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Cannabidiol and Δ^8-Tetrahydrocannabinol: Cannabinoids of Rising Interest and Concern

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ABSTRACT: Although much is known about Δ^9-tetrahydrocannabinol and its inactive open ring isomer, cannabidiol, far less is known about the effects, metabolism, and pharmacodynamics of Δ^9-tetrahydrocannabinol's double-bond isomer, Δ^8-tetrahydrocannabinol. With the passage of the so-called United States "Farm Bill," which was made law in order to allow legal hemp cultivation in the United States, more needs to be known about the effects of Δ^8-tetrahydrocannabinol, a double-bond isomer of Δ^9-tetrahydrocannabinol, and cannabidiol (CBD), which is an open-ring isomer of Δ^8-tetrahydrocannabinol. It is the aim of the review to summarize current knowledge of Δ^8-tetrahydrocannabinol and CBD, including the pharmacodynamics and pharmacokinetics of CBD. Also, plant genetics, the effect of cannabinoids on the current topic of viral entry into mammalian cells, and the current practice of vaping, dabbing, and dripping are covered.

KEYWORDS: Agriculture Improvement Act of 2018, cannabidiol, cannabidiol reactions, cannabinoid analytical methodology, dabbing, dripping, EVALI, Farm Bill, hemp, HHC-O, JWH-124, JWH-138, plant genetics, SCAR, sequence characterized amplified region, Δ^8-tetrahydrocannabinol, Δ^9-tetrahydrocannabinol; Δ^8-THC-O, Δ^8-THCjd, Δ^8-THCP, VALI, vaping, viral cell infection, vitamin E acetate.

INTRODUCTION

As a general observation, few drugs/drug classes except for ethyl alcohol have had more published about them than the cannabinoids, which are derived from *Cannabis sativa* L (Linneaus). Much of the open literature has focused on the most psychoactive component, Δ^9-tetrahydrocannabinol (Δ^9-THC), whose chemical structure is presented in **Figure 1A** [7,14,41] using the dibenzopyran numbering system. The older terpenoid system for numbering of this compound, Δ^1-tetrahydrocannabinol (Δ^1-THC) is presented in **Figure 1B** [41]. The dibenzopyran numbering system will be used throughout this article.

Δ^9-THC has two chiral or optically active centers (carbons 6a and 10a). As drawn, Δ^9-THC is in the R,R configuration [13] which makes the pyran and cyclohexenyl rings *trans* to each other at the 6a-10a bond. In chloroform, the naturally occurring R,R-form rotates polarized light to the left, making the R,R-form (–)-THC [13,93]. Δ^9-THC is formed primarily by the thermal decarboxylation of the naturally occurring tetrahydrocannabinolic acid [14], which exists as THCA-A (**Figure 1C**) and THCA-B (**Figure 1D**) [17].

As a synthetic pharmaceutical, (–)-Δ^9-THC is known as dronabinol, marinol, or syndros. (–)-Δ^9-THC also is included in a buccal solution known as nabiximols (Sativex) [7] which also contains cannabidiol (CBD). The isomerism of the tetrahydrocannabinols has been summarized in a recent presentation [22].

This review is an expanded version of a previous short review [114] with focuses on CBD, Δ^8-THC, and potential cannabinoids that may be derived from hemp.

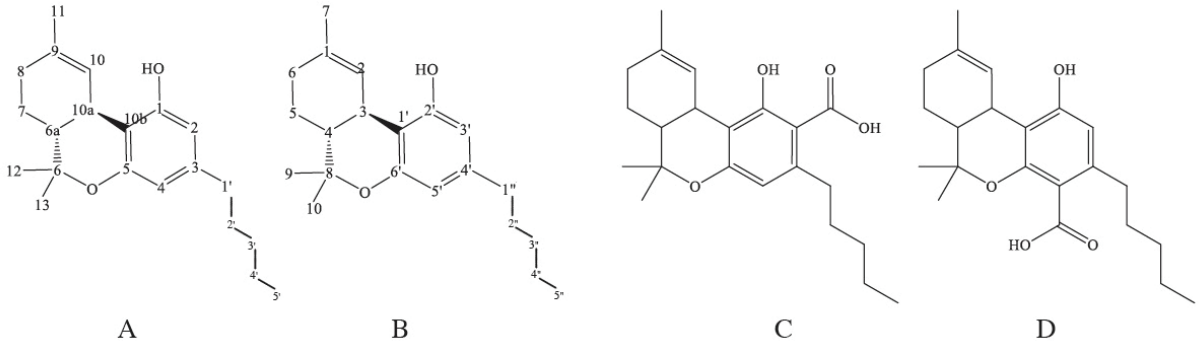

Figure 1. Chemical structures of: (A) Δ^9-tetrahydrocannabinol (Δ^9-THC; dibenzopyran numbering system); (B) Δ^1-tetrahydrocannabinol (Δ^1-THC; monoterpenoid numbering system); (C) Δ^9-tetrahydrocannabinolic acid-A; and (D) Δ^9-tetrahydrocannabinolic acid-B.

ABOUT THE AUTHOR

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Robert M. White, Sr. received a B.A. degree in chemistry from Vanderbilt University (Nashville, TN) in 1967 and a Ph.D. degree in physical organic chemistry from the University of Florida (Gainesville, FL) in 1972. Dr. White recently retired from the Center for Forensic Sciences, RTI International (Research Triangle Park, NC).

Upon completing his education, Dr. White served two and a half years of active duty in the US Army. He then undertook a postdoctoral in clinical chemistry with Dr. John Savory at the University of North Carolina (Chapel Hill, NC). Dr. White has served as the biochemist at Presbyterian Hospital (Charlotte, NC), director of life insurance testing at SmithKline-BioScience (Nashville, TN), co-director for chemistry and toxicology at Naples Community Hospital and Diagnostic Services (Fort Myers, FL), blood bank director at North American Biologicals, Inc. (Fort Myers, FL), and health care risk manager for Montgomery Eye Center (Naples, FL). Dr. White was also the scientific director for the Diagnostic Services, State of Florida Toxicology Laboratory and responsible person for the NLCP-certified laboratory (Fort Myers, FL). He also served as an adjunct professor at Florida Gulf Coast University and Hodges University in Naples/Fort Myers, FL. Dr. White was a full member of the Naples Community Hospital Department of Medicine (Naples, FL). He has qualified as an expert in toxicology in the criminal, administrative, and civil courts of the State of Florida and Federal administrative proceedings.

Dr. White's major research interests include oral fluid drug testing, biological matrix stabilization for drug testing, urine substitution and adulteration, hair drug testing, and method development. Dr. White is licensed as a clinical laboratory director in Florida with specialties in chemistry, serology/immunology, and molecular pathology. He is also licensed in the State of Tennessee as clinical laboratory personnel.

Dr. White is a member of the American Chemical Society, the American Association for Clinical Chemistry, the American Academy of Forensic Sciences, and the Society of Forensic Toxicologists. Dr. White is a fellow in the American Board of Forensic Toxicologists and a diplomate to the American Board of Clinical Chemistry in clinical chemistry, toxicological chemistry, and molecular diagnostics.