

Tocotrienols in Female Reproductive Cancers: A Long Way to Go

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Received: 11 June 2018

Published: 21 June 2018

Keywords: *Vitamin E; Tocotrienols; Tocopherols; Anticancer*

Abstract

The discovery of vitamin E was first documented in 1922 through the finding of a particular ‘anti-sterility Substance-X’ that was necessary for reproduction. However, the trends in the continuing studies involving vitamin E have directed the interest on vitamin E on its antioxidant properties. The ability of vitamin E to act as an anticancer was only reported in 1990s, in which from then on many researches have been conducted to understand its mechanisms of actions against cancer cells. A lot of study reports were documented, including its effect as an anticancer against breast, cervix, colon, liver, lung, ovary, pancreas, prostate, skin and stomach cancers. From these reports, the studies particularly on female reproductive cancers such as breast cancer have been widely made known, but the studies on the ovarian and cervical cancers are limited. This paper intended to summarize on the available reports on the effects of vitamin E on ovarian and cervical cancers conducted *in vitro*, which could possibly be useful in studying its importance for future clinical use.

Vitamin E

Vitamin E, which was first discovered by Evans and Bishop in 1922, has been reported as a potential reproductive protectant. This was following the finding of a particular ‘anti-sterility factor X’ that was necessary for reproduction [1]. Since then, vitamin E becomes well-recognized as an important lipid-soluble

antioxidant [2-4]. Vitamin E contains two major substances, tocopherols (TOCs) and tocotrienols (TCTs). These substances are present in eight different homologs, namely α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol and δ -tocotrienol [5]. Earlier reports on the benefits of vitamin E were emphasized mainly on the effects of TOCs, particularly alpha-TOC (α -TOC), where it has been claimed and continuously reported as the most powerful lipid-soluble antioxidant [2,6-15].

During the earlier period of vitamin E researches, TCTs was not been studied as extensively as TOCs. However, there were few reports stated that α -TCT possesses better antioxidant properties than α -TOC [16,17] due to the unsaturated side chain of TCTs that allows for efficient penetration through better distribution on tissue membranes with saturated fatty layer [18]. The benefits of TCTs have become into the attention only during the late 1980s, when their cholesterol-lowering potential [19] and anticancer effects were published [20,21]. Since then, the benefits of TCTs especially as an anticancer have been extensively reported including its effects on breast [22-25], cervix, colon [26,27], liver [28,29], lung [30,31], ovary, pancreas [32,33], prostate [34,35], skin [36,37] and stomach cancers [38].

Analyses on the available reports on anticancer effects of vitamin E particularly on the cervical and ovarian cancers (female reproductive cancers other than breast cancer) are very limited with only a few reports are available, as shown in Table 1.

Types of Cancer Cell	Types of Vitamin E	Effects / Mechanism of Action	References
Cervix	α -TOC α -TOC acetate γ -TCT	α -TOC and γ -TCT induced apoptosis through enhanced expressions of p53, Bax and Caspase-3, and the activity of Caspase-3 in cervical carcinoma CaSki cell	[39]
	α -TOC α -TCT γ -TCT δ -TCT	TCTs demonstrated a dose-dependent and time-dependent induction of cell death through cell cycle arrest at G2/M phase (downregulation of cyclin D3, p16, and CDK6 expression) and inhibition of HeLa cell proliferation through the upregulation of IL-6	[40]
	α -TOC Palm-TRF	Palm-TRF exerted the antiproliferative effects in CaSki cells through downregulation of the MEK-2 and ERK-2 protein expression	[41]
	γ -TCT	γ -TCT inhibits the spherical cell growth of cervical cancer cells	[42]
	d-alpha tocopheryl acetate	d-alpha tocopheryl acetate suppressed endogenous telomerase activity in ovarian cancer cells	[43]
Ovary	Palm-TRF Cyclophosphamide (CPA)	Co-administration of TRF with CPA confers protection against apoptosis in ovaries from chemotherapy associated damage	[44]
	Palm-TRF Cyclophosphamide (CPA)	TRF administration reversed the abnormal folliculogenesis with accompanied reduced ovulation rate, follicular edema, increased vascularity and inflammatory cell infiltration induced by CPA	[45]

Conclusion

Vitamin E has been widely known to have the ability to prevent cell proliferations in cancer cells. The limited reports on the effects of vitamin E on cervical and ovarian cancers are impeding the possible potential of using vitamin E to treat these diseases. This demands more researches in future to understand the mechanisms of actions of vitamin E against these two types of cancer cells. With the available little evidences, this marks a long way to go to make use of the research findings in initiating the development of new vitamin E-based drugs that could be used therapeutically to fight against cervical and ovarian cancers in females.

Bibliography

1. Evans, H. M. & Bishop, K. S. (1922). On the existence of a hitherto unrecognized dietary factor essential for reproduction. *Science*, 56(1458), 650-651.
2. Tappel, A. L. (1962). Vitamin E as the biological lipid antioxidant. *Vitam Horm*, 20, 493-510.
3. Burton, G. W. & Ingold, K. U. (1986). Vitamin E application of the principles of physical organic chemistry to the exploration of its structure and function. *Acc Chem Res.*, 19(7), 194-201.
4. Esterbauer, H., Dieber-Rotheneder, M., Striegl, G. & Waeg, G. (1991). Role of vitamin E in preventing the oxidation of low density lipoprotein. *Am J Clin Nutr.*, 53(1 Suppl), 314S-321S.
5. IUPAC-IUB Joint Commission on Biochemical Nomenclature. (1982). Nomenclature of tocopherols and related compounds. (Recommendations 1981). *Eur J Biochem.*, 123(3), 473-475.
6. Tappel, A. L. & Zalkin, H. (1960). Inhibition of lipid peroxidation in microsomes by vitamin E. *Nature*, 185, 35.
7. Tappel, A. L. (1980). Vitamin E and selenium protection from *in vivo* lipid peroxidation. *Ann NY Acad Sci.*, 355, 18-31.
8. Dillard, C. J., Litov, R. E. & Tappel, A. L. (1978). Effects of dietary vitamin E, selenium, and polyunsaturated fats on *in vivo* lipid peroxidation in the rat as measured by pentane production. *Lipids*, 13(6), 396-402.
9. Dillard, C. J., Sagai, M. & Tappel, A. L. (1980). Respiratory pentane: A measure of *in vivo* lipid peroxidation applied to rats fed diets varying in polyunsaturated fats, vitamin E, and selenium and exposed to nitrogen dioxide. *Toxicol Lett.*, 6(4-5), 251-256.
10. Burton, G. W. & Ingold, K. U. (1981). Autoxidation of biological molecules. I. The antioxidant activity of vitamin E and related chain-breaking phenolic antioxidants *in vitro*. *J Am Chem Soc.*, 103(21), 6472-6477.
11. Burton, G. W., Joyce, A. & Ingold, K. U. (1982). First proof that vitamin E is major lipid-soluble, chain-breaking antioxidant in human blood plasma. *Lancet*, 2(8293), 327.

12. Burton, G. W., Doba, T., Gabe, E., Hughes, L., Lee, F. L., Prasad, L. & Ingold, K. U. (1985). Autoxidation of biological molecules. 4. Maximizing the antioxidant activity of phenols. *J Am Chem Soc.*, 107(24), 7053-7065.
13. Pryor, W. A., Strickland, T. & Church, D. F. (1988). Comparison of the efficiencies of several natural and synthetic antioxidants in aqueous Sodium Dodecyl-Sulfate micelle solutions. *J Am Chem Soc.*, 110(7), 2224-2229.
14. Pryor, W. A., Cornicelli, J. A., Devall, L. J., Tait, B., Trivedi, B. K., Witiak, D. T. & Wu, M. (1993). A rapid screening test to determine the antioxidant potencies of natural and synthetic antioxidants. *J Org Chem.*, 58(13), 3521-3532.
15. Mukai, K., Kageyama, Y., Ishida, T., Fukuda, K., Okabe, K. & Hosose, H. (1989). Synthesis and kinetic study of antioxidant activity of new tocopherol (vitamin E) compounds. *J Org Chem.*, 54(3), 552-556.
16. Serbinova, E. A., Kagan, V., Han, D. & Packer, L. (1991). Free radical recycling and intramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol. *Free Radic Biol Med.*, 10(5), 263-275.
17. Serbinova, E. A. & Packer, L. (1994). Antioxidant properties of alpha-tocopherol and alpha-tocotrienol. *Methods Enzymol.*, 234, 354-366.
18. Suzuki, Y. J., Tsuchiya, M., Wassall, S. R., Choo, Y. M., Govil, G., Kagan, V. E. & Packer, L. (1993). Structural and dynamic membrane properties of alpha-tocopherol and alpha-tocotrienol: implication to the molecular mechanism of their antioxidant potency. *Biochemistry*, 32(40), 10692-10699.
19. Qureshi, A. A., Burger, W. C., Peterson, D. M. & Elson, C. E. (1986). The structure of an inhibitor of cholesterol biosynthesis isolated from barley. *J Biol Chem.*, 261(23), 10544-10550.
20. Kato, A., Yamaoka, M., Tanaka, A., Komiyama, K. & Umezawa, I. (1985). Physiological effect of tocotrienol. *J Jpn Oil Chem Soc.*, 34(5), 375-376.
21. Sundram, K., Khor, H. T., Ong, A. S. & Pathmanathan, R. (1989). Effect of dietary palm oils on mammary carcinogenesis in female rats induced by 7, 12-dimethylbenz(a)anthracene. *Cancer Res.*, 49(6), 1447-1451.
22. Guthrie, N., Gapor, A., Chambers, A. F. & Carroll, K. K. (1997). Inhibition of proliferation of estrogen receptor-negative MDA-MB-435 and -positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination. *J Nutr.*, 127, 544S-548S.
23. Hasani, N. A. H., Yusoff, P. A., Bak, K., Gapor, M. & Wan Ngah, W. Z. (2008). The possible mechanism of action of palm oil γ -tocotrienol and α -tocopherol on the cervical carcinoma CaSki cell apoptosis. *Biomed Res.*, 19(3), 194-200.

24. Pierpaoli, E., Viola, V., Pilolli, F., Piroddi, M., Galli, F. & Provinciali, M. (2010). Gamma- and delta-tocotrienols exert a more potent anticancer effect than alpha-tocopheryl succinate on breast cancer cell lines irrespective of HER-2/neu expression. *Life Sci.*, *86*(17-18), 668-675.
25. Pierpaoli, E., Viola, V., Barucca, A., Orlando, F., Galli, F. & Provinciali, M. (2013). Effect of annatto-tocotrienols supplementation on the development of mammary tumors in HER-2/neu transgenic mice. *Carcinogenesis*, *34*(6), 1352-1360.
26. Yang, Z., Xiao, H., Jin, H., Koo, P. T., Tsang, D. J. & Yang, C. S. (2010). Synergistic actions of atorvastatin with gamma-tocotrienol and celecoxib against human colon cancer HT29 and HCT116 cells. *Int J Cancer*, *126*(4), 852-863.
27. Kannappan, R., Yadav, V. R. & Aggarwal, B. B. (2010). γ -Tocotrienol but not γ -tocopherol blocks STAT3 cell signaling pathway through induction of protein-tyrosine phosphatase SHP-1 and sensitizes tumor cells to chemotherapeutic agents. *J Biol Chem.*, *285*(43), 33520-8.
28. Sakai, M., Okabe, M., Tachibana, H. & Yamada, K. (2006). Apoptosis induction by gamma-tocotrienol in human hepatoma Hep3B cells. *J Nutr Biochem.*, *17*(10), 672-676.
29. Sazli, F. A. R., Zakiah, J., Mariati, A. R., Karsani, S. A., Abdul Gapor, M. T. & Wan Ngah, W. Z. (2015). Gamma-tocotrienol treatment increased peroxiredoxin-4 expression in HepG2 liver cancer cell line. *BMC Complement Altern Med.*, *15*, 64.
30. Ji, X., Wang, Z., Geamanu, A., Sarkar, F. H. & Gupta, S. V. (2011). Inhibition of cell growth and induction of apoptosis in non-small cell lung cancer cells by delta-tocotrienol is associated with Notch-1 down-regulation. *J Cell Biochem.*, *112*(10), 2773-2783.
31. Ji, X., Wang, Z., Sarkar, F. H. & Gupta, S. V. (2012). Delta-tocotrienol augments cisplatin induced suppression of non-small cell lung cancer cells via inhibition of the Notch-1 pathway. *Anticancer Res.*, *32*(7), 2647-2655.
32. Kunnumakkara, A. B., Sung, B., Ravindran, J., Diagaradjane, P., Deorukhkar, A., Dey, S., Koca, C., Yadav, V. R., Tong, Z., Gelovani, J. G., Guha, S., Krishnan, S. & Aggarwal, B. B. (2010). {Gamma}-tocotrienol inhibits pancreatic tumors and sensitizes them to gemcitabine treatment by modulating the inflammatory microenvironment. *Cancer Res.*, *70*(21), 8695-8705.
33. Shin-Kang, S., Victoria, P. R., Lightner, J., Kanishka, C., William, S., Campbell, S., Shrikanth, A. G. R. & Koyamangalath, K. (2011). Tocotrienols inhibit AKT and ERK activation and suppress pancreatic cancer cell proliferation by suppressing the ErbB2 pathway. *Free Radic Biol Med.*, *51*(6), 1164-1174.
34. Sugahara, R., Sato, A., Uchida, A., Shiozawa, S., Sato, C., Virgona, N. & Yano, T. (2015). Annatto tocotrienol induces a cytotoxic effect on human prostate cancer PC3 cells via the simultaneous inhibition of src and stat3. *J Nutr Sci Vitaminol.*, *61*(6), 497-501.

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35. Yeganehjoo, H., DeBose-Boyd, R., McFarlin, B. K. & Mo, H. (2017). Synergistic Impact of d- δ -tocotrienol and geranylgeraniol on the growth and HMG CoA reductase of human DU145 prostate carcinoma cells. *Nutr Cancer.*, 69(4), 682-691.
36. Chang, P. N., Yap, W. N., Lee, D. T., Ling, M. T., Wong, Y. C. & Yap, Y. L. (2009). Evidence of gamma-tocotrienol as an apoptosis-inducing, invasion-suppressing, and chemotherapy drug-sensitizing agent in human melanoma cells. *Nutr Cancer.*, 61(3), 357-366.
37. Chung, S. Y., Nanjoo, S. & Ah-Ng, T. K. (2012). Does vitamin E prevent or promote cancer? *Cancer Prev Res.*, 5(5), 701-705.
38. Choe, E. & David, M. B. (2009). Mechanisms of antioxidants in the oxidation of foods. *Compr Rev Food Sci Food Saf.*, 8(4), 345-358.
39. Hasani, N. A. H., Yusoff, P. A., Bak, K., Gapor, M. & Wan Ngah, W. Z. (2008). The possible mechanism of action of palm oil γ -tocotrienol and α -tocopherol on the cervical carcinoma CaSki cell apoptosis. *Biomed Res.*, 19(3), 194-200.
40. Wu, S. J. & Ng, L. T. (2010). Tocotrienols inhibited growth and induced apoptosis in human HeLa cells through the cell cycle signaling pathway. *Integr Cancer Ther.*, 9(1), 66-72.
41. Hasani, N. A. H., Khalid, B. & Wan Ngah, W. Z. (2011). The anti-proliferative effect of palm oil γ -tocotrienol involves alterations in MEK-2 and ERK-2 protein expressions in CaSki cells. *Asian Biomed.*, 5(5), 601-609.
42. Gu, W., Indira, P., Meihua, Y., Fengxia, Z., Patrick, L., Yin, X. & Chengzhong, Y. (2015). Gamma tocotrienol targets tyrosine phosphatase SHP2 in mammospheres resulting in cell death through RAS/ERK pathway. *BMC Cancer.*, 15, 609.
43. Bermudez, Y., Ahmadi, S., Lowell, N. E. & Kruk, P. A. (2007). Vitamin E suppresses telomerase activity in ovarian cancer cells. *Cancer Detect Prev.*, 31(2), 119-28.
44. Saleh, H., Omar, E., Froemming, G. & Said, R. (2014). Tocotrienol rich fraction supplementation confers protection on the ovary from cyclophosphamide induced apoptosis. *Asian Pac J Trop Dis.*, 4(3), 234.
45. Saleh, H., Omar, E., Froemming, G. & Said, R. (2015). Tocotrienol preserves ovarian function in cyclophosphamide therapy. *Hum Exp Toxicol.*, 34(10), 946-52.