



## EFFICACY

# Unpicking the entourage effect

*The idea that compounds in cannabis act in synergy to magnify the drug's effects is intriguing but lacks solid evidence.*

BY TAMMY WORTH

Jenny Wiley was a consultant for the World Health Organization in 2018 when it conducted a major review of cannabis<sup>1</sup>. The committee considered input from various groups of people, including some that were touting the importance of the entourage effect — a purported synergy between the cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD), as well as other molecules found in the plant, known as terpenoids.

Such groups think that certain combinations of cannabis compounds can boost the potential medical benefits of THC, such as easing pain and inflammation, while lessening unwanted side effects such as memory impairment. But the evidence that the groups provided to support the claims were mostly anecdotal reports and communications from patients.

“There really isn't the science out there

to support it,” says Wiley, a behavioural pharmacologist at RTI International, an independent, non-profit research institute in Research Triangle Park, North Carolina. Given that the cannabis plant is known to contain more than 400 types of molecule, including 100 cannabinoids and a range of terpenoids, in various quantities, the concept is challenging to test scientifically. “It is a very complicated idea and, in some ways, may be unprovable,” she says.

## ENTOURAGE ORIGINS

The entourage effect was first proposed in 1998 by Raphael Mechoulam, a chemist at the Hebrew University of Jerusalem. Mechoulam and his colleagues were studying the molecule 2-arachidonoylglycerol (2-AG), which binds to the cannabinoid receptors CB<sub>1</sub> and CB<sub>2</sub>. They showed that, in the spleen, brain and gut of mice, 2-AG is typically found together with two other compounds: 2-linoleoylglycerol

and 2-palmitoylglycerol<sup>2</sup>. Although unable to bind to CB<sub>1</sub> and CB<sub>2</sub> themselves, the two molecules improved the ability of 2-AG to bind to the receptors and increased effects such as analgesia in the animals.

It's not a big leap to think that this concept could be extended to the chemicals in cannabis, says Ethan Russo, a neurologist and director of research and development at the International Cannabis and Cannabinoids Institute in Prague. For example, certain compounds could enhance and heighten the therapeutic effects of THC, the psychoactive component of cannabis. When Mechoulam's paper was published, Russo realized that the findings could lend support to his idea that THC wasn't the only pharmacological component of cannabis. For decades, he had been hearing anecdotes about strains of cannabis that affected people in different ways — one might be good for pain relief whereas another could improve sleep. Russo proposed that there were compounds other than THC in cannabis that could account for the differences. After learning about terpenoids, which include compounds known as essential oils that can be extracted from plants such as lavender and peppermint and are purported to have healing properties, he suggested that the compounds might be able to enhance the effects of THC.

Russo also contends that CBD might work to enhance THC's therapeutic effects. As evidence, he points to a 2010 clinical trial of Sativex (nabiximols), a botanical drug that comprises a mixture of THC and CBD extracted from cannabis. Developed by



GW Pharmaceuticals in Histon, UK, Sativex is used to treat neuropathic pain in people with multiple sclerosis. (Russo served as senior medical adviser to GW Pharmaceuticals in 2003–14.)

The study<sup>3</sup> involved 177 people experiencing pain from cancer and compared three approaches: one group of participants received a placebo, another was given a drug containing high levels of THC and a third group was treated with Sativex. Participants were asked to score their pain throughout the two-week study and to confirm at the end by how much their pain had lessened, if at all. A reduction in pain of 30% or more was considered clinically important. Around 40% of the people treated with Sativex reported this level of pain relief — almost twice as many as those who received either placebo or THC alone.

Mark Connor, a pharmacologist at Macquarie University in Sydney, Australia, says that the Sativex trial does not prove the existence of the entourage effect. However, it might be the first step in showing that drugs comprising variable ratios of natural products such as cannabinoids — as opposed to single compounds, which is the norm among pharmaceuticals — can yield benefits.

Other research that Russo cites in support of the entourage effect is a 2018 meta-analysis that studied 670 people with treatment-resistant epilepsy, who received either purified CBD or CBD-rich cannabis extracts<sup>4</sup>. Seventy-one per cent of those taking the extracts reported an improvement in the frequency of seizures, compared with 46% of people who were given purified CBD. However, there was no difference in the proportion of either group who saw at least a 50% reduction in the frequency of their seizures.

“We’ve got some proof at this point,” Russo says, although he concedes that it might not be enough to “satisfy the masses”.

## TEMPERING AND ENHANCING

Russo has collated evidence to suggest that terpenoids have the potential to reduce the psychosis and memory problems that THC can produce<sup>5</sup>. And such compounds might also augment THC’s more positive properties. Studies suggest that myrcene can improve sleep in people with chronic pain<sup>6</sup>, and that limonene might help to alleviate anxiety<sup>7</sup>. When used in concert, terpenoids, THC and CBD therefore provide an opportunity to fine-tune medications more effectively to fit the individual needs of patients, he says.

Some terpenoids have been shown to have antioxidative and analgesic properties<sup>8</sup>, says Adie Wilson-Poe, a neuroscientist at the Legacy Research Institute in Portland, Oregon, and chief executive of Smart Cannabis, a cannabis company also in Portland. But she concedes that there has been no research on finding appropriate combinations of molecules for various symptoms.

“When I hear ‘the entourage effect’, I think of

it as THC acting as a conductor of an orchestra,” she says. “Most of the therapeutic value is probably derived from THC, but the overall orchestra experience is really valuable.”

## SCIENTIFIC SCEPTICS

Wiley is sceptical about whether Mechoulam’s work in mice translates to plants.

Mechoulam realized that the molecules he was studying in the brain and gut had an important role — to help regulate the body’s cannabinoid system. But plants are not producing terpenoids to make cannabis a more effective medicine — they serve other purposes, including deterring predators. “It’s an idea, or theory, that has been co-opted from what it was never meant to cover,” Wiley says.

Connor also finds little evidence to support the entourage effect. The small number of studies conducted so far haven’t been able to determine the concentrations of terpenoids that reach the brain when someone consumes cannabis, he says. Essentially, no one knows how much reaches its target or how terpenoids might work when they do get there. “There could be something there,” Connor says, “but we are always looking for what the molecular basis might be — and at this point we can’t say.”

To gain a better understanding of how cannabis works in the body, Connor investigated how six common terpenoids interacted with THC in cells. In a March preprint, he found no evidence that the compounds could activate CB<sub>1</sub> and CB<sub>2</sub> or modify THC-induced signalling<sup>9</sup>. He is quick to note, however, that his results don’t rule out the possibility that terpenoids and THC interact in other ways. For instance, terpenoids could interact with proteins other than cannabinoid receptors, which his experiment didn’t address. This is the case for opioid drugs, as Connor explains: “When I started working, we thought there was one receptor,” he says. “Now we know there is potential for drug-binding sites at other places.”

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## THE ENTOURAGE PROMISE

Proponents and doubters agree that further research, including double-blind clinical trials, is needed to confirm whether the entourage effect exists and, if so, to understand how it works. “That way, you are taking out bias and expectation,” Wilson-Poe says.

Wiley agrees. “We have to have specified quantities and look at interactions one by one,” she says. But she worries that such work will not stop the attention being given to anecdotal claims of interactions. At the moment, many upholders of the entourage effect are people who smoke or ingest cannabis — they notice that different strains produce varied effects and take that as evidence that the entourage



Trichomes on leaves and buds produce the cannabis plant’s active compounds.

effect is real. The debate is becoming a “contest between the scientific method and anecdotal and personal experience”, Wiley says, and she is concerned that the effect will be used as a marketing tool — a reason for people to keep trying new strains of cannabis until one works for them.

Connor and Wilson-Poe think that cannabis will keep its place in the market as a natural option for easing pain, inflammation and sleep until researchers can demonstrate or disprove its therapeutic value. And the active components of cannabis might work together to produce beneficial effects in ways that are tricky to pinpoint using current methods.

Russo agrees, but hopes that the entourage effect will increase the pharmaceutical value of cannabis. Treatments for cancer commonly involve cocktails of drugs that are designed to tackle several aspects of the disease. Combinations of terpenoids, THC and CBD might similarly be tailored to symptoms such as spasticity, pain or anxiety. “For complex conditions, you need to do multiple things at once,” he says. “That can come from different drugs or one properly designed botanical.” ■

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