Chapter 11

Therapeutic Advantages of Cannabimimetic Plants: Can They Substitute Medical Cannabis?

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ABSTRACT

Cannabis has been used by humans both for recreational and therapeutic purposes since ancient times. Among 113 different cannabinoids from Cannabis, D9-trans-tetrahydrocannabinol (D9THCs) is primarily hallucinogenic and cannabidiol (CBD) is therapeutic. The growing interest in therapeutic uses of Cannabis has created interest in several other plants which are non-cannabinoid and have secondary metabolites similar to CBD known as cannabimimetic plants. The cannabimimetic plants are currently gaining attention and can be the potential alternative to Cannabis because of certain secondary metabolites with a similar mechanism of action binding with cannabinoid receptors. For example, phytoextracts from liverworts Radula marginata, amorfrutin in Amorpha fruticose and several Rhododendron species have been reported to have cannabinoid-like properties. This chapter is providing a complete review of cannabimimetic plants focusing on botanical, biochemical, and potential therapeutic aspects.

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INTRODUCTION

Secondary metabolites are found in plants as a result of evolutionary adaptation. Secondary metabolites are frequently used by plants to defend themselves against predators and diseases, and they have been used in biopharmaceutical applications. Cannabis is one of the most well-known genera in the angiosperm plant family Cannabaceae *and one of the oldest cultivated plants*. The plant has medicinal properties in addition to hallucinogenic properties. This plant, commonly known as hemp, has been used for centuries as a source of fibers, drugs for religious rituals, voluptuary and medicinal purposes (Bonini et al., 2018). The species is thought to have originated in central Asia (India and China) since ancient times (Russo et al., 2008). Based on its cultural significance, in India, three cannabis grades have been identified: bhang, ganja, and charas, which are determined by using dried shoot tips, resin-rich pistillate flower, or pure resins.

The plant has been used medicinally in India for over 3500 years. *The medicinal use of Cannabis sativa L. (C. sativa)* dates back to 5000 years ago (Abel 1980). According to the Chinese pharmacopeia seeds of this plant were used in treating various diseases such as eczema and psoriasis and for reducing pain and inflammation (Jeong et al., 2014).

The key phytocannabinoid, *trans*-Δ-9-tetrahydrocannabinol (D9-THC) from *Cannabis sativa* has been isolated by Gaoni and Mechoulam (1964) which opened the window to explore cannabinoids and medicinal use of this plant as a substitute to opioids in pain management (Cash et al., 2020). In the 1980s, Pfizer worked on the development of synthetic ligands of cannabinoid receptors (Pertwee, 2006). Subsequent breakthrough discovery of the cannabinoid type-1 (CB1) receptor in 1990, and the cannabinoid type-2 (CB2) receptor in 1993 (Pertwee, 2009) enlighten the mechanistic and biosynthesis of phytocannabinoids. Moreover, in the 1990s the two endogenous CB receptor ligands, arachidonoylethanolamine, and 2-arachidonylglycerol, were also discovered (Pertwee, 2009). The term "endocannabinoid system", which comprises endogenous ligands, receptors, and synthesis and degradation enzymes was coined by Di Marzo et al. (Di Marzo et al., 1994).

However, the debate on legal status of *Cannabis sativa* is still active in many western governments (McGinty et al., 2017). To date, the Food and Drug Administration (FDA) has not approved a marketing application for cannabis for the treatment of any disease or condition. The agency has, however, approved one cannabis-derived drug product: Epidiolex (cannabidiol), and three synthetic cannabis-related drug products: Marinol (dronabinol), Syndros (dronabinol), and Cesamet (nabilone) (US FDA, 2020). These approved drug products are only available with a prescription from a licensed healthcare provider. Importantly, the FDA has not approved any other cannabis, cannabis-derived, or cannabidiol (CBD) products currently available on the market. Eleven US states, and the District of Columbia, have enacted legal recreational cannabis regulations (Lancione et al. 2020). The legal age of cannabis possession matches the legal drinking age in all jurisdictions except one. Most consumption is in private residences only, with some provinces/territories permitting public consumption where tobacco is permitted (Lancione et al. 2020).

There is an urgent need to investigate non-cannabis plants that contain phytocannabinoids similar to *Cannabis*. The term "cannabimimetics" refers to a class of phytochemicals that can mimic the effects of phytocannabinoids in *Cannabis* and interact with the endocannabinoid system (ECS) (Gertsch et al. 2010). The primary source of phytocannabinoid in cannabimimetics is secondary metabolites from medicinal plants, spices, and herbs (Russo 2016). Furthermore, several authors have argued that molecules found in cannabimimetic plant extracts not only bind to CB1 and CB2 receptors but also regulate the

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