

## MECHANISM OF ACTION OF TUMORIGENESIS OF ANTICANCER MOLECULES OF PALM OIL TOCOTRIENOLS (*Elaeis guineensis* Jacq.): A SYSTEMATIC REVIEW

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### ABSTRACT

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*Palm oil contains vitamin E which comprises two structurally similar compounds namely tocopherols and tocotrienols. For many years tocopherols considered the best therapy in curing disease, but in recent research advances, tocotrienol has been widely used as a powerful therapy in several diseases, including cancer. We prepared this article to review and analyze the role of tocotrienols from palm oil as anticancer molecules and their mechanism of action in the process of tumorigenesis based on the literature from PubMed, Scopus, Science Direct, and ProQuest databases published from 2011 to 2020, and according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Nineteen English articles and abstracts according to the inclusion criteria, systematically reviewed and compiled. The results showed that tocotrienol acts on intracellular and extracellular targets involved in cell signaling pathways and*

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*suppresses the growth of various malignancies, including breast, lung, prostate, ovarian, liver, brain, colon, pancreatic, and myeloma cancers. This literature review shows that the molecular mechanism of action of tocotrienols has several advantages, namely a positive effect on cell proliferation, apoptosis, angiogenesis, metastasis, and inflammation, which when working together can function as effective agents in cancer therapy. The tocotrienol-mediated therapeutic action mechanism could help clinicians to design new strategies for cancer treatment.*

**KEYWORDS** Mechanism Of Action; Tocotrienols; Palm Oil; Therapy; Cancer



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## INTRODUCTION

Cancer is a deadly disease with an increasing incidence worldwide (Kashyap et al., 2017; Kashyap et al., 2018). Based on GLOBOCAN 2018 data, it is estimated that 18.1 million new cancer cases and 9.6 million deaths occurred in 2018. Conventional cancer treatment has focused on chemotherapy and radiotherapy, which sometimes have a detrimental effect on cancer patients. Therefore, the latest research is growing, especially in studying the molecular mechanism of tumorigenesis, as well as the development of new anticancer agents that are safe and effective. In recent decades, one of the main focuses of anticancer research has been on natural agents capable of fighting cancer cells (Kashyap et al., 2018).

Palm oil (*Elaeis guineensis* Jacq.), has been widely cultivated because the oil from the seeds and fruit is very beneficial for the industrial sector and has potential as a medicinal plant. Palm oil is also used as the main source of ingredients for kitchen needs and is widely consumed by people in Asia and Africa. More than 85% of palm oil production is provided by Indonesia and Malaysia as the main producers in the world (Mancini et al., 2015; Absalome et al., 2020).

Palm oil contains vitamin E which is an essential fat-soluble nutrient, obtained from food and supplements. In addition to their antioxidant activity, vitamin E components have the potential to influence various mechanisms underlying human health and disease. Vitamin E consists of two structurally similar compounds namely tocopherols and tocotrienols. The main theory states that tocotrienols have anticancer effects by inhibiting lipid peroxidation, antioxidant activity of tocotrienols can prevent oxidative damage to Deoxyribonucleic acid (DNA) and as a chemopreventive. Administration of tocotrienols in mice, rat, and human tumor cell lines has been shown to inhibit growth cancer cells (Catalgol, Batirel and Ozer, 2011; Bak et al., 2017).

Tocotrienols as a natural compound, it has been observed that it has antioxidant, antiproliferative, pro-apoptotic, anti-inflammatory, antiangiogenic, anti-invasive, and anti-metastatic activity, so it has potential as a chemopreventive or chemotherapeutic agent (Kashyap et al., 2018; M rarchi et al., 2018; Sethi et al., 2018). In addition, the beneficial effects that have been proven are effective in lowering cholesterol levels and as

neuroprotective, while in suppressing the growth of malignancies have been studied in the ovaries, liver, stomach, prostate, brain, blood, pancreas, and uterus (Rizvi et al., 2014; Kanchi et al., 2017).

In this literature review, we will summarize the latest data showing the unique anticancer effect, discuss the molecular mechanism of action of tumorigenesis of tocotrienols in various cancer models that can prove tocotrienols as promising chemopreventive and chemotherapeutic agents. Because in Indonesia there are so many and easy to find palm oil plants, it must be utilized as best as possible by exploring the possibility of using tocotrienols as a replacement therapy for conventional cancer treatment in Indonesia. Next we will highlight recent advances in the development and testing of tocotrienols-based cancer therapies.

## **RESEARCH METHOD**

The study selection of relevant articles previously published from 2011 to 2020 was obtained from the PubMed, Science Direct, Scopus and ProQuest databases, using the keywords (“palm oil” OR “*Elaeis guineensis* Jacq.”), AND (“vitamin E”), AND (“tocotrienols” OR “tocotrienols”), AND (“anti-cancer” OR “anticancer”), AND (“mechanism” OR “mechanisms”), AND (“action” ), AND (“tumorigenesis”). Articles and abstracts taken are in English, read, reviewed and arranged systematically.

The studies in the selected articles met four inclusion criteria, namely: (1) sources: tocotrienols from palm oil; (2) effect: anticancer; (3) mechanism: acts on intracellular and extracellular targets involved in cell signaling pathways and has been shown to suppress the growth of various malignancies, including breast, lung, prostate, ovarian, liver, brain, colon, pancreatic, and myeloma cancers; (4) results: positive effect on cell proliferation, apoptosis, angiogenesis, metastasis, and inflammation; And articles will be excluded if: (1) palm oil content is not tocotrienols molecules; (2) has an effect on chronic diseases other than cancer (3) irrelevant results.

## **RESULT AND DISCUSSION**

In a literature search we identified 2532 studies. Then 229 duplicate articles were removed and a further 2303 articles were carefully evaluated. Although 280 articles met the inclusion criteria, 261 were excluded because they were not eligible for this study. The number of articles analyzed was 19 articles. The study selection flowchart and reasons for rejection can be seen in Figure 1.

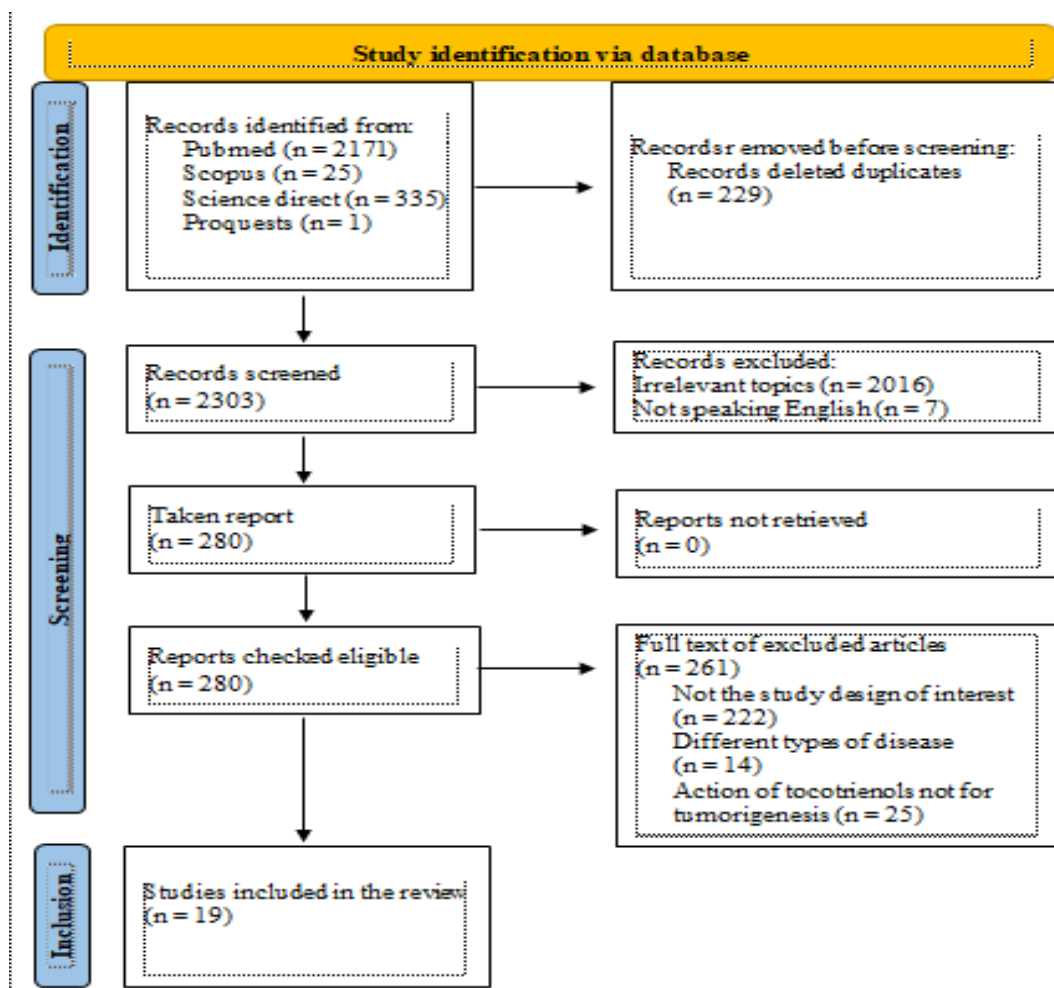
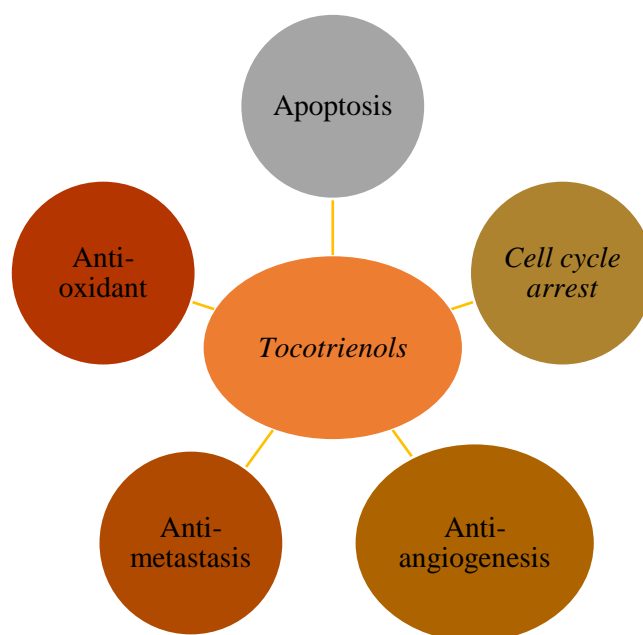


Figure 1. Study selection flowchart

### Main Functions of Tocotrienols as Anticancer

*Tocotrienols* is a natural form of the vitamin E group, which consists of four different isomers namely  $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\delta$ -tocotrienols (Peh et al., 2016). Tocotrienols are found in rice bran oil, palm oil and annatto seed (Rashid Khan et al., 2015). Tocotrienols are the main phytonutrients found in palm oil and can be found in the palm oil fraction known as the tocotrienol-rich fraction (TRF) (Subramaniam, Selvaduray and Radhakrishnan, 2019).

Various beneficial properties of tocotrienols have been reported in recent years. Tocotrienols act as cellular lipid antioxidants which are effective as anti-inflammatory, antiangiogenic, antiinvasive, and antimetastatic agents that are involved in disease cure and have potential as chemopreventive or chemotherapeutic agents although they have not been clinically tested on a large scale (Figure 2) (Mocchegiani et al., 2014; MÉRARCHI et al., 2018; Aggarwal et al., 2019).



**Figure 2.** Anticancer properties of tocotrienols

Its chemopreventive properties have been studied extensively in a number of animal models. In contrast to the effects of tocopherols on animal models of carcinogenesis (colon, prostate, breast and lung) which often yield inconsistent results, most of the studies on tocopherols have shown positive chemopreventive effects (Ling et al., 2012).

#### **Inhibition of Cell Proliferation and Induction of Apoptosis**

Apoptosis is an important process used as an innate defense mechanism against cancer initiation (Marcus et al., 2014). Several in vitro and in vivo experiments have confirmed that apoptosis can induce the potential of natural molecules. Tocotrienols are among several natural compounds with effective antitumor activity through apoptosis-inducing pathways. Tocotrienols downregulate the expression of several oncogenic gene products by inhibiting the NF- $\kappa$ B pathway and also cause substantial apoptosis in tumor cells (Aggarwal et al., 2019).

Inhibition of proliferation and induction of apoptosis has also been reported to be mediated through tocotrienols-induced activation of the EGR-1/BAX pathway, upregulation of miR-34a125, miR-429135, p27/CDKN1B136 and PPAR- $\gamma$ 137, impaired lipid formation and mitochondrial membrane modification and activation of pro-inflammatory genes. apoptosis. In addition, tocotrienols and their metabolite 13`-COOH modulate sphingolipid metabolism through inhibition of dihydroceramide desaturase (DEGS). In addition, pathway analysis of tocotrienols-induced gene expression profiling changes showed that -T3 and -T3 alter endoplasmic reticulum stress signaling and associated autophagy and cell death (Yang et al., 2020).

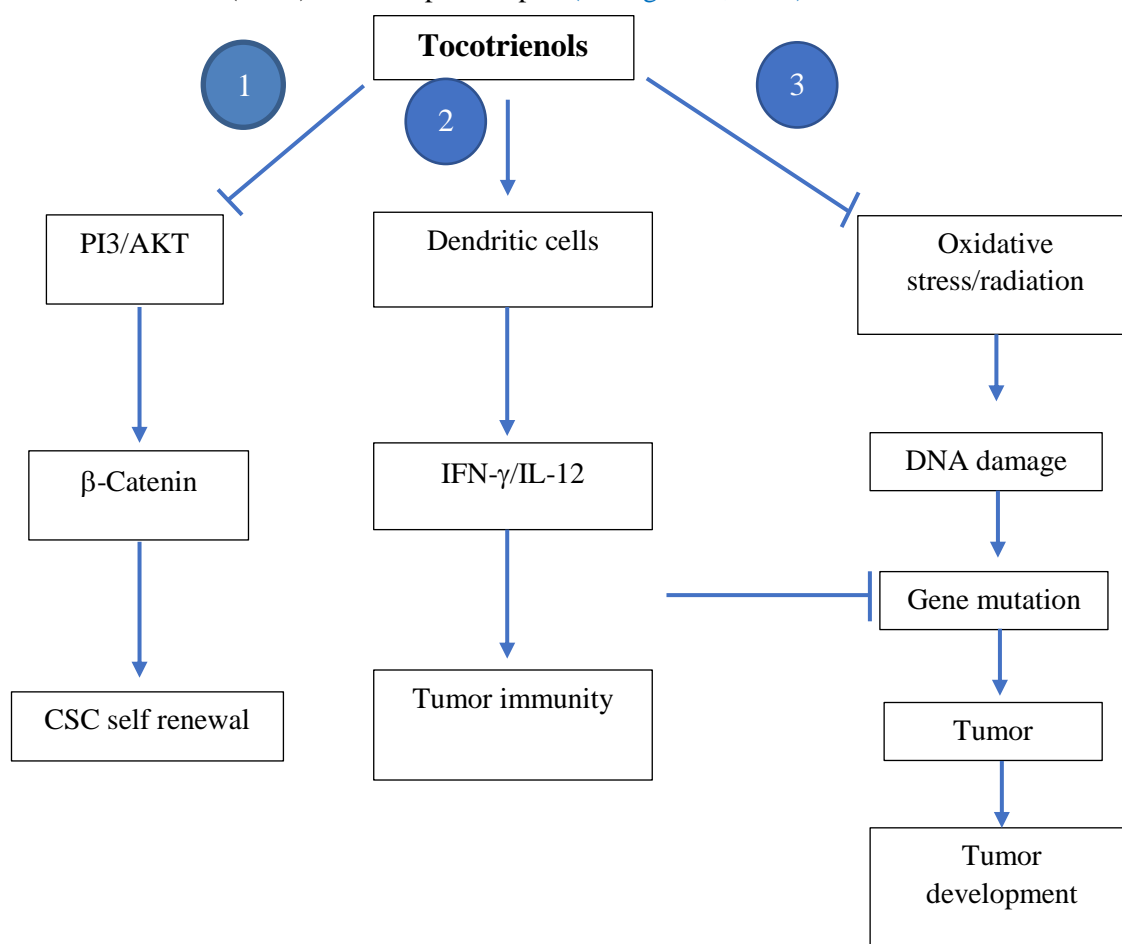
#### **Tocotrienols and Cancer-related Studies**

Research about cancer using tocotrienols has been studied extensively in humans. Many studies have shown that lower tocotrienols intake or nutritional status is associated with an increased risk of various types of cancer.

Cancer, as it is widely known, is a class of diseases in which cells show uncontrolled growth and can damage surrounding tissues, and can metastasize or spread to other locations in the body via the lymph or blood vessels. Interest in the use of alternative and complementary therapies, especially tocotrienols as a chemopreventive greatly increased especially for cancer treatment. In this study, chemoprevention by tocotrienols could slow the formation and delay the development of neoplasms. Regulation of signal transduction pathways associated with tumor formation (tumorigenesis) is considered a key point for slowing cancer progression (Catalgol, Batirel and Ozer, 2011). Figure 3 describes the mechanism of the chemopreventive effect of tocotrienols.

Increasing evidence supports the role of tocotrienols in cancer prevention. The theory about the effect of tocotrienols as anticancer is the inhibition of lipid peroxidation and with antioxidant activity it can prevent oxidative damage to DNA (Deng et al., 2019).

Research on vertebral bone metastases from prostate cancer patients using VcaP cell line NCr (-/-) nude mice of eight weeks old male injected subcutaneously with VcaP-luc cells in matrigel and given a mixture of tocotrienols for 8 weeks was able to inhibit the growth of prostate tumor xenografts. The concentration of tocotrienols and their metabolites increased significantly in the treatment group. Tocotrienols inhibit prostate tumor growth by suppressing cell proliferation, which is associated with cyclin-dependent induction of kinase (CDK) inhibitor p21 and p27 (Huang et al., 2017).



**Figure 3.** Chemopreventive effect of tocotrienols. Oxidative stress or radiation causes DNA damage and induces genetic mutations thereby promoting tumor development with CSCs being the tumor trigger population. The pathways occur through: 1. Suppressing CSCs self-renewal and tumorigenicity through inactivation of the PI3/AKT/b-catenin pathway; 2. Promote dendritic cell mediated tumor immunity, tocotrienols can facilitate the elimination of tumor cells in the early stages of tumor initiation and achieve chemopreventive effects; 3. Tocotrienols inhibit tumor development through blocking oxidative stress or radiation-induced DNA damage. Image modified from Ling et al., 2012.

In human breast cancer, several effects of tocotrienols have been shown to inhibit the growth of cancer cells. Cells were treated with 50 M Omega 3-docosahexaenoic acid (DHA) and 5 M vitamin E Delta-tocotrienol (Delta-T3) which showed that DHA could trigger an increase in lipid droplet (LD) biogenesis and the combination treatment with Delta-T3 was able to reduce biogenesis. LD. In addition, it was found that higher cytoplasmic LD was associated with higher malignancy and breast cancer cell proliferation (Pizato et al., 2019).

Immunotherapy research conducted Hafid and Radhakrishnan (2019) used dendritic cells with a tumor vaccine (DC vaccine) in combination with daily supplementation of TRF to enhance the antitumor immune response potency. DC vaccine immunotherapy together with TRF supplementation induces immunity to tumors. This study used female BALB/c mice induced by breast cancer (Hafid and Radhakrishnan, 2019).

Several cancer treatment and prevention studies are summarized in table 1.

**Table 1.** Results of clinical research on tocotrienols in various types of cancer

Writer	Study population	Treatment	Results	Significance
Behery et al., 2013	Metastatic - SA mammary epithelial cancer cell line	$\delta$ -tocotrienols analogs 10 and 38	Anti-proliferative activity	Tocotrienols increase the level and control the metastatic of breast malignancy
Zhang et al., 2015	Balb/c nude mice inoculated with cancer cells human colon SW620	Tocotrienol-rich fraction (TRF) from palm oil for 6 weeks	TRF significantly inhibits the growth of xenografts	The strong anticancer effect of TRF is associated with Wnt . signal pathway regulation
Springett et al., 2015	Pancreatic cancer	Vitamin E - tocotrienols (VEDT) at a dose of 200-3200mg per day	Biological activity, in the form of apoptotic induction, was seen to be significant in neoplastic cells as	The results are significant but require further clinical research from VEDT to

		for 13 days before surgery and a single dose on the day of surgery	measured by elevated levels of caspase-3	chemoprevention and/or pancreatic cancer therapy
Shanmugam et al., 2017	Preclinical several types of cancer	Tocotrienol	Several growth factors and their receptors such as VEGF/VEGFR, bFGF/FGFR, angiopoietin, and hypoxia-induced factors facilitate the development of angiogenesis and are anti-cancer targets	Tocotrienols exhibit prominent anti-angiogenic effects in a preclinical model of tumor angiogenesis
Fontana et al., 2019	Castration-resistant prostate cancer (CRPC)	Vitamin E-derived tocotrienols on selmCRPC (PC3 and DU145)	$\delta$ -TT provides cytotoxic/proapoptotic activity in CRPC cells	Apoptosis involves ER stress and autophagy (in autophagy-positive PC3 cells), and paraptosis is involved in anti-cancer activity $\delta$ -TT in CRPC cells.

## CONCLUSION

A wide variety of bioactive compounds isolated from natural products including tocotrienols, have various therapeutic benefits and potential for cancer prevention and treatment. The mechanism of action of tocotrienols at the cellular and molecular levels leads to the modulation of various cancer-associated signaling pathways. The tocotrienols-mediated therapeutic action mechanism could help researchers and clinicians to design new strategies for cancer treatment.

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