

Resveratrol in the treatment of asthma based on an animal model

Kamil Leis¹, Przemysław Gałązka¹, Jakub Kazik¹, Tomasz Jamrożek¹, Weronika Bereźnicka¹, Rafał Czajkowski²

¹Department of General and Oncologic Surgery for Children and Adolescents, Chair of Paediatrics, Haematology and Oncology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

²Chair of Dermatology and Venerology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

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Abstract

Resveratrol is a natural polyphenol found, for example, in red wine, grapes or nuts. One of the resveratrol's health properties is a cardioprotective activity – it is believed that resveratrol is responsible for the French paradox and anti-cancer activity. Moreover, the effectiveness of resveratrol in the treatment of asthma is confirmed by multiple research. Resveratrol displays a multiway impact on the reduction of the symptoms of the disease which contributes to the alleviation of inflammation i.a. by: inhibition of cellular infiltration, suppression of oxidative stress, reduction in the volume of mucus, relaxation of smooth muscle, stalling of the fibrosis affecting the respiratory tract or counteracting bronchial hyperresponsiveness. Resveratrol reduces the concentration of eosinophils, pro-inflammatory interleukins and interferes with many signal transduction pathways. In case of concomitance of obesity, resveratrol alleviates the course of asthma. The review juxtaposes the mechanisms of resveratrol activity and presents the results of the published research conducted on rodents.

Key words: resveratrol, natural polyphenol, asthma treatment.

Introduction

Resveratrol (3,4',5-trihydroxy-trans-stilbene) is a chemical compound that belongs to phytoestrogens and polyphenols. It is naturally found in many products such as nuts and blueberries. However, the highest concentration of resveratrol can be found in grapes and red wine. It exhibits a wide array of biological activities proven by multiple research. One of the most important is the cardioprotective effect which consists in a significant reduction in the risk of a cardiovascular event due to i.a. reduction in the LDL level and inhibition of the thrombocyte aggregation process. It is believed that resveratrol is responsible for the phenomenon called the “French paradox” – the French are renowned for high red wine consumption and despite the high-calorie diet, which abounds in monosaccharides and animal fats, the French are less frequently affected by cardiovascular diseases, such as cardiac infarction, when compared with other populations. The other resveratrol features include anti-cancer activity, antibacterial activity, antimycotic activity

and neuroprotective activity [1–8]. The references provide data that confirm anti-inflammatory impact of the polyphenol encountered in the course of numerous diseases including asthma.

Asthma is one of the most frequent respiratory tract diseases affecting approximately 235 million people according to WHO calculations [9]. Due to this fact, concomitant symptoms that frequently reduce the quality of life and rare cases of death, the effective treatment is the crucial issue for clinicians. Nowadays, β -agonists and glucocorticoids are the standard therapy, while the other pharmacotherapy models such as omalizumab are studied. Resveratrol appears to be another option that could be useful in the asthma treatment [10–13].

Mechanism of resveratrol activity in the treatment of asthma

Resveratrol exhibits a multiple activity against asthma by reducing its symptoms, alleviating inflammation, and improving biochemical parameters. Pharmacother-

Address for correspondence: Dr Kamil Leis, Department of General and Oncological Surgery for Children and Adolescents, Dr Antoni Jurasz University Hospital, Nicolaus Copernicus University, Medical College, 9 Skłodowskiej-Curie St, 85-094 Bydgoszcz, Poland, phone: +48 52 585 4015, fax: +48 52 585 4093, e-mail: kamil.leis13@gmail.com

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apy results in reduction of mucus volume in the respiratory tract, alleviation of the alveoli oedema, relaxation of the respiratory tract smooth muscle, and alleviation of bronchial hyperresponsiveness. The polyphenol suppresses cellular inflammatory infiltration, prevents the degranulation process affecting mast cells and inhibits the fibrosis advance by reduction in the hydroxyproline level. Resveratrol reduces levels of immunoglobulin E, immunoglobulin G2A, tumor necrosis factor (TNF) α (TNF- α), transforming growth factor- β (TGF- β), TGF- β calpain – a protein responsible for induction of the necrosis process [14, 15], cytokine-induced neutrophil chemoattractant-1 (CINC-1), and prostaglandin E2. The polyphenol displays an inhibiting activity against granulocyte-macrophage colony-stimulating factor (GM-CSF), phosphodiesterase 4, interleukin 4, interleukin 5 (however, the data are inconclusive), interleukin 6, interleukin 8, interleukin 13, and interleukin 17. Resveratrol has no impact on immunoglobulin G and cathepsin C – serine proteinase inhibitors, a protein which concentration increases in the course of the disease and which participates in asthma pathogenesis and is responsible for inflammation [16–29]. The compound's supply in all probability does not involve size reduction in the respiratory tract epithelial tissue [30].

The polyphenol reduces levels of CD3+CD4+, CD3+CD8+, CD4+IL4+, and elevates the concentration of CD4+CD25+FOXP3 and interleukin 10. The FOXP3 protein (forkhead box P3), induced by resveratrol, is an anti-inflammatory agent which is responsible for regulatory T cell production [24].

The compound has an impact on the respiratory tract chronic inflammation by blocking ERK1/2 pathway (through induction of the mitogen-activated protein kinase-1 mediated by the pathway of protein kinase A – cAMP) which results in increased activity of the anti-inflammatory protein MYD88 (myeloid differentiation primary response 88) [31].

Resveratrol reduces the concentration of eosinophils through the mechanism of the cell cycle suppression and intensification of the apoptosis. The increase in p21 and p51 protein activity and the inhibition of cyclin-dependent kinase 2 and cyclins A and E lead to the eosinophil cell cycle suppression during the G1/S phase. The apoptosis is achieved by the induction of Bcl-2-associated X protein (Bax) and Bcl-2-like protein 11 (Bim) and simultaneous suppression of B-cell lymphoma 2 protein (Bcl-2) activity [16–18, 20, 26, 27, 32].

The polyphenol participates in regulation of the Akt pathway by inducing expression of inositol polyphosphate 4-phosphatase which leads to a reduced level of Akt pathway kinase, thereby resulting in the decrease in phosphorylation processes within the pathway. Resveratrol re-establishes the function of PI3K-Akt pathway which reduces its hypersensitivity, thereby inhibiting inflammation and oxidative stress concomitant with asthma [17]. Moreover, the compound inhibits expression of the Syk

protein, activator protein-1 (AP-1), PTEN protein (phosphatase and tensin homolog deleted on chromosome 10) with participation of SIRT1 (NAD-dependent deacetylase sirtuin-1) and transcriptional protein NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) which additionally results in the decrease in matrix metalloproteinase 9 (MMP-9) activity leading to the reduction in inflammation [18, 20, 33]. Furthermore, resveratrol reduces inflammatory infiltration by its impact on cyclooxygenase-1 and cyclooxygenase-2 with participation of peroxidase and also through the agency of PPAR- α dependant pathways (peroxisome proliferator-activated receptor – PPAR) [20, 30].

Through its inhibiting activity on TGF- β 1, the polyphenol blocks expression of the p-Smad2, p-Smad3 and p-Smad4 proteins which results in inhibition of epithelial-mesenchymal transition (EMT) pathway that is overexpressed in asthma [19]. Resveratrol contributes to inhibition of miR-34A pathway (which is responsible for reduction in the FOXP3 level) and blockage of GATA3 expression (which is responsible for Th2 lymphocyte production and induction of inflammation within the respiratory tract) [24].

The compound reduces the mucus volume by reducing the concentration of mucin 5AC through activity within mCLCA3/hCLCA1 pathway and inhibiting murine calcium-activated chloride channel 3 and human calcium-activated chloride channel 1 [21].

As an antioxidant resveratrol blocks reactive oxygen species responsible for the elevated level of c-RAF (RAF proto-oncogene serine/threonine-protein kinase) and activity of Janus kinases – signal transducer and activator of transcription proteins (JAK-STAT) pathway in patients with asthma [34]. Moreover, it boosts mitochondrial activity and reduces the concentration of NADPH and 8-isoprostane. On the other hand, the polyphenol induces activity of total superoxide dismutase, glutathione peroxidase, catalase, and glutathione. It is also responsible for regulation of the “antioxidant defence unit” comprised of nuclear factor erythroid 2-related factor 2 (Nrf-2), and Kelch-like ECH-associated protein 1 (KEAP1) [17, 35, 36].

In case of obesity concomitant with asthma, resveratrol impairs activity of p47phox (neutrophil cytosolic factor 1), regulates AMPK pathway, activates superoxide dismutase, blocks nitric oxide synthase and reduces the level of reactive oxygen species [23].

In the course of asthma resveratrol induces insulin sensitivity improvement and enhancement of insulin transport within lung tissue (which is dysfunctional as a result of obesity). The main reason for that is increased activity (which was impaired due to obesity) of insulin receptor substrate 1, β type insulin receptors, and AKT, as well as inhibition of tyrosine nitration of aforementioned proteins and kinases NF- κ B and c-Jun N-terminal [37].

The molecular activity of resveratrol in asthma is shown in Table 1.

The summary of recent studies on effectiveness of resveratrol in the treatment of asthma

In 2009 Lee *et al.* assigned mice of BALB/c strain into several groups of 5–6 individuals and were administering 4 mg/kg of dexamethasone and 30 mg/kg of resveratrol to them. Asthma in the rodents was induced with a hen's egg. Subsequently, the rodents were given a 6.25–50 mg/ml dose of methacholine in aerosol. The researchers attested that the animals subjected to the polyphenol, independently of the methacholine concentration, exhibited decreased values of enhanced pause – Penh when compared with the stimulated group and slightly increased when compared with dexamethasone pharmacotherapy – the results there were comparable. Resveratrol led to a decrease in eosinophil activity of nearly 90% (when compared with the group subjected to allergisation solely) and to reduction of about 77% of cellular infiltration measured in the bronchoalveolar lavage fluid. Dexamethasone caused the reduction of the aforementioned parameters of nearly 98% and about 85%, respectively. Similar activity of the polyphenol was also found in perivascular and peribronchial connective tissue materials. Moreover, resveratrol reduced the total IgE level from the average concentration of 1793 mg/ml in the clinical control group to 662 mg/ml (the decrease of over 1000 mg/ml). The effect was significantly better when compared with dexamethasone. Additionally, the compound caused the decrease in specific IgE antibodies to the egg from 463 mg/ml to 232 mg/ml (the reduction of approximately 50%), and in specific IgG antibodies from about 2.5 mg/ml to about 1.2 mg/ml. Moreover, the researchers measured the cytokine levels after glucocorticoid and resveratrol administration. The polyphenol caused the decrease in interleukin 4 concentration (from 102 mg/ml in the control group to 64 mg/ml), and interleukin 5 (from 30.6 mg/ml to 4.6 mg/ml). It should be noted that the polyphenol suppressed the interleukin 5 concentration more effectively comparing with dexamethasone which reduced the interleukin 5 level to 11.4 mg/ml [16].

Chen *et al.* in 2015 conducted a research which consisted in sensitizing rodents with house dust mites. Subsequently, the rodents were given dexamethasone at a dose of 1 mg/kg and resveratrol at a dose of 50 mg/kg. It was observed that the intensity of the inflammation process had been significantly smaller in the group receiving the polyphenol when compared with the control group. The extent of the inflammation process in the control group was estimated at 4 on a 5-point scale, whereas in the resveratrol group at 2. The therapy with dexamethasone resulted in 1 point in the scale. The analysis of collagen indicated that the compound inhibited the fibrosis process. The polyphenol reduced the concentration of TNF- α from 12793 pg/ml in the control group to 1443 pg/ml, TGF- β from the average level of 141523 pg/ml

Table 1. Mechanism of action of resveratrol against asthma

Induce	Inhibit
<ul style="list-style-type: none"> • CD4+CD25+FOXP3 • Interleukin 10 • Myeloid differentiation primary response 88 	<ul style="list-style-type: none"> • Hydroxyproline • Immunoglobulin E • Immunoglobulin G2A • TNF-α • TGF-β • TGF-β1 calpain • CINC-1 • Prostaglandin E2 • GM-CSF • Fosfodiesterase-4 • Interleukin 4 • Interleukin 5 (?) • Interleukin 6 • Interleukin 8 • Interleukin 13 • Interleukin 17 • CD3+CD8+ • CD3+CD4+ • CD4+IL4+ • ERK 1/2 pathway • Eosinophils • Akt • PI3K-Akt • Syk • AP-1 • PTEN • NF-κB • Cyclooxygenase – 1 • Cyclooxygenase – 2 • p-Smad2 • p-Smad3 • p-Smad4 • EMT pathway • miR-34A pathway • GATA-3 • 5AC mucine • ROS • c-RAF • JAK-STAT • NADH • 8-isoprostane • p47phox

in the control group to 43963 pg/ml, interleukin 6 from the average concentration of 35073 pg/ml in the control group to 8816 pg/ml, and interleukin 17 from the average level of 179 pg/ml to 41 pg/ml. Dexamethasone exhibited a comparable effect. The Syk-dependent pathway (which is activated by immunoglobulin E) was also inhibited [18].

In 2017 Lee *et al.* published a similar analysis. The researchers were administering the egg protein to the mice for 3 months which triggered allergic asthma. The polyphenol was administered at doses of 10 mg/kg per day or 50 mg/kg per day starting from the 35th day until the end of the experiment. During the trial it was attested that resveratrol inhibits the respiratory tract remodeling and reduces inflammation (which is assessed on the basis of the amount of pro-inflammatory cytokines such

as interleukin 4, interleukin 5, and interleukin 13 and eosinophils present in bronchoalveolar fluid and peribronchial tissue). Additionally, the polyphenol reduced the level of hydroxyproline and consequently collagen level because hydroxyproline is the main component of collagen. Through suppression of the TGF- β 1 resveratrol also caused inhibition of the epithelial-mesenchymal transition – EMT pathway and its mediatory proteins such as p-Smad2, p-Smad3, and p-Smad4. The intensity of activity was directly proportional to the dose rate [19, 35].

Ni *et al.* in 2016 published the results of the conducted tests concerning resveratrol's impact on inflammation and the volume of mucus produced in the course of the disease. 30 mice of BALB/c strain were assigned into 3 groups of 10 individuals each. The control group received saline solution while the second and the third group were given the egg protein and the egg protein combined with resveratrol at a dose of 30 mg/day (within a period of 6-day pharmacotherapy), respectively. The histopathological examination of the sample derived from lung tissue indicated that the polyphenol administration resulted in alleviation of the inflammatory cell infiltration and also displayed inhibitory activity against mucogenesis. The inhibition of mucogenesis is possible due to the reduction in the mucin 5AC level (elevated in the groups exposed to the allergen) by inhibition of the transcription process which consists in suppression of mRNA mucin 5AC expression [21].

On the other hand, Royce *et al.* were administering resveratrol at a dose of 12.5 mg/day to asthmatic mice for 6 weeks. The mice were assigned into 3 groups counting 15 individuals each – the control group, the group receiving the egg protein and the group receiving the egg protein combined with resveratrol. The researchers noticed that the polyphenol administration results in considerable elevation of the inflammatory cells level and the immunoglobulin E level comparing with the group subjected to the allergen solely. The researchers assessed that the results were “comparable”. Further analysis of the inflammatory infiltration showed that in the group receiving resveratrol, the level of eosinophils was slightly increased, whereas the levels of monocytes and neutrophils were slightly decreased. However, the difference in the concentration of lymphocytes was noticeable. The average level of lymphocytes in the group subjected to allergen was about 2×10^7 /ml BAL, whereas in the group receiving resveratrol the concentration of lymphocytes was about 2.5×10^7 /ml BAL. The results prove that, in contrast to the previously discussed studies, the polyphenol may not only have no impact on the reduction of inflammatory infiltration, but also it can increase slightly. Further analyses showed that resveratrol reduced AHR and the size of subepithelial extracellular matrix. The polyphenol also slightly reduces the amount of AP-BAS goblet cells. The compound administration had no effect on the size of the respiratory tract epithelial tissue. The authors emphasized that resveratrol's activity in the field

of the respiratory tract remodelling was restricted to the inhibition of the fibrosis process [30].

In 2016 Andre *et al.* studied the impact of resveratrol on the course of asthma in mice with insulin resistance and obesity. The mice of C57/Bl16 strain were allergized with the egg protein. The polyphenol was administered to the mice at a dose of 100 mg/kg for 2 weeks. During the experiment the mice were on a natural or high-fat diet. The researchers attested that the course of asthma was more severe in case of obese mice (i.e. the eosinophilic infiltration was greater). Resveratrol triggered the alleviation of inflammation (the reduction in the cellular infiltration was about 2 times in case of mice on a natural diet and 8 times in mice on a high-fat diet), and reduced the concentration of eosinophils (about 1.75 times in mice on a normal diet and almost 5 times in mice on a high-fat diet) [23].

Moreover, the polyphenol had an impact on regulation of the AMPK pathway expression, displayed inhibitory activity against p47phox, boosted the activity of superoxide dismutase, and reduced the levels of nitric oxide synthase, reactive oxygen species, and TNF- α . Interestingly, that effect was not observed in case of non-obese mice on a natural diet. The polyphenol reduced the elevated concentration of phosphodiesterase 4 in mice on a normal diet as well as in mice on a high-fat diet and the effect was comparable [23].

The resveratrol's activity on the course of asthma in obese rats was studied by Li *et al.* in 2018. They assigned a total of 42 rodents into 7 groups counting 6 individuals each and administered 0.03% resveratrol in the food to 3 groups. The researchers attested that not only did the polyphenol improve metabolism, but also reduced the level of reactive oxygen species measured in the samples derived from the lung tissue, the renal tissue, and the cardiac muscular tissue (which is the effect of resveratrol's inductive impact on total superoxide dismutase, glutathione peroxidase, catalase, and glutathione). Furthermore, the compound triggered the decrease in Kelch-like ECH-associated protein 1 (KEAP-1) protein level and simultaneous increase in the nuclear factor erythroid 2-related factor 2 (Nrf-2) level. Both of the aforementioned compounds are part of the “antioxidant defence” [38].

Joskova *et al.* in 2013 conducted a comparative analysis of the effectiveness of resveratrol and quercetin in the treatment of asthma. The researchers triggered an allergic reaction in guinea pigs with the egg protein. Subsequently, they administered a 10 mg/kg dose of resveratrol per day, a 20 mg/kg dose of quercetin per day, and also medications containing the aforementioned compounds such as Flavin-7 at a dose of 2 ml/kg/day, and Provin at a dose of 20 mg/kg/day.

The polyphenols as well as their preparations triggered the trachea smooth muscle relaxation by counteracting the activity of histamine and acetylcholine.

Moreover, the compounds reduced the respiratory tract reactivity, and the concentrations of interleukin 4 and 5. The effect of the preparations was significantly stronger than the polyphenols alone (the researchers determined it as inconsiderable).

It was attested that quercetin reduced the amplitude of contraction (which was induced by the transmitters such as acetylcholine, and histamine measured during their incubation). Resveratrol, however, had no impact on the changes of the amplitude [39].

The recent studies on effectiveness of resveratrol in the treatment of asthma are shown in Table 2.

Summary

Based on the studies with rodents and *in vitro* tests, resveratrol proves to be an effective therapeutic option in the treatment of asthma. Until now the standard pharmacotherapy had consisted in β -blocking agents

and glucocorticoids (hormones that are produced in suprarenal glands and our skin) [40]. The polyphenol exhibits marginally weaker activity when compared with glucocorticoids. Its multiway mechanism consisting in the inflammation alleviation, the reduction in bronchial hyperresponsiveness or the volume of produced mucus are the reason why resveratrol is considered (provided that the outcome of the consecutive studies are positive) as a possible adjunctive pharmaceutical to the standard anti-asthmatic therapy. Moreover, resveratrol may be an effective alternative for the patients who are disqualified from the standard therapy due to their clinical condition. However, the references still provide a small number of studies that confirm the effectiveness of resveratrol in the treatment of asthma. The published articles refer to the small group of rodents (mice, rats, guinea pigs) and the results are inconclusive. Human involvement is still a necessary component of further molecular analyses.

Table 2. Recent studies on effectiveness of resveratrol in the treatment of asthma

Study	Model	Approach	Results
Lee <i>et al.</i> , 2009	Animal: mice of BALB/c strain	The therapy comprised of 4 mg/kg of dexamethasone and 30 mg/kg of resveratrol; asthma induced by egg protein	Reduction of IgE, IL-4 and IL-5 concentrations; lower Penh values, reduction in cell infiltration; eosinophilia alleviation; the efficiency slightly lesser in comparison with dexamethasone pharmacotherapy
Chen <i>et al.</i> , 2015	Animal: rodents	Administration of dexamethasone at a dose of 1 mg/kg and resveratrol at a dose of 50 mg/kg; asthma induced by house dust mites	Reduction in: inflammation, fibrosis progression and concentration of TNF- α , TNF- β , IL-6 and IL-16; the effectiveness of polyphenol and dexamethasone was comparable
Lee <i>et al.</i> , 2017	Animal: mice	Administration of resveratrol at a dose of 10 mg/kg or 50 mg/kg/day; asthma induced by egg protein	Reduction in inflammation, inhibition of respiratory tract remodelling progression, reduction in collagen, IL-4, IL-5, IL-13 and TGF- β 1 concentrations, reduction in eosinophilia
Ni <i>et al.</i> , 2016	Animal: mice of BALB/c strain	Administration of resveratrol at a dose of 30 mg/day for 6 days; asthma induced by egg protein	Reduction of inflammation, inhibition of mucogenesis by reducing mucin concentration
Royce <i>et al.</i> , 2011	Animal: mice of BALB/c strain	A 6-week pharmacotherapy of resveratrol at a dose of 12.5 mg/day; asthma induced by egg protein	Slightly increased concentration of inflammatory cells, eosinophils and IgE, reduction in neutrophils and monocytes concentration, reduction in AHR and respiratory tract fibrosis progression
Andre <i>et al.</i> , 2016	Animal: mice of C57/Bl16 strain; co-occurring obesity in some individuals	Administration of resveratrol at a dose of 100 mg/kg for 14 days; asthma induced by egg protein; normal or high-fat diet	Reduction in inflammation and eosinophils concentration; polyphenol exhibited more efficient activity in mice on a high-fat diet, inhibition of nitric oxide synthase activity and TNF- α only in mice on a high-fat diet
Li <i>et al.</i> , 2018	Animal: rats with co-occurring obesity	Food containing polyphenol at a concentration of 0.03%	Reduction in ROS concentration, antioxidant defence enhancement
Joskova <i>et al.</i> , 2013	Animal: guinea pigs	Comparison of resveratrol's and quercetin's effectiveness; administration of resveratrol at a dose of 10 mg/kg/day, quercetin at a dose of 20 mg/kg/day and preparations containing polyphenols at doses of 2 ml/kg and 20 mg/kg; asthma induced by egg protein	Reduction in muscle tone, smaller respiratory tract reactivity, reduction in IL-4 and IL-5 concentration caused by each type of pharmacotherapy; the authors stated that the activity of preparations containing quercetin was stronger than pharmacotherapy based solely on polyphenols

Conflict of interest

The authors declare no conflict of interest.

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