Resveratrol attenuates mast cell mediated allergic reactions: potential for use as a nutraceutical in allergic diseases?

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Keywords

Allergy; anti-inflammatory; mast cells; nutraceuticals; resveratrol

Abbreviations

AAM, arachidonic acid metabolites; AD, atopic dermatitis; AR, allergic rhinitis; β-hex, beta hexosaminidase; BMMCs, bone marrow-derived mast cells; COX, cyclooxygenase; CRSwNP, chronic rhinosinusitis with nasal polyps; CXCL, C-X-C motif chemokine ligand; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinases; hiMC, human intestinal mast cells; HO-1, heme oxygenase-1; IIR, intestinal ischemia-reperfusion; IκBα, inhibitor of NF-κB; JNK, c-Jun N-terminal kinase; LAD, Laboratory of Allergic Disease 2; LO, lipoxygenase; MAPK, mitogen-activated protein kinases; MCs, mast cells; NQO1, NADPH dehydrogenase quinone 1; Nrf2, nuclear erythroid 2-related factor 2; OVA, ovalbumin; PCA, passive cutaneous anaphylaxis; PGD, prostaglandin D; PKC, protein kinase C; PLC, phospholipase C; PMA, phorbol-12-myristate 13-acetate; PPAR, peroxisome proliferator-activated receptor; PtdIns, phosphatidylinositol; PTP1B, phosphorylation of protein tyrosine phosphatase 1B; RAGE, receptor for advanced glycation end products; RBL-2H3, rat basophilic leukemia mast cell line; RCT, randomized controlled trial; RESV, resveratrol; RIP, receptor interacting protein; Sirt1, sirtuin-1; ST2, Interleukin 1 receptor-like 1; STAT, signal transducer and activator of transcription; Syk, spleen tyrosine kinase; TLR, toll-like receptors; TNF-α, tumor necrosis factor alpha; TSLP, thymic stromal lymphopoietin;

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Abstract

Allergic diseases are one of the most common health disorders affecting about 30% of the world population. Mast cells (MCs) are key effector cells of allergic reactions by releasing pro-inflammatory mediators including histamine, lipid mediators and cytokines/chemokines. Natural substances like secondary plant substances such as resveratrol (RESV), which can contribute to prevention and treatment of diseases, are becoming increasingly interesting for use as nutraceuticals. In this review, the anti-inflammatory effects of RESV on MC-mediated allergic reactions in vitro and in vivo models were summarized. The studies indicate that RESV inhibits MC degranulation, synthesis of arachidonic acid metabolites, expression of cytokines and chemokines as well as activation of signal molecules involved in pro-inflammatory mechanisms. Also, beneficial impacts by this polyphenol were reported in randomized controlled trials with allergic rhinitis patients. Although it cannot yet be concluded that RESV can be used successfully in allergy patients in general, there are many results that indicate a possible role for resveratrol for use as an anti-inflammatory nutraceutical. However, strategies to favorably influence the poor bioavailability of RESV would be helpful.

1 Introduction

The prevalence of allergic diseases is high; almost 30% of the world population suffers from one or more allergic conditions.[1] In general, allergy is an overreaction of the immune system to ordinarily harmless foreign substances, usually proteins, resulting in skin rash, sneezing or swelling of mucous membranes.[2] Therefore, the term „allergy", which was discovered by Clemens von Pirquet (1874-1929) in the early 1900s, describes a constellation of clinical diseases like allergic rhinitis (AR), asthma, atopic dermatitis (AD), food allergy, drug allergy and the life threatening systemic mast cell (MC)-mediated reaction known as anaphylaxis.[3] MCs belong to the innate immune system. They play a crucial role in inflammatory and immediate allergic reactions by releasing inflammatory mediators such as histamine, proteases, chemotactic factors, cytokines and metabolites of arachidonic acid (AAM) that act among others on inflammatory cells.[4] Noteworthy, MC granules are described as the major source of histamine in humans.[3] The so-called degranulation can be induced by exogenous and endogenous stimuli, including immune mechanisms that may be Immunglobulin (Ig) E-dependent or IgE-independent.[4] IgE antibodies produced in response to a certain allergen bind to the high-affinity FcεRI receptor, expressed on the surface of MCs, and lead to their activation after they have been cross-linked by the allergen,[4,5] which is the so-called type I hypersensitivity allergic reaction.[6] Besides, interleukin (IL-) 33 released by exposure to allergens seems to play a role in IgE–dependent and -independent allergic inflammation via its receptor interleukin 1 receptor-like 1 (ST2).[7] IgE-mediated activation results in degranulation of preformed mediators such as proteases, and histamine or the de novo production of lipid mediators as well as cytokines influencing vascular permeability and adhesiveness.[4,8] Therefore, MCs are involved in several diseases such as allergic rhinitis, atopic dermatitis, asthma, but also in autoimmune disorders, atherosclerosis or mastocytosis. [8] Figure 1 shows MC activation via several stimuli leading to the release of de novo and pre-stored mediators implicated in several diseases.

Since there is an increase in life expectancy all around the world,[9] there is a growing interest in substances, which can contribute to healthy aging by preventing diseases or treating existing disorders. In this context, in the late 1980s the term nutraceutical, consisting of "nutrition" and "pharmaceutical", was introduced for food or food components which are praised for maintaining health.[10] As the term implies, it is assumed that they exhibit pharmaceutical benefit besides their nutritional value.[11] Nowadays, different types of nutraceuticals are available. They can be categorized based on the food sources in probiotics/prebiotics, polyunsaturated fatty acids, antioxidant vitamins, spices and polyphenols.[10] Latter comprise a large group of phenolic compounds, including flavonols, flavones, anthocyanins, coumarins or stilbenes.[10,12]

Resveratrol (trans-3,5,4'-trihydroxystilbene) (RESV) belongs to the best studied polyphenols, precisely to the group of stilbenes. Its two phenol rings are connected by an ethylene bridge.[13] Just like other secondary plant substances, RESV is synthetized to defend plants against bacterial or fungal infection or external stress, including UV irradiation.[14,15] Naturally, RESV occurs as cis and trans isoforms in > 70 plant species as well as different fruits, including blueberries, mulberries, raspberries or grapes.[14] Nevertheless, it is mainly found in grape skin, at a concentration of 50–100 µg/g.[16] However, trans-RESV exists in glycosylated form and therefore is more stable which is why it is considered to be the most abundant form.[14] As an aglycone, trans-RESV has 38% bioavailability and its exposure was approximately 46-fold lower than that of the glucuronide form.[14] In this

context, oral intake of 25 mg resveratrol resulted in a concentration peak of <10 ng/ml after 0.5 h.[15] The poor in vivo bioavailability of RESV is explained by its rapid metabolism to glucuronide and sulphate derivatives in the liver and intestine.[14] After RESV was discovered from white squash in the 1940s,[17] its possible beneficial effects have been examined in various studies. Therefore, RESV is probably best known for its antioxidant activities.[18] Also, anti-inflammatory,[19] anti-allergic,[20] anticancerogenic,[21] cardio-[22] and neuroprotective[23] or antipathogenic[24] effects of this polyphenol were shown in vitro and in vivo. It is even considered to mimic some aspects of caloric restriction,[25] which can extend lifespan.[26] Furthermore, clinical trials reported that RESV is safe and well tolerated.[27] Here, we summarize the immunomodulating activities of RESV on MCs in vitro and in vivo in the context of allergic conditions.

2 RESV inhibits MC degranulation in vitro and in vivo

MCs are located in mucosal and epithelial tissues where antigens can enter the host's body, such as the gastrointestinal tract, skin or the respiratory epithelium.[28] Their cytoplasm contain about 50–200 large granules with preformed and stored inflammatory mediators as mentioned above.[28] In various in vitro as wells as in vivo models, it could be shown that treatment with RESV inhibits MC degranulation (Table 1 and 2). Determination of β-hexosaminidase (β-hex) is used to evaluate the level of MC degranulation,[29] which can also be evaluated by detection of histamine. However, β-hex release is slower and the process persists for longer than histamine release does.[29] In the rat basophilic leukemia mast cell line (RBL-2H3), which is widely used to study the IgE-dependent degranulation of MCs,[29] the release of β-hex and/or histamine could be reduced by about 50% and more after the treatment with RESV (Table 1).[20,30,31] Naveen et al. explained the RESV-induced decrease of β-hex release by the inhibition of the type II phosphatidylinositol (Ptdlns) 4-kinase, which is usually activated upon FcεRI cross-linking.[31]

Using mouse bone marrow-derived MCs (BMMCs), Baolin et al. could detect an inhibition of IgE-mediated histamine release by RESV at concentration of 100 µM without any cytotoxic effects.[32] This reduction was greater than 90% (Table 1). However, lower doses did not result in a significant decrease.[32] RESV also attenuated IgE/antigen-mediated release of β-hex by mouse BMMCs.[33] Wang et al. reported a dose-dependent attenuation of compound 48/80 (C48/80)-induced β-hex and histamine release by RESV in the human Laboratory of Allergic Disease 2 (LAD2) mast cell line.[34] Here, the application of 200 µM RESV led to a decreased degranulation of mentioned mediators by about 80% (Table 1).[34] We measured a reduction of IgE-mediated β-hex release by about 75% of human intestinal mast cells (hiMC) in response to pre-treatment with 50 µM RESV and a complete inhibition after treatment with 100 µM RESV.[35] The transcription factor signal transducer and activator of transcription (STAT) 3 was found to be present in mitochondria, and that mitochondrial STAT3 plays a major role in IgE-antigen–mediated mast cell exocytosis.[36] Moreover, ERK1/2 has been shown to phosphorylate STAT3 on the serine 727 residue. We could show that in IgE/antigen-activated hiMC 50 µM of RESV inhibited the phosphorylation of both nuclear and mitochondrial STAT3 and ERK1/2 by almost 100%. Thus, it can be concluded that RESV prevents activation of MCs also by inhibiting this pathway.[35] Figure 2 summarizes signaling molecules and transcription factors in MC that have been shown to be affected by resveratrol treatment.

Regarding degranulation, in vivo experiments show similar results (Table 2). In BALB/c mice, a commonly used strain in models of allergic diseases,[37] administration of 10 mg/kg RESV (10 mg/kg in 100 mL solution) resulted in a reduction of plasma histamine concentration, by about 50%, which was enhanced in sensitized mice challenged with 2,4-dinitrophenol (DNP)-human serum albumin (HSA).[38] The reduced histamine levels were concomitant with the reduced phosphorylation of the protein kinase C (PKC)-μ, spleen tyrosine kinase (Syk) as well as the phospholipase (PLC)-γ.[38] In an ovalbumin (OVA)-induced model of food allergy using BALB/c mice, RESV (20 mg/kg BW) decreased the serum histamine level by about 50%.[20] Furthermore, β-hex levels were reduced to about 50% by RESV in the intestine of male Sprague-Dawley rats with intestinal ischemia-reperfusion (IIR).[39] C65BL/6 mice with pseudoallergy induced by C48/80 were pre-treated with RESV (5, 10, 20 mg/kg) which resulted in a dose-dependent decrease of serum histamine levels (Table 2).[34] In addition, the number of degranulated MCs was reduced in a dose-dependent manner, too, whereas the maximum application concentration (20 mg/kg) led to a greater reduction (~70%).[34]

3 RESV attenuates the synthesis of arachidonic acid metabolites in vitro and in vivo

Newly synthesized lipid mediators are AAM such as prostaglandin D_2 (PGD_2) or leukotrienes (LTs), which are produced and released after MC activation by antigens. In mouse BMMCs, which were sensitized with anti-DNP IgE and stimulated with DNP-bovine serum albumin (BSA), RESV reduced the release of LTs and PGD_2 at concentrations of both 100 μM and 10 μM (Table 2).[32] Moreover, the reduction of LTs was about 99% after the application of 100 μM RESV, whereas PGD_2 was decreased by ca. 50% at 100 μM.[32] RESV at a concentration of 10 μM was used in a study by Li et al.[33] Here, LTC_4 and PGD_2 releases were reduced after the treatment of mouse BMMCs with RESV by more than 70% (Table 1).[33] In in vivo experiments, lower doses of 5 mg/kg BW as well as 10 mg/kg BW RESV led to a decrease in synthesis of PGDs and LTC_4s in OVA-sensitized BALB/c mice (Table 2).[40] Responsible for this result is probably the inhibition of the pro-inflammatory enzymes cyclooxygenase 2 (COX2) and 5-lipoxygenase (5-LO), which catalyze the generation of PGD_2 and LTC_4 out of arachidonic acid (AA), since the expression of these pro-inflammatory enzymes was reduced after RESV treatment, too.[40]

4 RESV reduces the expression of cytokines and chemokines in vitro and in vivo

Different from lipid mediators such as PGD_2 or LTC_4, which are synthesized in lipid bodies or nuclear/endoplasmic reticulum (ER) membranes and released through active transporters, de novo synthesized cytokines and chemokines packaged in secretory vesicles are released through constitutive exocytosis.[41] In RBL-2H3 cells, stimulated with either anti-DNP/DNP-HSA[42] or IL-33[43] the release of pro-inflammatory cytokines and chemokines, such as tumor necrosis factor α (TNF-α), IL-6, IL-4, IL-3 as well as monocyte chemoattractant protein 1 (MCP-1), was suppressed by RESV (Table 1).[42,43] This effect could be explained by the reduced phosphorylation of mitogen-activated protein kinases (MAPK) p38, extracellular-signal regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) which occurred following the treatment with RESV in a dose-dependent manner.[42] Besides MAPK, nuclear factor kappa B (NF-κB) pathway plays an important role in cytokine release from human MCs.[43,44] After incubation of IL-33 and IgE/antigen-stimulated RBL-2H3 cells with 10 μM RESV the phosphorylation of p38, inhibitor of NF-κB α (IκBα) and NF-κB subunit p65 was reduced by more than 50%.[43]

A reduced release of TNF-α, IL-13, and IL-6 by more than 40% was also detected in mouse BMMCs stimulated with either IL-33 or anti-DNP-IgE/anti-IgE following the treatment with 25 µM of the polyphenol (Table 1).[7] Since it was found that the MAPK-activated protein kinase (MK)-2/3 mediated activation of phosphatidylinositol-3 kinase (PI3K)/Akt pathway is crucial for IL-33-induced IL-6 and IL-13 production in MCs[45] it can be suggested that RESV inhibits the synthesis of pro-inflammatory cytokines by targeting the MK2/3–PI3K/Akt axis.[7] Interestingly, the release of IL-6 and TNF-α was already diminished by about 60% in BMMC using a concentration of 10 µM RESV.[34] RESV treatment led to a decreased phosphorylation of protein tyrosine phosphatase 1B (PTP1B), which is suggested to be involved in FcεRI-dependent MC activation by regulating the Syk pathway.[33] Latter was deactivated, too, and it is known to be a central regulator of FcεRI signaling.[33]

Furthermore, Moon et al. and Kang et al. reported a reduction in mRNA expression of pro-inflammatory mediators like thymic stromal lymphopoietin (TSLP) by using human mast cell line (HMC)-1, which was stimulated with phorbol-12-myristate 13-acetate (PMA) and calcium ionophore A23187 prior to RESV incubation.[46,47] Higher doses of RESV (≥ 50 µM) resulted in a decreased release as well as mRNA expression of various cytokines and chemokines by about 60-70% (Table 1).[47] Following the treatment with 3 µM of RESV intracellular calcium levels were reduced resulting in a decreased production of receptor interacting protein (RIP) 2/caspase-1, which inhibited the activation of NF-κB or the phosphorylation of IκBα by about 50%.[46] The authors assumed that this effect was responsible for the reduced TSLP production by RESV.[46] As described above, the inhibition of NF-κB probably leads to an attenuation of allergic reactions by the decreased synthesis of other pro-inflammatory cytokines, too. Furthermore, Kang et al. reported inhibitory effects on degradation of IκBα by RESV, which prevents nuclear translocation of p65 NF-κB.[47] This could be, apart from the attenuated intracellular calcium levels, an explanation for the reduced expression of pro-inflammatory cytokines like IL-6 or TNF-α.[47]

In LAD2 the synthesis of MCP-1, TNF-α and IL-1β was suppressed by RESV by about 50%.[34] In addition, we detected a dose-dependent decrease in mRNA expression of different chemokines, particularly C-X-C motif chemokine ligand (CXCL) 8, CC-chemokine ligand (CCL) 2 and CCL4, after the incubation of hiMC with RESV with a complete inhibition in response to 100 µM RESV.[35] As mentioned above, we found that RESV inhibited IgE mediated phosphorylation of STAT3 and ERK1/2, known to be involved in MC cytokine expression,[48] in hiMC by almost 100%, so we concluded that RESV prevents also the cytokine expression by inhibiting this pathway.[35] Aside from inhibition of crucial pro-inflammatory signal molecules, RESV leads to promotion of the mRNA expression of genes involved in the suppression of allergic reactions. RESV treatment of C48/80-stimulated LAD2 resulted in an increase of nuclear erythroid 2-related factor 2 (Nrf2) expression as well as heme oxygenase-1 (HO-1) and NADPH dehydrogenase quinone 1 (NQO1) generation, which are target genes of Nrf2.[34] Because the Nrf2/HO-1 pathway has been reported to play a role in IgE-dependent allergy, Nrf2 could act as a target for the therapy of MC-mediated allergic disorders.[34]

Various in vivo models reported a reduced expression of pro-inflammatory cytokines and chemokines in response to treatment with RESV (Table 2). In IL-33-stimulated male Sprague-Dawley rats treated with 5 mg/kg RESV plasma levels of IL-6 (~50%), IL-13 (~40%), TNF-α (~60%) and MCP-1 (~50%) were reduced.[43] Also, a decrease in serum levels of TNF-α (~50%), IL-1β (~40%), IL-18 (~50%) and mRNA expression of IL-1β p17 (~60%) and IL-18 (~60%) was detected in rats suffering from IIR

treated with 15 mg/kg [39]. Further cytokines such as IL-4 (~40%), IL-5 (~80%) or MCP-1 (~50%) were less produced following the treatment with RESV in a models of passive cutaneous anaphylaxis (PCA) and eosinophilic rhinosinusitis with nasal polyps (CRSwNP) (Table 2).[40,38] Moreover, in female BALB/c mice with OVA-induced chronic allergic airway disease, transforming growth factor β1 (TGFβ1) expression in lung tissue was lowered by RESV (12.5 mg/kg).[49] Besides production of pro-inflammatory cytokines, the infiltration of chemokines, such as CXCL1, CXCL5 or CCL22, was inhibited by RESV in C65BL/6 gouty arthritis model (Table 2); however, the release of CXCL12 was promoted in joint tissue.[50] Thus, RESV increased the synthesis of sirtuin-1 (Sirt1) by 100% and the production of peroxisome proliferator-activated receptor (PPAR)-γ by about 60% in joints of gouty arthritis of C65BL/6 mice.[50] It is suggested that Sirt1 inhibits the infiltration of inflammatory cells as well as the secretion of pro-inflammatory molecules through its downstream molecule PPAR-γ.[50] Further, serum levels of IL-8 were suppressed by RESV in C65BL/6 mice with pseudoallergy (Table 2).[34] In an AD mouse model protein expression of TNF-α (~60%), IL-1β (~60%) and high-mobility-group protein (HMGB)-1 (~70%) was reduced in skin, whereas the levels of IL-4 (~70%) and interferon (IFN)-γ (~50%) were decreased in the serum after the treatment with RESV (20 mg/kg) (Table 2).[51] Binding of the nonhistone chromatin-associated protein HMGB1 to receptor for advanced glycation end products (RAGE) activates a signaling pathway through ERK and NF-κB.[51,52] Since the HMGB1 signaling induces the generation of pro-inflammatory mediators the authors suggested that this pathway might be a potential therapeutic target in skin inflammation.[51]

5 RESV attenuated symptoms of allergic rhinitis in randomized controlled trials

Not only in vitro and in vivo studies reported an attenuation of pro-inflammatory mediators and mechanisms. Beneficial effects of RESV on AR were additionally detected in randomized controlled trials (RCTs). AR is an IgE-mediated inflammatory disease of the upper respiratory tract, particularly of the nasal mucous membranes, which is caused by the interaction of allergens.[53] Diseases of the upper respiratory system are characterized by a common mechanism in the type 2 inflammatory pathway mediated by several inflammatory cells, such as eosinophils, mast cells, basophils, Th2 cells or IgE-producing B cells, which release several mediators, chemokines, and cytokines.[53,54] In this context, MC mediators are released upon IgE-dependent mechanism in AR, but they can also induce IgE generation in B cells.[53] Once produced, local IgE acts on the FcεRI receptors of tissue-resident MCs and basophils which results in the release of histamine or leukotrienes leading to edema, vasodilation, and bronchoconstriction.[54] Adult AR patients treated with RESV (100 µL/spray) showed a reduction in nasal symptoms compared to the placebo group. In this context, this polyphenol led to a decrease of IgE (~40%), IL-4 (~30%), TNF-α (~10%) and eosinophil levels (~80%) in the blood of the participants. Additionally, RESV treatment improved the quality of life of adults with AR (Table 3).[53] Furthermore, in children with pollen-induced AR, intranasal administered RESV (100 µL/spray) combined with carboxymethyl-b-glucan resulted in a significant reduction of nasal symptoms, including itching, sneezing, rhinorrhea & obstruction, and antihistaminic consumption (Table 3).[55] This indicates that RESV could be used as an adjuvant substance in AR to attenuate the symptoms in children and adults, not only because this polyphenol has been found to be safe and well-tolerated at up to 5 g/day.[56] However, it cannot yet be concluded that RESV can generally be used successfully in allergy patients. More studies are needed to prove the use of RESV as a potential substance in the treatment of allergic diseases.

6 Challenges in using RESV as anti-inflammatory nutraceutical

The effective RESV dosage found in vitro (micromolar range) can hardly be reached by oral administration in vivo due to its in vivo bioavailability, making it difficult to identify the concentration at which RESV should be administrated to human subjects.[57] Thus, although RESV was shown to be safe in vivo, arguably one of the biggest challenges regarding the use of resveratrol as a potential adjuvant substance in allergic diseases is its poor bioavailability. After oral administration, more than 70% of RESV is absorbed by the gastrointestinal tract.[57] It is rapidly metabolized by phase II enzymes in the intestine and liver leading to the accumulation of glucuronides and sulfate conjugates in plasma as well as urine, and hence the very low bioavailability of RESV.[27,57,58] Furthermore, 75% of the total consumed resveratrol is excreted, while the remaining amount of resveratrol is metabolized and the highest concentration of free resveratrol in the serum is 1.7–1.9%.[15] Since RESV has a limited dissolution rate in the aqueous environment, a small increase in solubility can enhance its bioavailability.[59] Topical administration of RESV has been shown to be more effective compared to oral application, as its oral intake results in quick metabolization and excretion.[27] RESV must be administrated orally at relatively high, i.e. mM, concentrations to achieve efficacy in cutaneous applications.[60]

In order to improve RESV's poor bioavailability, various methodological approaches have been developed, including several delivery systems such as RESV encapsulation in lipid nanocarriers or liposomes, emulsions, micelles, insertion into polymeric nanoparticles, solid dispersions, and nanocrystals.[59] Using 3T3-L1 fibroblasts, it was shown that trans-RSV encapsulated in lipid nanocarriers or liposomes increased cellular RESV content in cells, whereas RESV liposomes showed better biological activity due to its higher physical and chemical stability at room temperature.[59] Further, self-microemulsifying drug delivery systems with UDP-glucuronosyltransferase excipients have been developed to increase oral bioavailability by inhibiting enzyme mediated intestinal metabolism.[61] In vivo, the inhibitory excipients containing self-microemulsifying increased oral RESV bioavailability compared to free RESV- and excipients without inhibitory activities.[59,61] Besides, oral bioavailability of trans-RESV from a grapevine-shoot extract (Vineatrol30) was increased in healthy subjects by enhancing its absorption via micellar solubilization compared with the native powder.[62] As mentioned before, encapsulation in nanoparticles is another strategy to improve oral bioavailability of RESV. In this regard, RESV-loaded galactosylated nanoparticles enhanced the oral bioavailability of RESV in Sprague-Dawley rats as well as the anti-inflammatory efficacy of RESV-loaded galactosylated nanoparticles in RAW 264.7 cells.[63] In another work with Sprague-Dawley rats, the oral bioavailability of an amorphous solid dispersion of trans-RESV was examined by a Eudragit E/HCl solid dispersion prepared by a spray drying process.[64] The absolute oral bioavailability of trans-RESV from Eudragit E/HCl solid dispersion (10/90) was estimated to be 40%.[64] In addition, nanocrystals are a promising approach to improve the oral bioavailability of RESV. Plasma concentration profile of trans-RESV nanocrystals has been shown to be enhanced compared to trans-RESV.[59] Overall, there are several strategies to increase the oral bioavailability of RESV.[59] However, the actual biologically effective concentration range of RESV in vivo needs to be determined in further studies.[57]

7 Conclusion

Based on the studies included in this overview, it can be concluded that RESV is able to attenuate pro-inflammatory, particularly IgE-dependent MC-mediated reactions in vitro and in vivo. Beneficial effects of this polyphenol were also reported in RCTs; thus, it can be assumed that RESV might be successful in alleviation of allergic symptoms, especially allergic rhinitis, in humans. However, the poor bioavailability of RESV is a big challenge for using RESV as nutraceutical in allergic diseases in general. There are several strategies to favorably influence the pharmacokinetics of RESV and further clinical trials are needed investigating the oral bioavailability of RESV. Nevertheless, the inhibition of the release of pro-inflammatory mediators including β-hex, histamine or cytokines/chemokines by MCs serves as an explanation for the anti-inflammatory impact of this polyphenol. Since RESV is a natural, safe, and well-tolerated substance it could be considered in future studies as a potential adjuvant or an alternative drug, especially when medication compliance is low because of adverse events caused by conventional therapy methods.

Author contribution statement

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Conflict of interest

All authors declare no conflicts of interest

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Figure legends

Figure 1. MC activation via several stimuli leads to release of de novo and pre-stored mediators involved in several diseases. Sensitization and subsequent FcεRI crosslinking represent the most prominent activation cascade in MCs. Antigen presenting dendritic cells present allergens via major histocompatibility complex (MHC) and interact with T cell receptor (TCR). Th2 cell derived IL-4 and IL-13 stimulate B cells to produce IgE. IgE then binds to FcεRI receptors on MCs. If allergens bind to specific IgE, FcεRI is crosslinked, leading to MCs activation. Further, activation signals can be initiated via stimuli like substance P or compound 48/80 binding to Mas-related G-protein coupled receptor member X2 (MRGPRX2), bacterial components like LPS to toll-like receptors (TLR), IL-33 to ST2 receptor or SCF to CD117. Activation cascade leads to degranulation of pre-stored substances like histamine or β-Hexosaminidase or de novo synthesis of cytokines/chemokines. Inflammatory mediators are involved in several disease outcome, e.g. allergic rhinitis, atopic dermatitis, food allergy, mastocytosis, atherosclerosis, or autoimmune disorders.

Figure 1

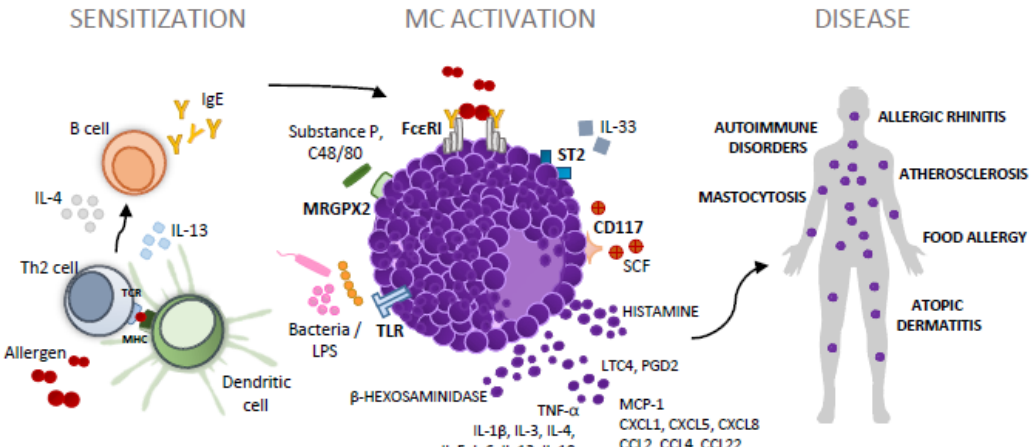

Figure 2. Signaling pathways in MCs affected by resveratrol. Activation of MCs is amongst others induced via receptors such as FcεRI, TLR, MRGPRX2 and ST2, leading to de novo synthesis of cytokines and chemokines as well as to release of pre-stored mediators like histamine. As stated in the text, resveratrol has been shown to affect various signaling molecules and transcription factors

in cytoplasm, mitochondria as well as in nucleus involved in these signaling pathways (marked in pink).

Figure 2

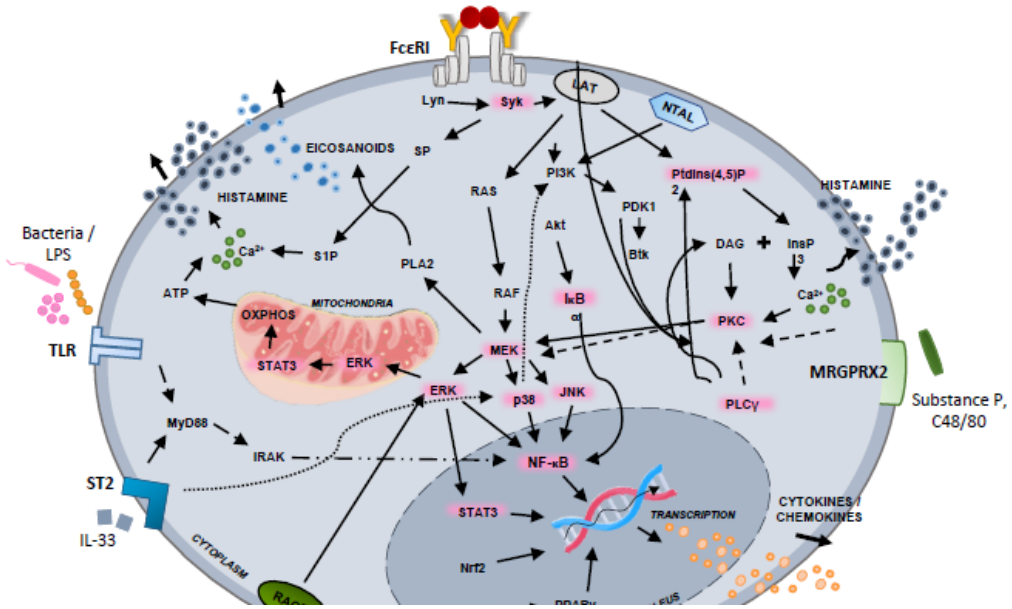

Table 1. Overview of the anti-inflammatory effects of RESV on MCs in vitro

Dosage RESV	*MC*	*Model*	*Stimulus*	*Degranulation*	*Arachidonic acid metabolites*	*Cytokines / Chemokines*	*Signaling*	*Others*	*Reference*
N/A	RBL-2H3		IgE/DNP-HSA	β-Hex ↓ (60%)	---	---	Ptdlns 4-kinase activity ↓ (90%)		[31]
1 - 25 μM	RBL-2H3		anti-DNP/ DNP-HSA	---	---	TNF-α, IL-4, IL-3 ↓ (dd)	p-p38 MAPK, p-ERK1/2, p-JNK & p-Src ↓ (dd)	mRNA expression *Fcεriγ* subunit ↓ (dd)	[42]
10 μM	RBL-2H3		DNP-BSA	β-Hex ↓		---	p-PLCγ1 & p-ERK1/2 ↓ (N/A)	---	[65]
10 μM	RBL-2H3		IL-33 (50 ng/ml) & IgE-antigen	---	---	IL-6, IL-13, TNF-α & MC	ST2, cytosolic pERK1/2/ERK, pJNK/JNK ↔ Cytosolic p-P38/P38, IκBα & NF-κB (p65)	cell viability ↓ (dd)	[43]

					P-1 ↓	proteins ↓ (~50-60%)		
10 µM	RBL-2H3	AHR ligands/ Iono-PMA	β-Hex ↓ (<50%)	---	*Il-6* ↓	---	---	[30]
5, 10 & 20 µg/ml	RBL-2H3	anti-DNP-IgE/DNP-BSA	β-Hex ↓ (dd; >50% with ≥10 µM) Histamine ↓ (dd; max. 50%)	---	---	---	---	[20]
≤ 25 mmol/l	RBL-2H3	anti-DNP-IgE/DNP-HSA	β-Hex ↓ (dd) Histamine ↓ (dd)	---	---	p-PKCµ & p-PKCθ ↓ p-PKCζ/λ ↑ p-Syk & p-PLCγ ↓	---	[38]
250	rPMC	C48/80	Histamine ↓ (82.4%)	---	---	---	---	[66]
1, 10 & 100 µM	mBMMC	IgE or Calcium ionophore A23187	Histamine ↓ (>90% with 100 µM)	LT ↓ (99.4% with 100 µM; 72% with 10 µM) PGD_2 ↓ (~33% with 10 µM; ~70% with 100 µM)	---	---	---	[32]
1 – 25	mBMMC	IL-33 & anti-DNP-IgE/anti-IgE	CD63 counts ↓ (~70% with 25 µM)	---	IL-6, IL-13 & TNF-α ↓ (dd; ~20-30% with 10 µM, ~40-50% with 25 µM)	p-IKKα/β & p-p65 ↔ p-p38 & p-MK2 ↔ p-Akt ↓	---	[7]
10 µM	mBMMC	anti-DNP-IgE/DNP-HSA	β-Hex ↓ (~65 %)	LTC_4 & PGD_2 ↓ (~80%)	IL-6 & TNF-α ↓ (~70%)	p-Akt, p-p38, p-Syk & p-PTP1B ↓	Intracellular Ca^{2+} ↓ (~50%)	[33]
0.03, 0.3 & 3 µM	HMC-1	PMA + calcium ionophore A23187	---	---	TSLP ↓ (dd; ~25% with 3 µM) *TSLP* ↓ (dd; ~80% with 3 µM)	RIP2 ↓ (~37% with 3 µM) & caspase-1 ↓ (~60% with 3 µM) NF-κB ↓ (~50% with 3 µM) & p-IκBα ↓ (~30% with 3 µM)	Intracellular Ca^{2+} ↓ (~30%)	[46]
Dosage RESV	***MC Model***	***Stimulus***	***Degranulation***	***Arachidonic acid metabolites***	***Cytokines / Chemokines***	***Signaling***	***Others***	***Reference***
10 – 50 µM	HMC-1	PMA + calcium ionophore A23187	---	---	*TNF, IL-6, IL-8* ↓ (~65-90% with 50 µM) TNF-α, IL-6 & IL-8 ↓ (~60-95%	*Cox-2* ↓ (~80% with 50 µM) COX-2 ↓ (~90% with 50 µM) p-ERK1/2/ERK1/2 ↓ (~66% with 50 µM) &	Intracellular Ca^{2+} ↓ (~80%)	[47]

					with 50 µM)	NF-κB activity ↓ (~66% with 50 µM) degradation of IκBα ↓		
50 µM	HMC-1	RESV &/or tocopherols	---	---	---	p-Akt ↓ (58%)	Cell proliferation ↓ (25% at 24h; 49% at 48h & 39% at 72h)	[67]
50, 100 & 200 µM	LAD2	C48/80	β-Hex ↓ (dd) Histamine ↓ (dd)	PGD_2 ↓	*MCP-1* ↓ (~40%), *TNF* ↓ (~60%) & *Il-1β* ↓ (~80%) TNF-α, IL-8 & MCP-1 ↓ (dd)	*Nrf2*, *Ho-1* & *Nqo-1* ↑ (~50-100%)	Intracellular Ca^{2+} (dd) ↓ *Mrgprx2* ↓ (~50%)	[34]
50 µM	hiMC	mAb 22E7 (IgE-dependent activation)	β-Hex ↓ (dd; ~75% with 50 µM)	---	*CXCL8*, *CCL2*, *CCL4* & *TNF* ↓ (dd; ~80-100%) & *CCL3* ↓ (dd; ~100%)	p-STAT3 & p-ERK1/2 in nuclear (~50-70%) & mitochondrial fractions (~60 -85%) ↓	---	[35]

Abbreviation: β-Hex, β-Hexosaminidase; AHR, aryl hydrocarbon receptor; Akt, protein kinase B; BSA, bovine serum albumin; C48/80, compound 48/80; Ccl2, CC-chemokine ligand 2; COX-2, cyclooxygenase-2; Cxcl8, chemokine (C-X-C motif) ligand 8; dd, dose-dependent; DNP, Dinitrophenol; ERK1/2, extracellular signal-regulated kinase 1/2 (ERK1/2); hiMC, human intestinal mast cells; HMC-1, human mast cell line 1; HSA, human serum albumin; HO-1, heme oxygenase 1; IgE, Immunoglobulin E; IL, Interleukin; IkBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IKKα/β, inhibitor of nuclear factor kappa-B kinase subunit alpha/beta; JNK, c-Jun N-terminal kinase; LAD2, Laboratory of Allergic Diseases 2; LT (C4), leukotriene (C4); mAb, monoclonal antibody; mBMMCs, (mouse)bone marrow-derived mouse mast cells; MC, mast cell; MCP-1, monocyte chemoattractant protein-1; MK-2, mitogen-activated protein kinase-activated protein kinase 2; MRGPRX2, MAS Related GPR Family Member X2; N/A, not available; NF-kB, nuclear factor k-light-chain-enhancer of activated B cells; NQO1, NAD(P)H quinone oxidoreductase-1; Nrf2, nuclear factor erythroid 2-related factor 2; p, phospho; p38 MAPK, p38 mitogen-activated protein kinase; PGD2, prostaglandin D2; PKC, protein kinase C; PLCg1, phospholipase C, gamma 1; PLCγ, phospholipase Cγ; PMA, phorbol myristate acetate; Ptdlns 4, Phosphatidylinositol 4-phosphate; PTP1B, protein-tyrosine phosphatase 1B; RBL-2H3, rat basophilic leukemia cells; RESV, resveratrol; RIP2, receptor-interacting protein 2; rPMC, rat peritoneal mast cells; ST2, Interleukin 1 receptor-like 1; STAT3, signal transducer and activator of transcription 3; Syk, spleen tyrosine kinase; TNF-α, tumor necrosis factor, alpha; TSLP, thymic stromal lymphopoietin;

Table 2. Overview of the anti-inflammatory effects of RESV on MCs in vivo

Dosage RESV	*MC Model*	*Stimulus*	*Degranulation*	*Arachidonic acid metabolites*	*Cytokines / Chemokines*	*Signaling*	*Others*	*Reference*
5	♂ Sprague Dawley rats (6 wk)	IL-33	---	---	Plasma levels ↓ IL-6 (~50%), IL-13 (~40%), TNF-α (~60%) & MCP-1 (~50%)	---	---	[43]
15	♂ Sprague Dawley rats (adult)	IIR	Intestinal β-Hex ↓ (~50%)	---	Serum levels ↓: TNF-α (~50%), IL-1β (~40%) & IL-18 (~50%) *Il-1β p17* ↓ (~60%) & *Il-18* ↓ (~60%)	Mucosal NLRP3 & caspase-1 p20 ↓ (~50%) Mucosal IL-1β p17 & IL-18 ↓ (~60%)	TUNEL positive cells ↓ (~50%)	[39]
0.5 mg/kg & 5 mg/kg	(N/A) BALB/c mice (4 wk)	CRSwNP (OVA-induced)	---	PGDs ↓ (~80% with 0.5 mg/kg & 5 mg/kg) LTC_4S ↓ (~75% with 0.5 mg/kg, ~50% with 5 mg/kg)	*Il-4* ↓ (~40% with 0.5mg/kg, ~60% with 5 mg/kg) & *Il-5* ↓ (~80% with 0.5 mg/kg & 5 mg/kg)	5-LO ↓ COX-2 ↓ (only with 5 mg/kg)	---	[40]
10	♂BALB/c mice (5 wk)	PCA (anti-DNP IgE / DNP-HSA)	MC degranulation in dorsal skin ↓ Plasma histamine ↓ (~50%)	---	MCP-1 ↓ (~50%) & MIP-2 (~40%) in dorsal dermis	p-Syk ↓ (~50%) p-PLC-γ ↓ (~60%) p-PKC-μ ↓ (~55%) in dorsal skin tissue	Vascular permeability (~75%) & thickness of ears (~50%) ↓	[38]
12.5	♀BALB/c mice (6 wk)	Chronic allergic airway disease (OVA-induced)	---	---	TGFβ1 in lung tissue ↓	---	total & differential BAL cell counts ↔ Inflammatory cell infiltration in airways ↓ (~15%) subepithelial thickness of ECM ↓ (~20%)	[49]
5, 10 & 20 mg/kg	♀ BALB/c mice (7-9 wk)	FA (OVA-induced)	Serum IgE ↓ (~30%, ~40%, ~40%, respectively) Serum histamine ↓ (~25% with 10 mg/kg, ~50%	---	Serum MCP-1 ↓ (~30% with 10 mg/kg, ~50% with 20 mg/kg)	---	DC number in SPL ↓ (~45% with 20 mg/kg) Th & Treg cells in SPL & MLN ↔ B cell number ↓ (~20% in SPL, ~25% in MLN) MC number ↓	[20]

			with 20 mg/kg)				(~20% in SPL, ~60% in MLN)	
30	r g / k g	♀BALB/c mice (6-8 wk)	AD (DNFB-induced)	---	---	number of IL-15-, IL-33- & TSLP-positive cells in skin epithelium ↓ (~20%, respectively)	Number of caspase-3 positive cells in skin epithelium ↓ (~25%)	Weight change ↔ Dermatitis score ↓ (~40%) Epithelial thickness ↓ (~50%)	[68]

Dosage RESV	***MC Model***	***Stimulus***	***Degranulation***	***Arachidonic acid metabolites***	***Cytokines / Chemokines***	***Signaling***	***Others***	***Reference***
10 & 50 mg/kg	♀BALB/c mice (7 wk)	AI (OVA-induced)	---	---	IL-4 ↓ (ns; ~50%), IL-5 ↓ (~60%; ~40%), IL-13 ↓ (~30%; ~50%) & TGFβ1 ↓ (ns; ~50%) in BAL fluid *Tgfβ1* in lungs ↓ (ns; ~70%) TGFβ1 in lungs ↓ (ns; ~60%) & BAL fluid ↓ (ns; ~20%)	p-smad2 ↓ (~30%, ~90%) & p-smad3 in lungs ↓ (ns; ns)	total cell counts ↓ (~40%, respectively) & eosinophils ↓ (~60%; ~70%) in BAL fluid; infiltration of peribronchial inflammatory cells in lungs ↓ Number of goblet cells ↓ (~40%; ~60%) α-SMA in peribronchium ↓ (~20%; ~40%) hydroxyproline in lungs ↓ (ns; ~60%)	[69]
5, 10 & 20 mg/kg	♂ C65BL/6 (8 wk old)	Pseudo-allergy (C48/80-induced)	Serum histamine ↓ (dd; ~60%; ~60%; ~70%) Degranulated MC number ↓ (dd; ns; ~50%; ~70%)	---	Serum MCP-1 ↓ (~50%, ~70%, ~80%) TNF-α ↓ (~30%, ~50%, ~70%) IL-8 ↓ (~20%, ~30%, ~50%)	---	Paw thickness ↓ (dd; ~20%; ~60%; ~60%) Evans blue extravasation ↓ (dd; ~20%; ~30%; ~50%)	[34]
10 & 20 mg/kg	(N/A) C65BL/6 (NA)	Gouty arthritis (MSU-induced)	---	---	Release in joint tissue ↓ : MCP-1 (~100%), IL-1β (~80%), IL-1α (~90%), IL-6 (~90%), TNF-α (~100%), IFN-r (~100%), CXCL-1 (~100%), CXCL-5 (~90%), CCL-22 (~70%) and CXCL-13 ↑ (~400%)	*Sirt1* ↑ (~100%) & *Pparγ* ↑ (~60%) in joint tissue ↑	Foot swelling ↓ Inflammation scores ↓ (~100%) Infiltration of inflammatory cells in joints ↓	[70]

20	r g / k g	♀NC/Nga mice (6 wk old)	AD (DfE-cream induced)	MC number in skin ↓ (~10%)	---	Protein expression in skin ↓ : TNF-α (~60%), IL-1β (~60%) & HMGB-1 (~70%) Serum IL-4 ↓ (~70%) & IFN-γ (~50%)	Protein expression in skin ↓ : p-PI3K (~70%), p-ERK1/2 (~40%) & p-NFκB (~70%)	Dermatitis score ↓ Protein expression in skin ↓ : TNFR1 (~50%), IL-2Rα (~70%), COX-2 (~60%) & GRP78 (~60%) CHOP (~80%), cleaved caspase-7 (~40%), TLR4 (ns), RAGE (~40%)	[51]

Abbreviation: ♂ male; ♀ female; 5-LO, 5-lipoxygenase; α-SMA, alpha-smooth muscle actin; AD: atopic dermatitis; AI: airway inflammation; BAL, bronchoalveolar lavage; β-Hex, β-Hexosaminidase; C48/80, compound 48/80; Ccl2, CC-chemokine ligand 2; CHOP, C/EBP homologous protein; COX-2, cyclooxygenase-2; CRSwNP, chronic rhinosinusitis with nasal polyps; Cxcl, chemokine (C-X-C motif) ligand; dd, dose-dependent; DC, dendritic cells; DfE, *Dermatophagoides farinae*; DNFB, 1-Fluoro-2,4-dinitrobenzene; DNP, Dinitrophenol; ECM, extracellular matrix; ERK1/2, extracellular signal-regulated kinase 1/2 (ERK1/2); FA, food allergy; GRP78, glucose regulated protein-78; HMGB-1, High mobility group box 1; HSA, human serum albumin; IFN, Interferon; IIR: intestinal ischemia reperfusion; IgE, Immunoglobulin E; IL, Interleukin; LT (C4) (s), leukotriene (C4) (synthase); MC, mast cell; MCP-1, monocyte chemoattractant protein-1; MIP-2, macrophage inflammatory protein; MLN, mesenteric lymph nodes; MRGPRX2, MAS Related GPR Family Member X2; MSU, monosodium urate; N/A, not available; NFkB, nuclear factor k-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; ns, not significant; OVA, Ovalbumin; p, phosho; PCA: passive cutaneous anaphylaxis; PGD (s), prostaglandin D (synthase); PI3Ks, Phosphoinositide 3-kinase; PKC, protein kinase C; PLCg1, phospholipase C, gamma 1; phospholipase Cγ (PLCγ); PPAR, proliferator-activated receptor; RAGE, receptor for advanced glycation endproducts; RESV, resveratrol; Sirt, sirtuin; smad, an acronym from the fusion of *Caenorhabditis elegans Sma* genes and the *Drosophila Mad*, Mothers against decapentaplegic; SPL: spleen; Syk, spleen tyrosine kinase; TGFβ1, Transforming growth factor beta 1; Th, T helper cells; TLR4, Toll Like Receptor 4; TNF-α, tumor necrosis factor, alpha; TNFR1, tumor necrosis factor receptor 1; Tregs, regulatory T cells; TSLP, thymic stromal lymphopoietin; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; wk, week

Table 3. Overview of the anti-inflammatory effects of RESV in randomized controlled trials

Dosage RESV	*Study type & duration*	*Study population*	*Results*	*Reference*
100 µL/spray	RCT (1 month)	N = 151 adults with severe persistent AR Age: 18-60 years	Nasal symptoms ↓ Blood levels of IgE ↓ (~40%), IL-4 ↓ (~30%) & TNF-α ↓ (~10%) Eosinophile number in blood ↓ (~80%)	[53]
RESV + carboxymethyl-β-glucan (100 µL/spray)	RCT (2 months)	N = 68 children with AR Mean age: 7.9 years	Itching, sneezing, rhinorrhea & obstruction ↓ Antihistamine use ↓	[55]

Abbreviation: AR, allergic rhinitis; IgE, Immunoglobin E; IL, Interleukin; RCT, double-blind randomized controlled trial; RESV, resveratrol; TNF-α, tumor necrosis factor alpha

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Graphical Abstract. Mast cells, stimulated via several stimuli and signaling pathways, produce and release a lot of inflammatory mediators implicated in mast cell-associated disease. Resveratrol inhibits mast cell activation and thereby mast cell-mediated disorders. Therefore, resveratrol may be successfully used as a potential adjuvant or alternative drug to alleviate inflammatory reactions in mast cell-associated diseases.

Graphical Abstract