ELSEVIER

Critical Reviews in Oncology/Hematology 83 (2012) 1–10

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

The intersection between cannabis and cancer in the United States

Daniel W. Bowles[a,b,c,*], Cindy L. O'Bryant[a,d], D. Ross Camidge[a], Antonio Jimeno[a,b]

[a] *Developmental Therapeutics Program, University of Colorado Cancer Center, Aurora, CO 80045, United States*
[b] *Head and Neck Cancer Program, University of Colorado Cancer Center, Aurora, CO 80045, United States*
[c] *Medical Marijuana Advisory Committee, Colorado Department of Public Health and Environment, Denver, CO 80246, United States*
[d] *University of Colorado School of Pharmacy, Aurora, CO 80045, United States*

Accepted 30 September 2011

Contents

Abstract

In the last 15 years there has been a major shift in the laws governing medical use of cannabis in the United States. Corresponding with this change there has been escalating interest in the role that cannabis, commonly referred to as marijuana, and cannabinoids play in the care of patients with cancer. This review will examine cannabis' and cannabinoids' current and potential roles in cancer care. Specifically, we will examine five areas of cannabis medicine: (1) pharmacologic properties of cannabis; (2) its potential role in the development of human cancers, particularly smoking-related malignancies; (3) cannabinoids' potential as anti-cancer therapies; (4) cannabis and cannabinoids in the palliation of common cancer-associated symptoms; (5) current legal status of cannabis for medical purposes in the United States.

Keywords: Cancer; Cannabinoids; Cannabis; Medical marijuana; Tetrahydrocannabinol

1. Introduction

Cannabis, commonly known as marijuana, is a natural product derived from the *Cannabis sativa* plant. The psychoactive properties of its active ingredients, cannabinoids,

* Corresponding author at: Developmental Therapeutics and Head and Neck Oncology Programs, University of Colorado Cancer Center, MS 8117, 12801 E. 17th Avenue, Aurora, CO 80045, United States.
Tel.: +1 303 724 3847; fax: +1 303 724 3889.
E-mail address: daniel.bowles@ucdenver.edu (D.W. Bowles).

1040-8428/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.critrevonc.2011.09.008

have led to its use for religious and medicinal purposes for thousands of years. Increasingly, cancer care professionals are expected to answer questions from patients and other health care providers on the role of cannabis and cannabinoids in clinical practice, often with little more information than the National Cancer Institute's PDQ® on cannabis and cannabinoids [1]. This review will explore the intersection of cannabis, synthetic cannabinoids, and cancer in the United States (US). We will examine the pharmacologic properties of cannabis and cannabinoids, the role that cannabis may play in cancer development and symptom palliation, as well as its potential as an anti-cancer therapy. Finally we will review the current legal status of medical cannabis in the United States. The epidemiology and non-cancer related effects of cannabis use have recently been reviewed elsewhere and will not be addressed here [2].

2. Pharmacology of cannabinoids

Cannabinoids are divided into phytocannabinoids, endogenous endocannabinoids, and synthetic cannabinoids. More than 60 phytocannabinoids have been identified within the cannabis plant [3]. The primary phytocannabinoid responsible for cannabis' psychoactive and physiological effects is Δ^9-tetrahydrocannabinol (THC) [3]. Cannabinoids mediate their actions through cannabinoids receptor type 1 (CB_1) and CB_2, two G-coupled receptors in the endocannabinoid signaling system. Activation of either receptor leads to the inhibition of adenylate cyclase, decreased production of cyclic adenosine monophosphate (cAMP), and activation of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways [3,4]. CB_1 receptors are found predominantly in the central and peripheral nervous systems and suppress neuronal excitability and transmitter release, leading to hypothermia, sedation, euphoria, and altered mental status [5]. CB_2 receptors are found in higher concentrations in immune tissues and may modulate the immune system via cytokine release. They are not related to psychoactive effects [3]. CB_1 and CB_2 are reviewed extensively elsewhere [6,7]. Cannabidiol (CBD), another phytocannabinoid, can also exert anti-inflammatory effects by activation of transient receptor potential vanillin (TRPV) channel proteins and inhibiting cyclooxygenase enzymes 1 and 2 (COX-1/2) [8,9].

Inhalation and oral ingestion are the most common routes of administration for natural and synthetic cannabis products but rectal, sublingual, transdermal, ophthalmic, intrathecal, and intravenous routes have also been developed. Concentrations of THC in natural cannabis preparations can vary significantly based on a number of factors including the plant variety, type of preparation (hash oil > hash > sinsemilla [seedless plant] > smoked or ingested leaves and flowers) and cultivation technique. There is evidence that cannabis' potency has doubled in the US and abroad since the 1980s [10,11]. Dronabinol (Marinol™), a synthetic THC, and nabilone (Cesamet™), a synthetic THC-mimetic, are FDA-approved cannabinoids. Nabiximols (Sativex™) is an oromucosal spray containing THC and cannabidiol extract approved in Canada and the United Kingdom that is currently undergoing clinical testing in the US and Europe.

Table 1
Pharmacokinetic properties of inhaled and orally ingested cannabinoids.

	Inhaled	Orally ingested
Peak blood levels (min)	3–10	60–120
Bioavailability (%)	10–40	<15
Time to peak psychoactive activity (min)	20	120–240
Maximal duration (min)	Dose dependant	240-360

THC's pharmacologic parameters vary based upon the delivery form (Table 1). THC is highly protein bound in the blood but the steady state volume of distribution is large (approximately 10 L/kg) due to its lipophilicity [4]. THC's half-life ($t_{1/2}$) is variable based on the route of administration and dose but can be generally characterized by an initial $t_{1/2}$ of 3–4 h, followed by a terminal $t_{1/2}$ of 25–36 h with low levels of drug being eliminated over a longer period of time due to its large volume of distribution [4]. Vaporized cannabis has a similar pharmacokinetic profile to smoked cannabis but with less carbon monoxide exposure [12]. THC is primarily metabolized in the liver by the CYP2C subfamily and is eliminated predominantly in the feces and less in the urine. 11-OH-THC is the principle metabolite formed when THC is ingested by mouth [13]. Detectable levels of THC can be found in the urine for up to 12 days after use due to extensive enterohepatic recirculation of metabolites; however, this period could be longer for regular users [4].

3. Cannabinoids and cancer development

One of the principle concerns over the medical use of cannabinoids, particularly inhaled cannabis, is their carcinogenic potential. There is little direct evidence that THC or other cannabinoids are carcinogenic. THC is not carcinogenic in skin tests on rodents [14] and THC and other cannabinoids are not mutagenic according to the Ames test [15]. By contrast, cannabis smoke is carcinogenic in rodents [16] and mutagenic in the Ames test [17]. Cannabis smoke contains several of the same carcinogens as tobacco smoke [18] at up to 50% higher concentrations [19,20] and with three times the tar per cigarette [21]. Respiratory mucosa exposed to chronic cannabis smoke shows pre-neoplastic histological and molecular changes [22,23]. Despite this *in vitro* and *in vivo* evidence, however, it has been difficult to strongly correlate cannabis use and the development of human cancers.

For instance, the epidemiologic data correlating head and neck squamous cell carcinoma (HNSCC) risk and cannabis are inconsistent. Three studies have found a statistically significant increased risk of HNSCC in cannabis users. In a