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Research Studies

Breast Cancer

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Breast Cancer

Globally, breast cancer represents one in four of all cases in women. According to a report by WHO, since 2008, worldwide breast cancer cases have increased by 20%! It is estimated that worldwide over 508,000 women died in 2011 due to breast cancer. In fact, breast cancer is the most commonly occurring cancer in women and the second most common cancer overall. There were over 2 million new cases in 2018. Currently, the average risk of a woman developing breast cancer sometime in her life is about 12 – 15%. This means there is a 1 in 8 chance she will develop breast cancer. Moreover in recent years, incidence rates have increased by 0.4% per year! Breast cancer is the second leading cause of cancer death in women. The chance that a woman will die from breast cancer is about 1 in 38 (about 2.6%).

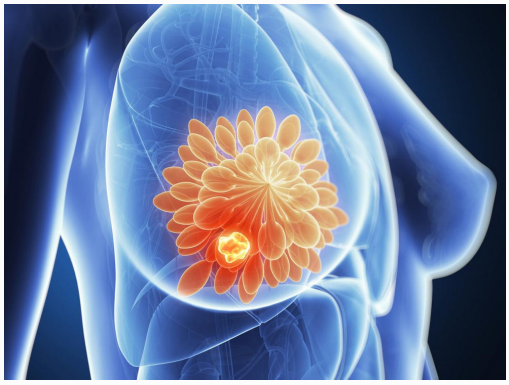
In the pursuit to fight cancer, researchers have discovered Tocotrienol which is supposed to exhibit anti-cancer activities. Several studies have been conducted over Annatto based Tocotrienol (DeltaGold – Eannatto). Several studies have been conducted on Tocotrienol for its effects against breast cancer like, 'miR-429 mediates Delta-Tocotrienol induced apoptosis in triple-negative breast cancer (TNBC) cells by targeting XIAP 'where the effects of Delta-Tocotrienol on exponentially growing TNBC cells, MDA_MB-231 and MDAMB-468 cells were observed. These cells are also known as human triple negative breast cancer cells which were treated in the presence of Delta-Tocotrienol (DeltaGold – Eannatto) for 24 hours, and the cell viability rate was measured using an MTT assay. It was observed that treatment with Delta-Tocotrienol inhibited the proliferation of MDA-MB-231 and MDA-MB-468 cells in a dose-dependent manner. Another study, 'Tocotrienols inhibit the growth of human breast cancer cells irrespective of estrogen receptor status' showed the potential anti – proliferative effects of Tocotrienols on the growth of both estrogen – responsive and estrogen – unresponsive (ER+) MCF7 human breast cancer cells and estrogen – unresponsive (ER-) MDA – MB – 231 human breast cancer cells.

"Study 1 - miR-429 mediates Delta-Tocotrienol induced apoptosis in triple-negative breast cancer (TNBC) cells by targeting XIAP"

The large number of etiological factors and the complexity of breast cancer pose challenges for prevention and treatment. Triple – negative breast cancer (TNBC) is histologically defined as an invasive carcinoma of the breast that lacks staining for estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor – 2 (HER2). TNBC is associated with high proliferative rates, early recurrence, and poor survival rates. Much effort has been spent on the study of the biological behavior of TNBC cells to develop effective treatment strategies.

MicroRNA (miRNAs) are small, non – coding RNAs of 19 – 25 nucleotides in length that are endogenously expressed in mammalian cells. miRNAs post – transcriptionally regulate gene expression by pairing with complementary nucleotide sequence in the 3' – UTRs of specific target mRNAs. miRNAs are involved in biological and pathological processes, including cell differentiation, proliferation, apoptosis, and metabolism. miR – 429, a member of the miR – 200 family of microRNAs, was reported to inhibit expression of transcriptional repressors ZEB1/δEF1 and SIP1/ZEB2 and regulate epithelial – mesenchymal transition. It is significantly down regulated in several cancers, including renal cell carcinoma and gastric cancer. Emerging evidence has shown that over – expression of miR – 429 can inhibit proliferation and induce apoptosis in human osteosarcoma cancer cell lines.

In this study, it was shown that miR – 429 was up regulated in TNBC cells treated with Delta – Tocotienol (DeltaGold – Eannatto). Inhibition of miR – 429 may partially rescue the apoptosis induced by Delta – Tocotienol (DeltaGold – Eannatto) in MDA – MB – 231 cells. It was also observed that the forced expression of miR – 429 was sufficient to lead to apoptosis inMDA – MB – 231 cells. Furthermore, it was identified that X – linked inhibitor of apoptosis protein (XIAP) as one of miR – 429's target genes. Human triple-negative breast cancer (TNBC) cells were seeded in 6 – well plates at a concentration of 2×104and cultured in medium without antibiotics for approximately 24 h before transfection. Cells were transiently transfected with miR – 429 precursor or inhibitor and negative control miRNA at a final concentration of 50 nM (precursor) or 100 nM (inhibitor) using Lipofectamine 2000 (Invitrogen, Carslbad, CA, USA) according to the manufacturer's protocol.



Result

1. Delta – Tocotrienol (DeltaGold – Eannatto) was observed to inhibit cell proliferation and induce apoptosis in TNBC cells.
2. miR mediated induction of apoptosis in TNBC cells treated with Delta – Tocotrienol.
3. Forced expression of miR – 429 induces apoptosis in TNBC cells via suppressing XIAP.

"Study 2 - Tocotrienols inhibit the growth of human breast cancer cells irrespective of estrogen receptor status."

Potential anti – proliferative effects of Tocotrienols on the growth of both estrogen – responsive and estrogen – unresponsive (ER+) MCF7 human breast cancer cells and estrogen – unresponsive (ER-) MDA – MB – 231 human breast cancer cells, and effects were compared with those of Alpha – Tocopherol (alpha T). The Tocotrienol – rich fraction (TRF) of palm oil inhibited growth of MCF7 cells in both the presence and absence of estradiol with a non – linear dose – response but such that complete suppression of growth was achieved at 8 microg/mL. MDA – MB – 231 cells were also inhibited by TRF but with a linear dose – response such that 20 microg/mL TRF was needed for complete growth suppression. Separation of the TRF into individual Tocotrienols revealed that all fractions could inhibit the growth of both ER+ and ER- and of ER+ cells in both the presence and absence of estradiol. However, the Gamma – and Delta – Tocotrienol fractions were the most inhibitory.

Complete inhibition of MCF& cell growth was achieved at 6 microg/mL of Gamma – Tocotrienol/Delta – Tocotrienol (Gamma – T3/Delta – T3) in the absence of estradiol and 10 microg/mL of Delta – Tocotrienol in the presence of estradiol, whereas complete suppression of MDA – MB – 231 cell growth was not achieved even at concentrations of 10 microg/mL of Delta – Tocotrienol. By contrats to these inhibitory effects of Tocotrienols, Alpha – Tocopherols had no inhibitory effect on MCF7 cell growth in either the presence or the absence of estradiol, nor on MDA – MB – 231 cell growth. These results confirm studies using other sub – lines of human breast cancer cells and demonstrate that Tocotrienols can exert direct inhibitory effects on the growth of breast cancer cells.

In searching for the mechanism in inhibition, studies of the effects of TRF on estrogen – regulated pS2 gene expression in MCF7 cells showed that Tocotrienols do not act via an estrogen receptor – mediated pathway and must therefore act differently from estrogen antagonists. Furthermore, Tocotrienols did not increase levels of levels of growth – inhibitory insulin – like growth factor binding proteins (IGFBP) in MCF7 cells, implying also a different mechanism from that proposed for retinoic acid inhibition of estrogen – responsive breast cancer cell growth. Inhibition of the growth of breast cancer cells by Tocotrienols could have important clinical implications not only because Tocotrienols are able to inhibit the growth of both ER+ and ER- phenotypes but also because ER+ cells could be growth – inhibited in the presence as well as in the absence of estradiol. Future clinical application of TRF could come from potential growth suppression of ER+ breast cancer cells otherwise resistant to growth inhibition by anti – estrogens and retinoic acid.

Summary

So why Tocotrienol?

- Antioxidants, especially Tocotrienol was observed to exhibit anti-cancer activity against breast cancer cells.
- Angiogenesis which is the process of formation of blood vessels in cancer cells like in your breast cancer. Tocotrienol promotes cancer cell death to a very great extent.
- Apoptosis is the programmed cell death which leads to the death of cancer cells. Tocotrienol induces apoptosis in breast cancer cells by increasing endoplasmic reticulum stress and autophagy thus helping in killing cancer cells.
- Cell Proliferation is the process by which cancer cells copy their DNA and divide into more cancer cells during mitosis thus lead to spreading cancer. According to several kinds of research, it has been observed Tocotrienols suppress the proliferation of breast cancer cells by altering the expression of oxidative stress modulatory enzymes GPX, SOD, NQO1, and NQO2.
- Chemoprevention and anti-cancer activity against breast cancer have been observed in Tocotrienols both in vitro and in vivo researches.
- Phenotypes of breast cancer cells, Estrogen-receptor-positive (ER+) and estrogen-receptor-negative (ER-) both were observed to be reduced by the action of Tocotrienol by inhibition of HMGCR activity.
- Lipid Raft Disruption is induced by Gamma-Tocotrienol which encourages anti-proliferative activity in breast cancer cells.
- K-Ras, H-Ras, and pERK expressions were observed to be inhibited by Gamma-Tocotrienol which inhibited mammary cancer cell growth.
- In Vitro (Procedure performed outside of a living organism) and In Vivo (Effects of an experiment in a living organism)studies of Tocotrienol have shown anti-cancer activities of Tocotrienol against breast cancer cells.
- Anti-Tumor effects on breast cancer have been observed by all kinds of Tocotrienols isoforms.

- Annatto-Tocotrienol which comprises of 90% of Delta-Tocotrienol and 10% of Gamma-Tocotrienol reportedly delayed the development of mammary tumor and reduced the number and size of the tumor via enhancing both apoptosis and senescent-like growth arrest in Her-2/neu transgenic mice.
- Cancer stem cell death has been observed by the action of Tocotrienols especially Delta – Tocotrienols (DeltaGold – Eannatto). Even after chemotherapies, radiation and surgeries, there are stem cells of those cancerous tissues left revolving in your body which can lead to your cancer coming back. Henceforth, their death is very necessary and Tocotrienols have been observed to kill cancer stem cells.

Dosage

- Under the study, 200-900 mg/day of Tocotrienols were used to treat breast cancer cells and no adverse effects were observed and the death of breast cancer cells was witnessed.
- Substances that complement Tocotrienol for cancer include Vitamins C, D, Selenium, B complex.

Why Tocotrienol and Not Tocopherol?

- Tocopherol, the enemy of Tocotrienol: Earlier, in a breast cancer clinical study a mixture of Tocotrienol and Tocopherol was used but then Tocopherol was replaced by Gamma-Tocotrienol because it witnessed interference of Tocopherol in the functioning of Tocotrienol! Tocopherol has been observed to attenuate cancer inhibition, inhibits absorption, reduces adipose storage, and compromises cholesterol and triglyceride reduction.
- Tocopherol, the antagonist in breast cancer treatment: Alpha-Tocopherolnot only interferedwith the functioning of Tocotrienol but also antagonized DHA's anticancer properties while Gamma-Tocotrienol enhanced DHA's effect.
- Tocotrienol, the protector of State: Tocotrienol has more mobility than Tocopherol due to its small structure so it can cover a larger area targeting more number of breast cancer cells.
- Small structure and less molecular weight: The higher anti-oxidant activity of Tocotrienols is due to their small structure and less molecular weight which assist in their integration of the cell, unlike Tocopherols.
- Absorption: As compared to Tocopherols, Tocotrienols absorb better in the body and Tocopherols have been observed to prevent absorption of Tocotrienols

References:

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- Tocotrienols: The Promising Analogues of Vitamin Efor Cancer Therapeutics https://doi.org/10.1016/j.phrs.2018.02.017
- miR-429 mediates Delta-Tocotrienol induced apoptosis in triple-negative breast cancer (TNBC) cells by targeting XIAP
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4658948/
- Tocotrienols inhibit the growth of human breast cancer cells irrespective of estrogen receptor status
- https://www.ncbi.nlm.nih.gov/pubmed/9625593

Note:

1. To read studies in detail, follow the references and links given.
2. The dosages given must not be taken as the advice of a medical practitioner. Consult your physician for the optimum dosage to be consumed.