REVIEW PAPER

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Resveratrol in prostate diseases – a short review

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Introduction. Resveratrol is a plant–derived polyphenol suggested to have many beneficial health effects, including antioxidant, anti–inflammatory, anti–proliferative, proapoptotic, and anti–angiogenic. It is even specu- lated that uptake of resveratrol by red wine consumption could be behind the so–called French paradox the lower incidence of cardiovascular diseases in the French population. These properties, together with good absorption and tolerance, would make it an attractive agent in prostatic diseases, especially in cancer prevention and treatment.

Material and methods. MEDLINE search (keywords "prostate res- veratrol") resulted in 39 research papers published since 2007. It has been shown that resveratol down–regulate androgen receptor expression, inhibit proliferation, and promote apop- tosis in prostate cancer cell lines and enhance their sensitivity to ionizing radiation. Several studies on animal prostate cancer development also suggest that resveratrol is able do delay or prevent carcino- genesis in prostate. Despite these promising results, there is no proof of any therapeutic properties of resveratrol in prostate diseases from human clinical trials nor any information about ongoing trials in this field.

Conclusions. Resveratrol is produced and sold as a nutritional supplement, there is not enough clinical evidence to justify a recommendation for the administration of resveratrol in humans at present.

Key Words: resveratrol ‹› prostate ‹› cancer

INTRODUCTION

Resveratrol (trans–3, 4', 5–trihydroxystilbene, $C_{14}H_{12}O_3$) is a plant–derived polyphenolic phytoalexin produced in response to environmental stress such as vicissitudes in climate, exposure to ozone, sunlight and heavy metals, and infection by pathogenic microorganisms. Resveratrol exists in both cis– and trans– stereoisomeric forms, the predominant trans– isomer is the biologically active one [1, 2, 3]. Exposure to heat and ultraviolet radiation can cause trans–resveratrol to isomerize to the cis–resveratrol. It is primarily found in the skin of grapes as well as in other fruits and plants, such as raspberries, blueberries, mulberries, Scots pine, Eastern white pine, and knotweed [1, 4].

It is speculated that uptake of resveratrol by red wine consumption could be behind the so–called French paradox – whereby the French population, in spite of a rather fatty diet, has a lower incidence of cardiovascular disease [1]. Resveratrol is also produced by chemical and biotechnological synthesis and sold as a nutritional supplement. It is well absorbed upon oral ingestion and metabolized to sulfate and glucuronate [1, 2].

Resveratrol has been reported do have a wide range of effects beneficial for health, including cardioprotective, neuroprotective, and immunomodulatory function as well as improving insulin sensitivity, but in relation to prostatic diseases, the following ones are the most interesting: anticancer – resveratrol has been reported to have antiproliferative and proapoptotic effects on prostate cancer cell lines LNCaP, DU–145, and PC–3; it also potentiates the effect of ionizing radiation and chemotherapeutic agents; potential chemopreventive properties; anti-inflammatory and antioxidant functions, which may

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be useful in treatment of prostate inflammation; and also play a role in chemoprevention, as a positive correlation between prostatitis and prostate cancer risk has been reported [5, 6].

Prostate cancer (PCa), being one of the most common malignancies and a major cause of cancer–related death in men, is a considerable health problem, especially in ageing populations, since it is typically diagnosed in men over the age of 50 [6, 7]. All these, together with its long latency, make PCa an attractive target for chemopreventive interventions [4, 6]. There is also a considerable amount of epidemiological data suggesting that certain nutritional factors may influence PCa occurrence [6, 8]. Consequently, several PCa risk reduction studies were conducted, but only in two of them – PCPT (finasteride) and REDUCE (dutasteride) – a reduction of PCa incidence was observed. The most important endpoint – the reduction of mortality, however, was not reached in either of them [9]. This may be partially due to the slow natural course of the disease, which would require an ideal observation period of around 20 years.

In this paper, recently published research articles on the application of resveratrol in prostate diseases have been reviewed in order to shed light on the evidence justifying its application in prevention and treatment of prostate diseases.

Mechanism of action

Resveratrol induces a broad range of effects on cell phenotype. Numerous studies have reported resveratrol to cause cell growth inhibition, modulation of cell cycle, induction of apoptosis in many different cell lines, including PCa ones [2, 10–45], and induction of differentiation in certain cell types [27, 46–49]. All these are important in cancer treatment and are exerted by modulating a complex range of cellular processes, including: receptor function, transduction pathways, and transcription factor activity. The detailed description of all the documented resveratrol mechanisms of action would exceed this paper.

Apart from these, resveratrol has been reported to exhibit other properties that may be useful in cancer treatment: inhibition of tumor invasion and angiogenesis as well as increase of radiosensitivity and chemosensitivity.

The expression of matrix metalloproteases (MMPs) correlates with tumor invasion and metastasis, which make them attractive pharmaceutical targets in cancer treatment [50]. Resveratrol reduced the expression of MMP–2 and MMP–9 in certain cell lines [51–55] and decreased the level of vascular epithelial growth factor (VEGF), a protein crucial for angiogenesis and maintaining tumor growth, thus inhibiting angiogenesis [56–60].

Another interesting property of resveratrol is its ability to increase prostate cancer cell lines sensitivity to ionizing radiation, which has a potential for clinical application in combination with radiotherapy – an important treatment in PCa [17, 19, 20, 43].

Resveratrol has also been shown to sensitize human cancer cell lines, including prostate carcinoma, to such chemotherapeutic agents as doxorubicin, cytarabine, actinomycin D, taxol, and methotrexate by down–regulating survivin expression and increasing apoptosis [61].

Inflammation has been proven to be a significant factor in the initiation/progression stages of cancer development by inducing oxidative damage and promoting cell growth [62, 63]. Cyclooxygenase–2 (COX–2) catalyzes the conversion of free arachidonic acid to prostaglandins, which can stimulate cell proliferation, promote angiogenesis, and suppress apoptosis all of which promote malignancy [64–66]. Resveratrol expresses anti–inflammatory activity by directly inhibiting COX–2 activity and suppressing NF□B by up–regulating MKP5 [44, 67].

Review of current studies

Resveratrol and its mechanisms of action have been intensively investigated and a large amount of evidence suggesting that it may be a promising molecule in both PCa treatment and prevention has been collected. MEDLINE search (keywords "prostate resveratrol") resulted in 39 research papers published since 2007 – the results of which are presented in Table 1. Surprisingly, a considerable number of *in vitro* and a few animal model experiments have been performed, with lack of human clinical trials. There are currently no published demonstrations of therapeutic or protective effects of resveratrol in appropriately designed clinical trials [64]. Web page http://www.clinicaltrials.org reported five ongoing trials of resveratrol in cancer, but none in prostate disease. The results of several resveratrol pharmacokinetics and metabolism studies in humans, however, have already been published and despite good absorption upon oral administration, poor bioavailability of unchanged resveratrol indicates that it would be difficult to achieve concentrations proven to be effective in *in vitro* studies [68, 69]. Additionally, a study by Klink et al., indicates that resveratrol may actually worsen the survival in certain prostate cancer xenograft models [70].

Among 38 research papers on resveratrol in prostate diseases published between 2007 and 2012, 35 were performed on cell lines and nine on *in vivo* models (five transgenic models of PCa development and five PCa xenografts). Seven studies concentrated on the

Table 1. *Studies on resveratrol in prostate diseases published in years 2007–2012*

Ref. no.	Model used	Observed effects and mechanism
72	SV–40 Tag rats	suppressed prostate cancer development
73	TRAMP mice	suppressed tumor growth in vivo
12	PC–3, TRAMP–C2 cell lines TRAMP mice	reduced cell proliferation; reduced prostate cancer in vivo; inhibits Hedgehog signaling
13	PTEN–CaP8 cell line prostate–specific PTEN–KO mice	reduces cell proliferation, induces apoptosis; decreased prostatic adenocarcinoma in vivo
14	COS7, LNCaP cell lines TRAP rats	induces apoptosis through androgen receptor down–regulation; suppressed tumur growth in vivo
70	mouse xenograft model of prostate cancer (LNCaP and LAPC–4)	worsens survival with LAPC–4 tumors, no difference with LNCaP tumours
71	mouse xenograft model of prostate cancer	inhibited tumor growth, metastasis and angiogenesis
15	LNCaP cell line mouse xenograft model of prostate cancer	reduces cell proliferation ***in vitro***; delayed tumor growth in vivo
16	PC–3M–MM2 cell line mouse xenograft model of prostate cancer	reduced cell viability, migration and invasiveness inhibited the tumor growth, decreased the incidence and number of metastases
17	LAPC4, CWR22, LNCaP, PC–3, DU–145 cell lines mouse xenograft model of prostate cancer	reduces cell proliferation ***in vitro***; no effect observed in vivo
18	PC–3 cell line	enhanced irradiation–induced apoptosis
19	PC–3, DU–145 cell lines	enhanced irradiation–induced apoptosis by up–regulation of the expression of perforin and granzyme B
20	PC–3, 22RV1, PNT1A cell lines	enhanced irradiation–induced apoptosis, arrests cell cycle
21	DU–145 cell line	enhanced irradiation–induced apoptosis
22	LNCaP cell line	inhibits the function of the androgen receptor
23	LNCaP cell line	inhibition of androgen–promoted growth, inhibition of androgen receptor transcriptional activity, effect synergistic with flutamide
24	LNCaP cell line	inhibition of androgen receptor transcriptional activity
25	LNCaP, PC–3 cell lines	decreased the post–translational androgen receptor level
26	LNCaP, PC–3 cell lines	decreased androgen receptor and estrogen receptor alpha protein levels
27	C4–2, LNCaP cell lines	stimulates PTEN expression through androgen receptor inhibition, inhibits EGFR phosphorylation decreasing AKT phosphorylation
28	LNCaP cell line	reduces cell proliferation, induces apoptosis; inhibited the phosphorylation of PI3K, AKT and mTOR
29	LNCaP cell line	induced cell cycle arrest and apoptosis
30	LNCaP cell line	reduces cell proliferation, induces apoptosis; sensitized cells to TRAIL
31	LNCaP, DU–145 cell lines	down–regulated oncogenic microRNAs and up–regulated tumor suppressor microRNAs
32	LNCaP, DU–145 cell lines	induces apoptosis; restores p53–signaling pathways
33	LNCaP, PC–3 cell lines	reduces cell proliferation, induces apoptosis; inhibits NFκB specific binding to DNA
34	LNCaP, PC–3, DU–145 cell lines	induces apoptosis, SOCS–3 reduced apoptosis in resveratrol–treated cells
35	LAPC4, LNCaP, PC–3, DU–145 cell lines	anti–inflammatory activity by up–regulation of MKP5
36	PZ–HPV–7, LNCaP, PC–3 cell lines	induced cell cycle arrest, reduced cell proliferation
37	C4–2, LNCaP cell lines	induces apoptosis
38	PC–3 cell line	inhibition of cell proliferation, down–regulation of expression of CAV1, IGF2, NR2F1, and PLAU genes, suppressed secretion of the urokinase plasminogen activator
2	PC–3, DU–145 cell lines	reduces cell proliferation; trans– isoform more active than cis–
39	PC–3, DU–145 cell lines	sensitized cells to TRAIL, Fas, TNFalpha
40	PC–3, DU–145 cell lines	down–regulated the expression of Bcl–2, Bcl–X(L) and survivin and upregulated the expression of Bax, Bak, PUMA, Noxa, Bim, TRAIL–R1/DR4 and TRAIL–R2/DR5
41	C4–2B, PC–3, DU–145, LNCaP, RWPE–1 cell lines	reduces cell proliferation; modulation of SIRT1/S6K signaling
42	22Rv1, PC–3, DU–145 cell lines	synergistic with AdΔΔ adenovirus, increases apoptosis
43	CWR22Rv1 cell line	reduced cell proliferation
44	RWPE–1, WPE1–NA22, WPE1–NB14, WPE1–NB26 cell lines	induced cell cycle arrest
45	ALVA–41, PC–3 cell lines	reduces cell proliferation, induces apoptosis; synergy with casein kinase 2 inhibition

role of androgen receptor and four on enhancement of radiosensitivity (Table 1). A short characteristic of PCa cell lines most commonly used in experiments listed in Table 1 – their androgen sensitivity, p53 and PTEN (proteins important in mechanism of action of resveratrol in PCa cells) are presented in Table 2. TRAMP, TRAP, and SV–40 Tag are transgenic animal models of PCa development – animals programmed to develop prostate cancer – were used to assess potential chemopreventive properties of resveratrol.

Table 2. *A short characteristic of PCa cell lines*

Cell line	androgen sensitivity	p53	PTEN
PC–3	AR–negative	mutant	mutant
DU–145	AR–negative	mutant	wild–type
C4–2B	androgen independent	wild–type	mutant
LNCaP	broad steroid specificity	wild–type	mutant
LAPC–4	wild–type	mutant	wild–type
CWR22rv1	androgen independent	mutant	wild–type

CONCLUSIONS

The anti–cancer potential of resveratrol has been well documented in many *in vitro* and *in vivo* studies. Down–regulation of androgen receptor and synergy with flutamide, as well as enhancement of radiosensitivity are the most interesting properties in treatment of prostate cancer.
Resveratrol has displayed a potential as prostate cancer chemoprevention in both *in vitro* and animal model studies.
Resveratrol is well–tolerated, but an optimal dose has not yet been determined.
There are no results from human clinical trials on therapeutic effects of resveratrol in prostate diseases.
Despite promising results from many studies, published evidence is not strong enough to justify chronic administration of resveratrol to humans.

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