Journal of Traditional and Complementary Medicine Vo1. 3, No. 4, pp. 227-233

Journal of Traditional and Complementary Medicine
Journal homepage http://www.jtcm.org

The Anticancer Properties and Apoptosis-inducing Mechanisms of Cinnamaldehyde and the Herbal Prescription Huang-Lian-Jie-Du-Tang (黃連解毒湯 Huáng Lián Jiě Dú Tang) in Human Hepatoma Cells

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ABSTRACT

Hepatocellular carcinoma (HCC) has long been one of the most important causes of cancer mortality in the world. Many natural products and traditional herbal medicines have been used to treat HCC in Asian countries such as Japan, Korea, Taiwan, and China. The present review aims to describe the anticancer properties and apoptotic mechanisms of cinnamaldehyde, the bioactive ingredient isolated from cinnamon trees, and the herbal prescription Huang-Lian-Jie-Du-Tang (黃連解毒湯 Huáng Lián Jiě Dú Tang; HLJDT) against human hepatoma cells *in vitro* and *in vivo*. Implication of their treatment for the development of targeted therapy against HCC is discussed.

Key words: Anticancer, Apoptosis, Cinnamaldehyde, Hepatoma, Huang-Lian-Jie-Du-Tang

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm with more than 750,000 new cases diagnosed every year and is the third leading cause of cancer-related mortality worldwide.[1,2] The normal hepatocytes may transform into liver tumor cells by risk factors such as viral hepatitis, alcohol consumption, fatty liver disease, dietary exposure to aflatoxin B1, smoking, obesity, and diabetes.[3-5] Viral hepatitis is the major causative factor of HCC and approximately 80% of HCC cases are associated with persistent infection by either hepatitis B virus (HBV) or hepatitis C virus (HCV).[6] Globally, chronic hepatitis B alone is responsible for about 50% of the underlying etiologies for the development of HCC.[7] With hepatitis C, it is estimated that the HCV-infected individuals are associated with 3-5% of HCC incidence worldwide.[8] More than 70% of all newly diagnosed liver cancers occur in Asia, a region which accounts for 75% of all those chronically infected with HBV in the world.[9] About 55% of global HCC cases occur in China.[10]

Surgery, liver transplantation, radiotherapy, chemotherapy, immunotherapy, and newer pharmaco/biological treatments are currently used for the management of HCC. Chemotherapy is

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DOI: 10.4103/2225-4110.119732

one of the major conventional HCC therapies, but the associated strong side effects and the development of drug resistance often affect the treatment outcome. Development of safe and effective chemopreventive agents is therefore necessary to better improve liver cancer morbidity and mortality. Both natural products and herbal medicines have also been used to prevent and treat liver diseases including hepatitis, liver cirrhosis, and HCC. They are still extensively adopted, particularly in Asian countries, due to their efficacy, availability/accessibility, lesser side effects, and improved quality of life. Ongoing research continues to explore their bioactivities against various cancers as well as characterize their underlying mechanism (s), which could lead to novel methods of treating cancers. In this review, we summarize the anti-HCC properties and mechanism (s) of action of the natural product cinnamaldehyde, as well as the herbal prescription Huang-Lian-Jie-Du-Tang (黃連解毒湯 Huáng Lián Jiě Dú Tāng; HLJDT) from recent studies.

CINNAMALDEHYDE

Cinnamaldehyde (CIN) [Figure 1] is an active constituent isolated from the stem bark of cinnamon trees such as *Cinnamomum cassia* Presl. (肉桂 Ròu Guì) (Lauraceae). This aromatic aldehyde has been widely investigated for its biological and pharmacological properties, including anticancer, antioxidative, anti-inflammatory, anti-diabetic, anti-mutagenic, and immunomodulatory activities.[11-16] CIN is the major component of cinnamon bark essential oil that is also widely used as a fragrance ingredient and as an antibacterial agent in the food industry.[17,18] Results from our study as well as other studies have shown that CIN can exert antiproliferative activity against various types of human cancer cells, including those derived from HCC such as PLC/PRF/5 and HepG2 cells.[19-25]

Effect of CIN on apoptosis modulated by the mitochondria and the Bcl-2 family members

Apoptosis is a major physiological process of the cell involved in the development of multicellular organism and the regulation of cellular homeostasis. Deregulation of the apoptotic program is linked to the pathogenesis of many diseases including cancer, autoimmune diseases, stroke, and neurodegenerative disorders.[26,27] The mitochondria are known to occupy a key position in the induction of apoptosis mediated by various apoptotic stimuli, including chemotherapeutic drugs, DNA damage, UV irradiation, reactive oxygen species (ROS), and other cellular stress factors.[28,29] Mitochondrial apoptosis is triggered by the collapse of mitochondrial membrane potential ($\Delta\psi m$) and generation of ROS, which are modulated by Bcl-2 family of proteins including pro-apoptotic (Bax, Bak, Bid, and Bad) and anti-apoptotic (Bcl-2, Bcl-x_L, Bcl-w, and Mcl-1) molecules.[30] In cancer treatment, apoptosis induced by many chemotherapeutic agents involves the cleavage of Bid to its truncated form (t-Bid) by caspase (CASP)-8. This event, in conjunction with a favorable ratio of pro-apoptotic to anti-apoptotic Bcl-2 family members, causes the release of cytochrome *c* from the mitochondria into the cytosol; cytochrome *c*, upon forming a complex with the apoptotic protease activating factor 1 (Apaf-1), leads to the activation of CASP-9 and the downstream CASP-3, eventually resulting in cell death.[31] The second mitochondria-derived activator of caspase (Smac/DIABLO) and/or Omi/HtrA2 are the factors released from the mitochondria, along with cytochrome *c* during apoptosis. These molecules function to promote caspase activation by eliminating the negative effect mediated by the inhibitor of apoptosis (IAP) family of proteins.[32,33]

Apoptosis due to CIN treatment has been shown to involve the mitochondria and Bcl-2 family of proteins in HCC cells. Specifically, treatment with CIN induces the PLC/PRF/5 hepatoma cells to accumulate in S phase, which is associated with loss of $\Delta\psi m$ and up-regulation of ROS formation and Bax expression.[21,25] An increased cytochrome *c* leakage from the mitochondria to the cytosol is also observed with the activation of CASP-8 and CASP-3, and with the resulting cleavage of targets such as Bid and poly (ADP-ribose) polymerase (PARP), respectively. Levels of Bcl-2, Mcl-1, and X-linked inhibitor of apoptosis protein (XIAP) expression are also down-regulated in hepatoma cells treated with CIN [Figure 2].[21,25] Furthermore, these mitochondria-related apoptotic effects triggered by CIN can be blocked by pretreatment with the mitochondrial permeability transition (MPT) pore inhibitor, cyclosporin A (CsA), and the general caspase inhibitor z-VAD-fmk, suggesting the involvement of the mitochondria in CIN-induced apoptosis.[22] It is also noteworthy that CIN treatment in conjunction with an antioxidant such as vitamin E has been observed to suppress the release of apoptotic factors from the mitochondria in the hepatoma cells.[25]

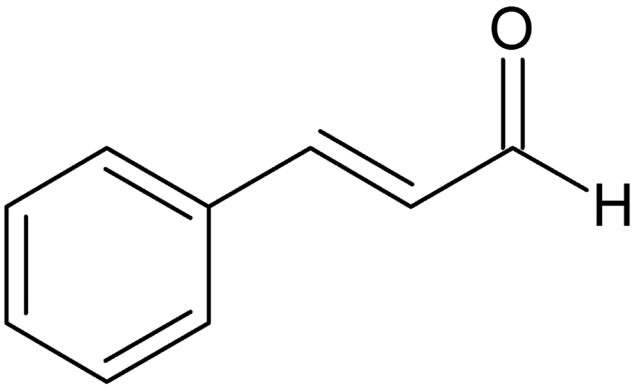

Figure 1. Chemical structure of cinnamaldehyde

Effect of CIN on the MAPK-mediated apoptosis

In mammalian cells, the mitogen-activated protein kinases (MAPKs) are a superfamily of proline-directed serine/threonine protein kinases that include the c-Jun N-terminal kinases (JNKs), extracellular signal-regulated kinases (ERKs), and p38.[34] Downstream targets of MAPKs can include mitogenic/pro-inflammatory enzymes and nuclear transcription factors, and thus, the MAPKs play a pivotal role in inflammation, cell proliferation, cell differentiation, and cell death. The activation of JNK and p38 has been associated with apoptosis, whereas ERK activation has been observed to enhance cell growth and differentiation.[35-37]

The apoptosis-inducing effect of many natural products involves MAPKs. It has been reported that the RRR-α-tocopheryl succinate induces cell death in human breast cancer cells through