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RESEARCH ARTICLE

THERAPEUTIC ROLE OF EDIBLE MUSHROOM *Pleurotus florida* (Mont.) ON THIOACETAMIDE INDUCED HEPATOTOXICITY IN RATS

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ABSTRACT

This study was carried out to investigate the therapeutic role of the aqueous extract of *Pleurotus florida* (PF) on thioacetamide induced hepatotoxicity in rats. Thioacetamide at the dose of 600mg/kg body weight orally produced liver damage in rats as manifested by the significant rise in serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, cholesterol and decreases the protein level compared with control. The body and liver weight of each animal was determined, to assess any possible weight gain or loss in experimental animals compared with control groups. Oral administration of aqueous extracts of *P. florida* (100, 200, 400mg/kg) and silymarin (25mg/kg) once daily for 28 days to thioacetamide treated rats shows lowered significantly where as protein level increased. It also shows a significant increase in body weight and decrease in liver weight. The extract alone treated rats did not adversely affect the serum biochemical estimation. Treatment with *P. florida* (100, 200, 400mg/kg) of the extract revealed a antihepatotoxic action compared with the rats that were administered thioacetamide alone. This study has shown that the aqueous extract of *P. florida* possesses antihepatotoxic property.

INTRODUCTION

Liver disease considered as one of the serious health problems, as it is an important organ for the detoxification and deposition of endogenous and exogenous substances. Steroids, vaccines and antiviral drugs which have been employed as a therapy for liver diseases, have potential adverse effects especially when administered for long terms. Hence hepatoprotective drugs from plant sources seem to be attractive alternative. Ayurveda is a traditional system of medicine being protected in Indian sub continent for over 5000 years. In ayurveda several herbal drugs have been prescribed as 'liver tonics' to reduce the toxicity due to ingested xenobiotics. It gives an elaborate amount of medical plants, their uses in herbal therapeutics based upon traditional wisdom and knowledge. Some plants mentioned in ayurveda are highly reputed for their potential benefits in the treatment of liver disorders (Sing and Handa, 1995).

Thioacetamide a selective hepatotoxin is well known to induce hepatic failure (Albrecht *et al.,* 1990) within a short period of time after the administration of the drug. It undergoes an extensive metabolism to acetamide and thioacetamide S-dioxide by the mixed function oxidase system (Chieli and Malvadi, 1984). Acetamide does not have liver necrotizing properties while thioacetamide S-oxide is further metabolized, atleast in part of cytochrome P-450 mono-oxygenase to sulfene, thioacetamide S-dioxide. The thioacetamide S-dioxide is a very highly reactive compound (Hounter *et al*., 1977; Porter *et al*., 1978). Its binding to tissue macro molecules might induce hepatic necrosis (Porter *et al*., 1978).

Thioacetamide was used as a fungicide to control decay of oranges (Childs and Siegler, 1944; Childs and Siegler, 1945) and presence of thioacetamide in orange juice revealed its heaptotoxic potential (Fitzhugh and Nelson, 1948). In the liver, thioacetamide is oxidized to a reactive metabolite via thioacetamide S-oxide a proximate reactive metabolite that is further oxidized to thioacetamide S-dioxide, which covalently binds to liver macromolecules and initiates liver injury (Porter *et al.,* 1979).

Thioacetamide was originally used as a fungicide to protect against decay of oranges (Childs, 1996). The compound has also been reported toxic for kidney and thymus (Barker and Smucklear, 1994). It is also reported that the chronic thioacetamide exposure produced cirrhosis in rats (Chieli and Malvadi, 1985). Cyt-P450 system is known to metabolize thioacetamide in rat liver. Mechanism of thioacetamide toxicity is due to the formation of thioacetamide S-oxide which is responsible for the change in cell permeability, increased intracellular concentration of Ca^{++} increase in nuclear volume and enlargement of nucleoli and also inhibits mitochondrial

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activity which leads to cell death (Ambrose *et al.,* 1949, 1950; Neal and Halpert, 1982). Thioacetamide is experimentally used for inducing fulminant hepatic failure (Bruck *et al*., 2002), necrosis (Landon *et al*., 1986), carcinogenesis (Kizer *et al*., 1985) and liver cirrhosis (Li XN *et al*., 1990). In a number of animal models, thioacetamide induced cirrhosis seem to resemble the important features of human diseases (Torres *et al.,* 1996).

Mushrooms are nutritionally functional food and a source of physiologically beneficial and nontoxic medicines (Wasser and Weis, 1999). They have been used in folk medicine throughout the world since ancient times. Attempts have been made in many parts of the world to explore the use of mushrooms and their metabolites for the treatment of a variety of human ailments. The significant medicinal effect of mushrooms and their metabolites are attention of the public (Jose and Janardhanan, 2000). *Pleurotus* species are commonly called Oyster mushrooms. There are about 40 species of this mushroom. They enjoy worldwide distribution, both in temperate and tropical parts of the world. Oyster mushrooms now rank second among the important cultivated mushrooms in the world (Chang, 1991).

The significant pharmacological effects and physiological properties of mushrooms are bioregulation (immune enhancement), maintenance of homeostasis and regulation of biorhythm, cure of various diseases and prevention and improvement from life threatening diseases such as cancer, cerebral stroke and heart diseases. Mushrooms are also known to have effective substances for antifungal, antiinflammatory, antitumor, antiviral, antibacterial, hepatoprotective, antidiabetic, hypolipedemic, antithrombotic and hypotensive activities (Wasser and Weis, 1999; Ajith and Janardhanan, 2007). Hence, search for new antihepatotoxic substances from mushrooms has been a matter of great importance.

MATERIALS AND METHODS

Procurement and rearing of experimental animals

Adult male albino rats (Wistar strain) were collected from Central Animal House, Rajah Muthiah Medical College, Annamalai University and were used for the present study. The rats were housed in polypropylene cages at room temperature (27 ± 2°C). The animals were randomized and separated into normal and experimental groups of body weight ranging from 180-190 g. The animals received a diet of standard pellets (Hindustan Lever Ltd., Bombay). Rats were provided free access to water *ad libitum* and food through the tenure of acclimatization to the environment for a minimum period of two weeks prior to commencement of experiment. All studies involving animals were done according to NIH guidelines, after getting the approval of the Annamalai University Institute's Animal Ethics Committee.

Preparation of aqueous extract

The collected *Pleurotus florida* were air dried and powdered. The powdered *Pleurotus florida* were kept in airtight containers in a deep freeze until the time of use. A sample containing 250 g of *Pleurotus florida* was mixed with 1000 ml of distilled water and stirred magnetically overnight (12 h) at 37°C. This was repeated three consecutive times. The residue was removed by filtration and the extract evaporated to dryness at a lower temperature (<40°C) under reduced pressure in a rotary evaporator. The residual extract was dissolved in normal physiological saline and used in the study. The yield of the extracts was approximately 15.4 g.

The suitable optimum dosage schedules were identified by administering the aqueous extract of *Pleurotus florida* extracts at different dosages (250, 500 and 1000 mg/kg body weight) in a day daily for twenty eight days. The optimum doses were selected as 250 and 500 mg/kg body weight of the animals for twenty eight days respectively.

EXPERIMENTAL DESIGN

The animals were divided into 6 groups of 6 rats each.

Group 1 *:*Control rats given physiological saline solution10 mL/kg body wt. ***Group 2:*** Rats given thioacetamide (600 mg/kg body wt.) orally were using an intragastric tube. ***Group 3:***Rats given thioacetamide + *Pleurotus florida* (250 mg/kg body wt.) administered orally using an intragastric tube.***Group 4:***Rats given thioacetamide + *Pleurotus florida* (500 mg/kg body wt.) administered orally using an intragastric tube. ***Group 5:***Rats given thioacetamide + silymarin (25 mg/kg body wt.) administered orally using an intragastric tube. ***Group 6:*** Rats given *Pleurotus florida* (500 mg/kg body wt.) alone administered orally using an intragastric tube.

At the end of the experimental period in 24 h after last treatment the animals were killed by cervical decapitation. Blood was collected without anticoagulant for the separation of serum. The liver tissues were excised immediately and washed with chilled physiological saline.

Biochemical analysis

Blood samples were taken into centrifuge tube with rubber caps, labeled and centrifuged at 3000 rpm for 15 minutes. Serum biochemical parameter such as Transaminases (AST and ALT), ALP, Bilrubin, cholesterol and protein levels were estimated according to standard methods (Reitman and Frankel, 1957; King and Armstrong, 1980; Malloy and Evelyn 1937; Zlatkis et al., 1953; Lowry et al., 1951).

Statistical analysis

Statistical analysis was done by analysis of variance (ANOVA) and the groups were compared by Duncan's multiple range test (DMRT). The level of statistical significance was set at $p \leq 0.05$(Duncan, 1957).

RESULTS

Body and liver weight changes

The body and liver weight changes were estimated in normal and experimental rats. Significant decreased in body weight and increase liver weight in rats treated with thioacetamide when compared with the corresponding control rats. Oral administration of aqueous extract of *Pleurotus florida 2*50 mg/kg, 500 mg/kg and silymarin to thioacetamide induced hepatic damaged rats caused a marked increased in the body weight whereas liver weight decreased. The extract alone treated rats did not show any significant alterations when compared with control group (Table 1).

Hepatic serum marker enzymes

The levels of serum AST, ALT and ALP were estimated in normal and experimental rats. Significant elevation in serum AST, ALT and ALP in rats treated with thioacetamide when compared with the corresponding control rats. Oral administration of aqueous extract of

Table 1. Body and liver weight changes in control and experimental groups

Groups	Body weight (g)		Liver weight (g)
	Initial	Final	
Control	185 ± 4.62	215 ± 6.36^{a}	6.52 ± 0.12^{a}
Thioacetamide (600 mg/kg)	180 ± 9.72	158 ± 4.22^{b}	7.35 ± 0.36^{b}
Thioacetamide □ *Pleurotus florida* (250 mg/kg)	192 ± 5.46	209 ± 7.42^{e}	6.95 ± 0.42^{e}
Thioacetamide □ *Pleurotus florida* (500 mg/kg)	183 ± 3.94	215 ± 5.84^{c}	6.64 ± 0.18^{c}
Thioacetamide □ Silymarin (25 mg/kg)	190 ± 9.12	212 ± 5.28^{d}	6.70 ± 0.24^{d}
Pleurotus florida (500 mg/kg) alone	187 ± 8.55	222 ± 9.45^{a}	6.45 ± 0.11^{a}

All the values are mean ± SD of six observations.
Values which are not sharing common superscript differ significantly at 5% level ($P < 0.05$).
Duncan Multiple Range Test (DMRT).

Table 2. Serum hepatic marker enzyme activities in control and experimental groups

Groups	AST (U/L)	ALT (U/L)	ALP (U/L)
Control	64.60 ± 8.23^{a}	40.68 ± 3.24^{a}	145.00 ± 7.44^{a}
Thioacetamide (600 mg/kg)	183.45 ± 11.65^{b}	135.23 ± 4.46^{d}	449.33 ± 14.52^{e}
Thioacetamide □ *Pleurotus florida* (250 mg/kg)	82.98 ± 5.74^{d}	59.83 ± 2.92^{c}	208.00 ± 9.16^{d}
Thioacetamide □ *Pleurotus florida* (500 mg/kg)	74.25 ± 6.12^{b}	47.22 ± 4.12^{b}	185.83 ± 8.38^{b}
Thioacetamide □ Silymarin (25 mg/kg)	77.53 ± 8.04^{c}	49.50 ± 3.38^{b}	198.66 ± 4.64^{c}
Pleurotus florida (500 mg/kg) alone	64.35 ± 7.95^{a}	40.00 ± 2.96^{a}	142.50 ± 6.98^{a}

All the values are mean ± SD of six observations.
Values which are not sharing common superscript differ significantly at 5% level ($P < 0.05$).
Duncan Multiple Range Test (DMRT).

Table 3. Serum bilirubin, cholesterol and protein levels in control and experimental groups

Groups	Bilirubin (mg/dL)	Cholesterol (mg/dL)	Protein (mg/dL)
Control	0.80 ± 0.03^{a}	82.67 ± 4.18^{a}	6.83 ± 0.15^{b}
Thioacetamide (600 mg/kg)	3.42 ± 0.13^{d}	148.00 ± 7.42^{e}	4.48 ± 0.31^{a}
Thioacetamide □ *Pleurotus florida* (250 mg/kg)	1.38 ± 0.08^{c}	112.33 ± 9.28^{d}	7.03 ± 0.15^{b}
Thioacetamide □ *Pleurotus florida* (500 mg/kg)	1.20 ± 0.04^{b}	92.00 ± 5.13^{b}	7.47 ± 0.21^{c}
Thioacetamide □ Silymarin (25 mg/kg)	1.28 ± 0.08^{bc}	97.33 ± 4.95^{c}	7.48 ± 0.22^{c}
Pleurotus florida (500 mg/kg) alone	1.79 ± 0.06^{a}	82.66 ± 5.36^{a}	6.86 ± 0.10^{b}

All the values are mean ± SD of six observations.
Values which are not sharing common superscript differ significantly at 5% level ($P < 0.05$).

Pleurotus florida 250 mg/kg, 500 mg/kg and silymarin to thioacetamide induced hepatic damaged rats caused a marked reduction in the activities of these enzymes. The extract alone treated rats did not show any significant alterations when compared with control group (Table 2).

Serum bilirubin, cholesterol and protein

The levels of serum bilirubin, cholesterol and protein were analysed in normal and experimental rats. There was a significant increase in bilirubin and cholesterol while the level of protein decreased in rats treated with thioacetamide when compared with the corresponding control group. Oral administration of aqueous extract of *Pleurotus florida* 250 mg/kg, 500 mg/kg and silymarin to thioacetamide treated rats exhibited a remarkable decrease in bilirubin and cholesterol while there was a significant increase in protein level when compared to thioacetamide alone treated rats. The extract alone treated rats did not show any alterations when compared with control group (Table 3).

DISCUSSION

Liver is an important organ actively involved in metabolic functions and is a frequent target of number of toxicants. One of the major functions of the liver is detoxification of xenobiotics and toxin (Mitra et al., 1998). Because liver performs many vital functions in the human body, damage of liver causes unbearable problems (Chattopadhyay, 2003). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most often used and most specific indicators of hepatic injury and represent markers

of hepatocellular necrosis (El-Gazzar et al., 2009). Assay of serum ALP activity has been recognized as a suitable marker of skeletal and hepatobiliary disorder. Moreover, an elevated serum level of ALP activity is frequently associated with various pathological conditions (Simko, 1991; Moss, 1989). Alkaline phosphate is a non-specific tissue enzyme widely spread, mainly in the ostaoblasts, live and biliary canaliculi (Poole and Lesile, 1989; Ringler and Dabich, 1979).

In the present study administration of thioacetamide treated rats showed an increase in the levels of ALT, AST and ALP activities when compared with control rats. Oral administration of aqueous extract of *Pleurotus florida* (250 and 500 mg/kg body wt.) and silymarin to thioacetamide treated rats showed an inhibition in the elevated levels of serum ALT, AST and ALP than thioacetamide alone treated rats. Similar changes noticed that oral administration of *Butea monosperma* to thioacetamide treated rats showed AST and ALT levels were decreased (Sehrawat *et al.,* 2005). Zaragoza *et al.* (2005) have reported that serum liver marker enzymes are (AST and bilirubin) increased in thioacetamide treated rats. Bassi *et al.* (2004) have reported that administration of thioacetamide caused significantly increased serum alanine aminotransferase (ALT), asparate aminotransferase (AST) and lactic dehydrogenase (LDH). Thioacetamide treated rats caused serum levels of AST and lipid peroxidation levels were elevated than control rats (Sun *et al.,* 2000). Anand *et al.* (2004) have noticed that administration of thioacetamide caused significantly increased serum alanine aminotransferase. Devi *et al.* (2005) have reported that increased level of alanine aminotransferase in thioacetamide treated rats.

Administration of leaf extract of *Andrographis paniculata* to high cholesterol diet fed rats showed significant reduction of serum marker enzymes (Zuraini *et al,* .2006). Kumar et al. (2004) have reported that administration of *Trianthema portulacastrum* against paracetamol and thioacetamide treated rats showed a significant lowering in the serum AST, ALT and bilirubin levels when compared to thioacetamide and paracetamol alone treated rats respectively. Similarly administration of jigrine to thioacetamide treated rats showed decreased in the levels of AST and ALT (Ahmad et al., 2002). Oral administration of extract of *Asteracantha longifolia* to alloxan treated rats shows reduce the elevated levels of transaminase (Muthulingam, 2010b).

Bilirubin is the conventional indicator of liver diseases (Achliya et al., 2004). Hyperbilirubinemia is a very sensitive test to substantiate the functional integrity of the liver and severity of necrosis which increases the binding, conjugating and excretory capacity of hepatocytes that is proportional to the erythrocyte degeneration rate (Rajesh et al., 2004). In the present investigation administration of thioacetamide exhibited profound increase in serum bilirubin level when compared with control rats. Oral administration of *Pleurotus florida* (250 and 500 mg/kg body wt.) and silymarin to thioacetamide treated rats showed decrease in bilirubin level significantly. Similarly administration of *Pistacia lentiscus* to thioacetamide treated rats showed significantly lowered bilirubin level (Ljubuncic *et al.,* 2005). Sankar *et al.* (2005) have reported that administration of *Cajanus indicus* to thioacetamide treated rats showed decreased bilirubin level when compared with control rats. Oral administration of extract of *Nymphaea pubescens* to acetaminophen treated rats shows minimize the increased levels of bilirubin (Muthulingam, 2010a)

Proteins are important organic constituents of the animal cells playing a vital role in the process of interactions between intra and extra cellular media. Being a part of cell membrane and as an enzyme, protein participate the intricately balanced subcellular fractions. The depletion in the protein levels might be because of their metabolism to liberate energy during cadmium toxicity. Protein and amino acids are very important nutrients. Protein plays a major role in the synthesis of microsomal detoxifying enzymes and helps to detoxify the toxicants which enter into the animal body (Ramasamy, 1987).

In the present investigation administration of thioacetamide exhibited profound decrease in serum protein level when compared with control rats. Oral administration of *Pleurotus florida* (250 and 500 mg/kg body wt.) and silymarin to thioacetamide treated rats showed increase in protein level significantly. Similarly oral administration of chloroform and ethylacetate extracts of *Astercantha longifolia* and also silymarin to CCl_4 treated rats result increase in serum protein in near normal (Muthulingam, 2002). Shirwaika and Sreenivasan (1996) have reported that oral administration of *Legenaria siceraria* to CCl_4 treated rats showed increase in serum protein level when compared to CCl_4 alone treated rats. Sangeetha and krishnakumari (2010) have noticed that administration of extract of *Tephrosia purpurea* to carbon tetrachloride treated rats showed increase in serum and liver protein levels.

Lipids are the most important cellular entities which are not only the constituents of cell membrane but also involved in many cellular functions, metabolic processes and are vital for energy production. Liver is the organ and involved in the synthesis of lipoproteins and metabolism of cholesterol. Honma and Sudha (1997) have reported that the changes in the level of plasma lipids could be sensitive and serve as a simple marker of assessing liver disorders.

In the present investigation administration of thioacetamide exhibited profound increase in serum cholesterol level when compared with control rats. Oral administration of *Pleurotus florida* (250 and 500 mg/kg body wt.) and silymarin to thioacetamide treated rats showed decrease in cholesterol level significantly. Kothavade *et al.* (1996) have reported that administration of livomyn to ketoconazole treated rats showed cholesterol level decreased. Muthulingam et al., (2010) have addressed that administration of *Indigofera tinctoria* extract to paracetamol induced liver damage rats shows decreased the levels of cholesterol.

Conclusion

Oral administration of *Pleurotus florida* (250 and 500 mg/kg body wt.) and silymarin to thioacetamide treated rats showed the elevated parameters were decreased where as decrease the protein levels increased by the action of *Pleurotus florida*. *Pleurotus florida* have some bioactive compounds that will minimize the toxic effect of thioacetamide.

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