

Chocolate Shake and Blueberry Pie..... or why Your Liver Would Love it

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ABSTRACT

“Let food be thy medicine and medicine be thy food.” proclaimed nobody less than Hippocrates, the Ancient Greek philosopher and doctor about 460 B.C. And indeed, the daily food intake is the most important exchange of our organism with the environment. Today, we know that the choice of comestible goods is an important contributor to our well-being and that the targeted use of specific nutrients and other bioactive molecules (e.g. secondary plant products) significantly helps in the regulation of metabolic processes in a variety of situations of particular requirements. However, next to a health protective diet, identifying the chemical compounds of a healthy natural food product allows us to characterize those compounds that are potential candidates for a new drug, and manufacturing it artificially, we can then change its structure in several different ways to see if we can improve its effectiveness or gain new insights as to how to design a more effective drug of a similar type. Chronic liver diseases are the fifth most frequent cause of death in the European Union, mostly caused by chronic alcohol abuse or virus hepatitides. Liver fibrosis, and ultimately liver cirrhosis, is the common end-stage of all chronic liver diseases. As chronic liver diseases entail multiple risks, such as portal hypertension, ascites, hepatic encephalopathy and, of course, hepatocellular carcinoma (HCC), pharmaceutical intervention at the stage of fibrogenesis therefore remains a major task in today’s medicine. This review focusses on established components of Western food, such as Curry, Coffee or Chocolate, in terms of their hepatoprotective effects and discusses the biochemical background of the epidemiological observations. It hopefully triggers both, motivation and curiosity, to open a new discussion on the future of the pharmacological treatment of chronic liver diseases and on the development of drugs based on natural compounds.

INTRODUCTION

Chronic liver diseases are the fifth most frequent cause of death in the European Union, as they entail multiple risks, such as portal hypertension, ascites, spontaneous bacterial peritonitis, hepatorenal and hepatopulmonary syndromes, hepatic encephalopathy and, of course, hepatocellular carcinoma (HCC)^[1,2].

Liver fibrosis, and ultimately liver cirrhosis, is the common end-stage of all chronic liver diseases. At the beginning of fibrogenesis stands a chronic inflammatory condition. But it is not the virus- or toxin-induced hepatocellular damage that primarily causes tissue-destruction and the formation of granulation tissue, but the activation of immunocompetent cells (e.g. Kupffer-cells) and the release of proinflammatory cytokines, such as tumor necrosis factor α (TNF- α), interleukin (IL)-6 and IL-12. These mediators and the accumulation of potentially toxic free fatty acids generate highly reactive oxygen species (ROS), which expose the hepatocyte to an oxidative stress, which, primarily via peroxidation of membrane lipids and DNA damage, leads to hepatocellular injury. In the meantime, it comes to an activation of mesenchymal cells, resulting in an increased synthesis and interstitial deposition of extracellular matrix components^[3]. These mesenchymal cells, hepatic stellate cells (HSC), also known as Ito cells, are pericytes found in the perisinusoidal space of the liver also known as the space of Disse. Following liver injury, HSC undergo “activation” which connotes a transition from quiescent vitamin A-rich cells into proliferative, fibrogenic, and contractile myofibroblasts (MFB). This pathway has long been, and probably still is, considered as the “canonical” pathway in the pathogenic understanding of liver fibrogenesis. The major phenotypic changes after activation include proliferation, contractility, fibrogenesis, matrix degradation, chemotaxis, retinoid loss, and white blood cell chemoattraction^[4].

In Europe, most frequent causes of chronic liver failure are of

nutritive-toxic origin: chronic alcohol abuse, followed by virus hepatitis. Hereditary causes such as hemochromatosis or Morbus Wilson, autoimmune processes such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) or autoimmune hepatitis (AIH), metabolic disorders, but also venous obstruction and liver congestion follow—at a distant third, however^[2].

More than 50 percent of all patients with complicated liver cirrhosis die within the first 17 years following diagnosis, mostly from HCC. In more than 90 percent of all cases, the HCC develops within a cirrhotic liver. Therefore, attenuation of the fibrogenic process can significantly lower morbidity^[1].

The daily food intake is the most important exchange of the organism with the environment. Today, we know that the choice of comestible goods is an important contributor to our well-being and that the targeted use of specific nutrients and other bioactive molecules (e.g. secondary plant products) significantly helps in the regulation of metabolic processes in a variety of situations of particular requirements.

Ever since the introduction of the written word about 5,000 years ago, the application of medicinal herbs prepared in formulas has been documented. But despite of this “old knowledge”, the effectiveness of medicinal herbs has long been denied, or at least questioned, by modern medicine. It is only a couple of years that the potential medicinal effects could be convincingly proven by large scale clinical studies.

This review presents the current knowledge on hepatoprotective properties of established food components such as curry, coffee, chocolate, garlic, and many more, and presents the history and folk use, the major chemical constituents and proven molecularbiological mechanisms responsible for the beneficial action of these foods in patients with chronic liver disease.

SPECIFIC AGENTS

Artichoke: *Cynara cardunculus*

Description: The cardoon (*Cynara cardunculus*), also called the artichoke thistle, cardone, cardoni, carduni or cardi, is a thistle-like plant in the aster family *Asteraceae*. The wild cardoon is a stout herbaceous perennial plant growing up to 1.5 m tall, with deeply lobed grey-green tomentose leaves up to 50 cm long, with yellow spines up to 3.5 cm long. The flowers are violet-purple, produced in a large, globose, massively spined capitulum up to 6 cm diameter^[5]. It is adapted to dry climates, occurring wild from Morocco and Portugal east to Libya and Greece and north to France and Croatia^[5].

There are two main cultivar groups, the cardoon (*Cynara cardunculus* Cardoon Group), selected for edible leaf stems, and the artichoke (*Cynara cardunculus* Scolymus Group), selected for edible flower buds. They differ from the wild plant in being larger (up to 2 m tall), much less spiny, and with thicker leaf stems and larger flowers. Today, main production areas are found in the USA, in Italy, Spain, Egypt, Argentina and France^[5].

History and Folk Use: Artichokes were already known in ancient Egypt and the Romans considered them a delicacy for the upper class. With the decease of the Roman Empire, the artichoke almost entirely disappeared from the European continent and only returned in the 15th century, when Arabs brought the vegetable back to France, and it is believed that its name derives from the Arabian word *al-harsuf*. From France, the artichoke was brought to America^[6]. The medico-pharmaceutical tradition of the artichoke could so far only be reconstructed in fragments. Whether the vegetable named *skolymus* mentioned in Dioskurides *Materia medica* is an artichoke, could not be finally proven. In the early middle ages, it was apparently known as

a medicinal plant named *cinara*, as references in the Pharmacopoeia of the German abbey of Lorsch suggest, however, further evidences in other books of cloister medicine are entirely lacking^[6]. First evidence that parts of the artichoke might have been used in the treatment of liver diseases appear in the 16th century *Kreütterbuch* of German botanist Hieronymus Bock (1498-1554), who called the vegetable *Welschdistel* or *Strobildorn*, and describes its anticholeretic and anti-icteric properties^[7], a suggestion also seized by the German professor Tabernaemontanus (1522-1590)^[6]. The hepatoprotective properties were still propagated in the 18th century, when German pharmacist and botanist Johann Wilhelm Weinmann (1683-1741) noted in his pharmacobotanic opus *Phythanthoza iconographia*, that a distillation of crowd and root of the artichoke would be a “glorious remedy” for the treatment of jaundice^[8]. In the 19th century, the medical value of the artichoke finally slid into obscurity. It was only in the mid-twentieth century, that the idea of the use of this vegetable as medicinal plant was revitalized, when scientists described a cholesterol-lowering effect of its major bioactive compound cynarin, therefore a suitability in the prevention of atherosclerosis. And in the 1970’s eventually, the hepatoprotective properties were made publically again as well^[6].

Functional Components: The main phenolic constituents of the artichoke leaf extract are a variety of mono- and dicaffeoylquinic acids (e.g. chlorogenic acid, cynarin [(1,3-Dicaffeoylquinic acid; (1R,3R,4S,5R)-1,3-Bis[[3-(3,4-dihydroxyphenyl)propenyl]oxy]-4,5-dihydroxycyclohexanecarboxylic acid]), caffeic acid and flavonoids (e.g. luteolin-7-O-glucoside) for which several pharmacodynamic effects have been observed *in vitro* and *in vivo*. However, *in vivo* not only the genuine extract constituents but also their metabolites may contribute to efficacy. In addition, all parts of the plant contain sesquiterpene lactone cynaropicrin and inulin^[9].

Hepatoprotective Activity: Cynarin and, to a lesser extent, caffeic acid exhibited hepatoprotective activity in carbon tetrachloride (CCl₄)-treated rats, however, a minimum of 1% polyphenols and 0.2% flavonoids in the dried leaves was required for the activity^[10]. A protective effect of cynarin was also observed for D-Galactosamine N (D-GalN) pretreated primary-cultured mouse and rat hepatocytes^[11].

A study by Gebhardt *et al* demonstrated that the protective properties of artichoke extracts may mostly be attributed to an enhancement of the antioxidative capacity of the liver. Triggering oxidative stress through application of the two hydroperoxides tert-butylhydroperoxide (t-BHP) or cumene hydroperoxide to cultured primary rat hepatocytes, this group found that artichoke extracts did not affect the cellular level of the antioxidant glutathione (GSH), but diminished the loss of total GSH and the cellular leakage of oxidized glutathione (GSSG) resulting from exposure to t-BHP. However, chlorogenic acid and cynarin accounted for only part of the antioxidative principle of the extracts. Addition of artichoke extracts also prevented the hydroperoxide-induced increase of malondialdehyde (MDA) formation in a concentration-dependent manner when presented simultaneously or prior to the peroxides, as well as hepatocyte necrosis induced by the hydroperoxides. The effective concentrations were well below the cytotoxic levels of the extracts^[12]. Next to its potent antioxidative properties, high-dose aqueous extracts from artichoke leaves were found to inhibit cholesterol biosynthesis in primary cultured rat hepatocytes in a dose-dependent manner, most likely through an inhibition at the level of hydroxymethylglutaryl-CoA (HMG-CoA) -reductase. Screening of several known constituents of artichoke extracts revealed that cynaroside and particularly its aglycone luteolin were mainly responsible for inhibition^[13]. As expected, artichoke extracts were also observed to significantly lower total serum cholesterol in the rat^[14].

Figure 1

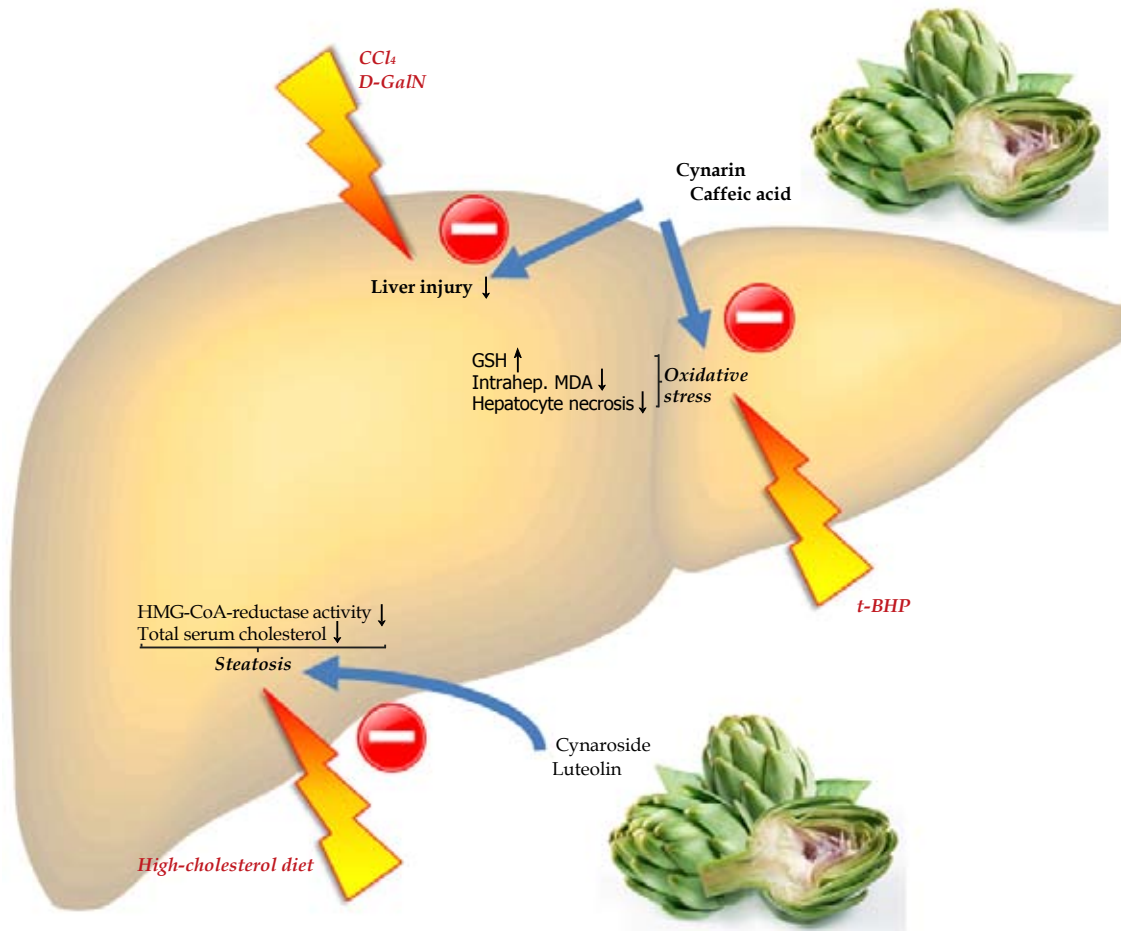


Figure 1 Effects of cynarin, caffeic acid, cynaroside, and luteolin, major biochemical compounds of the artichoke, on liver injury, oxidative stress and steatosis. Abbreviations: CCl₄: Carbon tetrachloride; D-GalN: D-galactosamine N; GSH: Glutathione; HMG-CoA-reductase, 3-hydroxy-3-methyl-glutaryl-CoA reductase; MDA: Malondialdehyde; t-BHP: tert-butylhydroperoxide.

Blueberries: *Vaccinium spp.*

Description: Blueberries (*Vaccinium spp.*) are a plant genus from the heath family (*Ericaceae*). All *Vaccinium* species grow as evergreen or deciduous, crawling, spread, standalone or climbing dwarf shrubs, bushes or trees. Characteristic of the species *Vaccinium* are its egg-shaped to round, fleshy berries, the actual blueberries. Blueberries are primarily native to the northern hemisphere (alone 92 subspecies are found in China alone^[15] and 25 in North-America^[16], whereas in tropical areas of Asia, Central- or Soutamerica it is only found in alpine areas. Some subspecies are also found in Africa and on Madagascar. An overview on the hepatoprotective effects of artichoke constituents is given in figure 1.

History and Folk Use: The use of blueberries as medicinal plant dates back as far as the 12th century, when German abess Hildegard von Bingen mentions their effectiveness in the treatment of gastrointestinal disorders. Proclaimed medicinal use by the Greek doctor Pedanios Dioskurides (circa 40-90 AD) could not finally be confirmed. In the Middle Ages and thereafter, blueberries were widely used, especially as folk remedy against diarrhea and abdominal typhus, and again, much propagated by the German botanist and doctor Tabernaemontanus^[17]. The species *Vaccinium* was first named and classified by the Swedish botanist and physician Carl Linnaeus (1707-1778) in his work *Species Plantarum* in 1753^[18].

Functional Components: Anthocyanins, natural pigments which are responsible for the blue colour of the berry, are one of the

major flavonoid classes, present in almost all plant species^[19]. Due to their particular chemical structure, flavonoids, and in particular anthocyanins, are characterised by an electron deficiency, which makes them very reactive toward ROS, and are consequently considered to be powerful natural antioxidants^[20,21]. Blueberries contain the following anthocyanins: malvidin 3-galactoside, delphinidin 3-galactoside, delphinidin 3-arabinoside, petunidin 3-galactoside, petunidin 3-arabinoside, malvidin 3-arabino-side, cyanidin 3-glucoside, cyanidin 3-galactoside, cyanidin 3-arabinoside, delphinidin 3-glucoside, malvidin 3-glucoside, peonidin 3-glucoside, peonidin 3-galactoside, peonidin 3-arabinoside, and peonidin 3-glucoside^[22].

Another important compound of the blueberry is pterostilbene. Pterostilbene is a stilbenoid chemically related to resveratrol and belongs to the group of phytoalexins. It has proven antiinflammatory, antimicrobial (in particular: antiviral), antineoplastic, and antioxidant actions by modulating target gene expression and enzyme activity^[23,24].

Hepatoprotective Activity: Blueberry extract was shown to have preventive and protective effects both, on CCl₄-induced hepatic fibrosis by reducing hepatocyte injury and on lipid peroxidation^[25], and on D-GalN induced acute hepatitis by reducing activities of pro-inflammatory cytokines, and by improving barrier functions and antioxidant activity^[26].

Blueberry extracts have high antioxidant potential and are able to increase phase II enzyme expression and activities. In a study performed by Wang *et al* with male mice receiving oral blueberry

Figure 2

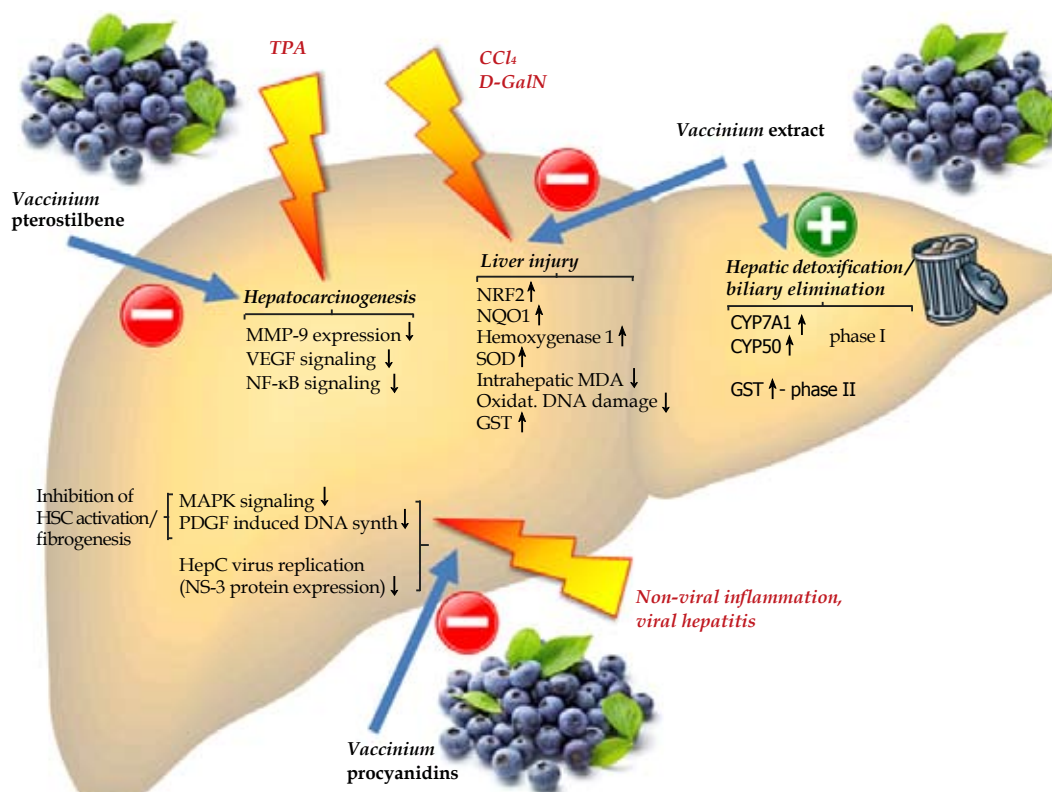


Figure 2 Effects of blueberry extract, as well as blueberry pterostilbenes and procyanidins, on liver injury, viral hepatitis, fibrogenesis, hepatocarcinogenesis and hepatic phase I and II detoxification.

CCl₄: carbon tetrachloride; CYP: cytochrome p450; D-GalN: D-galactosamine N; GST: glutathione S-transferase; MAPK: Mitogen-activated protein kinase; MDA: malondialdehyde; MMP: matrix metalloproteinase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NQO1: NAD(P)H dehydrogenase [quinone] 1; NRF2: Nuclear factor (erythroid-derived 2)-like 2; NS-3: hepatitis C virus nonstructural protein 3; PDGF: platelet derived growth factor; SOD: superoxide dismutase; TPA: tetradecanoylphorbol 13-acetate; VEGF: vascular endothelial growth factor.

extract it was shown that blueberry treatment significantly increased the expression of NF-E2-related factor-2 (*NRF2*), hemoxygenase-1, and NAD(P)H:quinone oxidoreductase (*NQO1*), which are important antioxidant components in the liver. Also hepatic SOD (superoxide dismutase) activities were higher and MDA levels were lower in the mice receiving blueberry extract compared to the control group^[27].

Another animal study with male Sprague-Dawley rats confirmed these findings showing that short-term supplementation with 1% blueberry flavonoids relevantly decreased oxidative DNA damage in the liver^[28].

An inhibitory role of procyanidins extracted from the leaves of blueberry *V. virgatum* on the fibrogenic process in the liver was proposed by Takami *et al*, who found a blueberry procyanidin dependent impairment of platelet derived growth factor (PDGF)-induced DNA synthesis and MAP-kinase signaling in activated hepatic stellate cells, thus an attenuation of the myofibroblastic differentiation of these cells, which is currently regarded a key process in the pathogenetic understanding of liver fibrogenesis^[3,29]. In line with these results, an interesting study from Japan suggested that the same procyanidins isolated from blueberry leaves could be of potential use as therapeutic agents in patients with hepatitis C virus (HCV) infection by inhibiting viral replication. They were able to show that purified procyanidin showed dose-dependent inhibition of expression of the neomycin-resistant gene and the NS-3 protein gene in the Hepatitis C virus (HCV) subgenome in replicon cells through interaction with the heterogeneous nuclear ribonucleoprotein A2/B1. The latter is indispensable for HCV subgenome expression in replicon cells^[30].

Blueberry products were furthermore found to increase hepatic

detoxification and bile production, as hamsters fed high-fat diets supplemented with blueberry pomace byproducts showed an upregulation of hepatic cytochrome p450 (CYP) 7A1 expression, and CYP51, suggesting that both bile acid and cholesterol synthesis were increased^[31], so were hepatic GST (glutathione S-transferase) activities, which are relevant for phase II detoxification processes^[28].

A study published in Carcinogenesis presented data revealing that pterostilbene extracted from blueberries efficiently inhibited invasion, migration and metastasis of human hepatoma cells (HepG2 cells) by downregulating procarcinogenic 12-O-tetradecanoylphorbol 13-acetate (TPA)-induced induced matrix metalloproteinase (MMP)-9 gene expression. In addition, pterostilbene was shown to inhibit TPA-induced vascular endothelial growth factor, and NF-kappaB signaling^[32]. Figure 2 gives a summary on the hepatoprotective mechanisms of the respective blueberry components.

Common fig: *Ficus carica*

Description: The Common fig (*Ficus carica*) is a deciduous tree belonging to the genus *Ficus* from the family Moraceae, native to southwest Asia and naturalized in the Mediterranean region and areas bordering from Pakistan to the Iberian Peninsula. It is growing to heights of up to 6 m in *Ficus carica* is well known for its fragrant leaves that are large and lobed. The fruit is 3-5 cm long, with a green skin, sometimes ripening towards purple or brown^[33].

History and Folk Use: The history of *Ficus carica* is long and fascinating. Not only that the Common Figure tree (*Ficus carica*) is the first plant cited in the Bible - in Genesis 3:7 Adam and Eve are described to cover themselves with fig leaves when figuring out

Figure 3

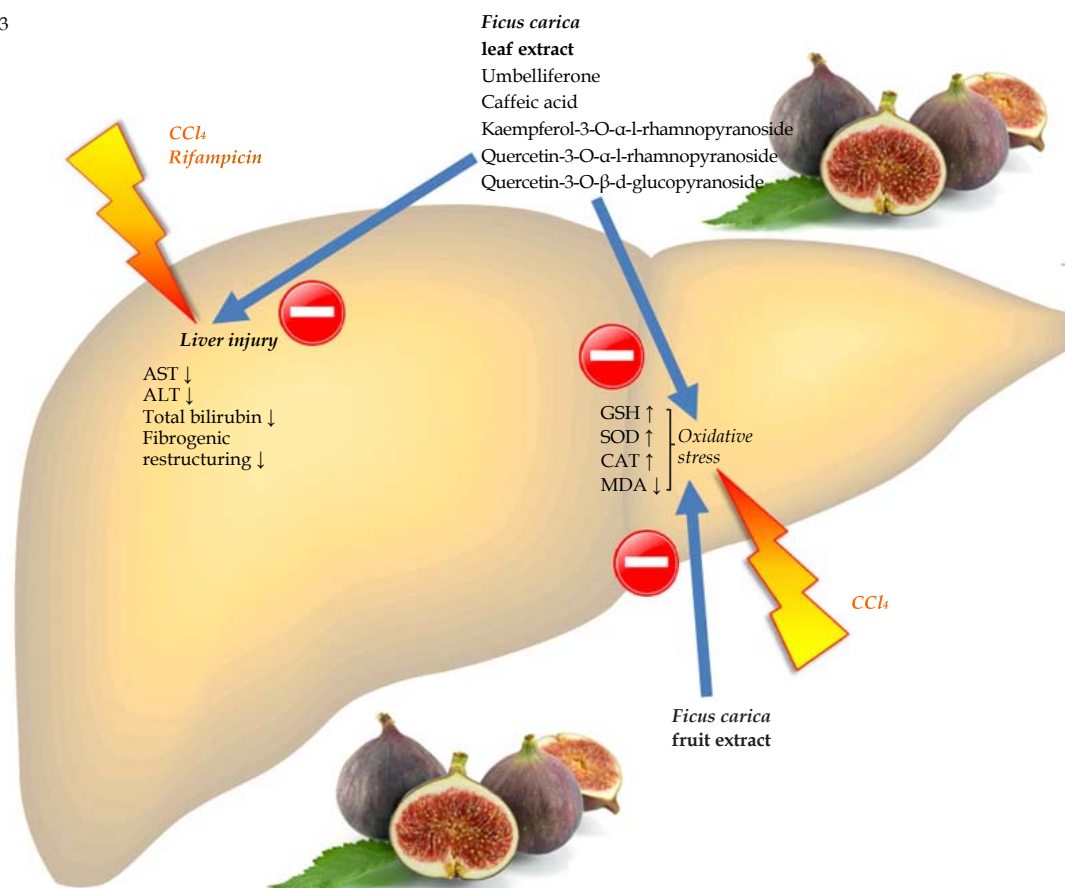


Figure 3 Effects of fig leaf and fruit extract, and the obtained biochemical compounds umbelliferone, caffeic acid, quercetin-3-O-β-d-glucopyranoside, quercetin-3-O-α-l-rhamnopyranoside, and kaempferol-3-O-α-l-rhamnopyranoside on liver injury, fibrogenesis, and oxidative stress. ALT: alanine aminotransferase; AST: aspartate aminotransaminase; CAT: catalase; CCl₄: carbon tetrachloride; GSH: glutathione; MDA: malondialdehyde; SOD: superoxide dismutase.

that they are naked – evidence of cultivation dates back as far as 9400-9200 BC. Nine subfossil figs of a parthenocarpic type from that time were found in the early Neolithic village Gilgal I in the Jordan Valley, just north of Jericho^[34,35]. Beneficial effects of the fruit have been described ever since: Hezekiah, king of Judah between 715 and 686 BC, cured local infections by applying figs to the affected spot (Isaiah xxxviii. 21). In ancient Rome, famous writer Ovid (43 BC-17 AD) told about the common New Year's Day custom to give friends and relatives fruits of fig and honey as a good omen for the New Year. According to Pliny the Elder (AD 23-79), eating figs «increases strength in young people, improves the health of old people and reduces wrinkles». Appropriately, figs were preferably consumed by Roman athletes and convalescents, thanks to their nutritional value and the easy digestibility. In the first half of the sixteenth century, the fig was brought to British Isles by the English Cardinal Pole (1500-1558), a few years before Hernán Cortés (1485-1547) introduced the tree to Mexico. Fig trees eventually reached North America in about 1790^[33,36].

The Latin designation *Ficus carica* was introduced by Carl Linnaeus and first published in 1753 in his work *Species plantarum*^[18,36]. Today, the United States, Turkey, Greece and Spain are the primary producing nations of dried figs.

Functional Components: Figs are one of the major plant sources of calcium and fiber, but are also rich in copper, manganese, magnesium, potassium, and vitamin K, relative to human needs. Figs furthermore contain many antioxidants: They are a good source of flavonoids and polyphenols^[37] including gallic acid, chlorogenic acid, syringic

acid, (+)-catechin, (–)-epicatechin and rutin^[38]. In one study, a portion of only 40-gram of dried figs (two medium sized figs) produced a significant increase in plasma antioxidant capacity^[39]. Figure 3 provides a schematic overview of the proposed hepatoprotective action of *Ficus carica* leaf and fruit extracts.

Hepatoprotective Activity: Despite its long history in medicinal use, only few reports have investigated the beneficial effects of components of the fig tree on liver pathophysiology so far.

Gond *et al* extracted dried leaves of *Ficus carica* using petroleum ether and applied the extract to rats with rifampicin induced toxic liver injury. Serum activities or concentrations of AST, ALT, bilirubin and histological changes in liver were assessed. They observed significant reversal of rifampicin dependent biochemical (AST, ALT, total bilirubin), histological and functional changes in those rats receiving the extract^[40].

Another study investigated the effect of intraperitoneal applications of either *Ficus carica* leaf or *Ficus carica* fruit methanolic extract to rats with CCl₄-induced toxic liver injury.

Both types of extract showed potent antioxidant and hepatoprotective activities by increasing serum GSH content, SOD-, and catalase (CAT) activities and by reducing MDA concentrations. Chromatographic investigation of the most active extract obtained from the *Ficus carica* leaf revealed umbelliferone, caffeic acid, quercetin-3-O-β-d-glucopyranoside, quercetin-3-O-α-l-rhamnopyranoside, and kaempferol-3-O-α-l-rhamnopyranoside as major compounds^[41].

Not just intraperitoneal, but also oral application of methanolic extract of *Ficus carica* leaves was evaluated for its hepatoprotective

Figure 4

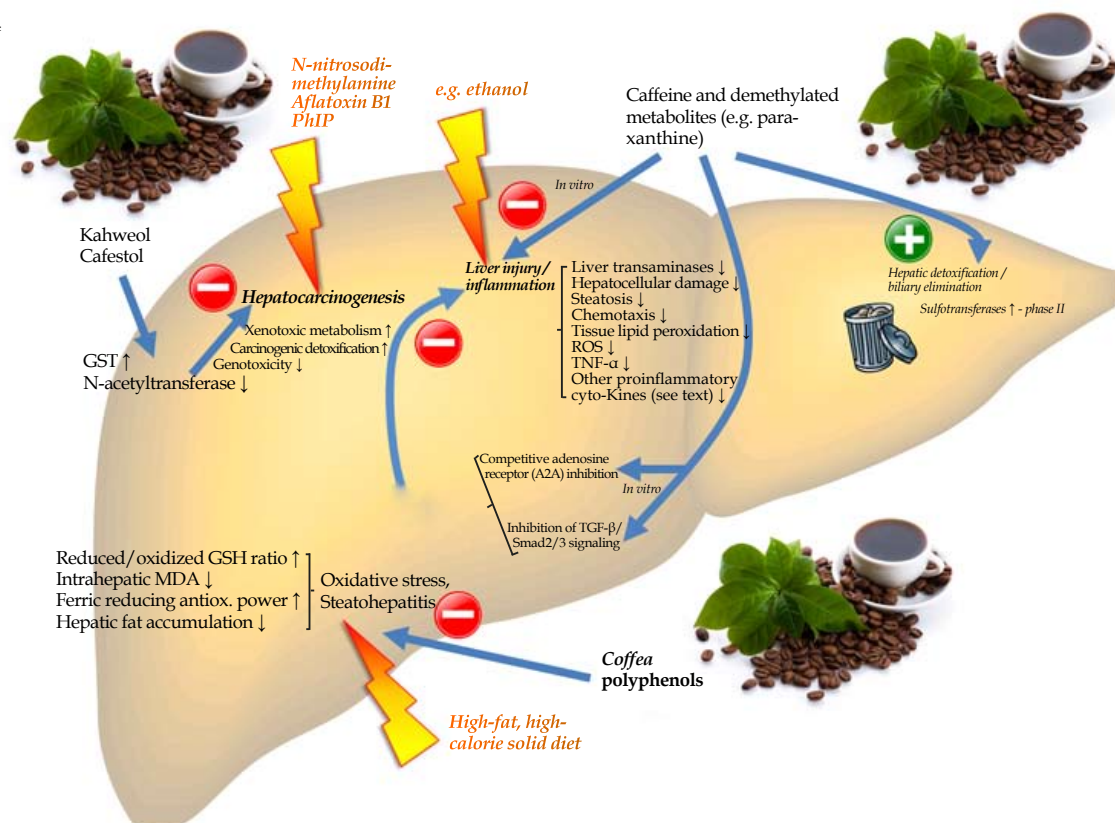


Figure 4 Effects of coffee methylxanthines (particularly caffeine), polyphenols, and diterpenes (kahweol, cafestol) on liver injury, inflammation, oxidative stress, steatosis/steatohepatitis, phase II detoxification and carcinogenesis.

GSH: glutathione; GST: glutathione S-transferase; MDA: malondialdehyde; PhIP: 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; ROS: reactive oxygen species; TGF: transforming growth factor; TNF: tumor necrosis factor.

activity in CCl₄-induced liver damaged rats by Krishna *et al.* An oral dose of 500 mg/kg exhibited a significant protective effect reflected by lowering the serum activities of AST, ALT, total serum bilirubin concentrations, and MDA equivalent, an indicator of lipid peroxidation of the liver^[42].

Coffee: *Coffea* spp.

Description: Coffee (*Coffea*) is a plant genus from the Rubiaceae family with about 90 species. Most famous are the mostly plantation grown Arabica (*Coffea arabica*) and Robusta (*Coffea canephora*) coffees. The plants are evergreen shrubs or small trees that may grow 5 m tall when unpruned. The leaves are dark green and glossy, usually 10-15 cm long and 6 cm wide. The flowers are axillary, and clusters of fragrant white flowers bloom simultaneously, followed by oval berries of about 1.5 cm^[43]. Green when immature, they ripen to yellow within 7-9 months, then crimson, before turning black on drying. Each berry usually contains two seeds, but 5-10% of the berries^[43] have only one; these are called peaberries^[44]. These semens serve as raw material for the hot drink coffee.

All coffee species have their origin in tropical Africa, especially in the highlands of Ethiopia and Sudan, Madagascar and on the Mascarene Islands. However today, it is grown as a cultivated plant in the tropical and semitropical zone worldwide^[43].

History and Folk Use: The origin of the name “coffee” is not fully known, but it seems to derive from the Arabic word “qahwah”. Some suggest that the Arab form may disguise a loanword from an Ethiopian or African source, suggesting Kaffa, a highland in southwestern Ethiopia as one, since the plant is indigenous to that area^[45,46].

There is mounting evidence that the ancestors of the Ethiopian Oromo people were the first to recognize the energizing effect of the

coffee bean plant. In their culture, the coffee plant was very likely merely considered a medicinal plant^[46].

From Ethiopia, coffee was brought to Arabia by slave traders in the 12th century, maybe even earlier. It was in about that Abu Bakr Muhammad ibn Zakariya ar-Razi (Rhases; 865-925), an Islamic physician, recommended coffee as a medicinal compound for gastric disorders. Another Persian doctor, Abū Alī al-Husain ibn Abdullāh ibn Sīnā (Avicenna; 980-1037), noted in his Pharmacopoeia the health properties of a plant he called “Bunchum”. Later, the name “Bunch” was used for coffee plants and their berries. First description of a coffee beverage is only documented for the middle of the 15th century. Coffee growing thereafter provided a monopoly position for Arabia. Commercial center was the port town of Mocha, the today's al-Mukha in Yemen^[46]. In the 16th century, coffee conquered the Osmanic empire, and around 1511, the first coffee houses are recorded for the city of Mecca. First evidence of coffee consumption in Cairo dates back as far as 1532. The first cultivation beyond Africa and Arabia was promoted by the Governor-General of the Dutch East Indies, Joan van Hoorn (1653-1711), who supervised the first agricultural tests on Sri Lanka in 1690 and on Java in 1696, with imported plants from Arabia. From these plantations, coffee trees eventually arrived in several botanical gardens in Europe, for example Amsterdam. In 1718, the Dutch again brought coffee plants to Suriname, the French in 1720 to Martinique, in 1725 to French Guyana, and in 1730 to Guadeloupe. The Portuguese brought the first plants to Brazil in 1727, which evolved as a major coffee producing country based on slavery and plantation economy^[46]. Already in the 17th century coffee houses set up in many European countries and coffee was increasingly appreciated as a beverage with stimulating effects on the central nervous system. The drink became popular in ever-larger parts of the population. In the 19th century, coffee has become a potential substitute for alcohol due

Figure 5

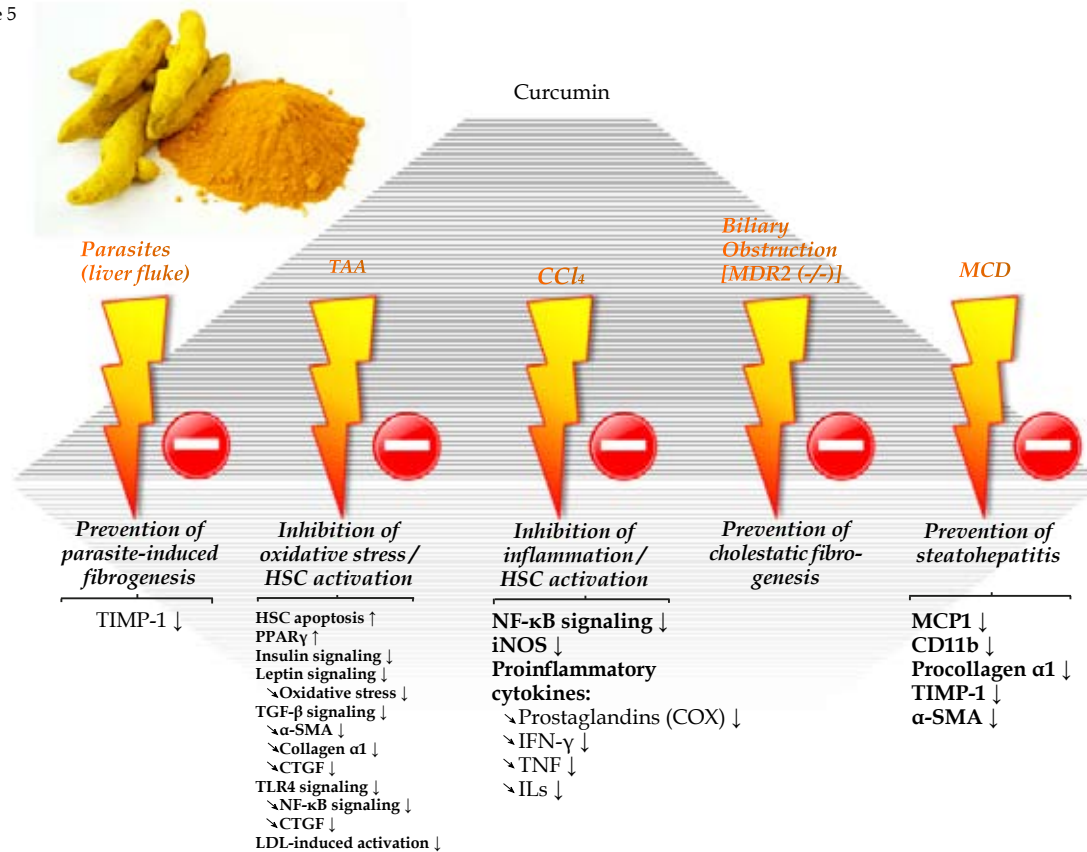


Figure 5 Effects of curry and its major compound curcumin on fibrogenesis and steatohepatitis.

CCl₄: carbon tetrachloride; CTGF: connective tissue growth factor; HSC: hepatic stellate cells; IFN: interferon; ILs: interleukins; iNOS: inducible nitric oxide synthase; MCD: methionine-choline diet; MCP1: monocyte chemoattractant protein1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PPAR: peroxisome proliferator-activated receptor; SMA: smooth muscle actin; TAA: thioacetamide; TGF: transforming growth factor; TIMP: tissue inhibitor of matrix metalloproteinases; TNF: tumor necrosis factor.

to its central stimulating effects.

At the behest of Johann Wolfgang von Goethe, Friedlieb Ferdinand Runge, a pharmacochemist from Wroclaw/Poland, was the first to look for the psychoactive substance in coffee. In 1820, he finally extracted chemically pure caffeine, from which the German scientists Christoph-Heinrich Pfaff and Justus von Liebig successfully deduced the structural formula C₈H₁₀N₄O₂ by burning analysis^[46].

Today, coffee plantations have become the economical backbone for many developing countries of the Third World. Especially African countries like Uganda, Burundi, Rwanda, and Ethiopia, as well as many countries in Central America economically rely on coffee production. The antifibrotic mechanisms of curcumin are summarized in figure 5.

Functional Components: Coffee contains a variety of biochemical compounds which differ a lot between the several *Coffea* species.

Next to carbohydrates (~24%; mostly water-indissoluble and water-dissolvable polysaccharides), proteins, fats/lipoids (~13%; components of the coffee oil, e.g. linoleic acid, palmitic acid, as well as the diterpene alcohols kahweol and cafestol, that are esterified with the primary hydroxyl group of, mostly, linoleic acid and palmitic acid) and water (~2.5%), acidic compounds make up ~5% of raw coffee. About 80 different acids in coffee have been described, among them citric-, acetic-, and malic acids. However, the main portion may be attributed to chlorogenic acids (particularly caffeoylquinic- and feruloylchiquina acids). Being polycarboxylic acids, chlorogenic acids belong to the secondary plant compounds with antioxidative

qualities^[47,48].

Among the alkaloids, which are detectable in coffee, caffeine is the major one with an amount of ~0.58-1.70%. In addition, coffee contains lesser amounts of further purine alkaloids, such as theobromine (~0.002%), theophylline (~0.001%), paraxanthine (traces), as well as other alkaloids such as trigonelline (Nicotinic acid N-methylbetaine), theacrine (traces), liberine (traces) and methyl-liberine (traces). The roasting process has little effect on the caffeine content. However, the trigonelline amount is reduced up to 75%, resulting in increased formation of vitamin B3/nicotinic acid (niacin, ~0.02%). A cup of coffee covers about one tenth of the daily requirement of niacin in the adult^[47,48].

Of the more than 800 volatile aroma compounds in coffee (approx. 0.1% of all coffee compounds) up to 100 are still not classified. Most important of the known compounds are the diterpenes atracylgenine, a diterpene of the kauran type, and its glycosides (atractyloside), as well as diterpene alcohols^[47,48].

The content of minerals strongly depends on the type of coffee as well as on the growing area and growing conditions. On average, an amount of about 4% related to all biochemical compounds in coffee is assumed, and more than 90% of these are found in the beverage. First and foremost is potassium, followed by calcium, magnesium and phosphorus. Traces of almost all other minerals also occur. But despite this advanced biochemical analysis, it should be noted that more than 30% of all substances in coffee have not been identified yet^[47,48].

Hepatoprotective Activity: Data on 5994 adult patients with chronic

liver disease, collected by US-American scientists during the third National Health And Nutrition Examination Survey (NHANES III) of the National Centers of Health Statistics, Disease Control and Prevention (CDC; Atlanta/GA, USA) proposed a hepatoprotective effect of increased coffee consumption^[49,50]. Similar results were obtained previously by NHANES I as well as during a recent study by the National Institute of Diabetes and Digestive and Kidney Disease/National Institute of Health (NIDDK/NIH; Bethesda/MD, USA)^[51].

In summary, these studies gave evidence that patients with higher coffee consumption displayed a milder course of fibrosis^[50,51], especially in alcoholic liver disease^[49,50,52] and lower serum activities of ALT and GGT^[49,52]. According to Ruhl *et al*, two cups of coffee daily were sufficient, to markedly reduce the risk of fibrosis progression^[50].

Scientists from Tohoku University Hospital in Sendai/Japan who evaluated 9-year data of coffee consumption of 60.107 subjects for the association of coffee intake and the risk of developing primary HCC found that regular coffee drinkers had a risk for suffering from HCC, which was significantly reduced compared to those who remained abstinent towards coffee consumption^[53].

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) investigated 110.688 cohort members aged 40-79 years in respect of their average coffee intake and calculated a hazard ratio of 0.50 for death due to HCC for drinkers of one and more cups of coffee per day. In contrast, the ratio for drinkers of less than one cup per day was 0.83, which therefore confirmed an inverse association between coffee consumption and HCC mortality^[54].

These findings were supplemented with a Swedish meta-analysis of the Karolinska Institute, Stockholm which evaluated the data of 9 cohort and case-control studies involving a total of 2260 cases and 239146 non-cases. All epidemiological studies that were considered reported an inverse relation between coffee consumption and risk of liver cancer, and in 6 studies the association was statistically significant. Overall, this meta-analysis revealed an association of an increase in consumption of 2 cups of coffee per day and a 43% reduced risk of developing HCC^[55]. Data were backed up by a concomitant Italian meta-analysis^[56].

Different mechanisms on the molecularbiological rationale behind coffee's hepatoprotective effect have been proclaimed.

Several authors suggested that the major chemical constituents responsible for physicochemical and therapeutic action of coffee are the methylxanthines, above all caffeine. Modi *et al* investigated the relationship between caffeine intake and liver fibrosis in 170 patients with chronic hepatitis C virus infection, and showed that daily consumption of coffee-derived caffeine above the 75th percentile for the cohort (308 mg=approximately 2.25 cups of coffee equivalents) was associated with reduced liver fibrosis. Of note, consumption of caffeine from sources other than coffee or of decaffeinated coffee was not associated with reduced liver fibrosis^[51]. Similar findings of a significant reduction in risk of fibrosis following oral intake of coffee caffeine were obtained by Molloy *et al* in 306 patients with nonalcoholic steatohepatitis (NASH)^[57]. All these data were mechanistically supported by several *in vitro* studies from our group, demonstrating that caffeine inhibits the synthesis of connective tissue growth factor (CTGF/CCN2) in liver parenchymal and nonparenchymal cells, primarily by inducing degradation of the transforming growth factor (TGF)- β effector Smad2 (and to a much lesser extent Smad3) and thus impairment of intracellular TGF- β signaling^[58-60]. CTGF and TGF- β play crucial roles in the fibrotic remodeling of various organs, and, ultimately, carcinogenesis^[61]. Antiinflammatory and antioxidative action as major hepatoprotective

mechanism of coffee consumption has been proposed by a Chinese group investigating the effect of caffeine on alcohol induced liver injury in the mouse model. Treatment with caffeine significantly attenuated elevated serum aminotransferase enzymes and reduced the severe extent of hepatic cell damage, steatosis and the immigration of inflammatory cells. Furthermore, caffeine decreased serum and tissue inflammatory cytokines levels, tissue lipid peroxidation and inhibited the necrosis of hepatocytes. Kupffer cells isolated from ethanol-fed mice produced high amounts of ROS and TNF- α , whereas Kupffer cells from caffeine treated mice produced less ROS and TNF- α ^[62]. Next to its anti-inflammatory/antioxidative action, caffeine was also shown to induce phase II drug-metabolizing enzymes, particularly sulfotransferase (SULT1A1, AST-IV) and rat hydroxysteroid sulfotransferase (rSULT2A1, STa), in the liver of rats^[63]. And eventually, a last mechanism for the antifibrotic effect of methylxanthines was proposed from an Israeli research team showing that activation of the adenosine A(2A) receptor promotes peritoneal fibrosis, which is equally attenuated by selective uncompetitive A(2A) receptor blockage by ZM241385 and competitive A(2A) receptor blockage by caffeine in the mouse model *in vivo* and *in vitro*^[64].

But apart from these beneficial effects of the methylxanthine caffeine itself, effects have also been described for other biochemical compounds of coffee. For example, animal models and cell culture studies indicate that kahweol, diterpenes and cafestol in coffee can function as blocking agents by modulating multiple enzymes involved in carcinogenic detoxification; these molecules were also shown to alter the xenotoxic metabolism by inducing the enzymes GST and inhibiting N-acetyltransferase^[65-67]. An Italian study demonstrated that oral intake of coffee polyphenols protected the liver from damage caused by a high-fat diet. This effect was mediated by a reduction in hepatic fat accumulation (through increased fatty acid β -oxidation) as well as through an attenuation of systemic and liver oxidative stress through the GSH system. They observed a two-fold reduced/oxidized GSH ratio in both serum and liver, reduced serum MDA, and increased ferric reducing antioxidant power. In addition, liver inflammatory activity was reduced through a modulation of genes, e.g. reduction of tissue transglutaminase, and TGF- β expression and increased expression of adiponectin receptor and peroxisome proliferator-activated receptor (PPAR) α . And eventually, the expression and concentrations of proteins and cytokines related to inflammation, eg. proinflammatory TNF- α and interferon (IFN)- γ were found to be reduced^[68].

As becomes obvious, a wide variety of molecularbiological mechanisms for the hepatoprotective activity of coffee and caffeine intake have been proclaimed and proven, discussing all these in depth would go beyond the scope of this review. For further information we refer to our review article published in Hepatology in 2009^[58], to our editorial published in Gastroenterology in 2010^[69], as well as to several other review articles discussing this topic (e.g.^[70-72])

Curry: *Curcuma*

Description: *Curcuma* is a genus of about 80 accepted species in the ginger family (*Zingiberaceae*) that contains such species as turmeric (*Curcuma longa*) and Temulawak (*Curcuma xanthorrhiza Roxb.*). It is a tropical mountain plant native to India and Southeast Asia, a reed-like, perennial plant with tuberous rhizome with orange flesh. The large bright green leaves may grow to a length of more than 1m and form an acaulescent just above the ground, from which an inflorescence with whitish, yellowish or pinkish blossoms of about 20 cm grows out^[73].

Figure 6

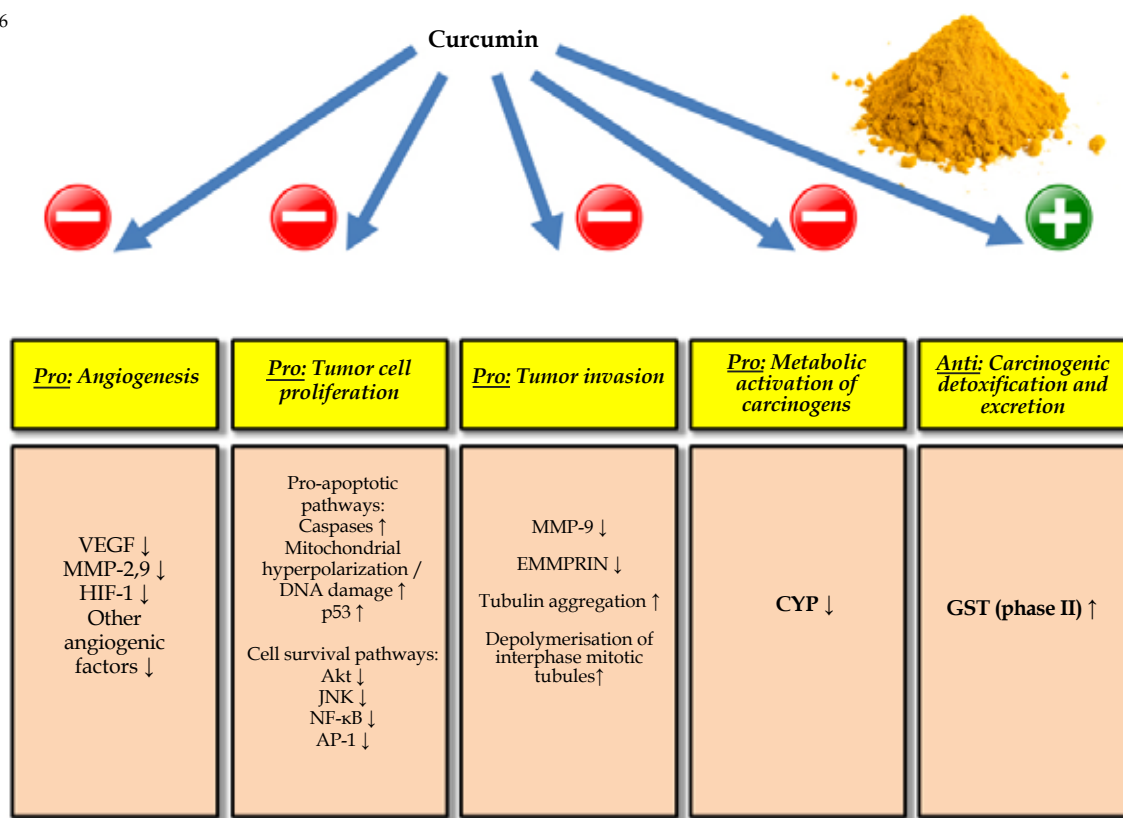


Figure 6 Effects of curry and its major compound curcumin on hepatocarcinogenesis.

AKT: protein kinase B; AP-1: activator protein 1 transcription factor; CYP: cytochrome p450; EMMPRIN: extracellular matrix metalloproteinase inducer; GST: glutathione S-transferase; HIF: hypoxia-inducible factor; JNK: c-Jun N-terminal kinase/stress-activated protein kinase; MMP: matrix metalloproteinase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; VEGF: vascular endothelial growth factor.

History and Folk Use: Already 3000 years ago, curcuma was known in India and Indonesia as medicinal plant and stain. The name derives from the Arabian word “kurkum” (=“turmeric”). Arabians brought *Curcuma longa* to the Mediterranean region via the classical caravan and trade routes. Returning from china in 1280, Marco Polo wrote in his notes, “there is also a plant that has all the estate of true saffron, as well as the smell and the color, and yet it is not really saffron”. In medieval Arabian sources, *Curcuma longa* is frequently referred to as “kurkum” and noted, that it may also be called “saffron”, because of the same color^[74]. Writers of herbal books from the Early Modern Age regarded *Curcuma longa*, then frequently referred to as *Cyperus indicus* or *Terra merita*, as an exotic drug and attributed to it healing powers against jaundice and liver complaints. In the 16th century, Tabernaemontanus recommends: “This root with saffron and incense taken on three consecutive mornings expells the jaundice”^[75]. Eventually, *Curcuma longa* entered the official pharmacy and is referred to in several international pharmacopoeiae, always in regard to its hepatoprotective and anti-icteric properties. During the 19th century, *Curcuma longa* slowly lost its importance as medicinal drug and was merely used as spice or stain and it was only in the first third of the 20th century, that with the introduction of a previously disregarded curcuma subtype, the Javanese *Temulawak* (*Curcuma xanthorrhiza* Roxb.) to the European market by the Dutch as commercial preparation named Heparlitol[®], curcuma was proposed again as medication for the treatment of liver- and biliary diseases.

While in the 1970’s, *Curcuma longa* was used as stain and spice, whereas *Curcuma xanthorrhiza* Roxb. was used for medical purposes, today, both are appreciated equally for their hepatoprotective, cholecystokinetic and choleric properties^[76].

Functional Components: Curcumin, a polyphenol (diferuloylmethane), is the main active compound found in *Curcuma*. Together with the curcumin-related demethoxy compounds demethoxycurcumin, bisdemethoxycurcumin and the first found cyclic derivative, cyclocurcumin, they are the four principal curcuminoids obtained from the extracts of dried roots of *Curcuma longa*. Although in most systems curcumin was found to be the most potent^[77,78], in some systems bisdemethoxycurcumin was found to exhibit higher activity^[73,79]. There are also suggestions that they might act synergistically^[41,80].

One of the most prominent features of curcumin is its extremely good tolerance and its very low toxicity and side effects. Curcumin is generally recognized as safe by the Food and Drug Administration, and this compound has been granted an acceptable daily intake level of up to 3 mg/kg by the Joint FAO and WHO Expert Committee on Food Additives^[81]. No studies in either animals^[82] or humans^[83] have found any toxicity associated with the consumption of curcumin even at very high doses. Figure 6 gives an overview on the anticarcinogenic effects of curcumin in the liver.

Hepatoprotective Activity: The antifibrotic and anticarcinogenic, thus hepatoprotective, action of curcumin mostly relies on its potent anti-inflammatory and antioxidant properties. Curcumin was shown to suppress prostaglandin synthesis by its effect on cyclooxygenase (COX)^[84], to suppress the production of cytokines such as IFN-γ, ILs and TNF, to inhibit the inducible nitric oxide synthase (iNOS), and to suppress the activation of NF-κB^[84-86]. By doing so, the anti-inflammatory capacity of curcumin has been compared to those of steroidal drugs and non-steroidal drugs such as phenylbutazone or

indomethacin^[87].

Several studies investigating the effect of curcumin on HSC activation, a key mechanism of liver fibrogenesis, have been performed. The results are congruent and stunning as it could be shown that curcumin can protect HSCs against activation (1) by attenuating oxidative stress^[88,89]; (2) by inhibiting TGF- β 1 induced α -smooth muscle actin (α -SMA) expression and collagen deposition^[90]; (3) by suppressing the gene expression of Toll-like receptor (TLR)-4, thus inhibiting NF- κ B and suppressing CTGF expression^[91]; (4) by inhibiting LDL (low-density lipoprotein)-induced activation^[92-94]; (5) by inhibiting leptin and leptin-induced oxidative stress^[95,96]; (6) by interrupting insulin signaling; (7) and by activating PPAR γ ^[97,98]. At higher concentrations, curcumin was shown to induce apoptosis in HSCs^[90,99]. Rodent models furthermore revealed the ability of curcumin to attenuate (1) parasitic liver fibrosis through an inhibition of TIMPs (tissue inhibitors of matrix metalloproteinases [MMPs])^[100]; (2) chronic cholangiopathy, and cholangiocyte proliferation in in Mdr2 (-/-) mice^[101]; (3) CCl₄ induced toxic liver injury and collagen deposition through an inhibition of NF- κ B expression and proinflammatory cytokine activity^[101]; (4) thioacetamide induced toxic liver injury and fibrosis through a reduction of oxidative stress as well as an inhibition HSC activation and collagen alpha 1 expression^[102]; (5) steatohepatitis in the MCD (methionine-choline diet) model through a blockage of the intrahepatic expression of monocyte chemoattractant protein1 (MCP1), CD11b, procollagen type I, TIMP-1 and α -smooth muscle actin (SMA)^[103], and to (6) improve hepatic antioxidant activity^[104-108].

Next to its antifibrotic actions, curcumin has been shown to modulate a variety of critical steps in carcinogenesis as well as in tumor progression. It is able to regulate angiogenesis, tumor cell proliferation and invasion, as well as the metabolic activation of carcinogens [e.g. inhibition of cytochrome P450 (CYP)] and the detoxification and excretion of such compounds (e.g. induction of GST). Of cancer therapeutic interest is the ability of curcumin to induce cell cycle arrest and apoptosis specifically in cancer cells^[109,110].

The growth of new blood vessels (=angiogenesis) is a central prerequisite for tumor growth and invasion. One of the prime factors regulating angiogenesis is vascular endothelial growth factor (VEGF), whereas matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases that degrade extracellular matrix, are important enzymes involved in tumor invasion. Not only VEGF but also several other angiogenic factors were shown to be inhibited by curcumin, so were MMPs^[111]. In the highly invasive SK-Hep-1 hepatocellular carcinoma cell line, curcumin displayed striking anti-invasion activity which was closely associated with blockage of MMP-9^[112]. In Hep1-6 hepatoma cells, sensitivity to curcumin was conferred by a knockdown of the extracellular matrix metalloproteinase inducer EMMPRIN (Basigin, CD147)^[113]. Also important for tumor invasion, curcumin was shown to induce tubulin aggregation and depolymerization of interphase and mitotic microtubules in HeLa and MCF-7 cells, thus regulating tumor cell mobility^[114].

Next to angiogenesis and tumor invasion, curcumin was also demonstrated to act anti-proliferatively through a modulation of tumor suppressor genes, oncogenes and/or cell cycle regulatory proteins and checkpoints, thus regulating apoptosis and cell cycle arrest. Major actions triggered by curcumin in this context are a stimulation of pro-apoptotic enzymes such as caspases or an inhibition of cell survival pathways such as AKT, JNK, NF- κ B, and AP-1^[115]. Also, curcumin induced G2/M cell cycle arrest and apoptosis in several hepatoma cell lines such as Huh7, Hep3B, SK-Hep-1, HepG2 and QGY-7703, either through mitochondrial hyperpolarization and mitochondrial DNA

damage or through a p53-dependent pathway, and inhibited hypoxia induced angiogenesis through a downregulation of hypoxia-inducible factor (HIF-1)^[116-120].

In the HCC cell line HA22T/VGH, curcumin exerted cell growth inhibitory and apoptotic effects alone as well as in combination with cisplatin or doxorubicin, at least partially due to changes in NF- κ B levels^[121].

The tumorprotective properties of curcumin could also be convincingly demonstrated in several in vivo models of hepatocellular carcinoma. In mice treated with N-bis (2-hydroxypropyl) nitrosamine, curcumin relevantly reduced liver adenoma formation and tumor growth^[122] and in mice with diethylnitrosamine-induced HCC, curcumin reduced both, tumor multiplicity and incidence^[123].

Further investigations that were performed tried to reveal the primary anticarcinogenic mechanisms of curcumin *in vivo*. In an orthotopic implantation model of hepatocellular carcinoma CBO140C12 cells curcumin suppressed intrahepatic metastasis but did not affect the growth of the implanted tumor itself^[124], suggesting that in vivo, curcumin primarily prevents tumor invasion rather than displaying cytotoxic chemotherapeutic actions. According to that, in HepG2 xenografts, tetrahydrocurcumin did not show any cytotoxic activity to HepG2 cells even at the highest doses but had antiangiogenic effects^[125-127].

Garden cress: *Lepidium sativum*

Description: Garden Cress or garden peppergrass (*Lepidium sativum*) is an annual plant of the family *Cruciferae*. The stalk may reach lengths between 30 and 60 cm and is profusely branched. It is early ripening and cold-resistant. While the lower leaves are mostly petiolar and either pinnately lobed or entire, the upper ones tend to be entire and sessile. The numerous flowers are white. The fruit of the garden cress is a small silicle^[128].

History and Folk Use: The exact origin of *Lepidium sativum* is not fully known but latest findings suggest it's origin to be in Ethiopia and neighbouring countries. Domestication of the plant presumably took place in western Asia. Cultivation was already known from ancient times in Greece and Italy, possibly also in Egypt. Nowadays, the garden cress is cultivated worldwide, including in most African countries, but mostly on a small scale as a garden crop^[128].

Functional Components: The oil obtained upon steam distillation of the seeds of *Lepidium sativum* is rich in oleic (31%), linoleic (29%) and uric acids, and also contains imidazole alkaloids. *Lepidium sativum* seeds are furthermore rich in flavonoids, glycosides, tannin, alkaloids, and amino acids like cysteine, glycine, and glutamine. The flavonoids and tannin are strong antioxidants themselves, whereas cysteine, glycine, and glutamate are intermediates for the synthesis of the endogenous antioxidant GSH^[128-130]. Current knowledge on the hepatoprotective mechanisms of *Lepidium sativum* is summarized in Figure 7.

Hepatoprotective Activity: CCl₄ treated rats receiving a methanolic extract of *Lepidium sativum* showed a significant reduction in all biochemical parameters of liver injury and a striking attenuation of CCl₄-induced fatty degeneration of the liver^[131]. Current data suggest, that extracts of *Lepidium sativum* extract its effects primarily through an inhibition of inflammation, a decrease of serum cholesterol, as well as through an enhancement of hepatic detoxification. *Lepidium sativum* seed oil decreased the release of inflammatory mediators such as NO, and leukotriene B₄, as well as to a lesser extent IL-2 and

Figure 7

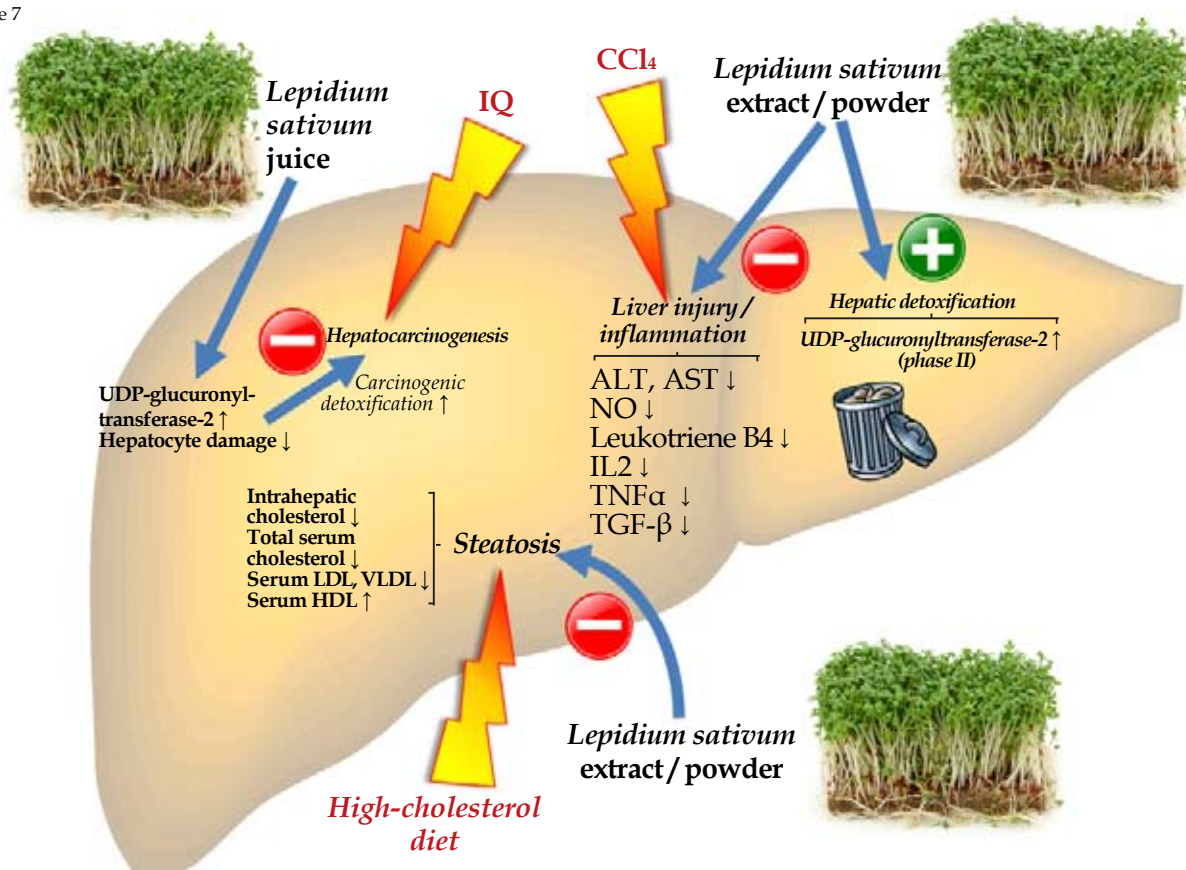


Figure 7 Effects of garden cress extract, powder and juice on liver injury/ inflammation, steatosis, phase II detoxification and carcinogenesis.

ALT: alanine aminotransferase; AST: aspartate aminotransaminase; CCl₄: carbon tetrachloride; HDL: high density lipoprotein; IL: interleukin; IQ: 2-amino-3-methyl-imidazo[4,5-f]quinoline; LDL: low density lipoprotein; NO: nitric oxide; TGF: transforming growth factor; TNF: tumor necrosis factor; UDP: uridine diphosphate; VLDL: very low density lipoprotein.

TNF- α from spleen lymphocytes, thus suggesting a role in alleviating inflammatory conditions favourably^[132]. In line with these findings, the study by Eddouks *et al* showed that oral administration of *Lepidium sativum* extract for 15 days significantly decreased the amount of urinary TGF- β 1, the profibrogenic master cytokine, in diabetic rats^[133].

At least two studies demonstrated a cholesterol-lowering effect of *Lepidium sativum* extract. Wafeka *et al* showed that rats receiving a high cholesterol diet for 11 weeks, plus an aqueous *Lepidium sativum* extract, and 10% *Lepidium sativum* powder had significantly lower serum cholesterol, LDL, and VLDL (very low density lipoprotein) values, whereas serum high density lipoprotein (HDL) concentrations were increased compared to those rats receiving the high-cholesterol diet alone. Of note, not just serum cholesterol, but also ALT and AST were significantly lowered in the *Lepidium sativum* extract treated animals, suggesting a preventive effect also in the development of steatohepatitis^[134,135]. Indeed, feeding rats with 10% *Lepidium sativum* seed oil significantly lowered intrahepatic cholesterol by more than 12% compared to the control group^[135].

Not just anti-inflammatory and antisteatotic, but also anticarcinogenic effects of *Lepidium sativum* on the liver have been reported. Oral treatment of F344 rats with fresh *Lepidium sativum* juice for three consecutive days caused a significant reduction in imidazo[4,5-f]quinoline-induced DNA damage in liver cells in the range of 75-92%. The reduction in hepatocyte damage was accompanied by a significant increase in the activity of hepatic UDP glucuronosyltransferase -2, suggesting that the chemoprotective effect of *Lepidium sativum* is mediated through an enhancement of detoxification of hepatotoxic or cancerogenous agents by the UDP

glucuronosyltransferase^[136].

Garlic: *Allium sativum*

Description: *Allium sativum*, commonly known as garlic, is a species in the onion genus, *Allium*. The *Allium sativum* plant has 6-12 long, narrow and flat like grass leaves, is perennial and can grow 60 cm high or more. With the exception of the single clove types, garlic bulbs are normally divided into 4 to 20 fleshy sections called cloves. The flowers rise direct from the bulb and are white in color^[137].

History and Folk Use: The exact origin of *Allium sativum* is not fully known. The closest wildform match is *Allium longicuspis* from the Tianshan mountains in the border region between China and Kirgistan, suggesting an origin in that geographical area. Of the about 700 species of genus *Allium*, many are native to Central Asia, the center of diversity ranging from the Himalayas to Turkestan^[137,138]. It then spread to China, the Near East, and the Mediterranean region before moving west to Central and Southern Europe, Northern Africa (Egypt) and Mexico^[139].

The name garlic derives from the Celtic words *gar* (a spear) and *lac* (a plant), in reference to its spear-shaped leaves.

Garlic has a long tradition as medicinal plant. Sanskrit records demonstrate its medicinal use more than 5000 years ago, and its application in traditional Chinese medicine finds first records earlier than 1000 BC. Also Babylonians, Egyptians, Phoenicians, Vikings, Greeks, and Romans used garlic frequently^[140]. Primary intention was the treatment of intestinal disorders, worms, flatulence, skin diseases, wounds, respiratory infections, symptoms of aging, but also of many

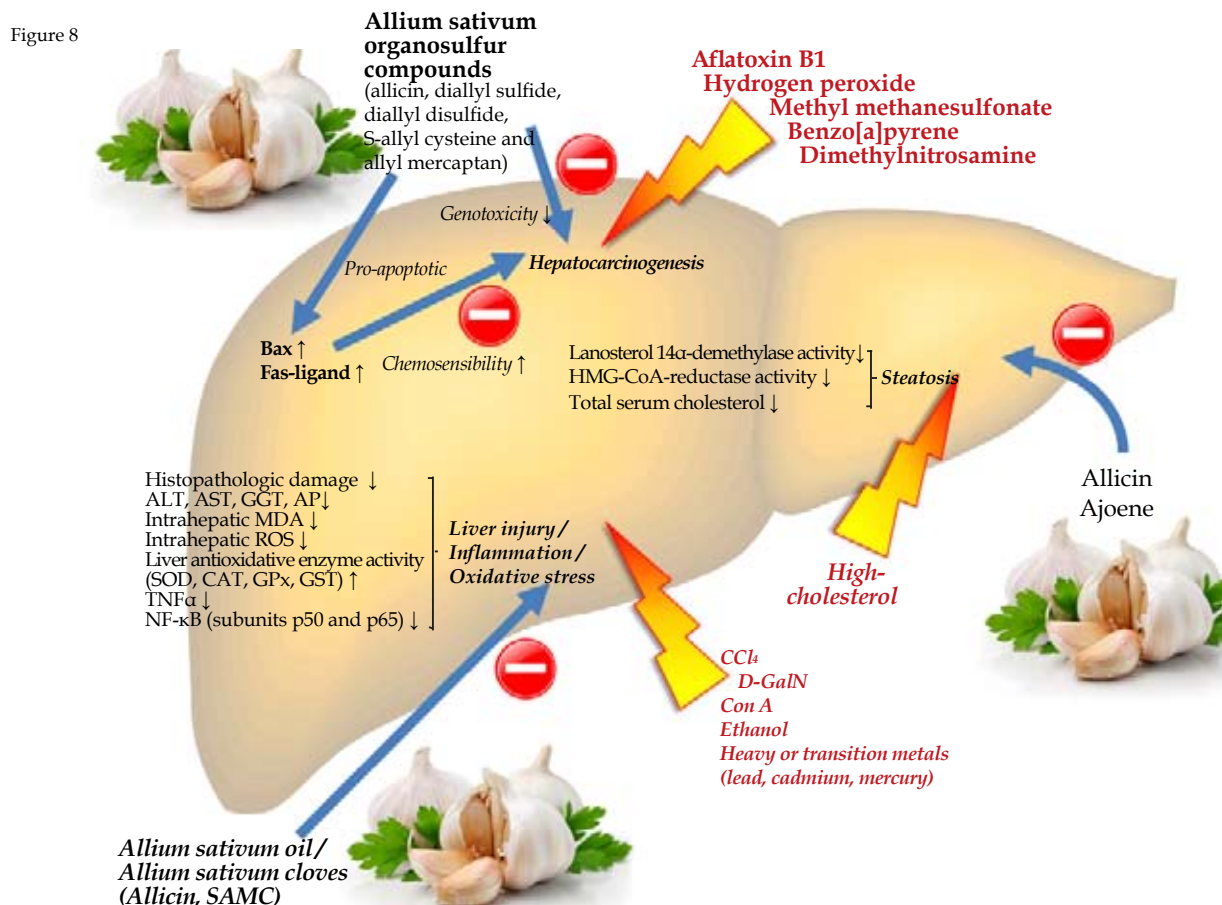


Figure 8 Effects of garlic and its compounds allicin, SAMC, ajoene, diallyl sulfide, diallyl disulfide, as well as S-allyl cysteine and allyl mercaptan on liver injury/ inflammation, oxidative stress, steatosis, and carcinogenesis.

ALT, alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; CAT: catalase; CCl₄: carbon tetrachloride; Con A: concanavalin A; D-GalN: D-galactosamine N; GGT: gamma-glutamyl transpeptidase; GPx: glutathione peroxidase; GST: glutathione S-transferase; HMG-CoA-reductase, 3-hydroxy-3-methyl-glutaryl-CoA reductase; MDA: malondialdehyde; NF- κ B: nuclear factor kappa-light-chain-enhancer of activated B cells; ROS: reactive oxygen species; SAMC: S-allyl-mercapto-L-cysteine; SOD: superoxide dismutase; TNF: tumor necrosis factor.

other ailments. Particularly its anti-infectious properties were widely valued: In 1858, Louis Pasteur (1822-1895) from Paris was the first to specify garlic's antibacterial activity. However, the use of garlic to treat wounds was well established already through the middle ages until World War II, when ground or sliced garlic was still applied directly to wounds of soldiers as an anti-infectious prophylaxis to prevent the development of gangrene^[141].

Functional Components: The health benefits of garlic likely arise from a wide variety of components, possibly working synergistically. It is known that the bulb of *Allium sativum* contains at least 33 sulfur-containing components (the highest concentration of sulfur compounds of all *Allium* species), as well as 17 amino acids, many enzymes and essential dietary minerals such as selenium.

The sulfur compounds are responsible both for garlic's odor and most of its medicinal effects. Whole garlic typically contains approximately 1% S-allyl cysteine sulfoxide (*alliin*), together with (+)-S-methyl-L-cysteine sulfoxide (*methiin*) and (+)-S-(trans-1-propenyl)-L-cysteine sulfoxide, γ -glutamyl-S-allyl-mercapto-L-cysteine, and S-(2-Carboxypropyl) glutathione, γ -glutamyl-S-allyl-L-cysteine, γ -glutamyl-S-(trans-1-propenyl)-L-cysteine^[142,143]. The pharmacodynamically more potent compound allicin (diallyl thiosulfinate or diallyl disulfide) is only released in cut or crushed garlic, as such injury to the garlic bulb results in a release of the enzyme allinase, which metabolizes *alliin* to *allicin*. *Allicin* again is the precursor of various transformation products, including ajoenes,

vinylthiines, oligo-sulphides and polysulphides, depending on the conditions^[144]. Chemically pure *allicin*, first isolated in the 1940's, was shown to have antibacterial, antiviral, antifungal and antiparasitic effects. Its biological activity may mostly be attributed to either antioxidant activity, thiol disulfide exchange and rapid reaction with thiol containing proteins^[145]. However, biologically active *alliin* or *allicin* is primarily found in fresh garlic or garlic powder, but not sufficiently in garlic oil, aged garlic and steam-distilled garlic^[146]. Antifibrotic and anticarcinogenic mechanisms of garlic in the liver are demonstrated in figure 8.

Hepatoprotective Potential

Administration of D-GalN is an established model of an acute fulminant hepatitis triggered by oxidative stress in the rodent, as it increases susceptibility of the hepatocyte towards lipopolysaccharide (LPS) within few hours after administration. In D-GalN/LPS-treated hepatitis rats a significant increase of lipid peroxidation accompanied by decreased liver antioxidant enzyme activities (GSH, GST, SOD, CAT, glutathione peroxidase [GPx]) are observed. Vimal and Devaki could show in their study, that pretreatment with allicin prevented these alterations^[147]. An antisteatotic effect by allicin and/or ajoene in rat hepatocytes and HepG2 cells on the level of HMG-CoA-reductase or lanosterol 14 alpha-demethylase was observed by German and Indian research teams suggesting a preventive effect of garlic consumption on periinflammatory steatosis^[148,149]. Strong antioxidant properties of allicin in the mouse liver were observed by Bruck *et al*,

who investigated the ability of allicin to prevent immune-mediated, concanavalin A (Con A)-induced liver damage in mice. They observed that the histopathologic damage in the liver, and the Con A-induced increase of transaminases and TNF- α were significantly inhibited in those animals that were pretreated with *allicin* before Con A injection. Further experiments revealed that *allicin* exerts its antioxidative and anti-inflammatory properties mostly through immunomodulatory effects on T cells and adhesion molecules as well as an inhibition of NF- κ B activation^[150].

Xiao *et al* focussed on another sulfur compound of garlic, S-allyl-mercapto-L-cysteine (SAMC) and found that administration of SAMC triggered the expression of antioxidant enzymes, reduced nitric oxide (NO)-dependent oxidative stress, and attenuated lipid peroxidation in CCl₄ treated mice. Co-treatment with SAMC furthermore mitigated CCl₄-induced hepatic inflammation through selective inhibition of NF- κ B subunits p50 and p65 (hereby confirming the study by Bruck *et al*), resulting in a reduced expression of pro-inflammatory cyto- and chemokines^[151].

The antioxidative properties described above are mostly the reason for the effects of garlic on the hepatic response towards toxic agents, such as heavy metals or ethyl alcohol. Ethanol is efficiently metabolized in the liver to cytotoxic acetaldehyde by the alcohol dehydrogenase. Acetaldehyde in turn is further oxidized to acetate by aldehyde oxidase or xanthine oxidase resulting in a production of ROS via cytochrome p (CYP) 450. Abdel-Naim *et al* showed in the combined ethanol/CCl₄ model of the rat that pretreatment with garlic oil reduced the ethanol/CCl₄-induced elevation of AST, ALT, GGT, AP serum activities as well as total bilirubin concentrations. It furthermore prevented the decline in total protein and the increase in triglycerides and total cholesterol resulting from ethanol/CCl₄-administration in rat liver homogenates. GSH levels reduced by ethanol/CCl₄ were found to be restored by garlic oil. Histopathological examination revealed that administration of garlic oil furthermore attenuated ethanol/CCl₄-induced centrilobular necrosis and nodule formation^[152]. These promising data could be transferred to the human by Mirunalini *et al* who found decreased serum concentrations of MDA as well as an increase of the activities erythrocytic antioxidant enzymes in patients with alcohol induced liver damage that were supplemented with two small sized garlic cloves per day for 45 d^[153]. Similar to chronic alcohol ingestion, exposure to heavy metals poses a risk for oxidative stress to the liver. The effect of garlic extract on heavy metal induced liver damage was investigated in three studies. In a recent paper, Nwokocha *et al* compared the effects of a raw garlic containing diet on oral mercury, cadmium and lead uptake in the rat with garlic being added to the diet either simultaneously with the metals, 7 d after exposure to heavy metals or 7 d before heavy metal exposure for 6 weeks. Of note, garlic offered the most hepatoprotective effect towards cadmium, followed by mercury and lead through the processes of uptake, assimilation and elimination of these metals. Strongest effects were observed in those rats receiving concomitant garlic administration^[154].

The research group around Ajayi showed that *post*-lead treatment with *Allium sativum* significantly reduced the lead-induced increase of both, ALT and AP serum activities^[155], which was confirmed by Kilikdar *et al*, demonstrating that also garlic extract fed orally to rats 1 h before lead acetate treatment strikingly reduced the lead-induced increase of activities of ALT and AP, of serum bilirubin concentrations and of the damage in the tissue morphology. In addition, they observed a reversal of almost all signs of lead-induced oxidative stress, such as decreased serum activity of SOD and from increased levels of lipid peroxidation and reduced GSH following oral ingestion

of aqueous garlic extract^[156]. Cadmium-induced oxidative stress in the liver could equally be reversed by pretreatment with heated garlic juice, as seen by a reduction of intrahepatic MDA and ROS as well as increased SOD and CAT activities compared to control rats receiving no garlic juice^[157]. Experimental studies have demonstrated the ability of garlic to reduce chemical carcinogenesis in different animal models, especially certain cancer incidences in the stomach, colon, mamma, and cervix^[158]. Only few studies investigating the effect of garlic on hepatocarcinogenesis are available so far, however. A French study revealed that the garlic organosulfur compounds allicin, diallyl sulfide, diallyl disulfide, S-allyl cysteine and allyl mercaptan displayed antigenotoxic activity in HepG2 cells, an immortalized hepatocellular carcinoma cell line. They found that Aflatoxin B1 genotoxicity was significantly reduced by all organosulfur compounds tested except by allyl mercaptan. Additionally, all organosulfur compounds studied were shown to decrease the genotoxicity of the direct-acting genotoxic compounds, hydrogen peroxide and methyl methanesulfonate. Diallyl disulfide was the most efficient organosulfur compound in reducing benzo[a]pyrene induced genotoxicity. Furthermore, S-allyl cysteine and allyl mercaptan significantly decreased DNA breaks in HepG2 cells treated with dimethylnitrosamine^[159]. This study is the first to suggest a direct antimutagenic effect of garlic in the carcinogenesis of the liver. However, these experimental data of an anticarcinogenic effect of garlic are supported by findings from China, demonstrating an induction of apoptosis and an upregulation of Bax and Fas ligand expression by allicin in a mouse model of HCC^[160].

Green Tea: *Camellia sinensis*

Description: The tea plant (*Camellia sinensis*) grows in subtropical monsoon climate with wet, hot summers and rather dry, cold winters. The range of cultivation is from the south of Japan and Korea to the southern half of China and North-East India. In southerly directions, tea plants are found in Laos, Myanmar, Thailand and Vietnam. In wilderness, it grows in the understory of evergreen forests. But because of the long history of cultivation by humans, the exact natural habitat is no longer definable^[161].

The tea plant grows as evergreen scrub or small tree up to a height of 5, seldom also 9, metres. The alternate dark green leaves have short peduncles, are of round or oval shape and 5 to 14 cm in diameter, with a dentated margin. The plant blossoms between October and February, with flowers of 2.5-3.5 cm in diameter^[161].

Green tea is a variety of tea processing. In contrast to black tea, the tea leaves are not fermented. After withering of the freshly picked leaves, a short heating, roasting or steaming of the tea leaves prevents their fermentation. For this reason, the inactivation or metabolic conversion of almost all active compounds contained in the fresh leaf is prevented.

History and Folk Use: A legend is told that in the year 2737 BC, tea was more or less coincidentally discovered when Chinese emperor Chen Nung accidentally dropped the leaves of a wild growing *Camellia sinensis* plant into a bowl of hot water. Not wanting to discard the water, he drank from the cup and found it refreshing and healing^[162].

For the following centuries, tea was exclusively used as a medicine to treat fatigue, rheumatic disorders, headache, lack of concentration or slight visual impairment. It took a couple of more centuries, until tea was eventually discovered as a luxury food. Around 400 BC, first records of teatime ceremonies in China emerge. The first written mention of tea dates back to 221 BC. The Chinese government levied a tax for tea which means that tea must have been relatively widespread and common at the time. The first known book about

Figure 9

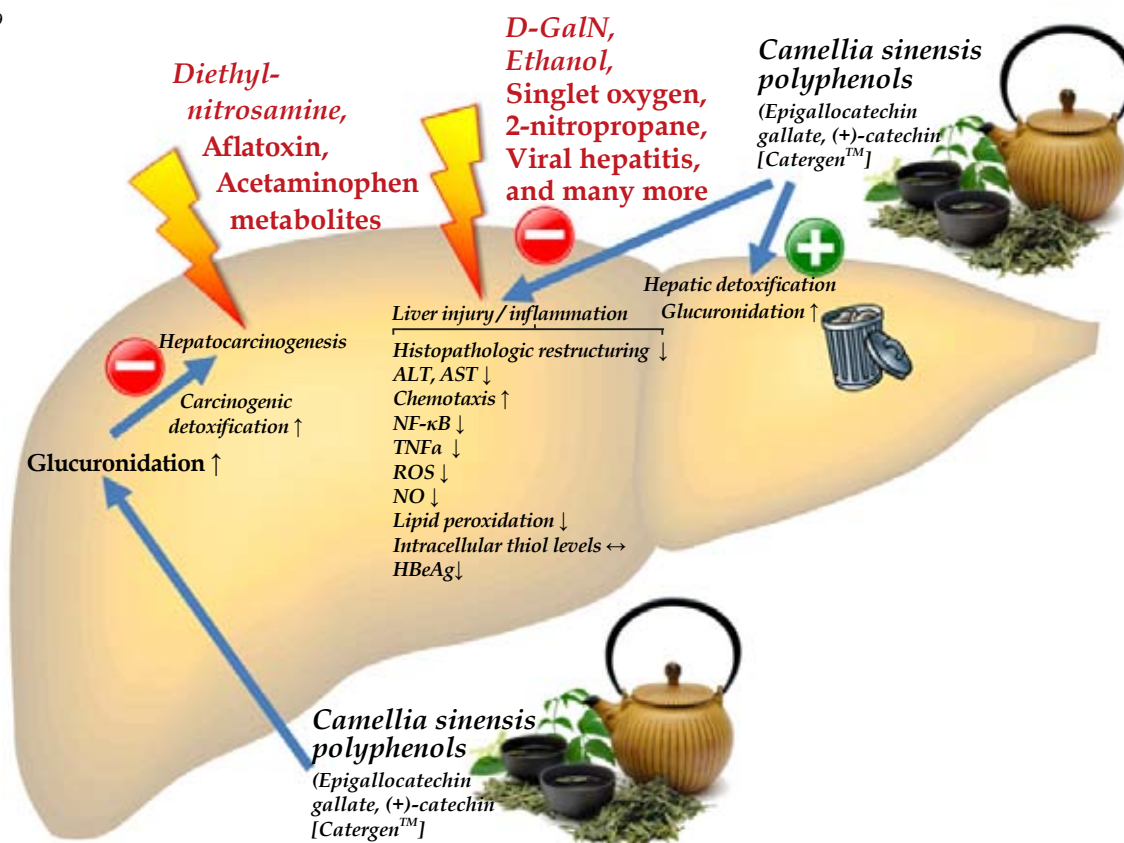


Figure 9 Effects of green tea polyphenols on viral and non-viral hepatitis, oxidative stress, phase II detoxification, fibrogenesis, and carcinogenesis.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; D-GalN: D-galactosamine N; HBeAg: hepatitis B envelope antigen; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NO: nitric oxide; ROS: reactive oxygen species; TNF: tumor necrosis factor.

tea was published in 780 AD by the Chinese Lu Yu (733-804) called "Cha Ching" (The classical book of tea). It was here, that green tea was first described as a new variety of tea processing. Because of his contribution to Chinese tea culture, Lu Yu is widely respected as the Sage of Tea. In the first centuries of its history tea was still only for the upper class. It was not until 4th-7th century that tea became affordable to every Chinese and displaced wine as the most popular beverage. The Chinese tea culture was booming, tea gardens were planted, some only to contribute the finest teas, plucked by virgins in the early morning mist, to the Chinese Emperor. Tea became a symbol of purity and a way to self-knowledge^[162].

The earliest mention of tea in the literature of Europe was in 1559. It appears as "Chai Catai" (Tea of China) in the book *Delle Navigazione et Viaggi* (Voyages and Travels) by Giovanni Battista Ramusio (1485-1557), an Italian geographer and travel writer.

Ramusio's book was a collection of narratives of voyages and discoveries in ancient and modern times, including those of the Persian merchant Hajji Mahommed, who visited Venice, who is credited with first bringing tea to Europe. The reference describing tea says, One or two cups of this decoction taken on an empty stomach removes fever, headache, stomach ache, pain in the side or in the joints . . . besides that, it is good for no end of other ailments, which he could not remember, but gout was one of them. He said "it is so highly valued and esteemed that everyone going on a journey takes it with him, and those people would gladly give a sack of rhubarb for one ounce of Chai Catai". The beverage was first called Cha, from the Cantonese slang for tea. The name changed later to Tay, or Tee, when the major British trading post moved from Canton (Guangzhou) to Amoy (Xiamen), where the word for tea is T'e^[162].

In 1610, the Dutch began shipping Chinese and Japanese teas to Europe from their Javanese trading posts. In the 1630s, the Dutch began selling teas to France, Germany, North America, and England. It was the Dutch who also brought tea to the American colonies around 1650 through their colony of New Amsterdam, now New York City. In the 1670's, tea houses were established in New Amsterdam. The introduction of tea had its biggest impact in England, where it was sold for the first time in 1657. In the middle of the 19th century, in England green tea was largely replaced by black tea, because of which green tea sunk into obscurity. Only in the last 50 years, green tea re-emerged as part of a healthy diet^[162].

Functional Components: Tea is rich in bioactive constituents, mostly polyphenols and alkaloids^[163].

While alkaloids are central in the psychostimulatory effects of tea drinking, they are not central to the medicinal effects attributed to this beverage. It is more the polyphenols, that provide the medicinal, and particularly hepatoprotective, effects, but also the bitter flavor of tea^[164-166].

In dry weight, green tea contains about 30-40% polyphenols, compared to only 3-10% in black tea. The averaged sized cup of tea contains somewhat between 50 and 150 mg of polyphenols^[163]. The polyphenols in tea are classified as catechins^[163], of which tea contains six primary ones: (+)- catechin, epicatechin, epicatechin gallate, gallic acid, epigallocatechin, and epigallocatechin gallate. The latter one is currently considered to be the most potent of the bioactive components^[165,167].

Hepatoprotective Activity: Green tea has been shown to possess

several hepatoprotective properties. In general, protective effects have been observed in ethanol^[168], D-GalN^[169,170], 2-nitropropane (an industrial solvent also found in cigarette smoke)^[171,172], and 1,4-naphthoquinone^[166] induced hepatitis and carcinogenesis.

As observed for most other foods described herein, most of the hepatoprotective action of green tea is due its antioxidative components, the polyphenols (catechins). In most rodent models of toxic hepatitis, such as singlet oxygen-, tert-butyl hydroperoxide and bromotrchloromethane-, or 1,4-naphthoquinone-induced hepatitis, green tea catechins were found to inhibit lipid peroxidation^[164, 166, 173].

For example, in 2-nitropropane induced hepatitis, administration of epigallocatechin gallate almost halved hepatic lipid peroxide levels at six hours and an attenuation of 30 percent was still found at 15 h post administration^[172].

However, next to its direct antioxidant activities, catechins of green tea have been shown to possess also indirect effects on the intracellular redox balance through the maintenance of intracellular protein thiol levels, which in turn influences the protein tertiary configuration. The latter mechanisms was suggested to be particularly important in the case of 1,4-naphthoquinone-induced hepatocellular damage^[166].

Pure green tea (+)-catechin, commercially known as *Catergen*, has been extensively studied in the human and, temporarily, also used to treat viral hepatitis. Rauch *et al* found that *Catergen* application to the mouse results in a dose-dependent activation of cytotoxic-T-lymphocytes, macrophages, and natural killer cells^[174]. An interesting study from 2011 then investigated a wide spectrum of possible cell signaling molecules suppressed by *Catergen* in a rat model of alcoholic liver disease. Key findings were that *Catergen* attenuated alcohol-induced liver injury most efficiently through a downregulation of the endotoxin-mediated activation of NF- κ B and, further downstream, TNF- α , nitric oxide and ROS - thus by enhancing the antioxidant profile. All observations correlated well with the respective hepatic histoarchitecture^[175]. A particular clinical effectiveness of *Catergen* was observed in patients with Hepatitis B. A Japanese double-blind study registered a significant drop in titers of antibodies against hepatitis B e antigen (HBeAg), equitable to an attenuation of disease activity. A 16 week treatment resulted in a reduction of 50% of the HBeAg titer in more than 30% of all patients (twice as many as in the placebo group), and HBeAg even completely disappeared in 11% of all cases. The patients whose HBeAg titer was lowered were largely those with chronic active hepatitis^[176]. In another study, twelve male patients with chronic hepatitis B infection were treated by the combination of recombinant human IFN- α and *Catergen* for 6 months. Four patients experienced clinical improvement in which serum HBeAg fell below the detection limit, and aminotransferase activities fell back to normal levels^[177].

However, these intriguing therapeutic effects of *Catergen* were overshadowed by a variety of side-effects: In some cases it caused hemolysis in treated patients^[178,179], possibly by triggering antibody formation against (+)-catechin, which cross-react with erythrocytes^[179]. Also, there are few reports on transient febrile reactions following application^[177]. When in September 1985, three deaths in Naples/ Italy occurred upon intake of *Catergen*, further worldwide distribution of the medication was eventually stopped^[180].

Next to its antioxidative and immunostimulatory properties, green tea administration were proven to efficiently enhance the phase II liver detoxification process in the rat, by increasing glucuronidation for as much as 100%^[181,182]. Increasing elimination in the presence of green tea extracts were observed for, but not only, aflatoxin and acetaminophen metabolites^[181].

It is very likely, that the enhancement of the detoxifying process

largely contributes to the anticarcinogenic effects of green tea in the liver, by facilitating the metabolism of chemical carcinogens into inactive, readily-excretable products^[183].

Several mouse model studies have given evidence that green tea significantly reduces or even prevents the formation, growth and metastatic spread of hepatic malignancies, e.g. those induced by diethylnitrosamine^[167]. Other researchers obtained comparable results in rats^[184,185].

All in all, despite few opponent literature^[186], the anticarcinogenic effect of green tea on the liver is certainly convincing. Going into depth with the tumorpreventive properties of green tea. Which has evolved as a major focus of green tea research, would go beyond the scope of the review. It may therefore be referred to the relevant literature^[187-191].

Liquorice: *Glycyrrhiza glabra*

Description: Liquorice (*Glycyrrhiza glabra*) is a member of the papilionaceae subfamily, belonging to the bean family (*Fabaceae*). It is native to mediterranean Europe and Western Asia.

Liquorice is a hardy perennial plant which grows upto 1 m in height. The leaves are pinnate, about 7-15 cm long, and have 9-17 leaflets. The flowers are purple to pale whitish blue and 0.8-1.2 cm long. The fruit is an oblong pod, 2-3 cm long, and contains numerous seeds. Liquorice grows best in deep valleys, well-drained soils, with full sun, and is harvested in the autumn, two to three years after planting^[192,193]. All medicinally active components derive from the dried root, *Liquiritiae radix* (syn. *Glycyrrhizae radix*, *Radix Glycyrrhizae*, *Radix Liquiritiae*).

History and Folk Use: *Glycyrrhiza glabra* originated in the Mediterranean and Middle East and has been used medicinally at least since 500 BC^[162]. The generic name *Glycyrrhiza*, already used in ancient times, derives from the greek words *glykys* (sweet) and *rhiza* (root). The latin species name *glabra* (bald, sticky) refers to the leaves that are glandular and sticky on the underside. Already in ancient Greece and Rome, liquorice was particularly appreciated. Already the greek philosopher Theophrastus (ca. 371-287 BC) and doctor Pedanius Dioscorides (ca. 40-90 AD) recommended the juice of *Glycyrrhizae radix* as a valuable medicine against cough and bronchial catarrh. The use of *Glycyrrhizae radix* as a drug also found much attention also in the Middle Ages, including in well-known in Pharmacopoeias. In the German city of Bamberg, for example, a "liquorice-culture" was introduced in the 15th century, a tradition that was even expanded in the following 16th century. At that time, liquorice was one of the most commonly prescribed herbs. Traditional uses included the treatment of peptic ulcers, asthma, pharyngitis, malaria, abdominal pain, and infections. Also in the Middle Ages, the renaming of the greek name *Glycyrrhizae* to latin *Liquiritia* as it exists today, took place^[162].

Nowadays, liquorice is used to flavor a wide variety of candies, gum, tobacco products, and drinks. However, the idea of it's use in medicine has not been abandoned. For example, it's major compound glycyrrhizic acid is now routinely used throughout Japan for the treatment and control of chronic viral hepatitis^[194].

Functional Components: Several flavonoids (liquiritin and isoliquiritin), a variety of isoflavonoids (isoflavonol, kumatakenin, licoricone, and glabrol) as well as chalcones, coumarins (umbelliferone, herniarin), triterpenoids, and phytosterols are biochemical components of the fresh root of *Glycyrrhiza glabra*. Most of these compounds are hydrolyzed during artificial drying. The major active constituents of

Figure 10

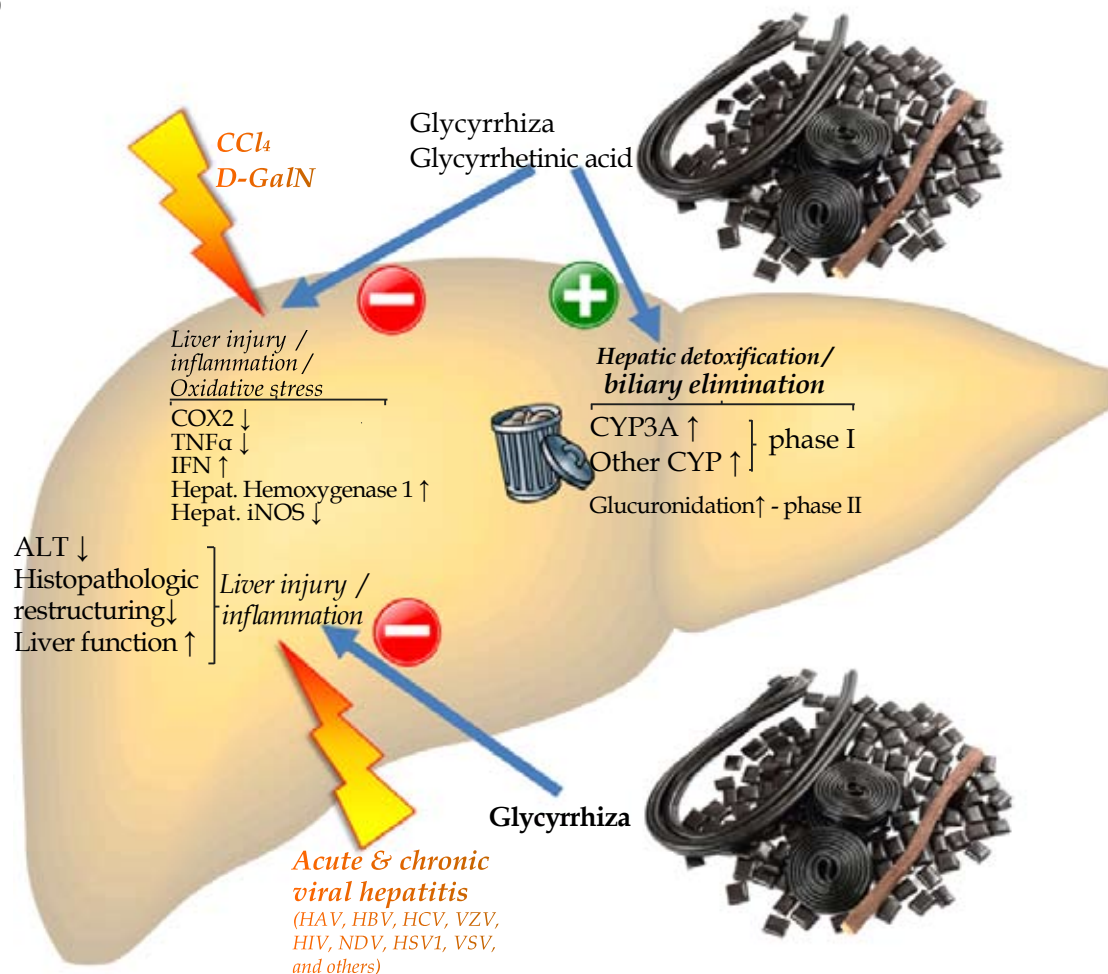


Figure 10 Effects of Glycyrrhiza and Glycyrrhetic acid, major compounds of liquorice, on viral and non-viral hepatitis, oxidative stress, as well as hepatic phase I and II detoxification.

ALT: alanine aminotransferase; CCl_4 : carbon tetrachloride; COX: cyclooxygenase; CYP: cytochrome p450; D-GalN: D-galactosamine N; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HSV1: herpes simplex virus type 1; IFN: interferon; iNOS: inducible nitric oxide synthase; NDV: Newcastle Disease virus; TNF: tumor necrosis factor; VSV: vesicular stomatitis virus; VZV: varicella zoster virus.

the dried root, as it relates to hepatic disorders, are the triterpenoid saponin glycoside Glycyrrhiza (also known as glycyrrhizic acid; 2-15%), its aglycone glycyrrhetic acid, and 24-hydroxy-18/glycyrrhetic acid, as well as several other saponoids^[163].

Hepatoprotective Activity: A strong hepatoprotective effect of Glycyrrhiza could be demonstrated in mouse models of CCl_4 ^[195,196] and D-GalN induced hepatitis^[197]. Also Glycyrrhiza has been demonstrated to have a significant free-radical quenching effect^[198]. And as for most other hepatoprotective foods described in this review, current data suggest the antioxidative/antilipid peroxidation effect of Glycyrrhiza as the major mechanism of its protective action against CCl_4 -induced hepatotoxicity^[195].

In mice, CCl_4 induced hepatic iNOS, COX-2, and TNF- α protein and mRNA expression were markedly attenuated and hepatic heme oxygenase-1 protein and mRNA expression markedly stimulated following oral glycyrrhizin administration^[199]. These findings were also confirmed in cell culture models of primary rat and mouse hepatocytes. An *in vitro* assay for antihepatotoxic activity using D-GalN-induced injury in primary-cultured mouse and rat hepatocytes confirmed that, among others, glycyrrhetic acid, and glycyrrhizin displayed significant antihepatotoxic activity^[111].

Glycyrrhiza is able to stimulate hepatic detoxification processes, mostly by activating CYP, phase I detoxification or by increasing hepatic glucuronidation. Oral application of extract from *Glycyrrhizae*

radix or chemically pure glycyrrhizin to Swiss Albino CD1 mice for 10 d enhanced the CYP, phase I detoxification of a variety of agents, such as pentoxyresorufin, p-nitrophenol, ethoxyresorufin, methoxyresorufin, and aminopyrine^[200]. A Chinese group observed a modest induction of CYP3A following administration of glycyrrhizin, resulting in enhanced midazolam detoxification^[201].

Rats subjected to oral intake of Glycyrrhiza tincture displayed a significant increase of the cumulative biliary (>150%) and urinary (>130%) elimination of acetaminophen-glucuronide conjugate within the first 120 min after the administration of acetaminophen. However, in this study, high concentrations of Glycyrrhiza were used that in humans would have likely caused unwanted side effects^[202].

Antiviral activity of intravenous Glycyrrhiza was shown in several studies: A Dutch double blind study showed its effectiveness in viral hepatitis, in particular chronic viral hepatitis. Glycyrrhizin up to 240 mg, thrice weekly, were found to lower serum ALT during treatment, but had no effect on HCV-RNA levels in patients with chronic hepatitis C, non-responders or unlikely to respond (genotype 1/cirrhosis) to interferon therapy^[203].

The same was found for oral application of Glycyrrhiza extract. In this study, all indicators of liver function returned to normal in 85 percent of subjects with *acute* hepatitis that received Glycyrrhiza within 30 d after first ingestion, compared to 35 percent in the control group treated with Poly I:C (polyinosinic-polycytidylic acid,

Figure 10

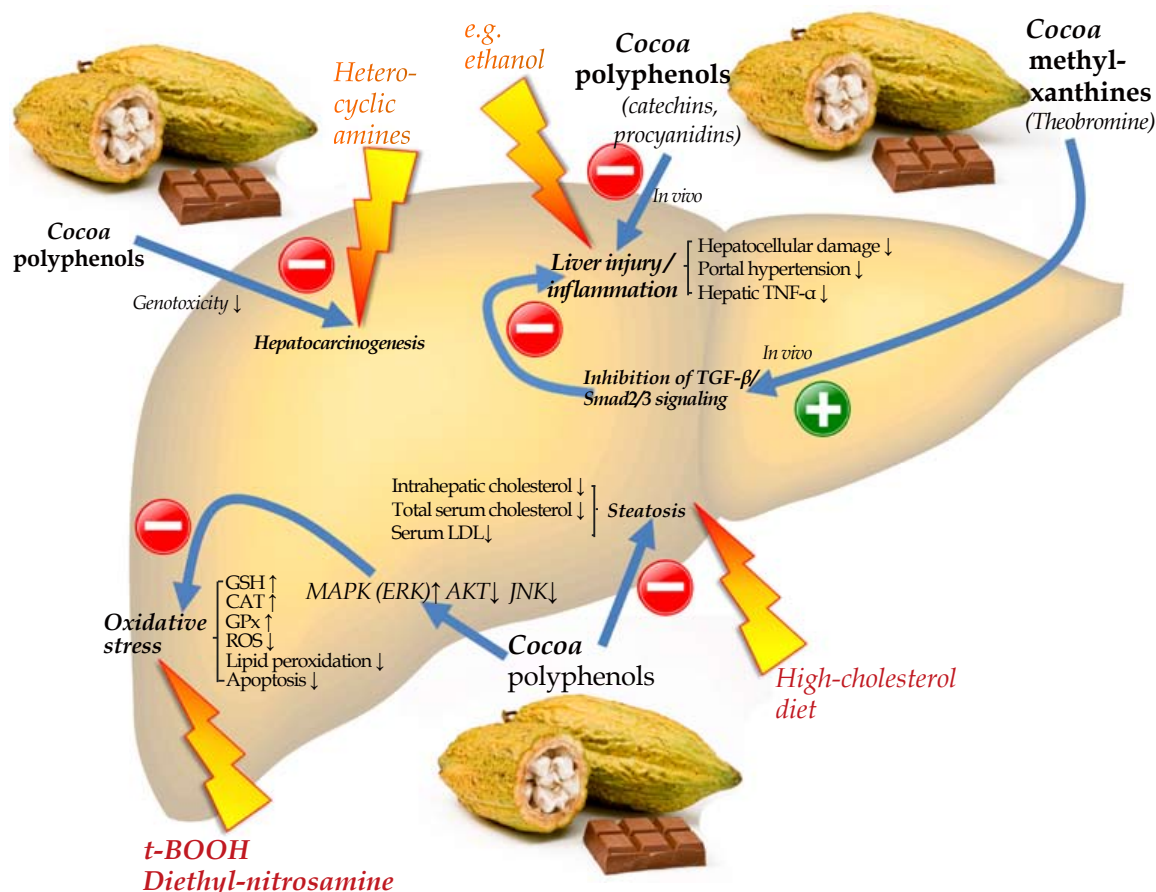


Figure 11 Effects of cocoa polyphenols and methylxanthines on liver injury/inflammation, oxidative stress, steatosis, and carcinogenesis. CAT: catalase; GPx: glutathione peroxidase; GSH: glutathione; LDL: low density lipoprotein; ROS: reactive oxygen species; t-BOOH: tert-butyl hydroperoxide; TGF: transforming growth factor; TNF: tumor necrosis factor.

an antiviral) and inosine intramuscularly. In patients with chronic hepatitis, 75 percent experienced normalization of liver function, compared to 10 percent in the control group^[204].

The reason for the observed antiviral effect seems to be a stimulation of IFN activity: Commercially available compositions of 0.9% saline solutions, cysteine, glycine, and Glycyrrhiza (Stronger Neo Minophagen-CTM, or SNMCTM) have shown to stimulate endogenous IFN production next to the already known antioxidant and detoxifying effects^[205]. A stunning 72% survival rate was noted for patients with subacute hepatic failure due to viral hepatitis who received SNMC treatment for 12 weeks, compared to a survival rate of only 31% in patients who received regular supportive therapy^[205].

Next to these general antiviral, i.e. immunostimulatory, effects, Glycyrrhiza has proven to also display specific antiviral activity against several viruses, including hepatitis A (HAV)^[206], hepatitis B (HBV)^[207], HIV^[208], varicella zoster (VZV)^[209], Newcastle disease (NDV)^[210,211], herpes simplex type 1 (HSV1)^[210,211], and vesicular stomatitis viruses (VSV)^[210,211]. Data are summarized in figure 10.

Cacao: *Theobroma cacao*

Description: Cacao (*Theobroma cacao*) belongs to the genus *Theobroma*. It is now classified under the family *Malvaceae*, the mallow family, comprising e.g. marshmallow, jute, kola nut, okra, and cotton. Cacao belongs to the subfamily *Sterculioideae*, along with the kola tree. The Cacao-Tree owes its name to Carl Linnaeus, who described it as *Theobroma cacao* (from greek “theos”=god and “broma”=food). Recent studies of *Theobroma cacao* genetics seem to show that the plant originated in the Amazon region of Brazil and was distributed by man throughout Central America and Mesoamerica.

Nowadays, the key growing areas are in Africa (Côte d’Ivoire, Ghana, Nigeria, Cameroon), South and Mesoamerica (Brazil, Ecuador, Colombia, Dominican Republic, Mexico) and Asia (Malaysia, Indonesia).

Even though the tree may reach a height of 15 m, in culture they are generally polled to a height of only 4-8 m. Leafs may get up to 35 cm long. The five-petalled flowers are located directly on the stem (cauliflory), the fruits have a leathery skin, are yellow-brownish, 15-20 cm long and weigh up to 500 g. Below the extremely hard shell here are 30-60 seeds arranged in 5 rows which are embedded in a white, sweet, mucous, delicious pulpa. It is the seeds from which, after a complicated food technological procedure, cocoa mass, powder and butter for manufacturing chocolate are obtained^[212].

History and Folk Use: The first use of chocolate, the raw or processed food produced from the seed of *Theobroma cacao*, can be traced back to the Mokaya and other pre-Olmec people of the Soconusco region in Mexico and parts of the Pacific coast of western Guatemala, with evidence of cacao beverages dating back as far as 1900 BC^[213,214].

Tradition continued, and chocolate played a special role in both Maya and Aztec royal and religious events and were traded like a currency^[214]. It is the word “xocolatl” from the Aztekan Nahuatl language, from which our word “chocolate” derives, made up from the words “xococ” meaning sour or bitter, and “atl” meaning water or drink^[214]. It is also from that time that first application of chocolate in medical purposes is described: The ancient Incas, Mayans, and Aztecs believed that cacao was a source of power, thus not knowing whether to call it food or medicine. Chocolate beverages were thought to

cure diarrhea and dysentery, and were believed to be an aphrodisiac. For example, Aztecan emperor Moctezuma I. (1390-1469) drank chocolate drinks in small amounts up to fifty times a day for increased virility^[214].

Christopher Columbus (1451-1506) was apparently the first European to encounter cacao beans on August 15, 1502, on his 4th and last voyage to the Americas. When Spanish conquistador Hernán Cortés (1485-1547) discovered the drink a few years later, he made it a major part of his soldiers' diet. Historical records show that those who drank it felt increased energy, focus, stamina, happiness, and virility. Cortez was the first to bring three full chests of cacao seeds back to Spain, followed soon by regular deliveries with the first official shipment from Veracruz to Seville in 1585. As societies from other countries more and more experienced the delicacy, chocolate became more widely available. Soon the French, English, and Dutch were cultivating cacao in their colonies in the Caribbean, and later, elsewhere in the world. This resulted in lower prices, so that soon, chocolate became a food product for the masses in Europe and the Americas^[214].

In the 17th centuries, chocolate was recommended for its euphorogenic and antidepressant properties. Also, chocolate was substituted by a variety of other ingredients. Quinine (major alkaloid from the Peruvian bark) was added as treatment for Malaria, and potassium iodide for patients with lues, lymph node tuberculosis or goiter. China chocolate contained Peruvian bark for the application in patients with "cold fever", and chocolate supplemented with extracts from Icelandic moss was used in cases of consumption, respiratory ailments or diarrhea^[214].

Medical effects of chocolate itself, however, more and more fell into oblivion. In the 19th century, eventually, chocolate was only consumed as a delicacy and no longer in medical intentions. After a long period of neglected possibilities, science eventually rediscovered the healthbeneficial effects of pure chocolate. It has only been a few decades, that studies promoted again potent antioxidative, anti-inflammatory, anticonvulsive, and cholesterol-lowering effects of *Theobroma Cacao*.

Functional Components: The seeds of *Theobroma cacao* consists to more than half of fat (*Oleum Theobromatis*, approx. 54%). Major fatty acids are oleic acid (33 to 39%), stearic acid (30 to 37%), and palmitic acid (24 to 31%). The fat portion delivers the cocoa butter required for chocolate production. It is won by a pressing technique by which up to 80% of the fat components are extracted. Depending on the degree of extrusion, weakly and highly de-oiled cocoa butter is differentiated. Cocoa butter is not-as the name maybe suggests-a firm, butter-like mass, but a liquid, golden brown oil. In addition, the seed contains purine alkaloids (3-4%) with the major alkaloid being theobromine, which accounts for 80% of all alkaloids in the seed, followed by caffeine (0.1-0.4%) and traces of theophylline. Other components are carbohydrates [starch and oligosaccharides 5-9%, monosaccharides (e.g. Saccharose, Glucose, Fructose) 2-4%], at least 17 polyphenolic compounds [13%; e.g. as (-)-epicatechin and (+)-catechin^[215,216], leukocyanidines, procyanidins, and anthocyanins (e.g. 3- α -l-arabinosyl cyanidin and 3- β -d-galactosyl cyanidin)], oxalates (0.6 - 1%), biogenic amines (e.g. β -phenylethylamine, tyramine, tryptamine, serotonin), and isoquinoline derivatives [e.g. Salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline)]^[217].

Hepatoprotective Activity: There is increasing interest in the potential health benefits of dark chocolate intake. Although still debated, a range of potential mechanisms through which dark

chocolate might exert its benefits have been proposed, including activation of nitric oxide and antioxidant, as well as antiinflammatory effects.

In a rodent model of alcohol-induced liver injury in which rats were fed high-fat liquid diets with or without ethanol and cocoa extract, enteral ethanol caused severe fat accumulation, mild inflammation, and necrosis in the liver, cocoa extract significantly blunted these changes. Increases in serum transaminase activity, liver TNF- α protein levels, and hepatic lipid peroxidation caused by ethanol were completely blocked by cocoa extract^[218]. In line with this, a study from our group showed that theobromine, the major alkaloid of *Theobroma cacao*, efficiently interrupted TGF- β signaling, the profibrogenic master cytokine and strong promoter of hepatic inflammation, and CTGF synthesis in primary rat hepatocytes by interfering with the Smad2/3 signaling pathways^[58,219].

However, most research traces the hepatoprotective effect of cacao intake back to the antioxidative capacity of the ingredients, particularly the phenolic compounds such e.g. catechins and procyanidins.

In N-nitrosodiethylamine-injected rats, a cocoa-rich diet furthermore almost entirely prevented the reduction of hepatic GSH concentration and CAT and GPx activities^[220]. Martin *et al* demonstrated in HepG2 cells that the induction of the two antioxidant enzymes, GPx and glutathione reductase (GSR), by cocoa polyphenols takes place through a stimulation of the classical MAP kinase pathway, primarily involving extracellular regulated kinases (ERK) activation^[221]. These findings were supplemented by *in vivo* data from a Malaysian group, examining the effect of polyphenolic cacao liquor extract on tumor marker enzymes such as AP, GGT, GST, and GSR activities - in plasma and/or liver tissue of rats, in which hepatocarcinogenesis was induced by diethylnitrosamine and 2-acetylaminofluorene. The findings showed that the polyphenolic compounds present in cacao liquor are able to lower the activity of all these marker enzymes of hepatocarcinogenesis in rats^[222].

Another *in vivo* study in rats with N-nitrosodiethylamine-induced hepatic damageshowed that application of N-nitrosodiethylamine caused a significant increase in damage markers, a decrease in hepatic GSH and p-ERK levels, and enhanced protein carbonyl content, caspase-3 activity and values of p-AKT and p-JNK. A cocoa-rich diet counteracted all these N-nitrosodiethylamine-induced changes^[220].

A Spanish study investigated 21 cirrhotic patients with end stage liver disease who received a standard liquid meal of dark chocolate (containing 85% cocoa, 0.55 g of dark chocolate/kg body weight) or a liquid meal containing white chocolate which is devoid of cocoa flavonoids. They found that the post-prandial physiological increase in hepatic venous pressure was markedly reduced in patients receiving dark chocolate, and resumed that dark chocolate contains potent antioxidants, i.e. flavonoids, which attenuate portal hypertension and endothelial dysfunction^[223].

A Japanese study investigated the impact of phenolic compounds of *Theobroma cacao*, in particular of cacao procyanidins, on serum cholesterol and hepatic steatosis in rats fed on either a normal diet, a high cholesterol diet or a high cholesterol diet supplemented with cacao procyanidins and found that these antioxidative constituents significantly decreased plasma and intrahepatic cholesterol concentrations to levels similar to those of the normal diet group. They suggested an inhibition of intestinal absorption of cholesterol as responsible mechanism^[224]. These data were confirmed by another group from Spain and supplemented by findings of a reduction of not just total, but particularly of LDL cholesterol following cocoa fiber intake in rats^[225].

Yamagishi *et al* studied the effect of polyphenols derived from

cacao liquor on hepatocarcinogenesis, particularly on the mutagenic action of heterocyclic amines *in vitro* and *ex vivo*. In the Ames test, a biological assay to assess the mutagenic potential of chemical compounds^[226], the cacao liquor polyphenols showed antimutagenic effects in bacteria treated with heterocyclic amines in the presence of an S-9 mixture. In a host-mediated assay in mice, a method used to estimate the potential carcinogenicity of chemicals *ex vivo*, oral administration of the cacao liquor polyphenols, reduced the number of colonies of revertant bacteria recovered from the liver, suggesting that the cacao liquor polyphenols have an antimutagenic effect not only *in vitro*, but also *ex vivo*^[227].

These phenomenological data received a molecularbiological rationale by data obtained from the human hepatocellular carcinoma cell-line HepG2 showing that cocoa polyphenols extract efficiently prevented tert-butyl hydroperoxide (t-BOOH)-induced apoptosis by reducing ROS generation and by modulating apoptotic pathways, mostly by interfering with caspase 3 signaling or by inducing autophagy^[228].

So overall, we got a good view on the antihepatocarcinogenic action of cocoa polyphenol extract which is a stimulation of cell survival, an inhibition of apoptosis, and an increase of the antioxidative capacity.

DISCUSSION

“Let food be thy medicine and medicine be thy food.” Proclaimed no one less than Hippocrates, the Ancient Greek philosopher and doctor about 460 BC. “Live a healthy life,” he said furthermore, “and you are not likely to fall ill, unless you have an accident or an epidemic occurs. If you do fall ill, proper regimen will give you the best chance of recovery”^[229].

After in the 19th century, nutritional science was established as a systematic, and analytical research of food and its components, the 20th (and 21st) century was/is merely characterized by the development of a conception of the causal relation of biochemical, ecological, epidemiological, functional and medical aspects of our nutrition^[230]. In this effort, next to the basic constituents carbohydrates, proteins and lipids, essential minerals, vitamins and, later, secondary bioactive compounds such as polyphenols were identified and studied^[230]. For centuries, the pharmacodynamics effects of these secondary plant products had been traditionally used in therapeutic intentions, but the actual bioactive compounds and their mechanism of action remained unknown^[230].

Next to upgraded methods for biochemical analysis, it is the epidemiological phenomena that eventually lead to the identification of specific secondary bioactive compounds. One example is the so called “French Paradox”, where statistical analysis revealed that despite a high-fat or high-cholesterol diet, French citizen are less likely to suffer from cardio-vascular diseases than their north European neighbors or people in the United States. Epidemiological survey, followed by biochemical analyses and *in vitro* as well as *in vivo* animal studies then revealed that it is the polyphenols in red wine, particularly the resveratrol (3,5,4'-trihydroxy-trans-stilbene), that are responsible for this phenomenon^[231-234].

With a balanced diet, every person ingests about 1.5 g of secondary plants compounds every day^[235], the most being polyphenols with an estimated intake of 1.0 g^[236].

Today, healthprotective properties of many secondary plant compounds could be convincingly proven, so that many well known institutions, such as the US National Cancer Institute or the German Association for Nutrition, have given recommendations for the intake of fruits or vegetables in respect to their content of secondary bioactive compounds. Furthermore, there are several databases

with information on the food-specific content of polyphenols. The currently largest database is the *USDA Database for the Flavonoid Content of Selected Food*, which was initiated by the US Department of Agriculture together with several co-operation partners^[237].

But it has to be emphasized that the isolated intake of nutritional supplements or secondary plant compounds does certainly not replace a healthy diet, but is sensible as addendum in situations of additional needs, i.e. during acute illness, chronic diseases or excessive stress (e.g. high work load, high-performance sport, sunbathing, etc.).

However, next to defining a healthprotective diet, identifying the chemical compounds of a healthy natural food product allows us to characterize those compounds that are potential candidates for a new drug, and manufacturing it artificially, we can then change its structure in several different ways to see if we can improve its effectiveness or gain new insights as to how to design a more effective drug of a similar type.

A few years ago, a comparative search between about 10000 components of traditional Chinese medicine and about 8000 drugs deriving from modern Western medicine identified 908 agent pairs had strong structural similarities and 327 agent pairs were even identical in structure^[238]. Very recently, the same group added further data showing that in the area of cancer, over the time frame from around the 1940s to date, of the 175 small molecules 74.8% are other than synthetic, with 48.6%, actually being either natural products or directly derived therefrom^[239].

But even though one may deduce that the pharmaceutical industry of today is based on the phytotherapeutic knowledge of past centuries, synthetic combinatorial chemistry and high throughput screening of potential drug targets nowadays almost disconnected the historical link between botany and pharmacology. In the meantime, the search for natural pharmacoactive products diminished, maybe also enforced by the common belief that phytotherapy is a soft science, based on scientifically dubious knowledge. However, from an evolutionary point of view, compounds derived from natural products frequently perform better than randomly synthesized drug compounds, as the primary and secondary metabolites, enzymes, and regulatory proteins used in phytotherapy originate from a limited number of parent molecules that adapted to provide the respective plant with a selection advantage in evolution^[240,241]. This gets obvious by the mere fact that natural metabolites very often have a much higher sterical complexity than chemically synthesized compounds^[242]. In addition, since natural compounds have not yet evolved as single therapeutic agents, their chemical structure and pharmacokinetic (and/or pharmacodynamics) properties, may even be further improved. Taking this and the fact, that more than 90% of all species in flora and fauna have not yet been thoroughly investigated for potential new leads and drugs for chemotherapy, into account, there is still a lot of work for us ahead. This review hopefully triggered both, motivation and curiosity, to approach this task.

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