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Potential of cannabinoids in the treatment of hepatocellular carcinoma

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1 INTRODUCTION

In 1964 the Δ9-Tetrahydrocannabinol was isolated and identified for the first time by Gaoni and Mechoulam. After 26 years, in 1990, the CB1 and CB2 receptors responsible for the action of these cannabinoids were identified, as well as the endogenous substances, derived from arachidonic acid, related to their activation (anandamide and 2-AG). The CB1 receptor is more present in presynaptic neurons, and is responsible for the great majority of the neurobehavioral effects of cannabinoids through a mechanism of inhibition of neurotransmitter release (regulating the action of ion channels). The CB2 receptor is mainly found on the immune system cells, where it acts modulating the release of cytokines.

The use of cannabinoids is currently studied for epilepsy, insomnia, spasms, pain, glaucoma, asthma, inappetence, Tourette's syndrome, nausea control, appetite stimulant, pain control and in the symptoms of Multiple Sclerosis, anxiety, inflammation, brain damage (as a neuroprotector), psychosis, and recently in the treatment of neoplasms, such as HCC.

Hepatocellular carcinoma (HCC) is the malignant neoplasm derived from hepatocytes, the main cells of the liver. It is the most common liver cancer, followed by cholangiocarcinoma and other rarer neoplasms. This carcinoma is indicated by the World Health Organization (WHO) as the second leading cause of death from cancer in humans. In Brazil, the incidence of HCC is higher in the states of Espírito Santo and Bahia.

HCC mainly affects developing countries. It is the fifth most common type of cancer in men and the seventh most common in women, and is diagnosed in more than half a million people worldwide each year. Recognized risk factors for hepatocellular carcinoma include chronic hepatitis B virus (HBV)

infection, hepatitis C virus (HCV) infection, aflatoxin exposure, liver steatosis, chronic alcoholic disease, obesity, smoking, diabetes, and iron overload.

As is common with cancers, HCC arises by monoclonal replication of a hepatocyte with compromised DNA that has lost control of its cell cycle and its tumor suppression mechanisms. The neoplasm mostly results from a cirrhotic liver with dysplastic nodules caused by underlying lesions. This neoplastic precondition comes from activation of hepatic stellate cells by paracrine signals of necrosis, causing their proliferation and production of collagen 1, leading to fibrosis and eventually cirrhosis.

Like other types of cancer, HCC does not result from just mutation and unbridled reproduction. For a tumor to originate and evolve, cells need to acquire mechanisms that allow them to survive in an organism made to destroy them. The most important mechanisms are self-sufficiency in growth, insensitivity to growth inhibitors, evasion of apoptosis and cell death, sustained angiogenesis, ability to invade and metastasize, reprogramming of energy metabolism, immune evasion, and genomic instability.

In addition to indirect damage resulting from cirrhosis, underlying diseases and some intoxications have direct mechanisms of DNA damage. The HBV virus, which is responsible for up to 80% of HCCs, integrates the HBx protein gene into cellular DNA. The viral protein activates multiple cell proliferation pathways and turns off tumor suppressor proteins, especially p53. Chronic infection with the even more aggressive HCV results in HCC in up to 30% of cases. The virus activates beta-catenin pathways and turns off p53, p73, and the RB.

Moreover, the underlying diseases in general and their associated cirrhosis generate production of reactive oxygen species, toxic metabolites, and accentuated exposure of the genome by the proliferation characteristic of the inflammatory microenvironment. The result is tumor cells with enormous heterogeneity, chromosomal instability, and high aggressiveness, as well as all the characteristics necessary for tumor development. Moreover, only part of HCCs have curative treatment, and, without intervention, death commonly occurs in about 10 months, which justifies the research and development of new treatments.

2 METHODOLOGY

The BVS, PUBMED and EBSCO databases were searched, and sixty-four (64) articles were found, leaving twelve (12) articles to be read in full. After applying the exclusion criteria, which were: adequacy to the theme, Portuguese or English language, date of publication beyond 2011, eight articles remained for the review. Several lines of research were found on the use of cannabinoids in the treatment of HCC, based mainly on CB2 receptor agonism and CB1 receptor antagonism.

3 CONCLUSION

Cannabinoids represent a pharmacological class studied in the treatment of ophthalmic, neurological, respiratory and many other diseases, including neoplasms. In the case of HCC, a prevalent

cancer of the liver, cannabinoids represent a therapeutic opportunity in a disease that lacks effective treatments.

Several biomolecular mechanisms explain the action of cannabinoids against HCC, mostly due to the activation of CB2 receptors and inhibition of CB1. The most studied pathways are the induction of apoptosis, autophagy and endoplasmic reticulum stress, the inhibition of angiogenesis and of invasion and metastasis.

Further, larger and more complex studies are still needed to elucidate the mechanisms and their applicability in clinical practice.

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