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Editorial Board of *World Journal of Gastrointestinal Oncology*, Rossana Berardi, MD, PhD, Director, Full Professor, Medical Oncology, Università Politecnica delle Marche, Ancona 60126, Italy. r.berardi@univpm.it

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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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MINIREVIEWS

Vitamin E in the management of pancreatic cancer: A scoping review

Sophia Ogechi Ekeuku, Effiong Paul Etim, Kok-Lun Pang, Kok-Yong Chin, Chun-Wai Mai

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Sophia Ogechi Ekeuku, Kok-Yong Chin, Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur 56000, Malaysia

Effiong Paul Etim, Faculty of Applied Sciences, UCSI University, Kuala Lumpur 56000, Malaysia

Kok-Lun Pang, Newcastle University Medicine Malaysia, Iskandar Puteri 79200, Johor, Malaysia

Kok-Yong Chin, Chun-Wai Mai, State Key Laboratory of Oncogenes and Related Genes, Renji-Med X Clinical Stem Cell Research Center, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

Chun-Wai Mai, Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur 56000, Malaysia

Corresponding author: Chun-Wai Mai, BPharm, PhD, Associate Professor, Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, UCSI University, No. 1, Jalan Menara Gading, UCSI Heights (Taman Connaught), Cheras, Kuala Lumpur 56000, Malaysia. mai.chunwai@gmail.com

Abstract

Pancreatic cancer is the leading cause of cancer mortality worldwide. Research investigating effective management strategies for pancreatic cancer is ongoing. Vitamin E, consisting of both tocopherol and tocotrienol, has demonstrated debatable effects on pancreatic cancer cells. Therefore, this scoping review aims to summarize the effects of vitamin E on pancreatic cancer. In October 2022, a literature search was conducted using PubMed and Scopus since their inception. Original studies on the effects of vitamin E on pancreatic cancer, including cell cultures, animal models and human clinical trials, were considered for this review. The literature search found 75 articles on this topic, but only 24 articles met the inclusion criteria. The available evidence showed that vitamin E modulated proliferation, cell death, angiogenesis, metastasis and inflammation in pancreatic cancer cells. However, the safety and bioavailability concerns remain to be answered with more extensive preclinical and clinical studies. More in-depth analysis is necessary to investigate further the role of vitamin E in the management of pancreatic cancers.

Key Words: Anti-cancer treatment; Pancreatic cancer; Scoping review; Tocopherol; Tocotrienol; Vitamin E

Core Tip: Vitamin E is a natural bioactive agent found in a variety of foods. Our scoping review found that it inhibits pancreatic tumor progression, and modulates key pathways in carcinogenesis. Vitamin E might support the current pharmacological approach for treating pancreatic cancer. However, more studies are needed to investigate its safety and efficacy.

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INTRODUCTION

Pancreatic cancer is a disease with a poor prognosis and high mortality rate[1,2]. Pancreatic ductal adenocarcinoma (PDAC) is categorized as an exocrine tumor that accounts for 80%-90% of pancreatic cancer cases. Less common types of exocrine tumors, such as squamous cell carcinoma and small cell carcinomas, constitute the remaining cases[2]. PDAC can evade from the host's cell death[3-5] and immune defense[5-8]. The lack of effective PDAC therapy emphasizes the need for the development of new treatment modalities.

Background

Just like other cancers, pancreatic cancer is characterized by uncontrolled proliferation and the ability to resist eradication[1]. Over the past few decades, there has been a dramatic surge in pancreatic cancer cases. The number of cases worldwide has increased from 196000 in 1991 to 495773 in 2010. The global number of new cases is expected to increase by 1.1% annually. By 2050, the incidence could rise to 18.6 cases for every 100000 individuals[9]. Mortality-wise, cases have increased by 53% in the last 25 years and as of 2020, there were 466003 deaths recorded and PDAC-linked deaths account for 4.6% of all cancer deaths[10]. The high fatality rate of pancreatic cancer is linked to the inability of detecting early malignancy. Hence, late diagnosis at an advanced stage is often the case with a 5-year survival rate of less than 5%.

The ability of pancreatic cancer cells to evade the host's apoptotic and immune pathways make intervention difficult[3-8]. The activation of the extrinsic death receptor-mediated apoptosis pathway is dependent on the ligand-receptor binding of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)[11]. Pancreatic cancer cells have also shown resistance to the apoptotic effects of TRAIL[11]. There are several pathways and mechanisms that drive the oncogenic progression of pancreatic cancer cells. Kirsten rat sarcoma viral oncogene homolog (KRAS) is the most frequently onset driver of pancreatic cancer. It captures the cell machinery *via* the phosphoinositide-3-kinases/protein kinase B (PI3K/AKT) and the rat sarcoma virus/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase (MAPK) kinase/extracellular signal-regulated kinase (Ras/Raf/MEK/ERK) signaling pathways [12]. The signal transducer and activator of transcription 3 (STAT3) pathway is constitutively activated in pancreatic cancer cells[13]. Pancreatic cancer disrupts the cancer-immunity cycle, supporting cancer cells to evade host immunity and immunotherapy[4-7]. Pancreatic cancer stem cells (CSCs) that break off from the primary tumor and metastases have made treatment and recovery options even more challenging as most patients go into relapse. This is because CSCs renew themselves, become tumorigenic, metastatic and develop differentiated progenies that further increases the resistance to treatment[14,15].

Unfortunately, treatment options available for patients with pancreatic cancer are limited. The only effective treatment method with the possibility of full recovery remains surgery either by pancreatic-duodenectomy (Whipple's procedure), distal or total pancreatectomy[16]. The risk associated with the procedure is daunting and less safe once metastasis ensues. Most patients are then given gemcitabine, the first-line chemotherapy used to eliminate pancreatic cancer, which only merely extends the survival rate marginally[17]. Other chemotherapeutic regimes, such as 5-fluorouracil, Partenariat de Recherche en Oncologie Digestive 24/Canadian Cancer Trial Group, and modified FOLFIRONOX (a combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin), and immunotherapy have shown some benefits among patients with pancreatic cancer[2]. However, pancreatic cancer eventually develops chemoresistance towards these clinically used agents. Many combination agents[7,18,19] and novel drug delivery methods[20-22] are currently under investigation in hope that a safe and effective treatment for pancreatic cancer patients can be found.

Dietary modulation is a good strategy with the potential for prevention and treatment of many disorders including cancers[23,24]. The naturally occurring vitamin E with all its isoforms have shown potential as a stand-alone treatment in disrupting the cancer mechanism pathways and in several combination treatments[25]. Vitamin E comprises a chromanol ring with an isoprenoid side chain (Figure 1)[26]. There are two common homologues of vitamin E, *i.e.* tocopherol (TP) and tocotrienols (TT). Natural occurring TPs exhibit three *R*-configuration asymmetric carbons, namely C2 (chromanol ring), C4′ and C8′ (side chain)[26]. For TT, the three double bonds are *all-trans* configuration. Both groups exist in α-, β-, γ- and δ-isomer, with different methyl groups. Stereoisomerism of TP and TT may have an impact on their biological activity. Both TP and TT can be prepared in ester forms, namely acetate, nicotinate, succinate or phosphate, at the hydroxyl group at the chromanol head to reduce the oxidation of TP or TT. Vitamin E isoforms can be prepared *via* total or semi-synthesis for industrial application[26]. Unfortunately, the investigation of α-TP as an agent of cancer prevention has only yielded disappointing results since it required a high anti-cancer dose *in vitro* but failed to suppress the growth in pancreatic carcinoma *in vivo*[27]. As a consequence, the study of α-TPs has not reached clinical trial and are not being investigated as treatment for pancreatic cancer[27]. Molecularly, TTs differ from TPs since the former have an unsaturated isoprenoid side chain (Figure 1). Compared to most TP isoforms, δ- and γ-TT possess stronger anti-cancer properties. This unsaturated side chain may confer an extra anticancer/anti-proliferative property that the TPs are lacking[28]. However, due to the strong binding of α-TP with α-TP transfer protein, TTs have a low bioavailability which might hinder their anti-cancer activities *in vivo* when present together with α-TP [27]. A study also showed that δ- and γ-TT exhibited a much stronger inhibitory effect on eicosanoid formation than α-TPs[27]. Moreover, compared to α-TP, TT has much stronger inhibitory effects on canonical inflammatory markers[27]. Thus, δ-TT and γ-TT are widely studied for their anti-cancer properties, but not β-TT probably because it is not commonly found in nature compared to other isoforms[25,27].

Purpose

Given the unique properties of TPs and TTs, this review aims to summarize the effects of vitamin E against PDAC cells lines, *in vivo* tumor models and pancreatic cancer patients. In addition to identifying research gaps in the existing literature, this study will look at the quantity, variety, and type of research activity that is currently available on this subject.

MATERIALS AND METHODOLOGY

This scoping review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines[29]. The methodology was according to the Arksey and O'Malley framework[30]. Steps of the literature search selection process, from identification, screening and eligibility for the inclusion of articles are shown in Figure 2. The protocol of this scoping review has not been registered before the study.

Research question

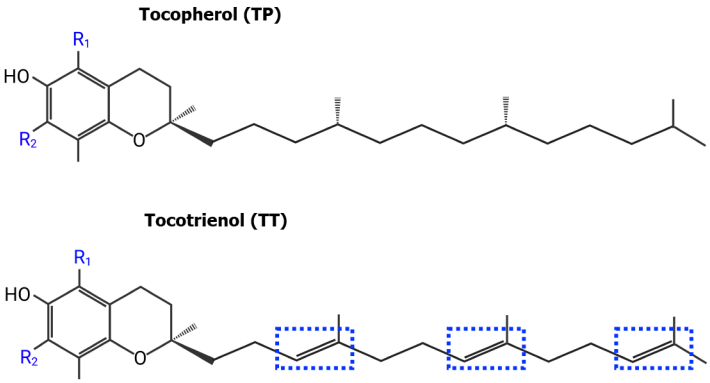
The research question for this scoping review was: *What are the effects of vitamin E on pancreatic cancer?* α-TP, α-, β-, γ- and δ-TT are different types of vitamin E included in the study. Pre-clinical models such as *in vitro* cell lines, *in vivo* mouse models and clinical trial findings from pancreatic cancer patients were included in the study. This scoping review has included findings from all stages of pancreatic cancer.

Study identification

A literature search was conducted by two authors (SOE and EPE) in October 2022 using PubMed and Scopus to identify studies on the association between vitamin E and pancreatic cancer. The search string used was ("vitamin E" OR TPs [MeSH] OR OR tocopheryl OR TTs [MeSH] OR TT) AND "pancreatic cancer".

Study selection

Studies with the following characteristics were included: (1) Studies that aimed at determining the effects of vitamin E (mixture or single isomer) on pancreatic cancer; (2) Studies published in English; and (3) Studies conducted on pancreatic cancer cells (primary culture or cell lines), animal models or patients with pancreatic cancers. We excluded: (1) Articles that did not contain original data, such as reviews, letters, commentaries, or opinions; (2) Conference abstracts, considering the results might have been published as full articles; and (3) Studies that use a combination of vitamin E and other compounds, whereby the effects of vitamin E could not be clearly delineated. The search results were organized using Mendeley software (Elsevier, Amsterdam). Duplicates were identified using Mendeley and confirmed by manual checking.



	α	β	γ	δ
R_1	CH_3	CH_3	H	H
R_2	CH_3	H	CH_3	H

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Figure 1 Chemical structure of vitamin E homologues, namely tocopherol, and tocotrienol. TP has a saturated phytyl side chain, while tocopherol has three double bonds (indicated in blue line dotted box) on the side chain. The α-, β-, γ-, δ-isomers differ in the position of the methyl group on the chromanol ring (R_1 and R_2).

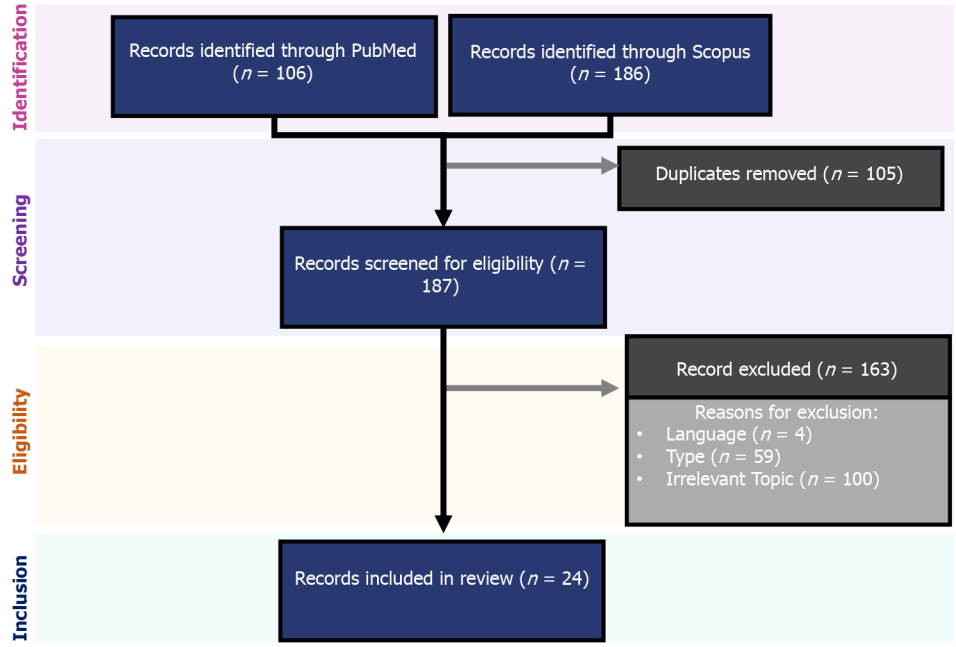

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Figure 2 Process of article selection in this scoping review.

Data charting

Two authors (SOE and EPE) screened the search results based on titles, abstracts and full texts. Any disagreement on the inclusion or exclusion of articles was resolved through discussion among the two authors. The corresponding author (CWM) had the final decision on articles included if a consensus could not be reached between authors. Data charting was performed by two authors (SOE and EPE) using a standardized table and validated by two other authors (KYC and KLP). The data extracted included researchers, years of inclusion, study design and major findings.

RESULTS

Selection of articles

The literature search yielded 292 results (106 from PubMed and 186 from Scopus). After removing the duplicated items (n = 105), 187 articles were screened for eligibility. During the screening, 163 articles were removed due to various reasons (100 articles were not relevant, 4 non-English articles, 41 review articles, 4 conference proceedings, 3 book chapters, 3 meta-analyses, 2 notes, 2 "Patients-Oriented

Evidence that Matters" articles, 1 editorial, 1 guideline, 1 letter and 1 short communication). Finally, 24 papers that met all the criteria were included in the current review.

Study characteristics

Articles that passed the inclusion criteria were published from 2000 to 2019. Three studies used vitamin E succinate (VES)[31-33], two studies used alpha-tocopheryl succinate (α-TPS)[34,35], four studies used α-TP[36-39], one study used α-TT[39], one study used β-TT[39], four studies used γ-TT[12,39-41], and 11 studies used δ-TT[39-51]. Nineteen studies were *in vitro* experiments using human pancreatic cancer cell lines, namely AsPC-1, BxPC-3, Capan-1, Capan-2, COLO-357, MIA PaCa-2, PANC-1, Pan02, Panc 28, PSN-1, SW1990, and L3.6pI[12,31,33-36,39-48,51,52]; human pancreatic cancer stem-like cells (PCSCs) [48] and primary culture of human pancreatic cancer cells[32]. The concentrations of vitamin E ranged from 0 to 500 μM *in vitro* up to 72 h[12,31,33-36,39-43,45-48,51,52]. In terms of animal studies, 11 studies used either athymic nude mice[41-43,48,51], severe-combined immunodeficient (SCID) nude mice[39] , $LSL^{KrasG12D/+}$; *Pdx-1-Cre* transgenic mice[47,50], $LSL^{KrasG12D/+}$; $LSL^{Trp53R172H/+}$; *Pdx-1-Cre* (KPC) transgenic mice [49] or Syrian hamsters[37,38]. The dose of vitamin E used in animal studies was between 4 to 400 mg/kg/day and the study duration ranged from 3 wk to 12 mo[37-39,41-43,47-51]. Only one Phase I clinical trial of vitamin E (NCT00985777) on patients diagnosed with pancreatic ductal neoplasia was reported [53]. It was a single-center, open-label, phase I dose escalation trial. Patients with presumptive premalignant (intraductal papillary mucinous neoplasm or mucinous cystic neoplasm of the pancreas) or malignant (pancreatic carcinoma) exocrine pancreas neoplasms were given 200-1600 mg vitamin E twice daily for 2 wk before surgery and once on the day of surgery[53].

Evidence from cell culture studies

As illustrated in Table 1, several *in vitro* studies applied various types of vitamin E in pancreatic cancer cell lines[12,31,33-36,39-43,45-48,51,52], PCSCs[48] and primary culture of human pancreatic cancer cells [32]. VES (0.000023-500 μM) reduced the growth[32-34] or proliferation[31] of pancreatic cancer cells after 24-72 h of treatment. Protein expression studies revealed that VES induced pancreatic cancer cell death with the increase of cleaved poly adenosine diphosphate ribose polymerase (cPARP), caspase-3, and p21 expression but decreased the cell division cycle protein 2 (Cdc2), survivin, and X-linked inhibitor of apoptosis protein (XIAP) expression[31]. Debele *et al*[35] reported that α-TPS and α-TPS-loaded poly(allylamine)-citraconic anhydride-poly(lactic-co-glycolic acid)-cystamine (PAH-SS-PLGA) micelle (PAH-SS-PLGA-TOS) exhibited cytotoxicity, apoptosis induction and G0/G1 and G2/M arrest in Pan02 cells. However, the effect of α-TPS was only significant at a higher concentration (100 μM). Husain *et al*[39] reported that α-TP at doses between 0-100 μM did not affect growth, survival, colony formation and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity in the pancreatic cancer cell lines. Independently, Greco *et al*[34] reported that pancreatic cancer cell lines were only responsive to the anti-proliferative effects of α-TPS at a concentration greater than 200 μM. Similarly, Blanchard *et al*[36] also reported decreased expression of interleukin 6 (IL-6) in both CAPAN 1 and CAPAN 2; IL-8 and NF-κB in CAPAN 2 pancreatic cancer cell lines at a high dose (500 μM). These results suggest that α-TP may only be effective against pancreatic cancer cell lines at high doses greater than 100 μM.

Independently, TTs also reduced proliferation, and modulated apoptosis of pancreatic cancer cells[12, 39,41,42,44-48]. TT suppressed pancreatic cancer cell proliferation as indicated by the downregulation of proliferation markers (cyclin D1, cellular myelocytomatosis or c-Myc) in a concentration-dependent manner[41]. After treatment with δ- or γ-TT (0-100 μM for 2-6 d), pancreatic cancer cells underwent apoptosis as downregulated anti-apoptotic proteins such as B-cell lymphoma 2 (Bcl2), Bcl-extra-large (Bcl-xL), XIAP, and cellular inhibitors of apoptosis protein (cIAP), as well as increasing the expression of apoptotic proteins namely, caspase 3, caspase 8, Bcl-2 associated X protein (Bax), early growth response factor (EGR) 1 , and poly(adenosine diphosphate-ribose) polymerase 1 (PARP-1)[39,41,42,48]. However, δ-TT (50 μM for 12 h) did not significantly affect Bcl-2, survivin, XIAP and cIAP1 protein expression, suggesting that TT has conflicting effects on anti-apoptotic markers of pancreatic cancer cells[47]. Additionally, γ-TT (40 μM for 2-6 d) induced apoptosis by upregulating ceramide synthesis in pancreatic cancer through stimulating the synthesis of serine palmitoyl transferase, ceramide synthase 6 and delta 4-desaturase, sphingolipid 1. As a result, γ-TT prevented the conversion of ceramides to sphingomyelin and glucosylceramide, which contributes to the apoptotic effect of γ-TT on pancreatic cancer cells[12].

NF-κB transcription factor in pancreatic cancer cells was significantly decreased after the treatment with 500 μM of α-TP for 18 h[36] or 50 μM of d- or γ-TT for 72 h[39] suggesting that vitamin E modulates inflammation in pancreatic cells. Both γ- and δ-TT (10-100 μM for 72 h) reduced MAPK/ERK activation and that of its downstream mediator ribosomal protein S6 kinase, as well as suppressed AKT activation. TT-mediated inactivation of MAPK, AKT and ERK through the induced expression of $p27^{Kip1}$, suggests that oncogenic signaling was inhibited through cell cycle inhibition[40,43,48]. Suppression of AKT phosphorylation by γ- and δ-TT led to downregulation of phosphorylated glycogen synthase kinase-3 beta and upregulation accompanied by nuclear translocation of forkhead box transcription factor-3a (Foxo3a). These effects were mediated by messenger-level receptor tyrosine-protein kinase erythroblastic oncogene B-2 downregulation[40]. Additionally, δ-TT (10-100 μM for 72 h) decreased the

Table 1 *In vitro* studies investigating effect of vitamin E on pancreatic cancer

Type	Pancreatic cells	Dosing regimen	Statistically significant effect (compared to negative control)	Ref.
VES	AsPC-1, COLO 357, PANC-1	10-80 μM; 24, 48, 72 h	↓ Proliferation; ↑ Apoptosis; ↑ Cell cycle arrest; ↓Antiapoptotic markers	[31]
VES	LPC 1-7 (Primary Culture)	0.001-1 μM; 48 h	↓ Proliferation	[32]
VES	MIA PaCa-2	0.000023 μM; 24, 48, 72 h	↓ Proliferation	[33]
α-TPS	BxPC-3, Capan-1,MIA PaCa-2, PANC1, PSN-1	5-500 μM; 72h	↓ Proliferation	[34]
α-TPS, PAH-SS-PLGA-TOS	Pan02	1.45-232.2 μM; 48 h	↓ Proliferation; ↑ Apoptosis; ↑ Cell cycle arrest	[35]
α-TP	Capan-1, Capan-2	500 μM; 18 h	↓ NF-κB activity; ↓ IL-6; ↓ IL-8	[36]
α-TP, α-TT, β-TT, γ-TT, δ-TT	AsPC1, MIA PaCa-2	0-100 μM; 72 h	↓ Proliferation; ↑ Apoptosis;↓ NF-κB activity; ↓ NF-κB DNA binding activity; ↓ Antiapoptotic markers	[39]
γ-TT, δ-TT	BxPC-3, MIA PaCa-2, PANC-1, Panc 28	10, 20, 40, 60, 80, 100 μM; 24 h	↑ Apoptosis; ↓ MAPK related markers	[40]
γ-TT	BxPC-3, MIA PaCa-2, PANC-1	10, 50 μM; 48, 96, 144 h	↓ Proliferation; ↓ NF-κB activity; ↓Antiapoptotic markers; ↓Angiogenesis markers; ↓ Invasion markers	[41]
γ-TT	BxPC-3, MIA PaCa-2, PANC-1	40 μM; 2, 4, 6 h	↑ Apoptosis	[12]
-TT	BxPC-3, MIA PaCa-2, SW1990	0-50μM; 24, 48, 72h	↓ Proliferation; ↑ Cell cycle arrest; ↓ MAPK related markers	[43]
δ-TT	BxPC-3, MIA PaCa-2, PANC-1	0-64 μM; 24-72 h	↓ Proliferation; ↑ Apoptosis	[44]
δ-TT	Human pancreatic cancer cells from ATCC	2.5-80 μM; 48 h	↓ Proliferation	[45]
δ-TT	PANC-1	12.5 μM; 48 h	↓ Proliferation	[46]
δ-TT	MIA PaCa-2	50 μM; 0-12 h	↓ Proliferation; ↑ Apoptosis; = Antiapoptotic markers	[47]
δ-TT	MIA PaCa-2, PCSCs	10-100 μM; 72 h	↓ MAPK related markers; ↓ Invasion markers; ↓ Angiogenesis markers	[48]
δ-TT	AsPc-1, BxPC-3, MIA PaCa-2, PANC-1, SW1990	20-100 μM; 72 h	↓ Proliferation; ↑ Apoptosis	[42]

"=" represents no difference; "↑" represents increase; "↓" represents reduction; PAH-SS-PLGA-TOS: Poly (allylamine)-citraconic anhydride-poly(lactic-co-glycolic acid)-cystamine micelle-α-tocopheryl succinate conjugate; α-TP: Alpha tocopherol; β-TT: Beta tocotrienol; γ-TT: Gamma tocotrienol; δ-TT: Delta tocotrienol; LPC: Low passage primary pancreatic cancer cells; ATCC: American Type Culture Collection; PCSC: Pancreatic cancer stem cells; NF-kappa B: Nuclear factor kappa-light-chain-enhancer of activated B cells; IL: Interleukin; MAPK: Mitogen-activated protein kinase.

pluripotency of pancreatic CSCs as shown by a reduction in the expression of Nanog, octamer-binding transcription factor 4 and sex-determining region Y-box 2 as well as blocking the Notch 1 receptor[48].

δ- or γ-TT (0-100 μM for 2-6 d) prevented the invasion, adhesion, and angiogenesis of pancreatic cancer cells by reducing the protein expression of matrix metalloproteinase 9 (MMP-9), intercellular adhesion molecule 1 (ICAM-1), vascular endothelial growth factor (VEGF) and C-X-C chemokine receptor type 4[41,48]. Additionally, TT increased the protein expression of the E-cadherin and reduced the expression of vimentin and N-cadherin in pancreatic cancer cells, indicating the role of TT in suppressing epithelial-to-mesenchymal tumor transition (EMT) of pancreatic cancer cells[48].

Evidence from animal studies

Several studies suggest that TT treatment can reduce the growth of pancreatic tumors *in vivo* (Table 2). A significantly smaller pancreatic tumor was observed after 100 mg/kg of δ-TT daily (3 wk)[43], 200mg/kg of δ-TT once/twice daily (4 wk)[42], 200 mg/kg of δ-TT twice daily (4 wk)[48], or 400 mg/kg of γ--TT (28 d)[41], was given to the athymic nude mice with pancreatic cancer cell line-derived xenografts. The xenografts were established using subcutaneous xenograft implantation in the flank of mice[42,43] or orthotopic xenograft implantation in the subcapsular region of the pancreas[41,48], or spleen[51] of the mice. In another subcutaneous xenograft of AsPC-1-induced pancreatic tumors[39], the team reported a 50% reduction, 42% reduction and 32% reduction of tumor volume after δ-TT, γ--TT

Table 2 *In vivo* studies investigating effect of vitamin E on pancreatic cancer

Type	Model	Dosing regimen	Statistically significant effect (compared to negative control)	Ref.
δ-TT	Subcutaneous xenograft of MIA PaCa-2 induced pancreatic tumor in athymic nude mice	PO 100 mg/kg, 1 x/day for 3 wk	↓ Tumor volume; ↓ Proliferation markers; ↓ MAPK related markers	[43]
δ-TT	Subcutaneous xenograft of MIA PaCa-2 induced pancreatic tumor in athymic nude mice	PO 200 mg/kg, 2 x/day during weekday & 1 x/day during weekend for 4 wk	↓ Tumor volume; ↑ Apoptotic markers	[42]
δ-TT	Subcutaneous xenograft of L3.6pl cells and PCSC- induced pancreatic tumor in athymic nude mice	PO 200 mg/kg, 2x/day for 4 wk	↓ Tumor volume; ↓ Proliferation markers; ↑ Apoptotic markers; ↓ Invasion markers; ↓ Angiogenesis markers	[48]
δ-TT	Orthotopic xenograft of MIA PaCa-2 induced pancreatic tumor in athymic nude mice	PO 400 mg/kg, 1 x/day for 28 d	↓ Tumor volume; ↓ Proliferation markers; ↓ NF-κB activity; ↓ Invasion markers; ↓ Angiogenesis markers	[41]
δ-TT	*LSL*$^{KrasG12D/+}$; *LSL*$^{Trp53R172H/+}$; *Pdx-1-Cre* (KPC) transgenic mice	PO 200 mg/kg, 2 x/day for 12 wk	↑ Survival; ↓ Tumor volume; = Body weight; ↓ Proliferation markers; ↑ Apoptotic markers; ↓ MAPK related markers	[49]
δ-TT	*LSL*$^{KrasG12D/+}$; *Pdx-1-Cre* transgenic mice	PO 200 mg/kg, 2 x/day for 12 mo	↑ Apoptotic markers	[47]
δ-TT	*LSL*$^{KrasG12D/+}$; *Pdx-1-Cre* transgenic mice	PO 200 mg/kg, 2 x/day for 12 mo	↑ Survival; ↓ Tumor progression; = Body weight; ↑ Apoptotic markers; ↓ NF-κB markers; ↓ MAPK related markers	[50]
δ-TT	Orthotopic xenograft of MIA PaCa-2 induced pancreatic tumours in athymic nude mice	PO 50-100 mg/kg, 2 x/day during weekday & 1 x/day during weekend for 6 wk	↑ δ-TT concentration in pancreas; = Body weight; = Histopathology	[51]
α-TT, β-TT, γ-TT, δ-TT	Subcutaneous xenograft of AsPC-1 induced pancreatic tumor in SCID mice	PO 200 mg/kg, 2 x/day for 4 wk	↓ Tumor volume; ↑ Apoptotic markers; ↓ Antiapoptotic markers; ↓ NF-κB activity and markers	[39]
α-TP	*N*-nitrosobis (2-oxopropyl) amine-induced pancreatic cancer in Syrian hamster	PO 4 mg/kg, 3 x/wk for 12 wk	= Tumor incidence; = Body weight; ↓ Liver metastasis incidence; = Liver metastasis number; = Liver metastasis size	[37]
α-TP	*N*-nitrosobis (2-oxopropyl) amine-induced pancreatic cancer in Syrian hamster	PO 4 mg/kg, 3 x/wk for 12 wk	= Tumor incidence; = Body weight;	[38]

"=" represents no difference; "↑" represents increase; "↓" represents reduction; α-TP: Alpha tocopherol; α-TT: Alpha tocotrienol; γ-TT: Gamma tocotrienol; δ-TT: Delta tocotrienol; SCID: Severe-combined immunodeficient; PO: Oral administration; PCSC: Pancreatic cancer stem cells; MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells.

and β-TT treatment, respectively. However, there was no tumor volume reduction after α-TT treatment. The treated tumor also showed a lower expression of Ki-67 protein expression among the treatment group compared to the negative controls[41,43,48]. Similarly, δ-TT of 200 mg/kg (12 wk) reduced the Ki-67 staining in pancreatic tumor formed among the KPC transgenic mice[49], indicating the role of TT in reducing pancreatic tumor proliferation and growth *in vivo*.

δ-TT treatment (200 mg/kg) for 12 wk[49], or 12 mo[47,50] induced apoptosis on the pancreatic tumors of KPC transgenic mice with a lower level of antiapoptotic protein Bcl-xL but increased expression of apoptotic proteins Bax, PARP-1, EGR1, and cleaved caspase-3. Similarly, increased apoptosis was found among the pancreatic cancer cell line-derived xenograft in the SCID nude mice[39] or athymic nude mice[42,48] upon δ-TT or -TT (200-400mg/kg) treatment for 4 wk. This was evidenced by an increase in Bax and PARP-1 protein expression; increased cPARP-1, caspase-3 and -8 protein activity and reduction of antiapoptotic proteins such as Bcl-xL, survivin, cFLIP and XIAP in the TT-treated tumors[39,42,48].

Tumor formation in the KPC transgenic mice treated with δ-TT (200mg/kg) for 12 wk[49] or *LSL*$^{KrasG12D/+}$; *Pdx-1-Cre* transgenic mice treated with δ-TT (200mg/kg) for 12 mo[50] expressed lower levels of KRAS related oncogenic events including AKT, MEK and ERK activation. Researchers also observed cell cycle arrest, as evidenced by an increase of $p27^{kip-1}$ (a cell cycle repressor protein)[49,50] and $p21^{Cip1}$ (a cycle-dependent kinase inhibitor)[49] in pancreatic cancer tumors. Similarly, Hodul *et al*[43] also reported an increase in $p21^{Cip1}$ protein expression in athymic nude mice carrying MIA PaCa-2 cell-induced pancreatic tumors treated with 100 mg/kg of δ-TT daily for 3 wk.

Husain *et al*[49] also reported a decrease in the invasion, adhesion, and angiogenesis in tumors from KPC transgenic mice treated with δ-TT (200mg/kg) for 12 wk. It was evidenced by a decrease in angiogenic factors such as VEGF and clusters of differentiation (CD) 31 immunoreactivity[49]. Similarly, athymic nude mice with pancreatic cancer cell line derived xenografts when being treated with 400 mg/kg of g-TT for 28 d[41] and 200 mg/kg of δ-TT (twice daily) for 4 wk[48] showed a reduction in VEGF, MMP-9, CD31 and CD44. The same group also reported an inhibition in EMT, shown by reduced expression of the mesenchymal markers (N-cadherin and vimentin), and increased expression of the epithelial marker (E-cadherin)[48,49]. Interestingly, 12 wk of oral administration of 4 mg/kg α-TP (thrice weekly) in the *N*-nitrosobis (2-oxopropyl) amine-induced pancreatic cancer in the Syrian hamster did not affect the incidence of pancreatic tumor formation[37,38]. However, α-TP treatment decreased the incidence of liver metastasis compared to the negative control but not the number and size of liver metastasis *per* animal compared to the negative control[37].

Evidence from human clinical trial

Based on the selection criteria for this review, only one human study (NCT0098577) passed our selection criteria, in which vitamin E was used as a single drug intervention with complete peer-reviewed response in pancreatic cancer[53]. In this single-center, open-label, dose-escalation phase I trial conducted by Springett *et al*[53], 25 patients with resectable pancreatic ductal neoplasia were treated with δ-TT (200, 300, 400, 800 and 1600 mg twice daily) for 2 wk before and one dose on the day of pancreatectomy (day 14)[53]. Dysplastic and malignant tissues excised from these patients showed increased caspase-3 staining suggesting that oral δ-TT has beneficial effects on patients with pancreatic cancer[53].

A total of 5 trials (including NCT0098577) were found on ClinicalTrials.gov registry (https://clinicaltrials.gov/; Accessed 1 September 2022) using the search term "Vitamin E" and "Pancreatic Cancer". Two of the trials (NCT01446952 and NCT01450046) investigated the safety profile of vitamin E by the same team and reported the finding in NCT0098577. No data were made available from these two trials, so they were excluded from this review. The other study (NCT02681601) was filed by the University of California Los Angeles Hirshberg Pancreatic Cancer Centre to investigate the clinical outcomes of a dietary supplement enriched with natural vitamin E for pancreatic cancer patients. This study was also excluded from our review because it was terminated due to a low number of participants with no data published by the research team. Moreover, the supplement is a combination of natural vitamin E and other ingredients, so the efficacy of vitamin E cannot be accurately determined from this study. Another study (NCT04315311) which was also excluded from our review because this study investigated the role of pancrelipase rather than vitamin E in a patient with exocrine pancreatic insufficiency other than pancreatic cancer. As a result, there is no other good quality vitamin E intervention studies on human pancreatic cancer except the cited study (NCT0098577)[53]. Therefore, further larger and multi-center clinical studies are warranted to understand the effects of oral vitamin E on pancreatic cancer.

Mechanistic studies of vitamin E in the treatment of pancreatic cancer

The development and progression of pancreatic cancer relies heavily on its capability to proliferate and resist cell death[1,7,54]. Early stages of pancreatic tumors development are associated with a fibrogenic response that favors cancer cell proliferation and survival[1,4,5]. Vitamin E could exhibit its promising anticancer effect by disrupting cancer proliferation. -TT suppresses cell proliferation in pancreatic cancer cells by downregulating cell proliferative markers, namely cyclin D1[41], c-Myc[41], and Ki-67[43,48,49]. Overriding the cell cycle checkpoint is a common phenomenon in carcinogenesis, allowing tumor cells to replicate indefinitely[1]. Cell cycle entry is modulated by cyclin-dependent kinases (CDK) activity and its inhibitors ($p21^{Cip1}$and $p27^{kip-1}$). Activating the checkpoint inhibitor is thus a logical approach to limit cancer cell proliferation[1]. α-TP succinate induced G0/G1 cell cycle arrest in pancreatic cancer[35], while -TT induced G1 cell cycle arrest through increased expression of $p21^{Cip1}$[49] and $p27^{kip}$[43,49,50]. VES[31] and α-TP succinate[35] induced G2/M cell cycle arrest by suppressing Cdc2 (CDK1)[31], resulting in reduced proliferation among the pancreatic cancer cells.

Apoptosis is essential for cell survival, and its dysregulation drives the development of several diseases, including pancreatic cancer[8]. One of the hallmarks of pancreatic cancer is the ability to avoid cell death (such as apoptosis) and thus creating a conducive tumor microenvironment for tumor progression[8]. The sensitivity of cancer cells to treatment is modulated by the pro- and anti-apoptotic genes[18,55-58]. Treatment with VES, - or -TT induced apoptosis in pancreatic cancers by upregulating the apoptotic markers (Bax, and caspase-3) and downregulating the anti-apoptotic markers[31,39,41,42,47-50]. - and -TT suppressed expression of anti-apoptotic proteins Bcl-2, Bcl-xL, cIAP-1, XIAP and c-Flip [39,41,42]. However, Wang *et al*[47] reported that -TT did not affect protein expression of Bcl-xL, cIAP-1 and XIAP, suggesting there might be a varied response by vitamin E in regulating anti-apoptotic proteins of pancreatic cancers.

Inflammation-induced cancer progression is one of the inevitable oncogenic events in pancreatic cancer[3]. Activation of NF-κB is known to interfere with apoptosis processes and enhance cell survival [59]. NF-κB will be activated when IkappaB kinase phosphorylates the NF-κB-bound IκBα, leading to the ubiquitin-degradation of IκBα, and the nuclear translocation of the NF-κB p65-p50 dimer. This process activates inflammation-induced proliferation and cell survival[3,60], α-TP succinate[36] and -TT

[41] suppressed NF-κB activity in pancreatic cancer cells. Husain *et al*[39] demonstrated that - and -TT prevented the degradation of IκBα, thus suppressing the nuclear translocation of p65/p50 dimer. As a nuclear factor, NF-κB controls the transcription of proteins related to proliferation, apoptosis and cell cycle[61]. Both intrinsic (Bcl-2 and Bcl-xL) and extrinsic (cIAPs, caspase-8, and c-Flip) pathways are regulated by NF-κB, and NF-κB activation frequently tips the scales in favor of anti-apoptotic markers such as cFlip or the IAP (cIAP1/2 and XIAP)[61].

Additionally, KRAS-induced inflammation is another key oncogenic event in PDAC[62]. However, KRAS remains "undruggable" because of a lack of efficient inhibitors[63]. KRAS mutation accounts for 90–95% of fatal and metastatic PDAC[64]. Even though oncogenic KRAS remains "undruggable", KRAS relies on the two major downstream pathways, namely: (1) PI3K/AKT; and (2) Ras/Raf/MEK/ERK pathways to promote proliferation, and survival. Therefore, a prospective method of treating these KRAS-driven pancreatic cancers could be achieved by inhibiting its KRAS downstream signals[63,65].

The PI3K/AKT survival pathway is primarily involved in cancer cell proliferation[66]. The dysregulation of PI3K/AKT accounts for nearly 60% of PDAC patients[66]. Through phosphorylation, AKT activates the Bcl-2-associated death promoter, glycogen synthase kinase 3 (GSK-3), and FoxO-related transcription factors, all of which mediate cancer cell proliferation[66]. AKT activation was suppressed by -TT[40] or -TT[40,43,48,50], as evidenced by a reduction in phosphorylated AKT (pAKT). By inhibiting pAKT, -TT or -TT also modulated GSK-3β and Foxo3a as well as nuclear translocation in pancreatic cancer cells[40]. Foxo3a suppresses tumor growth by promoting cell cycle arrest and apoptosis. Phosphorylated AKT inhibits Foxo3a, resulting in its cytoplasmic sequestration. Dephosphorylation of FoxO3a leads to nuclear translocation and transcriptional activity conducive to apoptosis or cell cycle arrest[40].

The RAS/RAF/MEK/ERK pathway is one of the critical pathways in MAPK, that regulates proliferation, apoptosis, and cell cycle. The G0–G1–S phase cell cycle progression is also regulated by the RAF–MEK–ERK pathway in response to growth factor stimulation or oncogene activation. As a result, the pathway regulates the expression/activity of CDK and CDK inhibitors ($p21^{Cip1}$ and $p27^{kip-1}$)[67]. -TT or -TT inhibited the RAS/RAF/MEK/ERK pathway by suppressing MEK and ERK activation, which subsequently increased the expression of $p27^{kip-1}$, leading to cell cycle arrest at G1[40,43,48-50].

Tumor angiogenesis is a tightly controlled process, in which new blood vessels form in the tumor environment to provide oxygen and support tumor growth[1]. Apart from its role in the maintenance of the primary tumor ecosystem, tumor angiogenesis promotes tumor cell invasion and dissemination and the formation of new secondary tumor ecosystems at metastasized sites[68]. This process necessitates extensive interactions between endothelial cells, angiogenic growth factors, and extracellular matrix *via* pro-angiogenic signals[1,68]. -TT reduced angiogenesis in pancreatic tumor cells and thus reduced the oxygen supply to the tumor cells and slowed their growth[41,43,48]. -TT also inhibited the angiogenic factor as confirmed by a reduction in the CD31 immunostaining in tumor blood vessels[48,50]. To direct the tip cell migration and stalk cell proliferation during sprouting angiogenesis, VEGF and Notch signaling are activated[69]. In a bid to promote Notch-dependent angiogenesis, VEGF can cause the production of jagged ligands, which in turn boosts Notch expression in cancer endothelial cells[69]. The Notch signaling pathway is important in cancer stem cell renewal, differentiation, and survival[70]. Husain *et al*[48] supported the application of -TT in targeting the PCSCs' self-renewal capacity by suppressing Notch 1 receptors and other pluripotent transcription factors.

Tumor cells will eventually gain the ability to metastasize, leaving the primary site and spreading throughout the body, causing severe organ failure and eventually death[71]. Invasion, the first step in tumor cell metastasis, begins when cancer cells detach from the tumor mass, acquire the ability to actively move, and invade surrounding tissues through the adjacent basement membrane[71]. - and -TT downregulated the tumor invasion biomarker MMP9 and prevented tumor invasion[41,48]. Adhesion is another critical step in metastasis, and it can occur directly between tumor cells and endothelial cells with the help of adhesion-associated proteins[72]. -TT also prevented the adhesion in cancer cells by suppressing the adhesion marker ICAM[41]. One of the key events in driving tumor metastasis is EMT, a complex biological process in which epithelial cells lose their phenotype and gain mesenchymal characteristics[73]. EMT is a potential target for cancer metastases due to the tight coupling of these growth factors that sustain the growth of cancer cells. Preventing the activation signal of EMT markers, such as E-cadherin, N-cadherin and vimentin, is one of the ways to target the EMT process in cancer [73]. On that note, -T3 treatment reversed EMT by increasing the expression of the epithelial marker (E-cadherin) and decreasing the expression of the mesenchymal markers (N-cadherin and vimentin)[48,49], indicating its potential in preventing metastasis in pancreatic cancer. Based on our scoping review, vitamin E modulates proliferation, cell death, inflammation angiogenesis, and metastasis in pancreatic cancer cells (Figure 3).

DISCUSSION

Safety and bioavailability concerns of vitamin E

There is a global initiative to promote the consumption of vitamin E *via* supplementation or vitamin E-

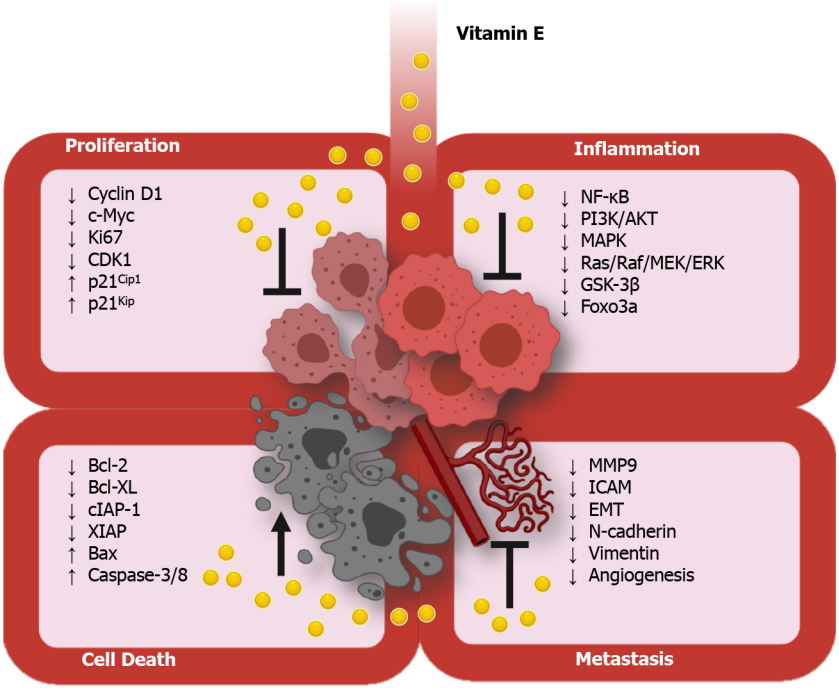

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Figure 3 Role of vitamin E in modulating proliferation, cell death, inflammation and metastasis in pancreatic cancer. c-Myc: Cellular myelocytomatosis; CDK1: Cyclin-dependent kinase 1; Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra-large; cIAP-1: Cellular inhibitor of apoptosis protein-1; XIAP: X-linked inhibitor of apoptosis protein; Bax: Bcl-2 associated X protein; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: Phosphoinositide 3-kinase; AKT, Protein kinase B; MAPKL Microtubule-associated protein kinase; Ras/Raf/MEK/ERK: Rat sarcoma virus/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase (MAPK) kinase/extracellular signal-regulated kinase; GSK-3β: Glycogen synthase kinase-3 beta; Foxo3a: Forkhead box transcription factor-3a; MMP9: Matrix metalloproteinase 9; ICAM-1, Intercellular adhesion molecule 1; EMT: Epithelial-to-mesenchymal tumor transition. The figure is created by author and generated using Biorender.com.

fortified food since the majority of the intake values are far below average[74]. As a result, the clinical safety and toxicity of vitamin E supplementation must be evaluated. Regrettably, there has been only a small number of conflicting reports on vitamin E safety evaluation in recent years[53,75-78]. For the present review, animal doses were translatable to human equivalent doses by multiplying the animal doses with a factor of 0.081 or 0.135 for mouse or hamster models, respectively, assuming a human adult's average weight is 60 kg[79]. In a meta-analysis by Miller *et al*[75], it was discovered that the elevated risk of death was only noticeable at a vitamin E dose of 2000 IU/d (1340 mg/d or 22.3 mg/kg), which is higher than the adult upper limit. According to El-Hak *et al*[76], subacute administration of 2000 mg/kg (324 mg/kg in humans) α-TP acetate for 30 d in male albino rats caused liver toxicity by altering the levels of alanine transaminase, aspartate transaminase, and the histological structure of the liver. However, no mortality or adverse reproductive effects was reported[76]. In contrast, female mice treated with 500 and 1000 mg/kg (40.5 and 81.08 mg/kg in humans) of palm vitamin E for 14 and 42 d had a higher bleeding and clotting time[77]. Serum creatinine and kidney weight were increased in these mice but no renal impairment was observed[77]. However, Kappus *et al*[78] noted that numerous scientifically credible studies consistently did not identify any significant negative effects related to α-TP supplementation at intakes up to 3200 IU/d (2144 mg/d or 35.7 mg/kg). A clinical trial recorded no adverse effects in pancreatic cancer patients treated with 3200 mg/d (53.33 mg/kg) of δ-TT[53]. More conclusive safety studies are warranted to investigate whether high-dose vitamin E is safe for humans.

One of the possible underlying reasons for variable efficacy and safety of vitamin E could be attributed to its poor oral bioavailability, particularly TTs[20,80]. In the mice given δ-TT (100 mg/kg for 6 wk), Husain *et al*[51] found that δ-TT was 10-fold more concentrated in the pancreas than in tumor, indicating that δ-TT may not be available for pancreatic tumor through oral administration. The pharmacokinetic limitation of TT is caused by its solubility, absorption, distribution, and rate of elimination[80]. In healthy human volunteers, the 24-hour area under the curve (0-∞) of TT rich fraction increased by roughly 2-fold in the fed state compared to the fasting state, showing that food consumption increased the absorption of vitamin E, thereby enhancing its bioavailability[81]. TTs reach their peak plasma concentration (Tmax) at 3-4 h after a meal but α-TP took 6 h to reach its Tmax[82]. However, α-TP achieved a higher peak plasma concentration compared to TTs (1.82-2.92 μM *vs* 0.89-1.92 μM, respectively)[82]. The elimination half-life (t1/2) of α-TP in humans ranged from 2.3 to 4.4 h for various TT isomers[83]. Therefore, TT supplementation is typically advised to be taken twice daily to maintain its bioactive levels[80]. This was used in most of the reviewed studies where TT was

administered twice daily to mice[39,42,43,47,48,50,51] and humans[53].

To address the issue of low bioavailability, researchers are altering or modifying the composition of TT isomers in a fraction, developing new emulsification with cyclodextrin, or constructing new nano-formulations such as nano-vesicles, solid-lipid nano-particles, nano-structured lipid carriers, nano-emulsions, and polymeric nano-particles[20,80]. However, very few studies have reported the bioavailability and toxicity profiles of nano-formulations[20,80]. Debele *et al*[35] illustrated that a nanoparticle-based drug delivery system using glutathione-sensitive micelle loaded with α-TP succinate (PAH-SS-PLGA-TOS), was more effective at increasing the cytotoxicity, apoptosis and G2/M cell cycle arrest in Pan02 pancreatic cancer cell compared to free α-TP succinate. The synergistic effects of the nano-formulated TOS in the study suggest that PAH-SS-PLGA micelles may be a good carrier for TOS, increasing the therapeutic potency of the compound[35]. Independently, Maniam *et al*[21] also showed the niosomes entrapped TT and gemcitabine can enhance activity of gemcitabine. More studies are therefore required to provide important insights into the various applications, toxicity, and pharmacokinetics of vitamin E formulations.

Limitations of the current preclinical and clinical models in evaluating the role of vitamin E in cancer

It is critical to select an appropriate cancer model to investigate the respective research hypothesis[84]. PDAC induced by nitroso-bis(2-oxopropyl) amine in the Syrian hamster shared common human genetic alteration including KRAS mutation. However, the development of concomitant malignancies in the liver and lung jeopardized this pancreatic cancer model[85]. Moreover, a rat-based PDAC model had a limited subset of tumor types and grades. Similar to other cancers, these limitations prompt the development of mouse xenograft and transgenic mouse models. These mouse models demonstrate a greater advantage given the animals' small size, lower cost, ease of breeding, short life span of 1-2 years, and ability to recapitulate genomic and pathological alteration in humans[84]. Only two studies used the *N*-nitrosobis(2-oxopropyl) amine-induced pancreatic cancer in Syrian hamsters[37,38]. Almost all animal studies reviewed used the subcutaneous[39,42,43] or orthotopic[41,48,51] tumor xenograft or transgenic[47,49,50] mouse model. Out of 291 registered trials under the search term 'vitamin E' (https://clinicaltrials.gov/; accessed on 22nd August 2022), only three trials were on pancreatic cancer. Two studies were conducted using multiple dosing δ-TT (NCT01450046) or single dosing (NCT01446952) in healthy humans. Only one study was conducted using δ-TT on patients with resectable pancreatic exocrine neoplasia (NCT00985777)[53]. Therefore, to better determine the effects of vitamin E for pancreatic cancer patients, we advocate for more studies using cutting edge genetical engineered mouse models[86-88], organoids[89,90] or organ-on-chip[91] to further evaluate the role of vitamin E in pancreatic cancer. A novel drug delivery system using a novel nanoformulation[20,80] or complex ion delivery system[54,92] may strengthen vitamin E's efficacy in cancer.

Considerations for clinical use of vitamin E as an anticancer treatment

Assuming a healthy adult is 60 kg in weight, the American Food and Nutrition Board recommends a daily upper limit of 1000 mg/day (or 16.67 mg/kg) of vitamin E[93]. The human equivalence dose (HED) of vitamin E used in hamsters (4-100 mg/kg) was only 0.54-8.1mg/kg, which is far from the adults' daily upper limit of 16.67 mg/kg. However, the HED doses in mice (200-400 mg/kg) were 16.216-32.43 mg/kg, which is approximate the adult's daily upper limit. Although 32.43 mg/kg exceeds the recommended intake for adults, Kappus and Diplock[78] noted that there was no significant negative effects associated with α-TP supplementation even up to 3200 IU/d (2144 mg/d or 35.7 mg/kg). Independently, Springett *et al*[53] also recorded no adverse effects in pancreatic cancer patients treated with 3200 mg/d (53.33 mg/kg) of δ-TT. All findings suggest that vitamin E could be a safe therapeutic agent even above the recommended daily intake.

Our review concluded α-TP supplementation failed to inhibit the growth of pancreatic carcinoma *in vivo*[37,38] and only suppressed the proliferation of pancreatic cancer cells growth at high doses[34-36]. None-the-less, mounting mechanistic and preclinical animal studies demonstrated that - and -TT have a significantly better pancreatic cancer-preventive activity than other forms of vitamin E. However, α-TP could reduce TT's antioxidant potential, impairs its anticancer effects and accelerates the breakdown of TT in the body[94,95]. As a result, it appears that TP-TT mixtures may not be efficient in preventing or treating pancreatic cancer. Furthermore, compared to -TT, -TT or gemcitabine alone, both - and -TT in combination with gemcitabine are more effective in the treatment of pancreatic cancer. - and -TT improve the antitumor efficacy of gemcitabine by inhibiting NF-κB, cell proliferation, and inducing apoptosis, implying that TT may be more effective as an adjuvant rather than a replacement for standard therapy in pancreatic cancer treatment.

LIMITATIONS OF THIS SCOPING REVIEW

We only considered articles that were indexed by PubMed and Scopus; therefore, studies published in non-indexed journals and grey literature may have been overlooked. Furthermore, no critical appraisal of evidence sources was performed since only a small number of papers were eligible for the review.

Future scoping review on the similar topic may include a critical appraisal when more peer-reviewed studies have been published.

To comprehend the molecular actions of vitamin E, only studies that focused on vitamin E or its isomers were included in this scoping review. In reality, vitamin E is present in many foods and it may interact with other nutrients to produce more complex pharmacokinetic and pharmacodynamic interactions. This aspect was not considered in the current study. Most studies did not compare the effect of vitamin E on cancer cells or tumors with standard therapy. We are not able to draw any conclusive remarks on this aspect as well. Thus, more thorough research is required to validate vitamin E as a clinical therapeutic option for PDAC.

CONCLUSION

Based on the available studies, vitamin E modulates proliferation, cell death, angiogenesis, metastasis and inflammation in pancreatic cancer cells (Figure 3). However, there are limited studies to address its safety concern and low bioavailability. Currently, available preclinical and clinical studies should be re-visited with a more in-depth analysis to further investigate the efficacy and safety of vitamin E in pancreatic cancer.

FOOTNOTES

Author contributions: Ekeuku SO, Etim EP, Pang KL, Chin KY, Mai CW were involved in the data collection and validation; Ekeuku SO, Etim EP provided the first draft of the manuscript; Ekeuku SO, Etim BP, Mai CW prepared the figures and tables; Ekeuku SO, Etim EP, Pang KL, Chin KY, Mai CW wrote and finalized the manuscript; Chin KY and Mai CW designed the outline and coordinated the writing of the paper.

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Country/Territory of origin: Malaysia

ORCID number: Sophia Ogechi Ekeuku 0000-0002-5485-4592; Effiong Paul Etim 0000 0001 6437 8772; Kok-Lun Pang 0000-0003-2219-6297; Kok-Yong Chin 0000-0001-6628-1552; Chun-Wai Mai 0000-0001-6532-184X.

Corresponding Author's Membership in Professional Societies: Chinese Society for Cell Biology, S233103897M; European Association for Cancer Research, EACR27345; International Pharmaceutical Federation, 36982; Royal Society of Chemistry, 538435; Malaysian Pharmaceutical Society, 8141.

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