

BIBLIOGRAFIA

INGREDIENTI FITOTERAPICI	ABSTRACT
Tè	1) Una meta-analisi sull'assunzione di tè verde e l'efficacia capacità delle catechine nella prevenzione del cancro alla prostata. 2) Report preliminare sulla chemioprevenzione del cancro prostatico a seguito di assunzione di catechine del tè verde in volontari con alto grado di neoplasia prostatica intraepiteliale protratta per un anno. 3) Follow-up a due anni sulla chemioprevenzione del cancro alla prostata umana dopo somministrazione di catechine del tè verde.
Melograno	1) Studio sulla terapia con acido ellagico in pazienti con cancro alla prostata refrattari alla terapia ormonale (HRPC) in chemioterapia standard. 2) Rassegna sulle attività antinfiammatorie e anticancro sia del melograno e sia del suo costituente: l'acido ellagico. Dati da studi preclinici e clinici.
Astragalo	Studio sull'isoflavone: formonnetina e inibizione del ciclo cellulare attraverso la downregulation di Akt/Cyclin D1/CDK4 nelle cellule umane di cancro alla prostata.
Bacche di Goji	I polisaccaridi contenuti nelle bacche di Goji inducono l'apoptosi nelle cellule umane di cancro alla prostata, come dimostrato in un modello animale (topo xenograft) di cancro alla prostata.
Licopene	Metaanalisi che dimostra come il licopene assunto con la dieta è associato ad un ridotto rischio di cancro alla prostata in modo dose-dipendente.
Ravanello	Metaanalisi sull'assunzione di verdure crocifere e riduzione del rischio di cancro alla prostata.
Resveratrolo	Rassegna sui benefici legati alla elevata capacità ossidante del resveratrolo e il suo potenziale per sostenere la prevenzione e il trattamento del cancro prostatico.

Green tea and the risk of prostate cancer

A systematic review and meta-analysis

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Abstract

Prostate cancer (PCa) now remains the 2nd most frequently diagnosed cancer. In recent years, chemoprevention for PCa becomes a possible concept. Especially, many phytochemicals rich foods are suggested to lower the risk of cancer. Among these foods, green tea is considered as effective prevention for various cancers. However, clinical trials and previous meta-analyses on the relationship between green tea consumption and the risk of PCa have produced inconsistent outcomes. This study aims to determine the dose-response association of green tea intake with PCa risk and the preventive effect of green tea catechins on PCa risk. Seven observational studies and 3 randomized controlled trials were retrieved from Cochrane Library, PubMed, Sciencedirect Online, and hand searching. The STATA (version 12.0) was applied to analyze the data. The relative risks (RRs) and 95% confidence intervals were pooled by fixed or random effect modeling. Dose-response relations were evaluated with categories of green tea intake. Although there was no statistical significance in the comparison of the highest versus lowest category, there was a trend of reduced incidence of PCa with each 1 cup/day increase of green tea ($P=0.08$). Our dose-response meta-analysis further demonstrated that higher green tea consumption was linearly associated with a reduced risk of PCa with more than 7 cups/day. In addition, green tea catechins were effective for preventing PCa with an RR of 0.38 ($P=0.02$). In conclusion, our dose-response meta-analysis evaluated the association of green tea intake with PCa risk systematically and quantitatively. And this is the first meta-analysis of green tea catechins consumption and PCa incidence. Our novel data demonstrated that higher green tea consumption was linearly reduced PCa risk with more than 7 cups/day and green tea catechins were effective for preventing PCa. However, further studies are required to substantiate these conclusions.

Abbreviations: CI = confidence interval, EGCG = (–)-epigallocatechin-3-gallate, HGPIN = high-grade prostatic intraepithelial neoplasia, HR = hazard ratio, IGF = insulin-like growth factor, OR = odds risk, PCa = prostate cancer, RCT = randomized controlled trial, RR = relative risk.

Keywords: dose-response, green tea, green tea catechins, meta-analysis, prostate cancer

Editor: Sumit Arora.

YMG and FZ contributed equally to this work.

Authorship: YMG and FZ contributed equally to this work. YMG, FZ, XHW, and XHZ conceived and designed the study. HX, QM, KKZ, YMG, and PC performed the electronic search, selected studies, extracted data, and performed quality assessment. YMG, FZ, and XHZ analyzed data and conducted meta-analysis. YMG, PC, and XHZ supervised the research, edited and drafted revisions to the article.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:13(e6426)

Received: 15 August 2016 / Received in final form: 24 February 2017 /

Accepted: 27 February 2017

http://dx.doi.org/10.1097/MD.00000000000006426

Research Article

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

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Abstract

Green tea catechins (GTCs) proved to be effective in inhibiting cancer growth in several experimental models. Recent studies showed that 30% of men with high-grade prostate intraepithelial neoplasia (HG-PIN) would develop prostate cancer (CaP) within 1 year after repeated biopsy. This prompted us to do a proof-of-principle clinical trial to assess the safety and efficacy of GTCs for the chemoprevention of CaP in HG-PIN volunteers. The purity and content of GTCs preparations were assessed by high-performance liquid chromatography [(–)-epigallocatechin, 5.5%; (–)-epicatechin, 12.24%; (–)-epigallocatechin-3-gallate, 51.88%; (–)-epicatechin-3-gallate, 6.12%; total GTCs, 75.7%; caffeine, <1%]. Sixty volunteers with HG-PIN, who were made aware of the study details, agreed to sign an informed consent form and were enrolled in this double-blind, placebo-controlled study. Daily treatment consisted of three GTCs capsules, 200 mg each (total 600 mg/d). After 1 year, only one tumor was diagnosed

among the 30 GTCs-treated men (incidence, ~3%), whereas nine cancers were found among the 30 placebo-treated men (incidence, 30%). Total prostate-specific antigen did not change significantly between the two arms, but GTCs-treated men showed values constantly lower with respect to placebo-treated ones. International Prostate Symptom Score and quality of life scores of GTCs-treated men with coexistent benign prostate hyperplasia improved, reaching statistical significance in the case of International Prostate Symptom Scores. No significant side effects or adverse effects were documented. To our knowledge, this is the first study showing that GTCs are safe and very effective for treating premalignant lesions before CaP develops. As a secondary observation, administration of GTCs also reduced lower urinary tract symptoms, suggesting that these compounds might also be of help for treating the symptoms of benign prostate hyperplasia. (Cancer Res 2006; 66(2): 1234–40)

Note: S. Bettuzzi and M. Brausi contributed equally to this work.

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©2006 American Association for Cancer Research.
doi:10.1158/0008-5472.CAN-05-1145

Cancer Res 2006; 66: (2). January 15, 2006

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available at www.sciencedirect.com
journal homepage: www.europeanurology.com



Letter to the Editor NOT referring to a recent journal article

Chemoprevention of Human Prostate Cancer by Green Tea Catechins: Two Years Later. A Follow-up Update

Prostate cancer (CaP) progresses slowly and clinical is usually diagnosed in very elderly men. Delaying disease onset by a few years would reduce incidence, which makes it an ideal target for chemoprevention strategies. We and others showed that both Green Tea Catechin (GTC) and EGCG possess anti-tumour activity *in vitro*, as well as *in vivo* in the TRAMP mouse model [1,2]. We suggested that administration of GTCs might be beneficial in the early stages of cell transformation but not later, when cancer had already developed.

We performed a clinical trial in 60 volunteers bearing HGPIN, the main pre-malignant lesion of CaP, to assess the efficacy of GTCs for chemoprevention, as published [3]. Volunteers consumed GTCs (600 mg per day tid) or placebo for 1 year. Subjects received two follow-up saturation biopsies [4], at 6 months and one year. Only 1 tumour was diagnosed in the GTCs-arm (incidence: 3%), while 9 cancers were found in the placebo-arm (incidence: 30%); no related adverse effects were reported.

Was CaP progression prevented definitively or simply delayed during treatment? We performed another round of prostate mapping in a subset of these patients. The mean follow-up from the end of GTCs dosing was 23.3 months for placebo-arm (range: 12–30) and 19.1 months for GTCs-arm (range: 12–30). Only 9 from the placebo-arm and 13 from the GTCs-arm underwent this third prostate mapping. Despite the high drop-out rate (57% and 55%, respectively), the two arms remained balanced and large enough for statistical analysis.

Figure 1 shows a Kaplan-Meier plot of study data. Three further cancer diagnoses appeared during

follow-up, two in the placebo arm and one in the GTCs-arm. The final difference in cancer prevalence is highly significant ($p < 0.01$) by χ^2 test analysis. These results suggest that the inhibition of prostate cancer progression achieved in these subjects after one year of GTCs administration was long-lasting. The early emergence of benefit observed at 6 months suggests a treatment effect on early lesions. Overall, treatment with GTCs led to an almost 80% reduction in CaP diagnosis, from 53% to 11%, suggesting that an important decrease of sanitary costs related to this disease could be achieved [5].

This chemoprevention approach in high risk patients would fulfil a significant therapeutic and social need, thus opening a new scenario for a novel and effective clinical approach for CaP. A larger confirmatory trial of these results is currently underway (Kumar N. et al, Moffitt Cancer Centre, Tampa Fl, USA; personal communication).

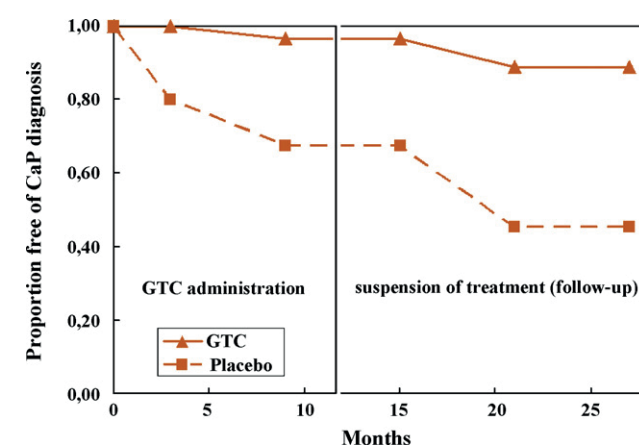


Fig. 1 – Kaplan-Meier analysis of final result showing the prevalence of prostate cancer at 6- and 12-mo check (previous study) as well as 2 years later following suspension of GTC administration (follow-up study).

Conflicts of interest: The authors have nothing to disclose.

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March 19, 2008
Published online ahead of print on April 4, 2008

Clinical Trial

Eur Urol. 2005 Apr;47(4):449–54; discussion 454–5.
doi: 10.1016/j.eururo.2004.12.001. Epub 2005 Jan 19.

Support ellagic acid therapy in patients with hormone refractory prostate cancer (HRPC) on standard chemotherapy using vinorelbine and estramustine phosphate

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- PMID: 15774240
- DOI: [10.1016/j.eururo.2004.12.001](https://doi.org/10.1016/j.eururo.2004.12.001)

Abstract

Background: Recent phase III studies in hormone refractory prostate cancer (HRPC) showed an improvement in terms of overall survival (OS), objective response (OR) and biochemical response (BR); however, chemotherapy is usually accompanied by negative side effects that determines poor quality of life (QoL) and only marginally improves individual clinical response (ICR) in terms of pain relief and performance status. Ellagic acid is a polyphenol that is found in many species of flowering plants. It is an antioxidant that determines apoptosis, down regulation of IGF-II, activates p21 (waf1/Cip1), mediates the cumulative effect on G1/S transition phase and prevents destruction of p-53 gene by cancer cells.

Endpoints: The aim of this study was to assess the effects of ellagic acid support therapy on toxicity, OR, ICR and BR in HRPC patients treated with estramustine phosphate and vinorelbine.

Materials and methods: Patients with HRPC were randomly distributed in two study groups: a control group (group A) who underwent chemotherapy with vinorelbine and estramustine phosphate, and an experimental group (group B) where chemotherapy regimen was associated with ellagic acid.

Results: The mean number of chemotherapy cycles/patient was 4 (range 3–8 cycles) and 6.5 (range 5–11) in group A and B patients, respectively. A reduction in systemic toxicity, statistically significant for neutropenia, associated with better results in term of OR rate, ICR, and BR were observed in group B compared with group A. On the contrary no significant difference in OS and PFS was detected between groups.

Conclusions: our study suggests that the use of ellagic acid as support therapy reduces chemotherapy induced toxicity, in particular neutropenia, in HRCP patients; however, further studies are required to confirm our results.

Antiinflammatory and anti-cancer activities of pomegranate and its constituent, ellagic acid: Evidence from cellular, animal, and clinical studies

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First published: 07 January 2020

<https://doi.org/10.1002/ptr.6565>

Citations: 26

SHARE

Abstract

Inflammation is commonly characterized as a defensive and protective reaction of the body to various exogenous or endogenous stimuli, which aims to maintain the body health. *Punica granatum* (pomegranate) and its constituent ellagic acid (EA) are recently more taken into accounts since their promising pharmacological effects. Therefore, we aimed to obtain a comprehensive review regarding antiinflammatory, anticancer, and antioxidant activities of both pomegranate and EA and their possible involved mechanisms. In the procedure, scientific databases, including Web of Science, PubMed, Scopus, and Google Scholar, were searched in the English language, until the end of January 2019. Pomegranate belonging to the *Punicaceae* has been used for medical purposes from ancient and in different cultures. Several studies have also supported that EA is the major active compound of pomegranate and possesses antimutagenic, antiinflammatory, antifibrosis, anticancer, and antiaging properties. It has been suggested that pomegranate and EA possess promising immunomodulatory effects in preclinical models as well as human studies through regulation of the T-cell function and suppressing humoral immunity. Hopefully, we wish that this review and information could be helpful for designing further experiments to investigate the potential protective effects of pomegranate and EA

Cellular Physiology and Biochemistry

Cell Physiol Biochem 2014;34:1351-1358
DOI: 10.1159/000366342
Published online: October 02, 2014
Accepted: August 13, 2014
© 2014 S. Karger AG, Basel
www.karger.com/cpb
1421-9778/14/0344-1351\$39.50/0
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Original Paper

Formononetin Promotes Cell Cycle Arrest via Downregulation of Akt/Cyclin D1/CDK4 in Human Prostate Cancer Cells

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Key Words

Formononetin • CDK4 • Cyclin D1 • Akt • Prostate cancer

Abstract

Background: Formononetin is an O-methylated isoflavone isolated from the root of *Astragalus membranaceus*. It has already been reported that formononetin could inhibit cell proliferation and induce cell apoptosis in several cancers, including prostate cancer. This study aimed to further investigate whether cell cycle arrest is involved in formononetin-mediated antitumor effect in human prostate cancer cells, along with the underlying molecular mechanism. **Methods:** Human prostate cancer cells PC-3 and DU145 were respectively treated with various concentrations of formononetin. The inhibitory effect of formononetin on proliferation of prostate cancer cells was determined using MTT assays and flow cytometry. Next, formononetin-induced alterations in cyclin D1, CDK4 and Akt expression in PC-3 cells were detected by real-time PCR and western blot. **Results:** Formononetin dose-dependently inhibited prostate cancer cell proliferation via the induction of cell cycle arrest at G0/G1 phase *in vitro*, which was more evident in PC-3 cells. Meanwhile, concomitant with reduced phosphorylation of Akt in PC-3 cells, formononetin remarkably downregulated expression levels of cyclin D1 and CDK4 in a dose-dependent manner. More interestingly, in the *in vivo* studies, formononetin showed a noticeable inhibition of tumor growth in recipient mice. **Conclusion:** Formononetin could exhibit inhibitory activity against human prostate cancer cells *in vivo* and *in vitro*, which is associated with G1 cell cycle arrest by inactivation of Akt/cyclin D1/CDK4. Therefore, formononetin may be used as a candidate agent for clinical treatment of prostate cancer in the future.

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Lycium barbarum polysaccharides induce apoptosis in human prostate cancer cells and inhibits prostate cancer growth in a xenograft mouse model of human prostate cancer

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- PMID: 19735167
- DOI: [10.1089/jmf.2008.1232](https://doi.org/10.1089/jmf.2008.1232)

Abstract

Lycium barbarum polysaccharides (LBPs) are important functional constituents in red-colored fruits of *L. barbarum* (Guo Qi Zi, a well-known traditional Chinese medicinal plant commonly known as Goji berry or wolfberry). The influence of LBP on human prostate cancer cells was systematically investigated in vitro and in vivo. The in vitro effects of LBP on two cell lines (PC-3 and DU-145) were examined by using trypan blue exclusion staining, single-cell gel electrophoresis, flow cytometry, terminal dUTP nick-end labeling assay, and immunohistochemical assay (assessment of Bcl-2 and Bax expression). The in vivo effect of LBP on PC-3 cells was assessed in the nude mouse xenograft tumor model. The in vitro results showed that LBP can dose- and time-dependently inhibit the growth of both PC-3 and DU-145 cells. LBP caused the breakage of DNA strands of PC-3 and DU-145 cells; the tail frequency and tail length were significantly higher than that of control cells. LBP also markedly induced PC-3 and DU-145 cell apoptosis, with the highest apoptosis rates at 41.5% and 35.5%, respectively. The ratio of Bcl-2/Bax protein expression following LBP treatments decreased significantly with a dose-effect relationship, which suggested that LBP can regulate the expression of Bcl-2 and Bax to induce apoptosis of PC-3 and DU-145 cells. The in vivo experimental results indicate that LBP might significantly inhibit PC-3 tumor growth in nude mice. Both the tumor volume and weight of the LBP treatment group were significantly lower than those of the control group.

Review

Prostate Cancer Prostatic Dis
. 2017 Dec;20(4):361-377.
doi: 10.1038/pcan.2017.25. Epub 2017 Apr 25.

Increased dietary and circulating lycopene are associated with reduced prostate cancer risk: a systematic review and meta-analysis

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- PMID: 28440323
- DOI: [10.1038/pcan.2017.25](https://doi.org/10.1038/pcan.2017.25)

Abstract

Background: Prostate cancer (PCa) is the fifth leading cause of cancer-related deaths worldwide. Many epidemiological studies have investigated the association between prostate cancer and lycopene, however, results have been inconsistent. This study aims to determine the impact of dietary and circulating concentrations of lycopene on PCa risk and to investigate potential dose-response associations.

Methods: We conducted a systematic review and dose-response meta-analysis for the association between dietary and circulating lycopene and PCa risk. Eligible studies were published before 1 December 2016 and were identified from PubMed, Web of Science and the Cochrane Library. We estimated pooled relative risk ratios (RR) and 95% confidence intervals (CI) using random and fixed effects models. Linear and nonlinear dose-response relationships were also evaluated for PCa risk.

Results: Forty-two studies were included in the analysis, which included 43 851 cases of PCa reported from 692 012 participants. Both dietary intake (RR=0.88, 95% CI: 0.78-0.98, P=0.017) and circulating concentrations (RR=0.88, 95% CI: 0.79-0.98, P=0.019) of lycopene were significantly associated with reduced PCa risk. Sensitivity analyses within the dose-response analysis further revealed a significant linear dose-response for dietary lycopene and PCa risk such that PCa decreased by 1% for every additional 2 mg of lycopene consumed (P=0.026). Additionally, PCa risk decreased by 3.5 to 3.6% for each additional 10 μgdl^{-1} of circulating lycopene in the linear and nonlinear models respectively ($p_{\text{linear}}=0.004$, $p_{\text{nonlinear}}=0.006$). While there were no associations between lycopene and advanced PCa, there was a trend for protection against PCa aggressiveness (RR=0.74, 95% CI: 0.55-1.00, P=0.052).

Conclusions: Our data demonstrate that higher dietary and circulating lycopene concentrations are inversely associated with PCa risk. This was accompanied by dose-response relationships for dietary and circulating lycopene. However, lycopene was not associated with a reduced risk of advanced PCa. Further studies are required to determine the mechanisms underlying these associations.

Cruciferous vegetables intake and risk of prostate cancer: a meta-analysis

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- PMID: 22121852
- DOI: [10.1111/j.1442-2042.2011.02906.x](https://doi.org/10.1111/j.1442-2042.2011.02906.x)

Abstract

Objective: To evaluate the relationship between cruciferous vegetables intake and risk of prostate cancer.

Methods: A systematic literature search up to June 2011 was carried out in PubMed, and the references of retrieved articles were screened. The summary relative risks with 95% confidence interval for the highest versus the lowest intake of cruciferous vegetables were calculated. Heterogeneity and publication bias were also evaluated.

Results: Seven cohort and six population-based case-control studies met the inclusion criteria of the meta-analysis. A significantly decreased prostate cancer risk was observed overall in the cruciferous vegetables intake group (relative risks = 0.90; 95% confidence interval 0.85-0.96) and the subgroup of case-control studies (relative risks = 0.79; 95% confidence interval 0.69-0.89), but not in cohort studies (relative risks = 0.95; 95% confidence interval 0.88-1.02). No heterogeneity and publication bias were detected across studies.

Conclusion: Cruciferous vegetables intake is related to the decreased risk of prostate cancer. Because of the limited number of studies, further prospective studies are needed to explore the protective effect of cruciferous vegetables on prostate cancer.

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THE OCCURRENCE OF RESVERATROL IN FOODSTUFFS AND ITS POTENTIAL FOR SUPPORTING CANCER PREVENTION AND TREATMENT. A REVIEW

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ABSTRACT

Over recent years, there has been increasing interest noted in those active substances derived from plants that show potential for preventing cancer development. The most promising candidate is resveratrol which can be found in large amounts in the skin of grapes, tomatoes and in red wine. Its beneficial effects on the human body are seen both in prevention and therapy. The anti-carcinogenic action of resveratrol is linked with its ability to neutralise reactive oxygen species and to modulate cellular processes such as apoptosis, and both cancerous cell proliferation and differentiation. This article presents the characteristics of resveratrol as a bioactive compound derived from natural sources exhibiting anti-cancer properties, which, because of a wide spectrum of biological activities may be used in the prevention of cancer. Many *in vitro* and animal-based studies have demonstrated such preventative anti-cancer action in the colon, prostate, breast and lungs. The beneficial effects of resveratrol are also presented when adopted as a support to conventional treatments of cancer using chemo- and radio-therapy.

Key words: *resveratrol, foodstuffs, chemo-prevention, cancer*

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