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ANTIOXIDANT AND ANTICANCER ACTIVITIES OF ETHANOLIC EXTRACT OF *FICUS GLOMERATA* ROXB. IN DMBA INDUCED RATS

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ABSTRACT: The present study was designed to evaluate the antioxidant and anticancer activities of the ethanolic leaf extract of *Ficus glomerata* Roxb. on the basis of enzymatic and non-enzymatic antioxidants, xenobiotic enzymes and histopathological parameters in 7, 12-dimethylbenz(a)anthracene (DMBA) induced mammary carcinoma in rats. *F. glomerata* is large evergreen tree, found all over India and South East Asia. DMBA at a dose of 20mg/kg body weight (gastric intubation) significantly reduce the enzymatic antioxidant such as superoxide dismutase (SOD), catalase (CAT), glutathione-s-transferase (GST), glutathione peroxidase (GPX), glutathione reductase (GR), glucose-6-phosphate-dehydrogenase (G6PD) and non-enzymatic antioxidant like vitamin-C, vitamin-E and total reduced glutathione (TRG) and lipid peroxidation (LPO) in group II rats. A significant increase in xenobiotic enzymes like cytochrome P_{450} and cytochrome b_5, in DMBA induced groups were observed. Treatment with ethanolic leaf extract of *F. glomerata* (150mg/kg body weight, orally) in group III rats were observed all these above mentioned parameters were reverted to near normal level when compared to control rats. Finally, we concluded that the *F. glomerata* leaf extract exerts equipotent anticancer and antioxidant activities in the experimental model of DMBA induced mammary carcinoma in rats.

INTRODUCTION: Cancer is one of the non-communicable diseases and a public health problem in the world. Cancer is a second major cause of death in the world.

More than 70% of all death due to cancer occurred in developing countries. One of main types of cancer is breast cancer in the world [1].

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The role of interactions between genes and environment in carcinogenesis is clearly demonstrated by phase I and II enzymes that constitute the central armamentarium against toxic chemicals and carcinogens. Several environmental carcinogens that are not chemically active undergo metabolic activation.

Cytochrome P_{450}, a family of phase I hemoproteins, represents a major adaptive response against chemical challenge from the environment and catalyzes the activation of various procarcinogens to ultimate carcinogens. The ultimate carcinogens in turn interact with DNA, resulting in chromosomal abnormalities and mutation [1] is in key

growth regulatory genes that eventually culminate in neoplastic transformation. Phase II enzymes detoxify pro- and ultimate forms of chemical carcinogens, thereby decreasing DNA damage.[2] It follows that control of environmentally induced cancers can be achieved by decreasing the rate of DNA damage through modulation of phase I and II biotransformation enzymes.

Mammary glands of several rat strains, mainly Sprague-Dawley and Wistar-Furth, are susceptible to transformation induced by chemical carcinogens and the two most widely used active chemical inductors of mammary carcinogenesis are 7, 12-dimethylbenz(a)anthracene (DMBA) and N-methylnitrosurea [4, 5].

Several markers have been developed to biomonitor chemoprevention. These are based on the fact that chemopreventive agents can exert their anticarcinogenic effects by one or a combination of the following mechanisms: inhibiting formation of reactive carcinogenic metabolizes, induction of enzymes that detoxify carcinogens, scavenging reactive oxygen species, influencing apoptosis and inhibiting cell proliferation [6, 7]. The tripeptide glutathione, a physiologically important nucleophile and the enzymes glutathione peroxidase (GPx), glutathione S-transferase (GST), which utilize reduced glutathione (GSH) as substrate have assumed significance as biomarkers of chemoprevention owing to their antioxidant and detoxification properties [8, 9, 10].

Many plants have antioxidant properties which protect our cells from oxidative damage, which is further linked to many diseases. These antioxidant properties of plants are due to various phytochemicals present in the plant.[11] India has a rich heritage of medicinal plants, many of which have been explored for the various bioactivities since ages. However, The radio protective potential of plants have been hardly explored, though a large number of compounds were isolated from various plant sources have been shown to possess antioxidant properties [12, 13].

One such plant is *Ficus glomerata* which has been used in traditional system of medicine for treating liver diseases, anemia and gastrointestinal disorders like constipation, diarrhoea, piles, asthma, leprosy and other ailments [14].

The fruits of *Ficus glomerata*, locally known as Gular have been used since olden times in the ethnomedicine for many varied medicinal purposes including as a remedy of diabetes mellitus [15]. In addition, this plant is considered to possess tonic, expectorant, emollient, stomachic and carminative properties [16]. The sap extracted from trunk of the tree is also considered curative in diabetes. Moreover, the powdered seeds mixed with pure bee-honey are prescribed to the diabetics in the folklore medicine [17].

The present research program was aimed to investigate anticancer and antioxidant activities of leaf extract of *Ficus glomerata* in DMBA induced mammary carcinoma rats.

MATERIALS AND METHODS:

Chemicals: DMBA (7, 12 Dimethylbenz(a) anthracene) was purchased from sigma chemical company St. Louis, MO, USA. All other chemicals used in this study were of analytical grade which were brought from Himedia laboratories private ltd., Mumbai, India.

Plant: *Ficus glomerata* leaves were collected from the trees located in and around Coimbatore. The leaf samples were authenticated by Dr.V.S.Ramachandran, Professor, Department of Botany, Bharathiar University, Coimbatore- 46.

Preparation of the extract: *F. glomerata* leaves were shade dried and powdered. 10gram of this powder was extracted with 250ml of ethanol in a soxhlet apparatus. The obtained residues were vaccum dried and used for the study.

Experimental animals: Female Sprague dawley rats (180-200g) obtained from the small animal breeding station, Mannuthy, Thrissur, Kerala, India. The animals were housed and maintained in clean polypropylene cages. The animals were fed with standard pellet diet (M/s.Hindustan lever ltd, Mumbai, India) and water *ad libitum*.

The experimental protocol was carried out according to the guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA), India and approved by the animal ethical committee.

Experimental design: A total of 30 rats were used. The animals were divided into five groups of six animals each as follows.

- Group I served as control rats receiving olive oil, a vehicle alone.
- Group II rats were induced with a single dose of DMBA (20mg/rat, dissolved in olive oil) by oral gavage at the first day of experimental period.
- Groups III rats received *F. glomerata* extract (150 mg/kg b.wt.) orally for 14 days after 90 days of DMBA induction.
- Group IV received Tamoxifen (20 mg/kg b.wt.) orally for 14 days after 90 days of DMBA induction.
- Group V rats received *F. glomerata* extract alone (150 mg/kg b.wt.) Orally for 14 days.

At the end of the experimental period (i.e. on the 15thday) all animals were euthanized and the liver, kidney, mammary tissues were excised immediately and rinsed with ice cold saline, dried with blotting paper, weighed, cut into pieces and 1 gram of each sample (liver, kidney, mammary tissue) was homogenized with 0.25M sucrose, 1mM Tris HCL and 1mM EDTA, (pH 7.2-7.4) using a motorized glass-Teflon homogenizer to get a 10% homogenate.

The 10% homogenate was centrifuged at 600x g for 5 minutes to remove the nuclear fraction and broken cell debris and then supernatant was collected. That supernatant was centrifuged at 1200x g for 10 minutes to sediment the mitochondrial fraction. Mitochondrial pellet was finally suspended in 0.25M sucrose solution. All operations were performed at 4°C. The mitochondrial fraction was used for the following biochemical studies.

Phase I mitochondrial xenobiotic enzymes: The mitochondrial fraction of liver, kidney, mammary tissue homogenates were used for assaying cytochrome P_{450} reductase [18] and Cytochrome b_5 reductase [19].

Phase II Antioxidant activities in mitochondrial fraction: The mitochondrial fraction of liver, kidney, mammary homogenate were used for assaying superoxide dismutase (SOD) [20], catalase (CAT) [21], glutathione peroxidase (GPx) [22], glutathione reductase (GR) [23], glutathione-S-transferase (GST) [24], glucose-6-phosphate dehydrogenase (G6PD) [25], total reduced glutathione (GSH) [26], vitamin-C [27], vitamin-E [28] and lipid peroxidation (LPO) [29].

Statistical analysis: The values were expressed as mean ± SD. Data were analyzed for the statistical significance by one way analysis of variance (ANOVA) followed by the group means were compared with Dunnett's multiple comparison test using a statistical software package SPSS version 10 and value of $P<0.05$ was considered to indicate a significant difference between the groups.

RESULTS AND DISCUSSION:

Phase I mitochondrial xenobiotic enzymes: The activities of mitochondrial xenobiotic enzymes such as cytochrome P_{450} reductase and cytochrome b_5 reductase in liver, kidney and mammary tissue of control and experimental rats were presented in **tables 1, 2 and 3**.

TABLE 1: EFFECT OF *FICUS GLOMERATA* ON PHASE I XENOBIOTIC ENZYMES IN LIVER MITOCHONDRIAL FRACTION OF CONTROL AND EXPERIMENTAL RATS

Parameters	Group I	Group II	Group III	Group IV	Group V
Cytochrome P_{450} reductase	0.55 ± 0.09	1.86 ± 0.16a	0.85 ± 0.35b	0.72 ± 0.03bc	0.57 ± 0.04ns
Cytochrome b_5 reductase	0.26 ± 0.06	0.88 ± 0.12a	0.50 ± 0.02b	0.38 ± 0.04bc	0.27 ± 0.06ns

TABLE 2: EFFECT OF *FICUS GLOMERATA* ON PHASE I XENOBIOTIC ENZYMES IN KIDNEY MITOCHONDRIAL FRACTION OF CONTROL AND EXPERIMENTAL RATS

Parameters	Group I	Group II	Group III	Group IV	Group V
Cytochrome P_{450} reductase	0.66 ± 0.17	1.97 ± 0.18a	0.89 ± 0.46b	0.78 ± 0.00bc	0.65 ± 0.21ns
Cytochrome b_5 reductase	0.09 ± 0.01	0.32 ± 0.02a	0.19 ± 0.02b	0.15 ± 0.03bc	0.11 ± 0.02ns

TABLE 3: EFFECT OF *FICUS GLOMERATA* ON PHASE I XENOBIOTIC ENZYMES IN MAMMARY TISSUE MITOCHONDRIAL FRACTION OF CONTROL AND EXPERIMENTAL RATS

Parameters	Group I	Group II	Group III	Group IV	Group V
Cytochrome P_{450} reductase	0.74 ± 0.14	2.40 ± 0.17A	1.01 ± 0.07B	0.97 ± 0.06BC	0.69 ± 0.11A
Cytochrome B_5 reductase	0.12 ± 0.02	0.29 ± 0.03A	0.18 ± 0.03B	0.19 ± .01BC	0.12 ± 0.02NS

Units: Cytochrome P_{450} reductase – µmol of NADPH oxidised/min/mg protein, **Cytochrome b_5 reductase** – µmol of NADH oxidised FeCN/min/mg protein; Values are mean ± SD of six observations. Comparisons are made between: a –Group I vs Group II & V; b – Group II vs Group III & IV; c – Group III vs Group IV. Statistical significance: a,b,c significant at $p<0.05$, ns-not significant.

The activities of xenobiotic enzymes like cytochrome P_{450} reductase and cytochrome b_5 reductase in liver, kidney and mammary tissue were significantly ($p<0.05$) increased in DMBA induced (Group II) rats when compared to control (Group I) rats. *F. glomerata* leaf extract treated (Group III) rats showed significant ($p<0.05$) decrease in the levels of cytochrome P_{450} reductase and cytochrome b_5 reductase when compared with DMBA induced rats. Tamoxifen administered (Group IV) rats also showed the above mentioned enzyme activities were near normal level when compared to control rats. Plant extract alone administered rats (Group V) did not show any significant changes when compared to control rats.

Hence, the effect of *F. glomerata* on phase I enzyme might be due to its flavonoid content that decrease cytochrome P_{450} activity either by increasing V_{max} or decreasing K_m for microsomal monoxygenase and enhancing the interaction with cytochrome P_{450} binding to the catalytic site. *F. glomerata* actively reduces the activity of cytochrome b_5 reductase in the cancer bearing animals, indicating its overall effect on phase I enzymes mediated by its flavonoids content [30].

Phase II enzymic and non enzymic antioxidant status in mitochondrial fraction: Tables 4, 5 and 6 shows the activities of mitochondrial enzymic antioxidants like SOD, CAT, GPX, GR, GST and G6PD and levels of non-enzymic antioxidants like GSH, Vitamins C and E in mitochondrial fractions of liver, kidney and mammary gland of control and experimental rats. The antioxidant status (both enzymic and non-enzymic) was found to be significantly lowered ($p < 0.05$) in mammary carcinoma bearing rats when compared with normal control rats. All these alterations were reverted to nearly control values on the administration of *F. glomerata* extract in Groups III animals. In *F. glomerata* extract treatment, the antioxidant levels were further increased when compared with standard Tamoxifen treated rats.

TABLE 4: EFFECT OF *FICUS GLOMERATA* ON THE LEVELS OF MITOCHONDRIAL ANTIOXIDANT STATUS IN LIVER

Parameters	Group I	Group II	Group III	Group IV	Group V
CAT	14.33 ± 0.33	7.10 ± 0.14a	9.02±0.03b	10.05±0.05bc	14.50±0.70a
SOD	15.46 ± 0.58	8.25 ± 0.24a	10.41 ± 0.42b	13.84 ± 0.26bc	15.75 ± 0.37a
GPx	4.72 ± 0.63	2.34 ± 0.35a	3.41 ± 0.28b	4.13 ± 0.25bc	4.8 ± 0.01a
GR	12.52 ± 0.89	5.71 ± 1.70a	11.57 ± 1.12b	11.81 ± 1.13b	12.98 ± 0.79ns
GST	3.50 ± 0.22	1.47 ± 0.03a	2.95 ± 0.40b	3.25 ± 0.43bc	3.83 ± 0.38a
G6PD	3.41 ± 0.57	1.11 ± 0.34a	3.11 ± 0.36b	3.05 ± 0.27b	3.96 ± 0.56a
GSH	16.69 ± 1.74	7.21 ± 0.36a	10.52 ± 0.51b	13.07 ± 0.24bc	17.19 ± 0.65a
VIT C	1.67 ± 0.04	0.82 ± 0.04a	1.80 ± 0.04b	1.70 ± 0.07bc	1.68 ± 0.03ns
VIT-E	2.91 ± 0.36	1.37 ± 0.28a	1.86 ± 0.12b	1.98 ± 0.08bc	2.91 ± 0.36ns

TABLE 5: EFFECT OF *FICUS GLOMERATA* ON THE LEVELS OF MITOCHONDRIAL ANTIOXIDANT STATUS IN KIDNEY

Parameters	Group I	Group II	Group III	Group IV	Group V
CAT	7.04 ± 0.04	3.04 ± 0.03a	5.42 ± 0.05b	7.05 ± 0.02bc	6.35 ± 0.03a
SOD	4.19 ± 0.36	1.88 ± 0.42a	4.17 ± 0.16b	4.33 ± 0.16b	4.64 ± 0.36a
GPx	3.35 ± 0.55	2.45 ± 0.52a	3.44 ± 0.27b	3.76 ± 0.31bc	3.39 ± 0.23ns
GR	8.47 ± 2.04	5.70 ±4.80a	8.50 ± 0.72b	8.48 ± 0.13b	8.58 ± 0.40ns
GST	2.65 ± 0.10	0.94 ± 0.04a	2.13 ± 0.16b	2.13 ± 0.08b	2.64 ± 0.33ns
G6PD	3.06 ± 0.67	1.07 ± 0.30a	1.89 ± 0.46b	2.48 ± 0.31bc	2.95 ± 0.21ns
GSH	13.50 ± 1.10	9.53 ± 1.13a	13.53 ± 1.71b	11.20 ± 0.78bc	14.24 ± 2.58a
VIT C	0.87 ± 0.07	0.48 ± 0.03a	0.85 ± 0.04b	0.85 ± 0.02b	0.94 ± 0.03a
VIT-E	2.33 ± 0.22	1.13 ± 0.19a	1.93 ±0.13b	1.73 ± 0.52b	2.34 ± 0.22ns

TABLE 6: EFFECT OF *FICUS GLOMERATA* ON THE LEVELS OF MITOCHONDRIAL ANTIOXIDANT STATUS IN MAMMARY GLAND

Parameters	Group I	Group II	Group III	Group IV	Group V
CAT	8.29 ± 0.02	5.58 ± 0.05a	6.12 ± 0.03b	7.02 ± 0.01bc	8.68 ± 0.02a
SOD	6.10 ± 0.88	2.81 ± 0.16a	5.29 ± 0.47b	5.30 ± 0.40b	6.05 ± 0.54ns
GPx	5.31 ± 1.02	4.34 ± 0.51a	4.00 ± 0.21b	4.37 ± 0.20b	4.95 ± 0.62a
GR	11.83 ± 1.53	5.29 ± 2.07a	8.80 ± 0.22b	8.58 ± 0.23b	11.92 ± 1.49ns
GST	2.85 ± 0.07	1.79 ± 0.07a	2.37 ± 0.11b	2.66 ± 0.18bc	2.91 ± 0.01ns
G6PD	3.38 ± 0.28	1.13 ± 0.00a	2.52 ± 0.38b	2.57 ± 0.13b	3.45 ± 0.57ns
GSH	13.34 ± 1.00	9.85 ± 0.82a	11.23 ± 1.38b	11.04 ± 1.35ab	13.37 ± 0.28ns
VIT C	1.10 ± 0.05	0.75 ± 0.02a	0.90 ± 0.06bc	1.05 ± 0.08bc	1.14 ± 0.02ns
VIT-E	2.33 ± 0.22	1.13 ± 0.19a	1.93 ± 0.13b	1.73 ± 0.52ab	2.34 ± 0.22ns

Units: SOD - Units/mg protein, **Catalase -** µmoles H_2O_2 decomposed /min/mg protein, **Gpx -** µgrams glutathione utilized /min/mg protein, **GR -** µmoles NADPH oxidized /min/mg protein, **G-S-T - µmoles** CDNB conjugate formed /min/mg protein, **G-6-PO$_4$ DEHROGENASE –** Units/mg protein, **TRG** – µmoles/g tissue, **Vitamin-C** – mg/g tissue, **Vitamin-E –** mg/g tissue
Values are mean ± SD of six observations. Comparisons are made between: a –Group I vs Group II & V; b – Group II vs Group III & IV; c – Group III vs Group IV. Statistical significance: a, b, c significant at $p<0.05$, ns-not significant.

Reactive oxygen species (ROS) that are formed during the metabolism of DMBA can diffuse from the site of generation to other targets within the cell or even propagate the injury outside to intact cells. The liver is especially vulnerable to such ROS-induced damage although endowed with a rich supply of antioxidants. Thus, ROS-induced lipid and protein oxidation with compromised antioxidant defenses [31, 32].

Low levels of GSH and reduced activities of GPx, SOD and CAT seen in mammary tumors and liver of DMBA treated animals in this study can cause accumulation of superoxide anion and H_2O_2 with deleterious consequences including oxidation of critical –SH groups and conformational changes in functional proteins leading to oxidative stress.

Table 7 represents the level of LPO in liver, kidney and mammary gland mitochondrial fraction of control and experimental rats. A significant ($p < 0.05$) increased LPO were observed in mammary carcinoma bearing rats. Tamoxifen and *F.glomerata* treatment resulted in a free radical quenching effect thereby, preventing the peroxidation of lipids significantly ($p < 0.05$).

TABLE 7: EFFECT OF *FICUS GLOMERATA* OF MITOCHONDRIAL LIPID PEROXIDATION IN LIVER, KIDNEY AND MAMMARY GLAND

	Group I	Group II	Group III	Group IV	Group V
Liver	2.81 ± 0.03	4.44 ± 0.07a	3.92 ± 0.08b	3.12 ± 0.05bc	2.80 ± 0.06ns
Kidney	1.23 ± 0.04	2.51 ± 0.02a	1.65 ± 0.06b	1.72 ± 0.05bc	1.21 ± 0.06ns
Mammary Gland	0.49 ± 0.01	0.65 ± 0.03a	0.52 ± 0.01b	0.52 ± 0.01ab	0.49 ± 0.01ns

Units: LPO – nmoles of MDA formed/dl. Values are mean ± SD of six observations. Comparisons are made between: a –Group I vs Group II & V; b – Group II vs Group III & IV; c – Group III vs Group IV. Statistical significance: a,b,c significant at $p<0.05$, ns-not significant.

Apart from the enzymic antioxidants, non-enzymic antioxidants such as GSH, Vitamins C and E play an excellent role in protecting the cells from oxidative stress. Mitochondrial GSH plays a critical role in maintaining cell viability through the regulation of mitochondrial inner membrane permeability by maintaining sulfhydryl groups in the reduced state [33]. The levels of these antioxidants were significantly lowered in cancer condition. This observation supports our finding where we have observed a decline in GSH levels with an increase in oxidative stress as evidenced by increased mitochondrial LPO. The GSH level was restored to near normalcy on combinatorial therapy, which may be due to the antioxidant activity of riboflavin to regenerate the glutathione pool by reduction of oxidized glutathione. α -Tocopherol is a powerful chain breaking antioxidant and free radical scavenger which inhibits peroxidation of mitochondrial membrane lipids. Vitamin E is one of the exclusive antioxidant that protects against carcinogenesis and tumor growth. Vitamin C acts as an antioxidant to protect Vitamin E within cell membranes.

Being water-soluble, vitamin C cannot directly protect the fat-soluble cell membranes. However, it does seem to protect any fat-soluble components coming into contact with the water-soluble phase. The observed decrease in the level of vitamins C and E in mammary carcinoma bearing rats may be due to the excessive utilization of these antioxidants for quenching enormous free radicals generated in cancer condition. Oral administration of combinatorial therapy restored the vitamins C and E levels to near normalcy.

F. glomerata having strong antioxidant that enhances the benefits of other antioxidants, such as vitamins C and E [34]. *F. glomerata* leaf extract significantly reduced the incidence of mammary tumors. *F. glomerata* leaf extract at a dose of 150 mg/kg bw were more effective in chemoprevention as well as in modulating phase I and phase II enzyme activities and oxidant–antioxidant status, inhibiting cell proliferation and inducing apoptosis

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