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Antiangiogenic Activities of Cinnamon, Black and Green Tea Extracts on Experimentally Induced Breast Cancer in Rats

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ABSTRACT

Breast cancer is the most frequent malignancy in women and its metastatic state represent the second most common cause of mortality. Inhibition of angiogenesis is considered to be an important strategy for cancer therapy. The currently available antiangiogenic agents that are used for treatment of breast cancer have serious side effects limiting their chronic use. Therefore, the current study was designed to investigate and compare the antiangiogenic effects of natural food sources; cinnamon, green and black tea on experimentally induced breast cancer in rats using 7,12-dimethylbenz(a)anthracene (DMBA). Animals were randomly divided into eight groups of seven animals each: four healthy groups and four breast cancer groups induced by a single dose of (20 mg kg^{-1}) of DMBA dissolved in 1.0 mL corn oil. Both healthy and breast cancer groups were treated aqueous extract of cinnamon, black and green tea (100 mg kg^{-1} b.wt. in 1.0 mL distilled water), given for 45 successive days intragastrically. Serum levels of some angiogenic stimulators and inhibitors were estimated using ELISA assays. The results showed significant increases in the serum levels of VEGF, sVEGFR-1 and bFGF in untreated breast cancer group when compared with untreated healthy rats. Also, there was a significant decrease in the serum levels of VEGF, sVEGFR-1 and bFGF in the treated groups with plants extracts when compared with breast cancer control group. The results of the present study suggested that extracts of these plants have antiangiogenic protective activities and supports the hypothesis that these plants help in the prevention of breast cancer.

Key words: Angiogenesis, 7,12-dimethylbenz(a)anthracene, breast cancer, black tea, green tea, cinnamon, complementary medicine

INTRODUCTION

Breast cancer is the most frequent diagnosed cancer in females and its metastatic state represents the second leading cause of death (Desantis *et al*., 2011). Recently, American Cancer Society reported that 2, 30, 480 of women were diagnosed as new cases of breast cancer in the United States and 39, 520 died from breast cancer in 2011 (ACS, 2011). In developing countries, breast cancer is the most prevalent cancer in women, representing 23% of the total cancer cases and it is the most leading cause of cancer death representing 14% of the cancer mortality (Jemal *et al*., 2011). Mammary tumor is usually resistant to standard therapeutic procedures (Pasqualini, 2004). It is well known that cancer metastasis including breast cancer need several interdependent processes including uncontrolled growth of cancer cells, their invasion to surrounding tissues, their

migration and adhesion to the other organs of the human body. Also, tumor growth and metastasis require angiogenesis mechanism because new vessel formation is necessary to supply nutrients for tumor cellular proliferation (Price *et al*., 1997).

Angiogenesis, the formation of new vessels from preexisting vasculature, plays a prominent role in tumor growth and metastasis (Kerbel, 2006). Inhibition of angiogenesis is considered to be an important strategy for cancer therapy and could lead to the inhibition of cancer metastasis and would eventually further increase survival of breast cancer patients (Jiang *et al*., 2012). Angiogenesis is a complex process regulated by a balance between proangiogenic and antiangiogenic factors (Hanahan and Folkman, 1996). Some angiogenic stimulators includes Vascular Endothelial Growth Factor (VEGF), Vascular Endothelial Growth Factor Receptor-1 (VEGFR1), basic Fibroblast Growth Factor (bFGF) and Platelets Drived Growth Factor-2 (PDGF-2) and some angiogenic inhibitors include endostatin and angiostatin. Angiogenesis is viewed as an attractive therapeutic target for the development of novel anticancer agents and a variety of approaches to inhibit VEGF activity are being assessed in preclinical and clinical trials (Ferrara and Kerbel, 2005).

Some drugs developed for their anti-angiogenic actions have been approved by the United States Food and Drug Administration (FAD) for treatment of patients with specific types of cancer. However, serious side effects that have been associated with currently available antiangiogenic drugs, such as hypertension, bleeding and gastrointestinal perforation, limiting their chronic use (Kamba and McDonald, 2007). Consequently, it has been a renewed interest in identifying natural food sources potentially rich in angiogenic inhibitors, given the advantage of proven safety for human use (Albini *et al*., 2007). Additionally, consumption of a plant-based diet has been implicated in the prevention of cancer development and progression (Fang *et al*., 2007).

Dietary components play an important role in the pathogenesis and control of cancer growth (Singh and Fraser, 1998). Therefore, the use of dietary compounds for the prevention and therapy of cancer would be of major importance overcome adverse effects of therapeutic drugs (Sukhthankar *et al*., 2008). A variety of foods including Cinnamon powder (*Cinnamomum zeylanicum*) as well as green and black tea (*Camellia sinensis*) are rich in polyphenols that are proposed to have antiangiogenic activities (Sartippour *et al*., 2008).

Cinnamon zeylanicum, dry bark, is one of the most popular and oldest spices. The bark and leaves of cinnamon are often added to food preparations to improve taste and aroma. Cinnamon extracts contain several active components such as essential oils (cinnamic aldehyde and cinnamyl aldehyde), tannin, mucus and carbohydrates (Wijesekera, 1978). These components have various biological functions including anti-oxidant, antimicrobial, anti-inflammation, anti-diabetic effects (Kim *et al*., 2006) and anti-tumor activity (Youn *et al*., 2008). However, further studies are necessary to explain working mechanisms of active compounds that linked with anti-tumor activity (Kwon *et al*., 2009).

Tea, produced from the leaves of *Camellia sinensis,* is a popular beverage consumed since ancient times that provides health benefits and reduces the risk of several human diseases including cancer (Boehm *et al*., 2009). Next to water, tea is the most widely consumed drink worldwide and it is available in four different forms such as green, black, oolong and white tea depending on the used manufacturing process. Green tea is consumed primarily in China and Japan and most widely studied for its health benefits. The most active constituents of green tea are polyphenols (catechins), including epigallocatechin 3-gallate (EGCG), epigallocatechin, epicatechin-3-gallate (ECG) and epicatechin (Anderson *et al*., 2001; Siddiqui *et al*., 2006).

Some of meta-analysis reported an inverse association between green tea intake and breast cancer risk (Adhami *et al*., 2009) and the results for black tea were conflicting; an inverse

association between black tea and breast cancer were observed (Sun *et al*., 2006), another study referred to a significant positive association between black tea intake and risk of breast cancer (Larsson *et al*., 2009), whereas others observed no association (Tang *et al*., 2009).

The 7,12-Dimethylbenz(a)anthracene (DMBA), potent carcinogen, induced mammary carcinoma in the rat and it is a commonly used model for studies of the prevention and treatment of breast cancer (Anbuselvam *et al*., 2007).

Therefore, the present study aimed to investigate and compare the antiangiogenic activities of an aqueous extracts for pure dried powder of cinnamon as well as green and black tea on experimentally induced breast cancer in rats using oral administration of 7,12-dimethylbenz(a) anthracene (DMBA). Moreover, the current study examined the effects caused by consuming these plants in healthy rats.

MATERIALS AND METHODS

Chemicals: 7,12-dimethylbenz(a)anthracene (DMBA) was purchased from Sigma Chemical Company (St Louis, MO, USA). Pure dried powder of cinnamon as well green and black tea were purchased from a public market in Al-Hufof, KSA.

Plant extraction: Dried granules of Green Tea (GT), Black Tea (BT) and dried bark of cinnamon (CINM) were obtained from the market (1000 g of each) and ground to fine powder and macerated with 1000 mL of 80% methanol and water for 72 h with occasional stirring, further the extraction procedure is repeated for three times to obtain hydroalcoholic extracts and obtained extracts were filtered and concentrated using vacuum evaporator to obtain the solid residue. The extracts were labeled and final weights were noted, stored in plastic containers and refrigerated until further use (Rusak *et al*., 2008). Proper weight of the yield for each extract was dissolved in water and doses for animal treatment were prepared (100 mg kg^{-1} b.wt. in 1.0 mL distilled water) (Anbuselvam *et al*., 2007).

Animals: Fifty six female white Western rats weighing (140±5 g) were obtained from the College of Veterinary Medicine and Animal Resources, King Faisal University, Al-Hufof, KSA. The animals were housed in well ventilated large spacious polypropylene cages (7 animals in each cage) and had 12±1 h light and dark cycles at constant temperature 25°C throughout the experimental period. Animals were acclimatised to laboratory conditions for a period of one week before the commencement of the experiments. Animals received a balanced diet of commercially available pellet rat feed (Standard rodent food pellets, ARASCO, Riyadh, KSA) and distilled water. The standard rodent food pellets contain cereals, wheat-bran, soya, molasses, alfalfa, minerals and vitamins. The amount of crude proteins, fats and fibres in the food pellets are 13, 2 and 10%, respectively. All animals were humanely treated in accordance with the WHO guideline for animal care and the study design will approved by the King Faisal University Research Ethics Committee.

Induction of mammary carcinoma: Mammary tumor was induced by oral administration of a single dose of (20 mg kg^{-1}) of 7,12-dimethylbenz(a)anthracene (DMBA) dissolved in 1.0 mL corn oil (Barros *et al*., 2004). Forty-five days after DMBA administration, all the experimental animals were sacrificed according to the method of Anbuselvam *et al*. (2007).

Experimental design and treatment schedule: Animals were randomly divided into 8 groups of seven animals each: four healthy groups and four breast cancer groups. In healthy groups, rats

were treated with saline and received orally 1.0 mL distilled water (healthy control group), cinnamon extract (100 mg kg^{-1} b.wt. in 1.0 mL distilled water), black tea extract (100 mg kg^{-1} b.wt. in 1.0 mL distilled water) and green tea extract (100 mg kg^{-1} b.wt. in 1.0 mL distilled water) given for 45 successive days intragastrically (Anbuselvam *et al*., 2007).

In breast cancer groups, the first group of rats were orally treated a single dose of 20 mg of DMBA dissolved in 1.0 mL corn oil, followed by 1.0 mL of distilled water (DMBA control group), the second group were orally treated a single dose of 20 mg of DMBA dissolved in 1.0 mL corn oil, followed by cinnamon extract (100 mg kg^{-1} b.wt. in 1.0 mL distilled water), the third group were orally treated a single dose of 20 mg of DMBA dissolved in 1.0 mL corn oil, followed by black tea aqueous extract (100 mg kg^{-1} b.wt. in 1.0 mL distilled water) and the last group were orally treated a single dose of 20 mg of DMBA dissolved in 1.0 mL corn oil, followed by green tea aqueous extract (100 mg kg^{-1} b.wt. in 1.0 mL distilled water), given for 45 successive days.

Blood sampling: At the end of the experimental period, day 45, all the rats were anesthetized with diethyl ether and sacrificed by decapitation. Trunk blood was collected into clean dry polypropylene test tubes without EDTA. The blood samples were allowed to clot for 30 min at room temperature, then centrifuged for 10 minutes at 5000 rpm. Sera were separated and immediately stored at -40°C until used for biochemical analysis.

Biochemical analysis: Quantitative measurement of serum levels of some hormones and some of angiogenic and antiangiogenic indices were performed using a competitive enzyme immunoassay kits according to the manufacturer's recommendations. Rat prolactin kit was supplied by SPI-Biobertin pharma, 10 bis avenue Ampere F-78480 Montignyle Bretonneux, France (Catalog No. A05101), Rat progesterone and Rat estradiol kits were supplied by Cayman Chemical Company, 1180 E. Ellsworth Rd. Ann Arbor, Ml 48108, USA (Catalog No. 582601 and 582251, respectively), Rat VEGF and Rat PDGF-AB kits were supplied by Quantikine, R and D Systems, Inc. 614 McKinley Place NE Manneapolis, MN 55413, USA (Catalog No. RRV00 and MHD00, respectively), bFGF2, VEGFR1, endostatin and angiostatin kits were supplied by USCN, Life Science Inc.108 Zhuanyang Avenue, economic and Technological Development Zone, Wuhan 430056, R.P. China (Catalog No. E90551Ra, E91818Ra, E90542Ra and E91254Ra, respectively).

Statistical analysis: The data were presented as Mean±SE. Statistical analysis were performed with One-Way Analysis of Variance (ANOVA, Tukey's Multiple Comparison Test) for the significant interrelation between the various groups (Turner and Thayer, 2001), using GraphPad Prism version 4.00 for Windows, GraphPad software, San Diego, CA, USA. p-values of <0.05, <0.01 and <0.001 will be considered statistically significant, highly significant and very highly significant, respectively.

RESULTS

Table 1 showed effect of cinnamon, green and black tea on the serum levels of prolactin, estradiol and progesterone hormones in DMBA induced breast cancer groups compared to the normal healthy control. The results showed significant decreased serum levels of prolactin in Cinm, BT and GT treated breast cancer groups compared to non treated groups (p-values; <0.05, 0.01 and 0.05, respectively). Also, the data showed significant decreased serum levels of prolactin in BT treated normal healthy rats compared to non treated control group (p-values <0.05). In addition, the results showed significant decreased serum levels of estradiol in BT treated breast cancer group

Table 1: The serum levels of prolactin, estradiol and progesterone hormones in DMBA induced breast cancer groups compared to the normal healthy control

	Prolactin (ng mL^{-1})	Estradiol (pg mL^{-1})	Progesterone (ng mL^{-1})
Cont.	26.83±2.73	63.88±14.80	6.74±0.85
Cont.+Cinm	26.53±3.69	82.88±55.78	7.17±0.97
Cont.+BT	18.91±4.61*	72.88±10.25	9.54±0.33**
Cont.+GT	22.10±3.04	29.70±6.73*	8.06±1.18
Breast cancer (DMBA)	32.69±2.35*	41.21±15.16	7.51±1.23
DMBA+Cinm	24.97±2.94†	53.71±20.66	4.52±1.26†
DMBA+BT	22.24±2.40††	18.87±3.00***†	6.64±0.83**
DMBA+GT	21.13±5.16†	28.35±7.00	9.22±1.10

DMBA: 7,12-dimethylbenz(a)anthracene, Cont.: Control, Cinm: Cinnamon, BT: Black tea, GT: Green tea, Values are Mean±SE, significantly different from that of the normal healthy control group at *p<0.05, **p<0.01, ***p<0.001, Value are significantly different from breast cancer group which received DMBA at †p<0.05, ††p<0.01, †††p<0.001

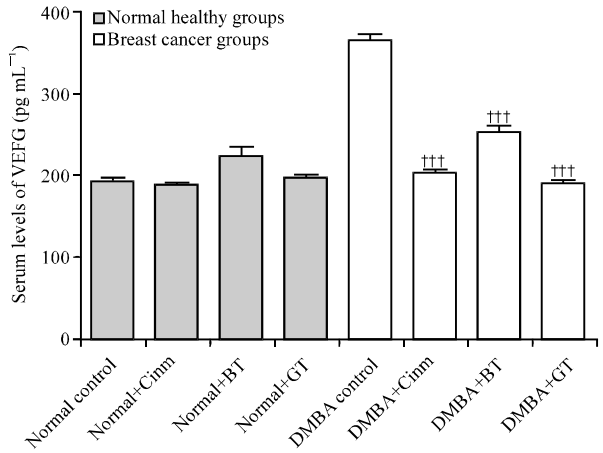

Fig. 1: Effect of cinnamon, black and green tea extracts on serum levels of VEGF in different groups of both breast cancer and normal healthy rats. VEGF: Vascular endothelial growth factor, DMBA: 7,12-dimethylbenz(a)anthracene, Cinm: Cinnamon, BT: Black tea, GT: Green tea. Values are Mean±SD, significantly different from that of the breast cancer group which received vehicle at †††p<0.001

compared to non treated groups of both breast cancer and normal healthy control (p-values; <0.05 and 0.001, respectively). Furthermore, decreased serum levels of progesterone was found in Cinm treated breast cancer group when compared to non treated breast cancer control (p<0.05).

The results showed a highly significant decrease in the serum levels of VEGF in breast cancer groups treated with cinnamon, black and green tea extracts when compared with DMBA control group (p<0.001). Also, green tea extract showed a significant decrease in the serum levels of VEGF in healthy rats when compared with DMBA control group (p<0.001) (Fig. 1).

The results showed a highly significant decrease in the serum levels of PDGF in breast cancer groups treated with cinnamon, black and green tea extracts when compared with both DMBA control group (p<0.001) and Normal healthy rats (p<0.01, 0.05 and 0.05, respectively) (Fig. 2).

The results showed a highly significant decrease in the serum levels of bFGF in breast cancer groups treated with cinnamon, black and green tea extracts when compared with DMBA control

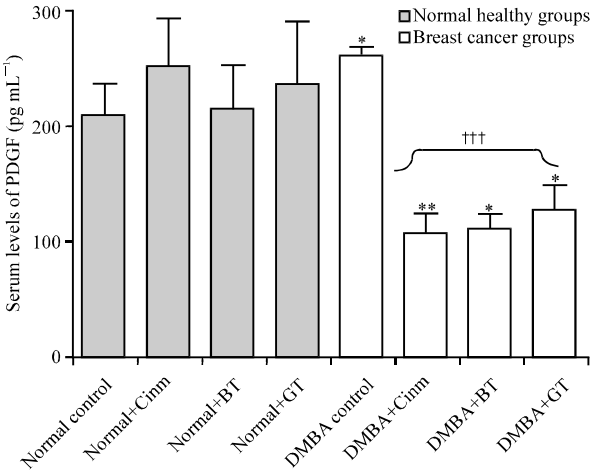

Fig. 2: Effect of cinnamon, black and green tea extracts on serum levels of PDGF in different groups of both breast cancer and normal healthy rats. PDGF: Platelets derived growth factor, DMBA: 7,12-dimethylbenz(a)anthracene, Cinm: Cinnamon, BT: Black tea, GT: Green tea. Values are Mean±SE, significantly different from that of the normal healthy control group at *p<0.05, **p<0.01, Values are significantly different from that of the breast cancer group which received vehicle at †††p<0.001

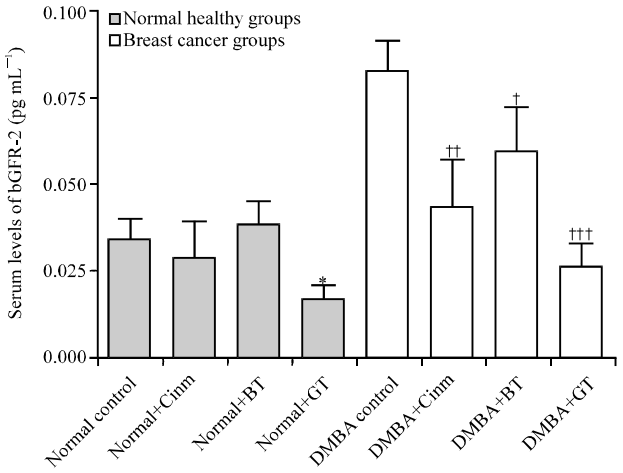

Fig. 3: Effect of cinnamon, black and green tea extracts on serum levels of bFGF in different groups of both breast cancer and normal healthy rats. bFGF: Basic fibroblast growth factor, DMBA: 7,12-dimethylbenz(a)anthracene, Cinm: Cinnamon, BT: Black tea, GT: Green tea, Values are Mean±SE, significantly different from that of the normal healthy control group at *p<0.05, Values are significantly different from that of the breast cancer group which received vehicle at †p<0.05, ††p<0.01 and †††p<0.001

group (p<0.01, <0.05 and <0.001, respectively). Also, significant decrease in the serum levels of bFGF were found in healthy group treated with green tea extract when compared with the normal control group (p<0.05) (Fig. 3).

The results showed a highly significant decrease in the serum levels of VEGFR1 in breast cancer groups treated with cinnamon, black and green tea extracts when compared with DMBA

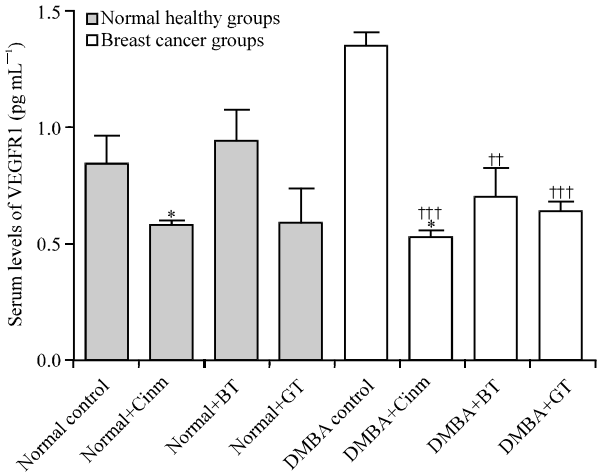

Fig. 4: Effect of cinnamon, black and green tea extracts on serum levels of VEGFR1 in different groups of both breast cancer and normal healthy rats, VEGFR1: Vascular endothelial growth factor receptor-1, DMBA: 7,12-dimethylbenz(a)anthracene, Cinm: Cinnamon, BT: Black tea, GT: Green tea, Values are Mean±SE, significantly different from that of the normal healthy control group at *p<0.05, Value are significantly different from that of the breast cancer group which received vehicle at ††p<0.01, †††p<0.001

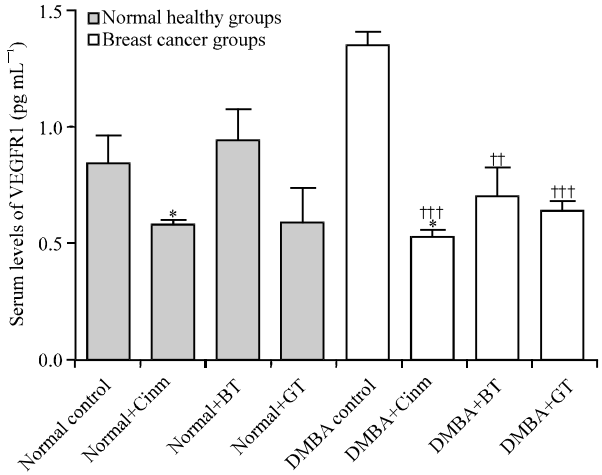

Fig. 5: Effect of cinnamon, black and green tea extracts on serum levels of endostatin in different groups of both breast cancer and normal healthy rats. DMBA: 7,12-dimethylbenz(a) anthracene, Cinm: Cinnamon, BT: Black tea, GT: Green tea, Values are Mean±SE, significantly different from that of the normal healthy control group at ***p<0.001, Values are significantly different from that of the breast cancer group which received vehicle at †††p<0.001

control group (p<0.001, 0.01 and 0.001, respectively). Also, significant decrease in the serum levels of VEGFR1 were found in breast cancer group treated with cinnamon extract when compared with normal healthy control group (p<0.05) (Fig. 4).

The results showed significant increase in the serum levels of endostatin in breast cancer group treated with green tea extracts when compared with both DMBA control group (p<0.001) and normal healthy rats (p<0.001). Also, a significant increase in the serum levels of endostatin were observed in normal rats treated with green tea compared with normal control (p<0.001) (Fig. 5).

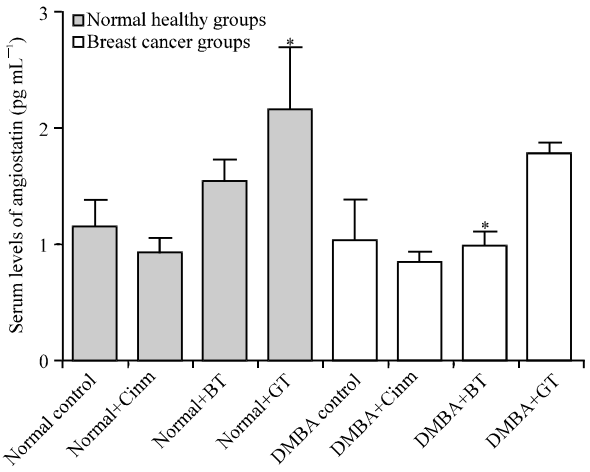

Fig. 6: Effect of cinnamon, black and green tea extracts on serum levels of Angiostatin in different groups of both breast cancer and normal healthy rats. DMBA: 7,12-dimethylbenz (a)anthracene, Cinm: Cinnamon, BT: Black tea, GT: Green tea, Values are Mean±SE, significantly different from that of the normal healthy control group at *$p<0.05$

The results showed significant increase in the serum levels of angiostatin in breast cancer group treated with green tea extracts when compared with DMBA control group ($p<0.001$). Also, a significant increase in the serum levels of angiostatin were observed in normal rats treated with green tea compared with normal control ($p<0.05$) (Fig. 6).

DISCUSSION

Breast cancer is the most prevalent malignancy in women and in its metastatic state, the second most common cause of mortality (Desantis *et al*., 2011). Angiogenesis is an important approach for cancer treatment and prevention and it is regulated by the balance between proangiogenic and antiangiogenic factors (Hanahan and Folkman, 1996). Consequently, it was reported that, when systemic concentrations of angiogenic inhibitors exceed those of stimulators, it could potentially prevent tumors from growing and metastasis to other organs (Lu *et al*., 2010).

It was established that Vascular Endothelial Growth Factor (VEGF) is one of the most critical and specific angiogenesis factors regulating normal physiological and tumor angiogenesis (Ferrara, 2002). It induces angiogenesis via binding to its two receptor tyrosine kinases expressed on endothelial cells, namely, Vascular Endothelial Growth Factor Receptor 1 (VEGFR1) (Flt-1) and Vascular Endothelial Growth Factor Receptor 2 (VEGFR2). VEGF is viewed as an attractive therapeutic target for the development of novel anticancer agents (Ferrara and Kerbel, 2005) and a variety of approaches to inhibit VEGF activity are currently being assessed in preclinical and clinical trials (Lu *et al*., 2010).

Many nutritional sources, contain certain phytochemicals, including polyphenols such as flavonoids, exert their protective effect from cancer via inhibition of tumor angiogenesis. Studying of the antiangiogenic activity of these nutritional sources is important not only for understanding the mechanism of the preventive effect but also for developing novel therapeutic interventions (Bellou *et al*., 2012). Polyphenols are abundant in a variety of foods including Cinnamon powder (*Cinnamomum zeylanicum*) as well as green and black tea (*Camellia sinensis*) (Sartippour *et al*., 2008). Therefore, the current study was designed to investigate and compare the effect of aqueous

extract of cinnamon as well as green and black tea on the balance between proangiogenic and antiangiogenic factors in experimentally induced breast cancer in rats using DMBA. In addition, the current study examined any effects caused by consuming these plants in healthy rats.

The results of the present study showed that Cinnamon extract decrease serum levels of proangiogenic factors VEGF, bFGF, PDGF and VFGFR1 in rat with breast cancer when compared with both DMBA control group (Fig. 1-4). But no significant differences in the serum levels of antiangiogenic factors; endostatin and angiostatin were observed in cinnamon treated rat with breast cancer when compared with both DMBA control and healthy groups (Fig. 5, 6). In addition, decreased serum levels of prolactin but no significant differences in the serum levels of progesterone and estradiol were found in cinnamon treated rats with breast cancer when compared with both DMBA and healthy controls (Table 1).

Similar findings were obtained by several recent studies on mouse melanoma suggesting that cinnamon extract has anticancer activity. Kwon *et al.* (2009) found that cinnamon extract strongly diminishes tumor growth, angiogenesis and vascularization by inhibiting of the expression of pro-angiogenic growth factors *in vitro* and by down-regulating pro-angiogenic factors and reducing levels of pro-angiogenic factors (EGF, VEGF-α, TGF-β and FGF) *in vivo*. The study revealed that antitumoral effects of cinnamon extract in mouse melanoma is mediated by modulation of angiogenesis and enhancement of cytotoxic activity of CD8+T cells in the tumor microenvironment which collectively leads to an active immune response to tumors. these results may be regarded as evidence of the potent anti-tumor activity of cinnamon together with a detailed mechanism of action (Kwon *et al.*, 2009).

Another study reported that cinnamon extract and specific characterized cinnamon extract components, type A procyanidin trimer and tetrameric procyanidins, effectively inhibited VEGFR2 kinase activity as well as VEGF signaling in endothelial cells. Also, the study revealed that Cinnamon extract inhibited various aspects of angiogenesis, including endothelial cell proliferation, migration and tube formation *in vitro*, sprout formation *ex vivo*, as well as tumor-induced blood vessel formation in mice. The study revealed that a novel biological function of cinnamon extract and suggested a possible molecular mechanism for its action (Lu *et al.*, 2010).

On another side of our study, black tea extract showed similar results to cinnamon extract targeting angiogenesis through down regulation of angiogenic stimulators but no significant effects on the serum levels of angiogenic inhibitors were observed. Green tea extract showed a significant increase in the serum levels of VEGF, sVEGFR-1 and bFGF in DMBA control group when compared with healthy rats supporting the fact that angiogenesis is an important mechanism used to promote growth of breast cancer (Kerbel, 2006). Also, a significant decrease in the serum levels of proangiogenic agents; VEGF, sVEGFR-1 and bFGF were observed in treated rat with breast cancer when compared with both DMBA control and healthy groups (Fig. 1-4). Furthermore, inversed effect were observed on the serum levels of angiogenic inhibitors; endostatin and angiostatin (Fig. 5, 6). In addition, significant positive correlations were found between VEGF and sVEGFR-1 in green tea treated groups ($r = 0.907$, $p<0.001$ and $r = 0.762$, $p<0.001$, respectively) suggesting that the increased VEGF concentrations observed in breast cancer may be due to an excessive production of the sVEGFR-1.

The antitumor effects of green tea catechins have been studied in colorectal cancer at the cellular level and the catechins are reported to have a potential antiangiogenic activity through suppressing the expression of proangiogenic factors such as VEGF and bFGF in colorectal cancer cells which could account for reduced angiogenesis and hence hamper tumor growth and metastasis

(Singh and Fraser, 1998). The study investigated the molecular mechanism involved in the suppression of bFGF by tea catechins and found that this occurred specifically through posttranslational modification. They also examined the transcriptional regulation of bFGF by catechins but they could not identify any changes in mRNA level or mRNA stability in the presence of these catechins in LoVo cells. Thus, posttranslational regulation of bFGF by catechins may fully account for the catechins -induced bFGF suppression. Another study reported that green tea may exert beneficial effects on breast carcinogenesis through inhibition of estrogen alone or in combination with other estrogen-inhibiting factors (Yuan *et al*., 2011). In the same direction, recent review on clinical studies critically assessed association between green tea consumption and the risk of cancer incidence and mortality (Thakur *et al*., 2012).

The current study hypothesized that consumption of green tea prior to clinical cancer onset was significantly associated with improved prognosis breast cancer and this association may be related to a modifying effect of green tea on angiogenesis of the cancer. This hypothesis was supported by another study reported the effects of Polyphenols treatment on growth and invasion in a breast carcinoma cell line resistant to tamoxifen (MCF-7Tam) and parental MCF-7 (Farabegoli *et al*., 2010).

Conversely, some studies reported that black tea does not appear to have protective effects on breast cancer incidence and may increase risk of hormone-dependent tumors. These studies recommended that future research is needed to elucidate the interactive role of tea catechins and other dietary cancer-inhibitory compounds in mammary carcinogenesis in humans (Yuan *et al*., 2011).

In conclusion, the present study suggested that cinnamon, as well as black and green tea extract have antiangiogenic activities that may be attributed to presence of polyphenols that regarded as potent angiogenic inhibitors and supports the hypothesis that these plants have beneficial effects and help in the prevention of breast cancer. But, it is still not clear, the preventive action of extracts due to antiangiogenic activities polyphenols alone or combined action with antioxidant activities of other components.

Further studies are required to evaluate the natural balance between the proangiogenic and antiangiogenic factors in breast cancer on molecular levels to find and explain the exact signaling mechanism of these antiangiogenic activities for cinnamon as well as black green tea extract.

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