



## The use of pomegranate flower extract or oil to increase the effectiveness of tamoxifen in breast cancer

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### ABSTRACT

Breast cancer is a type of cancer with an increasing incidence. Side effects of tamoxifen (TAM) and resistance to TAM over time are important problems in breast cancer patients. Pomegranate contain isoflavones genistein and coumestrol both are natural estrogens are investigated in numerous studies for cope with TAM resistance.

**KEYWORDS:** tamoxifen resistance, pomegranate, isoflavones, genistein

### INTRODUCTION

Increasing exposures to xenoestrogens and estrogens from sources such as natural and plastic bottles have also increased the incidence of breast cancer in men. Breast cancer cells can be formed by the effect of increased estrogen due to factors such as contraceptive pills, hormone replacement therapy (HRT), high-fat diets or alcohol intake (1).

Pathologically, breast cancer is divided into 3 classes mainly luminal A and luminal B

basal-like and HER2-positive ones (2,3). Basal-like breast cancer is also considered as triple-negative breast cancer (TNBC) in some cases, because TNBC is characterized as lacking the expression of these three biomarkers (4).

85% of diagnosed breast cancers are classified as luminal type A with positive prognosis for estrogen and progesterone receptors (data collected in ONCOLOGY, 2008 National Breast Cancer Awareness month issue).

Although estrogen and progesterone receptors are positive in luminal type B, the course of breast cancer is more rapid and requires a multimodal approach to treatment. These patients are treated with surgery, chemotherapy and radiotherapy as needed, hormone therapy including Tamoxifen (TAM). Studies have shown that a 5-year use of tamoxifen for all breast cancers reduces the 1-year breast cancer death rate by 31%. Side effects of TAM and resistance to TAM over time are important problems in breast cancer patients (5).

Numerous studies have been conducted and are being conducted to prevent resistance to TAM, to increase its effectiveness, and to reduce side effects (6). A meta-analysis published which included 93 studies, about breast cancer were shown to evidence of a

protective effect of healthy dietary products especially in postmenopausal, hormone receptor-negative and positive women (7).

Epidemiological studies also showed that consumption of vegetables especially soy products and fruits are reducing the risk and recurrence rate therefore increasing to survival rate of breast cancer [8,9]. For this reason, some studies have been done with pomegranate (10,11). The antiproliferative, anti-angiogenic, anti-inflammatory and apoptotic effects of pomegranate were investigated (*Punica granatum*) in skin, prostate and breast cancer. Pomegranate seeds and flower oil contain isoflavones genistein and coumestrol both are natural estrogens (12). ER positive, TAM susceptible MCF-7 breast cancer when TAM is co-administered with pomegranate extract. When TAM (1  $\mu$ M) with PFEs (300  $\mu$ g / ml) were administered for 48 hours, was found to be more effective than given alone in MCF-7 breast tumor cells (13,14).

It was observed that increasing to cell proportions in the G0-G1 phase and apoptosis ( $P < 0.01$ ). A greater apoptotic effect was observed when PFE and TAM was applied together. It is used for treatment in TAM, early or advanced metastatic breast cancer (15).

It shows its effect by reducing the effect of estradiol increasing proliferation and Bcl-2 expression in breast cancer patients with positive estrogen receptors (16). Studies have shown that PFEs mimic the effect of TAM. Resistance to TAM reduces TAM activity (6). Studies show that PFEs can reduce TAM resistance. Although the mechanism of action of PFEs in reducing resistance is not fully known, studies show that PFEs reduce the molecular barriers responsible for resistance.

**CONCLUSION:** More work is needed on this subject. It is thought that the use of PFE together with TAM may provide significant

improvements in the treatment of breast cancer in the future.

## REFERENCES

- 1.Hilakivi-Clarke L, Cho E, Cabanes A, DeAssis S, Olivo S, Helferich W, Lippman ME, et al.. Dietary modulation of pregnancy estrogen levels and breast cancer risk among female rat offspring. *Clin Cancer Res.* 2002;8:3601–3610.
- 2.Reis JS, Pusztai L. Breast Cancer 2 Gene expression profiling in breast cancer: Classification, prognostication, and prediction. *Lancet.* 2011;378:1812–1823.
- 3.Perou CM, Borresen-Dale AL. Systems biology and genomics of breast cancer. *Cold Spring Harb. Perspect. Biol.* 2011;3 doi: 10.1101/cshperspect.a003293.
- 4.Hudis CA, Gianni L. Triple-negative breast cancer: An unmet medical need. *Oncologist.* 2011;161:1–11. doi: 10.1634/theoncologist.2011-S1-01.
- 5.Banerjee S, Kambhampati S, Haque I, Banerjee SK. Pomegranate sensitizes Tamoxifen action in ER- $\alpha$  positive breast cancer cells. *J Cell Commun Signal.* 2011 Dec; 5(4): 317–324.
- 6.Kumar R, Zhang H, Holm C, Vadlamudi RK, Landberg G, Rayala SK. Extranuclear coactivator signaling confers insensitivity to tamoxifen. *Clin Cancer Res.* 2009;15:4123–4130. doi: 10.1158/1078-0432.CCR-08-2347.
- 7.Grosso G., Bella F., Godos J., Sciacca S., Del Rio D., Ray S., et al. Possible role of diet in cancer: Systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. *Nutr. Rev.* 2017;75:405–419.
- 8.Farvid MS, Chen WY, Michels KB, Cho E, Willett WC, Eliassen AH. Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer: Population based cohort study. *BMJ Br. Med. J.* 2016;353 doi: 10.1136/bmj.i2343.

9. Kim MK, Kim JH, Nam SJ, Ryu S, Kong G. Dietary intake of soy protein and tofu in association with breast cancer risk based on a case-control study. *Nutr. Cancer.* 2008;60:568–576.
10. Toi M, Bando H, Ramachandran C, Melnick SJ, Imai A, Fife RS, et al. Preliminary studies on the anti-angiogenic potential of pomegranate fractions in vitro and in vivo. *Angiogenesis.* 2003;6:121–128.
11. Bell C, Hawthorne S. Ellagic acid, pomegranate and prostate cancer – a mini review. *J Pharm Pharmacol.* 2008;60:139–144.
12. Pantuck AJ, Zomorodian N, Belldegrun AS. Phase-II Study of pomegranate juice for men with prostate cancer and increasing PSA. *Curr Urol Rep.* 2006;7:7. doi: 10.1007/s11934-006-0047-4.
13. Hayes DF, Robertson JF. Overview and concepts of endocrine therapy. In: Robertson JF, Nicholson RI, Hayes DF, editors. *Endocrine therapy of breast cancer.* London: Martin Dunitz Ltd; 2002. pp. 3–10.
14. Taylor IW, Hodson PJ, Green MD, Sutherland RL. Effects of tamoxifen on cell cycle progression of synchronous MCF-7 human mammary carcinoma cells. *Cancer Res.* 1983;43:4007–4010.
15. Ali S, Coombes RC. Estrogen receptor alpha in human breast cancer: occurrence and significance. *J Mammary Gland Biol Neoplasia.* 2000;5:271–281.
16. Wang TT, Phang JM. Effects of estrogen on apoptotic pathways in human breast cancer cell line MCF-7. *Cancer Res.* 1995;55:2487–2489.