Pharmacological effects of chlorogenic acid: an overview

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ABSTRACT

Chlorogenic acid, the ester of caffeic and quinic acid, has received considerable recent attention due to its multiple biological and pharmacological effects. Chlorogenic acid is found in a number of plants, including Phyllostachys edulis, Calluna vagaries and Hibiscus sabdariffa. It is rich in the eggplant fruits and abundant in coffee beans. Also, its presence is reported in the apple, pears, tomatoes, carrot, potato and blueberries. It is used as an additive in chewing gum, mints and coffee products. The present mini review discusses about its potent pharmacological effects and reported mechanism of action in brief.

Keywords: Chlorogenic acid; Cancer; Diabetes; Hepatotoxicity; Inflammation; Neuroprotection.

INTRODUCTION

Chlorogenic acid is an important biosynthetic intermediate in lignin biosynthesis. It is an ester formed between the combination of two molecules, caffeic acid and the 3-hydroxyl position of the L-quinic acid. Chlorogenic acid is found in several plants, including Phyllostachys edulis, Calluna vulgaris, and Hibiscus sabdariffa. It is also found in green tea, apple, tomatoes, blueberries and strawberries (Lallemand et al., 2012). Experimental studies reported that up to 8% of ingested chlorogenic acid by weight is absorbed as caffeic acid in the intestine. Human studies, however, noticed 1.7% of ingested chlorogenic acid in the urine after the consumption of 2g chlorogenic acid. Around 12 urinary metabolites of ingested chlorogenic acid has been reported, after digestion and metabolism of chlorogenic acid. Some of the important urinary metabolites of chlorogenic acid include caffeic acid and ferulic acid (Rohn et al., 2006). Chlorogenic acid is reported to have diverse biological activities including antioxidant, antidiabetic and hepatoprotective potential (Feng et al., 2016; Ye et al., 2016; Jaeschke 2016).

The structure of chlorogenic acid is given in the figure 1. This mini review highlights the pharmacological effects of chlorogenic acid reported so far in both in vitro and in vivo studies. For this particular review, the information on chlorogenic acid was collected from PUBMED resources and previous review articles as well as from cited references.

Hepatoprotective effect of chlorogenic acid

The liver, the major metabolic organ, plays a vital role in the detoxification of xenobiotics. Acute or chronic liver diseases always arise as a result of drug induced liver damage. (Feng et al., 2016) demonstrated the hepatoprotective and antioxidant efficacy of chlorogenic acid loaded liposome in the experimental mouse model. They concluded that liposomal formulation not only enhanced the oral bioavailability but also significantly increased the antioxidant potential of chlorogenic acid, which could be responsible for its hepatoprotective properties. (Feng et al., 2016) highlighted the protective role of chlorogenic acid against D-
galactose induced liver and kidney damage in mice. They suggested that the protective efficacy of chlorogenic acid might be attributed to its anti-inflammatory and antioxidant properties. (Pang et al., 2015) suggested that the potent antioxidant efficacy of chlorogenic acid prevented acetaminophen induced hepatic injury. Chlorogenic acid explored the hepatoprotective effect against acetaminophen induced hepatotoxicity in mice (Jaeschke, 2016). (Zheng et al., 2015) demonstrated the hepatoprotective effect of chlorogenic acid against acetaminophen induced hepatotoxicity. The protective effect is probably due to down regulation of TLR3/4 NFĸB signaling pathways. (Ji et al., 2013) suggested that the hepatoprotective potential of chlorogenic acid relies on its antioxidant efficacy in acetaminophen-induced liver injury. (Shi et al., 2016a) showed the chlorogenic acid protective efficacy on liver fibrosis both in vivo and in vitro. They suggested that chlorogenic acid attenuated liver fibrosis, though the inhibition of oxidative stress in hepatic stellate cells.

Anti-inflammatory effect of chlorogenic acid

Inflammation is the protective response raised by the body's white blood cells against bacteria and viruses, the foreign invaders. A substance that reduces inflammation is referred to as inflammatory agents. (Tsang et al., 2016) pointed out that chlorogenic acid suppressed the skin inflammation via inhibiting the release of cytokine IL6. (Hwang et al., 2015) explored the anti-inflammatory potential of chlorogenic acid loaded gold nanoparticles in in vitro model. They suggested that chlorogenic acid loaded gold nanoparticles significantly down regulated NFĸB mediated inflammatory network. (Guo et al., 2015) suggested that the anti-inflammatory efficacy of chlorogenic acid relies on its involvement in the suppression of TLR2/TLR9 MyD88 signaling pathways in HSV-1 induced responses in BV2 microglia. Chen and Wu (2014) pointed out that chlorogenic acid exhibited anti-inflammatory effect in human chondrocytes via inhibiting nitric oxide and prostaglandin E2 production as well as COX-2 and iNOS expression. (Hwang et al., 2014) demonstrated the anti-inflammatory effect of chlorogenic acid in lipopolysaccharides induced RAW 264.7 and BV2 microglial cells. They suggested that the anti-inflammatory effect of chlorogenic acid is due to its role in the inhibition of nitric oxide production COX-2 and iNOS expression. (Shi et al., 2013b) pointed out that the anti-inflammatory potential of chlorogenic acid is due to its inhibitory effect on LPS/ROS/NFĸB signaling pathways in the hepatic satellite cells. (Shi et al., 2013c) explored the anti-inflammatory role of chlorogenic acid in CCl4 induced liver inflammation and fibrosis. They suggested that chlorogenic acid exhibited anti-inflammatory efficacy via inhibition of TLR4/MyD88/ NFĸB signaling pathway. (Lou et al., 2015) pointed out that chlorogenic acid and luteolin in combination synergistically inhibited the inflammatory proliferation of synoviocytes in rheumatoid arthritis patients.

Neuroprotective effect of chlorogenic acid

Neuroprotection refers to the preservation of neuronal integrity against a neurodegenerative insult. (Kwon et al., 2010) pointed out that chlorogenic acid exerted a neuroprotective role against scopolamine induced amnesia in mice via improving the antioxidant defense mechanism and by decreasing the activity of acetylcholine esterase. Hao et al., (2015) explored the therapeutic potential of chlorogenic acid against cadmium-induced oxidative neuropathy in experimental rats. Heitman and Ingram (2014) reviewed the cognitive and neuroprotective potential of chlorogenic acid. Oboh et al., (2013) pointed out that chlorogenic acid inhibited oxidative stress induced neurodegeneration in rat brain cells. Mikami et al., (2015) explored the neuroprotective effect of chlorogenic acid against glutamate neurotoxicity.

Anticancer effect of chlorogenic acid

Malignant cancers are characterized by rapid and abnormal cell growth, invasion and metastasis. It has been estimated that around 15 million new cancer cases were reported by the year 2012 worldwide. In India, a total number of 3,00,000 cancer new cases are reported to occur every year. Epidemiological studies pointed out that consumption of chlorogenic acid containing beverages such as coffee could help to prevent several chronic disorders, including diabetes and cancer (Liang and Kitts, 2015). (Feng et al., 2005) reported that the chemo preventive efficacy of chlorogenic acid is due to its significant role in the up regulation of antioxidant enzymes as well as in the suppression of ROS – mediated NFĸB, MAPK, and AP-1 activation in A549 human cancer cells. Rakshit et al., (2010) have demonstrated that chlorogenic acid induced apoptosis in Bcr-Abl+CML cell via early accumulation reactive oxygen species. (Jiang et al., 2001) demonstrated chlorogenic acid induced cytotoxicity in human oral cancer cell lines. The cytotoxic effect is probably due to H2O2 mediated oxidative mechanism. Chlorogenic acid inhibited rat tongue carcinogenesis, when administered concomitantly with the carcinogen 4NQO (Tanaka et al., 1993). (Matsunaga et al., 2002) demonstrated the protective role of chlorogenic acid in azoxymethane-induced colon cancer in rats. (Shimizu et al., 1999) explored the antitumor efficacy of chlorogenic acid against methyl-nitrosourea induced stomach carcinogenesis. (Tanaka et al., 1990) showed the tumor inhibitory potential of chlorogenic acid in rat hepatocarcinogenesis. (Huang et al., 1988) pointed out the antitumor promoting potential of chlorogenic acid in skin carcinogenesis. (Mori et al., 1986) demonstrated the tumor inhibitory effect of chlorogenic acid in methyloxyazoxymethanol acetate induced large intestine and hepatocarcinogenesis. Chlorogenic acid significantly induced apoptotic cell death in leukemia cells via regulating caspase-3 pathways (Yang et al., 2012). Chlorogenic acid reduced the cell viability of colon cancer cells in vitro by causing S-
phase cell cycle arrest (Hou et al., 2016). (Park et al., 2015) suggested that chlorogenic acid played a vital role in the inhibition of hypoxia induced angiogenesis. The inhibitory effect of chlorogenic acid is due to its role in the down regulation of the HIF-1α/AKT pathway. (Liu et al., 2013) reported that chlorogenic acid inhibited the cell proliferation as well as induced the preprophase apoptosis in HL-60 cells.

**Anti-diabetic effect of chlorogenic acid**

Diabetes mellitus, a metabolic syndrome, occurs due to defects in insulin secretion and or function. The incidence of this metabolic disorder is rapidly increasing worldwide and around 400 million and 6 million people are affected by diabetes mellitus worldwide and in India respectively by the year 2014. Ye et al., (2016) reported that chlorogenic acid attenuated oxidative stress in streptozotocin mediated diabetic nephropathy in rats. (Meng et al., 2013) reviewed the efficacy of chlorogenic acid on glucose and lipid metabolism. (Ghadieh et al., 2015) focused the modulating effect of chlorogenic acid/chromium supplementation on glucose metabolism and obesity in mice. The suggested that chlorogenic acid/chromium supplementation played a vital role in maintaining glucose metabolism in high fat diet fed mice. (Hunyadi et al., 2012) suggested that chlorogenic acid exerted anti-hyperglycemic activity in type II diabetic rats.

**Other pharmacological effects of chlorogenic acid**

Topical administration of chlorogenic acid prevented the formation of trinitrobenzenesuphonic acid induced colitis in mice. The authors suggested that suppression of NFκB activation might be a possible mechanistic role of chlorogenic acid during TNBS induced colitis (Zatorski et al., 2015). (Liu et al., 2016) explored the analgesic efficacy of chlorogenic acid and suggested that the effect is due to promoting voltage-gated potassium channel activation. Bagdas et al., (2015) suggested that systemic chlorogenic acid therapy could have a beneficial effect on wound healing. Sotillo and Hadley (2002) reported that chlorogenic acid has a vast potential to modify the status of liver concentration of lipids and minerals in Zucker rats. (Amin et al., 2012) highlighted the dose dependent inhibitory effect of chlorogenic acid in collagen induced platelet aggregation. (Zhao et al., 2012) explored the mechanism for the antihypertensive effect of chlorogenic acid. (Fuentes et al., 2014) reported the inhibitory effect of chlorogenic acid on human platelet activation and thrombus formation. (Akila et al., 2017) suggested that the antioxidant efficacy of chlorogenic acid is responsible for the attenuation of isoproterenol induced myocardial oxidative stress in male albino wistar rats.

**CONCLUSION**

The present mini review explores the multiple pharmacological effects of chlorogenic acid. Based on the thorough and extensive literature survey, it is observed and concluded that chlorogenic acid exerted various pharmacological activities, mainly through its antioxidant potential. Thus, chlorogenic acid could be recommended as a therapeutic agent alone or in combination with the currently available in therapeutic drugs to treat various diseases.

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