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Review

Ellagic Acid - A Dietary Polyphenol with Anticancer Activity that Deserves More Consideration

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Abstract

Ellagic acid (EA) the principal polyphenol of pomegranate (*Punicca granatum*) is renowned for its beneficial therapeutic activity in several diseases including cancer. Studies have shown that EA exerts a carcinopreventive effect on many cancer cells, inducing cell cycle arrest and apoptosis, and limiting neovascularization and cell migration. In animal models, EA could reduce tumor development, number and size. Research detected that EA exerts its activity on cancer cells through several signaling pathways, without affecting the function and viability of normal cells. While the investigation of the carcinopreventive effect of EA has been carried out in great detail *in vitro*, research on animal models and clinical studies is rather scanty, leaving the impression that its potential value as a carcinopreventer is somewhat neglected. This work aims to review the effect of EA on different types of cancer and to attract researchers' attention to the potential of EA to serve as an adjuvant to anti-cancer drugs.

Keywords

Ellagic acid; cancer; polyphenols; chemoprevention; cytokines; immunity

1. Introduction

Pomegranate (*Punicca granatum*) has a long history of use as a delectable fruit and a remedy for various inflammatory and other illnesses [1, 2]. No wonder it makes sense that the fruit has been treasured by virtually all religions and is thought to have mystical characteristics [3]. Research showed that ellagic acid (EA), a polyphenol being the most active substance in pomegranate is found in more vegetables and fruits like strawberries, blackberries, raspberries, cranberries, pecans, wolfberries, and other plant foods. Along with EA, fruits and vegetables also contain a significant amount of polyphenols that have anti-inflammatory, antioxidant, and immunomodulatory activities, highlighting the health benefits of the Mediterranean diet [4]. Moreover, the discovery that polyphenols, particularly those in pomegranates, have an anticancer effect has stimulated scientific research to identify the processes underlying their detrimental impact on the development of cancer cells. Polyphenols, especially EA, may induce cancer cells to undergo a mitotic arrest at the G2/M phase, damage DNA, encourage apoptosis, alter glycolytic pathways, and interfere with mitochondrial function [5-8]. Incubation of normal human lung fibroblast cells (HEL299) serving as control, and colon (Caco2), breast (MCF-7 and 578T) and prostatic (DU145) cancer cells with 10-100 μM/L of EA for 24 hours resulted in increased adenosine triphosphate (ATP) and metalloproteinases production in the control cells, whereas that of the cancer cells was dose-dependently decreased, explaining their enhanced apoptosis and decreased viability observed after the EA effect [9]. EA has been demonstrated to influence the immunological balance between mononuclear cells and those from the HT-29 and RKO human colon cancer cell lines. Both lower and higher EA concentrations reduced IL-1β, IL-6, IL-1ra and IL-10 production by mononuclear cells, but had no impact on IFNγ generation. It was suggested that suppressed production of proinflammatory cytokines would attenuate inflammatory reactions and slow cancer development [2, 10]. Recent studies showed that EA might affect several hub genes and the cellular tumor antigen P53 and WNT signaling pathways in cancer cells leading to apoptosis and cell death [11, 12]. Additionally it was reported that EA interfered with the mitochondrial functions in colon carcinoma (HCT116) and breast adenocarcinoma (MCF7) cell lines by inhibiting Drp-1 mitochondrial dynamic protein which is essential for cell division [13]. Figure 1 demonstrates that EA damages cancer cells by inducing phagocytosis, autophagocytosis and necrosis. In addition to chemotherapy and radiotherapy, EA exerts a significant anticancer effect [14]. These and other studies indicate that EA is a promising additive to the armamentarium of anti-cancer remedies. On the other hand, the advantageous effects of EA were primarily seen when applied to animals or *in vitro*. With the hope that the hereby-reported findings will encourage clinical trials, this work aimed to review recent observations regarding the mechanism of the carcinopreventive effect of EA on the various forms of cancer.

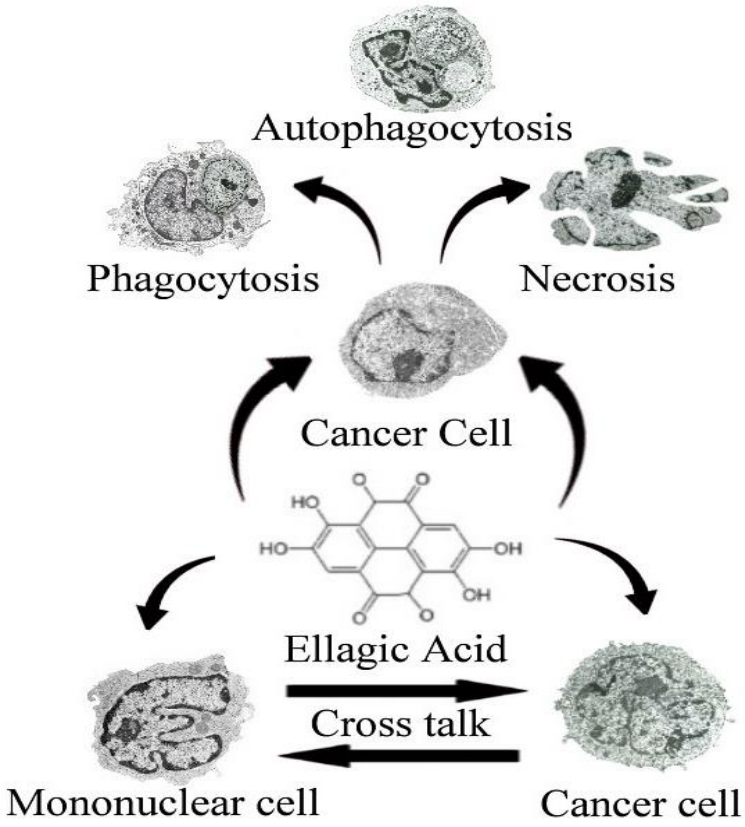

Figure 1 Ellagic acid exerts chemoprevention by inducing phagocytosis, autophagocytosis and even death of the cancers cells via various mechanisms detailed in the text. In addition, it activates mononuclear cells for cytokine production and a cross talk between immune and cancer cells.

2. Esophageal and Gastric Cancers - Table 1

Research on the carcinopreventive impact of EA on esophageal cancer has been carried out on rats with N-nitroso methyl benzylamine (NMBA)-induced carcinogenesis. The incidence of tumors in the tumor-bearing animals was reduced by EA administration to the animals by 66.7% as opposed to 100% in the untreated animals, but their multiplicity was unaffected [15]. Diets reach in phytochemicals, including EA have a protective effect against the onset and progression of gastrointestinal tract cancers [16-18]. This effect was attributed to an impaired NMBA cells' metabolism [19], a process observed in the liver microsomes and esophageal explants taken from rats NMBA bearing cancers fed with a diet containing EA and other polyphenols [20]. Studies in *vitro* indicate that EA is effective against gastric cancer development. Treatment with EA of AGS and SNU601 gastric cancer cells decreased the production of the matrix metalloproteinases MMP7 and MMP9 implicated in cell migration and metastasis, as well as lowering the activity of several proinflammatory factors, including cyclooxygenases 1 and 2 (COX1, COX2) [21]. Increased AGS cancer cells' death was reported *in vitro* and *in vivo* in immunosuppressed mice bearing human gastric cancer tumors following administration of EA. In these investigations the effect of EA processed through alterations of genes linked with apoptosis and inflammation including inhibited proinflammatory cytokine production, leading to a significant decrease in tumor size [22].

Table 1 Type of cancer, EA concentrations and parameters determined.

Type of cancer	**Type of experiment**		**Elagic acid dosage**	**Parameters measured***	**Ref No.**
	In vivo	*Cell Lines*			
Esophageal	Rats		0.4-4 mg/kg	Number of tumors	[15]
Esophageal	Rats		0.4-4 mg/kg	Number of antineoplastic lesions	[17]
Gastric		AGS, SNU601	3-10 μM	CDK1, COX1, COX2, Snail, Twist1, C-mucin	[21]
Gastric	Mice		10-50 mg/kg	MMP-2. MMP-9, P53, BAX, APAF1, BCL2, INOS, IL-8, TNFα	[22]
Gastric		SW480	10 M	Cell cycle, GF-II, P53, apoptosis	[23]
Colorectal	Rats		60 mg/kg	P53, cell proliferation, apoptosis	[24]
Colorectal		HCT-15	20-120 μM	Proliferation, apoptosis, ROS, AP, LDH, BCL-2, AKT, DNA	[25]
Colorectal		HCT-116, Caco-2	0-200 μg/ml	Cell cycle, proliferation, AKT phosphorylation	[26]
Colorectal		HCT-116	25 μM-150 μM	Change in gene expression, cell proliferation, apoptosis	[27]
Colorectal		HCT-116	0-150 μM	Cell cycle, TGF-β1/Smad3 pathway	[28]
Colorectal		HCT-116	20 μM-40 μM	Apoptosis, autophagy. AMPK/mTOR signaling pathway	[29]
Colorectal		HT-29		Proliferation, apoptosis. *BAX:BCL-2 ratio*	
Colorectal	Mice		10 mg/kg	Effect on colonic epithelium	[30]
Colorectal	Mice		10 mg/kg	Peroxidative damge induced by cisplatin	[31]
Colorectal		Caco-2	10 μM	MAPK signaling genes	[32]

*CDk1 -cyclin dependent kinase 1; Snail, Twist -transmission f-r; MMP -metaloproteinase; P53 - cell cycle regulator; BAX - apoptosis regulator; APAF1-Apoptotic protease activating f-r; BCL2 - B cell lymphoma regulator; INOS - inducible nitric oxide synthase; AP- alkaline phosphatase; LDH - lactic dehydrogenase; AKT - protein kinase B; TGF-β1/Smad3 pathway - transforming growth f-r β/cancer growth proteins; AMPK/mTOR - activated protein kinase; *BAX:BCL-2 - apoptosis regulator;* MAPK - mitogen activated protein kinase

3. Colorectal Cancer

Colorectal cancer gained a tarnished reputation being a malignancy with high morbidity and fatality rates. Ways to support surgical and medical treatment with natural polyphenols have shown promising results, however observed predominantly on colorectal carcinoma cells in vitro [33]. Treatment of SW480 colon cancer cells with EA caused apoptotic cell death mediated through activation of P53 and P21 and downregulation of insulin-like growth factor (IGF-II) which is highly expressed in this type of cancer cells [23]. In rats with 1,2-dimethylhydrazine (DMH)-induced colon cancer, ornithine oxidase expression was raised. After oral administration of EA to the animals, their antioxidant activities were severely compromised, resulting in decreased tumor progression [34]. Similar results under comparable experimental conditions showed enhanced production of the proapoptotic protein P53 and decreased malignant cell proliferation [24]. Given to mice bearing DMH-induced colon carcinoma, EA was found to be a potent anti-inflammatory mediator acting by reducing NF-kB, COX-2iNOS and the proinflammatory cytokines IL-6 and TNF-α [25]. The PI3K/AKT (phosphatidylinositol 3-kinase) pathway, which is essential for the maintenance of the normal cell cycle, was inactivated in subsequent investigations with HCT-15 colon cancer cells treated with EA and induced a cell cycle arrest at G2/M phase. Additionally, EA increased ROS production, encouraged apoptosis and inhibited cancer cell proliferation [25]. The anti-proliferative and pro-apoptotic activity of EA was detected to be dose-dependent in cells of the colorectal cancer lines HCT-116 and Caco-2, processes mediated by depression of p-AKT activity and reduced expression of the growth promotion protein K-Ras [26]. HCT-116 colon cancer cells treated with EA showed increased apoptosis and inhibited cell cycle and proliferation by altering the expression of many genes and TGF-β1/Smad3 signaling pathways [27, 28]. Reducing the phosphorylation of adenosine monophosphate-activated protein kinase AMPK/mTOR pathway is another mechanism by which EA induces apoptosis and autophagy and inhibits the growth of HCT116 cells [29]. Notable, not only EA may affect cancer cells. It has been reported that pomegranate juice inhibits proliferation and promotes apoptosis in HT-29 human colon cancer cells by targeting TNFα induced COX2 and suppressing activation of AKT, an essential protein needed for cell development [35]. EA exhibits complementary effects to traditional chemotherapy. When given together, EA boosted the cytotoxicity of 5-fluorouracil, the leading drug now available for the treatment of colon cancer, thus enhancing its ability to reduce the proliferation of colorectal carcinoma cells [36]. When EA and cisplatin were given together to mice with colon cancer caused by DMH, the damaged colon epithelium's appearance improved [30] and the cisplatin cytotoxicity was significantly subsided by reducing ROS injury sorafenib to the cells [31]. EA research has drawn attention to the anti-cancer effect of urolithin, a metabolite produced by gut microbiota from food-derived EA. It was shown that urolithin enhanced the effect of 5-fluorouracil, by increasing caspase 8 and 9 activation and the drug's ability to arrest the cell cycle at the G2/M phase [37]. When EA and urolithins were administered to Caco-2 cells, the inhibition of cell growth during the S- and G2/M phase was more pronounced. This effect was accompanied by altered expression of growth factor receptors and MARK signaling genes controlling cell cycle and proliferation [32]. The fundamental idea is that EA possesses a favorable effect in suppressing the growth of colon cancer cells, which should be further investigated and its quality as a chemoprevention should be affirmed.

4. Hepatocellular and Other Cancers - Table 2

Hepatocellular carcinoma has been recognized as one of the most malignant and deadly cancers. The lack of effective medications attracted researchers' interest in the carcinopreventive effects of nutrients and their phytochemicals, comprising EA [38]. Studies have shown that EA may restrain the advancement of hepatocellular carcinoma through several pathways [39]. Hepatocellular carcinoma HepG2 cells exposed to EA exhibited enhanced apoptosis and mitotic arrest at the G1 phase, activities brought on by activation of the p21 gene inducing DNA damage, and downregulation of the MCM2-7 genes involved in genome replication [40]. It was shown that EA alters lipid metabolism with a positive impact on liver disorders by inhibiting the secretion of the lipid transporter apolipoprotein B from human hepatoma cells HepG2, while increasing the secretion of apolipoprotein A [41]. Notably, pomegranate derivatives and metabolites may function as carcinopreventive agents in addition to EA. Pomegranate emulsion made from pomegranate aqueous extract and pomegranate seed oil administered in a diethylnitrosamine (DENA) induced model of rat hepatic carcinoma prompted the suppression of the oxidative stress associated with liver cancer progression through nuclear factor E2-related factor 2 (Nrf2)-mediated antioxidant mechanisms [42]. Rats with DENA hepatocellular tumors responded favorably to a combination of EA and cineole (eucalyptol), as evidenced by the reduction of tumor-related growth factors like transforming growth factor beta-1 (TGF-1), vascular endothelial growth factor (VEGF), metalloproteinase-9, and other tumor markers, as well as an improvement in histological findings [43]. In rats with hepatocellular carcinoma, the carcinopreventive effect of EA was compared with that of doxorubicin. When contrasted to untreated rats, treated animals significantly decreased their levels of VEGF, signal transducer and activator of transcription 3 (STAT3), transmission activator glypican-3, alpha-fetoprotein, and cytokine signaling 3 [44]. EA decreased the cardiotoxicity of doxorubicin in treated animals and enhanced the apoptotic and anti-viability effects of doxorubicin and cisplatin on hepatocellular cancer cells [45]. Similar results were obtained in a hepatocellular carcinoma model when EA was given together with sorafenib, a potent protein kinase inhibitor, an activity exerted by increasing ROS and the mitochondrial membrane potential of the cancer cells [46]. The EA intestinal metabolite, urolithin A, was found to wield an anti-inflammatory, anti-proliferative and antioxidant effect on the intestinal tract. In addition, it reduced Ras-related C3 botulinum toxin substrate 1 (Rac1) and p21-activated kinase (PAK1) activity involved in cancer cells' cytoskeleton reorganization, motility and growth [47], thus providing potential chemoprevention [48]. HepG2 hepatoma cells showed decreased proliferation and reduced oxidative stress mediated by inhibited activity of β-catenin, c-Myc and cyclin D1, cytoplasmic proteins that sustain normal intercellular adhesion and regulate cellular differentiation and proliferation. On the other hand, p53 and mitogen-activated protein kinase (p38-MAPK) expression was amplified [49]. EA enhanced the radiosensitizing effect on the development of HepG2 cells by increased ROS generation, an arrest in the G2/M phase and inhibited production of the proinflammatory mediators IL-6, COX-2 and TNF-α [50]. At the very least *in vitro*, EA appears to be a hopeful adjuvant in treating hepatocellular carcinoma.

Table 2 Type of cancer, EA concentrations and parameters determined.

Type of cancer	Type of experiment		Ellagic acid dosage	Parameters measured*	Ref No.
	In vivo	*Cell Lines*			
Hepatocellular		HepG2, Hep38, Hepa 1-6	0-50 µM	Mitotic arrest, activation of p21 gene, apoptosis	[40]
Hepatocellular		HepG2	Up to 50 µM	ApoA-1 and ApoB	[41]
Hepatocellular	Rats		60 mg/kg	Liver tests, mRNA, TGF-β1, FSCN1, MMP-9, and VEGF	[43]
Hepatocellular	Rats		50 mg/kg	Alfa fetoprotein, glycan-3, IL-3, VEGF	[44]
Hepatocellular		HepG2, SMMC-7221	20-60 µM	Caspases 3 and 9, PARP, Apoptosis	[45]
Hepatocellular	Rats	HCC	2-5 µM	ROS, cell viability, caspase-3, mitoch. membrane potential	[46]
Hepatocellular		HepG2	10 -100 µM	Cell viability and proliferation	[50]
Pancreatic		MIA PaCa-2, HPAF-II	3 µM	DNA fragmentation. Cell proliferation, tumor volume	[51]
Pancreatic		PANC-1	0.2.5-10 µg/ml	Cell growthan migration, COX-2, NF-kB, E-cadherin, vimentin	[52]
Pancreatic		MIA PaCa-2 PANC-1	10-50 mmol/L	Apotosis, NF-kB, caspase activation	[53]
Pancreatic	Mice	PANC-1	0-40 mg/kg	Cancer growth, AkT, Shh, Notch pathways	[54]
Pancreatic		PANC-1, AsPC-1, MIA PaCa-2	0-1000 µM	TGF-β, metalloproteinases 2,3 E-cathedrin	[55]
Lung	Mice		0, 40, 80 mg/kg	Cell growth, AMPK. HIF-1α	[56]
Lung	Mice		12 µg/ml of drinking water	GSH, NADPH-dependent lipid peroxidation	[57]
Breast		MCF-7	1-30 µg/ml	Cell cycle, TGF-β/Smads pathway	[58]
Breast		MCF-7, MDA-MB-231	1-10 µM	Proliferation, apoptosis, CDK6	[59]
Breast		MDA-MB-231	2.5-20 µM	Angiogenesis, proliferation, migration, VEGFR-2 pathway	[60]
Breast	Rats		400 ppm w/w Orally	microRNA modulation	[61]
Breast		MCF-7	10 µM	Apoptotic sensitivity to γ- radiation	[62]
Genital tract		SKOV-3, ovary	IC_{50} of 36.6 µmol/L	Beclin-1, ATG-5, LC31/II, Bax, mTORC1, AMPK	[63]
Genital tract		A2780, ES-2, ovary	10-15 µg/mL	MMP2, MMP9	[64]
Genital tract		A2780, ovary	10 µM	Migration, proliferation, apoptosis, ErbBr, ROS,	[65]

Genital tract		Ishikawa cells, endometrial	20 μM	ROS, NHE1 expression	[66]
Genital tract		KLE, AN3CA, endometrial	20 μM	Proliferation, apoptosis, PI3K, MMP9	[67]
Genital tract		HeLa, SiHa, C33A, cervical	0-30 μM	Proliferation, cell cycle, STAT3, Janus kinase 2	[68]
Genital tract		HeLa, cervical	2.5-10 μM	AKT/mTOR, IGFBP7	[69]
Genital tract		HeLa, cervical	20 μM	Cell cycle arrest	[70]
Genital tract		HeLa, cervical	0-60 μM	P53, ROS formation, DNA damage	[71]
Prostate		PC3	8-100 μM	Viability, STAT3, ERK, AKT, IL-6	[72]
Prostate		PC3	10-100 μM/L	Proliferation. PARP, Bax, Bcl-2, Procaspase-3, -6, -8, 9	[73]
Prostate		LnCap, HO1, HO-2 CYP2J2	25-50 μM	VEGF, OPG, mRNA	[74]
Prostate		PC3 human PLS10 rat	0, 25,50 μM	Motility, invasion, MMP-2	[75]
Prostate	Rats	LnCap, DU145, PC-3	25-125 μM	Suppressed carcinogenesis, caspase 3, Bax/Bcl-2 ratio	[76]
Bladder		TSGH8301	0-75 μM	Apoptosis, viability, mitotic arrest, P21, P53, CDC2, BAD, DNA	[77]
Bladder		T24, HT-1376, UM-UC3	5-60 μM	Cell invasiveness, VEGF-A, VEGFR-2, PD-L1	[78]
Melanoma		WM115, A375	40 μM	Migration, invasion, proliferation, EGFR, vimentin	[79]
Glioblastoma		U251	0-200 μM	Mitotic arrest, apoptosis, DR4, DR5, CHOP, GRP78	[80]

*ApoA-1, ApoB - lipoproteins; VEGF - vascular endothelial growth f-r; FSCN1 -fascin-actin binding protein; MMP -metalloproteinase; VEGF - vascular endothelial growth f-r; PARP - poly(ADP-ribose) polymerase; ROS -reactive oxygen species; NF-kB - nuclear f-r kappa-light-chain-enhancer of activated B cells; AkT - serine-threonine protein kinase; Shh -sonic Hedgehog proteins; Notch - immunomodulator; AMPK - activated protein kinase; HIF-α - hypoxia inducible f-r α; NADP - nicotinamide adenine dinucleotide phosphate; TGF-β/Smads - transforming growth f-r β/transcription protein; CDK6 - cyclin dependent kinase; ATG-5 - autophagy related protein; LC31/II - light chain protein; BAX - apoptosis protein; mTORC-1 - mediator of temporal control growth; AMPK - activated protein kinase; ErbBr - epidermal growth f-r receptor; NHE1 -Na^+/H^+ exchanger 1; PI3K - phosphoinositide 3-kinase; STAT3 - transcription transducer activator; AKT3 - protein kinase; IGEBBP7 = insulin growth f-r; ERK - extracellular regulated kinase; P53 -tumor antigen; OPG - osteoprotein; CgA - carcinoid marker; p75NGFR - nerve growth f-r; DNMT-1 - methyltransferase; CDC2 - cyclin dependent kinase; BAD - pro-apoptotic protein; PD-L1 - programmed death ligand; DR4 and DR5 - necrosis f-r receptors; CHOP - pro-apoptotic transmission f-r;GRP78 - glucose related protein.

5. Pancreatic Carcinoma

Despite advancements in surgery and chemotherapy, pancreatic carcinoma is notorious for having the worst fatality rates of all cancers. In order to act as therapeutic adjuvants, attempts are made to mobilize phytochemicals, along with EA. *In vitro* research has produced encouraging findings. Human pancreatic carcinoma cells MIA, PaCa-2 and HPAF-II treated with EA demonstrated increased apoptosis and reduced cell proliferation by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (Nf-kB) activity. This effect was augmented when EA was given with embelin, a phytochemical isolated from the herb *Ardisiae Japonicae* which operated by decreasing STAT-3 phosphorylation [51]. Cheng et al. [52] incubated human pancreatic cancer cells PANC-1 with EA and observed a dose-dependent suppression of cell growth, mitotic arrest at the G1 phase and reduced cell migration. EA-treated PANC-1 xenografted mice showed longer lifetimes and subdued tumor growth. The favorable effect of EA on tumor progression was explained by its restraining effect on COX-2 and Nf-kB activity. Triggering the mitochondrial pathway of apoptosis in the cancer cells and inhibiting Nf-kB activation are other ways by which EA attenuates tumor development [53]. In PANC-1 tumor-bearing nude mice, the decrease of growth, angiogenesis, and metastasis, and treatment with EA considerably inhibited tumor progression [54]. EA induced apoptosis on PANC-1, AsPC-1 and MIA PaCA-2 pancreatic cancer cell lines through activation of caspases 3 and 9, suppression of metalloproteinase 2 and 9 expression, as well as that of TGFβ (transforming factor β) which is mighty cell proliferation inhibitor [55]. The available information provides a strong foundation for future studies that will stabilize the prospect of using EA as an additional therapeutic option for this precarious type of cancer.

6. Lung Cancer

In vitro research suggests that polyphenols, particularly EA, may exhibit an anti-cancer effect in this malignancy. Lung cancer cells (A549) treated with 0.06 μM of EA showed a marked inhibition of sphingosine kinase 1 (SphK1) production, an enzyme critical for cancer cell proliferation and survival. In contrast, human embryonic kidney cells serving as control were not affected [81]. Duan et al. [56] have reported that EA inhibited lung cancer cell development by suppressing ATP level, the inner membrane mitochondrial potential on the one hand, and AMPK activation on the other. Also, when given to tumor-bearing mice, EA slowed tumor growth, reduced HIF1α level and raised AMPK production. The effect of EA on N-nitroso diethylamine-induced tumorigenesis mice was compared with that of quercetin, another polyphenol found in large quantities in fruits and vegetables. Quercetin could lower tumor incidence from 76.4% of the control values to 44.4%, whereas EA could reduce it to 20% from 72.2% of the control. Due to an increase in glutathione levels and a reduction in ascorbate-dependent lipid peroxidation, both polyphenols impacted tumor formation [57]. Notable, the growth of lung cancer cells can be affected not only by EA but also by pomegranate leaves extract which was shown to reduce the proliferation and halt the cell cycle in the G2/M phase in a dose-dependent matter in non-small lung carcinoma A549 and H-1299 cell lines. The extract decreased the quantity of ROS species and the mitochondrial membrane potential leading to enhanced apoptosis. When applied to the non-small lung carcinoma H-1299 cell line the extract prevented migration by reducing MMP-2 and MP-9 expression [82]. However, even though the *in vitro* results are impressive, additional basic and

clinical research is necessary to secure the position of EA as a helpful additive for treating lung cancer.

7. Breast Cancer

Breast cancer is one of the most often diagnosed cancers in women. Using pomegranate juice and EA as adjuvants in treating breast cancer has been shown to boost the effectiveness of standard chemotherapy and hormonal therapy with estrogen receptor modulators [83]. Estrogen receptor-positive MCF7 and estrogen negative MDA-MB-231 breast cancer cells treated with pomegranate juice reduced cancer cell proliferation, increased cell-to-cell adhesion and decreased cell migration without altering the function of normal breast cells [84]. Treatment of breast cancer WA4 stem cells with pomegranate extract containing EA, ursolic acid and luteolin-induced cell cycle arrest in the G0/G1 phase, inhibited cell viability and enhanced apoptosis [85]. Studies indicate that EA may prevent MCF-7 breast cancer cells' development through several mechanisms, such as inhibited cell proliferation by reducing the activity of the transforming growth factor (TGFβ/Smad3) signaling pathway [7], stopping the mitotic cycle in the G0/G1 phase and dysregulation of a total of 4,738 genes [58]. EA causes downregulation of cyclin-dependent kinase (CDK6), an enzyme with high proliferative activity in cancer cells presenting an additional way to trigger apoptosis and decrease colonization in breast cancer cells [59]. Shi et al. [86] observed that treatment of breast cancer cells with EA and GDC-0941, a PI3K (phosphatidylinositol 3-kinase) inhibitor that plays an essential role in cell development, leads to a decrease in cell growth and migration and enhanced apoptosis. Angiogenesis, a key factor in cancer expansion is also restricted by EA by down-regulation of the VRGFR-signaling pathway, a crucial promoter of vascular growth in breast cancer xenografts and restrained the development of MDA-MB-231 breast cancer cells [60]. Using an ACI inbred rat strain breast cancer model similar to estrogen-dependent human breast tumors Munagala et al. [61] detected that EA induces a dysregulation of many microRNA strains leading to inhibited breast cancer tumorigenesis. Notably, urolithin A, a protein generated from EA by the gut microbiota, may function as a breast cancer resistance protein (BCRP) that inhibits the development of drug resistance to chemotherapeutic drugs by acting as a xenobiotic transporter [87]. EA treatment made NIH3T3 breast cancer cells more sensitive to γ-irradiation. In MCF breast cancer cells combined administration of EA and γ-irradiation promoted apoptosis by upregulating the pro-apoptotic Bax protein and inhibiting Bcl-2, both proteins actively involved in apoptotic cell death [62].

8. Cancers of the Genital Tract

Female reproductive system tumors are prevalent and rank fourth in severity, behind colorectal, lung, and breast malignancies. Despite the significant advancement in diagnostic and treatment modalities, they continue to have a high mortality risk. Studies on the anticancer action of EA show that this polyphenol exhibits promising effects in these malignancies. Regrettably, research on the mechanism by which EA may affect cancers of the genital tract has been carried out primarily in vitro with ovarian, cervix and endometrial cancer cell lines. By activating Beclin-1, Baxh, AMPK, and other autophagy-related proteins, treatment of SKOV-3 ovarian cancer cells with EA suppressed cell proliferation and migration and accelerated apoptosis and autophagy. Inhibition of Akt, which is involved in cell migration and invasion, and mTORC1, a protein synthesis

activator, furthered this process [63]. In cells of the A2780 ovarian cancer cell line, proliferation and migration were suppressed under the influence of EA, luteolin, and pomegranate juice. This was explained by the inhibition of the activities of the matrix metalloproteinases MMP2 and MMP9 [64]. Intermittent treatment of cisplatin resistance-induced A2780 cells with EA for 26 weeks completely prevented the development of drug resistance, while promoting apoptosis, inhibition of cell growth and migration, and lesser ROS generation [65]. Endometrial cancer cells incubated with EA displayed reduced ROS generation and NHE1 levels, hampering the segment transmission of DNA to RNA and subsequently altering cancer cell development [66]. Cell cycle arrest, death, and reduced endometrial cancer cell survival were caused by EA's inhibition of the PIK3CA and PIK3R signaling pathways, which regulate cell proliferation and differentiation. When used on endometrial cancer-bearing mice, EA reduced the number of lung metastases [67]. EA caused cytotoxic and apoptotic effects in Hela and NIH-3T3 cervical cancer lines [88] and induced mitotic arrest at the G1 phase by suppressing the STAT3 signal transducer [68]. HeLa cells exposed to EA showed a strong antiestrogen activity proceeding primarily through estrogen receptor ERβ and to a lesser extent via ERα [89]. Remarkably, EA from pomegranate peel extract rather than the fruit itself may prevent the proliferation and differentiation of HeLa cells by blocking the AKT/mTOR intracellular signaling pathway, which controls the cell cycle. Additionally it increased the level of Insulin Growth Factor Binding Protein-7 (IGFBP7), which is crucial for cell growth and differentiation [69]. When administered in conjunction with the anticancer polyphenol curcumin, the suppressive effect of EA on the mitotic arrest of HeLa cells in the G2/M phase was doubled [70], the signaling pathway P53 was repaired and the impairment of ROS formation and DNA damage was amplified [71].

9. Prostate Cancer

Prostate cancer is a frequent malignancy in men and the second leading cause of mortality [72, 90]. While encouraging results from laboratory tests show that EA inhibits cancer cell development, angiogenesis, and metastatic qualities in this type of tumor, clinical investigations on the EA anti-cancer activity are still in the early stages [90, 91]. EA reduced PC3 human prostate cancer cells proliferation and viability by decreasing a few signaling proteins including STAT3, ERK (extracellular signal-regulated kinase) and AKT [72]. In addition EA promoted caspases activation, inhibited the anti-apoptotic protein BAX2 and increased BAX, the pro-apoptotic protein [73]. Applied on LnCap human prostatic cancer cells EA triggered an anti-angiogenic effect by significantly reducing heme oxygenase activity and several members of the MMP cytochrome enzymes family [74]. The chromatographic level of a key indicator of neuroendocrine tumors was decreased, while p75NGFR (low-affinity nerve growth factor receptor) was increased [92]. EA inhibited the migration of androgen-dependent human PC3 and rat PLS10 prostate cancer cell lines by a slight inhibition of MMP2 in both types of cells and the collagenase IV activity in cells from the PLS-10 line [75]. EA repressed cell proliferation and induced apoptosis in androgen-dependent LNCaP androgen-dependent cells by enhancing Bax/Bcl-2 ratio, caspase 3 activation and cell cycle-related tumor proteins. EA did not affect PC-3 or DU145 androgen-dependent human prostate cancer cells. Applied on an animal model with prostate cancer-bearing rats, EA suppressed tumor development by activating caspase 3 apoptosis and decreasing lipid peroxidation [76]. EA combined with the two pomegranate juice components, i.e., luteolin and

punicic acid inhibited the growth and migration of both hormone-dependent and independent prostate carcinoma cells through inhibition of CXCL12/CXCR4 axis which is crucial for tumor development, cell viability and metastasis. In addition the generation of IL-8 and VEGF was suppressed [93].

10. Other Sorts of Cancer

EA-induced apoptosis, GO/G1 mitotic arrest and DNA damage in TSGH8301 human bladder cells by enhancing p21, p53 and ROS species production and activation of mitochondria signaling pathways [77]. EA treatment reduced tumor infiltration and angiogenesis and improved mitomycin C activity in human bladder cancer xenografts. Due to VEGF-A (vascular endothelial growth factor-A) suppression caused by the treatment of four human bladder cancer lines with EA inhibited the development of these cancerous cells [78]. EA inhibited the cell growth and migration of WM115 and A375 melanoma cells through the downregulation of p-EGFR (epidermal growth factor receptor) and vimentin (filament protein preserving cell structure) [79]. The mitotic cell cycle in U251 human glioblastoma cells was blocked in the G0/G1 phase by EA upregulation of the mitogen-activated DR4, DR5 and MAP kinases leading to markedly increased apoptosis [80].

To sum up, studies conducted *in vitro* indicate that EA significantly inhibits the development, proliferation and mobility of cancer cells derived from different human cancer cell lines through several pathways. Nearly all reports conclude that conventional chemotherapy combined with EA may represent an effective therapeutic approach for cancer management. To accomplish this goal extensive clinical studies on the subject are advised. Although the positive effects of EA have been assessed in a limited number of individuals receiving conventional treatment for colorectal and prostate cancer [78], there is a critical need to extend the in vitro findings to other cancer types in both animal and clinical research.

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Author Contributions

The author did all the research work of the study.

Competing Interests

The author has no conflict of interest in the manuscript.

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