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The pharmacology of resveratrol in animals and humans ☆

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ABSTRACT

In addition to thousands of research papers related to resveratrol (RSV), approximately 300 review articles have been published. Earlier research tended to focus on pharmacological activities of RSV related to cardiovascular systems, inflammation, and carcinogenesis/cancer development. More recently, the horizon has been broadened by exploring the potential effect of RSV on the aging process, diabetes, neurological dysfunction, *etc.* Herein, we primarily focus on the *in vivo* pharmacological effects of RSV reported over the past 5 years (2009–2014). In addition, recent clinical intervention studies performed with resveratrol are summarized. Some discrepancies exist between *in vivo* studies with animals and clinical studies, or between clinical studies, which are likely due to disparate doses of RSV, experimental settings, and subject variation. Nevertheless, many positive indications have been reported with mammals, so it is reasonable to advocate for the conduct of more definitive clinical studies. Since the safety profile is pristine, an added advantage is the use of RSV as a dietary supplement. This article is part of a Special Issue entitled: Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes.

1. Introduction

Resveratrol (RSV) was first isolated in 1939 by Takaoka from *Veratrum grandiflorum* Loes. fil. (the root of the white hellebore) [1]. It is speculated that the name resveratrol was derived from the combination of its chemical structure and plant source used for isolation: a *res*orcinol derivative or polyphenol in the *res*in, occurring in *Veratrum* species which contains hydroxyl (–OH) groups (*-ol*). In addition to the most popular name, resveratrol, further nomenclature includes *trans*-resveratrol, (*E*)-resveratrol, 3,4′,5-trihydroxy-*trans*-stilbene, 3,4′,5-stilbenetriol, (*E*)-3,4′,5-trihydroxystilbene, *trans*-3,5,4′-trihydroxystilbene, 5-[(1*E*)2-(4-hydroxyphenyl)ethenyl]1,3-benzenediol, (*E*)2-(3,5-dihydroxyphenyl)1-(4-hydroxyphenyl)ethane, (*E*)5-(*p*-hydroxystyryl)resorcinol, Bioforte™, Regu®-Fade (for skin), resVida™, and SRT 501.

As a defense mechanism in plants, the production of RSV, one of the phytoalexins, can be triggered in response to fungi, rhizobacteria, UV irradiation, metallic salts, methyl jasmonate, *etc.* The main enzyme responsible for RSV biosynthesis is stilbene synthase which condenses one *p*-coumaroyl-CoA (4-coumaroyl-CoA) and three molecules of malonyl-CoA [2]. Stilbene synthase encoding genes have been identified in grapevine, pine, *Arachis hypogea*, *Parthenocissus henryana*, *Vitis riparia* cv Gloire de Montpellier, *Sorghum*, *etc.* [3].

Despite the early discovery, RSV gained little attention until an article coining the phrase 'the French paradox' was published, in which it was suggested that people of France, who consume a relatively high level of saturated fat, had a relatively low mortality from coronary heart disease, presumably as a result of wine consumption [4]. Later, RSV was touted as an active ingredient in red wine responsible for reduced serum lipids [5], but of course the concentration of RSV in wine is relatively low [6], and grapes are known to contain over 1600 phytochemicals [7]. As shown in Fig. 1, there has been an enormous upsurge of studies investigating the characteristics of RSV since 1997, undoubtedly due to the publication or our paper reporting cancer chemopreventive potential with a number of model systems [8].

Based on a search using SciFinder® [accessed July 18, 2014, using the RSV chemical structure (CAS 501-36-0)], 219 commercial sources are available and 679 reactions to yield RSV have been published. A large number of patents have been filed that are related to the effects of RSV in therapeutic, cosmetic and nutraceutical applications [9]. The response of the nutraceutical industry has been robust. Many dietary supplements containing RSV as a single component or in combination with other ingredients are on the market. Unit doses range from about 0.2 to 1000 mg (Google search, July 19, 2014). In some products RSV is encapsulated in liposomal formulations, micronized, or filled as a liquid capsule, ostensibly to improve the absorption.

In addition, a wide array of compounds and extracts are used in combination with RSV, including: *compounds* such as glucosamine, flavonoids (*e.g.*, quercetin, catechins, rutin, anthocyanins, and proanthocyanidins), stilbenoids (*e.g.*, piceid), phenolic acids (*e.g.*, ellagic acid), vitamins (*e.g.*, vitamins B6, B12 and C, folic acid, and coenzyme Q10), phosphatidylcholine, piperine, tocotrienols, lutein, lycopene, fatty acids

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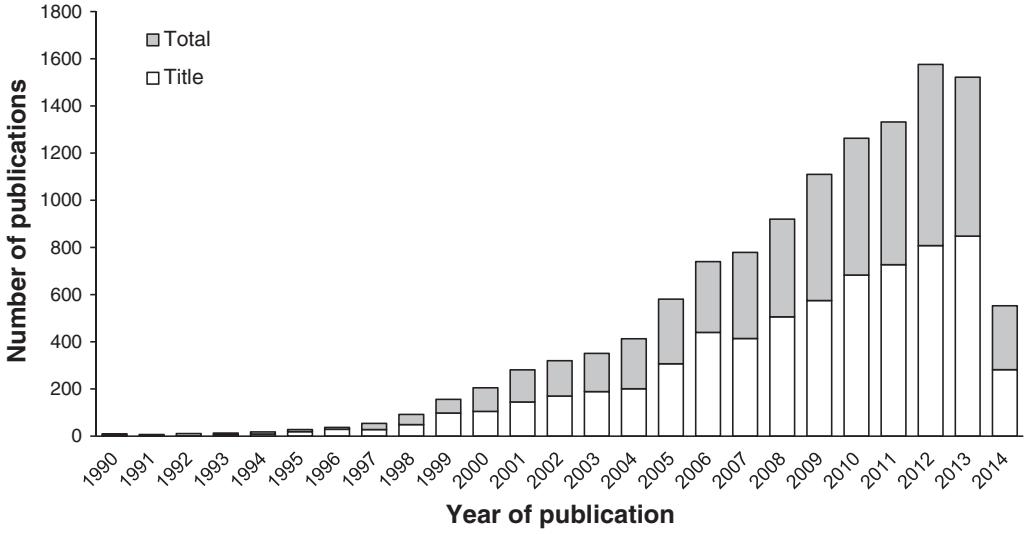

Fig. 1. Yearly publications related to RSV (1990–2014). The original search with the chemical structure of RSV (CAS number 501-36-0) followed by the removal of duplicate articles using the SciFinder® program yielded a total of 15,782 references (accessed July 18, 2014) as shown in 'total' bar (shaded). Within the 15,782 references, a total of 6664 articles include 'resveratrol' in the title ('title' bar, open).

(*e.g.*, docosahexaenoic acid, eicosapentaenoic acid), L-carnitine, and reduced L-glutathione; *extracts* from kelp, acai berry, blueberry, cherry, cranberry, pomegranate, olive, citrus fruits, melon, grape, French red wine, turmeric rhizome, black pepper fruit, potato, or calamari oil. Also, RSV has been used as an active ingredient in skin care products, with vitamin C, calcium, methylsulfonylmethane, polyphenols, or proanthocyanidins.

Although scores of *in vitro* studies have added to our understanding of the vast biological potential of RSV, it is common to use high concentrations that may not be of physiological relevance. Since RSV is known to have poor bioavailability in that it is rapidly metabolized and excreted, it is expected that the results of many *in vitro* studies will not have a good correlation with *in vivo* studies. Here, the discussion is limited to the *in vivo* biological effects of RSV, excluding work in which extracts or mixtures of compounds were investigated.

The review is largely based on a PubMed search using the search terms as 'resveratrol and animal model', 'resveratrol and in vivo', or 'resveratrol and animal study'. A literature search using SciFinder® (research topic: resveratrol, document type: review, publication year: –2008, accessed November 22, 2014) resulted in 244 review articles that include "resveratrol" in the titles. As an attempt to avoid redundancy, this article focuses on *in vivo* studies that were published during the time period of 2009 to 2014.

2. Carcinogenesis/cancer

Studies on the cancer chemopreventive effect of RSV increased dramatically following the paper published in 1997 describing the ability of RSV to inhibit skin carcinogenesis in an animal model [8]. Since comprehensive reviews on the cancer chemopreventive and anti-cancer potential of RSV have been published, we currently summarize data appearing over the past 5 years. Molecular alterations observed with different carcinogenesis/cancer models (including lung, breast, prostate and colon) are illustrated in Fig. 2.

2.1. Skin

The first report on the cancer chemopreventive potential of RSV was against skin carcinogenesis [8]. In rodent models, skin cancer can be induced by the treatment with 7,12-dimethylbenz[*a*]anthracene (DMBA) plus 12-*O*-tetradecanoylphorbol-13-acetate (TPA), benzo[*a*]pyrene (BP), and UV irradiation [10,11]. To evaluate the skin cancer chemopreventive or anti-cancer capacity of RSV, *in vivo* studies have been conducted using DMBA/TPA [8,12–16], DMBA alone [17–21], TPA alone [22–24], DMBA/croton oil [25], UVB exposure [26–29], BP [18], and xenograft [30] models. Topical application of RSV is the most commonly used route of treatment in skin cancer models. In DMBA/TPA models, RSV treatment reduced the incidence [8,12–15], multiplicity [8,12,14,15], and tumor volume [14–16], and delayed the onset of tumorigenesis [14]. At biomarker levels, RSV induced apoptosis: RSV decreased the expression levels of Bcl-2 while it increased p53 and Bax. Also, RSV enhanced the release of cytochrome c, induced apoptotic protease-activating factor-1(APAF-1), and cleaved caspase-9,-3, and poly (ADP-ribose) polymerase (PARP) [14]. On the other hand, it decreased cell survival-related proteins including phosphatidylinositol-3-kinase (PI3K) and Akt [17], and inflammatory markers including *interleukin* (*IL*)*-6*, *cyclooxygenase-2* (*COX-2*), and c-Jun [16].

With UVB models, RSV decreased bi-fold skin thickness [26,27], hyperplasia [27], infiltration of leukocytes [27], and incidence [28], and delayed the onset of tumorigenesis [28]. In addition, biomarkers were affected by RSV treatment. Activities of ornithine decarboxylase (ODC) [26] and COX [26] and expression levels of ODC [26], proliferating cell nuclear antigen (PCNA) [27], cyclin-dependent kinase (CDK)2, CDK6, and cyclinD2 [27], mitogen-activated protein kinase kinase (MEK) [27], extracellular signal-regulated kinase (ERK) [27], survivin, and phosphorylated (p-)survivin were downregulated. On the other hand, the expression of p21 [27], p53 [27], and Smac/DIABLO [28] was upregulated. Furthermore, RSV exerted the antioxidant effect with the reduction of H_2O_2 and lipid peroxidation in the skin [26].

Notably, oral administration of RSV, but not topical treatment, also resulted in positive effects, including decreases in the tumor multiplicity [29] and volume [29], and delay in the onset of tumorigenesis [29]. The anti-tumor effect of RSV was associated with decreased expression levels of TGF-β1 [29] and Rictor [31], and increased expression levels of E-cadherin [29].

With the human cutaneous skin squamous carcinoma A431 cell line xenograft model, tumor volume was decreased by RSV treatment, along with increased expression levels of p53 and ERK [30], and decreased levels of survivin [30,32]. Although ERK is considered as a proliferation and survival protein in general, ERK was also reported to form a complex with p53, leading to an increase in p53 phosphorylation and expression [30]. Also, RSV enhanced the activation of caspase-3 [32].

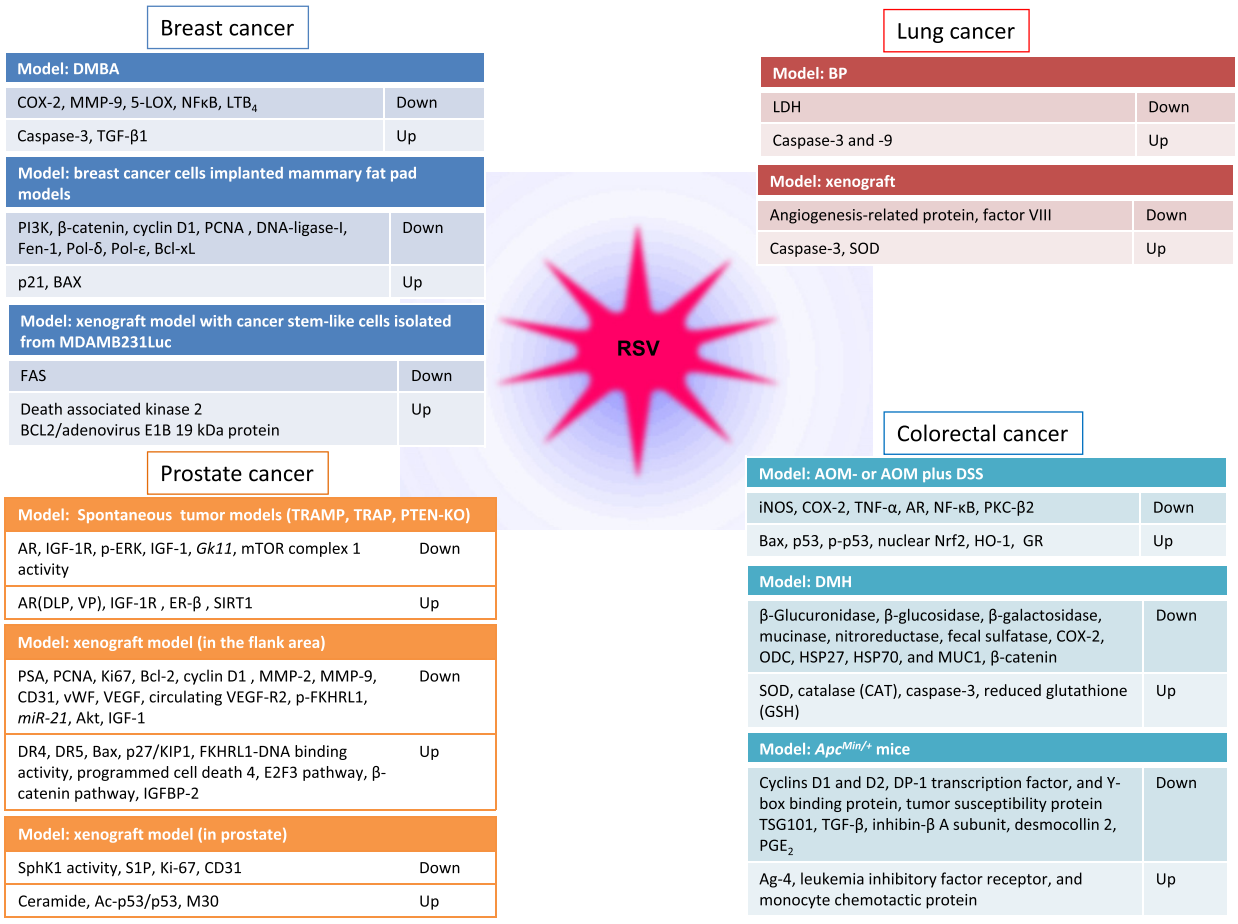

Fig. 2. Molecular alterations resulting from RSV intervention studies with select in vivo cancer models.

In addition, the antitumor effect of RSV was reduced with genetically engineered animals including TLR4 deficient C3H/HeJ mice in the DMBA model [19] and Sirtuin 1 (Sirt1)-null mice in the DMBA/TPA model [15].

Oral gavage of RSV inhibited the growth of a mouse melanoma (B16BL6 cell line) xenograft carried in mice, with decreased expression of Akt [33]. In another xenograft model with A2058 human melanoma cells, intratumoral injection of RSV reduced tumor volume and this was associated with inhibition of STAT3-DNA methyltransferase 1 (DNMT1) complex formation and the sequential decrease in the methylation of several tumor-suppressor gene (*PTPN6*, *CDKN2A*, and *SOCS3*) promoters [34]. On the other hand, tumor growth of other melanoma cell lines, including B16M [35], A375 [36], and Duke melanoma 738 xenografts in mice, was not attenuated by RSV, demonstrating limited potential as an anti-melanoma agent [37]. Topical administration of RSV reduced UVB-induced hyperpigmentation which is related to melanoma formation with a decrease in tyrosinase-related protein 2 in male brownish guinea pigs (KIWA:A1) [38].

The experimental conditions and outcomes with individual animal models are listed in Table 1.

2.2. Breast

Breast cancer is expected to be the most commonly diagnosed type of cancer and to rank second in cancer mortality among women in the United States in 2014, when excluding basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder [39]. RSV has displayed cancer chemopreventive and anti-cancer properties in certain types of breast cancer animal models. Chemically-induced mammary gland carcinogenesis models using DMBA [8], *N*-methyl-*N*-nitrosourea (MNU) [40], or estradiol [41], as well as spontaneous mammary tumor models using HER-2/*neu*-overexpressed [42] or *Brca1*-mutated (*K14cre*; $Brca1^{F/F}$; $p53^{F/F}$) mice [43], have been used to evaluate the preventive or curative effect of RSV. Among around 20 papers found from PubMed or SciFinder searches, the DMBA-induced model (7 publications) or xenograft in the hind flank region or the mammary fat pad (6 publications) is most commonly used.

Although some controversial studies exist indicating that RSV has no effect [43,44] or even enhances tumorigenesis [45,46], the majority of studies found that RSV can prevent tumorigenesis [34,40,42,47–51]. In DMBA-induced models, dietary supplementation with RSV reduced mammary tumor incidence associated with the alteration of biochemical markers in mammary tissue. RSV reduced the levels of lipid peroxidation [4-hydroxy-2-nonenal (4-HNE)] and DNA-single-strand breaks, inhibited the expression of COX-2, matrix metalloproteinase (MMP)-9, 5-lipoxygenase (5-LOX), nuclear factor-κB (NFκB), leukotriene B_4 (LTB_4; a main product of 5-LOX which can enhance proliferation and suppress apoptosis), and cyclin D1, and attenuated the activation of NFκB, while it increased caspase-3 activity and TGF-β1 expression in mammary tissues of rats [52,53]. With breast cancer cell implanted fat pad models using cigarette smoke condensate-transformed MCF-10A-Tr cells [50] or SUM159 cells [51], RSV downregulated the expression of cell proliferation/survival-related proteins (PI3K, β-catenin, cyclin D1, and PCNA), DNA repair-related proteins (DNA-ligase-I, Fen-1, Pol-δ, and Pol-ε), and anti-apoptotic protein (Bcl-xL), while it upregulated tumor suppressor gene, p21, and proapoptotic protein, Bax, in mammary tissue of mice [50,51].

Hyper-lipogenesis is a hallmark of cancer cell physiology [30]. RSV treatment suppressed the tumor growth of cancer stem-like cells isolated from MDAMB231Luc in a mouse xenograft model, accompanied by the suppression of fatty acid synthase (FAS) which is related

Table 1
Skin cancer preventive or anti-tumor effects of RSV in animal models (the entire period).

Species (F/M[1])	Dose	Duration	Model	Route	Major outcome	Marker	Year	Reference
CD-1 mice (F)	1,5,10,25 μmol	With TPA, twice/week for 18 weeks	DMBA/TPA	Topical	*Incidence↓ *Number of tumors per mouse↓	Not tested	1997	[8]
CD-1 mice (F)	1,5,10,25 μmol	30 min prior to TPA, for 4 h	TPA	Topical	Not applicable	*Activities*: MPO↓, GSSG reductase↓, SOD↑ *Expression*: c-*fos*↓, *TGF-β1*↓ H_2O_2↓, GSH↑	1998	[22]
ICR mice (F)	85 nmol	*One week prior initiation, *Twice/week with TPA for 20 weeks	DMBA/TPA	Topical	*Incidence↓ *Number of tumors per mouse↓	Not tested	2002	[12]
CD-1 mice	5,10,25 μmol	Twice/week with TPA for 18 weeks	DMBA/TPA	Topical	Incidence↓	Not tested	2002	[13]
SKH-1 mice	25 μmol	Single, 30 min prior to UVB exposure	UVB	Topical	*Bi-fold skin (dorsal and ear) thickness↓ *Infiltration of leukocytes↓	*Activities*: ODC↓, COX↓ *Expression*: ODC↓ H_2O_2↓, lipid peroxidation↓	2003	[26]
SKH-1 mice	10 μmol	7 times, alternate days, 30 min prior to UVB exposure	UVB	Topical	*Bi-fold skin thickness↓, *Hyperplasia↓, *Infiltration of leukocytes↓	*Expression*: PCNA↓, CDK2↓, CDK6↓, cyclin-D2↓, MEK↓, ERK2↓, p21↑, p53↑	2004	[27]
ICR mice (F)	1,5,25 μmol	Single, 30 min prior to TPA for 4 h	TPA	Topical	Not applicable	*Activities*: ERK↓, p38 MAPK↓ *DNA binding*: AP-1↓ *Expression*: COX-2↓, p-ERK↓	2004	[23]
SKH-1 mice (F)	25, 50 μmol	30 min before or 5 min after UVB exposure, twice/week for 28 weeks	UVB	Topical	*Incidence↓ *Onset of tumorigenesis↓	Survivin↓, p-survivin↓, smac/DIABLO↑	2005	[28]
Swiss albino mice (M)	50 μM, 200 μL (10 nmol)	RSV for 3 weeks → DMBA → TPA (3×/week, for 24 weeks)	DMBA/TPA	Topical	*Incidence↓ *Onset of tumorigenesis↓ *Number of tumors per mouse↓	Bcl-2↓, p53↑, Bax↑, release of cytochrome c↑, APAF-1↑, cleaved caspase-9,-3, and PARP↑	2008	[14]
Swiss albino mice (M)	50 μM, 200 μL (10 nmol)	DMBA → TPA (RSV 1 h prior to TPA, 3×/week, for 24 weeks)	DMBA/TPA	Topical	*Incidence↓ *Onset of tumorigenesis↓ *Number of tumors per mouse↓ *Tumor volume/mouse↓	Bcl-2↓, p53↑, Bax↑, release of cytochrome c↑, APAF-1↑, cleaved caspase-9,-3, and PARP↑	2008	[14]
Swiss albino mice (F)	16 μmol	Single, 1 h prior to BP for 24 h	BP	Topical	Not applicable	*Activity*: Ethoxy-resorufin dealkylase (ROD)↓, methoxy-ROD↓, penthoxy-ROD↓, NQO1↑	2008	[18]
Swiss albino mice (F)	16 μmol	Single, 1 h prior to DMBA for 24 h	DMBA	Topical	Not applicable	*Activity*: NQO1↓	2008	[18]
Balb/c mice (F)	16 μmol	Single, 15 min prior to TPA for 1–12 h	TPA	Topical	Not applicable	*Activity*: IKKβ↓, 20S proteasome↓ *Expression*: nuclear p65↓, IκBα↑, c-Jun↓, COX-2↓, iNOS↓ *DNA binding*: c-Jun↓, p65↓, p50↓	2008	[24]
TLR4 competent C3H/HeN mice, TLR4 deficient C3H/HeJ mice	10 μmol	1 h prior to DMBA, for 25 weeks	DMBA	Topical	*Incidence↓ *Number of tumors per mouse↓ *Tumor volume/mouse↓ (In C3H/HeJ mice: the effects were diminished.)	VEGF↓, MMP-2↓, MMP-9↓, IFN-γ↑, IL-12↑ (*The effects were diminished in C3H/HeJ mice.*)	2009	[19]
Normal ($SirT1^{+/+}$ or $SirT1^{+/-}$) and SirT1-null mice	25 μmol	With TPA, once/week for 15–22 weeks	DMBA/TPA	Topical	*Incidence↓ *Number of tumors per mouse↓ *Tumor volume/mouse↓ (The effects were reduced but not ablated in SirT1-null mice.)	None	2009	[15]
Swiss albino mice (F)	25, 50 μM/200 μL (5,10 nmol)	1 h prior to DMBA, thrice/week for 28 weeks	DMBA	Topical	*Incidence↓ *Number of tumors per mouse↓ *% of tumor free survival↓ *Tumor volume/mouse↓	p53↑, Bax↑, release of cytochrome c↑, caspases activation↑, Apaf-1↑, Bcl-2↓, PI3K↓, Akt↓ survivin↓	2009	[17]
SENCAR mice (F)	5 μmol/mouse 20 min prior to DMBA	Twice/week, for 4 weeks	DMBA	Topical	Epidermal thickness↓	Not significant	2010	[21]
Highly tumor-susceptible $p53^{+/-}$/SKH-1 mice	200 mg/kg/day	3×/week for 2 weeks prior to UVB exposure, total 27 weeks	UVB	Oral gavage	*Onset of tumorigenesis↓ *Number of tumors per mouse↓ *Tumor volume per mouse↓	TGF-β1↓, E-cadherin↑	2011	[29]
$p53^{+/-}$/SKH-1 mice	200 mg/kg/day	3×/week for 2 weeks prior to UVB exposure, total 27 weeks	UVB	Oral gavage		Rictor↓	2012	[31]
SENCAR mice (F)	2.5 μmol	20 min prior to DMBA	DMBA/TPA	Topical	*Number of tumors per mouse↓	*IL-6*↓, c-Jun↓	2013	[16]
SENCAR mice (F)	2.5 μmol	20 min prior to TPA, twice/week up to 14 weeks	DMBA/TPA	Topical	*Epidermal proliferation↓ *Epidermal thickness↓	*IL-6*↓, *COX-2*↓, c-Jun↓	2013	[16]
Nude mice	10, 20, 40 μg	14 days	Xenograft, A431 cells	i.p.	Xenograft volume↓	p53↑, ERK↑, survivin↓	2013	[30]

[1] F: female, M: male.

to lipogenesis and over-expressed in various cancers. Consequently, proapoptotic markers including death associated kinase 2 and BCL2/adenovirus E1B 19 kDa protein interacting protein 3, which are inhibited by FAS via ceramide synthesis, were induced by RSV [54].

In an estradiol-induced model with female ACI rats, RSV decreased the expression level of DNMT3b, miR21, -129, -204, and -489 in tumor but increased these factors in normal tissues [41]. Moreover, with rats, RSV prevented mammary carcinogenesis of offspring. Gestational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin leads to CpG methylation of the breast cancer-1 (BRCA-1) gene and the subsequent reduction of BRCA-1 expression in the mammary tissue of offspring. Pretreatment with RSV partially reversed the changes by upregulating the expression of aromatic hydrocarbon receptor (AhR) repressor (AhRR) [55].

A summary of studies is given in Table 2.

2.3. Prostate

Prostate cancer is expected to be the most commonly diagnosed type of cancer and to rank second in cancer mortality among men in the United States in 2014, when excluding basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder [39]. Two experimental models to evaluate the cancer chemopreventive or anti-cancer capacity of RSV were employed primarily, including spontaneous tumor models using genetically modified rodents or xenograft models in which prostate cancer cells were inoculated into the flank area subcutaneously, or into the prostate.

With transgenic mouse models, dietary consumption of RSV attenuated prostate tumorigenesis. For instance, with the transgenic adenocarcinoma mouse prostate (TRAMP) model, RSV reduced grade 4 and 6 lesions of prostatic adenocarcinoma and decreased cell proliferation in the dorsolateral (DLP) and ventral prostate (VP) [56]. With the transgenic rat for adenocarcinoma of prostate (TRAP) model, RSV reduced the content of prostatic neoplastic lesions [57,58] with inhibiting cell proliferation in the ventral prostate [58]. With prostate-specific phosphatase and tensin homolog (PTEN)-knockout mouse model, the incidence of both mouse prostatic intraepithelial neoplasia (mPIN) lesions [59] and high-grade prostatic intraepithelial neoplasia (HGPIN) lesions [60] was reduced by RSV, with a decrease in p-S6 kinase (S6K) and an increase of Sirt1 in prostate tissue. These results suggest that RSV exerts an anti-tumor effect via Sirt1/S6K-mediated autophagy [60].

In xenograft models with androgen receptor (AR)-positive LNCaP or LNCaP-Luc human prostate cancer cells, pretreatment and post-treatment of RSV upon cell inoculation exhibited different efficacies. Treatment with RSV via the diet (6 or 12 mg/kg/day) [61] and oral gavage (50 mg/kg/day, every other day) [62] starting 2 weeks prior to inoculation of cells in nude mice delayed tumor growth, whereas supplementation with RSV (50 mg/kg/day) in the Western diet 3 weeks after inoculation in SCID mice had no effect on survival [63]. In castrated nude mice, RSV (4 g/kg diet) intervention just 1 day after implantation, reduced tumor volume, and this was associated with a reduction of β-catenin-mediated AR function via downregulating the expression of hypoxia-inducible factor 1-alpha (HIF-1α) [64].

With AR-negative PC-3 human prostate cancer cell xenografts in the flank area of mice, post-treatment of oral RSV (30 mg/kg/day) reduced tumor volume with decreases in tumor cell proliferation and neovascularization and induction of apoptosis [65].

In addition, intraperitoneal post-treatment with RSV (25 mg/kg/day) reduced the tumor volume with PC-3 cell xenografts in the prostate of mice [66]. However, the anti-tumor effect of RSV diminished in xenografts with sphingosine kinase-1 (SphK1)-transfected PC-3 cells, which demonstrated that SphK1, an enzyme facilitating the conversion of the sphingosine (proapoptotic) into S1P (prosurvival), is a target for RSV. Also, intraperitoneal post-treatment of RSV (50 mg/kg/day) in orthotopic Du145 cell xenografts in the prostate reduced tumor growth, progression, local invasion, and spontaneous metastasis. The effect of RSV decreased with metastasis-associated protein 1 (MTA1)-knockdown Du145 cell xenografts indicating that MTA1 plays a crucial role in anti-tumor effect of RSV [67].

Experimental conditions and outcomes with individual animal models are listed in Table 3.

2.4. Lung

Lung cancer is expected to be the second most commonly diagnosed type of cancer and to rank first in cancer mortality among men and women in the United States in 2014, when excluding basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder [39]. In animal models, a variety of agents are known to induce lung carcinogenesis, including nitrosamine 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), diethylnitrosamine (DEN), BP, vinyl carbamate, uracil mustard, urethane, and MNU [11]. Using BP plus NNK [69] or BP only [70] in mouse models, RSV supplemented in the diet had no effect on lung tumor multiplicity [69], the expression levels of CYP1A1 and CYP1B1 [70], or the level of BP protein adduct [70]. On the other hand, RSV treatment in the BP-induced mouse lung carcinogenesis model reduced the level of BP diolepoxide (BPDE)-DNA adduct [71], improved ultrahistoarchitecture [72], decreased the development of tumor nodules with increased pulmonary caspase-3 and -9 activities, and decreased glucose uptake/turnover and serum lactate dehydrogenase (LDH) activity (It is elevated in cancer cells involving cancer cell metabolism) and p-p53 levels at Ser15 (Its hyperphosphorylation can lead to the inactivation of p53) [73].

With Lewis lung carcinoma cell xenograft models, RSV treatment attenuated tumor growth [74–77], and this was associated with increased apoptosis accompanied by elevated TUNEL-positive cells [75,76] and caspase-3 activity [75] and reduced angiogenesis-related protein, factor VIII [75] in tumors, and decreased oxidative stress along with an increase in superoxide dismutase (SOD) activity and a decrease in malondialdehyde (MDA) content in serum [77].

Over the past 5 years, it has been found that RSV treatment attenuated the growth of A549 [78,79] and MSTO-211H [80] xenografts in mice. Several biochemical/molecular alterations occurred with RSV administration: RSV suppressed tumor fluorodeoxyglucose (^{18}F-FDG) uptake (a marker for the tissue uptake of glucose) in Lewis lung carcinoma xenograft mice [81], increased cleavage of caspase-3 (apoptosis marker), and reduced specificity protein 1 (Sp1; highly expressed in various cancers) in MSTO-211H-bearing mice [80]. Forkhead box protein C2 (FOXC2) was reported to enhance tumor metastasis and induce epithelial to mesenchymal transition (EMT). One study with mice demonstrated that the anti-tumor effect of RSV in A549 xenografts was diminished in FOXC2—overexpressing A549 xenografts, suggesting that RSV possibly exerts anti-tumor activity via FOXC2 [79].

The experimental conditions and outcomes with individual animal models are listed in Table 4.

2.5. Colon

Colorectal cancer is expected to be the third most commonly diagnosed type of cancer and rank third in cancer mortality among men and women in the United States in 2014, when excluding basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder [39]. In addition to using genetically modified animals such as *Apc*$^{Min/+}$ mice and *Apc*$^{Pirc/+}$ rats, chemical carcinogens induce colon cancer, including azoxymethane (AOM), AOM plus dextran sulfate sodium (DSS), 2-amino-3-methylimidazo[4,5-*f*]quinoline, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine, and 1,2-dimethylhydrazine (DMH) [10,11,82]. The histopathological and pathophysiological manifestations/features of colon cancers can be observed, including hyperplasia, aberrant crypt foci (ACF), adenoma, and adenocarcinoma [82].

In AOM- or AOM plus DSS-induced models, oral administration (in the diet or gavage) of RSV reduced the incidence [83,84], multiplicity

Table 2
Breast cancer preventive or anti-tumor effects of RSV in animal models (the entire period).

Species (F/M[1])	Dose	Duration	Model	Route	Major outcome	Marker	Year	Reference
Sprague–Dawley rats (F)	10 and 100 mg/kg/day	5 days/week, 1 week before MNU injection, for ~17 weeks	MNU	Oral gavage	*Incidence↓ *Number of tumor/rat↓	Not available	2001	[40]
Sprague–Dawley rats (F)	100 μg/rat/day	1 week before DMBA, for 127 days	DMBA	In diet	*No effect on tumor volume *Incidence↓ *Multiplicity↓ *Latency period of tumor development↑	COX-2↓, MMP-9↓, NFκB activation↓	2002	[52]
FVB/N HER-2/*neu* mice (F)	4 μg/mouse/day	Starting from week 20, for ~2 months	Spontaneous mammary tumor	In drinking water	*Onset of tumorigenesis↓ *Tumor volume↓ *Multiplicity↓	HER-2/*neu* (mRNA)↓	2005	[42]
Sprague–Dawley CD rats (F)	50, 100 mg/kg/day	Whole life time	DMBA	In diet	*Multiplicity↓ *Latency period of tumor development↑ *Differentiated lobular structures of mammary glands↑ *Proliferative cells in mammary terminal ductal structures↓	Not available	2006	[47]
Athymic mice (F)	25 mg/kg/day	Daily after tumor size reached 40 mm^3 for 3 weeks	Xenograft with MDA-MB-231 cells	i.p.	*Tumor volume↓ *TUNEL staining↓ *Microvessel density↓	Not available	2006	[48]
Sprague–Dawley rats (F)	0.2 mg/kg/day	Daily, for ~14 weeks (from 40 days until 20 weeks of age)	DMBA	Oral gavage	*Number of 8-OHdG and 8-isoPGF$_{2\alpha}$ contents in tumors↓ *Incidence↓	Protein carbonyl (Oxidized protein)↓	2009	[49]
Sprague–Dawley rats (F)	100 μg/rat/day	19 weeks	DMBA	In diet	*Lipid peroxidation↓ *DNA damage↓ *Cell proliferation↓ *Apoptosis↑	*Activity*: Caspase-3↑ *Expression*: 5-LOX↓, TGF-β1↑, NFκB p65↓, LTB_4↓	2011	[53]
Athymic nude mice	25 mg/kg/day, twice/week starting when tumor volume reached ~150 mm^3	Day 7–26 (20 days)	Xenograft, MDA-MB468 cells	i.p.	Tumor volume↓	Not available	2012	[34]
Balb/c mice (F)	40 mg/kg/day	30 days	Xenograft in mammary fat pad with cigarette smoke condensate-transformed, MCF-10A-Tr cells	Oral gavage	Tumor volume↓	p21↑, PI3K↓, NFκB↓, Bcl-xL↓, cleaved PARP↑, BAX↑, PCNA↓, Fen-1↓, Pol-δ↓, Pol-ε↓, H2AX↑	2014	[50]
Nonobese diabetic/severe combined immunodeficient mice (NOD/SCID) (F)	100 mg/kg/d, daily	14 days	Xenograft in mammary fat pads with SUM159 cells	i.v.	*Tumor growth↓ *breast cancer stem cell population in tumor cells↓ *Aldehyde dehydrogenase-positive populations in tumor cells↓	β-Catenin↓, cyclin D1↓	2014	[51]

[1] F: female, M: male.

Table 3
Prostate cancer preventive or anti-tumor effects of RSV in animal models (the entire period).

Species (F/M[1])	Dose	Duration	Model	Route	Outcome	Marker	Year	Reference
Heterozygous TRAMP (M)	625 mg/kg diet	7 or 23 weeks	Spontaneous prostate tumor	In diet	*Incidence of poorly differentiated prostatic adenocarcinoma (Grade 6 lesions)↓ *Progression of well differentiated (Grade 4 lesions)↓	*Dorsolateral prostate* (*DLP*): Androgen receptor (AR)↑, ER-β↑, IGF-1↓, IGF-1R↑, p-ERK1↓ *Ventral prostate* (*VP*): IGF-1R↓, p-ERK1↓ p-ERK2↓	2007	[56]
Heterozygous TRAP rats (M)	7.6, 16.1, or 30.1 mg/kg/day	7 weeks	Spontaneous prostate tumor	Drinking water	*Serum testosterone↓ (not 200 μg/mL) *Prostatic neoplastic lesions↓ *Numbers of apoptotic cells↑ **No significant* differences in the incidences of PIN or adenocarcinoma **No difference* in Ki-67	*Serum*: testosterone↓ *Ventral prostate*: AR↓, androgen responsive gene, *Gk11*↓	2008	[57]
Athymic nude mice (Balb/cAnNCr-*nu*/*nu*) (M)	6 or 12 mg/kg/day	Starting 2 weeks before implantation, total 9 weeks	Xenograft, LNCaP cells	In diet	*Tumor growth↓ *Apoptosis↓ *Microvessel formation↑ (PECAM-1 staining↑)	Prostate-specific antigen (PSA)↓	2008	[61]
Homozygous PTEN knockout mice (M)	50 mg/kg/day	3 times a week, total 7 weeks	Spontaneous prostate tumor	Oral gavage	*The mean genitourinary tract and prostate weights↓ *The incidence of mouse prostatic intraepithelial neoplasia (mPIN) lesions↓ *Regression of adenocarcinomas↓	Not available	2009	[59]
TRAP rats (M)	15 mg/kg/day	30 weeks	Spontaneous prostate tumor	In diet	*Incidence (Grades 4–6)↓ *21% prostate cancer free (CTL: 2% free) *Cell proliferation in the VP↓ (not DLP) *Apoptosis in the VP↑	*Ventral prostate*: IGF-1↓, AR↑	2009	[58]
Athymic nude mice (Balb/c nu/nu)	30 mg/kg/day	Thrice/week, beginning when tumor volume reached about 100 mm^3, total 6 weeks	Xenograft, PC-3 cells	Oral gavage	*Tumor volume↓ *Cell proliferation↓ *Apoptosis↑ *Number of blood vessels↓	PCNA↓, Ki67↓, death receptor (DR4)↑, DR5↑, Bax↑, Bcl-2↓, p27↑, cyclin D1↓, MMP-2↓, MMP-9↓, CD31↓, von Willebrand Factor↓, VEGF↓, circulating VEGF-R2↓, p-FOXO3a↓, FOXO3a-DNA binding activity↑	2010	[65]
NMRI/Nu (*nu*/*nu*) mice (M)	25 mg/kg/day	Daily, 10 days after implantation, total 2 weeks	Intraprostatic xenograft, PC-3, PC-3/neo, or PC-3/SphK1 cells	i.p.	*Tumor volume↓ (no effect with PC-3/SphK1 cells)	SphK1 activity↓, ceramide↑, S1P↓	2010	[66]
SCID mice (M)	20 mg/kg/day	Alternate days, starting 1 week before implantation until the end of the study, total 39 days	Xenograft, PC-3 M-MM2 (highly invasive) cells	Oral gavage	*Tumor volume↓ *Tumor weight↓	*miR-21*↓, Akt↓, programmed cell death 4↑	2012	[68]
PTEN knockout mice	0.1% and 2% in diet	14 weeks	Spontaneous prostate tumor	In diet	*Prostate weight↓ *Incidence of high-grade prostatic intraepithelial neoplastic (HGPIN)↓	*Prostate*: mTOR complex 1 activity↓ Sirt1 expression↑	2013	[60]
Nude mice (M)	50 mg/day	2 weeks after implantation, total 42 days	Xenograft, CWR22 cells	Osmotic mini pump, s.c.	*No effect compared with controls*	Cyclin D1↓	2013	[37]
Nude mice		Alternate days, starting 2 weeks before implantation, total 7 weeks	Xenograft, LNCaP-Luc cells	Gavage	Tumor growth↓	Not available	2013	[62]
SCID mice	50 or 100 mg/kg/day	3 weeks after injection, total ~150 days	Xenograft, LAPC-4 cells	In Western diet	*Survival in 50 mg/kg/day (not 100 mg/kg/day)↑ *IGF-1/IGFBP-3 ratio (a measure of free IGF-1)↓	Insulin↓, IGF-1↓, E2F3 pathway↑, β-catenin pathway↑	2013	[63]
SCID mice	50 mg/kg/day	3 weeks after implantation, total ~150 days	Xenograft, LNCaP cells	In Western diet	No effect on survival	IGFBP-2↑	2013	[63]
Nude mice (M)	50 mg/kg/day	Daily, 14 days after implantation, total 6 weeks	Xenograft in anterior prostate, Du145-EV-Luc or Du145-MTA1shRNA-Luc	i.p.	*In Du145-EV-Luc*: *Tumor growth↓ *Progression, local invasion↓ *Spontaneous metastasis↓ *Angiogenesis↓ *Apoptosis↑	Ki-67↓, p53 acetylation↑, M30 (apoptosis)↑ CD31 (microvessel)↓	2013	[67]
Balb/cSlc-*nu*/*nu* castrated mice (M)	4 g/kg diet	1 day after implantation, total 40 days	Xenografts, LNCaP cells	In diet	*Tumor volume/weight↓	HIF-1α↓, hypoxia-responsive genes (*VEGF*, *PSA*)↓ cytosolic β-catenin↑	2014	[64]

[1] F: female, M: male.

Table 4
Lung cancer chemopreventive or anti-tumor effects of RSV in animal models (the entire period).

Species (F/M[1])	Dose	Duration	Model	Route	Outcome	Marker	Year	Reference
A/J mice	500 ppm in diet	Starting 1 week after the final dose of BP and NNK, 18 weeks	BP and NNK	In diet	No effect on lung tumor multiplicity	Not available	1999	[69]
C57BL/6 strain mice (F)	0.6, 2.5 or 10 mg/kg/day	Daily, 21 days	Xenograft, LLC tumors	i.p.	*Tumor volume/weight↓ *Metastasis to lung↓	Not available	2001	[74]
Balb/c mice	50 mg/kg/week	5 weeks	BP	s.c.	*BPDE-DNA adduct induction↓ *Apoptosis (TUNEL)↓ (a reversal to the normal condition)	CYP1A1↓	2003	[71]
A/JOlaHsd mice (F)	0.4% in diet (6–8 mg/kg/day)	1 week prior to BP exposure, 9 weeks or 9 weeks + 5 months	BP	In diet	*No significant effect on BP tetrol I-1 protein adducts *No effect on multiplicity	CYP1A1 (−)	2004	[70]
C57BL/6 mice (F)	20 mg/kg, daily	4 days after implantation, 17 days	Xenograft, LLC tumors	i.p.	*Tumor volume/weight↓ *Apoptosis (TUNEL)↑	Caspase-3↑, PCNA↓, Factor VIII↓	2006	[75]
Nude mice	15, 30, or 60 mg/kg	Daily after 7–8 days of implantation, 15 days	Xenograft, A549	i.v.	Tumor volume↓	Not available	2013	[78]
SCID mice	20 mg/kg/day	Daily, 6 weeks	Xenograft, A549/VC or A549/FOXC2	i.p.	Tumor volume↓ (the effect was decreased on A549/FOXC2 xenograft)	Not available	2013	[79]
Laka mice (M)	5.7 μg/mL	Thrice a week, 10 days before BP, total 22 weeks	BP	Oral gavage	*Tumor nodules↓	Caspase-3, -9 activity↑ LDH activity↓	2014	[73]

[1] F: female, M: male.

[83,85,86], and individual size [85] of ACF in rodent models with the alteration of biomarkers. RSV increased the expression of Bax [85], p53 and p-p53 at Ser15 [83], heme oxygenase-1 (HO-1) [86], glutathione reductase (GR) [86], and nuclear localized nuclear factor (erythroid-derived 2)-like 2 (Nrf2) [86], whereas it decreased the expression of inducible nitric oxide synthase (iNOS) [83,86], COX-2 [83,86], tumor necrosis factor alpha (TNF-α) [83], aldose reductase [86], NFκB [86], and p-protein kinase C-β2 (PKC-β2) [86]. It is suggested that RSV down-regulated aldose reductase-dependent activation of PKC-β2 and NFκB, with a subsequent decrease in the expression level of iNOS and COX-2 [86].

In DMH-induced models, RSV reduced the incidence [87], multiplicity [87–89], size [87,88] of ACF, histopathological lesions [87], and DNA damage in leukocytes [90]. The anti-tumor effect of RSV against colon carcinogenesis is accompanied by the alteration of enzyme activities: In rat models, the activities of antioxidant enzymes including SOD and catalase (CAT) in the intestine/colon [88], liver [91], and erythrocytes [90] were increased, while the activities of biotransforming enzymes including β-glucuronidase, β-glucosidase, β-galactosidase, mucinase, and nitroreductase in colonic mucosal and fresh fecal samples were decreased [87]. In addition, the expression levels which are altered by DMH in rats were normalized by RSV treatment: RSV reduced the expression levels of COX-2, ornithine decarboxylase (ODC), heat shock protein (Hsp)27, Hsp70, and MUC1 in colonic mucosa [92], and β-catenin in ACF [93], whereas it induced the expression levels of caspase-3 in colonic mucosa [92] and glutathione, reduced state (GSH), in the intestine/colon [88], liver [91], erythrocytes [90], and plasma [90]. With genetically modified mouse models (e.g. $Apc^{Min/+}$ mice [94–96], and mice with *APC* locus knockout and activated *Kras* [97]), supplementation with RSV inhibited the formation of colon tumors [94–97] and dysplasia occurrence [96]. At the mRNA level, RSV down-regulated i) cell survival-related mRNA (*cyclins D1* and *D2*, *DP-1 transcription factor*, and *Y-box DNA-binding protein*), and upregulated ii) recruitment and activation of immune cell-related mRNAs (*cytotoxic T lymphocyte Ag-4*, *leukemia inhibitory factor receptor*, and *monocyte chemotactic protein 3*), and iii) carcinogenic process and tumor expansion-related mRNA (*tumor susceptibility protein TSG101*, *TGFβ*, *inhibin-βA subunit*, and *desmocollin 2*) in small intestinal mucosa [94]. At the miRNA level, RSV induced the expression of *miR-96*, which regulates *Kras* translation [97]. In addition, RSV reduced levels of PGE_2 in the intestine [95].

The experimental conditions and outcomes with individual animal models are listed in Table 5.

2.6. Liver

Hepatocarcinogenesis can be induced by DEN, DEN plus phenobarbital, aflatoxin, CCl_4, thioacetamide, peroxisome proliferators, and a choline deficient diet in animal models. Also, it can be observed in genetically engineered models including hepatitis virus transgenic and Mdr2 knockout models [99]. RSV treatment, either at early or advanced stages of hepatocarcinogenesis, has been shown to be effective. The experimental conditions and outcomes with individual animal models are listed in Table 6.

From the late 1990s, the chemopreventive effects of RSV on liver carcinogenesis with decreased incidence [100,101] and nodules number [100,101] in animal models using chemical inducers [e.g., DEN [101–104], DEN plus phenobarbital [100], and DEN plus 2-acetylaminofluorene (2-AAF)] [105] or using transgenic mice [e.g., hepatitis B virus X protein (HBV X)-expressing transgenic mouse] [106], as well as the anti-tumor effects of RSV on xenograft models with hepatoma cell lines (e.g., AH-130 [107], H22 [108,109], AH109A [110], Bel-7402 [111], and HepG2 [112]) have been reported. The majority of studies showed that RSV reduced total tumor cell number [107], tumor growth [108,109], tumor weight [110], and angiogenesis/microvessel density [113] with rodent hepatoma

Table 5
Colon cancer preventive or anti-tumor effects of RSV (the entire period).

Species (F/M[1])	Dose	Duration	Model	Route	Outcome	Marker	Year	Reference
F344 rats (M)	200 μg/kg/day	Starting at 10 days before AOM treatment, total 100 days	AOM	In drinking water	*Number of ACF/colon↓ *Large ACF↓	*ACF*: Bax↑	2000	[85]
C57BL/6J *ApcMin* mice (M)	0.01% in drinking water (0.3–0.4 mg/kg/day)	From 5-week-old, total 7 weeks	Spontaneous tumor model	In drinking water	Colon and small intestinal tumors↓	*Small intestinal mucosa*: **Cyclins D1* and *D2*↓, *DP-1 transcription factor*↓, *Y-box DNA-binding protein*↓ **Cytotoxic T lymphocyte Ag-4*↑, *leukemia inhibitory factor receptor*↑, *monocyte chemotactic protein 3*↑ **Tumor susceptibility protein TSG101*↑, *TGFβ*↓, inhibin-βA subunit↑, *desmocollin 2*↑	2001	[94]
C57BL/6J $Apc^{Min/+}$ mice (M)	4, 20, or 90 mg/kg/day	From 43-day-old, total 7 weeks	Spontaneous tumor model	In diet	*No effect* on intestinal tumor load in the small or large intestine	*No changes in *COX-2* expression *PGE_2 levels of small intestinal tumors↓	2004	[98]
C57BL/6J $Apc^{Min/+}$(M)	0.05% or 0.2% in the diet (60 and 240 mg/kg/day)	From 4-week-old, total 3 weeks	Spontaneous tumor model	In diet	Adenoma load↓	*PGE_2* levels in the intestinal mucosa↓	2005	[95]
Wistar rats (M)	8 mg/kg/day	Daily, starting on the day of DMH injections till the end of study (the entire period), total 30 weeks	DMH	Oral	*Multiplicity, size, total number of ACF↓	*Intestine and colon*: *Levels*: Diene conjugates↑, lipid hydroperoxides↑, TBARS↑, GSH↑, vitamin C↓ α-tocopherol↓ *Activity*: SOD↑, CAT↑, GPx↓, GST↓, GR↑	2006	[88]
Wistar rats (M)	8 mg/kg/day	Daily, starting on the day of DMH injections till the end of study (the entire period), total 30 weeks	DMH	Oral gavage	*Incidence↓, *Tumor volume↓, *Tumor burden/rat↓ *Histopathological lesions DMH↓	*Colonic mucosal and fresh fecal samples*: *Activity*: β-Glucuronidase↓, β-glucosidase↓, β-galactosidase↓, mucinase↓, nitroreductase↓ *Fresh fecal samples*: sulfatase activity↓	2006	[87]
Wistar rats (M)	8 mg/kg/day	Daily, starting on the day of DMH injections till the end of study (the entire period), total 30 weeks	DMH	Oral gavage	*Number of argyrophilic nucleolar organizing region-associated proteins (AgNORs) per nucleus↓	*Liver*: SOD↑, CAT↑, GSH↑, TBARS↓	2006	[91]
Wistar rats (M)	8 mg/kg/day	Daily, starting on the day of DMH injections till the end of study (the entire period), total 30 weeks	DMH	Oral gavage	Not available	*Colonic mucosa*: COX-2↓, ODC↓, Hsp27↓, Hsp70↓, Caspase-3↑, MUC1↓	2009	[92]
Wistar rats (M)	4, 8, or 12 mg/kg/day	Daily, starting on the day of DMH injections till the end of study (the entire period), total 2 weeks for DNA damage study, total 30 weeks for oxidative stress	DMH	Oral gavage	DNA damage in the leukocyte↓	*Plasma*: TBARS↓, GSH↑, TRAP↑, vitamins C and E↑, β-carotene↑ *Erythrocyte*: *Levels*: GSH↑ *Activity*: SOD↑, CAT↑, GR↑, GPx↑, GST↑	2009	[90]
C57BL/6 mice (M/F)	300 ppm in diet (48 mg/kg/day)	62 days	AOM/DSS	In diet	*Colon tumor incidence↓ *Number of tumors/animal (multiplicity)↓ *Neutrophil infiltration [Number of neutrophils in mesenteric lymph nodes (MLN) and lamina propria (LP) sites]↓	*Colon*: iNOS↓, COX-2↓, TNF-α↓, p53↑, p-p53 (Ser15)↑ *T cells in MLN and LP*: *TNF-α↓, IFN-γ↓	2010	[83]
Sprague–Dawley rats (M)	60 mg/kg/day	49 days	DMH	Oral	*ACF↓ *Mucin depleted foci↓	Not available	2010	[89]
Balb/c mice (M)	50 or 250 ppm	Twice/week for 2 weeks (total 4 times) along with RSV 50, or 250 ppm in diet → RSV diet for 22 weeks, total 6 or 24 weeks	AOM	In diet	*Total number of aberrant crypt foci (ACF) and aberrant crypts (AC)↓ *Lymphoid nodule (LN) numbers↓	*Colonic mucosa*: *6 weeks after the first AOM injection* iNOS↓, COX-2↓, aldose reductase↓, HO-1↑, GR↑ *12 weeks after the first AOM injection* iNOS↓, COX-2↓, p-PKCβ2↓, and p-p65↓ *Colonic ACF*: Expression and nuclear localization of Nrf2↑, aldose reductase↓	2011	[86]
Wistar rats (M)	10, or 20 mg/kg/day	After induction of cancer, total 10 weeks	EDTA/DMH	Oral	Not available	β-Catenin in ACF↓	2012	[93]
Wistar rats (M)	2 g/kg diet	2 weeks after the last AOM, total 7 weeks	AOM	In diet	*ACF incidence↓ *Inflammation and oxidation-related metabolites↓ *Mitochondrial disruption↓ *Reversal of altered metabolites↑	*Colonic tissue*: Glucose↑, β-hydroxybutyrate (ketone body)↑, hypoxanthine↑, branched chain amino acids (isoleucine and valine)↓, tryptophan↓ *Serum*: Aminooxyacetate↓ *Urine*: 4-Hydroxyphenylacetate↓, xanthurenate↓	2012	[84]
Apc^{Min} mice (M)	45 μg/kg/day	From 6-week-old, co-administration with BP, total 60 days	BP	Oral gavage	*Number of colon adenomas↓ *Dysplasia occurrence↓	Not available	2013	[96]

[1] F: female, M: male.

Table 6
Liver cancer preventive or anti-tumor effects of RSV in animal models (the entire period).

Species (F/M[1])	Dose	Duration	Model	Route	Outcome	Marker	Year	Reference
Wistar rats (M)	1 mg/kg/day	Daily, 7 days	Xenograft, AH-130 cells	i.p.	*No effect on tumor volume *Total tumor cell number↓ *Cells in G2/M phase↑	Not available	1999	[107]
Balb/c mice	500, 1000, 1500 mg/kg/10 day	Starting on 2nd day after implantation, 10 days	Xenograft, H22 cells	i.p.	Tumor growth↓	Not available	2003	[108]
Balb/c mice	5, 10 or 15 mg/kg/day	Starting 24 h after implantation, 10 days	Xenograft, H22 cells	i.p.	Tumor growth↓	Cyclin B1↓, p34cdc2↓	2003	[109]
Donryu rats (M)	10, 50 ppm	20 days	Xenograft, AH109A cells	In diet	*RSV showed trends, but not significant.* *Tumor weigh↓ *Metastasis↓ *Excretion of neutral sterols and bile acids into feces↑	*Serum*: TBARS↓, triglyceride↓ (VLDL + LDL)-cholesterol↓	2003	[110]
Pathogen-free Sprague–Dawley rats (F)	50, 100 or 300 mg/kg/day	Starting 4 weeks prior to initiation, total 24 weeks	DEN/phenobarbital	In diet	*Incidence↓ *Total number and multiplicity of visible hepatocyte nodules↓ *Mean nodular volume and nodular volume as percentage of liver volume↓ *Cell proliferation↓ *Apoptotic cells↑	Bax↑, Bcl-2↓	2009	[100]
Balb/c-nu nude mice (F)	15 mg/kg/day	Daily, starting at day 10 after tumor cell inoculation, total 21 days	Xenograft, HepG2 cells with different stable transfectants (none, He-CAV1, He-CAVM1, He-CAVM2, He-GFP and He-CAVRNAi)	i.p.	*Tumor growth in HepG2 cells (wild type or expressing one of the various mutant constructs)↓ with more dominant in xenografts of HepG2 cells stably expressing CAV1	Not available	2009	[112]
Sprague–Dawley rats (F)	50, 100 or 300 mg/kg/day	Starting 4 weeks prior to initiation, total 24 weeks	DEN/phenobarbital	In diet	Not available	HSP70↓, COX-2↓ nuclear NFκB↓ cytosolic IκB↑	2010	[114]
Sprague–Dawley rats (F)	50, 100 or 300 mg/kg/day	Starting 4 weeks prior to initiation, total 24 weeks	DEN/phenobarbital	In diet	*Oxidative stress and inflammatory markers↓	*Liver*: TBARS↓, protein carbonyls↓, iNOS↓, 3-nitrotyrosine↓, Nrf2↑	2010	[103]
Sprague–Dawley rats (F)	50, 100 or 300 mg/kg/day	Starting 4 weeks before initiation, total 18 weeks	DEN/phenobarbital	In diet	*Nodule incidence↓ *hepatic tumor multiplicity↓ *RSV did not exhibit any cardiotoxicity but rather improved the cardiac function.*	Not available	2011	[101]
Wistar rats (M)	20 mg/kg body weight	Daily, for 15 days **Pre-treatment*: From day 1 of DEN injection **Post-treatment*: After the development of carcinoma	DEN/phenobarbital	Oral	*Total liver mass↓ *Body mass↑	*Serum*: α-fetoprotein↓ *Liver and serum*: ALP↓, ACP↓, 5′ND↓, γ-GT↓, LDH↓ *Liver*: PARP cleavage↑, caspase-3 activation↑, p53↑, cytochrome c release↑, Bax↑ Bcl2↓	2011	[104]
HBV X protein (HBx) transgenic mice	30 mg/kg/day	Daily, from 4-week-old	HBx	Oral gavage	*Onset of tumor↓ *HCC incidence↓	*Expression*: LXRα↓, Srebp1-c↓, PPARγ↓, ACC↓, Fas↓ *Activity*: Ampk↑, Sirt1↑	2012	[106]
SD rats (M)	60 mg/kg/day	Daily, 2 week after DEN injection, total 6 weeks	DEN/2-AAF	Oral gavage	*Area and number of GST-P-positive foci (a marker of hepatocarcinogenesis)↓ *Expression of GST-P and Cyp2e1 in both foci and surrounding liver tissue↓	*Liver* (*GST-P-positive foci and surrounding liver tissue*): Cyp2e1↓, GST-P↓ *Whole liver*: Cyp1a1↓, Cyp1a2↓, Cyp2b1↓	2013	[105]

[1] F: female, M: male.

xenograft models, with decreases in cell cycle-related markers including cyclin B1 and p34cdc2 [109], inflammatory IL-8 [111], and angiogenesis-related vascular endothelial growth factor (VEGF) [113], and an increase in the excretion of neutral sterols and bile acids into feces [110].

With chemically induced carcinogenesis models, RSV exerted apoptotic effects accompanied by the induction of proapoptotic markers (expression of Bax [100,104] and p53 [104], PARP cleavage [104], caspase-3 activation [104], cytochrome-c release [104]) and antioxidant/detoxification regulator (Nrf2) [103]. On the other hand, RSV reduced an anti-apoptotic marker in the liver (expression of Bcl-2 [100, 104]), inflammatory proteins in the liver (Hsp70 [114], COX-2 [114], nuclear NFκB [114], cytosolic inhibitor of kappa B (IκB) [114], TNF-α [102], IL-1β [102], IL-6 [102], and iNOS [103]), oxidative stress markers in the liver [thiobarbituric acid reactive substances (TBARS), protein carbonyls, 3-nitrotyrosine, and iNOS] [103], and other factors both in the liver and serum [alkaline phosphatase (ALP), acid phosphatase (ACP), 5′-nucleotidase (5′ND), γ-glutamyl transpeptidase (γ-GT), and LDH] [104], and a serum marker for liver cancer (α-fetoprotein) [104].

In the spontaneously induced hepatocellular carcinoma in HBV X-associated transgenic mice, RSV inhibited intracellular reactive oxygen species (ROS) and hepatic lipogenesis with the down-regulation of liver X receptor-α, sterol regulatory binding protein-1c, acetyl-CoA carboxylase (ACC), FAS and peroxisome proliferator-activated receptor γ (PPARγ). The expression of energy metabolism related proteins including 5′ AMP-activated protein kinase (AMPK) and Sirt1 was enhanced [106].

2.7. Other cancers in recent years (2009–2014)

High levels of post-translational modification with *O*-linked β-*N*-acetylglucosamine (*O*-GlcNAc) moieties are a manifestation of tumor progression, and one feature of chronic lymphocytic leukemia cells [115]. RSV treatment increased survival rate and reduced tumor burden with decreased spleen weight and high levels of *O*-GlcNAc (a marker of tumor progression) proteins in the spleen of both friend murine leukemia virus- or CB3 cell line-engrafted mouse erythroleukemias [115]. RSV could prolong the lifespan of mice engrafted with acute myeloblastic leukemia cells Kasumi-1, with the attenuation of signal transducer and activator of transcription 3 (STAT3) phosphorylation [116]. However, intraperitoneal or dietary RSV did not attenuate the progression of high risk human acute lymphoblastic leukemia with translocation t(4;11) [t(4;11) ALL] in mice engrafted with t(4;11) ALL cells [54,60].

RSV application prevented the incidence and growth of oral preneoplastic lesions and oral squamous cell carcinoma in DMBA-induced oral carcinogenesis in the hamster cheek pouch [117]. RSV treatment reduced tumor growth of human nasopharyngeal carcinoma cells (CNE-2Z cell line) [118], head and neck cancer-derived tumor-initiating cells (HNC-TICs) [119], and head and neck squamous cell carcinoma (HNSCC) cells (FaDu cell line) [120], in nude mouse xenograft models. With the anti-tumor effect of against head and neck cancer, RSV suppressed tumor stemness by reducing the expression of stemness markers (Oct4 and Nestin) and mesenchymal-like protein (Vimentin), and induced epithelial protein (E-cadherin) [119], increased cleaved caspase-3 (an apoptotic marker) and γ-histone 2AX (a DNA damage marker) [120].

RSV exerted anti-tumor and anti-angiogenic effects with decreases in microvessel density, plasma VEGF and intra-tumoral receptor type-2 (KDR/fetal liver kinase 1) levels with Ehrlich ascites carcinoma-bearing mice [121]. Intravesical instillation or RSV attenuated tumor growth with an increase in the expression of Sirt1 and p53, and a decrease in the expression of STAT3, p-STAT3, c-Myc, cyclin D1, survivin, and VEGF, in the orthotopic bladder transitional cell carcinoma (TCC) nude mouse model [122]. RSV inhibited tumor growth with a decrease in the expression of Ki67, cyclin D1, CDK4, and CDK6, and an increase in the expression of p21, p16, and β-Gal (a specific marker for mammalian senescent cells) in a gastric cancer xenograft nude mice model. The depletion of Sirt1 abolished the anti-tumor effect of RSV, demonstrating the involvement of Sirt1 in RSV action [123].

The forkhead transcription factors of the O class (FOXO) are involved in oxidative stress signaling, proliferation, and tumorigenesis. RSV suppressed the tumor growth of PANC-1 cells orthotopically implanted in nude mice with increased apoptosis/cell cycle arrest proteins including Bim, cleaved caspase-3, and p27, and decreased cell survival/proliferation markers including the expression of PCNA and phosphorylation of ERK, PI3K, Akt, p-FOXO1 (Ser256), and FOXO3a (Ser253) [124]. However, RSV did not show an anti-tumor effect with NuTu-19 ovarian cancers in rats [125], and one study demonstrated that RSV treatment did not affect tumor growth in the CWR22 xenograft model [37].

2.8. Metastasis

Oral treatment of RSV via gavage or diet (0.1–1 mg/kg body weight/day) exhibited anti-metastatic effects with melanoma [33, 126] or breast cancer cells [127] in mouse models. In a hepatic melanoma model with B16M cells, IL-18 is mainly involved in metastases. Oral treatment with RSV inhibited metastatic growth, decreased metastatic foci and metastatic volume in the liver of intrasplenically injected B16M cells, with a decrease in proinflammatory IL-18 levels in hepatic blood [126]. Oral treatment with RSV reduced lung metastasis (decreased tumor volumes) of melanoma cells (B16BL6 cells) with the down-regulation of Akt expression [33]. RSV inhibited cancer metastasis with a decrease in the number of pulmonary nodules and plasma MMP-9 activity with 4T1 mouse breast cancer cell line-injected mice [127].

In addition, in vitro treatment with RSV or via the intraperitoneal route resulted in suppression of metastasis. EMT has been linked to metastasis. Incubation with RSV inhibited LPS-induced EMT of K1735 melanoma cells in vitro, resulting in prolonged animal survival and reduced lung metastasis after tail vein injection of LPS-exposed K1735 cells in mice [128]. Intraperitoneal injection of RSV inhibited lung metastasis of A549/VC mice with a reduced number of colonies in the lung while the inhibitory effect was diminished in A549/FOXC2-injected mice, suggesting that FOXC2 is critical for RSV-mediated suppression of tumor metastasis [79].

3. Inflammatory diseases

Over the past five years, studies involving RSV treatment in rodent models of inflammatory diseases have demonstrated downregulation of inflammation-induced biomarkers including proinflammatory mediators [e.g., IL-1β, -6, and -23p19, TNF-α, monocyte chemoattractant protein-1 (MCP-1), IFN-γ, NFκB, COX-2, iNOS, and prostaglandin E synthase-1 (PGES-1)], oxidative stress markers [e.g., MDA, nitric oxide (NO)], and endogenous vasoconstrictors (e.g., angiotensin II, and endothelin), and upregulation of inflammation-reduced biomarkers including anti-oxidant protein (e.g., SOD) and anti-inflammatory protein (e.g., IL-10).

RSV treatment attenuated histopathologic changes (saponification spots in the intraperitoneal cavity, severe pancreatic edema, hemorrhage, necrosis, etc.) as well as elevated biochemical markers in blood plasma (renin activity and levels of angiotensin II, endothelin, and NO) in taurocholate-induced severe acute pancreatitis (SAP) in rats [129].

RSV reversed the decrease in SOD levels and the increase in MDA in intestine tissue. Also, RSV reversed the increase of TNF-α levels in serum. RSV prevented injury to the intestinal barrier in the rat SAP model [130].

RSV decreased inflammatory cytokines (IL-1β, IL-6, TNF-α, and TGF-β1) and the histologic fibrosis score in cecal tissue of peptidoglycan-polysaccharide-injected rats (animal model for Crohn's disease) [131].

RSV reduced cartilage destruction, the loss of matrix proteoglycan content in cartilage with a decrease in the apoptosis rate of chondrocyte and the level of NO in the synovial fluid in experimental osteoarthritis with rabbits [132].

RSV treatment 1) extended survival with increased numbers of regulatory T cells and intestinal epithelial cell proliferation/regeneration in the ileum mucosa, 2) decreased mucosal T lymphocyte and neutrophilic granulocyte numbers, 3) presented fewer proinflammatory enterobacteria and enterococci and higher anti-inflammatory lactobacilli and bifidobacteria loads, and 4) maintained intestinal barrier functions in a murine model of hyper-acute Th1-type ileitis following peroral infection with *Toxoplasma gondii*. This anti-inflammatory action accompanied an increase in anti-inflammatory cytokine IL-10 in ileum, mesenteric lymph nodes and spleen, and a decrease in proinflammatory cytokine expression (IL-6, IL-23p19, IFN-γ, TNF-α, and MCP-1) in the ileum [133].

With chronic DSS-induced colitis in mice, RSV treatment resulted in a higher survival than control with reduced clinical symptoms including loss of body weight, diarrhea and rectal bleeding, and improved the disease activity index and inflammatory score. The anti-inflammatory effect of RSV was concomitant with decreased levels of TNF-α, IL-1β, PGES-1, COX-2 and iNOS, and p-p38, and increased levels of IL-10 [134].

RSV treatment abrogated an increase in vascular permeability (increased peritoneal lavage) and neutrophil migration (in peritoneum) associated with a decreased release of serum IL-1β, IL-6, TNF-α, and macrophage inflammatory protein 1α (MIP)-1α in the C5 anaphylatoxin (C5a)-induced model of acute peritonitis [135].

RSV treatment attenuated mechanical ventilation-induced up-regulation of pulmonary NFκB activity but without alteration of other cytokines including IL-1β, IL-6, and keratinocyte-derived chemokine (KC) in the lung, and TNF-α, KC and, IL-6 in plasma [136].

Finally, RSV treatment reduced the incidence and severity of collagen-induced arthritis in a mouse model [137].

The summary of anti-inflammatory capacity of RSV in animal models is demonstrated in Table 7.

4. Cardiovascular diseases

According to the WHO (http://www.who.int/cardiovascular_diseases/about_cvd/en/), cardiovascular disease (CVD) includes disorders of the heart and blood vessels, including hypertension (high blood pressure), coronary heart disease (heart attack), cerebrovascular disease (stroke), peripheral vascular disease, heart failure, rheumatic heart disease, congenital heart disease, and cardiomyopathies. Rodent animal models have been frequently used to evaluate the therapeutic potential of drug candidates for the treatment of cardiovascular disease. However, various test agents selected from such animal studies have been found to be ineffective in clinical trials [138]. In terms of clinical relevance for the treatment of cardiovascular diseases, biological experimentation with pigs may offer an advantage over rodent studies, since there is a closer resemblance to the human in terms of anatomy, physiology, and genetics [139]. The effects of RSV on various cardiovascular diseases are summarized in Table 8.

4.1. Restenosis

During vascular repair after re-vascularization or aortic injury, restenosis might occur with neointimal hyperplasia. In earlier studies, RSV treatment was shown to attenuate restenosis [140–142] with reduced neointimal hyperplasia [140–144] in artery injury models of rabbits [140], rats [141,143,144] and mice [142]. In addition, RSV upregulated the expression of eNOS [141–143], p-eNOS [143], NO [142], Sirt1 [143], and p-AMPK [143] while it downregulated that of iNOS [143], platelet endothelial cell adhesion molecule (PECAM) [143], MMP-9 [143], 8-iso-PGF2α [144], MCP-1 [144], and IL-6 [144]. More recently, it has been found that RSV treatment prevented restenosis with a reduction of neointimal hyperplasia in carotid artery-injured [142–144] and femoral wire-injured [143] models with rodents. The suppressive activity of RSV on neointimal hyperplasia was abolished in ER-$\alpha^{-/-}$ mice [142], endothelial NOS (eNOS) knockout mice [143], and in N^G-nitro-L-arginine methyl ester (L-NAME)-co-treated mice [142] or rats [143], suggesting that RSV exerts the effect through ER-α-dependent NO production [142].

With clinical signs of the protective effect of RSV on restenosis, RSV induced arterial NOS activity and NO production in carotid artery injured mice with high-fat diet [142], and reduced inflammatory mediators including iNOS [143], platelet/endothelial cell adhesion molecule [143], MMP-9 [143], 8-iso-PGF2α [144], MCP-1 [144] and IL-6 [144], and induced eNOS, p-eNOS, Sirt1, and p-AMPK in carotid artery-injured rats [143].

4.2. Hypertension

Several experimental models with animals have been employed to elucidate the effect of resveratrol on hypertension. Studies using spontaneously hypertensive rats (SHRs) [145–152] showed that RSV treatment lowered systolic blood pressure (SBP) [145], prevented the development of concentric hypertrophy [149], reduced myocardial fibrosis [152], and improved endothelium-dependent vascular relaxation in response to acetylcholine (Ach) [145,147] and myocardial performance [148].

Also, RSV reduced oxidative DNA damage [146], glycoxidative stress [146], and oxidative stress [148,149,152]. The molecular alterations by RSV in SHRs were observed in the heart with decreases in HNE-LKB1 adduct and p-p70S6K expression, and increases in p-LKB1 and p-AMPK [148]. In arteries of SHRs, ERK signal [150], PCNA expression [150], and p-p70 S6 kinase [151] were decreased, but protein kinase G (PKG) activity [150] and the expression levels of p-eNOS [151], LKB1 [151], and AMPK [151] were increased by RSV intervention.

More recently, it has been shown that RSV supplementation attenuated monocrotaline-induced pulmonary hypertension in rats, with a decrease in right ventricular systolic pressure, right ventricular hypertrophy, and medial thickening of intrapulmonary arteries. Also, RSV increased pulmonary artery atrogin-1 expression [153].

RSV treatment improved survival without body weight loss, protected against cardiac and aortic endothelial dysfunction, and normalized reduced mitochondrial respiration, biogenesis, and mitochondrial fatty acid utilization. Related genes, including PPARα, carnitine palmitoyltransferase Ib (CPT-1b), and middle-chain acyl-CoA dehydrogenase, were normalized with RSV treatment in Dahl salt-sensitive rats fed a high-salt diet [154].

RSV decreased mean arterial pressure and heart rate, diastolic and systolic blood pressure, superoxide levels in the rostral ventrolateral medulla, and serum estradiol, with adult-cycling female rats in which hypertension was induced by chronic exposure of estradiol-17β [155]. RSV did not affect blood pressure, placental and renal blood flows in desoxycorticosterone acetate-induced hypertension in pregnant rats (preeclampsia model) [156].

RSV improved flow-mediated vasodilation, prevented increases in systolic blood pressure, reduced hypertrophic growth of the myocardium, decreased serum 4-HNE which is known to inhibit liver kinase B1 (LKB1) activity, together with increased phosphorylation of eNOS, LKB1, and AMPK, and reduced phosphorylation of p70 S6 kinase (pro-hypertrophic signaling) in mesenteric artery and ventricles in SHRs and angiotensin-II hypertensive mice (LKB1–AMPK–eNOS signaling axis) [151].

RSV treatment reduced the systolic blood pressure in rats with fructose-induced hypertension, concomitant with a decrease in

Table 7
Anti-inflammatory effects of RSV in animal models (2009–2014).

Species	Dose	Duration	Model	Route	Outcome	Year	Reference
Male BALB/c mice	10 mg/kg	6 h (RSV treatment 15 min before modeling)	C5a-induced model of acute peritonitis	i.p.	*Vascular permeability↓ (Increased peritoneal lavage↑) *Neutrophil migration in peritoneum↓ *Serum: IL-1β↓, TNFα↓, IL-6↓, MIP-1α↓	2009	[135]
C57BL/10ScSn (wild type) mice	20, 100, or 200 mg/kg/day, daily	10 days (RSV treatment 2 days before modeling)	Hyper-acute Th1-type ileitis following peroral infection with *Toxoplasma gondii*	Gavage	*Extended survival *Numbers of regulatory T cells and augmented intestinal epithelial cell proliferation/regeneration in the ileum mucosa↑ *Mucosal T lymphocyte and neutrophilic granulocyte numbers↓ *IL-10 in ileum, mesenteric lymph nodes and spleen↑ *Pro-inflammatory enterobacteria and enterococci loads↓ *Anti-inflammatory lactobacilli and bifidobacteria loads↑ *Intestinal barrier functions↑ *IL-23p19↓, IFN-γ↓, TNF-α↓, IL-6↓, MCP-1↓	2010	[133]
Female C57BL/6 mice	3 mg/kg/day	3 weeks (co-exposure: DSS for 5 days, RSV for 3 weeks)	Induction of chronic colitis by dextran sulfate sodium (DSS)	In diet	*Extended survival *Loss of body weight, diarrhea and rectal bleeding↓ *TNF-α↓, IL-1β↓, PGES-1↓, COX-2↓, iNOS↓, IL-10↑	2010	[134]
Sprague–Dawley rats	20 mg/kg, once	3, 6, 12 h (RSV treatment 5 min after modeling)	Taurocholate-induced severe acute pancreatitis (SAP) by injecting 4% sodium taurocholate at the hepatic portal site	i.v. (dorsal penile vein)	*Intestine: SOD↑, MDA↓, ICAM-1↑, VCAM-1↑ *Serum: TNFα↓	2012	[130]
Female Lewis rats	100 mg/kg/day	28 days, daily (RSV gavage 1 day after modeling)	Enterocolitis model by intramural injections of peptidoglycan-polysaccharide (PG-PS)	Gavage	*Histologic fibrosis score in cecal tissue↓ *No significant effect on IGF-I, and procollagen type III *Decreased IL-1β, IL-6, TNF-α, and TGF-β1	2012	[131]
Rabbit	50, 20, and 10 μmol/kg, daily	2 weeks (surgery 4 days before RSV)	Experimental osteoarthritis using the Hulth–Telhag modeling method	Knees injection	*Cartilage destruction, the loss of matrix proteoglycan content in cartilage↓ *Apoptosis rate of chondrocyte↓ *NO in the synovial fluid↓	2012	[132]
Sprague–Dawley rats	20 mg/kg, once	3, 6, 12 h (SAP + RSV)	Taurocholate-induced SAP induced by 4% sodium taurocholate in the retrograde pancreaticobiliary duct	i.v.	*Histopathologic changes (saponification spots in the intraperitoneal cavity, severe pancreatic edema, hemorrhage, necrosis, *etc.*)↓ *Reduced renin activity and levels of angiotensin II, endothelin, and NO in blood plasma	2013	[129]
Male DBA1 mice	20 mg/kg/day	8 weeks, daily (RSV co-treatment with modeling)	Collagen-induced arthritis	Gavage	*Incidence and severity of rheumatoid arthritis↓ (reduction of infiltrated cells in the joint, synovial hyperplasia, and adjacent cartilage, as bone erosion)	2013	[137]
Mice	10, 20, and 40 mg/kg/day	5 h (RSV 1 h before MV for 4 h)	Mechanical ventilation-induced inflammation	i.p.	*Pulmonary NFκB activity↓ *Lung: No effect on IL-1β, IL-6, keratinocyte-derived chemokine (KC) *Plasma: No effect on TNF-α, KC, and IL-6	2014	[136]

Table 8
Effects of RSV on cardiovascular diseases in animal models (2009–2014).

Species	Dose	Duration	Model	Route	Outcome	Marker	Year	Reference
Restenosis								
Female ER-$\alpha^{-/-}$ mice (B6.129 Esr1tm1KskN10) and their B6.129 wild-type littermates	50 mg/kg/day	4 weeks	Mouse carotid artery injury model with a *high-fat diet*	In diet	*Restenosis (attenuated neointimal hyperplasia)↓ *Arterial* eNOS activity↑*ER-α-dependent NO production↑	eNOS↑, NO↑	2010	[142]
Sprague–Dawley rats	4 mg/kg/day	17, and 31 days	Carotid artery injury model	s.c.	*Neointimal hyperplasia↓ *Reduced iNOS, PECAM, and MMP-9 *in the carotid artery at 4 days*. *Increased eNOS, p-eNOS *in the carotid artery at 4 days*. *Increased SirT1 and p-AMPK higher than *both untreated* and injured control carotid arteries at *4 days*.	iNOS↓, eNOS↑, p-eNOS↑, SirT1↑↑, p-AMPK↑↑, PECAM↓, MMP-9↓	2012	[143]
eNOS knockout mice	23 mg/kg/day	33 days	Femoral wire injury model	Oral	*Neointimal hyperplasia↓ (No effect on neointimal formation in eNOS-KO mice)	Not available	2012	[143]
Rats	1 mg/kg/day	7 or 14 days	Balloon injury model of rat carotid artery	i.p.	*Neointimal hyperplasia↓ *Decreased neointimal/medial area↓ *Serum 8-iso-PGF2α levels in serum↓ *MCP-1 and IL-6 in injured arteries↓	8-iso-PGF2α↓, MCP-1↓, IL-6↓	2013	[144]
Hypertension								
Dahl salt-sensitive rat	18 mg/kg/day	8 weeks	High-salt diet-induced hypertension model	In diet	*Survival↑ *Prevention from cardiac and aortic endothelial dysfunction *Normalization of the reduced mitochondrial respiration, biogenesis, and mitochondrial fatty acid utilization. *Increases in peroxisome proliferator-activated receptor α (PPARα), CPT-1β, and middle-chain acylCoA dehydrogenase (MCAD) expression.	PPARα↑, CPT-1b↑, MCAD↑	2011	[154]
Sprague–Dawley rats	0.84 g/kg of chow	41 days	Estradiol-17β-induced hypertension model	In diet	*Blood pressure↓ *Superoxide levels in rostral ventral lateral medulla↓ *Serum estradiol↓	Estradiol↓	2011	[155]
Sprague–Dawley rats	3 mg/kg/day	15 days	Monocrotaline-induced pulmonary hypertension model	Drinking water	*Right ventricular systolic pressure↓ *Right ventricular hypertrophy↓ *Medial thickening of intrapulmonary arteries↓ *Normalization of pulmonary artery *atrogin-1* expression	Atrogin-1↑	2012	[153]
Wistar albino rats	20 mg/kg/day, twice per day	During the whole pregnancy	Desoxycorticosterone acetate (DOCA)-induced hypertension model	Orogastric	*No effect on blood pressure *No effect on blood flows and placental pathology parameters		2012	[156]
Spontaneously hypertensive rats	~146 mg/kg/day	5 weeks	Spontaneously hypertensive rat model	In diet	*Vascular function↑ *Blood pressure↓ *Arterial eNOS and AMPK activities↑ *Cardiac HNE↓ *Left ventricular hypertrophy↓ *Cardiac LKB1/AMPK phosphorylation↑	*Artery*: p-eNOS↑, p-LKB1↑, p-AMPK↑, p-p70 S6 kinase↓	2013	[151]
C57BL/6 mice	~320 mg/kg/day	2 weeks	Angiotensin-II-induced hypertension model	In diet	*Vascular function↑ *Blood pressure↓ *Arterial eNOS and AMPK activities↑ *Cardiac HNE↓ *Left ventricular hypertrophy↓ *Cardiac LKB1/AMPK phosphorylation↑	*Artery*: p-eNOS↑, p-LKB1↑,p-AMPK↑, p-p70 S6 kinase↓	2013	[151]
Rats	10 mg/kg/day	1 week or 4 weeks	Fructose-induced hypertension model	In diet	*Systolic blood pressure↓ *NADPH oxidase subunits and ROS↓ *NO and SOD2 levels↑ *p-AMPK, Akt and neuronal NOS in the nucleus tractus solitarii↑	NADPH oxidase subunits↓, NO↑, SOD2↑, p-AMPK↑, Akt↑, nNOS↑	2014	[157]
Myocardial ischemia/infarction								
Yorkshire miniswine	100	11 weeks	Induced by implantation of an	In diet	*Regional wall motion abnormalities in the ischemic area↓	VEGF↑, p-eNOS↑, NFκB↑, p-Akt↑	2010	[164]

	mg/kg/day		ameroid constrictor on the left circumflex artery in pigs fed a high fat diet		*Myocardial blood flow↑ *Endothelium-dependent coronary vessel function↑ (a response to substance P↑) *Mean arterial blood pressure, diastolic blood pressure↓ *Total cholesterol↓ *Increases in expression of VEGF, p-eNOS (ser1177), NFκB, and p-Akt			
Yorkshire miniswine	100 mg/kg/day	11 weeks	Induced by implantation of an ameroid constrictor on the left circumflex artery in pigs fed a high fat diet	Diet	*Body mass index (BMI)↓ *Improved glucose tolerance, endothelial function, and myocardial function *Decreased free fatty acids, cholesterol, and c-reactive protein(CPR) levels and insulin resistance in serum *Induced insulin receptor substrate-1 (IRS), glucose transporters 1 (GLUT-1), and p-AMPK *Reduced retinol binding protein 4 (RBP4).	CRP↓, IRS-1↑, GLUT-1↑, p-AMPK↑, RBP4↓	2011	[165]
Rats	1 mg/kg/day, daily	4 weeks	Induced by permanent ligation of the left anterior descending artery	i.p.	*Increased expression of adenylate kinase 1 (AK1) and mitochondrial $NADP^+$-dependent isocitrate dehydrogenase (IDPm)	AK1↑, IDPm↑	2011	[159]
C57BL/6 mice	20 mg/kg/day, daily	42 days	Induced by the left coronary artery ligation	i.p.	*Survival↑ *Delayed progression of cardiac remodeling *Heart weight/body weight ratio↓ *Lung weight/body weight ratio↓ *Old infarct size↓ *Infarct size after global ischemia↓		2012	[158]
Rats	10 mg/kg, single dose	150 min	Induced by ischemia/reperfusion injury	i.p.	*Myocardial infarct area↓		2013	[160]
Male Wistar rats	25 mg/kg/day	7 days	Induced by ischemia/reperfusion injury	i.p.	*Recovery of post-ischemic ventricular functions↑ *Myocardial lipoperoxidation, free iron, and catalase activity ↓*Peroxidase activity, expression of Fe-SOD, and Mn-SOD↑	Fe-SOD↑, Mn-SOD↑, peroxidase activity↑, catalase activity↓	2013	[161]
Yorkshire swine	100 mg/kg/day	11 weeks	Induced by implantation of an ameroid constrictor on the left circumflex artery in pigs fed a high fat diet	Diet	*Body mass index↓ *No significant difference in insulin signaling (AMPK, p-AMPK, IRS2, p-IRS2, PI3K, Akt, p-Akt, FOXO1, p-FOXO1, GSK-3β, p-GSK-3β, PGC1α, GLUT1, and GLUT4)		2013	[163]
Atherosclerosis								
Rabbit	2 mg/kg/day	24 days	Induced by hypercholesterolemic diet	Diet	*Aortic atherosclerotic lesions↓ *Intima area and the intima/media layer area ratio↓ *Decreased VCAM-1, MCP-1, and IL-6 concentrations in descending aorta.	VCAM-1↓, MCP-1↓, IL-6↓	2012	[166]
Mini pigs	0.114 mg/kg/day	12 months	Induced by hypercholesterolemic diet	Diet	*No alteration on LCL-c, HDL-c, TG in plasma *No effect on ALT, GGT, ALT in serum *Reduced collagens (COL1A, COL3A), lipoprotein lipase (LPL) and fatty-acid binding proteins (FABPs) PBMNC	COL1A↓, COL3A↓, LPL↓, FABP↓	2012	[168]
Mini pigs	0.257 mg/kg/day	4 months	Induced by atherogenic diet	Diet	*Lipid drops in the intima of the aorta↓*Vascular oxidative stress↓ (superoxide anion↓) *Suppressor of cytokine signaling 1 (SOCS1) in male PBMNC↓ *Female PBMNC: SOCS3↓, vinculin (VCL)↑	SOCS1↓, VCL↑	2012	[169]
APOE*3-Leiden.CETP (E3L.CETP) mice	11 mg/kg/day	14 weeks	Induced by hypercholesterolemic diet	Diet	*Atherosclerotic lesion area in the aortic root↓ *Collagen/macrophage ratio in the atherosclerotic lesion↑ *Plasma cholesterol↓ *Macrophage function↑	Not available	2013	[167]
Others								
Sprague–Dawley rats	0.7 mg/kg/single dose	4 h 15 min	Angiotensin II (Ang-II)-induced arteriolar leukocyte adhesion model	i.v.	*Arteriolar leukocyte adhesion in the mesenteric arterioles↓ *Leukocyte–endothelial cell interactions in the postcapillary venules↓	Not available	2010	[175]
Sprague–Dawley rats	15 mg/kg/day, daily	30 days	Estrogen deficiency model by ovariectomy	Oral gavage (p.o.)	*Leukocyte adhesion to the arteriolar endothelium↓ (venular leukocyte–endothelial cell interactions↓) *CINC/KC, MCP-1, and MIP-1α in circulating system↓	CINC/KC↓, MCP-1↓, MIP-1α↓, P-selectin↓, VCAM-1↓	2010	[175]

(continued on next page)

Table 8 (*continued*)

Species	Dose	Duration	Model	Route	Outcome	Marker	Year	Reference
					*P-selectin and VCAM-1 in the arterial endothelium↓			
Sprague–Dawley rats	2.5 mg/kg/day, daily	24 days	Cardiac hypertrophy by pressure overload (abdominal aortic banding surgery)	Oral gavage	*Abnormalities in cardiac structure and function↓ *Oxidative stress in cardiac tissue↓		2010	[173]
C57BL/6J mice	100 mg/kg/day	6 weeks	Abdominal aortic aneurysm induced by periaortic application of $CaCl_2$	i.p.	*Aneurysm size (decrease in aortic diameter)↓ *Inflammatory cell infiltration in the aortic wall↓ **Aortic wall*: Expression of MCP-1, TNF-α, p-p65, ICAM-1, CD68, VEGF-A, p47, GPx1 and GPx3↓ 8-OHdG-positive, Mac-2-positive, CD31-positive, and 4-HNE-positive cells↓ *Activities of MMP-2 and -9↓	MCP-1↓, TNF-α↓, p-p65↓, ICAM-1↓, CD68↓, VEGF-A↓, p47↓, GPx-1↓, GPx-3↓, 8-OHdG↓, Mac-2↓, CD31↓, 4-HNE↓, MMP-2↓, MMP-9↓	2011	[176]
Sprague–Dawley rats	10 mg/kg/day, daily	21 days	Abdominal aortic aneurysm induced by *elastase*	Drinking water	*Abdominal aortic aneurysm expansion↓ *Vessel wall macrophage infiltration↓ *CD62L-monocyte subset expansion↓ *CD143 monocyte expression↓ **Plasma*: MMP-9 activity↓, TNFα↓ *Abdominal aortic segments: MMP-9↓, VEGF↓, and TNFα↓	CD62L↓, CD143↓, MMP-9 activity↓, TNFα↓, MMP-9↓, VEGF↓	2011	[177]
ICR WT mice ($Nrf2^{+/+}$), ICR Nrf2 KO mice ($Nrf2^{-/-}$)	2.4 g/kg diet	16 weeks	High fat diet-induced endothelial dysfunction	Diet	*Acetylcholine-induced vasodilations in skeletal muscle arterioles↑ *Oxidative stress and apoptosis in branches of the femoral artery↓ *Diminished RSV effects in $Nrf2^{-/-}$ mice.		2011	[177]
Sprague–Dawley rats	30 mg/kg/single dose	2 h 30 min	Trauma-hemorrhage and resuscitation model	i.v.	*Normalized cardiac output and left ventricular performance *Decreased DNA fragmentation (apoptosis), MPO activity, IL-6 levels, and ICAM-1 levels in cardiac tissue *Increased p-Akt in cardiac tissue	MPO activity↓, IL-6↓, ICAM-1↓, p-Akt↑	2012	[174]
C57BL/6 mice	10 mg/kg/single dose	18 h	Endotoxin-induced myocardial toxicity	i.p.	*Endotoxin-induced myocardial injury↓ *Decrease in serum creatine kinase (CK) and lactate dehydrogenase (LDH) *End diastolic left ventricular inner dimension (LVID)↓ *Ejection fraction↑ *Decreased TNFα, IL-1β, MIP1α, MCP in the heart **Possibly* induced Nrf2 activation with HO-1 and glutamate-cysteine ligase (GCLM) expression in heart tissue	CK↓, LDH↓, TNFα↓, IL-1β↓, MIP1α↓, MCP↓, HO-1↑, GCLM↑	2013	[170]
Female C57BL6 mice	~320 mg/kg/day, daily	8 weeks	Cardiac injury/toxicity induced by doxorubicin injection	Diet	*Left ventricle remodeling↓ *Recovered exercise capacity *Downregulated expression of molecular markers of cardiac dysfunction [(atrial natriuretic peptide (ANP) protein], and 4-HNE *Increased expression of mitochondrial function-related markers (mitochondrial electron transport chain complexes, and mitofusin-1 and -2)	ANP↓, 4-HNE↓, mitochondrial electron transport chain complexes↑, mitofusin-1↑ and -2↑	2013	[171]
Castrated male pigs	5 mg/kg/day, daily	14 days	Exposure to secondhand smoke	Oral	*Normalized cardiac function *Left ventricular end-diastolic volume, cardiac output↑*Plasma *nitrotyrosine* levels↓ *Decreased the increase in sarcomeric proteins (myosin light chain-1 (MLC1), β-myosin heavy chain fragment, and myosin-7 fragments) metabolic enzymes (pyruvate dehydrogenase and lactate dehydrogenase)	Nitrotyrosine, MLC1, β-myosin heavy chain fragment, myosin-7 fragment, pyruvate dehydrogenase, lactate dehydrogenase	2013	[182]
Wistar albino rats	20 mg/kg/day, daily	4 weeks	Cardiac injury/toxicity induced by doxorubicin injection	Oral gavage	*Body and heart weights↑ *Left ventricular necrosis and fibrosis↓ **Left ventricle*: lipid peroxidation↓, hydroxyproline↓, TNFα↓, and caspase-3↓, GSH↑, SOD↑ *Serum creatine kinase-myocardial band (CK-MB) activity↓	Hydroxyproline↓, TNFα↓, caspase-3↓, CK-MB↓, GSH↑, SOD↑	2014	[172]

NADPH oxidase subunits (p67, p22-phox) and ROS, and an increase in NO and SOD2, p-AMPK, Akt, and neuronal NOS [157].

4.3. Myocardial ischemia/infarction

RSV post-treatment increased survival and delayed the progression of cardiac remodeling with a reduced heart weight/body weight ratio, lung weight/body weight ratio, and old infarct size in a murine myocardial infarction model with global ischemia. In addition, RSV pretreatment decreased infarct size when ex vivo murine hearts were exposed to soluble fractalkine/chemokine (C-X3-C motif) ligand 1 (CX3CL1), which was reported to exacerbate heart failure [158].

RSV pretreatment reversed the decrease in expression of adenylate kinase 1 and mitochondrial $NADP^+$-dependent isocitrate dehydrogenase (known to increase myocardial energetic efficiency and reduce ROS-mediated damage) in surviving rats after permanent ligation of the left anterior descending artery under isoflurane anesthesia [159].

RSV decreased the myocardial infarct area in ischemia-reperfusion induced myocardial infarction in rats [160] and pretreatment improved the recovery of post-ischemic ventricular functions, with decreases in myocardial lipoperoxidation, free iron, and CAT activity, and increases in peroxidase activity, expression of Fe-SOD and Mn-SOD in ischemia/reperfusion (I/R)-induced injury with rats [161].

RSV supplements prevented an increase in body mass index and blood glucose levels after dextrose infusion, and reversed the decrease in cardioprotective autophagy in chronically induced ischemic myocardium in pigs fed a high cholesterol diet, with normalization of increased p-mammalian target of rapamycin (mTOR), decreased p70-S6K, lysosome-associated membrane protein 2 (LAMP-2), and LC3A-II, to levels of pigs fed a regular diet [162].

Although RSV supplement decreased body mass index, it did not significantly alter insulin signaling [AMPK, p-AMPK, insulin receptor substrate-2 (IRS2), p-IRS2, PI3K, Akt, p-Akt, FOXO1, p-FOXO1, glycogen synthase kinase 3β (GSK3β), p-GSK3β, PPARγ co-activator-1alpha (PGC-1α), glucose transporter 1 (GLUT1), and GLUT4] in chronically induced ischemic myocardium with pigs fed a high cholesterol diet [163].

RSV supplements attenuated regional wall motion abnormalities in the ischemic area, increased myocardial blood flow, preserved endothelium-dependent coronary vessel function with an improved response to substance P, and decreased mean arterial blood pressure, diastolic blood pressure, and total cholesterol, in chronically induced ischemic myocardium with pigs fed a high cholesterol diet, concomitant with greater expression of VEGF (a potent vasodilator), p-eNOS (ser1177) (which is involved in the generation of NO, a vasorelaxant), NFκB (a transcription factor for VEGF), and p-Akt (Thr308) (pro-survival protein), in studies conducted with pigs fed a regular diet or a high cholesterol diet [164].

With chronical ischemic myocardium in pigs fed a high cholesterol diet, supplemental RSV 1) lowered body mass index, and 2) improved each of the following: glucose tolerance with a decrease in blood glucose levels 30 min after dextrose infusion, endothelial function with an increase in microvascular relaxation response to ADP, and myocardial functions with decreases in systolic blood pressure, double product (pressure-rate product, indirect index of myocardial oxygen consumption), ventricular contractility assessment, and ventrical segmental shortening [165]. RSV treatment also decreased free fatty acids, cholesterol, insulin resistance, and C-reactive protein levels in serum. Notably, RSV treatment led to induction of the downstream molecules of Sirt1 including IRS1, GLUT1, and p-AMPK, and reduction of retinol binding protein 4 (RBP4), which inhibits glucose uptake and blocks insulin signaling, in chronically ischemic myocardium in pigs fed a high cholesterol diet [165].

4.4. Atherosclerosis

Both short-term (24 days [166] and 14 weeks [167]) with a higher dose (2 [166] and 11 [167] mg/kg/day) in rabbits [166] and mice [167], and long-term (12 [168] and 4 [169] months) with a lower dose (0.114 [168] and 0.257 [169] mg/kg/day) of RSV in mini pigs displayed a protective effect on atherosclerosis.

RSV treatment resulted in milder aortic atherosclerotic lesions, a reduced intima area and intima/media layer area ratio, and decreased vascular cell adhesion molecule 1 (VCAM-1), MCP-1, and IL-6 in the descending aorta of rabbits with hypercholesterolemic diet-induced atherosclerosis [166].

RSV treatment reduced the atherosclerotic lesion area of the aortic root, increased the collagen/macrophage ratio in atherosclerotic lesions (a marker of plaque stability) decreased plasma cholesterol levels, and improved macrophage function in APOE*3-Leiden.CETP (E3L.CETP) mice fed a cholesterol-rich diet [167].

RSV treatment reduced collagens (COL1A, COL3A), lipoprotein lipase and fatty-acid binding proteins in peripheral blood mononuclear cells (PBMNC) of high-fat diet pigs [168]. RSV treatment moderately alleviated atherosclerosis by reducing lipid drops in the intima of the aorta, decreasing vascular oxidative stress (decreased superoxide anion), decreasing suppressor of cytokine signaling 1 (SOCS1) in male PBMNCs, and decreasing SOCS3, and increasing vinculin in female PBMNCs in pigs fed an atherogenic diet [169].

4.5. Other cardioprotective effects

RSV pretreatment attenuated LPS-induced myocardial injury in mice (sepsis-related myocardial injury; septic cardiomyopathy), with decreased end diastolic left ventricular inner dimension, serum creatine kinase (CK) and LDH, as well as increased the ejection fraction. In addition, RSV inhibited the expression of proinflammatory mediators including TNF-α, IL-1β, MIP-1α, and MCP in heart tissue, while it induced the expression of HO-1 and glutamate-cysteine ligase regulated by Nrf2 activation [170].

RSV pretreatment attenuated left ventricular remodeling and led to a recovery in exercise capacity, with a decrease in the expression of molecular markers of cardiac dysfunction (atrial natriuretic peptide), and oxidative stress (4-HNE), and an increase in the expression of mitochondrial function-related markers (mitochondrial electron transport chain complexes, and mitofusin-1 and -2) in a doxorubicin-induced mouse cardiac injury model [171].

In a doxorubicin-induced rat cardiac injury model, RSV pretreatment attenuated a decrease in body and heart weights as well as an increase in left ventricular necrosis and fibrosis, reduced left ventricular lipid peroxidation, hydroxyproline, TNF-α, caspase-3 levels, and serum creatine kinase-myocardial band (CK-MB) activity, and restored left ventricular reduced glutathione content and SOD activity [172].

RSV post-treatment attenuated cardiac hypertrophy with a decrease in abnormalities in cardiac structure and function in pressure overload rats induced by abdominal aortic banding surgery [173].

RSV pretreatment normalized cardiac output and left ventricular performance ($\pm dP/dt_{max}$), with a decrease in DNA fragmentation (apoptosis), myeloperoxidase (MPO) activity, IL-6 levels, and intercellular adhesion molecule 1 (ICAM-1) levels, and an increase in p-Akt with cardiac tissues, with a trauma-hemorrhage and resuscitation model performed with rats [174].

4.6. Other vascular protective effects

RSV pretreatment inhibited angiotensin II-induced arteriolar leukocyte adhesion in mesenteric arterioles, and leukocyte–endothelial cell interactions, in the postcapillary venules of rats [175], and attenuated ovariectomy (animal model of estrogen deficiency)-induced 1) leukocyte adhesion to the arteriolar endothelium, 2) venular leukocyte–endothelial cell interactions, 3) increase of circulating levels of CINC/KC, MCP-1, and MIP-1α, and 4) upregulation of P-selectin and VCAM-1 in the arterial endothelium of rats [175]. Pretreatment also showed protective effects on abdominal aortic aneurysm in both $CaCl_2$-

induced mouse and elastase-induced rat models with a reduction in aneurysm expansion, inflammatory cell infiltration, and molecular markers related to inflammation, oxidative stress, matrix proteolysis, etc. [176,177].

RSV pretreatment attenuated the expansion of abdominal aortic aneurysm as judged by reduced aneurysm size (decrease in aortic diameter) and inflammatory cell infiltration in the aortic wall of mice. At the molecular level in the aortic wall, RSV decreased i) mRNA expression of *MCP-1*, *TNF-α*, *ICAM-1*, *CD68*, *VEGF-A*, *p47*, *glutathione peroxidase 1* (*GPx-1*), and *GPx-3*, ii) 8-hydroxy-2′-deoxyguanosine (8-OHdG)-positive, Mac-2-positive, CD31-positive, and 4-HNE-positive cells, iii) the activities of MMP-2 and MMP-9, and iv) phosphorylation of p65 [176]. With abdominal aortic segments from the rat with abdominal aortic aneurysm [177], RSV pretreatment decreased CD62L-monocyte subset expansion, CD143 monocyte expression, MMP-9 activity and TNF-α levels in plasma, and expression of MMP-9, VEGF, and TNF-α.

RSV supplementation displayed protective effects on high fat diet-induced endothelial dysfunction in Nrf2 wild type mice ($Nrf2^{+/+}$), with increased acetylcholine-induced vasodilations in skeletal muscle arterioles, decreased oxidative stress and apoptosis in branches of the femoral artery. The protective effects of RSV were partially abolished in $Nrf2^{-/-}$ mice receiving a high fat diet, suggesting that the RSV effects are mediated by Nrf2 [178].

RSV treatment increased renal blood flow (RBF) and decreased renal vascular resistance in rats. However, upon L-NAME (a NOS inhibitor) and tempol (a SOD mimetic) pretreatment, but not indomethacin (a COX inhibitor) pretreatment, the increase in RBF by RSV was diminished, indicating that the renal vasodilatory effect of RSV is related to NO production and superoxide scavenging [179].

RSV significantly accelerated re-endothelialization (decreasing the risk of thrombosis) in mice fed a high-fat diet with carotid artery injury [180].

Finally, RSV treatment increased muscle microvascular blood volume at 30, 60, and 90 min, and muscle microvascular blood flow at 30 and 60 min. However, systemic pretreatment with L-NAME (NOS inhibitor) and TNF-α (known to induce ROS generation) neutralized the vasodilatory effect of RSV on muscle microvasculature, suggesting that the effect is exerted by increasing vasorelaxant NO as well as reducing TNF-α-induced ROS production [181].

The effects of RSV on various cardiovascular diseases are summarized in Table 8.

5. Diabetes

With diabetic animal models, more than half of the reported studies involved induction of diabetes by treatment with streptozotocin (STZ). STZ is used for the production of insulin-dependent (type I) diabetes mellitus via damage of pancreatic beta-cells that occurs within 48 h and lasts for up to 4 months [183]. In line with this, the duration of studies with RSV varied from 6 days to 4 months which fall into the abovementioned range. RSV administration ameliorated diabetic symptoms, including body weight loss, polyphagia, polydipsia, delayed onset of insulin resistance, and increased glucose uptake by hepatocytes, adipocytes, and skeletal muscle, and hepatic glycogen synthesis in diabetic rodents. Diabetes eventually can lead to the onset of complications including cardiomyopathy, nephropathy, neuropathy (e.g., autonomic neuropathy predisposing to gastroparesis and peripheral sensory neuropathy predisposing to foot ulcers), ketoacidosis, vasculopathy (e.g., retinal vasculopathy), hypertension, stroke, and hyperosmolar hyperglycemic nonketotic syndrome [184]. Treatment with resveratrol resulted in the alleviation/amelioration of diabetic complications with normalized/recovered clinical/biochemical markers in diabetic animal models, suggesting potential anti-diabetic activity. In the component of this review dealing with animals, only effects of RSV with the STZ-induced model are described.

Although some studies have reported that RSV had no effect on blood glucose levels [185,186], the majority of publications show reduced blood glucose levels (hypoglycemic effect) [187–192]. In fact, RSV delayed the onset of insulin resistance with increased glucose uptake by hepatocytes, adipocytes, and skeletal muscle, and increased hepatic glycogen synthesis in diabetic rodents [187]. In addition, RSV treatment resulted in a hypolipidemic effect with decreased plasma trigylcerides [187].

Elevated levels of oxidative/nitrosative stress markers including i) MDA, xanthine oxidase (XO), and NO in the hippocampus, cortex, cerebellum, brain stem, and spinal cord [193], ii) MDA in plasma/blood [190,194,195], iii) peroxynitrite in plasma [194], and iv) TBARS in the kidney [186], were decreased by RSV treatment. The levels of Trx-1 [189] in the heart, and the activities of antioxidant enzyme including i) CAT in plasma/blood [194,195] and sciatic nerve [194], and ii) MnSOD in the heart [189] and SOD in the kidney [186], were increased by RSV treatment. Additional alterations observed with STZ-induced diabetic rats were also reversed by RSV intervention. RSV attenuated body weight loss [187], and reduced the symptoms of nephropathy by inhibiting the increase in kidney weight/body weight ratio [186], plasma creatinine level [186,191], blood urea nitrogen (BUN) [186], and blood urea [191].

RSV attenuated neuropathy, for instance, RSV reversed the STZ-induced enhancement of contractile responses to noradrenaline (NA) [190] and the decrease in the relaxation response to acetylcholine (Ach) [190]. Also, RSV suppressed polyphagia [187], polydipsia [187], cold allodynia [196], and hyperalgesia [194,196,197], while it normalized decreased motor nerve conduction velocity (MNCV) and nerve blood flow (NBF) [194].

RSV treatment decreased the enzyme activities of aspartate transaminase (AST), alanine transaminase (ALT), and ALP [191] in serum, and suppressed the expression levels of p38 and p53 in the kidney [186], Cav-1 [192] in the heart, and p-Akt (S473) in the soleus muscle [188]. On the other hand, RSV increased p-AMPK [192], p-Akt [189,192], p-eNOS [189,192], HO-1 [189], GLUT-4 [192], Cav-3 [192], and VEGF [189] in the heart, and SIR2, p-histone H3 in the kidney [186]. In addition, treatment improved left ventricular function throughout reperfusion with decreased infarct size and cardiomyocyte apoptosis in the global ischemia model [189].

Collectively, RSV ameliorated various diabetic symptoms and complications in STZ-induced diabetic animal models, with underlying molecular mechanisms including a reduction in oxidative/nitrosative stress and inflammation generated during high-glucose metabolism, and the induction in signaling pathways such as AMPK and Sirt.

Biomarkers altered by RSV in STZ-induced diabetic models are listed in Table 9.

5.1. Effects of RSV on circulating/systemic biomarkers

Recent studies report that the unfavorable alterations observed in the circulatory and vascular systems of STZ-induced diabetic rodents were improved by treatment with RSV. This includes amelioration of deregulated biomarkers related to hyperglycemia, hyperlipidemia, oxidative stress, inflammation, liver dysfunction, and renal dysfunction in the blood/serum/plasma of diabetic rodents. RSV treatment reduced STZ-induced hyperglycemia with 1) a decrease in blood/plasma glucose levels [187,189–192,203,207,211,222,226,228,229], plasma fructosamine (a glycated protein) [217], serum advanced glycation end products [200], and blood glycosylated hemoglobin (HbA1c) [211], and 2) an increase in plasma insulin [191,211], adiponectin [200] and C-peptide [200] levels.

Oxidative or nitrosative stress-related markers, which were altered in STZ-induced diabetic rodents, were reversed by RSV treatment. RSV treatment reduced plasma lipid peroxidation [211,222] with decreased levels of plasma MDA [190,194,195,207]. Additional decreases in reactive oxygen/nitrogen levels including blood NO [211], plasma

Table 9
Effects of RSV on biomarkers altered by STZ in animal models (2009–2014).

Marker	Tissue (A: activity, P: phosphorylation, E: expression, I/R: upon ischemia/reperfusion injury, ↑↑ higher than basal level)
Proteins	
Acetylcholinesterase (AChE)	Cerebral cortex synaptosome↓ [198], hippocampus↓ [199]
Advanced glycation end products (AGE)	Serum↓ [200]
Alkaline phosphatase (ALP), activity	Serum↓ [191,201], blood↓ [202]
5′ AMP-activated protein kinase (AMPK)	Lipid raft fraction in left ventricle↑P [192], kidney↑P/E [203], hippocampus↑P [204], liver↑A [205]
Alanine aminotransferase (ALT), activity	Serum↓ [206], kidney↓ [200], serum↓ [191,201,207]
Aspartate aminotransferase (AST), activity	Serum↓ [206], kidney↓ [200], serum↓ [191,201,207]
Aminolevulinate dehydratase (δ-ALA-D), activity	Liver↑ [206], kidney↑ [206]
AKT, phosphorylated	Left ventricle↑ [192], kidney↓ [208], I/R left ventricular tissue↑ [189] and I/R heart↑ [209]
Bilirubin	Serum↓ [201,207]
Catalase, activity	I/R brain↑ [210] liver↑ [201,206], kidney↑ [206], sciatic nerve sections↑E [194], blood↑ [202], red cell↑ [195], pancreas↑ [211]
Cav-1	Lipid raft fraction in left ventricle↓ [192]
Cav-3	Lipid raft fraction in left ventricle↑ [192]
Plasma ceruloplasmin	Plasma↑ [211]
Citrate synthase, activity	Heart↓A [212]
Collagen IV	Glomeruli↓ [213], cortex↓ [214]
COX-1	Heart ↔ [215], kidney ↔ [216]
COX-2	Heart ↔ [215], kidney ↔ [216]
ERK1/2	Aortic tissue↓A [217], kidney↓P [213]
Fibronectin	Glomeruli↓ [213], cortex↓ [214]
FoxO1	Kidney↑ [214]
FOXO3a	Corpora cavernosa↓ [218]
Fructosamine	Plasma↓ [217]
Fructose-1,6-bisphosphatase	Kidney↓ [219], liver↓ [219]
Glucose-6-phosphatase	Kidney↓ [219], liver↓ [219]
Glucose-6-phosphate dehydrogenase	Kidney↑ [219], liver↑ [219]
γ-Glutamiltransferase (γ-GT), activity	Serum↓ [206]
Glucose transporter type 4 (GLUT-4)	Lipid raft fraction in left ventricle↑ [192], soleus muscle↑ [188]
Glutathione	Cardiac tissue↑ [212], liver↑ [207], liver GSH↑ [201], blood↑ [202], plasma↑GSH [211]
Glutathione reductase, activity	Cardiac tissue↑A [212]
Glutathione peroxidase (GPx)	Liver↑ [201], blood↑ [202], pancreas↑ [211]
Glutathione-S-transferase	Liver↑A [207], pancreas↑A [211]
Glycogen synthase	Liver↑ [219]
Glycogen phosphorylase	Liver↑ [219]
Hexokinase, activity	Kidney↑ [219], liver↑ [219]
Histone H3	Kidney↓dephosphorylation [186]
HO-1	I/R left ventricle↑ [189]
β-Hydroxyacyl coenzyme-A dehydrogenase, activity	Heart↓A [212]
Insulin	Plasma↑ [191,211]
Intercellular adhesion molecule-1 (ICAM-1)	Thoracic aorta and carotid artery↓ [220], renal cortex↓ [208]
IL-1β	Serum↓ [220], plasma↓ [211], kidney↓ [200,203], liver↓ [201,221]
IL-6	I/R brain↓ [210], serum↓ [220], kidney↑ [203], kidney↓ [200], liver↓ [201], hippocampus↓ [204], plasma↓ [222], plasma↓ [211]
IL-10	I/R brain↑ [210]
Lactate dehydrogenase (LDH)	Kidney↓ [219], liver↓ [219]
MCP-1	Thoracic aorta and carotid artery↓ [220]
Myeloperoxidase (MPO)	I/R brain↓ [210]
MMP-9	Heart ↔ [215]
NFκB	Heart↔E [215] Aortic tissue↓E [217], thoracic aorta and carotid artery↓A/E [220], kidney↓E [208], kidney↓E [200], liver↓E [221], hippocampus↓E [204], gastrocnemius muscle↓A [205], polymorphonuclear cells↓A [222], pancreas↓A [211]
p-eNOS, endothelial, phosphorylated	Heart↑ [192], I/R left ventricular tissue↑ [189]
eNOS, endothelial	Heart↑ [209], microvessel↑↑(more than basal level) [223]
iNOS, inducible	Heart↓ [209]
nNOS, neuronal	Heart↓ [209], microvessel↑↑ [223]
NTPDase	Brain (cerebral cortex synaptosomes)↑A [198]
5′-Nucleotidase	Brain (cerebral cortex synaptosomes)↑A [198]
p38	Kidney↓ [186]
p53	Kidney↓ [186], corpora cavernosa↓ [218]
p62	Heart↓ [224]
PAI-1 expression	Renal cortex↓ [208]
Phosphoenolpyruvate carboxykinase (PEPCK)	Liver↑ [188]
Proliferation cell nuclear antigen (PCNA)	Aortic tissue↓ [217], glomeruli kidney↓ [208]
Pyruvate dehydrogenase, activity	Heart↑A [212]
Pyruvate kinase, activity	Kidney↑ [219], liver↑ [219]
Quinone reductase	Liver↑A [207]
Rab7	Heart↑ [224]
RAGE	Aortic tissue↓ [217]
SERCA2a	Heart↑ [225]
SirT1	Heart↑E [215,224], heart↑A [224,225], kidney↑E [214], liver↑A [205], corpora cavernosa↑E [218]
SIR2	Kidney↑E [186]
Smad2	Kidney↓P [213]
Smad3	Kidney↓P [213]
SOD, activity	I/R brain↑ [210], liver↑ [201,206,207,226], aortic tissue↑ [226], kidney↑ [206] kidney↑ [214], blood↑ [202,222], pancreas↑ [211], corpora cavernosa↑ [218]

(continued on next page)

Table 9 (*continued*)

Marker	Tissue (A: activity, P: phosphorylation, E: expression, I/R: upon ischemia/reperfusion injury, ↑↑ higher than basal level)
MnSOD, activity	I/R left ventricle↑A [189], liver↓E [221], spleen↑E [221]
TNF-α	I/R brain↓ [210], thoracic aorta and carotid artery↓ [220], kidney↑ [203], kidney↓ [200], liver↓ [201], hippocampus↓ [204], serum↓ [197], plasma↓ [211,222]
TGF-β	Glomeruli↓ [213]
Trx-1	I/R left ventricle↑ [189]
VEGF	I/R left ventricle↑ [189], hippocampus↓ [204]
Xanthine oxidase (XO)	Hippocampus, cortex, cerebellum, brain stem and spinal cord↓ [193]
Antioxidant-related	
Hydrogen peroxide	Liver↓ [201], plasma and pancreatic tissues↓ [211]
Hydroxyl radical	Kidney↓ [200]
Lipid peroxidation/lipid peroxide	Liver↓ [201,206], kidney↓ [206,227], plasma↓ [211,222], pancreas↓ [211]
Malondialdehyde (MDA)	I/R brain↓ [210], liver↓ [207,226], aortic tissue↓ [226], plasma↓ [190,194,195,207], kidney↓ [214], hippocampus, cortex, cerebellum, brain stem and spinal cord↓ [193], corpora cavernosa↓ [218]
Nitric oxide (NO)	Kidney↓ [200], liver↓ [201], brain↓ [197], hippocampus, cortex, cerebellum, brain stem and spinal cord↓ [193], blood↓ [211], I/R plasma↑ [209]
Nitrotyrosine	I/R heart↓ [209]
Non protein thiol	Liver↑ [206], kidney↑ [206]
Peroxynitrite	Plasma↓ [194]
Protein carbonyl	Kidney↓ [203], liver↓ [201,221], spleen↓ [221], plasma and pancreas↓ [211]
Superoxide anion	Kidney↓ [200,203], liver↓ [221], spleen↓ [221], I/R plasma↓ [209], brain↓ [223]
Vitamin C	Liver↑ [201,206], kidney↑ [206], plasma↑ [211]
Vitamin E	Liver↑ [201], plasma↑ [211]
Glucose-related	
Blood/serum glucose	↓ [187,189–192,203,211,222,226,228,229]
Glycogen, liver	↑ [187,219]
Glycosylated hemoglobin (HbA1c)	Blood↓ [211]
Kidney-related	
Creatinine	↓Plasma [203], serum↓ [206,227,228]
Kidney weight to body weight ratio	↓ [213]
Urea nitrogen	Blood↓ [203]
Urea	Serum↓ [206], kidney↓ [227]
Lipid-related	
Cholesterol, serum	↓ [206,207,229]
Fatty acid	Serum↓ [212]
Hypolipidemic	↑ [226]
Triglyceride, serum/plasma	↓ [187,206,207]
Nerve-related	
Cerebral infarction (cerebroprotective)	↓ [210]
Motor nerve conduction velocity (MNCV)	↑ [194]
Nerve blood flow (NBF)	↑ [194]
Other factors	
Autophagic dysfunction (autophagic flux)	↓ [224]
Weight	↑ [190,222]

peroxynitrite [194], plasma superoxide anion [209], plasma hydroperoxide [211], and plasma protein carbonyl [211] were reported as a result of treatment, along with increases in plasma levels of antioxidants including reduced glutathione [211], vitamin C [211], vitamin E [211], and ceruloplasmin [211], as well as the activities of antioxidant enzymes in blood including GPx [202], CAT [202], and SOD [202,222].

As mentioned above, hyperlipidemia, one of the diabetic complications, can be alleviated by RSV treatment [226], and this is associated with a decrease in total cholesterol [206,207,220,229], triacylglycerol [206,207,220], low-density lipoprotein (LDL) [207], and total cholesterol to high-density lipoprotein (HDL) ratio [207] in serum.

RSV treatment attenuated diabetic inflammation, accompanied by downregulated expression levels of IL-1β [211,220], IL-6 [211,220,222], NFκB [211], and TNF-α [197,211,222] in serum or plasma.

Liver function damage caused by STZ can be inhibited by RSV treatment with modification of related biomarkers. RSV treatment reversed the elevated enzymatic activities of alanine aminotransferase (ALT) [191,201,206,207], aspartate aminotransferase (AST) [191,201,206,207], γ-glutamiltransferase (γ-GT) [206], and ALP [191,201], and abolished the increased levels of bilirubin [201,207] in serum.

In relation to nephropathy, RSV treatment ameliorated renal dysfunction as judged by lowering plasma creatinine [203] and blood urea nitrogen [203].

5.2. Effects of RSV on blood vessels

RSV treatment inhibited STZ-induced vasculopathy [217] in rodents. RSV decreased i) vascular permeability in the aorta [217], retina [217], kidney [217], and blood–brain barrier [204], ii) vascular smooth muscle cell proliferation [217], and iii) aortic collagen deposition/cross-linking [217], whereas it normalized the impaired vascular reactivity/response (e.g., increased endothelium-dependent relaxation upon acetylcholine exposure in the aortic ring) [190,226]. In addition, the expression levels of biomarkers in blood vessels of diabetic rodents were altered by RSV treatment. The expression levels of ICAM-1 [220], MCP-1, chemokine (C-C motif) ligand 2 (CCL2) [220], TNF-α [220], and NFκB (total and nuclear) in the thoracic aorta and carotid artery [220] were downregulated. Also, the expression levels of PCNA [217], p-ERK1/2 [217], receptor for advanced glycation end product [217], and nuclear NFκB [217] in aortic tissue were decreased.

5.3. Effects of RSV on the heart

Treatment with RSV can alleviate heart dysfunction (diabetic cardiomyopathy), one diabetic complication, accompanied with reversion of the expression or activity of biomarkers or biochemical parameters which are altered in STZ-induced dibetic rodents. RSV treatment lessened i) cardiomyocyte apoptosis with downregulation of autophagic flux [224], ii) collagen deposition [225], and iii) atrial cardiac stem/progenitor cell loss [230].

RSV treatment increased i) the expression of Sirt1 [215], Rab7 (a crucial factor in the maturation of autophagosomes and their fusion with lysosomes) [224], GLUT4 [192], and caveolin-3 [192], eNOS [209], sarcoplasmic calcium ATPase 2a (SERCA2a; improves contractile dysfunction) [225], and glutathione [212], ii) enzymatic activities of pyruvate dehydrogenase [212], GR [212], and iii) phosphorylations of AMPK [192], eNOS [192], and Akt [192] were reverted to the normal condition with resveratrol treatment. Also, RSV decreased the expression of caveolin-1 [192], p62 protein [224], neuronal NOS (nNOS) [209], iNOS [209], the enzymatic activities of myocardial β-hydroxyacyl coenzyme-A dehydrogenase [212], and citrate synthase [212].

In addition, upon acute myocardial I/R injury, RSV treatment improved cardiac function upon I/R exposure, and decreased infarct size [189,209]. The downregulated expression of cardiac p-Akt (Ser473) [189,209], p-eNOS [189], thiredoxin-1 (Trx-1) [189], HO-1 [189], plasma NO, and the enzymatic activity of Mn-SOD [189], and upregulated cardiac nitrotyrosine and plasma superoxide anion, were reversed by RSV treatment in diabetic rats [209].

5.4. Effects of RSV on the kidney

RSV treatment ameliorated hyperglycemia-mediated renal dysfunction or diabetic nephropathy (e.g., oxidative damage [200], microalbuminuria [213]/proteinuria [227,228], glomerular hypertrophy [213], renal hypertrophy [228], glomerulosclerosis [213]), by lowering i) urinary levels of urea [206], creatinine [206,228], albumin [213], and albumin to creatinine ratio [208], ii) kidney weight to body weight ratio [208], iii) thickness of the glomerular basement membrane (GBM) [213], and iv) vascular leakage (capillary permeability) [217].

In renal tissue, RSV treatment attenuated increased levels of proinflammatory proteins including IL-1β [200,203], IL-6 [200,203], TNF-α [200,203], and NFκB [200,208]. However, RSV did not significantly affect the expression of renal COX-1 and -2 genes in diabetic rats [216].

RSV treatment might reduce renal tissue fibrosis, with the inhibition of TGF-β signaling by decreasing TGF-β [213] levels and the phosphorylation of smad2 [213] and smad3 [213], and subsequent expression of extracellular matrix molecules (fibronectin [213] and type IV collagen [213]) in diabetic glomeruli. Also, increased levels of fibronectin and type IV collagen in the renal cortex were decreased by RSV in STZ-induced diabetic rats [214]. RSV decreased p-ERK1/2 [213] which is related to hypertrophy and extracellular matrix accumulation in the renal tissue of rodents.

RSV treatment had effects on carbohydrate metabolism-related enzymes in diabetic kidney, with inhibition of enzymatic activities of LDH [219], glucose 6-phosphatase [219], and fructose 1,6-bisphosphatase [219], and induction of the enzymatic activities of hexokinase [219], pyruvate kinase [219], and glucose 6-phosphate dehydrogenase [219].

RSV treatment alleviated oxidative stress in the STZ-induced diabetic kidney in rodents, as judged by induction of the expression of Nrf2 [200], γ-glutamylcysteine synthetase heavy subunit [200], glutathione *S*-transferase (GST), mu 3 [200], and enhancing the enzymatic activities of CAT [200,206,214], SOD [200,206,214], GPx [200], GST [200], GR [200], glyoxalase-I [200] and aminolevulinic acid dehydratase (δ-ALA-D) [206]. RSV also increased the levels of nonprotein thiols (liver/renal), and vitamins C [200,203] and E [200], and reduced glutathione [200], while it decreased the levels of superoxide anion [200,203], TBARS levels [206], hydroxyl radical [200], NO [200], protein carbonyl [203], and MDA [214] in diabetic kidney.

In relation to vascular complications in the diabetic renal cortex, RSV treatment reversed the increased expression of plasminogen activator inhibitor-1 (PAI-1) (fibrosis and thrombosis) [208], intercellular adhesion molecule-1 (infiltration of leukocytes) [208], and the p-Akt/Akt ratio [208].

In relation to the glomerular filtration, RSV reversed the decrease of nephrin in the glomeruli of the diabetic kidney [213]. Also, in the diabetic kidney, RSV treatment enhanced the AMPK–Sirt1 pathway with upregulated expression levels of the p-AMPK [203], AMPK [203], Sirt1 [186,214], and FOXO1 [214], and decreased expression levels of dephosphorylated histone H3 [186] and p53 [186].

5.5. Effects of RSV on the hepatic system

RSV treatment resulted in the attenuation of liver dysfunction induced by STZ in rodent models. Treatment preserved the cellular function and structural integrity of hepatocytes from hyperglycemia-mediated oxidative damage [201], and demonstrated antihyperglycemic potential with improved hepatic glycogen content [219].

Treatment with RSV significantly decreased oxidative stress via i) reducing the levels of TBARS [206], superoxide anion [221], hepatic lipid peroxides [201], hydroperoxides [201], protein carbonyls [201], MDA [221,226], protein carbonyl [221], and NO [201], and ii) increasing the levels of reduced glutathione [207], vitamin C [201,206], vitamin E [201], reduced glutathione [201], nonprotein thiols [206], hepatic glycogen [219], Mn-SOD [221], as well as increased the enzymatic activities of GST [201,207], GR [201], NAD(P)H: quinone oxidoreductase (NQO) [207], CAT [201,206,207], SOD [201,206,207,226], δ-ALA-D [206], and GPx [201].

RSV treatment decreased inflammation markers including TNF-α [201], IL-1β [201,221], IL-6 [201], and NFκB [201,221], and normalized liver function-related enzymes, including downregulation of the enzymatic activities of hepatic aspartate transaminase (AST) [201], ALT [201], and ALP [201].

RSV attenuated STZ-induced alteration in carbohydrate metabolism-related enzymes by i) reducing the activity of LDH [219], glucose 6-phosphatase [219], fructose 1,6-bisphosphatase [219], glycogen phosphorylase [219], and phosphoenolpyruvate carboxykinase [188], and by ii) enhancing the activities of hexokinase [219], pyruvate kinase [219], glucose 6-phosphate dehydrogenase [219], and glycogen synthase [219] in the liver.

RSV treatment normalized energy metabolism with increased expression of hepatic AMPK and Sirt1, and mitochondrial biogenesis [205].

5.6. Effects of RSV on the central nervous system

Neurological complications or diabetic encephalopathy, including cognitive impairment with decreased hippocampal neurogenesis and synaptic plasticity, neuropathic pain, and cerebral infarction results from chronic hyperglycemia and subsequent oxidative stress. RSV treatment exhibited beneficial effects on diabetic brain with a decrease in neuropathic pain (thermal hyperalgesia [194,196,197], cold allodynia [196]), sensory neuropathy (e.g., thermal hypoalgesia with an increase in intraepidermal nerve fiber loss and the mean axonal diameter of myelinated axons of the tibial nerve [231]), cerebral infarction upon I/R exposure [210], neurodegeneration [204] (the reduction in motor nerve conduction velocity [194], nerve blood flow [194], DNA damage and apoptosis in sciatic nerve sections [194]), memory impairment [199], anxiety [232], and neuroinflammation (astrocytic activation) [204].

RSV decreased the apoptosis rate in the retina and sciatic nerve of diabetic rats [222], and exhibited a cerebroprotective effect against cerebral infarction, as judged by reduced oxidative stress markers (MPO

and MDA) and inflammatory markers (TNF-α and IL-6), and increased antioxidant (SOD and CAT) and anti-inflammatory markers (IL-10) in I/R-damaged brain tissue [210]. Inflammatory markers including TNF-α (hippocampus) [204,210], IL-6 (hippocampus) [204,210], and NFκB (hippocampus) [204] were inhibited, and Jak/Stat pathway-related genes including *IL-15*, *IL-22*, *Socs2*, and *Socs5* [233] were suppressed. Treatment altered oxidative stress-related markers indicated by a decrease in NO release [193,197] (hippocampus, cortex, cerebellum, brain stem and spinal cord), MDA [193] (hippocampus, cortex, cerebellum, brain stem and spinal cord), xanthine oxidase [193] (hippocampus, cortex, cerebellum, brain stem and spinal cord), and an increase in CAT (sciatic nerve sections) [194].

RSV treatment reversed the expression levels of genes related to neurogenesis, neurotransmission, and synaptic plasticity: RSV up-regulated Hdac4 and Wnt7a, while it down-regulated Hat1 and ApoE. RSV treatment inhibited the enzymatic activities of acetylcholinesterase (cerebral cortex synaptosomes [198] hippocampus [199], cerebral cortex [199], striatum [199]).

RSV improved energy metabolism/mitochondrial biogenesis with an increase in the activity of AMP-activated protein kinase (metabolic regulator that promotes insulin sensitivity and energy production) and mitochondrial number per neuron (hippocampus) [204].

In addition, treatment improved cerebrovascular dysfunction. Blood vessel permeability [204] was decreased, and the responses/reactivity/dilation of pial arterioles in response to ADP (eNOS-dependent agonist) and *N*-methyl-D-aspartic acid (nNOS dependent agonist) [223] was increased with diabetic rats.

5.7. Effects of RSV on the pancreas

Although there is a report that RSV treatment had no beneficial effect on glucose tolerance or graft survival on mouse islet engraftment [234]. RSV treatment protected beta cells from oxidative damage while maintaining their function and structural integrity [211]. In relation to the oxidative stress, the increased levels of lipid peroxides, hydroperoxides, and protein carbonyls and the decreased activities of SOD, CAT, GPx, and GST in diabetic pancreatic tissues were reversed by RSV treatment [211]. RSV treatment prevented apoptosis with decreased levels of cleaved forms of caspase-3 and PARP in the beta cells of the pancreas [235].

5.8. Effects of RSV on spleen

RSV treatment alleviated oxidative stress correlated with the down-regulated levels of superoxide anion content, protein carbonyl, and Mn-SOD in STZ-induced diabetic spleen. However, RSV treatment showed different effects on proinflammatory markers: RSV treatment decreased NFκB and IL-1β, whereas it increased TNF-α and IL-6 [221].

5.9. Effects of RSV on the reproductive system

RSV treatment improved/restored erectile function with increases in the intracavernous pressure to mean arterial pressure ratio [236], smooth muscle to collagen ratio in cavernosum tissue [218], and smooth muscle content of the cavernosum [218] of STZ-induced diabetic rats. Also, deregulated biomarkers in the corpora cavernosa were normalized by RSV treatment. For instance, Sirt1 expression and SOD activity were upregulated, whereas the expression of apoptotic p53 and oxidative stress-related FOXO3a was downregulated [236].

5.10. Effects of RSV on muscle/tendon

The reduced phosphorylation of Akt and GSK3 in both fast- and slow-twitch muscles in diabetes was reversed by RSV treatment [237]. RSV treatment improved the process of tendon healing with a higher ratio of newly synthesized collagen area to the healing region area [238].

5.11. Effects of RSV on embryonic development

RSV suppressed diabetes-induced impairment during embryonic development, along with reversal of decreased expression of retinoic acid receptors, retinoid X receptors, and p-ERK1/2, and increased expression of p-c-Jun N-terminal kinase (JNK) and p-p38 [239].

6. Obesity

With animal models, obesity is induced by providing high-caloric diet (e.g., excessive amount of dietary fat or sugar). Common markers for obesity include body weight and fasting serum levels of glucose and insulin. Of 13 studies [168,240–251], 11 [168,240–244,246,248–251] include a standard diet control. Among ten studies [168,240–244, 248–251] which provide the body weight of animals, eight with rat or swine models showed significant differences between standard diet and obesity-inducing diet [168,248]. Notably, RSV treatment is reported to reduce body weight [240,241,244,249] or have no effect [242,243,250, 251]. Eight [240–244,246,250,251] out of the abovementioned 11 studies [168,240–244,246,248–251] demonstrated that there is a significant difference in glucose tolerance between standard diet and fat/sugar-enriched diet controls. All eight studies [240–244,246,250,251] demonstrated that RSV regimens (dose range: 30–400 mg/kg body weight/day, duration: 1–20 weeks) improved glucose tolerance [240,242,243, 246,250,251] or lowered fasting glucose level [241,244] compared with obese controls with mice or swine models. Among the eight studies [240–244,248–250] providing fasting insulin levels in blood/serum, six studies [240–244,250] showed that treatment with RSV decreased circulating insulin in obese models using mice or pigs. However, a significant difference between a standard diet and a high-fat, high-sugar obese model in Rhesus monkeys was not detected [248,249].

A summary of the results from animal studies related to obesity is presented in Table 10. As illustrated by the trend analysis shown in Fig. 3, based on 13 reports in the literature, there is a tendency for RSV to improve glucose tolerance and decrease serum insulin, whereas alteration of body weight varies.

7. Central or peripheral nervous system diseases/disorders

In earlier studies (pre-2009), the neuroprotective properties of RSV with various stimuli have been reported. Neurotoxicity induced by kainic acid (excitotoxin) was alleviated by RSV treatment as judged by recovery of glutamate decarboxylase (GAD) activity in olfactory cortex and hippocampus [252], reduction in incidence of convulsions along with brain MDA levels [253], attenuation of hippocampal neuronal damage [254], and a decrease in activation of astrocytes and microglial cells [254] in rats. In middle cerebral artery (MCA) occlusion-induced cerebral ischemia models, RSV reduced the total volume of infarction [255–258], suppressed motor impairment [256], improved necrotic changes in the cortex and basal ganglia [259], ameliorated the neurological deficit [258], and decreased permeability of the blood–brain barrier [258]. RSV decreased levels of MDA [256, 260], reduced glutathione [256], MMP-9 in brain [259], TNF-α, and MPO activity [258], while it increased MMP-2 and VEGF [261]. Notably, RSV failed to protect the brain in PPARα knockout mice [257], suggesting that the neuroprotective mechanism of RSV is related to PPARα.

7.1. Effect of RSV on depression

According to a fact sheet from the World Health Organization (WHO) in 2012, depression is a common worldwide mental disorder with more than 350 million patients (http://www.who.int/mediacentre/factsheets/fs369/en/). To evaluate the antidepressant

Table 10
Effect of RSV on diet-induced obesity in animal models (2009–2014).

Animal	Obesity-inducing model	Diet composition	Treatment	Standard diet (SD) for comparison with conditioned diet	Route	Dose (mg/kg body weight/day)	Duration (RSV treatment/total diet)	Body weight	Glucose tolerance, serum	Insulin, serum	Year	Reference
Male C57BL/6 male mice	High-calorie diet (HCD) for 14 weeks → RSV treatment for 5 weeks with HCD	58% calories from fat	Diet → RSV	Included	Injection into cerebral lateral ventricles *via* mini pump	79.2 ng/day	5/19 weeks	Not affected	Decreased (fasting glucose)	Decreased	2009	[244]
Male Sprague–Dawley rats	HCD for 6 weeks with RSV	4.6 kcal/g, 200 g/kg sucrose, 195 g/kg lard, 30 g/kg soybean oil	Diet + RSV	Not included	In diet	6, 30, 60	6/6 weeks	Not affected	Not affected	Not affected	2009	[247]
Mice (wild type, or deficient in AMPKα1 or -α2)	High-fat diet (HFD)	40% calories from fat	Diet + RSV	Not included	In diet	400	12/12 weeks (3 months)	Reduced (no comparison between SD and HFD, no effect in AMPKα1$^{-/-}$ mice)	Improved	Decreased	2010	[245]
Male Yorkshire miniswines	HCD/HFD	500 g of a hypercholesterolemic diet daily, 4% cholesterol, 17.2% coconut oil, 2.3% corn oil, 1.5% sodium cholate	Diet + RSV	Included	In diet	100	11/11 weeks	Body mass index (reduced)	Improved	Not available	2010	[251]
Male C57Bl/6J mice (wild type, or Glp1r$^{-/-}$)	HFD	72% calories from fat	Diet + RSV	Included	In diet	60	5/5 weeks	Not available	Improved	Not available (increased portal plasma insulin)	2011	[246]
Yorkshire miniswines	HCD/HFD	2248 kcal/day, hypercholest-erolemic diet, 4% cholesterol, 17.2% coconut oil, 2.3% corn oil, 1.5% sodium cholate	Diet + RSV	Included	In diet	100	11/11 weeks	Reduced	Improved	Decreased	2011	[250]
Female and male mini pigs	HFD	20% fat, 280 mg of cholesterol in 100 g diet	Diet + RSV	Included	In diet	0.114	12/12 months	No difference from SD	No difference from SD	Not available	2012	[168]
Male C57BL/6J mice	HFD	60% fat in diet	Diet + RSV	Included	In diet	200	20/20 weeks	Not affected	Improved	Decreased	2012	[240]
Male C57BL/6 N mice	HFD	58% calories from fat	Diet → RSV	Included	In diet	30	2/20 weeks	Not affected	Decreased (fasting glucose)	Decreased	2012	[241]
Male C57BL/6J mice	HFD	Lard (30%, w/w)	Diet → RSV	Included	In diet	400	16/24 weeks	Reduced	Improved	Decreased	2012	[243]
Rhesus monkeys	High-fat, high-sugar diet (HFSD)	42.3% calories from fat, 41.9% calories from carbohydrate (27% sucrose w/w)	Diet + RSV	Included	In diet	80 (1st yr) → 480 (2nd yr)	24/24 months	No difference from SD	No difference from SD	No difference from SD	2013	[248]
Rhesus monkeys	HFSD	42% calories from fat, 27% sucrose (w/w)	Diet + RSV	Included	In diet	80 (1st yr) → 480 (2nd yr)	24/24 months	Not affected	No difference from SD	No difference from SD	2013	[249]
Male Kunming mice	HFD	50% calories from fat	Diet + RSV	Included	In diet	200	12/12 weeks	Reduced	Improved	Decreased	2014	[242]

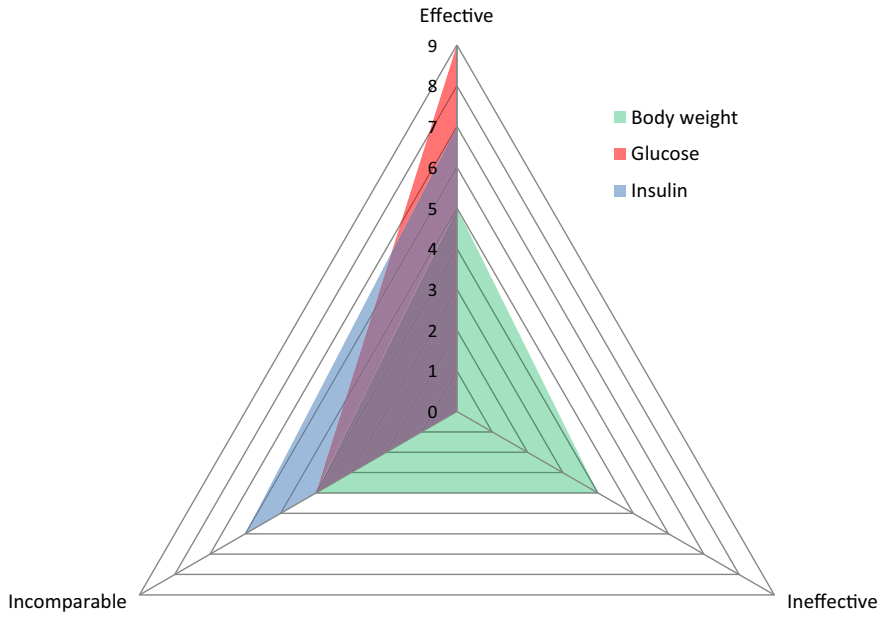

Fig. 3. Effects of RSV on glucose tolerance, serum insulin levels, and body weight with animal models used for studying obesity.

potential of compounds using animal models, multiple approaches have been adopted including behavioral tests and biochemical/neurochemical assays. In behavioral tests, the clinical symptoms/signs of depression including anhedonia (incapability to perform rewarded behaviors) and helpless behaviors can be measured/quantified using a sucrose preference test, forced swim test, tail suspension test, and shuttle box test (learned helplessness model) [262]. In relation to pharmacological aspects, it has been reported that monoamine deficiency, alteration/abnormality/dysfunction in hypothalamic–pituitary–adrenal (HPA) axis, reduction in neurogenetic/neurotrophic-growth factor, and dysregulation in the brain immune system are observed in depression models [263].

RSV was reported to exert antidepressant-like effects through alleviating depression-like symptoms/behaviors in rodent animal models. RSV treatment improved the helplessness symptom as judged by reducing the duration of immobility in the tail suspension or forced swimming tests in rats [264] and mice [265,266]. Also, under chronic stress conditions, an increase in immobility time in both forced swim and tail suspension tests [267], a decrease in sucrose preference [268], the learned helplessness using the shuttle box method [268], and an increase in adrenal gland/body weight [268], were reversed by RSV treatment in rats.

In addition, RSV treatment altered molecular markers related to depression. RSV induced brain-derived neurotrophic factor (BDNF) levels in the hippocampus of unstressed rats [264] and mice [269], as well as reversed the reduced expression of BDNF in the prefrontal cortex and hippocampus of chronic mild stress-exposed rats [270]. In addition, the reduced phosphorylation levels of cAMP response element-binding protein (CREB) and ERK, which is involved in learning, memory, and neuroplasticity, were normalized by RSV in stressed rats [270].

RSV can regulate the monoaminergic system. In the chronic stress rat model, RSV attenuated the decrease in serotonin (hippocampus, frontal cortex, hypothalamus), noradrenaline (hippocampus, frontal cortex, striatum, hypothalamus), and dopamine (frontal cortex), and the increase in monoamine oxidase-A (MAO-A) activity (hippocampus, frontal cortex) [268]. These effects also were found in the normal condition of mice: the levels of serotonin (hippocampus, frontal cortex, hypothalamus), noradrenaline (hippocampus, frontal cortex), and dopamine (frontal cortex) were increased while the activities of MAO-A and MAO-B (hippocampus, frontal cortex) were decreased [266]. In addition, it was shown that the anti-immobility effect of RSV was abolished by pretreatment with the serotonin antagonist *para*-chlorophenylalanine, demonstrating the possible involvement of RSV on the serotonergic system as related to its antidepressant potential [266].

As mentioned above, hyperactivity of the HPA axis along with upregulated corticosterone in serum was observed in animal models for depression. RSV reduced the upregulated serum concentration of corticosterone, which is known to increase during stress in chronically stressed-rats [267,270], as well as decreased serum corticosterone in unstressed mice [269].

7.2. Effect of RSV on epilepsy/seizure

Epilepsy affects about 50 million people worldwide. Reagents including kainite and pentylenetetrazole (PTZ) have been used to induce epileptic seizures in experimental animal models [271]. RSV reversed biomarkers that are altered in epileptic rat models. S100 calcium binding protein B that is mainly produced by astrocytes and released into serum and cerebral spinal fluid is a useful biochemical marker to evaluate brain damage after seizure [272]. RSV normalized the increase of brain damage markers in epileptic models. RSV reduced S100B protein levels in the cerebral spinal fluid and serum [272], neuron specific enolase levels in serum [273], and the expression of caspase-3 (an apoptosis marker) [273] and kainate receptor of the hippocampus [274] with PTZ-induced epileptic rats. Indeed, histological observations demonstrated a protective effect of RSV on damage in CA1 [273,274], hilus [273], or CA3a [274] of the hippocampus. In addition, altered oxidative stress parameters including increased MDA levels, reduced glutathione levels and CAT activity in epileptic brain of rats were reversed by RSV treatment [273]. Treatment with RSV increased seizure latency (delayed the onset of seizure) [272] and decreased seizure score [273].

The Morris water maze is used to measure the location memory ability (spatial probe test), and spatial learning and memory ability (place navigation test) [272]. RSV affected behavioral changes in epileptic rats. Treatment led to recovery of impairment in location memory ability [272] and spatial learning and memory ability [272], and decreased the number and rate of spontaneous seizures measured using

electroencephalography [274] in epileptic rats. However, RSV did not demonstrate protective effects on juvenile epileptic rats [275].

7.3. Effect of RSV on Alzheimer's disease

Alzheimer's disease (AD) is characterized by intraneuronal β-amyloid (Aβ) plaques and hyperphosphorylated tau, leading to neuronal cell death and progressive memory loss. RSV reduces cognitive impairment and has a neuroprotective role, decreasing the amyloid burden and reducing tau hyperphosphorylation [276].

RSV increased the mean life expectancy and maximal lifespan in SAMP8 (accelerated aging, a mouse model of sporadic and age-related AD) as well as their controls, the related strain SAMR1 [276]. RSV supplements (or RSV-fed animals) increased Sirt1 expression and consequent downregulation of apoptotic protein p53 in the cortex and hippocampus. Also, RSV supplements increased p-AMPK in the cortex and total AMPK in the hippocampus [276].

RSV affected AD-related markers. The expression of a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10; possessing α-secretase activity) was increased and the expression of p-tau (Ser396) was decreased by RSV in the cortex and hippocampus. CDK5 protein levels and the p25/p35 ratio were decreased and p-GSK3β (Ser9) was increased in the cortex, but not in the hippocampus. Levels of Aβ plaques in the hippocampus were decreased in this mouse model [276].

However, another study demonstrated that RSV neither improved cognitive function nor increased the expression of Sirt1 and acetylated p53 in the same mouse model [277]. This might be due to differences between the two studies, including the starting point of diet, duration, and dosage of RSV (e.g., starting at month 2 with 1 g/kg body weight for 7 months of treatment vs. starting at month 5 with 0.12 g/kg body weight for 2 months of treatment).

Aβ plaques are one of the unique features of AD. In animal models, AD can be induced by the administration of Aβ peptide accompanied by upregulation of iNOS and induction of HO-1 and neuronal apoptosis [278]. RSV improved spatial memory (decreased escape latency in the Morris water maze) with decreased accumulation of Aβ (25–35) and lipid peroxidation in the hippocampus. The biomarkers iNOS and HO-1, altered in Aβ-induced AD mice, were normalized by RSV [278].

Also, amyloid precursor protein (APP)/presenilin 1 (PS1) transgenic mice expressing a chimeric mouse/human APP, mutant human PS1, are frequently used for AD studies. Both early (starting at 15 weeks of age) [279] and late (at 50–53 weeks of age) [280] administration of RSV in APP/PS1 mice demonstrated the therapeutic potential of RSV as judged by altered biomarkers. Dietary RSV increased the expression of ACC [279], drebrin [280], and transthyretin [280], as well as the phosphorylation of AMPK [279], GSK3β (Ser9) [280], and tau (Ser396, Ser404) [280]. However, the effect on amyloid deposition differed from previous work, possibly due to the different starting points of diet, dosage, and duration.

7.4. Effect of RSV on Huntington's disease

Huntington's disease (HD) is caused by the mutation in huntingtin (*htt*) gene with clinical symptoms of involuntary hyperkinetic movements. HD models can be established in animals by toxins via inducing cell death either using excitotoxic agents including quinolinic acid and kainic acid, or disrupting mitochondrial machinery with 3-nitropropionic acid. Genetic models include transgenic mice such as R6/2, R6/1, N171-82Q, and YAC, or knock-in mice including HdhQ92, HdhQ111, CAG140, and CAG15O [281].

Sirtuins are NAD-dependent deacetylases that regulate important biologic processes including transcription, cell survival and metabolism. Activation of Sirt1, a mammalian sirtuin, extends longevity and increases neuronal survival. An important substrate of Sirt1 is PGC-1α, a principal regulator of energy metabolism, whose function is significantly impaired in HD [282]. Administration of RSV (SRT501-M) increased expression of PGC-1α, as well as its downstream targets, nuclear respiratory factor-1 and uncoupling protein-1, in brown adipose tissue with the N171-82Q transgenic mouse model of HD [282].

7.5. Effect of RSV on Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease that affects about 1% of the population over 55 years of age. Animal models of PD can be classified into neurotoxic [6-hydroxydopamine, 1-methyl-1,2,3,6-tetrahydropiridine (MPTP), paraquat, rotenone], and genetically mutated animal models (mutations in the genes encoding α-synuclein and LRRK2, PINK1/Parkin, or DJ-1) [283]. Oxidative stress is a hallmark in the pathogenesis of Parkinson disease (PD), which involves the selective loss of nigral dopaminergic neurons.

In one study, RSV protected dopaminergic neurons against MPTP-induced cell degeneration almost to the same extent as PGC-1α overexpression [284]. RSV treatment demonstrated behavioral improvements in PD animal models. RSV decreased abnormal rotational behavior in rats [285,286] and increased motor coordination skills in 6-hydroxydopamine-treated rats [287] and HtrA2 KO mice [288].

RSV showed neuroprotective effects in dopaminergic neurons with an increased number of tyrosine hydroxylase (TH)-positive cells in striatum and substantia nigra pars compacta in MPTP-treated mice [284] and in the nigral area of 6-hydroxydopamine-treated rats [285,286] along with an increase in dopamine and 3,4-dihydroxyphenylacetic acid levels in striatum [287] and nigrostriatum [289]. RSV increased the antioxidant activities in 6-hydroxydopamine-treated rats [286, 287]. TH is a rate-limiting enzyme in the synthesis of dopamine and is only present in dopaminergic neurons of the nigra area.

7.6. Effect of RSV on memory function

RSV treatment has been reported to improve memory in behavioral tests. Memory enhancement by RSV was blocked in Sirt1 mutant mice, suggesting that RSV improves memory via a Sirt1-dependent pathway [290].

Intraventricularlly-injected RSV ameliorated long-term memory formation and LTP induction from hippocampus CA1 in 8–9 month-old mice [290], and dietary treatment preserved cognitive function in aging mice with an improved cerebrovascular condition (higher microvascular density and a lower number of microvascular abnormalities), and had no effect on cholinergic cell number or fiber density [291].

A protective effect of RSV against chronic alcohol-induced cognitive dysfunction/deficits, and impaired learning and memory in both adults [292] and neonatal [293] rats, was reported to improved cognitive performance (spatial memory) in homocysteine-induced oxidative stress, apoptosis and cognitive impairment [294]. With the senescence-accelerated mouse (SAM), improved learning and memory ability, neuromuscular coordination, and sensorimotor capacity were reported [295].

RSV treatment has also be invested in the following systems: i) Prevention of memory decline in ovariectomized (OVX) rats chronically treated with D-galactose (D-gal) [296], ii) decreases in abnormality of pyramidal cells in the hippocampal CA1 sub-region in OVX rats chronically treated with D-gal [296], iii) prevention of CA1 cell injury and improved cognitive deficits in ischemia-exposed rats [297], iv) amelioration of impaired spatial learning and memory in hypoxia–ischemia-exposed neonatal rats [298], v) improved effects on learning and memory by acting on muscarinic cholinergic receptors in scopolamine- and mecamylamine-induced memory impaired rats [299], and vi) increases in spontaneous locomotor activity, working memory, and spatial memory performance in non-human primates, mouse lemurs (*Microcebus murinus*) [300].

Along with memory improvement, RSV treatment altered biochemical/molecular deficits. Reports have appeared indicating

i) decreased acetylation levels of PGC-1α in mouse hippocampus [290], ii) reduced acetylcholinesterase activity [292], iii) reduced levels of lipid peroxidation, nitrite, TNF-α, IL-1β, nuclear NFκB p65, and caspase-3 [292], iv) recovery of reduced glutathione [292], v) increased SOD [292] and CAT activities [292] in the cerebral cortex and hippocampus of chronic ethanol-administered adult [292] and neonatal rats [293], vi) reduced total homocysteine in plasma, reduced lipid peroxidase activity, DNA fragmentation, p53 expression in the hippocampus in homocysteine (which is known to cause apoptosis and impairment of neural plasticity in brain)-induced oxidative stress, apoptosis and cognitive impairment in rats [294], vii) increased gene expression and activity of SOD, and activity of GPx in the brain of SAM [295] and in the serum of OVX rats chronically treated with D-gal [296], viii) decreased MDA levels in the brain of SAM [295], and ix) decreased TBARS levels in the serum and hippocampus in OVX rats chronically treated with D-gal [296].

One study showed a negative effect of RSV in hippocampus-dependent spatial learning and memory with reduction of p-CREB and BDNF levels in the hippocampus [301].

7.7. Effect of RSV on ocular damage

RSV supplementation attenuated an increase in the expression of Bcl-2 and VEGF in the retina of neonatal rats with oxygen-induced retinopathy of prematurity [302]. Supplementation also shown to exert protective effects by inhibiting pathological parameters including TUNEL-positive retinal cells, outer nuclear layer thinning, and electroretinography changes in mice with light exposure (5000-lux white light for 3 h)-induced retinal degeneration. RSV reduced the activation of activator protein-1 and augmented Sirt1 activity in the retina [303]. RSV reduced the expression of eNOS and nNOS in an oxygen-induced (hyperoxia) retinopathy model with rats [304].

RSV treatment attenuated decreased electroretinogram (ERG) b-wave amplitudes, a loss of choline acetyltransferase indexing cholinergic amacrine cells, and increased vimentin levels (a marker of Müller cells), together with inhibition of upregulated MMP-9, HO-1, and iNOS, and recovery of downregulated Thy-1 (a marker of the neuron retinal ganglion cells) in high intraocular pressure-induced retinal ischemia with rats [305].

RSV treatment ameliorated impaired retinal function with increased ERG a- and b-wave amplitudes, ischemia-mediated thinning of the whole retina and, in particular, the inner retinal layers with a retinal ischemic injury model induced by elevation of intraocular pressure in the rat [306].

RSV inhibits tunicamycin (ER stress inducer)-induced vascular degeneration in the retina, together with inhibition of ER stress [downregulation of C/EBP homologous protein (CHOP), inositol-requiring enzyme-1α (IRE1α), Bip]. In addition, RSV inhibits retinal I/R-induced vascular degeneration, retinal I/R-induced upregulation of eukaryotic translational initiation factor 2α (eIF2α)-CHOP branch of ER stress, upregulation of IRE1α and Xbp1 splicing, and overexpression of Bip [307].

RSV prevented a cigarette smoke-induced increase in choroidal neovascularization following laser injury [308].

At the doses tested, no RSV effect was observed with the corneal neovascularization experimental model of corneal alkali burn in white Vienna rabbits [309].

7.8. Effect of RSV on nociceptive pain

RSV exhibited analgesic/antinociceptive effects in several animal models. RSV treatment prevented the licking behavior in acute nociception models induced by capsaicin or glutamate with mice. Interestingly, RSV downregulated capsaicin-induced c-Fos and COX-2 expression in the spinal cord and COX-2 expression in the cortex [310]. Treatment reduced IL-6 or plantar incision-induced allodynia in the mouse paw, and prevented the transition of allodynia to a chronic pain state (persistent nociceptive sensitization induced by PGE_2) in mouse paws [311].

RSV treatment attenuated mechanical allodynia and thermal hyperalgesia, with increased Sirt1 and decreased acetyl-histone H3 expression in the spine in rats subjected to a neuropathic pain model of chronic constriction injury (CCI) [312]. Spinal Sirt1 expression and deacetylase activity decrease after CCI surgery. RSV pretreatment alleviated CCI-induced neuropathic pain in mice, associated with thermal hyperalgesia and mechanical allodynia, which was reversed by intrathecal injection of the Sirt1 inhibitor EX-527, suggesting that the analgesic effect of RSV is mediated by Sirt1 deacetylase activity [313].

RSV pretreatment resulted in an antinociceptive effect of long-term morphine infusion induced antinociceptive/morphine tolerance in rats, associated with reversal of the upregulated *N*-methyl-D-aspartate receptor subunit NR1 and NR2B subunits in the synaptosome fraction and the postsynaptic density-95/NR1/NR2B complex in spinal cords. RSV pretreatment suppressed proinflammatory cytokines (IL-1β, IL-6, and TNF-α) in spinal cords [314].

7.9. Effect of RSV on other neuronal damage

RSV treatment resulted in varying neuroprotective outcomes with different study models involving neonatal rodents. RSV treatment did not prevent sevoflurane anesthesia-induced neuroapoptosis in neonatal mouse (six-day-old mice) brain [315]. However, prenatal RSV treatment alleviated early and late gestational stress-induced cognitive deficits/dysfunction in rats on postnatal day 40, without affecting reduced cerebral Na^+, K^+-ATPase activity which is related to memory consolidation [316].

RSV pretreatment to postnatal day 7 rat pups resulted in neuroprotection against ethanol-induced cerebellar toxicity/damage with an increase in the survival of cerebellar granule cells, a decrease in apoptotic events such as cleaved caspase-3 protein levels and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells, and a decrease in oxidative stress accompanied by increased levels of glutathione, nuclear Nrf2, QR1, and SOD2, and decreased levels of total thiol, MDA, and 8-iso-PGF2α (an oxidative stress marker for non-enzymatic lipid peroxidation) in the cerebellum [317].

In an experimental model of hypoxic-ischemic encephalopathy with postnatal day 7 rat pups, RSV treatment normalized the performances in righting reflex, rotarod and water maze tests with a reduction of infarct and preservation of myelination [298].

Chronic treatment of RSV attenuated disease onset and extended survival of transgenic mice overexpressing G93A-SOD1 (mutant SOD, a model of amyotrophic lateral sclerosis), with an increase in surviving motor neurons, levels of Hsp25 and Hsp70, and a decrease in acetylated heat shock factor 1 (HSF1) levels in spinal cords, demonstrating that the protective effect of RSV is mediated by Sirt1 with the deacetylation of HSF1 and subsequent upregulation of Hsps [318].

RSV exerted motor neuron protective activity. RSV abated fluphenazine-induced intensity of vacuous chewing movements, and attenuated the reduction in both locomotor and exploratory activities in an animal model of orofacial dyskinesia [319].

RSV exerted protective activity against neurodegenerative disorders. RSV treatment reduced the levels of $CD4^+$ T-helper 17 (T_H17) cells (by inhibiting the differentiation of $CD4^+$ T lymphocytes to IL-17A-positive T_H17 cells), IL-17A and MMP-2, -3, and 9, and elevated the levels of tight junction proteins (occludin and claudin-5) which improved Basso Beattle Bresnahan locomotor rating scale integrity in Ppt1-KO mice that mimic infantile neuronal ceroid lipofuscinosis [320].

RSV treatment i) alleviated fatigue symptoms with an increase in daily running activity, neurogenesis, and hippocampal BDNF expression, and a decrease in hippocampus atrophy, neuronal apoptosis, and hippocampal acetylated p53 expression in the fatigue mouse induced by *Brucella abortus* antigen [321], ii) resulted in unfavorable effects on hippocampal neurogenesis and cognitive function; RSV impaired

hippocampus-dependent spatial learning and memory, reduced the proliferation and survival of neural progenitor cells in the dentate gyrus of the hippocampus, associated with the elevated active form of AMPK, and the reduced p-CREB and BDNF in the hippocampus [301], iii) improved rat dorsal neuronal function with increased Basso Beattle Bresnahan locomotor rating scale scores, restored neural morphology, increased the number of neurons, increased SOD activity and Bcl-2 expression, and decreased MDA, IL-1β, IL-10, TNF-α, MPO, apoptosis (TUNEL-positive cells, Bax, and caspase-3) in of spinal cord injured rats [322], iv) elevated BDNF in the hippocampal tissues of rats [323], and v) reduced infarct volumes during the acute phase of ischemic stroke reducing brain injury in mice, with suppressed expression of IL-1β and TNF-α, microglial activation, and ROS production in the ischemic cortex (neuroprotective) [324].

RSV pretreatment prevented membrane lipid loss via reduction in the total content of gangliosides, phospholipids, and cholesterol in the hippocampi and cerebral cortex induced by global cerebral ischemia (ischemia/reperfusion injury) in rats [325]. Pretreatment also inhibited neuronal death, generation of ROS, lipid peroxidation and NO content while it improved oxidative stress parameters (decreased SOD and GPx, and increased CAT in the hippocampus; decreased SOD and the increased CAT in the cortex), and Na^+, K^+-ATPase (susceptible to free radical attacks, decreased after cerebral ischemia and in various chronic neurodegenerative disorders) activity in the cortex and hippocampus of rats with global cerebral ischemia [326].

RSV treatment reduced ischemic cell death in the first ischemic insult (mild stroke) and in the recurrent insult (recurrent stroke). Blood–brain barrier disruption and edema followed recurrent stroke [327].

8. Aging

Although it is controversial, some papers have indicated that RSV treatment can be beneficial for extending lifespan, reduce the aging process by inhibiting skin photoaging [38] caused by UV-B exposure, increase insulin sensitivity in old mice [328], maintain T-cell compartment and suppress proinflammatory markers in aging-hybrid mice [329], preserve mitochondrial function upon high-fat diet [330], enhance telomere length and telomerase activity in the aorta [331], improve aerobic performance and exercise capacity [331], and decrease oxidative stress/damage in the liver and skeletal muscle [332,333].

Topical application of RSV reduced hyperpigmentation (or suppressed melanin) in UV-B-stimulated guinea pig skin, with a reduction in skin tyrosinase-related protein 2 which is necessary for melanogenesis, supporting RSV as a potential depigmentation agent for treating hyperpigmentation and skin photoaging [38].

RSV treatment did not increase survival rates in old mice fed either standard diet or high-protein diet. Instead, RSV ameliorated insulin sensitivity in old mice fed standard diet with a decrease in resistin levels. However, RSV exhibited dual effects with an increase in serum inflammatory markers (CXCL1, and CCL5) and superoxide production and with a decrease in aortic distensibility in old mice fed high-protein diet [328].

RSV preserved the $CD4^+$ and $CD8^+$ T-cell compartment in splenocytes of old mice (30-months-old) similar to that of young mice (12-months-old). RSV treatment resulted in a reduction of proinflammatory cytokines such as IFN-γ, IL-6, and TNF-α, and attenuated oxidative DNA damage with decreased 8-OHdG levels in the spleen of old mice (30-month-old) [329].

RSV treatment induced the expression of Klotho which is known as an aging suppressor gene in the mouse kidney [334].

Treatment with RSV improved the downregulated mitochondrial biogenesis in the skeletal muscle and heart of mice fed a high-fat diet, with an increase in citrate synthase activity, mtDNA copy number, and mRNA expression of PGC-1α, mitochondrial mRNA expression of mitochondrial transcription factor A, and B2 (TFAM and TFB2M). The effect of RSV was abolished in animals lacking Sirt1, demonstrating that RSV function is mediated by Sirt1 [330].

Although the treatment of low dose of RSV (0.0015 mg/kg of chow) to rats for 6 months had no effect on lifespan, it resulted in increased/improved aerobic capacity, time of exercise tolerance, and endothelium-dependent relaxation by acetylcholine, with decreased expression of p53 and increased telomere length and telomerase activity in aortic tissue [331]. Treatment attenuated age-induced oxidative stress, with an increase in glutathione and GPx activity in the liver of old mice [332], and with induction of Mn-SOD activity, and reduction of hydrogen peroxide and lipid peroxidation levels in the skeletal muscle of middle-aged mice [333].

On the other hand, some papers have reported that RSV has no significant effects on extending lifespan. For example, RSV had no effect on the lifespan of genetically heterogeneous mice [335]. Similarly, RSV supplementation (1.5 or 6 mg/mouse/day) from 12 months of age had no significant effect on survival in genetically heterogeneous mice [336], nor did RSV extend the mean lifespan of Wrn mutant mice lacking the helicase domain of the WRN homolog [337].

9. Reproductive system diseases

RSV treatment has been reported to improve the reproductive capacity of female mice and male rabbits. Female (14–15-months-old) mice supplemented with RSV for one year from 2 to 3-months-old maintained fertility (to reproduce pups), with an increase in follicle pool, number and quality of oocytes. Also, RSV treatment resulted in an increase of telomerase activity, telomere length, and age-related gene expression of Sirt1 which was reported to increase telomerase activity, and a decrease of the senescence marker p21 in ovaries, similar to those of young mice (2–3-months-old) [338].

RSV treatment might improve erectile dysfunction induced by hypercholesterolemia, with increased vasorelaxation responses to acetylcholine in the corpus cavernosum isolated from cholesterol-fed male rabbits [339].

RSV showed a protective effect on endometriosis. RSV treatment in female rats with surgically induced endometriosis reduced implant size and histological changes in the endometriotic foci, with a decrease of VEGF levels in the peritoneal fluid and plasma, MCP-1, levels in the peritoneal fluid, and VEGF (angiogenesis marker, angiogenesis as a pathological alteration in endometriosis) expression in endometriotic tissue [340].

RSV treatment in female mice with surgically induced endometriosis resulted in a reduction in growth with reduced PCNA- and Ki67-positive stromal and glandular cells, and a decrease in angiogenesis of endometriotic lesions, with reduced microvessel density and CD31-positive endothelial cells in the neovascular lesions [341].

However, it may be necessary to be cautious about intake RSV during pregnancy. RSV treatment decreased maternal weight, placental inflammation, and liver triglyceride deposition, while it increased glucose tolerance, and uterine artery volume blood flow in pregnant nonhuman primates. The fetal pancreatic mass was abnormally enlarged by RSV treatment [342].

10. Irradiation injury

Total body irradiation (TBI) can lead to a decrease in survival, induction of bone marrow dysfunction and xerostomia. RSV exerted preventive effects with rodents undergoing TBI. RSV pretreatment increased survival, inhibited the reduction of WBCs and bone marrow nucleated cells (BMNs), and improved hematopoietic progenitor cells (HPCs) and hematopoietic stem cells (HSCs) with their clonogenic functions in bone marrow in mice undergoing TBI-induced long-term bone marrow injury [343]. In relation to molecular alterations, after TBI, RSV i) deceased ROS production and NOX4 expression, and increased SOD2 and GPx-1 expression in HSCs and HPCs, ii) decreased p16 and

acetylated p53 expression and increased Sirt1 expression in HSCs, and iii) increased enzymatic activity of SOD2 and GPx-1 in BM-MNCs [343].

RSV treatment attenuated acinar loss, ductal damage and cell necrosis, with an increase in glutathione levels and a decrease in MDA in both the parotid and submandibular glands of TBI-induced salivary gland dysfunction model with rats [344].

11. Clinical studies

Early clinical studies conducted with RSV explored pharmacokinetic properties to provide a rudimentary understanding of metabolism, bioavailability, etc., with healthy subjects. More recently, as shown in Fig. 4, the pharmacological features of RSV have been studied. Currently, the majority of clinical studies focus more on pharmacodynamics and, notably, clinical trials have been performed with overweight/obese, diabetic/metabolic syndrome, and cancer patients, as well as those with cardiovascular disease. A summary of clinical studies with RSV is listed in Table 11.

11.1. Cancer

In patients with colorectal cancer who consumed RSV before surgical resection, tumor cell proliferation was reduced, suggesting that RSV may serve as a colorectal cancer chemopreventive agent [345]. SRT501 (micronized RSV) supplementation with colorectal cancer and hepatic metastases patients resulted in increased levels of cleaved caspase-3 in malignant hepatic tissue [346]. However, SRT501 had no effect on the levels of IGF-I, Ki-67, p-Akt (ser473), Akt1, p-GSK3, GSK3, p-ERK, ERK, p-JNK, JNK, β-catenin, survivin, Bcl-2, Bax, or PARP [346].

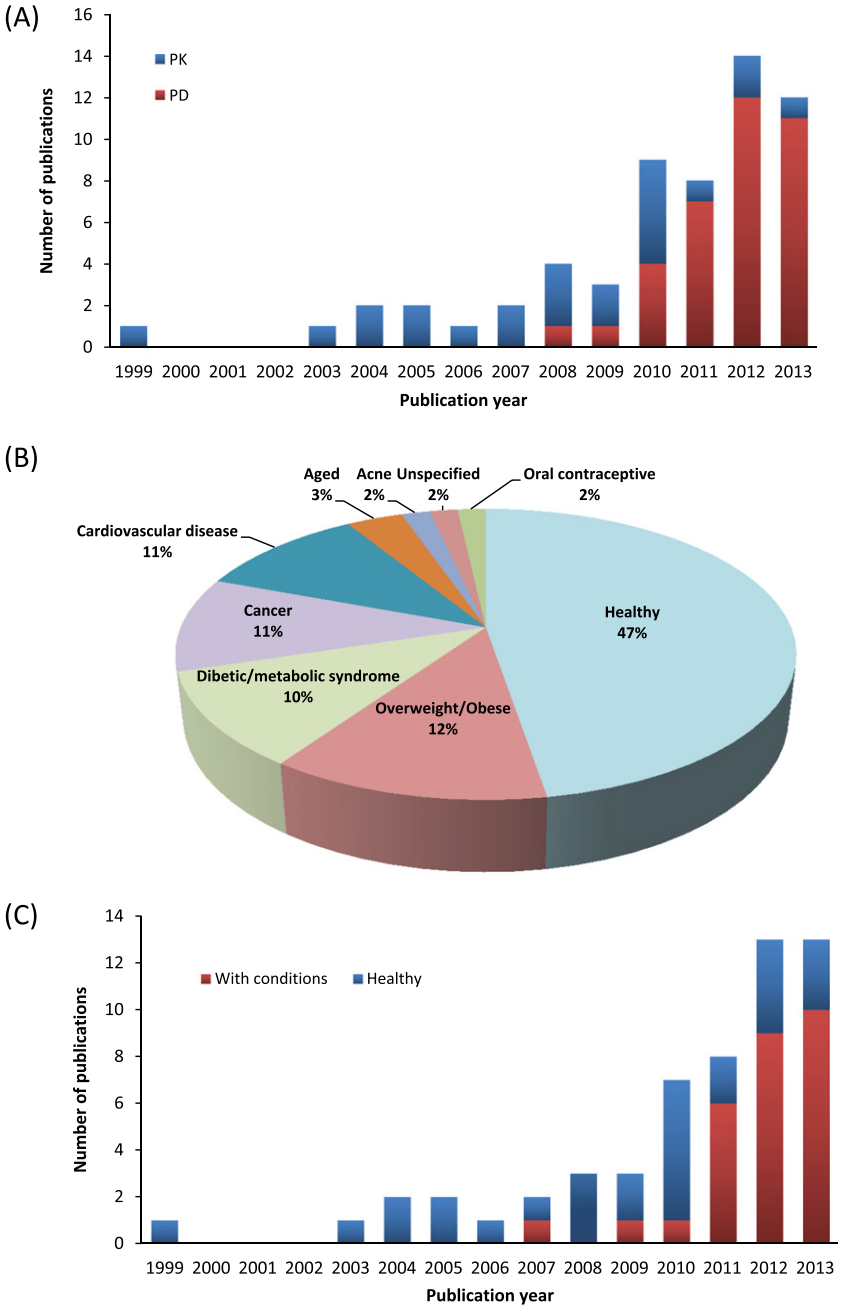

Fig. 4. Analysis of clinical trials conducted with RSV. (A) A chronological trend of clinical studies [pharmacokinetic-related studies (PK) vs. pharmacodynamic-related studies (PD)], (B) pie chart illustrating the health status of subjects participating in clinical trials, and (C) chronological trend of studies conducted with healthy patients vs. those with medical conditions.

Table 11
Effects of RSV in clinical trials (2009–2014).

Enrollment size (control/intervention)	Participants condition	Age(year) of RSV group (range)	Study design	Route	Amount per day	Duration	Outcome	Year	Ref.
Cancer									
20	Patients with histologically confirmed colorectal cancer	66.8 ± 17.2 (46–83)	Not available	Oral	0.5 or 1.0 g/day	8 days → surgical resection	Tumor cell proliferation (Ki-67)↓	2010	[345]
9 (3/6)	Patients with confirmed stage IV colorectal cancer and hepatic metastases had a life expectancy of less than 3 months → scheduled to undergo resection of liver metastases	68.5 ± 10.8 (18 years or older)	Pilot study, phase I, randomized (2:1), double-blind clinical trial	Oral (SRT501, micronized RSV in water)	5.0 g/day	~14 days (10–21 days) → surgical resection	*Cleaved caspase-3 in malignant hepatic tissue↑ *No significant differences in IGF-I, Ki-67, p-Akt (ser473), Akt1, p-GSK3, GSK3, p-ERK, ERK, p-JNK, JNK, b-catenin, survivin, Bcl-2, Bax, and PARP	2011	[346]
39	Adult women at increased breast cancer risk	Median age, 59.5 years in low dosage and 54 years in RSV high dosage	Randomized, double-blind, placebo-controlled	Capsule	*P. cuspidatum* with 5 or 50 mg of RSV, twice per day	12 weeks	*No significant effect on the methylation of 4 cancer-related genes (*p16*, *RASSF-1α*, *APC*, *CCND2*) *Positive correlation between RASSF-1α methylation and nipple aspirate fluid (NAF) PGE_2	2012	[347]
42	Healthy volunteers, 2 weeks of washout	40 (19–64)	Not available	Oral	1 g/day, once per day	4 weeks	*CYP3A4, CYP2D6, and CYP2C9↓ *CYP1A2↑	2010	[348]
Cardiovascular									
40 (20/20)	Post-infarction Caucasian patients (a history of myocardial infarction)	66.3 ± 8.9 (42–80)	Double-blind, randomized, placebo controlled trial	Capsule	10 mg/day	3 months	*Left ventricular diastolic function↑ *Endothelial function measured by flow-mediated dilatation (FMD) of the brachial artery↑ *Low-density lipoprotein (LDL) level↓ *Red blood cell deformability↑ *Platelet aggregation↓ *No changes in white cell count, platelet count, CRP, HgbA1c, TNFα, total cholesterol, triglyceride, HDL-cholesterol	2012	[349]
75 (25/25/25)	Statin-treated patients in primary cardiovascular disease prevention	62 ± 9	Triple-blind, randomized, placebo-controlled trial	Capsule	8 mg/day, daily RSV enriched grape extract (GE-RES), grape extract (GE, similar polyphenolic content but no resveratrol), or placebo (maltodextrin)	6 months	*LDLox/ApoB↓ (more than GE) *Non-HDL/ApopB↑ (more than GE) *No changes in GGT, AST, ALT, LDH, ALP, CPK, glucose, TSH, T4, bilirubin, creatinine, urate, albumin	2012	[350]
75 (25/25/25)	Patients on statin treatment for 3 months before inclusion and diabetes mellitus or hypercholesterolemia plus another CV risk factor.	62 ± 9 (18 to 80)	Randomized, triple-blinded, placebo controlled trial with 3 parallel arms	Capsule	GE-RES (RSV 8 mg, daily) for 6 months → GE-RES (16 mg, daily) for 6 months	12 months	*Glucose, glycated hemoglobin↓(more than GE) *Decreases in high-sensitivity CRP, TNF-α, PAI-1, and IL-6/IL-10 ratio *IL-10↑	2012	[351]
1000	1000 participants in the PREDIMED Study (479 men and 521 women)	65.0 ± 5.4	Large cross-sectional, parallel-group, multi-center, controlled, randomized clinical	Total resveratrol metabolite (biomarker of wine intake)	Not available	Not available	*Direct association between RSV consumption and lower concentrations of fasting blood glucose and triglycerides, also lower heart rate	2012	[352]
75 (25/25/25)	Stable-coronary artery disease patients	Between 18 and 80 years	Triple-blind, randomized, placebo-controlled, one-year follow-up, 3-arm pilot clinical trial	Capsule	GE-RES (RSV 8 mg, daily) for 6 months → GE-RES (16 mg, daily) for 6 months	12 months	*Glucose, GIHB↓ (better than GE) *Anti-inflammatory serum adiponectin↑ *Thrombogenic PAI-1↓ *Activation of transcription factor Kruppel-like factor 2 (KLF2)↑ *Inhibition of inflammation-related transcription factors [activator protein 1 (Ap-1)], proto-oncogene c-JUN (JUN), activating transcription factor 2 (ATF-2), cAMP response element-binding	2013	[353]

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Table 11 (*continued*)

Enrollment size (control/intervention)	Participants condition	Age(year) of RSV group (range)	Study design	Route	Amount per day	Duration	Outcome	Year	Ref.
							(CREB)-binding protein *Donwregulation of extracellular-space acting genes related to inflammation, cell migration and T-cell interaction signals in PBMCs		
27 (13/14)	Healthyindividuals	65 ± 1 (60–72)	Randomized double-blind placebo controlled design	Tablet	250 mg/day + high-intensity exercise training	8 weeks	*Maximal oxygen uptake↓ *Interstitial level of vasodilator prostacyclin↓ *Muscle thromboxane synthase↑ *Abolished the positive effects of exercise on low-density lipoprotein, total cholesterol/high-density lipoprotein ratio and triglyceride. *No alteration in the effect of exercise training on the atherosclerosis marker VCAM-1, Sirtuin 1	2013	[354]
40 (20/20)	Healthy individuals	≥18 years	Double-blind, randomized, placebo-controlled clinical trial	NA	400 mg/day	30 days	*Reduction of plasma IFN-γ and fasting insulin concentration	2013	[355]
Diabetes									
19 (9/10)	Subjects with type 2 diabetes (T2DM)	57.9 ± 7.9	Double-blind, placebo-controlled study	Oral	5 mg, twice/day, daily	4 weeks	*Decreased insulin resistance, and urinary ortho-tyrosine excretion. *Increased the pAkt:Akt ratio in platelets. *Had no effect on β-cell function.	2011	[356]
62 (29/28)	Subjects with T2DM	56.67 ± 8.91	Open-label, randomized, controlled trial	Oral	250 mg/day	3 months	*Decreased the mean hemoglobin A(1c), systolic blood pressure, low-density lipoprotein cholesterol (LDL-C), total cholesterol, urea nitrogen, and total protein in T2DM *No effect on high-density lipoprotein cholesterol (HDL-C)	2012	[357]
10 (0/10)	Subjects with impaired glucose tolerance	72 ± 3	Pilot study, randomized, take open-label RSV No control group	Oral	1, 1.5, and 2 g/day	4 weeks	*Improved insulin sensitivity (Matsuda index) and post meal plasma glucose. *No changes in weight, blood pressure, fasting plasma glucose and lipids	2012	[358]
24 (12/12)	Obese subjects	44.7 ± 3.5	Investigator-initiated, randomized, double blinded, placebo-controlled, parallel-group trial	Oral	Thrice (500 mg × 3 = 1.5 g/day)	4 weeks	*No changes in >Glucose turnover and insulin sensitivity >Endogenous glucose production and the turnover >Oxidation rates of glucose >Blood pressure >Resting energy expenditure >Oxidation rates of lipid >Ectopic or visceral fat content >Inflammatory biomarkers: TNFα, NFκB expression in adipose tissue >Metabolic biomarkers: p-AMPK, p-acetyl-CoA carboxylase, GLUT4, and PGC1α expressions, and total acetylation status of lysine residues in muscle	2013	[359]
35 (9/13/13 = Placebo/GE/GE-RES)	Hypertensive subjects with type 2 diabetes mellitus (T2DM)	63 ± 12	Randomized placebo-controlled, triple-blind, dose-response, 1-year follow-up with three parallel arms	Oral	GE-RES (RSV 8 mg), daily	12 months	*No changes in body weight, blood pressure, glucose, HbA1c or lipids *Altered biomarkers more significantly than in the GE group in comparison with placebo control. >Reduced ALP and IL-6 levels in serum >Reduced CCL3, IL-1β and TNF-α in PBMC >Increased LRRFIP-1 in PBMC >Increased miR-21, miR-663, miR-30c2	2013	[360]
24 (10/14)	T2DM subjects with diabetic foot syndrome	54.0 ± 10.1	Placebo-controlled, examiner-blinded, parallel-group randomized controlled pilot clinical	Oral	50 mg × 2/day	60 days	*Reduced parameters reflecting diabetic ulcer size *Declined plasma fibrinogen level *No effect on CRP	2014	[361]
66 (31/33)	Subjects with T2DM	52.45 ± 6.18	A randomized placebo-controlled	Oral	1 g/day	45 days	*Decreased systolic blood pressure, fasting blood glucose, hemoglobin A1c, insulin,	2013	[362]

			double-blinded parallel clinical trial				and insulin resistance *Increased HDL		
Obesity									
19 (19/19)	Overweight/obese with elevated blood pressure (BP) without diabetes	55 ± 2	Randomized, double-blind, placebo-controlled, crossover human intervention trial	Oral	RSV (resVida™) 30, 90 and 270 mg, weekly	1 h after consumption	*Increased plasma RSV and flow-mediated dilatation of the brachial artery (FMD)	2011	[363]
11 (11/11)	Obese without diabetes	52.5 ± 2.1	A randomized double-blind, placebo-controlled, crossover study	Oral	resVida™ 150 mg/day	30 days	*Reduced sleeping and resting metabolic rate *Decreased homeostasis model assessment (HOMA) index *Increased p-AMPK (Thr172), SIRT1 and PGC-1α protein levels, citrate synthase activity, muscle mitochondrial respiration on a fatty acid-derived substrate in muscle *Increased intramyocellular lipid levels *Decreased intrahepatic lipid content, circulating glucose, triglycerides, alanine-aminotransferase, leptin, and TNF-α in plasma	2011	[364]
45 (14/15)	Overweight, postmenopausal women without diabetes	58.2 ± 4.0	A randomized, double-blind, placebo-controlled trial	Oral	75 mg/day	12 weeks	*No effect on body composition, HOMA-IR score, resting metabolic rate, blood pressure, heart rate *No effect on insulin sensitivity in the liver, skeletal muscle, or adipose tissue *No effect on AMPK, SIRT1, NAMPT, and PPARGC1A, in either the skeletal muscle or adipose tissue *No effect on glucose, insulin, plasma lipids, adiponectin, leptin, CRP, IL-6 in plasma	2012	[365]
32 (10/12/10 = RES/RTP/CGSE)	Obese subjects without diabetes	36.5 ± 9.6	1 capsule per day of placebo for 28 days → 150 mg RSV, 300 mg RTP, or 400 mg CGSEf for 28 consecutive days	Capsule	150 mg/day	28 days	*Decreased GSH levels *Increased anti-oxidized low-density lipoproteins (oxLDL) *Decreased PON3, CCR4, MAZ, and TFRC. *Increased PRDX1, FTH1, CCL5, UBB, HYPB, and HERPUD1	2012	[366]
28 (28/28)	Obese subjects	61±1.3 (40-75)	Randomized, double-blind, placebo-controlled, crossover	Oral	75 mg/day	6 weeks	*FMD in the brachial artery↑ *No effects on blood pressure, arterial compliance, and all components of the Stroop Color-Word Test (maintaining healthy circulatory function)	2013	[367]
10	Obese subjects	52 ± 2	Randomized, double-blind, crossover design	Oral	resveratrol (Resvida®) 150 mg/day	30 days with 4 weeks washout	*No effect on fasting plasma concentrations or postprandial plasma responses of glucose-dependent insulinotropic polypeptide, or glucagon-like peptide-1, and incretin hormone levels *Postprandial glucagon responses↓	2013	[368]
8	Overweight or obese individuals with mild to moderate hypertriglyceridemia	45.8 ± 3.1	Randomized, double blind, placebo-controlled, crossover trial	Oral	1 g/day (500 mg twice/day) for 1st week, 2 g/day (1 g twice/day) for 2nd week	2 weeks per occasion (4–6 weeks apart between 2 occasions)	*No effect on insulin sensitivity *No effect on fasting or fed triglyceride concentrations in plasma *ApoB-48 production rate↓ *ApoB-100 production rate and fractional catabolic rate↓	2013	[369]
46 (23/23)	Overweight older individuals	50–75	Not available	Oral	200 mg/day	26 weeks	*Hippocampal functional connectivity↑ *HbA1c and body fat↓, leptin↑ *Memory performance↑	2014	[370]
Others									
22	22 healthy adults, 9 healthy men	24.8 (21–29)	Randomized, double-blind, placebo-controlled, crossover	Oral	250 or 500 mg	3 treatments 45 min before	*Cerebral blood flow during task performance↑	2010	[371]

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Table 11 (*continued*)

Enrollment size (control/intervention)	Participants condition	Age(year) of RSV group (range)	Study design	Route	Amount per day	Duration	Outcome	Year	Ref.
			study			cognitive tasks (7 days apart between occasions)			
	Patients affected by acne vulgaris	18–23	Single-blind study, pilot	Gel	daily, 0.001% w/w	60 days	*Global acne grading system score↓ *Lesions in areas↓	2011	[372]
12	Patients of reproductive age with a laparoscopic diagnosis of endometriosis, who were still reporting pain and breakthrough bleeding after the first 6 months of use of an oral contraceptive containing drospirenone + ethinylestradiol.	30 ± 5 (22–37)	Open office-based study	Oral	30 mg/day	2 months	*Pain scores↓ *Dysmenorrhea and pelvic pain↓	2012	[373]
42	Patients pelvic pain and/or infertility submitted to laparoscopy and hysteroscopy not only to confirm the diagnosis of endometriosis but also to treat the lesions	31 ± 4 (24–40)	Immunohistochemistry study	Oral	30 mg/day	2 months	*Inhibition of aromatase and COX-2 expression in eutopic endometrium of patients	2012	[373]
50	Healthy adult smokers		Randomized, double-blind, placebo-controlled, cross-over trial	Oral	Group 1: 500 mg/day, 30 days→ washout, 30 days→ placebo 30 days Group 2: placebo, 30 days → washout, 30 days → 500 mg/day, 30 days	30 days (total 90 days)	*CRP and triglyceride concentrations↓ *Total antioxidant status values↑ *No changes in uric acid, glucose, insulin, cholesterol, liver enzyme concentrations, and weight, waist circumference, and blood pressure values	2013	[374]
116 (29/29/29/29 = G1/G2/G3/CTL)	Most were in Canadian Cardiovascular Society angina class III at inclusion (62%), 30% were in class II, and 8% were in class IV	65 (42–83)	Randomized, double-blinded, active-controlled, parallel clinical trial	Oral	20 mg/day	60 days	*Left ventricular function marker (N-terminal prohormone of brain natriuretic peptide)↓	2013	[375]
783	783 community-dwelling men and women 65 years or older in 2 villages in the Chianti area	65 years or older	Prospective cohort study	Not available	None	Year 1998–2009	No significant alterations in serum CRP, IL-6, IL-1β, and TNF	2014	[376]

RSV supplementation decreased methylation of the tumor suppressor gene RASSF-1α which is directly related to a decrease in PGE_2 in adult women at increased breast cancer risk, demonstrating potential chemopreventive effects [347]. Also, RSV supplementation inhibited the phenotypic indices of CYP3A4, CYP2D6, and CYP2C9, while it induced the phenotypic index of 1A2 [348].

11.2. Cardiovascular disease

RSV supplementation i) improved left ventricular diastolic function, endothelial function measured by flow-mediated dilatation, and red blood cell deformability, and ii) decreased LDL levels and platelet aggregation, and unfavorable hemorheological changes in patients with coronary artery disease [349].

Stilvid® (RSV-enriched grape extract) supplementation exerted cardioprotective activity by decreasing oxidized LDL and apolipoprotein-B (ApoB) while increasing the ratio of non-HDLc (total atherogenic cholesterol load)/ApoB in statin-treated patients for primary cardiovascular disease prevention [350].

RSV-rich grape supplement (GE-RSV) improved inflammatory and fibrinolytic status, with a decrease in high-sensitivity C-reactive protein, TNF-α, plasminogen activator inhibitor type 1, and IL-6/IL-10 ratio, and an increase in anti-inflammatory IL-10, in patients who were on statins for primary prevention of CVD and at high CVD risk [351].

With the analysis of total urinary RSV metabolites (TRMs) in 1000 participants, RSV consumption was correlated with beneficial alterations in blood lipid profiles, fasting blood glucose, and heart rate [352].

With stable-coronary artery disease patients, consumption of RSV-containing grape extract (GE-RSV) resulted in an increase of the anti-inflammatory serum adiponectin, and a decrease of thrombogenic PAI-1, with downregulation of gene expression in peripheral blood mononuclear cells (PBMCs) of: Connective tissue growth factor (*CTGF*), cardiotrophin-like cytokine factor 1 (*CLCF1*), placental growth factor (*PGF*), insulin-like growth factor binding protein 4 (*IGFBP4*), gastrin (*GAST*), melanoma inhibitory activity (*MIA*), wingless-type MMTV integration site family member 10A (*WNT10A*), surfactant protein B (*SFTPB*), collagen, type XVIII, alpha 1 (*COL18α1*), thyrotropin-releasing hormone (*TRH*), *IL-1β-3*, *-8*, *-13*, *-17A*, *-17C*, and *-24*, chemokine (C–C motif) ligand 3 (*CCL3*), *CCL22*, chemokine (C–X–C motif) ligand 2 (*CXCL2*), *CXCL6*, *CX3CL1*, sonic hedgehog (*SHH*), lymphotoxin alpha (*LTA*), *IFNβ1* and *TNF* [353].

RSV supplementation abolished the positive effects by physical exercise training with i) a decrease in maximal oxygen uptake, interstitial level of vasodilator prostacyclin, and ii) an increase in muscle thromboxane synthase, LDL, total cholesterol/HDL ratio and triglyceride concentrations in blood, without altering atherosclerosis marker VCAM-1 and Sirt1 [354].

RSV supplementation led to the reduction in plasma IFN-γ and fasting insulin concentration [355].

11.3. Diabetes

In some cases, RSV treatment has been reported to improve insulin sensitivity and glycemic control in type 2 diabetic patients. RSV treatment for 4 weeks decreased insulin resistance (homeostasis model of assessment for insulin resistance) and urinary *ortho*-tyrosine excretion, while it increased the pAkt:Akt ratio in platelets. On the other hand, it had no effect on parameters that relate to β-cell function (i.e., homeostasis model of assessment of β-cell function) [356].

Treatment with RSV for 3 months improved mean hemoglobin A(1c), systolic blood pressure, LDL cholesterol, total cholesterol, urea nitrogen, and total protein in type 2 diabetes mellitus (T2DM). No significant changes in body weight and HDL cholesterol were observed in type 2 diabetes patients [357].

RSV treatment for 4 weeks improved glucose metabolism (fasting plasma glucose was unchanged, but peak post meal and 3-hour glucose AUC declined) in older adults with impaired glucose tolerance (IGT) [358].

RSV supplementation for 4 weeks in obese subjects had no effect on insulin sensitivity, endogenous glucose production and the turnover and oxidation rates of glucose, blood pressure, resting energy expenditure, oxidation rates of lipid, ectopic or visceral fat content, or inflammatory (TNF-α and NFκB) and metabolic (p-AMPK, p-ACC, GLUT4, and PGC-1α expressions) biomarkers [359].

RSV-enriched (8 mg) grape extract (GE-RSV) supplementation for 1 year showed beneficial immunomodulatory effects in hypertensive subjects with T2DM. GE-RSV treatment altered molecular markers more than GE treatment when compared with placebo. GE-RSV reduced serum inflammatory markers (ALP and IL-6 levels) and proinflammatory cytokines [C–C motif chemokine ligand 3 (CCL3), IL-1β and TNF-α] in PBMCs, while it increased the expression of the transcriptional repressor [leucine-rich repeat flightless-interacting protein 2 (LRRFIP-1)] and miRNAs (miR-21, miR-663, miR-30c2) in PBMCs [360].

RSV treatment in type 2 diabetic patients with newly diagnosed diabetic foot ulcers resulted in a reduction of diabetic ulcer size and plasma fibrinogen level [361].

RSV treatment exerted beneficial effects on T2DM subjects with a decrease in systolic blood pressure, fasting blood glucose, hemoglobin A1c, and insulin resistance, and an increase in HDL [362].

11.4. Obesity

In obese subjects, RSV exhibited a vascular protective effect [363, 367], mimicked calorie restriction [364], had an antioxidant effect [366], protected from deregulated glucose tolerance [368], had beneficial effects on hypertriglyceridemia [369], and improved memory performance (maintenance of brain health) [370].

RSV consumption increased flow-mediated dilatation of the brachial artery, a biomarker of endothelial function and cardiovascular health, in 19 overweight/obese men or post-menopausal women [363].

RSV intake modified clinical signs and molecular markers with obese men, including a decrease in i) the sleeping and resting metabolic rate, ii) homeostasis model assessment (HOMA) index (an indication of insulin sensitivity), iii) adipose tissue lipolysis and plasma fatty acid and glycerol in the postprandial state, iv) intrahepatic lipid content, and v) circulating glucose, triglycerides, alanine-aminotransferase, leptin (satiety hormone), and TNF-α, and an increase in i) intramyocellular lipid levels, ii) p-AMPK (Thr172), Sirt1, and PGC-1α protein levels, iii) citrate synthase activity, and iv) muscle mitochondrial respiration on a fatty acid-derived substrate [364].

RSV supplementation did not change i) body composition (intra-abdominal fat volume and intrahepatic triglyceride content), ii) blood pressure, iii) heart rate, iv) resting metabolic rate, and v) plasma adipokine levels (adiponectin and leptin) or inflammatory markers (C-reactive protein [CRP] and IL-6) insulin sensitivity in the liver, skeletal muscle, or adipose tissue in non-obese, postmenopausal women with normal glucose tolerance [365].

RSV supplementation reduced oxidative stress related markers in obese subjects. It decreased glutathione levels and increased oxidized LDLs, with alterations of gene expression related to oxidative stress and inflammation (decrease in *PON3*, *CCR4*, *MAZ*, and *TFRC*: increase *PRDX1*, *FTH1*, *CCL5*, *UBB*, *HYPB*, and *HERPUD1*) [366].

In further clinical trials, RSV supplementation i) resulted in an increase in flow-mediated dilatation without affecting blood pressure, arterial compliance, and all components of the Stroop Color-Word Test in obese but otherwise healthy adults [367], ii) had no impact on the levels of glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, and glucagon in fasting plasma, while it suppressed postprandial plasma glucagon responses [368], iii) reduced the production rate of triglyceride-rich apoB-48 and apoB-100 in overweight or obese individuals with mild hypertriglyceridemia [369], and iv) improved memory performance with an increase in functional connectivity between the

left posterior hippocampus and the medial prefrontal cortex, and improved glucose metabolism (decrease in HbA1c) in older adults [370].

11.5. Others

RSV treatment elevated cerebral blood flow during task performance [371], reduced the Global Acne Grading System (GAGS) score (the average area of microcomedones) of lesions in the face area caused by acne vulgaris [372], and reduced pain scores, with a decrease in dysmenorrhea and pelvic pain, in patients using oral contraceptives with endometriosis. RSV treatment also downregulated the expression of aromatase and COX-2 in the eutopic endometrium of patients with endometriosis and pelvic pain [373].

Finally, RSV treatment reduced CRP and triglyceride concentrations, and increased Total Antioxidant Status values in healthy smokers [374], and exhibited a beneficial effect with a decrease in left ventricular function marker, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) with stable angina pectoris patients with asymptomatic or symptomatic left ventricular dysfunction [375].

12. Discussion

As described herein, thousands of manuscripts have been published describing some aspect of resveratrol action, and generally the results are touted as correlating with some aspect of promoting better health. With the labyrinth of *in vitro* studies, however, it is frequently difficult to rationalize an actual relationship with pharmacological relevance since high concentrations of the parent compound are necessary to mediate a response. In most cases, achievable serum concentrations are many orders of magnitude below the concentrations used with *in vitro* studies. On the other hand, concentrations of metabolites such as RSV-3-*O*-glucuronide may be higher [262], and the mean plasma level of RSV itself can be enhanced by processes such as micronization [263]. Also, recent studies have suggested that improvements in RSV bioavailability can be realized through combination with other compounds. For example, co-treatment with piperine improved the bioavailability of RSV, increased maximum serum concentrations in mice [377], exerted a synergistic antidepressant-like effect with a mouse model [265], and enhanced bioefficacy on cerebral blood flow in human subjects [378]. In addition, many other factors come into play, such as enzymatic reconversion of RSV metabolites to the parent compound and the effect of combining RSV with other drugs or compounds, so clearly, additional work is required.

Although all of this is interesting from an academic or practical point-of-view, detailed discussion of such topics is beyond the scope of the current review. In this review, we have concentrated on results obtained with animal models and clinical trials involving human beings. The ultimate endpoint of greatest interest is the biological response mediated with a living mammal and, frankly, the array of responses reported over the past 5 years is simply amazing (Fig. 5). Amelioration of disease states and modulation of biomarkers is widespread over a large range of ailments. In many cases the *in vivo* investigations described herein allude to possible mechanisms, such as antioxidant, anti-inflammatory, and Sirt1 signal-activating capacities, but in actual fact it is difficult to pinpoint one truly critical target. Rather, it appears that the ability of RSV to mediate an overall response involves the weak modulation of a host of targets. As described previously, RSV is an extremely promiscuous molecule [379]. Taking advantage of this multifaceted pharmacological mode of action, additional uses of RSV have been suggested, such as exploitation as a probe for the rapid detection of Aβ and monitoring AD [380].

Considering the broad range of responses, it is tempting to view RSV as a panacea. It should be borne in mind, however, the effects are often statistically significant but relatively weak, so a definitive response or cure is not a reasonable expectation. This leads to the notion of creating analogs with greater potency and efficacy [381], but of course such an approach leads to greater developmental expenses, greater risk, and possibly adverse side-effects. It is noteworthy that RSV itself has not been found to exert adverse effects in animal models or clinical intervention studies.

As a distractor, a recent prospective cohort study, conducted in two villages in the Chianti area of Italy, revealed that total urinary RSV metabolite concentration did not correlate with inflammatory markers (serum CRP, IL-6, IL-1β, and TNF), cardiovascular disease, and cancer, nor was it predictive of all-cause mortality in 65-year-old or older subjects [376]. However, since this work is based on dietary levels, which

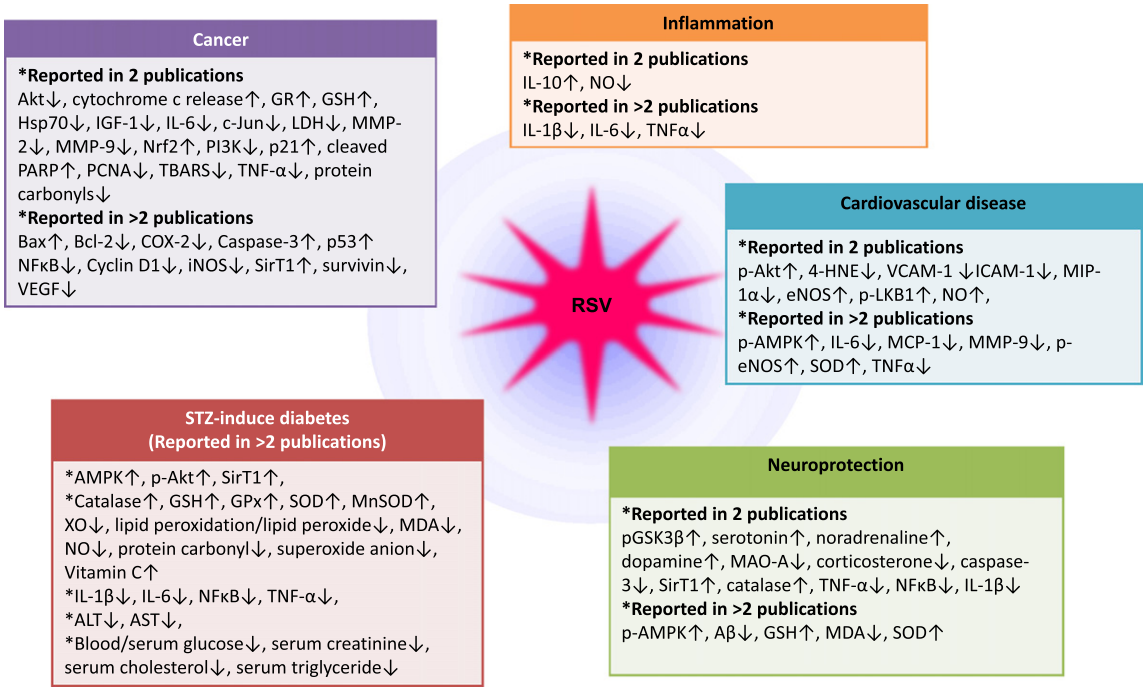

Fig. 5. Effect of RSV on molecular targets (biomarkers) determined with in vivo models of various disease states.

are miniscule, the study has little bearing on RSV action. The same negative conclusions could be drawn in regard to the other 1600 compounds associated with the grape [7], which are also present at very low concentrations, as well as the myriad of remaining constituents associated with the diet of free-living human beings.

In sum, to reach any definitive statements regarding the therapeutic potential of resveratrol, more detailed clinical trials with well-defined material and protocols are necessary. ClinicalTrials.gov lists approximately 80 RSV trials (https://clinicaltrials.gov/ct2/search/browse?brwse=intr_alpha_r; accessed September 9, 2014), so perhaps firmer expectations will be delineated over the next few years.

Abbreviation list

Aβ	β-Amyloid
ACC	Acetyl-CoA carboxylase
ACF	Aberrant crypt foci
AD	Alzheimer's disease
δ-ALA-D	Aminolevulinic acid dehydratase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMPK	5′ AMP-activated protein kinase
AOM	Azoxymethane
APP	Amyloid precursor protein
AR	Androgen receptor
AST	Aspartate aminotransferase
BP	Benzo[*a*]pyrene
BPDE	BP diolepoxide
BDNF	Brain-derived neurotrophic factor
CAT	Catalase
CCL2	Chemokine (C–C motif) ligand 2
COX-2	Cyclooxygenase-2
CREB	cAMP response element-binding protein
CRP	C-reactive protein
CVD	Cardiovascular disease
CX3CL	Chemokine (C–X3–C motif) ligand
DEN	Diethylnitrosamine
DMBA	7,12-Dimethylbenz[a]anthracene
DMH	1,2-Dimethylhydrazine
DSS	Dextran sulfate sodium
DR	Death receptor
EMT	Epithelial to mesenchymal transition
eNOS	Endothelial nitric oxide synthase
ERG	Electroretinogram
ERK	Extracellular signal-regulated kinase
FABP	fatty-acid binding protein
FAS	Fatty acid synthase
FOXC2	Forkhead box protein C2
FOXO	Forkhead transcription factors of the O class
GLUT	Glucose transporter
GSH	Glutathione, reduced state
GPx-1	Glutathione peroxidase 1
GR	Glutathione reductase
GSK3β	Glycogen synthase kinase 3β
GST	Glutathione *S*-transferase
γ-GT	γ-Glutamiltransferase
HBV X	Hepatitis B virus X protein
HD	Huntington's disease
HDL	High-density lipoprotein
HIF-1α	Hypoxia-inducible factor 1-alpha
4-HNE	4-Hydroxy-2-nonenal
HO-1	Heme oxygenase-1
HPA	Hypothalamic–pituitary–adrenal
HPC	Hematopoietic progenitor cells
HSC	Hematopoietic stem cells
HSF	Heat shock factor 1
Hsp	Heat shock protein
IGF-1	Insulin-like growth factor 1
IGFBP	Insulin-like growth factor binding protein
I/R	Ischemia/reperfusion
IκB	Inhibitor of kappa B
ICAM-1	Intercellular adhesion molecule 1
IL	Interleukin
iNOS	Inducible nitric oxide synthase
i.p.	Intraperitoneal
IRS	Insulin receptor substrate
i.v.	Intravenous
JNK	c-Jun N-terminal kinase
KC	Keratinocyte-derived chemokine
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LKB1	Liver kinase B1
LPL	Lipoprotein lipase
L-NAME	N^G-Nitro-L-arginine methyl ester
5-LOX	5-Lipoxygenase
MAO	Monoamine oxidase
MCP-1	Monocyte chemoattractant protein-1
MDA	Malondialdehyde
MMP-9	Metalloproteinase 9
MPO	Myeloperoxidase
MPTP	1-Methyl-1,2,3,6-tetrahydropiridine
MTA1	Metastasis-associated protein 1
mTOR	Mammalian target of rapamycin
MNU	*N*-Methyl-*N*-nitrosourea
NFκB	Nuclear factor kappa B
NO	Nitric oxide
NQO	NAD(P)H: quinone oxidoreductase
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
8-OHdG	8-Hydroxy-2′-deoxyguanosine
O-GlcNAc	*O*-Linked β-*N*-acetylglucosamine
OVX	Ovariectomized
p-	Phosphorylated
PAI-1	Plasminogen activator inhibitor-1
PARP	Poly ADP ribosyl polymerase
PBMNC	Peripheral blood mononuclear cells
PCNA	Proliferation cell nuclear antigen
PD	Parkinson's disease
PGC-1α	Peroxisome proliferator-activated receptor gamma co-activator-1alpha
PGES-1	Prostaglandin E synthase-1
PKC-β2	Protein kinase C-β2
PPAR	Peroxisome proliferator-activated receptor
PS1	Presenilin 1
PSA	Prostate-specific antigen
PTZ	Pentylenetetrazole
RBF	Renal blood flow
RBP4	Retinol binding protein 4
ROS	Reactive oxygen species
RSV	Resveratrol
S6K	S6 kinase
SAM	Senescence-accelerated mouse
SAP	Severe acute pancreatitis
s.c.	Subcutaneous
SHRs	Spontaneously hypertensive rats
Sirt1	Sirtuin 1
SOCS1	Suppressor of cytokine signaling 1
SOD	Superoxide dismutase
STAT3	Signal transducer and activator of transcription 3
STZ	Streptozocin
TBARS	Thiobarbituric acid reactive substances
TBI	Total body irradiation
TH	Tyrosine hydroxylase

TNF-α	Tumor necrosis factor alpha
TPA	12-*O*-Tetradecanoylphorbol-13-acetate
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling
VCAM-1	Vascular cell adhesion molecule 1
VEGF	Vascular endothelial growth factor
VLDL	Very-low-density lipoprotein

Transparency Document

The Transparency Document associated with this article can be found, in the online version.

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