example, Parkinson's disease), cancer and diabetes. Cannabis-based medicines are known to be effective treatment for a wide range of illnesses, from multiple sclerosis to HIV, and can also fight chronic pain as well as the side effects of chemotherapy.

As Prof Yew tells *The Business Times*: "What we are concerned about is, ultimately, to be able to get some of these cannabinoids out into the therapeutic area."

## What makes it medicine

More than 100 different cannabinoids are found in resin produced by the leaves and buds of the cannabis plant, of which two are well known.

The first is delta-9-tetrahydrocannabinol, or THC, which gives marijuana its mind-altering effect. Prof Yew says that THC is not of interest to researchers here.

What is of interest to them is cannabidiol, or CBD. Unlike THC, CBD does not give users a mental high. CBD has risen in importance in medicine as more people are learning about its usefulness as a less-toxic alternative to older drugs for treating a range of diseases and disorders.

For instance, CBD can modulate chemical and electrical activity in the brain to reduce seizures.

In the US, a civil movement has sprung up around getting medical marijuana to children who suffer from epilepsy. A high-CBD, low-THC strain of marijuana known as Charlotte's Web has been bred in Colorado for this purpose.

And in October last year, London-based GW Pharmaceuticals submitted Epidiolex, a CBD-based epilepsy drug to the US Food and Drug Administration (FDA) for approval.

Three other synthetic cannabinoid drugs already have the FDA's green light to treat chemotherapy-induced nausea and vomiting.

These include Marinol from AbbVie and Syndros from Insys Therapeutics, which both use dronabinol, a synthetic form of THC. Cesamet, from Valeant Pharmaceuticals, contains a synthetic cannabinoid similar in structure to THC.

All three are sold, however, with a litany of warnings on possible side effects – from dizziness to mental disorientation and a caution against dependency.

Prof Yew says: "CBD is already in clinical trials for certain diseases (overseas). Because of the acceptance of cannabinoids having therapeutic use, the research can go on at a faster rate.

"There's always two sides to a story. Cannabis, if abused, can be very detrimental to human health, but if used appropriately, it could be very beneficial. This is the same with all drugs concerned."

What remains to be proven is whether CBD, and other medical cannabinoids, would be a more efficient substitute to the drugs being used now.

As Prof Yew frames it: "Can doctors use it at a lower concentration, a lower dose, while getting the same results – so you don't have tolerance, resistance or toxicity?"

## Synthetic biology

It must be noted that the NRF's decision to fund work in marijuana research does not mark a softening of Singapore's stance on drugs.

The NRF, a department within the Prime Minister's Office, told BT: "We continue to take a firm stance against drug abuse. The Synthetic Cannabinoid Biology Programme does not study the psychoactive compounds of the cannabis plant.

"Instead, the programme will identify cannabinoid genes for the sustainable production of medicinal cannabinoids. We do not need the cannabis plant for the research, and our aim to produce cannabinoids through synthetic biology means we do not have to grow the plant to reap the benefits of medicinal cannabinoids."

In Singapore, CBD is not a controlled substance because it's not psychoactive.

Prof Yew's work, which began last year, involves discovering new pathways to synthesise CBD and other lesser-known cannbinoids in high quantities and in pure form.

By placing the right enzymes in microbes like yeast, he can induce yeast to make cannabinoids.

Meanwhile, fellow scientists are working on a parallel project to establish proprietary national strains of yeast and bacteria for commercialisation.

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(Prof Yew also leads a team rewiring probiotics – such as lactobacillus found in probiotic drinks – to produce substances that bring about caloric restriction without the adverse effects associated with dieting, with the ultimate goal of extending lifespan).

Combining the new pathways with proprietary national strains will create cannabinoids that suit the needs of pharmaceutical companies, since they require compounds to be free of any intellectual property burden in order to be commercially viable.

"In a couple of years we should be able to synthesise therapeutically-useful cannabinoids using proprietary national strains of yeast and bacteria," Prof Yew says.

The private sector is already taking an interest in Singapore's synthetic cannabinoid programme. Multinational firms in the field of drug research have started contacting the NRF to seek out collaborative ventures.

## Green rush

Worldwide spending on legal marijuana is expected to hit US$57 billion by 2027, with recreational spending to account for US$38.3 billion, and medical spending US$19.1 billion, according to the Arcview Market Research report.

The US and Canada spent US$9.2 billion on legal pot last year, and this is projected to reach US$47.3 billion by 2027, at a compound annual growth rate of 18 per cent.

Pot is poised to go mainstream in Canada, where recreational weed could be legalised and sold in stores by 2019. Canada legalised medical marijuana in 2001, and more than 80 companies tied to pot currently trade on its exchanges.

Canopy Growth Corp, the world's largest pub-

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licly traded medical marijuana producer, rings in quarterly sales of C$21.7 million (S$21.8 million) and has a market cap of C$6.6 billion. It recently sold a minority stake to US-based Constellation Brands, which distributes Corona beer and now wants to develop drinkable cannabis products.

Beyond marijuana, physicians are now pushing into the outer reaches of psychedelic drugs, marking a return to research that began in the 1950s and ended in the 1970s when psychedelic drugs were declared a controlled substance in the US, making them illegal.

Small trials over the last two years have shown that psilocybin, a hallucinogenic compound found in magic mushrooms, can lift people out of severe depression if taken under the right conditions. A start-up backed by tech mogul Peter Thiel plans to commence the largest international study of psilocybin this year. The trial for treatment-resistant depression will involve 400 patients across Europe and potentially, the US.

In Silicon Valley, people are finding that taking microdoses of lysergic acid diethylamide, or LSD, with their breakfast boosts their mood, creativity and productivity. LSD's long-term effects remain unclear, but microdosing at a fraction of what recreational drug users consume doesn't cause one to hear colours or see sounds, say users. To map out future directions for clinical studies, psychologist James Fadiman and his team have gathered data from over 1,500 microdosers.

While psychedelics remain outlawed in Singapore and most other places on earth, scientists as well as government bodies are slowly shrugging off decades of taboo to pursue and support research into the use of controlled drugs as prescribed medication.

The cannabis corral, meanwhile, draws all sorts.

Last year, Oxford University joined up with private equity firm Kingsley Capital Partners to set up Oxford Cannabinoid Technologies (OCT), a biotech firm that aims to create new therapies for cancer and inflammatory diseases.

Kingsley, which has also invested in a halal meat business, will pump £10 million (S$18.6 million) into cannabinoid research.

"People were surprised, but nobody said: 'What are you doing?' No one said that at any stage last year," managing partner Neil Mahapatra tells BT by phone.

He first delved into medical marijuana literature during his mother's battle with cancer.

"That's when you start to read. I read most of the papers to see what the potential was, but there wasn't enough. It's not been researched enough," he adds.

"I've met a few of these people, who say their tumours have shrunk after they consumed cannabis oil, but that's the problem – they're all anecdotes.

"Nobody really knows how these cannabinoids and other molecules in the cannabis plant like terpenes (the chemicals that give pot its signature scent) interact with each other."

Mr Mahapatra read biology at Oxford before going into finance, and decided to start OCT after getting his former biology professor on board. OCT is preparing for clinical trials in the next two years.

"Because of legality issues cannabis wasn't being explored as a source for drugs. (But) plants have always been a significant source of medicine," Mr Mahapatra reasons.

"The fact that Singapore is doing this is great news. This is nothing but good."

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Syndros, Cesamet and Marinol cannabinoid medication – these three synthetic cannabinoid drugs already have the US FDA's green light to treat chemotherapy-induced nausea and vomiting.



Charlotte's Web, a low-THC, high-CBD strain of cannabis, has been bred specifically for medical use by children suffering from epilepsy.
PHOTO: CNN

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