

## Protective and Therapeutic Effect of Green Tea (*Camellia sinensis*) against Rat Prostate Cancer

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### ABSTRACT

*This investigation was conducted to evaluate the protective and therapeutic effect of green tea to ameliorate the deleterious effects of prostate cancer in rats. The obtained data revealed a significant elevation in tumor markers (PSA, TAP and PAP levels) after induction of cancer prostate in rats in comparison with the normal control one. Also, there was a significant decrease in total testosterone, free testosterone and DHEA-S concentrations, but the serum MDA level was increased significantly in rats with cancer prostate as compared with the corresponding levels in control rats. On the other hand, administration of green tea before or/and after induction of prostate cancer in rats led to a considerable improvement in the previous parameters but, their values did not revert to normal level. Any how, the results of the present investigation showed that the green tea when taken before and after induction of cancer prostate gave the prophylactic and therapeutic effects. The underlying mechanisms through which green tea counteracted cancer prostate were discussed.*

**Key words:** Green tea, Prostate cancer, Tumor markers, Rats.

### INTRODUCTION

Prostate cancer (PCa) is one of the biggest killers of men and is often referred to as the hidden cancer because it can develop without any obvious symptoms. It has become the second leading cause of related death<sup>(1,2)</sup>. It is a malignant tumor which was considered a major cause of morbidity and mortality in men<sup>(3)</sup>. It is therefore necessary to forward efforts to diagnose and manage that disease early through developing novel approaches for its diagnosis, prevention and treatment.

Chemoprevention involving the use of natural agents to prevent or reverse the process of carcinogenesis could be an effective approach to reduce the progression of PCa<sup>(4)</sup>. Development of effective chemopreventive and agents against PCa in human, however, requires conclusive evidence of their efficacy in animal models that closely emulate human disease and possess surrogate endpoint biomarkers for rapid evaluation of chemopreventive and/or therapeutic agents<sup>(5)</sup>.

Tea polyphenols have been proposed as potential

chemopreventive agents<sup>(1,6,7)</sup>. Both green and black tea and their constituents have been extensively studied both *in vitro* and in animal models of carcinogenesis<sup>(7,8)</sup>. Green tea is derived from the plant *Camellia sinensis*, which is widely consumed all over the world<sup>(5)</sup>. It is chemically characterized by the presence of large amount of polyphenolic compounds known as catechins including epicatechin gallate (ECG), epicatechin (EC), epigallocatechin 3-gallate (EGCG), and epigallocatechin (EGC)<sup>(9)</sup>.

The role of tea in cancer prevention is supported by results from a large number of studies in animal models carried out over more than a decade<sup>(9,10)</sup>. Using the transgenic adenocarcinoma mouse prostate model of prostate carcinogenesis, it was demonstrated that oral consumption of 0.1% of green tea polyphenols decreased tumor incidence by 65%<sup>(1,6,11)</sup>.

Based on the standing of animal models of carcinogenesis and the bioavailability of the tea polyphenol, the present article was planned to explain the potential relevance of these models to cancer protection in rats.

## MATERIALS & METHODS

Fifty adult male albino rats (*Rattus rattus*) at 8 weeks of age were obtained from the Animal House of Nuclear Research Center, Inshas, Egypt. They were maintained in plastic cages at 23°C, housed in a well ventilated animal house and kept under the same managerial and environmental conditions. The

animals were fed to appetite on a standard laboratory animal diet according to the National Research Council (NRC)<sup>(12)</sup>. Deionized water was available all time.

Rats were divided randomly into five equal groups (ten for each). Rats of the first group (negative control) were injected subcutaneously with 500µl of physiological saline (0.9% Na Cl) daily for 8 weeks. Members of the second group (positive control) received orally 50 mg cyproterone acetate (Sigma Chem. Co., St. Louis, Mo, USA)/kg body weight daily for 21 consecutive days. Cyproterone acetate inhibits androgen secretion from the testis, thereby causing atrophy of prostatic epithelial cells. Starting on the day after the last injection of cyproterone acetate, rats received s.c. injections of 100 mg testosterone propionate (Sigma Chem. Co., St. Louis, Mo, USA)/kg body weight daily for another 21 days. That sequence of antiandrogen treatment followed by androgen treatment synchronizes and stimulates cell proliferation in the prostate and thereby maximizes neoplastic development in response to a single dose of chemical carcinogen<sup>(13)</sup>. Twenty four hours after the last dose of testosterone propionate, rats received 50 mg N-methyl-N-nitrosurea (MNU) (Sigma Chem. Co., St. Louis, Mo, USA) dissolved in sterile saline (pH 5.0)/kg body weight as a single i.v injection<sup>(14)</sup>. After induction of cancer prostate, blood samples were withdrawn from tail vein of rats and PSA was assayed in order to determine the incidence of prostate cancer. Rats of the third group received green tea as a drinking

water for 8 weeks before induction of prostate cancer by the same previous method. Green tea solution was prepared freshly every day as follow, 5 g of commercial green tea (Arab Co. for Pharm. and Medicinal Plants (MEPACO), Inshas, Egypt) were boiled in 100 ml boiling water for five minutes, allowed to stand at room temperature an hour before use. In the fourth group prostate cancer was induced firstly by previous method then green tea was administered in the same dose for 8 weeks. The last group received green tea four weeks before and four weeks after prostate cancer induction. At the end of the experimental period (8 weeks), rats were scarified by decapitation and the blood samples were collected from each group of the rats in clean dry test tubes and sera were separated and stored frozen under -20°C until analysis.

Serum total acid phosphatase (TAP) activity was determined kinetically using commercial kits (Bio Merieux Co., Mary-L-Eolilie, Chorbouneries, Les- Brain, France)<sup>(15)</sup>. Prostatic acid phosphatase (PAP) activity was assessed by ELISA using commercial kits (IBL-Gesellschaft, Hamburg, Co., Germany)<sup>(16)</sup>. Testosterone<sup>(17)</sup>, free testosterone<sup>(18)</sup> and dehydroepiandrosteron sulfate (DHEA-S)<sup>(19)</sup>, prostatic specific antigen (PSA)<sup>(20,21)</sup> levels were estimated by radioimmunoassay (RIA) using solid phase system. The kits were purchased from Diagnostic Product Corporation (DPC) USA. Serum malondialdehyde (MDA)<sup>(22)</sup> was determined by ELISA technique

using commercial kit (Cayman Chem. Co., USA).

All data were statistically analyzed using one way analysis of variance (ANOVA) followed by Duncan's multiple range test according to *Snedecor and Cochran*<sup>(23)</sup> using a computer program (Costate).

## RESULTS & DISCUSSION

The incidence of prostate tumors was reported to increase exponentially with age including benign prostatic hyperplasia, which tends to occur in the transitional zone and adenocarcinoma, which arises mainly in the peripheral zone<sup>(23)</sup>. Cancer is a fermentative disease caused by a compromised robust oxidative mechanism, giving uncontrolled cellular growth<sup>(25,26)</sup>.

In the current study, it is obvious that rats treated with N-methyl-N-nitrosurea in the presence of cyproterone acetate an inhibitor of androgen secretion and testosterone propionate as stimulator of cell proliferation in the prostate, showed a significant ( $P < 0.05$ ) elevation in the activity of TAP and PAP beside the levels of PSA and MDA in serum as compared to negative control one (Table 1). PSA is a specific tumor marker for prostate carcinoma, thus these results are anticipated and promoted to the occurrence of prostate cancer. *Ruddon*<sup>(27)</sup> reported that the level of PSA in serum is liable to detection if there is a tumor in the prostate. Many authors attributed the elevation in the tumor marker level due to the elevation of free radical production, lipid peroxidation, DNA

damage, mutation in DNA, abnormalities of gene sequence and disturbance in the cytochrome P450<sup>(1,2,28)</sup>. TAP and PAP leaks into the serum from the damaged prostate gland and elevation in its activity suggest the presence of metastatic prostatic carcinoma or at least prostatic damage as the level of increased activity depends upon the size of lesion<sup>(29)</sup>. These results are in harmony with those obtained by *Heibashy and Badie-Bakshwan*<sup>(30)</sup>.

It has been postulated that carcinogen may increase tissue oxidative stress with accelerated lipid peroxidation which subsequently induces DNA damage<sup>(29,31)</sup> or synthesis of prostaglandins and leukotrienes that stimulate prostate cancer cell proliferation<sup>(32)</sup>, that could explain the elevated MDA level in prostate cancer group of the current study (Table. 1). As, lipolysis of stored fat releases glycerol and fatty acid oxidation of which are increased in cancer patients<sup>(33)</sup>. Also, *Ruddon*<sup>(27)</sup> reported that tumor cells are found to have abnormal activities of antioxidant enzymes and this explain the elevated level of MDA. As well, *Heibashy*<sup>(28)</sup> found that tumor cells are low in activities of SOD and catalase.

Dehydroepiandrosterone (3 beta-hydroxy-5-androstene-17 one; DHEA) and its conjugates are abundant circulating steroids that originate largely from the adrenal cortex and to a lesser extent by the testes and ovaries. It is a precursor in the body for synthesis of testosterone, estradiol and a number of other steroid hormones<sup>(34)</sup>. DHEA and DHEA-S have shown protection against tumors by blocking carcinogen-induced cell

transformation and depressing the mitogenic effects of carcinogens<sup>(35)</sup>, also they were shown to inhibit prostate cancer induction in rats<sup>(36)</sup>. In the present work, rats with prostate cancer exhibited lower level of DHEA-S corresponding to higher levels of PSA, PAP, TAP and MDA (Table. 1). These results may explain the oxidative stress that, can play a major role in induction of prostate cancer. Moreover, DHEA-S is able to inhibit certain enzymes involved in the formation of free radicals by increment the levels of reduced glutathione<sup>(3)</sup> and enhancement of the activity of superoxide dismutase, glutathione peroxidase and catalase<sup>(34)</sup>. Also, DHEA-S reduces the lipid peroxidation level by preserving the cellular reduced glutathione<sup>(3)</sup>. Another study found that, DHEA may also be effective in enhancing the function of the immune system, which may play a role in cancer defense<sup>(37)</sup>.

In relation to reproductive performance, the obtained data showed a significant ( $P < 0.05$ ) reduction in total testosterone and free testosterone in rats with cancer prostate group (positive control) when compared to negative control one. These results may be attributed to either the conversion of testosterone to dihydrotestosterone (DHT) which is an important factor in the development of prostate cancer as it stimulates the growth and proliferation of cancerous prostate cells and therefore is the primary fuel for the growth of prostate cancer<sup>(14,38)</sup>, or may be due to the negative feedback caused by injected testosterone.

The obtained data in (Table. 1) showed a significant improvement in prostate tumor markers (PSA, TAP and PAP) levels as well as total testosterone, free testosterone, DHEA-S and MDA concentrations, when green tea were either given before cancer induction, after cancer induction and/or when taken before and after cancer induction when compared to rats with cancer prostate but all of these parameters did not return to their normal levels.

Green tea is particularly rich in polyphenols, including catechins, theaflavins and thearubigins, which are thought to contribute to the health benefits of tea. These polyphenols act as antioxidants *in vitro* by scavenging reactive oxygen and nitrogen species and chelate redox-active transition metal ions. They may also act indirectly as antioxidants through **I**) inhibition of the redox-sensitive transcription factors, nuclear factor- $\beta$  and activator protein-1; **II**) inhibition of "pro-oxidant" enzymes, such as inducible nitric oxide synthase, lipoxygenases, cyclooxygenases and xanthine oxidase; and **III**) induction of phase II and antioxidant enzymes, such as glutathione S-transferases and superoxide dismutases<sup>(39)</sup>.

The results of the present study showed that administration of green tea may have chemopreventive effect on prostate cancer. The most interesting point observed in the current investigation is the improvement in all determined parameters as a result of green tea administration. These results are in parallel with the results of previous study which mentioned that, the polyphenols present in green tea help

to prevent the spread of prostate cancer by targeting molecular pathways that shut down the proliferation and spread of tumor cells, as well as inhibiting the growth of tumor nurturing blood vessels<sup>(40)</sup>. These results may be due the role of green tea polyphenols (GTP) in modulating the insulin-like growth factor-1 (IGF-1), by reducing its levels or by increasing the levels of one of the binding proteins for IGF-1. This explanation bears a significance in light of studies that indicated an increase in the levels of IGF-1 which associated with increased risk of several cancers, such as prostate, breast, lung and colon. Moreover, GTP also caused a reduction in the expression of proteins known to be associated with the metastatic spread of cancer cells, as it inhibited the level of urokinase plasminogen activator as well as matrix metalloproteinases 2 and 9, cellular molecules linked to the metastasis. GTP contributed to minimize tumor development by governing the amount of vascular endothelial growth factor (VEGF) in the serum of the prostate cancer mouse model. The reduction of VEGF may result from GTP-induced suppression of IGF-1 levels. VEGF acts to recruit and develop new blood vessels that carry nutrients to developing tumors. By reducing the amount of VEGF, GTP works to minimize nutrients flowing and supporting tumor growth<sup>(40)</sup>.

Furthermore, the protective effect of GTP may be due to its blockage effect on the production of oxygen free radicals derived during carcinogenesis, enhancement of the levels of antioxidants defense

enzymes system by increasing the activities of some enzymes which convert the oxidized molecules to their reduced form<sup>(39)</sup>. *In vivo*, some studies have shown that, catechins are hypothesized to help protection against ROS by increasing total plasma antioxidant activity<sup>(41,42)</sup>. So, the decrement in the level of MDA shown in prostate cancer rats after treated with green tea (Table 1), may be attributed to catechins present in the tea which have a direct or indirect antioxidant effect<sup>(41,43)</sup>. Also, GTP exhibit modifying influence on the protein phosphorylation process<sup>(44)</sup> and following catalytic activities of many enzymes especially the oxidant ones<sup>(45)</sup>.

The tea polyphenols consist of strong metal ion chelators such as iron and copper which are required for generation of reactive oxygen radicals by means of Benton and Haber Weiss reactions<sup>(46)</sup>. Moreover, oral feeding of green tea leaves to rats resulted in enhanced SOD activity in serum and catalase activity in liver and an increased concentration of glutathione in the liver<sup>(47)</sup>. Thus, antioxidants present in green tea could contribute to the preventive effect on cancer<sup>(48)</sup>.

Interaction of tea flavonoid with pro-carcinogens plays a prominent role of the beneficial effects of tea against cancer initiation. *Masuda et al.*<sup>(49)</sup> examined the influence of EGCG and ECG on protein kinase activator, EGCG blocks the interaction between proteins and ligands while, both EGCG and ECG inhibit the gap functional intracellular communication caused by tumor promoters. Thus, tea polyphenol can interact with enzymatic defense

mechanisms in cells and contribute to cancer prevention at the early stage of carcinogenesis<sup>(11,49,50,51)</sup>.

Flavonoids present in tea can also exert a protective effect on cancer promotion. They maintain normal growth by blocking the activation of an oncogene activator protein (AP), maintain cell-cell communication and apoptosis of malfunctioning cells<sup>(48,52)</sup>. Prevention of cancer may be also studied through anti-mutagenic protective properties of green tea. EGCG has reactive oxygen species (ROS) scavenger property and the most potent antimutagenic agent protecting DNA scissions and nonenzymatic interception of superoxide anions. ECG emerges as the most potent enzymatic scavenger amongst the green tea polyphenol<sup>(11,53,54)</sup>.

Although, numerous health benefits have been proposed for the consumption of tea, the effectiveness of tea as a cancer preventive agent in human remains unclear because animal models of carcinogenesis may be different from the human situation. Judging from the inhibitory activities of tea polyphenols observed in the present study in animal model, it is likely that there are multiple mechanisms by which tea constituents induce inhibitory effects against prostate cancer either as prophylactic and therapeutic agent. To this end information on the biotransformation, bioavailability and tissue level of theaflavins, EGCG, ECG and other tea constituent should be a vital goal for future mechanistic researches. Further studies are required to determine the best dosage and route by which tea constituents deliver to

certain organ. More detailed molecular cellular mechanism studies in animals and humans are needed because the results of the previous

researches will help to verify the effects of tea in humans by comparison with studies in animals.

**Table (1): Chemo protective effects of green tea on prostate cancer in rats**

Treatment Groups Parameters	Group I	Group II	Group III	Group IV	Group V
PSA (ng/ml)	0.152 ± 0.04 <sup>a</sup>	1.752 ± 0.23 <sup>b</sup>	1.416 ± 0.19 <sup>c</sup>	1.138 ± 0.24 <sup>d</sup>	0.639 ± 0.18 <sup>e</sup>
TAP activity (U/L)	1.974 ± 0.09 <sup>a</sup>	3.056 ± 0.17 <sup>b</sup>	2.754 ± 0.19 <sup>c</sup>	2.458 ± 0.19 <sup>d</sup>	2.249 ± 0.15 <sup>e</sup>
PAP activity (U/L)	0.642 ± 0.05 <sup>a</sup>	1.787 ± 0.023 <sup>b</sup>	1.493 ± 0.22 <sup>c</sup>	1.107 ± 0.16 <sup>d</sup>	0.899 ± 0.09 <sup>e</sup>
Testosterone (ng/ml)	1.827 ± 0.08 <sup>a</sup>	0.659 ± 0.07 <sup>b</sup>	0.881 ± 0.11 <sup>c</sup>	1.128 ± 0.08 <sup>d</sup>	1.367 ± 0.09 <sup>e</sup>
Free Testosterone (Pg/ml)	0.693 ± 0.01 <sup>a</sup>	0.181 ± 0.02 <sup>b</sup>	0.237 ± 0.03 <sup>c</sup>	0.416 ± 0.05 <sup>d</sup>	0.589 ± 0.02 <sup>e</sup>
DHEA-S (µg/dl)	260.17 ± 1.94 <sup>a</sup>	127.89 ± 1.46 <sup>b</sup>	151.46 ± 1.73 <sup>c</sup>	192.36 ± 1.62 <sup>d</sup>	227.13 ± 1.76 <sup>e</sup>
MDA (Um/dl)	0.132 ± 0.02 <sup>a</sup>	0.319 ± 0.09 <sup>b</sup>	0.271 ± 0.09 <sup>c</sup>	0.218 ± 0.08 <sup>d</sup>	0.194 ± 0.06 <sup>e</sup>

*a,b,c,d,e means in the same row with no common superscript are significantly different at (P<0.05).*

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## الدور الوقائي والعلاجي للشاي الاخضر ضد مرض سرطان البروستاتا في الجرذان

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اجريت هذه الدراسة لإلقاء الضوء على الدور الوقائي والعلاجي للفينولات المتعدده بالشاي الاخضر ضد مرض سرطان البروستاتا في الجرذان.  
أظهرت النتائج المتحصل عليها إن سرطان البروستاتا يتسبب في حدوث زيادة ذات قيمه احصائيه في مستويات كل من الفوسفاتاز الحمضي الكلي ، الفوسفاتاز الحمضي البروستاتي، انتيجين البروستاتا النوعي وثنائي الدهيدالمالون بينما يحدث انخفاضاً ذات قيمه احصائيه لمستويات كل من التستوستيرون الكلي والتستوستيرون الحر و الدهياس وذلك بالمقارنة بنتائج المجموعة الضابطة.  
وأوضحت أيضا نتائج الدراسة قدرة الشاي الاخضر في تحسين قيم جميع القياسات البيوكيميائية المتحصل عليها بالرغم من إنها لم تصل إلى نفس مستويات مثيلاتها في جرذان المجموعة الضابطة.  
و لوحظ ان التأثير العلاجى للشاي الاخضر عندما تم اعطاه قبل وبعد احداث السرطان افضل من التأثير الوقائى وعلى أي حال فنتائج هذا البحث أوضحت أن الشاي الاخضر بما يحتويه من مضادات الأكسدة يمتلك فوائد كامنة تسهم في تقليل خطر بعض قياسات الدم المصاحبة لمرض سرطان البروستاتا في الجرذان.  
وقد نوقشت النتائج وتم إلقاء الضوء على أسبابها المحتملة و لا بد من استمرار عمل الدراسات لمعرفة افضل جرعه و الوقت المناسب للوصول الي افضل النتائج.