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Review

Coffee and liver diseases

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ABSTRACT

Coffee consumption is worldwide spread with few side effects. Interestingly, coffee intake has been inversely related to the serum enzyme activities gamma-glutamyltransferase, and alanine aminotransferase in studies performed in various countries. In addition, epidemiological results, taken together, indicate that coffee consumption is inversely related with hepatic cirrhosis; however, they cannot demonstrate a causative role of coffee with prevention of liver injury. Animal models and cell culture studies indicate that kahweol, diterpenes and cafestol (some coffee compounds) can function as blocking agents by modulating multiple enzymes involved in carcinogenic detoxification; these molecules also alter the xenotoxic metabolism by inducing the enzymes glutathione-S-transferase and inhibiting N-acetyltransferase. Drinking coffee has been associated with reduced risk of hepatic injury and cirrhosis, a major pathogenic step in the process of hepatocarcinogenesis, thus, the benefit that produces coffee consumption on hepatic cancer may be attributed to its inverse relation with cirrhosis, although allowance for clinical history of cirrhosis did not completely account for the inverse association. Therefore, it seems to be a continuum of the beneficial effect of coffee consumption on liver enzymes, cirrhosis and hepatocellular carcinoma. At present, it seems reasonable to propose experiments with animal models of liver damage and to test the effect of coffee, and/or isolated compounds of this beverage, not only to evaluate the possible causative role of coffee but also its action mechanism. Clinical prospective double blind studies are also needed.

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Contents

1. Introduction . . . 298
   1.1. Coffee and liver enzymes . . . 298
   1.2. Coffee and fibrosis/cirrhosis . . . 298
      1.2.1. Cirrhosis/fibrosis . . . 298
      1.2.2. Some factors involved in fibrosis . . . 298
   1.3. Development of liver cirrhosis and coffee . . . 299
   1.4. Coffee and hepatocellular carcinoma . . . 300
2. Cafestol and kahweol . . . 301
3. Possible anti-tumorigenic mechanism for diterpenoids . . . 301
   3.1. Phase I-mediated mechanisms . . . 301
   3.2. Inhibition of phase I activating enzyme expression . . . 301
   3.3. Inhibition of phase I enzymatic activity . . . 302

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3.4. Induction of phase II detoxifying enzymes . . . 302
3.5. Molecular mechanism of induction, Nrf2/ARE signal pathway . . . 302
3.6. Regulation of Nrf2/ARE signaling pathways by coffee components . . . 302
4. Coffee and drugs . . . 302
4.1. Caffeine . . . 303
4.2. Caffeine and drug interactions . . . 303
5. Conclusions . . . 303
Acknowledgments . . . 304
References . . . 304

1. Introduction

Coffee has had an important place in human society for at least 1200 years and is one of the most widely consumed beverages in the world. Coffee is appreciated for its aroma and flavor, but caffeine plays also a role in its popularity. Coffee is a mixture of thousands different compounds, like carbohydrates, lipids, vitamins, alkaloids, nitrogenous molecules, and phenolic compounds [1]. Most of the studies on the beneficial properties of coffee on humans are observational. Concerns about deleterious effects of coffee and caffeine raised by epidemiological observations in the past were likely exacerbated by high intakes of coffee and its association with cigarette smoking and inactivity [2]. Recently, coffee consumption has been related with reduction of various chronic diseases [3]. This review focused on the beneficial/deleterious effects of coffee drinking in the presence/development of liver diseases in both animal models and in humans.

A growing body of evidence on a potentially favorable effect of coffee on hepatic diseases has accumulated over the last 20 years. The beneficial effects span from positive effects on liver enzymes to cirrhosis and hepatocellular carcinoma (HCC). The evidence comes from epidemiological observations to experiments performed in animal models of liver injury [4].

1.1. Coffee and liver enzymes

Coffee consumption has been associated with a decrease in gamma-glutamyltransferase (GGT) expression [4–7]. This inverse relationship was particularly high in risk subjects, including heavy drinkers of alcohol [4]. Alanine aminotransferase (ALT) is a cytosolic enzyme of the hepatocyte and is a marker of liver necrosis when it increases in serum. In Italy and Japan, liver damage was also inversely correlated with consumption of coffee [5,8–10]. Recently, a cross-sectional study conducted in about 6000 adults at high risk of liver damages from various etiologies, found that coffee and caffeine consumption reduces the risk of elevated serum alanine aminotransferase activity [10]. It has been found that hepatic injury inhibits caffeine metabolism, raising the possibility that people with liver disease drink less coffee because they are more likely to experience caffeine adverse effects. On the other hand, the inverse relationship between serum ALT activity and coffee consumption was the same in subjects with impaired or normal liver function [10]. The possibility for liver disease to impair caffeine clearance indicates the importance of distinguishing between former coffee drinkers and non drinkers in future epidemiological studies.

1.2. Coffee and fibrosis/cirrhosis

1.2.1. Cirrhosis/fibrosis

Chronic injury to the liver may result in liver fibrosis that is characterized by the accumulation of extracellular matrix (ECM) proteins [11]. The main causes of hepatic fibrosis/cirrhosis include chronic hepatitis C or B virus (HCV and HBV) infections, alcohol abuse, parasites and non alcoholic steatohepatitis (NASH). The accumulation of ECM proteins distorts the hepatic architecture of the liver by producing fibrous scars, and the subsequent development of nodules of regenerating hepatocytes defines cirrhosis. Cirrhosis includes dysfunction of hepatocytes and increased intrahepatic resistance to blood flow that result in hepatic insufficiency and portal hypertension, respectively [12].

1.2.2. Some factors involved in fibrosis

A large body of evidence shows that the hepatic fibrogenic process is highly regulated by TGF-β1 (transforming growth factor-β1) (Fig. 1) [13–16]. In addition to hepatic stellate cells (HSC), which are induced by TGF-β to differentiate into myofibroblasts and to produce increased amounts of ECM proteins, hepatocytes are now recognized as important cells that actively participate in the fibrogenic process [13–15]. Transition of hepatocytes to fibroblast like cells induced by TGF-β show the pathogenetic importance of these cells in addition to HSC [17].

It was reported that hepatocytes synthesize CTGF (connective tissue growth factor) in culture and in damaged liver and that CTGF is up-regulated by TGF-β (Fig. 2) [18,19] and that hepatocytes are probably the principal cellular source of CTGF in the liver [20]. CTGF is then suggested as an important downstream modulator of TGF-β, thus amplifying the profibrogenic action of this cytokine in the liver and in other tissues [21]. The crucial role of CTGF in fibrogenesis is shown by important up-regulation in fibrotic livers [22–24]; in addition, it is worth noting that utilization of small interfering RNA (siRNA) to attenuate CTGF leads to prevention or decrement of experimental fibrosis [25,26]. Therefore, CTGF appears as an interesting target to fight against fibrosis and cirrhosis.

1.2.2.1. Caffeine decreases TGF-β. Interestingly for this review, the cyclic adenosine mono phosphate (cAMP) was identified as one inhibitor of CTGF induction by TGF-β (Fig. 2) [27], and caffeine (Fig. 3) and other methylxantines are well known to elevate intracellular cAMP levels by inhibiting phosphodiesterase activity [28]. All these information provide molecular evidence that coffee, in such case caffeine, may constitute an

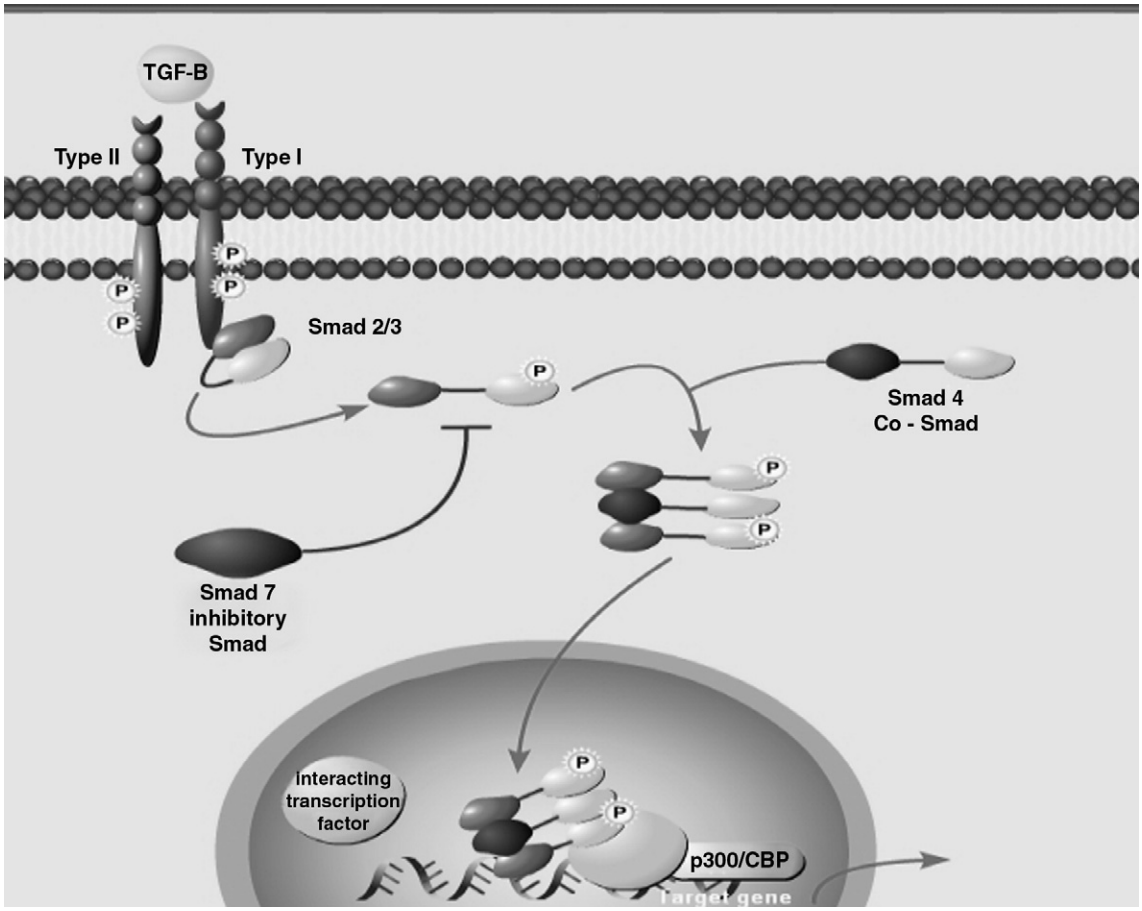

Fig. 1. The TGFb superfamily signaling pathway. Binding of TGFb superfamily ligands triggers the formation of a heteromeric complex of serine/threonine kinase receptors. The type II receptor kinase then transphosphorylates and activates the type I receptor, which in turn phosphorylates and activates R-Smads. The activated type I receptor kinase phosphorylates receptor-specific Smads, which, for the TGF-b pathway, include Smad2 and Smad3. This step can be inhibited by Smad7. Phospho-Smad2 and 3 form complexes with the co-Smad (Smad4) and move into the nucleus, where they may interact with other transcription factors or coactivators and corepressors to regulate transcription.

interesting approach to fight against fibrosis and cirrhosis. Gressner et al. [29] investigated the beneficial effect of caffeine on CTGF as the profibrogenic modulator of TGF-β actions. They found that caffeine inhibits the expression of CTGF in liver cells by inducing proteasomal degradation of the TGF-β signal mediator SMAD 2, by the inhibition of phosphorilation of SMAD 3 and 1, and by the up-regulation of peroxisome proliferator-activated receptor γ (PPARγ) expression of its receptor [29]. Therefore, long-term caffeinization appears as an interesting option for antifibrotic trials in chronic liver diseases in animals and humans.

1.3. Development of liver cirrhosis and coffee

The above information provides molecular evidence of the possible beneficial effects of coffee in the development of liver fibrosis and cirrhosis. The effect of coffee on human liver enzymes, previously described, also supports the role of this beverage in long-term hepatic injury. Several works have related the risk of cirrhosis to coffee intake [30–35].

In the prospective study conducted by Klatsky et al. [30] an inverse coffee–cirrhosis relation was reported for the first time. Drinking coffee but not tea was inversely related to alcoholic cirrhosis risk with persons who drank four or more cups per day at one-fifth the risk of those who did not drink coffee [31].

Tverdaland and Skurtveit [32] followed up more than 50,000 adults undergoing screening for cardiovascular disease. During 17 years 4207 deaths occurred, 53 from cirrhosis. This study provides evidence of a favorable role of coffee beverage consumption on the risk of death from hepatic cirrhosis; mortality was distinctively lower amongst people drinking 3 or more cups of coffee compared with persons drinking less than 2 cups. This relationship was valid for both those with alcoholic cirrhosis and patients developing cirrhosis secondary to other factors.

Corrao et al. [33] performed a study of 732 subjects (274 cases and 458 controls) and found a dose-response relationship between coffee intake and risk of liver cirrhosis with the odds ratio (OR) for cirrhosis of the liver decreasing from 1.0 for abstainers to 0.47, 0.23, 0.21, and 0.16 for 1, 2, 3 or 4 cups of coffee, respectively. The role of caffeine was also evaluated by assessing the effect of other caffeine-containing beverages on the development of hepatic cirrhosis. Interestingly, unlike

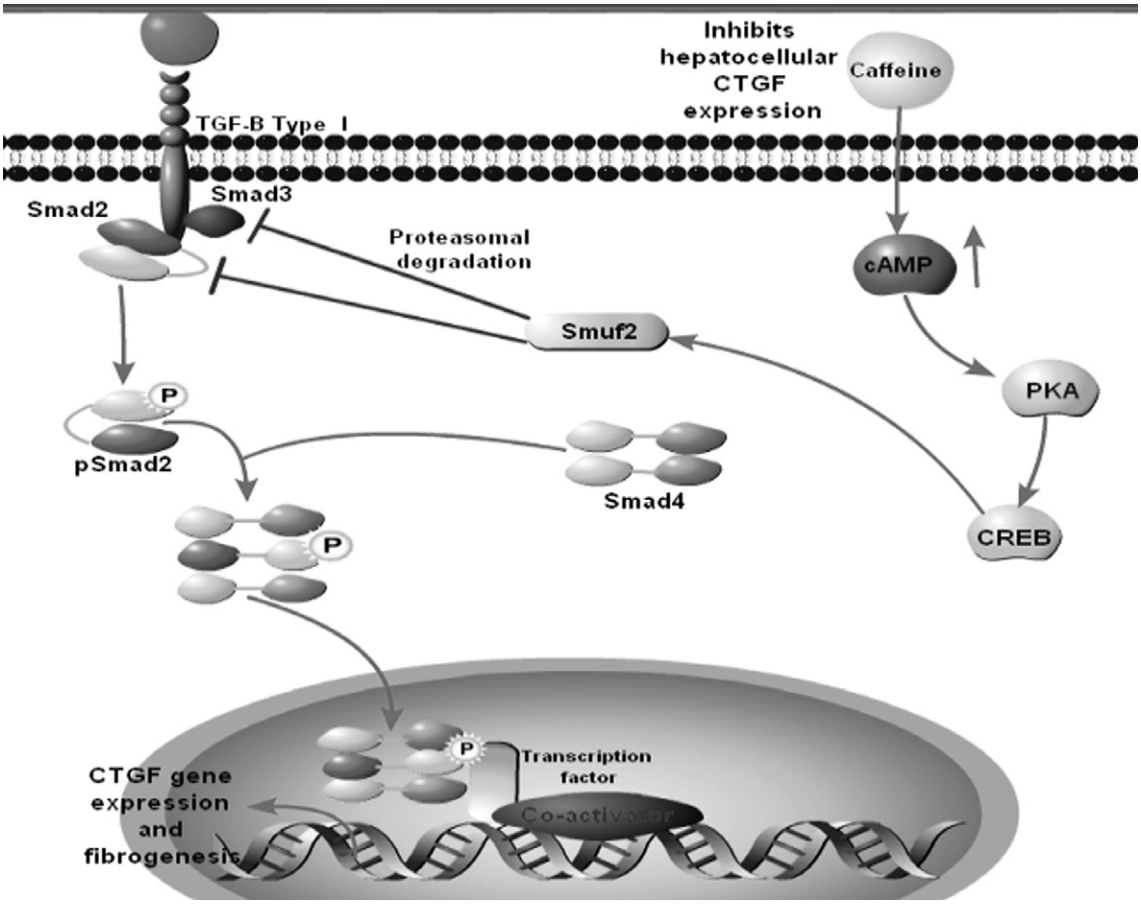

Fig. 2. Model for TGF-β induced CTGF expression in hepatocytes and fibrogenesis. Via intracellular activation of the kinase domain of the Alk5-receptor it triggers Smad2 but not Smad3-phosphorylation leading to nuclear translocation with the common mediator Smad4 and subsequent CTGF expression. Simplified and schematic overview of the proposed signaling pathway of caffeine mediated CTGF suppression in hepatocytes. Caffeine inhibits hepatocellular CTGF expression through an elevation of intracellular cAMP concentrations leading to enhanced ubiquitination/proteasomal degradation of the TGF-β effector Smad2 by the ubiquitin–ligase Smurf2, which displays high sensitivity towards this particular Smad as well as to the TGF-β receptor complex. Also observed is an inhibition of Smad3 phosphorylation but only little degradation of the total Smad3 protein, which is in contrast to Smad2.

coffee, intake of caffeine in other beverages did not show any relationship with cirrhosis [33], suggesting that other components of coffee may play a role in liver diseases. These observations were later confirmed by case-control studies with morbidity of liver cirrhosis as end point [33,34]. Additional support for the reduction in cirrhosis risk by coffee consumption comes from a study performed by Gallus et al. [35], since they observed that coffee drinkers presented less cirrhosis.

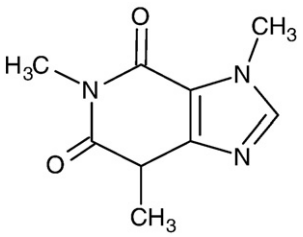

Fig. 3. Chemical structure of caffeine.

Taken together these epidemiological results indicate that coffee consumption is inversely related with hepatic cirrhosis; however, they fail to demonstrate a causative role of coffee with prevention of liver injury. Controlled prospective clinical studies and basic research are needed before a conclusion or recommendation would be reached.

1.4. Coffee and hepatocellular carcinoma

Cell culture and animal models indicate that some coffee compounds (including kahweol, diterpenes and cafestol) can function as blocking compounds by modulating multiple enzymes involved in carcinogenic detoxification [36,37]. These molecules also alter the xenotoxic metabolism by inducing the enzymes glutathione-S-transferase and inhibiting N-acetyltransferase [38]. Coffee has been associated with reduced risk of hepatic injury and cirrhosis [30–35], a major pathogenic step in the process of hepatocarcinogenesis [39–41]. Thus, the benefit that produces coffee consumption on hepatic cancer may be attributed to its inverse relation with cirrhosis, although allowance for clinical history of

cirrhosis did not completely account for the inverse association. Therefore, it seems to be a continuum of the beneficial effect of coffee consumption on liver enzymes, cirrhosis and HCC.

However, it is difficult to find causality on the basis of these descriptive studies alone. These inverse relationship may be false and due to the fact that patients with gastrointestinal illness, including liver diseases may reduce their coffee consumption. However, avoidance of coffee is not routinely recommended to patients with hepatic injury, and an inverse relation was observed among persons with self-reported or serological evidence of hepatitis. The study of Tanaka et al. [42] provides additional evidence that coffee consumption inversely correlates with HCC. They recruited 209 incident HCC and three different controls (1308 community controls, 275 hospital controls and 381 patients with chronic liver disease without cancer), coffee use during the last one or two years was associated with a decreased risk against any control group.

Observational studies included in the meta-analysis by Bravi et al. [43] are prone to various biases and are confounding. An important issue deals with the assessment of coffee intake, based on patients' self-reporting; however, recall of coffee drinking was satisfactorily valid and reproducible [44,45] The inverse relation between coffee intake and HCC in cohort and case-control studies, and in populations from Japan and southern Europe favors a major role of information or selection bias in these studies [43]. In addition, the fact that the inverse relation remained despite including major risk factors for HCC, like cirrhosis, hepatitis B and C, and other liver diseases, tobacco smoking and alcohol drinking supports the hypothesis of a strong inverse relationship between coffee and HCC. In the meta-analysis of Bravi et al. [43] they observed a 41% reduction in the risk of HCC among coffee drinkers compared with non-coffee drinkers; similar results were obtained in case control and prospective studies.

There are at least three lines of evidence for possible beneficial effects of coffee drinking in the liver: (1) several numbers of cross-sectional and cohort studies have shown a very consistent inverse association between coffee consumption and serum liver enzyme levels [4–10]; (2) various case control and cohort studies have shown a consistent protective association between coffee drinking and the risk of liver cirrhosis [30–35]; and (3) a few animal experiments showed that the incidence of cancer is lower in rodents given coffee than in placebo animals [46,47]. These observations support the possibility that coffee drinking may reduce or prevent liver diseases including HCC.

2. Cafestol and kahweol

As mentioned above, various compounds are responsible for the chemoprotective effects of coffee. Caffeine and polyphenols including chlorogenic acids and their degradation products were considered potentially responsible for the chemoprotective effects of coffee [48]. Some evidence supports that the anti-tumorigenic effect may in part be due to the uptake of the diterpenes. The major constituents of this fraction were found to be diterpenes cafestol and kahweol (C + K) (Fig. 4) [49]. These specific coffee constituents are very difficult to isolate independently, and kahweol is highly unstable when purified. Therefore, the biological properties of these compounds have been studied traditionally using a mixture of both [50]. Recently, attention has been focused on the biological effects of these diterpenes. The mechanisms responsible for the chemoprotective effects of C + K are not fully understood. Recent reports further confirm that C + K preventive effects may be mediated by both an inhibition of bioactivation and a stimulation of detoxification. Mechanisms of these compounds are discussed below.

3. Possible anti-tumorigenic mechanism for diterpenoids

3.1. Phase I-mediated mechanisms

Activation of some carcinogens with phase I activating enzymes is a prerequisite stage for the initiation of carcinogenesis. Thus, agents targeting at inhibiting the protein level or decreasing the activity of phase I activating enzymes are another anti-tumorigenic therapy. C + K, are suggested to function at this stage.

3.2. Inhibition of phase I activating enzyme expression

Reduction of carcinogen activation was shown to play an important role in the C + K mediated prevention of carcinogen DNA binding besides stimulation of detoxification processes. Long-term treatment with diets containing C + K significantly decreases the hepatic expression of the cytochrome P450 CYP3A2 at both mRNA and protein levels as well as the decreased enzymatic activity [36]. Other P450s were altered by C + K treatments. For example, the expression of the male-specific P450 CYP2C11 was also significantly

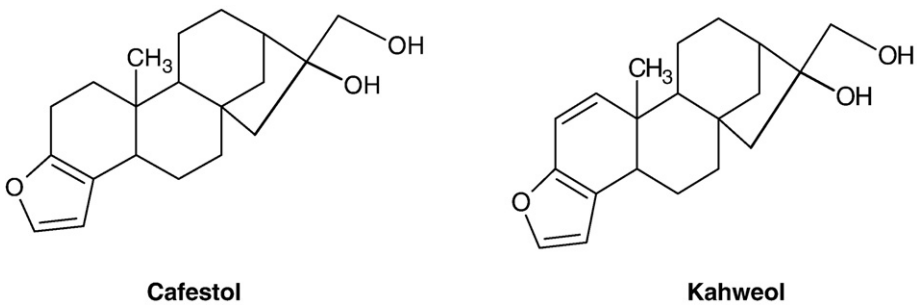

Fig. 4. Chemical structures of the coffee specific diterpenes cafestol and kahweol.

decreased by 35% at 2300 ppm and 88% at 6200 ppm of C + K in the diet as compared with control level [36]. These effects on CYP3A2 and CYP2C11 were confirmed in rat primary hepatocyte cultures. Since CYP2C11 and CYP3A2 are the major P450s responsible for the bioactivation of AFB1 (aflatoxin B1) into AFBO in the rat, it was hypothesized that a reduction in the expression of these genes may contribute to the C + K-mediated prevention of AFB1–DNA adducts [51]. These data support a role for the decrease in phase I enzyme expression in the chemoprotective effects of C + K against AFB1 genotoxicity.

3.3. Inhibition of phase I enzymatic activity

A direct inhibition of P450 enzymatic activity without any effects on protein expression is an additional phase I-mediated mechanism through which the coffee diterpenes may act. For example C + K has been shown to produce an inhibition of P 4501A1 activity in liver cells which resulted in a reduction of B[a]P activation (benzo[*a*]pyrene is a procarcinogen) and DNA binding. Similar inhibitory effects were found with human CYP 2B6, a human P450 responsible for AFB1 bioactivation [52]. In addition, it is suggested that the reduction of PhIP–DNA adducts found in C + K treated rats involves an inhibition of the PhIP-activating enzymes CYP 1A2 and N-acetyl transferase (NA) [53,54]; C + K was also found to reduce the N-hydroxylation of 4-amino biphenyl in vitro [55].

3.4. Induction of phase II detoxifying enzymes

It is known that the initiation of tumor formation consists of a permanent modification of DNA with electrophilic or oxidant metabolites derived from activated carcinogen. Members of phase II detoxifying enzymes act through an inhibition of the formation and/or the stimulation of the detoxification of the electrophilic or oxidant intermediates, resulting in decreased DNA damage and in the blocking of initiation. Induction of these enzymes is an important antitumorigenic therapy. Early studies indicated that C + K induced glutathione S-transferase (GST) activity in mouse liver and small intestine [56]. Since GST is known to detoxify electrophilic compounds through conjugation with glutathione, these data led to the hypothesis that C + K may possess the properties of blocking agents. Recent studies further confirm this hypothesis and show that C + K-preventive effects may be mediated by both an inhibition of bioactivation and a stimulation of detoxification. The effects of C + K on the expression of various GST subunits were studied in the rat [36,57]. The most striking effects identified are the strong dose-dependent induction of the GST Pi subunit Yp and the alpha subunit Yc2 (rGST A5) in the liver at the mRNA and protein levels following long-term treatment with diet containing C + K. Meanwhile, C + K-mediated induction of GST-P occurs within a few days. Moreover, it is shown that the increased expression is dependent on the continuous presence of C + K in the diet and reversible following removal of C + K [36]. In agreement with this, levels of overall GST activity, as measured with chlorodinitrobenzene (CDNB), increased two- to three-fold during a 10-day dietary exposure to 2000 ppm C + K, but returned to pretreatment levels 10 days after removal of the treatment diet [53]. In rats fed 0.2% C + K, strong increases in the liver and kidneys (two- to three-fold as compared to controls) are observed [58]. In addition to the effects on GST expression, C + K are found to strongly induce several other phase II xenobiotic metabolizing enzymes such as UGT and NQO1 (quinine oxidoreductase1) activities [59].

3.5. Molecular mechanism of induction, Nrf2/ARE signal pathway

The cis-acting antioxidant-responsive-element (ARE) sequence has been identified on the promoter of several genes involved in detoxification processes [60]. It has been suggested that altering the expression of these genes through ARE-mediated transcriptional activation is likely to be a key molecular mechanism explaining how many blocking agents may prevent mutagenesis (Fig. 5). bZip Nrf (nuclear factor erythroid related factor) proteins have been found to activate gene induction through this specific enhancer [61]. The role of Nrf2 (nuclear factor erythroid 2-related factor) transcription factor in the C + K-mediated activation of liver detoxifying enzymes has been addressed using a mouse line bearing a targeted disruption of the gene encoding this factor [62]. These results demonstrate the key role of this transcription factor in the chemoprotective activity of C + K in the small intestine.

3.6. Regulation of Nrf2/ARE signaling pathways by coffee components

Extensive studies in recent years have provided more evidence that components of coffee can regulate Keap1/Nrf2/ARE signaling pathways thus prevent carcinogenesis. Nrf2 activation is constitutively repressed by its binding with a citosolic protein known as Keap1 and to the cytoskeleton. This interaction promotes the permanent Nrf2 degradation by the proteosome, implying that the primary control of Nrf2 function lies on its subcellular distribution rather on its *de novo* synthesis [63,64]. Keap1 is a cysteine-rich protein and some of the 27 cysteine residues in Keap1 are postulated to play a sensory role in detecting oxidants and xenobiotics [65]. In addition, certain cysteine residues (C257, C273, C288, and C297) reportedly interact with the N-terminal Neh2 domain of Nrf2 [66]. C + K disrupt the cytoplasmic Keap1/Nrf2 complex through thiol modification of cysteine residues in Keap1, thereby releasing Nrf2 and permitting its translocation to the nucleus where it transcriptionally activates ARE-dependent genes [67]. Caffeine is reported to activate MAPK/ERK signal pathway so as to phosporate Nrf2 and then release and permit its translocation to the nucleus where it transcriptionally activates ARE-dependent genes [68]. Those ARE-dependent genes include genes encoding phase II detoxifying enzymes and antioxidant proteins, Nrf2. The increased expressions of these protein products thus prevent carcinogenesis at the above-mentioned stages (Fig. 5).

4. Coffee and drugs

Coffee is among the most widely consumed beverages in the world; many people use drugs and drink coffee at a time. Different studies show that caffeine may cause pharmacokinetic interactions at the CYP1A2 enzyme which may cause

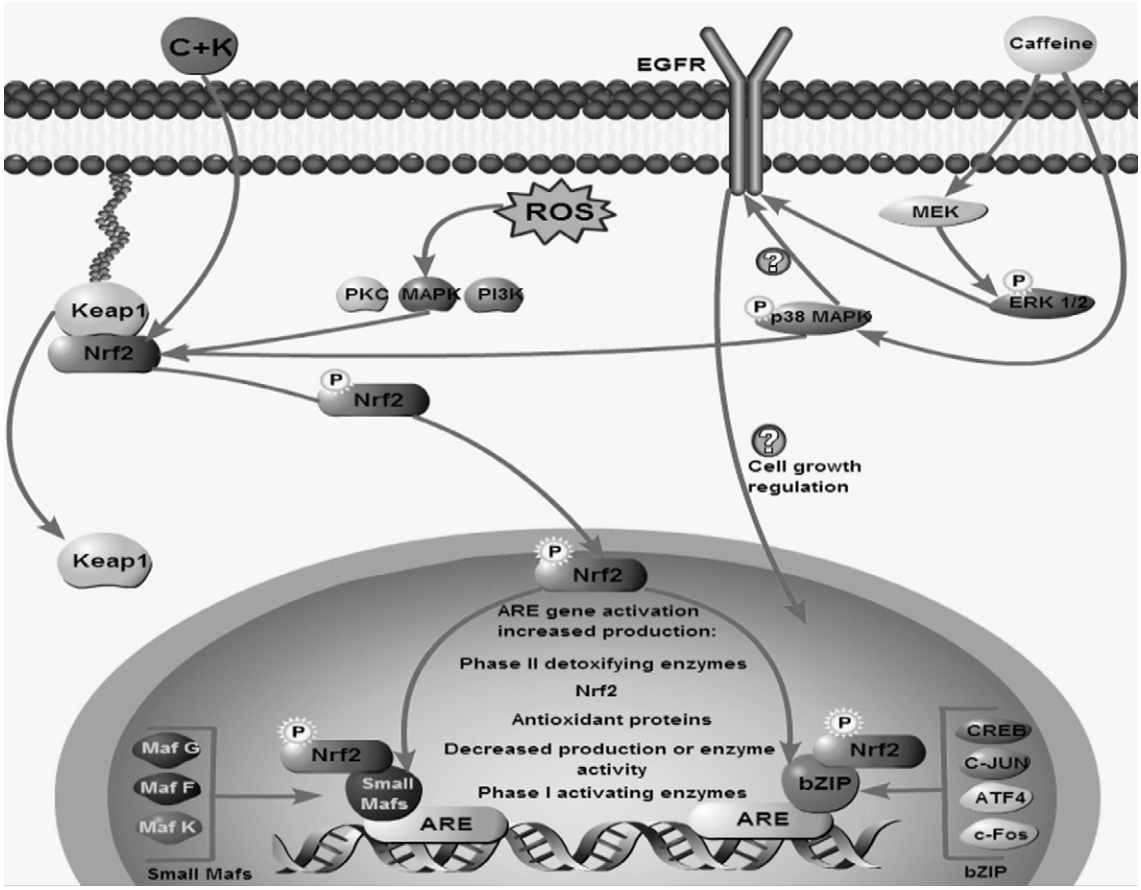

Fig. 5. Coffee components stimulate the ARE-regulated signal transduction for cancer prevention. Caffeine phosphorates Nrf2 via MAPK pathway and C + K makes thiol modification of cysteine residues in Keap1, which disrupt the cytoplasmic Keap1/Nrf2 complex, thereby releasing Nrf2 and permitting its translocation to the nucleus where it transcriptionally activates ARE-dependent genes.

toxic effects during concomitant administration of caffeine and certain drugs used.

4.1. Caffeine

Caffeine (1,3,7-trimethylxanthine) (Fig. 3) is a purine alkaloid that occurs naturally in coffee beans. In experiments with liver microsomes and CYP1A-specific inhibitors or antibodies, it has been shown that human CYP1A2 plays a pivotal role in caffeine metabolism, especially in catalyzing N-demethylation reactions [69–71]. Further studies with selected cDNA-expressed CYP isoforms, or CYP1A2 and CYP2E1 cell lines, have indicated that caffeine 3-N-demethylation is most efficiently catalyzed by CYP1A2, while the CYP3A subfamily is the main isoenzyme catalyzing C-8-hydroxylation to 1,3,7-trimethyluric acid. In addition, CYP2E1 may also contribute to 1-N- and 7-N-demethylation [72–74]. A caffeine concentration value of approximately 100 μM may be considered "the maximum therapeutic concentration in humans". However, some individuals may consume more than 1 g/day (about 15 mg/kg/day) and even up to 3.5 g/day (about 50 mg/kg/day) of caffeine in a caffeinism syndrome which leads to caffeine concentrations above 100 μM in their blood plasma [75–77]. There are some observations that point to the autoinduction of caffeine metabolism.

4.2. Caffeine and drug interactions

Interactions of caffeine with other drugs such as allopurinol, antimycotics, cardiovascular drugs, histamine H2 receptor antagonists, idrocilamide, methylxanthines (i.e. furafylline, theophylline), nonsteroidal anti-inflammatory drugs (paracetamol), oral contraceptives, phenylpropanolamine, proton pump inhibitors, psoralens, and quinolones have also been observed [76]. Use of ketamine in combination with caffeine enhances its stimulant responses and lethal risk, suggesting that a potentially toxic interaction exists between ketamine and caffeine [78]. The caffeine and antiepileptic drugs, result in increased seizure frequency. The epileptic patients should limit their daily intake of caffeine [79]. Numerous drug interactions may occur between caffeine and neuroactive drugs or other pharmacological medications. Therefore, patients taking caffeine-containing medicine or coffee drinkers taking drugs that interact with CYP1A2 may require proper dosage adjustments upon caffeine ingestion.

5. Conclusions

There is a growing body of evidence supporting the favorable effect of coffee beverages on liver function and disease. Epidemiological studies strongly suggest that drinking

around 3 cups of coffee will reduce the risk or severity of liver damage caused by a variety of etiological agents. Basic, mechanistic studies indicate that there are molecular basis to believe that coffee is good for the liver. Various components of coffee have been related to such a favorable effect, including caffeine, coffee oils kahweol, cafestol, and antioxidant substances from coffee beans, but no definite evidence is available for any of these components. At this point, studies utilizing animal models of liver damage, including HCC are urgently needed to establish if coffee plays a causative role in prevention of liver diseases and to determine its action mechanism(s). Prospective double blind studies in patients are also encouraged. In addition, numerous drug interactions may occur between caffeine and neuroactive drugs or other pharmacological medications. Therefore, patients taking caffeine-containing medicine or coffee drinkers taking drugs that interact with CYP1A2 may require proper dosage adjustments upon caffeine ingestion.

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