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An update on ellagic acid as a natural powerful flavonoid

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Abstract

Ellagic acid is a polyphenol compound present in many fruits, nuts, and seeds, such as pomegranates, black raspberries, raspberries, strawberries, walnuts, and almonds. Some studies in the past indicated that ellagic acid showed powerful free radical scavenging action, and also has anti-diabetic, chemoprotective, anti-apoptotic, anti-inflammatory and anti-tumorigenic properties. While ellagic acid and its complex derivatives such as ellagitannins (ETs) play an important role in human nutrition and endowed with numerous biological properties, thus this substance may be suitable as a defensive factor against free radicals. Hence the aim of this paper is to review current research into the therapeutic potential of ellagic acid in prevention and treatment of some chronic conditions such as cancers or various chronic disease due to its main role as a potent scavenger of oxygen species.

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Introduction

The administration of botanical extracts to prevent and therapy of diseases is an old-fashioned phenomenon (1). Epidemiological studies have revealed a correlation between dietary habits and disease risks. Recently, growing proportion of papers have proposed a connection between phytochemicals, plant-derived metabolites and reduced risk of various chronic diseases such as diabetes, cancer and cardiovascular disorders (2). Polyphenols, valuable types of phytochemicals, are known for their rich antioxidant properties. In recent years, rising proportion of investigations have also focused on their anti-inflammatory, anti-proliferative and apoptosis-inducing impacts. Numerous type of polyphenols have also been recommended to have the possible influence on counteracting to toxic effects created by chemotherapy in cancer (1-3).

Ellagic acid is a polyphenol compound present in various fruits, nuts and seeds, such as pomegranates, black raspberries, raspberries, strawberries, walnuts, and almonds (3).

Ellagic acid is known as a naturally occurring phenolic lactone compound which is degraded product of hydrolysable plant tannins (4-7). With more than 500 natural products characterized so far, ellagic acid and its complex derivatives such as ellagitannins (ETs) play an important role in human nutrition and endowed with numerous biological properties, including antibacterial, antioxidant, anti-hepatotoxic, anti-atherosclerotic, anti-inflammatory and anti-HIV replication activities. Recently interests on ellagic acid have raised due to its anti-mutagenic and anti-carcinogenic actions (7). ETs are differentiated by a complicated chemical construction. They are subjected to spontaneous lactonization expulsion hexahydroxydiphenoic acid which possibly converted into ellagic acid. It was reported that intake of food rich of ETs can help to improve the health and prevention of several chronic diseases (including cardiovascular, neurodegenerative diseases and cancer). The anticancer activity of ETs and their metabolites is associated with their ability to scavenging free radicals. For this reason, ETs decrease or inhibit the oxidative

Core tip

This paper has given a view on ellagic acid and also the reasons for its widespread administration as a polyphenolic compound originated in the numerous foods. Various investigations have been reported the therapeutic and preventive effects of this substance including anti-mutagenic and anti-carcinogenic, anti-tumorigenic and even anti-diabetic potentials in order to play an important role as a functional food.

stress (OS) process, which can otherwise induce various diseases such as cancer, atherosclerosis and cardiovascular diseases (8-10).

Some studies in the past indicated that ellagic acid showed free radical scavenging action, anti-cataractogenic, cardio-protective, gastro-protective, ulcer healing, anti-fibrotic, anti-diabetic, hypolipidemic, anti-atherosclerotic, chemo-protective, anti-apoptotic, anti-inflammatory and anti-carcinogenic properties that make it interesting for further studies in different disorders particularly cancer cell systems (11-15). Due to its effects on a variety of hard curable diseases, ellagic acid has attracted the attention of a lot of scientists. This article was aimed to provide more detailed investigations regarding the effects of ellagic acid as a natural powerful antioxidant on some chronic conditions such as cancer and diabetic nephropathy.

Materials and Methods

In this review, a variety of sources have been used by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following keywords and, or their equivalents; Ellagic acid, cancer, free radicals, reactive oxygen species, diabetes mellitus, antioxidants, oxidative stress and renoprotective effects.

Antioxidant and anti-tumorigenic activity

Free radicals are extremely high reactive intermediate chemicals and have the potential damage to cells. They are created when an atom or a molecule either gains or loses an electron. They are formed naturally in the body and play an important role in several cellular signaling in the normal cells (15,16). It was documented that free radicals at high concentrations can be hazardous to the body and cause harm the all main ingredients of cells (such as DNA, proteins, and cell membranes). The damage to cells (especially to DNA) induced by free radicals, can play a vital role in the triggering and development of cancer and other health conditions (15,20). ellagic acid is a powerful flavonoid which plays the main role as a potent scavenger of oxygen species. A diet rich in polyphenols has been suggested to have positive health properties and to diminish the risk of diseases (18-21). ellagic acid as a polyphenolic compound is found in the different types of berry and nuts and it has received meticulous concentration because of its vast collection of biological goods. It has been shown that DPPH has a free radical scavenging activity and also inhibits the lipid peroxide (LPO) generation in the V79-4 cells treated with hydrogen peroxide (H_2O_2).

Furthermore, it was detected that ellagic acid increased the activity of several main antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT), which these enzymes changed to the different disorders including free radical attack (18). Moreover, it protects from DNA double helix against alkylating agent damage (20-23). Therefore, a diet rich in antioxidants is essential to prevent pathogenic conditions. In this paper, ellagic acid has been introduced as one of the most powerful agents in the prevention and also treatment some type of hard diseases. For example, recent studies detected that prostate cancer as the fourth most popular cancer in the men older than 50 years is one of the cancers usually diagnosed late. Thus, preventive factors can be really effective (24). Interestingly, the molecular mechanism of ellagic acid on the induction of apoptosis in prostate cancer cells was evaluated in recent studies. These investigations showed that ellagic acid has anti-proliferative effects through blocking the activation of mammalian target of rapamycin and decreasing the intracellular values of β-catenin in the LNCaP cell line. On the basis of recent investigations, administration of ellagic acid in the form of food and fruit will be one of the preventive strategies. Previous studies have identified major ETs-type phytochemicals in different types of berry fruit extracts, which are distinguished via biological activities including anti-cancer (such as leukemia, prostate and colon cancers), anti-neurodegenerative and anti-viral properties (25,26).

Moreover the other type of cancer affected by ellagic acid is cervical cancer. Although, polyphenol-rich raspberry extracts were made and fractioned through reverse chromatography on C_{18} solid phase, indicating that, one of the extracted compounds identified as ellagic acid detected having the capability to inhibit *in vitro*, the proliferation of HeLa cells. This potency could explain that ellagic acid, from ETs, cause triggering of apoptosis signaling by mitochondrial-mediated or intrinsic pathway. Additionally, it was reported that ellagic acid (10-100 μM) is capable of preventing the proliferation of ovarian carcinoma cells (PA-1 and ES-2 cells) in a time and dose -related fashion through arresting all cell lines at the G phase. Likewise, ellagic acid can perform these impacts by raising the presentation of p53 and Cip1/p21 and lessening the presentation of cyclins E and D1.

Accordingly, it was found that ellagic acid can induce caspase-3 activation and consequently induction of apoptosis by growing the Bax/Bcl-2 ratio. This is the major phenomenon that control apoptosis signaling, and restore anoikis (27-29). Interestingly, ellagic acid at elevated concentrations (10-50 mmol/L) can accelerate the cell death via apoptosis mode and also diminish the viability of the human pancreatic adenocarcinoma cell lines MIA PaCa-2 and PANC-1. Previous investigations had detected that ellagic acid can perform these effects through the declining nuclear factor-kappa B (NF-κB) activity, thus activating the death cell by mitochondrial-mediated pathway. This pathway is associated with loss of mitochondrial membrane potential (Δψm), caspase-3 activation and cytochrome C release. A new investigation has directed that ellagic acid at low concentration (0.5-3 μM) can induce the apoptosis signaling and diminish the viability of the human pancreatic cancer cell lines MIA PaCa-2 and also HPAF-II cells.

Also, it has been found that ellagic acid induces similar

apoptotic impacts on other cancer cell lines such as pancreatic stellate cells and the progenitor cells of pancreatic cancer.

In vivo data showed that dietary alone with ellagic acid could induce decreasing of size and viability of a tumor in a subcutaneous xenograft mouse model of pancreatic cancer. Another in vivo investigation denoted that ellagic acid can prevent pancreatic cancer growth in Balb/C nude mice. This inhibitory influence by ellagic acid was accompanied with the decrease of cell proliferation, activation of caspase-3, and stimulation of poly (ADP-ribosyl) polymerase (PARP) cleavage. Additionally, ellagic acid weakened the expression of Bcl-2, cyclin D1, CDK2, and CDK6, whereas caused the presentation of the Bax as a pro-apoptotic protein in the various tumor tissues as compared with untreated control tissues (29).

Numerous molecular target mechanisms have been proposed to be involved in cell cycle activity and proliferation modifications by ellagic acid, such as raised levels of p53 and raised levels and/or activation of p21cip1. Down-regulation of cyclins A and B1 or cyclin D1, and up-regulation or decreased levels of cyclin E has also been associated with ellagic acid-induced cell cycle modifications. ellagic acid is also a powerful inhibitor of CK2, an important protein kinase involved in the neoplasia and tumor proliferation activated down-stream of Wnt-signaling.

Recently, it has been reported that ellagic acid induces the down-regulation of insulin-like growth factor II (IGF-II), and it plays a main role in the transcription and protein levels of the mitogen-activated protein kinase (MAPK), kinases p38, and MEKK1(2,30-32).

Preclinical point of view

Strawberries are good sources of vitamin C and polyphenolics like flavonoids, particularly anthocyanins and flavonols, and ellagic acid products, to which many beneficial effects have been recognized (32). The different parts of the gastrointestinal tract were affected the bioavailability of free ellagic acid and ETs, in which these compounds are absorbed. It was shown that several conditions such as acidic gastric environment and the presence of gastric enzymes were affected the stability of ETs and undergone neither hydrolysis to free ellagic acid nor degradation. Neutral pH is the best conditions for hydrolysis of ET. Acidified chyme is transported in small portions of the stomach to further sections of the gastrointestinal tract, where pH is higher and more suitable for hydrolysis of ETs (pH 7.1-8.4) such as duodenum and small intestine (10,33-35).

More recently, Zhang et al detected that ellagic acid is a natural phenolic compound and induces anti-carcinogenic impacts through decreasing tumor cell proliferation, prompting apoptosis, breaking the binding of carcinogens to DNA, and inhibiting the infections with the virus, and also decreasing the inflammation, angiogenesis (29).

In another study, Bharati et al showed that ellagic acid has a chemoprotective effect due to strong antioxidant properties which lead reducing OS (36). Likewise, recent experimental investigations revealed that phytochemicals play a protective role against OS, which is induced by heavy metals in animals. At sub-lethal dose of mercuric chloride treated rat liver tissue shows hepatic cell damage and alteration of its metabolic activities by the way of liver marker enzymes. Also, the liver protective effect of hesperidin and ellagic acid was found to be effective against liver toxicity induced by mercuric chloride ($HgCl_2$).

It was reported that the administration of ellagic acid and hesperidin on $HgCl_2$ intoxicated rats not only decreased the levels of liver markers enzymes, bilirubin or cholesterol, but also maintained their level to near normal condition (37,38).

A recent study by Ahad et al revealed that diabetic nephropathy (DN) as a serious complication of diabetes is linked to inflammation. They mentioned that nephroprotective effects of oral treatment of ellagic acid in high fat diet/low dose streptozotocin (HFD/STZ)-induced type 2 diabetic Wistar rats. After induction of diabetes, the treatment of ellagic acid for 16 weeks could significantly decrease the renal dysfunction and OS. ellagic acid significantly inhibited the renal NF-rB activation. Moreover, ellagic acid significantly lowered renal pathology and suppressed transforming growth factor-beta (TGF-ß) and fibronectin expressions in renal tissues. Also, it was shown that ellagic acid significantly decreased the serum amounts of pro-inflammatory cytokines, such as interleukin-1beta (IL-1b), IL-6 and tumor necrosis factor-alpha (TNF-a) (39-44). While, diabetes mellitus (DM) is one of the most widespread diseases in the world, however, all attempts to its treatment have been unsuccessful.

Although, the management of this disease by administration of oral anti-diabetic drugs and dietary therapy has shown some promise. More recent studies detected functional foods contains antioxidant nutrients with insulin secreting, insulin sensitizing and insulin mimetic properties. They found among various foods with this property, ellagic acid and gallic acid play insulinotropic roles (42,43).

Ellagic acid and diabetic kidney disease

Today, the incidence of diabetes DM (especially type-2) as a global health problem is growing. Diabetic kidney disease, one of the most serious micro-vascular complications of DM advances as a result of extended hyperglycemia and eventually leads to end stage renal disease. In recent years, several studies have documented that the inflammation pathways play a major role in the pathophysiology of diabetic kidney disease (40,41). In this context, NF-κB, a well-known transcription factor, has received much attention. NF-κB is produced by almost all cell types and is activated by a wide variety of cell-stress stimuli including hyperglycemia, obesity, raised plasma levels of free fatty acids, OS, hypertension, vasoactive agents, proteinuria, bacteria, cytokines and growth factors (40-43). NF-κB is

activated in renal fibrosis and its inhibition has resulted in a significant amelioration of diabetic kidney disease, suggesting its importance as a potential therapeutic target for the treatment of diabetic nephropathy. The application of dietary therapy in the treatment of this disease is one of the options aimed at controlling diabetes-induced hyperglycaemia. Thus, in some researches ellagic acid introduced as anti-diabetic functional foods and also a good source of insulin secreting, insulin sensitizing and insulin mimetic properties (42-44).

Conclusion

This paper has given a view on ellagic acid and also the reasons for its widespread administration as a polyphenolic compound originated in the numerous foods. Various above-mentioned investigations have been reported the therapeutic and preventive effects of this substance including anti-mutagenic and anti-carcinogenic, anti-tumorigenic and even anti-diabetic potentials in order to play an important role as a functional food.

Authors' contribution

SK searched and gathered the related articles as well as writing. SK prepared the draft. HN edited the final manuscript several times. Both authors read and signed the final paper.

Conflicts of interest

The authors like to declare that HM and SK are the current staffs of the journal. The peer-review process of the current article has been performed in accordance with the COPE guidelines.

Ethical consideration

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Khodadadi S, Rafieian-Kopaei M. Herbs, health and hazards; a nephrology viewpoint on current concepts and new trends. Ann Res Antioxid. 2016;1:e05.
2. Alfredsson CF. Effects of ellagic acid in human neuroblastoma cells [dissertation] Karlstad University Studies; 2013.
3. Rafieian-Kopaei M, Baradaran A, Rafieian M. Oxidative stress and the paradoxical effects of antioxidants. J Res Med Sci. 2013;18:628-.
4. Sato T, Kataoka M. Molecular structure and electronic spectrum of ellagic acid: semi-empirical molecular orbital calculation. J heterocyclic Chem. 1997;34:665.
5. Nasri H. Herbal drugs and new concepts on its use. J Prev Epidemiol. 2016;1:e01.
6. Bahmani M, Shirzad H, Majlesi M, Shahinfard N, Rafieian-Kopaei M. A review study on analgesic applications of Iranian medicinal plants. Asian Pac J Trop Med. 2014;7:S43-53.
7. Landete JM. Ellagitannins, ellagic acid and their derived metabolites: a review about source, metabolism, functions and health. Food Res Int. 2011;44:1150–60.
8. Sarrafchi A, Bahmani M, Shirzad H, Rafieian-Kopaei M. Oxidative stress and Parkinson's disease: new hopes in treatment with herbal antioxidants. Curr Pharm Des. 2016; 22:238-46.
9. Zhang T, Chen HS, Wang LF, Bai MH, Wang YC, Jiang XF, et al. Ellagic acid exerts anti-proliferation effects via modulation of Tgf-β/Smad3 signaling in MCF-7 breast cancer cells. Asian Pac J Cancer Prev. 2014;15:273-6.
10. Lipińska L, Klewicka E, Sojka M. Structure, occurrence and biological activity of ellagitannins: a general review. Acta Sci Pol Technol Aliment. 2014;13:289-99.
11. Galano A, Francisco Marquez M, Pérez-González A. Ellagic acid: an unusually versatile protector against oxidative stress. Chem Res Toxicol. 2014;27:904-18.
12. Kannan MM, Quine DS**.** Ellagic acid ameliorates isoproterenol induced oxidative stress: Evidence from electrocardiological, biochemical and histological study. Eur J Pharmacol. 2011;659:45–52.
13. Weisburg JH, Schuck AG, Reiss SE, Wolf BJ, Fertel SR, Zuckerbraun HL, et al. Ellagic acid, a dietary polyphenol, selectively cytotoxic to HSC-2 oral carcinoma cells. Anticancer Res. 2013;33:1829-36.
14. Rafieian-Kopaei M. Medicinal plants for renal injury prevention. J Renal Inj Prev. 2013;2:63-5.
15. Warpe VS, Mali VR, Arulmozhi S, Bodhankar SL, Mahadik KR. Cardioprotective effect of ellagic acid on doxorubicin induced cardiotoxicity in wistar rats. Journal of Acute Medicine. 2015;5:1e8.
16. Nankar RP**,** Doble M. Ellagic acid potentiates insulin sensitizing activity of pioglitazone in L6 myotubes. J Funct Foods. 2015;15:1–10.
17. Lin MC, Yin MC. Preventive effects of ellagic acid against doxorubicin-induced cardio-toxicity in mice. Cardiovasc Toxicol. 2013;13:185-93.
18. Diplock AT, Charleux JL, Crozier-Willi G, Kok FJ, Rice-Evans C, Roberfroid M, et al. Functional food science and defense against reactive oxygen species. Br J Nutr. 1998;80 Suppl 1:S77-112.
19. Aleebrahim-Dehkordy E, Khodadadi S, Mousavipanah Z, Nasri H. Herbal antioxidants and kidney. Ann Res Antioxid. 2016;1:e10.
20. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39:44-84.
21. Mişe Yonar S, Yonar ME, Yöntürk Y, Pala A. Effect of ellagic acid on some haematological, immunological and antioxidant parameters of rainbow trout (*Oncorhynchus mykiss*). J Anim Physiol Anim Nutr (Berl). 2014;98:936-41.
22. Abuelsaad ASA, Mohamed I, Allam G, Al-Solumani AA. Antimicrobial and immunomodulating activities of hesperidin and ellagic acid against diarrheic Aeromonas hydrophila in a murine model. Life Sci. 2013;93:714-22.
23. Khodadadi S. Role of herbal medicine in boosting immune system. Immunopathol Persa. 2015;1:e01.
24. Dubey A, Park DW, Kwon JE, Jeong YJ, Kim T, Kim I, et al. Investigation of the biological and anti-cancer properties of ellagic acid-encapsulated nano-sized metalla-cages. Int J Nanomedicine. 2015;10:227-40.
25. Shirzad H, Taji F, Rafieian-Kopaei M. Correlation between antioxidant activity of garlic extracts and WEHI-164 Fibrosarcoma tumor growth in BALB/c mice. J Med Food. 2011;14:969-74.
26. Sepúlveda L, Ascacio A, Rodríguez-Herrera R, Aguilera-Carbó A, Aguilar CN. Ellagic acid: biological properties and biotechnological development for production processes. African J Biotechnol 2011;10:4518-23.
27. Mishra S, Vinayak M. Role of ellagic acid in regulation of apoptosis by modulating novel and atypical PKC in lymphoma bearing mice. BMC Complement Altern Med. 2015;15:281.
28. Shirzad H, Burton RC, Smart YC, Rafieian-Kopaei M, Shirzad M. Natural cytotoxicity of NC-2(+) cells against the growth and metastasis of WEHI-164 fibrosarcoma. Scand J Immunol. 2011;73:85-90.
29. Zhang H, Zhao L, Li H, Xu H, Che W, Tao L. Research progress on the anticarcinogenic actions and mechanisms of ellagic

acid. Cancer Biol Med. 2014;11:92-100.
30. Ahmed T, Setzer WN, Nabavi SF, Orhan IE, Braidy N, Sobarzo-Sanchez E, et al. Insights into effects of ellagic acid on the nervous system: a mini review. Curr Pharm Des. 2016;22(10):1350-60.
31. Ho CC, Huang AC, Yu CS, Lien JC, Wu SH, Huang YP, et al. Ellagic acid induces apoptosis in TSGH8301 human bladder cancer cells through the endoplasmic reticulum stress- and mitochondria-dependent signaling pathways. Environ Toxicol. 2014;29:1262-74.
32. Da Silva Pinto M, Lajolo FM, Genovese MI. Bioactive compounds and quantification of total ellagic acid in strawberries (Fragaria x ananassa Duch.). Food Chem. 2008;107:1629–35.
33. Akkoyun HT, Karadeniz A. Investigation of the protective effect of ellagic acid for preventing kidney injury in rats exposed to nicotine during the fetal period. Biotech Histochem. 2016;91:108-15.
34. Lipińska L, Klewicka E, Sojka M. Structure, occurance and biological activity of ellagitannin: a general review. Acta Sci Pol Technol Aliment 2014;13:289-299.
35. Rafieian-Kopaie M, Baradaran A. Plants antioxidants: From laboratory to clinic. J Nephropathol. 2013;2:152-3.
36. Bharathi E, Jagadeesan G. Antioxidant potential of hesperidin and ellagic acid on renal toxicityinduced by mercuric chloride in rats. Biomed Prev Nutr. 2014;4:131-6.
37. Baradaran A, Nasri H, Rafieian-Kopaei M. Protection of renal tubular cells by antioxidants: current knowledge and new trends. Cell J. 2015;16:568-71.
38. Jagadeesan G, Bharathi E. In vivo restoration of hepatic and nephroprotective potential of hesperidin and ellagic acid against mercuric chloride intoxicated rats. Biomed Aging Pathol. 2014;4:219–22.
39. Nasri H, Shirzad H, Baradaran A, Rafieian-Kopaei M. Antioxidant plants and diabetes mellitus. J Res Med Sci. 2015;20:491-502.
40. BenSaad LA, Kim KH, Quah CC, Kim WR, Shahimi M. Anti-inflammatory potential of ellagic acid, gallic acid and punicalagin A&B isolated from Punica granatum. BMC Complement Altern Med. 2017;17:47.
41. Ahad A, Ganai AA, Mujeeb M, Siddiqui WA. Ellagic acid, an NF-κB inhibitor, ameliorates renal function in experimental diabetic nephropathy. Chem Biol Interact. 2014;219:64-75.
42. Amin MM, Arbid MS. Estimation of ellagic acid and/or repaglinide effects on insulin signaling, oxidative stress, and inflammatory mediators of liver, pancreas, adipose tissue, and brain in insulin resistant/type 2 diabetic rats. Appl Physiol Nutr Metab. 2017;42:181-92.
43. Mali VR, Bodhankar SL, Mohan V, Thakurdesai PA. Subacute toxicity of ellagic acid in cholesterol fed hyperlipidemic rats. Toxicol Int. 2008;15:91-5.
44. Fontaine BM, Nelson K, Lyles JT, Jariwala PB, García-Rodriguez JM, Quave CL, et al. Identification of ellagic acid rhamnoside as a bioactive component of a complex botanical extract with anti-biofilm activity. Front Microbiol. 2017 Mar 23;8:496.