Chapter 5

Anti-Tumor Effects of Cannabinoids in Brain, Lung, Breast, Prostate, Colorectal, and Pancreatic Cancers: A Systematic Review of the Literature

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ABSTRACT

In search for new cancer treatments, the anti-tumor effects of cannabinoids are under investigation. This study systematically reviews the experimental and clinical evidence for benefits of cannabinoids in cancer. Literature search was conducted through PubMed, EBSCO Host, and ProQuest electronic databases. The text words "medical marijuana," "cannabis," "cannabinoids," "cannabidiol (CBD),"

DOI: 10.4018/978-1-6684-5652-1.ch005

and "Δ9-Tetrahydrocannabinol (THC)," with the Boolean operator "AND" "cancer" either "brain," "lung," "breast," "prostate," "colorectal," or "pancreatic" were used to identify studies on anti-tumor effects of cannabinoids. Treatment with cannabinoids decreased cell proliferation, tumor size, angiogenesis, adhesion, migration, and metastasis, and promoted cell cycle arrest, apoptosis, and autophagy in tumor cells and xenograft models and overall survival in cancer patients. There is strong experimental evidence for anti-tumor effects of cannabinoids. Clinical trials are warranted, and further experimental studies are needed to elucidate the pharmacologic potential for cannabinoids in oncology.

INTRODUCTION

In 2020, worldwide cancer incidence included 2.26 million new cases of breast cancer, 2.21 million of lung cancer, 1.93 million of colorectal cancer, 1.41 million of prostate cancer, 495,000 of pancreatic cancer, and 308,000 new cases of brain cancer (WHO, 2020). Despite biotechnological advancements that have supported numerous novel approaches for cancer treatment, cancer-related deaths still accounted for approximately ten million deaths,1 in 6 deaths worldwide, with 1.80 million deaths from lung cancers, 916,000 deaths from colorectal cancers, 685,000 deaths from breast cancers, 466,000 deaths from pancreatic cancers, 375,000 deaths from prostate cancer, and 251,000 deaths from central nervous system cancers in 2020 (WHO 2020).

The endocannabinoid system encompasses several classes of receptors including type 1 and type 2 cannabinoid receptors (CB1 and CB2) that are activated by endogenous cannabinoids, anandamide (AEA), 2-arachidonoylglycerol (2-AG), as well as G protein-coupled receptor 55 (GPR 55), and transient receptor potential channels of the vanilloid subtype (TRPVs) (Shahbazi et al., 2020). Potential therapeutic applications involving the manipulation of the endocannabinoid system arise from neuroprotective, anti-inflammatory, anti-convulsive, anti-emetic, anti-inflammatory, and anti-tumor effects that have been described in animals and humans with various cancers and neuropsychiatric conditions (Akinyemi et al., 2020; Pagano et al., 2021; Longoria et al., 2022). Although the most studied cannabinoids for medicinal purposes have been cannabidiol (CBD) and Tetrahydrocannabinol (THC), there are more than 140 phytocannabinoids found in *Cannabis sativa* and other plant extracts. The proportions of different cannabinoids, terpenes and flavonoid compounds detected in cannabis end-products vary depending on how the plants are cultivated, and on the conditions before and after harvesting, including temperature, humidity, carbon dioxide levels, mineral concentrations, storage methods and length of storage times. Chemical composition characterizes ten distinct subclasses, or 'chemovars', that contain predominantly either CBG, delta-9-THC, CBD, CBC, CBN, delta-8-THC, CBL, CBND, CBE, or CBT (Procaccia et al., 2022). Four main 'cultivars' are marketed as either Type III containing predominantly CBD with more than 15% CBDA (CBD acid), Type II containing mixed CBD and THC with more than 10% CBDA plus more than 4% of THCA (THC acids), Type I containing predominantly THC with no CBD, and Type IV lacking any CBD or THC but containing more than 6% of their precursor CBGA (Procaccia et al., 2022). In the USA, recreational marijuana outlets are not permitted to carry Δ^9-THC containing products, although are allowed to market products containing the less potent Δ^8-THC.

Renewed interest in the anti-tumor effects of medical cannabis is currently driving in-depth scientific investigation of the cellular and molecular mechanisms of cannabinoids in primary cancer cell cultures, cancer cell lines, animal models of cancer, cancer xenograft models, as well as cancer patients. A review of studies in cancer revealed that the anti-tumor effects vary by cancer type, dosage and formulation