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HEPATOPROTECTIVE ACTIVITY OF PLANT BASED DRUGS AGAINST D-GALN.

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ABSTRACT

Liver disorder may cause liver inflammation or tissue injury and affects liver physiologic condition. Natural products that are found in the form of vegetables, fruits, plant extract, herbs, and animals, have been traditionally and clinically used for treating liver disorders. They are specific chemical compounds that usually have biological activities for use in drug evaluation and design. Many herbal products have been clinically available as potent anti-hepatotoxic agents against commonly occurring liver disorders. This review summarizes the current progress in the basic, clinical, and traditional research on herbal products in treatment of various liver disorders. Also, we will rivet on the discovery and biological evaluation of the herbal products, which shows potential as a new anti-hepatotoxic agent of liver disorders.

KEYWORDS: **Antioxidant enzyme, Hepatotoxicity, D-Galactosamine, Flavanoide, Free radical, Hepatoprotective activity, Herbal medicine, Ant inflammation.**

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INTRODUCTION

A liver in injury is closely related to human hepatitis; D-Galactosamine is well defined heapatotoxicant & plays an important role in evolution of hepatoprotection. D Galn heapatotoxicant is an experimental model which mainly causes acute hepatitis & it not affect other organs. D-Galn has a greater affinity with liver because liver cell have high affinity with galactokinase & galactose 1-uridytransferase&also it inhibit synthesis of uridylate nucleotide[1]. D Galn induced hepatotoxicity by inhibiting the synthesis of RNA & protein via reduction of cellular U.T.P a substrate for RNA polymerase[2] D-Galn breaks the enzyme that transfers the substrate to mitochondria & modifies the composition of phospholipids of membrane this bring about change in mitochondria also[3]. A single injection with d-galactosamine can decrease the uracil nucleotides in the liver and heart.[4] It alter the synthesis of essential uridylate nucleotide, depletion of these nucleotide impaired the synthesis of glycoprotein lead to change of cell membrane resulting change in permeability of membrane & finally leakage of enzyme from cell[5].It cause metabolic disturbance. The main source of damaging cell membrane & stimulation of lipid peroxidase is due to formation of highly reactive hydroxyl radical (oH*) [6]. Oxidative stress is one major problem of D Galn induction due to excessive formation of free radical resulting from oxidative stress damage macromolecule as lipid & D-Gal injection decreased GSH, SOD,& CAT who show that that D Galn intoxicant increased TBRS level which are a typical parameter for lipid peroxidase[7] Oxidation is common procedure of body, free radical are formed when body breakdown food into energy it is highly unstable molecule that alter many vital function of body. Free radical causes damage known as “oxidative stress” & key role in production of state like alzimer, cancer, heart disease, Parkinson, rheumatoid arthritis[8]

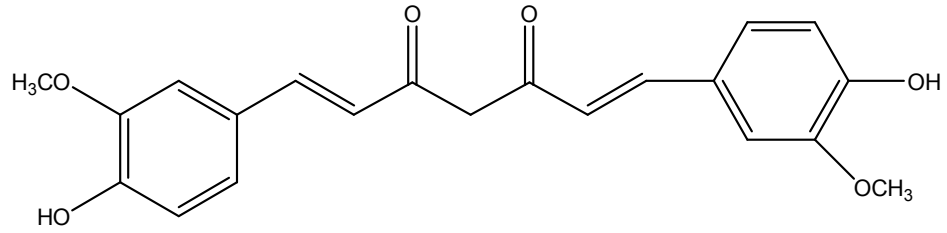
HEDYOTIS CORYMBOSA

Hedyotis corymbosa (L.) also known as Oldenlandia corymbosa Lam, belonging to family Rubiaceae,is a weed which distributed throughout India. In traditional medicine of Kerala It is commonly known as ‘Parppatakapullu’. There are approx 180 species in which 35 species found in Malaysia. Plant extract given in liver deasese, jaundice, heat eruptions, and vitiated conditions. Increased level of AST, ALT, ALP and GT in serum Caused by D-Galn alters by the treatment with HC extract at 100 mg & 200 mg/kg does. Recovery getting normelisation that extract of HC causes parenchyma cell regeneration in liver thus protecting membrane fragility, decreasing enzyme leakage and extract mediated decreased level of increased bilirubin. Suggested HC extract able to stabilize billiary dysfunction. D-Galn treatment causes decrease in level of antioxidative enzyme activities. Extract of HC arises the antioxidant parameter and decreased oxidative stress which appeared in decreasing the mean value of liver TBARS and compared to D-GalN. The level of GSH, SOD & CAT decreased out the hepatic damage with D-Galn administration but treatment with 100 & 200 mg/kg of treatment show significant increase in these enzymes and controls the level of LPO which indicate antioxidant activity of HC. Histopathology examination of HCE at Different Dose levels offers hepatoprotection, but 200mg/kg is more effective than other lower dose.

CURCUMIN

Curcumine is main compound found in plant curcuma longa was first isolated two centuries ago. It is used from long time in Indian tradition to treat various disorders like body ache, skin diseases rheumatism, intestinal worms, diarrhea, hepatic disorders, biliousness, urinary discharges, intermittent fevers, leukoderma, amenorrhea, and colic. Viewing its medicinal importance, interest has been focused on curcumine due to its treatment of wide variety of disease such as Alzheimer’s disease,

psoriasis, cardiovascular, arthritis, cancer, diabetes & so many by modulation of various molecular target[9]. Curcumine inhibit many factors like nuclear factor-kappa.



Chemical structure of various natural products: Curcumin from the plant CurcumaLonga.

Curcumine control many pro-inflammatory and profibrotic cytokines and its antioxidant properties proved a rational use in liver disease. Curcumin could attenuate liver injury induced by ethanol, thioacetamide, iron overdose, cholestasis[10]

ENICOSTEMMA AXILLARE

Enicostemma axillare Raynal Belonging from Family Gentianaceae is a perennial glabrous herb found throughout India common in coastal areas. In Indian tradition it is used in the treatment of hepatic diseases and a blood purifier. Swertiamarin is a main content found in Enicostemma axillare in the form of alkaloids, steroids, saponins, triterpenoids, flavanoids, phenolic acids and xanthenes were isolated from Enicostemma axillare. Swertiamarin Treatment at 100 and 200 mg/kg show a significant reversed the level of liver enzyme, produced by D-Galn & recover towards normalize. Extract of Enicostemma caused increase level in CAT, SOD, & GSH & Minimize the level of TBARS in serum, kidney and liver show a significant role that it restored these antioxidant action in the problem caused by D-Galn hence the mechanism of hepatoprotection of Swertiamarin is mainly by its antioxidant property. Swertiamarin is one of the treatments at 200 mg/kg body wt administrated orally for 8 day to normalize animal and also show better hepatoprotective action[11]. This result given by histological sdudes. Extracted Swertiamarin is 100% pure, which can be evaluated by HPTLC. In Acute toxicity evaluation Swertiamarin up to 2000 mg/kg show no any toxicity & mortality when given orally. Swertiamarin (200 mg/kg) dose to d-GalN intoxicated rats showed a maximum hepatoprotection.

GLYCYRRHIZIN

Glycyrrhizin is an aqueous extract of the liquorice root (*Glycyrrhiza glabra*) and used from ancient time in traditional medicine to treat bronchitis, jaundice and gastritis. The main chemical constitute are flavanoids, hydroxycoumarins, glycyrrhetic acid, and beta-sitsterol, with some extent with glucocorticoide and mineral corticoid properties. A standard extract containing, cysteine and glycine, glycyrrhizin, used to treat chronic hepatitis as Stronger Neominophagen C (SNMC) in Japan. Daily treatment with Glycyrrhizin with 80 mg/kg/day administration iv for 2 week lowered the elevated level of alanine transaminase[12]. SNMC mainly available in the united state as tablet & liquid powder. In cell culture experiments, glycyrrhizin modifies glycosylationand blocks sialylation of hepatitis B surface antigen (HBsAg), leading to its retention in the trans-Golgi apparatus[13.] There is no any experimental evidence for antiviral activity of Glycyrrhizin, but it is due to membrane-stabilizing effect proposed by in vitro hepatotoxicity model study[15].

MELOCHIA CORCHORIFOLIA

The extract of Arial part of plant Melochia Corchorifolia shows presence of different phytochemicals constituents like steroid, flavanoids, alkaloid, tannins, and carbohydrates. The extract gives nega due to its potent pharmalogicale activity, economic

viability and toxicity. The main antioxidant property is due to its reflecting electron donation capacity of bioactive compound[15]. By donating electrons, antioxidant substances are able to block radical chain reaction by converting reactive oxygen species to more stable products. The antioxidant properties of plant that promote health protection by counteracting reactive oxygen species (ROS) [16]. The phenolic content in Arial part of *M. corchorifolia* were found to be from (16.28+_0.52) to (34.22+_0.43) mg/g. Methanol extract contains more phenolic content i.e. (34.22_+0.43) mg/g than other extracts and the alkaloid content was ranging from (18.46+_0.34) to (26.37+_0.16) mg/g. Also methanolic content have more alkaloid content (26.37+_0.16) mg/g than other extracts[17].

S.no.	Name of the extract	Total phenolic content (mg/g)	Total alkaloid content (mg/g)
1	Hydro alcoholic (Ethanol70%)	29.34±0.69	21.86±0.39
2	Ethyl acetate	24.69±0.47	20.58±0.43
3	Hexane	16.28±0.52	18.46±0.34
4	Methanol	34.22±0.43	26.37±0.16

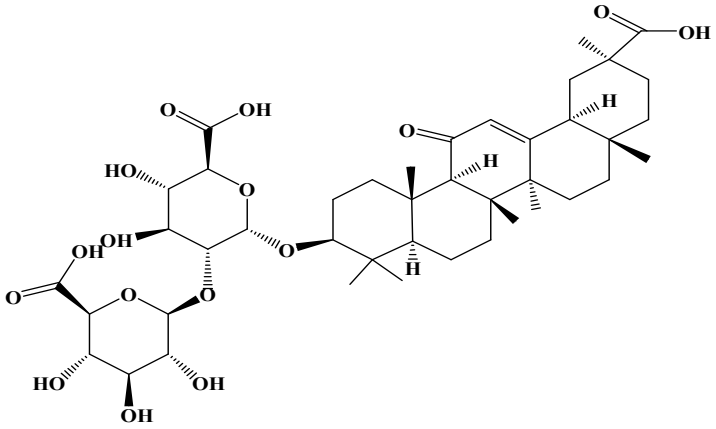
On comparing with the silymarin plant extract at 500mg/kg produce normalize the level of sGOT, sGPT, ALP and TBRS level. The main protective effect is arises due to stabilizing of membrane of liver and scavenging the free radical or by both mechanism. Methanolic extract of *M. corchorifolia* show better antioxidant and hepatoprotective properties due to the presence of important antioxidative factors like phenolic, alkaloid and flavanoids compounds[18-24].

IN VITRO ANTI OXIDANT ACTIVITY

In this studied the hydro alcoholic, methanol, ethyl acetate extract of *M.corchorifolia* were found concentration dependent scavenging activity on tested free radicals (superoxide, hydroxyl and DPPH). The mean IC50 values for superoxide radical of hydro alcoholic, methanol, ethyl acetate and hexane extracts of *M. corchorifolia* were found to be 206 µg, 127µg, 530µg and 901 µg respectively. The mean IC50 values for hydroxyl radical of methanol extract is 240µg, 384µg for hydroalcoholic, ethyl acetate was found to be 490µg and 501µg respectively. The IC50 value for DPPH radical of methanol, hydro alcoholic, ethyl acetate and hexane was found to be 179µg, 286µg, and 470µg and 971µg respectively[8].

POLYGONUM CUSPIDATUM

The main chemical constituents of *Polygonum cuspidatum* is resveratrol, a polyphenolic phyto chemicals mainly found in grapes wine and berries, several study show that its potent treatment in the liver ailments. The hepatoprotection of *Resveratrol* is due to inflammatory cytokines and free radicals induce antioxidant enzyme and increase the level of Glutathione and modulate varied signal transduction pathway of hepatotoxicity.



Chemical structure of Resveratrol from Polygonum cuspidatum

Many studied such as cultured cell, purified enzymes and laboratory animal show that its antioxidant, anti-inflammatory, anti-carcinogenic and anti-aging properties that might be relevant to chronic diseases and/or longevity in humans[25]. Resveratrol reduces the elevated level of TNF-a and IL-6, mRNA and normalize the number of kuffer cells in the damaged liver. It also promoted liver cell regenerations and minimizes fibrosis that enhances the survival of BDL mice. Resveratrol is also used in cholestasis liver injury[26]. Another hepatoprotection of this plant derived by suppressing oxidative stress and apoptosis. Either Pretreatment or advanced stage of hepatocarcinogenesis is treatment show equally effective by activation of the apoptotic pathway in rodent[27]. The activity Resveratrol on vascular endothelial growth factor and angiogenesis in hepatocellular carcinoma caused by suppression of the activation of NF-kappa B in HepG2 cell[28]. It also protects liver from methotreaxate liver injury[29]. Oral treatment with Resveratrol (20 mg/kg daily for 4 weeks) remarkably inhibit the DMN-induced loss in liver, body weight, and inhibited the elevated level of serum alanine transaminase, aspartate transaminase, alkaline phosphatase and bilirubin levels[30].

Bei Chaihu (Bupleurum Chinese)

D-Galn is important heapatotoxicant producing hepatic injury model. It causes inhibition of RNA & protein synthesis through loss of uridine nucleotide and aggregation of UDP hexosamines in liver cell. In a study it found that D-Galn induced hepatotoxicity increase sensitivity to TNF which cause hepatic injury during inflammation. Aminotransferase catalysis of amino transfer reaction is a major diagnosis of hepatotoxicity. Serum AST, ALT, and TNF in blood are main point for evolution of hepatoprotection. In estimation of the hepatoprotective effect of B. Chinese polysaccharide rat's treated with different concentration of WBCP after D-Galn injection. As in table D-Galn significantly increased serum AST and ALT level outcome compared with control gp, and treatment with WBCP decrease this elevated level when given in different dose dependent manner. When treated with WBCP, AST found to be decreased level at 11.9%, 33.4% and 40.3% at the different dose of 100, 200 and 400 mg/kg, respectively, and ALT activity by 8.0%, 19.4% and 30.6%, and LDH activity by 14.9%, 26.9% and 37.9%, respectively on dose dependent manner. ALP is main agent for removing phosphate gp from nucleotide and protein which formed in liver and key role in heapatic function's-Galn increased level of ALP level[31].

Group	Dose (µmol/mg protein)	AST (µmol/mg protein)	ALT (µmol/mg protein)	ALP (µmol/mg protein)	LDH (µmol/mg protein)
Normal		107.44±9.25	74.41±7.44	501.23±69.42	710.61±69.72
Control		932.23±86.46	635.21±79.32	821.59±110.55	1929.45±242.46
WBCP	100	821.34±77.52	584.44±95.24	753.43±99.19	1641.48±196.42
	200	621.03±92.42*	512.74±63.48*	671.56±90.26*	1411.53±241.28
	400	556.22±86.42**	441.06±84.41**	592.46±94.99**	1197.46±243.98**

Values are expressed as mean ±SD (n = 10).
**** p < 0.05.***
***** p < 0.01 vs. control***

Hedyotis corymbosa

The effect on various doses of HCE was studied on serum marker enzymes and total bilirubin in D-GalN intoxicated animal. It showed no any toxicological effect at 100 and 200 mg/kg body wt. thearfore 200 mg/kg dose of plant extract is effective for its pharmacological effect's D-Galn injury cause significantly change in marker enzyme like, AST - 172.35%, ALT by 188.04%, ALP by 119.9%, γ-GT by 112.33% and total bilirubin by 57.73% on comparing with control group. The percentage protection in marker enzyme of treated group at 100 mg/kg as AST 7.83 (P< 0.01), ALT 12.47 (P< 0.05), ALP 8.4 (P< 0.01), γ-GT 7.03 and total bilirubin 10.67(P<0.01) on comparing with toxic group while maximum protection percentage in marker enzyme at the dose of 200 mg/kg and silymarin (100mg/kg) as AST 38.38 (P< 0.001), 56.34 (P< 0.001),ALT 32.65 (P< 0.001), 46.76 (P< 0.001), ALP 36.93 (P< 0.001), 45.94 (P< 0.001), γ-GT 26.3 (P< 0.01), 38.53 (P<.001), and total bilirubin 24.27 (P< 0.001), 32.03 (P< 0.001) which is almost comparable to the group treated with silymarin. Silymarin is a potent hepatoprotective which used as standard drug[32].

Table

Effect of HCE on serum AST (U/L), ALT (U/L), ALP (U/L), Total Bilirubin (TBL) level (mg/dl), and γ-GT (U/L) against D-galactosamine induced liver.

Group	ALT	AST	ALP	TBL	γ-GT
Control	32.38 ±2.7	72.2 ±3.2	98.27 ± 2.2	0.67 ± 0.02	1.54 ± 0.09
D-Galn	93.27 ± 4.6*	213.20± 5.24*	216.1 ± 5.8*	1.03 ± 0.04*	3.27 ± 0.23*
HCE100	81.67 ± 4.2a	196.50 ± 4.2b	197.8 ± 4.1b	0.92 ± 0.03b	3.04 ±0.2n
HCE 200	62.81 ± 3.8c	131.35 ± 3.8c	136.28 ± 3.2c	0.78 ± 0.02c	2.41 ± 0.19b
Silymarin	49.65 ± 3.1c	93.08 ± 3.5c	116.81 ± 2.9c	0.7 ± 0.02c	2.01± 0.17c

Mean ± S.E.M. of 6 rats in each group
n: no significant.
P values: *<0.001 compared with respective control group me.
P values: a<0.05, b<0.01, c<0.001 compared with group II (D-Gal).

Allium sativum

Allicin is main active constitute of freshly *Allium sativum (*garlic) cloves. In D-Galn induced hepatotoxicity in rat resulting increase in level of lipid per oxidation and deacresd antioxidant property of liver. Treatment with allicin prevents these alterations. The concentration of sGOT level decreased that found in liver cell, pancreas, lungs, leukocytes, skeletal muscle, kidneys, brain, and erythrocytes. In tissue sGOT occurs in two locations, the cytosol and mitochondria but sGPT show highest concentration in liver cell.[33] sGPT show more specific test for assessing hepatocellular damage then test of sGOT. On comparing both sGOT as well as sGPT level that assessed the hepatic damage caused by D-Galn. Heapatotoxicant (D-Galn) gp B compared with Control gp A, Through treatment gp, with the allicin 0.3 and 0.4 mg/kg for 15 and 22 days respectively show highest efficacy and potency in decreasing the sGOT and sGPT levels, the dose with low concentration and less number of days (0.3 mg/kg for 15 days) showing better protection for the liver against d-Galn induced hepatotoxicity as shown in table.

Effect of different doses of allicin and the reference drug silymarin on sGOT and sGPT activities in d-GalN-treated rats.

Group	sGOT			sGPT		
	8day	15day	22day	8day	15day	22day
Control (A)	110.6 ± 3.1	107.5 ± 3.4	109.0 ± 3.9	60.0 ± 1.8	58.2 ± 1.7	61.7 ± 2.1
GalN-intoxicated (B)	340.6± 25.4□□	329.0± 23.2□□	333.2± 26.4□□	215.8± 22.1□□	199.4± 21.6□□	204.4± 24.2□□
Silymarin (C)	140.3± 16.5□	129.2 ± 9.3□	136.1 ± 8.7□	102.5 ± 8.3□	59.1 ± 2.2□	58.7 ± 1.7□
Allicin, 0.2 mg/kg (D)	163.0 ± 9.3□□	149.0 ± 8.5□□	141.0 ± 7.6□□	143.2 ± 6.3□□	74.4 ± 6.2□□	68.2± 2.3□□
Allicin, 0.3 mg/kg (E)	151.5 ± 7.2□	134.0 ± 6.7□	131.0 ± 5.7	123.7 ± 7.9□	60.1 ± 3.1□	59.7 ± 1.7□
Allicin, 0.4 mg/kg (F)	149.3 ± 6.3□	133.0 ± 6.1□	127.3 ± 5.7□	121.5 ± 8.2□	59.9 ± 2.7□	58.3 ± 4.2□

Values are represented as mean ± S.E. (n = 6) and analyzed by one-way analysis of variance (ANOVA). Further analysis between the groups was statistically evaluated by the Newman–Keults test. P-value <0.05 was regarded as significant. (A) Saline-treated control; (B) Galactosamine (300 mg/kg per day) and lip polysaccharide (30 µg/kg per day) i.p. on the last day of treatment protocol and the animals were sacrificed 24 h after administration.

□***P < 0.01***

□□***P < 0.05***

D-Galn hepatotoxicity significant increases the level of lipid per oxidation as well as increased the level of iron and ferritin as compared with control rats.

Table

Effect of allicin on lipid per oxidation and its antioxidant properties

Parameters	Group I normal control	Group II allicin pretreated (A)	Group III GalN/ LPS-intoxicated (B)	Group IV(A + B)
Iron	171 ± 16.70	169 ± 16.56	369.45 ± 17.60†	181.12 ± 16.87†
SOD	6.46 ± 0.75	7.01 ± 0.67	3.36 ± 0.47†	7.46 ± 0.69†
CAT	77.56 ± 7.38	79.12 ± 7.1	36.51 ± 2.97†	67.13 ± 7.81†
LPO	1.39 ± 0.16	1.41 ± 0.13	2.35 ± 0.24†	1.46 ± 0.17†
GSH	5.65 ± 0.49	5.13 ± 0.48	2.97 ± 0.21†	4.63 ± 0.39†
GST	11.16 ± 1.21	11.25 ± 1.31	5.26 ± 0.48†	9.59 ± 0.89†
GPX	81.12 ± 7.86	83.11 ± 8.14	52.56 ± 4.97†	77.63 ± 7.11†
Ferritin	27.71 ± 2.67	25.67 ± 2.49	79.16 ± 7.36†	31.54 ± 3.09†
Ceruloplasmin	39.46 ± 3.43	36.13 ± 3.52	17.12 ± 1.65†	31.23 ± 2.96†

Values expressed as mean ± S.D, n = 6; Group III vs. Group I; Group IV vs. Group III; Student's t-test.

Activity of tissue antioxidants is expressed as: nmol/g liver tissue for GSH; _mol of GSH oxidized/min/mg of protein for GPX; unit/min/mg of protein for GST; 50% inhibition of epinephrine auto-oxidation for SOD; µmoles of hydrogen peroxide decomposed/min/mg of protein for CAT. Activity of ceruloplasmin in serum is expressed as mg/dl. (A) Allicin (0.3 mg/kg per day) diluted in 1% of gum acacia; (B) Galactosamine (300 mg/kg per day); lip polysaccharide (30µg/kg per day) i.p. on the last day. †P < 0.001. This studied show that oral pre treatment with allicin for 15 days with different dose show significantly normalizes the elevated level of lipid per oxidation and other. Most of the effect is due to its strong SH modifying and antioxidant properties [33].

Tridax procumbens

Tridax weed belonging from family Compositeae found all over India and used as indigenous medicine for various hepatotoxicities. It also used from traditionally in Indian medicine as antifungal and insect repellent, anticoagulant, in bronchial catarrh, diarrhea and dysentery. Tridax procumbens also found in 'Bhringraj' which perform a key role in herbal medicine for hepatotoxicity.[34]

Lygodium flexuosum

Lygodium belonging to family lygodiacea is a climbing fern. It also known as vallipanna and distributed all over India mainly in Western Ghats of Kerala. Lygodium flexuosum is very important medicinal plant in Indian ayurveda tradition some scholar state that plant may be 'Rudra jata' its medicinal properties show by all

part of the plant. 'Rudra jata' is an intermediate drug in Ayurveda system. The rhizomes' used in the treatment of jaundice. The root is also used to treat stomach pain by Mech, Oraon and Rabha tribes in Jalpaiguri district of West Bengal, India[35]. D-Galn at dose of 800mg/kg causes elevation in serum AST, ALT, and LDH. When n hexen extract of Lygodium flexuosum given at dose of 100mg/kg and 200mg/kg body wt it show remarkably decrease in elevated level of marker enzyme and also protect the live from increasing hepatic malondialdehyde [MDA] formation & normalize the level of glutathione (GSH) in d-galactosamine treated rats. 200mg/kg dose show more effective than 100mg/kg. Histopathology report show its membrane stabilizing effect and hepatoprotection action is due to inhibiting UDP-sugar derivatives & biosynthesis of glycoprotein[35]. On treatment with Lygodium flexuosum for 2, 24 & 48h after D-Galn injection the free radical generated wear scavenged by the extract as evidence from normal liver MDA and GSH level. And its hepatoprotection action is due to inhibiting UDP-sugar derivatives[35]

Table

Effect of Lygodium flexuosum extracts and Silymarin on GSH and MDA in d-galactosamine intoxicated rats (post-treatment groups)

Treatment gp	MDA(nmol/mg tissue)	GSH(nmol/mg Protein)
Normal control	0.635 ± 0.001	0.522 ± 0.002
Lygodium flexuosum (200 mg/kg) + d-galactosamine	0.637 ± 0.003†	0.520 ± 0.002†
D-galactosamine control (800 mg/kg; i.p.)	1.089 ± 0.006*	0.400 ± 0.003*
Lygodium flexuosum (100 mg/kg) + d-galactosamine	0.676 ± 0.002†	0.498 ± 0.001†
Silymarin (50 mg/kg) + d-galactosamine	0.658 ± 0.002†	0.503 ± 0.001†

Values are means's., n=6.
**** p≤0.05 vs. normal control.***
† p≤0.05 vs. d-galactosamine control.

CONCLUSION

In the above study we discussed about laboratory finding and clinical trial study of natural hepatoprotective plant. Main focused on the natural extract which contain bioactive molecule which show hepatoprotection. Herbal plant extract are used from ancient time to treat various disease associated with liver and now they become a promising therapy for pathological liver state. This time many natural plant and there potent extract are available which show hepatoprotection. These phytochemicals can be extracted and developed as separate drugs, with quality and standards of recent medicinal system. It's very critical time for the pharmaceutical industry in drug discovery process which are going very expensive, inefficient and riskier. In Indian tradition natural plant play key & wide source of drug many pharmaceutical preparation contain these herbals to enhance their efficacy. Half of Indian medicine preparation contains these natural plants that of the modern concept of evidence-based medicinal evaluation, standardization of herbal products and randomized placebo-controlled clinical trials to support clinical efficacy. Herbal drug served as a materia medica of our living lifestyle, and becoming a promising treatment for pathological liver disorder.

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