

PRELIMINARY COMMUNICATION

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Trans-, *cis*-, and *dihydro*-resveratrol: a comparative study

Natalia YU Anisimova¹, Mikhail V Kiselevsky¹, Andrey V Sosnov², Sergey V Sadovnikov³, Ivan N Stankov³ and Andrei A Gakh^{4*}**Abstract**

Background: Recent studies showed that moderate consumption of red or white wines increased the chances of breast cancer, while similar consumption of red wines, rich in *trans*-resveratrol (*trans*-**R**), decreased the rate of prostate cancer. This prompted us to explore the role of various forms of **R** in cancer proliferation.

Results: *Trans*-**R** was found to be the most potent antiproliferative agent. *Cis*-**R** demonstrated somewhat less potency compared to *trans*-**R**. Unlike *cis*-**R** and *trans*-**R**, *dihydro*-**R** exhibits moderate proliferative effect on androgen-independent prostate cancer cell lines PC-3 and DU-145 at picomolar concentrations. At higher concentrations, *dihydro*-**R** caused proliferation inhibition, similar to *cis*-**R** and *trans*-**R**. The proliferative effect of *dihydro*-**R** at low concentrations can be reversed by *trans*-**R** which acts as a partial antagonist in the presence of *dihydro*-**R**. Mixtures of *dihydro*-**R** and *trans*-**R** demonstrated complex non-monotonic cross-modulation activity patterns.

Conclusions: *Dihydro*-**R** exhibits proliferative effects in androgen-independent prostate cancer cells at picomolar and nanomolar concentrations. While the exact mechanism of these effects requires further evaluation, our preliminary results point to hormone receptor modulation activity. We also observed strong cross modulation between *trans*-**R** and *dihydro*-**R** at sub-picomolar concentrations. The role of *dihydro*-**R** in cancer proliferation related to moderate consumption of red wine remains an open question because *dihydro*-**R** has a very complex activity pattern in the presence of *trans*-**R**.

Background

The term “French Paradox” was introduced by S. Renaud in the early 1990s to describe the low incidence of heart disease and obesity among the French in contrast to their relatively high-fat diet [1]. It is widely believed that consumption of red wine, rich in *trans*-resveratrol (*trans*-**R**) and other dietary polyphenols, is the primary cause of this paradox. Given the well-documented anticancer properties of *trans*-**R**, it is natural to expect that the moderate consumption of red wine might bring additional benefits of lower cancer rates, especially the most frequent forms of cancer such as breast and prostate cancer. However, recent studies have unequivocally demonstrated that even moderate consumption of red or white wines markedly increased

the chances of breast cancer [2-4], while moderate consumption of red wine substantially decreased the rate of prostate cancer [5]. It was also reported that moderate consumption of white wine or beer does not affect prostate cancer rate [5]. Although the alcohol content should be considered as a prime factor responsible for this intriguing disparity between the cancer types [2-5], this unusual situation prompted us to further explore the role of resveratrol (**R**) in prostate cancer proliferation.

Like any food product, red wine contains a complex mixture of structurally related organic compounds. One of these compounds is **R**. The predominant *trans*-**R** comes along with a lesser-known companion, *cis*-resveratrol (*cis*-**R**), and they are almost always present in red wine together (Figure 1). We recently discovered [6] that the GC-MS peak of *cis*-**R** was usually accompanied by a close peak of another polyphenol having molecular weight 2 Da higher than *cis*-**R**. Independent synthesis

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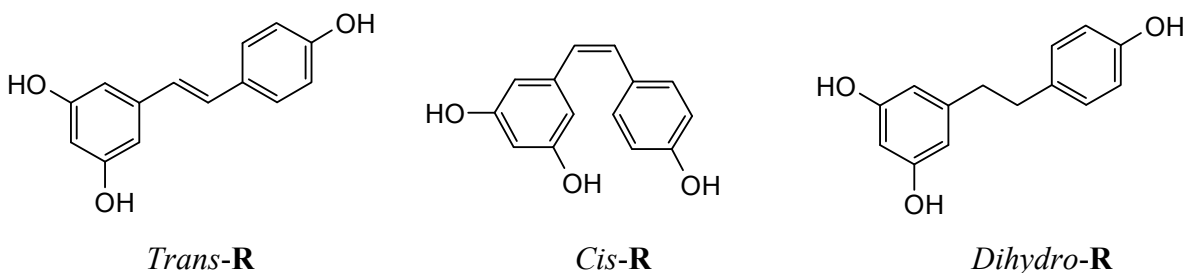


Figure 1 Structures of *trans*-resveratrol (*trans*-R), *cis*-resveratrol (*cis*-R), and *dihydro*-resveratrol (*dihydro*-R) isomers.

confirmed that this peak is the peak of the third form of **R**, *dihydro*-resveratrol (*dihydro*-R). *Dihydro*-R is a well-known metabolite of *trans*-R [7], but it had not been identified in red wines before the study [6].

In our experiments *dihydro*-R demonstrated strong proliferative properties in hormone-dependent cell lines (such as MCF-7) at picomolar (10^{-12} M) concentrations [6]. The effect was not observed in cell lines without estrogen receptors, and the proliferative effect could be reversed by the action of estrogen antagonists, such as the known breast cancer drug Tamoxifen. This is consistent with the assumption that *dihydro*-R is a potent phytoestrogen, even though the conformationally flexible chemical structure of *dihydro*-R makes it a very unlikely analog of 17β -estradiol and other synthetic nonsteroidal estrogens such as diethylstilbestrol (DES) [6].

Given the preceding, it is reasonable to assume that the presence of *dihydro*-R in red wines could be partially responsible for the difference observed between breast cancer and prostate cancer in relation to moderate wine consumption. To explore this further, we initiated a comparative study of the biological effects of the three forms of **R** found in red wines on two androgen-independent human prostate cancer cell lines (PC-3 and DU-145) and one hormone-dependent breast cancer cell line (MCF-7) in vitro. This paper presents the results of our work.

Results and Discussions

To investigate the ability of *trans*-R, *cis*-R, and *dihydro*-R to control the growth of PC-3 prostate cancer cells, various concentrations of these compounds were added to tumor cell cultures and then incubated for 48 h. Figures 2 and 3 show the tumor cell viability after exposure to these agents.

The cytotoxic effect of *trans*-R was observed at concentrations of 1×10^{-7} to 1×10^{-4} M. Similarly, the cytotoxic effect of *cis*-R was observed at concentrations 1×10^{-6} to 1×10^{-4} M. The results indicated that *trans*-R is somewhat more effective as an anticancer agent than *cis*-R. *Dihydro*-R, in contrast to *trans*-R and *cis*-R, had a biphasic effect. At high concentrations (1×10^{-5}

to 1×10^{-3} M), *dihydro*-R showed the typical for this class of compounds decrease in the growth rate of tumor cells. However, treatment with 1×10^{-10} to 1×10^{-7} M of *dihydro*-R significantly increased the growth of PC-3 prostate cancer cells (Figure 2).

Further comparative evaluation of the biological activity of *trans*-R and *dihydro*-R was performed using the DU-145 prostate cancer cell line. Again, *trans*-R displayed only cytotoxic properties whereas *dihydro*-R had a biphasic effect, similar to the one observed in PC-3 cells. At high concentrations (1×10^{-5} to 1×10^{-3} M), *dihydro*-R decreased the rate of growth of DU-145 tumor cells. Treatment with low concentrations (1×10^{-10} to 1×10^{-8} M) of *dihydro*-R significantly increased the growth of DU-145 prostate cancer cells (Figure 3).

The observed cytotoxic effects of both *trans*-R and *cis*-R in androgen-independent prostate cancer cell lines are in agreement with the previously reported data. *Trans*-R is a known inhibitor of human prostate cancer cell growth at concentrations of 1×10^{-6} to 1×10^{-4} M (e.g., $GI(50) = 2.41 \times 10^{-5}$ M, DU-145 [8]) depending on the prostate cancer cell line and experimental conditions [9]. The biphasic action of the third form of **R**, *dihydro*-R, in

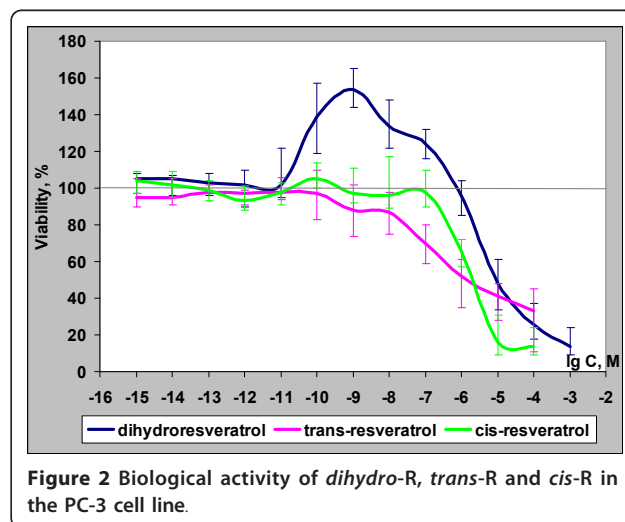
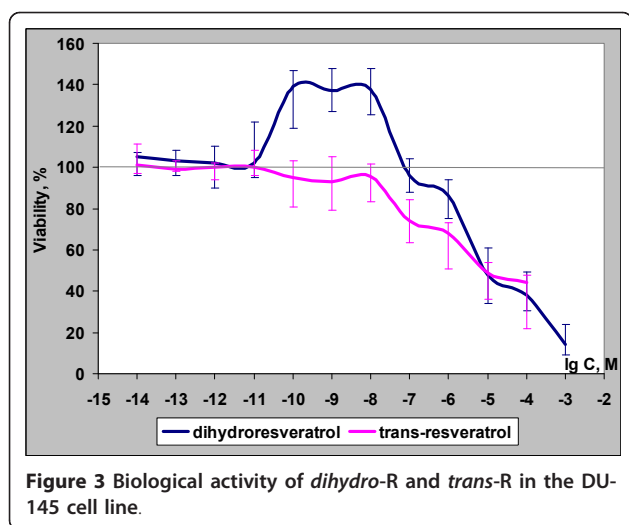


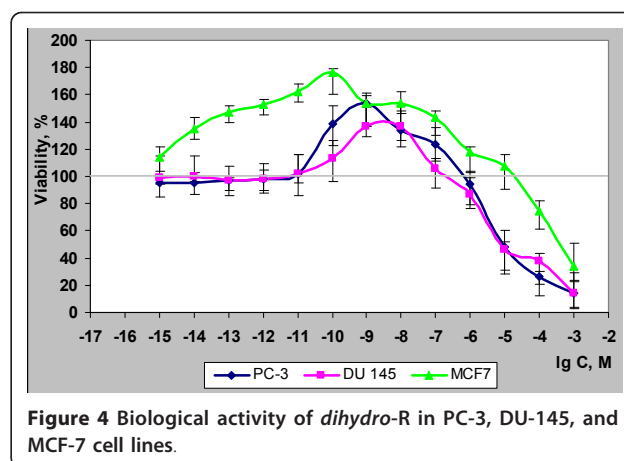
Figure 2 Biological activity of *dihydro*-R, *trans*-R and *cis*-R in the PC-3 cell line.



comparison with the better studied *trans-R* requires further evaluation, especially in relation to estrogen receptors [6] present in both the PC-3 and the DU-145 prostate cancer cell lines [10-14].

The biological effects of *trans-R* in androgen-independent prostate cancer cell lines can be attributed to a variety of specific molecular targets, including estrogen and androgen receptors [15]. Unfortunately, the exact mechanism of the hormone receptor-mediated activity of *trans-R* is poorly understood because of the apparent complexity of the underlying biological functions of these receptors in prostate cancer cells. For example, it is well documented that 17β -estradiol (E2) inhibits growth of androgen-independent PC-3 cells [10] but stimulates growth of androgen-dependent LNCaP cells, presumably via its own receptor [16]. The situation is even further complicated by the existence of two estrogen receptors (ERs), ER- α and ER- β , in prostate cancer cells [11]. As a result, growth of PC-3 cells, which have both ER subtypes, can be effectively inhibited by estrogens as well as antiestrogens [17]. In contrast, DU-145 cells express only ER- β , and their growth can be inhibited only by antiestrogens [11].

Given the convolution of hormone receptor functions in prostate cancer cells [18], it could only be presented as a working hypothesis that, similar to MCF-7 breast cancer cells [6], the observed growth stimulation of PC-3 and DU-145 cells by nanomolar concentrations of *dihydro-R* can be attributed to the hormone receptor modulation activity of this compound. A direct comparison between the three cell lines (MCF-7 [6], PC-3, and DU-145, Figure 4) reveals substantial similarities in *dihydro-R* biphasic proliferative action. As expected, the proliferative effects are more pronounced in the "classic" ER- α -dependent MCF-7 cells compared to PC-3 cells (ER- α and ER- β) and then DU-145 cells (only ER- β).



Additional credence is given to our assumption that *dihydro-R* is a hormone receptor modulator by the recent observation that another dietary polyphenol with a similar biological profile, genistein (Figure 5), also exhibits biphasic behavior in the regulation of prostate cancer cell growth [19]. It was reported that low (5×10^{-7} M) concentrations of genistein caused increased proliferation of PC-3 cells whereas a pharmacologic dose (5×10^{-5} M) decreased proliferation. Estrogen signaling is mentioned as one of the possible mechanisms of this biphasic action [19] (genistein is a well-known phytoestrogen [14,20,21]).

To explore our working hypothesis further, we evaluated the cancer cell growth effects of *dihydro-R* in the presence of *trans-R*. *Trans-R* is capable of acting as both an estrogen and an antiestrogen [22-26], including non-genomic action [25], but this compound by itself does not significantly affect the growth of PC-3 prostate cancer cells at concentrations below 1×10^{-7} M. Our experiments clearly demonstrated the interference between *dihydro-R* and *trans-R* (Figure 6). In these experiments *trans-R* acted as a *dihydro-R* antagonist at low concentrations. The maximum antagonistic effect was observed at nanomolar concentrations (1×10^{-10} to 1×10^{-8} M). Similar biphasic agonistic/antagonistic properties of *trans-R* in MCF-7 cells in the presence of E2 were reported previously [24].

Somewhat stronger interference between *dihydro-R* and *trans-R* was observed in "classic" ER- α -dependent MCF-7 cells (Figure 7). As we mentioned previously, *dihydro-R* proliferative action at very low concentrations was more pronounced in the MCF-7 cell line than the PC-3 cell line (Figure 4). As a result, cross-modulation effects of *dihydro-R* and *trans-R* in MCF-7 cells were notable even at sub-picomolar concentrations (1×10^{-16} to 1×10^{-13} M). This modulation appeared to be non-monotonic and showed a very complex concentration dependence pattern. For example, maximum proliferation effects of a 1/1

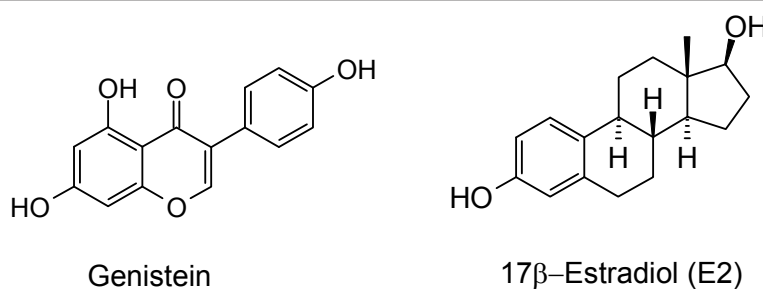


Figure 5 Structures of genistein and E2.

mixture of *dihydro-R* and *trans-R* were observed at 1×10^{-14} and 1×10^{-7} M concentrations, whereas intermediate concentrations (1×10^{-11} to 1×10^{-9} M) showed little, if any, proliferative activity (Figure 7). Non-monotonic dose response is a well-documented feature of steroid hormone receptors [27,28].

Experimental Section

Trans-R was obtained from Sigma (St. Louis, Missouri, USA). *Cis-R* was prepared from *trans-R* by photoisomerization [29]. *Dihydro-R* was synthesized from *trans-R* by catalytic hydrogenation according to [7,29]. The purity of the compounds was monitored by a combination of high performance liquid chromatography, ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR. MCF-7, a human breast cancer cell line, and PC-3 and DU 145, human prostate cancer cell lines, were obtained from the American Type Culture Collection, Rockville, Maryland. Cell lines were cultured at 37°C in a 5% CO_2 humidified atmosphere and maintained in RPMI-1640 (Sigma, USA) supplemented with 10% heat-inactivated (56°C , 30 min) fetal calf serum (Hyclone Laboratories, Logan, UK), 2 mM L-glutamine, and antibiotics (100 $\mu\text{g}/\text{ml}$ penicillin sodium salt and 100 $\mu\text{g}/\text{ml}$ streptomycin sulfate [Sigma, USA], herein referred to as complete medium [CM]). Resveratrol samples were dissolved in

dimethyl sulfoxide (DMSO) (Sigma, USA) at a concentration of 200 mM, and diluted in culture medium just before use. Tumor cells were harvested, counted, suspended in CM, seeded into 96-well tissue culture plates (Costar, France) in 200 $\mu\text{l}/\text{well}$ at a concentration of 1×10^5 cell/ml, and allowed to adhere overnight (required for particular cell lines to be in log phase). After that, CM was removed from sample wells. Compound sample solutions in CM were added to tumor cells. Final concentrations in sample wells amounted to 1×10^{-15} - 1×10^{-3} M. The plates were incubated at 37°C in a 5% CO_2 humidified atmosphere for 48 h. Three replica wells were used for controls and each compound concentration. The control samples contained DMSO concentrations corresponding to target compound dilutions. Every 24 h cells underwent microscopy and were photographed with the help of an AxioVision 4 system (Zeiss, Germany; see additional file 1). Cell viability assays were performed using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) reduction. After a 48 h incubation of tumor cells (control or drug-treated), MTT solution (5 mg/ml) was added to each well. A 4 h incubation at 37°C was stopped by the addition of 100 μl of DMSO. The absorbances of the samples were measured on a microplate reader Multiscan MS

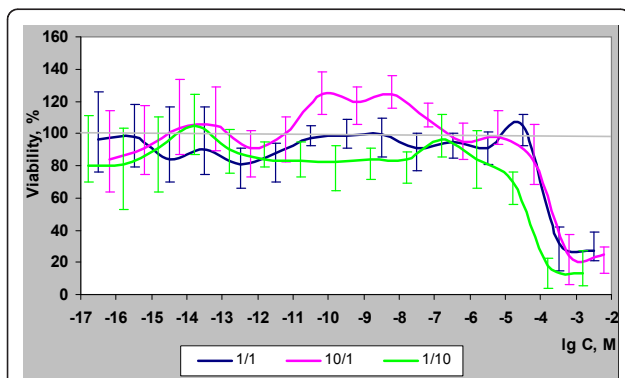


Figure 6 Biological activity of *dihydro-R* and *trans-R* mixtures (1/1; 10/1; 1/10) in PC-3 cells.

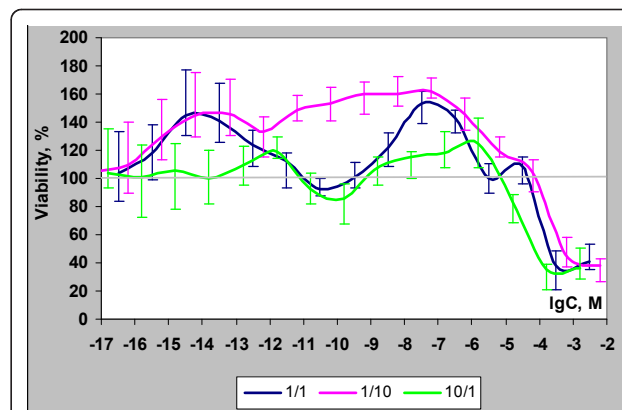


Figure 7 Biological activity of *trans-R* and *dihydro-R* mixtures (1/1; 1/10; 10/1) in MCF-7 cells line.

(Labsystem, Finland) at 540 nm after 30 min incubation at 37°C. Cell viability was expressed as a relative viability of tumor cells (percent of control cultures incubated with medium only) and was calculated as follows: relative viability = $[(Ae - Ab)/(Ac - Ab)] \times 100$, where *Ab* is the background absorbance, *Ae* is the experimental absorbance, and *Ac* is the absorbance of untreated controls. The Statistica software package, version 6.0 (Stat-Soft) was used for statistical analysis.

Conclusions

We demonstrated that the biphasic proliferative effects of *dihydro-R* at picomolar and nanomolar concentrations are not limited to hormone-dependent breast cancer cells but also present, albeit in a reduced scale, in androgen-independent prostate cancer cells. While the exact mechanism of these effects requires further evaluation, our preliminary results point to hormone receptor modulation activity. A significant similarity exists between the phytoestrogens genistein and *dihydro-R*. We also observed strong cross modulation between *trans-R* and *dihydro-R*, which is noticeable even at subpicomolar concentrations. The role of *dihydro-R* in breast cancer and prostate cancer proliferation related to moderate consumption of red wine remains an open question because *dihydro-R* exhibits proliferative activity in both prostate and breast cancer cells at low concentrations and has a very complex activity pattern in the presence of *trans-R*.

Note Added in Proof

The anti-cancer properties of *trans-R* go beyond direct growth inhibition of cancer cells. It is known that natural killer (NK) cells, such as mononuclear leukocytes (ML), are capable to kill tumor cells. We subsequently studied immunotropic activity of *trans-R* (Table 1, additional file 2). It was found that 10^{-6} M of *trans-R* significantly activated lysis of K-562 cells by ML compared to intact ML: $61 \pm 6.8\%$ vs. $46 \pm 5.8\%$ for K-562/ML cell ratio 1:10; and $53 \pm 8.7\%$ vs. $26 \pm 7.3\%$ for K-562/ML cell ratio 1:5.

Our results are consistent with the general trends observed in the previous in vitro studies [30]. The

Table 1 NK-activity of ML after coincubation with *trans-R*.

Concentration <i>trans-R</i> in medium, M	NK-activity		
	K-562/ML ratio 1:10	K-562/ML ratio 1:5	K-562/ML ratio 1:2
10^{-5}	$52 \pm 7.9\%$	$48 \pm 10.8\%$	$7 \pm 2.2\%$
10^{-6}	$61 \pm 6.8\%$	$53 \pm 8.7\%$	$5 \pm 3.4\%$
10^{-7}	$45 \pm 5.7\%$	$28 \pm 3.8\%$	$4 \pm 1.9\%$
Control	$46 \pm 5.8\%$	$26 \pm 7.3\%$	$7 \pm 2.7\%$

authors [30] reported that in vitro exposure to *trans-R* produced a biphasic effect on the anti-CD3/anti-CD28-induced development of both IFN-gamma-IL2 and -IL4-producing CD8+ and CD4+ T-cells. *Trans-R* was found to induce a significant enhancement of NK cell cytotoxic activity at low concentrations and to induce suppression at high concentrations.

Additional material

Additional file 1: Cytotoxic activity of *dihydro-R* and *trans-R* mixtures. Microscopic evaluation of the cytotoxic activity of *dihydro-R* and *trans-R* mixtures in MCF-7 and PC-3 cell lines.

Additional file 2: Immunotropic activity of *trans-R*. Microscopic evaluation of the immunotropic activity of *trans-R* in K-562 cell line.

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Authors' contributions

NUA carried out biological experiments, participated in design of the study, and drafted the manuscript. MVK and AVS participated in coordination and design of the study. SVS carried out analysis of **R** samples, and participated in design of the study. INS carried out analysis of **R** samples. AAG participated in design and coordination of the study and edited the manuscript for publication. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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