Hepatoprotective activity of medicinal plants: A mini review

Divya Jain, Priya Chaudhary, Aarti Kotnala, Rajib Hossain, Kiran Bisht and Mohammad Nabil Hossain

DOI: https://doi.org/10.22271/plants.2020.v8.i5c.1212

Abstract

A phytotherapeutic approach for the development of modern drug agents can provide various vital drugs from the conventional medicinal plants. Exploration of pure phytocompounds as drug agent is expensive and time taken. Various plants and their herbal formulations are found to be useful for the cure of liver diseases. However, in some cases, the results of treatment are not up to the mark but experimental studies are carried out on a number of valuable plants and their formulations. The therapeutic efficacy is tested against some chemically induced liver damages in liver cancer cell lines and animal models. Antioxidants from the medicinal plants and common dietary sources can provide protection against the liver damages caused by the chemicals and oxidative stress mechanism.

Keywords: Antioxidants, liver diseases, liver cancer cell line, herbal formulation, hepatoprotective, phytotherapeutic

Introduction

In severe cases of liver damage, most of the cells either die or changes to fibrotic state. In such cases, the treatment option includes some agents along with the therapeutic agents which can stimulate the proliferation of liver cell. Human liver cell lines procured from the cancerous tissue or by the genetic engineering of primary liver cells are broadly utilized in In vitro studies due to their better availability. The stable metabolism and larger capacity of proliferation of these cells make them an acceptable one for In vitro investigation under reproducible and standardized condition. Hepatoma cell line HepG2 is mostly used for In vitro studies for the development of cancer therapy. Reports highlighted the importance of cell line for the investigation of metabolic pathways or to test a particular drug candidate solely or in combination for a cancer therapy [1, 2].

For the development of remarkable herbal agent to treat different diseases of liver, medicinal plants have to be validated for their properties such as liver regeneration, antihapatotoxic, and antiviral activity. The plants with above mentioned properties have to be selected. Single plant cannot fulfill all the desired activities. An amalgam of various herbal fraction/extracts can likely to fulfill desired properties to treat liver diseases. Production of these herbal formulations with standards of efficacy, purity and safety can revitalise the treatment of liver ailments. However, plants such as Aegle marmelos Correa, Ficus syedopalma Blanco, Picrorhiza kurroa Royle, Cochlospermum angolensis, Semecarpus anacardium, Humulus japonicas, Pleurotus pulmonarius, Caesalpinia bonducella, Symphlocos racemose, Berberis vulgaris, Urtica dioica L, Terminalia arjuna, Withania somifera, Punica granatum, Morinda citrifolia, and Morinda pubescens (Hyoscyamine) plays an important role in the human wellbeing due to the presence of various primary and secondary metabolites [3, 4, 5, 6].

Around 80% of the globe population is dependent upon the use of conventional medicine which is based on the medicinal plants [7]. The conventional medicine refers to a wide range of natural wellbeing practices including tribal/folk practices as well as Unani, Amchi, Siddha, and Ayurveda. It is determined that around 7,500 plants are utilized in tribal and rural part of India. Out of them, the exact therapeutic value of more than 4,000 plants is still unknown or little known to the large population. The traditional system of medicine such as Tibetan, Unani, Amchi, Siddha, and Ayurveda utilized around 1200 species of plants [8]. A complete investigation of plants applied in local wellbeing traditions and their pharmacognostical evaluation can lead to the production of crucial plant drugs for many untreatable diseases [9].
Liver diseases
Liver plays an important role in the regulation of many of the physiological processes. It is included in various vital functions such as storage, secretion, and metabolism. Detoxification of many xenobiotics and drugs can occur in liver. The bile acid of the liver with some other things directs the digestion process. Liver diseases are one of the severe ailments. It may be categorized as chronic or acute (inflammatory ailment), cirrhosis (results liver fibrosis), and hepatitis (non-inflammatory ailment). They are mainly occurred because of many risk factors which damage the cells of liver by directing peroxidation of lipids and other oxidative damages due to the generation of oxidative stress in liver. Enhanced peroxidation of lipid during the microsomal ethanol metabolism in liver may results in hepatitis and cirrhosis [10].

Risk factors for liver cancer
Chronic infection with Hepatitis C and B virus is found to be the common factor responsible for causing liver cirrhosis [11]. Hepatitis C and B viruses can transmit from one individual to another through the use of contaminated needles and blood sharing. This chance of transmission can be reduced via blood test prior to the transfusion of blood [12]. Another risk factor is the alcohol abuse which is the cause of liver cirrhosis leading to hepatic cancer [13]. Tobacco use, obesity, diabetes and smoking can also raise the possibilities of getting liver cancer [14]. Heavy metals exposure through the portable water can also develop a risk in developing some types of hepatic cancer [15]. Further, long-term exposure to thorium dioxide (X-ray chemical), vinyl chloride, aflatoxin can raise the chances of cirrhosis and liver cancer in individual [16].

Table 1: Medicinal plant with antioxidant activity in liver cell

| Plant                     | Compounds                          | Plantparts                  | IC50/ dose concentration | Proposed mechanism                                                                 | Test system       | Reference |
|---------------------------|------------------------------------|-----------------------------|--------------------------|-----------------------------------------------------------------------------------|-------------------|-----------|
| *Tinospora cordifolia*    | Jatrorrhizine, Saponarin, Galactoarabinan | Whole plant                | 300 mg/kg                | Increase SOD, CAT, GPx and GSH level and reduce LPO enzyme.                        | Male wister albino rats. | [27]      |
| *Kleinhovia hospita*      | Eleuthero l                         | Leaves                     | IC50 = 491.8 IM          | Scavenged the radical                                                             | DPPH radical scavenging method | [28]      |
| *Morinda pubescens*       | Hyoscyamine                        | Leaves                     | IC50 = 289.33±62.14 μg/mL | 58.40% DPPH radical scavenging                                                   | DPPH method using L-Ascorbic acid | [29]      |
| *Terminalia arjuna*       | Terminoside A                      | Bark                       | 400 mg/kg                | Increase SOD, CAT, GPx and GSH level and reduce LPO enzyme.                        | Male wistar albino rats. | [30, 31] |
| *Rosmarinus officinalis*  L. | Rosmanol, Carnosol                | Whole plant                | 0 to 120 g/mL            | 50% increased antioxidant activity.                                               | Human liver carcinoma HepG2 cells | [21]      |
| *Pleurotus pulmonarius*   | Ergosta-5, 7, 22-trien-3β-ol        | Whole plant                | 0.25 mg/ml to 4 mg/ml    | DPPH scavenging activity                                                          | Mice               | [25]      |
| *Humulus japonicus*       | Luteolin-8-C-glucoside             | Whole plant                | 0.1-2 mg/ml              | DPPH radical and hydroxyl radical scavenging activities of methanol extracts of Humulus japonicus were 60% and 35%, respectively | DPPH radical scavenging method | [20]      |
| *Semecarpus anacardium*   | Anacardoside, Galbuahvanone         | Nut                        | 200 mg/kg                | Increase glutathione                                                              | Male wistar albino laboratory rats | [34]      |
| *Cochlospermum angolensis* | Gallic acid, Protocatechuic acid   | Whole plant                | EC50 ≤ 170 μg/mL         | Increase DPPH scavenging activity                                                 | Human liver carcinoma HepG2 cells | [22]      |
| *Picrorhiza kurroa*       | Picrorhiza acid                     | Whole plant                | 2 μg/mL                  | Radical scavenging assays (DPPH* and *OH), ferric reducing antioxidant property (FRAP) and thiobarbituric acid (TBA) assay for testing inhibition of lipid peroxidation | Hep3B (human hepatocellular carcinoma) | [19]      |
| *Ficus pseudopalma*      Blanco | Lupeol                             |                            | DPPH (IC50=331.76 μg/mL), nitric oxide (IC50=19.81 μg/mL) and DPPH, nitric oxide, and FRAP scavenging activity | Hepatocellular Carcinoma (HepG2) cells | [23]      |
### Potential of phytochemicals

Many phytochemicals are found to be the potential one against hepatocarcinoma. Structures of some of the phytochemicals is presented in figure 1. Curcumin was found to induce both mitochondrial and nuclear DNA damage \[36\]. DNA damage was detected previously through the use of comet assay where DNAs were formed as single strand breaks. From those studies, it was also found that the mitochondrial DNA was more damaged than the nuclear DNA. As a result, hepatoma cells are increased by curcumin \[37\]. Besides, a natural alkaloid named berberine, which is found in plants was previously used to secure the plasmid DNA by destroying the damaging characteristics and oxidative stress of H2O2 \[38\]. The DNA damaging events in promyelocytic cancer cells (HL-60) are also found through this single phytochemical \[39\]. Berberine was also responsible for the demonstration of cell cycle arrest and the death of apoptotic cells in the cancer cells \[37\].

| Plant                          | Phytochemicals                  | FRAP (IC50=53.04 µg/mL) | Suppress lipid peroxidation (LPO), xanthine oxidase (XO) | Male Sprague–Dawley rats |
|-------------------------------|--------------------------------|-------------------------|--------------------------------------------------------|--------------------------|
| Aegle marmelos Correa         | Marmin unbelliferone            | 25 and 50 mg/Kg b. wt. orally | Increased the levels of antioxidants (CAT, GR and SOD) enzyme and increase MDA | Wistar rats [18]          |
| Urtica dioica L.              | p-coumaric acid Seeds           | 2 mL/day                | GPx and SOD activities increased, lowered NO level     | Male Sprague–Dawley rats [32] |
| Berberis vulgaris             | Cannabis G                      | 0.2-1 mg/ml             | GPx, SOD and DPPH assay                                | GPx, SOD and DPPH assay [24] |
| Symlocos racemosa             | Symplquinone A, B, C Bark       | 100 and 200 mg/kg       | Increase glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD), reduce LPO. | Hepatocellular carcinoma rats [15] |
| Caesalpinia bonducella        | 5-hydroxyxythiacanal Whole plant | 100 and 200 mg/kg       | Reduce lipid peroxidation, increased nonenzymatic antioxidants (GSH), and antioxidant enzymes (SOD and CAT) levels, | Hepatocellular carcinoma rats [17] |
| C. lansium (Lour.)            | 8-hydroxypsoralen Fruits        | For DPPH 25, 50, 75 and 100 µg/ml, and for superoxide anion 12.5, 25, 75 and 50 µg/ml | Increase DPPH radical and superoxide anion scavenging activity | DPPH and superoxide anion assay [33] |
| Artemisia annua L.            | Gentisic acid Whole plant       | 0.50 mg/g dry matter in 80% (v/v) | Reduced lipid peroxidation and DNA damage | 2,7-dichlorofluorescein (DCF) assay [26] |
Interaction process of few Phytochemicals

1. Curcumin
Curcumin plays an important role as a phytochemical. Basically, curcumin is a kind of polyphenol found in Curcuma longa plants. The molecular targeting systems and alarming signaling pathways are mainly triggered by the polyphenol of curcumin in order to prevent cancer [40]. From various studies it has been found that the ‘inflammatory pathway disorder’ increases the risk of cancer growth [41]. There are several pro-inflammatory molecules which are produced and increased by this single inflammation process such as cytokines, ROS, cyclooxygenase (COX-2), transcription factors including nuclear factor κB (NF-κB), protein kinases B (AKT), activator protein 1 (AP1), signal transducer and activator of transcription 3 (STAT3) and so on. Undoubtedly, all these molecules play an important role in the development of cancer, as these are inflammatory pathways [42, 43]. In this case, curcumin participates in interaction process with the help of some immune mediators through its immunomodulatory characteristics and proves itself as an anticancer drug [40].

2. Camptothecin
Camptothecin is known to be a natural alkaloid which is procured from the Mappia foetida, Canzptotheca acriminata, and many other plant species. It has an antitumor potential and mainly acts upon topoisomerase I, an enzyme responsible for the DNA supercoiling relaxation [44, 45]. Many derivatives of camptothecin are in clinical trial stages. In phase I trial, 20-(S)-9-nitrocamptothecin and 20-(S)-camptothecin were given to 29 and 59 patients having tumor, respectively. These compounds are found to be effective in different patients with skin, prostate, breast, and liver cancer [46].

3. Quercetin
Carbon tetrachloride (CCl₄) directed hepatic carcinoma has been broadly studied in the field of hepatology. The radicals of CCl₄ make covalent interaction with the components of cell and inhibits the secretion of lipoproteins and thus results steatosis. On reaction with oxygen, they lead to the formation of CCl₃-OO, which introduce peroxidation of lipid and results in programmed cell death. Quercetin is known to be a natural flavonoid with various therapeutic effects. It provides protection to the liver against CCl₄-directed liver injury via anti-inflammation and antioxidative stress. The main mechanism responsible behind the protection leads to the inhibition of MAPK (mitogen-activated protein kinases) phosphorylation and Toll-like receptor 4 (TLR4) and Toll-like receptor 2 (TLR2) activation which ultimately directs the NF-κB (nuclear factor kappa light chain enhancer of activated B cells) inactivation and decreases the production of inflammatory cytokines in liver [47, 48].

4. Berberine
The hepatoprotective activity of berberine was investigated in mice which were administered with doxorubicin to induce hepatotoxicity. Berberine pre-treatment remarkably decreases the histologic damages and functional hepatic tests [49]. The mechanism underlying to reduce the hepatotoxicity was also determined in case of CCl₄-directed hepatotoxicity.
Berberine reduces the nitrosamine and oxidative stress and also changes the inflammatory response in the liver. Further, it prevents the increase in peroxidation of lipid and decrease in the activity of superoxide dismutase (SOD) and contributes in the reduction of iNOS, COX-2, and TNF-α level. Decrease in the level of transaminase provide support in relation to the hypothesis, according to which berberine is found to be effective in maintaining the integrity of liver cell membrane [50, 51].

Conclusion
The aim of ethnopharmacological investigation in case of medicinal plants is not limited to find pure isolated compound as a therapeutic drug. Active fraction, extracts or mixture of extracts can be used as an effective drug option. The drugs obtained from plant (either individual or combination) for hepatic diseases are proved to be sufficient in the cure of hepatic diseases caused because of the intake of alcohol, viruses, and chemicals. Effective formulation is needed to be developed by the use of indigenous variety of plants, with all validation in terms of pharmacological experimentation and pre-clinical and clinical trials. In order to make plant drugs globally acceptable, the manufacturing of plant-based drugs should be governed properly according to the standard of efficacy or safety.

Conflict of interest
There is no conflict of interests.

References
1. Zeilinger K, Freyer N, Damm G, Seehofer D, Knössel F. Cell sources for in vitro human liver cell culture models. Exp. Biol. Med. 2016;241(15):1684-1698. https://doi.org/10.1177/1535370216657448
2. Samatiwat P, Takeda K, Satarug S, Ohba K, Kukongviriyapan V, Shibahara S. Induction of MITF expression in human cholangiocarcinoma cells and hepatocellular carcinoma cells by cyclopamine, an inhibitor of the Hedgehog signaling. Biochem Biophys Res Commun 2016;470:144-9.
3. Chaudhary P, Kotnala A, Negi N, Janneda P. Ayurvedic approach: a natural way to cure diabetes (Madhumeha). Vigyana Varta 2020;1(4):12-15.
4. Jain D, Uniyal N, Mitra D, Janneda P. Traditional resources and use of aromatic and ethanomedical plants in Uttarakhand: Compliment of nature. Int. J Herb. Med 2020;8(5):88-95.
5. Prakash A, Jain D, Tripathi R, Janneda P. Pharmacognostical analysis of different parts of Cyperus rotundus L. Plant Sci. Today 2019;6:607-612. https://doi.org/10.14719/pst.2019.6.sp1.679
6. Verma D, Madbul G, Chaudhary P, Mahakur B, Mitra D, et al. Medicinal plants of Uttarakhand (India) and their benefits in the treatment of tuberculosis: current perspectives. GJBB 2020;9(3):75-85.
7. WHO, Regional Office For The Western Pacific, Research Guidelines For Evaluating The Safety And Efficacy Of Herbal Medicines, Manila, WHO 1993.
8. Push pangadan P. Role of Traditional Medicine in Primary Health Care. In: Iyengar PK, Damodaran VK, Push pangadan P, Editors. Science for Health. Published By State Committee On Science, Technology And Environment, Govt. Of Kerala 1995.
9. Aszalos A, Editor. Antitumor Compounds of Natural Origin. Boca Raton, CRC Press 1982.
10. Smucker EA. Alcoholic Drink: Its Production and Effects. Fed Proc 1975;34:2038-44.
11. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. J Gastroenterol. 2012;142(6):1264-1273.e1. https://doi.org/10.1053/j.gastro.2011.12.061
12. Coppola N, De Pascalis S, Onorato L, Calò F, Sagnelli C, Sagnelli E. Hepatitis B virus and hepatitis C virus infection in healthcare workers. World J Hepatol 2016;8(5):273-281. https://doi.org/10.4254/wjh.v8.i5.273
13. Addolorato G, Mirijello A, Leggio L, Ferrulli A, Landolfi R. Management of alcohol dependence in patients with liver disease. CNS Drugs 2013;27(4):287-299. https://doi.org/10.1007/s40263-013-0043-4.
14. EL-Zayadi AR. Heavy smoking and liver. World J Gastroenterol. 2006;12(38):6098-6101. https://doi.org/10.3748/wjg.v12.i38.6098
15. Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda K. Toxicity, mechanism and health effects of some heavy metals. Interdiscip Toxicol 2014;7(2):60-72. https://doi.org/10.2478/intox-2014-0009
16. Rapisarda V, Loreto C, Malaguarnera M, Ardiri A, Proti M, Rigano G et al. Hepatocellular carcinoma and the risk of occupational exposure. World J Hepatol 2016;8(13):573-590. https://doi.org/10.4254/wjh.v8.i13.573
17. Gupta M, Mazumder UK, Sambath Kumar R, Sivakumar T, Gomathi P et al. Antioxidant defense system induced by a methanol extract of Caeasalpinia bonducella. in rat liver. Pharm Biol 2005;43(5):411-419.
18. Khan TH, Sultana S. Antioxidant and hepatoprotective potential of Aegle marmelos Correa. against CCl4-induced oxidative stress and early tumor events. J Enzyme Inhib Med Chem 2009;24(2):320-327.
19. Rajkumar V, Guha G, Kumar RA. Antioxidant and anti-neoplastic activities of Pierorhiza kurroa extracts. Food Chem Toxicol 2011;49(2):363-369.
20. Lee YR, Kim KY, Lee SH, Park HJ, Jeong HS. Antioxidant and antitumor activities of methanolic extracts from Hamulus japonicus. Korean J Food & Nutr 2012;25(2):357-361.
21. Vicente G, Molina S, González-Vallinas M, García-Risco MR, Fornari T et al. Supercritical rosemary extracts, their antioxidant activity and effect on hepatic tumor progression. J Supercrit Fluids 2013;79:101-108.
22. Pereira C, Calhelha RC, Barros L, Ferreira IC. Antioxidant properties, anti-hepatocellular carcinoma activity and hepatotoxicity of artichoke, milk thistle and horseradish. Ind Crops Prod 2013;49:61-65.
23. Bueno PR, Buno CB, Santos DL, Santiago LA. Antioxidant activity of Ficus pseudopalma Blanco and its cytotoxic effect on hepatocellular carcinoma and peripheral blood mononuclear cells. Curr ResBio Pharma Sci 2013;2:14, 21.
24. Abd El-Wahab AE, Ghareeb DA, Sarhan EE, Abu-Serie MM, El Demellawy MA. In vitro biological assessment of Berberis vulgaris and its active constituent, berberine: antioxidants, anti-acyethylcholinesterase, anti-diabetic and anticancer effects. BMC complement Altern. Med 2013;13(1):218.
25. Xu WW, Li B, Lai ETC, Chen L, Huang JHH et al. Water extract from Pleurotus pulmonarius with antioxidant activity exerts in vivo chemoprophylaxis and chemosensitization for liver cancer. Nutr Cancer 2014;66(6):989-998.
26. Kim MH, Seo JY, Liu KH, Kim J-S. Protective Effect of Artemisia annua L. Extract against Galactose-Induced Oxidative Stress in Mice. PLoS ONE. 2014;9(7):e101486Management of alcohol dependence in patients with liver disease. CNS Drugs 2014;27(4):287-299. https://doi.org/10.1007/s40263-013-0043-4.

27. Jayaprakash R, Ramesh V, Sridhar MP, Sasikala C. Antioxidant activity of Ethanolic extract of Tinospora cordifolia on N-nitrosodimethylamine (dimethylnitrosamine) induced liver cancer in male Wistar albino rats. J. Pharm. Bioallied Sci 2015;7(1):S40.

28. Arung ET, Kusuma IW, Purwatiningsih S, Roh SS, Yang CH et al. Antioxidant activity and cytotoxicity of the traditional Indonesian medicine Tahongai (Kleinhovia hospita) L. extract. J Acupunct Meridian Stud 2009;2(4):306-308.

29. Kumar DJ, Santhi RJ. Antioxidant and cytotoxic effects of hexane extract of Morinda pubescens leaves in human liver cancer cell line. Asian Pac. J Trop Med 2012;5(5):362-366.

30. Sivalokanathan S, Ilayaraja M, Balasubramanian MP. Antioxidant activity of Terminalia arjuna bark extract on N-nitrosodimethylamine induced hepatocellular carcinoma in rats. Mol Cell Biochem 2006;281(1-2):87.

31. Verma N, Vinayak M. Effect of Terminalia arjuna on antioxidant defense system in cancer. Mol. Biol. Rep 2009;36(1):159.

32. Yener Z, Celik I, Ilhan F, Bal R. Effects of Urtica dioica L. seed on lipid peroxidation, antioxidants and liver pathology in aflatoxin-induced tissue injury in rats. Food Chem Toxicol 2009;47(2):418-424.

33. Prasad KN, Xie H, Hao J, Yang B, Qiu S et al. Antioxidant and anticancer activities of 8-hydroxypsoralen isolated from wampee [Clausena lanium (Lour.) Skeels] peel. Pecl. Food Chemist 2010;118(1):62-66.

34. Premalatha B, Sachidanandam P. Semecarpus anacardium L. nut extract administration induces the in vivo antioxidant defence system in aflatoxin B1 mediated hepatocellular carcinoma. J Ethnopharmacol 1999;66(2):31-139.

35. Vijayabaskaran M, Yuvaraja KR, Babu G, Sivakumar P, Perumal P et al. Hepatoprotective and antioxidant activity of Symplocos racemosa bark extract on DMBA induced hepatocellular carcinoma in rats. IJCT 2010;1(3):147-158.

36. Cao J, Liu Y, Jia L, Zhou HM, Kong Y et al. Curcumin induces apoptosis through mitochondrial hyperpolarization and mtDNA damage in human hepatoma G2 cells. Free Radic. Biol. Med 2007;43(6):968-975. https://doi.org/10.1016/j.freeradbiomed.2007.06.006.

37. Kaur V, Kumar M, Kumar A, Kaur K, Dhillon VS et al. Pharmacotherapeutical potential of phytochemicals: Implications in cancer chemoprevention and future perspectives. Biomed Pharmacother. 2018;97(2017):564-586. https://doi.org/10.1016/j.biopha.2017.10.124.

38. Choi D-S, Kim S-J, Jung MY. Inhibitory Activity of Berberine on DNA Strand Cleavage Induced by Hydrogen Peroxide and Cytochrome c. Biosci. Biotechnol. Biochem. 2001;65(2):452-455. https://doi.org/10.1271/bbb.65.452.

39. Khan M, Giessrigl B, Vonach C, Madlener S, Prinz S et al. Berberine and a Berberis lyceum extract inactivate Cdc25A and induce α-tubulin acetylation that correlate with HL-60 cell cycle inhibition and apoptosis. Mutat Res 2010;683(1-2):123-130. https://doi.org/10.1016/j.mrfmmm.2009.11.001.

40. Giordano A, Tommonaro G. Curcumin and cancer. Nutrients 2019;11(10):1-19. https://doi.org/10.3390/nu11102376.

41. Mantovani A. Molecular pathways linking inflammation and cancer. Curr. Mol. Med 2010;10(4):369-373.

42. Catanzaro M, Corsini E, Rosini M, Racchi M, Lanni C. Immunomodulators Inspired by Nature: A Review on Curcumin and Echinacea. Molecules 2018;23(11):2778. https://doi.org/10.3390/molecules23112778.

43. Mohamed SIA, Jantan I, Haque MA. Naturally occurring immunomodulators with antitumor activity: An insight on their mechanisms of action. Int. Immunopharmacol 2017;50:291-304. https://doi.org/10.1016/j.intimp.2017.07.010.

44. Netelson EA, Giovanelia BC, Verschraegen CF, Fehir KM, De Ipolyi PD, Harris N et al. Phase I clinical and pharmacological studies of 20-(S)-camptothecin and 20-(S)-9-nitrocamptothecin as anticancer agents. Ann N Y Acad Sci 1996;803:224-230.

45. Li QY, Zu YG, Shi RZ, Yao LP. Review Camptothecin: current perspectives. Curr Med Chem 2006;13:2021-2039.

46. Hosseini A, Ghorbani A. Cancer therapy with phytochemicals: evidence from clinical studies. Avicenna J Phytopharm 2015;5(2):84-97.

47. Ma JQ, Li Z, Xie WR, Liu CM, Liu SS. Quercetin protects mouse liver against CCl4-induced inflammation by the TLR2/4 and MAPK/NF-κB pathway. Int. Immunopharmacol 2015;28(1):531-539.

48. Li S, Tan HY, Wang N, Cheung F, Hong M, Feng Y. The potential and action mechanism of polyphenols in the treatment of liver disease. Oxid. Med. Cell. Longev 2018. https://doi.org/10.1155/2018/8394818.

49. Zhao X, Zhang J, Tong N, Chen Y, Luo Y. Protective effects of berberine on doxorubicin-induced hepatotoxicity in mice. Biol Pharm Bull 2012;35(5):796-800.

50. Domitrovic R, Jakovac H, Blagojevic G. Hepatoprotective activity of berberine is mediated by inhibition of TNF-α, COX-2, and iNOS expression in CCI4-intoxicated mice. J Toxicol 2011;280(1-2):33-43.

51. Neag MA, Mocan A, Echeverria J, Pop RM, Boczan CI, Crisan G. Berberine: botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorder. Front. Pharmacol 2018;9:557. https://doi.org/10.3389/fphar.2018.00557.