Safety concerns associated with cannabidiol-rich cannabis extract

Igor Koturbash, MD, PhD

Associate Professor and Vice-Chair,

Department of Environmental and Occupational Health

Co-Director, Center for Dietary Supplements Research

University of Arkansas for Medical Sciences, Little Rock, AR

Advancing Dietary Supplements Research

Fay W. Boozman
College of Public Health

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The center's mission is to provide industry, regulatory agencies and the public with credible information, assessments, expert opinions and risk communication, as well as professional and educational services relating to the efficacy and safety of dietary supplements.

Center for Dietary Supplements Research
https://publichealth.uams.edu/cdsr/

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Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

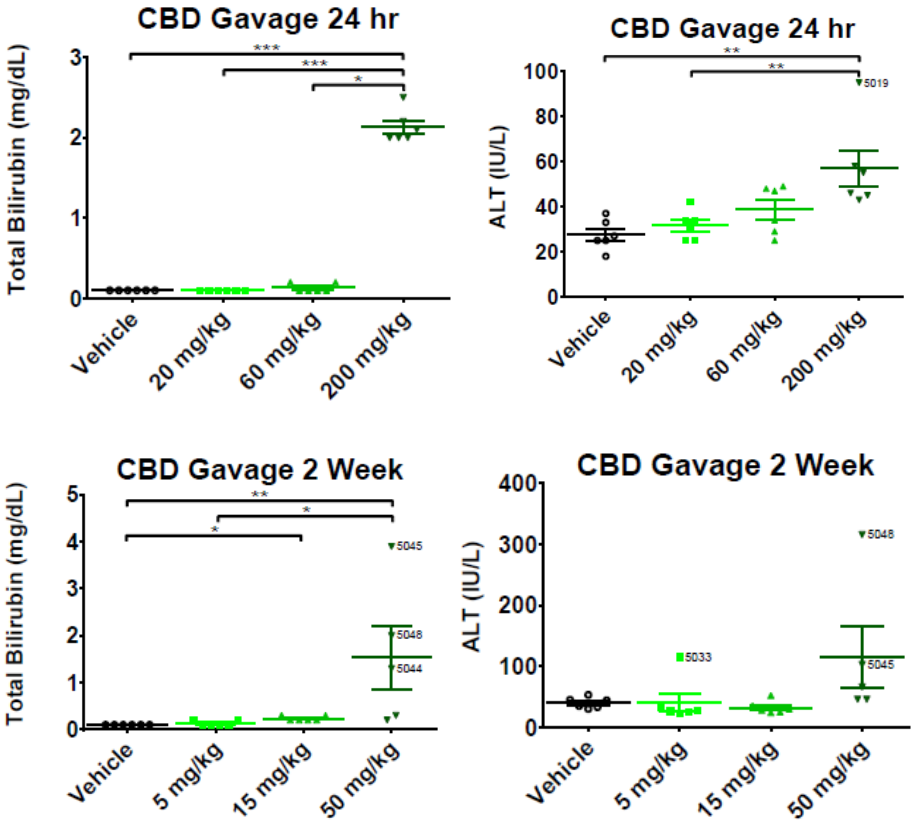
Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

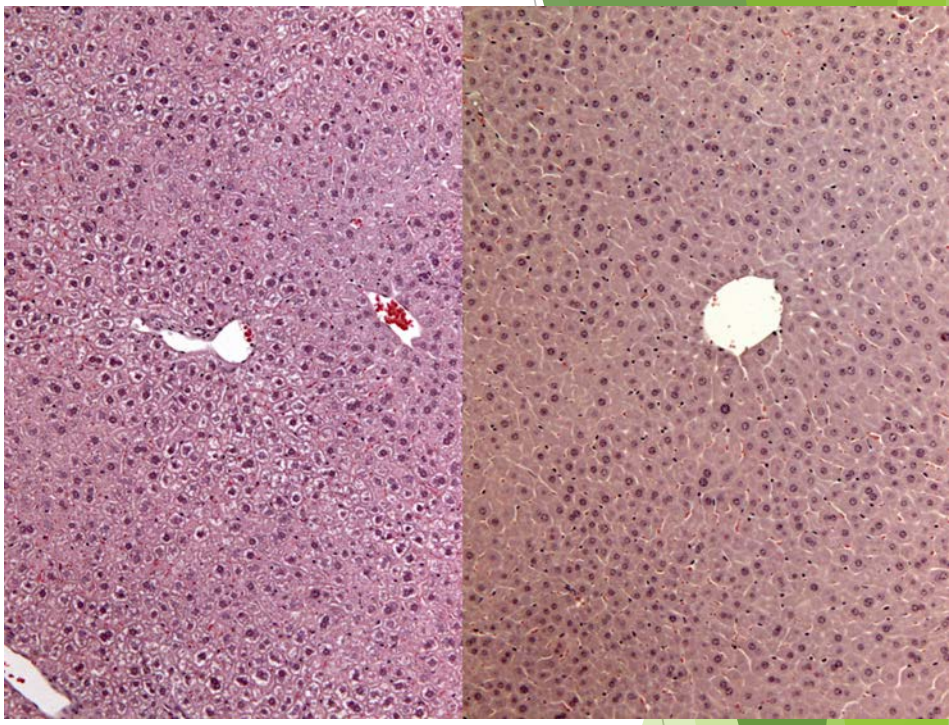
----------**WARNINGS AND PRECAUTIONS**----------

- Hepatocellular Injury: EPIDIOLEX can cause transaminase elevations. Concomitant use of valproate and higher doses of EPIDIOLEX increase the risk of transaminase elevations. See Full Prescribing Information for serum transaminase and bilirubin monitoring recommendations. (5.1)

Studies on Cannabidiol-Rich Cannabis Extract (CRCE)

CRCE-induced hepatotoxicity

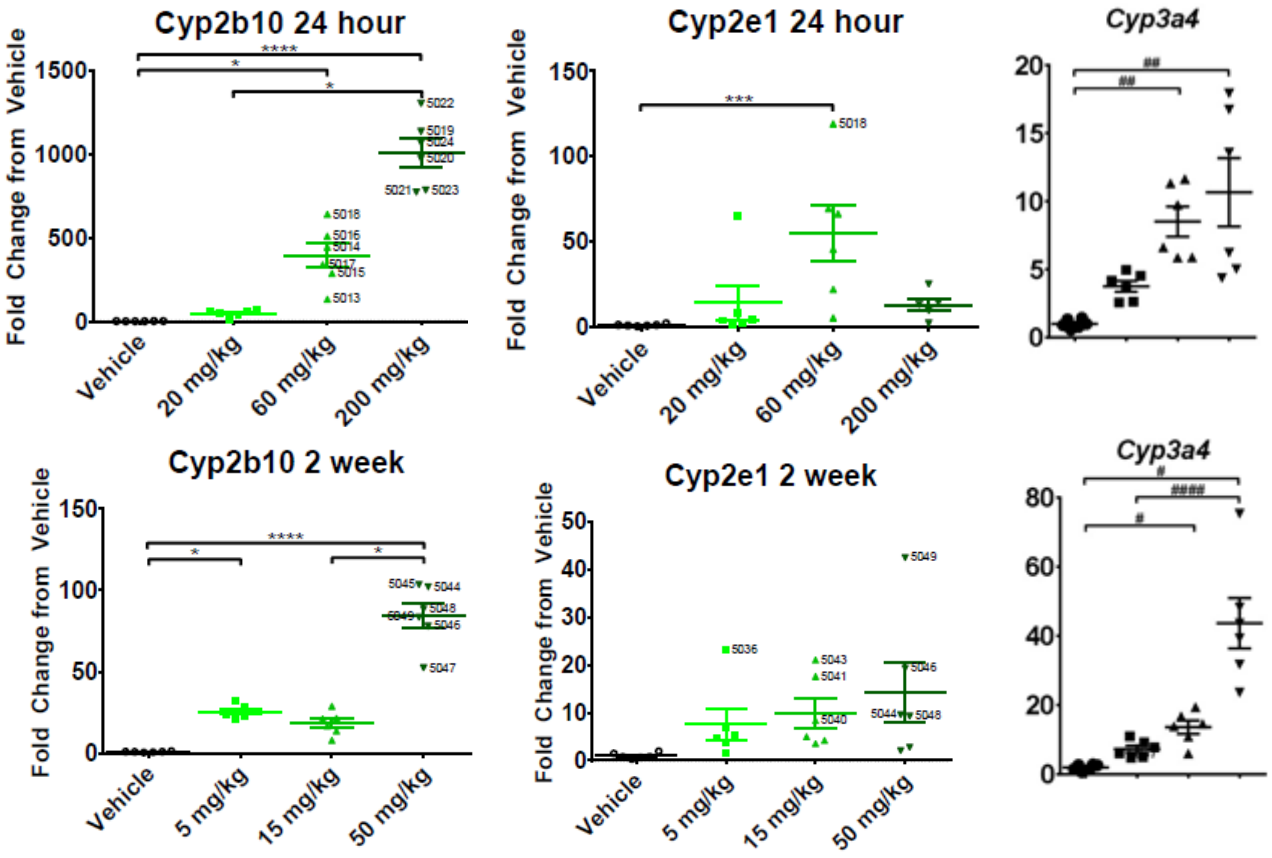


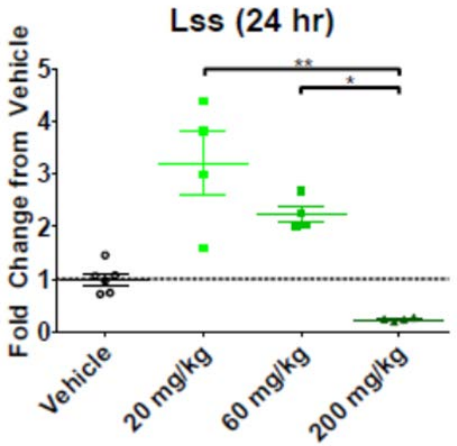


Pan-hepatic cytoplasmic swelling (on the right) as a result of administration of 50 mg/kg CBD for 2+ days.

- Administration of CRCE either in a single dose of 200 mg/kg or chronically at doses of 50 mg/kg results in hepatotoxicity, exhibited by spiking levels of total bilirubin, increased plasma levels of liver enzymes (ALT, AST) and pan-hepatic cytoplasmic swelling.

Potential for CRCE/drug interaction

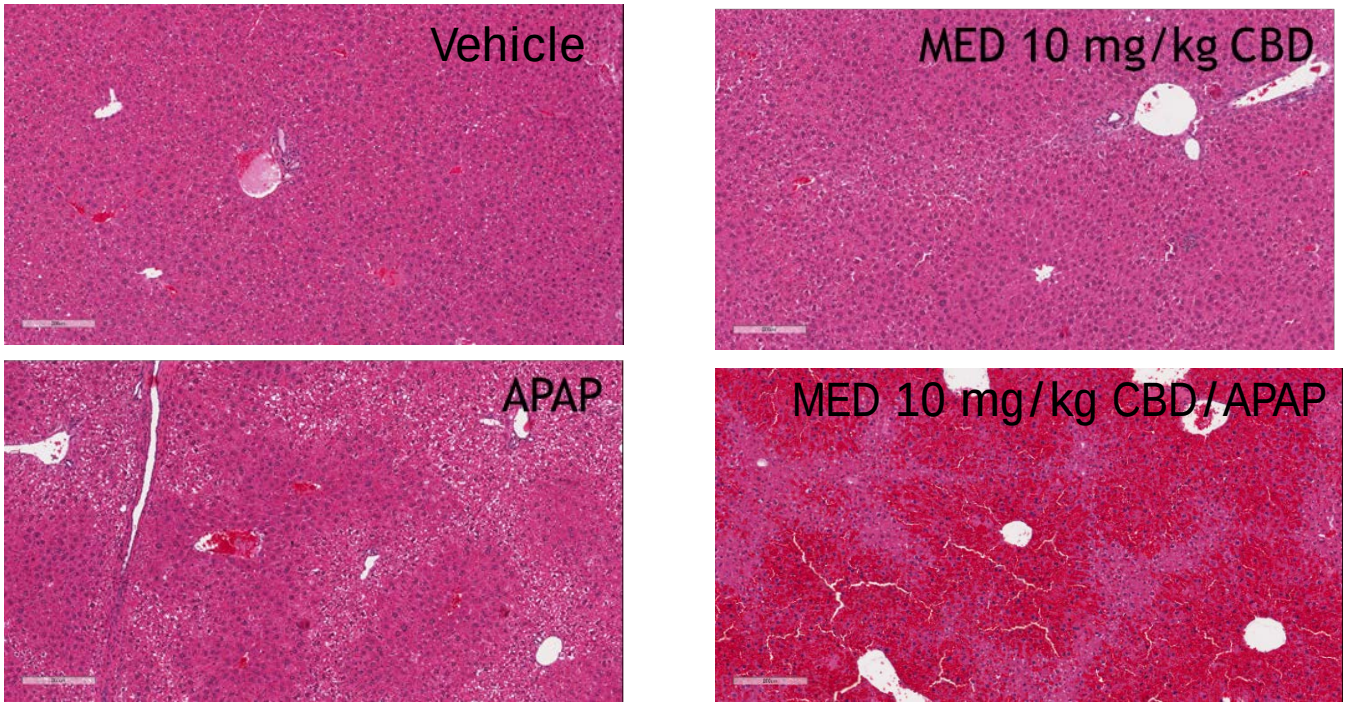




Differential gene expression regulation after administration of low dose(s) *vs* high dose(s).

- CRCE is a potent activator of a number of cytochromes, including those involved in metabolism of anesthetics (*Cyp2b10*) as well as acetaminophen and ethanol (*Cyp1e2* and C*yp2e1*).

CRCE/Acetaminophen-induced liver injury



- Concomitant administration of CRCE and APAP resulted in sinusoidal obstruction syndrome-like liver injury;
- Mortality (3 out of 8 mice) was observed in female CD-1 mice administered lower dose – 116 mg/kg (MED10 mg/kg) of CRCE.

molecules

MDPI

Article

Hepatotoxicity of a Cannabidiol-Rich Cannabis Extract in the Mouse Model

Laura E. Ewing [1,2], Charles M. Skinner [1,3], Charles M. Quick [4], Stefanie Kennon-McGill [1], Mitchell R. McGill [1,2,3], Larry A. Walker [5,6], Mahmoud A. ElSohly [5,6,7], Bill J. Gurley [3,8] and Igor Koturbash [1,3,*]

1 Department of Environmental and Occupational Health, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA; leewing@uams.edu (L.E.E.); cmskinner@uams.edu (C.M.S.); skennonmcgill@uams.edu (S.K.-M.); mmcgill@uams.edu (M.R.M.)
2 Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA
3 Center for Dietary Supplements Research, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA; gurleybillyj@uams.edu
4 Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA; quickcharlesm@uams.edu
5 National Center for Natural Products Research, University of Mississippi, University, MS 38677, USA; lwalker@olemiss.edu (L.A.W.); melsohly@olemiss.edu (M.A.E.)
6 ElSohly Laboratories, Inc. (ELI), Oxford, MS 38655, USA
7 Department of Pharmaceutics and Drug Delivery, School of Pharmacy, University of Mississippi, University, MS 38677, USA
8 Department of Pharmaceutical Sciences, University of Arkansas for Medical Sciences, Little Rock, AR 72223, USA
* Correspondence: ikoturbash@uams.edu; Tel.: +1-501-526-6638; Fax: +1-501-526-6931

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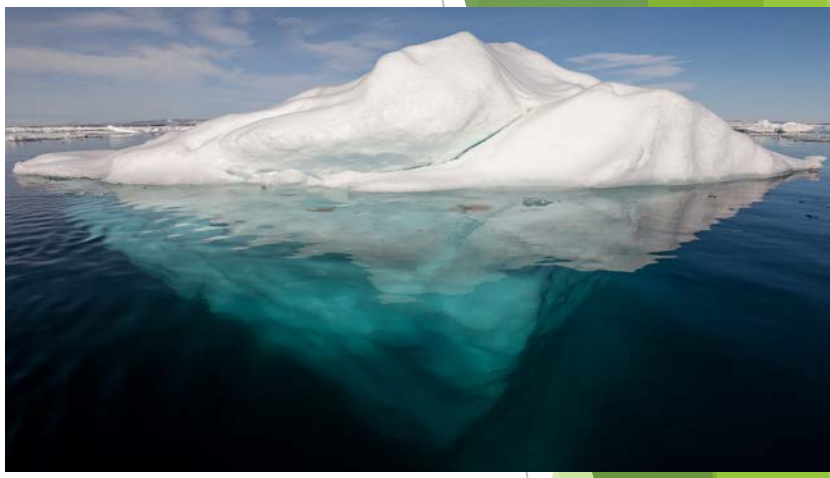
…what do we know is just a tip of an iceberg…

- CRCE poses significant potential for hepatotoxicity
- CRCE holds significant potential for CBD/drug interaction
- CRCE may exacerbate other agents-induced hepatotoxicity



Further research is clearly needed to understand safety and drug interaction potential of CBD and CBD-containing products