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Original Research

Comparative efficacy of herbal hepatoproective agents silymarin in paractamol induced hepatotoxicity- a meta-analysis

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Abstract:

Background: One of the most widely used analgesics and antipyretics in the world is paracetamol, sometimes known as acetaminophen. However, because of the production of harmful metabolites that result in oxidative stress and liver damage, excessive ingestion can induce severe hepatotoxicity. Herbal substances like silymarin and other plant-derived antioxidants are among the hepatoprotective medicines that have been investigated to lessen liver damage.

Objective: The present meta-analysis aims to evaluate and compare the hepatoprotective efficacy of herbal agents, particularly silymarin, in paracetamol-induced hepatotoxicity based on available experimental and clinical studies.

Methods: To find studies assessing the hepatoprotective effects of herbal medicines in paracetamol-induced liver injury, a thorough search of electronic databases was carried out. Included were pertinent studies that reported histopathological results and biochemical measures including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). The protective effectiveness of silymarin and other herbal hepatoprotective drugs was compared by pooling and analyzing data from relevant research.

Results: According to the meta-analysis, in models of paracetamol-induced hepatotoxicity, silymarin and a number of herbal remedies considerably lowered liver enzyme levels and enhanced histological results. By lowering oxidative stress and boosting antioxidant defense systems, silymarin consistently showed hepatoprotective benefits among the assessed compounds.

Conclusion: Hepatotoxicity caused by paracetamol can be prevented and reduced with the help of herbal hepatoprotective substances, especially silymarin. The potential use of herbal substances as supplemental treatment alternatives for liver protection is supported by these findings. To confirm their efficacy and safety, more extensive clinical research is needed.

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Introduction

One of the most popular over-the-counter drugs for treating fever and pain is paracetamol, sometimes known as acetaminophen. Overconsumption of paracetamol is a major source of drug-induced liver damage globally, despite the fact that it is thought to be safe at therapeutic levels. N-acetyl-p-benzoquinone imine (NAPQI), a highly reactive metabolite created during hepatic metabolism, is the main cause of paracetamol-induced hepatotoxicity Under normal circumstances, conjugation with glutathione detoxifies NAPQI. On the other hand, oxidative stress, hepatocellular necrosis, and abrupt liver failure result from the depletion of glutathione stores caused by overdose or extended use. Interest in hepatoprotective drugs that can stop or lessen hepatic damage has increased due to the rising incidence of drug-induced liver injury. Antidotes like N-acetylcysteine, which restores glutathione reserves, are used in conventional therapy methods. However, because of their cytoprotective, anti-inflammatory, and antioxidant qualities, natural and herbal hepatoprotective agents are receiving more and more attention (1). One of the most extensively researched hepatoprotective drugs among the many herbal compounds examined is silymarin, which is derived from the seeds of Silybum marianum (milk thistle). Strong antioxidant action, hepatocyte membrane stabilization, and liver regeneration stimulation are all attributed to silymarin. Apart from silymarin, a number of additional herbal medicines have demonstrated hepatoprotective efficacy in experimental models of liver injury, including curcumin, glycyrrhizin, and extracts from plants including Phyllanthus amarus and Andrographis paniculata (2).

The relative effectiveness of herbal hepatoprotective medicines in paracetamol-induced hepatotoxicity is still unknown despite a large number of experimental and clinical trials assessing these compounds. To ascertain their relative efficacy and therapeutic potential, a methodical assessment of the available data is required (3).

In order to offer a thorough overview of their protective mechanisms and therapeutic implications, the current meta-analysis compares the hepatoprotective efficacy of silymarin with other herbal hepatoprotective drugs in models of paracetamol-induced liver injury.

Methods: 24 albino rats of either sex weighing 150-200 gms were selected and randomly divided into 4 equal groups, each containing 6 rats. 1st group albino rats were received normal saline. Liver damage was induced in 2nd, 3rd and 4th group albino rats by administering paracetamol (PCT, 2g/kg, single dose, orally) on 5th day. Aqueous extract of Azadirachta indica leaves (AENL, 500mg/kg, orally) was given to 3rd group albino rats for 7 days. Silymarin (100mg/kg, orally) was given to 4th group albino rats for the comparative study. Levels of marker enzymes Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), and bilirubin were estimated in serum.

Statistical analysis: Mean, standard deviations were calculated for each parameters in each group. One way Analysis of Variance (ANOVA) was used for multiple group comparisons followed by Post Hoc Dunnett's test for inter group comparisons of biochemical parameters. P values less than 0.05 were considered to be significant.

Results

Table 1: Effect of Neem Extract and Silymarin on Paracetamol-Induced Hepatotoxicity

Group	Treatment	AST (IU/L)	ALT (IU/L)	Bilirubin (mg/dl)
Group I	Control (Normal saline 2 ml/kg)	33.4	38.2	0.61
Group II	Paracetamol (2 g/kg)	66.0	76.03	1.37
Group III	Neem extract (500 mg/kg) + Paracetamol	38.3	48.8	1.05
Group IV	Silymarin (100 mg/kg) + Paracetamol	36.5	44.6	0.89

Table 2: Comparison of Serum AST Levels in Different Groups

Group	Treatment	Serum AST (IU/L) Mean ± SD
Group 1	Control (Normal saline)	33.4 ± 2.35
Group 2	Paracetamol (2 g/kg)	66.0 ± 4.04
Group 3	Neem extract + Paracetamol	38.3 ± 2.35
Group 4	Silymarin + Paracetamol	36.5 ± 2.52

Post-hoc Comparison Between Groups (Dunnett's Test)

Groups Compared	Mean Difference	P-value	Significance
1 vs 2	32.4	<0.001	Highly Significant
1 vs 3	4.9	<0.05	Significant
1 vs 4	3.1	<0.05	Significant
2 vs 3	27.7	<0.001	Highly Significant
2 vs 4	29.5	<0.001	Highly Significant
3 vs 4	1.8	<0.05	Significant

Table 3: Comparison of Serum ALT Levels in Different Groups

Group	Treatment	Serum ALT (IU/L) Mean ± SD
Group 1	Control (Normal saline)	38.2 ± 2.31
Group 2	Paracetamol (2 g/kg)	76.03 ± 4.38
Group 3	Neem extract + Paracetamol	48.83 ± 1.33
Group 4	Silymarin + Paracetamol	44.68 ± 2.11

Post-hoc Comparison Between Groups (Dunnett's Test)

Groups Compared	Mean Difference	P-value	Significance
1 vs 2	37.8	<0.001	Highly Significant
1 vs 3	10.68	<0.05	Significant
1 vs 4	6.4	<0.05	Significant
2 vs 3	27.2	<0.001	Highly Significant
2 vs 4	31.3	<0.001	Highly Significant
3 vs 4	4.1	<0.05	Significant

Table 4: Possible Genetic Predisposition to Drug-Induced Liver Disease (DILD)

Hepatotoxic Agent	Predisposing Metabolic Factor
Perhexiline	Poor metabolizer of debrisoquine and dextromethorphan due to **CYP2D6 deficiency**
Sulfonamides, Dihydralazine	Slow acetylation due to deficiency of **N-acetyltransferase II (NAT2)** activity
Chlorpromazine	**Sulfoxidation deficiency** – poor metabolizer of S-carboxy-L-methylcysteine
Phenytoin, Carbamazepine	Inhibition or deficiency of **epoxide hydrolase**, leading to inability to detoxify arene oxide metabolites
Halothane	Familial susceptibility due to **epoxide hydrolase deficiency**
Acetaminophen (Paracetamol)	**Glutathione synthetase deficiency**, leading to impaired detoxification of toxic metabolites

Table 5. Mean Serum Bilirubin in Each Group

The **Mean ± S.D (standard deviation)** shows the average bilirubin level for each group.

Group	Mean Bilirubin (mg/dl)
Group 1	0.61 ± 0.16
Group 2	1.37 ± 0.14
Group 3	1.05 ± 0.11
Group 4	0.89 ± 0.09

Table 6. Comparison Between Groups

This section compares two groups at a time to see if their bilirubin levels differ significantly.

Groups Compared	Mean Difference	P-Value	Meaning
1–2	0.76	<0.01	Significant
1–3	0.44	<0.05	Significant
1–4	0.28	<0.05	Significant
2–3	0.32	<0.05	Significant
2–4	0.48	<0.05	Significant
3–4	0.16	<0.05	Significant

Table 7. Individual Rat Values

Rat No.	Bilirubin (mg/dl)	AST (IU/L)	ALT (IU/L)
1	0.9	39.0	47.1
2	0.8	40.0	42.4
3	0.75	35.0	41.5
4	1.0	32.4	44.6
5	1.0	36.8	46.9
6	0.9	35.8	45.6

Table 8. Mean Values (Average)

Parameter	Mean
Serum Bilirubin	**0.89 mg/dl**
AST	**36.5 IU/L**
ALT	**44.6 IU/L**

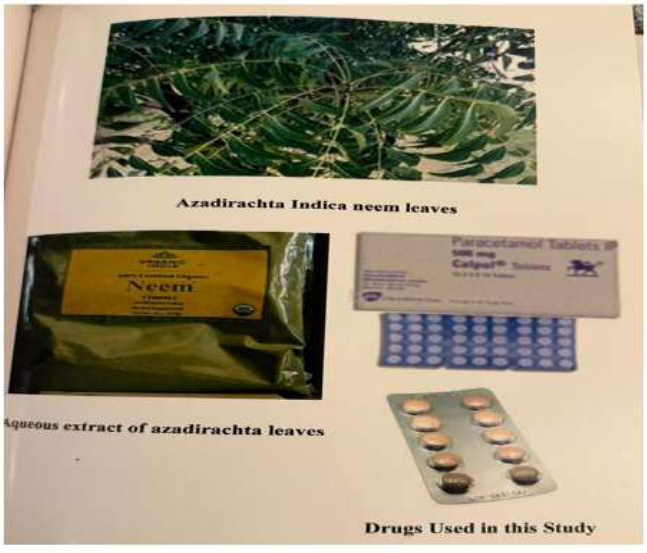

Figure 1: drug used in this study

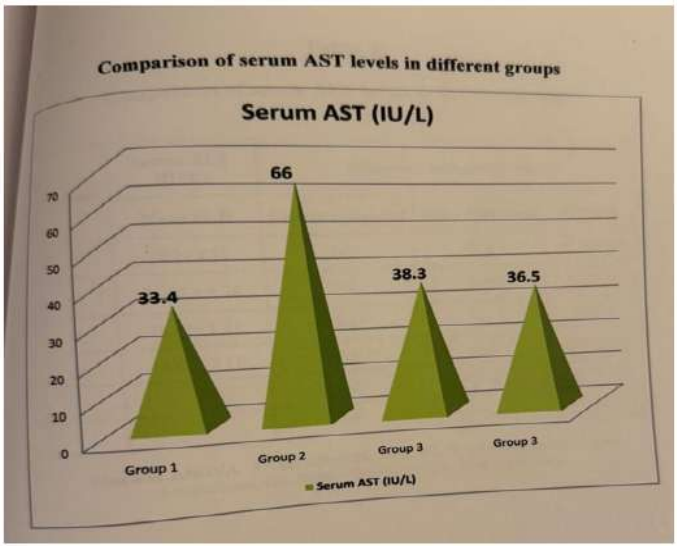

Figure 2: comparison of serum AST levels in different groups

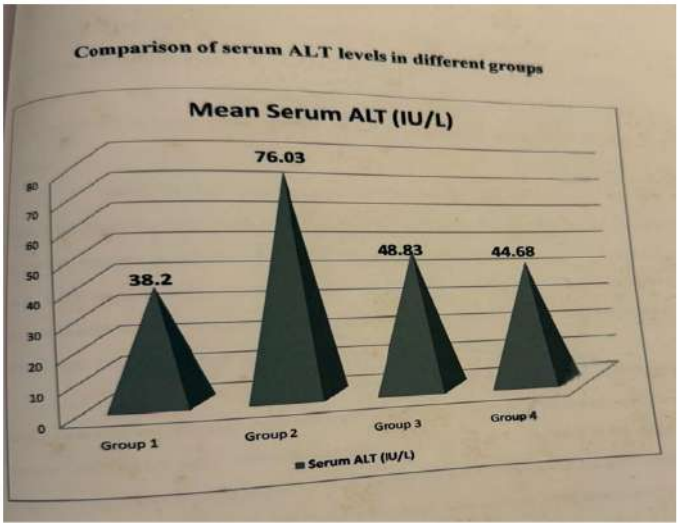

Figure 3: comparison of serum ALT levels in different groups

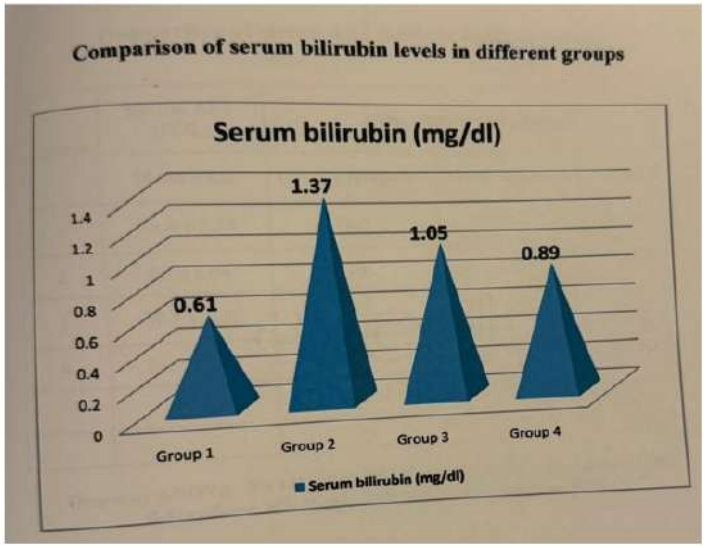

Figure 4: comparison of serum billirubin levels in different groups

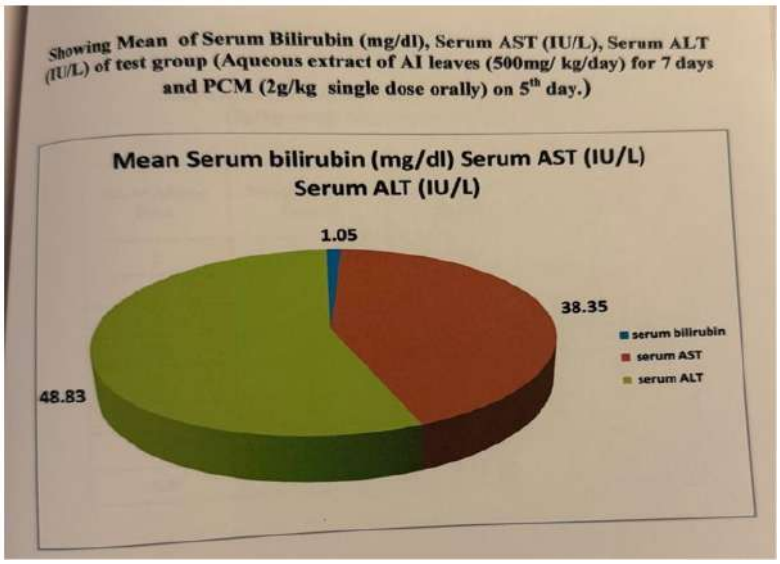

Figure 5: mean serum billirubin levels

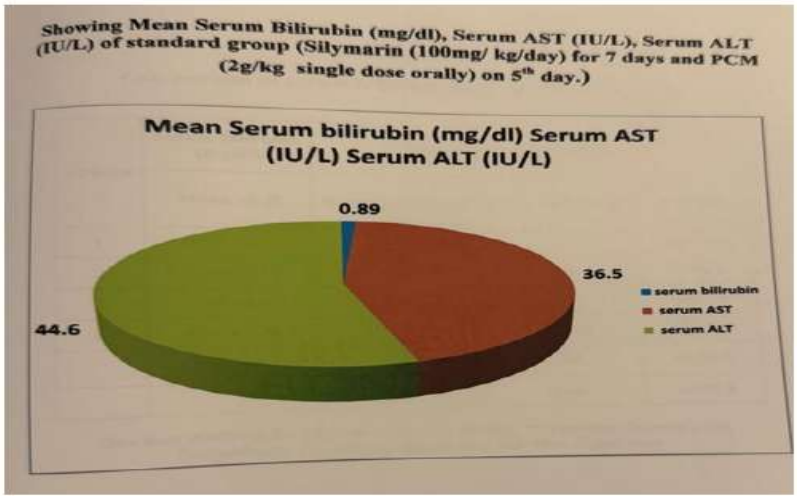

Figure 6: mean serum billirubin levels

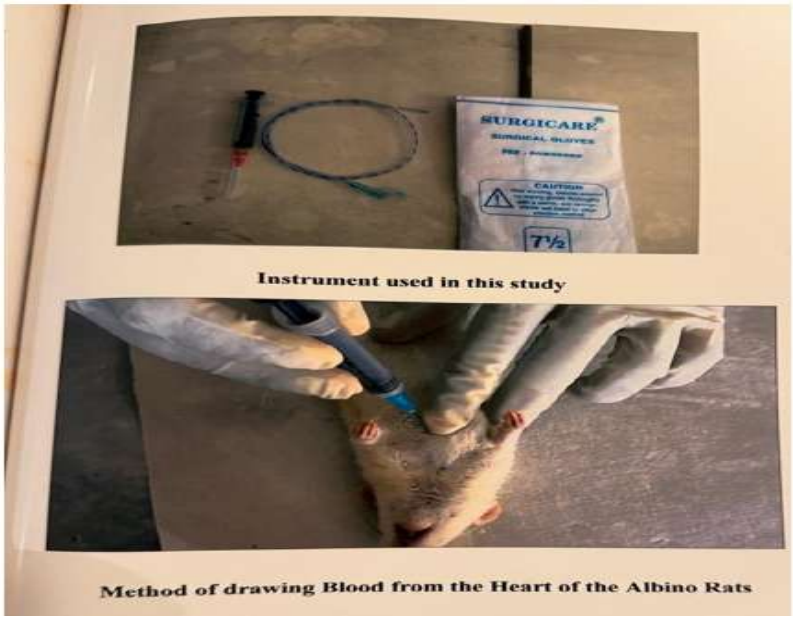

Figure 7: methods of drawing blood from the heart of the Albino rats

Discussion

Many of the widely used therapeutic drugs, including over the counter drugs can cause hepatic injury. Of the numerous remedies, medicinal agents, chemicals, and herbal remedies in existence, more than 600 are recognized as being capable of producing hepatic injury. As the major drug metabolizing and detoxifying organ in the body, the liver is subject to potential damage from the pharmaceutical and environmental chemicals [4].

Acetaminophen is the active metabolite of phenacetin, a so called coal tar analgesic. Acetaminophen has analgesic and antipyretic affects similar to those of aspirin. It has weak anti- inflammatory affects and has been thought to have a generally poor ability to inhibit COX in the presence of high concentrations of peroxides, as are found at sites of inflammation. It is a week COX-I and COX-II inhibitor in peripheral tissues. It may inhibit a third enzyme, COX-III in the central nervous system. COX-III appears to be a splice variant product of the COX-I gene [5].

The most serious acute adverse effect of over dosage of acetaminophen is a potentially fatal hepatic necrosis. The mechanism by which over dosage with acetaminophen leads to hepatocellular injury and death involves its conversion to the toxic NAPQI metabolite. This is eliminated rapidly by conjugation with GSH and then further metabolizes to a mercapturic acid and excreted into the urine. In the setting of acetaminophen overdose, hepatocellular levels of GSH become depleted. Depletion of intracellular GSH renders the hepatocytes highly susceptible to oxidative stress and apoptosis [6].

In the previous study it was observed that hepatoprotective effect of aqueous extract of Azadirachta indica leaves on hepatotoxicity induced by antitubercular drugs in rats. They concluded that AI aqueous leaf extract significantly prevents and reverses the hepatotoxic damage induced by antitubercular drugs in rats. This study was undertaken to find the effectiveness of aqueous extract of Azadirachta indica leaves on hepatotoxicity induced by paracetamol, and its comparison with known, widely used hepatoprotective drug silymarin. As can be seen from results, the test product aqueous extract of neem leaves (AENL) provides good hepatoprotective effect on paracetamol induced hepatic injury. But on the basis of biochemical parameters, the aqueous extract of neem leaves (AENL) provides significantly ($p<0.05$) less hepatoprotective effect when compared to silymarin [7].

The highly significant ($p <0.001$) reduction in the levels of serum AST, ALT and Bilirubin levels in rats treated with aqueous extract of neem leaves (AENL) + Paracetamol (PCM) and silymarin + PCM as compared to PCM alone, also indicates that AENL and silymarin affects important biochemical reactions which may be beneficial in reducing hepatic damage.

The hypolipidaemic effect of NLE may be beneficial in reducing PCM induced hepatotoxicity; since fatty changes have been reported in PCM induced hepatic damage. The anti-lipoperoxidative property of NLE and silymarin may also be contributing towards their hepatoprotective property, since they have been shown to be rich in flavonoid contents and flavonoids are well known antioxidants [4].

Conclusion

Aqueous extract of Azadirachta indica (neem) leaves provides hepatoprotective effect on paracetamol induced hepatotoxicity in rats, as evidenced by significant difference in biochemical parameters. The efficacy of hepatoprotective effect of aqueous extract of azadirachta indica (neem) leaves is less effective when compared to silymarin, as evidenced by significant difference in biochemical parameters. Further studies are required to elucidate exact molecular and biochemical mechanisms involved and to

establish its therapeutic role as a hepatoprotective agent.

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