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RESEARCH ARTICLE

MOLECULAR MECHANISM OF BENEFICIAL EFFECT OF COFFEE ON LIVER: A SYSTEMIC REVIEW

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ABSTRACT

In this brief systematic review, we will discuss the key components in coffee that have a significant role in prevention of various liver diseases. The main components are chlorogenic acid (CGA), trigonelline, diterpenes kahweol, cafestol, 16-O-methylcafestol , melanoidins and caffeine. There are very few retrospective or prospective studies done to evaluate the association between coffee and liver. Most of the studies have been done on mice and rats at molecular level. These studies give us very extensive and in depth reviews of the mechanism by which coffee and its components help prevent liver diseases.

INTRODUCTION

Coffee is composed of various biochemical that play a significant role in prevention of non-alcoholic liver disease, liver cirrhosis and even liver cancer. [1] In this brief systematic review, we will discuss about the key components in coffee that have a significant role in prevention of various liver diseases. The main components are chlorogenic acid (CGA), trigonelline, diterpeneskahweol, cafestol, 16-O-methylcafestol, melanoidins and caffeine. There are very few retrospective or prospective studies done to evaluate the association between coffee and liver. Most of the studies have been done on mice and rats at molecular level. These studies give us a very extensive and in depth reviews of the mechanism by which coffee and its components help prevent liver diseases.

Effect of coffee in prevention of inflammation and progression to NASH/NAFL/fibrosis: Various published studies demonstrate an inverse association between coffee consumption and liver fibrosis. Manyoutstanding reviews examine this hypothesis in further detail, and the overwhelming inference is that this inverse association is factual– coffee drinking reduces liver fibrosis. He Wang et al in there in vitro cell study established that caffeine inhibited the production of procollagen I via PKA-SRCERK1/2 and procollagen III via P38 MAPK 0 pathway and hence prevents liver fibrosis. [1]

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Another in vitro study established that trigonelline suppresses reactive-oxygen-species (ROS)-potentiated invasive activity and thereby progressing of liver fibrosis. [2] Two studies done on rats have reported that caffeine down-regulates cAMP/PKA/CREB pathway in rat hepatostellate cells and thereby prevents liver fibrosis. [2,3] Vitaglione, P et al in a study on rats showed that coffee/polyphenol modulates gene and protein expression of several mediators of inflammation, insulin sensitizers, and hepatic fat b-oxidation by up-regulation of PPAR-alpha and adipo R2, and down regulation of THF alpha, TGF beta and tTG gene which decreases the progression to NASH. They further report that it reduces IFN gamma and GST actvity and increase the concentration of IL 4 , IL10 and GSH/GSSG which also play a role in decreasing the progression to NASH.[4]Another study on ratsdemonstrated that caffeine prevents liver fibrosis by increasing hepatostellate cell apoptosis and intracellular F-actin and cyclic adenosine monophosphate expression. It also inhibits expression of procollagen type Ic and α-SMA and Transforming growth factor-β. [5] Coffee has also been shown to have anti-inflammatory properties. Paur I et al in their study on mice showed that melanoidins, reduces inflammation by a 63% inhibition of nuclear factor-jB activation which has been associated with the progression of liver fibrosis.[6] Chlorogenic acid prevents liver fibrosis by inhibition of TLR4/ myeloid differentiation factor 88 / nuclear factor -B signaling pathway. It attenuates hepatic mRNA expression and serum levels of tumor necrosis factor- (TNF-), interleukin-6 (IL-6) and interleukin-1 (IL-1).[7] Brandt, A. et al in their study on mice modelshowed that coffeeprevents nonalcoholic fatty liver

disease by down regulating inducible NO-synthase protein levels and 3-nitrotyrosine protein adducts found in proximal small intestine. [8] Chang, C. C., et al reported that caffeineprevents liver fibrosis and intrahepatic angiogenesis by down regulating hepatic VEGF/Rho-A protein expressions but study reported that the pulmonary inflammation and angiogenesis-related protein expressions were not significantly altered by caffeine.[9]Caffeinealso attenuates progression to cirrhosis through its antioxidant properties and by down regulating expression of transforming growth factor-beta (TGF-b), connective tissue growth factor (CTGF), alpha-smooth muscle actin (a-SMA), and matrix metalloproteinase (MMP)-2, 9 and 13.[10] Coffee and its components have also been found to have protective role in prevention of hepato-cellular carcinoma. [2] One hospital-based control study conducted in Italy concluded that compared to non-coffee consumers, the risk of HCC was lower by 20% with an intake of 1–2 cups per day, by 60% for 3–4 cups and by 70% for >5 cups.[11] Two meta-analyses concluded that an increase in coffee consumption of one cup per day was associated with a 22–25% lower risk of liver cancer.[12,13]

Coffee and its effect on preventing free radical injury though its anti-oxidant property: A review study mentions role of diterpeneskahweol, cafestol and 16-O-methylcafestol, in prevention of NAFLD by inducing phase II detoxifying enzymes, and regulation of Nrf2/ARE signaling pathways, and hence enhances the endogenous defense systems against oxidative damage.[14] Chlorogenic acid and caffeic acid have been found to exhibit protective effects against ischemic reperfusion injury in the rat small intestine through its antioxidant properties as shown by an study done bySato, Y. et al. [15] A study showed that coffee improved liver injury in rats with NAFLD by enhancing the expression of chaperones, located in mitochondria and endoplasmic reticulum, ensuring correct protein folding, and by increasing the expression of antioxidant proteins. [16] Kolb, H. et al found that phenolic phytochemicals induce cell stress, causing activation of an adaptive cell defense response, via activation of the Nrf2 system, translocation of Nrf2 to the nucleus and increased expression of Nrf2-dependent antioxidant and other cytoprotective genes.[17]Kalthoff S et al in their in vitro study and study on mice model reported that coffee increases antioxidant activity by directly activating Nrf2 (nuclear factor erythroid 2-related factor) transcription factor or indirectly increasing the expression of UDP glucuronosyl transferase in hepatocytes.[18]

Coffee and its anti-inflammatory property: Ma et al in their experimental study on mice showed that chlorogenic acid (CGA), a component in coffee prevents mice from diet-induced obesity and obesity related metabolic syndrome. CGA also improves liver steatosis, insulin sensitivity and reduces chronic inflammation in obese mice. These findings provide direct evidence in support of the potential health benefits of CGA in managing obesity and obesity-associated metabolic disorders. [19] Tajik, N.et al in their review study reportedchlorogenic acid up regulates PPAR alpha, CPT, AMPK, which affects pro-inflammatory cytokines and chemokines which stimulates anti-inflammatory activity by reducing reactive oxygen species. [20] Paur I et al in their study on mice showed that melanoidins, reduces inflammation by a 63% inhibition of nuclear factor-jB activation. [6]

Effect of coffee on altering lipid level in blood: Most studies that shown that caffeine, chlorogenicacid, and polyphenols play a significant role in decreasing lipid level in blood. Velázquez, A. M. et al reports that polyphenols has the following mechanism by which it decreases lipid level in blood and prevent free radical injury, 1)up-regulates acyl-CoA oxidase 1 and PPAR-α gene expression - responsible for the β-oxidation. 2) Up-regulates liver X receptor-α (LXR-α), intestinal ATP-binding cassette subfamily A1 (ABCA1) and ATP-binding cassette subfamily G1 (ABCG1) gene expression, reducing circulating cholesterol3) up-regulation of free fatty acid receptor-1 (FFAR-1) mRNA expression-hence reduces lipid digestion. 4) Up-regulates zonulin-1 and claudin gene expression, reducing gut permeability for lipids. 5) Controls body weight through increased energy expenditure and fat oxidation through amelioration of insulin sensitivity and a negligible up-regulation of intestinal peptide YY (PYY) gene expression.[21] A similar study done on mice proposed that polyphenolsenhances energy metabolism and reduces lipogenesis by down regulating mRNA levels of sterol regulatory element-binding protein (SREBP)-1c, acetyl-CoA carboxylase-1 and -2, stearoyl-CoA desaturase-1, and pyruvate dehydrogenase kinase-4 in the liver, which leads to the suppression of body fat accumulation.[22] A review study reportedchlorogenic acid up regulates PPAR alpha, CPT, AMPK, which positively regulates lipid/glucose metabolism. [20] Few studies also came to a similar conclusion that chlorogenic acid and caffeine play a role in reduction of hepatic TG levels. [23, 24] Caffeineworks by reducing intra-hepatic lipid content and stimulates β-oxidation in hepatic cells and liver via an autophagy-lysosomal pathway by down regulation of mTOR signaling and alteration in hepatic amino acids and sphingolipid levels.[25,26]An in vitro study demonstrated thatcaffeine induces auto-phagosome formation in HepG2 cells which reduced hepatic lipid content and thus playing a protective role in prevention of NAFLD.[27,28]Some studies have even demonstrated beneficial effect of decaffeinated coffee by decreasing lipid level in blood by down-regulating IL-1b gene expression in the livers of high fat diet-fed mice given decaffeinated coffee.[29] In summary, multiple studies done in mice, rats and in vitro laboratory testing have proved that coffee through its various component have a beneficial effect on liver by lowering lipid level in blood, decreasing free radical injury, decreasing inflammation and preventing progression of fibrosis in liver.

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