Effect of *Albizia lebbeck* on liver and kidney function of *Plasmodium berghei* infected mice

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Abstract:

Purpose- Drug resistance to antimalarials has been a major hindrance in the treatment of malaria. The present study was aimed at investigating the biochemical and histopathological effect of ethanolic bark extract of *Albizia lebbeck* (EBEAL) on *Plasmodium berghei* infected mice.

Methods- To assess the schizonticidal activity, animals were infected with parasite on D0 and orally administered EBEAL concentrations (100-1000 mg/kg; G4-G8) along with normal control (G1), infected control (G2) and CQ, 5mg/kg (G3) respectively. Serum activity of ALP, SGOT, SGPT and levels of bilirubin were assessed as biomarkers of liver function and creatinine and urea as indicators of renal sufficiency on D7.

Results -Significant increase ($p<0.0001$) in enzyme activities of infected control than normal were observed on D7. Serum ALP activity was elevated in G4-G8 while SGOT and SGPT levels were within the normal range contrary to the positive control (CQ) which exhibited significant increase ($p< 0.0001$) in enzyme activities on D7. In all the extract treated groups, bilirubin levels were slightly elevated. However, kidney function tests were within normal range in treated groups but increased in infected control (G2) on D7. Transverse sections of infected liver illustrated gross lesions whereas slight changes in hepatic architecture were also evident in CQ (5 mg/kg) and EBEAL (100 mg/kg) treated liver exhibiting sinusoidal dilations and haemozoin depositions on D28. This indicates safety of extract to host liver. Necrotic changes in renal morphology was evident in *P. berghei* infected kidney. CQ treated group exhibited impaired renal morphology, whereas, haemozoin deposition was observed in kidney after EBEAL (100 mg/kg) treatment.

Conclusions-The present study has established that administration of EBEAL has no adverse effect on the liver and kidney of mice infected with malaria.

Keywords- *Plasmodium berghei*, *Albizia lebbeck*, liver function tests, kidney function tests, histopathological studies.

INTRODUCTION

Malaria remains a devastating global health problem. It is known as the world's most important tropical parasitic infectious disease to humans. Each year, there are approximately 5.5 million cases of malaria, causing the death of about one to three million people, the majority of whom are under 5 years of age and pregnant women **(1)**.

At least for 4.5 billion people on Earth, plant-based traditional medicine is the dominant, or perhaps only, form of accessible primary health care. Over 80% of the population in developing countries depends directly on plants for their medical requirements **(2)**. Traditional medicine is a key element among the rural communities in developing countries for the provision of primary health care especially where there are inadequate primary health care systems. The existence of traditional medicine depends on plant species diversity and related knowledge of their use as herbal medicines **(3)**. Traditional medicines are being practiced in the developing countries for their primary health care. In most developing countries, the use of traditional medicine as a normative basis for the maintenance of good health has been widely observed **(4).**

The emergence of drug-resistant *Plasmodium* parasite has already compromised the efficacy of many antimalarials leaving artemisinin-based combination therapies as one of the few treatment regimens whose efficacy is assured **(5).** The development of traditional herbal medicines for malaria, bioscreening and modern drug development are not mutually exclusive **(6).**

Liver has a pivotal role in regulation of physiological processes. It is involved in several vital functions such as metabolism, secretion and storage. Malaria parasites avoid the immune system when they move from the liver to the red blood cells. Malaria parasites head to the liver after arriving in a human body leading to its detachment from its neighbour. Most of the hepatic damage also, thus, occurs mainly during malaria [2].

Clinically significant renal involvement is associated with infections by *Plasmodium falciparum* and *P.malariae*. Infection with *P.falciparum* produces only acute manifestations, ranging from asymptomatic urinary abnormalities and mild electrolyte disturbances to acute renal failure (ARF) requiring dialysis support.

Albizia lebbeck (Family: Leguminosae) is an astringent, also used by some cultures to treat boils, cough, eye flu, gingivitis, lung problems, pectoral problems and abdominal tumours. Stem bark of *A. lebbeck* has been used in Ayurveda for treatment of bronchitis, asthma, leprosy, eczema, pruritus, paralysis, gum inflammation and worm infestation. It has been found to possess anti-histaminic and mast cell stabilizing properties **(7).** The anti-histaminic activity is supposed to be due to saponins and catechins **(8).** Kumar *et al.* **(2)** has observed antibronchial property of stem bark decoction of *A. lebbeck.* Anti-fungal and antimicrobial activities of hydroalcoholic extract of *A. lebbeck* was noticed by Kajaria *et al.* **(9)** in polyherbal drug Shrishadi. Phytochemical screening of plant extract showed the presence of alkaloids, phenols, flavonoids, saponins, phytosterols and terpenes. Antiplasmodial activity of EBEAL against *P.berghei in vitro* has been reported from our laboratory with IC_{50} less than 10µg/ml **(10).**

In the present work, effect of ethanolic bark extract of *Albizia lebbeck* (EBEAL) on biochemical and histological parameters had been investigated to assess its hepatoprotective and nephrotoxic activities.

MATERIALS AND METHODS

Experimental animals and Parasite strain

White Swiss mice *Mus musculus* of BALB/c strain of either sex and weighing about 25-30 g, were used as experimental models for present study. Mice were obtained from and kept in Central Animal House, Panjab University, Chandigarh and fed on standard pellet diet and water *ad libitum*. The treatment of the mice was done according to the guidelines of committee for the purpose of control and supervision on experiments on animals (Animal ethical clearance registration no. 45/1999/CPCSEA).

Plasmodium berghei (NK 65) strain was maintained *in vivo* in mice by weekly passage of blood from infected to normal mice. Asexual blood stages were passaged by intraperitoneal inoculation of $1x10^6$ infected RBCs from infected to naïve mice in citrate saline [0.85% (w/v) sodium chloride, 3.8% (w/v) sodium citrate].

Preparation of plant extract /Phytochemical screening

The stem bark of *A. lebbeck* was collected from Shimla Distt., Himachal Pradesh, India. Voucher specimen (No.17865) was obtained from Department of Botany, Panjab University, Chandigarh, where identification of plant was confirmed. Stem bark of plant was washed thoroughly with water, dried at room temperature and then powdered.

Ethanolic bark extract of *A. lebbeck* (EBEAL) was prepared by Soxhlet extraction method **(11).** Approximately 300 ml of ethanol was added to 100g of dried powdered stem bark, and extraction was carried out till the solvent became colourless in the siphon. The extract obtained was evaporated to dryness in a rotary evaporator and dried residue was stored in screwed capped vials at -4^0C.

100g of dried stem bark of *A. lebbeck* gave 10.22g of dried residue after ethanolic extraction and drying in Rota evaporator. Phytochemical examination of the extract was carried out for detection of alkaloids, phenols, flavonoids, tannins, saponins, phytosterols, terpenes, glycosides and steroids following the method of Tiwari *et al.* **(12).**

Experimental groups

Animals were randomly divided into 8 groups of six mice each. Animals in G1 were designated as normal control and were not inoculated with the parasite. Each mouse in other groups (G2-G8) was inoculated on D0 intraperitoneally with 0.2 ml of infected blood containing about 1 x 10^6*P. berghei* parasitized RBCs. Treatment was given for 4 days (D0-D3) by orally dosing mice of all groups. The administration of different treatments (0.2 ml/mouse/OD) which lasted from D0-D3, is as follows:

G1- uninfected mice (distilled water).

G2- infected mice (distilled water).

G3- Positive control (Chloroquine, 5mg/kg)

G4- 100 mg/kg (EBEAL) in SSV.

G5- 250 mg/kg (EBEAL) in SSV.

G6- 500 mg/kg (EBEAL) in SSV.

G7- 750 mg/kg (EBEAL) in SSV.

G8- 1000 mg/kg (EBEAL) in SSV.

Parasitaemia was evaluated on D4, D7, D14, D21 and D28 respectively, by screening for malaria parasites in tail blood of infected animals after fixing in methanol and staining with Giemsa stain **(13).** The percentage of chemosuppression was determined by following formula:

$$(A-B)/A\times 100,$$

where A= Average Parasitaemia in negative control, B= Average Parasitaemia in extract/drug treated control

Mice of all the groups were proceeded for liver and kidney function tests through biochemical studies and histopathological studies.

Biochemical assays

The biochemical assays were performed by taking blood from tail of mice (G1-G8) by tail vein incision on D7. The blood samples were left undisturbed for 1 h and serum was obtained by centrifugation at 800g for 10 minutes. Biochemical assays were performed by using diagnostic kits supplied by Reckon Diagnostics Pvt. Ltd. Gorwa, Vadodara, Gujarat, India and Transasia Bio-medicals Ltd. Nalagarh road, Baddi, Distt. Solan, Himachal Pradesh, India.

Liver function tests

These were performed by assessing serum ALP, SGOT and SGPT activities and bilirubin levels using kits (Table 1). The quantitative estimation of alkaline phosphatase activity in serum was determined by using p-NPP method with stabilized substrate **(14).** Estimation of SGOT activity in serum was done by IFCC method **(15).** Estimation of SGPT activity in serum was done by IFCC method **(15).** Quantitative estimation of total bilirubin in serum was done by Jendrassik and Grof method **(16).**

Table 1 : Evaluation of schizonticidal activity along with liver and kidney function tests in various experimental groups on day 7.

Group	Schizonticidal activity		Liver Function Tests				Kidney Function Tests	
	CS (%)	MST (days)	SGPT (IU/L)	SGOT (IU/L)	ALP (IU/L)	BILIRUBIN (mg/dl)	UREA (mg/dl)	CREATININE (mg/dl)
G1	-		13.3± 0	8.84±0	108.5±0	1.0±0.3	38.3±1.4	0.8±0.3
G2	-	7.8±0.8	[a]75.4±0	[a]30.9±0	[a]257.7±0	[a]2.3±0.3	[a]147.5±3.4	[b]1.8±0.5
G3	96.8	[a]25.2±6.2	[a]41.7±2.8	[a]50.2±2.8	[a]228.1±0.7	[a]1.05±0.3	[a]45.3±2.4	[d]1.2±0.7
G4	69.4	[a]23±7.6	[a]8.84	[a]44.2±12.4	[a]325.4±38.3	[a]1.2±0.2	[a]22.3±3.8	[a]0.4±0.3
G5	71.4	[b]24.1±3.9	[a]17.7	[a]17.7	[a]73.9±10.5	[a]1.2	[a]7.4±1.3	[a]0.2±0.1
G6	71.9	[a]20.8±7.8	[b]8.8	[b]30.9±31.2	[d]400.1±18.2	[a]1.2±0.2	[a]13.7±4.9	[c]0.8±0.6
G7	79.8	[a]27.5±0.6	[a]17.7	[a]26.5	[d]542.6±1.8	[a]1.2	[a]19.5±9.5	[d]3.2±2.1
G8	84.7	[a]25.2±6.2	[a]61.9	[a]26.5	[d]278.0±20.3	[a]3.9	[a]8.3	[c]2.3

(a= p<0.0001,extremely significant, b= p<0.001,very significant, c= p<0.05,significant, d= p<0.05,not significant); CS=Chemosuppression ; MST= Mean survival time

Kidney function tests

These were assessed by estimating serum urea and creatinine levels (Table 1). The estimation of urea was done by modified Berthelot method **(17)** and that of creatinine was done by alkaline picrate method **(18).**

Statistical analysis

All experimental data was expressed as mean± SD. The student's t-test was performed to calculate p-value by employing Graphpad software 3. Value of $p \leq 0.05$ has been termed as statistically significant.

(a=$p<0.0001$= extremely statistically significant, b=$p<0.001$ = very statistically significant, c= $p<0.05$ = statistically significant, d=$p>0.05$ = not statistically significant).

Histopathological studies

For histopathological studies, mice of normal, *P. berghei* infected and drug/extract-treated groups were sacrificed after light anesthesia with diethyl ether. Liver and kidney were removed on D7 (normal and infected control) and on D28 (CQ and G4) respectively and washed properly in 0.9% saline solution. Tissues

were fixed in Bouin's fixative and stained with Haematoxylin/eosin staining technique **(19)** for studying the histology.

Results and Discussion

There is a great need for the optimal use of available drugs and the development of new approaches to antimalarial chemotherapy. For safety reasons, phytochemical, pharmacological and biochemical investigations on medicinal plants traditionally used as antimalarials are urgently needed. Till now, about 1277 plants belonging to 160 families have shown good antimalarial activity **(4).**

The present investigation describes biochemical and histological changes associated with treatment of malaria with extract of traditionally used medicinal plant *Albizia lebbeck*. EBEAL with IC_{50}<10 µg/ml can be categorised as a promising antimalarial agent. Acute toxicity evaluation proved that extract is toxicologically safe for oral administration at higher doses (LD_{50} >5g/kg). Moreover, according to classification given by Munoz *et al.* **(20),** on the basis of *in vivo* antiplasmodial activity, this plant can be categorized as good antimalarial as the extract displayed more than 50 % growth inhibition of parasite at a dose of 100 mg/kg during the schizonticidal activity. EBEAL contains alkaloids, phenols, flavonoids, saponins, phytosterols and terpenes which have also been reported to be responsible for antimalarial efficacy. In Peter's 4 day test, there was a dose- dependent increase in chemosuppression on D7 after oral administration of different concentrations of the extract. The standard drug chloroquine caused a chemosuppression of 96.8%, whereas, concentrations of 100, 250, 500, 750 and 1000 mg/kg/day caused chemosuppression of 69.4%, 71.4%, 71.9%, 79.8% and 84.7% respectively (Table 1). This good antimalarial activity has also been exhibited by other traditional medicinal plant species such as *Xanthium strumarium* and *Ajuga bracteosa* in our laboratory **(21, 22, 23).** There are also several reports of phytochemicals like flavonoids being promising antiplasmodial compounds within clinically tolerant and non-toxic concentrations owing to their anti- inflammatory and antioxidant activities **(24).**

Enzymes are necessary for normal cellular metabolism including that of the liver. The degenerative changes in the hepatocytes due to the *Plasmodium* infection may alter the activities of its enzymes. Hepatic dysfunction is a common complication in malaria characterized by significant increase in liver enzyme activities such as serum SGOT, SGPT and alkaline phosphatase (ALP) **(25).** Similar observations have been made in the present study, where serum levels of these enzymes were significantly ($p<0.0001$) increased in the infected control as compared to normal.

ALP activity in the serum of normal mice was found to be 108.5±0 IU/L which increased remarkably ($p<0.0001$) in the infected mice (257.7 ±0 IU/L). Levels were observed to rise in all treated groups except G4, with G7 recording maximum elevation in ALP level (542.6±1.8 IU/L) (Table 1). SGOT activity increased three times in infected control (G2) which was statistically significant ($p<0.0001$) as compared to normal. SGOT activity was elevated as compared to normal with significant p-value (<0.0001). Serum SGPT activity was significantly ($p<0.0001$) elevated in infected control (G2) as compared to normal (13.3±0 mg/dl). However, in EBEAL treated groups (G5, G6 and G7), SGPT activity was comparable to normal. These studies also concorded with previous studies in which chloroquine, the standard antimalarial drug, has been found to elevate liver biomarker enzymes in Wistar rats which reflects damage to hepatocytes and increased cellular permeability resulting from developed oxidative stress **(26).**

Centilobular liver damage is one of the factors involved in hepatic dysfunction in acute malaria infection, leading to hyperbilirubinaemia **(27).** In case of serum bilirubin concentration, infected control (G2) exhibited a 2-times increase in total bilirubin as compared to the normal (1.05±0.3 mg/dl) indicative of jaundice or hyperbilirubinaemia in the host due to impaired drainage capacity of liver. Among extract treated mice, slight elevation in serum bilirubin concentration was evident in all groups (G4-G8) which was significantly less as compared to infected control (G2) on D7. The absence of hepatocellular damage at these tested concentrations revealed that the conjugating ability of the liver was not much compromised, especially from the total bilirubin levels obtained.

Meanwhile, non-hepatocellular damage as revealed by SGOT and SGPT values was further supported by histological revelation. Histology of normal liver revealed polyhedral hepatic cells with eosinophilic cytoplasm having distinct nuclear membrane and nucleus. Central vein with normal RBC's and portal triad were also visible (Fig 1 A). *P. berghei* infected liver showed irregular lobules with distorted cells, portal infiltration, sinusoidal dilation, increased number of Kupffer cells and haemozoin deposition (Fig 1 B). These observations are in accordance with previous studies which report that hepatocyte abnormalities are associated with infiltration of parasitized red blood cells and haemozoin depositions inside degenerated hepatocytes. Histology of CQ (Fig 1 C) treated liver also exhibited distorted morphology with irregular hepatic cords. Histology of G4 (100 mg/kg) liver showed altered morphology of hepatic chords. Haemozoin depositions, distorted endothelial lining of central vein and sinusoidal dilations were also observed (Fig 1 D). CQ has also been reported to result in development of oxidative stress in hepatic and renal tissues **(28).** These findings

indicate that the extract administration does not harm the overall integrity of liver.

Kidneys maintain optimum chemical composition of the body fluids by acidification of urine and removal of metabolite wastes as urea, uric acid, creatinine and ions. During renal disease, the concentrations of these metabolites increase in blood. Increase in urea levels has been observed in acute and chronic renal disease associated with malaria **(29).** In the present study, the amount of urea in EBEAL treated groups was observed to be lower than that in the normal mice (Table 1). Increased urea levels ($p<0.0001$) were also observed in chloroquine treated (positive control) mice on D7. The serum creatinine level was also increased ($p<0.001$) in *P. berghei* infected mice as compared to normal. The concentration of serum creatinine was also observed to be comparable to normal in EBEAL treated groups (G4, G5 and G6) on D7, which was extremely significant ($p<0.0001$) as compared to infected control (G2).

Histopathological studies on normal kidney revealed division of capsule into outer cortex and inner medulla (Fig 2 A). Proliferative changes in the glomeruli have been reported in *P. falciparum* in humans **(29).** Similar observations were made in the present study where necrotic changes in epithelium of renal capsule and convoluted tubules and abnormal proliferation of mesangial cells between loops and swelling and shrinkage of renal corpuscles was evident in *P. berghei* infected kidney (Fig 2 B). Treatment with chloroquine (Fig 2 C) caused slight changes in renal morphology which supported the previous report of oxidative stress induced nephrotoxicity of CQ at recommended doses **(26).** However, haemozoin deposition and glomerular infilteration in kidney were observed in EBEAL (100 mg/kg) treated kidney (Fig 2 D) than that of positive control.

Conclusion

To conclude, the present study has established that administration of *A.lebbeck* extract has no adverse effect(s) on the liver and kidney of mice infected with malaria. Further studies pertaining to isolation of active antimalarial principles can be undertaken to establish new leads against the disease.

Acknowledgements

Ms. Shagun Kalia is thankful to UGC, New Delhi for BSR fellowship for meritorious students. Authors are also thankful to PURSE program of DST for financial assistance.

Competing Interests

The authors declare that they have no competing financial or other interests regarding this work.

Contribution of Authors

Ms. Shagun Kalia and Mr.Varun Gorki contributed to the execution of various techniques and analysis of data. Dr. Upma Bagai contributed towards designing of the study and framing and final editing of the manuscript.

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LEGENDS TO FIGURES

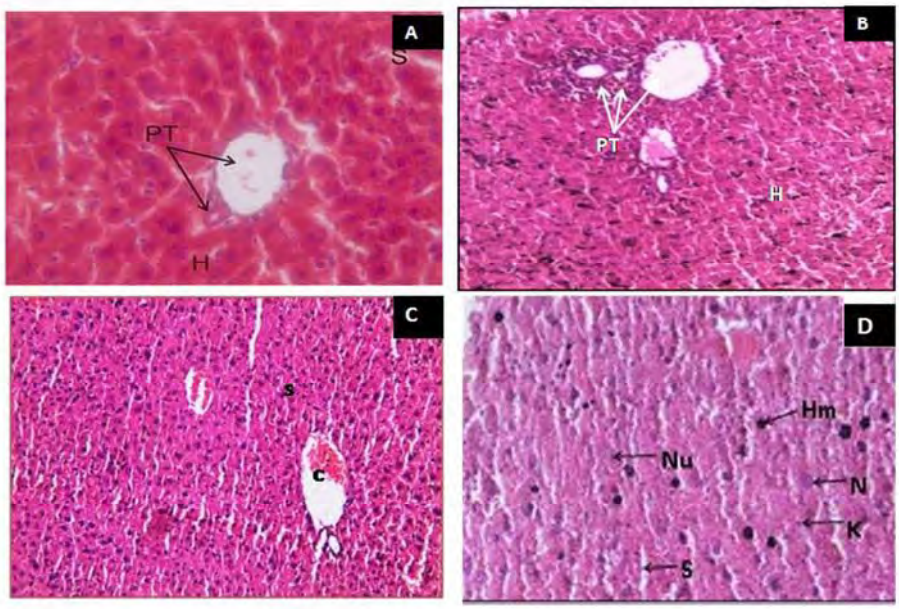

Fig 1:Haematoxylin/eosin stained transverse sections of liver of normal (A), *P.berghei* infected (B), chloroquine (5 mg/kg) treated (C) and EBEAL (100 mg/kg) treated (D) mice, respectively. [Magnification = 100 X]

(PT- Portal triad, S- Sinusoids, H- Hepatocyte, C-Central vein, N-Nucleus, Nu- Nucleolus, Hm- Haemozoin, K- Kupffer cells)

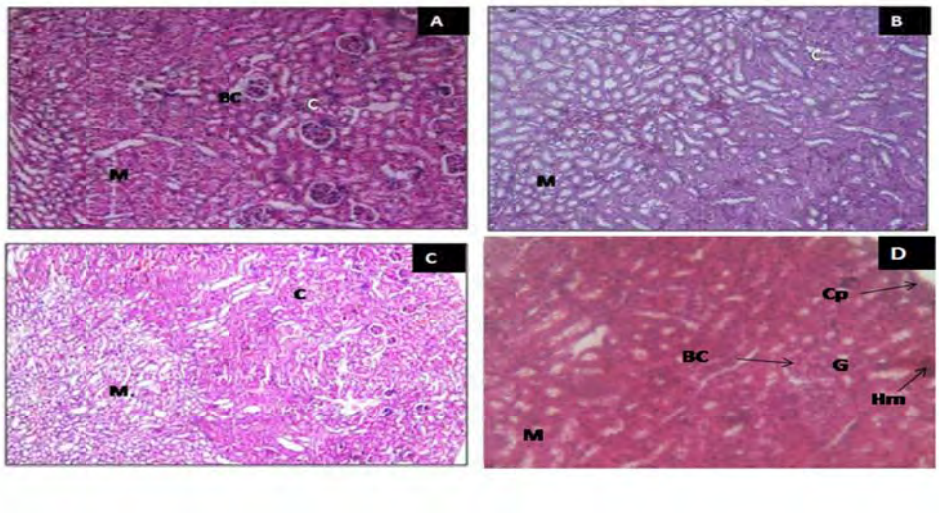

Fig 2:Haematoxylin/eosin stained transverse sections of kidney of normal (A), *P.berghei* infected (B), chloroquine (5 mg/kg) treated (C) and EBEAL (100 mg/kg) treated (D) mice, respectively. [Magnification= 100 X]

(C-Cortex, M-Medulla, BC-Bowman's Capsule, Cp- Capsule, G- Glomerulus)

Author's Profile

Dr. Upma Bagai (Corresponding Author) has received M.Sc (Zoology Honours) and Ph.D degrees from Kurukshetra University, Kurukshetra (1987) and Panjab University, Chandigarh (1992), respectively. Her major research areas include Immunology and Protozoology. She is currently working as an Associate Professor in the Department of Zoology, Panjab University, Chandigarh.

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