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Combined Supplementation of Soy and Garlic modulate Biochemical Parameters of 7,12-dimethylbenz[α]anthracene Induced Mammary Cancer in Female *Albino* Rats

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Abstract: The study was designed to investigate the chemoprotective effect of Combined Supplementation of soy and garlic on 7,12-dimethylbenz[α]anthrance (DMBA) induced mammary cancer in female *Albino* rats. Animals (eighty rats) where equally divided into four groups, (twenty rats each). Group I: each rat received 1 mL of 0.1% saline daily for twenty days. Group II: received 1 mL of 0.1% saline given orally once a day for twenty days after DMBA infusion (30 mg kg^{-1}) and these rats served as controls (cancer control) for groups III and IV. Group III: were post treated with garlic after Infusion with DMBA. Group IV: Treated with Combined Supplementation of Soy and Garlic after DMBA infusion. Biochemical measurement were carried out on liver tissues and serum of experimental animals. Circulating levels of lactate dehydrogenase (LDH), glutamate oxaloacetate transaminase (GOT) and glutamate pyrovate transaminase (GPT) were elevated, while the activities of glutathione-s-transferase (GST) and superoxide dismutase (SOD) and the levels of reduced glutathione (GSH) were reduced in liver tissues in DMBA infused rats as compared to normal. Combined Supplementation of Soy and Garlic treatment altered the above mentioned biochemical parameters towards normal values. Present findings indicate that combined supplementation of soy and garlic got more marked effect on DMBA infused rats as compared to a group of rats received only garlic treatment.

Key words: Dimethylbenz[α]anthracine (DMBA), mammary cancer, garlic, soy, liver function, antioxidant enzymes, protective effect

INTRODUCTION

There are conflicting reports on the effect of soy and its components on mammary carcinogenesis in adult female rats, mainly because of different rodent models that are used in chemoprevention studies (Constantinou *et al*., 2001), while Barnes (1997) reported that soy protein preparations containing isoflavonoid conjugates have chemopreventive activity in carcinogen-induced rat models of breast cancer. Khataibeh *et al*. (2006) reported the effect of garlic extract on DMBA induced mammary cancer in albino rats. The present study was undertaken to compare the tumor-preventative effects of Combined Supplementation of soy with garlic with only garlic treatment.

The importance of garlic (*Allium sativum*) was recognized many centuries ago in early Egyptian, Chinese and Indian civilizations as a herbal or traditional medicine, today in many parts of the world both for prophylaxis and for the cure of variety of diseases including acute and chronic infections, gastritis, dysentery, typhoid fever, cholera, tuberculosis, pneumonia, diabetes-mellitus, heart disease and hyper tension (Wargovich *et al*., 2006; Gilani and Rahman, 2005).

Prevention of cardiovascular disorders and retardation of hyperglycemia by and antiseptic activities of garlic have been documented by a number of researchers (Borek, 2006; Ahmad and Ahmed, 2006). One of the most important biological effects observed recently with garlic is prevention of cancer which is reported in various experimental systems with mouse and rats (Wargvich *et al*., 2006; Lin *et al*., 2006; Khataibeh *et al*., 2006). Diet is an important factor in the development of almost 40% of all human neoplasias (O'Hanlon, 2006; Kraunz *et al*., 2006). Epidemiological studies indicated that dietary factors influence the development of breast cancer and experimental analysis suggests that natural or synthetic constituents of diet can act as an anticancer

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agents to inhibit breast cancer (Wang *et al*., 2006; Veena *et al*., 2006; Garcia-Solis and Avceves, 2005). Genistein (5,7,4'-trihydroxyisoflavone), a flavonoid abundant in soy, shows an anticancer activities against breast cancer cells (Nakagawa *et al*., 2000). Constantinou *et al.* (2001) reported that daidzein and soy protein isolate (with normal or low levels of isoflavones) are effective inhibitors of DMBA-induced mammary tumors in adult rats.

In addition, Barnes (1995) reported that two-thirds of studies on the effect of genistein-containing soy materials in animal models of cancer, the risk of cancer (incidence, latency or tumor number) was significantly reduced. Genistein (5,7,4'-trihydroxyisoflavone), one of two major isoflavonoids in soy, has anti-proliferative effects on mitogen-stimulated cell growth of human breast cancer cells in culture and is a candidate for use in the prevention of breast cancer (Barnes, 1997). Barnes (1997) mentioned that, Soy protein preparations containing isoflavonoid conjugates have chemopreventive activity in carcinogen-induced rat models of breast cancer.

Garlic (*Allium sativum*), fresh garlic extracts, garlic compounds or synthetically prepared substitutes may be another food item that significantly affects human health (Leelarungrayub *et al*., 2006; Bunowes and VanHouten, 2006; Tattelman, 2005). Although not all epidemiologic studies support the theory that consumption of garlic reduces the risk of cancer (Dorant *et al*., 1993; Milner, 1996). Malekzadeh *et al.* (2005) and Bespalov *et al.* (2004) shown that breast cancer risk was shown to decrease as consumption of garlic increase. However, another study showed garlic supplement was not associated with breast cancer (Dorant *et al*., 1995). In contrast to epidemiologic studies, laboratory investigations have provided adequate evidence that garlic-containing substances inhibits a variety of chemically-induced tumors in animals (Xiao and Singh, 2006; Park *et al*., 2005; Khataibeh *et al*., 2006). Literature survey revealed that no study have been reported on the chemoprotective effect of combined supplementation of soy and garlic on 7,12-dimethylbenz[α]anthrance (DMBA) induced cancer. Therefore, the present study was initiated to investigate the chemoprotective effect of treatment of combined supplementation of Soy and Garlic on DMBA-induced mammary cancer in female *Albino* rats.

MATERIALS AND METHODS

We conducted this study from December 2005 to October 2006, in the Laboratories of Medical Technology Department, Applied Science University.

Eighty female Spraque-Dawley rats weighing approximately forty grams and 40±5 days old each, were randomly divided into four equal groups designated as group I, II, III and IV.

Group I (20 rats): In this group, each rat received 1 ml of 0.1% saline daily for twenty days, they were kept at laboratory conditions till the termination of the experiment. Group II (20 rats): One milliliter 0.1% saline were given orally once a day for twenty days after single dose (30 mg kg^{-1} body weight) infusion with DMBA. These rats served as control (cancer control) for groups III and IV.

Groups III (20 rats): One milliliter of garlic extract (25 g/100 mL in 0.1% saline) were administered orally once a day for twenty days after cancer induction with DMBA infusion.

Group IV (20 rats): Combined Supplementation of soy and garlic: One milliner of garlic extract (25 g/100 mL in 0.1% saline same dose as given to group III animals) and 1 mL of soy extract (20 g/100 mL in 0.1%saline) were administered orally once a day for twenty days after 24 h to an oral infusion of DMBA (30 mg kg^{-1} body weight).

All animals were given food and drinking water *ad libitum*: All the four different groups were sacrificed after hundred days of the commencement of the experiment. Blood was collected in tubes without anticoagulant and the separated serum samples were kept frozen at -30°C. Liver tissues were collected too and kept frozen with normal saline.

Serum samples were used for the assay of GOT, GPT, LDH, while liver tissues were subjected for the estimation of GST, SOD and total, free and protein bound GSH.

Throughout the study, student t-test was used for statistical analysis, a value of $p<0.05$ was considered significant difference.

RESULTS

DMBA induced mammary cancer in female rats: Groups II (cancerous groups) showed significance alteration in an above mentioned different biochemical parameters as compared to normal controlled group. The serum levels of GOT, GPT and LDH were significantly elevated ($p<0.001$) as compared to control rats (Table 1).

As compared to the normal control values, the activities of GST, SOD and the levels of total, free and protein bound GSH were significantly decreased ($p<0.001$) in liver tissues of DMBA treated rats (Table 2).

Effect of combined supplementation treatment with soy and garlic on DMBA induced cancer: The study was designed to determine the action of combined

Table 1: Effect of combined supplementation treatment with garlic and soy on serum LDH, GOT and GPT levels in DMBA induced cancerous rats

			DMBA induced cancer	
Parameters	Normal (10)	DMBA induced cancer (10)	Treatment with garlic only (10)	Combined supplementation (soy and garlic) (10)
LDH (U mL^{-1})	117.17±12.00	189.00±13.29	141.60±7.86	133.40±6.88
SGOT (IU mL^{-1})	13.55±1.867	49.26±1.581	56.06±1.03	55.94±1.74
SGPT (IU mL^{-1})	8.86±1.195	40.89±1.453	48.05±1.450	47.84±1.66

Table 2: The levels of GST and SOD in liver tissues of normal, DMBA induced cancer only, garlic treated and combined supplementation (soy and garlic) treated rats

			DMBA induced cancer	
Parameters	Normal (10)	DMBA induced cancer (10)	Treatment with garlic only (10)	Combined supplementation (soy and garlic) (10)
SOD (Units mg^{-1} tissues)	2.640±0.111	1.723±0.026	22.33±0.043	2.326±0.108
SGT (Units mg^{-1} protein)	169.300±1.440	109.300±0.732	151.580±0.639	156.200±0.970

Table 3: The liver tissue levels of total, free and protein bound GSH in normal, DMBA induced cancer and cancerous rats with garlic only and combined supplementation (soy and garlic) treated rats

			DMBA induced cancer	
Parameters	Normal (10)	DMBA induced cancer (10)	Treatment with garlic only (10)	Combined supplementation (soy and garlic) (10)
Total GSH (μmole min^{-1} g^{-1} of tissues)	8.613±0.264	6.047±0.245	7.265±0.094	7.323±0.112
Free GSH (μmole g^{-1} of tissues)	1.480±0.061	1.042±0.037	1.255±0.033	1.362±0.056
Protein bound GSH (μmole g^{-1} of tissues)	7.115±0.230	5.054±0.039	6.020±0.061	6.301±0.191

supplementation of soy and garlic on DMBA induced cancer in female rats. When animals were post treated with garlic after the induction of cancer with DMBA, the changes recorded in the above mentioned biochemical parameters were less marked than in untreated animals except in the activities of GOT and GPT in serum were further elevated (Table 1-3). Even though the cancer was developed but the conditions of rats were better than those garlic untreated DMBA infused cancerous rats.

Treatment of rats with combined supplementation of garlic and soy after DMBA infusion brought about changes in all above parameters to bring these more closer to the values in control animals as compared to only garlic treated rats, except in serum, the activities of GOT and GPT were further elevated as compared to DMBA infused rats (Table 1-3).

The effectiveness of combined supplementation of garlic and soy treatment is more marked on DMBA-induced cancer as compared to post treatment with garlic only.

DISCUSSION

Present findings, indicate that combined supplementation with garlic and soy has a remarkable an anti carcinogenic effect apparent in the alteration of the biochemical parameters (LDH, GSH, GST and SOD) towards normal values.

The efficacy of combined supplementation with garlic and soy was evaluated in terms of extent of reversion of mentioned biochemical parameters from untreated DMBA infused toward normal values. Thus the combined supplementation treatment with garlic and soy was found effective in preventing DMBA carcinogenesis.

The efficacy of various drugs or compounds on inhibition or promotion of experimental cancer was evaluated in terms of number of observed tumors per animal and the rate of tumor development, which have their own limitations (Kokoska *et al*., 1993; Dunson and Dinse, 2000). On the other hand, in the present study the effect of the indigenous drugs on DMBA induced mammary carcinogenesis is evaluated in terms of altered biochemical parameters in cancer.

Epidemiological studies have shown that ingestion of isoflavone-rich soy products is associated with a reduced risk for the development of breast cancer (Steiner *et al*., 2006). While Barnes (1995) reported that in only two-thirds of studies on the effect of genistein-containing soy materials in animal models of cancer, the risk of cancer (incidence, latency or tumor number) was significantly reduced. Asian women consuming a traditional diet high in soy have a low incidence of breast cancer, yet when they emigrate to the USA the second but not the first generation lose this protection (Fritz *et al*., 1998).

Potential protective dietary elements include tomatoes/lycopene, other carotenoids, cruciferous vegetables, vitamin E, selenium, fish/marine omega-3 fatty acids, soy, isoflavones and polyphenols Increases the evidence that supports the important role of nutrition in cancer prevention (Chan *et al*., 2005; Allred *et al*., 2004).

Genistein modulates the expression of glutathione s-transferases (GSTs) in human breast cells, exposure to

genistein significantly increased, GST catalytic activity and intracellular glutathione concentrations (Steiner *et al*., 2006).

Known tumor promoter on topical application depletes the reduced glutathione content (GSH) and down regulates the activities of its metabolizing enzyme, glutathione-s-transferase (GST) and the activities of antioxidant enzymes (Sultana *et al*., 2004). Steiner *et al*. (2006) reported that Genistein protects human mammary epithelial cells from several potent carcinogenic compounds by modulating the glutathione/glutathione s-transferase system conclude that soy isoflavones are potentially protective against TPA induced biochemical alterations (Sultana *et al*., 2004).

Chemical induction of mammary tumors in female rats has been used to determine that exposure of the mammary gland to soy isoflavones prior to tumor induction is protective against tumor formation and also, purified genistein delayed mammary tumor appearance in association with increased cell differentiation in mammary tissue in rats treated with 7, 12-dimethylbenz [a] anthracene (Allred, 2004; Lamartiniere *et al*., 2002).

Lamartiniere *et al*. (2002) concluded that dietary genistein protects against mammary and prostate cancers by regulating specific sex steroid receptors and growth factor signaling pathways. Due to the estrogenic properties of soy-derived isoflavones, many postmenopausal women are using these compounds as a natural alternative to hormone replacement therapy (Allred *et al*., 2004).

The preventive or curative effects of garlic residues in its water and oil soluble organo-sulfur components reported by Aggrawal and Shishodia (2006), which are shown to markedly inhibit tumor growth. The results of Amagase and Milner (1993), Dorai and Aggrawall (2004) and Gunadharrin *et al*. (2005) are mainly in agreement with our results.

To explain the mechanism of action of given course of treatment, the following explanations could be a possible answer. the combined action of these compounds seems to be mediated through alteration of neurohumoral and free radical metabolizing enzymes and thereby changing the levels of neurohumors and free radicals. The increase in glutathione level by garlic treatment could be due to the selenium present in garlic (Sundaram and Milner, 1996). Glutathione treatment (Rao *et al*., 2001; El-Bayoumi *et al*., 2003; Steele *et al*., 2002) and chemoprevention (Schwartz and Shklar, 1996; Rao *et al*., 2001) or increased levels of glutathione due to selenium treatment (Schwartz and Shklar, 1996) is shown to reduce tumor burden.

Moreover, the antioxidants are also shown to enhance the immune response in tumor (Schwartz *et al*., 1990). Similar to present findings the levels of glutathione and GST have been shown to be enhanced following consumption of garlic or sulfur compounds (Sumiyoshi and Wargovich, 1990). Selenium probably decreased the binding of DMBA metabolites to mammary cell DNA and thus reduce incidence of chemically induced tumor (Liu *et al*., 1991). Similarly, garlic as well because of the selenium content reduces the binding of DMBA metabolites to mammary cell DNA (Liu *et al*., 1992; Amagase and Milner, 1993). The dietary selenium is also reported to enhance the efficacy of garlic as an anti-carcinogenic agent (Peters *et al*., 2006). Garlic powder inhibits the incidence of 7, 12-dimethylbenz [a] anthracene (DMBA) induced mammary tumor. However, cancer prevention studies in preclinical models have not revealed any significant differences between the inorganic form of selenium and those naturally occurring forms of selenium (Rao *et al*., 2001; El-Bayoumy *et al*., 2003; Peters *et al*., 2006). The enhanced GST and SOD and reduced glutathione (GSH) levels after treatment with garlic extracts may help in management of H_2O_2 produced by macrophages in responses to altered immune system. The level of LDH, the tumor marker is also decreased towards normal values after garlic treatment (Sheen *et al*., 1999), showing a decreased lactate metabolism. Thus, combined supplementation with soy and garlic treatment both the immune and free radical metabolizing responses are enhanced and the condition of rats is improved, which is also evident by a revert in the level of GST and GSH and by a decrease in the levels of LDH towards normal after treatment, while a further increase in GOT and GPT levels was observed. Similar to our findings, Pale *et al*. (1995) has also reported that some clinical conditions induce increases in serum activities of LDH, GOT and GPT and after treatment the LDH reverted toward normal values with a slight increase in GOT and GPT levels. At the end of the experiment all of combined supplementation with soy and garlic and even with only garlic treated animals were still alive. Thus it can be concluded that combined treatment with soy and garlic preventive effect on promotion of DMBA carcinogenesis is more marked and because of garlic pharmacological safety, it can be used to prevent cancer and in combination with current cancer therapies (Dorai and Aggrawal, 2004), why not with using soy isoflavones compounds which are considered as a natural alternative to hormone replacement therapy (Allred *et al*., 2004). Further research can be done for elucidating the exact mechanism of action and identifying the most active compound in both garlic and soy those work together producing this marked anticarcinogenic effect.

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