Tea and lycopene protect against prostate cancer

Article *in* Asia Pacific Journal of Clinical Nutrition · April 2007

Source: PubMed

3 authors, including:

Le Jian
Curtin University
74 PUBLICATIONS **2,903** CITATIONS
SEE PROFILE

Colin Binns
Curtin University
643 PUBLICATIONS **17,734** CITATIONS
SEE PROFILE

Original Article

Tea and lycopene protect against prostate cancer

Le Jian MD PhD[1, 2], Andy H Lee PhD [2] and Colin W Binns MBBS PhD [2]

[1]*Medical College of Zhejiang University, Hangzhou, PR China*
[2]*School of Public Health, Curtin University of Technology, Western Australia*

Prostate cancer is the most common male cancer in developed countries and is increasing in the developing world. Its long latency and geographical variation suggest the possibility of prevention or postponement of onset by dietary modification. To investigate the possible joint effect of lycopene and green tea on prostate cancer risk, a case-control study was conducted in Hangzhou, China, with 130 prostate cancer patients and 274 hospital controls. Information on tea and dietary intakes, and possible confounders was collected using a structured questionnaire. The risk of prostate cancer for the intake of tea and lycopene and their joint effect were assessed using multivariate logistic regression models. Prostate cancer risk was reduced with increased consumption of green tea. The protective effect of green tea was significant (odds ratio 0.14, 95% CI: 0.06-0.35) for the highest quartile relative to the lowest after adjusting for total vegetables and fruits intakes and other potential confounding factors. Intakes of vegetables and fruits rich in lycopene were also inversely associated with prostate cancer risk (odds ratio 0.18, 95% CI 0.08-0.39). Interaction analysis showed that the protective effect from tea and lycopene consumption was synergistic (p<0.01). This study suggests that habitual drinking tea and intakes of vegetables and fruits rich in lycopene could lead to a reduced risk of prostate cancer in Chinese men. Together they have a stronger preventive effect than either component taken separately. This is the first epidemiological study to investigate the joint effect between tea drinking and lycopene intake.

Key Words: green tea, lycopene, prostate cancer, joint effect, China

Introduction

Prostate cancer is the most commonly diagnosed non-skin cancer in men in western countries. In contrast, the incidence in developing countries such as China is considerably lower (age standardized rate, ASR 1.7/100,000). Large difference in incidence has been noted between different racial and ethnic groups with the highest in the USA (ASR 104/100, 000).[1, 2] Studies on immigrants from Asian countries to North America revealed that the incidence of prostate cancer increased in immigrants compared with their native population.[3, 4] The geographic variations in incidence rate and the increased incidence in immigrants suggest a significant role of environmental factors, including nutrition, for developing the disease. The sharp increase incidence of prostate cancer worldwide in recent decade can be partly attributed to the increase in PSA screening. Whilst PSA testing is popular in China, PSA screening is not widespread and prostate cancer is typically diagnosed at an advanced stage. Thus, it is important to put forward strategies for primary prevention.

Recent studies have shown that regular drinking tea and consumption of diet rich in vegetables and fruits are associated with the reduced risk of cancers.[5-8] Green tea may induce apoptosis and inhibit cancer cell growth through their antioxidant properties and by causing cell cycle arrest.[9, 10] Two recent case-control studies evaluated green tea and prostate cancer risk in Asian countries.[6, 11] Both studies received high methodological quality ratings from the US FDA.[12] The Chinese study showed drinking three cups of green tea per day was significantly associated with a reduced risk of prostate cancer (odds ratio 0.27, 95% CI 0.15-0.48).[6] However the Japanese study reported that drinking two to ten cups of green tea per day was not significantly associated with prostate cancer risk (odds ratio 0.67, 95% CI 0.27-1.64).[11] A double-blind, placebo-controlled clinical trial in Italy using 600 mg/d green tea catechins has shown encouraging results.[7]

Red-orange, dark green vegetables and fruits are rich sources of carotenoids, including lycopene, carotene, lutin, zeaxanthin and cryptoxanthin. Lycopene gives the red color to foods including tomatoes, tomato products, watermelon, pink grapefruit, apricots, papaya and pink guavas. In Western countries, over 80% of dietary lycopene comes from the consumption of tomatoes and tomato-based products including tomato sauce/juice/soup, spaghetti sauce, salsa, chili, pasta and pizza sauce.[14, 15] The ability of lycopene to act as an antioxidant and scavenger of free radicals is considered as the most likely mechanism that could account for the hypothesized beneficial effects on human health. Lycopene may quench singlet oxygen, interact with reactive oxygen species and prevent oxidative damage to lipoproteins and DNA.[13] It may increase cell cycle arrest and induction of apoptosis in human prostate cancer cell lines.[16, 17] A well-designed animal study compared the effects of different diets on rats (n=194).[18]

Corresponding Author: Dr Le Jian, School of Public Health, Curtin University of Technology, GPO Box U 1987, Perth, WA, 6845, Australia
Tel: +61-8-92664250; Fax: +61-8-92662958
Email: L.Jian@exchange.curtin.edu.au

Rats fed with tomato powder experienced a significant (26%) decrease in prostate cancer specific mortality. The epidemiological study providing the strongest evidence thus far concerning tomatoes and prostate cancer prevention was a cohort study in the USA.[19] This study followed 47,894 men. Raw tomatoes and tomato sauce were the only fruits or vegetables from a 131-item FFQ found to be associated with a reduced risk of prostate cancer with RR=0.74 (95% CI: 0.58-0.93) and RR=0.66 (95% CI: 0.49-0.90), respectively. Our recent case-control study in Chinese men also showed a protective effect of red-orange vegetables and fruits rich in carotenoids against prostate cancer.[20]

The majority of studies so far have focused on individual foods or nutrients. However free-living populations are simultaneously exposed to a variety of food items in one meal. Phytochemicals in whole meals may behave differently to individual compounds given in experimental situations. These complex exposure situations may result in different health outcomes. Thus, investigating the health benefit of different diets and phytochemicals in terms of their joint effects is necessary in order to understand their underlying protective mechanism against cancers. This study aims to assess the possible joint effect of tea and lycopene on prostate cancer risk.

Methods

Subjects

The subjects were men residing in Zhejiang Province for at least 10 years and over 45 years of age. They were recruited during 2001 and 2002 at eight public hospitals in Hangzhou, capital of Zhejiang Province located in southeast China. Potential participants with a history of stroke or Alzheimer's disease were excluded to avoid memory error. Cases were confirmed by histopathological reports of prostate adenocarcinoma. Controls were recruited in the same hospitals during the same period and had no previous diagnosis of malignancies confirmed by physical examination, x-ray, operation or biopsy. Among the 140 cases recruited, 130 (93%) were interviewed and 10 (7%) declined to participate in the study, including one with Alzheimer's disease. Of the 284 eligible controls identified, 274 (96.5%) participated in the study. Two men (3.5%) with Alzheimer's disease and one with a history of stroke were excluded.

Data collection

The interviews were conducted using a structured questionnaire which included a quantitative FFQ component. The interviewer was blind to the final diagnosis when doing the interviews. The study protocol included instructions to follow the printed questionnaire exactly to avoid bias. The reproducibility and validity of the FFQ were assessed by several methods.[21] Information on demographic characteristics, family history of prostate cancer, height, weight and physical activity, and medical history were also collected. A reference recall period (5 years before diagnosis for cases and 5 years before interview for controls) was adopted. Interviews were usually conducted in the presence of next-of-kin to assist in recall. The study was approved by the Human Research Ethics Committee of Curtin University, the Zhejiang hospital administration and the doctors in charge of the relevant wards. Informed consent was sought prior to interview.

Dietary assessment

The FFQ contained questions on 130 food items including all foods in the usual diet of Zhejiang residents. The habitual frequencies and quantities of foods consumed per meal were recorded.

Tea assessment

Tea drinking questions included both qualitative and quantitative measurements. Participants were first classified as "ever" or "never" (less than once per month) habitual tea drinkers. Information on consumption pattern was then collected from those "ever" tea drinkers. The details of measurement can be obtained from our previous paper.[6]

Physical activity assessment

Information on habitual physical activity was assessed in terms of type, intensity and duration. Daily metabolic equivalent task (MET) scores were calculated by multiplying the reported duration of any activity by the respective intensity score and then summing over all activities.[22]

Statistical analysis

The data analysis was undertaken using the SPSS package (version 11; SPSS Inc., Chicago, IL, USA). Independent-samples t, Mann-Whitney and Chi-square tests were used to compare the demographic characteristics and potential risk factors between cases and controls. Energy and nutrient intakes were calculated using the Chinese nutrient database established by the Institute of Nutrition and Food Health, Chinese Academy of Preventive Medicine.[23] Conversion of lycopene from food items was undertaken using the U.S. Department of Agriculture Database (USDA) because of no available Chinese database.[24] The level of supplementations among the participants were very low, therefore, they were not included in the analysis. Risk of prostate cancer for the intake of tea and lycopene and their joint effect were assessed by odds ratios (ORs) and their 95% confidence intervals (95% CI) using unconditional multivariate logistic regression models. Each fitted regression equation adjusted for age, height, weight, body mass index (BMI), locality, education, income, marital status, family history of prostate cancer, physical activities (MET), intakes of fat and caloric. The quantities of tea and lycopene intakes were classified into quartiles. Adjusted ORs were obtained with the lowest quartile as the reference category. In addition, when assessing green tea consumption, fresh vegetables and fruits were included for adjustment in the model. Meanwhile, when assessing lycopene intakes, green tea intakes were weighted in the model. When assessing their joint effect, a new variable (joint effect of tea and lycopene) was generated according to the match of each pair of established quartiles. For example, if the case was both in the lowest quartile of green tea and lycopene consumptions, he was classified into the lowest quartile of the new variable, and vice versa. If intakes of green tea and lycopene were not in the same category (level) e.g. green tea intake was in the lowest quartile but lycopene intake wasn't, they were

Table 1. Characteristics of participants

	Cases (*N* =130)	Controls (*N* =274)
Age at interview, mean years (SD)	72.7 (7.1)	71.4 (7.2)
Height, mean cm (SD)	168 (5.3)	169 (5.6)
Weight*, mean kg (SD)	66 (10.3)	65 (9.9)
BMI*, mean kg m^{-2} (SD)	23.4 (3.1)	22.7 (3.1)
Locality of residence, N (%)		
Urban	97 (74.6)	207 (75.5)
Rural	33 (25.4)	67 (24.5)
Education, N (%)		
No formal education	18 (13.8)	29 (10.6)
Primary	37 (28.5)	78 (28.5)
Secondary	44 (33.8)	110 (40.1)
Tertiary	31 (23.8)	57 (20.8)
Personal monthly income in 2000(RMB), N (%)		
≤ 500	24 (18.5)	50 (18.2)
501-1000	55 (42.3)	113 (41.2)
1001-2000	43 (33.1)	99 (36.1)
≥ 2001	8 (6.2)	12 (4.4)
Marital status, n (%)		
Married,	114 (87.7)	245 (89.4)
Widowed, divorced, separated	16 (12.3)	29 (10.6)
Prostate cancer in first-degree relatives*, N (%)		
No	111 (85.4)	241 (88.0)
Yes	3 (2.3)	0 (0.0)
Unclear	16 (12.3)	33 (12.0)
Weekly MET	157 (59.2)	157 (55.4)
Fat, mean g day^{-1}(SD)	60.3 (24.6)	56.2 (20.7)
Calorie, mean kcal day^{-1}(SD)	2386 (809)	2333 (619)
Fresh vegetables and fruits*, mean g day^{-1}(SD)	500 (321)	865 (478)
Drink tea*, N (%)		
No	58 (44.6)	55 (20.1)
Yes	72 (55.4)	219 (79.9)

* $p<0.05$

Table 2. Quartiles of green tea, lycopene and their joint effect on prostate cancer risk

	Cases	Controls	Crude OR	(95.0 % C.I.)	OR†	(95.0% C.I.)
Green tea leaves (g day^{-1})						
(1) 0	58	53	1.00		1.00	
(2) 0.3-2.9	50	110	0.42	(0.25-0.69)	0.45	(0.25-0.82)
(3) 3.0-4.9	13	48	0.25	(0.12-0.51)	0.24	(0.10-0.57)
(4) ≥5	9	63	0.13	(0.06-0.29)	0.13	(0.05-0.32)
Lycopene (μg day^{-1})						
(1) <1609	55	68	1.00		1.00	
(2) 1609-3081	32	69	0.57	(0.33-0.99)	0.47	(0.25-0.86)
(3) 3081-4917	30	69	0.54	(0.31-0.94)	0.40	(0.21-0.77)
(4) >4917	13	68	0.24	(0.12-0.47)	0.17	(0.08-0.39)
Joint effect of tea & lycopene						
(1) Low	24	15	1.00		1.00	
(2) Other combinations ‡	92	192	0.30	(0.15-0.60)	0.28	(0.13-0.59)
(3) Middle	11	31	0.22	(0.09-0.57)	0.21	(0.08-0.57)
(4) High	3	36	0.05	(0.01-0.20)	0.03	(0.01-0.16)

†Variables adjusted for: age at interview, locality (urban, rural), education (none, primary, secondary, tertiary), family income (RMB, ≤500, 501-1000, 1001-2000, ≥2001), marital status (married, widowed/divorced/separated), family history of prostate cancer (yes, no, uncertain), MET, BMI, fat intakes and calories. In addition, when analyzing green tea leaves intakes, total fresh vegetables and fruits were adjusted and when analyzing lycopene intakes, green tea consumption was adjusted. ‡Intakes of green tea and lycopene were not in the same category (level) e.g. green tea intakes in the lowest quartile bur lycopene intakes in the highest quartile

categorized as "other combinations".

Results

Table 1 shows the characteristics of the participants. Demographic characteristics such as age, education, income and marital status were similar in both groups, as well as fat and caloric intakes. Compared with the controls, cases tended to have higher BMI, more prostate cancer patients in the family, drank less tea and ate less fresh vegetables and fruits.

The relationships between green tea drinking, lycopene intakes and prostate cancer risk are presented in Table 2.

Table 3. Interactions of tea and lycopene on prostate cancer using binary variables

	Lycopene intakes	Cases (%)	Controls (%)	Adjusted OR (95%CI)	*p*
Green tea drinking					
Low	Low	74 (56.9)	88 (32.1)	1.00	
Low	High	34 (26.2)	75 (27.4)	0.44 (0.25-0.78)	0.005
High	Low	13 (10.0)	49 (17.9)	0.26 (0.13-0.54)	0.000
High	High	9 (6.9)	62 (27.6)	0.11 (0.05-0.26)	0.000
Interaction				0.20 (0.09-0.44)	0.000

[†]Variables adjusted for: age at interview, locality, education, family income, marital status, family history of prostate cancer, MET, BMI, fat intakes and calories.

After adjusting for age, family history of prostate cancer and other demographic characteristics, BMI, MET, fat, caloric and fresh vegetables and fruits intakes, the OR was 0.13 (95% CI 0.05-0.32) for men who consumed at least 5 g green tea leaves daily compared with non-tea drinkers. Similarly, men who consumed over 4917μg of lycopene daily had adjusted OR 0.17 (95% CI 0.08-0.39) compared with the lowest quartile (<1608.6μg day^{-1}) of intake.

The possible joint effects and interactions of tea and lycopene on prostate cancer risk are presented in Table 2 and Table 3. Compared with the independent effects of tea and lycopene on the cancer risk, the joint effect was 0.03 (95% CI 0.007-0.164) in high dose combination group relative to low dose combination group. The adjusted OR was 0.11 (95%CI 0.05-0.26) for high dose of both green tea and lycopene intakes relative to low dose of tea and lycopene intakes.

Discussion

Many risk factors such as age, race, and family history cannot be controlled. However, research on risk of prostate cancer suggests that some environmental and lifestyle factors might be modified to achieve better outcome in terms of decreasing the risk of the cancer.[5, 6, 14, 25] In this study, we observed the synergistic protective effect of green tea and lycopene against prostate cancer.

In recent years, there are increasing number of epidemiological studies on "functional food" and their correlations with cancers. Phytochemicals in plants are often considered as the major bioactive compounds with human health benefits linked to their antioxidant activities. Unfermented green tea leaves contain up to 30 percent dry weight of tea polyphenols.[24] Lycopene is the most abundant carotenoid in tomatoes, tomato products and watermelon. While both green tea and lycopene have been shown to prevent prostate cancer, we have found no published studies examined their joint effects on prostate cancer. As prostate cancer is a multifactor disease and food is consumed in meals, studies of the interactions of protective factors may provide useful information on prevention. The joint effects and the high consumption of tea and fresh vegetables and fruits in Asian countries may partially explain the different clinical incidence of prostate cancer between countries. To the best of our knowledge, this is the first report that investigated the possible joint effect of green tea and lycopene consumption on prostate cancer risk in Chinese people, a population with low risk of the cancer.

Nevertheless, attempt to investigate the joint effect of dietary factors on the risk of prostate cancer via a case-control study is vulnerable to selection and information bias. However, effort has been made to minimize the selection bias by recruiting participants from eight major public hospitals including four provincial hospitals and four city hospitals in Hangzhou. The low refusal rate of participation in both case and control groups may also indirectly demonstrate our effort in minimizing selection bias. Because of the latency of the cancer, the reference recall period was set at five years before diagnosis for cancer cases and five years before interview for controls. Therefore, the food and tea consumptions could represent habitual intakes before the onset of the disease. More detailed information on tea and food consumption was collected in our study than other studies such as a recent cohort study from Japan, in which, only one question related to tea consumption and 36 on food items.[26] In addition, the relationship of tea, lycopene, and prostate cancer risk was not established at the time of interview, so that information bias could be assumed to be minimum. Furthermore, people with Alzheimer' disease or recent stroke were excluded to avoid memory error. For participants who neither shopped for food nor cooked meals, 97% of interviews were conducted in the presence of participants' next of kin to confirm the usual quantities and frequencies of habitual food and beverage consumption. Standard containers were shown to the participants to help in recall. To avoid inter-interviewer bias, a single interviewer conducted all interviews following the same protocol. In addition, the risk of prostate cancer was assessed using adjusted OR and accounted for possible confounders. In the logistic regression analysis, three sets of models were used separately to exam potential joint effects.

In summary, diets rich in lycopene and green tea are inversely related to the prostate caner risk, together, they offer stronger preventive effect. This preliminary study may provide an example for nutritional cancer epidemiological studies for assessing the joint effect of foods and nutrients on cancer risks. Further laboratory study is needed to understand the molecular mechanism and biochemistry of the joint effect between phytochemicals.

Acknowledgments

The authors would like to thank the following doctors for their kind permission to interview patients in their hospitals: Professor Li Ping Xie, the First Affiliated Hospital of Zhejiang University; Professor Chuan Jun Du, the Second Affiliated Hospital of Zhejiang University; Dr Da Hong Zhang, Sir Run Run Shaw Hospital; Dr Fang Mei, Hangzhou Fifth Hospital; Dr Yu Guo

Hou, Hangzhou Traditional Chinese Medicine Hospital; Dr Zheng Yong Li, Hangzhou Fourth Hospital; Dr Yu Min Pan, Hangzhou First Hospital; Dr Qiang Zhou, Zhejiang Province Peoples Hospital.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5. In. version 2.0 ed. Lyon: IARCPress; 2002.
2. Stewart BW, Kleihues P. Would Cancer Report. Lyon: IARC Press; 2003.
3. Cook LS, Goldoft M, Schwartz SM, Weiss NS. Incidence of adenocarcinoma of the prostate in Asian immigrants to the United States and their descendants. J Urol 1999;161:152-5.
4. Watanabe M, Nakayama T, Shiraishi T, Stemmermann GN, Yatani R. Comparative studies of prostate cancer in Japan versus the United States. A review. Urologic Oncology 2000;5:274-283.
5. Donaldson MS. Nutrition and cancer: a review of the evidence for an anti-cancer diet. Nutr J 2004;3:19.
6. Jian L, Xie LP, Lee AH, Binns CW. Protective effect of green tea against prostate cancer: a case-control study in southeast China. Int J Cancer 2004;108:130-5.
7. Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. Cancer Res 2006;66:1234-40.
8. Williams MT, Hord NG. The role of dietary factors in cancer prevention: beyond fruits and vegetables. Nutr Clin Pract 2005;20:451-9.
9. Kazi A, Smith DM, Zhong Q, Dou QP. Inhibition of bcl-x(l) phosphorylation by tea polyphenols or epigallocatechin-3-gallate is associated with prostate cancer cell apoptosis. Mol Pharmacol 2002;62:765-71.
10. Shenouda NS, Zhou C, Browning JD, Ansell PJ, Sakla MS, Lubahn DB, et al. Phytoestrogens in common herbs regulate prostate cancer cell growth in vitro. Nutr Cancer 2004;49:200-8.
11. Sonoda T, Nagata Y, Mori M, Miyanaga N, Takashima N, Okumura K, et al. A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. Cancer Sci 2004;95:238-42.
12. FDA. Letter Responding to Health Claim Petition dated January 27, 2004: Green Tea and Reduced Risk of Cancer Health Claim. In. Maryland: Department of Health and Human Services, Center for Food Safety & Applied Nutrition; 2004.
13. Hadley CW, Miller EC, Schwartz SJ, Clinton SK. Tomatoes, lycopene, and prostate cancer: progress and promise. Exp Biol Med (Maywood) 2002;227:869-80.
14. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst 2002;94:391-8.
15. Agarwal S, Rao AV. Tomato lycopene and its role in human health and chronic diseases. Cmaj 2000;163:739-44.
16. Tang L, Jin T, Zeng X, Wang JS. Lycopene inhibits the growth of human androgen-independent prostate cancer cells in vitro and in BALB/c nude mice. J Nutr 2005;135:287-90.
17. Hwang ES, Bowen PE. Cell cycle arrest and induction of apoptosis by lycopene in LNCaP human prostate cancer cells. J Med Food 2004;7:284-9.
18. Boileau TW, Liao Z, Kim S, Lemeshow S, Erdman JW, Jr., Clinton SK. Prostate carcinogenesis in N-methyl-N-nitrosourea (NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy-restricted diets. J Natl Cancer Inst 2003;95:1578-86.
19. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 1995;87:1767-76.
20. Jian L, Du CJ, Lee AH, Binns CW. Do dietary lycopene and other carotenoids protect against prostate cancer? Int J Cancer 2005;113:1010-4.
21. Jian L, Binns C, Lee A. Validity of a Food Frequency Questionnaire for Elderly Men in Southeast China. Public Health Nutrition 2006: 9: 928-33.
22. Jian L, Shen ZJ, Lee AH, Binns CW. Moderate physical activity and prostate cancer risk: a case-control study in China. Eur J Epidemiol 2005;20:155-60.
23. Institute of Nutrition and Food Hygiene CAopM. Table of Food Components (National representative values). 1 ed. Beijing: People's Hygiene Press; 2000.
24. USDA. USDA Database for the Flavonoid Content of Selected Foods. In. Beltsville: USDA; 2003.
25. Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. J Natl Cancer Inst 2000;92:61-8.
26. Kuriyama S, Shimazu T,Ohmori K, Kikuchi N, Nakaya N, Nishino Y, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and al causes in Japan: the Ohsaki study. JAMA. 2006;296:1255-65.

Cureus

Open Access Review Article

DOI: 10.7759/cureus.43156

A Review of the Dietary Intake, Bioavailability and Health Benefits of Ellagic Acid (EA) with a Primary Focus on Its Anti-Cancer Properties

Review began 07/17/2023
Review ended 08/02/2023
Published 08/08/2023

Philip Harper [1]

1. Life Sciences, University of Southampton, Southampton, GBR

Corresponding author: Philip Harper, philip.harper8@btinternet.com

Abstract

Ellagitannins (ET) and ellagic acid (EA) are polyphenols, present in common foods, which may exhibit significant health benefits against inflammation, infection and cancer. EA is metabolised by the gut flora to produce urolithins, which are absorbed into the systemic circulation. Urolithins are widely documented to reduce oxidative stress associated with many diseases including cancer, heart disease and liver damage. In particular, Urolithin C and D have been shown to have high anti-oxidant properties through the inhibition of reactive oxygen species (ROS). The anti-inflammatory properties of EA have been demonstrated through the down-regulation of pro-inflammatory enzymes such as COX-2 and iNOS as well as decreasing the expression of adhesion molecules. EA also regulates the gut microflora and possesses antimicrobial activity against various strains of harmful bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) and Helicobacter pylori. Numerous studies have documented the anticarcinogenic benefits of EA and have been performed on, but not limited to, prostate, colon and breast cancer cell lines and in vivo models. Conventional treatments for cancer, such as chemotherapy, can often be associated with significant side effects such as fatigue, hair loss and alopecia. Naturally-occurring food substances such as ETs potentially offer a risk-free preventative measure against cancer and could perhaps be used in synergy with current treatments. More level 1 studies are required to inform the evidence-base on this topic.

Categories: Oncology, Nutrition
Keywords: antimicrobial, cancer, anti-inflammatory, antioxidant, polyphenol, ellagitannin, ellagic acid

Introduction And Background

Polyphenols are a large group of phytochemicals which form part of a plant's immune system protecting them from bacteria, viruses and fungi. Ellagitannins (ETs) and ellagic acid (EA) are commonly occurring polyphenols present in certain fruits, nuts and seeds including pomegranate, raspberries, strawberries, walnuts and almonds. In recent years, polyphenols have been extensively researched due to their potential health benefits. They represent a major source of antioxidant in our diet and have been shown to have beneficial health effects in cancer, cardiovascular disease, inflammation, diabetes and Alzheimer's disease [1].

This review explores the bioavailability, metabolism and health effects of ET and EA with a primary focus on their anti-cancer properties. A narrative review of the literature was conducted using PubMed, Web of Science, Scopus and reference lists of chosen articles. Keywords including 'polyphenol', 'ellagitannins', 'anti-inflammatory', 'anti-oxidant' and 'cancer' were used to narrow the search. Only English-written papers were included and the full text of each paper was reviewed prior to its inclusion in this review. Recently published articles were prioritized. References were managed using Endnote software.

Review

Dietary intake

Various studies have attempted to estimate the average dietary intake of polyphenols and ETs. In a Spanish diet, the mean daily intake of total polyphenols was estimated between 2,590 and 3,016 mg/day [2]. France and Denmark produced similar results of 1,193 ± 510 mg/day and 1,786 mg/day, respectively. Finland and Greece had more modest estimations with average daily intakes of 863 ± 415 mg/day and 744 mg/day, respectively. The daily intake of ET was 12 mg/day in Finland, 13 mg/day in America and only 5 mg/day in Germany [3]. In France, the average person consumes around 1.7 kg of strawberries every year, which is their primary source of ETs. This would correspond to a daily consumption of around 0.4 mg/day total EA [4]. As demonstrated by these studies, polyphenol and ET intake varies drastically between countries. Accurately measuring the daily intake of polyphenols is extremely challenging due to the inability to control all aspects of a subject's diet.

Bioavailability and metabolism

EA can occur in either its free form, EA glycosides, or bound as ETs. ETs are hydrolysed to EAs under physiological conditions and then metabolised by the intestinal gut flora to produce urolithins, which are absorbed into the circulation. The low bioavailability of ETs are likely due to their large size and high polarity with the presence of C-C linkage. ETs which are sensitive to hydrolysis in the stomach and duodenum release EAs which are also poorly bioavailable due to low water solubility, extensive degradation before absorption and its irreversible binding to DNA, which may affect transcellular absorption [5]. When mice were given ETs (from raspberries or pomegranates) 10% of the total EA dose was detected in the urine and faeces. However, there was virtually no trace of it in the blood or tissues [6]. In a human subject, EA was detected in plasma at a maximum concentration after one hour of ingesting pomegranate juice but was rapidly eliminated after four hours [7].

Studies have shown that urolithins are much more readily bioavailable and appear in human systemic circulation within a few hours of pomegranate ingestion reaching maximum concentrations between 24 and 48 hours. They were found to exist in both free and conjugated forms in the plasma and urine [8,9]. In view of this they are considered the bioactive forms of ETs.

Toxicity of ET

Before delving into the potential health benefits of ETs and EA, one must consider the negative effects associated with their intake. Tasaki et al. performed a toxicity study on EA using F344 rats with doses ranging between 9.4 and 42.3 g/kg of body weight. Haematology and serum biochemistry revealed sporadic alterations in mean corpuscular volume (MCV), aspartate transaminase (AST) and ALP observed in both genders but this was not felt to be treatment-related. Histological testing revealed sporadic lesions in the lungs, heart, liver and kidneys. However, incidence of lesions was similar to the control group. Body weight gain was slightly decreased in the female group but not to the extent of affecting biochemical markers. In conclusion, the no-observed-adverse-effect level in female rats was estimated to be 3,254 mg/kg/day, significantly higher than normal dietary amounts [10].

Polyphenols bind iron in the intestines and can prevent it from being absorbed. This can have a beneficial impact in cases of iron overload and preventing formation of oxygen free radicals which will be discussed later [11]. However, it can also be detrimental and may increase the risk of iron-deficient anaemia.

Binding of polyphenols to digestive enzymes such as amylase, protease and lipase can impair their function and disturb the function of the gastrointestinal system. This could be particularly harmful to people with food intolerances who lack certain enzymes such as gluten and lactose intolerance, coeliac disease or cystic fibrosis. Further to this, elderly people are at higher risk of digestive enzyme deficiency and ingestion of a high polyphenol diet could exacerbate this [12]. Other negative impacts include disturbing the gut microbiome and impacting the metabolism of certain drugs by either increasing or diminishing their therapeutic effect.

Antioxidant effects

The cellular injury caused by oxidative stress and free radicals has been associated with many diseases including cancer, heart disease and liver damage. Polyphenols are widely considered to have strong anti-oxidant potency acting as reactive oxygen species (ROS) scavengers (Type 1 antioxidants), peroxide decomposers and electron donors (type 2 antioxidants) [13]. EA exerts its effects against free radicals using type 1 and type 2 mechanisms. Importantly, it inhibits the endogenous production of radial hydroxyl which is responsible for tissue and DNA damage. It also chelates and subtracts metal ions such as Fe2+ and copper ions involved in the production of free radicals [14]. As previously mentioned, only trace amounts of EA have ever been found in human blood whereas their metabolites, urolithins, are readily absorbed into the systemic circulation.

Urolithin A, when tested as a direct radical scavenger showed an IC50 OF 152.66mM in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) test compared to EA which had an IC50 of 6.6 mM. However, rather than being prolific free radical scavengers Urolithin A exerted most of its antioxidant effects through the inhibition of oxidase enzymes, such as MAO-A and tyrosinase, with IC50 values of 71.44 and 29.4 mM, respectively [15]. Bialonska et al. demonstrated that Urolithin C and D exerted the highest antioxidant activity with IC50 values of 0.16 and 0.33 µM, respectively, when compared to IC50 value of 1.1 of the EA. Urolithin C had superior lipophilicity and hence was more bioavailable that Urolithin D [16].

Anti-inflammatory effects

The effects of pomegranate extract (POMx) have been tested on collagen-induced arthritis (CIA) in mice. POMx is a highly rich source of ETs. It was found that consumption of POMx delayed the onset and reduced the incidence of CIA at doses of 13.6 mg/kg and 34 mg/kg. Activated macrophages produce several inflammatory mediators and infiltrate joints in arthritis. One such mediator is nitric oxide (NO). POMx was shown to significantly inhibit NO production in LPS-stimulated macrophages at a dose of 20 µg/ml. The POMx-fed mice demonstrated reduced joint infiltration by the inflammatory cells and levels of interleukin-6 (IL-6) were significantly decreased [17].

Endothelial cell expression of adhesion molecules has been recognized as an early step in inflammation. Papoutsi et al examined the effect of EA from walnuts on the expression of vascular cell adhesion molecule (VCAM)-1 and intracellular adhesion molecule (ICAM)-1 in human aortic endothelial cells. Results showed that EA significantly decreased the TNF-α-induced endothelial expression of both VCAM-1 and ICAM-1 at a concentration range of 0·1-10 μm [18]. Mirzaie et al. conducted a randomised controlled trial where individuals with Inflammatory Bowel Disease (IBS) received 180mg of EA per day for two months. They found a significant reduction in the IBS severity score in the treatment group owing to less severe abdominal pain/distension and frequency of symptoms [19].

Anti-microbial and probiotic effects

It has been shown that EA can influence the gut microflora by either destroying harmful bacteria or enhancing the growth of beneficial bacteria. When EA-rich foods, such as pomegranate, are consumed the ETs accumulate in the large intestines, where they interact with and promote the gut microflora. Using fluorescence in situ hybridization (FISH) analysis, POMx enhanced the growth of total bacteria, bifidobacterium spp and Lactobacillus spp using human faecal samples. These two groups of bacteria are associated with many health benefits. POMx did not influence the Clostridium coccoides-Eubacterium rectale group and the C. histolyticum group. The lack of growth enhancement in the latter group has clinical significance as it contains proteolytic bacteria, the metabolism of which have been linked to IBS and colorectal cancer [20].

EA along with other pomegranate-containing compounds have antimicrobial activity when assayed against various strains of bacteria including E. coli and methicillin-resistant Staphylococcus aureus (MRSA) [21]. They elicited a dose-dependent bactericidal effect in Helicobacter pylori by inhibiting the action of Arylamine N-acetyltransferase and Staph. aureus with an IC50 value of 0.47 mM through the inhibition of N-acetylation of 2-aminofluorene [22,23]. They are believed to disrupt the cell membrane in both gram positive and gram negative bacteria through direct binding or binding with biomolecules such as peptidoglycans in cell membranes [24]. Mycobacterium abscessus (Mabs) is a cause of various types of infection including respiratory infection in patients with cystic fibrosis. EA demonstrated antimicrobial activity against Mabs due to its high binding affinity to Dihydrofolate reductase at a minimum inhibitory concentration of 1.56 mg/mL and bactericidal concentration of of 3.12 mg/mL [25].

Unfortunately, the inhibitory effect of polyphenols is not just limited to pathogens. The inhibitory effect of a variety of polyphenols on the gut microbiome is noted in multiple studies including myricetin inhibiting the effect of intestinal lactic acid bacteria, epigallocatechin inhibiting non-pathogenic E.coli and quercetin inhibiting Ruminococcus gauvreauii [26-28].

Anti-cancer effects

Polyphenols mediate their anti-cancer effects through antioxidant, anti-inflammatory and anti-proliferative mechanisms as well as influencing subcellular signalling pathways and inducing cell-cycle arrest and apoptosis. Many different types of cancer have been investigated in vitro. This review will focus on prostate, colon and breast cancer.

Prostate Cancer

EA treatment of prostate cancer PC3 cells resulted in decreased cancer cell proliferation through a reduction of phosphorylated STAT3, ERK and AKT signalling proteins after 72 hours in a dose-dependent manner (0-100 μM) [29]. Other studies have reached similar conclusions by assessing different components of pomegranate such as the peel, juice seeds and seed oil (rich sources of ETs) on various prostate cancer cell lines. They consistently demonstrated pro-apoptotic and inhibitory effects on cancer cell proliferation. In vivo they demonstrated potent inhibition of PC3 xenograft growth in mice [30,31]. Urolithins have also been shown to inhibit the growth of both androgen-dependent and androgen-independent prostate cancer cell lines in vitro with IC50 values lower than EA, however, the exact mechanisms by which they exert these effects need to be investigated [32]. Furthermore, the IC50 values of urolitihins were higher than what is physiologically achievable.

Inflammation is a hallmark of many cancers, in particular prostate cancer, and is dependent on the transcription factor NF-kB. NF-kB activation leads to immune activity, inflammation and cell proliferation whilst also upregulating the transcription genes that produce collagenases, cell adhesion molecules and inflammatory cytokines. It is also associated with the transcription of genes involved in cell survival and inhibiting apoptosis. Inflammation can result in persistent oxidative stress in cancer cells and ROS may give these cancer cells a survival advantage. EA has been shown to prevent prostate cancer growth, by inhibiting inflammatory pathways including the NF-kB pathway [32].

Another hallmark of cancer is angiogenesis. Sartipour et al. administered oral POMx to severe combined immunodeficient mice which had been previously injected with LAPC4 human prostate cancer cells. After four weeks of treatment POMx decreased prostate cancer xenograft size, tumour vessel density, vascular endothelial growth factor (VEGF) levels and HIF-1 alpha expression, thereby suggesting that POMx has an

inhibitory effect on tumour-associated angiogenesis [33].

A clinical trial was carried out which looked at the effects of pomegranate juice on rising prostate specific antigen (PSA) in prostate cancer patients after surgery or radiotherapy was conducted. The mean length of time for PSA to double was significantly prolonged following daily pomegranate juice consumption [34].

Colon Cancer

EA was extracted from the pulp and seeds of five different types of raspberries and exerted antiproliferative effects against human colon carcinoma cells in vitro. The extent of this effect was correlated with the content of EA in the extract [35]. The activation of Wnt signalling pathways are known to play a key role in human colon carcinogenesis. Using the 293T colon cancer cell line it was observed that Urolithin A inhibited the Wnt signalling pathway at physiologically relevant concentrations - IC50 of 39 μM [36]. The doses of ET and EA needed to inhibit Wnt signalling were unfortunately not physiologically relevant.

Cytochrome p450-1 (CYP1) enzymes are involved in the activation of procarcinogens into cancer-inducing chemicals. ET and urolithins showed a significant dose-dependent inhibition of CYP1 enzymes in HT-29 colon cancer cells, whilst also demonstrating anti-proliferative effects mediated through cell cycle arrest in the G0/G1 and G2/M stages followed by induction of apoptosis [37]. González-Sarrías et al. reached similar conclusions and found that EA, Urolithin A and Urolithin B modulated phase I and phase II detoxifying enzymes in colon cancer Caco-2 cells. The three compounds induced the expression and activity of CYP1A1 which, unlike the other CYP enzymes, is involved in detoxification [38].

5-Fluorouracil (5-FU) remains a first line treatment for colorectal cancer. However, only 10-15% of patients with advanced colorectal cancer respond positively to 5-FU monotherapy. Therefore, new strategies to enhance the 5-FU effectiveness are critically needed. The co-treatment of 5-FU with Urolithin A, resulted in decreased IC50 values for 5-FU and cell cycle arrest at the G2/M phase together with a slight increase in caspases 8 and 9 activation. Urolithin A may therefore potentiate the effects of 5-FU on colon cancer cells. This potentially means that lower doses of 5-FU could be used to achieve therapeutic effects thereby decreasing the likelihood of adverse effects [39].

Black raspberries have a high concentration of phenolic compounds including ETs and flavonoids. A clinical trial examined the effects of concentrated berry power in 20 colorectal cancer (20g freeze dried berry powder diluted in 100ml of water consumed x3 times a day for 1-9 weeks). Immunohistochemistry demonstrated that blackberries protectively modulated a number of anti-cancer proteins including β-catenin (Wnt pathway), Ki-67 (cell proliferation), terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) (apoptosis) and CD105 (angiogenesis) [40]. Smad4 is a tumour suppressor gene, which, when poorly expressed, is associated with worse outcomes in colorectal cancer. Colorectal specimens from patients who had ingested black raspberries showed increased Smad4 expression in the epithelium compared to control subjects [41]. Upregulating Smad4 expression in the colonic epithelium could reduce the risk of malignant transformation in colonic tumours. Of course, a limitation with foods such as blackberries is the varying concentrations of phenolic compounds within them, which thereby lessens the reliability and consistency of chemopreventive effects.

Breast Cancer

Polyphenols from fermented juice, pericarp and oil inhibited the growth of breast cancer cell lines in vitro. This effect was greater in the oestrogen-dependent MCF-7 line than the oestrogen-independent MB-MDA-231 line. Fermented pomegranate juice polyphenols consistently showed about twice the anti-proliferative effect as fresh pomegranate juice polyphenols. Oestrogen synthesis was inhibited by a 60-80% reduction in aromatase activity.

As previously mentioned, a tumour needs to receive sufficient nutrients and oxygen and have the ability to evacuate waste in order to sustain growth. It achieves this through angiogenesis and VEGF is the most potent stimulator of this process. EA markedly inhibits angiogenesis-associated activities including proliferation, migration/invasion and capillary formation on VEGF-stimulated endothelial cells in vitro at doses of 2.5 to 20 μM. It directly inhibited VEGFR-2 tyrosine kinase activity and its downstream signalling pathways including MAPK and PI3K/Akt in endothelial cells. In vivo, EA inhibited vessel formation in chick chorioallantoic membrane and sprouts formation of chicken aorta. In breast cancer xenografts, EA significantly inhibited MDA-MB-231 cancer growth and P-VEGFR2 expression. The authors concluded very low toxicity of EA given there were no abnormal morphological changes to the cancer cell lines and in vivo there was sprout recurrence from the chick aortic arch once EA was removed [42]. To our knowledge, there have been no clinical studies performed regarding the effects of EA on breast cancer.

Synergistic Effects of Polyphenols

EA is widely considered the key compound in pomegranate in terms of its anti-carcinogenic

effects. However, it is believed that its action is enhanced by other polyphenols present in pomegranate. Seeram et al. compared the effect of pure pomegranate juice with individual polyphenols (EA and punicalagin) on human oral, prostate and colon cancer cells. It found that the polyphenols independently decreased the viable cell number of cancer cells but not nearly as much as the pure pomegranate juice. The juice also had a more profound effect on inducing apoptosis compared with the separated polyphenols [43].

Conclusions

In recent years, an abundance of research has led to the idea that ETs, EA and their derived metabolites may be protective against many diseases including cancer. The prospect of natural chemotherapy is very appealing because medical chemotherapy often produces distressing side-effects, which may hinder compliance. The in vitro and in vivo evidence of ET health benefits is strong, however, there is a dearth of research assessing the effects of ETs in human subjects. The clinical significance of many of the aforementioned studies isn't clear as ET are not readily found in the bloodstream following ingestion of ET-rich foods. Studies involving EA and/or urolithins are perhaps more clinically revelant as these have better bioavailability. EA and urolithins have been shown to accumulate in the prostate and intestines where they may exert their most potent anti-cancer effects. It is unclear why they localise here in relation to other organs.

Clinical studies investigating the timing of ET-rich supplements in cancer therapy would be useful. For example, neo-adjuvant versus adjuvant treatment and in combination with other existing therapies such as chemoradiotherapy or hormone therapy. Current evidence on urolithins potentiating the effects of chemotherapy agents such as 5-FU are very promising and could significantly improve the quality of life of patients undergoing chemotherapy treatment. There is also benefit in the cost-effectiveness of chemopreventive foods which may represent a more affordable option for developing countries than pharmacological agents. Randomised controlled trials should be carried out to investigate recurrence rates following primary cancer treatment used in conjunction with ET supplementation. Finally, the therapeutic doses of EA and urolithins need to be better defined in order to analyse the risk-benefit profile of oral supplementation. The negative health impacts of polyphenols and their metabolites have been discussed and should be considered when conducting clinical trials.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Sharma J, Maity A: Pomegranate phytochemicals: nutraceutical and therapeutic values . Fruit Vegetable Cereal Sci Biotechnol. 2010, 4:56-76.
2. Saura-Calixto F, Serrano J, Goni I: Intake and bioaccessibility of total polyphenols in a whole diet . Food Chem. 2007, 101:492-501. 10.1016/j.foodchem.2006.02.006
3. Ovaskainen ML, Törrönen R, Koponen JM, Sinkko H, Hellström J, Reinivuo H, Mattila P: Dietary intake and major food sources of polyphenols in Finnish adults. J Nutr. 2008, 138:562-6. 10.1093/jn/138.3.562
4. Clifford MN, Scalbert A: Ellagitannins-nature, occurrence and dietary burden . J Sci Food Agriculture. 2000, 80:1118-25. 10.1002/(SICI)1097-0010(20000515)80:7<1118::AID-JSFA570>3.0.CO;2-9
5. Whitley AC, Stoner GD, Darby MV, Walle T: Intestinal epithelial cell accumulation of the cancer preventive polyphenol ellagic acid—extensive binding to protein and DNA. Biochem Pharmacol. 2003, 66:907-15. 10.1016/s0006-2952(03)00413-1
6. Smart RC, Huang MT, Chang RL, Sayer JM, Jerina DM, Conney AH: Disposition of the naturally occurring antimutagenic plant phenol, ellagic acid, and its synthetic derivatives, 3-O-decylellagic acid and 3,3'-di-O-methylellagic acid in mice. Carcinogenesis. 1986, 7:1663-7. 10.1093/carcin/7.10.1663
7. Seeram NP, Lee R, Heber D: Bioavailability of ellagic acid in human plasma after consumption of ellagitannins from pomegranate (Punica granatum L.) juice. Clin Chim Acta. 2004, 348:63-8. 10.1016/j.cccn.2004.04.029
8. Villalba KJ, Barka FV, Pasos CV, Rodríguez PE: Food ellagitannins: structure, metabolomic fate, and biological properties. Tannins: Structural Properties, Biological Properties and Current Knowledge. IntechOpen, 2019. 26-46. 10.5772/intechopen.86420
9. Quideau S, Deffieux D, Douat-Casassus C, Pouységu L: Plant polyphenols: chemical properties, biological activities, and synthesis. Angew Chem Int Ed Engl. 2011, 50:586-621. 10.1002/anie.201000044
10. Tasaki M, Umemura T, Maeda M, et al.: Safety assessment of ellagic acid, a food additive, in a subchronic toxicity study using F344 rats. Food Chem Toxicol. 2008, 46:1119-24. 10.1016/j.fct.2007.10.043
11. Wang X, Li Y, Han L, Li J, Liu C, Sun C: Role of flavonoids in the treatment of iron overload . Front Cell Dev Biol. 2021, 9:685364. 10.3389/fcell.2021.685364
12. Ahmed T, Haboubi N: Assessment and management of nutrition in older people and its importance to

health. Clin Interv Aging. 2010, 5:207-16. 10.2147/cia.s9664
13. Porter WL: Recent trends in food applications of antioxidants . Autoxidation in Food and Biological Systems. Simic MG, Karel M (ed): Springer, Boston, USA; 1980. 295-365. 10.1007/978-1-4757-9351-2_19
14. Galano A, Mazzone G, Alvarez-Diduk R, Marino T, Alvarez-Idaboy JR, Russo N: Food antioxidants: chemical insights at the molecular level. Annu Rev Food Sci Technol. 2016, 7:335-52. 10.1146/annurev-food-041715-033206
15. Cásedas G, Les F, Choya-Foces C, Hugo M, López V: The metabolite urolithin-A ameliorates oxidative stress in neuro-2a cells, becoming a potential neuroprotective agent. Antioxidants (Basel). 2020, 9:177. 10.3390/antiox9020177
16. Bialonska D, Kasimsetty SG, Khan SI, Ferreira D: Urolithins, intestinal microbial metabolites of pomegranate ellagitannins, exhibit potent antioxidant activity in a cell-based assay. J Agric Food Chem. 2009, 57:10181-6. 10.1021/jf9025794
17. Shukla M, Gupta K, Rasheed Z, Khan KA, Haqqi TM: Consumption of hydrolyzable tannins-rich pomegranate extract suppresses inflammation and joint damage in rheumatoid arthritis. Nutrition. 2008, 24:733-43. 10.1016/j.nut.2008.03.013
18. Papoutsi Z, Kassi E, Chinou I, Halabalaki M, Skaltsounis LA, Moutsatsou P: Walnut extract (Juglans regia L.) and its component ellagic acid exhibit anti-inflammatory activity in human aorta endothelial cells and osteoblastic activity in the cell line KS483. Br J Nutr. 2008, 99:715-22. 10.1017/S0007114507837421
19. Mirzaie Z, Bastani A, Hesami S, Pouryousefi E, Kavianpour M, Haghighian HK: Improving effect of ellagic acid on sleep quality and gastrointestinal symptoms in patient with irritable bowel syndrome: randomized double-blind clinical trial. Turk J Gastroenterol. 2021, 32:937-44. 10.5152/tjg.2021.20344
20. Bialonska D, Ramnani P, Kasimsetty SG, Muntha KR, Gibson GR, Ferreira D: The influence of pomegranate by-product and punicalagins on selected groups of human intestinal microbiota. Int J Food Microbiol. 2010, 140:175-82. 10.1016/j.ijfoodmicro.2010.03.038
21. Reddy MK, Gupta SK, Jacob MR, Khan SI, Ferreira D: Antioxidant, antimalarial and antimicrobial activities of tannin-rich fractions, ellagitannins and phenolic acids from Punica granatum L. Planta Med . 2007, 73:461-7. 10.1055/s-2007-967167
22. Chung JG: Inhibitory actions of ellagic acid on growth and arylamine N-acetyltransferase activity in strains of Helicobacter pylori from peptic ulcer patients. Microbios. 1998, 93:115-27.
23. Lu HF, Tsou MF, Lin JG, Ho CC, Liu JY, Chuang JY, Chung JG: Ellagic acid inhibits growth and arylamine N-acetyltransferase activity and gene expression in Staphylococcus aureus. In Vivo. 2005, 19:195-9.
24. Yoda Y, Hu ZQ, Zhao WH, Shimamura T: Different susceptibilities of Staphylococcus and Gram-negative rods to epigallocatechin gallate. J Infect Chemother. 2004, 10:55-8. 10.1007/s10156-003-0284-0
25. Moraes-Neto RN, Coutinho GG, Ataíde AC, et al.: Ethyl acetate fraction of Bixa orellana and its component ellagic acid exert antibacterial and anti-inflammatory properties against Mycobacterium abscessus subsp. massiliense. Antibiotics (Basel). 2022, 11:87. 10.3390/antibiotics11060817
26. Puupponen-Pimiä R, Nohynek L, Meier C, Kähkönen M, Heinonen M, Hopia A, Oksman-Caldentey KM: Antimicrobial properties of phenolic compounds from berries . J Appl Microbiol. 2001, 90:494-507. 10.1046/j.1365-2672.2001.01271.x
27. Vattem DA, Lin Y-T, Ghaedian R, Shetty K: Cranberry synergies for dietary management of Helicobacter pylori infections. Process Biochem. 2005, 40:1583-92. 10.1016/j.procbio.2004.06.024
28. Duda-Chodak A: The inhibitory effect of polyphenols on human gut microbiota . J Physiol Pharmacol. 2012, 63:497-503.
29. Eskandari E, Heidarian E, Amini SA, Saffari-Chaleshtori J: Evaluating the effects of ellagic acid on pSTAT3, pAKT, and pERK1/2 signaling pathways in prostate cancer PC3 cells. J Cancer Res Ther. 2016, 12:1266-71. 10.4103/0973-1482.165873
30. Lansky EP, Jiang W, Mo H, et al.: Possible synergistic prostate cancer suppression by anatomically discrete pomegranate fractions. Invest New Drugs. 2005, 23:11-20. 10.1023/B:DRUG.0000047101.02178.07
31. Albrecht M, Jiang W, Kumi-Diaka J, et al.: Pomegranate extracts potently suppress proliferation, xenograft growth, and invasion of human prostate cancer cells. J Med Food. 2004, 7:274-83. 10.1089/jmf.2004.7.274
32. Heber D: Multitargeted therapy of cancer by ellagitannins . Cancer Lett. 2008, 269:262-8. 10.1016/j.canlet.2008.03.043
33. Sartippour MR, Seeram NP, Rao JY, et al.: Ellagitannin-rich pomegranate extract inhibits angiogenesis in prostate cancer in vitro and in vivo. Int J Oncol. 2008, 32:475-80. 10.3892/ijo.32.2.475
34. Pantuck AJ, Leppert JT, Zomorodian N, et al.: Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. Clin Cancer Res. 2006, 12:4018-26. 10.1158/1078-0432.CCR-05-2290
35. Stoner GD: Foodstuffs for preventing cancer: the preclinical and clinical development of berries . Cancer Prev Res (Phila). 2009, 2:187-94. 10.1158/1940-6207.CAPR-08-0226
36. Sharma M, Li L, Celver J, Killian C, Kovoor A, Seeram NP: Effects of fruit ellagitannin extracts, ellagic acid, and their colonic metabolite, urolithin A, on Wnt signaling. J Agric Food Chem. 2010, 58:3965-9. 10.1021/jf902857v
37. Kasimsetty SG, Bialonska D, Reddy MK, Ma G, Khan SI, Ferreira D: Colon cancer chemopreventive activities of pomegranate ellagitannins and urolithins. J Agric Food Chem. 2010, 58:2180-7. 10.1021/jf903762h
38. González-Sarrías A, Azorín-Ortuño M, Yáñez-Gascón MJ, Tomás-Barberán FA, García-Conesa MT, Espín JC: Dissimilar in vitro and in vivo effects of ellagic acid and its microbiota-derived metabolites, urolithins, on the cytochrome P450 1A1. J Agric Food Chem. 2009, 57:5623-32. 10.1021/jf900725e
39. González-Sarrías A, Tomé-Carneiro J, Bellesia A, Tomás-Barberán FA, Espín JC: The ellagic acid-derived gut microbiota metabolite, urolithin A, potentiates the anticancer effects of 5-fluorouracil chemotherapy on human colon cancer cells. Food Funct. 2015, 6:1460-9. 10.1039/c5fo00120j
40. Wang LS, Arnold M, Huang YW, et al.: Modulation of genetic and epigenetic biomarkers of colorectal cancer in humans by black raspberries: a phase I pilot study. Clin Cancer Res. 2011, 17:598-610. 10.1158/1078-0432.CCR-10-1260
41. Huang YW, Lin CW, Pan P, et al.: Black raspberries suppress colorectal cancer by enhancing Smad4

expression in colonic epithelium and natural killer cells. Front Immunol. 2020, 11:570683. 10.3389/fimmu.2020.570683

42. Wang N, Wang ZY, Mo SL, et al.: Ellagic acid, a phenolic compound, exerts anti-angiogenesis effects via VEGFR-2 signaling pathway in breast cancer. Breast Cancer Res Treat. 2012, 134:943-55. 10.1007/s10549-012-1977-9
43. Seeram NP, Adams LS, Henning SM, Niu Y, Zhang Y, Nair MG, Heber D: In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. J Nutr Biochem. 2005, 16:360-7. 10.1016/j.jnutbio.2005.01.006

Home > Chinese Journal of Integrative Medicine > Article

Potential Benefits of Green Tea in Prostate Cancer Prevention and Treatment: A Comprehensive Review

Herbal and Botanical Review | Published: 02 April 2024
Volume 30, pages 1045–1055, (2024) Cite this article

Chinese Journal of Integrative Medicine

Aims and scope →

Submit manuscript →

Gui-hong Liu, Ze-qin Yao, Guo-qiang Chen, Ya-lang Li & Bing Liang

Abstract

Prostate cancer is a prevalent and debilitating disease that necessitates effective prevention and treatment strategies. Green tea, a well-known beverage derived from the *Camellia sinensis* plant, contains bioactive compounds with potential health benefits, including catechins and polyphenols. This comprehensive review aims to explore the potential benefits of green tea in prostate cancer prevention and treatment by examining existing literature. Green tea possesses antioxidant, anti-inflammatory, and anti-carcinogenic properties attributed to its catechins, particularly epigallocatechin gallate. Epidemiological studies have reported an inverse association between green tea consumption and prostate cancer risk, with potential protection against aggressive forms of the disease. Laboratory studies demonstrate that green tea components inhibit tumor growth, induce apoptosis, and modulate signaling pathways critical to prostate cancer development and progression. Clinical trials and human studies further support the potential benefits of green tea. Green tea consumption has been found to be associated with a reduction in prostate-specific antigen levels, tumor markers, and played a potential role in slowing disease progression. However, challenges remain, including optimal dosage determination, formulation standardization, and conducting large-scale, long-term clinical trials. The review suggests future research should focus on combinatorial approaches with conventional therapies and personalized medicine strategies to identify patient subgroups most likely to benefit from green tea interventions.

Principali conclusioni della review (aprile 2024)

- **Proprietà biologiche confermate**: il tè verde, grazie alle catechine (soprattutto EGCG), esercita **effetti antiossidanti, anti-infiammatori e antitumorali**, modulando vie molecolari rilevanti nella carcinogenesi prostatica, come proliferazione cellulare, apoptosi e segnalazioni chiave .
- **Studi epidemiologici**: alcuni suggeriscono un'associazione inversa tra consumo regolare di tè verde e rischio di carcinoma prostatico, soprattutto nelle forme aggressive; tuttavia, i dati non sono uniformi e restano tentativi da consolidare PubMedResearchGate.

- **Evidenza clinica**: alcuni studi su umani mostrano una **riduzione moderata dei livelli di PSA** e di altri marcatori tumorali, oltre a un potenziale rallentamento della progressione, ma i risultati non sono omogenei né definitivi.
- **Limitazioni critiche**:
    - Dosaggi variabili e poco standardizzati tra gli studi;
    - Formulazioni differenti (estratti vs tisane vs integratori), con effetto dose-dipendente;
    - Dimensioni campionarie ridotte e durata insufficiente dei trial clinici;
    - Mancanza di follow-up a lungo termine e limitata identificazione dei sottogruppi di pazienti che ne trarrebbero maggiore beneficio PubMedResearchGate.
- **Raccomandazioni future**:
    - Necessità di **studi su larga scala**, con protocolli RCT ben disegnati;
    - **Standardizzazione del dosaggio**, della forma di somministrazione e delle formulazioni (es. concentrazione di EGCG);
    - Approcci **combinati** con terapie convenzionali;
    - Ricerca orientata alla **medicina personalizzata**, per identificare chi può trarne vantaggio, potenzialmente in base a caratteristiche biologiche/genetiche