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Will Herbal-Paracetamol *Combination* Drug Prevent both Liver and Kidney Disease? - Results and Possibilities

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ABSTRACT

An attempt has been made to briefly review the existing information on herbal compounds which could combat acetaminophen (paracetamol) toxicity. A careful perusal of literature revealed that acetaminophen overdose not only damages liver but also the kidney. Nevertheless, the kidney was badly ignored in studies aimed at preventing paracetamol toxicity with herbal drugs. On account of such major neglect, so far no herbal-paracetamol combination could be made. Milk thistly is only well researched drug which appears as a suitable future candidate, but its action towards the kidney must be studied. The importance of such studies in the future is discussed.

Key words: Acetaminophen/paracetamol, hepatoxicity, Nephrotoxicity, Herbal Drugs/combination.

INTRODUCTION

Acetaminophen (Paracetamol: N-acetyl-p-aminophen) is an effective analgesic - antipyretic drug which is often used to treat pain and fever. Acetaminophen is available without prescription in many parts of the world (Goodman and Gilman 1996).

The most serious adverse effect of acute overdose of acetaminophen is dose-dependent, potentially fatal hepatic necrosis (Thomas 1993) which may be associated with renal tubular necrosis (Goodman and Gilman 1996). The number of self poisoning suicides with acetaminophen has grown alarming in recent years (Goodman and Gilman 1996; Gyamlani and Parikh 2002). According to a study in USA paracetamol was found to be associated with more than 10, 00, 00 cases of poisoning, 56000 visits to emergency departments, 26000 hospitalization and 450 deaths a year (BMJ 2002). Also acetaminophen was the drug most commonly taken in United Kingdom (Howton *et al* 1997) causing substantial number of deaths (Bray 1993). Cases of overdoses of acetaminophen in India are also not uncommon (Sharka *et al.* 1999).

The principal antidotal treatment is the administration of sulphydryl compound like N-acetyl-cysteine which act by replenishing hepatic stores of glutathione. This drug is effective only if given orally or intravenously within less than 10 hours after ingestion (Smilkstein *et al* 1988).

BRIEF REVIEW OF EXISTING REPORTS

In the past, several herbal compounds have also been screened to test their ability to reduce and / or nullify acetaminophen induced hepatotoxicity. These reports are given subsequently. It is of interest to mention here that only in two studies both liver and kidney were taken into consideration (Lee *et al.* 2002 and Bagchi *et al.* 2002) otherwise the kidney is badly ignored. However, quite earlier it was suggested that *special caution* should be taken in patients with liver and kidney disease while using paracetamol (Brzeznicka and Piotrowsi 1989).

S. No.	Worker	Year	Model	Name of the herbal Compound	Hepato protective property	Nephro protective property	Parameters		
							Lethality test	Histo - pathology	Biochemical / clinical /other parameters
1	Akintonwa *et al.*	1990	Rat	*Garcinia Kola*	Yes	No	Yes	Yes	Glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT)
2	Handa *et al.*	1990	Rat	*Andrographis paniculata* (andrographolide)	Yes	No	No	Yes	GOT, GPT, ALP, bilirubin, triglycerides
3	Donatus *et al.*	1990	Rat hepatocytes	*Curcuma longa* (Curcumin)	Yes (cytoprotectivity)	No	No	No	lipid peroxidation, LDH - leakage, GSH - depletion
4	Ansari *et al.*	1991	Rat	*Picrorhiza kurrooa* (Picrolive)	Yes	No	No	Yes	Various biochemical parameters
5	Chattopadhyay *et al.*	1992	Rat	*Azadirachta indica*	Yes	No	No	Yes	GOT, GPT, acid phosphatase, alkaline phosphatase
6	Muriel *et al.*	1992	Rat	*Silymarin*	Yes	No	No	No	Liver glutathione,lipid peroxidation, glycogen & serum alkaline phasphotase(AP)gamma-glutamyltranspeptidase,(GGT P) glutamic pyruvic transaminase (GPT)
7	Yamada *et al*.	1993	Rat	*Scizandra fruits*(gomisin A)	Yes	No	No	Yes (degeneration and necrosis of hepatocytes)	Serum amino transferase activity and hepatic lipoperoxides content, glutathione
8	Gilani *et al.*	1993	Mice & Rat	*Artemisia scoparia*	Yes	No	Yes	No	GOT, GPT
9	Cheng *et al.*	1994	Mice & Rat	*Hippophae rhammoides*	Yes	No	No	Yes	MDA), GPT, GOT, GSH
10	Lin *et al.*	1994	Mice	*Wedelia chinensis*	Yes	No	No	Yes	GOT, GPT
11	Lin *et al*.	1995	Rat	'teng-khia-u' Taiwan folk medicine (Elephantopus scaber L. E.mollis H.B.K. and Pseudoelephantopus spicatus(Juss.)Rohr.)	Yes	No	No	No	GOT, GPT
12	Singh *et al.*	1995	Rat	*Apium graveolens & Hygrophila auriculata*	Yes	No	No	Yes	GOT, GPT, alkaline phosphates (ALP), sorbitol dehydrogenase (SDH), glutamate dehydrogenase, bilirubin, tryglycerides
13	Thabrew *et al.*	1995	Mice & cutured Rat Hepatocytes	*Osbeckia octandra*	Yes	No	No	Yes	Blood Normotest, glutathione level, plasma aspartate amino transferase, cell viability, lactate dehydrogenase (LDH).
14	Janbaz *et al.*	1995	Mice & Rat	*Artemisia maritima*	Yes	No	Yes	No	GOT, GPT
15	Gilani *et al.*	1995	Mice & Rat	*Cyperus scariosus*	Yes	No	Yes	No	Alkaline phosphatase (ALP), GOT, GPT
16	Rasheed *et al.*	1995	Mice	*Teucrium stocksianum*	Yes	No	Yes	No	Aspartate amino transferase, bilirubin, GSH, liver weight, pento barbitone induced sleeping time.
17	Chin *et al.*	1996	Rat	'Ham-hong-Chho' Taiwan folk medicine *(Bidens pilosa* L..*var minor* (Blume)Sherff, *B. Pilosa L.* and *B. Chilensis* DC)	Yes	No	No	Yes	GOT, GPT
18	Gilani *et al.*	1996	Mice & Rat	*Fumaria parviflora*	Yes	No	Yes	No	ALP, GOT, GPT
19	Wang *et al.*	1996	Mice	Garlic	Yes	No	No	Yes	ALT, LDH & GSH
20	Lin *et al.*	1997	Rat	*Scutellaria rivularis* (Ban-zhi-lian)	Yes	No	No	Yes	GOT, GPT
21	Subramoniam *et al.*	1998	Rat	*Trichopus zeylanicus*	Yes	No	No	Yes	Serum marker enzymes, level of lipid peroxides in liver
22	Ryu *et al.*	1998	Rat	*Artemisia asiatica* (DA - 9601)	Yes	No	No	Yes (centrilobular necrosis, vacular degeneration, inflammatory cell infitration)	ALT, AST, LDH, GSH
23	Rusu *et al.*	1999	Rat	*Corylus avellana*	Yes	No	No	Yes	GOT, GPT, SDH, GtDH, G-6 Pase and ATPase,steatosis by sudan black staining.
24	Jafri *et al.*	1999	Rat	*Cassia occidentalis*	Yes	No	No	Yes	AST, ALT, ALP, cholesterol, Total lipid
25	Karan *et al.*	1999	Rat	*Swertia chirata*	Yes	No	No	-	-
26	Lin *et al.*	2000	Rat	*Acathopanax senticosus*	Yes	No	No	Yes	AST, ALP
27	Janbaz *et al.*	2000	Rat	*Berberis aristata* (Berberine)	Yes	No	No	No	ALP, AST, ALT
28	Lin *et al.*	2000	Rat	*Anoectochilus formosanus Gynostemma pentaphyllum*	Yes	No	No	Yes (necrosis in the centrilobular area, sinosoidal congestion, infiltration of the lymphocytes and kupffer cells around the hepatic central vein, loss of cell boundaries and ballooning degeneration.	AST, ALT
29	Mandal *et al.*	2000	Rat	*Ficus hispida*	Yes	No	No	Yes	GOT, GPT, bilirubin, ALP
30	Ray *et al.*	2000	Mice	IH 636 Grape seed proanthocya- nidine extract	No	Yes	No	Yes (apoptosis + necrosis , DNA fragmentation)	ALT, BUN, CPK
31	Yang *et al.*	2000	Mice	Yang-Gan-Wan	Yes	No	No	Yes (necrosis)	ALT, SDH
32	Emmanuel *et al.*	2001	-	*Wedelia calendulacea* (Coumestans)	Yes	No	No	No	LDH, ALT, AST, ALP
33	Wang *et al*	2001	Mice	*Astragalus* (total flavonoids)	Yes	No	No	Yes (hepatocellular necrosis)	ALT paracetamol prolonged pentobarbital induced sleeping time,paracetamol and its metabolites in mice urine
34	Ali *et al.*	2001	Mice	*Rhazya stricta*	Yes	No	Yes	Yes	Pentobarbitone induced sleeping time, GSH, AST, ALT, gamma glutamyl transferase (GGT), cholesterol, liver weight

35	Datta *et al.*	2001	Mice	herbal protein CI-1 (from *Cajanus indicus*)	Yes	No	No	Yes (ultrastructure)	No
36	Bhakta *et al.*	2001	Rat	*Cassia fistula*	Yes	No	No	No	GOT, GPT, bilirubin, ALP
37	Wu *et al.*	2001	Rat	Legumes (Mung bean, adzuki bean, black been and rice been)	Yes	No	No	No	GOT, GPT
38	Ahmed *et al.*	2001	Rat	*Ambrosia maritima*	Yes	No	No	No	AST, ALT, ALP malondialdehyde (MDA), glutathione (GSH), glutathione reductase (GSH-R), glutathione peroxidase (GSH-Px), glutathione - S - trasferase (GST)
39	Reen *et al.*	2001	Cultured Rat Hepatocytes	*Swertia species*	Yes	No	No	No	GSH, leakage of LDH as biological end - points of toxicity
40	Ye *et al.*	2001	Mice and Rat	*Angelica sinensis*	Yes	No	No	No	ALT, hepatic nitric oxide synthase (NOS) activities, GSH, MDA
41	Lin *et al.*	2001	Rat	*Terminilia catappa* (Punicalagin and Punicalin)	Yes	No	No	Yes	AST, ALT
42	Hittori *et al.*	2001	Mice	Ajoene (a garlic derived sulfur-contaning compound)	Yes	No	No	No	GSH, GPT, hepatic protein thiol content
43	Echard *et al.*	2001	Rat	Combination of medicinal herbs	Yes	No	No	No	AST, ALT
44	Lee *et al.*	2002	Rat	Chinese yam	Yes	Yes	No	Yes (renal tublar degranulation changes,necrosis,disintegration. inflammation of central vein and necrosis of liver tissue)	-
45	Bagchi *et al.*	2002	Mice	Grape seed proanthocyani-dine extract	Yes	Yes	No	Yes (apoptosis + necrosis + DNA damage)	Serum chemistry
46	Ko *et al.*	2002	Rat	*Silene aprica*	Yes	No	No	No	Morphological and biochemical observations.
47	Janbaz *et al.*	2002	Mice & Rat	Menthol	Yes	No	Yes	No	ALP, AST, ALT
48	Janbaz *et al.*	2002	Mice & Rat	Rutin	Yes	No	Yes	No	AST, ALT
49	Bhattacharyya *et al.*	2003	Rat	Himolive (a polyherbal formulation)	Yes	No	No	No	GOT, GPT, ALP, thiobarbituric acid - reacting substances (TBARS) SOD.
50	Gamal el-din *et al.*	2003	Mice	Arabic gum	Yes	No	No	No	ALT, AST, lipid peroxidation, nitrate + nitrities
51	Kumar *et al.*	2004	Rat	*Trianthema portulacastrum*	Yes	No	No	No	GOT, GPT, ALP, bilirubin, total Protein
52	Devi *et al.*	2004	Rat	*Premna tomentosa*	Yes	No	No	No	Cholesterol, tryglycerides, free fatty acids, phospholipids, serum lipoproteins, lipid metabolizing enzymes.
53	Tabassum *et al.*	2004	Mice	*Eclipta alba Hassk*	Yes	No	No	Yes (centrizonal and local necrosis, ballooning in liver)	ALT
54	Shon *et al.*	2004	Mice	Moutan Cortex	Yes	No	No	DNA fragmentation	ALT, GSH, Cyt P450 $2E_1$- dependent aniline and p-nitrophenol hydroxylases activities
55	Han *et al.*	2004	Rat	Adzuki bean hulls	Yes	No	No	No	GSH, GSH-R, GSH-Px, AST, catalase, phosphatidylcholine hydroperoxide, phosphatidyl ethanolamine hydroperoxide
56	Rao *et al.*	2004	Rat	*Ulva reticulata*	Yes	No	No	No	Aspartate transaminase, alanine transaminase, lipid peroxides, superoxide dismutase, catalase, glutathione, Vit. E and C.
57	Gupta *et al.*	2004	Rat	*Bauhinia racemosa*	Yes	No	No	No	GOT, GPT, ALP, SOD, CAT, LPO, GSH, bilirubin, total Protein
58	Kim *et al.*	2004	Rat & cultured rat hepatocytes	*Alnus japonica*	Yes	No	No	No	Lipid peroxidation, superoxide dismutase, Catase
59	Mroueh et al.	2004	Rat	*Centaurium erythraea*	Yes	No	No	Yes	GPT, GOT, LDH
60	Porchezhian *et al.*	2005	Rat	*Abutilon indicum*	Yes	No	No	No	Enzymatic examination
61	Murugesh *et al.*	2005	Rat	*Berberis tinctoria*	Yes	No	No	No	GOT, GPT, ALP, bilirubin, total protein, lipid peroxidation GSH, SOD, catalase activity
62	Oliveira *et al.*	2005	Mice	*Protium heptaphyllum* (alpha- and beta- amyrin)	Yes	No	Yes	Yes (centrilobular necrosis, cell infiltration)	ALT, AST, GSH, pentobarbital sleeping time
63	Raghavendran *et al.*	2005	Rat	*Sargassum polycystum* (Brown alga)	Yes	No	No	No	Lipid peroxides, SOD, CAT, GSH, GPx, GST
64	YJ *et al.*	2006	-	*Boswellia serrata* (Oleo-gum-resin)	Yes	No	No	Yes	Serum marker enzymes and liver weight
65	Kim *et al.*	2006	Rat	*Glycyrrhizae radix* (liquiritigenin)	Yes	No	No	Yes (hepatic necrosis,inflammation)	ALT , LDH
66	Baheti *et al.*	2006	Rat	*Hemidesmus indicus*	Yes	No	No	No	GPT, GOT, ALP, Bilirubin
67	Iwalokun *et al.*	2006	Mice	*Vernonia amygdalina*	Yes	No	No	No	GPT, GOT, LDH, ALP, bilirubin, catalase , iron & total protein concentrations, lipid peroxidation products thibarbituric acid- reactive substances (TBARS)
68	Sadasivan *et al.*	2006	Rat & In vitro	*Hedyotis corymbosa*	Yes	No	No	Yes	SGPT,SGOT, SAKP, bilirubin, hexobarbitone- induced sleeping time, antilipid peroxidant effect in vitro.
69	Shyamal *et al.*	2006	Rat	*Pittosporum neelgherrens wight & Arn.*	Yes	No	No	Yes	GOT, GPT
70	Pandey *et al.*	2006	Rabbit	Livol, *Eclipta alba and Silybum marianum*	Yes	No	No	Yes (varying degree of congestion, degeneration and necrosis, areas of focal mononuclear cell infiltration enlarged biliary ducts and periportal oedema)	-
71	Yemitan *et al.*	2006	Rat	*Zingiber officinale*	Yes	No	No	Yes	ALT, AST, ALP, LDH, SDH, glutamate dehydrogenase.

72	Parial *et al.*	2006	Rat	*Carica papaya*	Yes	No	No	No	GOT, GPT, ALP, Total biliribun,
73	Sener *et al.*	2006	Mice	*Ginkgo biloba*	Yes	No	No	Yes	ALT, AST, tumor necrosis factor apha (TNF-alpha) in blood, GSH, MDA, myeloperoxidase (MPO) activity, collagen content in liver tissues,luminol and lusigenin CL levels.
74	Roy *et al.*	2006	-	*Psidium guajava*	Yes	No	No	Yes	AST, ALT, ALP, bilirubin, liver weight.
75	Yen *et al.*	2007	Rat	*Cuscuta chinensis*	Yes	No	No	Yes	GOT, GPT, ALP, SOD, catalase glutathione peroxidase (GPx) and malondialdehyde (MDA)
76	Lin *et al.*	2007	Rat	*Chai-Hu-Ching-Kan-Tang*	Yes	No	No	Yes (central necrosis,fatty changes)	GOT, GPT, lipid peroxides, SOD, GPx
77	Setty *et al.*	2007	Rat	*Calotropis procera*	Yes	No	No	No	GPT, GOT, ALP, biliribuin, cholesterol, HDL, tissue GSH.
78	Chaturvedi *et al.*	2007	Rat	*Raphanus sativus*	Yes	No	No	No	Thiobarbituric acid reactive substances (TBARS), GOT, GPT, GSH, catalase.
79	BR *et al*	2008	Rat	*Phyllanthus polyphyllus*	Yes	No	No	Yes	AST, ALT, ALP,total bilirubin, gamma glutamate transpeptidase (GGPT), lipid peroxidase (LPO), total protein, SOD, catalase, GPx, glutathione S- transferase (GST)

DISCUSSION

Only for brevity and convenience current status of knowledge on herbal drugs versus paracetamol poisoning is discussed under following separate headings:

1. Many factors enhance paracetamol toxicity:

Alcohol, many drugs rifampicin, phenobarbital, isoniazid, phenytoin and carbamazepin increase paracetamol toxicity (Whitecomb and Block, 1994: Willacy, 2007). Even fasting greatly increases the chances of liver damage by paracetamol (White comb and Block, 1994). Tobacco is found as an independent risk factor in paracetamol poisoning (Schmidt and Dalhoff, 2003).

2. Some herbal drugs can reduce paracetamol toxicity

Chinese medicine *Artemisia asiatica. & A. Maritima* (DA-9601) has been reported to reduce liver damage induced by paracetamol (Ryu *et al.*, 1998, Janbaz and Gilani, 1995). Another chinese herbal medicine 'gomsin-A', a lignan component of *Schisandra chinesis* has also been reported to be hepatoprotective against paracetamol. It must be noted that *inadequate clinical research with human subjects has been conducted* on these herbal drugs to confirm the value of these herbal therapies against the toxic side effects of paracetamol (IBIS medical com., 2000). A literature review on herb-drug interaction also mentions that reported herb-drug interactions were based on case reports and were of *limited* clinical observations (Hu *et al*., 2005). On account of such badly ignored limited clinical observations on herb-drug interaction *so far no herbal paracetamol combination drug could be made*. On the contrary recently nitroparacetamol (NCX-701) has been introduced as a novel analgesic drug (Sandoval *et al*., 2007). *Silybum marianum* (milk thistle) reduces paracetamol induced hepatotoxiciy in animals. *This is a well research herbal drug in animals and humans and has good future (Pradhan and Girish, 2006) but its preventive action towards kidney needs detail studies.*

3. Problem in developing country like India:

In developing country like India where self medication with herbal and other drugs without prescription is a common practice hence chances of accidental or intentional overdose always exists. Moreover general public is not aware of drug abuse and its antidotal management under such circumstances paracetamol induced liver and kidney damage may go unnoticed and affected individual may die. Citizen and villagers know use paracetamol but none of them know about its hepatonephrotoxicity and about its principal antidotal drug N-acetylcysteine.Liver transplantation is also out of reach of general public. This drug is effective only when administrated within 10 hours of paracetamol poisoning and this drug is not available every where in India.

CONCLUSION

It is needless to say that paracetamol induced hepatonephrotoxicity and its management with herbal drugs also deserves serious attention, no matter, renal insufficiency occurs in about 1-2 percent cases of paracetamol overdose.

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