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RESEARCH ARTICLE

HEPATIC ANTIOXIDANT AND LIPID PEROXIDATIVE EFFICACY OF *Caralluma attenuata* (WIGHT) AGAINST ANTITUBERCULOSIS DRUG RIFAMPICIN INDUCED HEPATOTOXICITY IN MALE ALBINO WISTAR RATS

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ABSTRACT

India is the largest producer of medicinal plants. The medicinal plants have very important role in the health of human beings as well as animals. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. The Indian Traditional Medicine like Ayurveda, Siddha and Unani are predominantly based on the use of plant materials. The usage of medicinal plants for primary health care needs by millions of people in developing world is still occupying a prominent position. The aqueous extract of *Caralluma attenuata* leaves was investigated for its antioxidant and lipid peroxidative efficacy on antituberculosis drug rifampicin (1 g/kg) induced liver damage in male albino wistar rats. Antioxidant and lipid peroxidative activity was measured by using biochemical parameters such as superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), glutathione reductase (GR), glutathione-s-transferase (GST) and TBARS in liver. Oral administration of the aqueous leaf extract of *Caralluma attenuata* at the doses of (125, 250 and 500 mg/kg) to rifampicin treated rats produced significant antihepatotoxic effect by decreasing the level of TBARS and enhance the levels of antioxidant activity in liver. The effects aqueous leaf extract of *Caralluma attenuata* were comparable to standard drug silymarin. These results suggest that aqueous leaf extract of *Caralluma attenuata* have potential therapeutic value in the treatment of liver diseases, probably by its antioxidative efficacy in liver.

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INTRODUCTION

The liver is a key organ regulating homeostasis within the body. It has wide range of functions, including detoxification, protein synthesis and production of biochemicals necessary for digestion. This organ plays a major role in metabolism and has a number of functions in the body including glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production and detoxification (Thalla and Pentela, 2011). Antioxidant enzymes are involved in scavenging superoxide anion to form hydrogen peroxide, hence reducing the toxic effect caused by these radicals. SOD and CAT are important enzymes in the enzymatic antioxidant defense system (Curtis *et al.,* 1972). Decreases in their activities may result in a number of deleterious effects (Okokon *et al.,* 2017).

Rifampicin and isoniazid, alone or in association, are still widely used in most antitubercular chemotherapeutic regimens. However, these drugs are also well known as hepatotoxic agents (Prabakan *et al.,* 2000; Saraswathy and Devi, 2001). Oxidative stress is one of the mechanisms with a central role involved in the pathogenesis of antitubercular drugs (isoniazid and rifampicin)-induced hepatitis (Attri *et al.,* 2000). It is the result of excessive production of oxidant species and/or depletion of intracellular antioxidant defenses, leading to an imbalance in the redox status of the hepatic cells (Sodhi *et al.,* 1998; Jeyakumar *et al.,* 2008). Hepatotoxicity implies chemical-driven liver damage. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins (Aashish *et al.,* 2012). Protective agents of plant origin with antiperoxidative and antioxidant properties play an important role in protecting the liver against drug-induced toxicity (Santosh kumar *et al.,* 2014). The plant, *Caralluma attenuate* belongs to the family Asclepiadaceae, is a thick, succulent perennial herb growing wild in dry hill slope regions of southern India. It is known as Kallimulaiyan indigenously and is commonly used in traditional medicine as decoction for the treatment of many diseases and also used as a vegetable. Certain species of *Caralluma* are used in folk medicine as antipyretic, antirheumatic and reported to possess significant anti-

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inflammatory (Ahmad *et al.,* 1983) antihyperglycemic (Venkatesh *et al.,* 2003) diabetic (Kalaivani and Mary Violet Hristy, 2011) ulcer healing activity (Garg *et al.,* 2016). *Silybum marianum*, commonly known as 'milk thistle' is one of the oldest and thoroughly researched plants in the treatment of liver diseases. The plant itself grows as a stout thistle in rocky soils with large purple flowering heads. The leaves are characterized by milky veins, from which the plant derives its name (Luper, 1998). The extracts of milk thistle is being used as a general medicinal herb from as early as 4th century B.C. and first reported by Theophrastus (Schuppan *et al.,* 1999). In the 1st century A.D., Dioskurides used this plant as emetic as well as a general medicinal herb (Schuppan *et al.,* 1999). It became a favoured medicine for hepatobiliary diseases in 16th century and the drug was revived again in 1960 in central Europe (Luper, 1998; Schuppan *et al.,* 1999). The active constituents of the plant are obtained from the dried seeds and consist of four flavonolignans, which are collectively known as silymarin. Silymarin is extracted from the dried seeds of milk thistle plant, where it is present in higher concentrations than in other parts of the plant (Luper, 1998). The preclinical studies using different hepatotoxic substances showed that silymarin has multiple actions as a hepatoprotective agent. The antioxidant property and cell-regenerating functions as a result of increased protein synthesis are considered as most important (Kosina *et al.,* 2002). There is no available report on the effect of *Caralluma attenuata* on rifampicin induced liver damage. Therefore, the present investigation to evaluate the antioxidant and lipid peroxidatative efficacy of aqueous extract of *Caralluma attenuata* on rifampicin induced liver injury in rats.

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±2ºC). The animals were randomized and separated into normal and experimental groups of body weight ranging from 150-180 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. The study was approved by the Institutional Animal Ethical Committee of Rajah Muthiah Medical College and Hospital (160/1999/CPCSEA), Annamalai University, Annamalainagar, Chidambaram.

Preparation of aqueous extract

The collected plant, *Caralluma attenuata* were air dried and powdered. The powdered *Caralluma attenuata* were kept in airtight containers in a deep freeze until the time of use. A sample containing 250 g of *Caralluma attenuata* 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 (<40ºC) 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 28.5 g. The suitable optimum dosage schedule were identified by administering the aqueous extract of *Caralluma attenuata* extracts at different dosages (125, 250, 500 and 1000 mg/kg body weight) in a day daily for twenty eight days. The optimum doses were selected as 125, 250 and 500 mg/kg body weight of the animals for twenty eight days respectively.

Experimental design

The animals were divided into 7 groups of 6 rats each.

Group 1 : Control rats given physiological saline solution 10 mL/kg body wt.
Group 2 :Rats given rifampicin (1 g/kg body wt./p o) for one day only.
Group 3 :Rats given rifampicin + *Caralluma attenuata (*125 mg/kg body wt/p o)
Group 4 :Rats given rifampicin + *Caralluma attenuata (*250 mg/kg body wt/p o)
Group 5 :Rats given rifampicin + *Caralluma attenuata* (500 mg/kg body wt/p o)
Group 6 :Rats given rifampicin + silymarin (25 mg/kg body wt/p o)
Group 7 :Rats given *Caralluma attenuata* (500 mg/kg body wt/p o) alone

At the end of the experimental period in 24 h after last treatment the animals were killed by cervical decapitation. The liver tissues were excised immediately and washed with chilled physiological saline.

Biochemical analysis

Liver tissues were taken into centrifuge tube with rupper caps labeled and centrifuged at 3000 rpm for 15 minutes. Biochemical parameter such as lipid peroxidation (TBARS), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT), glutathione reductase (GR), glutathione-s-transferase (GST) activities were estimated according to standard methods (Niehaus and Samuelson, 1968; Ellman, 1959; Kakkar *et al.,* 1984; Sinha, 1972; Horn and Burn, 1978; Habig *et al.,* 1974) respectively.

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 $p < 0.05$ (Duncan, 1957).

RESULTS AND DISCUSSION

The liver plays vital role in maintenance, performance, regulation of homeostasis, secretions of bile, storage of vitamins (Ahsan *et al.,* 2009) and detoxification in the body. It participates in all the biochemical pathways to growth, immune system, nutrient supply and energy provision (Ward and Daly, 1999; Saleem and Naseer, 2014). Hepatic cell injury caused by various toxicants like chemotherapeutic agents, antituberculosis drugs, carbon tetrachloride, paracetamol, chronic alcohol consumption and pathogenic microbes were well reported (Priya *et al.,* 2010). Fig. 1 shows the results of lipid peroxidation and antioxidant activities in control and experimental rats. Oral administration of antituberculosis drug, rifampicin induced hepatic damage rats caused an increased lipid peroxidation with a concomitant decline in SOD, CAT, GSH, GR and GST activities in liver.

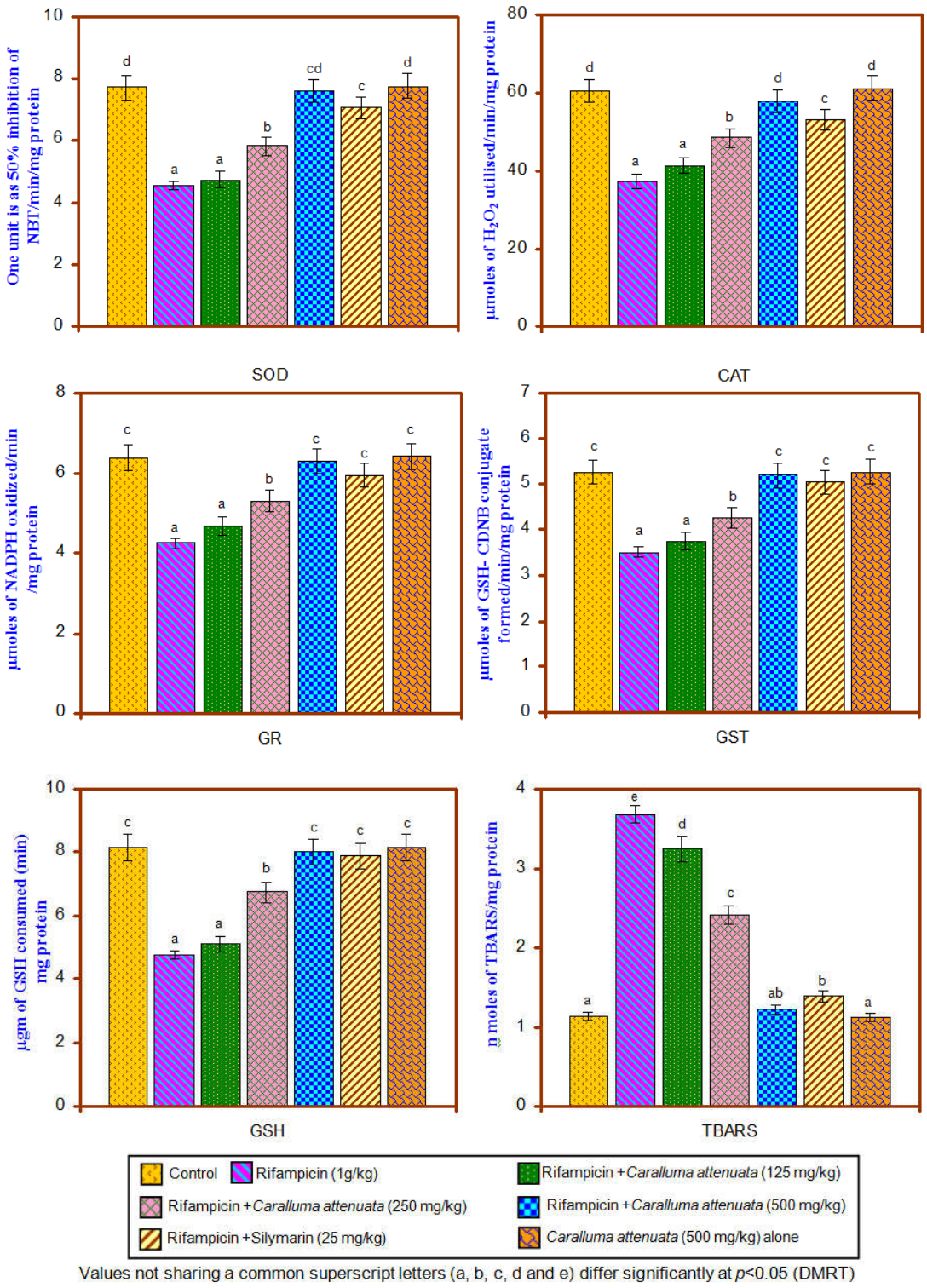

Fig.1. Activities of SOD, CAT, GR, GST, GSH and TBARS in liver of control and experimental groups

This confirms that rifampicin accentuates lipid peroxidation as an indicator of tissue damage and antioxidant enzymes are presumed to be important endogenous defense mechanisms against peroxidative destruction of cellular membranes. Antioxidant enzymes are involved in scavenging superoxide anion to form hydrogen peroxide, hence reducing the toxic effect caused by these radicals. SOD and CAT are important enzymes in the enzymatic antioxidant defense system (Jude *et al.,* 2017). Superoxide dismutase (SOD) and catalase (CAT) are essential for the endogenous antioxidative defense system to scavenge reactive oxygen species and maintain the cellular redox balance (Molina *et al.,* 2003; Parimoo *et al.,* 2014; Singh *et al.,* 2014). SOD is the primary step of the defense mechanism in the antioxidant system against oxidative stress by catalyzing the dismutation of superoxide radicals (O^{2-}) into molecular oxygen and hydrogen peroxide (H_2O_2). H_2O_2 is neutralized by the action of catalase (Salvi *et al.,* 2007; Singh *et al.,* 2014). The body has an effective defense mechanism to prevent and neutralize the free radical induced damage. This is proficient by a set of endogenous antioxidant enzymes such as SOD and CAT. These enzymes constitute a mutually supportive team of defense against ROS (Amresh *et al.,* 2007a,b).

Glutathione reductase is a very important enzyme of the in ascrobate glutathione cycle that protects cell against oxidative damage maintaining a high GSH/GSSG ratio (Foyer and Noctor, 2005). Glutathione-S-transferase (GST) consists of a large family of GSH utilizing enzymes and plays an important role in detoxification of chemicals in mammalian systems (Singh and Rana, 2007). GST is a soluble protein located in cytosol and plays an vital role in the detoxification and excretion of xenobiotics (Simons and Jagt, 1980; Masukawa and Iwata, 1986). Glutathione is an important endogenous antioxidant system that is found in particularly high concentration in liver and it is known to have key functions in protective processes (Sinclair *et al.,* 1991; Aftab *et al.,* 2002). GSH is a primary cellular non-protein antioxidant to protect cells against reactive oxygen species (ROS). Moreover, reduced glutathione content is often used to evaluate, oxidative stress in biological systems (Songa *et al.,* 2016; Peng *et al.,* 2017). GSH, the major non-protein thiol in body tissues, is considered the main detoxifying and antioxidant molecule produced by cells. It becomes conjugated to foreign compounds to eliminate their toxic effects (Brattin *et al.,* 1985; Wills *et al.,* 2012; Zhang *et al.,* 2013; Ahmed *et al.,* 2016). The protective effects of GSH cause it to be a crucial indicator of chronic injuries in liver tissues (Ayatollahi *et al.,* 2014). GSH is one of the most abundant tripeptide, non-enzymatic biological antioxidants present in the hepatocytes, which is a key component of the overall antioxidant defense system that protects the membrane protein thiols of hepatocytes from deleterious effects of reactive oxygen metabolites such as hydrogen peroxide and superoxide radicals (Meister *et al.,* 1994; Sing *et al.,* 2014).

Lipid peroxidation has been identified as one of the basic reactions involved in oxygen free radical induced cellular damages (Halliwell and Gutteridge, 1992). Peroxidation reactions in biological systems are the underlying causes for a variety of pathological condition (Estuo and Hiroyuki, 1990). Lipid peroxidation is a measurement of function of cellular membranes. The levels of TBARS are an indirect measurement of the lipid peroxidation (Halliwell *et al.* 1995). The reactive free radicals initiate cell damage through two major mechanisms of covalent binding to cellular macromolecules and lipid peroxidation (Slater, 1984). The free radicals initiate lipid peroxidation and could produce a range of enzymatically damaging consequences and could result in membrane disorganization by peroxidizing mainly the highly unsaturated and polyunsaturated fatty acids by attacking the methylene bridge hydrogen (Slater, 1972). The protective action of antioxidants is usually due to the inhibition of free radical chain reaction and the resultant prevention of peroxidative deterioration of structural lipids in membranous organelles. Circulating antioxidants mainly vitamin C and vitamin E and tissueenzymatic and non-enzymatic such as superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) play important role in alleviating tissue damage due to the formation of free radicals (Rajagopal *et al.,* 2003). In the present study administration of rifampicin treated rats showed minimize the activities of superoxide dismutase, catalase, reduced glutathione, glutathione reductase and glutathione-s-transferase whereas lipid peroxidation level was enhanced when compared with control rats. Oral administration of aqueous extract of *Caralluma attenuata* (125, 250 and 500 mg/kg body wt.) and silymarin to rifampicin treated rats showed an elevated levels of superoxide dismutase, catalase, reduced glutathione, glutathione reductase and glutathione-s-transferase whereas lipid peroxidation level was reduced significantly than rifampicin alone treated rats.

Similarly administration of *Astercantha longifolia* extract and silymarin to CCl_4 treated rats showed increased the activities of SOD, CAT and GSH whereas lipid peroxidation level was decreased when compared with CCl4 alone treated rats (Muthulingam, 2002). Oral administration of *Cajanus indicus* to thioacetamide treated rats showed an increase in SOD and CAT activity where as lipid peroxidation level was decreased (Sarkar *et al.,* 2005). Administration of HD-03, a herbal formulation to paracetamol treated rats showed lipid peoxidation level was decreased and GSH activities was increased (Mitra *et al.,* 1998). Oral administration of *Agaricus blazei* to Ccl_4 treated rats showed that SOD, CAT and GSH activities were enhanced where as lipid peroxidation level was minimized (Muthulingam *et al.,* 2013). Annie Felicia and Muthulingam (2013) reported that SOD, CAT and GSH activities were significantly enhanced whereas lipid peroxidation level was decreased in administration of *Indigofera tinctoria* to paracetamol induced hepatotoxicity rats. Administration of *Luffa acutangula* to carbontetra chloride and rifampicin treated rats showed increased the reduced levels of SOD, CAT and GSH whereas lipid peroxidation level was decreased (Jadhav *et al.,* 2010). Administration of various doses of methanolic extract of *Leucas aspera* to carbontetra chloride induced liver injury rats showed completely prevented the lowering of antioxidant activities (SOD, CAT, GSH, GST and GPx) and suppressed the level of lipid peroxidation in liver (Latha and Latha, 2013). Minimized the level of lipid peroxidation and enhance the activity of reduced glutathione in the liver of *Zingiber officinale* treated to paracetamol induced hepatotoxicity rats (Lebda *et al.,* 2013). Treatment with ethanolic extract of *Tridax procumbens* to N–Nitrosodiethylamine induced experimental hepatocellular carcinoma rats liver showed an increase in the activities of SOD, CAT, GPx, GR and GSH when compared with to N–Nitrosodiethylamine alone treated rats (Ameesh and Murugan, 2016).

Conclusion

In the present study showed that the aqueous extract of *Caralluma attenuata* shows significantly elevated the activities of super oxide dimustase, catalase, reduced glutathione, glutathione reductase and glutathione-s-transferase whereas lipid peroxidation level was reduced. It is concluded that treatment with aqueous extract of *Caralluma attenuata* decreases the rifampicin induced toxicity by enhances the significant antioxidant activities as compared with silymarin.

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