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Sustainment of Antioxidant Enzymes by *Drosera peltata* in Ehrlich's Ascites Carcinoma (EAC) Bearing Mice

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Research Article

History

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ABSTRACT

The purpose of this study was to measure the antioxidant status of animals treated with 250 and 500 mg/kg doses of ethanol and aqueous extract of *Drosera peltata* on Erich ascites carcinoma (EAC) inoculated mice. A total of 70 mice were divided into 7 groups, each group with ten mice. The first group received normal food and water for 14 days and was under normal control. The second group also received normal food and water for 14 days, which was cancer control. Third group received 5- fluorouracil (20 mg/kg, i.p) for 14 days. The fourth and fifth group animals received 250 and 500 mg/kg of ethanol extracts of *D. peltata* (EEDP) whereas the sixth and seventh groups of mice received 250 and 500 mg / kg of aqueous extracts of *D. peltata* (AEDP), orally for 14 days. All the groups were inoculated with EAC (2×106 cells/mouse, i.p.) except Group I, 24 hours before the commencement of the drug treatment. After the completion of treatment, blood was drawn retro-orbitally and sacrificed to isolate the liver, lungs, kidneys, and brain for observing tissue antioxidant status. The parameters analyzed were total protein (TP), catalase (CAT), malondialdehyde (MDA), superoxide dismutase (SOD), peroxidase (P), and glutathione (GSH) from the tissues apart and the protein carbonyl content (PCC) also measured from the blood sample. Treatment with EEDP and AEDP significantly lowers the MDA levels from 23 to 10 mmol/ml in the blood whereas 28 to 4 nm/g tissue isolates the liver, lungs, kidneys, and brain. It also raised the TP, GSH, SOD, CAT, and P levels in the blood and the tissues sample of the cancer cell line inoculated animals, and their levels are maintained similarly to normal group animals. The results proposed that both the extracts of *D. peltata* retained the various tissue antioxidant statuses in mice with EAC cancer lines.

Keywords: Antioxidant status, *Drosera peltata,* Erich ascites carcinoma, Malondialdehyde, Total protein.

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Introduction

Ayurveda, the Indian medical system, treats a variety of illnesses, including cancer, primarily using herbal medicines or formulations. It is one of the oldest medical systems covering thousands of medical concepts and hypotheses. Interestingly, Ayurveda can treat many chronic diseases that modern medicine cannot treat, such as cancer, diabetes, arthritis, and asthma (Parasuraman et al., 2014). Cancer is one of the prominent causes of death reported by WHO (WHO, 2022). There are several ways to treat cancer in modern medicine. These include chemotherapy, radiation therapy, and surgery. Chemotherapy is currently considered to be the most effective way to treat cancer. The high toxicity of most anti-cancer drugs has facilitated the development of less toxic and cheaper complements. Plants have long been used to treat cancer. An important strategy for developing effective anti-cancer drugs is the study of anti-cancer drugs derived from natural resources. Plant-derived anticancer drugs and their derivatives are effective in cancer treatment. Natural plant-derived substances such as flavonoids, terpenoids, and steroids have received a great deal of attention in recent years due to their various pharmacological actions, such as antioxidant and antitumor (Desai et al., 2008). Similarly, they have proven useful in the prevention and control of adverse pathophysiological conditions and complex diseases including cancer. One of the plants rich in therapeutically important as well as used in Ayurvedic formulation is Drosera. The genus Drosera is commonly known as Sandew. It is one of the largest genera of more than 170 species of carnivorous plants belonging to the Droseraceae family. In India, three Drosera plants were found namely *Drosera indica* L, *Drosera burmannii* Vahl, and *Drosera peltata* J.E.Sm. These include 1,4 naphthoquinone, plum bagin, ramantaseon and its glucosiderosoliside, and flavonoids such as quercetin and hyperosid. In both Plumbaginaceae and Droseraceae family, a yellow color pigment was found as a main phytoconstituent, named Plumbagin (5 hydroxy 2 methyl 1,4 naphthoquinone). Plumbagin is a major active ingredient with a variety of pharmacological actions, including anti-fertility, anti-malaria, anti-viral, anti-bacterial, anti-convulsant, anti-cancer, and Leishmania drugs. Plumbagin and quercetin are the important biologically active phytoconstituents found in drosera. Pharmacological actions are based on the number of constituents present in each plant (Raju Asirvatham & Arockiasamy Josphin Maria Christina, 2018). HPTLC method was used to quantify the plumbagin and quercetin content among the three Indian Drosera species (Raju Asirvatham et al., 2020). The above species are used in several clinical manifestations, such as memory loss, vision loss, infertility, general weakness of the body, the development of premature aging, and bronchial asthma. It is used as an important ingredient in Ayurveda preparations ('Swarnabhasma' -Golden ash) for rheumatoid arthritis, diabetes, and neuropathy (Asirvatham and Christina, 2013). Cold decation of *D. indica* is used to remove corn and these species are mentioned in the list of endangered medicinal plants (Reddy et al., 2001). Earlier in this report, the in-vitro antioxidant and anticancer potential as well as the in-vivo effect of *D. peltata* have been reported for different in-vitro antioxidant and anticancer models. This study aimed to determine the ability of cells to recover and retain the antioxidant enzymes with the treatment of ethanol and an aqueous extract of 250 and 500 mg/kg *D. peltata* in EAC-bearing mice.

Material and Methods

Plant materials and extracts

The whole plant of *D. peltata* was collected from Munnar, Kerala, India in December 2008. Air-dried, coarsely powdered whole plants (350 g) were defatted with petroleum ether (60-80°C), and followed the merc was extracted with ethanol solvent in a Soxhlet extractor for 72 hours. The obtained ethanol extract was concentrated and allowed to dry under a controlled temperature (40-50°C). The obtained merc was soaked in chloroform water for 2 days, filtered, concentrated, and allowed dry to get the aqueous extract. Ethanol extract of *D. peltata* (EEDP) and aqueous extract of *D. peltata* (AEDP) were reconstituted with distilled water for animal study.

Experimental animal and study approval

The treatment protocol (A. Raju 0903PH2254/JNTUH 2009) was presented before the institutional animal ethical committee. After reviewing the procedure, the committee had permitted to conduct the study. Adult male and female Swiss albino mice weighing approximately 20 to 25 g were acclimated to experimental conditions for approximately two weeks before subjecting to the experimental procedure. Tumor cell line- Erich ascites carcinoma (EAC) cells were obtained from the Amala Cancer Institute in Thrissur, Kerala, India. EAC cells were maintained in mice by weekly intraperitoneal (i.p.) inoculation of 2 x 106 cells/mouse.

Treatment protocol

It was a 14-days study, in which a total of 70 mice were divided into seven groups containing ten animals in each (Christina et al., 2004). All the mice were inoculated with EAC cells (2 × 106 cells/mouse, i.p.) 24 hours before the commencement of the drug treatment, except mice belonging to Group I.

Group 1, the animal received normal food and water for 14 days

Group 2, EAC control and received normal food and water for 14 days

Group 3, EAC cells and received 5- fluorouracil (20 mg/kg, i.p) for 14 days

Group 4, EAC cells and received EEDP (250 mg/kg, p.o) for 14 days.

Group 5, EAC cells and received EEDP (500 mg/kg, p.o) for 14 days.

Group 6, EAC cells and received AEDP (250 mg/kg, p.o) for 14 days.

Group 7, EAC cells and received AEDP (500 mg/kg, p.o) for 14 days.

On the 15th day, blood was collected by retro-orbital puncture and was allowed to stand for 45 minutes at room temperature. Serum was collected after centrifugation at 2500 rpm at 30 ° C for 15 minutes to estimate antioxidant enzyme levels (Senem et al ., 2011) in serum such as malondialdehyde (MDA), catalase (CAT), glutathione (GSH), superoxide dismutase (SOD) and protein carbonyl content (PCC).

After the collection of blood, mice were sacrificed with excessive anesthesia, and the liver, lung, kidney, and brain samples were removed for the measurement of tissue antioxidant status. To estimate the content of antioxidants in the tissue, the isolated organ was divided into two parts to prepare tissue homogenates (Vani et al., 1990). The first homogenate (10 % w / v) was prepared with potassium chloride (KCl, 0.15 M) and the content was centrifuged at 8000 rpm for 10 minutes, and the supernatant was used to measure total protein (TP), peroxidase (P), catalase (CAT), and malondialdehyde (MDA). Similarly, the second homogenate (10 % w / v) was prepared with sucrose phosphate buffer (5 M, pH 7.4) and the test tube content was centrifuged at 8000 rpm for 10 minutes, and the supernatant was used for the measurement of glutathione peroxidase (GSH) and superoxide dismutase (SOD). All the above antioxidant enzymes level from tissue homogenate were done by COBAS MIRA PLUS – S autoanalyzer (Roche, Switzerland) using antioxidant estimation assay kits from Agappe Diagnostics, India (Salwa et al., 2022).

Statistical analysis

The results obtained after statistical analysis were expressed in terms of mean ± S.E.M. The data were evaluated to present as results using a one-way ANOVA followed by Newman Keul's multiple comparison tests.

Results

Table 1 shows the status of various blood antioxidants in EAC- cancer cell line-carrying mice. In this study, MDA levels were increased significantly (p <0.001) with EAC control mice when compared to normal controls. After the treatment with EEDP and AEDP at the doses of 250, and 500 mg/kg, levels of MDA were reduced and the other free radical protective enzymes were more or less significantly increased when compared to the cancer control group. Similarly, serum PCC was raised in EAC-controlled group mice, but 14 days of extract treatment at doses of 250, 500 mg/kg EEDP and AEDP significantly re-established PCC (p <0.001) like the normal group mice.

EAC cells inoculation caused a significantly increased level of MDA levels in the tissues of the liver, brain, lungs, and kidneys when compared to the normal control animals simultaneously significant (p <0.001) reductions in SOD, TP, GSH, P, and CAT levels were also observed in the above tissue samples. 14 days of continuous treatment with EEDP (250 and 500 mg/kg) brought back the alteration of internal antioxidant status to normal (Tables 2-5). Most of the parameters were turned to like normal levels upon the treatment of a high dose of EEDP and AEDP. Almost the same results were seen with 5 flurouracil-treated mice. EEDP at 250 mg / kg and AEDP at 250 mg/kg treatment showed non-significant (p> 0.05) effect on the restoration of P in the liver and kidney.

Table 1. Effect of EEDP and AEDP on blood antioxidant status of EAC bearing mice

Parameters BLOOD	CAT U/mL serum	SOD U/mL serum	P U/mL serum	GSH U/L	MDA nmol/ml	PCC nmol/mg protein
Normal	14.4±0.13	7.5±0.67	34.5±1.25	73.98±0.51	8.65±0.17	1.9±0.8
EAC Control	5.9±0.32	3.5±0.15	21.6±0.48	45.08±0.24	23.15±0.26	9.5±1.2
EAC+5FU (20mg/kg)	14.6±0.42	7.35±0.1	33.93±0.69	74.23±0.15	9.03±0.26	2.8±0.7
EAC+EEDP250	11.9±0.29^{a}	6.18±0.24^{a}	29.38±0.84^{a}	68.08±1.08^{a}	12.4±0.13^{a}	4.6±0.75^{a}
EAC+EEDP500	14.4±0.3^{a}	7.3±0.2^{a}	34.15±0.26^{a}	75.05±0.26^{a}	10±0.25^{a}	2.5±1.06^{a}
EAC+AEDP250	6.7±0.22^{c}	5.55±0.17^{a}	23.88±0.47^{b}	56.05±0.95^{a}	19.5±0.47^{a}	7.2±0.2^{a}
EAC+AEDP500	10.95±0.4^{a}	5.95±0.34^{a}	28.2±0.4^{a}	64.83±1.09^{a}	15.9±0.27^{a}	6.4±0.4^{a}

The data were expressed as mean ± SEM, n = 10, where a: p<0.001.

Table 2. Effect of EEDP and AEDP on the liver antioxidant status of EAC- bearing mice

Parameters (Liver)	TP mg / dL	CAT U/mg tissue	SOD U/mg tissue	P nm/100mg tissue	GSH nm/100mg tissue	MDA nm/g protein
Normal conrtrol	12.25± 0.66	10.45± 0.1	4.35± 0.06	22.78± 0.29	53.05± 0.21	4.65± 0.06
EACControl	6.7± 0.17	2.25± 0.06	16.08± 0.26	19.07± 0.53	45.25± 0.52	28.43± 0.85
EAC+ 5FU (20mg / kg)	12.5± 0.41	8.95± 0.29	5.38± 0.36	22±0.65	51.93±0.83	5.75±0.59
EAC+EEDP250	11.45±0.15^{a}	8.4±0.13^{a}	5.53±0.54^{a}	21.43±0.39^{d}	54.05±0.54^{a}	5.57±0.19^{a}
EAC+EEDP500	12.7±0.38^{a}	9.08±0.08^{a}	3.45±0.1^{a}	25.08±0.73^{a}	56.35±0.44^{a}	4.35±0.15^{a}
EAC+AEDP250	9.75±0.26^{a}	7.63±0.23^{a}	8.22±0.31^{a}	19.98±0.14^{d}	50.4±0.41^{a}	13.4±0.23^{a}
EAC+AEDP500	10.98±0.31^{a}	8.83±0.08^{a}	6.53±0.25^{a}	22.18±0.79^{c}	53.85±0.19^{a}	8.45±0.15^{a}

The data were expressed as mean ± SEM, n = 10. where a: p<0.001, c: p<0.05, d: p>0.05

Table 3. Effect of EEDP and AEDP on the kidney antioxidant status of EAC- bearing mice

Parameters (Kidney)	TP mg/dL	CAT U/mg tissue	SOD U/mg tissue	P nm/100mg tissue	GSH nm/100mg tissue	MDA nm/g protein
Normal control	22.68± 0.27	11.48± 0.14	23.55± 0.4	77.5± 3.23	101.85± 0.61	12.87± 0.67
EAC Control	18.08±0.22	7.07±0.45	14±0.41	55.5±6.99	50.85±0.31	29.84±0.2
EAC+ 5 FU (20 mg/kg)	22.45±0.06	11.63±0.14	22.05±0.31	75.43±2.2	96.75±1.19	12.26±0.24
EAC+EEDP250	22.25±0.85^{a}	11.48±0.15^{a}	20.43±0.11^{a}	75.93±0.59^{b}	84.57±1.53^{a}	11.2±0.25^{a}
EAC+EEDP500	23.28±0.55^{a}	12.08±0.37^{a}	24±0.48^{a}	80.48±0.66^{a}	96.8±0.57^{a}	10.7±0.32^{a}
EAC+AEDP250	20.68±0.11^{a}	11.1±0.37^{a}	16.75±1.37^{b}	63.9±4.45^{c}	67.23±1.5^{a}	15±0.25^{a}
EAC+AEDP500	22.45±0.11^{a}	12.13±0.16^{a}	20.32±0.08^{a}	73.2±0.81^{b}	72.55±2.58^{a}	15.8±0.13^{a}

The data were expressed as mean ± SEM, n = 10, where a: p<0.001, b: p<0.01, c: p<0.05

Table 4. Effect of EEDP and AEDP on the brain antioxidant status of EAC- bearing mice

Parameters (Brain)	TP mg/dL	CAT U/mg tissue	SOD U/mg tissue	P nm / 100mg tissue	GSH nm/100mg tissue	MDA nm/g protein
Normal	41.82±2.83	22.1±0.59	33.3±0.58	34.66±0.66	82.48±0.94	8.48±0.38
EAC Control	9.5±0.24	9.58±0.53	15.68±0.47	10.24±0.46	39.02±0.57	28.04±0.58
EAC+ 5 FU (20 mg/kg)	40.78±0.59	23.08±1.13	32.6±0.37	29.74±1.28	77.48±1.47	9.92±0.37
EAC+EEDP250	24.06±4.57a	15.86±0.58a	25.5±0.76a	24.02±1.0a	69.02±1.34a	13.82±1.03a
EAC+EEDP500	41.46±0.44a	23.54±0.53a	29.46±1.42a	32.82±1.02a	80.38±0.61a	9.18±0.29a
EAC+AEDP250	26.22±0.63a	15±0.55a	23.56±0.72a	19.34±0.93a	54.46±1.01a	14.68±0.97a
EAC+AEDP500	33.24±1.06a	19.46±0.69a	28.02±0.45a	32.2±0.33a	68.76±0.28a	12.72±1.03a

The data were expressed as mean ± SEM, n = 10, where a: p<0.001

Table 5. Effect of EEDP and AEDP on the lung antioxidant status of EAC- bearing mice

Parameters (Lung)	TP mg/dL	CAT U/mg tissue	SOD U/mg tissue	P nm/100mg tissue	GSH nm/100mg tissue	MDA nm/g protein
Normal	26.55± 0.39	20.55± 0.28	13.63± 0.28	42.18± 0.51	62.73± 0.35	7.65± 0.17
EAC Control	12.8± 0.38	7.6± 0.14	5.2± 0.09	32.05± 0.13	26.43± 0.5	25.6± 0.29
EAC+ 5 FU (20 mg/kg)	26.6± 0.37	21.33± 0.19	14.45± 0.66	41.4± 0.45	62.15± 0.29	8.13± 0.19
EAC+EEDP250	26.13±0.34[a]	19.95±0.17[a]	13.13±0.13[a]	42.23±0.27[a]	60.95±0.29[a]	6.6±0.04[a]
EAC+EEDP500	28.67±0.55[a]	20.95±0.23[a]	10.47±0.08[a]	43.58±0.18[a]	64.38±0.26[a]	8.38±0.17[a]
EAC+AEDP250	24.58±0.33[a]	18.8±0.11[a]	10.67±0.19[a]	41.55±0.45[a]	53.43±0.38[a]	12.5±0.24[a]
EAC+AEDP500	26.75±0.2[a]	21.08±0.19[a]	12.5±0.25[a]	42.5±0.77[a]	60.85±0.35[a]	7.6±0.31[a]

The data were expressed as mean ± SEM, where a: p<0.001

Discussion

Ayurvedic treatment is very effective, but the proper pharmacovigilance, mechanism of action, pharmacokinetics, and other important aspects of Ayurvedic drugs are not yet fully understood. Moreover, due to the lack of evidence, the basic ideologies in Ayurveda are not scientifically acceptable. With the help of advanced research methodologies, validated research, and advanced technology make the Western medicine system is almost at the forefront of the medical system. Therefore, there is an urgent need for research methodologies to validate the fundamental concept of Ayurveda treatment because a perfect health restoration including maintenance is possible in Ayurvedic drug treatment (Parasuraman et al., 2014).

The generation of free radicals is the basic etiology in most human diseases condition, and there is an increasing need to develop techniques for measuring free radicals and their responses in vivo. These free radicals are so reactive that they have a short lifespan because of that, are not suitable for direct assays, and are determined by indirect methods where various end products of the target molecule like lipids, proteins, and DNA are measured quantitatively (Sara et al., 2012). The end product formed from the reactions of free radicals and biomolecules is more stable than free radicals. Measurements of these end products concerning the oxidation target are an important aspect of the treatment modulation. MDA and PCC are the by-products of lipid peroxidation and oxidized proteins respectively (Rizwan et al., 2008).

Medicinal plants have various phytoconstituents which are an excellent source of lead to develop therapeutic drugs including anticancer agents. Therefore, many studies have been conducted on herbs for various ethnobotany reasons (Cragg and Nweman, 2009) The antitumor properties of these plant species extract have already been reported (Raju et al., 2012). This study was conducted to estimate the antioxidant status in blood and various organs and the effectiveness of EEDP and AEDP on the restoration of these enzymes in cancer-bearing animals. Significantly increased levels of MDA and SOD in serum, liver, brain, lung, and kidney were found in the tumor-bearing animal which causes tissue damage and loss of functional completeness of cell membranes (Gupta et al., 2004). Lipid peroxidation is an autocatalytic chain reaction imitated by free radicals which affect the pathological state of cells. MDA, the marker compound of lipid peroxidation, is high in cancerous tissues than in normal organs (Yagi, 1987). GSH, an effective inhibitor of neoplastic cell processes, being a part of the endogenous antioxidant system plays an important role in cell proliferation. It occurs especially in high concentrations in the liver and is known to have important functions in the protection process (Imam et al., 2006). Excessive production of free radicals leads to oxidative stress and damage to macromolecules which affects many functions of important organs, especially in the liver, kidneys, brain, and lungs, even if the tumor site does not directly interfere with these organs. (DeWys, 1982). The generated oxygen radicals destruct the cell membranes by lipid peroxidation and can lead to tissue and/or organ damage (Koca et al., 2005) followed by the reduction I of other enzyme systems such as SOD, CAT, and GSH that counteract the harmful effects of reactive oxygen species (Ichimura et al., 2004). The reduction in SOD, CAT, GSH, and P in the EAC group is due to the loss of $Mn2^{+}$ in mitochondria (Sun et al., 1989). Tumor growth also reduces the level of SOD and CAT and arrests the functional activity in cancer-bearing mice.

The PCC of blood has increased significantly in disease control mice. The carbonyl content of proteins has been reported to be a sensitive and early marker of oxidative stress on tissues compared to lipid peroxidation (Rajesh et al., 2004). Elevated levels of PCC have been reported in patients with brain tumors. Elevated values strongly suggest that oxidative stress (OS) may play a vital role in the carbonylation of protein in the brain which is an oxidation reaction mediated by Fe^{2+} and Cu^{2+}. Free radicals bind to the cation binding site of a protein in presence of H_2O_2 or O_2, which converts the side chain of the amino acid to a carbonyl group. Accumulation of carbonyl groups in a protein causes many chemical modifications to form the oxidation product of the protein (Rodney et al., 2000). In this study, a significant increase in PCC levels in EAC-carrying mice. It recovered once after the administration of two doses of EEDP and AEDP. Administration of EEDP and AEDP significantly increased the SOD and CAT levels.

Plant extracts containing antioxidative components such as plumbagin have been reported to be cytotoxic to tumor cells (Ruby et al., 1995) and have antitumor activity in experimental animals (Ming et al., 1998). Induction of apoptosis and cell cycle arrest during the G2 / M phase are the two main mechanisms behind the antioxidant with antitumor activity. The effects of free radicals on the development of cancer are well documented (Putul et al., 2000). Mice that were treated with 250, 500 mg/kg EEDP and AEDP showed inhibition of lipid peroxidation, reflected as a reduction in MDA and PCC, similarly, it also restored the blood, liver, brain, kidney, and lung-containing antioxidant enzyme system to almost normal levels.

Conclusion

Natural antioxidants may enhance the endogenous antioxidant defenses against ROS disruption and restore optimal balance by neutralizing active species. They are becoming more and more important because of their important role in disease prevention. Ethanol extracts showed significant activity than the aqueous extracts. The possible mechanism of antitumor activity may be due to its antioxidant activity. Maintaining endogenous antioxidant status during the treatment of cancer has the advantage of minimization of serious adverse effects and reducing the treatment course period. A medicinal plant that has both anticancer as well as antioxidant help a better outcome from the disease condition.

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