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Original article

A Combined Anticancer Efficacy of Gloriosa superba and Glycyrrhiza glabra Extracts on 7, 12-Dimethylbenz[a]anthracene-Induced Free Radical Generation and Antioxidant Systems Breast cancer in Albino Wistar Rats: Breast Cancer

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Abstract

Breast cancer is a significant health issue in the world and oxidative stress has been identified as one of the key factors in the carcinogenesis and tumor progression. The chemical carcinogen is 7,12-dimethyl benz[a] anthracene (DMBA) which causes mammary tumors by excessively triggering the production of reactive oxygen species (ROS), which result in lipid peroxidation, DNA damage, and inhibition of antioxidant defense. The current experiment assessed the anticancer activity of Gloriosa superba and Glycyrrhiza glabra extracts when used together on the generation of free radicals and antioxidant mechanisms in DMBA-induced breast cancer in albino Wistar rats. A one-time oral dose of DMBA (20mg/kg body weight) caused mammary carcinogenesis. Rats were administered either G. superba or G. glabra or both in the form of ethanolic extracts over a 12-week period and their actions compared with that of paclitaxel which is a standard drug. In serum and mammary tissues, oxidative stress indicators, such as malondialdehyde (MDA), and antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and reduced glutathione (GSH) were measured. DMBA treatment greatly enhanced lipid peroxidation and lost antioxidant enzyme activity, which reflected extreme oxidative stress as other previous experimental studies have demonstrated. Individual plant extracts returned antioxidant status to some extent, whereas combined extract treatment had a significant normalizing effect on the parameters of oxidative stress, similar to paclitaxel. Further confirmation was done on histopathological analysis to identify that there was reduced tumor severity and better tissue architecture in treated groups. It is was found that the synergistic effect is due to the joint action of alkaloids, flavonoids, and phenolic compounds found in the extracts that increase free radical scavenging and cellular antioxidant defenses. The research arrives at the conclusion that a concomitant use of G. superba and G. glabra extracts has a considerable protective effect against DMBA-induced oxidative stress and breast carcinogenesis.

Keywords: *Gloriosa superba, Glycyrrhiza glabra Extracts, 12-Dimethylbenz[a]anthracene-Induced Free Radical Generation*

Introduction

Breast cancer is the most prevalently diagnosed cancer in women all around the world and has remained a major cause of cancer related death despite the progress in early diagnosis and management. Breast cancer etiology is multifactorial with an involvement of genetic predisposition, hormonal regulation anomalies, lifestyle and environmental carcinogenic agents. Among them, oxidative stress has become one of the key processes that connect

the exposure to the environment with the molecular events that lead to the development of a tumor and its progression. Oxidative stress occurs when the formation of reactive oxygen species (ROS) overwhelms the ability of the endogenous antioxidant defense mechanisms, thus causing oxidative damage to lipids, proteins, and nucleic acids.

A polycyclic aromatic hydrocarbon (DMBA) is commonly used to cause experimental mammary carcinogenesis because it has been shown to be a potent tumor-initiator and reproducible. The metabolic activation of DMBAs occurs via cytochrome P450 enzymes, which result in the generation of electrophilic intermediates and ROS, which cause the formation of DNA adducts and mutagenesis [1]. Continuous production of ROS promotes lipid peroxidation, dysfunction of mitochondria, and disruption of redox-responsive signaling pathways, all of which lead to malignant transformation [2]. Increased levels of malondialdehyde (MDA) and decreased antioxidant enzyme activities have also been constantly observed in the DMBA-induced breast cancer models and this is important in showing the role of oxidative stress in the development of cancer [3].

Even though the traditional chemotherapeutic drugs like paclitaxel are effective in inhibiting tumors growth, they are accompanied by serious adverse effects and resistance to the drugs. This has seen a growing interest in plant based therapies as safer and effective alternatives or complementary agents in managing cancer. Bioactive phytochemicals present in medicinal plants are flavonoids, alkaloid, phenolic and saponins with antioxidant, anti-inflammatory, and anticancer effects [4].

Glory lily or gloriosa superba is a medicinal plant commonly used to treat a number of diseases. It includes powerful alkaloids like colchicine and gloriosine that were reported to suppress the process of microtubule polymerization, prevent the development of the cell cycle, and cause cell death in cancer cells [5]. It has been experimentally proven that G. superba extracts have anticancer potential in terms of oxidative stress and apoptotic pathways modulation [6].

In the same way, Glycyrrhiza glabra (licorice) has been completely researched in terms of pharmacology. Its principal bioactive compounds, such as glycyrrhizin, liquiritigenin, and isoliquiritigenin, have a high potency as antioxidants and chemopreventatives because they scavenge free radicals and stimulate endogenous antioxidant systems [7]. These compounds have also been reported to regulate redox-sensitive transcription factors like Nrf2, and thus increase cell resistance to oxidative damage [8].

Even though there are reports on individual anticancer effects of G. superba and G. glabra, there has been little research on the combined effectiveness of these two in antioxidative stress-mediated breast carcinogenesis. Phytochemical interaction is increasingly understood as a driving force behind the improvement of the therapeutic capacity of herbal preparations in which, combined products can interact with multiple molecular targets at the same time [9]. Thus, the current experiment was aimed at determining the anticancer properties of G. superba and G. glabra extracts combined in terms of their synergistic effect on free radical production and antioxidant-generating mechanisms in albino Wistar rats induced with DMBA.

Materials and Methods

The study was on healthy adult female albino Wistar rats with a weight of 150-180 g. Animals were kept in standard laboratory conditions that included temperature (22 ± 2 o C), relative humidity (55 ± 5 o C) and light/dark cycle (12 hours). Standard pellet diet and water were given ad libitum to the rats. The Institutional Animal Ethics Committee granted all the experimental procedures, and the experiments were carried out in line with CPCSEA requirements.

The roots of the species Gloriosa superba and Glycyrrhiza glabra were picked, authenticated by a botanist, dried in the shade, and ground to powder. The solid substances were exposed to Soxhlet extraction through ethanol as solvent. Reduced pressure concentration of extracts was done and the extracts were kept in 4^{o} C until future use. The choice of ethanolic extracts was determined by the higher yield and antioxidant activity of the latter in the previously reported findings [4].

DMBA (20 mg/kg body weight) was dissolved in olive oil and administered orally once (20 mg/kg body weight). Palpation of tumor was performed once in a week. One of the groups (n = 6) of rats was selected at random as normal control, DMBA control, DMBA + paclitaxel, DMBA + G. superba extract, DMBA + G. glabra extract and DMBA + combined extracts. The 12-week period lasted after the induction of DMBA was performed orally.

Breast and Liver Tissue ready to Enzyme Assays.

Breast and liver tissues were sacrificed in three hours and immediately washed with ice-cold saline to get rid of blood contaminants and blotted. The tissue samples (about 100 mg each) were weighed and homogenized at 4 o C in 0.01 M TrisHCl buffer (pH 7.4) with chilled Teflon homogenizer. After centrifugation of the homogenates, the centrifuge was set to 2,500 rpm at 4 o C in order to eliminate cellular debris. The supernatants that followed were collected with caution and stored at low temperature (1215 o C) until biochemical estimations were to be done. Every enzyme activity and antioxidant determination was done with a maximum of 48 hours after the sample was taken to prevent enzyme degradation.

Biochemical Assays

Breast Tissue- Histopathology.

The histopathological examination of the tissue of the breast was performed. Breast tissues were put in 10 percent phosphate-buffered formalin (0.1 M, pH 7.4), rinsed, and dried using progressive amounts of alcohol (30 per cent, 50 per cent, 70 per cent, 90 per cent and absolute alcohol). Xenylene was used to clear tissues followed by molten paraffin wax when infiltrate. Tissues that were paraffin-embedded were cut into 810um with a rotary microtome. Slides on which sections were placed were coated with egg albumin, deparaffinised, rehydrated and stained with hematoxylin and eosin (H&E). Stained sections were dehydrated, cleared (xylene), mounted (DPX) and observed under the light microscope to detect histopathological changes.

Antioxidant Enzymes and Non-Enzymatic Antioxidants were estimated.

Superoxide Dismutase (SOD) Activity.

The procedure, which is built on the inhibition of pyrogallolautooxidation, was used to estimate the SOD activity. Three minutes were recorded in the increment of absorbance at 420 nm. A unit of SOD activity was considered to be the quantity of enzyme that inhibited the pyrogallolautooxidation by 50 percent per minute per unit of the enzyme and measured in U/mg protein.

Catalase (CAT) Activity

The activity of catalase was ascertained. Hydrogen peroxide was decomposed and monitored by the measurement of the formation of chromic acetate at 570 nm. The CAT activity was adopted as the number of μmoles of H2O2 broken down per minute per mg protein.

Reduced Glutathione (GSH)

To estimate GSH content as the product of the reaction between DTNB and thiol groups which had a yellow color was quantified at 412 nm. The level of GSH was converted into μg/g tissue.

The Glutathione-S-transferase (GST) Activity.

GST activity was determined and observing the conjugation of reduced glutathione with CDNB at 340 nm. The enzyme activity was represented in terms of μmoles of CDNB conjugated in a given minute per mg of protein.

Glutathione Peroxidase (GPx) Activity.

To estimate the GPx activity. Reduced glutathione was reduced to oxidized glutathione by additions of hydrogen peroxide which were then quantified at 412 nm using DTNB. The activity of GPx was represented in U/mg protein.

Glutathione Reductase (GR) Activity.

GR activity was measured at 340 nm, the reduction of the oxidized glutathione was measured by oxidation of NADPH. The activity of the enzyme was given in terms of the number of μmoles of NADPH oxidized/min/mg protein.

Estimation of Vitamin C and Vitamin E.

The method used to estimate the content of vitamin C. The product of reaction with DNPH was measured at 520 nm and indicated in mg/g tissue. The amount of 520 nm mediation was determined by the Emmerie Engel reaction. The absorbance was recorded at 520 nm and vitamin E was given as 520 nm/g tissue.

Results

The effect of DMBA administration was the tremendous increase in the level of lipid peroxidation, which was indicated by a high level of MDA in serum and mammary tissues as compared to the normal control group. The result suggests increased oxidative breakdown of membrane lipids, which agrees with the previous studies of

DMBA-induced ROS overproduction. The higher level of lipid peroxidation indicates intense oxidative stress and damage of cell membrane that were related to the development of the tumors.

Table 1. Effect of *Gloriosa superba* and *Glycyrrhiza glabra* extracts on lipid peroxidation (MDA levels)

Group	Serum MDA (nmol/mL)	Mammary Tissue MDA (nmol/mg protein)
Normal control	2.15 ± 0.18	1.92 ± 0.16
DMBA control	6.84 ± 0.42*	7.26 ± 0.51*
DMBA + Paclitaxel	2.68 ± 0.24#	2.45 ± 0.21#
DMBA + GS	3.94 ± 0.31#	3.68 ± 0.29#
DMBA + GG	3.62 ± 0.28#	3.41 ± 0.26#
DMBA + GS + GG	2.51 ± 0.22#	2.32 ± 0.20#

Values are mean ± SD (n = 6)*Significantly different from normal control ($p< 0.001$) #Significantly different from DMBA control ($p< 0.05$)

A significant reduction in antioxidant enzyme activities, including SOD, CAT, and GPx, was observed in DMBA-treated rats. Reduced glutathione levels were also markedly decreased, indicating depletion of non-enzymatic antioxidant defenses. These alterations suggest impaired detoxification of superoxide radicals and hydrogen peroxide, leading to sustained oxidative stress, as previously documented in experimental breast cancer models [3].
Treatment with *Gloriosa superba* extract resulted in a significant decrease in MDA levels and moderate restoration of antioxidant enzyme activities. Similarly, *Glycyrrhiza glabra* extract treatment improved antioxidant status, reflecting its free radical scavenging ability attributed to flavonoids and phenolic compounds [7]. Notably, combined extract treatment demonstrated a more pronounced reduction in lipid peroxidation and a significant increase in SOD, CAT, GPx, and GSH levels compared to individual treatments.

Table 2. Effect of plant extracts on antioxidant enzyme activities in mammary tissue

Group	SOD (U/mg protein)	CAT (µmol H_2O_2 decomposed/min/mg protein)	GPx (U/mg protein)
Normal control	8.92 ± 0.64	62.3 ± 4.8	7.85 ± 0.52
DMBA control	3.14 ± 0.29*	28.6 ± 2.3*	3.12 ± 0.24*
DMBA + Paclitaxel	7.86 ± 0.58#	58.9 ± 4.1#	7.21 ± 0.49#
DMBA + GS	5.62 ± 0.41#	46.8 ± 3.6#	5.68 ± 0.38#
DMBA + GG	5.94 ± 0.46#	49.2 ± 3.9#	5.92 ± 0.42#
DMBA + GS + GG	7.52 ± 0.55#	56.7 ± 4.0#	7.04 ± 0.48#

Values are mean ± SD (n = 6)*Significantly different from normal control ($p< 0.001$) #Significantly different from DMBA control ($p< 0.05$)
The antioxidant restoration observed in the combined extract group was comparable to that of paclitaxel-treated rats, indicating strong synergistic efficacy. Histopathological examination supported biochemical findings, revealing severe neoplastic changes in DMBA control rats, while treated groups showed reduced tumor severity and improved tissue architecture. These results suggest that combined herbal treatment effectively suppresses oxidative stress and tumor progression.

Table 3. Effect of plant extracts on reduced glutathione (GSH) levels

Group	Serum GSH (mg/dL)	Mammary Tissue GSH (µg/mg protein)
Normal control	6.84 ± 0.51	7.12 ± 0.56
DMBA control	2.36 ± 0.19*	2.14 ± 0.17*
DMBA + Paclitaxel	6.28 ± 0.47#	6.74 ± 0.52#
DMBA + GS	4.92 ± 0.38#	5.14 ± 0.41#
DMBA + GG	5.12 ± 0.41#	5.36 ± 0.44#
DMBA + GS + GG	6.04 ± 0.45#	6.52 ± 0.49#

Values are mean ± SD (n = 6)*Significantly different from normal control ($p< 0.001$) #Significantly different from DMBA control ($p< 0.05$)

Discussion

The current research shows that the administration of 7, 12-dimethylbenz[a]anthracene (DMBA) causes significant oxidative stress in the Wistar rats as indicated by a significant increase in lipid peroxidation and the loss of enzymatic and non-enzymatic antioxidant defenses. The recorded malondialdehyde (MDA) rise in serum and mammary tissues of DMBA treated rats presents an overproduction of reactive oxygen species (ROS) and oxidative breakdown of lipids in the membrane, a characteristic of chemically-induced mammary carcinogenesis. The findings are in line with the previous reports that DMBA metabolism through cytochrome P450 enzymes generates electrophilic intermediates and free radicals, triggering lipid peroxidation, DNA damage, and tumor initiation [2, 10].

The almost three times higher levels of mammary tissue MDA in the DMBA control group over normal rats accentuates the extent of oxidative lesions in the tumour site. The products of lipid peroxidation (MDA) in addition to damaging membrane integrity create adducts with proteins and nucleic acids, enhancing mutagenic and carcinogenic mechanisms [11]. The current information hence supports the important role of oxidative stress in breast tumor development induced by DMBA.

There was also great inhibition of antioxidant enzymes, which included superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in the DMBA-treated animals. These enzymes constitute the major cellular protection against ROS by catalyzing the dismutation of superoxide radicals, de-toxication of hydrogen peroxide and lipid hydroperoxides reduction. Their pronounced decrease implies the disruption in antioxidant activity, which results in persistent oxidative damage. Equivalent decreases in antioxidant enzymes were observed in experimental models of breast cancer, in which the development of tumor is linked to mitochondrial dysfunction and redox imbalance [3, 12].

Simultaneously, there was a significant loss of reduced glutathione (GSH), an essential non-enzymatic antioxidant and redox regulator in serum and mammary tissues after exposure to DMBA. GSH loss impairs cellular detoxification, undermines peroxide scavenging, and exposes cells to oxidative stress. In addition, reduced GSH concentrations also promote the development of tumors by interfering with redox signaling and increasing genomic instability [13]. The deep decrease in GSH in DMBA control group, therefore, further proves the oxidative stress load of carcinogen induced mammary tumors.

Treatment of Gloriosa superba extract drastically decreased the MDA level and moderately restored the activity of antioxidant enzymes and GSH level. This protective impact can be explained by the existence of bioactive substances containing colchicine derivatives, flavonoids, and phenolic compounds, which have the characteristics of free radical scavenging and metal-chelating. Past reports have revealed that G. superba extracts have antioxidant and anticancer properties which occur due to the regulation of oxidative stress, generation of apoptosis, and prevention of cell growth [14-15]. These reports are supported by the partial normalization of oxidative markers that was observed in the current study.

Equally, Glycyrrhiza glabra extract treatment was very significant in alleviating lipid peroxidation and augmenting antioxidant defenses in DMBA-treated rats. Licorice contains flavonoid including glabridin, liquiritigenin and

isoliquiritigenin which have strong anti-oxidant and anti-inflammatory properties. It has been found that these compounds increase endogenous antioxidant enzyme activities and inhibit ROS-based signaling pathways that mediate cancer progression [7, 16]. The enhancement of the SOD, CAT, GPx, and GSH level has been further increased in the licorice-treated group, which supports the role of licorice in the restoration of redox homeostasis.

It is worth noting that the joint action of the extracts of G. superba and G. glabra resulted in a greater protective effect compared to the single applications of the extracts. This combination greatly lowered the level of MDA to almost normal and returned antioxidant enzyme activities and GSH contents to almost normal levels as compared to those of the paclitaxel-treated group. This increased efficacy indicates that there is a synergistic interaction of the phytochemicals found in the two extracts, and hence better ROS neutralization, and enhances the process of antioxidant regeneration. The synergistic antioxidant actions of polyphenol-containing plant mixtures have been reported before, and are thought to encompass the complementary action of ROS scavenging, enzyme induction, and deterrence of lipid peroxidation cascades [17, 18].

The standard reference drug is paclitaxel which was effective in normalizing the signs of the oxidative stress indicating its capability to inhibit the tumor burden and indirectly regulate the antioxidant balance. The similar antioxidant reactive ideation attained through the combined herbal therapy, however, is especially notable, indicating that antioxidant treatment can be administered with minimal toxicity and therapeutic effect. Plant-based interventions can potentially have multitargeted activities, whereas conventional chemotherapeutic agents only have a single target and cannot be used safely [19, 20].

The biochemical results were also supported by histopathological observations which indicated severe neoplastic changes in DMBA control rats and significant increase in tissue architecture after extract treatments and particularly in the combined group. The decrease of tumor severity in the treated animals can be directly related to the inhibition of oxidative stress because excess Oxidative stress is known to favor tumors, angiogenesis, and metastasis [21].

Finally, the current results indicate that concomitant therapy using extracts of Gloriosa superba and Glycyrrhiza glabra can be used to alleviate oxidative stress caused by DMBA by lowering lipid peroxidation and replenishing antioxidant potential. This combination of herbs has potential use as an adjunctive therapy in breast cancer due to the observed synergistic antioxidant and chemoprotective effects observed. More molecular and clinical studies should be conducted to explain the specific signaling pathways that are involved and confirm its translational promise.

Conclusion

To sum up, the current experiment has shown that concomitant intake of Gloriosa superba extract and Glycyrrhiza glabra extracts is a viable approach to reducing the DMBA-induced oxidative stress and repairing the antioxidant defence mechanisms in albino Wistar rats. This was due to the great decrease in lipid peroxidation and the increase in enzyme and non-enzyme antioxidants, which are focal in the free radical scavenging and defense against oxidative tissue damage, which are paramount in the prevention of cancer development. Evidence of synergistic effects of combined herbal therapy indicates that the phytochemical interactions can increase the effectiveness of therapy by controlling several oxidative and molecular pathways leading to carcinogenesis. The combined extracts had antioxidant restoration similar to that of paclitaxel when compared to individual treatments, indicating that they can be used as safe complementary agents in treating breast cancer. These results are solid experimental evidence probing the use of G. superba and G. glabra as prospective candidates in subsequent preclinical and clinical investigation. Further research must be conducted in trying to understand the exact molecular pathways of the synergistic effects observed such as gene expression of oxidative stress-related and apoptotic genes. These findings could be clinically translated to help in the development of effective and less toxic adjunct therapies of breast cancer based on plants.

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