Hepatotoxicity: A Major Complication with Critical Treatment

Abstract

Hepatotoxicity in one of the major parameters need to be consider in drug therapy, behind the reason that drugs given either in single or in combination for a prolonged period causes liver damage. Most of drug withdraw from the market and pending for approval due to causing hepatotoxicity (Lefluconamide, Flutamide, Disulphiram, and Triglitazone) and may be chance to criticize the use based on this toxicity. Hepatoprotective agent opposes this effect while the agent who generates called hepatotoxins. There is no plant in this Universe which is non-medicinal and which cannot be made of use for many purposes and by many modes. This definition rightly suggests that in principle all plants have a potential medicinal value. Medicinal plants have been considered as important therapeutic aid for alleviating ailment of humankind. The present review is aimed at compiling data on promising Phytochemical from medicinal plants that have been tested in hepatotoxicity model using modern scientific system and mechanisms of free radicals toxicity with scavenger which revealed their toxicity belongs to synthetic or herbal product.

Keywords: Liver Diseases; Herbal Treatment; Free Radicals; CYP450

Abbreviations: SGOT/AST: Serum Glutamate Oxaloacetate Transaminase; SGPT/ALT: Serum Glutamate Pyruvate Transaminase; MDA: Malondialdehyde; NP-SH: Non-Protein Sulfhydryls; ROS: Reactive Oxygen Species; H$_2$O$_2$: Hydrogen Peroxide; HO•: Hydroxy Radical; RNS: Reactive Nitrogen Species; •NO: Nitric oxide; PBN: Alpha Phenyl t-Butyl Nitrone; CAR: Constitutive Androstane Receptor; RXR: Retinoid-X-Receptor; rGSTA1/A2: Glutathione S-Transferase A1/A2; PPAR: Peroxisome Proliferator-Activated Receptors; CPT 1: Carnitine Palmitoyl Transferase-1; FAO: Fatty Acid Oxidation

Introduction

The liver is most sensitive target of xenobiotic due to its working processes such as metabolism and detoxification. Liver toxicity is a leading cause of morbidity and mortality throughout the world and increases day by day. Nearly 20,000 deaths and 2,50,000 new cases observed each year [1,2]. Liver damage or failure is always associated with hepatocytes necrosis and elevated levels of biochemical parameters like serum glutamate oxaloacetate transaminase (SGOT/AST) and serum glutamate pyruvate transaminase (SGPT/ALT), triglycerides and malondialdehyde (MDA), non-protein Sulfhydryls (NP-SH), bilirubin and alkaline phosphatase [3,4]. The agents responsible for hepatic trouble may be parasitic and viral infections, autoimmune diseases, genetic predisposition and intoxication with various xenobiotics such as chlorinated solvents, alcohol, alphatoxin, drugs, herbal medicines, food toxins, peroxidized oils, fungal toxins, industrial pollutants and radioactive isotopes [5]. Most of the hepatotoxic chemicals damage liver cell mainly by including lipid peroxidation, DNA damage, depletion of Sulfhydryls, altered calcium homeostasis or mitochondrial permeability transition (MPT) [6,7] and other oxidative damages in liver. Most of drug withdraw from the market due to drug-induced liver injury (DILI) [8] or criticize the use of many drugs, including Isoniazid, Labetalol, Trovafloxacin, Tolcapone, and Felbamate [9].

Although tremendous scientific advancement in modern medicines, hepatic disease remains a global health problem, thus the search for new drugs is still ongoing. Hepato protective are a class of therapeutic agents that includes synthetic as well as natural product which offer protection to liver from damage or help in regeneration of hepatic cells. Plants are significant source of hepatoprotective drugs. It has been claimed that about 170 phyto constituents isolated from 110 plants belonging to 55 families with different genera do possess hepatoprotective activity which contain a variety of chemical constituents like phenols, coumarins, curcuminoids, lignans, essential oils and terpenoids. Clinical research has also shown that herbs have genuine utility in the treatment of liver diseases. Only a few hepato protectives are evaluated and documented used in local health traditions and pharmacological importance of these plants and their taxonomical relatives can lead to the development of invaluable plant drugs for many dreaded diseases [10]. The classical systems of medicine such as Ayurveda, Siddha, Unani and Tibetan use about 1,200 plants. Random screening of plants has not proved economically effective. The present review study give evidential explore mechanism of action of medicinal plants against experimentally animal models induced hepatotoxicity and give many links to develop the future trials.

Hepatoprotective

Hepatoprotective drugs are defined as the drugs which prevent liver diseases. The literature review reveals that a large number of drugs obtained from plant are endowed with hepatoprotective claims either directly or indirectly. Hepatoprotective effects of herbal formulations as well as allopathic are studied against various toxic chemicals like alcohol CCl$_4$, β-Galactosamine, Thioacetamide, Paracetamol, Nimusulide, Isoniazid, Rifampicin at different dose with variant time duration which may be in-vitro or in-vivo. Most of toxicity case included oxidative stress (ROS), hydrogen peroxide (H$_2$O$_2$), hydroxyl radical (HO•) and peroxo...
radicals of biomolecules, depletion of glutathione, low production of ATP and increases permeability of cell membrane. So detoxify of ROS required antioxidant, restoring cofactors and repairing altered biomolecules therapy [11-13]. In the absence of reliable liver protective drugs in allopathic medical practices, herbs play important role in the management of various liver diseases. These are divided in two categories.

**Synthetic hepatoprotective**

There are no specific allopathic medicines used as hepatoprotective, although different research works are going on some drug like, Ursodeoxycholic acid, S-Adenosyl-L-methionine. Ursodeoxycholic cause decreasing immunoglobulin production by B lymphocytes as well as interleukin-1 and interleukin-2 from T lymphocytes that produced beneficial effect on plasma membrane [14] and on mitochondrial oxidation [15], and recovery of liver prostaglandin level [16]. It also upward regulation of glucocorticoid receptor in hepatocytes [17]. Some authors believe that Penicillamine and polyphenol derivative act as metal chelator, neutralizing the pro-oxidant effect of iron, copper, lead and mercury while amphotergulin serving as anti-apoptotic action by activation of transcription-3 survival pathways, and by up-regulated Bd-xl expression. Silymarin, S-adenosyl-L-methionine, betulinic acid [33] that showing antioxidant activities (Table 1). The antioxidants enzymes(catalase, glutathione peroxidase), vitamins (A,C,E,K), flavonoids(isoflavones, quercetin, isocatechin), organic acids, saponins, glycosides, (ellagic acid, gallic acid, tannins), coumarins, lignans, essential oil, monoterpenes, carotenoids, minerals(zinc, chromium, copper, manganese, iodine, selenium), saponins, glycosides, flavonoids(isoflavones, quercetin, isocatechin), organic acids, enzymes(catalase, glutathione peroxidase), vitamins (A,C,E,K), lipids, alkaloids, xanthenes, curcuminoids, and terpenoids [5,22-25] that showing antioxidant activities (Table 1).

**Herbal hepatoprotective**

The medicinal plants and their derivatives with or without combination have been used as hepatoprotective from several decades, starting with the Ayurvedic treatment, and extending to the Chinese, European and other systems of traditional medicines. Herbal drugs are recently more popular because of them are in expensive, better cultural acceptability, better compatibility, with the human body and minimal side effects [20]. The 21st century has shifted towards therapeutic evaluation of herbal products in the trend of the modern concept of evidence based medicinal evaluation, standardization and randomized placebo controlled clinical trials to support clinical efficacy and revealed strengths of the traditional medicinal systems. It is interesting that India is known as "Botanical Garden of the world" due to larger production of medicinal plants, more than 93 plants are used in 40 patented and proprietary multi ingredient plant formulations [21] which include variety of chemical constituents like polyphenols (ellagic acid, gallic acid, tannins), coumarins, lignans, essential oil, monoterpenes, carotenoids, minerals(zinc, chromium, copper), manganese, iodine, selenium), saponins, glycosides, flavonoids(isoflavones, quercetin, isocatechin), organic acids, enzymes(catalase, glutathione peroxidase), vitamins (A,C,E,K), lipids, alkaloids, xanthenes, curcuminoids, and terpenoids [5,22-25] that showing antioxidant activities (Table 1). The antioxidants may cure different diseases by protecting the cells from damage caused by free radicals having highly reactive oxygen and nitrogen containing molecules [26-29].

**Table 1: Plants with Phyto constituents and their screening methods.**

| Chemical Classification | Botanical Name | Part Used | Screening Method | Phytoconstituent |
|-------------------------|----------------|----------|-----------------|-----------------|
| Phenols                 | Salacia reticulata | Plant     | COI, Paracetamol | Mangiferin [30] |
|                         | Rhodiolasachalinensis | Root    |                 | Salidrose [31]  |
|                         | Picrorra kurnoa     | Root     |                 | Picroside-1 [32]|
| Flavonoids              | Tecomella undulata  | Leaves   | COI, CO1         | Betulinic acid  |
|                         | Uncaria gambir      | Heart-wood|                 | Catchin         |
| Alkaloids               | Berberis vulgaris   | Leaves   | COI, CO1         | Berberine [34]  |
|                         | Pumaria indica      | Plant    | CO1, CO1         | Protepine [35]  |
|                         | Peumus boldus       | Plant    | CH100, Ibuprofen | Boldine [36]    |
|                         | Boerrhavia diffusa  | Plant    |                 | Punarnavine [37]|
| Xanthines               | Coffea Arabica      | Seed     | COI, D-galactosmine | Caffeine |
|                         | Swertia japonica    | Root     |                 | Tetrahydroxertswir-tilinol [38] |
| Monoterpenes            | Psoinea coryfolia   | Plant    | Tacrine         | (S)-bakuchiol [39] |
| Diterpens               | Andrographis paniculata | Whole-plant | Ethanol | Andrographolide [40] |
|                         | Acanthopanax koreanum | Root bark | D-galactosamine | Acanthoic acid [41] |
| Triterpens              | Glycryrrhiza glabra | Roots    | CO1, Acetaminophen | Glycyrrhizin [42] |
|                         | Protium heptaphyllum | Trunk    | CO1, Acetaminophen | β-Amyrin [43]   |
|                         | Tetrapanax papyriferum | Leaves |                  | Papyrogenin A [44] |
| Coumarins               | Solanum lyratum     | Plant    | CO1, D-galactosamine | Scoptoletin [45] |
|                         | Artemisae capillaris | Plant    |                 | Esculetin [46]  |
|                         | Smilax officinalis  | Roots    |                 | Hesmesidemine [47] |
| Essential oil           | Anethum graveolens  | Fruits   | Paracetamol     | α-phellandrene [48] |
|                         | Azadirachta indica  | Leaves   | Paracetamol     | azadirachtin-A [49] |
|                         | Cynara scolymus     | Plant    | Paracetamol     | Cynarin [50]    |
| Lignans                 | Silybum marianum    | seed     | Thio acetamide  | Silybin [51]    |

**DOI:** 10.15406/mojt.2015.01.00016

**Citation:** Sharma MK, Sharma GN, Vishal V, Ranjan B (2015) Hepatotoxicity: A Major Complication with Critical Treatment. MOJ Toxicol 1(3): 00016.
Mechanism of hepatoprotective

The hepatoprotective herbal drugs act through various mechanisms to protect against various deleterious effects. By involving through one or more mechanisms, they act on the hepatocyte liver directly or indirectly and help in proper functioning the mechanism involved elevated antioxidant level/ minimise generation of free radicals by Reactive Oxygen Species (ROS) as well as reactive nitrogen species (RNS), downward regulation of cytochrome 450, immuno modulative and phagocytic, preventing lipid peroxidation and enhance the level of natural antioxidant endowed body.

Source and control of ROS and RNS level: The production of oxygen based radicals is the Bane to all aerobic species. ROS and RNS generated during cellular redox process by endogenous or exogenous sources. Endogenous system included mitochondrial electron transport of aerobic respiration or by oxido reductase enzymes and metal catalyzed oxidation immune cell activation, inflammation, energy production, mental stress, excessive exercise, ischemia, infection, by vascular endothelium to neutralise nitric oxide [65,66], regulate cell growth and differentiation, the respiratory burst, cancer, aging while exogenous result from air and water pollution, cigarette smoke, alcohol, heavy or other metal containing proteins, vitamin A, NADPH and urate [71-75] which came from diet or not. Other metal catalyzed oxidation immune cell activation, inflammation, energy production, mental stress, excessive exercise, ischemia, infection, by vascular endothelium to neutralise nitric oxide [65,66], regulate cell growth and differentiation, the respiratory burst, cancer, aging while exogenous result from air and water pollution, cigarette smoke, alcohol, heavy or other metal containing proteins, vitamin A, NADPH and urate [71-75] which came from diet or not. One of the bioactive compounds of extracellular free radicals (such as nitric oxide, superoxide, hydrogen peroxide) can react with enzymes and other macromolecules and damage the cell. This damage can be prevented by the natural antioxidants present in the body. The natural antioxidants include vitamin C, vitamin E, selenium, coenzyme Q10, and others. These antioxidants can neutralize the free radicals and prevent them from damaging the cell.
Melatonin (N-acetyl-5-methoxytryptamine) is also a powerful endogenous antioxidant, having significance roles in regulation of circadian rhythms, sleep, immune system activity and elimination of oxygen free radicals [76,77] and worked through G protein dependent receptors which lead to the induction of anti oxidant enzyme synthesis [78]. In this way, melatonin neutralizes the effects of both oxygen and nitrogen-based reactive molecules [79]. Melatonin induces the activity of glutamyl cysteine synthetase, thereby stimulating the production of another intracellular antioxidant, glutathione [80].

**Inhibition of cytochrome P450:** Cytochrome P450, a super family of heme-proteins metabolizes and activates many toxicologically important substrates, including ethanol, carbon tetrachloride, acetaminophen, and N-nitroso dimethyl amine, to more toxic products [81-84] and metabolic clearance of numerous xenobiotics in the liver. They also play a critical role in the production of cholesterol, steroids, prostacyclins and thromboxane A₂. There are more than 50 CYP450 enzymes identified in humans, metabolize >90% of the clinically most important drugs [85,86]. For example, the CYP3A enzymes metabolize over 40% of the drugs currently approved by the United States Food and Drug Administration. Impairment of cytochrome P450 activity, which may be either genetic or environmental (inducer or inhibitor), may lead to toxicity caused by the parent compound itself. Various enzyme affected CYP450 family by up and down regulation such as- Barbiturates and chemicals that induce CYP2B initially interact with the constitutive androstane receptor (CAR) that translocate to the nucleus and dimerizes with the retinoid-X-receptor (RXR) and glutathione S-transferase A1/A2 (rGSTA1/A2). The dimer then binds to specific response elements, resulting in transcriptional activation of genes regulating P450 expression [87]. Other hand Peroxisome proliferator-activated receptors (PPAR) are members of the steroid hormone receptor super family [88] ankszcv1, and PPAR-α is associated with pleotropic responses induce PPAR activity, resulting in liver enlargement by stimulating the proliferation of hepatocyte peroxisomes and inducing the fatty acid oxidation enzyme CYP4A [89].

**Inhibition of mitochondrial fatty acid β-oxidation:** Recent studies show that tamoxifen, amiodipine and Valproicacid (VPA, or diproplactacid acid) is an analogue of medium chain fatty acid which freely enters the mitochondrion and generates a coenzyme A ester [90,91] within the mitochondrial matrix. This VPA-CoA derivative can inhibit carnitine palmitoyltransferase-1 (CPT 1), an enzyme catalysing the rate limiting step of the mitochondrial entry and b-oxidation of long-chain fatty acids [92]. Furthermore, the generation of the VPA-CoA ester reduces mitochondrial levels of CoA, which is a cofactor mandatory for fatty acid oxidation (FAO). A second mechanism which could play a major role in VPA-induced inhibition of FAO is the cytochrome P450 (CYP)-mediated generation of D4-VPA [93,94]. Indeed this metabolite also enters the mitochondrion to generate D2, 4-VPA-CoA, a reactive metabolite able to covalently bind to (and thus inactivate) FAO enzymes but above hypotheses are controversial.

**Regulation of Interleukin 6 pathway:** IL-6, pro-mitogenic and anti-apoptotic in nature for hepatocytes having both to delay and accelerate liver regeneration by down regulate Jak/STAT activation, e.g., transforming growth factor, granulocyte/macrophage colony-stimulating factor (GM-CSF), and angiotensin II [95-97]. When IL-6 binds to its soluble receptor, sIL-6r, which binds to the gp130 receptor, resulting in the activation of Janus Kinase (JAK). This leads to activation of the MAPK pathway and activation of Stat3 by tyrosine (Y) phosphorylation. Homo dimerized Stat3 [98] is able to translocate into the nucleus and activate gene transcription. In the liver, this process promotes liver regeneration [99], the acute-phase response and hepato protection against Fas and toxic damage [100-102,97].

**Conclusion**

Several medicinal plants are now prevalent for the treatment of various liver diseases. Most of them are potential heptogenic/heptoprotective against hepatotoxicity. They are considering as high safety margin, efficacy and cost effectiveness. Although different herbal drugs are used from long times ago but no precise their mechanism of action. While Considering the enormous...
biodiversity resources of India and coordinated research involving biomedical scientists, nutritionist, scholars working the field of pharmacology, therapists.

Pharmacognosy and other health professionals provided a big chance to develop evidence based alternative medicine to cure different kinds of liver diseases, included various pathways and molecules with their action. Research on free radicals and antioxidants involving these is one such effort in the right direction. This may be beneficial in the era of hepatoprotective.

References
1. Sharma B, Sharma UK (2010) Hepatoprotective activity of some indigenous plants. Int J Pharm Techn Res 2: 568-572.
2. Meganathan M, Madhana Gopal K, Saikala P, Mohan J, Gowdhaman N, et al. (2011) Evaluation of antioxidant effect of Omega 3-fatty acid against paracetamol induced liver injury in albino rats. Global J Pharmacol 5(1): 50-53.
3. Mossa JS, Tarig M, Mohsin A (1991) Am J Chin Med 19: 223.
4. Mascolo N, Sharma R, Jain SC, Capasso F (1998) J Ethnopharmacol 22: 211.
5. Evans WC (2002) An overview of drugs with antihepatotoxic and oral hypoglycyaemic activities. In: Evans WC (Ed.), Trease and Evans pharmacognosy. Scotland, pp. 414-420.
6. Bhavari K, Gopala Reddy A, Rao GS, Ravikumar P, Rajasekhar Reddy A, et al. (2010) Reversal of cadmium induced oxidative stress and its bioaccumulation by culinary herbs Murraya koenigii and Allium sativum. Research Journal of Pharmacology 4(3): 60-65.
7. Habeebusu S, Liu J, Klaassen CD (1998) Cadmium induced apoptosis in mouse liver. Toxicol Appl Pharmacol 149(2): 203-209.
8. Russmann S, Gerd A, Grattaglioni (2009) Current Concepts of Mechanisms in Drug-Induced Hepatotoxicity. Current Medical Chemistry 16(23): 3041-3053.
9. Temple R (2001) Hepatotoxicity through the Years: Impact on the FDA. Food & Drug Administration.
10. Trease GE, Evans WC (1983) Pharmacognosy. Balliere Tindall Press, London, pp. 56-57.
11. Sies H (1986) Biochemistry of oxidative stress. Angewandte chemie-international ed 25: 1058-1071.
12. Fernandez V, Videla LA (1996) Biochemical aspects of cellular antioxidant systems. Biological Research 29(2): 177-182.
13. Droege W (2002) Free radicals in the physiological control of cell function. Physiological Reviews 82(1): 47-95.
14. Oliva L, Beaufe F, Choquart D, Montet AM, Gautou M, et al. (1998) Ursodeoxycholic acid alleviates alcoholic fatty liver damage in rats. Alcohol Clin Exp Res 22(7): 1538-1543.
15. El-Sherbiny G, Taye A, Abdel-Rahmeem I (2009) Role of ursodeoxycholic acid in prevention of hepatotoxicity caused by amoxicillin-clavulanic acid in rats. Annals of Hepatology 8(2): 134-140.
16. Lukowitzka O, Maskевич A, Budo V (2001) Effect of ursodeoxycholic acid on prostaglandin metabolism and microsomal membranes in alcoholic fatty liver. Alcohol 25(2): 99-105.
17. Kotb MA (2012) Molecular mechanisms of ursodeoxycholic acid toxicity & side effects: ursodeoxycholic acid freezes regeneration & induces hibernation mode. International Journal of Molecular Sciences 13(7): 8882-8914.
18. Budo V, Sadovnichy V (1996) Cytchrome P-450 and free radical gene-nation in rat liver microsomes under the influence of prostaglandin E1. Biochem Mol Biol Inter 39(6): 1177-1184.
19. Budo V, Artsukhevich A, Mal'tsev A, Nikitin V, Ignatenko K, et al. (1994) Effect of polyunsaturated phosphatidylcholine on lipid structure and cAMP-dependent signal transduction in the liver of rats chronically intoxicated with ethanol. Exp Toxic Pathol 46(4-5): 375-382.
20. Rathee JS, Patro BS, Mula S, Gamre S, Chattopadhyay S (2006) Antioxidant activity of Piper betel leaf extract and its constituents. Journal of Agricultural and Food Chemistry 54(24): 9046-9054.
21. Handa SS, Sharma A, Chakraborti KK (1986) Natural products and plants as liver protecting drugs. Fitoterapia 57: 307-351.
22. Laper S (1998) A review of plants used in the treatment of liver disease part I. Altern Med Rev 3(6): 410-421.
23. Seef LB, Lindsay KL, Bacon B, Kresina TE, Hoofnagle JH (2002) Complementary and alternative medicine in chronic liver disease. Hepatology 34(3): 595-603.
24. Thyagarajan S, Jayaram S, Gopalakrishnan V, Hari R, Jeyakumar P, et al. (2002) Herbal medicines for liver diseases in India. J Gastroenterol Hepatol 17 Suppl 3: S370-S376.
25. Latha PG, Suja SR, Shyamal S, Rajasekar H (2005) Some hepatoprotective garden plants. Natural Product Radiance 4(4): 278-279.
26. Prajapati ND, Purohit SS, Sharma AK, Kumar T (2003) A Handbook of medicinal plants. Agrobios, India.
27. Gupta VK, Sharma SK (2006) Plants as natural antioxidants. Nat Prod Rad 5(4): 326-334.
28. Kaur C, Kapoor HC (2002) Antioxidants activity and total phenolic content of some Asian vegetables. Int J Food Sci Tech 37: 153-161.
29. Roy G, Hussan SA (2002) Oxidant, Antioxidant and carcinogenesis. Indian J Exp Biol 40(11): 1213-1232.
30. Das J, Ghosh J, Roy A, Sil PC (2012) Mangiferin in exerts hepatoprotective activity against D-galactosamine induced acute toxicity and oxidative/ nitrosative stress via Nrf2-NF-kB pathways. Toxicol Appl Pharmacol 260(1): 45-47.
31. Senthil Kumar R, Chandran R, Parmelazhagan P (2014) Hepatoprotective effect of Rhodola imbricata rhizome against paracetamol-induced liver toxicity in rats. Saudi Journal of Biological Sciences 21(5): 409-416.
32. Basu K, Dasgupta B, Bhattacharya SK, Debnath PK (1971) Chemistry and pharmacology of apocynum, isolated from Picrorrhiza kurroa Royle ex Benth. Current Science 40(22): 603-604.
33. Jain M, Kapadia R, Jadeja RN, Thounaojam MC, Devkar RW, et al. (2012) Hepatoprotective potential of Tecomella undulata stem bark is partially due to the presence of betulinic acid. Journal of Ethnopharmacology 143(1): 194-200.
34. Imanshahidi M, Hosseinizadeh H (2008) Pharmacological and therapeutic effects of Berberis vulgaris and its active constituent, berberine. Phytother Res 22(8): 999-1012.
35. Rath A, Srivastava AK, Shriwakar A, Singh AK, Mehrotra S (2008) Hepatoprotective potential of Fumaria indica Pugsley whole plant extracts fractions and an isolated alkaloid protopine. Phytomedicine 15(6-7): 470-477.
36. Lanbers MC, Joyce B, Souliman R, Fleurentin J, Sayag M, et al. (1991) Hepatoprotective and Anti-Inflammatory Effects of a Traditional Medicinal Plant of Chile, Peumus boldus. Planta Medica 57(2): 110-115.

Citation: Sharma MK, Sharma GN, Vishal V, Ranjan B (2015) Hepatotoxicity: A Major Complication with Critical Treatment. MOJ Toxicol 1(3): 00016. DOI: 10.15406/mojt.2015.01.00016
37. Chandan BK, Sharma AK, Anand KK (1991) Boerhaavia diffusa: A study of its hepatoprotective activity. Journal of Ethnopharmacology 31(3): 299-307.

38. Hase K, Li J, Basnet P, Xiong Q, Takamura S, et al. (1997) Hepatoprotective principles of Swertia japonica Makino on D-galactosamine/lipo polysaccharide-induced liver injury in mice. Chemical & pharmaceutical bulletin 45(11): 1823-1827.

39. Hyun C, Jun YJ, Song EK, Kang KH, Baek HY, et al. (2001) Baku chol: A hepatoprotective compound of Psoralea corylifolia on tacrine-induced cytoxity in Hep G2 cells. Planta Medica 67(8): 750-751.

40. Chandler R, Srivastava V, Tandon JS, Kapoor NK (1995) Antihypertensive activity of diterpenes of Andrographis paniculata (Kalmegh) against Plasmodium berghei induced hepatic damage in Mammotus natalensis. International Journal of Pharmacognosy 33(2): 135-138.

41. Park EJ, Zhao YZ, Young HK, Jung JL, Dong HS, et al. (2004) Acathoic acid from Acanthopanax koreanum protects against liver injury induced by tert-butyl hydroperoxide or carbon tetrachloride in vitro and in vivo. Planta Medica 70(4): 321-327.

42. Yamamura Y, Katoh H, Tanaka N, Aikawa T, Sawada Y, et al. (1997) The pharmacokinetics of glycyrrhetin and its restorative effect on hepatic function in patients with chronic hepatitis and in chronically carbon-tetrachloride-intoxicated rats. Biopharmaceutics & Drug Disposition 18(8): 717-772.

43. Oliveira FA, Chaves MH, Almeida FR, Lima RC JR, Silva RM, et al. (2005) Protective effect of alpha- and beta-aminor, a triterpene mixture from Protostimul lamelliforme (Aubl.) March, Trunk wood resin, against acetaminophen-induced liver injury in mice. Journal of Ethnopharmacology 98(1-2): 103-108.

44. Hikino H, Kiso Y, Amagaya S (1984) Antihepatotoxic actions of papyriogenins and papyriosides, triterpenoids of Tetrapanax papyrifera leaves. Journal of Ethnopharmacology 12(2): 231-235.

45. Kang SY, Sung SH, Park JH, Kim YC. (1998) Hepatoprotective activity of scopoletin, a constituent of Solanum lyratum. Archives of Pharmacal Research 21(6): 718-722.

46. Gilani AH, Janbaz KH, Shah BH. (1998) Esculetin prevents liver damage induced by Paracetamol and CCl4, Pharmacological Research 37(1): 31-35.

47. Murali A, Purnima A, Madhavan V. (2013) Antioxidant and hepatoprotective effects of the roots of Hemidesmus indicus. Asian Journal of Pharmaceutical Research and Education 3(1): 07-16.

48. Shanthasheela R, Chitra R, Vijayachitra M. (2007) Evaluation of Hepatoprotective Activity of combination of Anethum graveolens and Agave Americana on CCL4, Intoxicated Rats. Indian Drugs-Bombay 44(12): 950-952.

49. Baligar NS, Adalakatti RH, Ahmed M, Hiremath MB. (2014) Hepatoprotective activity of the neem-based constituent azadirachta-A in carbon tetrachloride intoxicated Wistar rats. Can J Physiol Pharmacol 92(4): 267-277.

50. Azdet T, Camarasar J, Launa JC. (1987) Hepatoprotective activity of polyphenolic compounds from Cynara scolymus against CCl4, toxicity in isolated rat hepatocytes. J Nat Prod 50(4): 612-617.

51. Hikino H, Kiso Y, Wagner, Fiebiq M (1984) Antihepatotoxic actions of Scopoletin, a constituent of Solanum lyratum. Archives of Pharmacal Research 12: 512.

52. Hikino H, Sugai T, Kanno C, Hashimoto I, Treasma S, et al. (1979) Liver protective Principle of Thuropsis dolabrata leaves. Planta Medica 36(2): 156-163.

53. Krittika R, Verma R. (2014) Ameliorative effects of phyllanthin on carbon tetrachloride-induced hepatic oxidative damage in mice. Asian Pacific Journal of Tropical Disease 4(1): S64-S70.

54. Huang ZS, Wang ZW, Liu MP, Zhong SQ, Li QM, et al. (1999) Protective effects of polydatin against CCl4-induced injury to primarily cultured rat hepatocytes. World Journal of Gastroenterology 5(1): 41-44.

55. Chen J, Zhang J, Zhuang Q, Zhang S, Lin X. (2007) Electrochemical study of bergenin on a poly-(2-pyridylazo)-resorcinol modified glassy carbon electrode and its determination in tablets and urine. Talanta 72(5): 1805-1810.

56. Rios JL, Recio MC, Giner RM, Manez S. (1996) An update review of saffron and its active constituents. Phytotherapy research 10: 189-193.

57. Anand KK, Singh B, Saxena AK, Chandan BK, Gupta VN, et al. (1997) Hepatoprotective activity of indigotine: A bioactivefraction from Indigofera tinctoria Linn. Phytotherapy Research 15(4): 286-288.

58. Rao KS, Mishra SH. (1998) Antihypertensive activity of monomethyl fumarate isolated from Fumaria indica. Journal of Ethnopharmacology 60(3): 207-213.

59. Singh B, Saxena AK, Chandan BK, Bhardwaj V, Gupta VN, et al. (2001) Hepatoprotective activity of bergenin against tert-butyl hydroperoxide-induced liver injury in mice. Journal of Ethnopharmacology 71(1): 19-28.

60. Hou YC, Janczuk A, Wang PG. (1999) Current trends in the development of bergenin on a poly(4-(2-pyridylazo)-resorcinol) modified glassy carbon electrode and its determination in tablets and urine. Talanta 51: 1805-1810.
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(1996) Resistance of lipo-protein(a) to lipid peroxidation induced by oxygenated free radicals produced by gamma radiolysis: a comparison with low-density lipoprotein. Biochem J 314: 277-284.

72. SE Stait, Leake DS (1996) The effects of ascorbate and dehydroascorbate on the oxidation of low-density lipoprotein. Biochem J 320(pt 2): 37-81.

73. Hall L, Williams K, Perry AC, Frayne J, Jury JA (1998) The majority of human glutathione peroxidase type 5 (GPX5) transcripts are incorrectly spliced: implications for the role of GPX5 in the male reproductive tract. Biochem J 333(pt 1): S9.

74. Patterson RA, Leake DS (1998) Human serum, cysteine and histidine inhibit the oxidation of low-density lipoprotein at acid pH. FEBS Lett 434(3): 317-321.

75. Stahl W, Jungheas A, de Boer B, Dromina ES, Brivida K, et al. (1998) Caredonetin protects multilamellar liposomes against oxidative damage: synergistic effects of lycopene and lutein. FEBS Lett 427(2): 305-308.

76. Allegra M, Reiter RJ, Tan DX, Gentile C, Tesoriere L, et al. (2003) The chemistry of melatonin's interaction with reactive species. J Pineal Res 34(1): 1-10.

77. Tan DX, Manchester LC, Reiter RJ, Plummer BE, Limson J, et al. (2000) Melatonin directly scavenges hydrogen peroxide: a potentially new metabolic pathway of melatonin biotransformation. Free Radical Biology and Medicine 29: 1177-1185.

78. Abdel-Wahab MH, Abdu-Allah AR (2001) Possible protective effect of melatonin and/or desferrioxamine against streptozotocin-induced hyperglycaemia in mice. Pharmacol Res 41(5): 533-537.

79. Sudakovich EJ, Maksimich YZ, Zabrodskaya SV, Kubshyll VN, Lapshina EA, et al. (2007) Melatonin attenuates metabolic disorders due to streptozotocin-induced diabetes in rats. European Journal of Pharmacology 563(1-3): 180-187.

80. Winiariska K, Kraczek T, Malinska D, Drozak J, Bryla J (2006) Melatonin attenuates diabetes-induced oxidative stress in rabbits. J Pineal Res 40(2): 168-176.

81. Guengerich FP, Kim DH, Iwasaki M (1991) Role of human cytochrome P450 BE1 in the oxidation of many low molecular weight cancer suspects. Chem Res Toxicol 4(2): 168-179.

82. Koop DR (1992) Oxidative and reductive metabolism by cytochrome P4502E1. FASEB J 6(2): 724-730.

83. Anzenbacher P, Anzenbacherova E (2001) Cytochromes P450 and metabolism of xenobiotics. Cell Mol Life Sci 58(5-6): 737-747.

84. Dahm LJ, Jones DP (1996) Mechanisms of chemically induced liver disease. Zakin D, Boyer TD (Eds.) Hepatology: a textbook of liver disease. 3rd edn., pp. 875-890.

85. Wilkinson GR (2005) Drug metabolism and variability among patients in drug response. N Engl J Med 352(2): 2211-2221.

86. Slaughter RL, Edwards DJ (1995) Recent advances: the cytochrome P450 enzymes. Ann Pharmacother 29(6): 619-624.

87. Liang Q, He JS, Falco AJ (1995) The role of Barbie box sequences as cis-acting elements involved in the barbiturate-mediated induction of cytochromes P450BM-1 and P450BM-3 in Bacillus megaterium. J Biol Chem 270(9): 4438-4450.

88. Peters JM, Cartley RC, Gonzalez FJ (1997) Role of PPAR alpha in the mechanism of action of the nongenotoxic carcinogen and peroxisome proliferator Carcinogenesis 18(11): 2029-2033.

89. Aoyama T, Peters JM, Iritani N, Nakajima T, Furihata K, et al. (1998) Altered constitutive expression of fatty acid-metabolizing enzymes in mice lacking the peroxisome proliferator-activated receptor alpha (PPAR alpha). J Biol Chem 273(10): 5678-5684.

90. Rettenmeier AW, Prickett KS, Gordon WP, Bjorge SM, Chang SL, et al. (1985) Studies on the biotransformation in the perfused rat liver of 2-npropyl-pentenoic acid, a metabolite of the antiepileptic drug valproic acid. Evidence for the formation of chemically reactive intermediates. Drug Metab Dispos 13(1): 81-96.

91. Silva MF, Ruijer JP, Illst L, Jakobs C, Duran M, et al. (2001) Differential effect of valproate and its Delta2- and Delta4-un saturated metabolites, on the beta-oxidation rate of long-chain and medium-chain fatty acids. Chem Biol Interact 137(3): 203-212.

92. Fromenty B, Pessayre D (1995) Inhibition of mitochondrial beta-oxidation as a mechanism of hepatotoxicity. Pharmacol Ther 67(1): 101-154.

93. Baldwin GS, Murphy VJ, Yang Z, Hashimoto T (1998) Binding of non steroidal anti inflammatory drugs to the a-subunit of the trifunctional protein of long chain fatty acid oxidation. J Pharmacol Exp Ther 286(2): 1110-1114.

94. Fromenty B, Freneaux E, Labbe G, Deschamps D, Larrey D, et al. (1989) Tianeptine, a new tricyclic antidepressant metabolized by beta-oxidation of its heptanoic side chain, inhibits the mitochondrial oxidation of medium length chain fatty acids in mice. Biochem Pharmacol 38(21): 3743-3751.

95. Sengupta TK, Schmitt EM, Ivaschik LB (1996) Inhibition of cytokines and Jak-STAT activation by distinct signaling pathways. Proc Natl Acad Sci USA 93(18): 9499-9504.

96. Bhat GJ, Abraham ST, Baker KM (1996) Angiotensin II interferes with interleukin-6-induced STAT3 signaling by a pathway involving mitogen-activated protein kinase kinase 1. J Biol Chem 271(37): 22447-22452.

97. Takeda K, Noguchi K, Shi W, Tanaka T, Matsumoto M, et al. (1997) Targeted disruption of the mouse Stat3 gene leads to early embryonic lethality. Proc Natl Acad Sci USA 94(8): 3801-3804.

98. Dittrich E, Renfrew-Haft C, Muyss L, Heimrich PC, Graeve L (1996) A di leucine motif and an upstream serine in the interleukin-6 (IL-6) signal transducergp130 mediate ligand-induced endocytosis and down-regulation of the IL-6 receptor. J Biol Chem 271(10): 5487-5494.

99. Levy DE, Lee CK (2002) What does Stat3 do? J Clin Invest 109(9): 1143-1146.

100. Hirano T, Ishihara K, Hibi M (2000) Roles of STAT3 in mediating the cell growth, differentiation and survival signals relayed through the IL-6 family of cytokine receptors. Oncogene 19(21): 2540-2556.

101. Bowman T, Garcia R, Turkson J, Jove R (2000) STATs in oncogenesis. Oncogene 19(21): 2474-2488.

102. Li W, Liang X, Kellendonk C, Poli V, Taub R (2002) STAT3 contributes to the mitogenic response of hepatocytes during liver regeneration. J Biol Chem 277(32): 28411-28417.

Citation: Sharma MK, Sharma GN, Vishal V, Ranjan B (2015) Hepatotoxicity: A Major Complication with Critical Treatment. MOJ Toxicol 1(3): 00016. DOI: 10.15406/mojt.2015.01.00016.