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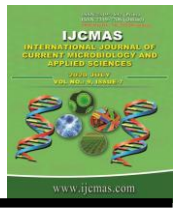

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Therapeutic Effect of *Idivallathi mezhugu* on Lipid Peroxidation and Antioxidant System in 7, 12-dimethylbenz[a]anthracene Induced Mammary Tumour in Female Sprague-Dawley Rats

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The study was undertaken for 150 days on female Sprague-Dawley rats to evaluate antioxidant effects on DMBA induced mammary tumours. A total of 80 rats were randomly allotted to 5 groups with 18 rats in 4 groups and 12 rats to the control group distributed to DMBA, DMBA + Tamoxifen and DMBA + Idivallathi mezhugu (*IM*) and *IM* groups. Rats were administered with 4 weekly doses of 5 mg DMBA/rat in olive oil by oral gavage beginning at 42nd day of age. From the day of first dosing of DMBA, tamoxifen (100 µg/kg/ BW/Day) was given in gingelly oil to DMBA + Tamoxifen group and *IM* (300 mg/kg BW/daily) in palm jaggery to DMBA+*IM* and *IM* groups by oral gavage till the end of study. DMBA group showed significant ($P<0.05$) increase in lipid peroxidation and antioxidants catalase (CAT) and superoxide dismutase (SOD) levels besides reduced glutathione (GSH). Whereas, *IM* and tamoxifen treated groups did not show any significant difference in lipid peroxidation and oxidative stress with no increase in the antioxidant level compared to the control. Selective growth advantage of tumour cells over their surrounding normal counterpart was evident in the DMBA group and inhibited lipid peroxidation and oxidative stress was evident in the *IM* group.

Introduction

In recent years, there has been a growing interest in studying the role played by lipid peroxidation (LPO) and antioxidant status. Proper balance between LPO and antioxidants should be maintained in the cell because of their potential importance in the pathogenesis of various pathologic diseases including cancer. Neoplastic cells may sequester essential antioxidants from circulation to supply the demands of growing tumor. Reactive oxygen species (ROS) are involved in the initiation and progression of carcinogenesis. Moreover, the ROS-induced oxidative damage causes a decrease in the efficiency of antioxidant defense mechanism (Padmavathi *et al.,* 2006). Hence, oxidative

damage considered as a main factor contributing to carcinogenesis and evolution of cancer. *Idivallathi mezhugu* (*IM*) is a herbomercuric Siddha formulation has a combination of 15 ingredients. It exhibits properties such as antiinflammatory, analgesic, antifungal, antirheumatic, antiarthritic and anti-ulcer effects (Gaidhani *et al.,* 2005). Antilipid-peroxidative and antioxidant mechanism was attributed by *P.longum* with its active principle piperine (Senthil *et al.,* 2007 a, b) and with a ferin in *W.somnifera* (Manoharan *et al.,* 2009) in the *IM* there by structural integrity of cell surface and cell membrane were maintained. Therefore, it is of interest to investigate the anticancer property of *IM* on DMBA induced breast cancer and to provide the scientific rationale for use the drug *IM* as an alternative agent against breast cancer.

Materials and Methods

Eighty-four virgin female (IAEC Approval Lr.No.1614/DFBS/B/2014, Dated 16.06.2014) 35-days-old Sprague-Dawley rats weighing 60g obtained from National Institute of Nutrition, Hyderabad were acclimatized for 7 days and were randomized and equally (n=18) distributed to five groups expect control (n=12) based on their body weight (g). The experiment was starts from 42th day of age. Group 1 is control. Group 2 (DMBA) was administered with 5 mg of DMBAin olive oil/animal/week/per os for 4 weeks. Group 3 was DMBA + tamoxifen. Group 4 was DMBA + *IM*. Group V was *IM*. Tamoxifen was administered in gingelly oil at a dose rate 100 µg/kg BW/day//peros. *IM* was obtained from M/s. The Indian Medical Practitioners Cooperative Pharmacy and Stores Ltd (IMPCOPS) Chennai, Tamil Nadu and stored at room temperature) was dissolved in palm jaggery and administered orally at the dose rate of 300mg/kg BW/day till the end of 150 days study.

In the DMBA group, out of 31 tumours recorded in 18 animals, 15 were benign tumours and 15 were carcinomas and one was a fibrosarcoma. In the tamoxifen group, out of 28 tumours recorded in 12 tumour bearing rats, 16 were benign tumours and 10 were carcinomas and two were fibrosarcoma. In the DMBA+*IM* group, out of 13tumoursrecorded in six animals nine were benign tumours and four were carcinomas. Normal and malignant mammary tumour samples (n=6) were collected in sterile normal saline for lipid peroxidation and antioxidant profile. Tissue protein was estimated as per the method of Lowry *et al.,* (1951). Glutathione peroxidase (GPx) was measured as per the method of Rotruck*et al.,* (1973). Superoxide dismutase (SOD) was measured as per the method of Marklund and Marklund (1974). Reduced glutathione (GSH) were estimated as per the method of Meron *et al.,* (1979). Lipid peroxidation (MDA) assay was determined as thiobarbiturc acid reactive substances (TBARs) as per the method of Yagi (1976). Catalase (CAT) was assayed as per the method of Caliborne (1985). The data generated from different parameters of the experimental study were subjected to one-way analysis of variance (ANOVA) test using SPSS software version 20 for windows.

Results and Discussion

Mean (± SE) lipid peroxidation and antioxidant values of DMBA induced mammary tumour in DMBA + tamoxifen and DMBA + *IM* treated Sprague-Dawley rats presented in Table 1.Group II cancer-bearing animals showed a significant increase in the lipid peroxidation and CAT, SOD and GSH values in the mammary tumour tissues when compared to that of the control. GPx value significantly reduced in DMBA group when compared to the control groups. Administration of tamoxifen in Goup III animals significantly decrease in antioxidant

levels when compared to group II animals. No significant changes were observed in Group IV drug control animals when compared to Group I animals.

Increased levels of lipid peroxidation playan important role in the early phases of tumor growth (Rice-Evans and Burdon, 1993). In the present study, DMBA group showed significantly increased lipid peroxidation and antioxidants levels except GPX value. Which were in accordance with the findings of Jalantha *et al.,* (2013) who had suggested that increased lipid peroxidation and host antioxidant defences mechanism were associated with the development of breast cancer which might offer a selective growth advantage to tumour cells over their surrounding normal counterparts and these were significantly reduced after treatment with tamoxifen and *IM*.

There is balance between the amount of free radicals produced from the body and antioxidant defense mechanism that scavenge them and protect the body against their deleterious effects (Kolanjiappan *et al.*, 2002). Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) constitute the enzymic antioxidant system, which scavenges ROS and lipid peroxidation.

SOD protects the body cells against superoxide and hydrogen peroxide-mediated LPO. In the present study, we have also observed an increased SOD and catalase activities. This increased level of superoxide anion have the capacity to produce the deleterious effect at sites far from the tumor (Oberley and Buettner, 1979).

GPx reacts with hydrogen peroxide thereby preventing the intracellular damage. There was adecline in the activities of GPx in the present study, which maybe due the altered antioxidant defense system caused byenormous production of free radicals in DMBA-induced carcinogenesis (Daniel and Joyce, 1983).In the present study, increased GSH activity and decreased GPx activity supported tumour growth in the DMBA treated group

Table.1 Mean (± SE) lipid peroxidation and antioxidant values of DMBA-induced mammary tumour in DMBA + Tamoxifen and DMBA+*IM* treated Sprague-Dawley rats

Parameters	Lipid peroxidation	Catalase	SOD	GPx	GSH
Control	182.57^{a}±1.50	1.04^{a}±0.15	143.05^{a}±1.90	9.71^{b}±0.24	198.18^{a}±1.72
DMBA	341.84^{b}±1.60	1.87^{b}±0.05	232.76^{b}±2.87	5.02^{a}±0.061	723.32^{b}±2.85
DMBA+Tamoxifen	185.60^{a}±1.46	1.39^{a}±0.15	149.02^{a}±1.80	9.20^{b}±0.27	205.67^{a}±3.07
DMBA+*IM*	183.37^{a}±3.84	1.10^{a}±0.12	145.58^{a}±1.56	9.49^{b}±0.06	200.26^{a}±2.59

Means with same superscript within a row do not differ from each other (P>0.05)

IM and tamoxifen treatment may enhances the cell membrane integrity and significantly reduces the extent of lipid peroxidation. This leads to decrease in the antioxidant levels in both the treatment groups when compared to the control group. Increased level of lipid peroxidation and enhanced host antioxidant defense mechanism play an important role in development of tumour cells in DMBA group. Whereas, *IM* and tamoxifen groups inhibits

the lipid peroxidation and oxidative stress with no increase in the antioxidant levels when compared with the control group.

This experiment concluded that, *Idivallathi mezhugu* can positively control the antioxidant activity and reduces the lipid peroxidation by detoxifying the oxygen free radicals induced by DMBA.

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