Original Article

Nimesulide Induced Oxidative Stress and Herbal Remedy

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ABSTRACT

Objective: To find the antioxidant activity of Picrorhiza Kurroa(Pk) in liver against nimesulide induced oxidative stress.

Study Design: Experimental animal study on mice

Place and Duration of Study: This study was conducted at the National Institute of Health, Islamadad from Feb 2013 to March 2014.

Materials and Methods: Heapatotoxicity was induced in mice by giving 750 mg/kg body weight of nimesulide foe 3 days and for establishing hepatoprotective activity, Picrorhiza kurroa was given for 14 days in two doses of 250 mg/kg and 500 mg/kg. Liver function analysis was carried out and serum glutathione peroxidase levels were measured to assess the antioxidant role of Picrorhiza Kurroain liver.

Results: Our study showed significant results for serum bilirubin and alanine aminotransferase (ALT) in mice receiving the two doses of Picrorhiza Kurroa. Similarly significant result was seen in serum glutathione peroxidase (GPx) showing Pk as a potent antioxidant against nimesulide toxicity.

Conclusion: This study demonstrated Pk as a strong antioxidant against nimesulide induced hepatic damage and the mechanism of hepatoprotection is by production of free radicals.

Key Words: Nimesuide, Picrorhiza Kurroa (Pk), hepatotoxicity, oxidative stress, glutathione peroxidase

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INTRODUCTION

Hepatotoxicity occurs either due to an insult by a medicinal agent or other non-infectious agents leading to deranged liver function.[1] Incidence of drug induced hepatotoxicity in general population was recently noted to be 14/100,000. Drugs are responsible for causing acute liver damage in10- 52 % of patients.[2] NSAIDs are among the agents displaying very simple chemical structure but manifesting potent analgesic, antiplatelet, antipyretic and anti-inflammatory response. However bleeding tendency, severe gastric upset, kidney and liver damage are their few common side effects.[3]

Many research studies have shown that an apoptotic event starts due to the presence of intracellular reactive oxygen species and may serve as an important indicator of NSAIDs associated liver damage. Due to excessive production of these reactive particles an environment of oxidative stress is produced leading to cell dysfunction and death of cell.[4]Other reason of mitochondrial failure is covalent modification of proteins by reactive oxidative species. Further aggravating factors are sensitivity to drug and gene related factors.

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Research demonstrates a positive role of nimesuide in generating oxidative stress in liver. Biochemical assays of many antioxidant enzymes are greatly reduced by nimesulide[5]

Picrorhiza kurroa (common name Kutki) is widely used both in modern medicine and in traditional medicine for asthma, jaundice and liver disorders. Apart from hepatoprotective activity other distinct properties of Pk are anti-inflammatory, anti-anaphylactic and free radical scavenging activities.[6]Picrorhiza kurroa has proved its hepatoprotective effect in several investigations against different hepatotoxic chemicals and convincing results were seen.[7]

Many animal studies have confirmed antioxidant effect of Picrorhiza kurroa. In one study different free radicle scavenging assays were used to establish antioxidant activity of aqueous extract of Pk against ethanol.[8] Picrorhiza kurroa methanolic and aqueous extracts obtained from the rhizome are able to show antiapoptotic and cytotoxic activity apart from strong antioxidant potential.[9]

When pretreatment of rats was done with Picrorhiza kurroa, they depicted significant p values of glutathione peroxidase activity.[10]Picroside II is an isolated glycoside obtained from Picrorhiza kurroa is also helpful in preventing liver damage in animals. This was established by noticing markedly decreased levels of ALT against paracitamol and carbon tetrachloride induced hepatotoxicity. Picroside II showed its antioxidant potential by lowering the concentration of malonaldehyde in serum remarkably, whereas serum glutathione and superoxide dismutase levels were

increased. Furthermore increased activity of ATPase and histological improvement was shown by Picroside II against paracitamol.[11]

At yet we have no alternative for detoxification of nimesulide induced damage. One such herb we can rely is Picrorhiza kurroa. No scientific research data documents the hepatoprotective potential for Pk and its glycosides against nimesulide. We conducted our study to note the hepatoprotective effect of Pk glycosides and how they produce hepatoprotection.

MATERIALS AND METHODS

We conducted this study at animal house of National Institute of Health, Islamabad from Feb 2013 to March 2014. Our experimental model for this study was adult Balb C mice. Standard laboratory diet was provided to mice in proper ventilated rooms. Stas Ottos method for glycosidal extraction was used for obtaining glycosidal extract of Pk.[12]There were four groups of 20 mice. Pk was administered to group 1 in a dose of 250 mg/kg for 14 days. 750 mg/kg nimesulide was administered for 3 days to group 2.[13] For group 3, 750 mg/kg nimesulide was given for 3 days and then 250 mg/kg[14]Pk for two weeks and in group 4, 3 days nimesulide administration was followed by 14 days administration of Pk in a dose of 500 mg/kg. At the end liver assesment and serum glutathione peroxidase were assessed by using colorimetric assay.

RESULTS

Animal model of hepatotoxicity was made administring 750 mg/kg nimesulide in high doses to mice. Nimesulide led to significant (p value < 0.000) increase in serum bilirubin from 0.69 mg/dl in group 1 to 1.78 mg/dl in group 2 and serum ALT (p value < 0.000) from 31.9 IU/L in group 1 to 163.2 IU/L in group 2. When nimesulide was given serum GPx levels were lowered from mean value of 91.8 m U/ dl in control group to 63.3 m U/ dl in nimesulide group.

Table No.1: Comparison of ALT between Different Groups

Groups	Mean ALT(IU/L)	P value
Control	31.9	0.000
Nimesulide	163.2	
Nimesulide	163.2	0.000
Low dose Pk	33.0	
Nimesulide	163.2	0.000
High dose Pk	31.7	

Results were analysed by using Tukey's test for serum GPx which demonstrated significant p value (0.000) when group 1 and 2 were compared. Pk demonstrated its curative potential by reversing serum bilirubin. Serum bilirubin was significantly (p value < 0.000) lowered to 0.33mg/dl in group 3 and 0.32 mg/dl in group 4. Similarly mean serum ALT was significantly (p value < 0.000) decreased to 33.0 IU/L in group 3 and 31.7 IU/Lin group 4. Similarly for serum GPx significant p value was seen when comparison of group 2 was made with group 3 and 4.

Table No.2: Comparison of GPx between different Groups

Groups	Mean GPx (mU/dl)	P value
Control	91.8	0.000
Nimesulide	63.3	
Nimesulide	63.3	0.000
Low dose Pk	92.0	
Nimesulide	63.3	0.000
High dose Pk	91.5	

DISCUSSION

Nimesulideis a frequently prescribed NSAID having nitroaromaticsulphonanilide structure which gives nimesulide marked analgesic, anti-inflammatory and antipyretic qualities. Despite therapeutic usefulness, safety profile and dire necessity of NSAIDs, many case reports of idiosyncratic drug induced hepatic injury have been noted.[15]

Literature search demonstrates nimesulide induced hepatotoxicity. Both biochemically and histologically, in doses as low as 20 mg/kg in rats.[16]

In our study nimesulide treated group showed significantly higher values of bilirubin than mean bilirubin of control group. There was 146% increase from normal in serum bilirubin,indicating hepatotoxicity. Pk administration on daily basis in low and high dose groups decreased the high levels of bilirubin (p value 0.000) showing a 52% decrease. Similarly ALT showed 409% increase in nimesulide group and then a decrease to 6.4 % by Picrorhiza kurroa.

Nimesulide induced oxidative stress in group 2 in terms of decreasing GPx significantly upto 45% when comparison was made with control group. Interestingly group 3 and 4 recovered from oxidative stress showing p value < 0.000.

Results of our study were supported by a research work conducted by Jeyakumar R where bilirubin and ALT was decreased by Pk. In that study the mechanism of hepatoprotection against antitubercular drugs was through Pk antioxidant activity in rats.[17]

Furthermore Girish C et al in his research also demonstrated that altered histological and biochemical parameters caused by paracitamol were reversed by prior treatment of mice with picrolive, which is a Pk glycoside against silymarin.[18]

A recently conducted study by K Kant demonstrated same results of Pk activity present in the leaves of Pk instead of using rhizomes of Pk establishing a new source of naturally occurring antioxidants.[19]

The protective potential of Picrorhiza kurroa on liver in cases who are prescribed lipid lowering drugs is also demonstrated by Harban S and Sharma where it proved itself as anticholestatic, antioxidant and demonstrated reduction in glutathione depletion.[20]

However no supporting or refuting data is available in literature to show the protective effect of Pk on plasma GPx activity after nimesulide administration.

CONCLUSION

It is concluded that the antioxidant effect of Picrorhizakurroa on liver occurred by potentiating the activity of antioxidant enzyme GPx which lead to an increased scavenging of free radicals which were produced by nimesulide. Based on these protective qualities of Pk we can give the community a better therapeutic alternative for nimesulide induced hepatorenal toxicity.

Author's Contribution:

Concept & Design of Study:	Afsheen Siddiqui
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Data Analysis:	Yasir Gaillani, Saadia Shahzad Alam
Revisiting Critically:	Afsheen Siddiqui, Yasir Gaillani
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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