

Pain relief without the high

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Researchers at Leiden University led by Mario van der Stelt (Leiden Institute for Chemistry) have set 'gold standards' for developing new painkillers based on the medicinal effects of cannabis. Publication in *Nature Communications*.

Medicinal marihuana

Medicinal marihuana is in frequent use as a painkiller, but its psycho-active side-effects are a major disadvantage. The pharmaceutical industry is desperately seeking a synthetic form of cannabis that inhibits inflammation and pain, but without the high. Leiden researchers have now brought the development of such drugs a step closer. In an article in *Nature Communications* they set out 'gold standards' for the use of reference substances, to improve trials with synthetic cannabis.

Many of the clinical trials carried out to date with with synthetic cannabis have failed, with no measurable effect being recorded in patients. One of the causes of these failures can be found in the pre-clinical lab, during testing with animals. Substances are often used in these tests whose biochemical and molecular-pharmaceutical effects have never been properly characterised. As a result, there have been a lot of contradictory publications on research findings, the results of which cannot be reproduced. This is having a major effect on the allocation of research funding, the use of animal testing and the exposure of patients to non-active substances.

International and public-private collaboration

Marjolein Soethoudt, a PhD candidate in Van der Stelt's research group, studied together with 12 international academic groups, the National Institute of Health (US) and pharmaceuticals concern Hoffman-LaRoche (Switzerland), the 18 most commonly used reference substances, including the psychoactive ingredient in marijuana, Δ 9-THC. They carried out their studies under standardised conditions in 36 different tests, to analyse the molecular pharmacological characteristics of the substances. They hoped to be able to identify the most suitable reference substances for the research on [synthetic cannabis](#). The research led to three 'gold standards' that should make it possible to give an impetus to the development of new painkillers and anti-inflammatories.

Cannabinoid CB2 receptor

Δ 9-THC binds to two types of proteins in the human body: the cannabinoid CB1 receptor in the brain and the cannabinoid CB2 receptor in the immune system. Activating the CB1 receptor in the brain makes you high, while activating the CB2 receptor has an anti-inflammatory effect. The three 'gold standards' are molecules that are highly selective in activating only the CB2 receptor and ignoring the CB1 receptor. These three gold standards also appeared to cause the fewest side-effects, nor did they give the mice a high. Earlier studies have shown that these [substances](#) do have an analgesic and anti-inflammatory effect. The researchers advise that these three gold standards should be used in future in research on new medicines that rely on the activation of the cannabinoid CB2 receptor for their effectiveness.

The research has been published in *Nature Communications* and has been funded in part by an ECHO-STIP subsidy from NWO Chemical Sciences.

More information: Marjolein Soethoudt et al. Cannabinoid CB2

receptor ligand profiling reveals biased signalling and off-target activity, *Nature Communications* (2017). [DOI: 10.1038/ncomms13958](https://doi.org/10.1038/ncomms13958)

Provided by Leiden University

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