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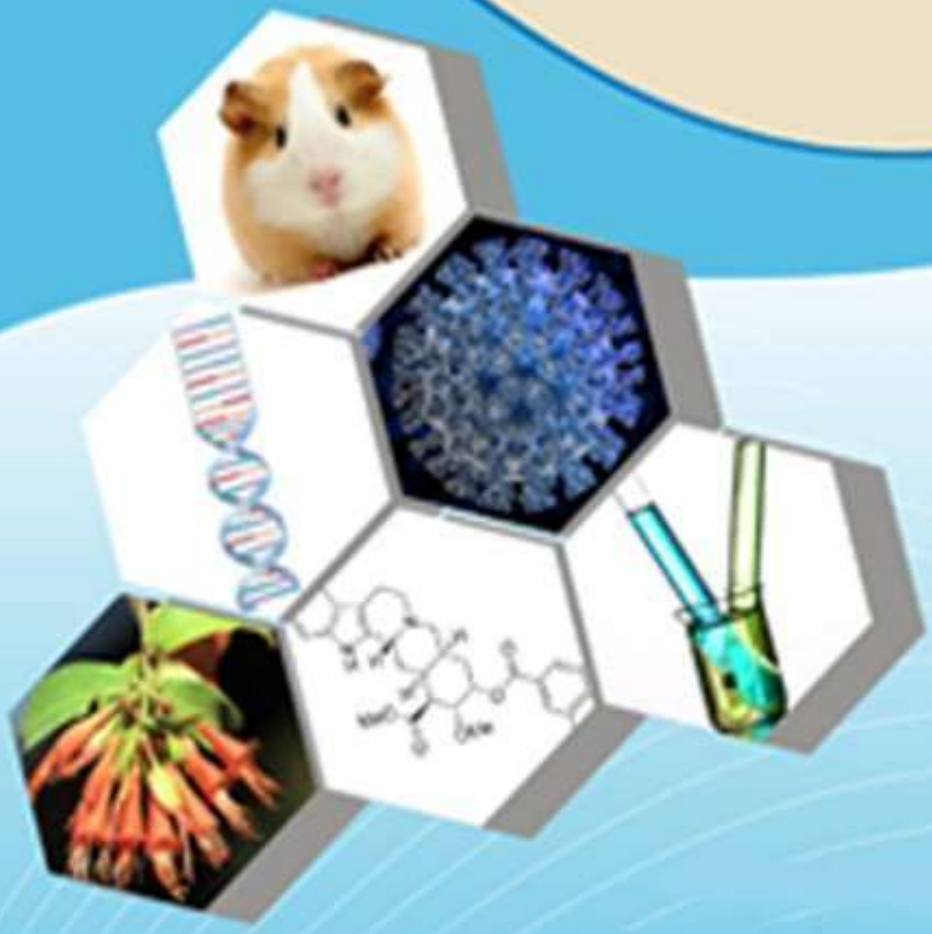

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Hepatoprotective Effects of Dawa-Ul-Kurkum, a Unani Polyherbal Preparation and the Possible Mechanisms in Experimental Model of Ethanol Induced Liver Damage in Rats

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Abstract Objective: Necrosis, elevated oxidative stress indicators such the Nitrates and Nitrites (NOx) test, Malondialdehyde levels, decreased glutathione (GSH) levels depletion, and elevated liver markers are all symptoms of hepatotoxicity. Methods: Hepatic derangement and an increase in several liver indicators were induced in rats by daily dosing with ethanol, simulating the effects of ethanol poisoning in humans. The effectiveness of various pharmaceutical interventions was evaluated using several indicators of liver damage. In addition, hepatic necrosis, fatty alterations, and hydropic degeneration were seen during histological analysis. A comparison of the hepatoprotective benefits of Dawa-ul-Kurkum and Hydro-alcoholic extract therapy with those of conventional medicine treatment showed similar outcomes for both. Higher levels of Malondialdehyde and Nitrates and Nitrites (NOx) test were found in alcoholic liver injury, but reduced glutathione (GSH) levels were found to be lower. Dawa-ul-Kurkum and Hydro-alcoholic therapies both reduced oxidative stress, although to varying degrees. The results show that Dawa-Ul-Kurkum therapy and its extract were effective in lowering hepatotoxic damage indicators in rats exposed to ethanol.

Keywords: Histopathology, hepatotoxicity, ethanol, and the Dawa-Ul-Kurkum

Introduction: The liver plays a crucial role in the body by aiding in digestion, storing nutrients, secreting hormones, and eliminating harmful substances. Hepatotoxicity may develop from excessive alcohol use over time, endangering the liver's regular functioning. The ethanol metabolism produces toxic metabolites that induce oxidative stress and hepatotoxicity [1]. The ingestion of alcohol, a psychoactive substance, has been related to several health problems [2]. One of the primary mechanisms of ethanol-induced hepatotoxicity is oxidative stress. Ethanol is metabolized by alcohol dehydrogenase into acetaldehyde, which is subsequently oxidized by acetaldehyde dehydrogenase into acetate [3-6]. The enzyme cytochrome P450 (CYP2E1) is responsible for converting excess ethanol to acetaldehyde, which has been linked to the generation of reactive oxygen species (ROS) [7-9]. A rise in reactive oxygen species (ROS) and a decline in antioxidant defenses leads to oxidative stress. Recent studies [10, 12] reveal that oxidative stress caused by ethanol is a major contributor to the onset and progression of alcoholic liver disease.

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Indo-American Journal of Pharma and Bio Sciences

Vol. 14, Issuse 1, Jan 2021

There are now no drugs that may halt or reverse the progression of alcoholic liver damage; new treatments are desperately required. Researchers are interested in medicinal plants and their active phytochemicals as prospective treatments against alcoholic liver damage due to their high antioxidant capacity and minimal adverse effect profiles. There is presently little scientific evidence to support the use of medicinal plants as a treatment or prevention for many ailments [13], despite the fact that their popularity has skyrocketed in recent decades. Using medicinal plants for the prevention and treatment of illness is one of the many complementary and alternative medicine practices that have gained popularity in the last decade. With the use of cutting-edge medical technology, these polyherbal drugs have been shown to be effective in treating a wide range of complicated pathophysiological conditions. Traditional herbal remedies for immunomodulation and hepatoprotection need to be tested in light of current scientific knowledge. In cases of liver malfunction, anorexia, ascites, and stomach discomfort, Dawa-ul-Kurkum, a polyherbal Unani preparation, might be helpful. Sunbul- ut-Teeb, Mur Makki, Saleekha, Qust, Shagufa-e-Izkhir, Darcheeni, Zafran, plus Sharab-e-musallas and Qand Safaid [14] are all part of this polyherbal. The purpose of this research is to examine the potential hepatoprotective effects of Dawa-ul-Kurkum and the mechanisms behind these effects in ethanol-induced liver injury in rats.

Methods

Drugs and Chemicals

The drug and chemicals are taken from different suppliers like Dawa-Ul- Kurkum provided by Central Research Institute of Unani Medicine, Hyderabad, Silymarin were purchased from Sigma and other chemicals were taken from SRL, New Delhi. Biochemical kits were purchased fromERBA.

Animals

The study employed either a male or female Wistar strain. Animals were seized from the Central Animal House Facility, Hamdard University and kept in a controlled environment. They were provided with unlimited food and drink. Animals were cared for according to CPCSEA criteria for animal usage, which were approved by the Institutional Animal Ethics Committee (IAEC) protocol number 1768 (Registration number 173/GO/ReBi/S/2000/CPCSEA).

The Investigational Drug

Dawa-ul-Kurkum, was provided by Central Research Institute of Unani Medicine (CRIUM), Ministry of AYUSH, Govt. of India with a batch no. 3-1/2018-19/CRIUM. This preparation is composed of Sunbul-ut-Teeb, Mur Makki,

Saleekha, Qust, Shagufa-eIzkhir, Darcheeni, Zafran with Sharab-e-musallas and QandSafaid QS [15]. The formulation is well documented in standard Unani literature and is certified to have been prepared as per traditional classical Unani text by CRIUM. Dawa-ul-Kurkum is a semi-solid preparation created with the ingredients listed below in the formulation [Table 1].

HPTLC of alcoholic extract of Dawa-Ul-kurkum

Dawa-Ul-Kurkum an important polyherbal formulations used for unani medicine. Standardization was carried out by Densitogram of alcoholic extract of Dawa-ul-kurkum at UV 366nm and UV 254nm [Table 2, 3 and Figure 1].

Table 1: Formulation Composition

S.No	Name	Botanical/sci. name	Qty	Part
1.	Sumbul-ut-tib	*Nordostachys jatamansi* DC. Syn. *Valeriana jatamansi*	1 Part	Dried Rhizomes
2.	Murmakki	*Commiphora myrrha*	1 Part	Gum resin
		(Nees) Engl.		
3.	Saleekha	*Cinnamomum cassia* Blume	1 Part	Bark
4.	Qust	*Saussurea lappa* C.B. Clarke	1 Part	Dried roots
5.	Shagofa Izkher	*Cymbopogon jwarancusa* Schult Syn. *Andropogon*	1 Part	Flower

Indo-American Journal of Pharma and Bio Sciences

Vol. 14, Issuse 1, Jan 2021

		Jwarancusa Jones		
6.	Darchini	*Cinnamomum zeylanicum* Blume	1 Part	Bark
7.	Zafran	*Crocus sativus* Linn.	1 Part	Style and stigma
8.	Sharab Musallas	-	Q.S	-
9.	Asal OR Qand Safaid	-	Q.S	-

Table 2: Peak list of alcoholic extract of Dawa-ul-kurkum at UV 366nm

Peak no	Y-Pos	Area	Area %	Height	Rf value
1	9.7	1731.46	84.02	747.93	0.01
2	24.2	12.96	0.63	10.16	0.21
3	30.4	56.38	2.74	31.68	0.29
4	44.7	19.06	0.93	8.98	0.49
5	79.0	240.80	11.69	86.68	0.96

Table 3: Peak list of alcoholic extract of Dawa-ul-kurkum at UV 254nm

Peak no	Y-Pos	Area	Area %	Height	Rf value
1	9.8	930.19	39.85	519.16	0.01
2	14.3	137.38	5.89	116.47	0.07
3	34.5	925.77	39.66	370.07	0.35
4	72.7	94.11	4.03	29.85	0.87
5	79.6	246.78	10.57	132.46	0.97

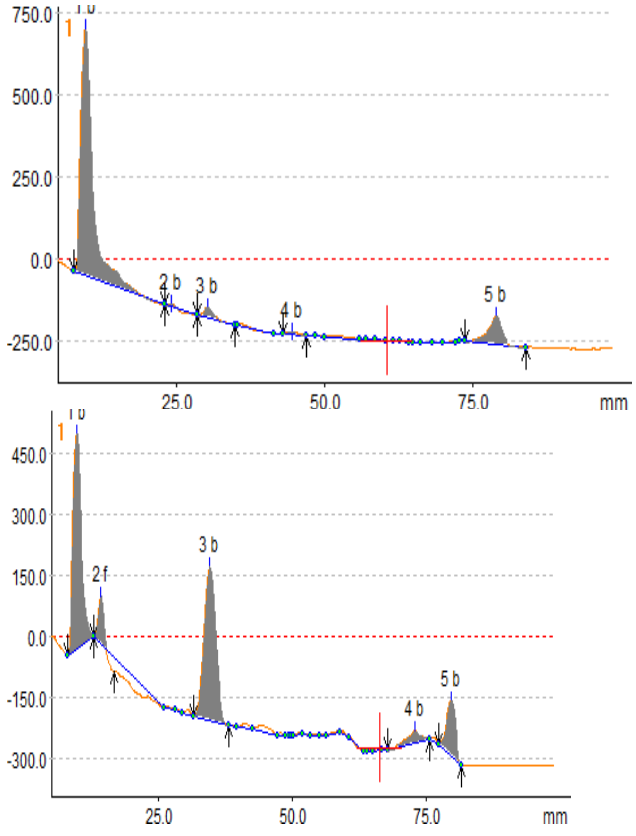


Figure 1: Densitogram of alcoholic extract of Dawa-ul-kurkum at UV 366nm and UV 254nm

Experimental Procedure (Ethanol induced liver damage in rats)

The rats in this experiment were given a diet of commercial rat food and water on a "as needed" basis before being randomized into seven groups of five. Each rat in Group I received an extra 2 ml/100 gm/day of distilled water as a control. For six weeks, members of Group II in the experiment were given 2 ml (0.5 g)/100 gm of body weight in an aqueous solution of 30% v/v ethanol. Group III served as the positive control and received 50 mg/kg p.o. of silymarin; Groups IV and V received Dawa-ul-Kurkum prepared according to Unani specifications (250 and 500mg/kg, p.o.); and Groups VI and VII received a HA extract of Dawa-ul-Kurkum prepared according to Unani standards (500 and 1000mg/kg, p.o.). All the animals were slaughtered at the end of the sixth week, and their hearts were punctured to draw blood while they were under a light anesthetic. Histopathological examinations and calculation of oxidative stress parameters were performed on tissue samples, and biochemical indicators of liver damage were measured in the blood samples [1].

Biochemical Estimations

Serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST) and serum alkaline phosphatase (ALP) were estimated by Kinetic method of International Federation of Clinical Chemistry (IFCC), serum bilirubin and total protein were estimated by End Point assay as per the instruction of the Kit Manufacture's manual.

Estimation of MDA levels

Malondialdehyde (MDA) is often employed as a biomarker of oxidative stress in the field of biomedicine. The 2-thiobarbituric acid-reactive substance (TBARS) in the liver homogenate supernatant is a spectrophotometric indicator of lipid peroxidation. Sodium dodecyl sulfate (8.1%), acetic acid (20%), and 2-thiobarbituric acid (0.8%) were added to 0.1 milliliter of supernatant. Finally, distilled water was added to bring the total volume of the reaction mixture up to 4.0 ml.Following a one-hour incubation at 95°C, samples were cooled with running water before being mixed with five milliliters of butanol and one milliliter of pyridine in a 15:1 (v/v) ratio. After ten minutes of shaking, the mixture was centrifuged at four thousand revolutions per minute. Next, a spectrophotometric reading was recorded of a butanol-pyridine layer at 532 nm. Values for TBARS are given in terms of their MDA equivalents. Standardization was performed using 1, 1, 3, 3-tetramethoxypropane (TMP) [16].

Assay of reduced glutathione (GSH) levels

Glutathione (GSH) levels were estimated by the method of Ellman [17]. This assay is based on the enzymatic recyclingprocedure in which glutathione was sequentially oxidized by the DTNB and reduced by NADPH in the presence of glutathione reductase. For assay, an equal quantity of samplewas mixed with 10% trichloroacetic acid and centrifuged to separate the

Indo-American Journal of Pharma and Bio Sciences

Vol. 14, Issuse 1, Jan 2021

proteins. To 0.1 ml of this supernatant, 2 ml of phosphate buffer (pH 8.4), 0.5 ml of 5'5-dithiobis (2-nitrobenzoic acid) and 0.4 ml of double distilled water was added. The mixture was vortexes and absorbance was read at412 nm within 15 min. The concentration of 2-nitro-5-benzoic acid formation was measured and reduced glutathione isexpressed as µmol/mg protein.

Nitrates and Nitrites (NOx) assay

NOx concentrations were determined by using the Griess reaction described by Tracey et al. 50µl of supernatant, 20µl of 310 mM phosphate buffer (pH 7.5) and 10µl each of 0.86 mM NADPH, 0.11 mM flavin adenine dinucleotide (FAD) and 10µl Nitrate reductase (1 U/ml) in individual wells of a 96-well plate. Plate was thereafter incubated for 1 h at room temperature in the dark. 200µl of Griess reagent [1:1 mixture of 1% sulfanilamide (1% solution with 5% orthophosphoric acid) and 0.1% N(1-naphthyl) ethylenediamine (NEDA) (1% solution with distilled water)] was added to each well andthe plate was incubated

of Lowry et al [18]. Concentration of total nitrate and nitrite (NOx) in liver homogenates was calculated from the standardcurve and expressed as nM/mg protein.

Histopathological examination

All groups were subjected to histological examination. Microscopic examination was done by a qualified pathologist using hemotoxylin and eosin staining in a blinded fashion.

Statistical Analysis

The values were expressed as mean ± standard error of the mean. One-way analysis of variance (ANOVA) followed by appropriate post hoc test (Tukey test) were used for analysis. $P < 0.05$ was considered as statistically significant.

Results

Effects of Dawa-Ul-Kurkum and its hydro-alcoholic extract on body weight and liver weight in ethanol induced liver damage in rats

The mean body weight was measured in all groups at1st day and last day of 6th week and liver weight was also measured on last day after various drug treatments. The results showed that dose of ethanol daily dose caused less increase in the body weight and change in the liver weight when compared to that control rats. Interestingly, treatment with Dawa-Ul-Kurkum with two different doses (250 and 500 mg/kg), 50% hydro-alcoholic extract of two different doses (500 and 1000mg/kg) and silymarin blocked the effects of ethanol and resulted in increase in the body weight with no significant changes in the liver weight. The increase in body weight can be due to improvement in appetite which may have due to hepatoprotective effect of Dawa-Ul-Kurkum. The results are shown in [Table 4].

Effects of Dawa-Ul-Kurkum and its hydro-alcoholic extract on Liver Function test (LFT) in ethanol induced liver damage in rats

In experimental control group, ethanol given 6weeks resulted in significant increase in serum levels of SGOT($p<0.05$), ALP ($p>0.05$), total bilirubin ($p>0.05$), direct bilirubin ($p<0.05$), non-significant increase in SGPT, and reduction in total protein as compared to normal control rats. This suggests that notable degree of hepatotoxicity and tissue injury in the rat liver and validated our model of ethanol induced liver damage. In Group 4 and 5, treatment with Dawa-Ul-Kurkum at two different doses 250 and 500mg/ kg for 6weeks significantly attenuated the effects of ethanol and reduced level of serum SGOT ($p < 0.05$ at 250 dose), SGPT, ALP, total bilirubin and direct bilirubin ($p < 0.05$ at both doses) and increased level of serum total protein as compared to that in Experimental control group. Similarly, in Group 6 and 7 treatment with two different doses of 50% hydro-alcoholic (500 and 1000mg/kg) produced hepatoprotective effect as it reduced significantly the levels of serum SGOT($p < 0.01$ at 1000mg/kg dose), SGPT($p < 0.05$ atboth doses), ALP ($p < 0.05$ at 500mg/kg dose), total bilirubin ($p < 0.05$ at 1000 mg/kg dose) and direct bilirubin ($p < 0.05$ at both doses), significantly increased total protein($p < 0.05$ at 500mg/kg dose) as compared to that in Experimental control. Pretreatment with silymarin also significant reduced the hepatotoxic effects of ethanol and reduced the levels of serum SGOT ($p<0.05$), SGPT ($p<0.005$), ALP ($p<0.05$),
Total bilirubin ($p<0.005$), and direct bilirubin ($p<0.005$)
but non-significantly increase in total protein as compared to that in Experimental control. The results of Dawa-Ul- Kurkum and its hydro-alcoholic extract are comparable to that of Silymarin. The results are shown in [Figure 2, 3 and table 5].

Effects of Dawa-Ul-Kurkum and its hydro-alcoholic extract on oxidative stress parameters in ethanol induced liver damage

In experimental control group, ethanol given daily dose for 6 weekly resulted in increase in stable metabolites of nitric oxide (NOx) ($P<0.05$) and MDA($P<0.05$) in supernatant of liver homogenates and significant reduction in GSH ($P<0.05$) as compared to control rats. This suggests a notable degree ofhepatotoxicity and tissue injury in the rat liver and corroborated

Table 4: **Effects of Dawa-Ul-Kurkum and its hydro-alcoholic extract on body and liver weight**

Treatment	Initial body weight (g)	Final body weight (g)
Control	223.2±2.059	263.8±14.68
Experimental control	271.4±15.24	279.6±16.18
Silymarin	264.4±10.32	272.0±10.07
DK 250	281.0±4.266	292.0±18.81

Indo-American Journal of Pharma and Bio Sciences

Vol. 14, Issuse 1, Jan 2021

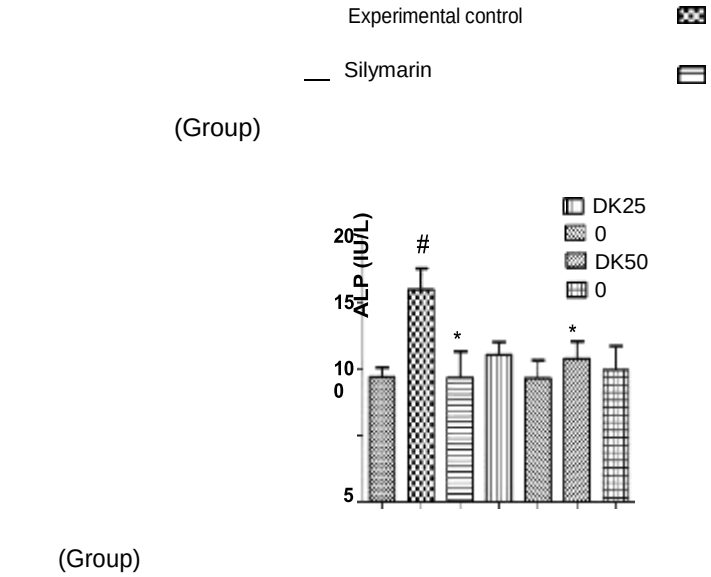
DK500	280.6±11.59	298.0±22.34	**HA1000**	7.6	2.56	296.8±7.605	
HA500	233.8±7.144	248.0±7.622	4.78	10.04±1.312	4.048		

SGPT(IU/L)

50

Indo-American Journal of Pharma and Bio Sciences

Vol. 14, Issuse 1, Jan 2021



igure 2: (a-c) Effects of Dawa-Ul-Kurkum and its hydro-alcoholic extract on (a) SGOT (b) SGPT and (c) ALP. DK-Dawa-ul-kurkum; HA-Hydroalcholic extract of DK

The values are expressed as mean ± SEM; (#=p<0.05 vs control group; *=p<0.05 and**=0.01 vs Experimental control. The data were analyzed using one-wayANOVA followed by Tukey`s test.

to validate this model of hepatotoxicity. In Group 4 and 5, treatment with Dawa-Ul-Kurkum at two different doses 250 and 500mg/kg for 6 weeks significantly attenuated the effects of ethanol and reduced level of homogenate supernatant NOx($p < 0.05$ at 250 mg/kg doses), MDA ($p < 0.05$ at 250 mg/kg doses) and significantly increased GSH ($p < 0.05$ at 250mg/ kg, dose) as compared to that in Experimental control group. Similarly, in Group 6 and 7 treatment with 50% hydro- alcoholic extract of two different doses (500 and 1000mg/kg) produced hepatoprotective effect as it significantly reduced the levels of NOx in homogenate supernatant ($p < 0.05$ at dose 500 mg/kg), MDA ($p < 0.05$ at 500 mg.kg doses) and significant increased GSH ($p < 0.05$ at dose 1000 mg/kg) as compared to that in Experimental control group. Pretreatment with silymarin also significantly reduced the hepatotoxic effects of ethanol and reduced the levels of NOx, MDA ($p > 0.05$) and increased GSH ($p<0.05$) as compared to that in Experimental control group. The results of Dawa-Ul-Kurkum and its hydro-alcoholic extract are comparable to that of Sily marin. The results are shown in [Figure 4].Histopathological examination

Histopathological examination of the liver sections of vehicle treated (control) rats showed most of the hepatic parenchymal cells appeared normal. Few inflammatory cell infiltrate seen. In experimental control group, administration of ethanol daily 6weeks showed hydropic degeneration, fatty changes and hepatocellular necrosis is seen. Mild periportal inflammatory cell infiltrate and peri biliary fibrosis is also evident. This was suggestive of notable degree of hepatotoxicity and tissue injury in the rat liver and validated our model of hepatotoxicity. Silymarin treated group showed hydropic degeneration and Focal areas of inflammatory cell infiltrate are also seen. Mild peri biliary fibrosis is also seen. In Group IV and V, treatment with Dawa-Ul-Kurkum at doses 250 and 500mg/kg respectively showed hepatocytes mostly appeared normal. Mild peri biliary fibrosis and inflammatory cell infiltrate is seen. In Group VI and VII treatment with 50% hydro-alcoholic extract of Dawa-Ul-Kurkum (500 and 1000mg/kg) also showed hydropic degeneration and

Indo-American Journal of Pharma and Bio Sciences

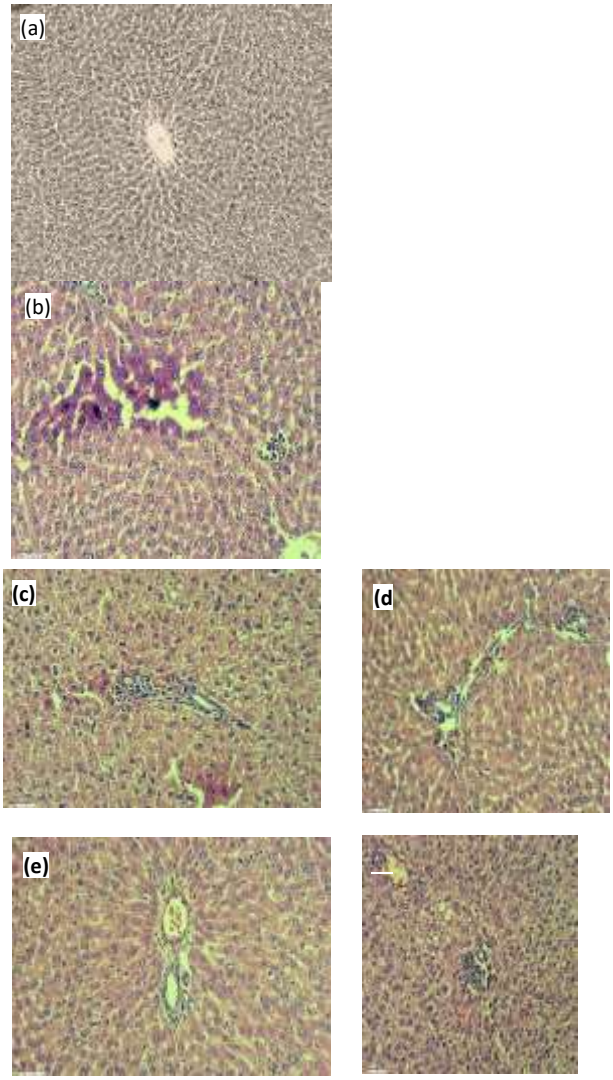
Vol. 14, Issuse 1, Jan 2021

Figure 3: (a-b) Effects of Dawa-Ul-Kurkum and its hydro-alcoholic extract on (a) Total bilirubin (b) Direct bilirubin

The values are expressed as mean ± SEM; (#=p<0.05 vs control group; *=p<0.05 and**=0.01 vs Experimental control. The data were analyzed using one-wayANOVA followed by Tukey`s test.

Figure 4: Effects of Dawa-Ul-Kurkum and its hydro-alcoholic extract on (a) stable metabolites of nitric oxide (NOx), (b) MDA and (c) GSH

The values are expressed as mean ± SEM; (#=p<0.05 vs control group; *p<0.05 vs Experimental control. The data were analyzed using one-way ANOVAfollowed by Tukey`s test.



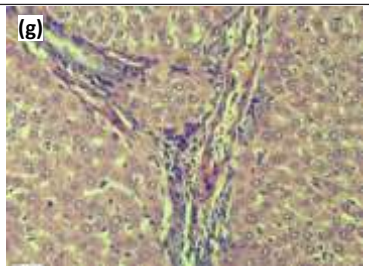


Figure 3: Histopathological picture of liver sections after various drug treatment in rats. a) Control; b) Experimental control; c) Silymarin; d) DK250; e) DK500; f) HA500; and g) HA1000. All groups except control group were treated with ethanol.

fatty change is seen in some part of the liver. Periportal inflammatory cell infiltrate is also seen. Peri biliary fibrosis is also seen. The results are shown in [Figure 5].

Discussion

Changes in weight growth were seen after long-term ethanol treatment in rats. Histological abnormalities in liver tissue and biochemical alterations in the blood and liver were discovered as a result of ethanol-induced liver damage. Chronic oral administration of ethanol significantly suppressed mean body weight increase, in comparison to the control groups. Continuous ethanol treatment has been shown to inhibit mean body weight increase in rats by Macdonald, Olusola, and Osaigbovo [19]. It's possible that the reduced rise in bodyweight (MEOS) is due to energy loss associated with ethanol metabolism through the microsomal ethanol oxidizing mechanism. The main routes for alcohol metabolism are the alcohol dehydrogenase and MEOS pathways. In the case of chronic alcohol use, ethanol is mostly metabolized through the MEOS pathway. By oxidizing ethanol without releasing chemical energy, activation of mitochondrial electron transport chain enzyme (MEOS) causes a shift in energy consumption and weight gain [20].

Consistent alcohol use may have devastating consequences on the liver, the primary site of ethanol metabolism. Hepatocyte necrosis and apoptosis are caused by the ethanol metabolic byproducts acetaldehyde and reactive oxygen species [21]. This lipid peroxidation in the cell membrane sets off a chain reaction of inflammatory processes.

Cellular leakage and the release of cytosolic enzymes like AST, ALT, and ALP into the

Indo-American Journal of Pharma and Bio Sciences

Vol. 14, Issuse 1, Jan 2021

circulation are direct consequences of hepatic damage, which compromises cell integrity. In the present study, prolonged exposure to ethanol increased blood levels of hepatic damage markers in rats, suggesting that ethanol use may lead to liver damage. According to Rajakrishnan and Menon [22], the blood levels of indicators of liver injury were elevated in rats after chronic alcohol treatment.

Lipid peroxidation due to oxidative stress was measured by estimating MDA levels in liver homogenate. The levels of MDA in the control group considerably increased after exposure to ethanol. This increase was statistically significant when compared to the non-alcohol-treated control group. It is possible that ethanol metabolic byproducts, which are very reactive, sped up lipid peroxidation. Alcoholic beverages, according to Macdonald et al. [15], enhance lipid peroxidation in a rat model. Dawa-Ul-Kurkum and the hydro-alcoholic extract were both much more effective than the experimental control group in decreasing MDA levels in liver homogenate, hence preventing lipid peroxidation. Decreased levels of malondialdehyde (MDA) in the liver homogenate of the treatment group indicate that dawa-ul-kurkum provides considerable protection against ethanol-induced lipid peroxidation.

Current results showed that combining ethanol with Dawa-Ul- Kurkum and 50% Hydro-alcoholic extract effectively decreased serum SGOT, SGPT, ALP, total bilirubin, and direct bilirubin elevations. Furthermore, ethanol-induced increases in MDA and NOx levels, as well as significantly increased GSH levels, were mitigated by Unani polyherbal preparations and hydroalcoholic extracts, as measured by oxidative stress parameters in liver homogenates. On an index measuring oxidative stress, the effects of DK were comparable to those of HA extract. Dawa-Ul-Kurkum and HA extract showed similar degrees of protection against ethanol-induced liver damage, with the former showing mostly normal hepatic tissue and the latter showing some peri biliary fibrosis. In contrast, Dawa-Ul-Kurkum and HA extract showed some protective properties. According to these results, both Dawa-Ul-Kurkum and its HA formulation are useful hepatoprotective drugs that may be used to ward against liver necrosis.

Conclusion

Ethanol induced was found to be potentially hepatotoxic to Wistar rats, as evidenced by changes in biochemical markers, oxidative stress, and histological examinations. The combination of Dawa-Ul-Kurkum and 50% hydro-alcoholic extract was found to be effective against ethanol induced liver damage in rats, significantly reducing hepatotoxic damage. Such translational studies using the reverse pharmacology approach could aid in the integration of traditional and modern medicinal concepts in the greater interest of drug development and rational use.

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The research was supported by grants from the CCRUM, Ministry of AYUSH, New Delhi, which is duly acknowledged. The authors wish to thank CRIUM, Hyderabad for providing standardized Dawa-Ul-Kurkum preparations.

Authors Contributions

Mohd. Rafi Reshi was involved in the conduct of experiments, acquisition and analysis of data and drafting of the manuscript. Kavita Gulati was involved in conceptualization, planning and designing of the study. She also helped in the analysis of data and critical review of the manuscript. Maaz Naqvi and Nafaa Hassan also help during experiment work. Arunabha Ray was involved in planning of the study, interpretation of data and critical reviewing of manuscript. All authors approved the final version of the manuscript.

Conflict of interest

No conflict of interest

Funding

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Ethical statement

Ethical approval was required as this study involve
laboratory animals.

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Indo-American Journal of Pharma and Bio Sciences

Vol. 14, Issuse 1, Jan 2021

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