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Original article

Protective Role of Licorice and Gloriosa superba Root Extracts against Oxidative Stress in DMBA-Induced Mammary Carcinogenesis

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Abstract

Oxidative stress is a major factor in the initiation and progression of breast cancer which is one of the major causes of cancer-related fatalities among women in the world. In the present study, the protective effect of the root extracts of Glycyrrhiza glabra and Gloriosa superba against oxidative stress of mammary carcinogenesis induced by 7, 12-Dimethylbenz[a]anthracene (DMBA) in Wistar rat models were assessed. The animals were divided into five experimental groups: Normal control, DMBA control, DMBA with Licorice root extract, DMBA with Gloriosa superba root extract and DMBA with Paclitaxel. Biomarker of oxidative stress level (superoxide dismutase SOD, catalase CAT, glutathione peroxidase GPx, reduced glutathione GSH and lipid peroxidation LPO) and histopathological examination of the mammary tissue were studied. The administration of DMBA resulted in very high level of lipid peroxidation and marked downfall of antioxidant enzyme activities, thus suggesting the occurrence of severe oxidative damage in mammary tissues. Both the herbal extracts significantly restored antioxidant status and oxidative stress significantly decreased compared to DMBA. The extracts also showed a reduction in the incidence of tumors, tumor load and histopathological abnormalities. Of the treatments, Licorice extract had the highest antioxidant activity, while Gloriosa superba had significant anti-proliferative activity similar to Paclitaxel. The results indicate that the extracts of Licorice and Gloriosa superba roots have great potential to protect against mammary carcinogenesis induced by oxidative stress by enhancing the endogenous antioxidant defense mechanisms. These medicinal plants could be beneficial complementary therapeutic agents in breast cancer care.

Keywords: *Breast cancer, mammary carcinogenesis, 7, 12-Dimethylbenz[a]anthracene, Oxidative stress*

Introduction

Breast cancer is one of the most prevalent cancers among women globally and remains a significant contributor to cancer deaths. The pathogenesis of breast cancer is a complex process that relies on several genetic, hormonal, environmental and biochemical factors which promote unchecked proliferation and development of tumors. Of these mechanisms, oxidative stress has been found to play a significant role in carcinogenesis by causing excessive production of ROS, which can damage DNA, cause lipid peroxidation, putatively cause protein oxidation, and cause mitochondrial dysfunction [1]. Increased oxidative stress leads to alteration of cellular homeostasis and to activation of signaling pathways linked to inflammation, angiogenesis and tumor growth [2]. Several studies have shown increased levels of oxidative stress biomarkers and decreased antioxidant defense systems in breast cancer patients, which make protection afforded by antioxidant molecules of crucial importance in preventing initiation and progression of breast cancer [3]. Oxidative injuries also cause mutations in oncogenes and tumor suppressors, which in turn leads to a greater acceleration of the process of malignant transformation in mammary tissues, where, as in other organs, it is triggered by persistent damage to tissues by oxygen free radicals [4-10].

The present study aimed to assess the protective effect of Licorice and Gloriosa superba root extract against oxidative stress induced in mammary carcinogenesis in Wistar rat model induced by DMBA. This study aimed at evaluating the levels of oxidative stress markers, antioxidant enzyme activity, lipid peroxidation, tumor incidence and histopathological changes in mammary tissues after treatment with herbal extracts. Comparative evaluation was also carried out with Paclitaxel to assess the therapeutic efficacy of plant extracts in reducing the oxidative stress mediated carcinogenesis. This study's results could be used to help develop plant-based anti-oxidant drugs for breast cancer treatment and prevention.

Materials and Methods

The present study carried out on healthy adult female Wistar rats (8-10 weeks old and weighing around 150-200 g). Female rats were chosen as the subjects because the mammary carcinogenesis produced by 7, 12-Dimethylbenz[a]anthracene is similar to the human hormone-dependent breast cancer. The animals were purchased from an approved experimental animal breeding farm and kept in good laboratory conditions at 22 ± 2°C, 55–65%RH and 12 hours light/dark cycle. The rats were kept in polypropylene cages with sterile paddy husk bedding and fed standard pellet feed and water were available ad libitum during the experiment. All experimental procedures were followed along the guidelines recommended by the CPCSEA for care and use of laboratory animals.

Collection and Authentication of Plant Materials

Roots of Glycyrrhiza glabra and Gloriosa superba were procured from well authenticated herbal sources in Tamilnadu, India. The plant materials were identified and authenticated by the qualified botanist of Department of Botany and the voucher specimens were deposited for future reference. The collected roots were thoroughly washed with distilled water to wash away the soil and the debris and then they were shade dried at room temperature for 2 weeks, and then these were powdered to coarse powder form by mechanical powdering.

Preparation of Plant Extracts

Soxhlet extraction of the powdered root materials of Glycyrrhiza glabra and Gloriosa superba was done with 70% ethanol as solvent. Around 500 g of the powdered material was extracted continuously for 72 h until there was complete exhaustion of phytoconstituents. The extracts were filtered through Whatman No.1 filter paper and then subjected to a rotary vacuum evaporation to concentrate the extract. All the semisolid extracts collected were dried, weighed and stored in airtight containers at 4°C for further use. Weight of plant powder used was used as the basis for calculating the percentage yield of extracts.

Induction of Mammary Carcinogenesis

Carcinogenesis of mammary gland was induced by a single dose of DMBA in olive oil. The intragastric feeding needle was used for the administration of the carcinogen to the animals after overnight fasting. Animals were inspected periodically for the appearance of tumours in the mammary glands after a period of DMBA administration. The oxidative stress and mammary tumor development induced by DMBA administration, by its capacity to generate reactive metabolites and DNA adducts, makes it a good experimental model for the studies of breast cancer.

Experimental Design

The animals were randomly divided into six groups of 6 rats. The healthy controls were group I animals, which were given normal saline during the experiment. The carcinogen control group II animals were injected with DMBA alone. Plant extracts were (oral) administered to groups III and IV after mammary carcinogenesis induction. The animals of group V were given Paclitaxel as a standard treatment. For the evaluation of the synergistic therapeutic effects, group VI animals were given combination of herbal extracts. The treatment was continued for 8 weeks after the induction of DMBA.

Standard drug and administration of plant extracts.

Both the roots of Glycyrrhiza glabra and Gloriosa superba were extracted by ethanol and were suspended in distilled water and given by intragastric tube. Plant extracts doses were determined from previous toxicological and pharmacological studies that showed their therapeutic safety and efficacy. Paclitaxel was intraperitoneally injected as it is used in standard experimentations of anti-cancer drugs. Body weight, feed consumption, behavioral changes and signs of toxicity were closely monitored in animals over the course of the treatment.

Biochemical Analysis of Oxidative Stress Markers

The animals were sacrificed under mild anaesthetic at the end of the experimental period and the mammary tissues were removed at once for biochemical analyses. Tissue homogenates were made using phosphate buffered saline and centrifuged for the collection of the supernatants. Oxidative stress markers and antioxidant enzyme activities were estimated by using standard biochemical methods.

Lipid Peroxidation (LPO): Level of lipid peroxidation was determined by measuring the formation of malondialdehyde (MDA) by thiobarbituric acid reactive substance (TBARS) assay, as described. The higher the levels of MDA, the more oxidatively damaged cellular membranes are. Superoxide Dismutase (SOD): catalyzes the conversion of superoxide radicals to hydrogen peroxide and oxygen which protects cells from oxidative stress. Catalase (CAT): Catalase is an enzyme that breaks down hydrogen peroxide to water and oxygen, and is crucial in cellular antioxidant defense. Glutathione Peroxidase (GPx): GPx works to prevent oxidative damage to cells by reducing hydrogen peroxide and lipid peroxides.

Histopathological Examination

Tissues of the mammary glands were fixed in 10% neutral buffered formalin for 24 hours, then processed using standard histological procedures. Tissues were paraffin-embedded, cut into 5 µm sections and stained with hematoxylin and eosin (H&E) and examined under the microscope. Histopathological examination was conducted to evaluate structural changes such as hyperplasia, necrosis, and inflammatory infiltration, changes in nuclear size and shape, and abnormal cell proliferation. The digital light microscope was used for taking the photomicrograph to perform comparative analysis between the various treatment groups.

Statistical Analysis

The data obtained were presented as mean ± SD. One-way analysis of variance (ANOVA) was performed to find statistical significance among experimental groups with Tukey's multiple comparison post hoc tests. Values of < 0.05 were deemed to be statistically significant.

Results

Effect of Licorice and Gloriosa superba Root Extracts on Body Weight

Animals treated with 7, 12-Dimethylbenz[a]anthracene showed a significant reduction in body weight compared to the normal control group, indicating systemic toxicity and progressive tumor burden associated with mammary carcinogenesis. The decrease in body weight observed in the DMBA control group may be attributed to increased oxidative stress, altered metabolism, reduced food intake, and rapid proliferation of tumor cells. In contrast, treatment with Glycyrrhiza glabra and Gloriosa superba root extracts resulted in significant improvement in body weight when compared to the DMBA-induced cancer control group. Animals treated with the herbal extracts maintained better physiological conditions and exhibited reduced signs of cachexia throughout the experimental period. The improvement in body weight may be associated with the antioxidant and protective effects of phytoconstituents present in the extracts, which reduced oxidative tissue damage and improved metabolic activity. Treatment with Paclitaxel also improved body weight compared to the DMBA control group; however, mild weight reduction persisted due to chemotherapy-associated toxicity.

Effect on Tumor Incidence and Tumor Volume

Mammary carcinogenesis was successfully induced in animals fed DMBA which developed mammary tumors. The incidence of tumors, tumor burden and tumor volume was the highest in the DMBA control group when compared with all the experimental groups. Several weeks after carcinogen administration, tumors manifested themselves as palpable nodules in the mammary gland area. The extracts of Licorice and Gloriosa superba root were found to significantly lower the incidence of tumours in animals. The decrease in the incidence of tumors indicates that the herbal extracts had notable anti-cancer activities against DMBA-induced carcinogenesis through inhibiting oxidative stress-induced cell proliferation. The extract treated groups showed significant reduction in the tumour size over the DMBA control group. Licorice extract among the herbal treatments showed a relatively higher reduction in tumor size which might be explained by the strong antioxidant and anti-proliferative properties of flavonoids and glycyrrhizin present in the roots of Licorice. Tumor growth showed significant inhibition in gloriosa superba treatment which may be related to colchicine like alkaloids inhibiting the mitotic activity and oxidative damage. The

group treated with paclitaxel showed significant decrease in tumour load in accordance with its known anti-cancer activity.

Effect on Lipid Peroxidation Levels

There was a significant increase in the level of lipid peroxidation in the mammary tissues of the DMBA control group when compared to the normal groups. An increase in malondialdehyde (MDA) levels is a sign of higher levels of oxidative degradation of membrane lipids, which is an excessive production of reactive oxygen species during carcinogenesis. Increased lipid peroxidation is responsible for the instability of membranes, damage to DNA and tumor progression in mammary tissues. Both Glycyrrhiza glabra and Gloriosa superba root extracts were significantly effective in reducing lipid peroxidation levels in comparison to DMBA group. This reduction in MDA content in treated animals indicates a good scavenging of free radicals and protection from oxidative membrane damage. The flavonoids and phenolic compounds in the extract of Licorice found to have strong antioxidant activity contributed to its pronounced inhibition of lipid peroxidation. Likewise, Gloriosa superba treatment improved the integrity of membrane by decreasing the formation of lipid radicals and oxidative injury. The lipid peroxidation levels were also lowered by the paclitaxel treatment, but were also comparable to the antioxidant efficacy of the herbal extracts, possibly with lower systemic toxicity.

Activity of Super Oxide Dismutase (SOD)

Significantly reduced activity of superoxide dismutase (SOD) was observed in the mammary tissues of DMBA-induced cancer-bearing animals as compared to normal controls. Decreased SOD activity is a sign of decreased antioxidant response to oxidative stress-associated superoxide radicals. Loss of SOD leads to an increase in the accumulation of ROS, and the resulting damage to the cells during mammary carcinogenesis. There was a significant recovery of SOD activity after administration of Licorice and Gloriosa superba root extracts in DMBA group. An increase in the activity of SOD represents better-endogenous antioxidant defense mechanisms in treated animals. The treatment with Glycyrrhiza glabra showed significant improvement in the SOD activity, probably because of its strong free radical scavenging properties and its antioxidant effect in the stabilization of antioxidant systems within the cells. Gloriosa superba treatment also increased SOD activity indicating decreased oxidative stress-mediated tissue injury. In the paclitaxel treated animals, the levels of SOD showed moderate recovery whereas antioxidant restoration was comparatively higher in the animal groups treated with the herbal extract.

Effect on Catalase Activity

The activity of catalase was significantly decreased in the DMBA control group than in normal animals, suggesting a failure of the ability to neutralize hydrogen peroxide produced during carcinogenesis. The decrease in catalase activity allows the accumulation of hydrogen peroxide which causes damage to proteins, lipids, and nucleic acids in the mammary tissue. Treatment with Licorice and Gloriosa superba extracts significantly increased the catalase activity, when compared with the cancer control group. Improvement in catalase levels implies an improvement in cellular antioxidant defense system and a decrease in oxidative stress. The antioxidant activity of glycyrrhizin and flavonoids resulted in the substantial improvement of catalase activity observed in Licorice extract. The treatment of Gloriosa superba also brought catalase activity to normal level by decreasing the production of reactive oxygen species and protecting the cell structures from oxidative damage. Treatment with paclitaxel showed moderate recovery of catalase activity in comparison to DMBA treated animals.

Level of Glutathione Peroxidase and Reduced Glutathione.

Glutathione peroxidase (GPx) activity and levels of reduced glutathione (GSH) were seen to be significantly decreased in the cancer control group induced by DMBA in comparison to normal control animals. The depletion of GPx and GSH levels are a sign of high oxidative stress and detoxification failure in mammary tissue in carcinogenesis. Reduced glutathione is a major antioxidant intracellular substance that neutralizes free radicals and maintains the cellular redox balance. Glycyrrhiza glabra and Gloriosa superba extracts significantly reduced the levels of DMBA.GSH levels and GPx activity were significantly increased by the administration of Glycyrrhiza glabra and Gloriosa superba extracts when compared to the DMBA control groups. The rise in antioxidant enzyme level indicates that herbal extracts were able to positively influence the endogenous antioxidant response to oxidative damage. Licorice extract performed the best on restoring GSH content which might be explained by the

ability of flavonoids to regenerate antioxidant molecules and protect cellular thiol groups. In addition, the levels of GPx and GSH also increased significantly in the treated plants of G. superba reducing the oxidative tissue damage. The activity of antioxidant enzymes was partially restored in paclitaxel treatment but it was still lower than in the groups treated with the herbal extract.

Table 1. Effect of Herbal Extracts on Oxidative Stress Biomarkers

Parameters	Normal Control	DMBA Control	Licorice	Gloriosa superba	Paclitaxel
SOD (U/mg protein)	8.92 ± 0.41	3.15 ± 0.28	7.46 ± 0.35	6.98 ± 0.33	6.51 ± 0.30
CAT (U/mg protein)	62.4 ± 2.1	28.6 ± 1.8	55.2 ± 1.9	51.8 ± 2.0	49.4 ± 1.7
GPx (U/mg protein)	12.5 ± 0.6	5.2 ± 0.4	10.8 ± 0.5	9.9 ± 0.4	9.2 ± 0.5

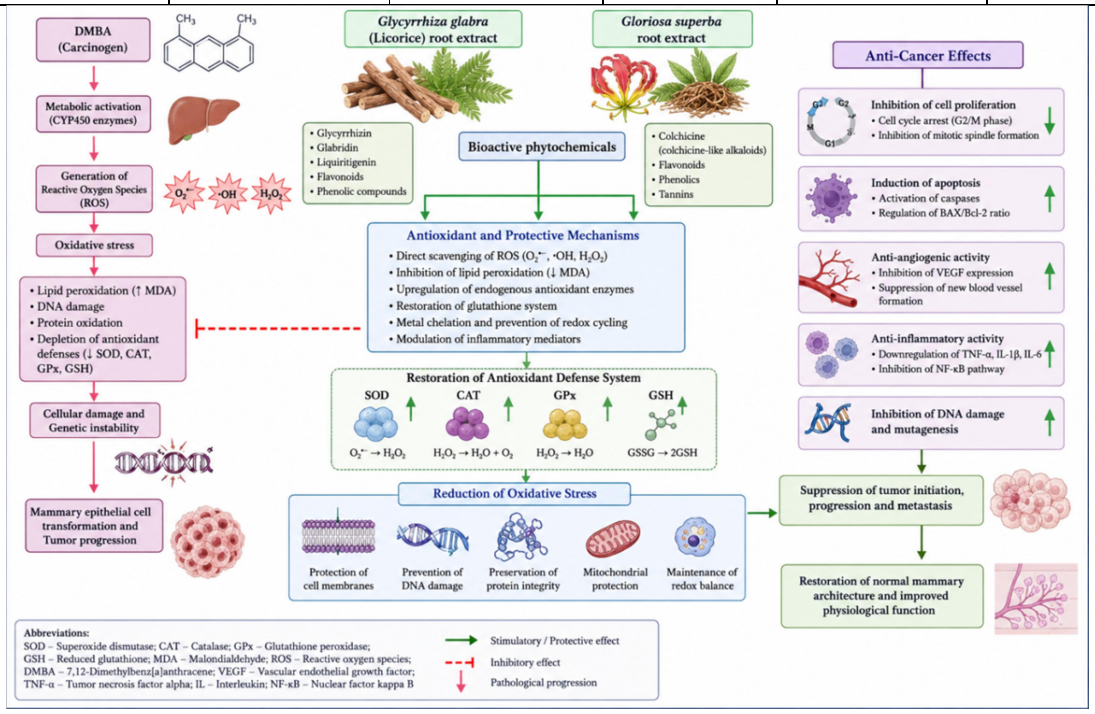

Figure 1 Proposed mechanism of antioxidant-mediated anti-cancer activity of Licorice and Gloriosa superba root extracts in mammary carcinogenesis.

Histopathological Findings

Histopathological examination of mammary tissues from the normal control group showed normal architecture with intact epithelial lining and absence of neoplastic changes. In contrast, mammary tissues from the DMBA control group demonstrated severe pathological alterations including hyperplasia, pleomorphic nuclei, inflammatory cell infiltration, necrosis, abnormal mitotic figures, and disorganized tissue architecture. Extensive tumor cell proliferation and destruction of normal mammary gland structure confirmed successful induction of mammary carcinogenesis. Treatment with Glycyrrhiza glabra root extract markedly improved mammary tissue architecture and reduced neoplastic alterations. Animals treated with Licorice extract showed decreased inflammatory infiltration, reduced hyperplasia, and restoration of normal epithelial organization. Similarly, Gloriosa superba-treated animals demonstrated moderate to significant improvement in histological appearance with reduced tumor cell proliferation and necrosis. The histopathological recovery observed in herbal extract-treated groups may be attributed to their antioxidant and anti-proliferative properties. Paclitaxel-treated tissues exhibited reduced tumor burden and improved cellular morphology; however, mild degenerative changes persisted in certain regions, possibly due to chemotherapy-associated toxicity.

Discussion

In the present study, 7, 12-Dimethylbenz[a]anthracene-induced mammary carcinogenesis Wistar rat models were used to study the antioxidant activity of Glycyrrhiza glabra and Gloriosa superba root extracts. The results showed that both herbal extracts decreased oxidative stress, antioxidant enzyme activities and inhibited the growth of tumors and histopathological architecture of mammary tissues. The study also showed that the antioxidant and anti-carcinogenic activities of the herbal extracts were similar to those of Paclitaxel treatments, indicating their therapeutic relevance in the treatment of breast cancer. Oxidative stress is believed to play a significant role in the onset and development of breast cancer. During the carcinogenesis process, the generation of ROS may lead to lipid peroxidation, DNA mutations, mitochondrial dysfunction, and activation of oncogenic pathways which lead to tumor development [11]. In the current study, DMBA administration led to elevated tumor incidence and tumor burden as well as a significant reduction in endogenous antioxidant systems. However, DMBA is metabolically activated to produce reactive intermediates that produce excess free radicals which cause damage to the cellular macromolecules leading to malignant transformation of mammary tissue [6]. Increased lipid peroxidation was seen in the DMBA control group, which further reveals increased oxidative damage and destabilization of membranes while mammary carcinogenesis takes place. The same results have been observed in other breast cancer experimental models in which DMBA was administered and resulted in a marked elevation of oxidative stress markers and advancement of breast cancer [5]. Licorice root extract significantly lowered lipid peroxidation and restored antioxidant enzyme activities such as superoxide dismutase, catalase, glutathione peroxidase and reduced glutathione. The lowering of malondialdehyde in Licorice treated animals suggests that it was effective in inhibiting the oxidative membrane damage and free radical mediated cellular damage. The protective effects may be due to the presence of bioactive phytochemicals like glycyrrhizin, glabridin, liquiritigenin and flavonoids in the roots of Licorice [12]. Flavonoids are known for their free radical scavenging and ability to stabilize the cellular antioxidant systems by donating hydrogen atoms to the reactive oxygen species [10]. Glabridin, one of the main flavonoids of Licorice, is reported to inhibit lipid peroxidation and increase the activity of antioxidant enzymes in experimental models of oxidative stress [15]. Enhanced activities of antioxidant enzymes found in the present investigation indicate that Licorice extract was effective in enhancing the antioxidant defense system against the oxidative injury caused by carcinogen. Likewise, the oxidative stress markers and the antioxidant enzyme status were significantly lowered in mammary tissues upon treatment with root extract of Gloriosa superba. Anti-cancer activity of Gloriosa superba could be linked with the presence of colchicine related alkaloids and phenolic compounds that inhibit the proliferation of the tumor cells and oxidative injury [16]. Colchicine derivatives are known to interfere with the polymerization of microtubules and inhibit the formation of the mitotic spindle which leads to suppression of rapid division of tumour cells [17]. Gloriosa superba extract exhibited strong anti-mitotic properties, significant antioxidant activity and also acts to restore glutathione-dependent defense mechanisms and to lower the generation of ROS. An increase in glutathione peroxidase and reduced glutathione results in better detoxification of hydrogen peroxide and the maintenance of redox balance in the cell. The effects of reduced oxidative stress could play a major role in the inhibition of tumor progression in treated animals. The increase of SOD and catalase activities in the herbal extract treated groups further substantiates the antioxidant effect of these medicinal plants in the mammary carcinogenesis. The loss of these enzymes in the DMBA group is indicative of a high level of oxidative stress and antioxidant defense deficiency. The antioxidant enzyme activities resulted in significant normalization in the case of Licorice and Gloriosa superba extracts, indicating effective free radical scavenging activity produced during carcinogenesis. Previously, it has been shown that treatment with antioxidants from plants can induce the endogenous enzyme defence pathway and block oxidative DNA damage linked to tumour development [11]. The beneficial effect of the herbal extracts was further substantiated by histopathological analysis of the mammary tissues. Hyperplasia, pleomorphism, necrosis, inflammatory infiltration and disorganized epithelial architecture were severe pathological changes observed in mammary tissues in the DMBA control group. Such histological changes are common characteristics of mammary carcinogenesis and are markers of tumor progression. The treatment with the extracts of Licorice and Gloriosa superba significantly enhanced tissue architecture and decreased the neoplastic changes significantly. The anti-inflammatory infiltration and the restoration of normal epithelial organization in treated groups could be related to the antioxidant and anti-proliferative activity of the phytochemicals contained in

the extracts. The histopathological enhancement seen in the present study is in accordance with previous reports showing the anti-cancer properties of herbal antioxidant in experimental models of breast cancer [14]. Both herbal extracts were found to be effective against cancer in comparison with Paclitaxel treatment with comparatively lower oxidative damage. The major mechanism of action of paclitaxel is the stabilization of microtubules and inhibition of mitosis of rapidly growing tumor cells. Paclitaxel showed good activity in reducing the size of the tumor, but it was also found that some tissues had some degenerative changes and toxic effects of the drug. The herbal extracts, however, inhibited tumor growth and stimulated endogenous antioxidant mechanisms, which indicates that there are more antioxidant affects that would protect against oxidative tissue damage. The results indicated the possible application of medicinal plant extracts as additional therapeutic agents that may lessen the toxic side effects of chemotherapy. The anti-tumor effect of the present investigation may be mediated through various mechanisms such as ROS scavenging, anti-lipid peroxidation effects, induction of antioxidant enzyme activity, inhibition of inflammatory response, and modulation of cellular signaling pathways involved in apoptosis and proliferation. The combined effect of the different phytochemicals present in Licorice and Gloriosa superba may be responsible for their overall therapeutic effects against mammary carcinogenesis. Medicinal plants are known to possess natural antioxidants that are able to act on several stages of tumor development with low systemic toxicity [9]. The results of this study conclude that Licorice and Gloriosa superba root extract have remarkable antioxidant and anti-carcinogenic activity against mammary cancer induced by DMBA. The observed reduction in oxidative stress, restoration of antioxidant defenses, suppression of tumor progression, and improvement in histopathological architecture suggest that these medicinal plants may serve as promising candidates for the development of plant-based therapeutic strategies in breast cancer management. Further molecular investigations and clinical studies are necessary to elucidate the precise mechanisms underlying their anti-cancer activity and to evaluate their potential application in human breast cancer therapy.

Conclusion

The results of the present research showed that the root extracts of Glycyrrhiza glabra and Gloriosa superba have considerable protective potential against oxidative stress of 7, 12-Dimethylbenz[a]anthracene-induced mammary carcinogenesis in Wistar rats. The administration of DMBA lead to significant oxidative damage as indicated by increased lipid peroxidation, reduced antioxidant enzyme activities, higher incidence of tumors and extensive histopathological alterations in the mammary tissue. The herbal extracts used effectively decreased oxidative stress and re-established endogenous antioxidant defense mechanisms such as superoxide dismutase, catalase, glutathione peroxidase, and reduced glutathione levels.

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