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The Protective and Curative Role of Methanolic Extract of *Pistacia integerrima* Stew Ex-brandis Galls in Nimesulide Induced Hepatorenal Intoxication in Rabbits

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Abstract. We investigated the defensive and curative role of methanolic extract of *Pistacia integerrima* (PI) galls in Nimesulide induced hepatorenal intoxication in rabbits. Extracts of PI galls were administered orally at 100, 300 and 500 mg/Kg/day along with Nimesulide (5 mg/Kg/day), while the same doses of extracts were administered in healing phase (pre-intoxication with Nimesulide). Nimesulide resulted in a remarkable elevation of hepato-specific enzymes ($P<0.05$) and mild increase ($P<0.05$) in the renal biomarkers, as compared to normal. All the investigated doses of the methanolic extract of PI galls showed more pronounced hepato-protection ($P<0.05$) than standard (Silymarin at 50 mg/Kg/day). Extract of PI galls administered at 300 mg/Kg/day revealed the same reno-protective response ($P>0.05$) as observed in the standard (vitamin-C at 40 mg/Kg/day) and showed better response ($P<0.05$) in renal protection than other two doses of extracts. This study showed that methanolic extract of PI galls have significant protective and curative role in the hepatorenal toxicity induced by Nimesulide.

Keywords: *Pistacia integerrima*, hepato-protective, reno-protective, Nimesulide

Introduction

The metabolism of drugs and other chemical substances is the main important role of liver. Due to this role, it became the main targeted area for the toxicities induced by chemicals, including drugs (Patel *et al*., 1998). The effect on the optimal secretion of bile is the indication towards liver dysfunction (Patel *et al*., 1998; Strautnieks and Bull, 1998). Alcohol, hypoxemia and hepatic damage due to drugs are the main causes of inflammation in liver. The increase in inflammatory condition causes the increase in phagocytic cells in liver (Laskin and Laskin, 2001; Jaeschke and Smith, 1997; Jaeschke *et al*., 1986) which causes not only the removal of dead cells bus also active against the normal cells of the liver (Jaeschke and Gores, 2002). The alcoholic metabolism also exacerbates the level of free radicals and causes hepatotoxicity (Wu and Cederbaum, 2009).

Certain hormonal activities, excretion of biochemicals and balance of electrolytes are the main functions of the kidney. Pathological and drug induced factors are responsible for the damage of kidneys (Perazella, 2009). Cardiac output directly increases the flow of blood to kidney and thus distributes all the chemical substances and drugs to kidneys. Many indigenous and exogenous substances, which are responsible for the damage of kidneys, accumulates in renal cells (Basile *et al*., 2012). Renal metabolism is an ongoing process, which generates the metabolites and free radicals, and therefore some time causes renal damage (Basile *et al*., 2012; Aleksa *et al*., 2005).

Nimesulide is a nonsteroidal anti-inflammatory drug, which inhibits cyclooxygenase-2 (COX-2) enzyme selectively (Thawani, 2003). Nimesulide has gained importance due to frequent and fatal reports of hepatotoxicity. As compared to other NSAIDs, Nimesulide is considered of having few adverse effects on kidney (DerNiepen *et al*., 2002). However, health care providers and patients should be cautious about the renal impairment induced by Nimesulide, which has been observed in few cases of Nimesulide therapy (Conforti *et al*., 2001). NSAIDs are claimed to be the cause of abnormality in mitochondrial function and the production of reactive oxygen species (ROS) (Salah-Eldin *et al*., 2012).

Herbal drugs are cost effective and have no or few side effects. They are considered to be strong antioxidants

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(Merlani *et al*., 2001). Because of these properties herbal drugs are fruitful in liver diseases like gallbladder disorders, poisoning from the chemicals and environmental toxins (Ramadan *et al*., 2011). Compounds obtained from plants have the properties to be used in the treatment of incurable diseases now days (Uddin *et al*., 2011). *Pistacia integerrima* plant is growing at height of almost 400 meters in the sub mountainous areas of Himalaya. It is 25 m in height with deep roots, red flowers and rounded fruits. This plant contains galls of leaf with many chemical entities and used for medicinal purpose (Upadhye and Rajopadhye, 2010). The galls are known as "Shnaee" locally available in the northern areas of Pakistan. Galls are formed due to Pemphigus, an insect, on the petioles of the leaves. The blended galls are bitter in taste with an astringent effect (Khan *et al*., 2004). *Pistacia integerrima* galls have pharmacological activities against high level of uric acid and inflammation. Traditionally utilized for scorpion stings, epistaxis, loss of appetite, bronchial problems and liver (Jindal, 2012). The protective action of different organs by herbal drugs may be the effect of some flavonoids and phenolic constituents, which are strong antioxidants (Tungmunnithum *et al*., 2018; Abdullah *et al*., 2017; Khan *et al*., 2011).

This study reports the *in-vivo* protective and curative activity of a methanolic extract of *P. integerrima* galls in the nimesulide induced hepatorenal toxicity.

Material and Methods

Plant collection and extraction. *P. integerrima* galls were collected from Swat, Pakistan. The galls were dried under shade, powdered and soaked in methanol for two weeks. The extract was obtained through filtration and concentrated in a rotary evapourator at 40 °C.

Chemicals and reagents. Standard drug selected for the protective effect on kidney was ascorbic acid (vit-C), while for hepatoprotection, silymarin was used.

Experimental animals. Rabbits were purchased from local market, placed in cages for one week to acclimatization. They were given water and grasses as food, with 12 h light and dark cycle. Departmental approval from Ethical committee was obtained.

Dosage and administration of drugs. Seven groups, each compsrised of six animals were given Nimesulide at a dose of 5 mg/Kg/day (Lecomte *et al*., 1991). Group NS group was administered with normal saline (5 mL/Kg/day). Nimesulide only, was administered to N group. Plant extracts, to groups P1, P2 and P3, were administered in doses of 100, 300 and 500 mg/Kg/day respectively, along with the concomitant administration of nimesulide at 5 mg/Kg/day to all the three groups. Group C received vit-C at 40 mg/Kg/day (Raafat *et al*., 2009) with Nimesulide at a dose of 5 mg/Kg/day. Similarly, group S was administered with silymarin at 50 mg/Kg/day (Maryam *et al*., 2010) along with Nimesulide at 5 mg/Kg/day. The duration of the study was 44 days.

Sampling for laboratory investigations. Ear marginal vein was used for collection of blood samples. The serum was separated by centrifugation at 3000 rpm for 15 min and used for the determination of levels of different biomarkers. Days 1st, 11th, 22nd and 44th were selected for the determination of the levels of serum creatinine (S.Cr), alanine transaminase (ALT), total leukocyte count (TLC), serum bilirubin (S.Br), hemoglobin (Hb) and blood urea nitrogen (BUN).

Curative phase. On day 22nd, three rabbits from each group of N, P1, P2, P3, C, S and NS, were sacrificed to obtain the biopsies of kidneys and livers and to study the histopathological changes. The other three rabbits in ecah group were deprived of Nimesulide and continued with previously administered drugs and doses till 44th day, except the N group which was started with normal saline 5 mL/Kg/day. The hepatorenal functions at the curative phase, in the absence of Nimesulide, were calculated through the estimation of hepatorenal biomarkers and their histopathlogical studies on day 44th.

Procedure to study histopathology. Histopathological studies were conducted on days 22nd and 44th. Kidneys and livers were separated, washed through sodium chloride (0.9%). For 24 h the tissues were fixed in 10% buffered formalin. Water was removed in various grades of xylene and ethanol. For sectioning in a microtome, the tissue was first placed in liquid paraffin. Eosin and hematoxylin dyes were used for staining the tissue. The tissues after staining were studied under microscope for histopathological changes, through different magnifications.

Statistical analysis. One way ANOVA with post-hoc Tukey test was applied. Moreover, $P<0.05$ as a significant value, was analysed statistically through SPSS software.

Results and Discussion

The protective and curative role of *P. Integerrima* galls was investigated in Nimesulide induced hepato-renal intoxication. Various histopathological, hematological and biochemical studies were performed to evaluate the effects on liver, kidney and on blood component as well.

Liver study. Figure 1-2 showed the same levels of S.Br and ALT (P>0.05) on 1st day, among all the groups. Group N showed high levels of ALT & S.Br throughout the study after day 1st, which showed strong liver toxicity induced by Nimesulide at a dose of 5 mg/Kg/day in comparison to normal (NS) group (P<0.05). In S group, taken as standard, the bilirubin and ALT levels were higher than NS (P<0.05) and were little bit lower than N group, which revealed no hepato-protection by standard group against toxicity induced by Nimesulide. P2 group (methanolic extract at 300 mg/Kg/day) showed a remarkable liver protection as compared to standard (P<0.05), P1and P3 groups. Groups P1 and P3 administered with methanolic extracts at 100 and 500 mg/Kg/day respectively, also showed prominent protection against toxicity induced in liver, as compared to standard (P<0.05).

As compared to NS, group N showed high level of liver biomarkers on day 44th but were decreased from, as measured on 11th and 22nd days. This showed a curative response as the Nimesulide was discontinued. In curative phase, the levels of S.Br and ALT, in groups administered with methanolic extract of galls, reduced rapidly to normal especially in P2 group. Standard group (S) also showed low level of liver biomarker as compared to the levels measured on day 11th and 22nd.

Renal study. Figure 3-4 showed that all the groups have same levels (P>0.05) of renal biomarkers (BUN and S.Cr) on day 1st. As compared to normal group (NS), N group reveals higher level of BUN and S.Cr (P<0.05) on day 11th and day 22nd. This indicates a mild to moderate renal toxicity induced by Nimesulide. *P. integerrima* extract at 300 mg/Kg/day (P2) showed the same levels of S. Cr and BUN as observed in standard (vitamin-C) P>0.05 and showed much better levels than P1 and P3 (P<0.05).

On day 44th it was observed from the result of BUN and S. Cr that group N have low levels than those observed on day 11th and 22nd. In the absence of Nimesulide, N group revealed some curative response. A much better reno-protective and curative response was observed in P2 at the discontinuation of Nimesulide, on day 44th. It was also observed on day 44th that P1 and P3 groups showed healing response but not better than P2 group (P<0.05).

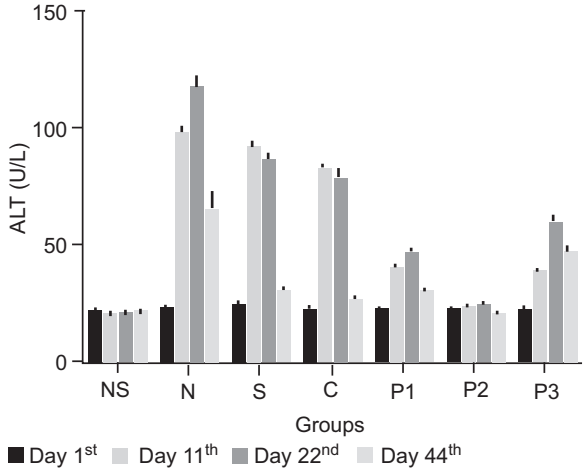

Fig. 1. Effect of nimesulide (N) at 5 mg/Kg/day, silymarin (S) at 50 mg/Kg/day, vitamin-C (C) at 40 mg/Kg/day, normal saline (NS) at 5 mL/Kg/day and different doses (100, 300 and 500 mg/Kg/day) of *P.i.* galls extract on ALT.

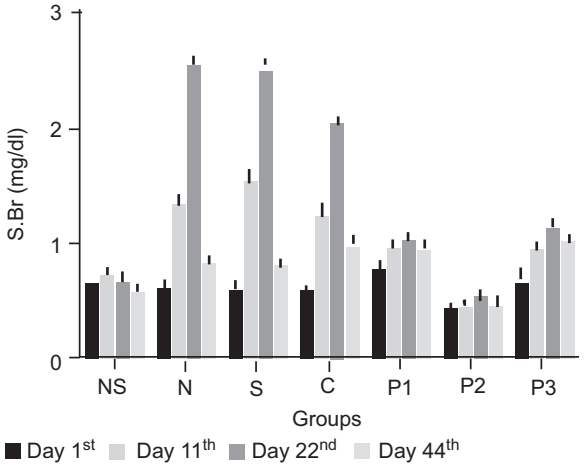

Fig. 2. Effectof nimesulide (N) at 5 mg/Kg/day, silymarin (S) at 50 mg/Kg/day, vitamin-C (C) at 40 mg/Kg/day, normal saline (NS) at 5 mL/Kg/day and different doses (100, 300 and 500 mg/Kg/day) of *P.i.* galls extract on S.Br.

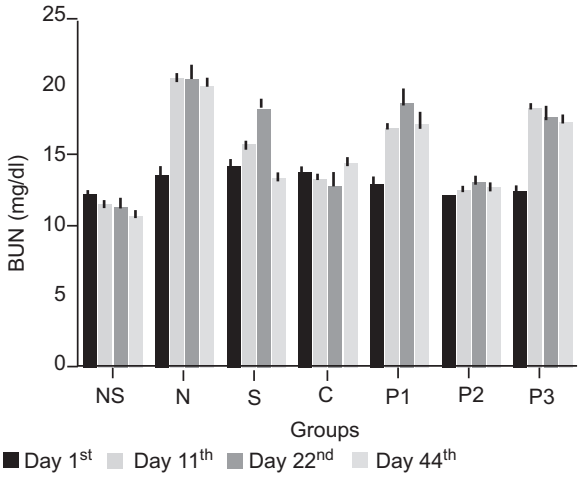

Fig. 3. Effectof nimesulide (N) at 5 mg/Kg/day, silymarin (S) at 50 mg/Kg/day, vitamin-C (C) at 40 mg/Kg/day, normal saline(NS) at 5 mL/Kg/day and different doses (100, 300 and 500 mg/Kg/day) of *P.i.* galls extract on BUN.

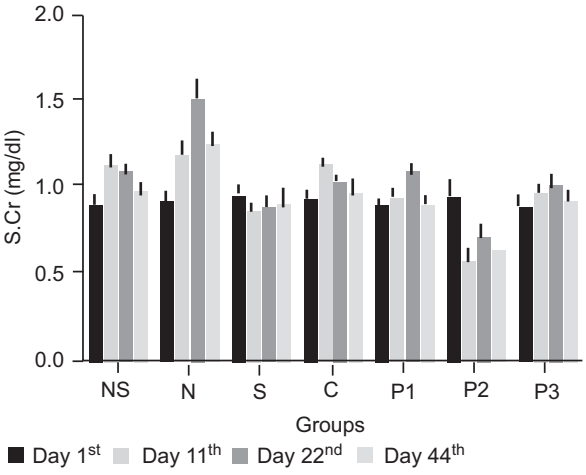

Fig. 4. Effectof nimesulide (N) at 5 mg/Kg/day, silymarin (S) at 50 mg/Kg/day, vitamin-C (C) at 40 mg/Kg/day, normal saline (NS) at 5 mL/Kg/day and different doses (100, 300 and 500 mg/Kg/day) of *P.i.* galls extract on S.Cr.

Hematology. Hb levels of all the groups were observed same (P>0.05) as shown in Fig. 5. In Fig. 6, the levels of TLC on day 1st and day 11th were also the same in all the groups (P<0.05). Group N resulted in lower level of TLC on day 22nd as compared to normal group (P<0.05). On day 44th, after the discontinuation of Nimesulide all the groups were showing a slight increase in the levels of TLC.

Histopathology of liver. Figure 7a, b, c, d, e and f (Liver histology) revealed mild to severe liver injuries. Table 1 showed a moderate degeneration of central vein with moderate infiltration of lymphocytes, ballooning degeneration, inflammation, fibrosis and apoptosis by Nimesulide (N group). Among all the test doses of methanolic extracts of *P. integerrima* galls, a dose at 300 mg/Kg/day (P2) resulted in better liver protection, revealed from the curative response regarding degene-ration of central vein, infiltration of lymphocytes, ballooning degeneration, inflammation, fibrosis and apoptosis. The other groups at doses of extracts at 100 and 500 mg/Kg/day (P1 and P2), showed mild degeneration of central vein with mild inflammatory foci, infiltration of lymphocytes and fibrosis.

Histopathology of kidney. Histological observations (Fig. 8a, b, c, d, e and f, in kidney histology) showed mild to moderate kidney injury in N group at 5 mg/Kg/day dose of Nimesulide. Cellular vacuolization and necrosis are the features, shown as kidney damage. The renal histological features of the group P2 administered with extract at 300 mg/Kg/day are like that of the group administered with vitamin-C (standard group). The

Table 1. Effect of *Pistacia integerrima* on Nimesulide induced histopathological changes in liver

Observation	Normal (NS)	Nimesulide (N)	Silymarin (S)	P1	P2	P3
Fibrosis	-	+++	_	+	-	+
Inflammatory foci	-	+++	+	+	+	+
Apoptosis	-	+++	-	+	-	-
Ballooning degeneration	-	+++	+	-	-	-
Lymphocyte infiltration	-	+++	+	+	+	+
Central vein degeneration	-	++	-	+	-	+

(-) = absent; (+) = mild; (++) = moderate; (+++) = severe; (++++) = extremely severe.

histology of P1 and P3 revealed a mild renal injury compared to P2 and standard group.

Liver is a vital organ that performs the role of bridge between the gastrointestinal tract and the target site of the drugs. It metabolises the drugs and xenobiotics absorbed from the gastrointestinal tract (William, 2003). The factors involved in the hepatotoxicity are the drugs, alcohol, age, sex, diseases (e.g. HIV or diabetes) and genetic makeup (Verma and Kaplowitz, 2009). The hepatobiliary diseases may be exaggerated by drug induced liver toxicity. In clinical use, dose related hepatotoxicity is caused by some drugs. Most of the drug induced liver diseases are unpredictable. Immune mediated hypersensitivity and idiosyncratic reactions

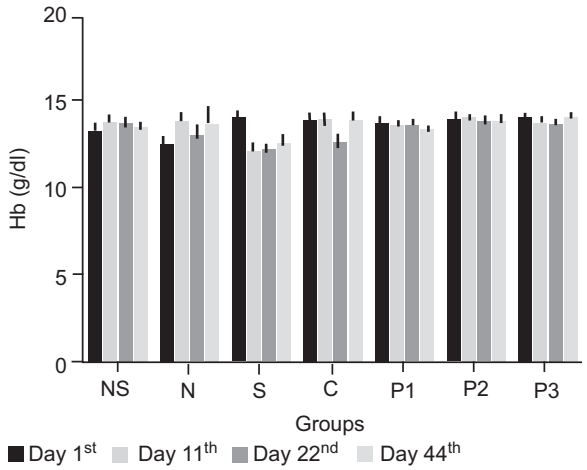

Fig. 5. Effect of nimesulide (N) at 5 mg/Kg/day, silymarin (S) at 50 mg/Kg/day, vitamin-C (C) at 40 mg/Kg/day, normal saline (NS) at 5 mL/Kg/day and different doses (100, 300 and 500 mg/Kg/day) of *P.i.* galls extract on Hb.

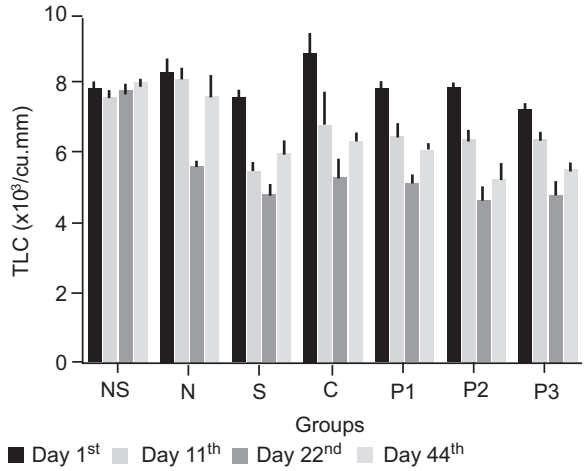

Fig. 6. Effect of nimesulide (N) at 5 mg/Kg/day, silymarin (S) at 50 mg/Kg/day, vitamin-C (C) at 40 mg/Kg/day, normal saline (NS) at 5 mL/Kg/day and different doses (100, 300 and 500 mg/Kg/day) of *P.i.* galls extract onTLC.

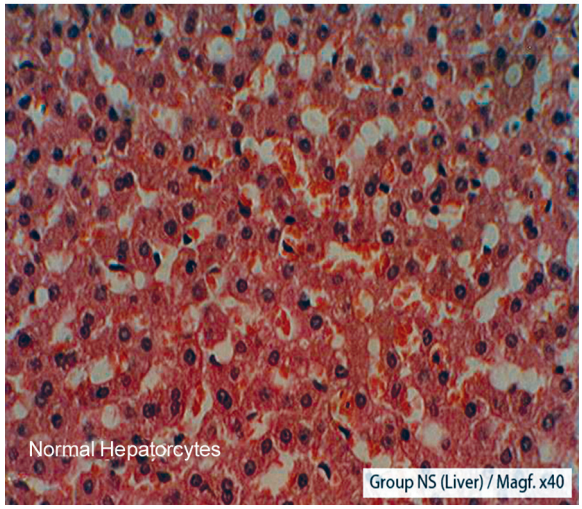

Fig. 7a. Liver histology of NS group (administered with normal saline at 5 mL/Kg/day).

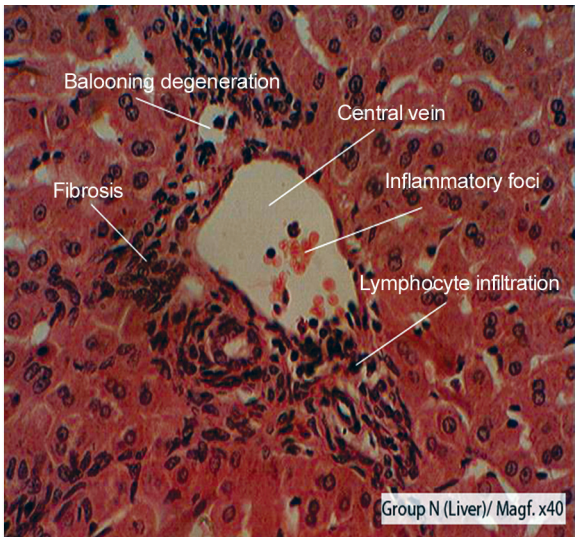

Fig. 7b. Liver histology of N group (administered with nimesulide only at 5 mg/Kg/day).

are sometime the cause of liver toxicity (Chalasani and Björnsson, 2010).

Kidney performs the most important functions of the body including endocrine function, acid-base balance, and control of volume status and clearance of endogenous waste products (Perazella, 2009). Kidney receives 25% of blood during resting cardiac output. It eliminates the drugs and their metabolites from the blood (Decloedt and Maartens, 2011). Humans are frequently exposed to the toxic substances which affects the kidney. Some of the immuno-suppressive drugs, analgesics, chemotherapeutic drugs and antimicrobials are nephrotoxic

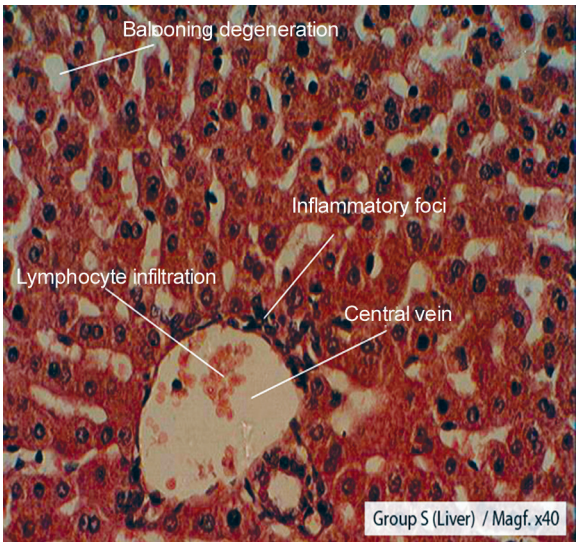

Fig. 7c. Liver histology of S group (administered with silymarin at a dose of 50 mg/Kg/day) and nimesulide at 5 mg/Kg/day.

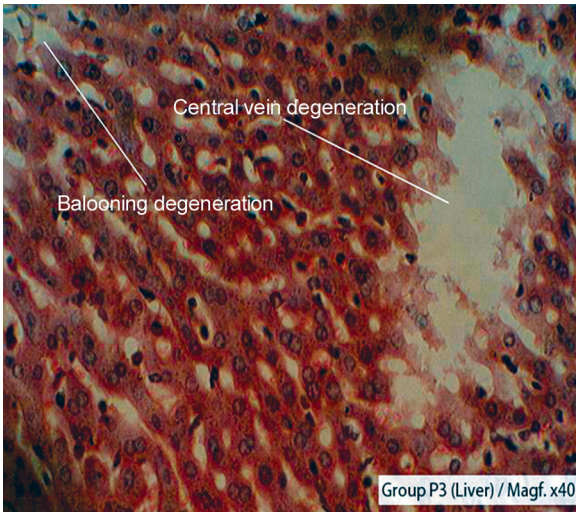

Fig. 7e. Liver histology of P2 group (administered with *P. integerrima* galls extract at 300 mg/Kg/day) and nimesulide at 5 mg/Kg/day.

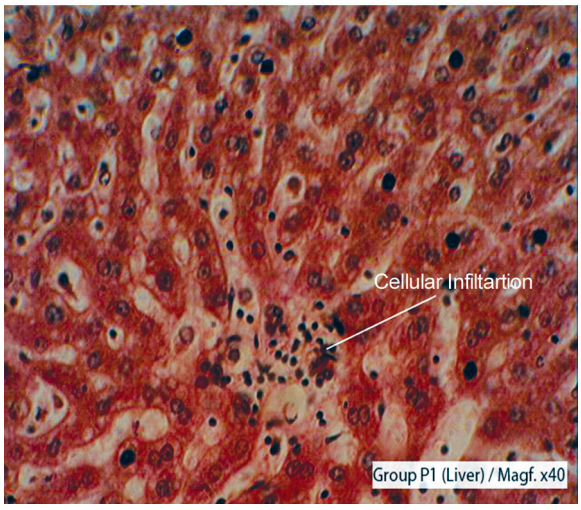

Fig. 7d. Liver histology of Pl group (administered with *P. integerrima* galls extract at 100 mg/Kg/day) and nimesulide at 5 mg/Kg/day.

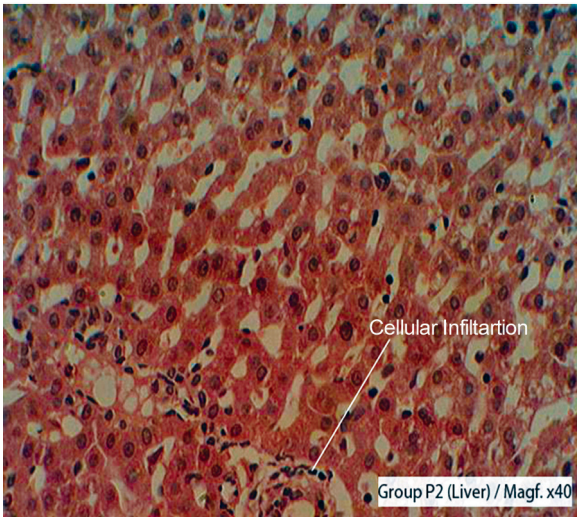

Fig. 7f. Liver histology of P3 group (administered with *P. integerrima* galls extract at 500 mg/Kg/day) and nimesulide at 5 mg/Kg/day.

(Schet *et al*., 2005; Lamieire *et al*., 2005). Some of the environmental substances also cause nephrotoxicity e.g. bismuth, uranium, copper, cadmium, lead and mercury (Brewster and Perazella, 2004; Yu *et al*., 2004; Vleet and Schnellmann, 2003).

NSAIDs have inhibitory effects on cyclooxygenases 1 and 2 (COX-1 and COX-2) which then cause the inhibition of thromboxane and prostaglandin. Anti-pyretic, anti-inflammatory and analgesic are efficient COX-2 inhibitors. COX-1inhibitors showed renal and gastrointestinal side effects more than COX-2 (Famaey, 1997). It was demonstrated in a study that diphenylamine group of NSAIDs is responsible for causing liver cell injuries by decreasing ATP (Bort *et al*., 1999). Liver toxicity is an increasing issue related to the utilization of NSAIDs (Gay *et al*., 1990). Because of the fewer adverse effects related to gastrointestinal tract, the use of Nimesulide has been increased (Hawkey, 1999). Despite frequent use, Nimesulide has been linked with

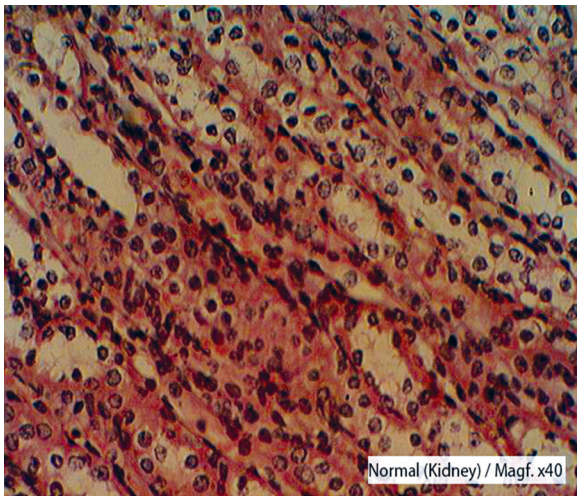

Fig. 8a. Kidney histology of NS group (administered with normal saline at 5 mL/Kg/day).

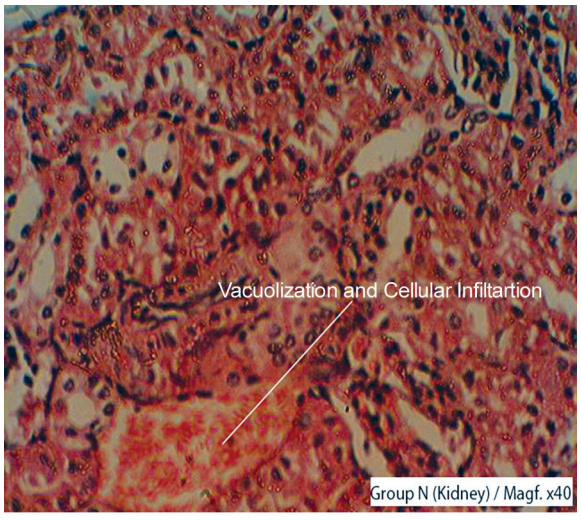

Fig. 8b. Kidney histology of N group (administered with nimesulide only at 5 mg/Kg/day).

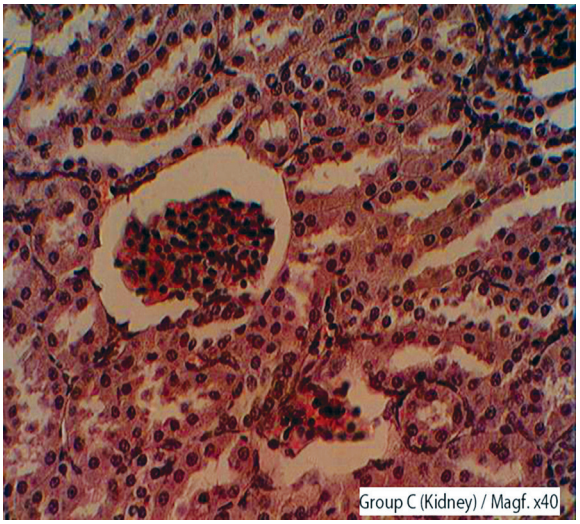

Fig. 8c. Kidney histology of group C (administered with vitamin C at 40 mg/Kg/day) and nimesulide with 5 mg/Kg/day.

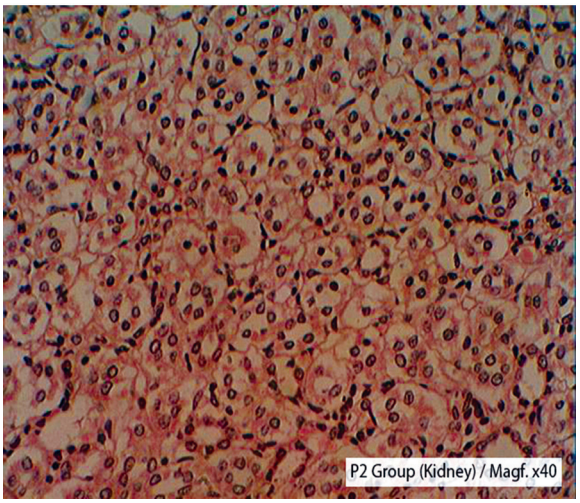

Fig. 8d. Kidney histology of P2 group (administered with *P. integerrima* galls extract at 300 mg/Kg/day) and nimesulide at 5 mg/Kg/day.

severe hepatotoxicity (Bessone, 2010; Walker and Kennedy, 2008; Tan *et al*., 2007; Boelsterli, 2002; Merlani *et al*., 2001; Schattner *et al*., 2000). The reported liver disorders associated with use of Nimesulide are reversibly increased levels of liver enzymes, cholestasis, hepato-cellular damage, acute hepatitis, and fatal acute liver failure (Bernardes *et al*., 2015).

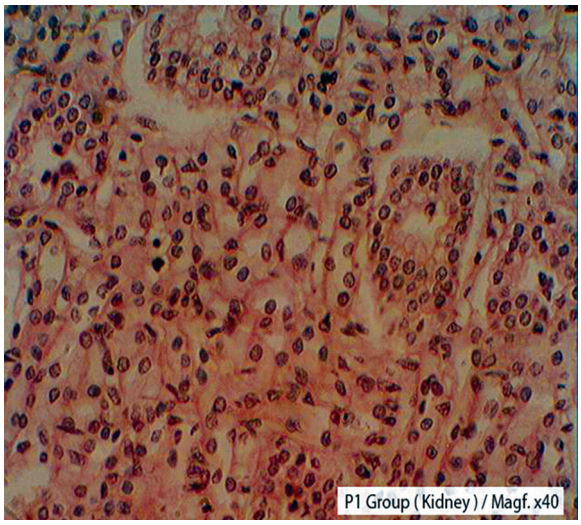

Fig. 8e. Kidney histology of P1 group (administered with *P. integerrima* galls extract at 100 mg/Kg/day) and nimesulide at 5 mg/Kg/day.

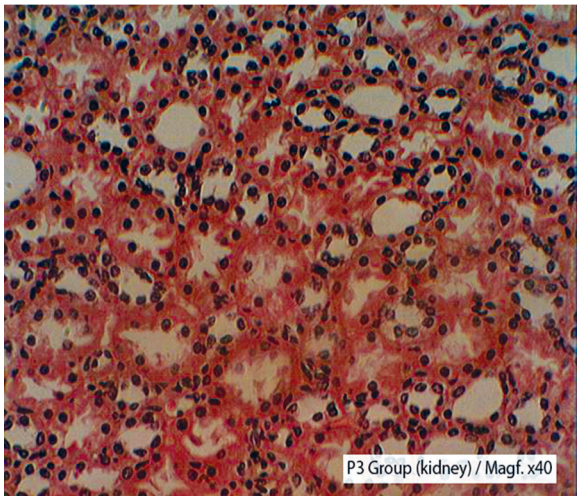

Fig. 8f. Kidney histology of P3 group (administered with *P. integerrima* galls extract at 500 mg/Kg/day) and nimesulide at 5 mg/Kg/day.

Beside hepatotoxicity, hyperplasia of bile ducts and generation of reactive metabolites take place with Nimesulide intake in some cases. This reactive metabolite induces oxidative stress of free radicals and mitochondrial damage (Singh and Tripathi, 2012; Singh and Tripathi, 2010). In one case 100 mg of nimesulide induced acute kidney failure with lymphocyte infiltration into the kidney and diffuse ischemic lesions, similar as in the case of nephritis due to NSAIDs (Apostolou *et al*., 1997). The underlying mechanism of Nimesulide induced toxicity is not fully understood yet. However, it is suggested that Nimesulide generates reactive oxygen species and mitochondrial injury (Borku *et al*., 2008). Nimesulide caused nephropathy due to crystalline obstruction in renal cells which resulted in acute kedney failure (DerNiepen *et al*., 2002). COX-2 inhibition at kideny level by nimesulide has given a clue to clinicians as a toxicity induced by it and can further be evaluated on this ground (Conforti *et al*., 2001). Oxidative stress produced can also effect the renal functions adversely (Squadrito and Pryor, 1998). Different extracts of various parts of the *P. integerrima* plants act as free radical scavenger due to the presence of flavonoids and phenolic compounds (Rauf *et al*., 2014; Khan *et al*., 2011; Joshi *et al*., 2010). These extracts also have anti-inflammatory activity (Naseem *et al*., 2010). The antioxidant compounds are gallic acid and quercetin (Joshi *et al*., 2008). Another study proved that methanolic and aqueous extract of *P. integerrima* galls has glycosides, flavonoids, tannins and phenolic constituents (Uttara and Mishra, 2009; Selvi and Uma, 2007).

This study was designed to evaluate whether the concomitant use of *P. integerrima* galls extract would have protective and curative roles in the Nimesulide induced hepatorenal intoxication. *P. integerrima* galls extracts exhibited better hepatorenal protective role, both in the presence and absence of nimesulide. Additionally, this study has supported the evidence that Leukopenia is associated with the use of NSAIDs (Strom *et al*., 1993). In this study Nimesulide was observed as the main cause of decreased level of TLC, on day 22nd. It was also observed that the groups administered with different doses of *P. integerrima* galls extracts, there was no effect on the levels of TLC both in the presence and absence of Nimesulide. In this study, from the levels of liver biomarkers (ALT and S.Br) P2 group showed better hepatoprotection against the toxicity induced by Nimesulide as compared to S2, P1 and P3, which was also supported by the histopathological

studies. The biochemical and histological study of kidney showed that standard (vit-C) and P2 groups have protective role against mild to moderate renal toxicity induced by Nimesulide.

Conclusion

It is concluded that methanolic extracts of *P. Integerrima* galls, especially administered at a dose of 300 mg/Kg/day, have exhibited a protective as well as a curative role in the hepatorenal intoxication, induced through the human therapeutic dose (5 mg/Kg/day) of Nimesulide. These findings are encouraging to plan clinical studies of herbal drugs in such type of drug induced toxicities.

Conflict of Interest. The authors declare that they have no conflict of interest.

References

Abdullah, K.M.A., Ahmad, W., Ahmad, M., Nisar, M. 2017. Hepatoprotective effect of the solvent extracts of *Viola canescens* Wall. ex. Roxb. against CCl4 induced toxicity through antioxidant and membrane stabilizing activity: *BMC Complementary and Alternative Medicine*, **17:** 1-11.

Aleksa, K., Matsell, D., Krausz, K., Gelboin, H., Ito, S., Koren, G. 2005. Cytochrome P450 3A and 2B6 in the developing kidney: implications for ifosfamide nephrotoxicity. *Pediatric Nephrology*, **20:** 872-885.

Apostolou, T., Sotsiou, F., fanti, Y., Andreadis, G.E., Nikolopoulou, N.E., Diamantopoulos, E., Billis, A. 1997. Acute renal failure induced by nimesulide in a patient suffering from temporal arteritis. *Nephrology Dialysis Transplantation*, **12:** 1493-1496.

Basile, D.P., Anderson, M.D., Sutton, T.A. 2012. Pathophysiology of acute kidney injury. *Comprehensive Physiology*, **2:** 1303.

Bernardes, S.S., Souza-Nogueira, A., Moreira, E.G., Kishima, M.O., Guembarovski, A.F., Turini, T.L., Turini, C.A. 2015. Nimesulide-induced fatal acute liver failure in an elderly woman with metastatic biliary adenocarcinoma: a case report. *Sao Paulo Medical Journal*, **133:** 371-376.

Bessone, F.2010. Non-steroidal anti-inflammatory drugs: what is the actual risk of liver damage. *World Journal of Gastroenterology*, **16:** 5651-5661.

Boelsterli, U.A. 2002. Mechanisms of NSAID-induced hepatotoxicity: focus on nimesulide. *Drug Safety*, **25:** 633-648.

Borku, M.K., Guzel, M., Karakurum, M.C., Ural, K., Aktas, S. 2008. Nimesulide-induced acute biliary tract injury and renal failure in a kitten: a case report. *Veterinary Medicine*, **3:** 169-172.

Bort, R., Ponsoda, X., Jover, R., Gomez-Lechon, M.J., Castell, J.V. 1999. Diclofenac toxicity to hepatocytes: a role for drug metabolism in cell toxicity. *Journal of Pharmacology and Experimental Therapeutics*, **288:** 65-72.

Brewster, U.C., Perazella, M.A. 2004. A review of chronic lead intoxication: an un-recognized cause of chronic kidney disease. *American Journal of the Medical Sciences*, **327:** 341-347.

Chalasani, N., Björnsson, E. 2010. Risk factors for idiosyncratic drug-induced liver injury. *Gastroenterology*, **138:** 2246-2259.

Conforti, A., Leone, R., Moretti, U., Mozzo, F.,Velo, G. 2001. Adverse drug reactions related to the use of NSAIDs with a focus on nimesulide: results of spontaneous reporting from a northern Italian area. *Drug Safety*, **24:** 1081-1090.

Decloedt, E., Maartens, G. 2011. Drug-induced renal injury: the kidney plays an important role in the elimination of many drugs and their metabolites. *Continuing Medical Education*, **29:** 252-255.

DerNiepen, P.V., Van Doorn, K.J., Den Houte, K.V., Verbeelen, D. 2002. Nimesulide and acute renal failure caused by oxalate precipitation. *Nephrology Dialysis Transplantation*, **17:** 315-316.

Famaey, J.P. 1997. *In vitro* and *in-vivo* pharmacological evidence of selective cyclooxygenase-2 inhibition by nimesulide: an overview. *Inflammation Research*, **46:** 437-446.

Gay, G.R.1990. Another side effect of NSAIDs. *Journal of the American Medical Association*, **264:** 2677-78.

Hawkey, C.J. 1999. COX-2 inhibitors. *Lancet*, **353:** 307-314.

Jaeschke, H., Smith, C.W., Clemens, M.G, Ganey, P.E., Roth, R.A.1986. Mechanisms of inflammatory liver injury: adhesion molecules and cytotoxicity of neutrophils. *Toxicology and Applied Pharmacology*, **l139:** 213-226.

Jaeschke, H., Gores, G.J. 2002. Mechanisms of Hepatotoxicity. *Toxicological Sciences*, **65:** 166-176.

Jaeschke, H., Smith, C.W.1997. Mechanisms of neutrophil-induced parenchymal cell injury. *Journal of Leukocyte Biology*, **l61:** 647-653.

Jindal, A. 2012. Physiochemical and phytochemical evaluation of *Pistacia integerrima* stew ex beandis. *Journal of Global Pharma Technology*, **4:** 24-27.

Joshi, U.P., Mishra, S.H. 2010. *In-vitro* antioxidant and hepatoprotective activity of isolated compounds from *Pistacia Integerrima*. *Australian Journal of Herbal Medicine*, **22:** 763-768.

Joshi, U.P., Mishra, S.H. 2008. Evaluation of aqueous and methanol extracts of *Pistacia integerrima* galls as potential immunomodulator. *Pharmacognosy Magazine*, **4:** 126-131.

Khan, M.A., Khan, J., Ullah, S., Malik, S.A., Shafi, M. 2011. Hepatoprotective effects of *Berberis lycium*, *Galium aparine* and *Pistacia integerrima* in carbon tetrachloride (CCl_4)-treated rats. *Journal of Post-graduate Medical Institute*, **22:** 91-94.

Khan, M.A., Malik, S.A., Shad, A.A., Shafi, M., Bakht, J. 2004. Hepatocurative potentials of *Pistacia integerrima* in CCl_4-treated rats. *Sarhad Journal of Agriculture*, **20:** 279-285.

Lamieire, N.H., Flombaum, C.D., Ronco, C. 2005. Acute renal failure in cancer patient. *Annals of Medicine*, **37:** 13-25.

Laskin, D.L., Laskin, J.D. 2001. Role of macrophages and inflammatory mediators in chemically induced toxicity. *Toxicology*, **160:** 111-118.

Lecomte, J., Monti, T., Pochobradsky, M.G. 1991. Antipyretic effects of nimesulide in paediatric practice: a double-blind study. *Current Medical Research and Opinion*, **12:** 296-303.

Maryam, A.S., Bhatti, A., Shahzad, A.W. 2010. Protective effects of silymarin in isoniazid induced hepatotoxicity in rabbits. *Annals of King Edward Medical University*, **16:** 43-47.

Merlani, G., Fox, M., Oehen, H.P., Cathomas, G., Renner, E.L., Fattinger, K., Schneemann, M., Kullak-Ublick, G.A. 2001. Fatal hepatotoxicity secondary to nimesulide. *European Journal of Clinical Pharmacology*, **57:** 321-326.

Naseem, S.A., Akbar, W., Muhammad, F., Aisha, Q. 2010. Analgesic and anti-inflammatory effects of *Pistacia integerrima* extracts in mice. *Journal of Ethnopharmacology*, **129:** 250-253.

Patel, T., Roberts, L.R., Jones, B.A., Gores, G.J. 1998. Dysregulation of apoptosis as a mechanism of liver disease: an overview. *Seminars in Liver Disease*, **18:** 105-114.

Perazella, M.A. 2009. Renal vulnerability to drug toxicity. *Clinical Journal of the American Society of Nephrology*, **4:** 1275-1283.

Raafat, B.M., Shafaa, M.W., Rizk, R.A., Elgohary, A.A., Saleh, A. 2009. Ameliorating effects of vitamin C against acute lead toxicity in albino rabbits. *Australian Journal of Basic and Applied Sciences*, **3:** 3597-3608.

Ramadan, S.I., Shalaby,M., Banna, H.E., Afif, N. 2011. Hepatoprotective and antioxidant effects of *Silybum marianum* plant in rats. *International Journal for Agro Veterinary and Medical Sciences*, **5:** 541-547.

Rauf, A., Uddin,G., Khan, H., Roohullah. 2014. Preliminary antioxidant profile of *Pistacia integerrima* Stewart. *Pakistan Journal of Pharmaceutical Sciences*, **27:** 855-8.

Salah-Eldin, O., Abd El-Azim, S.A., Eldeib, K.M., Barakat, M.M. 2012. Is lysosomal enzymes changes important in the pathogenesis of liver and kidney injury induced by short and long term administration of some NSAID'drugs in rats. *Life Science Journal*, **9:** 1102-1113.

Schattner, A., Sokolovskaya, N., Cohen, J. 2000. Fatal hepatitis and renal failure during treatment with nimesulide. *Journal of Internal Medicine*, **247:** 153-155.

Schet, M., Dasta, J., Goldstein, S., Golper, T. 2005. Drug-induced acute kidney injury. *Current Opinion in Critical Care*, **11:** 555-565.

Selvi, S., Uma, D.P. 2007. Antibacterial efficacy and phytochemical observation of some Indian medicinal plants. *Ancient Science of Life*, **3:** 16-22.

Singh, B.K.,Tripathi, M. 2012. Natural terpenes prevent mitochondrial dysfunction, oxidative stress and release of apoptotic proteins during nimesulide-hepatotoxicity in rats. *PLoS One*, **7:** e34200.

Singh, B.K., Tripathi, M. 2010. Nimesulide aggravates redox imbalance and calcium dependent mitochondrial permeability transition leading to dysfunction *in vitro*. *Toxicology*, **275:** 1-9.

Strautnieks, S.S., Bull, L.N. 1998. A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis. *Nature Genetics*, **20:** 233-238.

Squadrito, G.L., Pryor, W.A. 1998. Oxidative chemistry of nitric oxide: the roles of superoxide, peroxynitrite, and carbon dioxide. *Free Radical Biology and Medicine*, **25:** 392-403.

Strom, B.L., Carson, J.L., Schinnar, R., Snyder, E.S., Shaw, M., Lundin, F.E. 1993. Nonsteroidal anti-inflammatory drugs and neutropenia. *Archives of*

Internal Medicine, **153:** 2119-2124.

Tan, H.H., Ong, W.M., Lai, SH., Chow, W.C. 2007. Nimesulide-induced hepatotoxicity and fatal hepatic failure. *Singapore Medical Journal*, **48:** 582-585.

Thawani, V., Sontakke, S., Gharpure,K., Pimpalkhute, S. 2003. Nimesulide: the current controversy. *Indian Journal of Pharmacology*, **35:** 121.

Tungmunnithum, D., Thongboonyou, A., Pholboon, A., Yangsabai, A.2018. Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects: an overview. *Medicines* (Basel), **5:** 93.

Uddin, G., Rauf, A., Rehman, T.U., Qaisar, M. 2011. Phytochemical screening of *Pistacia chinensis* var. integerrima. *Middle-East Journal of Scientific Research*, **7:** 707-711.

Upadhye, A.S., Rajopadhye A. 2010. Pharmacognostic and phytochemical evaluation of leaf galls of Kakadshringi used in Indian system of medicine. *Journal of Scientific and Industrial Research*, **69:** 700-704.

Uttara, P.J., Mishra, S. 2009. *In-vitro* antioxidant activity of galls of *Pistacia integerrima*. *Pharmacology*, **2:** 763-768.

Verma, S., Kaplowitz, N. 2009. Diagnosis, management and prevention of drug-induced liver injury. *Gut*, **58:** 1555-1564.

Vleet, T.R., Schnellmann, R.G. 2003. Toxic nephropathy: environmental chemicals. *Seminars in Nephrology*, **23:** 500-508.

Walker, S.L., Kennedy, F., Niamh, N., McCormick, P.A. 2008. Nimesulide associated fulminant hepatic failure. *Pharmaco-epidemiology and drug safety*, **17:** 1108-1112.

William, M.L. 2003. Drug-induced hepatotoxicity. *New England Journal of Medicine*, **349:** 474-485.

Wu, D., Cederbaum, A.I. 2009. Oxidative stress and alcoholic liver disease. In: *Seminars in Liver Disease*, **29:** 141-154.

Yu, C.C., Lin, J.L., Lin-Tan, D.T. 2004. Environmental exposure to lead and progression of chronic renal diseases: a four-year prospective longitudinal study. *Journal of the American Society of Nephrology*, **15:** 1016-1022.