Chapter 15

Tea (*Camellia sinensis* L. Kuntze) as Hepatoprotective Agent: A Revisit

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1. INTRODUCTION

Liver plays a cardinal role in most metabolic processes, digestion (bile synthesis), and excretion of waste metabolites, and a pathological liver will invariably affect the health and life of an individual.[1] Liver, the chemical factory of the body, has remarkable ability to regenerate and maintain function. However, in aging the ensuing biochemical and histological changes reduce the overall physiological functioning of the liver and this at times compromises the health of the individual.[2–4]

Diet has a substantial influence on liver functions, health, and aging,[5] and numerous studies have shown that *Camellia sinensis* (L) Kuntze, commonly know as tea, possesses beneficial effects and also acts as a hepatoprotective agent against various hepatotoxins.[6] Globally, tea is the second most widely consumed beverage after water and has been cultivated and consumed by humans for thousands of years.[7] Historical evidence suggests that the tea plant was a native of China, Burma, Thailand, Laos, and Vietnam but today is also cultivated in Sri Lanka, India, and Japan.[7]

Depending on the way the leaves are harvested and processed, the tea is categorized as green, black, and oolong tea powder. Green tea (unfermented), oolong tea (partially fermented), and black tea (fully fermented) are manufactured from the same tea plant, *C. sinensis*.[7–9] Of the total commercial tea production worldwide, about 80% is consumed in the form of black tea, 18% in the form of green tea, and 2% as oolong tea. Black tea is consumed principally in Europe, North America, and North Africa; green tea throughout Asia; and oolong tea in China and Taiwan.[7–9]

2. PHYTOCHEMISTRY OF TEA

Tea is one of the most investigated plants, and detail information on the phytochemical constituents is available. The active compounds of green are the catechins (-epicatechin [EC], -epigallocatechin [EGC], -epicatechin-3-gallate [ECG], and -epigallocatechin-3-gallate [EGCG]), proanthocyanidins, flavonols (kaempferol, quercetin, and myricetin in the form of glycosides), gallic acids, and theanine, whereas that of black tea are thearubigins and theaflavins (Fig. 15.1). The relatively less commonly used oolong tea is reported to contain monomeric catechins, theaflavins, and thearubigins (Fig. 15.2).[7] Tea leaves also contain about 2%–5% of the alkaloids, caffeine, and small quantities of theobromine and theophylline. Other related compounds in this class include isotheaflavins, neotheaflavins, theaflavic acids, epitheaflavic acids, theafulvins, and theacitrins.[7]

3. VALIDATED USES

In traditional systems of medicine, black tea is used for improving mental alertness and cognitive performance. It is also used for headache, hypotension, atherosclerosis, and myocardial infarction, preventing Parkinson's disease and reducing the risk of gastrointestinal cancer, lung cancer, ovarian cancer, and breast cancer.[10,11] Studies have also shown that tea is useful in various conditions such as body weight control and energy metabolism; impaired glucose tolerance and diabetes; cardiovascular disease; bone mineral density; cognitive function and neurodegenerative disease; and cancers of stomach, esophageal, ovarian, and colon.[10–15] In addition to these multiple studies, it has been shown that tea possesses protective effects against various hepatotoxic agents. In the following section these observations are addressed.

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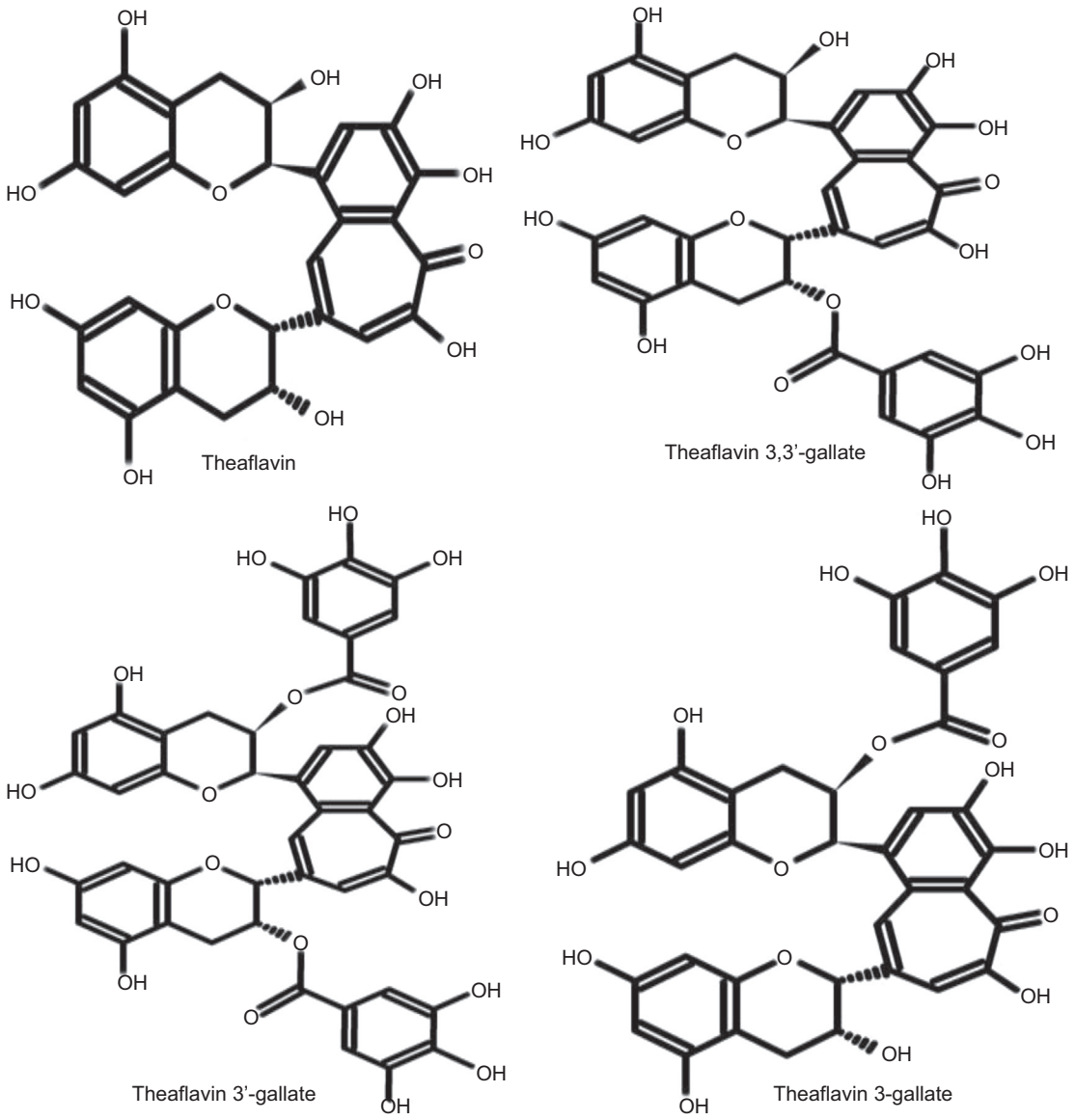

FIGURE 15.1 Phytochemicals of black tea.

4. TEA PROTECTS AGAINST THE ALCOHOL-INDUCED HEPATOTOXICITY

Alcohol toxicity is one of the world's major health problems, and chronic consumption of high doses of ethanol is proved to cause liver cirrhosis and cancer.[1] Preclinical studies have shown that tea protects against alcohol-induced hepatotoxicity by ameliorating ethanol-induced oxidative stress and preventing subsequent oxidation of lipids and proteins. Luczaj et al.[16] studied the hepatoprotective effects of black tea in rats and observed that administering black tea decreased ethanol-induced (chronically) increased lipid and protein oxidation products and increased the levels of sulfhydryl groups in liver tissue. Additionally, studies have also shown that epigallocatechin-3-gallate (EGCG), the most abundant catechin polyphenol in green tea, showed protection against alcohol-induced, cytochrome P 450–dependent liver damage and formation of fatty liver. Dietary supplementation with EGCG (3 g/L with liquid diet, 7 weeks) prevented increase in serum ALT and AST and ameliorated the reduced hepatic phospho-acetyl CoA carboxylase (p-ACC) and carnitine palmitoyltransferase 1 (CPT-1) levels.[17]

In vitro studies have also shown that theanine, a unique amino acid found in green tea protects against ethanol-induced hepatocytotoxicity, indicated by amelioration of decreased viability and increased release of LDH and AST. L-Theanine inhibited ethanol-induced L02 cell apoptosis and loss of mitochondrial membrane potential and prevented cytochrome c

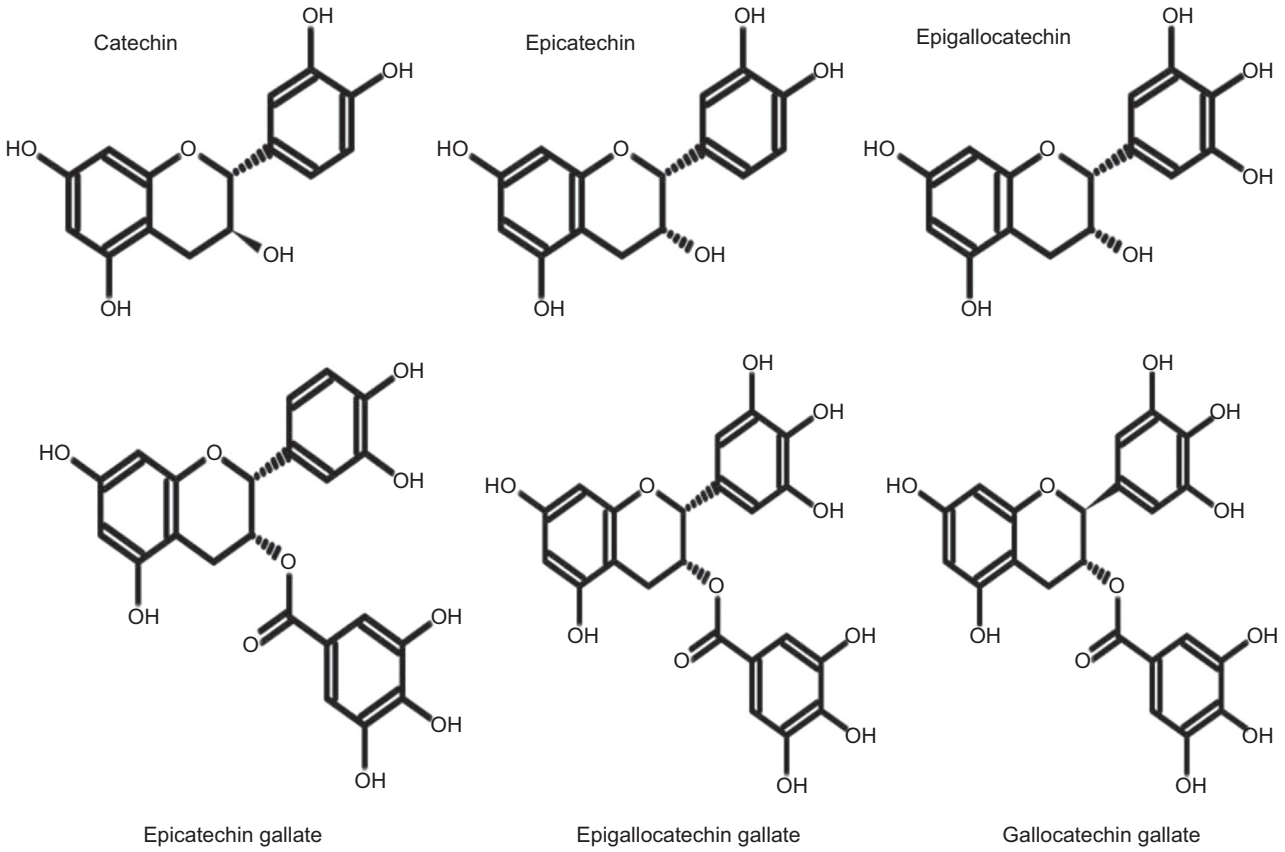

FIGURE 15.2 Phytochemicals of green tea.

release from mitochondria in ethanol-treated L02 cells. L-Theanine also prevented ethanol-triggered reactive oxygen species (ROS) and MDA generation in L02 cells.[18] In mice chronically intoxicated with ethanol, L-theonine prevented depletion of antioxidants in hepatocytes and release of hepatic enzymes LDH, AST, and ALT into the blood.[18]

5. TEA PROTECTS AGAINST CARBON TETRACHLORIDE–INDUCED HEPATOTOXICITY

Carbon tetrachloride (CCl_4) is a well-known toxin frequently used in preclinical experiments for xenobiotic-induced hepatotoxicity.[19,20] Green tea extract has been shown to be effective in decreasing the elevated serum levels of ALT and AST and ameliorating reduced liver GSH and elevated liver lipid peroxide levels in rats subjected to carbon tetrachloride toxicity.[19] Supplementation of the diet with black or green tea has been shown to prevent increase in plasma levels of aminotransferases (ALT and AST) and decrease in plasma total antioxidant capacity in rats intoxicated with carbon tetrachloride.[20] Green or black tea in diet has also shown to ameliorate oxidative stress in liver as indicated by preventing decrease in GSH and increase in MDA in liver.[20] Additionally, studies have also shown that the polyphenol-enriched extract from the Huangshan Maofeng green tea was effective in mitigating the CCl_4-induced hepatic damage in mice. Pretreatment with tea extract (200, 400, and 800 mg/kg bw) prior to CCl_4 injury significantly decreased the serum ALT, AST, and ALP activities and prevented an increase in hepatic MDA levels.[21] Mechanistic studies indicated that the protective effects were mediated at least in part by the free radical scavenging and antioxidant activities.[21]

With respect to the phytochemicals, experiments have shown that L-theanine, the amino acid constituent of black tea, prevented hepatotoxicity from carbon tetrachloride. In mice pretreated orally with L-theanine (50, 100, or 200 mg/kg, once daily for 7 days) before carbon tetrachloride dose, there was prevention of increase in serum ALT and AST and bilirubin level as well as carbon tetrachloride–induced liver histopathological changes.[22] L-Theanine significantly prevented CCl4-induced production of lipid peroxidation and decrease of hepatic GSH content and antioxidant enzymes activities. L-Theonine was shown to downregulate CYP 2E1 expression, inhibit increase of TNF-alpha and interleukin-1beta in serum, and suppress expression of inducible nitric oxide synthase and cyclooxygenase-2 in liver. It also prevented CCl_4-induced activation of apoptotic-related proteins including caspase-3 and PARP in mouse livers.[22]

6. EFFECT OF TEA ON *N*-ACETAMINOPHEN-INDUCED HEPATOTOXICITY

Acetaminophen, also known as paracetamol or *N*-acetyl-p-aminophenol, is one of the most commonly utilized compounds worldwide; its use as an antipyretic or analgesic drug has been predominant since 1955, particularly due to the fact that it is easily accessible in various formulations as an over-the-counter medication. Acetaminophen hepatotoxicity occurs through formation of the noxious *N*-acetyl-para-benzoquinone imine (NAPQI) metabolite, which is present in excessive quantities, as augmented by features of glutathione (GSH) depletion, oxidative stress, and mitochondrial dysfunction leading to depletion in adenosine triphosphate stores. Other mechanisms of hepatotoxicity include the formation of toxic free radicals, such as peroxynitrite, from the reaction of superoxide and nitric oxide, subsequently forming nitrotyrosine adducts inside the mitochondria.[23]

Black tea extract (BTE) and its main phenolic compounds, thearubigins, have been shown to have protective effect against hepatotoxic action of acetaminophen. Administration of BTE (3%, 4.5%, intraperitoneal) or thearubigins (60, 70 mg/kg, intraperitoneal) immediately after acetaminophen injection had significant effects. BTE and thearubigins caused significant amelioration of increased activities of aminotransferases, increased level of malondialdehyde in blood, decreased glutathione in blood, and central lobular hepatic necrosis.[24] Administration of EGCG (0.54%, in diet, 1 week) before an overdose of acetaminophen caused significant reduction in metabolism of acetaminophen, decrease in the levels of metabolites of acetaminophen in plasma and urine, and amelioration of increased activities of aminotransferases in serum in rats.[25] Salminen et al. investigated the effect of green tea extract on acetaminophen toxicity in mice. Administration of green tea extract prior to acetaminophen was beneficial in preventing/mitigating hepatotoxicity of acetaminophen. One of the proposed mechanisms was decreased binding of acetaminophen to protein, thereby reducing the formation of reactive metabolites. Supplementation of green tea extract after acetaminophen dose, caused potentiation of hepatotoxicity of acetaminophen. Green tea extract along with acetaminophen was shown to cause significant glutathione depletion.[26]

7. TEA IS EFFECTIVE IN VIRAL HEPATITIS

Globally, hepatitis caused by hepatotropic viruses is the most common cause for various liver diseases and cancers. Of the various viruses, the hepatitis B and C are responsible for most of the liver diseases. Hepatitis C virus (HCV) is a major cause of liver cirrhosis and hepatocellular carcinoma.[27,28] Green tea catechins, such as EGCG and its derivatives, epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC), have been found to exert antiviral and antioncogenic properties. EGCG potently inhibited cell culture–derived HCV (HCVcc) entry into hepatoma cell lines as well as primary human hepatocytes. Treatment with EGCG directly during inoculation strongly inhibited HCV infectivity.[27] A study performed by Li et al.[28] demonstrated the effect of catechins against viral hepatitis in Beijing ducklings. It was observed that the catechins were effective in reducing the levels of DHBsAg and DHBV-DNA and also reversed the histopathological changes in the liver.

8. EFFECT OF TEA ON ISCHEMIA-REPERFUSION INJURY

Ischemia-reperfusion injury induced by free radicals is one of the major complications of liver transplantation. Efforts have been made worldwide to prevent the hepatic damage due to reperfusion injury.[29] As the polyphenolic constituents of *C. sinensis* have been shown to be potent scavengers of ROS, it can be developed as a potential agent to prevent this injury. An animal study conducted with fasted Sprague–Dawley rats showed that a single dose of green tea extract was highly effective in reducing the ischemia-reperfusion injury.[29] Green tea extract acts by improving the sinusoidal circulation and also by decreasing cellular activation.[29]

In a recent study, Tao et al.[30] observed that administration of tea polyphenol extract 1 h prior to the ischemia-reperfusion injury resulted in significant attenuation of liver damage in mice. The beneficial effect of tea polyphenols was evident from the significant amelioration of increased activities of aminotransferases and amelioration of reduced ratio of GSH/GSSG. Ischemia-reperfusion injury significantly decreased the mRNA and protein expression levels of cytokine-induced nitric oxide synthase in liver tissues, and this was attenuated by pretreatment with tea polyphenols. Pretreatment with tea attenuated the increase in liver cell apoptosis and the expression level and activity of proapoptotic proteins in the liver. These findings indicate that tea polyphenols protect the liver against ischemia-reperfusion-induced injury by inhibiting oxidative stress and apoptosis.[30]

9. EFFECT OF TEA ON FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) is a common pathological condition, encompassing a range of conditions caused by lipid deposition within liver cells. To date, no approved drugs are available for the treatment of NAFLD despite the fact that it represents a serious and growing clinical problem. In a double-blind, placebo-controlled, randomized clinical

trial on patients with NAFLD, administration of green tea extract supplement (500 mg tablet for 90 days) and activities of ALT and AST in serum decreased significantly indicating beneficial effect of green tea.[31]

Administration of 1% green extract for six consecutive weeks decreased the levels of lipids and serum ALT in obese mice. It also decreased the mRNA expression of adipose sterol regulatory element-binding protein-1c, fatty acid synthase, stearoyl CoA desaturase-1, hormone-sensitive lipase, and serum nonesterified fatty acid concentrations. Immunohistochemical data indicated that steatotic livers from obese mice had extensive accumulation of tumor necrosis factor-α (TNF-α), whereas GTE at 1% decreased hepatic TNF-α protein and inhibited adipose TNF-α mRNA expression. Hepatic total glutathione, malondialdehyde, and Mn- and Cu/Zn-superoxide dismutase activities in obese mice fed GTE were normalized to the levels of lean littermates. Also, GTE increased hepatic catalase and glutathione peroxidase activities, and these activities were inversely correlated with ALT and liver lipids.[32] Wang and coworkers observed that oxidized tea polyphenols were effective in preventing accumulation of lipids in liver tissue in rats.[33] Contradictory to the abovementioned reports, prolonged supplementation of green tea extract (1%, 6 weeks) with high-cholesterol diet increased the cholesterol-induced hepatosteatosis, inflammation, and oxidative stress in liver and serum bile acids in mice.[34]

10. EFFECT OF TEA ON HEPATOTOXICITY OF LEAD

Exposure to lead through occupational and environmental settings is of major concern globally. Various studies on potential hepatotoxicity of lead in experimental animal systems and in humans exposed environmentally reported alterations in hepatic xenobiotic metabolism, cholesterol metabolism, liver cell proliferation, and DNA synthesis indicative of lead-induced hepatic hyperplasia.[35] An animal study conducted on Sprague–Dawley rats to determine the hepatoprotective effects of green tea extract on lead-induced liver toxicity showed that administration of green tea extract produced significant reduction in the levels of ALT, AST, and ALP, thus proving its protective effects on the hepatic cells.[35]

11. EFFECT OF TEA ON HEPATOTOXICITY OF ARSENIC

Arsenic increases the generation of ROS, which enhances lipid peroxidation and cellular damage in the hepatic tissues. Chronic arsenic-mediated oxidative stress consequentially activates the JNK and p38 MAPK pathways and induces apoptosis in the hepatocytes. Arsenic-induced oxidative stress induces hepatic apoptosis by upregulation of proapoptotic proteins.[36] An in vitro study has demonstrated antimutagenic, free radical scavenging, and DNA damage–preventing action of green tea in a rat experimental model. Green tea also showed SOD-protecting effect.[37]

12. EFFECT OF TEA ON PHENOBARBITOL-INDUCED LIVER DAMAGE

Hepatotoxicity is an infrequent but fatal adverse effect of phenobarbitol toxicity. Phenobarbitol has been shown to induce CYP, oxidative stress, and, consequently, liver damage.[38] An animal study conducted on diethylnitrosamine-initiated male Wistar rats showed that administration of epicatechin complex extracted from green tea along with the administration of phenobarbitol during hepatocarcinogenesis produced significant inhibition to the promotive effects of phenobarbitol.[39] Further studies with green tea extract must be conducted to develop it as a potential agent against hepatocarcinogenesis promoted by phenobarbitol.

13. EFFECT OF TEA ON HEPATOTOXICITY OF MICROCYSTIN

Microcystins are cyclic nonribosomal peptides produced by cyanobacteria, and microcystin, the most common heptapeptide of this group, is known to cause severe hepatic damage principally by inhibiting protein phosphatases.[40] Pretreatment with green tea (12 g/L, 18 days), prior to administration of microcystin decreased the serum levels of ALT, AST, and MDA and increased SOD and GSH.[40] Studies have shown that the phytochemical quercetin protected mice against the MC-LR-induced hepatotoxicity and decreased the levels of serum transaminases and hepatic activity of protein phosphatase in mice.[41]

14. EFFECT OF TEA ON HEPATOTOXICITY OF AFLATOXINS

Aflatoxins are a group of mycotoxins produced by *Aspergillus flavus* and *Aspergillus parasiticus* and are potent inducers of hepatotoxicity. Aflatoxin treatment of 30 days caused significant impairment in liver structure and function. Administration of black tea infusion (2%, along with drinking water, orally) restored the liver structure and function. Black tea caused

amelioration of aflatoxin-induced reduction of liver weight and increase in activities of serum aminotransferases.[42] Oxidized tea polyphenols have been shown to form complex with AFB1 (aflatoxin), thus inhibiting the absorption of AFB1 in intestine, promoting the elimination of AFB1 in feces, and inhibiting the liver injury caused by AFB1 in rats.[43]

15. EFFECT OF TEA ON HEPATOTOXICITY OF AZATHIOPRINE

Azathioprine (AZA) is a purine analogue used as an immunosuppressive drug in organ transplantation and autoimmune diseases. The pharmacological action of this compound is mediated through its metabolite 6-thioguanine nucleotides, which are believed to induce apoptosis of activated T lymphocytes, hence leading to suppression of the overactive immune defense mechanisms.[44] AZA-induced hepatotoxicity is believed to be a rare adverse event manifested as nodular regenerative hyperplasia, veno-occlusive disease, peliosis hepatis, fibrosis, and sinusoidal dilatation.[44] The polyphenols present in green tea were shown to mitigate the hepatotoxicity of AZA.[44] Green tea prevented the elevation of enzymes such as ALT, AST, and ALP and increased the levels of GSH, GPx, CAT, and GSSG contributing to its antiinflammatory activity. It also decreased the levels of tumor necrosis factor alpha (TNF-α) and caspase-3, thus reducing apoptosis.[44]

16. EFFECT OF TEA ON GALACTOSAMINE- AND LIPOPOLYSACCHARIDE-INDUCED LIVER DAMAGE

D-Galactosamine (GalN) is an important experimental hepatotoxin, and the pathogenesis it causes is akin to that in acute hepatitis. GalN causes insufficiency of UDP-glucose and UDP-galactose and alters the intracellular calcium homeostasis, consequently affecting the cell membranes, cell organelles, energy metabolism, and the synthesis of proteins and nucleic acids.[45] Studies performed on rats have demonstrated the protective effects of tea against D-galactosamine-induced liver damage and confirmed that the extract from tea attenuated the levels of plasma ALT and AST.[45] Lipopolysaccharide (LPS) causes hepatotoxicity by induction of oxidative stress and consequent oxidative damage to biomolecules.[46] Pretreatment with tea polyphenols attenuated LPS-induced liver injury and blunted the rise of serum TNF-alpha levels and lipid peroxidation and the induction of expressions of TNF-alpha and iNOS in the liver of rats.[47]

17. EFFECT OF TEA ON HEPATOTOXICITY OF INSECTICIDES

Cypermethrin is a synthetic pyrethroid used as an insecticide in large-scale commercial agricultural applications as well as in consumer products for domestic purposes. Induction of CYP system and oxidative stress has been implicated as the key mechanisms in the hepatotoxic effects of these insecticides. Preclinical studies have observed protective effects of BTE against hepatotoxicity of chlorpyrifos and cypermethrin.[48] Administering aqueous BTE at a dose of 200 mg/mL to mice before the combination dose of chlorpyrifos and cypermethrin (20 mg kg (−1) each) on alternate days over a 15-day period prevented and mitigated elevation in serum levels of enzymes ALP, AST, and ALT; decreased hepatic antioxidant enzymes SOD, GPx, GR, GST, and CAT in liver; and increased lipid peroxidation in liver, when compared with insecticide-alone treated cohorts.[48]

18. EFFECT OF TEA ON HEPATOCARCINOGENESIS

N-nitrosodiethylamine (DEN) is a potent hepatocarcinogenic dialkylnitrosamine extensively found in varieties of products such as milk products, meat products, soft drinks, alcoholic beverages, and tobacco smoke. *N*-nitrosodiethylamine is a commonly used xenobiotic agent in experimental animal model systems.[49] Various preclinical studies have observed protective effects of tea against hepatic carcinogenesis induced/initiated by nitrosodiethylamine. Purified epicatechin complex (87% concentration) isolated from green tea inhibited DEN-initiated, phenobarbitol-promoted proliferation of precancerous liver cells.[39] Green tea (2.5%) administered to rats before and following DEN treatment effectively inhibited hepatocarcinogenesis.[49]

Catechin components of green tea have been shown to possess anticarcinogenic properties possibly related to their antioxidant activity. Studies by Klaunig,[50] examined a catechin containing green tea extract for its effect on three previously defined properties of liver tumor promoters: induction of cytolethality, inhibition of gap junctional intercellular communication, and induction of cell proliferation. Green tea extract prevented the induction of hepatocyte cytolethality by glucose oxidase, xanthine oxidase, and paraquat (all oxygen free radical inducers) in a dose-responsive manner. Green tea extract prevented the inhibition of gap junctional–mediated intercellular communication by phenobarbital, lindane, and paraquat in a dose-dependent manner. The effect of green tea extract on hepatocyte DNA synthesis was examined in male mice containing preneoplastic liver lesions induced by diethylnitrosamine. Green tea extract significantly decreased the labeling

index in hepatic preneoplastic foci.[50] Mice which were administered green or BTEs (1.25%, total 40 weeks treatment) prior to, during, and after DEN treatment showed a decrement in the number of hepatic tumor cells, when compared with DEN-alone treated cohorts.[51]

Tea catechins, BTE, and oolong tea extract (0.05% or 0.1%) were shown to significantly decrease the number and area of preneoplastic glutathione S-transferase placental form-positive foci in the liver in rats with DEN-induced hepatocarcinogenesis.[52] Green tea extract has been shown to possess anticarcinogenic effect in DEN-initiated hepatocarcinogenesis without chronic hepatocyte damage but not effective in inhibiting lesion development in hepatic carcinoma with liver cirrhosis.[53] Tea polyphenols and tea pigments have been observed to effectively reduce the GST-Pi expression at both transcription and translation levels, and thus inhibition of carcinogen-induced expression of GST-Pi has been suggested as one of the mechanisms in the anticarcinogenic effect of phytochemicals in tea.[54] Tea polyphenols and pigments have been shown to modulate the phase detoxifying enzymes by inhibiting the overexpression of GST-Pi and promoting the expression of GST-alpha and GST-mu, thus inhibiting the occurrence and development of the precancerous lesions of rat liver.[55] Green tea was effective in inhibiting hepatocarcinogenesis in mice with DEN-induced, pentachlorophenol-promoted hepatic carcinoma.[56]

Black tea is shown to have hepatoprotective action. The principal phytochemical theophylline(TF)-enriched BTE when administered orally (40% TF-BTE, 50 or 100 mg/kg) to rats showed significant hepatoprotective action against DEN-induced hepatotoxicity. Theophylline-enriched BTE caused significant attenuation of elevated aminotransferases in serum and ameliorated necrosis, bile duct proliferation, and inflammation caused by DEN. It also inhibited the expression of liver alpha-smooth muscle action and transforming growth factor –beta 1 protein.[57]

Recent studies have confirmed beneficial effect of tea polyphenols in inhibition of hepatocarcinogenesis.[58–60] Studies with laboratory mouse have shown that the simultaneous prevention of liver and tongue carcinogenesis in mice by the tea polyphenols epigallocatechin gallate and theaflavin.[58] The cancer-restricting action of these polyphenols was associated with modulation in cellular proliferation/apoptosis and prevalence of CD44 positive population. The upregulation of self-renewal Wnt/β-catenin, Hh/Gli1 pathways, and their associated genes Cyclin D1, cMyc, and EGFR along with downregulation of E-cadherin seen during the carcinogenesis processes were found to be modulated during the restriction processes by EGCG/TF.[58] The experiment lasted for 13 weeks. Kujawska and coworkers reported that daily intake of yellow tea extract (800 mg/kg body weight, 13 weeks) alleviated the carcinogenic effect of DEN as evidenced by normalization of histological architecture of liver, decreased lipid peroxidation and oxidative stress, and improved antioxidant levels.[59]

Fumonisin B1 is the member of a family of toxins called fumonisins, produced by several species of fusarium molds. It is known to be a carcinogenic substance. Treatment with green tea polyphenols was effective in people who were exposed to fumonisin B1 through cereals and at high risk with hepatocellular carcinoma. Supplementation with green tea polyphenols (1000 mg, 3 months) resulted in decreased urinary excretion of fumonisin B1, sphingosine, sphinganine and ratio of sphinganine to sphingosine. This study indicates beneficial anticarcinogenic effect of green tea polyphenols.[60]

Procyanidins are a group of flavonoids and are of great interest in medicine and nutrition. They have been shown to exhibit antioxidant activity. Tea is one of the major sources of procyanidins. Procyanidins were shown to inhibit the activities of the three phosphatases of regenerating liver (PRL). Treatment with procyanidin C2 led to a decrease in cell migration of PRL-1- and PRL-3 overexpressing cells, suggesting the compound-dependent inhibition of PRL-promoted cell migration. Treatment with procyanidin B3 led to selective suppression of PRL-1 overexpressing cells, thereby corroborating the selectivity toward PRL-1 over PRL-3 in vitro. These studies suggest anticancer effect of procyanidins and that PRLs are the potential targets of chemotherapy of cancer.[61]

Obesity associated with insulin resistance, type 2 diabetes, and proinflammatory status of the body is a potential risk factor for hepatic cancer. Abnormal activation of the insulin-like growth factor (IGF)/IGF-1 receptor (IGF-1R) axis is also involved in obesity-related liver tumorigenesis. Tea phytochemical EGCG (0.1%, 34 weeks) administered to obese mice (db/db model of obese, type 2 diabetic mice) with DEN treatment inhibited the phosphorylation of IGF-IR, ERK (extracellular signal-regulated kinase), GSK-3beta (glycogen synthase kinase-3beta), and c-Jun NH-terminal kinase in the liver. EGCG also decreased the serum levels of insulin, IGF-1, IGF-2, free fatty acids, and TNF-alpha and downregulated the hepatic expression of mRNAs of TNF-α and interleukins. The antitumorigenic actions of EGCG have been suggested to be brought out by improving hyperinsulinemia and attenuating chronic inflammation.[62]

19. CONCLUSIONS

Observations from the scientific studies carried out in the recent past have clearly shown that tea possesses hepatoprotective action against diverse xenobiotic agents and hepatotoxic agents. Several mechanisms are likely to account for the observed pharmacological effects, the most important being the free radical scavenging, antioxidant, antiinflammatory, increase in the antioxidant enzymes, modulation of Phase I and II enzymes, and possible antiviral effects.

However, although considerable work has been done to exploit the hepatoprotective effects, countless possibilities for investigation still remain. Further in-depth mechanistic in vitro studies, relevant animal studies especially with old mice, and rationally designed clinical trials are required. The outcomes of such studies may be useful for further clinical applications of tea in humans and may open up a new therapeutic avenue.

LIST OF ABBREVIATIONS

ALT Alanine aminotransferase
AST Aspartate aminotransferase
AZA Azathioprine
CAT Catalase
CCl_4 Carbon tetrachloride
COX-2 Cyclooxygenase-2
CPT-1 Carnitine palmitoyltransferase 1
DEN *N*-nitrosodiethylamine
EC Epicatechin
ECG Epicatechin-3-gallate
EGC Epigallocatechin
EGCG Epigallocatechin-3-gallate
ERK Extracellular signal-regulated kinase
FAS Fatty acid synthase
GalN D-Galactosamine
GPx Glutathione peroxidase
GR Glutathione reductase
GSH Glutathione
GSK-3β Glycogen synthase kinase-3beta
GST Glutathione S-transferase
GST-mu Glutathione S-transferase mu
GST-Pi Glutathione S-transferase pi
GST-α Glutathione S-transferase alpha
HCV Hepatitis C virus
IGF Insulin-like growth factor
IGF-1R IGF-1 receptor
IL1β Interleukin-1beta
iNOS Inducible nitric oxide synthase
LDH Lactate dehydrogenase
MDA Malondialdehdye
NAFLD Nonalcoholic fatty liver disease
NAPQI *N*-acetyl-para-benzoquinone imine
p-ACC Phospho-acetyl CoA carboxylase
PARP Poly (ADP-ribose) polymerase
PRL 1 Phosphatases of regenerating liver 1
PRL 2 Phosphatases of regenerating liver 2
ROS Reactive oxygen species
SOD Superoxide dismutase
SREBP-1c Sterol regulatory element–binding protein-1c
TNF-α Tumor necrosis factor alpha
TNF-α Tumor necrosis factor-α
Δ-9-Desaturase Stearoyl CoA desaturase-1

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