

Review

Cannabinoids in medicine: A review of their therapeutic potential

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Abstract

In order to assess the current knowledge on the therapeutic potential of cannabinoids, a meta-analysis was performed through Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human. The research also included the reports and reviews published in English, French and Spanish. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded.

Seventy-two controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Cannabinoids present an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma. © 2006 Elsevier Ireland Ltd. All rights reserved.

Keywords: Cannabinoids; Cannabis; Therapeutic potential; Controlled clinical trials; Efficacy; Safety

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1. Introduction

Originating from Central Asia, cannabis is one of the oldest psychotropic drugs known to humanity. The beginnings of its use by humans are difficult to trace, because it was cultivated and consumed long before the appearance of writing. According to archeological discoveries, it has been known in China at least since the Neolithic period, around 4000 BC (McKim, 2000).

There are several species of cannabis. The most relevant are *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. *Cannabis sativa*, the largest variety, grows in both tropical and temperate climates. The two main preparations derived from cannabis are marijuana and hashish. Marijuana is a Mexican term initially attributed to cheap tobacco but referring today to the dried leaves and flowers of the hemp plant. Hashish, the Arabic name for Indian hemp, is the viscous resin of the plant (Ben Amar and Léonard, 2002).

The Emperor of China, Shen Nung, also the discoverer of tea and ephedrine, is considered to be the first to have described the properties and therapeutic uses of cannabis in his compendium of Chinese medicinal herbs written in 2737 BC (Li, 1974). Soon afterwards, the plant was cultivated for its fibre, seeds, recreational consumption and use in medicine. It then spread to India from China (Mechoulam, 1986).

In 1839, William O'Shaughnessy, a British physician and surgeon working in India, discovered the analgesic, appetite stimulant, antiemetic, muscle relaxant and anticonvulsant properties of cannabis. The publication of his observations quickly led to the expansion of the medical use of cannabis (O'Shaughnessy, 1838–1840). It was even prescribed to Queen Victoria for relief of dysmenorrhea (Baker et al., 2003).

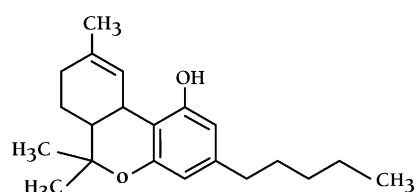
In 1854, cannabis is listed in the United States Dispensatory (Robson, 2001). It is sold freely in pharmacies of Western countries. It would be available in the British Pharmacopoeia in extract and tincture form for over 100 years (Iversen, 2000).

However, after prohibition of alcohol was lifted, the American authorities condemned the use of cannabis, making it responsible for insanity, moral and intellectual deterioration, violence and various crimes. Thus, in 1937, under pressure from the Federal Bureau of Narcotics and against the advice of the American Medical Association, the U.S. Government introduced the *Marihuana Tax Act*: a tax of \$1 per ounce was collected when marijuana was used for medical purposes and \$100 per ounce when it was used for unapproved purposes (Solomon, 1968; Carter et al., 2004). In 1942, cannabis was removed from the United States Pharmacopoeia, thus losing its therapeutic legitimacy (Fankhauser, 2002).

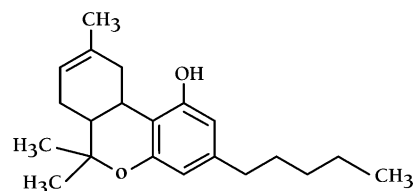
Great Britain and most European countries banned cannabis by adopting the 1971 Convention on Psychotropic Substances instituted by the United Nations.

Cannabis contains more than 460 known chemicals, more than 60 of which are grouped under the name cannabinoids (Ben Amar, 2004). The major psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol, commonly known as THC. Other cannabinoids present in Indian hemp include delta-8-tetrahydrocannabinol (Δ^8 THC), cannabinal (CBN), cannabidiol (CBD), cannabicyclol (CBL), cannabichromene

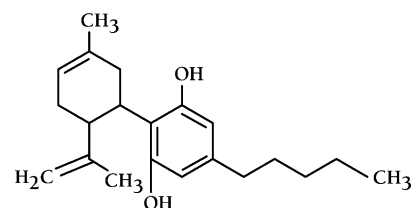
(CBC) and cannabigerol (CBG), but they are present in small quantities and have no significant psychotropic effects compared to THC (Smith, 1998; McKim, 2000). However, they may have an impact on the product's overall effect (Ashton, 2001). Cannabinoids exert their actions by binding to specific receptors: the CB₁ cannabinoid receptors, discovered by Devane et al. (1988), then cloned by Matsuda et al. (1990) and the CB₂ cannabinoid receptors, identified by Munro et al. (1993). Both cannabinoid receptors are part of the G-protein coupled class and their activation results in inhibition of adenylate cyclase activity. The identification of agonists (anandamide and 2-arachidonylglycerol, the most studied endocannabinoids, participate in the regulation of neurotransmission) and antagonists of these receptors has stimulated interest in the medical uses of cannabis (Baker et al., 2003; Iversen, 2003; Di Marzo et al., 2004).



Δ^9 - tetrahydrocannabinol (THC)



Δ^8 - tetrahydrocannabinol



Cannabidiol (CBD)

Despite its illegality, patients have continued to obtain cannabis on the black market for self-medication. In 1978, in response to the success of a lawsuit filed by a glaucoma patient (Robert Randall) who had begun treating himself by smoking marijuana after losing a substantial part of his vision, the U.S. Government created a compassionate program for medical marijuana: 20 people suffering from debilitating diseases legally received marijuana cigarettes from the National Institute on Drug Abuse (NIDA), after approval by the Food and Drug Administration (FDA). This program was closed to new candidates in 1991 by President Bush, but still recently seven people continued to receive their marijuana (Mirken, 2004).

In Canada, 14 years after the 1988 arrest of Terrance Parker (an Ontario patient who had discovered that marijuana con-

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