ISSN: 2231-6078

INTERNATIONAL JOURNAL OF DRUG DISCOVERY AND HERBAL RESEARCH (IJDDHR)
1(2): April-June: (2011), 65-73

Review Article

Ethnobotany and literature survey of hepatoprotective herbal drugs

Nikita Rajlaxmi Rana, Pushpendra Goswami and Shilpa Subhedar

1, Swami Vivekanand College of Pharmacy, Indore, M.P., India
2, Central India Institute of Pharmacy, Indore, M.P., India

Abstract

Hepatic disease (Liver disease) is a term for a collection of conditions, diseases, and infections that affect the cells, tissues structures, or functions of the liver. Liver has a wide range of functions, including detoxification, protein synthesis, and production of biochemical necessary for digestion and synthesis as well as breakdown of small and complex molecules, many of which are necessary for normal vital functions.

There are no specific allopathic medicines used as hepatoprotective, although different research works are going on some drug. Herbal drugs are more widely used than allopathic drugs as hepatoprotectives because they are inexpensive, have better cultural acceptability, better compatibility with the human body and minimal side effects. In the current review, it had been tried to redefine the use of important herbal hepatoprotective drugs like Tionospora Cordifolia, Terminalia Arjuna, Plumbago Zeylanica and Berberis Aristata that consist of specific chemical constituents who have their specific hepatoprotective activity against hepatotoxicant like ethanol, drugs, chemicals and others. These herbal drugs have shown the ability to maintain the normal functional statues of the liver with or without fewer side effects. These are the reasons why herbal hepatoprotectives are mostly preferred by medical practitioners, as well as over- the- counter.

Keywords: Hepatoprotectives, Ethanobotny, *Tionospora Cordifolia*, IL-6/Stat3 pathway.

Introduction

The liver is the first line of defense against damage by a variety of insults including viral hepatitis, poisons, xenobiotics and drugs. . Hepatic injury by these agents frequently results in both hepatic necrosis and apoptosis [1] It is well known that oxidative damage plays a prominent role in hepatic injury mediated by drugs and poison, whereas viral hepatitis and immune-mediated liver damage are believed to occur largely via activation of the Fas apoptotic death pathway. The link between Fas-mediated damage and the induction of reactive oxygen species (ROS) and oxidative damage has only recently been established [2–6] . Growth factors and cytokines, such as HGF and IL-6, promote hepatic survival by stimulating liver regeneration and providing hepatoprotection in a variety of liver-injury models, including Fas-mediated injury, toxic damage caused by hepatotoxins (such as CCL_4), and ischemic liver injury [1, 7–11]. These growth factors provide protection against chronic liver injury that ultimately leads to cirrhosis. Part of this protection is mediated by induction of anti apoptotic proteins that regulate the caspase cascade. A new study demonstrates that IL-6/ Stat 3 pathway provide hepatoprotection against Fas- mediated apoptotic liver damage.

***Corresponding Author**

E.mail: goswami.pushpendra@yahoo.in
Mob.: +919977406640

Mechanism Of Action Of Hepatoprotective Drugs :

Hepatoprotection Via The Il-6/Stat3 Pathway

Stat3 is a vital transcription factor that is activated downstream of the gp{glycoprotein}130 receptor, primarily via IL-6 signaling in adult liver. A new study demonstrates that Stat3 provides hepatoprotection against Fas-mediated apoptotic liver damage by two mechanisms: direct inactivation of caspases and reduction of reactive oxygen species.Acute liver failure is caused by a variety of insults, including viral hepatitis, toxic liver damage by poisons or drugs, and ischemia. The liver is the main site of detoxification against of ingested agents, including xenobiotics and drugs. Hepatic injury by these agents frequently results in both hepatic necrosis and apoptosis. In this issue of the JCI, Haga and colleagues demonstrate that signal transducer and activator of transcription-3 (Stat3), a key signaling molecule in pathways regulated by IL-6 and related cytokines, blocks apoptotic injury in two ways: induction of anticaspase{a.apoptotic} regulators; and reduction of oxidative injury via upregulation of an antioxidant protein, Ref-1{neucleus +} [12]. These findings provide new insights into common mechanisms of hepatoprotection in both Fas-mediated and toxin-mediated acute liver injury and allow predictions about potential therapeutic interventions that could prove beneficial in a variety of liver insults.

Signal Transducers And Activation Of Transcription::: Stat3

The IL-6 signal transduction pathway in liver injury and regeneration

IL-6 is a critical proregenerative factor and acute-phase inducer in the liver that also confers resistance to liver injury by hepatic toxins, ischemia, and Fas (Figure 1). Its effects are mediated almost exclusively on hepatocytes within the liver. Although the source of IL-6 within the liver has not been unequivocally established, studies with bone marrow transplantation provide evidence that hepatic Kupffer cells (liver macrophages) are responsible for production of IL-6 in response to liposaccharide or TNF [13]. Secreted IL-6 acts on neighboring hepatocytes in a paracrine fashion to stimulate liver regeneration and repair. IL-6 bound to the soluble IL-6 receptor signals via gp130 and Janus kinase-1 (JAK-1), leading to activation of the Stat3 transcription factor and the MAPK signal transduction cascade. IL-$6^{-/-}$ livers induce little Stat3 in response to IL-6 activation during liver regeneration after partial hepatectomy, hepatic injury, or acute-phase induction, suggesting that Stat3 may mediate many of the effects of IL-6 [1, 7–10]. Conditional Stat3 knockout mice have been used to show that Stat3 is an important component of the IL-6 response during liver regeneration and the acute-phase response, but Stat3 does not account for all of the effects of IL-6, particularly those that are mediated by MAPK{mitogen activated prot. Kinase} activation [14]. Up to 40% of the immediate-early genes induced during liver regeneration are regulated at least in part by IL-6, and a significant subset of these are also regulated by Stat3.

Figure 1
Model for IL-6/Stat3 signaling pathway. 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. Dimerized Stat3 is able to translocate into the nucleus and activate gene transcription. In the liver, this process promotes liver regeneration, the acute-phase response, and hepatoprotection against Fas and toxic damage. P, phosphate.

Anti Apoptotic Effects Of Il-6/Stat3 Pathway

Modulation of Stat3 levels in liver cells points to its critical role in hepatocyte survival

Stat3 is a vital, ubiquitously expressed protein that is activated by a number of ligands in addition to IL-6 [15, 16] It has important roles in mitogenesis and antiapoptosis. Stat3 has been shown to be involved in the transcriptional upregulation of many genes, not only acting by direct DNA binding, but acting in some cases as a coactivator of transcription factors such as activator protein-1 and hepatocyte nuclear factor-1 [17]. Stat3 knockout results in early embryonic lethality, but conditional knockouts provide useful tools to examine the actions of Stat3 in specific tissues. In the study by Haga et al. [12], two animal models were used to examine the effects of Stat3 modulation in Fas-mediated liver injury: mice injected with adenoviruses expressing constitutively active Stat3 and other proteins; and mice with hepatocyte-specific Stat3gene deletions. Adenoviruses injected intravenously normally home to the liver, infecting more than 80% of hepatocytes and allowing for expression of encoded proteins. Haga et al. demonstrate that constitutively active Stat3 provided protection against Fas-mediated liver injury, and that Stat3 deficiency led to Fas sensitivity. The antiapoptotic proteins FLIP, Bcl-2, and Bcl-XL, which block caspase activation, are elevated in IL-6–treated livers [9]. Haga and colleagues report here that these proteins were also elevated in Stat3-overexpressing livers, providing evidence that Stat3 mediates the major antiapoptotic effects of IL-6 (Figure 2). Whereas IL-6–mediated elevation of antiapoptotic proteins is largely posttranscriptional [9], mRNA for these proteins was elevated in the Stat3-overexpressing livers [12]. This difference could be due to the massive overexpression of Stat3 and the fact that adenovirus infection confers a degree of transcriptional induction not seen in normal mice.

Figure 2
Proposed model for the actions of IL-6 and Stat3 that result in hepatoprotection against Fas activation. Interaction of FasL with its receptor activates the caspase cascade that is blocked by IL-6 and Stat3 through the upregulation of FLIP, Bcl-2, and Bcl-XL. Fas activation also generates an oxidative stimulus that is blocked by the upregulation of Ref-1. FADD, Fas-associated death domain; Rac1, RAS-related C3 botulinum toxin substrate 1; Apaf1, apoptotic protease activating factor; Bax, Bcl2-associated X protein; Bid, BH3-interacting domain death agonist.

This mechanistic evaluation was taken to another level by the demonstration that not only anticaspase agents, but also the antioxidant N-acetyl cysteine, were able to provide some protection against the effect of Stat3 deficiency on Fas-mediated apoptosis [12]. Having identified ROS as a component of Fas-mediated liver injury, Haga et al. identified an endogenous antioxidant, Ref-1, as a target of Stat3. Expression of Ref-1 provided hepatoprotection, strongly suggesting that Ref-1 is a critical component of Stat3-mediated hepatoprotection. Ref-1, a dual-function protein upregulated by increases in ROS, is an endonuclease in the base excision repair pathway and a reducing agent that facilitates the DNA-binding properties of redox-sensitive transcription factors [18–21] Ref-1 is able to supgress ROS generation and hepatic apoptosis (Figure 2).

Hepatoprotection by redox-dependent and -independent mechanisms

These findings provide important insights into the hepatoprotective properties of IL-6 and its major anti-injury mediator Stat3 [12]. Though not yet shown, it is expected that IL-6 induces Ref-1, as IL-6 is the major regulator of Stat3 activation in Fas- and toxin-mediated liver injury. Stat3 has not yet been shown to be hepatoprotective in toxic liver damage, but based on these findings, Stat3 is predicted to be hepatoprotective in liver injury. Toxin-mediated liver injury occurs largely through the generation of ROS and direct mitochondrial damage, leading to hepatic necrosis with a lesser degree of apoptosis [1]. The level of oxidants may be so high that glutathione is depleted, thereby precluding the activation of caspases, a glutathione-dependent process. By inducing both antioxidant Ref-1 and caspase inhibitors such as Bcl-2, FLIP, and Bcl-XL, IL-6, Stat3, and similar cytokines are hepatoprotective in a broad spectrum of liver injuries mediated by Fas and liver toxins [22]. Cytokines such as IL-6 also promote liver regeneration, another component of the hepatoprotective mechanism that restores liver mass after necrotic or apoptotic injury has occurred. The link between intracellular signals resulting in mitogenic and antiapoptotic effects of these agents remains to be completely dissected.

Footnotes

Nonstandard abbreviations used: reactive oxygen species (ROS); signal transducer and activator of transcription-3 (Stat3).

ETHNOBOTANY

TINOSPORA CORDIFOLIA

English name: Gulancha tinospora
Common name: Guduchi
Family: Menispermaceae
Part used: All parts

Traditional uses[1-5] :

Tinospora cordifolia is mentioned in various texts of ayurvedic system of medicine for treatment of various ailments like leprosy, fever, asthma, anorexia, jaundice, gout, diabetes, skin infections, diarrhea and dysentery. It is considered as a rejuvenator, bitter tonic, astringent, diuretic and aphrodisiac.

Phytochemistry[2]:

T.cordifolia contains number of chemical constituents belonging to the different groups, viz. terpenoids, alkaloids, lignans, and steroids. Leaves of *T.cordifolia* are rich in protein (11.2%) and are fairly rich in calcium and phosphorus[6,7]. Stem of

T.cordifolia has reported to contain alkaloids like berberine, palmatine, tembetarine and magnoflorine. *T.cordifolia* roots have reported to contain other alkaloids like choline, tinosporin, isocolumbin, palmatine, tetrahydropalmatine and mangnoflorine[8-13].

Pharmacology:

T.cordifolia has show to have immunomodulatory activities[14,15] in clinical studies. In hepatitis patients T.cordifolia has shown normalization of the liver function[16] and significant decrease in all symptoms of allergic rhinitis in rhinitis patients[17].Pre-clinical studies of *T.cordifolia* has shown various pharmacological activities like anti-cancer[18-20], anti-diabetic and hypoglycemic[21-25], anti-inflammatory[26], antioxidant[27], anti-stress[28], antiulcer[29], digestive[30], hypolipidaemic[31], immunobiological activity[32-35]. It has also reported to be effective in the treatment of liver disorders[36], mental disorders[37], urinary calculi[38] and uraemia[39]

Indication:

Immune health

TERMINALIA ARJUNA

English name: Arjuna
Common name: Arjun
Family: Combretaceae
Part used: Bark

Traditional uses [43,42]:

Pacifies Kapha and Pitta. The herb Arjuna is used in Ayurveda in various types of ailments, main formulations in Ayurveda are: Arjunarishta, Arjuna ghrita and Kumkumadi churan.

Phytochemistry[43,42]:

Tannins and flavonoids are responsible for its anticancer properties.

Its stem bark possesses glycosides, large quantities of flavonoids, tannins and minerals. Flavonoids have been detected to exert antioxidant[42], anti-inflammatory[43] and lipid lowering effects while glycosides are cardiotonic, thus making Terminalia arjuna unique amongst currently used medicinal plants.

Pharmacology[40,41,44,45]:

Its bark exerts significant inotropic and hypotensive effect, increase in coronary artery flow and protection of myocardium against ischemic damage. It has also been detected to have mild diuretic, antithrombotic, prostaglandin E2 enhancing and hypolipidaemic[44] activity. It has a beneficial effect in coronary artery disease alone and along with statin.

It has the potential to correct dyslipidemia[45], reduce left ventricular mass and increase left ventricular ejection fraction.

In alleviating the pain of angina pectoris

In treating heart failure and coronary artery disease.

Treating hypercholesterolemia[40]

The cardioprotective effects of terminalia are thought to be caused by the antioxidant nature of several of the constituent flavonoids and oligomeric proanthocyanidins, while positive inotropic effects may be caused by the saponin glycosides. In addition to its cardiac effects,

Protective against gastric ulcers, such as those caused by NSAIDs[41].

Indication[40-45]:

Adjuvent in Ischemic heart disease.

In hypertriglyceridemia.

Mild to moderate hypertension

Preventive medicine in indivisuals susceptible to Ischemic heart disease.

PLUMBAGO ZEYLANICA

English name: Plumbago and Leadwort
Common name: Chitrak
Family: Plumbaginaceae
Part used: Fruit

Traditional uses[46] :

Plumbago zeylanica (known as "Chitrak") is a useful Indian medicinal plant. The plant and its constituents are credited with potential therapeutic properties including anti-atherogenic, cardiotonic, hepatoprotective and neuroprotective properties

The ability of the sap to create lead-colored stains on skin and the plant was a cure for lead poisoning.

Phytochemistry[47]

It consists of naphthoquinone, plumbagin, chloro plumbagin, biplumbagin, chitranone, zeylinone, isozelynone, plumbagic acid etc

Pharmacology[47] :

It has various pharmacological uses like, antipyretic, apgetizer, antibacterial, uterotonic, antifungal, antifertility, anticancer, anticoagulant, antitumor, cytotoxic, and hepatoprotective[47]

Indication[48]:

Antioxident[49].

It is used as a stimulant adjunct to other preparations. In small doses it is stimulant of mucus membrane of digestive organs.

BERBERIS ARISTATA

English name: Indian Berberry
Common name: Daruhaldi, Darhald
Family: Berberidaceae
Part used: Root

Traditional uses:
The roots form a reputed drug in Ayurvedic medicine and possess cholagogue, stomachic, laxative, diaphoretic, antipyretic and antiseptic[50].

Phytochemistry:
The alkaloids in the bark and root of Berberis aristata are berberine, berbamine, aromoline, karachine, palmatine, oxyacanthine and oxyberberine[50].

Pharmacology:
It has antibacterial and anti-inflammatory activity on acute, subacute and chronic types of inflammations produced by immunological and non-immunological methods[51].
The drug is regarded as a bitter tonic and is apgarently used as a cholagogue, stomachic, laxative, diaphoretic, antipyretic and antiseptic. It is administered externally in painful eye affections, indolent ulcers and hemorrhoids. The root is very useful in periodic neuralgia and menorrhagia.

Indication:
Antibacterial and Anti-inflammatory[52]

LITERATURE SURVEY:

A] Tinospora Cordifolia:

Common survey for all parts:

1. P.K. Raveendran Nair et al, Immune stimulating properties of a novel polysaccharide from the medicinal plant: Tinospora cordifolia, International Immunopharmacology, Volume 4, Issue 13, 2004, Pg 1645-1659
2. J. K. Grover et al evaluated Anti-hyperglycemic effect of Tinospora cordifolia lyophilized powder of plant, Journal of Ethnopharmacology, Volume 73, Issue 3, 2000, Pg 461-470.
3. Sudhakarn, Immunostimulatory effect of Tinospora cordifolia Miers leaf extract, Indian Journal of Experimental Biology , 2006, Vol.44.

For particular part:root:

1. P. Stanely et al, Antioxidant activity of Tinospora cordifolia roots, Journal of Ethnopharmacology, Volume 65, Issue 3, 1999, Pg 277-281
2. P. Stanely et al, Hypoglycaemic and other related actions of Tinospora cordifolia roots, Journal of Ethnopharmacology, Volume 70, Issue 1, April 2000, Pages 9-15
3. D. N. K. Sarma et al evaluated "Antistress Activity of *Tinospora cordifolia* and *Centella asiatica* Extracts" Phytotherapy Research, 1996, Volume 10, Issue 2, pages 181–183
4. D. N. K. Sarma et al, Antiulcer Activity of *Tinospora cordifolia* Root, Phytotherapy Research, Volume 9, Issue 8, pg 589–590, 1995

For hepatoprotective activity:

1. B Bishayi et al, Hepatoprotective and immunomodulatory properties of Tinospora cordifolia, J. Toxicol. Sci., 2002, Vol. 27: No. 3, Pg 139-146
2. SS Singh et al, Indian journal of pharmacy 2003, 35: Pg 83-91
3. T. S. Panchabhai et al, Protective effect of Tinospora cordifolia, Phyllanthus emblica and their combination against antitubercular drugs induced hepatic damage: an experimental study, Phytotherapy Research, 2008, Volume 22, Issue 5, pg 646–650

B] Terminalia Arjuna

Common survey for all parts:

1. Minakshi Chaudhari et al, Evaluation of phytoconstituents of Terminalia arjuna For Wound Healing Activity In Rat, Phytotherapy Research, 2006, Volume 20, Issue 9, pg 799–805
2. Fayez E. Kandil, A tannin anti-cancer promotor from Terminalia arjuna, Phytochemistry, Volume 47, Issue 8, 1998, Pg 1567-1568

For particular part:*bark:-*

1. Hua-Yew Cheng et al,., Antiviral: bark of Terminalia arjuna Linn, Antiviral Research, 2002, Volume 55, Issue 3, Pg 447-455.
2. Antioxidant activity of phenolic components present in barks of Terminalia arjuna, Department of Chemistry, University of Agriculture, Faisalabad 38040, Pakistan And Department of Chemistry and Biochemistry, University of Lethbridge, Alberta, Canada, Food Chemistry, Volume 104, Issue 3, 2007, Pg 1106-1114
3. K. Kaur et al, , Antimutagenic activities of acetone and methanol fractions of Terminalia arjuna bark, Food and Chemical Toxicology, Volume 40, Issue 10, 2002, Pg 1475-1482.
4. A.K. Khanna et al, Terminalia arjuna *bark :* an Ayurvedic Cardiotonic, Regulates Lipid Metabolism in Hyperlipaemic Rats, Phytotherapy Research, 1996, Volume 10, Issue 8, pg 663–665
5. Ramesh Chander et al, evaluated Antidyslipidemic and antioxidant activities of stem bark,Biomedical And Life Sciences, Indian Journal Of Clinical Biochemistry, Volume 19, Number 2, pg: 141-148

For hepatoprotective activity:

1. Girish et al, Hepatoprotective activity of six polyherbal formulations in CCl_4-induced liver toxicity in mice, Research Journals, Indian Journal of Experimental Biology, Vol.47 (04), 2009
2. Prasenjit Manna et al, Aqueous Extract Of Terminalia Arjuna Prevents Carbon Tetrachloride Induced Hepatic And Renal Disorders, Research Article, BMC Complementary And Alternative Medicine *2006.*
3. Venkataranganna et al, evaluated hepatoprotective activity, Indian Veterinary Medical Journal (2001): (25), June, pg: 157-160.

C] Plumbago Zeylanica

Common survey for all parts:

1. Yue Dai et al, Inhibition of Immediate Allergic Reactions by Ethanol Extract, Biological & Pharmaceutical Bulletin, Vol. 27 2004 , No. 3 429
2. S. Satish et al Antibacterial activity Volume 28, Issue 2, pg 145–147, 1999
3. L. M. van der Vijver et al, Antibacterial Activity In Roots, Planta Med 1971; 20(3): 8-13
4. Yuan-Chuen Wang et al Anti-*Helicobacter pylori* activity FEMS Immunology & Medical Microbiology Volume 43, Issue 3, pg 407–412, 2005
5. O.O.Oyedapo et al, Bioactivity of the Root Extract 1996, Vol. 34, No. 5 , Pg365-369
6. Arina Z et al Effect on multidrug resistant bacteria of clinical origin, World Journal Of Microbiology And Pharmacology, Volume 16, Numbers 8-9, 841-844
7. George Varughese et al antiplasmodial activity Journal of Ethnopharmacology Volume 74, Issue 2 2001 Pg 195-204

8. Dr. J. A. Olagunju et al hyperglycaemia treated with ethanol root extract Phytotherapy Research1999 Volume 13, Issue 4, pg 346–348
9. C. P. Bopaiah et al, Central nervous system stimulatory action from the root extract Phytotherapy Research, 2001, Volume 15, Issue 2, pages 153–156
10. Tilak et al Antioxidant properties Redox Report, Volume 9, Number 4, 2004 , pg 219-227(9)

Survey for particular part:

1. I.Ahmad et al, Antimicrobial and phytochemical studies Journal of Ethnopharmacology, 2001,Vol 74, pg 113-123
2. S.gopinath et al, Simultaneous Estimation of Plumbagin and Embelin by Reverse Phase-High Performance Liquid Chromatographic method, 2009, (1) 1: 135-142

Survey for hepatoprotective activity:

1. Purkayastha et al, Biological activities of ethnomedicinal claims of some plant species of Assam, 2006 pg229-236
2. Ansar M. patel et al, formulation and evaluation of polyherbal formulation for their hepatoprotective activity, International journal of pharmatech research, Vol 2, No. 1, pg 305-309.
3. Rajesh kumar et al, hepatoprotective activity of aerial parts International Journal of Pharmacy And Pharmaceutical Science, 2009, Vol.1, supg.1.

D] Berberis Aristata:

Common survey for all parts:

1. Bhupesh Chander Semwal et al, Antidiabetic Activity Of Stem Bark, The Internet Journal of Pharmacology, 2008, Volume 6 Number 1.
2. Padmaja V. Josh et al, Antidiarrheal activity, Chemical And Toxicity Profile, 2010
3. Suresh Kumar Gupta et al, Anti-inflammatory Effects investigative Ophthalmology and Visual Science. 2008; 49:4036-4040, Reprint: All India Institute Of Medical Sciences, New Delhi, India.
4. M. Čerňáková et al, Antimicrobial activity,Folia Microbiologica, Volume 47, Number 4, Pg:375-378
5. Sa Weon Hong et al, Antimicrobial Activity, Planta Med. 2000; 66(4): 361-363
6. Silvia Letašiováa et al Antiproliferative Activity, Vol.239, Issue 2, 2006, Pg:254-262

Survey for particular part:

1. Jyotsna Singh et al, Antihyperglycemic And Antioxidant Effect of *Berberis aristata* Root Extract, Journal of Ethnopharmacology, Volume 123, Issue 1, 2009, Pg 22-26
2. L. Iauk et al, Activity of *Berberis* Root extracts on *Candida* strains, Fitoterapia Volume 78, Issue 2, 2007, Pg 159-161
3. M. Shahid et al, Ethnobotanical Studies On *Berberis aristata* DC. Root Extracts, African Journal of Biotechnology, 2006, Vol. 8 (4), pg 556–563

Survey for hepatoprotective activity:

1. K. H. Janbaz et al, Studies On Preventive And Curative Effects Of Berberine On Chemical-Induced Hepatotoxicity, Fitoterapia 2000,Vol 71, Issue 1, Pg 25-33
2. Sharma et al, Hepatoprotective Effect of Few Ayurvedic Herbs, 2004, pg: 391-396
3. Chun-Kwan Wong et al Preventive and curative effects of *Berberis aristata* Fruit extract on paracetamol- and CCl_4-induced hepatotoxicity, Numbers 1-3, Volume 512, , Pg: 267-270
4. Anwar-Ul Hassan Gilani et al, Hepatoprotective Effect Of Fruit Extract Phytotherapy Research, 2006, Volume 9, Issue 7, pg 489–494

CONCLUSION

Liver is the main site for detoxification of certain drugs and toxins by either oxidation, hydrolysis, reduction or conjugation and excretes out toxic metabolites through bile. Hepatic injury can be caused by a variety of insults like viral hepatitis, poisons, drugs etc. which can result in both hepatic necrosis and apoptosis. The signal transducer and activator of Transcription-3 (Stat-3), a key molecule in pathways regulated by IL-6, blocks apoptotic injury in two ways: induction of anticaspase regulators and reduction of oxidative injury via up regulation of antioxidant protein. In this context, plants like Tinospora Cordifolia, Terminalia Arjuna, Plumbago Zeylanica and Berberis Aristata, have anti-oxidant and anti-inflammatory properties that help in preventing hepatic injury by certain hepatic insults.

This study so far concludes that plants like Tionospora Cordifolia, Terminalia Arjuna, Plumbago Zeylanica and Berberis Aristata have anti-oxidant and anti-inflammatory properties and thus prevent hepatic injury from various insults to the liver. Liver being the main site for detoxification of certain drugs and toxins, either by oxidation, hydrolysis, reduction or conjugation excretes out toxic metabolites through bile. Hence, this can open a new era of treatment for hepatotoxicity.

References

A] INTRODUCTION and MECHANISM OF ACTION:

1) Kaplowitz, N.K., and DeLeve, L.D. 2003. Drug-induced liver disease. Marcel Dekker Inc. New York, New York, USA, Pg 773.
2) Matsumura, H, et al. Necrotic death pathway in Fas receptor signaling. J. Cell Biol. 2000, vol 151, pg 1247-1256.
3) Pinkoski, MJ, Brunner, T, Green, DR, Lin, T. Fas and Fas ligand in gut and liver. Am. J. Physiol. Gastrointest. Liver Physiol. 2000.278:G354-G366.
4) Kanzler, S, Galle, PR. Apoptosis and the liver. Semin. Cancer Biol. 2000. 10:173-184.
5) Suzuki, Y, Ono, Y, Hirabayashi, Y. Rapid and specific reactive oxygen species generation via NADPH oxidase activation during Fas-mediated apoptosis. FEBS Lett. 1998. 425:209-212.
6) Jayanthi, S, Ordonez, S, McCoy, MT, Cadet, JL. Dual mechanism of Fas-induced cell death in neuroglioma cells: a role for reactive oxygen species. Brain Res. Mol. Brain Res. 1999. 72:158-165.
7) Taub, R, Greenbaum, LE, Peng, Y. Transcriptional regulatory signals define cytokine-dependent and independent pathways in liver regeneration. Semin. Liver Dis. 1999. 19:117-127.
8) Kovalovich, K, Increased toxin-induced liver injury and fibrosis in interleukin-6 deficient mice. Hepatology. 2000. 31:149-159.
9) Kovalovich, K. Interleukin-6 protects against Fas-mediated death by establishing a critical level of anti-

apoptotic hepatic proteins FLIP, Bcl-2, and Bcl-xL. J. Biol. Chem. 2001. 276:26605-26613.
10) Galun, E, Zeira, E, Papgo, O, Peters, M, Rose-John, S. Liver regeneration induced by a designer human IL-6/sIL-6R fusion protein reverses severe hepatocellular injury. FASEB J. 2000. 14:1979-1987.
11) Ozaki, M, Haga, S, Zhang, H, Irani, K, Suzuki, S. Inhibition of hypoxia/reoxygenation-induced oxidative stress in HGF-stimulated anti-apoptotic signaling: role of PI3-K and Akt kinase upon rac1. Cell Death Differ. 2003. 10:508-515.
12) Haga, S, et al. Stat3 protects against Fas-induced liver injury by redox-dependent and -independent mechanisms. *J. Clin. Invest.* 2003.112:989-998. doi:10.1172/JCI200317970.
13) Debonera, F, et al. Activation of interleukin-6/STAT3 and liver regeneration following transplantation. *J. Surg. Res.* 2001. 96:289-295.
14) Li, W, Liang, X, Kellendonk, C, Poli, V, Taub, R. STAT3 contributes to the mitogenic response of hepatocytes during liver regeneration.*J. Biol. Chem.* 2002. 277:28411-28417.
15) Levy, DE, Lee, C-K. What does Stat3 do? *J. Clin. Invest.* 2002. 109:1143-1148. doi:10.1172/JCI200215650.
16) Hirano, T, Ishihara, K, Hibi, M. Roles of STAT3 in mediating the cell growth, differentiation and survival signals relayed through the IL-6 family of cytokine receptors. *Oncogene.* 2000. 19:2548-2556.
17) Leu, JI, Crissey, MA, Leu, JP, Ciliberto, G, Taub, R. Interleukin-6-induced STAT3 and AP-1 amplify hepatocyte nuclear factor 1-mediated transactivation of hepatic genes, an adaptive response to liver injury. *Mol. Cell. Biol.* 2001. 21:414-424.
18) Ozaki, M, Suzuki, S, Irani, K. Redox factor-1/APE suppgresses oxidative stress by inhibiting the rac1 GTPase. *FASEB J.* 2002. 16:889-890.
19) Ozaki, M, Inhibition of the Rac1 GTPase protects against nonlethal ischemia/reperfusion-induced necrosis and apoptosis in vivo.*FASEB J.* 2000. 14:418-429.
20) Grosch, S, Fritz, G, Kaina, B. Apurinic endonuclease (Ref-1) is induced in mammalian cells by oxidative stress and involved in clastogenic adaptation. *Cancer Res.* 1998. 58:4410-4416.
21) Nakamura, H, Nakamura, K, Yodoi, J. Redox regulation of cellular activation. *Annu. Rev. Immunol.* 1997. 15:351-369.
22) Hecht, N, Hyper-IL-6 gene therapy reverses fulminant hepatic failure. *Mol. Ther.* 2001. 3:683-687.

B] ETHANOBOTANY

1) Charaka, Charaka Samhita, part I and II, edited by Rajeshwar Datta Shastri et al., (Chaukhambha Vidyabhawan, Varanasi), 1961.
2) Sushruta, Sushruta Samhita, edited by Jadavji Trikamji Acharya, (Chaukhambha OrientalisVaranasi and Delhi), 1992
3) Misra B, Bhava Prakash Nighantu, Vol. I, (Chaukhambha Vidyabhawan, Varanasi), 1969: pg 269.
4) Vaagbhata, Ashtanghridayam, edited by Paradkara, (Chaukhambha Orientalis, Varanasi and Delhi),1982.
5) Watt G, A Dictionary of Economic Products of India, Vol. 6, reprinted edition, (Periodical Experts, Delhi),1972: pg 63.
6) Zhao THF Planta Med, 1991: Vol 57: pg 505
7) Kumar SJ Med Arom Plant Sci, 200: Vol 22: pg 61.
8) Pachaly P Arch Pharmacol, 1981, Vol 314: pg 251-256
9) Qudrat-I-Khuda M Sci Res (Decca), 1964: Vol 1: pg 177-183.
10) Sharma DNK Fitoterapia, 1998 Vol : 69: pg 541-542.
11) Padhya MA Indian Drug, 1986 Vol: 24: pg 47-48.
12) Wadood N Planta Med, 1992 Vol: 58(2): pg 131-136
13) Bisset NG Planta Med. 1983: Vol 48: pg 275-279
14) Rege N , Indian J Med Res, 1989: Vol 90: pg 478-483.
15) Rege N l, Indian J Gastroenterol, 1993: Vol 12: pg 5-8.
16) Prakash S , J Res Ayurv Siddha, 1996: 17(1-2): pg 58.
17) Badar VA , J Ethnopharmacol. 2005, Vol 96(3): pg 445-9.
18) Jagetia GC , Cancer Lett, 1998: Vol 127 (1-2): pg 71-82
19) Metthew S , Fitoterapia, 1999 Vol: 70: pg 35-43.
20) Dhuley JN, J Ethnopharmacol. 1997: 58(1): pg 15-20
21) Chi CW , Life Sci. 1994: Vol 54:pg 2099-2107.
22) Stanely P , J Ethnopharmacol, 2000: Vol 70(1): pg 9-15.
23) Kar A J Ethnopharmacol, 2003 Vol: 84(1): pg 105-108.
24) Grover JK , J Ethnopharmacol, 2003: Vol 76(3): pg 233-238.
25) Raghunathan K J, Res Ind Med, 1969: Vol 3(2): pg 203
26) Patel SR , J Res Ind Med, 1977: Vol 13(2): pg 46.
27) Methew S , J Exp Clin Cancer Res, 1997: Vol 16: pg 407-411.
28) Sarma DNK , Phytother Res, 1996: Vol 10: pg 181-183.
29) Sarma DNK , Phytother Res, 1995: Vol 9(8): pg 589-590.
30) Sohni YR J, Ethnopharmacol, 1995: Vol 45(1): pg 43-52.
31) Singh KP , J Res Ind Med, 1975: Vol 10(1): pg 9
32) Manjreker PN . Fitoterapia, 2000: Vol 71: pg 254-257.
33) Atal CK J, Ethnopharmacol, 1986: Vol 18(2): pg 133-141.
34) Kapil A J, Ethnopharmacol, 1997: Vol 58(2): pg 89-95.
35) Thatte U, Indian Drugs, 1987: Vol 25(3): pg 95-97.
36) Rege N, Indian Drugs, 1984: Vol 21: pg 544-555
37) Kulkarni SK, Indian Drugs, 1993: Vol 30: pg 97
38) Rai M J, Res Ind Med, 1967: Vol 2(1): pg 115.
39) Prince P , J Ethnopharmacol, 1998, Vol: 64(1): pg 53-57.
40) Miller AL (1998). "Botanical influences on cardiovascular disease". Altern Med Rev 3 (6): 422–31. PMID 9855567
41) Devi RS, Narayan S, Vani G, Shyamala Devi CS (2007). "Gastroprotective effect of Terminalia arjuna bark on diclofenac sodium induced gastric ulcer.". Chem Biol Interact 167 (1): 71–83. doi:10.1016/j.cbi.2007.01.011. PMID 17327128.
42) Baillie, J K; A A R Thompson, J B Irving, M G D Bates, A I Sutherland, W Macnee, S R J Maxwell, D J Webb (2009-03-09). "Oral antioxidant supglementation does not prevent acute mountain sickness: double blind, randomized placebo-controlled trial". QJM: Monthly Journal of the Association of Physicians 102 (5): 341–8. doi:10.1093/qjmed/hcp026.
43) http://www.ncbi.nlm.nih.gov/pubmed/19273551.Retrieved 2009-03-25.
44) Mathison RD, Christie E, Davison JS. The tripeptide feG inhibits leukocyte adhesion. J Inflamm (Lond). 2008 May 20;5:6.

45) Burke, Don (2005). The Complete Burke's Backyard: the Ultimate Book of Fact Sheets. Murdoch Books. p. 268. ISBN 9781740457392
46) http://www.ayurvedaconsultants.com/herb_consult.aspx?commonName=CHITRAK
47) Chakravarti , sci indurst Res, 1950, 9B, 161; Atta-ur-& Banerjee, ibid, 1953, 30, 705; 13 Chatterjee, ibid, 1940 Rahman & Ansari, J chem Soc Pakist, 1983, 5, 282 and Plant med. 1980, Supg 185.
48) Halder et. al., "Antioxidant properties of Plumbago zeylanica, an Indian medicinal plant and its active ing. Ind. J. Pharmac., 1970, 2,26.Redox Rep (2004), vol 9, pg 219-27.
49) Desai, S.K., V.S. Gawali, A.B. Naik and L.L. D`souza, 2008. "Potentiating effect of piperine on hepatoprotective activity of Boerhaavia diffusa to combat oxidative stress". Int. J. Pharmacol., vol 4, pg393-397
50) Chakravarti *et. al.*, sci indurst Res, 1950, 9B, 161; Atta-ur-& Banerjee, ibid, 1953, 30, 705; 13 Chatterjee, ibid, 1940 Rahman & Ansari, J chem Soc Pakist, 1983, 5, 282.
51) Halder *et. al.*, Ind. J. Pharmac., 1970, 2,26.
52) Jin-Ming Hwang *et al*, Biomedical and Life Sciences Archives of Toxicology, Organ Toxicity and Mechanisms, Volume 76, Number 11, pg. 664-670

D] LITERATURE SURVEY

TINOSPORA CORDIFOLIA

1) P.K. Raveendran Nair, Sonia Rodriguez, Reshma Ramachandran et al, "Immune stimulating properties of a novel polysaccharide from the medicinal plant *Tinospora cordifolia",* International Immunopharmacology, 2004, Volume 4, Issue 13, Pg 1645-1659
2) J. K. Grover, V. Vats, and S. S. Rathi, "Anti-hyperglycemic effect of Tinospora cordifolia lyophilized powder of plant" , Journal of Ethnopharmacology, 2000, Volume 73, Issue 3, Pg 461-470.
3) Sudhakarn, "Immunostimulatory effect of Tinospora cordifolia Miers leaf extract" , Indian Journal of Experimental Biology , ISSN 0019-5189, CODEN IJEBA6 , 2006, vol. 44, n°9, pg. 726-732 [7 page(s) (article)]
4) P. Stanely, "Antioxidant activity of Tinospora cordifolia roots", Journal of Ethnopharmacology, 1999, Vol 65, Issue 3, Pg 277-281
5) P. Stanely, Mainzen Prince and Venugopal P. Menon "Hypoglycaemic and other related actions of Tinospora cordifolia roots" , Journal of Ethnopharmacology, 2000, Vol 70, Issue 1, Pg 9-15
6) D. N. K. Sarma evaluated "Antistress Activity of *Tinospora cordifolia* and *Centella asiatica* Extracts" Phytotherapy Research, 1996, Vol 10, Issue 2, pg 181–183
7) D. N. K. Sarma, R. L. Khosa, J. P. N. Chansauria, M. Sahai, "Antiulcer Activity of *Tinospora cordifolia* Root" , Phytotherapy Research, 1995, Vol 9, Issue 8, pg 589–590
8) B Bishayi, Roy chawdhury S, Ghosh S, Sengupta M, " Hepatoprotective and immunomodulatory properties of Tinospora cordifolia in CCl4 intoxicated mature albino rats." , J. Toxicol. Sci., 2002, Vol. 27: No. 3, Pg 139-146
9) SS Singh, SC Pandey, S Srivastava, VS Gupta, B Patro, "Chemistry and medicinal properties of *Tinospora cordifolia*" Indian journal of pharmacy 2003, Vol 35, Issue : 2, pg 83-91
10) T. S. Panchabhai, S. V. Ambarkhane, A. S. Joshi, B. D. Samant, N. N. Rege, *Protective effect of *Tinospora cordifolia*, Phyllanthus emblica and their combination against antitubercular drugs induced hepatic damage: An experimental study, Phytotherapy Research, 2008, Volume 22, Issue 5, pg 646–650

TERMINALIA ARJUNA

11) Minakshi Chaudhari, Sushma Mengi " Evaluation of phytoconstituents of Terminalia arjuna For Wound Healing Activity In Rat" , Phytotherapy Research, 2006, Vol. 20, Issue 9, pg 799–805
12) Fayez E. Kandil, Mahmoud I. Nassar "A tannin anti-cancer promotor from Terminalia arjuna, Phytochemistry" , 1998, Vol. 47, Issue 8, Pg 1567-1568
13) Hua-Yew Cheng, Chun-Ching Lin and Ta-Chen Lin " Antiviral: bark of Terminalia arjuna Linn" , Antiviral Research, 2002, Vol. 55, Issue 3, Pg 447-455.
14) "Antioxidant activity of phenolic components present in barks of Terminalia arjuna" , Department of Chemistry, University of Agriculture, Faisalabad 38040, Pakistan And Department of Chemistry and Biochemistry, University of Lethbridge, Alberta, Canada, Food Chemistry, 2007, Vol104, Issue 3, Pg 1106-1114
15) K. Kaur, **S.** Arora, S. Kumar and A. Nagpal , "Antimutagenic activities of acetone and methanol fractions of Terminalia arjuna bark" , Food and Chemical Toxicology, 2002, Vol 40, Issue 10, Pg 1475-1482.
16) A.K. Khanna et al, "Terminalia arjuna *bark :* an Ayurvedic Cardiotonic, Regulates Lipid Metabolism in Hyperlipaemic Rats", Phytotherapy Research, Indian Journal of Clinical Biochemistry, Vol 19, pg 141-148
17) Ramesh Chander et al, evaluated Antidyslipidemic and antioxidant activities of stem bark, Biomedical And Life Sciences, Indian Journal Of Clinical Biochemistry, Volume 19, Number 2, pg: 141-148
18) Girish et al, "Hepatoprotective activity of six polyherbal formulations in CCl_4-induced liver toxicity in mice", Research Journals, Indian Journal of Experimental Biology, NISCAIR publ., 2009, Vol.47, issue 04, pg 257-263
19) Prasenjit Manna, Mahua Sinha and Parames C Sil, "Aqueous Extract Of Terminalia Arjuna Prevents Carbon Tetrachloride Induced Hepatic And Renal Disorders" Research Article, BMC Complementary And Alternative Medicine *2006*
20) Venkataranganna, "Preliminary investigation on the hepatoprotective activity of Liv.52 Protec (Poultry Feed Supglement)", Indian Veterinary Medical Journal 2001, Vol. 25, pg: 157-160.

PLUMBAGO ZEYLENICA

21) Yue Dai et al, "Inhibition of Immediate Allergic Reactions by Ethanol Extract of *Plumbago zeylanica*

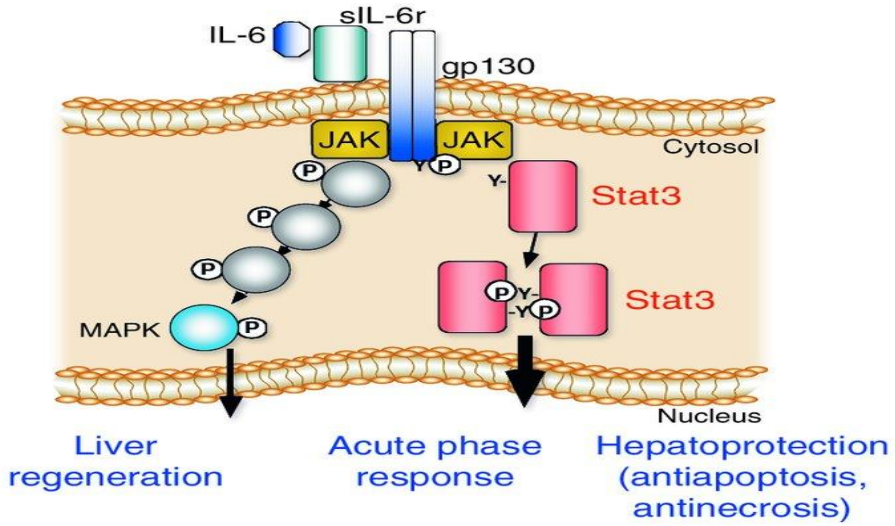
stems*"*, Biological & Pharmaceutical Bulletin, 2004, No. 3, Vol. 27, pg 429

22) S. Satish K. A. Raveesha, G. R. Janardhana, "Antibacterial activity on phytopathogenic *Xanthomonas campestris*" 1999, Vol. 28, Issue 2, pg 145–147
23) L. M. van der Vijver, A. P. Lötter, "Antibacterial Activity In Roots of *Plumbago zeylanica"*, Planta Med 1971, Numb.3, Vol.20, pg 8-13
24) Yuan-Chuen Wang, Tung-Liang Huang "Anti-*Helicobacter pylori* activityof *Plumbago zeylanica*" FEMS Immunology & Medical Microbiology, 2005, Vol 43, Issue 3, pg 407–412
25) O.O.Oyedapo " Bioactivity of the Root Extract of *Plumbago zeylanica* " Pharmaceutical Biology,1996, No. 5, Vol. 34, Pg 365-369
26) Arina Z Beg, Iqbal Ahmad "Effect on multidrug resistant bacteria of clinical origin", World Journal Of Microbiology And Pharmacology, Numb. 8-9, Vol16, pg 841-844
27) George Varughese et al "In Vitro Screening Of Indian Medicinal Plants For Antiplasmodial Activity" Journal of Ethnopharmacology, 2001, Vol 74, Issue 2 Pg 195-204
28) Dr. J. A. Olagunju, A. A. Jobi[1], O. O. OyedapO, "Hyperglycaemia treated with ethanol root extract of *Plumbago zeylanica*" Phytotherapy Research,1999 Vol 13, Issue 4, pg 346–348
29) C. P. Bopaiah, N. Pradhan, "Central Nervous System Stimulatory Action From The Root Extract Of *Plumbago zeylanica* In Rats", Phytotherapy Research, 2001, Vol 15, Issue 2, pg 153–156
30) Tilak, Adhikari, Soumyakanti, Devasagayam, Thomas "Antioxidant properties of *Plumbago zeylanica*, an Indian medicinal plant and its active ingredient, plumbagin" Redox Report, Numb.4, 2004 , Vol 9, pg 219-227(9)
31) I.Ahmad, Arina Z. Beg, "Antimicrobial and phytochemical studies on 45 Indian medicinal plants against multi-drug resistant human pathogens" Journal of Ethnopharmacology, 2001,Vol 74, pg 113-123
32) S.gopinath , S. Muralidharan, S. Rajan and S. P. Danaphal, "Simultaneous Estimation of Plumbagin and Embelin by Reverse Phase-High Performance Liquid Chromatographic method" 2009, Numb.1, Vol.1, Pg 135-142
33) Purkayastha, Jubilee Nath, Subhan C, "Biological activities of ethnomedicinal claims of some plant species of Assam" , 2006, Research Journals , Indian Journal of Traditional Knowledge, 2006, Vol.5, pg 229-236
34) Ansar M. patel, Snehal S. Darade, Pankaj G. Jain, Ashish M. Kandalkarl, "Formulation and Evaluation Of Polyherbal Formulation For Their Hepatoprotective Activity", International Journal Of PharmaTech Research, No.1,Vol 2, pg 305-309.
35) Rajesh kumar, Sushil Kumar, Arjun Patra, S. Jayalaxhmi, "Hepatoprotective activity of aerial parts Of *Plumbago Zeylenica* against CCL4 Induced Hepatotoxicity In Rats" International Journal of Pharmacy And Pharmaceutical Science, 2009, Vol.1, sup.1.

BERBERIS ARISTATA:

36) Bhupesh Chander Semwal, "Antidiabetic Activity Of Stem Bark of *Berberis aristata* in alloxan induced diabetic rats", The Internet Journal of Pharmacology, 2008, Number 1. Vol. 6
37) Padmaja V. JoshAtul A Shirkhedkar[1], Krishnan Prakash[2], Vijay L Maheshwari, "Antidiarrheal activity, Chemical And Toxicity Profile Of *Berberis aristata*", Pharmaceutical Biology, 2010, Pg 1-7
38) Suresh Kumar Gupta et al, "Anti-inflammatory Effects investigative Ophthalmology and Visual Science" 2008, Numb.9, Vol.49, 4036-4040, Reprint: All India Institute Of Medical Sciences, New Delhi, India.
39) M. Čerňáková, D. Košťálová, "Antimicrobial activity" Biomedical And Life Sciences, Folia Microbiologica, Numb. 4, Vol. 47, Pg:375-378
40) Sa Weon Hong et al, "Antimicrobial Activity of 9-*O*-Acyl- and 9-*O*-Benzoyl-Substituted *Berberrubines*", Planta Med. 2000, Vol. 66, Issue 4, pg 361-363
41) Bipul R. Acharya, Bhabatarak Bhattacharyya, Gopal Chakrabarti "The Natural Naphthoquinone *Plumbagin* Exhibits Antiproliferative Activity and Disrupts the Microtubule Network through Tubulin Binding" *Biochemistr*y, 2008, Vol .47 Issue 30, pg 7838–7845
42) Jyotsna Singh, Poonam Kakka "Antihyperglycemic And Antioxidant Effect of *Berberis aristata* Root Extract", Journal of Ethnopharmacology, 2009, Vol123, Issue 1, Pg 22-26
43) L. Iauk et al, "Activity of *Berberis* Root extracts on *Candida* strains" Fitoterapia , 2007,Vol.78, Issue 2, Pg 159-161
44) M. Shahid et al "Ethnobotanical Studies On *Berberis aristata.* Root Extracts", African Journal of Biotechnology, 2009, Numb.4, Vol. 8, pg 556–563
45) K. H. Janbaz, A. H. Gilani, "Studies On Preventive And Curative Effects Of Berberine On Chemical-Induced Hepatotoxicity", Fitoterapia, 2000, Vol. 71, Issue 1, Pg 25-33
46) Sharma, Y K. Singh , Harbans Mehra, B L " Hepatoprotective Effect of Few Ayurvedic Herbs", Research Journals, Indian Journal of Traditional Knowledge, 2004, Vol.3, pg: 391-396
47) Chun-Kwan Wong, V. E. C. Ooi, P. O. Ang "Preventive and curative effects of *Berberis aristata* Fruit extract on paracetamol- and CCl_4-induced hepatotoxicity*"* Phytotherapy Research, 1995, Numb. 1-3, Vol 512, Pg: 267-270
48) Anwar-Ul Hassan Gilani. Khalid Hussain Janbaz "Hepatoprotective Effect Of Fruit Extract" Phytotherapy Research, 2006, Vol 9, Issue 7, pg 489–494

Figure 1: Hepatoprotection via the IL-6/Stat3 pathway



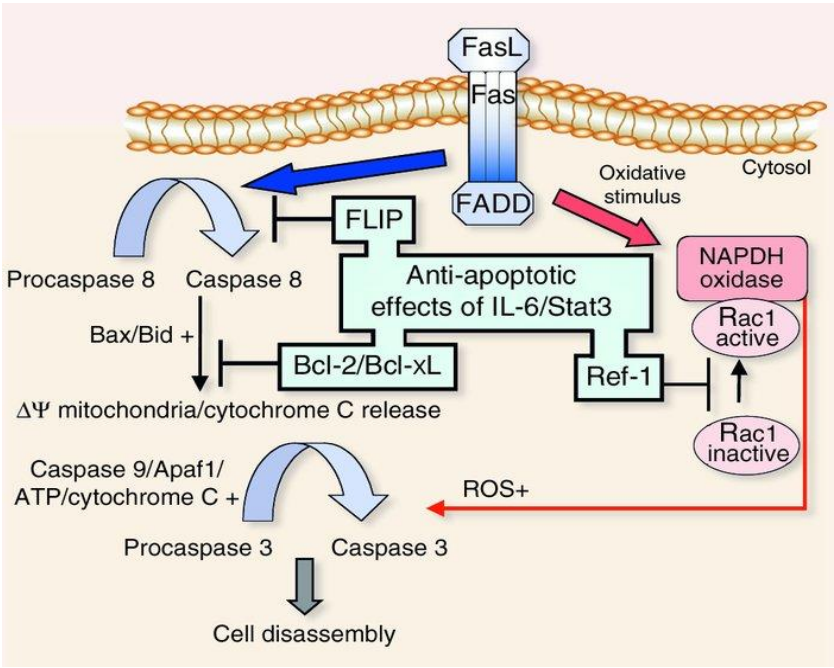


Figure 2:
Bcl:oncogeness found in b cell lymphoma. C.elegance prot.{A.APOPTOTC.-BCL-X}
BIM,BAK,BAX: PRO APOPTOTIC PROT.
Apaf 1: apoptosis actv. Fact.1
Aif:apopt.inducing fact.
Cystiene aspartate lyasase---3,6 wrk in xecution phase
CD31: apoptotic cells' marker