

## After HCV Eradication with Sovaldi<sup>®</sup>, Can Herbs Regenerate Damaged Liver, Minimize Side Effects and Reduce the Bill?

Nada M Mostafa and Abdel Nasser Singab\*

Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

### Abstract

**Objective:** Hepatitis C virus is a major health burden. It has infected millions of people worldwide with the highest prevalence in Egypt. Sofosbuvir (Sovaldi<sup>®</sup>) has been recently approved for treating chronic hepatitis C virus infections. Herbal medicine has been searched for centuries for the remedy of liver diseases.

**Key ings:** Plants contain phytochemicals that proved to demonstrate hepatoprotective activity *in vitro* in various hepatotoxic models. Herbal drugs also proved efficacy in many clinical trials in reducing the viral load and improving the clinical manifestations in patients suffering hepatitis C virus.

**Conclusions:** A hypothesis is postulated for the possibility of the use of a herbal mixture of plants, which are known for their hepatoprotective activity, in a combination therapy with directly acting antiviral drugs such as Sovaldi<sup>®</sup> to help regenerate the liver, improve the clinical condition and reduce both the cost and side effects for hepatitis C virus patients.

**Keywords:** Hepatitis C virus; Herbal medicine; Sovaldi<sup>®</sup>; Hepatoprotective; Liver regeneration

### Introduction

Hepatitis C virus (HCV) is considered a significant public health problem [1]. It currently infects more than 170 million people worldwide. The great majority of patients develop chronic HCV infection, which can ultimately result in hepatic cirrhosis, failure or hepatocellular carcinoma, leading to about 350,000 deaths each year [2,3]. Egypt shows the highest prevalence (15%) of hepatitis C virus worldwide. It also has the highest predominance of HCV- 4 (67%), especially subtype 4a (55%). The history of infection and the disease progression are influenced by various factors such as level of HCV viremia, age at the onset of infection, sex, co-infection with hepatitis B virus and duration of infection [4].

Sofosbuvir (Sovaldi<sup>®</sup>) Sofosbuvir is a new antiviral candidate against multiple Hepatitis C virus genotypes [1]. It is a nucleotide analogue that is a potent inhibitor of NS5B polymerase in HCV. NS5B is a non-structural protein which is essential for viral RNA replication and has been a valuable target for many directly acting antiviral agents [3]. Numerous *in vitro* studies show promising results against all genotypes of HCV. Sovaldi<sup>®</sup> is approved by the Food and Drug Administration for the treatment of chronic HCV infection [1]. It has shown high efficacy in combination with other drugs in antiviral treatment regimen. This drug is of special interest among directly acting antiviral drugs due to its high potency, oral administration, low side effects and high barrier to resistance [3].

Liver is the main organ responsible for the detoxification processes in our bodies and it is likely to be injured regularly by ingested toxins. The regenerative properties of the liver are in fact logical adaptation procedures carried out by organisms, for which liver damage depends on for recovery [5]. Liver regeneration is achieved through a complex network consisting of liver cells (hepatocytes, Kupffer cells, hepatic stellate cells, sinusoidal endothelial cells and stem cells); and extrahepatic organs such as thyroid gland, pancreas, adrenal gland, duodenum and autonomous nervous system [6]. Liver regeneration is achieved by both cell proliferation and cell growth of hepatocytes, which are induced via stimulations of cytokines and growth factors. Restoration of liver volume depends mainly on hepatocyte proliferation, which includes initiation, proliferation and termination phases [5,6].

In the absence of reliable liver-protective drugs in the modern medicine, a variety of medicinal preparations are recommended for the treatment of liver disorders [7]. Herbal drugs contain a wide number of phytochemicals that occur naturally in the plants, and may have potential protective or disease preventive properties [8-12]. Thus, studying the potential biological activity of crude drugs can result in the discovery of novel lead drugs for certain diseases and can lead to combining the strength of traditional application of herbal therapy with the modern concept of standardization, evidence-based pharmacological evaluation and controlled clinical trials in order to support clinical efficacy [13,14].

### Hepatoprotective Plants

Some fruits (grapefruit, grapes, cranberries and cactus pear fruit); plants such as chamomile and resin (propolis), which are consumed frequently by humans, in addition to some phytochemicals extracted from fruits, plants, algae, and yeasts have been evaluated in different models of hepatotoxicity and demonstrated hepatoprotective capacity [15]. A number of hepatoprotective plants have been tested in hepatotoxicity experimental models, which are often supported by histopathological examination of liver, thus provide an insight to the use of these plants against liver disorders in addition to regeneration of damaged hepatic tissues [16]. Some examples of these plants are listed below.

#### *Glycyrrhiza glabra* (Leguminosae)

Glycyrrhizic acid is a triterpene glycoside found in the roots of liquorice (*Glycyrrhiza glabra*). It possesses a variety of pharmacological

\*Corresponding author: Singab AN, Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, 11566, Cairo, Egypt, Tel: +20224051120; Fax: +20224051107; E-mail: [dean@pharma.asu.edu.eg](mailto:dean@pharma.asu.edu.eg) (or) [abdelnasser.sengab@pharma.asu.edu.eg](mailto:abdelnasser.sengab@pharma.asu.edu.eg)

Received June 16, 2016; Accepted June 30, 2016; Published July 04, 2016

**Citation:** Mostafa NM, Singab AN (2016) After HCV Eradication with Sovaldi<sup>®</sup>, Can Herbs Regenerate Damaged Liver, Minimize Side Effects and Reduce the Bill? Med Aromat Plants 5: 257. doi:10.4172/2167-0412.1000257

**Copyright:** © 2016 Mostafa NM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

activities such as anti-inflammatory, antiviral effects, immune regulatory actions, and inhibition of hepatic apoptosis, necrosis and antitumor effects [17]. In addition, glycyrrhizin and 18 $\beta$ -glycyrrhetic acid (active components in liquorice) have been shown to protect against a number of hepatotoxicants such as CCl<sub>4</sub> and D-galactosamine [18].

#### ***Silybium marianum* (Asteraceae)**

Silymarin is a mixture of flavonolignans isolated from the seeds of milk thistle. It is known for its hepatoprotective action. It has been used to treat many liver disorders, including acute or chronic viral hepatitis, toxin drug-induced hepatitis, cirrhosis and alcoholic liver diseases [16]. The mechanism of its action includes inhibition of hepatotoxin binding to the receptor sites on hepatocyte membranes, reduction of glutathione oxidation in order to enhance the level of hepatocytes in liver. It lowered the elevated serum level of bilirubin, AST, and ALT in various experimental models [19]. Silymarin acts as an antioxidant, regulator of the intracellular glutathione, stabilizer and regulator of cell membrane permeability to prevent entering of hepatotoxic substances into hepatocytes; it also promotes ribosomal RNA synthesis simulating regeneration of the liver, in addition, it inhibits the transformation of liver stellate cells into myofibroblasts thus prevents deposition of collagen fibres in liver [16,20].

#### ***Cynara scolymus* (Asteraceae)**

Artichoke has been traditionally used in treating liver diseases. It contains caffeoylquinic acids that have powerful hepatic regenerating effects similar to silymarin. Caffeoylquinic acids can protect, regenerate liver cells, eliminate toxins from the blood, help in treating liver damage and insufficiency [21,22].

#### ***Taraxacum officinale* (Asteraceae)**

The hepatoprotective activity of aqueous extract of dandelion was evaluated against D-galactosamine induced hepatitis in rats and supported by histological examination of liver sections. Results suggest that dandelion could be used as a potential therapeutic agent for treating chemically induced or viral hepatitis. Dandelion also possesses liver-healing properties. It enhances bile flow and improves both hepatitis and jaundice [23].

#### ***Cichorium intybus* (Asteraceae)**

*Cichorium intybus* is commonly known as Chicory, traditionally reputed as a liver tonic. It has been used as for gall and liver disturbances and it forms an important component of several liver preparations [24]. In preclinical studies its alcohol extract was found to be effective against chlorpromazine induced hepatic damage in albino rats. Using ethanolic extract of *Cichorium intybus* in dose of 300 mg/kg, showed significant increase in circulating leukocytes and relative weights of liver, as compared with alcohol alone which proves the liver protective effects of the herb [24].

#### ***Phyllanthus niruri* (Euphorbiaceae)**

Traditionally, the decoction of this plant has historically been used in jaundice. Extracts of *Phyllanthus niruri* have exerted hepatoprotective effect against both CCl<sub>4</sub> induced HepG2 cell damage in rabbits and paracetamol induced acute liver damage in rats [25]. In a preliminary study, treating carriers of hepatitis B virus with a preparation of *Phyllanthus niruri* for 30 days; 59% of the treated patients had lost hepatitis B surface antigen when they were tested 15-20 days after the end of the treatment. No case has the surface antigen returned. Preclinical studies demonstrate that *Phyllanthus niruri*

extract inhibits endogenous DNA polymerase of hepatitis B virus and binds to the surface antigen of hepatitis B virus [16].

#### ***Curcuma longa* (Zingiberaceae)**

The ethanol extract of *Curcuma longa* showed hepatoprotective activity against paracetamol-induced liver damage in rats. Pretreatment of rats with the ethanol extract of *Curcuma longa* prior to paracetamol dosing, statistically lowered the serum liver enzyme (AST, ALT and ALP) activities [26].

#### ***Ginkgo biloba* (Ginkgoaceae)**

The *Ginkgo biloba* exhibits many pharmacological properties such as antioxidant, membrane stabilizing effect, increase in blood fluidity, hepatoprotective effect and improvement in cognitive function. Its extract (0.24 mg of ginkgo flavon-glycosides/g of dry extract) reduces the AST, ALT and ALP levels in hepatotoxicity induced by CCl<sub>4</sub> in rats [16,27].

#### ***Zingiber officinale* (Zingiberaceae)**

Hepatoprotective effects, as documented by a decrease in liver enzymes, were observed by aqueous ethanol extract of *Zingiber officinale* against single dose of acetaminophen induced (3 g/kg, orally) acute hepatotoxicity in rat [28].

#### ***Camellia sinensis* (Theaceae)**

The leaves of *Camellia sinensis* contain a number of catechins (flavanols) especially epigallocatechin gallate that possess antioxidant property, and have the ability to stabilize cell membranes [29]. Its aqueous extract given orally to rats with CCl<sub>4</sub> induced hepatotoxicity, reduced serum liver enzymes and lipid peroxide and significantly increase serum total protein, albumin and liver glutathione (GSH), superoxide dismutase (SOD) and catalase enzyme (CAT) as compared to rats treated by carbon tetrachloride alone [30].

### **Herbs for Relief of Drugs Adverse Effect**

Sofosbuvir (Sovaldi®) has shown a good safety profile in clinical trials. The adverse effects reported in patients being treated with it are headache, insomnia, fatigue, nausea, dizziness, pruritis, upper respiratory tract infections, rash, back pain, grade 1 anemia, and grade 4 lymphopenia [3]. Headache, being the most common side effect observed, can be overcome by a variety of herbs well known for their effectiveness against migraine and headache. Most of herbs are available and not expensive thus herbal drugs can be an ally to HCV patients suffering from the acquisition high cost of treatment (\$1,000 per pill of Sovaldi®) [1].

Below are presented some plants that can be used in medicinal preparations to relieve headache:

***Tanacetum parthenium* (feverfew)** has been used traditionally to treat migraine. It is suggested to have serotonin 5-HT receptor blocking effects [31]. Feverfew inhibits the release of serotonin and histamine from platelets, and decreases the smooth muscle response to endogenous vasoactive substances, such as norepinephrine, prostaglandins, acetylcholine, histamine, bradykinin and serotonin. It has also been shown to produce a dose-dependent inhibition of the inflammatory leukotrienes and thromboxane B<sub>2</sub> [32,33].

***Salix alba* (white willow)** has been traditionally used to relieve various pains including headache. It was shown to strongly inhibit binding to serotonin 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors in a similar mode to *T. parthenium*. However, in contrast to *T. parthenium*, *Salix alba*

interact strongly with 5-HT<sub>1D</sub> receptors. Thus raising the possibility that combining *T. parthenium* with *S. alba* might provide more effective prophylaxis than *T. parthenium* alone [31].

**Zingiber officinale (ginger)** contains active ingredients (gingerols and shogaols), which are capable of inhibiting platelet aggregation [34]. Ginger ethanol extract completely inhibited *in vitro* arachidonate-induced platelet aggregation [35]. It was reported that gingerols are potent inhibitors of prostaglandin synthetase and inhibitors of leukotriene biosynthesis. Through inhibition of these inflammatory neurotransmitters, ginger may play an important role in migraine prevention [36].

**Ginkgo biloba (ginkgo)** extract has been shown to contain three specific platelet-activating factor (PAF) antagonists [37]. In clinical trials conducted on Ginkgo extract in France, they suggested that Ginkgo may be beneficial in migraine patients [38].

## Herbs in Clinical Trials

A number of clinical trials were conducted to prove the effectiveness of herbal medicine in combination with antiviral therapy in hepatitis patients. Here presented below are some of those trials reported.

Liu et al. conducted ten randomized trials, which included 517 patients with chronic hepatitis C. They evaluated ten different medicinal herbs, versus a number of control interventions (two other herbs, four placebo and four interferon). The herbal compound Bing Gan Tang when combined with interferon (INF)-alpha showed significantly better clearance of serum HCV RNA and better effect on normalization of serum ALT activity than INF-alpha alone. While, the herbal compound Yi Zhu decoction demonstrated a significant effect on the clearance of serum HCV RNA and the normalization of ALT levels as compared to glycyrrhizin in addition to ribavirin. Tang also showed similar significant effect on normalizing serum ALT, as compared to silymarin plus glucuro lactone. No significant efficacy of the other examined herbs was observed [39].

Kainuma et al. evaluated the effectiveness of combining a herbal medicine (Mao-to) with natural interferon-beta in patients with chronic hepatitis C having a high serum viral load and genotype 1b, who seem to be resistant to interferon therapy. Their study was conducted on eighteen patients and they concluded that Mao-to administration with IFN-beta treatment could increase the patient's biochemical response rate and reduce liver fibrosis [40].

McCulloch et al. examined the efficiency of Chinese herbal medicine (alone or with interferon alfa) in the treatment of chronic hepatitis B. They found that Chinese herbal medicine was equivalent to interferon alfa in the seroreversion of both HBeAg and hepatitis B virus DNA. The herbal medicine when combined with interferon alfa significantly raised the seroreversion of HBeAg, HBsAg and HBV DNA. The active component, bufotoxin, when combined with interferon alfa increased significantly HBeAg and HBV DNA seroreversion. While the active component, kurorinone, was equivalent to interferon alfa in the seroreversion of both HBeAg and HBV DNA [41].

Motoo et al. suggested that the herbal medicine Ninjinyoeito (NYT) can reduce the ribavirin-induced anemia in a clinical trial conducted on twenty-three patients with chronic HCV [42].

Barakat et al. examined the efficacy of *Nigella sativa* in thirty patients with HCV infection, who were not eligible IFN/ribavirin therapy. They concluded that *N. sativa* administration to those patients was safe, tolerable; it decreased the viral load and improved the clinical condition, oxidative stress and glycemic control in diabetic patients [4].

Shawkat et al. conducted a clinical trial on eighty-two patients with chronic HCV. They concluded that adding-on a herbal medicine Viron® tablet to the oral directly acting antiviral therapy of those patients can benefit in decreasing the viral load and offer better clinical manifestations and quality of life [43].

## Conclusion

The ultimate goal of this article is to highlight the role of crude herbal drugs in helping HCV patients, which extends from aiding in liver regeneration after elimination of the virus, to reducing some of the cost burden on those patients and offering a concomitant relief of their main medication side effect, which is headache. This can draw our attention to the possibility of formulating a herbal medication with a mixture of those magnificent crude drugs to help HCV patients satisfaction and relief. Yet, further clinical studies should be performed for the efficacy of such formulations.

The author(s) declare(s) that they have no conflicts of interest to disclose.

## Funding

This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## References

1. Cha A, Budovich A (2014) Sofosbuvir: a new oral once-daily agent for the treatment of hepatitis C virus infection. *PT* 39: 345-352.
2. Authors Chevaliez S, Pawlotsky JM (2013) HCV Genome and Life Cycle. *HCV Genome and Life Cycle*.
3. Bhatia HK, Singh H, Grewal N, Natt NK (2014) Sofosbuvir: A novel treatment option for chronic hepatitis C infection. *J Pharmacol Pharmacother* 5: 278-284.
4. Barakat EM, El Wakeel LM, Hagag RS (2013) Effects of *Nigella sativa* on outcome of hepatitis C in Egypt. *World J Gastroenterol* 19: 2529-2536.
5. Taub R (2004) Liver regeneration: from myth to mechanism. *Nat Rev Mol Cell Biol* 5: 836-847.
6. Fujiyoshi M, Ozaki M (2011) Molecular mechanisms of liver regeneration and protection for treatment of liver dysfunction and diseases. *J Hepatobiliary Pancreat Sci* 18: 13-22.
7. Singab AN, Ayoub NA, Ali EN, Mostafa NM (2010) Antioxidant and hepatoprotective activities of Egyptian moraceous plants against carbon tetrachloride-induced oxidative stress and liver damage in rats. *Pharm Biol* 48: 1255-1264.
8. Mostafa NM, Eldahshan OA, Singab AB (2014) The genus *Jacaranda* (Bignoniaceae): an updated review. *Pharmacognosy Communications* 4: 31-39.
9. Mostafa NM, Eldahshan OA, Singab AB (2013) *Pyrostegia venusta* (Ker Gawl.) Miers: a botanical, pharmacological and phytochemical review. *Medicinal Aromatic Plants*. 2: 123.
10. Mostafa NM, Eldahshan OA, Singab AB (2015) Chemical composition and antimicrobial activity of flower essential oil of *Jacaranda acutifolia* Humb. and Bonpl. against food-borne pathogens. *European Journal of Medicinal Plants* 6: 62-69.
11. Singab AB, Mostafa NM, Eldahshan OA, Ashour ML, Wink M (2014) Profile of volatile components of hydrodistilled and extracted leaves of *Jacaranda acutifolia* and their antimicrobial activity against foodborne pathogens. *Natural Product Communications* 9: 1007-1010.
12. Ayoub N, Singab AN, Mostafa N, Schultze W (2010) Volatile constituents of leaves of *Ficus carica* Linn. grown in Egypt. *Journal of Essential Oil Bearing Plants* 13: 316-321.
13. Mostafa NM, Ashour ML, Eldahshan OA, Singab AN (2015) Cytotoxic activity and molecular docking of a novel biflavonoid isolated from *Jacaranda acutifolia* (Bignoniaceae). *Natural Product Research* 23: 1-8.
14. Singab AN, Mostafa NM (2016) Molecular Pharmacognosy: A Promising and Prospective Scope in the Field. *Medicinal Aromatic Plants* 5: e172.

15. Madrigal-Santillán E, Madrigal-Bujaidar E, Álvarez-González I, Sumaya-Martínez MT, Gutiérrez-Salinas J, et al. (2014) Review of natural products with hepatoprotective effects. *World Journal of Gastroenterology* 20: 14787–14804.
16. Kashaw V, Nema AK, Agarwal A (2011) Hepatoprotective prospective of herbal drugs and their vesicular carriers—A review. *International Journal of Research in Pharmaceutical and Biomedical Sciences* 2: 360-374.
17. Li JY, Cao HY, Liu P, Cheng GH, Sun MY (2014) Glycyrrhizic acid in the treatment of liver diseases: literature review. *Biomed Res Int* 2014: 872139.
18. Jeong HG, You HJ, Park SJ, Moon AR, Chung YC, Kang SK, Chun HK (2002) Hepatoprotective effects of 18-glycyrrhetic acid on carbon tetrachloride induced liver injury inhibition of cytochrome P450 2E1 expression. *Pharmacological Research* 46: 221-227.
19. Magliulo E, Gagliardi B, Fiori GP (1978) Results of a double blind study on the effect of silymarin in the treatment of acute viral hepatitis, carried out at two medical centres (author's transl). *Med Klin* 73: 1060-1065.
20. Crocenzi FA, Roma MG (2006) Silymarin as a new hepatoprotective agent in experimental cholestasis: new possibilities for an ancient medication. *Curr Med Chem* 13: 1055-1074.
21. Aksu Ö, Altinterim B (2013) Hepatoprotective effects of artichoke (*Cynara scolymus*). *Bilim ve Genclik Dergisi* 1.
22. Behara RY (2011) Pharmacological studies on artichoke leaf extract - An edible herb of Mediterranean origin. *Journal of Pharmaceutical and Biomedical Sciences*, p: 11.
23. Singh A, Malhotra S, Subban R (2008) Dandelion (*Taraxacum officinale*) Hepatoprotective Herb with Therapeutic Potential. *Pharmacognosy reviews* 2: 163-167.
24. Sadeghi H, Nikbakht M, Ghaitasi I, Sabzali S (2008) Hepatoprotective effect of *Cichorium intybus* on CCl<sub>4</sub>- induced liver damage in rats. *African Journal of Biochemistry Research* 2: 141-144.
25. Tabassum N, Chattervedi S, Aggrawal SS, Ahmed N (2005) Hepatoprotective studies on *Phyllanthus niruri* on Paracetamol Induced Liver cell Damage in Albino Mice. *Experimental Medicine* 12: 211-212.
26. Kiso Y, Suzuki Y, Watanabe N, Oshima Y, Hikino H (1983) Antihepatotoxic principles of *Curcuma longa* rhizomes. *Planta Med* 49: 185-187.
27. Shenoy KA, Somayaji SN, Bairy KL (2001) Hepatoprotective effects of *Ginkgo biloba* against carbon tetrachloride induced hepatic injury in rats. *Indian Journal of Pharmacology* 33: 260-266.
28. Yacout GA, Elguindy NM, El Azab EF (2007) Amelioratic Effect of *Zingiber officinale* on Experimentally Induced Liver Fibrosis in Rats. *Journal of Medical Research Institute* 28: 154-159.
29. Cao J, Xu Y, Chen J, Klaunig JE (1996) Chemopreventive effects of green and black tea on pulmonary and hepatic carcinogenesis. *Fundam Appl Toxicol* 29: 244-250.
30. Sengottuvelu S, Duraisami S, Nandhakumar J, Duraisami R, Vasudevan M (2008) Hepatoprotective activity of *Camellia sinensis* and its possible mechanism of action. *Iranian Journal of Pharmacology & Therapeutics*, 7: 9-14.
31. Shrivastava R, Pechadre JC, John GW (2006) *Tanacetum parthenium* and *Salix alba* (Mig-RL) combination in migraine prophylaxis: a prospective, open-label study. *Clin Drug Investig* 26: 287-296.
32. Sinclair S (1999) Migraine headaches: nutritional, botanical and other alternative approaches. *Altern Med Rev* 4: 86-95.
33. Sumner H, Salan U, Knight DW, Hoult JR (1992) Inhibition of 5-lipoxygenase and cyclo-oxygenase in leukocytes by feverfew. Involvement of sesquiterpene lactones and other components. *Biochem Pharmacol* 43: 2313-2320.
34. Verma SK, Singh J, Khamesra R, Bordia A (1993) Effect of ginger on platelet aggregation in man. *Indian J Med Res* 98: 240-242.
35. Dorso CR, Levin RI, Eldor A, Jaffe EA, Weksler BB (1980) Chinese food and platelets. *N Engl J Med* 303: 756-757.
36. Kiuchi F, Iwakami S, Shibuya M, Hanaoka F, Sankawa U (1992) Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. *Chem Pharm Bull (Tokyo)* 40: 387-391.
37. Lamant V, Mauco G, Braquet P, Chap H, Douste-Blazy L (1987) Inhibition of the metabolism of platelet activating factor (PAF-acether) by three specific antagonists from *Ginkgo biloba*. *Biochemical Pharmacology* 36: 2749-2752.
38. DeFeudis FV (1991) *Ginkgo biloba* extract (EGb761): Pharmacological activities and clinical applications. Paris: Elsevier 142.
39. Liu JP, Manheimer E, Tsutani K, Gluud C (2001) Medicinal herbs for hepatitis C virus infection. *Cochrane Database Syst Rev* : CD003183.
40. Kainuma M, Ogata N, Kogure T, Kohta K, Hattori N, et al. (2002) The efficacy of a herbal medicine (Mao-to) in combination with intravenous natural interferon-beta for patients with chronic hepatitis C, genotype 1b and high viral load: a pilot study. *Phytomedicine* 9: 365-372.
41. McCulloch M, Broffman M, Gao J, Colford JM Jr (2002) Chinese herbal medicine and interferon in the treatment of chronic hepatitis B: a meta-analysis of randomized, controlled trials. *Am J Public Health* 92: 1619-1628.
42. Motoo Y, Mouri H, Ohtsubo K, Yamaguchi Y, Watanabe H, et al. (2005) Herbal medicine *Ninjinjyoeito* ameliorates ribavirin-induced anemia in chronic hepatitis C: a randomized controlled trial. *World J Gastroenterol* 11: 4013-4017.
43. Shawkat H, Yakoot M, Shawkat T, Helmy S (2015) Efficacy and safety of a herbal mixture (*Viron®* tablets) in the treatment of patients with chronic hepatitis C virus infection: a prospective, randomized, open-label, proof-of-concept study. *Drug Des Devel Ther* 9: 799-804.