Comprehensive REVIEWS in Food Science and Food Safety

Curcumin and Liver Disease: from Chemistry to Medicine

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Abstract: Curcumin, the natural yellow-colored active principle, also called turmeric yellow, extracted from the perennial herb *Curcuma longa* L., has potent biological and pharmacological properties such as antioxidant, anti-inflammatory, antifungal, antibacterial, anti-ischemic, antitumor, and anticancer actions. The molecular mechanism of the hepatoprotective action of curcumin is due to its antioxidant properties and inhibitory activity against nuclear factor (NF)-κB that regulates different proinflammatory and profibrotic cytokines. Overall, scientific reports demonstrate that curcumin has high therapeutic ability for treating hepatic disorders. Here is a systematic discussion of the hepatoprotective activity of curcumin and its possible mechanisms of actions.

Keywords: antioxidant, curcumin, hepatic disorders, nuclear factor-kB, turmeric

Introduction

The liver is a multifunctional vital organ with the primary role in maintenance of body homeostasis. Among the various liver functions are plasma protein synthesis (Tacke and others 2009), production of hormones, processing dead red blood cells, detoxification (Zhao and others 2009; Yu and others 2011), and glucose and lipid metabolism (Liu and others 2012a). The crucial role of liver in maintaining human health status means that liver diseases can severely affect health status and threaten human life (Åberg and others 2009). Generally, hepatocellular carcinoma (HC, liver cancer), hepatitis, cirrhosis, and fatty liver are the most common types of liver diseases (Bellentani and others 2005). Among these diseases, liver cancer and hepatitis are the most prevalent and serious global public health problems (Sun and Karin 2008). Hepatitis or liver inflammation is caused by one of the hepatitis viruses (A, B, C, D, and E) (Hu 2008; Sun and Karin 2008). The World Health Organization (WHO) estimates that about one-third of the world's population is infected with hepatitis B virus (HBV) during a lifetime, while about 17.5% remain chronically infected. According to WHO statistics, an estimated 5% of all humans in the world are HBV carriers and a quarter of those would develop serious liver diseases such as chronic hepatitis, cirrhosis, and primary HC. It is now known that HBV infection accounts for more than 1 million deaths every year (Verhoef and others 2002; Lavanchy 2005; Perz and others 2006; Farinati and others 2007; Sun and Karin 2008).

Liver cancer (which consists mainly of HC, a malignant hepatoma) is the 5th most common cancer in men and the 7th in women (Chuan-Xing and others 2011). It also represents the 3rd cause of cancer-related deaths in the world (Vara and others 2011). According to WHO statistics, the incidence rate of HC in men is about 9 times higher than that of women, and the disease is more prevalent in one-third of all the countries than in the rest (Alsohaibani and others 2011).

Nonalcoholic fatty liver disease is another very common type of liver disease; its prevalence is more than 70% than that of type II diabetics, over 50% in obese people and nearly 100% in patients with both conditions (Morisco and others 2008). The heavy consumption of alcohol, which leads to alcoholic fatty liver disease and different types of cancer, is one of the most common preventable causes of death in the world (Stokkeland and others 2010).

Numerous medical studies have demonstrated the important role of nuclear factor-kappaB (NF-kB) signaling pathways (Sun and Karin 2008; Lee and others 2010b) and oxidative stress (Caraglia and others 2011; Tanaka and others 2013) in the pathogenesis of liver diseases and have proved the ameliorative role of dietary antioxidants (Bishayee and others 2010; Nabavi and others 2012c).

Curcumin is a bright yellow-colored phenolic compound that was initially isolated from *Curcuma longa* L. (turmeric) rhizomes in 1815 (Gupta and others 2013). The genus Curcuma is a member of Zingiberaceae family, growing in India, Southeast Asia, and other tropical areas (Martin and others 2012).

The yellow color of turmeric, with its principal component curcumin, has a long history in traditional medicine and as a food ingredient (Benzie and Wachtel-Galor 2011; Martin and others

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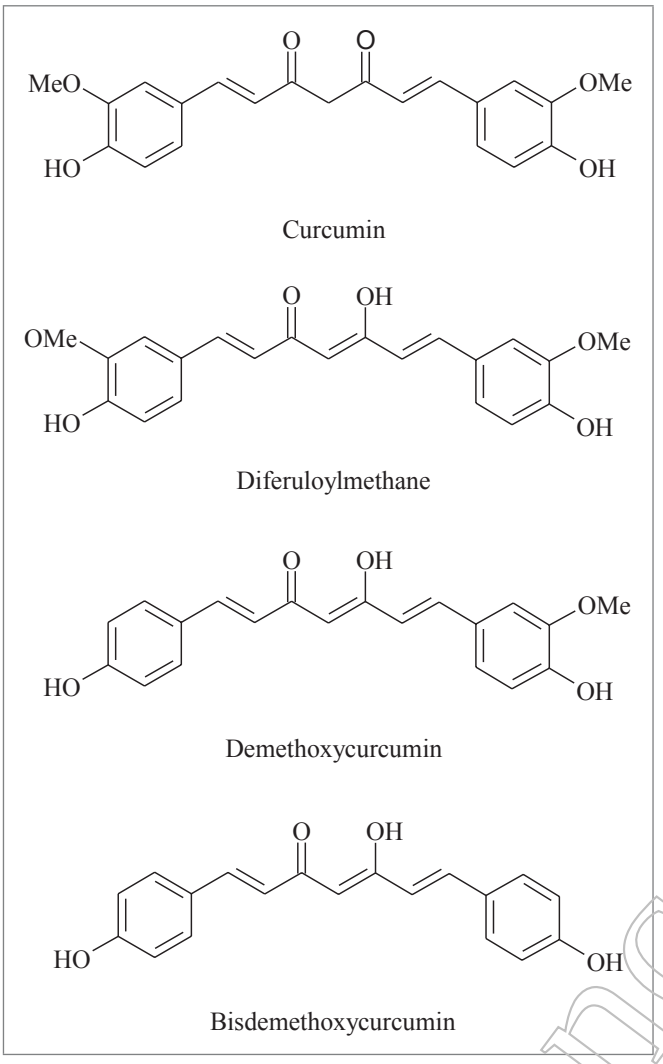

Figure 1–Chemical structure of curcumin and 3 common analogs.

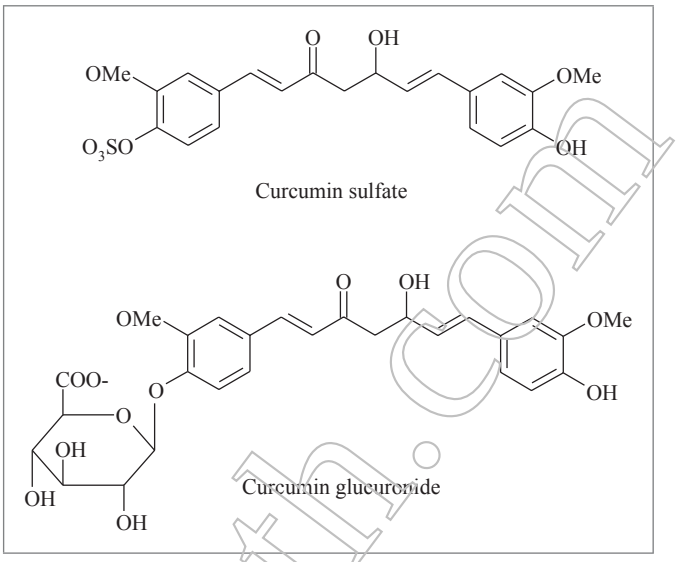

Figure 2–Chemical structures of curcumin metabolic products following oral administration.

2012). Three different analogs of curcumin have been isolated from *C. longa* L. rhizome, diferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin (Figure 1).

Current commercial curcumin preparations consist of diferuloylmethane (77%), demethoxycurcumin (18%), and bisdemethoxycurcumin (5%) that are all hydrophobic substances and usually dissolved in dimethylsulfoxide, organic solvents, or oils (Shehzad and Lee 2010). The curcumin UV-Vis absorption spectrum shows an absorption maximum approximately at $\lambda = 420$ nm (Priyadarsini 2009). In acidic solution, the color of curcumin changes from yellow to deep red (Lin and Lin-Shiau 2009).

Nowadays, many attentions have been paid to clinical utilization of curcumin (Hatcher and others 2008). More than 84 clinical studies, including randomized blind placebo-controlled, nonrandomized phase II/III trials, and so on (www.ClinicalTrials.gov), are investigating the effects of curcumin on human disorders (for example, mild cognitive impairment, asthma, Alzheimer's disease, dermatitis, adenomatous polyposis, multiple myeloma, type 1 and 2 diabetes, schizophrenia, irritable bowel syndrome, prostate cancer, pancreatic cancer, colorectal cancer, head and neck cancer, glioblastoma, myelodysplastic syndrome, knee osteoarthritis, rheumatoid arthritis, major depressive disorder, bipolar disorder, ulcerative colitis, osteosarcoma, Leber's hereditary optic neuropathy, chronic obstructive pulmonary disease, chemotherapy-induced mucositis, abdominal aortic aneurysm, proteinuric chronic kidney disease, nonsmall cell lung cancer, aberrant crypt foci in the human colon, kidney allografts, hyperprolactinoma, oral lichen planus, diabetes Crohn's disease, chronic psoriasis vulgaris, fibromyalgia, and cystic fibrosis) when given alone or conjunction with other drugs or nutriceuticals. Early studies evaluated safety and pharmacokinetics of curcumin in normal and/or patient population. While other studies evaluate efficacy of curcumin associated with aforementioned aspects (Goel and others 2008).

Following oral administration, curcumin is known to be metabolically converted to curcumin sulfate and curcumin glucuronide (Basnet and Skalko-Basnet 2011) (Figure 2), while intraperitoneal administration leads to the formation of hexahydrocurcuminol, hexahydrocurcumin, and tetrahydrocurcumin (Marczylo and others 2009) (Figure 3).

Chemistry

The chemical structure of curcumin (1, 7-bis [4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione, Figure 1) reveals its various functional groups. The 2 aromatic phenol rings (rings A and B) are connected by 2 sets of α, β-unsaturated carbonyl groups (Pullakhandam and others 2009) that are a good Michael acceptor and can react with glutathione and other nucleophiles (Scapagnini and others 2011). The 2 aryl methoxyl groups at the ortho position, the hydroxyl moiety as well as the conjugated β-diketone moieties of curcumin, which are conjugated, are other important structural features (Nabavi and others 2012a) (Figure 1).

The different methoxy substitutions in the chemical structure of diferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin (Figure 1) are responsible for a range of differential biological and pharmacological activities of these compounds (Anand and others 2008). There are, however, negligible systematic studies showing the correlation between the physicochemical and molecular characteristics of these compounds with their biological and/or pharmacological activities. Some scientific reports have demonstrated that diferuloylmethane displays better

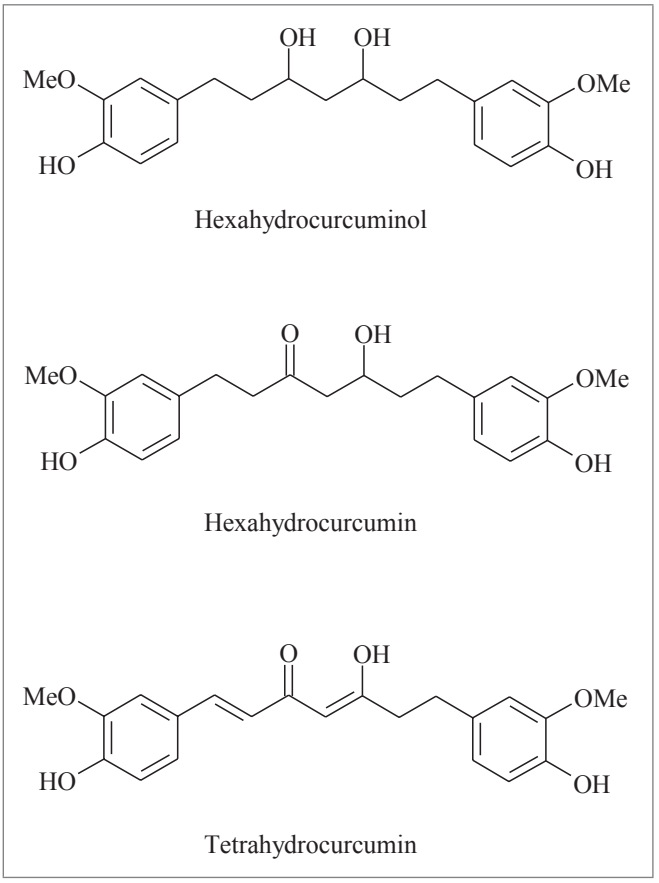

Figure 3–Chemical structures of curcumin metabolic products following intraperitoneal administration.

antioxidant activity than demethoxycurcumin and bisdemethoxycurcumin (Somparn and others 2007), while other reports have shown demethoxycurcumin to have better antioxidant effect than bisdemethoxycurcumin (Somparn and others 2007; Anand and others 2008). These observations suggest that the o-methoxy substitutions (OMe) are responsible for the differential antioxidant activities of diferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin (Singh and others 2011). It has also been suggested that hydrogen-bonding interaction between the phenol rings (hydroxyy and o-methoxy groups) in diferuloylmethane significantly affects the energy of O–H bond and hydrogen-donating potential, leading to better antioxidant action (Anand and others 2008). Transition metal chelation property is known as another antioxidant mechanism of curcumin, which is attributed to the diketone and the o-methoxy phenol moieties (Anand and others 2008).

The heme oxygenase-1 and NF-kB suppression by diferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin has been suggested to be attributed to α,β-unsaturated diketone structural moieties, which can act as a Michael reaction acceptor (Jeong and others 2009; Rajasekaran 2011).

Tetrahydrocurcumin is also known to be produced after intraperitoneal administration of curcumin through hydrogenation of the heptadiene moiety. When compared with curcumin, this metabolite displays a significantly higher antioxidant activity and reduced antitumor and anti-inflammatory abilities (Somparn and others 2007; Itokawa and others 2008; Teiten and others 2010).

It is further reported that when the o-methoxy phenol groups do not occur in conjugation with the β-diketone moiety, as in the case of tetrahydrocurcumin, the antioxidant activity is significantly increased (Anand and others 2008). This reaction leads to oxidative cleavage of the C-C bond at the active methylene carbon of the β-diketone moiety, leading to smaller o-methoxy phenol derivatives with better antioxidant potential (Leu and Maa 2002). Other reports also suggest that the α, β-unsaturated diketone moiety, in conjugation with phenolic rings, has a crucial role in NF-kB activity and ROS-generating activity of curcuminoids (Sandur and others 2007).

Molecular Targets

Curcumin is able to bind and inhibit various enzymes, metals, proteins such as albumin, growth factor receptors, and other important biomolecules (Goel and others 2008). Curcumin also demonstrates anti-inflammatory action and inhibitory effects against reactive oxygen-generating enzymes such as xanthine dehydrogenase/oxidase, lipoxygenase/cyclooxygenase, and inducible nitric oxide synthase (Lin 2007). Potent heme oxygenase-1-inducing (Chen and others 2012) and potent protein kinase C (PKC) (Watson and others 2010), EGF-receptor tyrosine kinase (Aggarwal and Sung 2009), and IκB kinase β (IKKβ) kinase inhibitory actions (Kim and others 2011) of curcumin have also been previously reported for curcumin. Furthermore, potent inhibitory activities of curcumin on NF-kB activation and expressions of some oncogenes such as Akt, CDKs, NIK, MAPKs, ERK, ELK, PI3K, c-jun, c-fos, c-myc, and inducible nitric oxide synthase have been reported (Das and others 2010). It is well known that the major upstream molecular targets of curcumin are EGFR tyrosine kinase, PKC, and mTOR, while downstream molecular targets include CDKs, FAS, c-jun, c-fos, c-myc, and inducible nitric oxide synthase (Lin 2007). In the target cells, curcumin suppresses tumor development by blocking some key signal transduction pathways (Shehzad and others 2010). Compounds like trifluoroacetic acid (oxidant tumor promoter) are known to activate PKC through reaction with zinc thiolates of the regulatory domain (Lin 2007). Likewise, the oxidized form of curcumin induces oxidation to vicinal thiols in the catalytic domain leading to activation of PKC (Das and others 2010). Recently, it has also been reported that ubiquitin proteasome-mediated degradation plays a crucial role in some cellular regulatory processes such as cell cycle, differentiation, proliferation, and apoptosis (Adams 2004). Moreover, curcumin induces apoptosis in cells via ubiquitin-proteasome pathway impairment and blocking the loss of misfolded N-CoR protein (Ng and others 2011).

Source and Bioavailability

C. longa, the main source of curcumin, is a short-stemmed rhizomatous perennial plant of the Zingiberaceae family (Figure 4) (Hayakawa and others 2011). The plant is widely cultivated in different countries of Asia such as India and China (Hayakawa and others 2011). In traditional medicine, *C. longa* has been used for mitigation of rheumatism and inflammatory and ulcerative diseases (Nabavi and others 2012b). The bright orange-colored rhizome of *C. longa* is commonly used as a spice in Asian and many other countries (Chaturvedi 2009). The main coloring constituent of the *C. longa* rhizome, "curcumin," has been isolated and its chemical structure determined in 1910 (Agrawal and Mishra 2009).

The poor bioavailability of curcumin limits the translation into clinically relevant strategies (Bar-Sela and others 2010). Low absorption, rapid metabolism, and quick elimination are known as the main complications that limit its bioavailability and have

Figure 4–*C. longa;* the main source of curcumin.

prompted the researchers to investigate not only the biofunctional and therapeutic properties in clinical studies, but also to develop new delivery systems (Bar-Sela and others 2010; Mythri and others 2012). Curcumin is poorly dissolved in water (Kakran and others 2012). Furthermore, UV light can degrade curcumin solution and therefore photochemical degradation is another limitation of its uses (Priyadarsini 2009). There are several methods for increasing its bioavailability, such as using adjuvants such as piperine, nanoparticles, liposomal curcumin, complexes of curcumin with phospholipids, and structural analog of curcumin (Mohanty and Sahoo 2010; Yadav and others 2012).

Safety

The FAO and WHO Expert Committee on Food Additives in 1996 reported that the acceptable daily intake (ADI) of curcumin is up to 3 mg/kg body weight. It is well known that curcumin is a natural product with a long history of consumption in the human diet, but there appear to be few scientific studies on its toxicity to both animals and humans, especially at high doses (Rivera-Espinoza and Muriel 2009). Previous studies showed that high concentration of curcumin causes chromosome aberrations, astrocyte cell death, teratogenic effect, embryo-, and reproductive toxicities (Ganiger and others 2007; Wu and others 2007; Burgos-Morón and others 2010; Romero-Hernández and others 2013). Rasyid and Lelo (1999) found that curcumin should not recommend for gallstones patients inasmuch as it induces contraction of human gallbladder.

In 2010, the European Food Safety Authority (EFSA) concluded that the literature data support an ADI of 3 mg/kg bw/day (EFSA Panel on Food Additives and Nutrient Sources Added to Food 2010). More systematic toxicity studies are needed to fully address the safety of curcumin (Rivera-Espinoza and Muriel 2009).

Biological and Pharmacological Actions

Several reports have documented the potent antioxidant capacity of curcumin whereby mitigation of lipid peroxidation and oxidative stress in several tissues were demonstrated (Nabavi and others 2011a, 2012b). These protective actions are due to the curcumin ability to modify antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (Nabavi and others 2011a, 2012b). In this context, curcumin has been shown to be more active than vitamin E (Shishodia and others 2006). Curcumin is also known as a Michael acceptor that reacts with the thiol group of glutathione and thioredoxin 1 (Adams and others 2005). It is well known that the phenolic hydroxyl groups play an important role in the antioxidant activity of curcumin (Feng and Liu 2009). The role of the β-diketone moiety in the antioxidant action of curcumin has also been reported in studies regarding dimethyltetrahydrocurcumin (Anand and others 2008). Furthermore, it has been reported that the ortho alkoxy group plays a significant role in the antioxidant activity of curcumin (Amorati and others 2009). Under *in vivo* conditions, the position of the hydroxyl group having a crucial role in the improvement of antioxidant activity of curcuminoids (Somparn and others 2007). As evidenced from tetrahydrocurcumin, a reduction of the C-C of the C7 linker apparently does not have any effect on antioxidant activity (Rajasekaran 2011).

The anti-inflammatory effect of curcumin is partly mediated through inhibition of IkB kinase activity leading to suppression of NF-kB activation. It has been shown that the saturation of the alkene and the decrease of carbonyl functions lead to diminish the anti-inflammatory effect (Pan and others 2000; Anand and others 2008). According to Nurfina and others (1997), the presence of a 4-hydroxyphenyl moiety is necessary for the anti-inflammatory activity of curcumin. They also found that the anti-inflammatory effect could be enhanced if additional alkyl or alkoxy groups occur at the 3- and 5-positions on the phenyl ring (Hong and others 2004). It has also been shown that acylation and alkylation of the phenolic hydroxyl group of curcumin severely reduce its anti-inflammatory activity (Anand and others 2008). Hong and others (2004) further demonstrated that the presence of phenolic hydroxy groups is necessary for the COX-1 inhibitory effect of curcumin. To date, several scientific reports have documented the anticancer effects of curcumin in various experimental models (Duvoix and others 2005; Johnson and Mukhtar 2007; Wilken and others 2011; Yan and others 2012). These effects include blocking of cell transformation (Bakhshi and others 2008), tumor promotion (Dance-Barnes and others 2009), tumor initiation (Huang and others 1992), angiogenesis (Kunnumakkara and others 2007), invasion (Kim Im and others 2008), and metastasis (Kunnumakkara and others 2008). Curcumin potential in suppressing carcinogenesis in the forestomach, colon, liver, and skin (Sethi and others 2009) has also been established. Moreover, the antiproliferative effects of curcumin against different types of tumor cells, such as colon carcinoma (Nautiyal and others 2010), B-cell and T-cell leukemia (Angelo and Kurzrock 2009), epidermoid carcinoma (Chan and others 2003), and several types of breast carcinoma cells (Liu and others 2009) have been reported by various authors. Structurally, the anticancer effect of curcumin is evident from its classical Michael acceptors, which are associated with reduction of intracellular glutathione (GSH) in human colon cancer cells (Adams and others 2005; Anand and others 2008). The presence of hydroxyphenyl groups further contributes to the chemoprotective action of curcumin, partly due to its ability in inducing phase II detoxification enzymes (Pullakhandam and others 2009).

Curcumin has a potent effect against several types of viruses such as human immunodeficiency virus-1 (Chai and others 2005), herpes simplex virus-1 (Kutluay and others 2008), hepatitis C virus (Kim and others 2010), influenza virus (Chen and others 2010), human papillomaviruses (Prusty and Das 2004), and so on. The treatment with curcumin significantly prevents lung and kidney injuries in different experimental models (Gunaydin and others 2012; Liu and others 2012b; Nabavi and others 2012a; Ueki and others 2012). It has also been reported that consumption of curcumin incurs a protective role against atherosclerosis (Shin and others 2011) and myocardial infarction (Wang and others 2012), an effect widely believed to be mediated through inhibition of proliferation of vascular smooth muscle cells (Chen and Huang 2009) and peripheral blood mononuclear cells (atherosclerosis) (Ahmed and others 2011), low-density lipoprotein oxidation (Kang and Chen 2009), oxidative stress in cardiac tissues (Nabavi and others 2011b), and platelet aggregation (myocardial infarction) (Shah and others 1999).

The antirheumatic and antiarthritic effects of curcumin could also be explained by its ability to modify COX2, tumor necrosis factor alpha (TNF-α), and other proinflammatory protein targets (Khanna and others 2007). Curcumin has also been shown to suppress allergic encephalomyelitis by blocking interleukin-12-signaling in T cells (Natarajan and Bright 2002). In experimental models of Alzheimer's disease, treatment with curcumin has been shown to ameliorate oxidative stress (Lim and others 2001), cognitive impairment (Baum and others 2008), and amyloid accumulation in the brain tissues (Yang and others 2005). Furthermore, treatment with curcumin significantly mitigates inflammatory bowel disease (Holt and others 2005) and diarrhea (Conteas and others 2009). It has also been reported that curcumin can modify cystic fibrosis defects by preventing mutations in the transmembrane conductance regulator gene (Egan and others 2004).

The abilities of curcumin in the mitigation of several skin diseases such as psoriasis (Kurd and others 2008), scleroderma (Thangapazham and others 2007), and skin carcinogenesis (Limtrakul and others 1997) have previously been reported. Also, it is well known that curcumin accelerates wound-healing *via* inhibition of NF-κB (Sidhu and others 2002). Quenching of free radicals (Thangapazham and others 2007), inhibition of NF-κB (Sidhu and others 2002), transforming growth factor (TGF)-β (Pratsinis and others 2004), and mitogen-activated protein kinase pathway (Chun and others 2003) have been shown to have an important role for the skin protection effect of curcumin. Other studies suggest that curcumin ability in modifying phase II detoxification enzymes has a crucial role in detoxification reactions and oxidative stress (Anand and others 2008).

Curcumin improves life and health span *via* modulation of expression of different aging-related genes such as *mth, thor, InR*, and JNK in *Drosophila melanogaster* (Lee and others 2010a). The protective role of curcumin against chronic cerebral ischemia is due to its ability in the modification of the protein levels of UCP2, oxidative stress (Gao and others 2012), and expression of α-synuclein (Yu and others 2012). Curcumin mitigates gastric ulcer by stimulating angiogenesis and collagen fiber restitution and modification of matrix metalloproteinase (MMP)-2, TGF-β, and vascular endothelial growth factor (VEGF) expression (Sharma and others 2012). In diabetes, administration of curcumin mitigates renal dysfunctions *via* inhibition of p300 and NF-κB (Pan and others 2013). In alloxan-induced diabetic models, curcumin has been shown to decrease blood sugar, hemoglobin, and glycosylated hemoglobin levels (Arun and Nalini 2002). Furthermore,

modification of plasma concentrations and abnormalities in the excretion of albumin, creatinine, urea, and inorganic phosphorus have been reported for curcumin (Suresh Babu and Srinivasan 1995). The ability of curcumin in the mitigation of retinal oxidative stress and inflammation in diabetes has also been reported (Kowluru and Kanwar 2007). Behavioral and biochemical studies further showed that curcumin ameliorates diabetic encephalopathy in experimental rats (Kuhad and Chopra 2007).

Liver Diseases

Hepatitis B

HBV is a small DNA member of the genus *Orthohepadnavirus* (Hepadnaviridae family) (Glebe 2007). HBV causes liver infections that lead to different hepatic disorders such as hepatitis, cirrhosis, and HC (Jazayeri and others 2009; Liaw and Chu 2009). The best clinical protocol for the management of hepatitis B viral infection is through the use of nucleotide/nucleoside analog (Fung and others 2011). These drugs suppress HBV *via* modification of polymerase/reverse-transcriptase activity (Balsano and Alisi 2008). It has been, however, reported that long-term treatment of polymerase inhibitors increases the risk of escape mutants emerging (Zoulim 2004b). Therefore, the search for finding of a better anti-HBV therapy has been intensified in recent years (Zoulim 2004a). During hepatitis B viral infection, the metabolic regulator PGC-1α coactivates the transcription of HBV *via* the forkhead transcription factor FOXO1 and the nuclear receptor HNF4α (Ganem and Prince 2004; Quasdorff and others 2008; Quasdorff and Protzer 2010). It has been reported that repression of PGC-1α leads to downregulation of HBV expression under the fed and starvation states (Shlomai and others 2006). Targeting PGC-1α is therefore a viable strategy for anti-HBV therapy (Ganem and Prince 2004). A recent report shows that curcumin downregulates PGC-1α and significantly suppresses HBV gene expression (Rechtman and others 2010). Furthermore, HBV has susceptible potential to manipulations of crucial molecular metabolic pathways of the liver such as gluconeogenesis (Duclos-Vall and others 1998). It has been further suggested that the combination of curcumin with nucleotide/nucleoside analog can synergistically suppress HBV replication and the risk of escape mutants emerging may be prevented (Rechtman and others 2010).

Hepatitis C

The hepatitis C virus with positive-sense single-stranded 9.6 kb RNA genome is a member of the *Flaviviridae* family (De Francesco 1999), which causes chronic hepatitis, fibrosis (Poynard and others 1997), cirrhosis, and HC (Degos and others 2000). Current estimates indicate that hepatitis C viral infection affects more than 170 million people all over the world (Alavian and others 2009).

It is well known that the combination of pegylated interferon-α and ribavirin is the best method for treating hepatitis C viral infection (Muir and others 2004). It has been reported, however, that nearly one-half of infected patients do not show any positive response to exogenous pegylated interferon-α (Mathew and others 2006). Therefore, studies for finding novel treatment protocols with lower side effects and more efficacious anti-hepatitis C viral infection are urgently needed.

A recent report shows that curcumin inhibits hepatitis C virus replication by suppressing PI3K/Akt-SREBP-1 pathway (Kim and others 2010). It can also be concluded that curcumin may decrease the risk of hepatitis C virus-related HC through its protective role against hepatitis C virus infection (Kubo and others 2002; Kim and others 2010).

Alcoholic liver disease

According to the WHO, alcohol-related death and disability accounted for nearly 4% of the total global burden of disease in the year 2000. In the U.S.A., one of the most important preventable causes of death is the excessive consumption of alcohol, which is associated with multiple adverse health consequences, such as acute and chronic liver damages and different types of cancers (Mokdad and others 2004; Paula and others 2010; Chen and others 2011; Jemal and others 2012; Simard and others 2012). Hence, a close correlation between alcohol consumption and alcoholic liver disease has been established (Hart and others 2010). However, liver cirrhosis occurred in few groups of heavy alcohol drinkers and its incidence risk rises with increasing consumption over 30 g alcohol per day (Bellentani and others 1997; Lucey and others 2009). According to some statistical reports, the incidence rate of cirrhosis is up to 5.7% in people consuming 120 g alcohol daily (heavy alcohol drinkers)(Lucey and others 2009). Alcohol consumption, just for a few days, leads to liver steatosis (commonly called fatty liver) (Adachi and Brenner 2005; Suter and Tremblay 2005), which is defined as the status in which hepatocytes contain macrovesicular droplets of triglycerides (Lucey and others 2009). Fatty liver can be a temporary or a long-term condition, which is not harmful itself but may induce some other disease conditions. Left untreated, it can contribute to the development of hepatic fibrosis (Jepsen and others 2009; Bataller and others 2011; Naveau and others 2013) and cirrhosis. Obviously, this disorder can be mitigated by alcohol avoidance (Lucey and others 2009).

The protective action of curcumin against experimental models of alcoholic liver diseases has been reported previously (Nanji and others 1999). It was shown that treatment with dietary curcumin reduced fatty liver, necrosis, and inflammation. Curcumin is also known to inhibit oxidative stress and lipid peroxidation, activation of NF-kB, and the expression of TNF-α, IL-12, MCP-1, MIP-2, COX-2, and iNOS (Nanji and others 1999). Animal studies have further shown that curcumin decreases the ethanol-induced increase in malondialdehyde, decreases the levels of lactate dehydrogenase (LDH) and aspartate aminotransferase (AST), and increases the GSH levels (Bao and others 2010). Although the protective role of NF-kB activation modulator against alcoholic liver injury has been documented previously (Nanji and others 2003), clinical studies on the protective role of curcumin against alcohol-induced liver injury are limited and therefore required for a comprehensive assessment of curcumin's overall therapeutic potential in this field.

Nonalcoholic fatty liver disease

Pathological studies have revealed that nonalcoholic fatty liver diseases were similar to alcoholic liver injury but they occurred in patients who did not consume alcohol (Angulo 2002; Clark and Diehl 2003). Nonalcoholic fatty liver diseases are the most important liver diseases; they affect more than 20% of people in the U.S.A. (Clark and Diehl 2003; Kim and Younossi 2008). Nonalcoholic fatty liver diseases consist of a variety of liver pathologies that range from simple steatosis to steatohepatitis, fibrosis, and cirrhosis (Brea and others 2005). Nonalcoholic fatty liver disease is closely correlated with obesity, overweight, metabolic syndrome, and type 2 diabetes in adult and pediatric individuals (Fabbrini and others 2009; Ortiz-Lopez and others 2012). According to some histological studies, nonalcoholic fatty liver disease causes a variety of changes, including macrovesicular steatosis (Tiniakos and others 2010), lobular inflammatory infiltrate, hepatocellular ballooning (Brunt 2010), perisinusoidal fibrosis (Brunt 2012), and Mallory's hyaline (Puri and Sanyal 2012). It has been reported

that intraperitoneal administrations of curcumin mitigates fibrosis and modifies intrahepatic gene expression of monocyte chemoattractant protein-1, CD11b, procollagen type I, NF-κB, ICAM-1, COX-2, TNF-α, and protein levels of α-smooth muscle-actin (Leclercq and others 2004; Vizzutti and others 2009). Curcumin also inhibits oxidative stress *via* modification of mitochondrial reactive oxygen species (Ramirez-Tortosa and others 2009) and 8-OH deoxyguanosine levels (Vizzutti and others 2009). Moreover, curcumin inhibits reactive oxygen species production in myofibroblastic hepatic stellate cells and modifies secretion of tissue inhibitor of metalloprotease-1 (Vizzutti and others 2009). Curcumin is also known to modify the abnormal increase in the level of aminotransferases (Ramirez-Tortosa and others 2009). Histologically, curcumin has been demonstrated to mitigate steatosis and necro-inflammation in the hepatic tissues. In conclusion, curcumin effectively mitigates nonalcoholic fatty liver diseases *via* its antioxidant and anti-inflammatory actions (Vizzutti and others 2009).

Drug-induced hepatotoxicity

Hepatotoxicity is known as a common side effect of over 1000 drugs, but its prevalence for many drugs is lower than 1 case in 10000 (Kaplowitz 2005; Navarro and Senior 2006). According to some U.S.A. statistical data, drug-related hepatotoxicity accounts for 50% of liver injuries including both chronic and acute liver diseases (Lee 2003). In most cases, cessation of the drug and consequent supportive care are the only effective solutions for the treatment of drug-induced hepatotoxicity (Navarro and Senior 2006). For example, in the U.S.A., suicide attempts account for over two-thirds of acetaminophen-related liver injury, whereas accidental overdose accounts for only one-third of the cases. Using *N*-acetylcysteine after an intentional or unintentional overdose of acetaminophen (Woodhead and others 2012) is the most known exception for the aforementioned intervention approach.

Drug-induced hepatotoxicity is one of the most important reasons that is cited for withdrawing drugs from the market by the U.S. Food and Drug Administration (FDA) (Lee 2003). Drugs or their metabolites can cause direct cellular damage or stimulate immune response that may lead to apoptosis or necrosis in hepatocytes (Liu and Kaplowitz 2002; Kaplowitz 2004). General mechanisms, which are involved in drug-induced hepatitis, include reactive metabolite formations, oxidative stress, GSH depletion, and protein alkylation (Grattagliano and others 2009). These processes directly influence the normal function of several organelle including mitochondria, the cytoskeleton, endoplasmic reticulum, microtubules, and/or the nucleus (Kaplowitz 2004; Gunawan and Kaplowitz 2007). Also, they can change cellular organelle functions through changes in the activation or inhibition of signaling kinases, transcription factors, and protein expression (Kaplowitz 2004; Gunawan and Kaplowitz 2007). These intracellular stresses were observed to be associated with deregulation of Jun-N-terminal kinase-1 (Nakagawa and others 2008), B-cell lymphoma-2 protein family (Bmf, Bim, Bax, and Bak) (Kaplowitz 2004), and c/EBP homologous protein-10 (Pessayre and others 2010). It has been further reported that the activation of B-cell lymphoma-2 protein family members causes massive mitochondrial injury through formation of pores in the outer mitochondrial membrane and triggers chromatin condensation and DNA fragmentation (Mohamad and others 2005). Moreover, mitochondrial dysfunction reduces energy production and causes release of nucleases through change in membrane potential collapse, which is caused by changing membrane permeability (Grattagliano and others 2009). Reactive metabolites can also stimulate immune response and cause immune-mediated injury by either covalently binding with liver proteins, such as cytochrome P450 enzymes, or involving hapten-like action (Wu and others 2010; Vogel and Manns 2012). Although the exact mechanism of immune-mediated liver injury is not fully understood, it is assumed that FasL and the perforin/granzyme B pathways have a crucial role in drug-induced immune-mediated hepatocyte apoptosis (Warrington 2012).

The ameliorative effect of curcumin and its derivatives against liver injury induced by several drugs, such as paracetamol (Girish and others 2009), chloroquine (Dattani and others 2010), methotrexate (Hemeida and Mohafez 2008), erythromycin estolate (Pari and Murugan 2004), isoniazid, rifampicin, and pyrazinamide (Adhvaryu and others 2007), has been reported. Antioxidant ability of curcumin and its derivatives is shown to be the main protective mechanism against drug-induced liver damages (Negi and others 2008). Curcumin, as a strong inhibitor of cytochrome P450 (Thapliyal and Maru 2001), can normalize antioxidant enzymes and nonenzymatic antioxidant compounds such as GSH (Oetari and others 1996). Bulku and others (2012) also demonstrated that curcumin ameliorates acetaminophen-induced liver damage through normalization of proapoptotic (Bax, caspase-3) and antiapoptotic signaling pathways the curcumin chemopreventive potential is further shown by it capacity to inhibit COX-2 and iNOS expression through NF-kB pathways that are considered another possible ameliorative mechanism against drug-induced liver damage (Puri and Sanyal 2012).

Liver cancer

Numerous annual reports demonstrate that HC is responsible for more than 696000 deaths all over the world, and accounts for about 90% of all cases of liver cancer and is the 3rd most common cause of cancer mortality (9.2%) (Ferlay and others 2010). Despite many approaches for treating liver cancer, the prognosis remains poor. According to WHO statistics, the incidence rate of HC in men is higher than in women. This suggests that gender and gender-related factors are important factors in HC (El-Serag 2004). Although the reason of the high HC incidence is unclear, there are systematic differences in the microRNA expression patterns of liver tissues in men and women (Ji and others 2009). A recent report on the inhibitory activity of estrogen on interleukin-6 induction in Kupfer cells may have crucial role in the observed gender difference of HC incidence (Wands 2007).

Liver cancer is also commonly associated with viral infections, as a high incidence is reported in hepatitis B and C sufferers (Benvegnù and others 2006). Although surgical methods are the most effective procedures for treating HC, only 20% of patients are eligible to go through this scheme (Shi and others 2007). Treatment *via* interferon α and transcatheter arterial chemoembolization have a key role in prolonging the survival time of patients with HC (Sun and others 2006; Peng and others 2009).

Many studies demonstrate the overexpression of Bcl-2 members (Chang and Xu 2000) and inhibitors of apoptosis proteins (IAPs) occurring during HC (Augello and others 2009). It is well known that IAPs (c-IAP-1, c-IAP-2, XIAP, NAIP surviving, and livin-α) and X-linked inhibitor-of-apoptosis protein (XIAP) through inhibiting effector caspases can inhibit cell death (Deveraux and Reed 1999; Vucic and others 2000; Kasof and Gomes 2001; Notarbartolo and others 2005; Augello and others 2009). Moreover, XIAP X-chromosome-linked inhibitor of apoptosis proteins (XIAP) can initiate proteasome degradation of caspases and 2nd

mitochondria-derived activator of caspases (Smac) (MacFarlane and others 2002). Recently, overexpression of Smac in HC tumors is used as an effective strategy for cancer treatment (Zhao and others 2006) because Smac sensitizes tumor cells to chemotherapeutic drugs (Zhao and others 2006). It is further known that NF-kB upregulates the expression level of XIAP and other IAPs as well as other NF-kB target genes in HC tumor cells (Wang and others 1998; Mitsiades and others 2002). Besides NF-kB, HC cells can control cell proliferation and growth through expression of other transcription factors, such as AP-1 and STATs (Liu and others 2002). Curcumin is well known for its potent NF-kB inhibitory activity (Chan 1995, Darvesh and others 2012). It can also interact with AP-1 and STATs (Notarbartolo and others 2005). Therefore, curcumin influences NF-kB, AP-1, and STATs, apoptotic mechanisms in human HC (Aggarwal and others 2003; Notarbartolo and others 2005). Recent evidence further shows that p38 activation-induced FasL expression signaling in human HC Huh7 cells has a crucial role in apoptosis-inducing activity of curcumin (Wang and others 2013).

MicroRNAs (miRNAs) deregulation is another mechanism that is involved in human HC (Ladeiro and others 2008; Iorio and Croce 2009). miRNAs are noncoding small RNAs composed of about 22 nucleotides that function in the transcriptional and posttranscriptional regulation of target genes (He and Hannon 2004; Chekulaeva and Filipowicz 2009). Most of the mammalian mRNAs are conserved targets of about 1000 miRNAs that are encoded by the human genome (John and others 2004; Chang and Mendell 2007; Guo and others 2010). Previous studies have shown that miRNAs are implicated in different biological processes including development, apoptosis, differentiation stress response, proliferation, and so on (Croce and Calin 2005). Over the past several years, numerous reports have shown that miRNAs levels are deregulated in most of human tumors (Calin and Croce 2006; Deng and others 2008; Garzon and others 2009). Ladeiro and others (2008) reported that dysregulation of miR-224 miR-200c, miR-200, miR-21, miR-224, miR-10b, and miR-222 has important roles in initiation or malignancy of hepatocellular carcinoma (HCC) tumors. Another study showed that HC caused a decrease in miR-199a/b-3p level and there was a close correlation between miR-199a/b-3p level and survival of patients (Hou and others 2011). As a function of microRNA, miR-199a/b-3p targets tumor-promoting PAK4 and represses tumor growth through suppressing the PAK4/Raf/MEK/ERK pathway (Hou and others 2011). Other studies report significant elevations of E2F1 and oncoproteins Bcl-2 level in human HC (Ladu and others 2008; Yang and others 2011). Curcumin administration showed a significant decrease in E2F1 and Bcl-2 protein levels (Li and others 2007). Hassan and Al-Olayan (2012) also showed that curcumin administration can normalize the expression levels of miR-199 and miR-200 families. Curcumin not only influences the expression of miR-21 and miR-34a, but also upregulates tumor suppressor let-7a miRNA (Subramaniam and others 2012).

Liver cancer promotes neovascularization and angiogenesis in HC tumors (Semela and Dufour 2004) that are regulated by different molecular signaling pathways including extracellular signal-regulated kinase 1/2 and serine/threonine kinase AKT (Schmitz and others 2008). Extracellular signal-regulated kinase is a mitogen-activated PKC cascade that is involved in different cell cycle processes including growth and proliferation (Zhang and Liu 2002; Wada and Penninger 2004). It has been reported that extracellular signal-regulated kinase is activated by VEGF (Rousseau and others 1997). The AKT pathways also have crucial role in cell cycles (Liang and Slingerland 2003). On the basis of previous reports, it has been suggested that elevation of phosphor extracellular signal-regulated kinase 1/2 and AKT expression levels are associated with aggressive tumor behaviors in HC (Schmitz and others 2008). Curcumin administration can significantly repress different angiogenic biomarkers such as VEGF, and cyclooxygenase-2 (COX-2) expression (Yoysungnoen and others 2006; Binion and others 2008). It has recently been demonstrated that PI-3/AKT, MAP kinase/ERK, and signal transducer and activator of transcription 3 (STAT3) pathways influence COX-2 and VEGF-stimulating pathways (Niu and others 2002; Kwon and others 2003; St-Germain and others 2004; Lo and others 2010). Moreover, it has been reported that the repression effect of curcumin on STAT3 (Yoysungnoen and others 2006) and hypoxia-inducible factor-1α expression in human HC leads to reduced tumor angiogenesis and progression (Bae and others 2006). Hence, the above-mentioned pathways are possible tumor angiogenesis suppression mechanism of curcumin (Bae and others 2006). Another possible antiproliferative mechanism of curcumin against HC is through induction of endoplasmic reticulum stress and mitochondrial dysfunction (Cheng and others 2010). Lin and others (1998) showed that the suppression effect of curcumin on MMP-9 secretion is its anti-invasion mechanism in HC SK-Hep-1 cells.

Biliary cirrhosis

Primary biliary cirrhosis is an autoimmune chronic cholestatic liver inflammation that slowly blocks the flow of bile and subsequently causes liver scarring, fibrosis, and cirrhosis (Dienes and others 1997; Leuschner 2003; Kaplan and Gershwin 2005). According to the histopathological studies, primary biliary cirrhosis causes nonsuppurative interlobular bile duct destruction (Talwalkar and Lindor 2003). It is well known that immunological and genetic factors have an important role in initiation and progression of this disease (Tanaka and others 2001). The sex ratio of primary biliary cirrhosis shows that affected patients are commonly middle-aged women with an asymptomatic increase in serum hepatic factors (sex ratio is 9 : 1, female : male) (Invernizzi and others 2004; Danielsson and others 2005). Fatigue, fatty deposits under the skin, itching, jaundice, and xanthelasma are the most commonly symptoms of primary biliary cirrhosis (Kaplan and Gershwin 2005; Sargent 2008). Ursodeoxycholic acid is the most common medical treatment of primary biliary cirrhosis, and it is approved by U.S. Food and Drug Administration (Lindor 2007).

TGF-β is an important profibrogenic cytokine in the development of fibrosis (Yao and others 2012). TGF-β stimulates the production of extracellular matrix and blocks its removing procedures (Branton and Kopp 1999). It is well known that TGF-β has a crucial role in activation of trans-differentiation of hepatic stellate cells to myofibroblasts in liver fibrogenesis (Shen and others 2003). Curcumin inhibits the profibrotic role of TGF-β and prevent fibrosis in fibrotic lung and kidney disorder (Gaedeke and others 2004; Reyes-Gordillo and others 2008; Punithavathi and others 2009).

It has also been reported that curcumin ameliorates cirrhosis induced by bile duct ligation through downregulation of TGF-β and inhibition of oxidative stress (Reyes-Gordillo and others 2008). Numerous reports suggest the role of TGF-β in the expression of different profibrotic genes (Gaedeke and others 2004; Leask and Abraham 2004). Curcumin inhibits upregulation of TGF-β mRNA and TGF-β protein expressions in hepatic tissues of bile duct-ligated rats (Reyes-Gordillo and others 2008). The preventive role of curcumin against fibrosis induced by

biliary cirrhosis could be attributed to its antioxidant action and its downregulation effects on NF-kB and TGF-β (Leask and Abraham 2004; Dohmen and others 2004; Salunga and others 2007; Reyes-Gordillo and others 2008).

Primary sclerosing cholangitis

Primary sclerosing cholangitis is a chronic cholestatic liver disease that causes inflammation, fibrosis, scarring, and destruction of the bile ducts at intrahepatic and extrahepatic levels (Cullen and Chapman 2003; Harrison and others 2005). The disease is a progressive immune-mediated disorder that culminates in cirrhosis, hepatic decompensation, and portal hypertension (Chapman and others 2010). About 70% of primary sclerosing cholangitis patients are young and middle-aged men (Mendes and Lindor 2010). More than 87% of primary sclerosing cholangitis patients are shown to have ulcerative colitis and 13% of them have Crohn's disease (Lee and Kaplan 2002). This pathology is often associated with inflammatory bowel disease (Jørgensen and others 2012). Other studies indicate that some of the primary sclerosing cholangitis patients have autoimmune disorders, chronic pancreatitis, and sarcoidosis (Saich and Chapman 2008; Kamisawa and others 2009; Bowlus 2011). It has also been reported that choledocholithiasis and infections (in the liver, bile ducts, and gallbladder) can cause primary sclerosing cholangitis (Mendes and Lindor 2010). Chronic fatigue, jaundice, itching, malabsorption, cirrhosis, enlarged liver, enlarged spleen, weight and appetite loss, and infection of the bile duct are the most common symptoms of primary sclerosing cholangitis (Miura and Miyachi 2009; Bowlus 2011; Elfaki and Lindor 2011; Ibrahim and Lindor 2011; Singal and others 2011; Azizi and others 2012). There are different medications for the treatment of primary sclerosing cholangitis such as cholestyramine (Mendes and Lindor 2010), ursodeoxycholic acid (Lindor and others 2009), antibiotics (Elfaki and Lindor 2011) (for treatment of bile duct infections), and some immunosuppressive drugs such as prednisone, azathioprine, cyclosporine, and methotrexate (Tabibian and Lindor 2013). Treatments with some vitamins such as vitamin D, vitamin E, vitamin A, and vitamin K have also shown to have some beneficial effects (Ibrahim and Lindor 2011). In addition to drug treatments, surgical procedures may be useful for primary sclerosing cholangitis (Aljiffry and others 2011).

It has been known that curcumin mitigates cholangiopathy and biliary fibrosis in Mdr2$^{-/-}$ mice *via* targeting the activation of PPARγ in cholangiocytes, inhibiting the TNF-α-induced inflammatory activation and the marker vascular cell adhesion molecule-1 expression in cholangiocytes (Baghdasaryan and others 2010). Through these mechanisms of action, curcumin decreases the attraction of neutrophil granulocytes and myofibroblasts in the portal fields. Furthermore, curcumin inhibits proliferation and portal myofibroblast activation through extracellular signal-regulated kinases1/2 phosphorylation inhibition, and therefore reduced fibrogenesis in Mdr2$^{-/-}$ mice (Baghdasaryan and others 2010).

Conclusion and Recommendation

In conclusion, curcumin shows therapeutic actions in different liver diseases, namely, hepatitis B, hepatitis C, alcoholic liver disease, nonalcoholic fatty liver disease, drug-induced hepatotoxicity, liver cancer, biliary cirrhosis, and primary sclerosing cholangitis. It is a potent free radical scavenger with good hydrogen-donating ability. It is also well known for its good metal chelating effect, especially iron and copper. The molecular mechanisms of curcumin therapeutic actions showed that its antioxidant and inhibitory effects on NF-kB, which is able to regulate different proinflammatory and profibrotic cytokines, have a crucial role in the mitigation of liver diseases. It is well known that oxidative stress has a crucial role in the initiation and progression of several liver diseases. NF-kB is known as one of the most important oxidative damage-responsive transcription factors and is crucial as an inflammatory transcriptional regulator in liver diseases.

Abundance of research shows that NF-kB plays cytoprotective effect and suppresses TNF-α-induced ROS formation through different mechanisms (Bubici and others 2006). NF-kB-mediated overexpression of ferritin heavy chain gene is one of them. Moreover, free iron can easily produce highly reactive hydroxyl radicals through Fenton and Haber–Weiss reactions, so decreasing of free iron level in the cells is necessary and vital (Pham and others 2004). Upregulation of ferritin heavy chain leads to inhibition of TNF-R-induced JNK signaling and cell death (Papa and others 2006). On the other hand, a plethora of information shows that ferritin heavy chain upregulated in tumor cell during their progression in response of oxidative stress (Baldi and others 2005; Aung and others 2007). Hence, NF-kB-promoted ferritin heavy chain over expression may cause tumor progression, anaplasia, and cancer resistance. Upregulation of Mn-SOD is another NF-kB-mediated antioxidant mechanism (Delhalle and others 2002). Pham and others 2004 reported that upregulation of Mn-SOD is dependent of both TNF-α and NF-kB and causes little or even no protection against TNF-R-mediated killing. Although this finding suggests that Mn-SOD probably not involves in the protective role of NF-kB against programmed cell death; there is evidence on correlation between Mn-SOD and pro-oncogenic actions of NF-kB (Bubici and others 2006). Synergism between Mn-SOD and ferritin heavy chain seems essential for suppressing redox homeostasis. Such anticancer agents cause increasing of ROS/JNK signaling in cancerous cells, and hence it is reasonable that blockage of the NF-kB-mediated procedures can commence and reinforce triggering of necrosis signaling in cancerous cell (Pham and others 2007).

Curcumin activates PPAR-γ, inhibits ERK, elevates the cellular GSH content, and inhibits toll-like receptor-4 gene expression leading to downregulation of NF-kB in hepatic stellate cells (Zheng and Chen 2006; Chen and Zheng 2008; Oconnell and Rushworth 2008). These procedures result in the suppression of TGF-β receptor gene expression that leads to inhibiting of TGF-β signaling and suppression of connective tissue growth factor gene expression. The above-mentioned procedures result in the reduction of the production of extracellular matrix from activated hepatic stellate cells and the mitigation of liver injuries (Zheng and Chen 2006). Curcumin ability to inhibit the growth stimulatory pathways such as insulin-like growth factor-1 plays important role in its antiproliferative effects (Xia and others 2007).

In the hepatitis B viral infection, curcumin modifies the PGC-1α level and inhibits the gene expression of HBV. Antioxidant actions of curcumin play a crucial role in its therapeutic actions in hepatitis C viral infection. Also, curcumin suppresses hepatitis C virus replication via PI3K/Akt-SREBP-1 pathway inhibition. In cases of alcoholic liver disease, the protective role of curcumin is due to its mitigating role in alcohol-induced oxidative stress and lipid peroxidation. Curcumin modifies the activation of NF-kB, and also the expression of different cytokines and chemokines. In nonalcoholic fatty liver disease, curcumin ameliorates histopathological abnormality *via* modification of expression of different cytokines and chemokines. The antioxidant activity of curcumin also plays an important role in its therapeutic action in nonalcoholic fatty liver disease. The antioxidant and anti-inflammatory effects

of curcumin appear to have an effective role in the management of drug-induced hepatotoxicity.

There are numerous mechanisms for the beneficial effects of curcumin against liver cancer. In fact, curcumin, as a classical Michael acceptor, and due to the presence of phenolic groups, plays an important role as an anticancer substance. In cases of biliary cirrhosis, antioxidant ability of curcumin and its potential in downregulation of NF-kB and TGF-β play an important role in the mitigation of chronic cholestatic liver inflammation and fibrosis. The preventive role of curcumin against fibrosis may be the result of its antioxidant action. In primary sclerosing cholangitis, curcumin inhibits the attraction of neutrophil granulocytes and myofibroblasts. The following recommendations are important for utilizing curcumin as a validated hepatoprotective agent:

- More basic and clinical studies must be performed on bioavailability, pharmacokinetics, and pharmacodynamic action of curcumin and its derivatives.
- More studies on the improvement of curcumin bioavailability, such as liposomal curcumin, curcumin nanoparticles, curcumin phospholipid complex, and use of curcumin analog must be performed.
- Further studies for ascertaining the best effective dose for the mitigation of liver diseases are needed.

References

Åberg F, Rissanen AM, Sintonen H, Roine RP, Höckerstedt K, Isoniemi H. 2009. Health-related quality of life and employment status of liver transplant patients. Liver Transplant 15(1):64–72.

Adachi M, Brenner DA. 2005. Clinical syndromes of alcoholic liver disease. Dig Dis 23(3–4):255–63.

Adams BK, Cai J, Armstrong J, Herold M, Lu YJ, Sun A, Snyder JP, Liotta DC, Jones DP, Shoji M. 2005. EF24, a novel synthetic curcumin analog, induces apoptosis in cancer cells via a redox-dependent mechanism. Anti-cancer Drug 16(3):263–75.

Adams J. 2004. The proteasome: a suitable antineoplastic target. Nature Rev Can 4(5):349–60.

Adhvaryu MR, Reddy N, Parabia MH. 2007. Effects of four Indian medicinal herbs on isoniazid-z, rifampicin and pyrazinamide-induced hepatic injury and immunosuppression in guinea pigs. World J Gastroenterol 13(23):3199–205.

Agrawal DK, Mishra PK. 2009. Curcumin and its analogues: potential anticancer agents. Med Res Rev 30(5):818–60.

Aggarwal BB, Kumar A, Bharti AC. 2003. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res 23(1A):363–98.

Aggarwal BB, Sung B. 2009. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. Trend Pharmacol Sci 30(2):85–94.

Ahmed T, Pathak R, Mustafa MD, Kar R, Tripathi AK, Ahmed RS, Banerjee BD. 2011. Ameliorating effect of N-acetylcysteine and curcumin on pesticide-induced oxidative DNA damage in human peripheral blood mononuclear cells. Environ Monit Assess 179(1):293–9.

Alavian SM, Ahmadzad-Asl M, Lankarani KB, Shahbabaie MA, Ahmadi AB, Kabir A. 2009. Hepatitis C infection in the general population of Iran: a systematic review. Hepat Mon 9(3):211–23.

Aljiffry M, Renfrew PD, Walsh MJ, Laryea M, Molinari M. 2011. Analytical review of diagnosis and treatment strategies for dominant bile duct strictures in patients with primary sclerosing cholangitis. HPB 13(2):79–90.

Alsohaibani F, Porter G, Al-Ashgar H, Walsh M, Berry R, Molinari M, Peltekian KM. 2011. Comparison of cancer care for hepatocellular carcinoma at two tertiary-care referral centers from high and low endemic regions for viral hepatitis. J Gastrointest Cancer 42(4):228–35.

Amorati R, Menichetti S, Mileo E, Pedulli GF, Viglianisi C. 2009. Hydrogen-atom transfer reactions from ortho-alkoxy-substituted phenols: an experimental approach. Chemistry Eur J 15(17):4402–10.

Anand P, Thomas SG, Kunnumakkara AB, Sundaram C, Harikumar KB, Sung B, Tharakan ST, Misra K, Priyadarsini IK, Rajasekharan KN, Aggarwal BB. 2008. Biological activities of curcumin and its analogues (congeners) made by man and mother nature. Biochem Pharmacol 76(11):1590–611.

Angelo LS, Kurzrock R. 2009. Turmeric and green tea: a recipe for the treatment of B-chronic lymphocytic leukemia. Clin Cancer Res 15(4):1123–5.

Angulo P. 2002. Nonalcoholic fatty liver disease. N Engl J Med 346(16):1221–31.

Arun N, Nalini N. 2002. Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. Plant Food Human Nutr 57(1): 41–52.

Augello C, Caruso L, Maggioni M, Donadon M, Montorsi M, Santambrogio R, Torzilli G, Vaira V, Pellegrini C, Roncalli M, Coggi G, Bosari S. 2009. Inhibitors of apoptosis proteins (IAPs) expression and their prognostic significance in hepatocellular carcinoma. BMC Cancer 9(1):125.

Aung W, Hasegawa S, Furukawa T, Saga T. 2007. Potential role of ferritin heavy chain in oxidative stress and apoptosis in human mesothelial and mesothelioma cells: implications for asbestos-induced oncogenesis. Carcinogenesis 28(9):2047–52.

Azizi L, Raynal M, Cazejust J, Ruiz A, Menu Y, Arrivé L. 2012. MR imaging of sclerosing cholangitis. Clinics Res Hepatol Gastroenterol 36(2):130–8.

Baghdasaryan A, Claudel T, Kosters A, Gumhold J, Silbert D, Thüringer A, Leski K, Fickert P, Karpen SJ, Trauner M. 2010. Curcumin improves sclerosing cholangitis in Mdr2−/− mice by inhibition of cholangiocyte inflammatory response and portal myofibroblast proliferation. Gut 59(4):521–30.

Bakhshi J, Weinstein L, Poksay KS, Nishinaga B, Bredesen DE, Rao RV. 2008. Coupling endoplasmic reticulum stress to the cell death program in mouse melanoma cells: effect of curcumin. Apoptosis 13(7): 904–14.

Baldi A, Lombardi D, Russo P, Palescandolo E, De Luca A, Santini D, Baldi F, Rossiello L, Dell'Anna ML, Mastrofrancesco A, Maresca V, Flori E, Natali PG, Picardo M, Paggi MG. 2005. Ferritin contributes to melanoma progression by modulating cell growth and sensitivity to oxidative stress. Clin Cancer Res 11(9):3175–83.

Balsano C, Alisi A. 2008. Viral hepatitis B: established and emerging therapies. Curr Med Chem 15(9):930–9.

Bae MK, Kim SH, Jeong JW, Lee YM, Kim HS, Kim SR, Yun I, Bae SK, Kim KW. 2006. Curcumin inhibits hypoxia-induced angiogenesis via down-regulation of HIF-1. Oncology Rep 15(6):1557–62.

Bao W, Li K, Rong S, Yao P, Hao L, Ying C, Zhang X, Nussler A, Liu L. 2010. Curcumin alleviates the ethanol-induced hepatocytes oxidative damageinvolving heme oxygenase-1 induction. J Ethnopharmacol 128:549–53.

Bar-Sela G, Epelbaum R, Schaffer M. 2010. Curcumin as an anti-cancer agent: review of the gap between basic and clinical applications. Curr Med Chem 17(3):190–7.

Basnet P, Skalko-Basnet N. 2011. Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment. Molecules 16(6):4567–98.

Bataller R, Rombouts K, Altamirano J, Marra F. 2011. Fibrosis in alcoholic and nonalcoholic steatohepatitis. Best Pract Res Clin Gastroenterol 25(2):231–44.

Baum L, Lam CW, Cheung SK, Kwok T, Lui V, Tsoh J, Lam L, Leung V, Hui E, Ng C, Woo J, Chiu HF, Goggins WB, Zee BC, Cheng KF, Fong CY, Wong A, Mok H, Chow MS, Ho PC, Ip SP, Ho CS, Yu XW, Lai CY, Chan MH, Szeto S, Chan IH, Mok V. 2008. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. J Clin Psychopharmacol 28(1):110–3.

Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, Crocè LS, Sasso F, Pozzato G, Cristianini G, Brandi G. 1997. Drinking habits as cofactors of risk for alcohol-induced liver damage. Gut 41(6): 845–50.

Bellentani S, Tiribelli C, Saccoccio G, Sodde M, Fratti N, De Martin C, Christianini G. 2005. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. Hepatology 20(6): 1442–9.

Benvegnù L, Fattovich G, Noventa F, Tremolada F, Chemello L, Cecchetto A, Alberti A. 2006. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis. A prospective study. Cancer 74(9):2442–8.

Benzie IFF, Wachtel-Galor S. 2011. Herbal medicine: biomolecular and clinical aspects. 2nd ed. Boca Raton, FL: CRC Press.

Binion DG, Otterson MF, Rafiee P. 2008. Curcumin inhibits VEGF-mediated angiogenesis in human intestinal microvascular endothelial cells through COX-2 and MAPK inhibition. Gut 57(11):1509–17.

Bishayee A, Darvesh AS, Politis T, McGory R. 2010. Resveratrol and liver disease: from bench to bedside and community. Liver Intl 30(8):1103–14.

Bowlus CL. 2011. Primary sclerosing cholangitis. In: Lawrence S. Friedman, Emmet B. Keeffe, editor. Handbook of liver disease. Philadelphia, PA: Elsevier. p 208.

Branton MH, Kopp JB. 1999. TGF-β and fibrosis. Microbes Infect 1(15):1349–65.

Brea A, Mosquera D, Martín E, Arizti A, Cordero JL, Ros E. 2005. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis. A case–control Study. Arterioscler Thromb Vasc Biol 25(5):1045–50.

Brunt EM. 2010. Pathology of nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 7(4):195–203.

Brunt EM. 2012. Histological assessment of nonalcoholic fatty liver disease in adults and children. Clin Liver Dis 1(4):107–10.

Bubici C, Papa S, Dean K, Franzoso G. 2006. Mutual cross-talk between reactive oxygen species and nuclear factor-kappa B: molecular basis and biological significance. Oncogene 25(51):6731–48.

Bulku E, Stohs JS, Cicero L, Brooks T, Halley H, Ray SD. 2012. Curcumin exposure modulates multiple pro-apoptotic and anti-apoptotic signaling pathways to antagonize acetaminophen-induced toxicity. Curr Neurovasc Res 9(1):58–71.

Burgos-Morón E, Calderón-Montaño JM, Salvador J, Robles A, López-Lázaro M. 2010.The dark side of curcumin. Intl J Cancer 126(7):1771–5.

Calin GA, Croce CM. 2006. MicroRNA signatures in human cancers. Nat Rev Cancer 6(11):857–66.

Caraglia M, Giuberti G, Marra M, Addeo R, Montella L, Murolo M, Sperlongano P, Vincenzi B, Naviglio S, Prete SD, Abbruzzese A, Stiuso P. 2011. Oxidative stress and ERK1/2 phosphorylation as predictors of outcome in hepatocellular carcinoma patients treated with sorafenib plus octreotide LAR. Cell Death Dis 2(4):e150.

Chai H, Yan S, Lin P, Lumsden AB, Yao Q, Chen C. 2005. Curcumin blocks HIV protease inhibitor ritonavir-induced vascular dysfunction in porcine coronary arteries. J Am Coll Surg 200(6):820–30.

Chan MMY. 1995. Inhibition of tumor necrosis factor by curcumin, a phytochemical. Biochem Pharmacol 49(11):1551–6.

Chan WH, Wu CC, Yu JS. 2003. Curcumin inhibits UV irradiation-induced oxidative stress and apoptotic biochemical changes in human epidermoid carcinoma A431 cells. J Cell Biochem 90(2):327–38.

Chang TC, Mendell JT. 2007. MicroRNAs in vertebrate physiology and human disease. Annu Rev Genomics Hum Genet 8:215–39.

Chang YC, Xu YH. 2000. Expression of Bcl-2 inhibited Fas-mediated apoptosis in human hepatocellular carcinoma BEL-7404 cells. Cell Res 10(3):233–42.

Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ. 2010. Diagnosis and management of primary sclerosing cholangitis. Hepatology 51(2):660–78.

Chaturvedi TP. 2009. Uses of turmeric in dentistry: an update. Ind J Dent Res 20(1):107–9.

Chekulaeva M, Filipowicz W. 2009. Mechanisms of miRNA-mediated post-transcriptional regulation in animal cells. Curr Opin Cell Biol 21(3):452–60.

Chen A, Zheng S. 2008. Curcumin inhibits connective tissue growth factor gene expression in activated hepatic stellate cells in vitro by blocking NF-κB and ERK signalling. Br J Pharmacol 153(3):557–67.

Chen HW, Huang HC. 2009. Effect of curcumin on cell cycle progression and apoptosis in vascular smooth muscle cells. Br J Pharmacol 124(6):1029–40.

Chen MH, Lee MY, Chuang JJ, Li YZ, Ning ST, Chen JC, Liu YW. 2012. Curcumin inhibits HCV replication by induction of heme oxygenase-1 and suppression of AKT. Intl J Mol Med 30(5):1021–8.

Chen DY, Shien JH, Tiley L, Chiou SS, Wang SY, Chang TJ, Lee YJ, Chan KW, Hsu WL. 2010. Curcumin inhibits influenza virus infection and haemagglutination activity. Food Chem 119(4):1346–51.

Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. 2011. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. JAMA 306(17):1884–90.

Cheng CY, Lin YH, Su CC. 2010. Curcumin inhibits the proliferation of human hepatocellular carcinoma J5 cells by inducing endoplasmic reticulum stress and mitochondrial dysfunction. Intl J Mol Med 26(5):673–8.

Chuan-Xing L, Xu H, Bao-Shan H, Yong L, Pei-Jian S, Xian-Yi Y, Xiao-Ning L, Li-Gong L. 2011. Efficacy of therapy for hepatocellular carcinoma with portal vein tumor thrombus: chemoembolization and stent combined with iodine-125 seed. Cancer Biol Ther 12(10):865–71.

Chun KS, Keum YS, Han SS, Song YS, Kim SH, Surh YJ. 2003. Curcumin inhibits phorbol ester-induced expression of cyclooxygenase-2 in mouse skin through suppression of extracellular signal-regulated kinase activity and NF-κB activation. Carcinogenesis 24(9):1515–24.

Clark JM, Diehl AM. 2003. Nonalcoholic fatty liver disease. JAMA 289(22):3000–4.

Conteas CN, Panossian AM, Tran TT, Singh HM. 2009. Treatment of HIV-associated diarrhea with curcumin. Dig Dis Sci 54(10):2188–91.

Croce CM, Calin GA. 2005. miRNAs, cancer, and stem cell division. Cell 122(1):6–7.

Cullen S, Chapman R. 2003. Primary sclerosing cholangitis. Autoimmun Rev 2(6):305–12.

Dance-Barnes ST, Kock ND, Moore JE, Lin EY, Mosley LJ, D'Agostino Jr RB, McCoy TP, Townsend AJ, Miller MS.2009. Lung tumor promotion by curcumin. Carcinogenesis 30(6):1016–23.

Danielsson Ä, Boqvist L, Uddenfeldt P. 2005. Epidemiology of primary biliary cirrhosis in a defined rural population in the northern part of Sweden. Hepatology 11(3):458–64.

Darvesh AS, Aggarwal BB, Bishayee A. 2012. Curcumin and liver cancer: a review. Curr Pharm Biotechnol 13(1):218–28.

Das T, Sa G, Saha B, Das K. 2010. Multifocal signal modulation therapy of cancer: ancient weapon, modern targets. Mol Cell Biochem 336(1):85–95.

Dattani JJ, Rajput DK, Moid N, Highland HN, George LB, Desai KR. 2010. Ameliorative effect of curcumin on hepatotoxicity induced by chloroquine phosphate. Environ Toxicol Pharmacol 30(2):103–9.

De Francesco R. 1999. Molecular virology of the hepatitis C virus. J Hepatol 31:47–53.

Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, Trinchet JC, Beaugrand M, Chevret S. 2000. Hepatitis C virus-related cirrhosis: time to occurrence of hepatocellular carcinoma and death. Gut 47(1):131–6.

Delhalle S, Deregowski V, Benoit V, Merville MP, Bours V. 2002. NF-kappaB-dependent MnSOD expression protects adenocarcinoma cells from TNF-alpha-induced apoptosis. Oncogene 21(24):3917–24.

Deng S, Calin GA, Croce CM, Coukos G, Zhang L. 2008. Mechanisms of microRNA deregulation in human cancer. Cell Cycle 7(17):2643–6.

Deveraux QL, Reed JC. 1999. IAP family proteins-suppressors of apoptosis. Genes Dev 13(3):239–52.

Dienes HP, Lohse AW, Gerken G, Schirmacher P, Gallati H, Löhr HF, zum Büschenfelde KM. 1997. Bile duct epithelia as target cells in primary biliary cirrhosis and primary sclerosing cholangitis. Virchows Arch 431(2):119–24.

Dohmen K, Mizuta T, Nakamuta M, Shimohashi N, Ishibashi H, Yamamoto K. 2004. Fenofibrate for patients with asymptomatic primary biliary cirrhosis. World J Gastroenterol 10(6):894–8.

Duclos-Vall JC, Capel F, Mabit H, Petit MA. 1998. Phosphorylation of the hepatitis B virus core protein by glyceraldehyde-3-phosphate dehydrogenase protein kinase activity. J Gen Virol 79(7):1665–70.

Duvoix A, Blasius R, Delhalle S, Schnekenburger M, Morceau F, Henry E. 2005. Chemopreventive and therapeutic effects of curcumin. Cancer Lett 223(2):181–90.

EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS). 2010. Scientific opinion on the re-evaluation of curcumin (E 100) as a food additive. EFSA J 8(9):1–46. Doi: 10.2903/j.efsa.2010.1679.

Egan ME, Pearson M, Weiner SA, Rajendran V, Rubin D, Glöckner-Pagel J, Canny S, Du K, Lukacs GL, Caplan MJ. 2004. Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects. Science 304(5670):600–2.

Elfaki DAH, Lindor KD. 2011. Antibiotics for the treatment of primary sclerosing cholangitis. Am J Ther 18(3):261–5.

El-Serag HB. 2004. Hepatocellular carcinoma: recent trends in the United States. Gastroenterology 127(5):S27–S34.

Fabbrini E, Sullivan S, Klein S.2009. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. Hepatology 51(2):679–89.

Farinati F, Cardin R, Bortolami M, Burra P, Russo FP, Rugge M, Guido M, Sergio A, Naccarato R. 2007. Hepatitis C virus: from oxygen-free radicals to hepatocellular carcinoma. J Viral Hepat 14(12):821–9.

Feng JY, Liu ZQ. 2009. Phenolic and enolic hydroxyl groups in curcumin: which plays the major role in scavenging radicals? J Agric Food Chem 57(22):11041–6.

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. 2010. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Intl J Cancer 127(12):2893–917.

Fung J, Lai CL, Seto WK, Yuen MF. 2011. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B. J Antimicrob Chemother 66(12):2715–25.

Gaedeke J, Noble NA, Border WA. 2004. Curcumin blocks multiple sites of the TGF-β signaling cascade in renal cells. Kidney Intl 66(1):112–20.

Ganem D, Prince AM. 2004. Hepatitis B virus infection – natural history and clinical consequences. N Engl J Med 350(11):1118–29.

Ganiger S, Malleshappa HN, Krishnappa H, Rajashekhar G, Ramakrishna Rao V, Sullivan F. 2007. A two generation reproductive toxicity study with curcumin, turmeric yellow, in wistar rats. Food Chem Toxicol 45(1):64–9.

Gao M, Liu L, Zhang P, Yu G, Li Y. 2012. Neuroprotective effect of curcumin involved in increasing the protein levels of UCP2 and inhibiting oxidative stress induced by chronic cerebral ischemia in vitro. Mol Neurodegener 7:S26.

Garzon R, Calin GA, Croce CM. 2009. MicroRNAs in cancer. Annu Rev Med 60:167–79.

Glebe D. 2007. Hepatitis B virus taxonomy and hepatitis B virus genotypes. World J Gastroentrol 13(1):14–21.

Goel A, Kunnumakkara AB, Aggarwal BB. 2008. Curcumin as "Curecumin": from kitchen to clinic. Biochem Pharmacol 75(4):787–809.

Grattagliano I, Bonfrate L, Diogo CV, Wang HH, Wang DQ, Portincasa P. 2009. Biochemical mechanisms in drug-induced liver injury: certainties and doubts. World J Gastroenterol 15(39):4865–76.

Girish C, Koner BC, Jayanthi S, Rao KR, Rajesh B, Pradhan SC. 2009. Hepatoprotective activity of picroliv, curcumin and ellagic acid compared to silymarin on paracetamol-induced liver toxicity in mice. Fundam Clin Pharmacol l23(6):735–45.

Gunawan BK, Kaplowitz N. 2007. Mechanisms of drug-induced liver disease. Clin Liver Dis 11(3):459–75.

Gunaydın M, Guzel A, Guzel A, Alacam H, Salis O, Murat N, Gacar A, Guvenc T. 2012. The effect of curcumin on lung injuries in a rat model induced by aspirating gastrointestinal decontamination agents. J Pediatr Surg 47(9):1669–76.

Guo H, Ingolia NT, Weissman JS, Bartel DP. 2010. Mammalian microRNAs predominantly act to decrease target mRNA levels. Nature 466(7308):835–40.

Gupta SC, Kismali G, Aggarwal BB. 2013. Curcumin, a component of turmeric: from farm to pharmacy. BioFactors 39:2–13.

Hatcher H, Planalp R, Cho J, Torti FM, Torti SV. 2008. Curcumin: from ancient medicine to current clinical trials. Cell Mol Life Sci 65(11):1631–52.

Harrison RF, Davies MH, Neuberger JM, Hubscher SG. 2005. Fibrous and obliterative cholangitis in liver allografts: evidence of recurrent primary sclerosing cholangitis? Hepatology 20(2):356–61.

Hart CL, Morrison DS, Batty GD, Mitchell RJ, Smith GD. 2010. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. Br Med J 340:C1420.

Hassan ZK, Al-Olayan EM. 2012. Curcumin reorganizes miRNA expression in a mouse model of liver fibrosis. Asia Pac J Cancer Prev 13(11):5405–8.

Hayakawa H, Minaniya Y, Ito K, Yamamoto Y, Fukuda T. 2011. Difference of curcumin content in curcuma longa L.(Zingiberaceae) caused by hybridization with other Curcuma species. Am J Plant Sci 2(2):111–9.

He L, Hannon GJ. 2004. MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Gen 5(7):522–31.

Hemeida RA, Mohafez OM. 2008. Curcumin attenuates methotraxate-induced hepatic oxidative damage in rats. J Egypt Natl Cancer Inst 20(2):141–8.

Holt PR, Katz S, Kirshoff R. 2005. Curcumin therapy in inflammatory bowel disease: a pilot study. Dig Dis Sci 50(11):2191–3.

Hong J, Bose M, Ju J, Ryu JH, Chen X, Sang S, Lee MJ, Yang CS. 2004. Modulation of arachidonic acid metabolism by curcumin and related β-diketone derivatives: effects on cytosolic phospholipase A2, cyclooxygenases and 5-lipoxygenase. Carcinogenesis 25(9):1671–9.

Hou J, Lin L, Zhou W, Wang Z, Ding G, Dong Q, Qin L, Wu X, Zheng Y, Yang Y, Tian W, Zhang Q, Wang C, Zhang Q, Zhuang SM, Zheng L, Liang A, Tao W, Cao X. 2011. Identification of miRNomes in human liver and hepatocellular carcinoma reveals miR-199a/b-3p as therapeutic target for hepatocellular carcinoma. Cancer Cell 19(2):232–43.

Hu KQ. 2008. Hepatitis B virus (HBV) infection in Asian and Pacific Islander Americans (APIAs): how can we do better for this special population & quest. Am J Gastroenterol 103(7):1824–33.

Huang MT, Wang ZY, Georgiadis CA, Laskin JD, Conney AH. 1992. Inhibitory effects of curcumin on tumor initiation by benzo[a]pyrene and 7,12-dimethylbenz[a]anthracene. Carcinogenesis 13(11):2183–6.

Ibrahim SH, Lindor KD. 2011. Current management of primary sclerosing cholangitis in pediatric patients. Pediatr Drugs 13(2):87–95.

Invernizzi P, Miozzo M, Battezzati PM, Bianchi I, Grati FR, Simoni G, Selmi C, Watnik M, Gershwin ME, Podda M. 2004. Frequency of monosomy X in women with primary biliary cirrhosis. Lancet 363(9408):533–5.

Iorio MV, Croce CM. 2009. MicroRNAs in cancer: small molecules with a huge impact. J Clin Oncol 27(34):5848–56.

Itokawa H, Shi Q, Akiyama T, Morris-Natschke SL, Lee KH. 2008. Recent advances in the investigation of curcuminoids. Chin Med 3:11.

Jazayeri SM, Alavian SM, Carman WF.2009. Hepatitis B virus: origin and evolution. J Viral Hepat 17(4):229–35.

Jemal A, Simard EP, Xu J, Ma J, Anderson RN. 2012. Selected cancers with increasing mortality rates by educational attainment in 26 states in the United States, 1993–2007. Cancer Causes Control 2012:1–7.

Jeong SO, Oh GS, Ha HY, Soon Koo B, Kim HS, Kim YC, Kim EC, Lee KM, Chung HT, Pae HO. 2009. Dimethoxycurcumin, a synthetic curcumin analogue, induces heme oxygenase-1 expression through Nrf2 activation in RAW264. 7 macrophages. J Clin Biochem Nutr 44:79–84.

Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. 2009. Clinical course of alcoholic liver cirrhosis: a danish population-based cohort study. Hepatology 51(5):1675–82.

Ji J, Shi J, Budhu A, Yu Z, Forgues M, Roessler S, Ambs S, Chen Y, Meltzer PS, Croce CM, Qin LX, Man K, Lo CM, Lee J, Ng IO, Fan J, Tang ZY, Sun HC, Wang XW. 2009. MicroRNA expression, survival, and response to interferon in liver cancer. N Engl J Med 361(15):1437–47.

John B, Enright AJ, Aravin A, Tuschl T, Sander C, Marks DS. 2004. Human microRNA targets. PLoS Biol 2(11):e363.

Johnson JJ, Mukhtar H. 2007. Curcumin for chemoprevention of colon cancer. Cancer Lett 255(2):170–81.

Jørgensen KK, Grzyb K, Lundin KE, Clausen OP, Aamodt G, Schrumpf E, Vatn MH, Boberg KM. 2012. Inflammatory bowel disease in patients with primary sclerosing cholangitis: clinical characterization in liver transplanted and nontransplanted patients. Inflamm Bowel Dis 18(3):536–45.

Kakran M, Sahoo NG, Tan IL, Li L. 2012. Preparation of nanoparticles of poorly water-soluble antioxidant curcumin by antisolvent precipitation methods. J Nanoparticle Res 14(3):1–11.

Kamisawa T, Takuma K, Anjiki H, Egawa N, Kurata M, Honda G, Tsuruta K. 2009. Sclerosing cholangitis associated with autoimmune pancreatitis differs from primary sclerosing cholangitis. World J Gastroenterol 15(19):2357–60.

Kaplan MM, Gershwin ME. 2005. Primary biliary cirrhosis. N Engl J Med 353(12):1261–73.

Kang Q, Chen A. 2009. Curcumin suppresses expression of low-density lipoprotein (LDL) receptor, leading to the inhibition of LDL-induced activation of hepatic stellate cells. Br J Pharmacol 157(8):1354–67.

Kaplowitz N. 2004. Drug-induced liver injury. Clin Infect Dis 38:S44–8.

Kaplowitz N. 2005. Idiosyncratic drug hepatotoxicity. Nat Rev Drug Dis 4(6):489–99.

Kasof GM, Gomes BC. 2001. Livin, a novel inhibitor of apoptosis protein family member. Sci Signal 276(5):3238–46.

Khanna D, Sethi G, Ahn KS, Pandey MK, Kunnumakkara AB, Sung B, Aggarwal A, Aggarwal BB. 2007. Natural products as a gold mine for arthritis treatment. Curr Opin Pharmacol 7(3):344–51.

Kim Im H, Huang H, Cheepala S, Huang S, Chung J. 2008. Curcumin inhibition of integrin ($\alpha 6\beta 4$)-dependent breast cancer cell motility and invasion. Cancer Prev Res 1(5):385–91.

Kim K, Kim KH, Kim HY, Cho HK, Sakamoto N, Cheong J. 2010. Curcumin inhibits hepatitis C virus replication via suppressing the Akt-SREBP-1 pathway. FEBS Lett 584(4):707–12.

Kim SG, Veena MS, Basak SK, Han E, Tajima T, Gjertson DW, Starr J, Eidelman O, Pollard HB, Srivastava M, Srivatsan ES, Wang MB. 2011. Curcumin treatment suppresses IKKβ kinase activity of salivary cells of patients with head and neck cancer: a pilot study. Clin Cancer Res 17:5953–61.

Kim CH, Younossi ZM. 2008. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. Cleveland Clin J Med 75(10):721–8.

Kowluru RA, Kanwar M. 2007. Effects of curcumin on retinal oxidative stress and inflammation in diabetes. Nutr Metab (Lond) 4:8.

Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H. 2002. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. Br J Surg 89(4):418–22.

Kuhad A, Chopra K. 2007. Curcumin attenuates diabetic encephalopathy in rats: behavioral and biochemical evidences. Eur J Pharmacol 576(1):34–42.

Kunnumakkara AB, Anand P, Aggarwal BB. 2008. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Lett 269(2):199–225.

Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB. 2007. Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-κB–regulated gene products. Cancer Res 67(8):3853–61.

Kurd SK, Smith N, VanVoorhees A, Troxel AB, Badmaev V, Seykora JT, Gelfand JM. 2008. Oral curcumin in the treatment of moderate to severe psoriasis vulgaris: a prospective clinical trial. J Am Acad Dermatol 58(4):625–31.

Kutluay SB, Doroghazi J, Roemer ME, Triezenberg SJ. 2008. Curcumin inhibits Herpes simplex virus immediate-early gene expression by a mechanism independent of p300/CBP histone acetyltransferase activity. Virology 373(2):239–47.

Kwon YW, Kwon KS, Moon HE, Park JA, Choi KS, Kim YS, Jang HS, Oh CK, Lee YM, Kwon YG, Lee YS, Kim KW. 2003. Insulin-like growth factor-II regulates the expression of vascular endothelial growth factor by the human keratinocyte cell line HaCaT. J Invest Dermatol 123(1):152–8.

Ladeiro Y, Couchy G, Balabaud C, Bioulac-Sage P, Pelletier L, Rebouissou S, Zucman-Rossi J. 2008. MicroRNA profiling in hepatocellular tumors is associated with clinical features and oncogene/tumor suppressor gene mutations. Hepatology 47(6):1955–63.

Ladu S, Calvisi DF, Conner EA, Farina M, Factor VM, Thorgeirsson SS. 2008. E2F1 inhibits c-Myc-driven apoptosis via PIK3CA/Akt/mTOR and COX-2 in a mouse model of human liver cancer. Gastroenterology 135(4):1322–32.

Lavanchy D. 2005. Worldwide epidemiology of HBV infection, disease burden, and vaccine prevention. J Clin Virol 34:S1–S3.

Leask A, Abraham DJ. 2004. TGF-β signaling and the fibrotic response. FASEB J 18(7):816–27.

Leclercq IA, Farrell GC, Sempoux C, Horsmans Y. 2004. Curcumin inhibits NF-κB activation and reduces the severity of experimental steatohepatitis in mice. J Hepatol 41(6):926–34.

Lee WM. 2003. Drug-induced hepatotoxicity. N Engl J Med 349(5):474–85.

Lee YM, Kaplan MM. 2002. Management of primary sclerosing cholangitis. Am J Gastroenterol 97(3):528–34.

Lee KS, Lee BS, Semnani S, Avanesian A, Um CY, Jeon HJ, Seong KM, Yu K, Min KJ, Jafari M. 2010a. Curcumin extends life span, improves health span, and modulates the expression of age-associated aging genes in *Drosophila melanogaster*. Rejuv Res 13(5):561–70.

Lee KH, Yeh MH, Kao ST, Hung CM, Liu CJ, Huang YY, Yeh CC. 2010b. The inhibitory effect of hesperidin on tumor cell invasiveness occurs via suppression of activator protein 1 and nuclear factor-kappaB in human hepatocellular carcinoma cells. Toxicology Lett 194(1):42–9.

Leu TH, Maa MC. 2002. The molecular mechanisms for the antitumorigenic effect of curcumin. Curr Med Chem-Anti-Cancer Agent 2(3):357–70.

Leuschner U. 2003. Primary biliary cirrhosis-presentation and diagnosis. Clin Liver Dis 7:741–58.

Li M, Zhang Z, Hill DL, Wang H, Zhang R. 2007. Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway. Cancer Res 67(5):1988–96.

Liang J, Slingerland JM. 2003. Multiple roles of the PI3K/PKB (Akt) pathway in cell cycle progression. Cell Cycle 2(4):336–42.

Liaw YF, Chu CM. 2009. Hepatitis B virus infection. Lancet 373(9663):582–92.

Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. 2001. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J Neurosci 21(21):8370–7.

Limtrakul P, Lipigorngoson S, Namwong O, Apisariyakul A, Dunn FW. 1997. Inhibitory effect of dietary curcumin on skin carcinogenesis in mice. Cancer Lett 116(2):197–203.

Lin JK. 2007. Molecular targets of curcumin. In: Aggarwal, Bharat B.; Surh, Young-Joon; Shishodia, S. editor.,The molecular targets and therapeutic uses of curcumin in health and disease. New York NY, USA: Springer. p. 227–43.

Lin LI, Ke YF, Ko YC, Lin JK. 1998. Curcumin inhibits SK-Hep-1 hepatocellular carcinoma cell invasion in vitro and suppresses matrix metalloproteinase-9 secretion. Oncology 55(4):349–53.

Lin JK, Lin-Shiau SY. 2009. Turmeric (curcumin). In: Bharat B. Aggarwal, Ajaikumar B. Kunnumakkarap, editors. Molecular targets and therapeutic uses of spices: modern uses for ancient medicine. Singapore: World Scientific. p.403.

Lindor K. 2007. Ursodeoxycholic acid for the treatment of primary biliary cirrhosis. N Engl J Med 357(15):1524–9.

Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, Harnois D, Jorgensen R, Petz J, Keach J, Mooney J, Sargeant C, Braaten J, Bernard T, King D, Miceli E, Schmoll J, Hoskin T, Thapa P, Enders F. 2009. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology 50(3):808–14.

Liu ZX, Kaplowitz N. 2002. Immune-mediated drug-induced liver disease. Clin Liver Dis 6(3):755–74.

Liu P, Kimmoun E, Legrand A, Sauvanet A, Degott C, Lardeux B, Bernuau D. 2002. Activation of NF-kappaB, AP-1 and STAT transcription factors is a frequent and early event in human hepatocellular carcinomas. J Hepatol 37(1):63–71.

Liu Q, Loo WT, Sze SCW, Tong Y. 2009. Curcumin inhibits cell proliferation of MDA-MB-231 and BT-483 breast cancer cells mediated by down-regulation of NFκB, cyclinD and MMP-1 transcription. Phytomedicine 16(10):916–22.

Liu Q, Yuan B, Lo KA, Patterson HC, Sun Y, Lodish HF. 2012a. Adiponectin regulates expression of hepatic genes critical for glucose and lipid metabolism. Proc Natl Acad Sci 109(36):14568–73.

Liu K, Chen HL, Huang H, Jing H, Dong GH, Wu HW, You QS. 2012b. Curcumin attenuates cardiopulmonary bypass-induced lung oxidative damage in rats. J Cardiovasc Pharmacol Ther 17(4):395–402.

Lo HW, Cao X, Zhu H, Ali-Osman F. 2010. Cyclooxygenase-2 is a novel transcriptional target of the nuclear EGFR-STAT3 and EGFRvIII-STAT3 signaling axes. Mol Cancer Res 8(2):232–45.

Lucey MR, Mathurin P, Morgan TR.2009. Alcoholic hepatitis. N Engl J Med 360(26):2758–69.

MacFarlane M, Merrison W, Bratton SB, Cohen GM. 2002. Proteasome-mediated degradation of Smac during apoptosis: XIAP promotes Smac ubiquitination in vitro. J Biol Chem 277(39):36611–6.

Marczylo TH, Steward WP, Gescher AJ. 2009. Rapid analysis of curcumin and curcumin metabolites in rat biomatrices using a novel ultraperformance liquid chromatography (UPLC) method. J Agric Food Chem 57(3):797–803.

Martin RC, Aiyer HS, Malik D, Li Y. 2012. Effect on pro-inflammatory and antioxidant genes and bioavailable distribution of whole turmeric vs curcumin: similar root but different effects. Food Chem Toxicol 50(2):227–31.

Mathew A, Peiffer LP, Rhoades K, McGarrity T. 2006. Sustained viral response to pegylated interferon α-2b and ribavirin in chronic hepatitis C refractory to prior treatment. Dig Dis Sci 51(11):1956–61.

Mendes F, Lindor KD. 2010. Primary sclerosing cholangitis: overview and update. Nat Rev Gastroenterol Hepatol 7(11):611–9.

Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Richardson PG, Hideshima T, Munshi N, Treon SP, Anderson KC. 2002. Biologic sequelae of nuclear factor-κB blockade in multiple myeloma: therapeutic applications. Blood 99(11):4079–86.

Miura H, Miyachi Y. 2009. IgG4-related retroperitoneal fibrosis and sclerosing cholangitis independent of autoimmune pancreatitis. A recurrent case after a 5-year history of spontaneous remission. JOP 10:432–7.

Mohamad N, Gutiérrez A, Núñez M, Cocca C, Martín G, Cricco G, Medina V, Rivera E, Bergoc R. 2005. Mitochondrial apoptotic pathways. Biocell 29(2):149–61.

Mohanty C, Sahoo SK. 2010. The in vitro stability and in vivo pharmacokinetics of curcumin prepared as an aqueous nanoparticulate formulation. Biomaterials 31(25):6597–611.

Mokdad AH, Marks JS, Stroup DF, Gerberding JL. 2004. Actual causes of death in the United States, 2000. JAMA 291(10):1238–45.

Morisco F, Vitaglione P, Amoruso D, Russo B, Fogliano V, Caporaso N. 2008. Foods and liver health. Mol Asp Med 29(1):144–50.

Muir AJ, Bornstein JD, Killenberg PG. 2004. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. N Engl J Med 350(22):2265–71.

Mythri BR, Srinivas M, Bharath M. 2012. Curcumin: a potential neuroprotective agent in Parkinsons disease. Curr Pharmaceut Des 18(1):91–9.

Nabavi SF, Eslami S, Moghaddam AH, Nabavi SM. 2011a. Protective effects of curcumin against fluoride-induced oxidative stress in the rat brain. Neurophysiology 43(4):287–91.

Nabavi SF, Moghaddam AH, Eslami S, Nabavi SM. 2012a. Protective effects of curcumin against sodium fluoride-induced toxicity in rat kidneys. Biol Trace Element Res 145(3):369–74.

Nabavi SF, Nabavi SM, Abolhasani F, Moghaddam AH, Eslami S. 2012b. Cytoprotective effects of curcumin on sodium fluoride-induced intoxication in rat erythrocytes. B Environ Contam Toxicol 88:486–90.

Nabavi SF, Nabavi SM, Ebrahimzadeh MA, Eslami S, Jafari N, Moghaddam HA. 2011b. The protective effect of curcumin against sodium fluoride-induced oxidative stress in rat heart. ArchBiol Sci 63(3):563–9.

Nabavi SM, Nabavi SF, Eslami S, Moghaddam AH. 2012c. In vivo protective effects of quercetin against sodium fluoride-induced oxidative stress in the hepatic tissue. Food Chem 132(2):931–5.

Nakagawa H, Maeda S, Hikiba Y, Ohmae T, Shibata W, Yanai A, Sakamoto K, Ogura K, Noguchi T, Karin M, Ichijo H, Omata M. 2008. Deletion of apoptosis signal-regulating kinase 1 attenuates acetaminophen-induced liver injury by inhibiting c-Jun N-terminal kinase activation. Gastroenterology 135(4):1311–21.

Nanji AA, Jokelainen K, Rahemtulla A, Miao L, Fogt F, Matsumoto H, Tahan SR, Su GL. 1999. Activation of nuclear factor kappa B and cytokine imbalance in experimental alcoholic liver disease in the rat. Hepatology 30(4):934–43.

Nanji AA, Jokelainen K, Tipoe GL, Rahemtulla A, Thomas P, Dannenberg AJ. 2003. Curcumin prevents alcohol-induced liver disease in rats by inhibiting the expression of NF-κB-dependent genes. Am J Physiol-Gastrointest Liver Physiol 284(2):G321–7.

Natarajan C, Bright JJ. 2002. Curcumin inhibits experimental allergic encephalomyelitis by blocking IL-12 signaling through Janus kinase-STAT pathway in T lymphocytes. J Immunol 168(12):6506–13.

Nautiyal J, Banerjee S, Kanwar SS, Yu Y, Patel BB, Sarkar FH, Majumdar AP. 2010. Curcumin enhances dasatinib-induced inhibition of growth and transformation of colon cancer cells. Intl J Cancer 128(4):951–61.

Navarro VJ, Senior JR. 2006. Drug-related hepatotoxicity. N Engl J Med 354(7):731–9.

Naveau S, Dobrin AS, Balian A, Njiké-Nakseu M, Nohra P, Asnacios A, Prévot S, Perlemuter G. 2013. Body fat distribution and risk factors for Fibrosis in patients with alcoholic liver disease. Alcohol Clin Exp Res 37:332–8.

Negi AS, Kumar JK, Luqman S, Shanker K, Gupta MM, Khanuja SPS. 2008. Recent advances in plant hepatoprotectives: a chemical and biological profile of some important leads. Med Res Rev 28(5):746–72.

Niu G, Wright KL, Huang M, Song L, Haura E, Turkson J, Zhang S, Wang T, Sinibaldi D, Coppola D, Heller R, Ellis LM, Karras J, Bromberg J, Pardoll D, Jove R, Yu H. 2002. Constitutive Stat3 activity up-regulates VEGF expression and tumor angiogenesis. Oncogene 21(13): 2000–8.

Ng APP, Chng WJ, Khan M. 2011. Curcumin sensitizes acute promyelocytic leukemia cells to unfolded protein response–induced apoptosis by blocking the loss of misfolded N-CoR protein. Mol Cancer Res 9(7):878–88.

Notarbartolo M, Poma P, Perri D, Dusonchet L, Cervello M, D'Alessandro N. 2005. Antitumor effects of curcumin, alone or in combination with cisplatin or doxorubicin, on human hepatic cancer cells. Analysis of their possible relationship to changes in NF-kB activation levels and in IAP gene expression. Cancer Lett 224(1):53–65.

Nurfina AN, Reksohadiprodjo MS, Timmerman H, Jenie UA, Sugiyanto D, van der Goot H. 1997. Synthesis of some symmetrical curcumin derivatives and their antiinflammatory activity. Eur J Med Chem 32:321–8.

Oconnell MA, Rushworth SA. 2008. Curcumin: potential for hepatic fibrosis therapy? Br J Pharmacol 153(3):403–5.

Oetari S, Sudibyo M, Commandeur JN, Samhoedi R, Vermeulen NP. 1996. Effects of curcumin on cytochrome P450 and glutathione S-transferase activities in rat liver. Biochem Pharmacol 51(1):39–45.

Ortiz-Lopez C, Lomonaco R, Orsak B, Finch J, Chang Z, Kochunov VG, Hardies J, Cusi K. 2012. Prevalence of prediabetes and diabetes and metabolic profile of patients with nonalcoholic fatty liver disease (NAFLD). Diabetes Care 35(4):873–8.

Pan MH, Lin-Shiau SY, Lin JK.2000. Comparative studies on the suppression of nitric oxide synthase by curcumin and its hydrogenated metabolites through down-regulation of IkappaB kinase and NFkappaB activation in macrophages. Biochem Pharmacol 60:1665–76.

Pan Y, Zhu G, Wang Y, Cai L, Cai Y, Hu J, Li Y, Yan Y, Wang Z, Li X, Wei T, Liang G. 2013. Attenuation of high-glucose-induced inflammatory response by a novel curcumin derivative B06 contributes to its protection from diabetic pathogenic changes in rat kidney and heart. J Nutr Biochem 24(1):146–55.

Papa S, Bubici C, Zazzeroni F, Pham CG, Kuntzen C, Knabb JR, Dean K, Franzoso G. 2006. The NF-κB-mediated control of the JNK cascade in the antagonism of programmed cell death in health and disease. Cell Death Differ 13(5):712–29.

Pari L, Murugan P. 2004. Protective role of tetrahydrocurcumin against erythromycin estolate-induced hepatotoxicity. Pharmacol Res 49(5):481–6.

Paula H, Asrani SK, Boetticher NC, Pedersen R, Shah VH, Kim WR. 2010. Alcoholic liver disease-related mortality in the United States: 1980–2003. Am J Gastroenterol 105(8):1782–7.

Peng BG, He Q, Li JP, Zhou F. 2009. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Surg 198(3):313–8.

Pessayre D, Mansouri A, Berson A, Fromenty B. 2010. Mitochondrial involvement in drug-induced liver injury. Adv Drug React 2010: 311–65.

Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. 2006. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 45(4):529–38.

Pham CG, Bubici C, Zazzeroni F, Knabb JR, Papa S, Kuntzen C, Franzoso G. 2007. Upregulation of Twist-1 by NF-κB blocks cytotoxicity induced by chemotherapeutic drugs. Mol Cell Biol 27(11):3920–35.

Pham CG, Bubici C, Zazzeroni F, Papa S, Jones J, Alvarez K, Jayawardena S, De Smaele E, Cong R, Beaumont C, Torti FM, Torti SV, Franzoso G. 2004. Ferritin heavy chain upregulation by NF-kappaB inhibits TNFalpha-induced apoptosis by suppressing reactive oxygen species. Cell 119(4):529–42.

Poynard T, Bedossa P, Opolon P. 1997. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet 349(9055):825–32.

Pratsinis H, Giannouli CC, Zervolea I, Psarras S, Stathakos D, Kletsas D. 2004. Differential proliferative response of fetal and adult human skin fibroblasts to transforming growth factor-β. Wound Repair Regen 12(3):374–83.

Priyadarsini KI. 2009. Photophysics, photochemistry and photobiology of curcumin: studies from organic solutions, bio-mimetics and living cells. J Photochem Photobiol C Photochem Rev 10(2):81–95.

Prusty BK, Das BC. 2004. Constitutive activation of transcription factor AP-1 in cervical cancer and suppression of human papillomavirus (HPV) transcription and AP-1 activity in HeLa cells by curcumin. Intl J Cancer 113(6):951–60.

Pullakhandam R, Srinivas PNBS, Nair MK, Reddy GB. 2009. Binding and stabilization of transthyretin by curcumin. Arch Biochem Biophys 485(2):115–9.

Puri P, Sanyal AJ. 2012. Nonalcoholic fatty liver disease: definitions, risk factors, and workup. Clin Liver Dis 1(4):98–102.

Punithavathi D, Venkatesan N, Babu M. 2009. Curcumin inhibition of bleomycin-induced pulmonary fibrosis in rats. Br J Pharmacol 131(2):169–72.

Quasdorff M, Hösel M, Odenthal M, Zedler U, Bohne F, Gripon P, Dienes HP, Drebber U, Stippel D, Goeser T, Protzer U. 2008. A concerted action of HNF4α and HNF1α links hepatitis B virus replication to hepatocyte differentiation. Cell Microbiol 10(7):1478–90.

Quasdorff M, Protzer U. 2010. Control of hepatitis B virus at the level of transcription. J Viral Hepat 17(8):527–36.

Rajasekaran SA. 2011. Therapeutic potential of curcumin in gastrointestinal diseases. World J Gastrointest Pathophysiol 2(1):1–14.

Ramirez-Tortosa MC, Ramirez-Tortosa CL, Mesa MD, Granados S, Gil Á, Quiles JL. 2009. Curcumin ameliorates rabbits steatohepatitis via respiratory chain, oxidative stress, and TNF-α. Free Rad Biol Med 47(7):924–31.

Rasyid A, Lelo A. 1999.The effect of curcumin and placebo on human gall-bladder function: an ultrasound study. Aliment Pharmacol Ther 13(2):245–9.

Rechtman MM, Har-Noy O, Bar-Yishay I, Fishman S, Adamovich Y, Shaul Y, Halpern Z, Shlomai A. 2010. Curcumin inhibits hepatitis B virus via down-regulation of the metabolic coactivator PGC-1α. FEBS Lett 584(11):2485–90.

Reyes-Gordillo K, Segovia J, Shibayama M, Tsutsumi V, Vergara P, Moreno MG, Muriel P. 2008. Curcumin prevents and reverses cirrhosis induced by bile duct obstruction or CCl4 in rats: role of TGF-β modulation and oxidative stress. Fundam Clin Pharmacol 22(4):417–27.

Rivera-Espinoza Y, Muriel P. 2009. Pharmacological actions of curcumin in liver diseases or damage. Liver Intl 29(10):1457–66.

Rousseau S, Houle F, Landry J, Huot J. 1997. p38 MAP kinase activation by vascular endothelial growth factor mediates actin reorganization and cell migration in human endothelial cells. Oncogene 15(18):2169–77.

Romero-Hernández MA, Eguía-Aguilar P, Perézpeña-Diazconti M, Rodríguez-Leviz A, Sadowinski-Pine S, Velasco-Rodríguez LA, Cáceres CJ, Arenas-Huertero F. 2013.Toxic effects induced by curcumin in human astrocytoma cell lines. Toxicol Mech Methods. Available from http://informahealthcare.com/doi/pdf/10.3109/15376516.2013.826768.

Saich R, Chapman R. 2008. Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease. World J Gastroenterol 14(3):331–7.

Salunga TL, Cui ZG, Shimoda S, Zheng HC, Nomoto K, Kondo T, Takano Y, Selmi C, Alpini G, Gershwin ME, Tsuneyama K. 2007. Oxidative stress-induced apoptosis of bile duct cells in primary biliary cirrhosis. J Autoimmun 29(2):78–86.

Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, Limtrakul P, Badmaev V, Aggarwal BB. 2007. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. Carcinogenesis 28(8):1765–73.

Sargent S. 2008. Diagnosing and treating a patient with primary biliary cirrhosis. Br J Nurs 17(9):566–70.

Scapagnini G, Sonya V, Nader AG, Calogero C, Zella D, Fabio G. 2011. Modulation of Nrf2/ARE pathway by food polyphenols: a nutritional neuroprotective strategy for cognitive and neurodegenerative disorders. Mol Neurobiol 44(2):192–201.

Schmitz KJ, Wohlschlaeger J, Lang H, Sotiropoulos GC, Malago M, Steveling K, Reis H, Cicinnati VR, Schmid KW, Baba HA. 2008. Activation of the ERK and AKT signalling pathway predicts poor prognosis in hepatocellular carcinoma and ERK activation in cancer tissue is associated with hepatitis C virus infection. J Hepatol 48(1):83–90.

Semela D, Dufour JF. 2004. Angiogenesis and hepatocellular carcinoma. J Hepatol 41(5):864–80.

Sethi G, Sung B, Aggarwal BB. 2009. In: Ramawat K. G., editor. The role of curcumin in modern medicine, Herbal drugs: ethnomedicine to modern medicine. Berlin Heidelberg: Springer. p. 97–113.

Shah BH, Nawaz Z, Pertani SA, Roomi A, Mahmood H, Saeed SA, Gilani AH. 1999. Inhibitory effect of curcumin, a food spice from turmeric, on platelet-activating factor-and arachidonic acid-mediated platelet aggregation through inhibition of thromboxane formation and Ca $^{2+}$ signaling. Biochem Pharmacol 58(7):1167–72.

Sharma AV, Ganguly K, Paul S, Maulik N, Swarnakar S. 2012. Curcumin heals indomethacin-induced gastric ulceration by stimulation of angiogenesis and restitution of collagen fibers via VEGF and MMP-2 mediated signaling. Antioxid Red Signal 16(4):351–62.

Shehzad A, Lee YS. 2010. Curcumin: multiple molecular targets mediate multiple pharmacological actions: a review. Drug Future 35:113–9.

Shehzad A, Wahid F, Lee YS. 2010. Curcumin in cancer chemoprevention: molecular targets, pharmacokinetics, bioavailability, and clinical trials. Arch Pharmazie 343(9):489–99.

Shen H, Huang GJ, Gong YW. 2003. Effect of transforming growth factor beta and bone morphogenetic proteins on rat hepatic stellate cell proliferation and trans-differentiation. World J Gastroenterol 9(4):784–7.

Shi M, Guo RP, Lin XJ, Zhang YQ, Chen MS, Zhang CQ, Lau WY, Li JQ. 2007. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg 245(1):36–43.

Shin SK, Ha TY, McGregor RA, Choi MS. 2011. Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism. Mol Nutr Food Res 55: 1829–40.

Shishodia S, Sethi G, Aggarwal BB. 2006. Curcumin: getting back to the roots. Annu New York Acad Sci 1056(1):206–17.

Shlomai A, Paran N, Shaul Y. 2006. PGC-1α controls hepatitis B virus through nutritional signals. Proc Natl Acad Sci 103(43):16003–8.

Sidhu GS, Singh AK, Thaloor D, Banaudha KK, Patnaik GK, Srimal RC, Maheshwari RK. 2002. Enhancement of wound healing by curcumin in animals. Wound Repair Regener 6(2):167–77.

Simard EP, Ward EM, Siegel R, Jemal A.2012. Cancers with increasing incidence trends in the United States: 1999 through 2008 CA: A Cancer J Clin 62:118–28.

Singal AK, Stanca CM, Clark V, Dixon L, Levy C, Odin JA, Fiel MI, Friedman SL, Bach N. 2011. Natural history of small duct primary sclerosing cholangitis: a case series with review of the literature. Hepatol Intl 5(3):808–13.

Singh U, Barik A, Singh BG, Priyadarsini KI. 2011. Reactions of reactive oxygen species (ROS) with curcumin analogues: structure-activity relationship. Free Rad Res 45(3):317–25.

Somparn P, Phisalaphong C, Nakornchai S, Unchern S, Morales NP. 2007. Comparative antioxidant activities of curcumin and its demethoxy and hydrogenated derivatives. Biol Pharm Bull 30(1):74–78.

St-Germain ME, Gagnon V, Parent S, Asselin E. 2004. Regulation of COX-2 protein expression by Akt in endometrial cancer cells is mediated through NF-κB/IκB pathway. Mol Cancer 3(1):7.

Stokkeland K, Ebrahim F, Ekbom A. 2010. Increased risk of esophageal varices, liver cancer, and death in patients with alcoholic liver disease. Alcohol Clin Exp Res 34(11):1993–9.

Subramaniam D, Ponnurangam S, Ramamoorthy P, Standing D, Battafarano RJ, Anant S, Sharma P. 2012. Curcumin induces cell death in esophageal cancer cells through modulating notch signaling. PLoS One 7(2): e30590.

Sun B, Karin M. 2008. NF-κB signaling, liver disease and hepatoprotective agents. Oncogene 27(48):6228–44.

Sun HC, Tang ZY, Wang L, Qin LX, Ma ZC, Ye QH, Zhang BH, Qian YB, Wu ZQ, Fan J, Zhou XD, Zhou J, Qiu SJ, Shen YF. 2006. Postoperative interferon α treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial. J Cancer Res Clin Oncol 132(7):458–65.

Suresh Babu P, Srinivasan K. 1995. Influence of dietary curcumin and cholesterol on the progression of experimentally induced diabetes in albino rat. Mol Cell Biochem 152(1):13–21.

Suter PM, Tremblay A. 2005. Is alcohol consumption a risk factor for weight gain and obesity? Crit Rev Clin Lab Sci 42(3):197–227.

Tabibian JH, Lindor KD. 2013. Primary sclerosing cholangitis: a review and update on therapeutic developments. Exp Rev Gastroenterol Hepatol 7(2):103–14.

Tacke F, Luedde T, Trautwein C. 2009. Inflammatory pathways in liver homeostasis and liver injury. Clin RevAllergy Immunol 36(1):4–12.

Talwalkar JA, Lindor KD. 2003. Primary biliary cirrhosis. Lancet 362(9377):53–61.

Tanaka A, Borchers AT, Ishibashi H, Ansari AA, Keen CL, Gershwin ME. 2001. Genetic and familial considerations of primary biliary cirrhosis. Am J Gastroenterol 96(1):8–15.

Tanaka S, Miyanishi K, Kobune M, Kawano Y, Hoki T, Kubo T, Hayashi T, Sato T, Sato Y, Takimoto R, Kato J. 2013. Increased hepatic oxidative DNA damage in patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. J Gastroenterol. Doi:10.1007/s00535-012-0739-0.

Teiten MH, Eifes S, Dicato M, Diederich M. 2010. Curcumin—the paradigm of a multi-target natural compound with applications in cancer prevention and treatment. Toxins 2(1):128–62.

Thangapazham RL, Sharma A, Maheshwari RK. 2007. Beneficial role of curcumin in skin diseases. In: Aggarwal, Bharat B.; Surh, Young-Joon; Shishodia, S., editors. The molecular targets and therapeutic uses of curcumin in health and disease. New York, NY, USA: Springer. p 343–57.

Thapliyal R, Maru GB. 2001. Inhibition of cytochrome P450 isozymes by curcumins in vitro and in vivo. Food Chem Toxicol 39(6):541–7.

Tiniakos DG, Vos MB, Brunt EM. 2010. Nonalcoholic fatty liver disease: pathology and pathogenesis. Annu Rev Pathol 5:145–71.

Ueki M, Ueno M, Morishita J, Maekawa N. 2012. Curcumin ameliorates cisplatin-induced nephrotoxicity by inhibiting renal inflammation in mice. J Biosci Bioeng 115(5):547–51.

Vara D, Salazar M, Olea-Herrero N, Guzmán M, Velasco G, Díaz-Laviada I. 2011. Anti-tumoral action of cannabinoids on hepatocellular carcinoma: role of AMPK-dependent activation of autophagy. Cell Death Differ 18(7):1099–111.

Verhoef C, Valkema R, De Man RA, Krenning EP, Yzermans JNM. 2002. Fluorine-18 FDG imaging in hepatocellular carcinoma using positron coincidence detection and single photon emission computed tomography. Liver 22(1):51–6.

Vizzutti F, Provenzano A, Galastri S, Milani S, Delogu W, Novo E, Caligiuri A, Zamara E, Arena U, Laffi G, Parola M, Pinzani M, Marra F. 2009. Curcumin limits the fibrogenic evolution of experimental steatohepatitis. Lab Invest 90(1):104–15.

Vogel A, Manns MP. 2012. Mimics of autoimmune hepatitis: drug-induced and immune mediated liver disease. Autoimmun Hepat 2012:93–113.

Vucic D, Stennicke HR, Pisabarro MT, Salvesen GS, Dixit VM. 2000. ML-IAP, a novel inhibitor of apoptosis that is preferentially expressed in human melanomas. Curr Biol 10(21):1359–66.

Wada T, Penninger JM. 2004. Mitogen-activated protein kinases in apoptosis regulation. Oncogene 23(16):2838–49.

Wands J. 2007. Hepatocellular carcinoma and sex. N Engl J Med 357(19):1974–6.

Wang WZ, Li L, Liu MY, Jin XB, Mao JW, Pu QH, Meng MJ, Chen XG, Zhu JY. 2013. Curcumin induces FasL-related apoptosis through p38 activation in human hepatocellular carcinoma Huh7 cells. Life Sci 92(6–7):352–8.

Wang CY, Mayo MW, Korneluk RG, Goeddel DV, Baldwin Jr AS. 1998. NF-κB antiapoptosis: induction of TRAF1 and TRAF2 and c-IAP1 and c-IAP2 to suppress caspase-8 activation. Science 281(5383):1680–3.

Wang NP, Wang ZF, Tootle S, Philip T, Zhao ZQ. 2012. Curcumin promotes cardiac repair and ameliorates cardiac dysfunction following myocardial infarction. Br J Pharmacol 167:1550–62.

Warrington R. 2012. Drug allergy: causes and desensitization. Hum Vaccine Immunother 8(10):1513–24.

Watson JL, Greenshields A, Hill R, Hilchie A, Lee PW, Giacomantonio CA, Hoskin DW. 2010. Curcumin-induced apoptosis in ovarian carcinoma cells is p53-independent and involves p38 mitogen-activated protein kinase activation and downregulation of Bcl-2 and survivin expression and Akt signaling. Mol Carcinog 49(1):13–24.

Wilken R, Veena MS, Wang MB, Srivatsan ES. 2011. Curcumin: a review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Mol Cancer 10(12):1–19.

Woodhead JL, Howell BA, Yang Y, Harrill AH, Clewell 3rd HJ, Andersen ME, Siler SQ, Watkins PB. 2012. An analysis of N-acetylcysteine treatment for acetaminophen overdose using a systems model of drug-induced liver injury. J Pharmacol Exp Ther 342(2):529–40.

Wu Z, Han M, Chen T, Yan W, Ning Q. 2010. Acute liver failure: mechanisms of immune-mediated liver injury. Liver Intl 30(6):782–94.

Wu JY, Lin CY, Lin TW, Ken CF, Wen YD. 2007. Curcumin affects development of zebrafish embryo. Biol Pharm Bull 30(7):1336–9.

Xia Y, Jin L, Zhang B, Xue H, Li Q, Xu Y. 2007. The potentiation of curcumin on insulin-like growth factor-1 action in MCF-7 human breast carcinoma cells. Life Sci 80(23):2161–9.

Yadav A, Lomash V, Samim M, Flora SJ. 2012. Curcumin encapsulated in chitosan nanoparticles: a novel strategy for the treatment of arsenic toxicity. Chem-Biol Interact 199(1):49–61.

Yan G, Graham K, Lanza-Jacoby S. 2012. Curcumin enhances the anticancer effects of trichostatin a in breast cancer cells. Mol Carcinog 52(5): 404–11.

Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM. 2005. Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 280(7):5892–901.

Yang Y, Zhu J, Gou H, Cao D, Jiang M, Hou M. 2011. Clinical significance of Cox-2, Survivin and Bcl-2 expression in hepatocellular carcinoma (HCC). Med Oncol 28(3):796–803.

Yao QY, Xu BL, Wang JY, Liu HC, Zhang SC, Tu CT. 2012. Inhibition by curcumin of multiple sites of the transforming growth factor-beta1 signalling pathway ameliorates the progression of liver fibrosis induced by carbon tetrachloride in rats. BMC Complment Altern Med 12(1):156.

Yoysungnoen P, Wirachwong P, Bhattarakosol P, Niimi H, Patumraj S. 2006. Effects of curcumin on tumor angiogenesis and biomarkers, COX-2 and VEGF, in hepatocellular carcinoma cell-implanted nude mice. Clin Hemorheol Microcirc 34(1):109–15.

Yu YD, Kim KH, Lee SG, Choi SY, Kim YC, Byun KS, Cha IH, Park KY, Cho CH, Choi DH. 2011. Hepatic differentiation from human embryonic stem cells using stromal cells. J Surg Res 170:e253–61.

Yu G, Liu L, Zhang P, Li Y. 2012. Protective effect of curcumin on chronic cerebral ischemia by altering expression of α-synuclein in 2VO model. Mol Neurodegener 7:S33.

Zhang W, Liu HT.2002. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. Cell Res 12(1):9–18.

Zhao D, Chen S, Cai J, Guo Y, Song Z, Che J, Liu C, Wu C, Ding M, Deng H. 2009. Derivation and characterization of hepatic progenitor cells from human embryonic stem cells. PloS One 4(7):e6468.

Zhao J, Jin J, Zhang X, Shi M, Dai J, Wu M, Wang R, Guo Y. 2006. Transfection of Smac sensitizes tumor cells to etoposide-induced apoptosis and eradicates established human hepatoma in vivo. Cancer Gene Ther 13:420–7.

Zheng S, Chen A. 2006. Curcumin suppresses the expression of extracellular matrix genes in activated hepatic stellate cells by inhibiting gene expression of connective tissue growth factor. Am J Physiol Gastrointest Liver Physiol 290(5):G883–93.

Zoulim F. 2004a. Antiviral therapy of chronic hepatitis B: can we clear the virus and prevent drug resistance? Antivir Chem Chemother 15(6): 299–305.

Zoulim F. 2004b. Mechanism of viral persistence and resistance to nucleoside and nucleotide analogs in chronic hepatitis B virus infection. Antivir Res 64(1):1–15.