

Special Section: Cannabinoid Signaling in Human Health and Disease—Commentary

The National Center for Complementary and Integrative Health: Priorities for Cannabis and Cannabinoid Research

David Shurtleff, Angela Arensdorf, Patrick C. Still, Steven W. Gust, Sekai Chideya, David Craig Hopp, and Inna Belfer

National Center for Complementary and Integrative Health, National Institutes of Health, Bethesda, Maryland

Received February 8, 2024; accepted May 7, 2024

ABSTRACT

The National Center for Complementary and Integrative Health (NCCIH), which is part of the US National Institutes of Health (NIH), has a broad interest in studying the biologic activities of natural products, especially those for which compelling evidence from preclinical research suggests biologic activities that may be beneficial to health or have a potential role in disease treatment, as well as products used extensively by the American public. As of 2023, use of cannabis for medical purposes is legal in 38 states and Washington, D.C. Such use continues to climb generally without sufficient knowledge regarding risks and benefits. In keeping with NCCIH's natural product research priorities and recognizing this gap in knowledge, NCCIH formally launched a research program in 2019 to expand research on the possible benefits for pain management of certain substances found in cannabis: minor cannabinoids and terpenes. This Viewpoint provides additional details and the

rationale for this research priority at NCCIH. In addition, NCCIH's efforts and initiatives to facilitate and coordinate an NIH research agenda focused on cannabis and cannabinoid research are described.

SIGNIFICANCE STATEMENT

Use of cannabis for purported medical purposes continues to increase despite insufficient knowledge regarding risks and benefits. Research is needed to help health professionals and patients make knowledgeable decisions about using cannabis and cannabinoids for medical purposes. The National Center for Complementary and Integrative Health, along with other NIH Institutes, Centers, and Offices, is expanding study on the safety, efficacy, and harms of cannabis—a complex mixture of phytochemicals that needs to be studied alone and in combination.

Natural products from diverse organismal sources (i.e., plants, animals, or microorganisms) continue to be a valuable source of novel analgesic small molecule scaffolds and biologics, serving as lead molecules and as drugs approved by the US Food and Drug Administration (McCurdy and Scully, 2005; Newman and Cragg, 2020; Chakraborty and Majumdar, 2021). Growing evidence points to analgesic properties of the cannabis plant and its constituents, but research on this topic has been slow due to both scientific and regulatory challenges (Cooper et al., 2021). Overall, cannabis contains a complex mixture of constituents, with over 100 unique phytocannabinoids and terpenes (Booth and Bohlmann, 2019; Radwan et al., 2021). Many phytochemicals found in cannabis may have not only analgesic properties but also other therapeutic benefits and fewer adverse effects than

the major cannabinoid Δ^9 -tetrahydrocannabinol, or Δ^9 -THC (Izzo et al., 2009). Additional research, therefore, needs to focus on other constituents of cannabis, including minor cannabinoids and terpenes, for their potential therapeutic benefits when used alone or in combinations.

Research on the biologic activities of products derived from natural sources is a priority for the National Center for Complementary and Integrative Health (NCCIH). Products of interest include secondary metabolites from diverse taxa and complex mixtures of these compounds (Still et al., 2022), as well as vitamins, probiotics, prebiotics, dietary supplements, and botanicals (including cannabis). NCCIH emphasizes research on products for which preclinical research supports potential biologic activity that may have a health benefit or lead to the development of an intervention, as well as research on natural products that Americans commonly use. NCCIH's mission is to determine, through rigorous scientific investigation, the fundamental science, usefulness, and safety of complementary and integrative health approaches and their roles in improving health and

This work received no external funding.

No author has an actual or perceived conflict of interest with the contents of this article.

dx.doi.org/10.1124/jpet.124.002173.

ABBREVIATIONS: CBD, cannabidiol; CBG, cannabigerol; ICOs, NIH Institutes, Centers, and Offices; NCCIH, National Center for Complementary and Integrative Health; NIH, National Institutes of Health; Δ^8 -THC, Δ 8-tetrahydrocannabinol; Δ^9 -THC, Δ 9-tetrahydrocannabinol.

health care. Research includes the study of a diverse group of nutritional, psychologic, and physical practices that may have originated outside of conventional Western health care. Those showing efficacy are gradually incorporated into mainstream care to manage symptoms, such as pain and other conditions treated initially through primary care.

Cannabis use presents unique challenges. Changes in medical and adult use of cannabis and related laws, regulations, and policies have moved ahead of the science. As of 2023, 38 US states, four territories, and Washington, D.C. had legalized or decriminalized medical and/or adult use of cannabis. However, the US Food and Drug Administration has approved only three natural and synthetic cannabinoids (i.e., dronabinol, nabilone, and Epidiolex) for treating specific health conditions. Adequate evidence on efficacy and safety does not exist for many of the conditions for which medical use of cannabis has been approved in Canada, Australia, various European countries, and certain US states (Hall et al., 2019). In addition, patients are using, and physicians are recommending cannabis products without an understanding of the medical impacts of dose, timing, concentration, strain type (i.e., mixture of phytochemicals), route of administration, mechanism of action, population-specific effects, interactions with other medications or substances, and potential adverse effects.

The National Institutes of Health (NIH) is actively addressing the chasm between medical use of cannabis and research that informs safety and efficacy. NCCIH, for example, is leading and coordinating a cannabis and cannabinoid interest group that includes several partner NIH Institutes, Centers, and Offices (ICOs) that share an interest in both the potential therapeutic benefits and the adverse effects of the cannabis plant and substances derived from it.

One issue of particular interest to NCCIH is the potential analgesic properties of cannabis and its constituents. Chronic pain is a major public health concern. The Medical Expenditure Panel Survey, which collected data from a nationally representative sample of US adults, found that between 1997/1998 and 2013/2014, the proportion who had a painful health condition grew from 32.9% (120.2 million) to 41.0% (178.0 million)—a 25% increase. Furthermore, in 2013/2014, 68 million individuals with painful health conditions reported that pain had a moderate or severe adverse effect on their activities at work or at home (Nahin et al., 2019).

The cannabinoid Δ^9 -THC has demonstrated analgesic properties (Whiting et al., 2015; Weizman et al., 2018; Casey et al., 2022), but it also has psychoactive effects and a potential for abuse that limit its usefulness (Murray and Srinivasa-Desikan, 2022). Cannabis, with its numerous chemotypes, cannot be considered analogous to Δ^9 -THC, but rather is a mixture of phytochemicals and their metabolites that may have antagonistic, additive, or synergistic actions that could cause different physiologic and behavioral effects, some of which may modulate the putative therapeutic actions of various combinations (Russo, 2019; LaVigne et al., 2021; Rodriguez et al., 2022; Moore et al., 2023). The cannabis chemotype primarily containing Δ^9 -THC, however, is the most widely available and consumed cannabis product for medical and adult use; one path forward is to develop and test more complex chemotypes or mixtures for potential therapeutic benefit (Lewis et al., 2018; Russo, 2019).

In 2019, NCCIH issued the funding opportunity “Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes.” This vanguard initiative resulted

in 11 grants totaling approximately \$3 million in the first year for all awards supported by NCCIH to investigate the potential analgesic effects of phytochemicals from cannabis and their mechanisms of action. Both minor cannabinoids (those other than Δ^9 -THC) and terpenes were included in this initiative. Along with some prior-funded cannabinoid research, in subsequent years NCCIH expanded this research program to support additional research grant applications. Some highlighted features of this research program include:

- Identifying the mechanisms of action by which cannabidiol (CBD) affects chronic pain associated with arthritis
- Testing individual cannabinoids and terpenes and combinations of these compounds for analgesia in rodent models of pain and determining their interactions with morphine
- Exploring the effects of rare cannabinoids on microglia
- Investigating CBD and terpenoid interactions in amygdala regulation of pain states
- Conducting therapeutic and mechanistic evaluation of terpenes in neuropathic pain models
- Initiating computation-assisted discovery of bioactive minor cannabinoids from hemp
- Chemical synthesis of rare cannabinoids not available commercially
- Evaluating the impact of CBD on gamma-aminobutyric acid (GABA) signaling in the brain
- Identifying the potential ability of myrcene and β -caryophyllene to replace THC and opioids
- Studying the effects of CBD on sleep and pain in multiple sclerosis
- Exploring cannabis’s effects on social anxiety disorder
- Conducting observational research on the effects of edible cannabis and cannabinoids on pain

A recent published report supported by NCCIH showed that the minor cannabinoid cannabigerol (CBG) relieved chemotherapy-induced peripheral neuropathy pain without evidence of tolerance in an experimental model of female and male mice, suggesting CBG could be used as a long-lasting pain treatment medication (Nachnani et al., 2023). Another NCCIH-supported study demonstrated that the cannabinoids CBD and CBG, which do not have significant psychotropic effects, have analgesic effects in a mouse model for tibial fracture. Interestingly, these cannabinoids also promoted bone healing through several mechanisms (Khajuria et al., 2023).

NCCIH is also working with other NIH ICOs to further investigate minor cannabinoids and terpenes. In 2022, NCCIH coordinated an effort to release the notice of special interest “Promoting Mechanistic Research on Therapeutic and Other Biological Properties of Minor Cannabinoids and Terpenes.” Minor cannabinoids include but are not limited to Δ^8 -tetrahydrocannabinol, CBD, CBG, cannabichromene, cannabinal, tetrahydrocannabinolic acid, cannabichromevarin, tetrahydrocannabivarin, tetrahydrocannabivarin acid, carmagerol, and cannabicitran. It should be noted that increased concentrated amounts of minor cannabinoids such as Δ^8 -tetrahydrocannabinol can be manufactured from hemp-derived CBD beyond what is “naturally” present in the plant material. Terpenes of interest include limonene, linalool, myrcene, α -humulene, α -terpineol, α -phellandrene, α -pinene, β -pinene, β -terpinene, and β -caryophyllene. The notice of special interest supports innovative basic research, either in appropriate

model organisms or with research participants, to investigate mechanisms underlying potential therapeutic effects of minor cannabinoids and terpenes. In addition to NCCIH, components of NIH participating in this initiative include the National Institute on Aging, National Institute on Drug Abuse, National Institute on Alcohol Abuse and Alcoholism, National Cancer Institute, National Institute of Dental and Craniofacial Research, National Eye Institute, National Institute of Neurological Disorders and Stroke, Office of Dietary Supplements, and Office of Research on Women's Health. All applications submitted under this notice of special interest should fall within the mission of at least one of these NIH ICOs.

To explore the pharmacokinetic properties of and interactions between natural and conventional medications, NCCIH supports the Center of Excellence for Natural Product–Drug Interaction Research, which provides leadership in studying natural product–drug interactions. Natural Product–Drug Interaction Research recently compared the pharmacokinetics and pharmacodynamics of orally administered Δ^9 -THC-dominant and CBD-dominant cannabis extracts; the study showed greater adverse effects from the CBD-dominant extract at the same dose of Δ^9 -THC. The results conflict with the popular belief that CBD lessens Δ^9 -THC's adverse effects (Zamarripa et al., 2023). Additional research is needed to further investigate interactions between cannabinoids and interactions of cannabinoids with drugs to help inform decisions about both the therapeutic and nontherapeutic uses of cannabis products.

Another new NIH activity is support of a Resource Center for Cannabis and Cannabinoid Research through a request for applications. The request for applications requested applications from the extramural research community to support a Center that will help investigators overcome challenges and barriers to conducting research on cannabis and its constituents, including regulatory concerns as well as scientific issues. The Center is also intended to help investigators successfully produce rigorous basic and clinical research evidence in multiple domains. The Center is expected to be a focal point for investigators who are new to cannabis research. It will support research tool development to facilitate cannabis research, and over time, it is expected to change the landscape of this field. Finally, NCCIH is coordinating and hosting the website “NIH-Supported Research on Cannabis, Cannabinoids, and Related Compounds.” The website consolidates information about the NIH cannabis and cannabinoid research program, and it includes NIH research priorities, relevant NIH program staff contacts for each ICO, active notices of funding opportunity, and access to funded active research grant applications.

Trends in the use of cannabis products for health-related purposes continue to climb (Mahabir et al., 2020) without sufficient knowledge regarding risks and benefits. More research is needed to help health professionals and patients make knowledgeable choices about whether to use cannabis and cannabinoids for health-related purposes. NIH is expanding its study on the safety, efficacy, and harms of cannabis, recognizing that cannabis is a complex mixture of phytochemicals that need to be studied both alone and in combination. Although this work is challenging, NCCIH and our NIH partners are committed to helping researchers navigate the current regulatory guidelines and advance this field of research.

Only through rigorous and innovative research can we fully understand and harness the therapeutic potential of cannabis constituents while clearly articulating safety concerns to address this public health imperative.

Data Availability

This article contains no datasets generated or analyzed during the current study.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Shurtleff, Arensdorf, Still, Gust, Chideya, Hopp, Belfer.

References

- Booth JK and Bohlmann J (2019) Terpenes in *Cannabis sativa* - From plant genome to humans. *Plant Sci* **284**:67–72.
- Casey SL, Mitchell VA, Sokolaj EE, Winters BL, and Vaughan CW (2022) Intrathecal Actions of the Cannabis Constituents $\Delta(9)$ -Tetrahydrocannabinol and Cannabidiol in a Mouse Neuropathic Pain Model. *Int J Mol Sci* **23**:8649.
- Chakraborty S and Majumdar S (2021) Natural Products for the Treatment of Pain: Chemistry and Pharmacology of Salvinorin A, Mitragynine, and Collybolide. *Biochemistry* **60**:1381–1400.
- Cooper ZD, Abrams DI, Gust S, Salicrup A, and Throckmorton DC (2021) Challenges for Clinical Cannabis and Cannabinoid Research in the United States. *J Natl Cancer Inst Monogr* **2021**:114–122.
- Hall W, Stjepanović D, Caulkins J, Lynskey M, Leung J, Campbell G, and Degenhardt L (2019) Public health implications of legalising the production and sale of cannabis for medicinal and recreational use. *Lancet* **394**:1580–1590.
- Izzo AA, Borrelli F, Capasso R, Di Marzo V, and Mechoulam R (2009) Non-psychoactive plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci* **30**:515–527.
- Khajuria DK, Karuppagounder V, Nowak I, Sepulveda DE, Lewis GS, Norbury CC, Raup-Konsavage WM, Vrana KE, Kamal F, and Elbarbary RA (2023) Cannabidiol and Cannabigerol, Nonpsychoactive Cannabinoids, as Analgesics that Effectively Manage Bone Fracture Pain and Promote Healing in Mice. *J Bone Miner Res* **38**:1560–1576.
- LaVigne JE, Hecksel R, Keresztes A, and Streicher JM (2021) *Cannabis sativa* terpenes are cannabimimetic and selectively enhance cannabinoid activity. *Sci Rep* **11**:8232.
- Lewis MA, Russo EB, and Smith KM (2018) Pharmacological Foundations of Cannabis Chemovars. *Planta Med* **84**:225–233.
- Mahabir VK, Merchant JJ, Smith C, and Garibaldi A (2020) Medical cannabis use in the United States: a retrospective database study. *J Cannabis Res* **2**:32.
- McCurdy CR and Scully SS (2005) Analgesic substances derived from natural products (natureceuticals). *Life Sci* **78**:476–484.
- Moore CF, Marusich J, Haghdost M, Lefever TW, Bonn-Miller MO, and Weerts EM (2023) Evaluation of the Modulatory Effects of Minor Cannabinoids and Terpenes on Δ -9-Tetrahydrocannabinol Discrimination in Rats. *Cannabis Cannabinoid Res* **8** (S1):S42–S50.
- Murray CH and Srinivasa-Desikan B (2022) Chronic Cannabigerol as an Effective Therapeutic for Cisplatin-Induced Neuropathic Pain. *Conscious Cogn* **102**:103357.
- Nachmani R, Sepulveda DE, Booth JL, Zhou S, Graziane NM, Raup-Konsavage WM, and Vrana KE (2023) Chronic Cannabigerol as an Effective Therapeutic for Cisplatin-Induced Neuropathic Pain. *Pharmaceuticals (Basel)* **16**:1442.
- Nahin RL, Sayer B, Stussman BJ, and Feinberg TM (2019) Eighteen-Year Trends in the Prevalence of, and Health Care Use for, Noncancer Pain in the United States: Data from the Medical Expenditure Panel Survey. *J Pain* **20**:796–809.
- Newman DJ and Cragg GM (2020) Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *J Nat Prod* **83**:770–803.
- Radwan MM, Chandra S, Gul S, and ElSohly MA (2021) Cannabinoids, Phenolics, Terpenes and Alkaloids of *Cannabis*. *Molecules* **26**:2774.
- Rodriguez CEB, Ouyang L, and Kandasamy R (2022) Antinociceptive effects of minor cannabinoids, terpenes and flavonoids in *Cannabis*. *Behav Pharmacol* **33**:130–157.
- Russo EB (2019) The Case for the Entourage Effect and Conventional Breeding of Clinical Cannabis: No “Strain,” No Gain. *Front Plant Sci* **9**:1969.
- Still P, Chen W, Weber W, and Hopp DC (2022) NCCIH Priorities for Natural Products Research. *Planta Med* **88**:698–701.
- Weizman L, Dayan L, Brill S, Nahman-Averbuch H, Hendler T, Jacob G, and Sharon H (2018) Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity. *Neurology* **91**:e1285–e1294.
- Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, et al. (2015) Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA* **313**:2456–2473.
- Zamarripa CA, Spindle TR, Surujunarin R, Weerts EM, Bansal S, Unadkat JD, Paine MF, and Vandrey R (2023) Assessment of Orally Administered Δ -9-Tetrahydrocannabinol When Coadministered With Cannabidiol on Δ -9-Tetrahydrocannabinol Pharmacokinetics and Pharmacodynamics in Healthy Adults: A Randomized Clinical Trial. *JAMA Netw Open* **6**:e2254752.

Address correspondence to: Dr. David Shurtleff, National Institutes of Health, Bethesda, Maryland. E-mail: David.Shurtleff@nih.gov