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ARTICLE

The science of cannabis

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Abstract

For reasons we are all too familiar with, cannabis has taken the spot as one of the least researched plants in peer-reviewed literature. The gap in peer-reviewed research is currently being addressed as new legislations favours growing of cannabis and encourages scientists to submit proposals for research to public funding bodies. Many questions are currently being addressed, including, but not limited to: Can cannabinoids cure cancer and other non-communicable diseases? How effective are cannabinoids in pain treatment? Is cannabis an untapped resource for mental health? How important is cannabis fibre and oil as a source for sustainable materials and commodities? The list of questions is endless, owing to the huge gap between historical and anecdotal as well as circumstantial evidence on the one side, and laboratory, field-based and clinical research (or lack thereof) on the other. In this article we address some of these questions and narrow down to the main scientific channels through which cannabis performs its most effect actions.

Key words: Cannabis; Science

Cannabis and mainstream science

I know that I know nothing

—Plato

For reasons we are all too familiar with, cannabis has taken the spot as the least researched crop plant in peer-reviewed literature. This doesn't mean that there is no scientific literature available on cannabis, on the contrary, much has been written in monographs and books (Kalant *et al.*, 1999; Grotenhermen and Russo, 2002; Iversen, 2009; WHO, 2018). The gap in peer-reviewed research is currently being addressed as new legislations favours growing of cannabis and encourages scientists to submit proposals for research to public funding bodies. Many questions are currently being addressed, including, but not limited to: Can cannabinoids cure cancer and other non-communicable diseases? How effective are cannabinoids in pain treatment? Is cannabis an untapped resource for mental health? How important is cannabis fibre and oil as a source for sustainable materials and commodities? The list of questions is endless, owing to the huge gap between historical and anecdotal as well as circumstantial evidence on the one side, and laboratory, field-based and clinical research (or lack thereof) on the other. In an ideal world, one side would be able to back up the other, such as in traditional Chinese medicine, to name but one example of a widely recognised knowledge system.

Notwithstanding the many millennia in which cannabis has accompanied mankind as a crop, Western medicine (which this author is most familiar with) has first documented cannabis in their pharmacopeia during the times of the Romans (Dioscorides, 1554). According to Hao and Jiang, traditional Chinese medicine has first documented cannabis (大麻) more than 1000 years earlier (Hao and Jiang, 2015). Concurrently, cannabis products from the rest of the plant have been used in food, feed, textiles, engineering and the built environment and many more sectors of daily life.

Economically, cannabis has always been a constant factor in our lives. However, there is no doubt, that during the past few years a renaissance of interest in cannabis has contributed to the generation of much needed facts and myths, the latter lesser needed. An ongoing discourse relates to the biology of cannabis. The number of cannabis species is disputed in the internet, for examples on Wikipedia. It is important to know that botanists have always been very clear about there being only one *species*, which is named *sativa* (Small and Cronquist, 1976; Small, 2015; Pollio, 2016). Botanists recognize four discernible groups as *varieties*(not species): *sativa, indica, spontanea, kafiristanica*. These varieties have resulted of domestication in geographically distinct areas,

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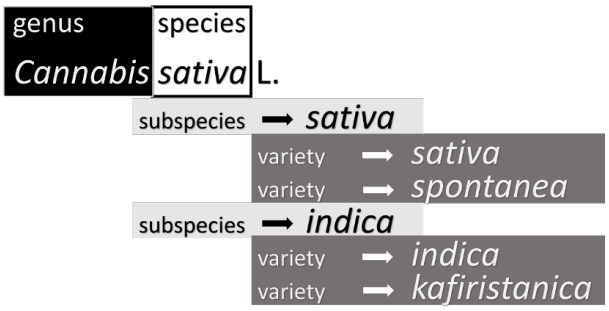

Figure 1. The four discernible cannabis varieties as recognised by botanists (Small and Cronquist, 1976; Small, 2015; Pollio, 2016).

but they all originate from species: *Cannabis sativa* L.

It is widely understood that cannabis product properties have been governed by domestication. For example, the difference in THC: CBD ratio of several cannabis varieties is a result of breeding. As such, the plant has been domesticated according to the product properties, which were ultimately required by the breeder. Tensile strength of cannabis fibre is an important property of the crop if the ultimate product was rope. The psychoactive products, tetrahydrocannabinol, cannabidiol and many more, produced by cannabis and their relative abundance is an important property of the crop. Its ultimate use is for medical and/or recreational purposes.

There have been attempts to categorize cannabis in chemical phenotypes (ElSohly *et al.*, 2017) ("chemotaxonomy"), depending on the level of psychoactive compounds. However, the limits between the ratios of these compounds are arbitrary. Furthermore, abundance of psychoactive compounds within plants does not necessarily correlate with pharmacological significance (Shevyrin *et al.*, 2016; Mudge, Murch and Brown, 2018), because there is strong evidence which suggests that efficacy is based on the synergy of cannabinoids, and not on the action of individual cannabinoids (Russo, 2011).

That said, research on the chemistry of cannabinoids is progressing in full steam. To this date, hundreds of cannabinoids have been isolated, characterized and described in much detail. This work has been performed *in vitro*, using physico-chemical methods coupled with state-of-the-art analytical methods which can distinguish between cannabinoids that are very similar in structure and have previously been unknown.

Research on cannabinoid receptors (Shao *et al.*, 2016) *in vivo* is also progressing at a fast rate and new results are published every week. Such research focusses on answering cause-and-effect questions. The availability of a constant and reproducible source of cannabinoids for this type of research is, however, a major bottleneck. This is due to a variation in plant cultivation methods. The slightest variation in growth parameters will result in cannabis producing a variation of cannabinoid spectrum, quality and abundance. This in turn is bad for research, because the validity and reproducibility of a study depends entirely on the perfectly reproducible supply of cannabinoids. Therefore, cannabis growth must be perfected in order to ensure that the cannabinoid spectrum, quality and abundance is constant, batch-by-batch and year-by-year. Quality control must be done using in vitro analysis, as mentioned above, using state-of-the-art analytical methods (Shevyrin *et al.*, 2016).

The most widely researched and characterized phytocannabinoid acids are delta-9-tetrahydrocannabinolic acid ($_3$THCA), cannabinolic acid ($_4$CBDA), cannabichromenenic acid ($_5$CBCA), tetrahydrocannabivarinic acid ($_6$THCVA),

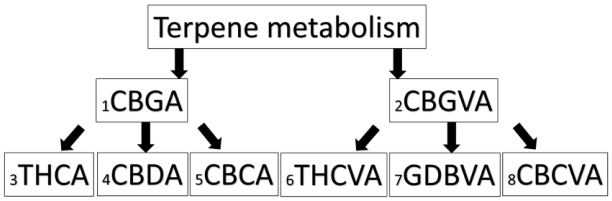

Figure 2. The biosynthetic pathway to produce the major cannabinoid acids.

cannabidivarinic acid ($_7$CBDVA) and cannabichromevarinic acid ($_8$CBCVA). THCA, CBDA and CBCA have a common precursor cannabigerolic acid ($_1$CBGA). THCVA, CBDVA and CBCVA have a common precursor cannabigerovarinic acid ($_2$CBGVA). Terpene metabolism is the big overarching metabolic pathway which produces phytocannabinolic acids in cannabis. Terpenes are a large and diverse class of tens of thousands of chemicals which are produced by all living organisms.

Due to a lack of analytical data, only THCA and CBDA are considered in clinical research. Recent advances in clinical research have demonstrated the combined activity of THCA and CBDA in various ratios. According to these studies, cannabinoids are used in the treatment of pain (Linher-Melville *et al.*, 2020; Vigil *et al.*, 2020), cancer (Afrin *et al.*, 2020), multiple sclerosis (Mecha *et al.*, 2020), epilepsy (Morano *et al.*, 2020), kidney disease (Rein, 2020), and autism (Agarwal, Burke and Maddux, 2019).

However, all the above cited peer-reviewed publications, without exception, mention in their conclusion that there is still too little evidence to support a strong pharmacological correlation between phytocannabinoid administration and healthcare benefits. Every single publication identifies research gaps and recommends that additional studies must be conducted.

Future studies must be based on well-studied phytocannabinoids and therefore botanical, horticultural and chemical knowledge. At present, the variation in abundance and levels of phytocannabinonids in various cannabis extracts is much too great to be useful for research. Scientific research is very costly, however, in the interest of healthcare and a sustainable cannabis economy, funding bodies must invest at full force.

Further reading

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Glossary of terms

- Cannabis – *Cannabis sativa* L.
- Peer-reviewed – other experts (usually between two and five individuals) in the field are determining the validity, reproducibility, significance and originality of the study.
- Cannabinoids – a class of chemicals including a) plant-based (phytocannabinoids), b) animal-based (endocannabinoids) as well as c) laboratory-based

(synthetic cannabinoids). Although their chemical structure is diverse, they all share the ability to bind to cannabinoid receptors in animals, including humans.

- Pharmacopeia – Greek for "drug making". An instruction manual written and used by pharmacists to standardize drug manufacture.
- *Cannabis sativa* L. – Systematic name for hemp, marijuana, dagga, ganja, etc. The L. stands for Carl von Linné, Botanist, *1707 †1778.
- Chemotaxonomy – systematic classification of plants solely based on the chemicals they produce.
- *in vitro* – Latin for "in a glass/test-tube". A research methodology which is studying processes in an isolated environment outside of a living organism.
- *in vivo* – Latin for "in a living organism". A research methodology which is studying processes as they happen inside a living organism.
- Phytocannabinoids – see cannabinoids
- Endocannabinoids – see cannabinoids
- Synthetic cannabinoids – see cannabinoids
- Pharmacology – study of drug or medication action

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Philasande Cele is a multi-talented innovator in the urban agriculture and cannabis space and also an MSc student and researcher at the University of the Witwatersrand, Johannesburg, The "Chilli of Soweto" he developed and grows has been added to the international Ark of Taste catalogue of heritage foods. He is the founder and director at Siyazenzela Plant Biotech and Agricultural Consultants, co-founder of Izindaba Zokudla (a small farmers platform), and Director of propagation, cultivation and processing at Afrocannabist (Pty) LTD.