Inhibition of hepatitis C virus replication by herbal extract: Phyllanthus amarus as potent natural source.

Ravikumar YS, Ray U, Nandhitha M, Perween A, Raja Naika H, Khanna N, Das S.

Source
Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore 560012, India.

Abstract
Hepatitis C virus infection is a major health problem worldwide. Developing effective antiviral therapy for HCV is the need of the hour. The viral enzymes NS3 protease and NS5B RNA dependent RNA polymerase are essential enzymes for polyprotein processing and viral RNA replication and thus can be potential targets for screening anti-HCV compounds. A large number of phytochemicals are present in plants, which are found to be promising antiviral agents. In this study, we have screened inhibitory effect of different plant extracts against the NS3 and NS5B enzymes of hepatitis C virus. Methanolic extracts were prepared from various plant materials and their inhibitory effects on the viral enzymes were determined by in vitro enzyme assays. Effect on viral RNA replication was investigated by using TaqMan Real time RT-PCR. Interestingly, Phyllanthus amarus root (PAR) extract showed significant inhibition of HCV-NS3 protease enzyme; whereas P. amarus leaf (PAL) extract showed considerable inhibition of NS5B in the in vitro assays. Further, the PAR and PAL extracts significantly inhibited replication of HCV monocistronic replicon RNA and HCV H77S viral RNA in HCV cell culture system. However, both PAR and PAL extracts did not show cytotoxicity in Huh7 cells in the MTT assay. Furthermore, addition of PAR together with IFN-α showed additive effect in the inhibition of HCV RNA replication. Results suggest the possible molecular basis of the inhibitory activity of PA extract against HCV which would help in optimization and subsequent development of specific antiviral agent using P. amarus as potent natural source.
Sección Virología, Facultad de Ciencias, Universidad de la República, 11400 Montevideo, Uruguay.

**Abstract**

Herpes simplex virus type 1 (HSV-1) infection has a prevalence of 70% in the human population. Treatment is based on acyclovir, valacyclovir, and foscarnet, three drugs that share the same mechanism of action and of which resistant strains have been isolated from patients. In this aspect, innovative drug therapies are required. Natural products offer unlimited opportunities for the discovery of antiviral compounds. In this study, 28 extracts corresponding to 24 plant species and 4 alga species were assayed in vitro to detect antiviral activity against HSV-1. Six of the methanolic extracts inactivated viral particles by direct interaction and 14 presented antiviral activity when incubated with cells already infected. Most interesting antiviral activity values obtained are those of Limonium brasiliense, Psidium guajava, and Phyllanthus niruri, which inhibit HSV-1 replication in vitro with 50% effective concentration (EC(50)) values of 185, 118, and 60 μg/mL, respectively. For these extracts toxicity values were calculated and therefore selectivity indexes (SI) obtained. Further characterization of the bioactive components of antiviral plants will pave the way for the discovery of new compounds against HSV-1.


**Lignans with Anti-Hepatitis B Virus Activities from Phyllanthus niruri L.**


**Source**

Department of Chemistry, Guangxi University, Nanning, 530004, People's Republic of China. chewxwei@yahoo.com.cn.

**Abstract**

One new lignan, nirtetralin B, along with its two known stereoisomers were isolated from Phyllanthus niruri L. The structure of the new compound was determined by spectroscopy experiments and x-ray diffraction analysis. These lignans were assayed for anti-hepatitis B virus activities in vitro. Nirtetralin and nirtetralin A, B effectively suppressed the secretion of the HBV antigens in a dose-dependent manner with IC(50) values for HBsAg of 9.5 μm (nirtetralin A), 16.7 μm (nirtetralin B) and 97.2 μm (nirtetralin), IC(50) values for HBeAg of 17.4 μm (nirtetralin A), 69.3 μm (nirtetralin B) and 232.0 μm (nirtetralin), respectively. Copyright © 2011 John Wiley & Sons, Ltd.
Phytochemicals from Phyllanthus niruri Linn. and their pharmacological properties: a review.

Bagalkotkar G, Sagineedu SR, Saad MS, Stanslas J.

Source
Department of Biomedical Sciences, University Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.

Abstract
This review discusses the medicinal plant Phyllanthus niruri Linn. (Euphorbiaceae), its wide variety of phytochemicals and their pharmacological properties. The active phytochemicals, flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins and saponins, have been identified from various parts of P. niruri. Extracts of this herb have been proven to have therapeutic effects in many clinical studies. Some of the most intriguing therapeutic properties include anti-hepatotoxic, anti-lithic, anti-hypertensive, anti-HIV and anti-hepatitis B. Therefore, studies relating to chemical characteristics and structural properties of the bioactive phytochemicals found in P. niruri are very useful for further research on this plant as many of the phytochemicals have shown preclinical therapeutic efficacies for a wide range of human diseases, including HIV/AIDS, hepatitis C and hepatitis B.

Effects of an extract from Phyllanthus niruri on hepatitis B and woodchuck hepatitis viruses: in vitro and in vivo studies.

Venkateswaran PS, Millman I, Blumberg BS.

Abstract
An aqueous extract of the plant Phyllanthus niruri inhibits endogenous DNA polymerase of hepatitis B virus and binds to the surface antigen of hepatitis B virus in vitro. The extract also inhibits woodchuck hepatitis virus (WHV) DNA polymerase and binds to the surface antigen of WHV in vitro. The extract, nontoxic to mice, was tested for antiviral activity in woodchucks (Marmota monax). In a trial using six long-term WHV-carrier woodchucks, five treated animals showed a faster decrease in woodchuck hepatitis virus surface antigen titer compared to one untreated control. In animals recently infected with WHV, the extract was effective when administered i.p. in three out of four animals in reducing and within 3-6 weeks eliminating both the surface antigen titer and DNA polymerase
activity in serum. The treatment was discontinued after 10 weeks, and the treated animals have remained free of detectable markers of WHV for more than 45 weeks. In contrast, three untreated controls remained positive for both markers for WHV. One of the controls died after 8 weeks; the other two controls have remained positive for WHV markers for more than 45 weeks. In a third trial with long-term carriers, test animals treated subcutaneously with the extract for 12 weeks did not respond; but on switching the mode of administration to i.p., two out of the five animals showed a significant decrease in woodchuck hepatitis virus surface antigen titer compared to controls.


Effects of Andrographis paniculata extract and Andrographolide on hepatic cytochrome P450 mRNA expression and monooxygenase activities after in vivo administration to rats and in vitro in rat and human hepatocyte cultures.


Source
Laboratoire de Toxicologie Cellulaire, EA 4267, IFR 133, UFR Pharmacie, Place Saint-Jacques, 25030 Besançon, France.

Abstract
The expression of cytochrome P450 (CYP) is regulated by both endogenous factors and foreign compounds including drugs and natural compounds such as herbs. When herbs are co-administrated with a given drug in modern medicine it can lead to drug-herb interaction that can be clinically significant. The ability of Andrographis paniculata extract (APE) and Andrographolide (AND), the most medicinally active phytochemical in the extract, to modulate hepatic CYP expression was examined in vivo in rats and in vitro in rat and human hepatocyte cultures. After in vivo administration, APE at dose levels of 0.5 g/kg/day (i.e. 5 mg/kg/day AND equivalents) and at 2.5 g/kg/day (i.e. 25 mg/kg/day AND equivalents) and AND at dose levels of 5 and 25 mg/kg/day significantly decreased CYP2C11 activity. In primary cultures of rat and human hepatocytes, treatment with AND 50 microM and APE-containing 50 microM AND also resulted in significant decreases in CYP2C expression and activity. In addition, in human hepatocytes, treatment with APE and AND 50 microM resulted in a decrease in CYP3A expression and activity. In conclusion, this study suggests that AND and APE could cause herb-drug interactions
Andrographis paniculata ameliorates carbon tetrachloride (CCl(4))-dependent hepatic damage and toxicity: diminution of oxidative stress.

Koh PH, Mokhtar RA, Iqbal M.

Source
Biotechnology Research Institute, Universiti Malaysia Sabah, Malaysia.

Abstract
Andrographis paniculata (hempedu bumi) is a plant that possesses many medicinal values in treating several diseases and for health care maintenance. However, its hepatoprotective activity and mechanism of action have not been fully investigated. Therefore, this study aimed to evaluate the hepatoprotective effects of A. paniculata and its mechanism of action in rats. Carbon tetrachloride (CCl(4)) challenge of rats at a dose of 1.2 ml/kg body weight-induced oxidative stress in the liver. This was evidenced by augmentation in lipid peroxidation, which was accompanied by a decrease in the activities of antioxidant enzymes and depletion in the level of reduced glutathione (P < 0.05). Parallel to these changes, CCl(4) challenge too, enhanced hepatic damage as evidenced by sharp increase in serum transaminases (e.g. alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase) (P < 0.05). Additionally, the impairment of liver function corresponded to histopathological changes. However, most of these changes were reversed in a dose-dependent fashion by pre-treatment of animals with A. paniculata (P < 0.05). The ability of A. paniculata to scavenge the 2,2-Diphenyl-2-picrylhydrazyl radical was determined through its EC(50) value. The EC(50) value of A. paniculata was 583.60 ± 4.25 µg/ml. In addition, A. paniculata was found to contain 65.37 ± 1.20 mg/g total phenolics expressed as gallic acid equivalent. From these studies, it is concluded that A. paniculata could be used as a hepatoprotective agent and possesses the potential to treat or prevent degenerative diseases where oxidative stress is implicated.

PMID: 21801496 [PubMed - indexed for MEDLINE]
paniculata and Swertia chirayita.
Nagalekshmi R, Menon A, Chandrasekharan DK, Nair CK.
Source
Amrita School of Pharmacy, Kochi 682041, Kerala, India. naga.lekshmi1@gmail.com

Abstract
Andrographis paniculata (Family: Acanthaceae) and Swertia chirayita (Family: Gentianaceae) are two controversial medicinal plants used as Kiriyattu, having similar therapeutic action and are used as a hepatoprotective and hepatostimulative agent. A. paniculata grows in southern parts of India and S. chirayita in the Himalayan region. The present work concerns on the ability of the extracts of these plants to offer protection against acute hepatotoxicity induced by paracetamol (150 mg/kg) in Swiss albino mice. Oral administration of A. paniculata or S. chirayita extract (100-200mg/kg) offered a significant dose dependent protection against paracetamol induced hepatotoxicity as assessed in terms of biochemical and histopathological parameters. The paracetamol induced elevated levels of serum marker enzymes such as serum glutamate pyruvate transaminase (GPT), serum glutamate oxaloacetate transaminase (GOT), alkaline phosphatase (ALP), and bilirubin in peripheral blood serum and distorted hepatic tissue architecture along with increased levels of lipid peroxides (LPO) and reduction of superoxide dismutase (SOD), catalase, reduced glutathione (GSH) and glutathione peroxidase (GPx) in liver tissue. Administration of the plant extracts after paracetamol insult restored the levels of these parameters to control (untreated) levels. Thus the present study revealed that the extracts of A. paniculata or S. chirayita offered protection against hepatotoxicity induced by paracetamol.

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PMID: 21983487 [PubMed - indexed for MEDLINE]

Free radical induced damages to rat liver subcellular organelles: inhibition by Andrographis paniculata extract.
Tripathi R, Kamat JP.
Source
Biotechnology Department, V B S Purvanchal University, Jaunpur, 222001, India.

Abstract
Aqueous extract of Andrographis paniculata was examined for antioxidant activity using rat liver subcellular organelles as model systems. The study deals with two important biological oxidative agents, ascorbate-Fe(+2) and AAPH generating hydroxyl and peroxyl radical, respectively. Oxidative damage was examined against the inhibition of membrane peroxidation, protein oxidation and restoration in decreased SOD and catalase activity. The antimutagenic activity of Ap was examined following inhibition in AAPH induced strand breaks in plasmid pBR322 DNA. Extract was a potent scavenger of DPPH, ABTS radicals, exemplified by ESR signals, O2-*, *OH and H2O2, displayed excellent reducing power, FRAP potentials to reduce Fe (III) --> Fe (II) and had considerable amount of phenolics/ flavonoids contents, an effective antioxidant index. The observed antioxidant effect might be primarily due to its high scavenging ability for ROS. Effect was confirmed ex vivo following inhibition in peroxidation, restoration in SOD enzyme, SOD band intensity and protein degradation in Ap fed liver homogenate. Based on these results, it was concluded that the aqueous extract of Andrographis paniculata might emerge as a potent antiradical agent against various pathophysiological oxidants.

PMID: 18072540 [PubMed - indexed for MEDLINE]

In vitro studies on the effect of certain natural products against hepatitis B virus.

Mehrotra R, Rawat S, Kulshreshtha DK, Patnaik GK, Dhawan BN.

Source

ICMR Advance Centre for Pharmacological Research on Traditional Remedies, Central Drug Research Institute, Lucknow.

Abstract

Picroliv (active principle from Picrorrhiza kurroa), its major components picroside I, catalpol, kutkoside I, kutkoside, andrographolide (active constituent of Andrographis paniculata), silymarin and Phyllanthus niruri extract were tested for the presence of anti hepatitis B virus surface antigen (anti HBs) like activity. HBsAg positive serum samples obtained from hepatitis B virus (HBV) associated acute and chronic liver diseases and healthy HBsAg carriers were used to evaluate the anti-HBs like activity of compounds/extract. The latter were mixed with serum samples and incubated at 37 degrees C overnight followed by HBsAg screening in the Elisa system. A promising anti-HBsAg like activity was noted in picroliv (and its major components) catalpol, P. niruri which differed from the classical viral neutralization. Picroliv also inhibited purified HBV antigens
HBsAg and HBsAg) prepared from healthy HBsAg carriers. The in vitro testing system appears to be a suitable model to identify an agent active against HBV, prior to undertaking detailed studies.


**Clinical studies on kalmegh (andrographis paniculata nees) in infective hepatitis.**

Chturvedi GN, Tomar GS, Tiwari SK, Singh KP.

**Source**

Institute of Medical Sciences, Banaras Hindu University, Varanasi-221 005, India.

**Abstract**

Infective hepatitis ia an acute inflammatory condition of liver. It is usually manifested in the form of Jaundice. In this clinical study Kalmegh(Andrographis paniculata Nees) was given in the decoction form to the patients of infective hepatitis. The results were assessed on the basis of clinical and biochemical parameters. A marked symptomatic improvement in majority of the cases was observed. A statistically highly significant decrease was noted in various liver function tests viz., serum bilirubin, thymol turbidity, alkaline phosphatase, S.G.O.T.; S.G.P.T. and serum globulin fraction of protein. Moreover it increased significantly total serum globulin fraction of protein. Moreover it increased significantly total serum protein level along with albumin fraction. On the total assessment 80% cases of this series were cured and 20% patients were relieved. Therefore, Kalmegh appears to be a useful remedy for the treatment of infective hepatitis.

PMID: 22556984 [PubMed] PMCID: PMC3336768 Free PMC Article


**Boerhaavia diffusa: a study of its hepatoprotective activity.**

Chandan BK, Sharma AK, Anand KK.

**Source**

Department of Pharmacology, Council of Scientific and Industrial Research, Jammu Tawi, India.

**Abstract**

An alcoholic extract of whole plant Boerhaavia diffusa given orally exhibited hepatoprotective activity against experimentally induced carbon tetrachloride hepatotoxicity in rats and mice. The extract also produced an
increase in normal bile flow in rats suggesting a strong choleretic activity. The extract does not show any signs of toxicity up to an oral dose of 2 g/kg in mice.

PMID: 2056758 [PubMed - indexed for MEDLINE]


Studies on the protective effects of Boerhaavia diffusa L. against gamma radiation induced damage in mice.

Manu KA, Leyon PV, Kuttan G.

Source
Amala Cancer Research Centre, Amala Nagar, Kerala State, India.

Abstract
The radioprotective effect of the hydro-alcoholic extract of Boerhaavia diffusa was studied using the in vivo mice model. The sublethally irradiated mice (600 rads, single dose) were treated intraperitoneally with 20 mg/kg of the extract. The animals were sacrificed at different time periods after the whole-body radiation. The most affected tissues--bone marrow and intestine--were considerably protected by the intraperitoneal administration of B. diffusa as estimated by bone marrow cellularity, maturing monocytes, and intestinal glutathione. Total white blood cell count was lowered drastically after radiation exposure (ninth day, 1500 +/- 500 cells/mm(3)). When the animals were exposed to radiation and treated with B. diffusa, the total white blood cell count was lowered only to 4000 +/- 400 cells/mm(3) on the third day, and it reached an almost normal level (6250 +/- 470 cells/mm(3)) by the ninth day. The elevated level of serum and liver alkaline phosphatase after radiation exposure was reduced in the B. diffusa-treated group. The serum and liver glutamate pyruvate transferase, which were elevated after radiation exposure, were also reduced by treatment with B. diffusa compared to the control. The lipid peroxidation level also increased in the irradiated animals both in the liver and serum, but in B. diffusa-treated animals, there was a significant reduction in lipid peroxidation levels. The agarose gel electrophoresis of DNA isolated from bone marrow of mice exposed to gamma radiation showed heavy damage that was reduced by treatment with B. diffusa. These results are indicative of the radioprotective effect of the whole-plant extract of B. diffusa.

PMID: 18048886 [PubMed - indexed for MEDLINE]
Antioxidant activity and hepatoprotective property of leaf extracts of Boerhaavia diffusa Linn against acetaminophen-induced liver damage in rats.

Olaleye MT, Akinmoladun AC, Ogunboye AA, Akindahunsi AA.

Source
Department of Biochemistry, School of Sciences, Federal University of Technology, PMB 704, Akure, Nigeria.

Abstract
Extracts of Boerhaavia diffusa leaves were evaluated for antioxidant and hepatoprotective properties in the acetaminophen-induced liver damage model. Antioxidative evaluation of ethanolic extract gave total phenolic content, total flavonoid content, vitamin C content and vitamin E content and the levels of selenium and zinc as 6.6+/−0.2 mg/g tannic acid equivalent, 0.092+/−0.003 mg/g quercetin equivalent, 0.21+/−0.03 mg/g, 0.054+/−0.002 mg/g, 0.52+/−0.05 ppm and 9.28+/−0.16 ppm, respectively. The DPPH scavenging capacity and the reductive potential were 78.32+/−2.41% and 0.65+/−0.02 mg/g ascorbic acid, respectively. Pretreatment with aqueous and ethanolic extracts decreased the activities of alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, and the level of bilirubin in the serum that were elevated by acetaminophen. The two extracts also ameliorated the elevation in the activities of the enzymes in the liver. Acetaminophen intoxication led to reduction in serum and liver albumin levels which were not significantly increased by pretreatment with the extracts. The extracts also protected against acetaminophen induced lipid peroxidation. These results indicated that leaf extracts from B. diffusa possess hepatoprotective property against acetaminophen-induced liver damage which may be mediated through augmentation of antioxidant defenses.

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PMID: 20553784 [PubMed - indexed for MEDLINE]
**Source**
Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002, Thailand. kanok_ja@kku.ac.th

**Abstract**
Modulatory influence of Andrographis paniculata crude extract on cytochrome P450 (CYP) enzymes was performed by administration of the crude extract of Andrographis paniculata to ICR male mice. Total hepatic P450 content was not significantly modified by either the aqueous or the alcoholic extracts of Andrographis paniculata. Assessment of hepatic microsomal P450 activities by alkoxyresorufin O-dealkylations noted that both the aqueous and alcoholic extracts of Andrographis paniculata significantly increased ethoxyresorufin O-dealkylase and pentoxyresorufin O-dealkylase activities, while those of methoxyresorufin O-dealkylase activities were not elevated. These results suggested that Andrographis paniculata might effectuate hepatic cytochrome P450 enzymes of which CYP1A1 and CYP2B are the responsive P450 isoforms.

PMID: 16406417 [PubMed - indexed for MEDLINE]

**Source**

**Antihepatotoxic effects of major diterpenoid constituents of Andrographis paniculata.**

Kapil A, Koul IB, Banerjee SK, Gupta BD.

**Source**
Department of Pharmacology, Regional Research Laboratory, Jammu, India.

**Abstract**
The diterpenes andrographolide (I), andrographiside (II) and neoandrographolide (III) isolated from Andrographis paniculata were investigated for their protective effects on hepatotoxicity induced in mice by carbon tetrachloride or tert-butylhydroperoxide (tBHP) intoxication. Pretreatment of mice with the diterpenes (I, II & III; 100 mg/kg, i.p.) for 3 consecutive days produced significant reduction in malondialdehyde formation, reduced glutathione (GSH) depletion and enzymatic leakage of glutamic-pyruvate transaminase (GPT) and alkaline phosphatase (AP) in either group of the toxin-treated animals. A comparison with the known hepatoprotective agent silymarin revealed that I exhibited a lower protective potential than II and III, which were as effective as silymarin with respect to their effects on the formation of the degradation products of lipid peroxidation and release of GPT and AP in the serum. GSH status was returned to normal only by III. The greater protective activity of II and III could be due to their glucoside groups which may act as strong...
antioxidants.
PMID: 8347130 [PubMed - indexed for MEDLINE]

**Protective Role of Tinospora cordifolia against Lead-induced Hepatotoxicity.**
Sharma V, Pandey D.

**Source**
Bioscience and Biotechnology Department, Banasthali University, Banasthali - 304 022, Tonk, Rajasthan, India.

**Abstract**
The importance of Tinospora cordifolia stem and leaves extract was investigated for its possible hepatoprotective effect in Swiss albino male mice against lead nitrate induced toxicity. Oral administration of plant extracts prevented the occurrence of lead nitrate induced liver damage. The decreased level of tissue enzymes, i.e., superoxide dismutase (SOD), catalase (CAT) and increased level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and acid phosphatase (ACP) were observed in mice treated with lead. Administration of aqueous stem extract (400 mg/kg body weight, orally) and aqueous leaves extract (400 mg/kg body weight, orally) along with the lead nitrate (5 mg/kg body weight, i.p. for 30 days) increased the activities of SOD and CAT and decreased the levels of AST, ALT, ALP, and ACP enzymes in mice. These biochemical observations were supplemented by histopathology/histological examinations of liver section. Results of this study revealed that plant extract could afford protection against lead-induced hepatic damage.

**Restoration of antioxidant defence by ethanolic Tinospora cordifolia root extract in alloxan-induced diabetic liver and kidney.**
Prince PS, Padmanabhan M, Menon VP.

**Source**
Department of Biochemistry, Annamalai University, Annamalainagar, Tamil Nadu, India.

**Abstract**
The present study investigates the effect of oral administration of an alcoholic extract of Tinospora cordifolia roots on antioxidant defence in
alloxan-induced diabetes in rats. A significant increase in the concentration of thiobarbituric acid reactive substances (TBARS) in liver and kidney was observed in diabetic rats. Decreased concentration of glutathione (GSH) and decreased activities of superoxide dismutase (SOD), and catalase in liver and kidney of diabetic rats were also noted. Alcoholic Tinospora cordifolia root extract (TCREt) administered at a dose of 100 mg/kg body weight to diabetic rats orally for six weeks normalized the antioxidant status of liver and kidney. The effect of Tinospora cordifolia root extract was more potent than glibenclamide (600 microg/kg body weight). Insulin (6 units/kg) restored all the parameters to normal status.

Hepatoprotective and immunomodulatory properties of Tinospora cordifolia in CCl4 intoxicated mature albino rats.

Bishayi B, Roychowdhury S, Ghosh S, Sengupta M.
Source
Department of Physiology, Immunology Laboratory, University of Calcutta, 92, A.P.C. Road, Calcutta-700 009, India.

Abstract
Effect of Tinospora cordifolia extract on modulation of hepatoprotective and immunostimulatory functions in carbon tetrachloride (CCl4) intoxicated mature rats is reported here. Administration of CCl4 (0.7 ml/kg body weight for 7 days) produces damage in the liver as evident by estimation of enzymes such as serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase (ALP) as well as serum bilirubin level. CCl4 administration also causes immunosuppressive effects as indicated by phagocytic capacity, chemotactic migration and cell adhesiveness of rat peritoneal macrophages. However, treatment with T. cordifolia extract (100 mg/kg body weight for 15 days) in CCl4 intoxicated rats was found to protect the liver, as indicated by enzyme level in serum. A significant reduction in serum levels of SGOT, SGPT, ALP, bilirubin were observed following T. cordifolia treatment during CCl4 intoxication. Treatment with T. cordifolia extract also deleted the immunosuppressive effect of CCl4, since a significant increment in the functional capacities of rat peritoneal macrophages (PM phi) was observed following T. cordifolia treatment. The results of our experiment suggest that treatment by T. cordifolia extract may be the critical remedy for the adverse effect of CCl4 in liver function as well as immune functions.
**Modulation of Kupffer cell activity by Tinospora cordifolia in liver damage.**

Nagarkatti DS, Rege NN, Desai NK, Dahanukar SA.

Source
Dept of Pharmacology, Seth GS Medical College, Parel, Bombay.

Abstract
Kupffer cells are major determinants of outcome of liver injury. Their activity was therefore studied in a model of chronic liver disease. The effect of Tinospora cordifolia, an indigenous agent with proven hepatoprotective activity, was evaluated on Kupffer cell function, using carbon clearance test as a parameter. Rats were divided into two major groups. In Gp I which served as normal control t1/2 of carbon was 9.48 +/- 4.14 min. GpII received horse-serum in a dose of 0.5 ml/100 gm b.w. i.p. for a period of 12 weeks and was divided into three sub-groups. In Gp IIA at the end of 12 weeks half-life of carbon was found to be significantly increased to 19.86 +/- 7.95 min (p < 0.01). Indicating suppressed Kupffer cell function in chronic liver damage. In Gp IIB treated with vehicle for 4 more weeks there was significant prolongation of half-life to 38.32 +/- 10.61 min (p < 0.01), indicating perpetuation of damage in absence of damaging agent. Whereas in Gp IIc, treated with Tinospora cordifolia t 1/2 was decreased to 14.24 7.74 min (p < .01), as compared to vehicle control indicating a significant improvement in Kupffer cell function and a trend towards normalization.

**Hepatoprotective effects of Eclipta alba on subcellular levels in rats.**

Saxena AK, Singh B, Anand KK.

Source
Department of Pharmacology, Regional Research Laboratory, Jammu-Tawi, India.

Abstract
The hepatoprotective effect of the ethanol/water (1:1) extract of Eclipta alba (Ea) has been studied at subcellular levels in rats against CCl4-induced hepatotoxicity. Ea significantly counteracted CCl4-induced inhibition of the hepatic microsomal drug metabolising enzyme amidopyrine N-demethylase and membrane bound glucose 6-phosphatase,
but failed to reverse the very high degree of inhibition of another drug metabolising enzyme aniline hydroxylase. The loss of hepatic lysosomal acid phosphatase and alkaline phosphatase by CCl4 was significantly restored by Ea. Its effect on mitochondrial succinate dehydrogenase and adenosine 5'-triphosphatase was not significant. The study shows that hepatoprotective activity of Ea is by regulating the levels of hepatic microsomal drug metabolising enzymes.

PMID: 8145570 [PubMed - indexed for MEDLINE]


**Antihepatotoxic activity of eclipta alba, tephrosia purpurea and boerhaavia diffusa.**

Murthy VN, Reddy BP, Venkateshwarlu V, Kokate CK.

**Source**
Faculty of Pharmecutical Sciences, Kakatiya University, Warangal 506 009, India.

**Abstract**
Alcoholic and chloroform extracts of E. alba, T. purpurea and B. diffusa were screened for antihepatotoxic activity. The extracts were given after the liver was damaged with CCl4. Liver function was assessed based on liver to boy weight ratio, pentobarbitone sleep time, serum levels of transaminase (SGPT, SGOT), alkaline phosphatase (SALP) and bilirubin. Alcoholic extract of E. alba was found to have good antihepatotoxic activity.

PMID: 22556585 [PubMed] PMCID: PMC3336594


**In vivo hepatoprotective activity of active fraction from ethanolic extract of Eclipta alba leaves.**

Singh B, Saxena AK, Chandan BK, Agarwal SG, Anand KK.

**Source**
Division of Pharmacology, Regional Research Laboratory, Jammu Tawi-180 001.

**Abstract**
The alcoholic extract of fresh leaves of the plant Eclipta alba (Ea), previously reported for is hepatoprotective activity was fractionated into three parts to chemically identify the most potent bioactive fraction. The hepatoprotective potential of the fraction prepared from extract was studied in vivo in rats and mice against carbon tetrachloride induced hepatotoxicity.
The hepatoprotective activity was determined on the basis of their effects on parameters like hexobarbitone sleep time, zoxazolamine paralysis time, bromosulphaline clearance, serum transaminases and serum bilirubin. Fraction Eall (10-80 mg/kg, p.o.) containing coumestan wedelolactone and desmethylwedelolactone as major components with apigenin, luteolin, 4-hydroxybenzoic acid and protocateuic acid as minor constituents exhibited maximum hepatoprotective activity and is the active fraction for hepatoprotective activity of Eclipta alba leave. The acute toxicity studies have shown that like Ea, Fraction Eall also high safety margin.

PMID: 11883149 [PubMed - indexed for MEDLINE]

In vitro antioxidant studies and free radical reactions of triphala, an ayurvedic formulation and its constituents.

Naik GH, Priyadarsini KI, Bhagirathi RG, Mishra B, Mishra KP, Banavalikar MM, Mohan H.

Source
Radiation Chemistry and Chemical Dynamics Division, Bhabha Atomic Research Centre, Trombay, Mumbai-400085, India.

Abstract
The aqueous extract of the fruits of Emblica officinalis (T1), Terminalia chebula (T2) and Terminalia bellerica (T3) and their equiproportional mixture triphala were evaluated for their in vitro antioxidant activity. gamma-Radiation induced strand break formation in plasmid DNA (pBR322) was effectively inhibited by triphala and its constituents in the concentration range 25-200 microg/mL with a percentage inhibition of T1 (30%-83%), T2 (21%-71%), T3 (8%-58%) and triphala (17%-63%). They also inhibited radiation induced lipid peroxidation in rat liver microsomes effectively with IC(50) values less than 15 microg/mL. The extracts were found to possess the ability to scavenge free radicals such as DPPH and superoxide. As the phenolic compounds present in these extracts are mostly responsible for their radical scavenging activity, the total phenolic contents present in these extracts were determined and expressed in terms of gallic acid equivalents and were found to vary from 33% to 44%. These studies revealed that all three constituents of triphala are active and they exhibit slightly different activities under different conditions. T1 shows greater efficiency in lipid peroxidation and plasmid DNA assay, while T2 has greater radical scavenging activity. Thus their mixture, triphala, is expected to be more efficient due to the combined activity of the individual constituents.
Cytochrome P450 inhibitory potential of Triphala—a Rasayana from Ayurveda.

Ponnusankar S, Pandit S, Babu R, Bandyopadhyay A, Mukherjee PK.

School of Natural Product Studies, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India. naturalproductm@gmail.com

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:
'Triphala' is one of the age-old, most commonly used polyherbal preparation from Ayurveda as Rasayana drug.

AIM OF THE STUDY:
This study was aimed at evaluating the effect of 'Triphala' on drug modulating enzymes to assess its safety through its potential to interact with co-administered drugs.

MATERIALS AND METHODS:
The cytochrome P450 inhibitory effect of 'triphala' formulation was investigated on rat liver microsomes using CYP450-CO complex assay and on individual isoform such as CYP3A4 and 2D6 using fluorescence screening. RP-HPLC method was developed to standardize 'triphala' and its individual components using gallic acid as analytical marker compound.

RESULTS:
RP-HPLC analysis demonstrated the presence of gallic acid (4.30±2.09 mg/g) in the formulation. The formulation showed 23% inhibition of the rat liver microsomes through CYP450-CO complex assay which is comparatively less when compared with the individual components. Further, the effect of standardized formulation dissolved in ethanol showed CYP3A4 and CYP2D6 inhibitory activity at the IC(50) values of 119.65±1.91 μg/ml and 105.03±0.98 μg/ml respectively. Gallic acid was also found to inhibit both the isoforms at the IC(50) values of 87.24±1.11 μg/ml and 92.03±0.38 μg/ml respectively.

CONCLUSIONS:
Various concentrations of the formulation and its individual components showed significantly less inhibitory activity (p<0.001) on individual isoforms when compared with the positive control. Assessment on the in vitro effect
of 'triphala' on drug modulating enzymes has important implications for predicting the likelihood of herb-drug interactions if these are administered concomitantly.

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Potential of traditional ayurvedic formulation, Triphala, as a novel anticancer drug.

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Source
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Abstract
The cytotoxic effects of aqueous extract of Triphala, an ayurvedic formulation, were investigated on human breast cancer cell line (MCF-7) and a transplantable mouse thymic lymphoma (barcl-95). The viability of treated cells was found to decrease with the increasing concentrations of Triphala. On the other hand, treatment of normal breast epithelial cells, MCF-10 F, human peripheral blood mononuclear cells, mouse liver and spleen cells, with similar concentrations of Triphala did not affect their cytotoxicity significantly. The drug treatment was found to induce apoptosis in MCF-7 and barcl-95 cells in vitro as determined by annexin-V fluorescence and proportion of apoptotic cells was found dependent on Triphala concentration. MCF-7 cells treated with Triphala when subjected to single cell gel electrophoresis, revealed a pattern of DNA damage, characteristic of apoptosis. Studies on Triphala treated MCF-7 and barcl-95 cells showed significant increase in intracellular reactive oxygen species (ROS) in a concentration dependent manner. ROS increase was, however, found to be insignificant in MCF-10 F as well as in murine spleen and liver normal cells. In vivo, direct oral feeding of Triphala to mice (40 mg/kg body weight) transplanted with barcl-95 produced significant reduction in tumor growth as evaluated by tumor volume measurement. It was also found that apoptosis was significantly higher in the excised tumor tissue of Triphala fed mice as compared to the control, suggesting the involvement of apoptosis in tumor growth reduction. These results suggest that Triphala possessed ability to induce cytotoxicity in tumor cells but spared the normal cells. The differential effect of Triphala on normal and tumor cells seems to be related to its ability to evoke differential response in intracellular ROS generation. The differential response of normal and
tumor cells to Triphala in vitro and the substantial regression of transplanted tumor in mice fed with Triphala points to its potential use as an anticancer drug for clinical treatment.

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Chemoprotective role of triphala against 1,2-dimethylhydrazine dihydrochloride induced carcinogenic damage to mouse liver.

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Abstract The present study was carried out to investigate the protective role of Triphala (a combination in equal proportions by weight of fruit powder of Terminalia belerica, Terminalia chebula and Emblica officinalis) against 1,2-dimethylhydrazinedihydrochloride (DMH) induced Endoplasmic reticulum stress (ER stress) in mouse liver. An oral dose of 3 mg/kg body wt in drinking water for 5 weeks significantly (P < 0.001) increased the levels of serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), serum Alkaline phosphatase (ALP) and total bilirubin thus suggesting damage to mouse liver and biliary dysfunction. The DMH administration invariably led to increase in the liver microsomal proteins of molecular weight of about 29 (ERp29) and 53 kDa (ERp53) and decrease in the protein of molecular weight of 36 kDa (ERp36) thereby suggesting the interference of DMH and its metabolites with normal protein biosynthesis and folding, in the reticular membranes of the liver cells thus developing ER stress. Histological studies show necrosis, large sized hepatocytes with increased N:C ratio, aberrant mitotic figures and prominent nucleoli in the liver of DMH treated mice. In animals fed 5% Triphala in diet (w/w) during DMH administration, there was significant decrease in the above changes in the liver suggesting the suppression of DMH induced ER stress in liver. Triphala significantly (P < 0.05) decreased lipid peroxidation and also the activity of lactate dehydrogenase (LDH) in mouse liver. It simultaneously increased the level of reduced glutathione (GSH) and the activity of glutathione-S-transferase (GST) thereby suggesting that it prevents peroxidative damage and also diverts the active metabolites (electrophiles) of DMH from their interactions
with critical cellular bio-molecules which could be responsible for its protective action against DMH.


**Effect of Azadiractha indica on paracetamol-induced hepatic damage in albino rats.**

Yanpallewar SU, Sen S, Tapas S, Kumar M, Raju SS, Acharya SB.

**Source**
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**Abstract**
Azadiractha indica, a plant used widely in Ayurveda, has been reported to have anti-inflammatory, immunomodulatory and adaptogenic properties. The present study evaluates its hepatoprotective role. Fresh juice of tender leaves of Azadiractha indica (200 mg/kg body wt. p.o.) inhibited paracetamol (2 g/kg body wt. p.o.)-induced lipid peroxidation and prevented depletion of sulfhydryl groups in liver cells. There was an increase in serum marker enzymes of hepatic damage (aspartate transaminase, alanine transaminase and alkaline phosphatase) after paracetamol administration. Azadiractha indica pretreatment stabilized the serum levels of these enzymes. Histopathological observations of liver tissues corroborated these findings.

PMID: 12834004 [PubMed - indexed for MEDLINE]


**Possible mechanism of hepatoprotective activity of Azadiractha indica leaf extract: part II.**

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**Abstract**
Hepatoprotective activity of Azadiractha indica leaf extract against paracetamol induced hepatic damage in rats has already been reported. In the present investigation effects of Azadiractha indica leaf extract on blood and liver glutathione, Na+K(+)-ATPase activity and thiobarbutiric acid reactive substances against paracetamol induced hepatic damage in rats
have been studied with a view to elucidate possible mechanism behind its hepatoprotective action. It was interesting to observe that Azadirachta indica leaf extract has reversal effects on the levels of above mentioned parameters in paracetamol hepatotoxicity. Possible mechanism behind the results are discussed.

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