

Antimutagenic Effect of Resveratrol

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Abstract

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Evidence exist from population-based and laboratory studies that some phytochemicals have protective effects against tumors or other diseases and reveal antimutagenic activity. We studied the protective effect of the plant phytoalexin resveratrol on the mutagenic activity of three mutagens, i.e. aflatoxin B₁ (AFB₁), 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) and N-nitroso-N-methylurea (MNU) using the Ames and the micronucleus tests. In the Ames test, we proved a significant antimutagenic activity only against the indirect mutagens AFB₁ and IQ, not against the direct mutagen MNU. A significant decrease of mutagenicity of all three mutagens was detected by the micronucleus test.

Keywords: resveratrol; aflatoxin B₁; 2-amino-3-methylimidazo[4,5-f]quinoline; N-nitroso-N-methylurea

The use of natural chemicals allowing the suppression, retardation, or inversion of carcinogenic process is a promising approach for the prevention of tumors. Most of the chemopreventive agents are plant extracts which prevent carcinogenic activation as blocking agents or inhibit malignant cell proliferation as suppressing agents which have low or none side effects or toxicity.

One of these phytochemicals with such a pleiotropic effects is phytoalexin resveratrol-apolyphe-nolic compound present in grapes and other plants. Resveratrol (3,5,4'-trihydroxystilbene) is produced in the plant as a response to injury, ultraviolet irradiation, or fungal attack, and can be found mainly in the skin of grapes and in derived products such as red wine. It has a range of biological and pharmacological activities *in vitro* as well as *in vivo*. Resveratrol is well known as anti-inflammatory, anti-oxidative, and anti-carcinogenic agent and

has also a positive effect on the immune system (FREMONT 2000).

Multiple lines of evidence from epidemiological studies indicate an inverse relationship between the red wine consumption and the risk of cardiovascular diseases (LIN & TSAI 1999).

Resveratrol as a proven antioxidant which “quenches” peroxy radicals (SATO *et al.* 2000; RIMANDO *et al.* 2002; BOYCE *et al.* 2004) can prevent oxidative DNA damage, which plays an important role in the activity of many genotoxic substances (DAMIANAKI *et al.* 2000; SGAMBATO *et al.* 2001). Resveratrol participates in the prevention of carcinogenesis by the inhibition of P450, an enzyme of phase I (CHANG *et al.* 2001; GUSMAN *et al.* 2001), and through the induction of phase II xenobiotic metabolising enzymes (SAVOURET & QUESNE 2002; KUNDU & SURH 2004). Resveratrol can induce the activation of p53 and the subsequent apoptosis

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occurring through p53-dependent pathway (DONG 2003; BODE & DONG 2004), but it can also induce apoptosis independently of p53 (MAHYAR-ROEMER & ROEMER 2001). Resveratrol can modulate signal transduction pathways by the inhibitory effect on the activation of transcription factors such as NF- κ B and AP1 (KUNDU & SURH 2004). Resveratrol, as a selective inhibitor of cyclooxygenase 2 (COX-2), is also a strong inhibitor of the dioxygenase activity of lipoxygenase (LOX) (PINTO *et al.* 1999).

Many authors have described the effect of resveratrol in the prevention of cardiovascular diseases (so-called French paradox). Resveratrol modulates lipid metabolism, inhibits the oxidation of LDL and thrombocyte aggregation (PACE-ASCIAK *et al.* 1995), and has a vasodilatation activity (FRE-MONT 2000; GUSMAN *et al.* 2001). LIN and TSAI (1999) studied the balance between free oxygen radicals and endogenous antioxidants. This effect is connected with the cardioprotective action of resveratrol which results from the inhibition of the formation of the oxidised form of LDL (WU *et al.* 2001).

In our work, we studied chemopreventive effects of resveratrol on the mutagenicity of three known mutagens, two indirect mutagens aflatoxin B₁ (AFB₁) and 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), and a direct mutagen N-nitroso-N-methylurea (MNU), using the Ames test on *Salmonella typhimurium* and the micronucleus test on mice.

MATERIAL AND METHODS

Chemicals. The following chemicals were used for both tests: AFB₁ (Alexis Corporation, USA), IQ (ICN Biomedicals, Inc., Germany), MNU (Sigma-Aldrich Co, Lousiana, USA), resveratrol (Sigma-Aldrich Co, Lousiana, USA). Chemicals were diluted with dimethyl sulfoxide (DMSO) (Sigma-Aldrich Co, Lousiana, USA).

Ames test. The Ames test with *Salmonella typhimurium* TA98 and TA100 (AMES 1971; AMES *et al.* 1975; ČERNÁ *et al.* 1989) was used for the evaluation of the antimutagenic effect of resveratrol *in vitro*.

The mutagenic substances were used in the following concentrations: AFB₁ in concentrations of 10 μ g, 1 μ g, and 0.1 μ g per plate with both strains TA98 and TA100, IQ in concentrations of 0.1 μ g, 0.01 μ g, and 0.001 μ g per plate with the strain TA98, in concentrations of 10 μ g, 1 μ g, and 0.1 μ g with the strain TA100, MNU in concentrations of

1000 μ g, 100 μ g, and 10 μ g only with the strain TA100 as these concentrations had no effect on the strain TA98. Each concentration of each mutagen was combined with four different concentrations of the antimutagen (300 μ g, 30 μ g, 3 μ g, and 0.3 μ g of resveratrol per plate). All chemicals were diluted with DMSO. For the metabolic activation, the S9 fraction of liver homogenate from laboratory rats induced by a mixture of polychlorinated biphenyls Delor was used (MARON & AMES 1983). Each combination of mutagen and antimutagen was tested in two separate experiments with three plates in each experiment.

Percentage of inhibition of mutagenicity was calculated by the formula:

$$\text{No of revertants of mutagen} - \frac{\text{No of revertants of mixture of mutagen and resveratrol}}{\text{No of revertants of mutagen}} \times 100$$

For statistical analysis, Student's *t*-test was used.

Experimental animals. *In vivo* experiments (bone marrow micronucleus test) were carried out on ten-week-old male Balb C mice, each weighing 22–26 g (purchased from BIOTEST, Konárovice, CZ). The animals were housed under controlled light regime of 12/12 h, temperature of $20 \pm 2^\circ\text{C}$, relative humidity of $60 \pm 10\%$, and complete air recirculation 10–14-times per hour. The animals were supplied with water *ad libitum* and were fed with a commercial granulated mixture for laboratory rodents. These animals were divided into groups of 10 mice each.

Micronucleus test. The mouse bone marrow micronucleus test was carried out according to SCHMID (1975). An increased frequency of micronuclei in polychromatophilic erythrocytes in comparison with the control groups indicates that the substance tested induces chromosomal damage in nucleated erythrocytes in the bone marrow. A total of 1000 polychromatophilic erythrocytes were scored per animal by the same observer for evaluating the frequencies of micronucleated polychromatophilic erythrocytes. Each experiment was run three times. As the negative control, mice were treated orally by a 7% solution of DMSO. For statistical analysis, Student's *t*-test was used.

Substances tested. The following concentrations of mutagens were used for *in vivo* test: AFB₁ 1 mg per kg of body weight (b.w.), IQ 20 mg/kg b.w., MNU 20 mg/kg b.w. Resveratrol was applied to mice at the dose of 5 mg/kg b.w. by the gavage for three sequential days. Carcinogens were applied in

one dose on the third day. The controls received 7% DMSO. All of the substances (diluted with DMSO) were applied in volumes of 100 µl/10 g b.w.

RESULTS

Ames test

The results of the Ames test are summarised in Tables 1–3. All results presented in tables are expressed also as percentage of inhibition of the mutagenic activity of a sample of mutagen with antimutagen in comparison with the mutagenic activity of the respective mutagen.

Resveratrol at concentrations of 30 and 300 µg per plate revealed to possess a remarkable and dose dependent antimutagenic effect against all

concentrations of AFB₁ (10, 1, and 0.1 µg per plate) in both strains TA98 and TA100. The only exception was the concentration of 30 µg per plate of resveratrol in combination with 10 µg per plate of AFB₁ in TA100. This concentration, similarly as other lower doses of resveratrol in both strains, did not reduce the mutagenic activity of AFB₁, except the lower resveratrol dose – 3 µg per plate which significantly reduced the activity of 1 µg of AFB₁ in the strain TA100 (Table 1).

A strong dose dependent effect of resveratrol was discovered also against the second indirect mutagen IQ used in concentrations of 0.1, 0.01, and 0.001 µg per plate with the strain TA98, and 10, 1, and 0.1 with TA100. In this case not only two highest resveratrol concentrations, but also the concentration of 3 µg per plate was antimuta-

Table 1. Effect of resveratrol on mutagenicity of AFB₁ – Ames test (*S. typhimurium* TA98, TA100)

AFB ₁ + RES dose (µg/plate)	<i>S. typhimurium</i> TA98 + S9		<i>S. typhimurium</i> TA100 + S9	
	revertants ± SD	% inhibition	revertants ± SD	% inhibition
10 + 0	1407 ± 144		1540 ± 236	
10 + 0.3	1460 ± 103	+4	1550 ± 273	+1
10 + 3	1561 ± 49	+11	1835 ± 205	+19
10 + 30	1195 ± 71*	–15	1850 ± 318	+20
10 + 300	177 ± 26**	–87	586 ± 33**	–62
1 + 0	896 ± 242		1490 ± 417	
1 + 0.3	902 ± 152	+1	1084 ± 371	–27
1 + 3	757 ± 88	–16	869 ± 341*	–42
1 + 30	324 ± 21**	–64	626 ± 241**	–58
1 + 300	67 ± 9**	–93	205 ± 33**	–86
0.1 + 0	252 ± 130		504 ± 124	
0.1 + 0.3	275 ± 103	+9	511 ± 175	+1
0.1 + 3	217 ± 56	–14	397 ± 92	–21
0.1 + 30	87 ± 13*	–65	225 ± 17**	–55
0.1 + 300	36 ± 5**	–86	145 ± 6**	–71
Control (DMSO)	37 ± 7		116 ± 19	
0 + 0.3	36 ± 2		139 ± 4	
0 + 3	33 ± 2		139 ± 8	
0 + 30	31 ± 5		139 ± 7	
0 + 300	29 ± 5		142 ± 15	

statistically significant difference of the sample with antimutagen and mutagen from the mutagen alone * $P \leq 0.05$; ** $P \leq 0.01$
SD – standard deviation

Table 2. Effect of resveratrol on mutagenicity of IQ – Ames test (*S. typhimurium* TA98, TA100)

IQ + RES dose (µg/plate)	<i>S. typhimurium</i> TA98 + S9		IQ + RES dose (µg/plate)	<i>S. typhimurium</i> TA100 + S9	
	revertants ± SD	% inhibition		revertants ± SD	% inhibition
0.1 + 0	830 ± 143		10 + 0	1877 ± 73	
0.1 + 0.3	702 ± 150	–15	10 + 0.3	1584 ± 244	–18
0.1 + 3	508 ± 87**	–39	10 + 3	1400 ± 264*	–25
0.1 + 30	219 ± 16**	–74	10 + 30	592 ± 126**	–69
0.1 + 300	30 ± 7**	–96	10 + 300	129 ± 11**	–93
0.01 + 0	174 ± 44		1 + 0	1100 ± 157	
0.01 + 0.3	181 ± 47	+4	1 + 0.3	734 ± 170**	–33
0.01 + 3	115 ± 24*	–34	1 + 3	401 ± 67**	–64
0.01 + 30	57 ± 15**	–67	1 + 30	174 ± 11**	–84
0.01 + 300	26 ± 6**	–85	1 + 300	106 ± 8**	–90
0.001 + 0	67 ± 31		0.1 + 0	278 ± 51	
0.001 + 0.3	65 ± 32	–3	0.1 + 0.3	176 ± 51**	–37
0.001 + 3	44 ± 8*	–34	0.1 + 3	150 ± 39**	–46
0.001 + 30	36 ± 7*	–46	0.1 + 30	108 ± 15**	–61
0.001 + 300	25 ± 6*	–63	0.1 + 300	104 ± 14**	–63
Control (DMSO)	21 ± 3		Control (DMSO)	102 ± 15	
0 + 0.3	27 ± 4		0 + 0.3	112 ± 17	
0 + 3	24 ± 5		0 + 3	110 ± 7	
0 + 30	24 ± 2		0 + 30	110 ± 12	
0 + 300	23 ± 4		0 + 300	115 ± 14	

statistically significant difference of the sample with antimutagen and mutagen from the mutagen alone * $P \leq 0.05$; ** $P \leq 0.01$
SD – standard deviation

genic and significantly decreased the activity of IQ (Table 2). The lowest concentration of 0.3 µg per plate was effective only against 1 and 0.1 µg of IQ per plate with TA100.

However, resveratrol was not effective against any of the tested concentrations of the direct mutagen MNU (Table 3), the decrease of mutagenic activity was only insignificant, even with the highest dose of resveratrol.

Micronucleus test

In the controls treated with 7% DMSO no significant increase in the frequency of micronuclei was observed in comparison with the intact animals.

The numbers of micronuclei in the animals influenced by resveratrol alone did not differ from

those of the control group. On oral application of the combination of resveratrol (3 times 5 mg/kg b.w.) and AFB₁ in one dose (1 mg/kg b.w.), the number of micronuclei in polychromatophilic erythrocytes was lower in a statistically significant degree in comparison with the laboratory mice treated with AFB₁ alone.

A similar effect appeared on the application of the IQ mutagen. Resveratrol (3 times 5 mg/kg b.w.) in combination with one dose of IQ (20 mg/kg b.w.) significantly reduced its mutagenic effect.

Similarly, the treatment of mice with the combination of the same doses of resveratrol and one dose of MNU (50 mg/kg b.w.) led to a significant reduction of the number of micronuclei in comparison with the number of micronuclei elicited by MNU alone. The results are presented in Table 4.

Table 3. Effect of resveratrol on mutagenicity of MNU – Ames test (*S. typhimurium* TA100)

MNU + RES dose (µg/plate)	<i>S. typhimurium</i> TA100	
	revertants ± SD	% inhibition
1000 + 0	2675 ± 187	
1000 + 0.3	2577 ± 237	–4
1000 + 3	2591 ± 208	–3
1000 + 30	2590 ± 140	–3
1000 + 300	2496 ± 179	–7
100 + 0	2356 ± 65	
100 + 0.3	2098 ± 305	–11
100 + 3	2103 ± 172	–11
100 + 30	2185 ± 131	–7
100 + 300	2160 ± 183	–8
10 + 0	452 ± 191	
10 + 0.3	439 ± 74	–3
10 + 3	429 ± 83	–5
10 + 30	408 ± 109	–10
10 + 300	357 ± 64	–21
Control (DMSO)	146 ± 35	
0 + 0.3	151 ± 32	
0 + 3	142 ± 31	
0 + 30	144 ± 29	
0 + 300	151 ± 31	

SD – standard deviation

DISCUSSION

New information about chemoprotective effects of phytochemicals from the field of molecular biology and biochemistry increases the interest of scientists and clinicians in the chemoprevention of malignant diseases and stimulate significant progress in experimental genotoxicology (MORSE & STONER 1993; KELLOFF *et al.* 1996; METTLIN 1997). Anticarcinogenic and antimutagenic activities of plant substances were proved by many authors in both *in vitro* and *in vivo* systems. BOYCE *et al.* (2004) found resveratrol to be potent in blocking the mutagenicity of the food-derived heterocyclic amines: 2-amino-1-methyl-6 phenylimidazol[4,5-*b*]pyridine (MeIQx) and 2-amino-3,8dimethylimidazo[4,5-*f*]quinoxaline (PhIP) in the Ames test and in chinese hamster V 79 cells. Also, in our previous experi-

Table 4. Effect of resveratrol on mutagenicity of the mutagens AFB₁, IQ and MNU – micronucleus test

Substance	Number of micronuclei	SD
Control 7% DMSO	0.6	0.4
Resveratrol	0.8	0.7
AFB ₁	3.8*	1.1
AFB ₁ + resveratrol	2.8**	0.9
IQ	4*	1.6
IQ + resveratrol	2.5**	1.6
MNU	42.4*	5.7
MNU + resveratrol	31.8**	9.3

*significantly higher number of micronuclei as against the negative control (DMSO)

**significantly higher number of micronuclei as against mutagen alone

SD – standard deviation

mental studies we demonstrated antimutagenic and immunomodulatory effects of some substances occurring in plants (ŠMERÁK *et al.* 2002).

It is probable that multiple mechanisms including the effect on the metabolic activation of mutagens or the influence on detoxification enzymes and blocking DNA-adducts formation are involved in the antimutagenic effect of resveratrol.

It has previously been shown using the Ames assay that resveratrol can suppress the induction of mutations by 3-amino-1,4-dimethyl-5H-pyrido[4,3-*b*]indole (TRP-p-1) (UENOBE *et al.* 1997), N-methyl-N'-nitro-N-nitrosoguanidin (MNNG) (KIM *et al.* 2002), or by methylmethansulphonate and benzopyrene (FU *et al.* 2004).

In our experiments on *Salmonella typhimurium*, resveratrol revealed a much stronger effect on the mutagenicity of the indirect mutagens AFB₁ and IQ in comparison with the effect on the mutagenicity of the direct mutagen MNU. Our results support the fact that resveratrol is very active in the suppression of metabolising phase I enzymes (GUSMAN *et al.* 2001) and are in agreement with the results of BOYCE *et al.* (2004) who proved the antimutagenic effect of resveratrol on the mutagenicity of the indirect food mutagen MeIQx. It has been also stated that high concentrations of resveratrol can inhibit cellular proliferation (BOYCE *et al.* 2004), but this was not detected in our experiments on prokaryotic cells.

A significant decrease of the mutagenicity of all three mutagens, AFB₁, IQ, and MNU, by resveratrol was detected in micronucleus test. Also Fu *et al.* (2004) proved that resveratrol prevents cyclophosphamide-induced micronucleus formation in the dose dependent manner.

Diet (nutrition) may be considered as a very important factor influencing favourably pathophysiological processes in organism and may be a very effective factor in the prevention strategy against various diseases, including diseases with genotoxicological ethiology.

The study of chemoprotective effects of phytochemicals or the study of their interactions and knowledge of the mechanisms of their effect should lead us to a wider use of these substances as dietary supplements or as a part of functional foods in the prevention of many diseases including tumors.

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