IJPSR (2013), Vol. 4, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 September, 2012; received in revised form, 19 October, 2012; accepted, 22 December, 2012

HEPATOPROTECTIVE ACTIVITY OF *LAGENARIA SICERARIA* (MOLINA) STANDLEY FRUITS AGAINST PARACETAMOL INDUCED HAPATOTOXICITY IN MICE

C.V. Panchal*[1], Jyotiram A. Sawale [2], B. N. Poul [1] and K.R. Khandelwal [3]

Maharashtra College of Pharmacy [1], Nilanga, Dist. Latur- 413 521, Maharashtra, India
IES College of Pharmacy [2], Kalkheda Ratibad Main road, Bhopal- 462 001, Madhya Pradesh, India
Rajarshi Shahu College of Pharmacy and Research [3], Tathwade, Pune-33 Maharashtra, India

Keywords:
Antioxidant, Bhopla, Cucurbitaceae, DPPH

Correspondence to Author:

Chandrawadan V. Panchal

Assistant Professor, Maharashtra College of Pharmacy, Nilanga, Dist. Latur- 413 521, Maharashtra, India

E-mail: cvpanchal.mcpnilanga@gmail.com

QUICK RESPONSE CODE

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ABSTRACT

Aim and Objectives: Fruit juice of *Lagenaria siceraria* (LS) belonging to Cucurbitaceae family, has been used traditionally to treat jaundice and to cure certain liver disorders. Antioxidants are well known for their hepatoprotective effect and in curing liver disorders. In this study, hepatoprotective and antioxidant effects of fruits were investigated.

Materials and Methods: The coarsely powdered plant material was extracted successively with petroleum ether (PE) and ethanol (ETH) using soxhlet. PE & ETH, were then evaluated for their hepatoprotective and antioxidant activities against paracetamol induced hepatotoxicity and different *in vitro* assays respectively. Hepatoprotective activity was evaluated at three oral dose levels of 250, 500 and 1000 mg/kg.

Results: Both extracts, PE and ETH exhibited a significant hepatoprotective and antioxidant activity. The ETH (1000 mg/kg) showed maximum hepato-protection. ETH also showed better antioxidant activity, in comparison to PE, in all the antioxidant assays.

Conclusions: ETH has shown better hepatoprotective activity than PE, which could be due to its better antioxidant activity. Moreover, better activity can also be attributed to the presence of phenolic compounds as these were absent in the PE.

INTRODUCTION: *Lagenaria siceraria* locally called as 'Bhopla' is a large softly pubescent annual climber distributed in Asia, America and tropical Africa, wild or cultivated in all warmer regions as a vegetable [1, 2]. The fruit is reported as diuretic and antipyretic. A decoction of leaves mixed with sugar is given in jaundice [3].

The seeds are being used to cure cough, fever, earache, as brain tonic and anti-inflmmatory [2, 3]. The fruit contains saponins and some authors have already reported saponins as hepatoprotective [4, 5, 6].

Despite no pre-clinical or clinical data is available, use of fruit juice of *Lagenaria siceraria* has been found effective in the prevention and cure of chronic diseases of liver, heart and also in cancer.

In the present study, fruits of *Lagenaria siceraria* were evaluated for its hepatoprotective activity against paracetamol induced hapatotoxicity. The fruits were also evaluated for its antioxidant activity by lipid peroxidation, DPPH, superoxide radical scavenging and ferric reducing power assays.

MATERIALS AND METHODS:

Chemicals: Folin-phenol reagent, Trichloroacetic acid (TCA), Iron chloride ($FeCl_3$), Dimethyl sulfoxide (DMSO), Methanol (AR grade), Potassium chloride, Glacial acetic acid and Ammonium ferrous sulphate were obtained from Qualigens Fine Chemicals, Mumbai, Maharashtra, India. Gallic acid, Sodium carbonate, Ascorbic acid, Nicotinamide adenine dinucleotide (NADH), Phenazine methosulphate (PMS) and Thiobarbituric acid (TBA) were purchased from LOBA Chemie, Mumbai, Maharashtra, India. Potassium ferricyanide was obtained from Thomas Baker & Co., London; Nitro blue tetrazolium (NBT) was purchased from Central Drug House, New Delhi and 1, 1-Diphenyl-2-picrylhydrazyl (DPPH) was purchased from HIMEDIA Laboratories Ltd., Mumbai

Preparation of Plant Extract: The fruits of *Lagenaria siceraria* (1 kg) were collected from Pune region and authenticated by Botanical Survey of India, Pune. A voucher specimen (PCV 1) was deposited at Botanical Survey of India, Pune. Dried fruits were ground and extracted successively by petroleum ether (60^o-80^o) and ethanol (95%) using soxhlet apparatus. Yield of petroleum ether (PE) and ethanolic (ETH) extracts were found to be 10.9g (1.09%w/w) and 126.8g (12.68% w/w), respectively.

Animals: The Swiss albino mice of either sex weighing 20-35 g were procured from Animal house, Padm. Dr D.Y. Patil Medical College, Pimpri, Pune, India. The animals were maintained at 12-12 hr day and night cycles, temperature between 20±5^{o}C and relative humidity 45±5%. The animals were housed in large spacious hygienic polypropylene cages during the course of the experimental period. The animals were fed with pellet feed supplied by M/s. Amrut Feeds, Sangli, India and water *ad libitum*. All experiments were conducted in accordance with guidelines of local animal ethical committee (Registration no. 198/CPCSEA).

***In vitro* Assays:** The extracts and standard drugs were evaluated in triplicate.

Lipid Peroxidation Assay: In this method lipid peroxidation was induced in mouse liver by Fe^{2+}/Ascorbate system [7].

Free Radical Scavenging Activity by DPPH method: Antioxidants on interaction with DPPH, either transfer electron or hydrogen atom to DPPH and thus neutralizing its free radical character, and convert it to 1,1- diphenyl- 2- picryl- hydrazine and the degree of discoloration indicates the scavenging activity of the drug. The change in the absorbance produced at 517 nm, has been used as a measure of antioxidant activity [8].

Superoxide Radical Scavenging Assay: Superoxide anions were generated from the dissolved oxygen by PMS/NADH coupling reaction that reduces the NBT (yellow dye) to blue colored product called formazan. Drugs possessing super oxide scavenging activity thereby decrease the reduction of NBT, which is a measure of superoxide anion scavenging activity. The assay was originally based on method as described [9] and the present procedure used was slightly modified [10].

Ferric Reducing Power Assay: The reducing capability was measured by the transformation of Fe^{3+}- Fe^{2+} in the presence of different extracts at 700nm as per the reported method [11]. Increased absorbance of the reaction mixture indicates increased reducing power.

Acute Toxicity Study: Toxicity studies conducted as per internationally accepted protocol drawn under OECD guidelines 420 using Swiss albino mice at the dose levels of extracts from 5, 30, 2000 and 5000mg/kg.

Dose preparation and Drug treatments: All the doses were prepared by suspending the test extract and standard drug, sylimarin, in 5% aqueous solution of gum acacia. PE and ETH were evaluated for their hepatoprotective activity at three oral dose levels of 250, 500 and 1000mg/kg, respectively. Sylimarin and paracetamol were used at doses of 100 and 400mg/kg, respectively. Plant extracts were administered 2 hr after the paracetamol administration.

The treatments were continued for 3 days and on fourth day of the experiment all animals were anesthetized with anesthetic ether and blood was withdrawn for various biochemical estimations as shown below. Finally, animals were sacrificed and liver was dissected out for the histopathological investigations.

***In-vivo* Hepatoprotective Activity:** The animals were divided into following nine groups consisting six mice in each group;

Group I: control (treated with 5% gum acacia)

Group II – VII: Test groups (received different doses of PE and ETH)

Group VIII: Sylimarin group

Group IX: Paracetamol group

Biochemical Estimations: Blood was collected by puncturing retro-orbital plexus by using fine glass capillary and collected in plain sterile centrifuge tubes and allowed to clot. Serum was separated by centrifugation at 5000 rpm for 15 min. at 5^{o}C. The separated serum was used for estimation of alanine aminotransferase (ALT), Alkaline phosphatase(ALP) and Total bilirubin [12].

Total Polyphenolic Content: The total polyphenolic content was measured by Folin -Phenol reagent method. In this method, the blue colour formed due to the presence of polyphenols in the extract was measured at 760 nm using UV Spectrophotometer and was expressed as g/100g of gallic acid equivalent [13].

Statistical Analysis: The results are expressed as mean ± S.E.M. and analysed using one way ANOVA followed by Dunnet's test. P value < 0.05 was considered to be statistically significant.

RESULTS:

***In-vitro* Assays:**

Lipid Peroxidation Assay: In this assay (**Table 1 and 1a**), PE, ETH and vitamin E showed inhibition of free radicals mediated by ferrous / ascorbate system at different concentrations in dose dependent manner.

TABLE 1: LIPID PEROXIDATION ASSAY

Concentration(µg/mL)	% Inhibition (PE)	% Inhibition (ETH)	IC_{50} value (µg/mL) PE	IC_{50} value (µg/mL) ETH
100	32.36	42.65	987.5	187.5
250	36.93	60.72		
500	39.79	65.01		
1000	49.15	69.31		
1500	53.31	73.21		
2000	59.55	76.98		

TABLE 1A: LIPID PEROXIDATION OF VITAMIN E

Concentration (µg/mL)	% Inhibition	IC_{50} value (µg/mL)
10	31.25	42
20	40.68	
40	48.62	
60	58.97	
80	64.68	
100	70.60	

DPPH Radical Scavenging Assay: PE, ETH and ascorbic acid showed significant DPPH radical scavenging activity at different concentrations in dose dependent manner with their IC_{50} values (**Table 2 and 2a).**

TABLE 2: DPPH RADICAL SCAVENGING ASSAY

Concentration (µg/mL)	% Inhibition (PE)	% Inhibition (ETH)	IC_{50} value (µg/mL) PE	IC_{50} value (µg/mL) ETH
250	12.04	22.40	163	585
500	21.00	48.17		
1000	32.21	61.62		
1500	46.49	76.75		
2000	59.38	91.03		

TABLE 2A DPPH RADICAL SCAVENGING ASSAY OF ASCORBIC ACID

Concentration (µg/mL)	% Inhibition	IC_{50} value (µg/mL)
20	42.01	
40	51.82	
60	58.54	38.5
80	65.54	
100	71.70	

Superoxide Radical Scavenging Assay: PE, ETH and ascorbic acid showed significant superoxide radical scavenging activity at different concentrations in a dose dependent manner (**Table 3 and 3a**).

TABLE 3: SUPEROXIDE SCAVENGING ASSAY

Concentration (µg/mL)	% Inhibition (PE)	% Inhibition (ETH)	IC_{50} value (µg/mL) PE	IC_{50} value (µg/mL) ETH
250	3.49	53.76		
500	16.66	62.50		
1000	45.83	65.45	113.5	487.5
1500	67.06	74.45		
2000	75.26	78.22		

TABLE 3A SUPEROXIDE SCAVENGING ASSAY FOR ASCORBIC ACID

Concentration (µg/mL)	% Inhibition	IC_{50} value (µg/mL)
10	47.36	
20	67.90	
30	73.15	12
40	84.48	
60	90.83	

Reducing Power Assay: Reducing power assay was carried out for PE, ETH and ascorbic acid. Both the extracts showed increase in absorbance as there is increase in concentration (**Table 4 and 4a**)

TABLE 4: REDUCING POWER ASSAY (PE AND ETH)

Concentration (µg/mL)	Absorbance (Mean ± S.E.M)	
	PE	ETH
250	0.222 ± 0.0120	0.196 ± 0.0028
500	0.273 ± 0.0012	0.233 ± 0.0027
1000	0.307 ± 0.0013	0.311 ± 0.0097
1500	0.343 ± 0.0006	0.400 ± 0.0067
2000	0.396 ± 0.0040	0.539 ± 0.0095

TABLE 4A: REDUCING POWER ASSAY FOR ASCORBIC ACID

Concentration (µg/mL)	Absorbance (Mean ± S.E.M)
10	0.135 ± 0.0011
20	0.151 ± 0.0008
30	0.159 ± 0.0017
40	0.174 ± 0.0020
60	0.199 ± 0.0055

Total Polyphenolic Content determination:

TABLE 5: TOTAL POLYPHENOLIC CONTENT OF ETH

Sr. No.	Extract	Polyphenolic content (%w/w)
1.	ETH	5.8245

Biochemical parameters: Administration of paracetamol (400 mg/kg, i.p.) produced significant ($p<0.01$) increase in the levels of ALT, ALP and total bilirubin. PE and ETH at doses of 250, 500 and 1000mg/kg, p.o. separately, significantly ($p<0.01$) reduced the ALT, ALP and total bilirubin levels in mice (**Table 6**).

TABLE 6 EFFECT OF PE AND ETH ON DIFFERENT BIOCHEMICAL PARAMETERS IN PARACETAMOL INDUCED HEPATOTOXICITY IN MICE

Sr. No.	Groups	ALT (Units/mL)	ALP (KA units)	Total Bilirubin (mg/100mL serum)
1.	Control	56.66 ± 1.33	18.73 ± 0.53	1.075 ± 0.12
2.	Intoxicated	190 ± 2.36# #	47.611 ± 0.5# #	3.55 ± 0.11# #
3.	Positive control	65.6 ± 2.92**	19.386 ± 0.35**	1.902 ± 0.10**
4.	PE (250mg/kg)	165 ± 2.06**	42.622 ± 1.89**	3.186 ± 0.12
5.	PE (500mg/kg)	70 ± 3.22**	19.114 ± 0.64**	2.156 ± 0.10**
6.	PE (1000mg/kg)	98 ± 8.31**	22.508 ± 0.24**	2.492 ± 0.13**
7.	ETH (250mg/kg)	114 ± 8.60**	23.788 ± 0.71**	3.528 ± 0.23
8.	ETH (500mg/kg)	89.6 ± 2.63**	21.308 ± 0.63**	2.536 ± 0.14
9.	ETH (1000mg/kg)	62.4 ± 3.12**	18.38 ± 0.57**	2.084 ± 0.13**

n=6; # # $p < 0.01$ versus control; ** $p < 0.01$ versus intoxicated group

Histopathology: Fig. 1-9 showed liver with focal areas of necrosis and inflammatory infiltrate with distorted architecture in paracetamol treated group. However PE and ETH at doses of 250, 500 and 1000mg/kg reversed the toxic effects of paracetamol on tissue organization. Silymarin (100 mg/kg) significantly reverses all the biochemical, and histopathological alterations as compared to intoxicated group, and the results were comparable to that of control.

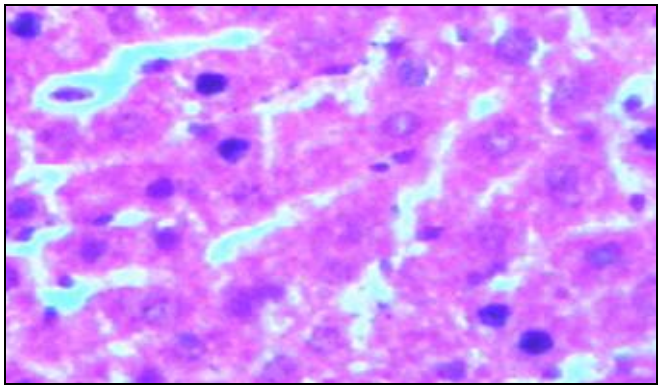

FIG. 1: SECTION OF NORMAL (5% GUM ACACIA P.O.) MICE LIVER SHOWING PROMINENT NUCLEI, HEPATOCYTES AND SINUSOIDAL SPACES. STAINED WITH H AND E, 40×10=400X

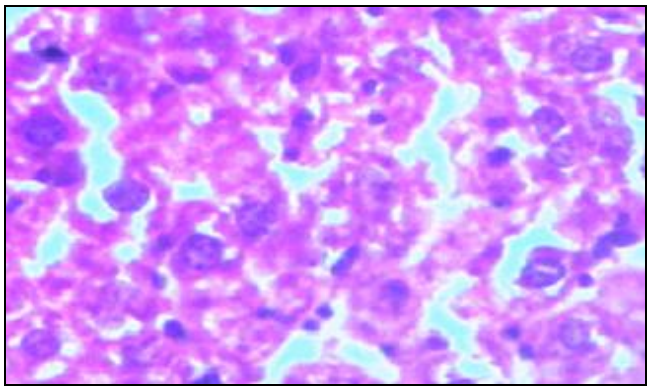

FIG.2: SECTION OF INTOXICATED (PARACETAMOL 400MG/KG I.P.) MICE LIVER SHOWING NECROSIS, AND CLOUDY SWELLING STAINED WITH H AND E, 40 × 10 = 400 X

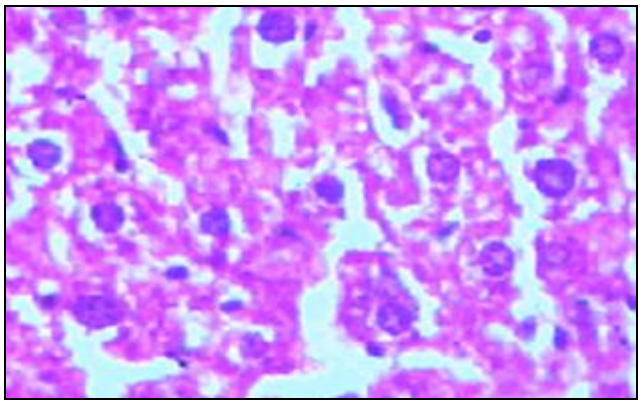

FIG. 3: SECTION OF PE (250MG/KG) + PARACETAMOL (400MG/KG I.P.) IN MICE LIVER STAINED WITH H AND E, 40 × 10 = 400 X

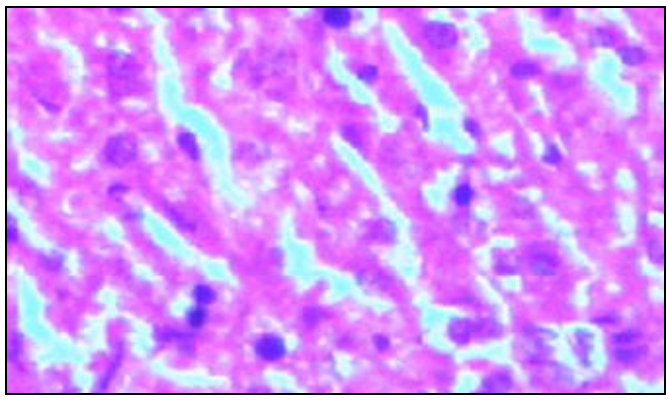

FIG. 4: SECTION OF PE (500MG/KG) + PARACETAMOL (400MG/KG I.P.) IN MICE LIVER STAINED WITH H AND E, 40 × 10 = 400 X

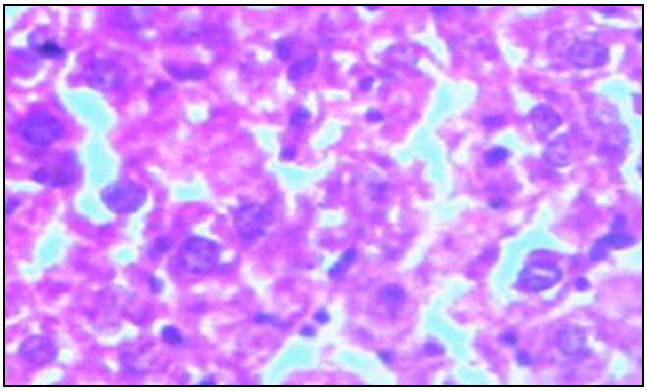

FIG. 5: SECTION OF PE (1000 MG /KG) + PARACETAMOL (400MG/KG I.P.) IN MICE LIVER STAINED WITH H AND E, 40 × 10 = 400 X

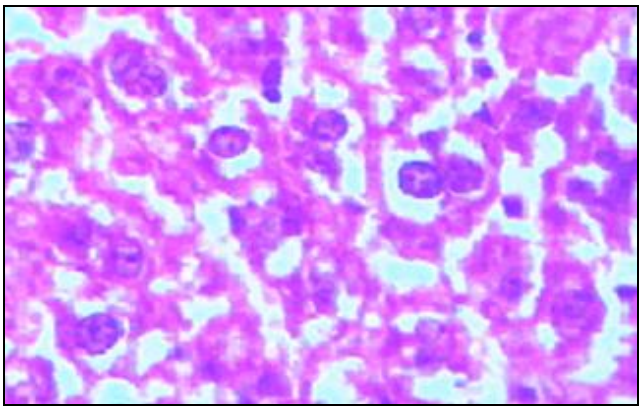

FIG. 6: SECTION OF ETH (250MG/KG) + PARACETAMOL (400MG/KG I.P.) IN MICE LIVER STAINED WITH H AND E, 40 × 10 = 400 X

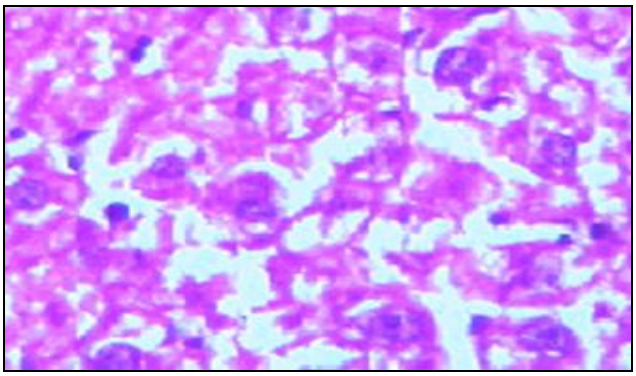

FIG. 7: SECTION OF ETH (500 MG /KG) + PARACETAMOL (400MG/KG I.P.) IN MICE LIVER STAINED WITH H AND E, 40 × 10 = 400 X

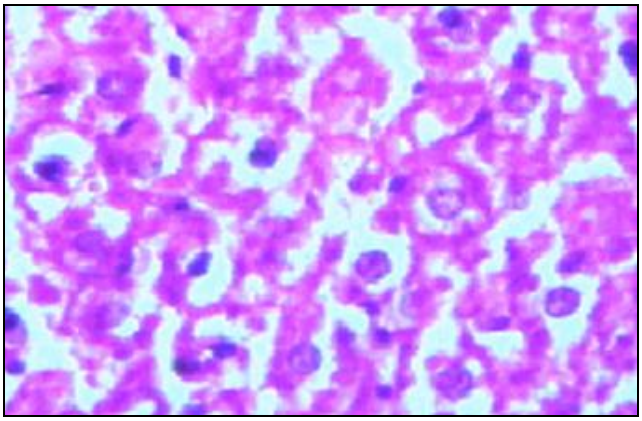

FIG. 8: SECTION OF ETH (1000 MG /KG) + PARACETAMOL (400MG/KG I.P.) IN MICE LIVER STAINED WITH H AND E, 40 × 10 = 400 X

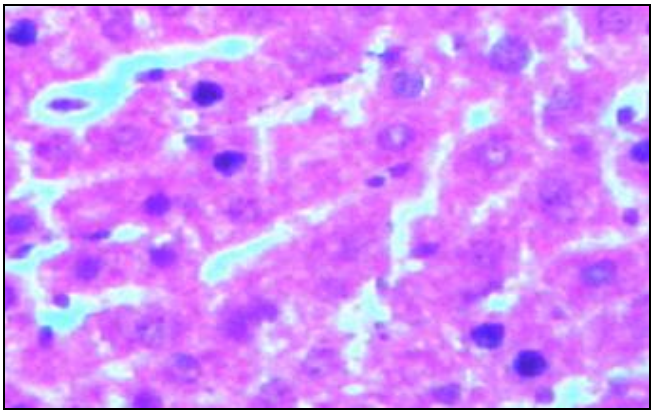

FIG. 9: SECTION OF POSITIVE CONTROL (SILYMARIN 100 MG /KG) + PARACETAMOL (400 MG/KG I.P.) IN MICE LIVER STAINED WITH H AND E, 40 × 10 = 400 X

DISCUSSION: *In-vitro* antioxidant assay: Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are various forms of activated oxygen and nitrogen [14]. ROS and RNS have been implicated in more than one hundred diseases including liver diseases, malaria, acquired immunodeficiency syndrome, heart diseases, stroke, arteriosclerosis, diabetes and cancer [15]. Hence, in the present study PE and ETH were screened for *in-vitro* antioxidant activity using different standard methods like reducing power, superoxide radical scavenging, DPPH radical scavenging and lipid peroxidation assays.

Polyunsatured fatty acids are extremely susceptible to oxidation, which may further lead to oxidative stress [16]. Lipid peroxides generated by the induction of Fe^{2+}/ascorbate on mice liver homogenate was found to be inhibited by the addition of the extracts, ETH showed potent lipid peroxidation effect (IC_{50} 187.5µg/mL) than PE (IC_{50} 987.5µg/mL). Flavonoids, phenolic compounds and tannins may be the origin of the exhibited antioxidant activity particularly ETH.

The DPPH radical scavenging assay is a common method to evaluate the antioxidant activity of several natural compounds. DPPH radical was highly scavenged by ETH (IC_{50} 585 µg/mL) than PE (IC_{50} 163µg/mL).

Superoxide scavenging is important to prevent oxidative damage because in cellular oxidation reactions superoxide radical produces other kinds of cell damaging free radicals and oxidizing agents. The superoxide anion radical has been linked to oxidant-mediated DNA damage, cancers and increased superoxide radical generation is implicated in many human diseases [17] . ETH showed the high scavenging activity of superoxide radical with an IC_{50} value of 487.5µg/mL while PE IC_{50} value 113.5µg/mL. In ferric reducing power assay, the reduction and consequent formation of the ferrous product is monitored by formation of Perl's Prussian blue at 700 nm. An increasing absorbance is indicative of potent antioxidant activity. The reducing powers of both extracts displayed a dose–dependant behavior. The ETH showed potent activity than PE [18].

The results suggest that ETH may contain phytoconstituents, which can donate electrons and react with free radicals, and then convert them into more stable metabolites and terminate the radical chain reaction but the difference in quantitative reduction activities might be a consequence of phyto-constituents differing in mechanism of antioxidation [19]. The potent antioxidant activity of the ETH may be due to the presence of higher amount of polyphenols.

***In- vivo* Hepatoprotective Activity:** The present study revealed the evaluation of hepatoprotective effect of *Lagenaria siceraria* fruits against paracetamol induced heptotoxicity. Paracetamol is a common NSAID'S agent which is safe in therapeutic doses but can produce fatal necrosis in man, rats and mice with toxic doses [20, 21] which was evident by the elevation in serum ALT, ALP and total bilirubin due to liver injury and disturbances in the transport functions of hepatocytes, thus resulting in leakage of enzymes in serum. ETH (1000mg/kg) and PE (500mg/kg) reduced the elevated serum ALT, ALP and total bilirubin to almost near normal levels, but former was very much comparable to silymarin.

There was a dose dependant response with ETH on all parameters, while PE did not show a dose dependent response; instead there was a very slight elevation in all serum parameters as the dose increased from 500 to 1000mg/kg.

In histopathology, paracetamol in high dose disturbed the normal hepatocytes arrangement i.e. centri-olobular necrosis, periportal infiltration, congestion and degeneration. Results obtained from the histo-pathological examination supports the biochemical evaluation in the groups treated with both PE and ETH separately and thus showing liver protective activity.

Free radical mediated reactions are involved in inflammatory response and can contribute to liver necrosis [22]. Antioxidants such as vitamin-C, ellagic acid[23]. and curcumin [24] have been reported to protect liver injury and fibrosis induced by hepatotoxins. Similarly hepatoprotective effect of ETH and PE is related mostly to their antioxidant property. Thus protection against oxidative damage and liver necrosis could be obtained by ETH and PE.

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How to cite this article:
Panchal CV, Sawale JA, Poul BN and Khandelwal KR: Hepatoprotective activity of *Lagenaria siceraria* (Molina) Standley fruits against Paracetamol induced Hepatotoxicity in mice. *Int J Pharm Sci Res*. 2013; 4(1); 371-377.