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Resveratrol: A "miracle" drug in neuropsychiatry or a cognitive enhancer for mice only? A systematic review and meta-analysis

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ABSTRACT

Background: Over the last decade resveratrol has been trialled for the prevention and treatment of cognitive decline; however, the results have shown a conflict between human studies compared with animal studies, especially on cognition, blood pressure, neuroimaging, and mood.
Methods: Human clinical trials and animal studies published prior to January 2020, were identified searching across major electronic databases. PRISMA guidelines were used for data extraction, which was independently performed by two authors. Pooled standard mean difference (SMD, random effect model) and odds ratios (ORs) were calculated.
Results: Most publications on animal models reported positive outcomes on cognition and brain function following exposure to resveratrol or grape seed extracts. By contrast, 11 meta-analyses of data from human placebo vs resveratrol, grape or wine treatment trials identified no statistically significant effect on a variety of measures, including cognitive and mood assessments, grey matter volume and blood pressure.
Conclusions: Based on currently available data, the promising effects of resveratrol in animal models is not replicated in human clinical trials. The effects, if any, of resveratrol on human cognition are likely to be small. This work may be useful for the design and implementation of future pre-clinical and clinical studies using resveratrol in a neurological setting.

1. Introduction

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterised by the subtle onset, then steady progression of cognitive impairment and functional decline, following from impairment or loss of functional neurons (Hansen et al., 2008). The neuropathological hallmarks of AD are extracellular senile plaques containing abnormal amyloid beta (Aβ) aggregates and intracellular neurofibrillary tangles (NFTs) composed of hyper phosphorylated tau protein (Wightman, 2017).

Five drugs are currently approved by the U.S. Food and Drug Administration (FDA) as prescription medicines for AD patients; they are donepezil, galantamine, rivastigmine, memantine and a combination of donepezil and memantine (Bond et al., 2012). These drugs may alleviate symptoms in some patients for a limited time but do not have disease modifying actions, and can have a variety of adverse effects. Consequently, studies have been directed towards finding an appropriate treatment utilising natural products with efficacy but fewer side effects (Di Santo et al., 2013; Hansen et al., 2008; Molino et al., 2016; Tomé-Carneiro et al., 2013; Wightman, 2017).

Numerous studies have shown that grapes are full of polyphenolic compounds and flavonoids, and have suggested that its clinical utility is mainly attributed to these compounds (Anekonda, 2006; Beheshti and Aghaie, 2016; Jefremov et al., 2007; Pezzuto, 2008). Resveratrol (RSV) is a natural polyphenol (stilbenoid) which is present in a variety of plants and plant extracts, including grapes (particularly the skin) and red wine, peanuts and fruits such as blueberries, bilberries, pomegranates, mulberries and strawberries (Ahmed et al., 2017; Huang and Mazza, 2011; Tomé-Carneiro et al., 2013). The potential health benefits of RSV have been widely explored with some promising results in animal

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Table 1
Clinical studies used for meta-analysis of effects of resveratrol on cognitive and physiological parameters.

Study Design	Population cohort	Age	Sample size	Intervention	Dose	Administration	Duration	Pathology measure	Cognitive outcome	Adverse Effect	References
Randomized, placebo-controlled, double-blind, multi-site, phase 2 trial	Alzheimer's Disease Cooperative Study	N/A	119	synthetic resveratrol powder (encapsulated)	500 mg	orally once daily (with a dose escalation by 500-mg increments every 13 weeks, ending with 1000 mg twice daily)	52 weeks	↓CSF MMP9 ↑ CSF MDC ↑CSF IL-4 ↑CSF FGF-2 ↓CSF Aβ42 ↔CSF Tau ↑Plasma MMP10 ↓Plasma IL-1R4 ↓Plasma IL-12P40 ↑Plasma TNF-α ↓Plasma RANTES/ CCL5 ↓Plasma IL-12P70 ↓Plasma IL-8	N/A	Weight loss	(Moussa et al., 2017)
Prospective, placebo-controlled, double-blinded randomized trial	mild decline in cognition (50 % female)	mean, 72.2 ± 4.7 years	10	freeze-dried grape powder; Placebo	72 g/day	Orally	6 months	No change	Mini-mental. Improvement in memory in the group which takes grape compare with placebo group	N/A	(Lee et al., 2017)
Double-blind, placebo-controlled trial	overweight men and women	65 years old and older	32	Resveratrol; Placebo	two doses of resveratrol (300 mg/day and 1000 mg/day)	oral capsule twice daily, immediately following breakfast and dinner	90 days	N/A	↑Psychomotor speed in 1000 mg group only	diarrhea, constipation, muscle cramps, fatigue, allergies/ upper respiratory infection, difficulty swallowing, rash, and headache	(Anton et al., 2018)
Randomized, double-blind interventional study	Patients with mild cognitive impairment (MCI)	50–80 years	40	Resveratrol; Placebo	200 mg/ d 1015 mg/d olive oil	oral capsule	26 weeks	N/A	No significant differences in memory function compared with placebo group	No adverse effect	(Köbe et al., 2017)
Placebo-controlled, double-blinded randomized trial	Healthy overweight older	50–75 years	23	Resveratrol; Placebo	200 mg/d	orally	26 weeks	N/A	Significant effect on words retention in resveratrol group compare with placebo group	N/A	(Witte et al., 2014)
Randomised, double-blind,	healthy adults	19–34 years	23			orally	14 days			N/A	(Wightman et al., 2014)

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Table 1 (*continued*)

Study Design	Population cohort	Age	Sample size	Intervention	Dose	Administration	Duration	Pathology measure	Cognitive outcome	Adverse Effect	References
placebo-controlled, cross-overtrial				Trans-Resveratrol; Trans-Resveratrol + piperine; Placebo	250 mg 250 mg + 20 mg piperine			No change on blood pressure	No significant effect on cognitive function, mood		
Randomised, double-blind, placebo-controlled (parallel comparison) dietary intervention trial	post-menopausal women	45–85 years	80	Resveratrol	75 mg twice daily	orally	14 weeks	N/A	Cognitive performance improvement in resveratrol group compared with placebo	N/A	(Evans et al., 2017)
Randomised, double-blind, placebo-controlled trial	Mild cognitive impairment (MCI)	68 years old and older	21	Concord grape juice	6.3−7.8 mL/kg	orally	16 weeks	N/A	Improvement neural activation in cortical regions Positive effect on memory function	N/A	(Krikorian et al., 2012)
Randomised, double-blind, placebo-controlled crossover study	obese but otherwise healthy adults	40−75 years	28	Resveratrol	75 mg	orally	12 weeks	N/A	↑FMD, No effect on cognitive function	No adverse effect	(Wong et al., 2013)
Randomised, double-blind, placebo controlled, cohort study	normal healthy adults	18−30 years	60	Resveratrol	500 mg	orally	28 days	N/A	No effect on cognitive function, ↓fatigue	N/A	(Wightman et al., 2015)
Randomised, double-blind, placebo controlled, cohort study	normal healthy adults	60–79 years	60	Resveratrol + Quercetin	200 mg resveratrol + 320 mg quercetin	orally	26 weeks	N/A	no significant effect	stomach-aches, skin changes, mood changes, diarrhea, flatulence, decrease in eyesight	(Huhn et al., 2018)
Randomised, double-blind, placebo-controlled trial	Overweight older adults	73 ± 7 years	32	Resveratrol	300 mg/day 1000 mg/day (twice daily)	orally	90 days	No significant effect on Blood pressure	No cognitive assessment	diarrhea, constipation, muscle cramps, fatigue, allergies/ upper respiratory infection, difficulty swallowing, rash, and headache	(Anton et al., 2014)

*In this case data was estimated from a bar graph representation, as it was not presented as a numerical value in a table or text. N/A indicates that data was not available within the manuscript.

Table 2
Rodent models used for systematic review of the effects of resveratrol supplementation on brain function.

Model	Sample size	Source	Duration of treatment	Dose	Route of Administration	Outcome	Reference
Rats exposed to ovariectomy combined with injection of D-galactose (100 mg/kg).	60	resveratrol	12 weeks	20, 40, 80 mg/kg	perfusion	↓glial fibrillary acidic protein (GFAP) ↓TNF-α activation of astrocytes	(Cheng et al., 2015)
Tg19959 mice expressing the mutant human amyloid protein precursor APPSweInd, which bears both the Swedish (K670 N/M671 L) and the Indiana (V717 F) mutations, under the control of the Syrian hamster prion protein promoter.	19	standard AIN-93 G plus 0.2 % resveratrol	45 days	300 mg/kg (3 g food per day for a 20 g mouse)	orally	↓ Amyloid Plaques in medial cortex (- 48 %) ↓ Amyloid Plaques in striatum (- 89 %) ↓ Amyloid Plaques in hypothalamus (-90 %) ↓brain glutathione (21 %) ↑brain cysteine (54 %)	(Karuppagounder et al., 2009)
AβPPswe/PS1dE9 mice expressing a chimeric mouse/human (Mo/Hu) AβPP-695 with mutations (KM 593/594 N L) linked to familial AD.	10	mouse chow (Harlam Diet) containing 1% resveratrol	10 months	4 mg/kg/day (mean of food intake of 4 g/animal/day)	orally	↓amyloid burden ↑mitochondrial complex IV protein ↑activation of Sirtuin 1 ↑activation of AMPK ↑IL1β gene expression ↑TNF gene expression Preventing memory loss	(Porquet et al., 2014)
Hippocampal injection of $A\beta_{1-42}$ in adult male Sprague–Dawley (SD) rats	138	resveratrol	7 days	0.005 nmol, 0.0125 nmol, 0.025 nmol, 0.05 nmol, 0.22 nmol, and 0.44 nmol	injection	Prevent learning and memory loss ↑SIRT-1 expression ↑ cAMP response binding protein (CREB) activation	(Wang et al., 2017)
Male APP/PS1 transgenic mice containing human transgenes for both APP bearing the Swedish mutation and PSEN1 containing an L166 P mutation, both under the control of the Thy1 promoter.	16	resveratrol	15 weeks		Oral	↑Cytosolic calcium levels ↑AMPK activation ↓Aβ accumulation ↑Acetyl-CoA carboxylase (ACC) expression	(Vingtdeux et al., 2010)
APP/PS1 mice containing human transgenes for both APP bearing the Swedish mutation and PSEN1 containing an L166 P mutation, both under the control of the Thy1 promoter.	18	resveratrol	16 weeks	174 mg/kg/d	oral	No decrease Aβ plaque formation ↑GSK3-b phosphorylation	(Varamini et al., 2014)
Male 3xTg-AD transgenic mice containing three mutations associated with familial Alzheimer's disease (APP Swedish, MAPT P301 L, and PSEN1 M146 V).	46	resveratrol	10 months	100 mg/kg	Oral	Improve memory function ↓anxiety ↓Aβ ↓p-tau ↑AMPK protein levels ↑SIRT1 ↑CREB ↑PGC-1α	(Corpas et al., 2018)
Adult female Tg2576 mice overexpressing a mutant form of APP (isoform 695) with the Swedish mutation (KM670/671 N L)	16	grape seed polyphenolic extract (GSPE)	5 months	200 mg/kg	Oral	Improve memory function ↓Aβ	(Wang et al., 2008)
Female Tg2576 mice overexpressing a mutant	18	Muscadine wine	10 months		Oral	Improve cognitive function ↓Aβ	(Ho et al., 2009)

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Table 2 (*continued*)

Model	Sample size	Source	Duration of treatment	Dose	Route of Administration	Outcome	Reference
form of APP (isoform 695) with the Swedish mutation (KM670/671 N L)							
Female Tg2576 mice overexpressing a mutant form of APP (isoform 695) with the Swedish mutation (KM670/671 N L)	14	grape seed polyphenolic extract (GSPE)	5 months	200 mg/kg	Oral	Improve cognitive function ↓Aβ	(Liu et al., 2011)
Aged male Fischer 344 rats	15	resveratrol	4 weeks	40 mg/Kg	intraperitoneal injections	Improvement in Learning, memory and mood function ↑net neurogenesis ↑microvasculature ↓astrocyte hypertrophy ↓microglial activation	(Kodali et al., 2015)
Aged Wistar female rats	60	resveratrol	12 weeks	20, 40 and 80 mg/kg	Oral	↓Aβ1–42 ↓advanced glycation end products (RAGE) ↓ (MMP-9) ↓NF-κB ↑Claudin-5	(Zhao et al., 2015)
SAMP8 mice – senescence accelerated prone mouse	216	trans-resveratrol	7 months	1 g/kg	oral	SIRT1 ↑ AMPK ↑ P53 acetylation ↓ ↓ cognitive impairment ↓ amyloid burden ↓tau hyperphosphorylation.	(Porquet et al., 2013)
SAMP8 mice – senescence accelerated prone mouse	32	resveratrol	8 weeks	120 mg/kg	Oral	No improvement in cognitive function No increasing in the level of SIRT-1 No enhancement in acetylated p53	(Chang et al., 2012)
SIRT1Dex4/Nestin-Cre mice (floxed SIRT1Dex4 allele7,8 with Nestin-Cre)	20	resveratrol	1 week	0.5 μL was injected into each side	intraventricular injection	Improvement in memory function	(Zhao et al., 2013)
Aged male C57Bl/6 mice	60	resveratrol	12 months	150 μg/ gr	oral	Improved cognitive function Improved cerebrovascular condition	(Oomen et al., 2009)
Aged Male Wistar albino rats	24	resveratrol	30 days	20 mg/kg	oral	Improve cognitive function ↓DNA fragmentation ↓Homocysteine ↓P53 Expression	(Koz et al., 2012)
Aged female Wistar rats	60	resveratrol	12 weeks	20 mg/kg 40 mg/kg 80 mg/kg	injection	(Morris water maze test) Improvement in memory ↓T-SOD ↓GSH-Px	(Zhao et al., 2012)
Aged male Wistar rats	44	resveratrol	2 weeks	12.5, 25 and 50 mg/kg	Oral	Improvement memory function	(Gacar et al., 2011)
Aged male mouse lemurs)	33	resveratrol	18 months	200 mg.kg	oral	↑spontaneous locomotor activity ↑working memory ↑spatial memory performance	(Dal-Pan et al., 2011)
Aged Male C57BL/6 mice	20	resveratrol	14 DAYS	10 mg/kg	Injection	↓spatial Memory function ↓p-CREB level ↓BDNF level	(Park et al., 2012)
Aged Wistar-albino rats	20	resveratrol	12 weeks	50 mg/kg	Oral	(MWM test) ↑retention scores ↓TNFα	(Gocmez et al., 2016)

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Table 2 (*continued*)

Model	Sample size	Source	Duration of treatment	Dose	Route of Administration	Outcome	Reference
						↓IL1β ↑learning and memory impairment	
Aged male BALB/c mice	48	AIN-93 G plus 0.4 % resveratrol	4 weeks		orally	↓LPS-induced deficits in aged animals ↓LPS-induced interleukin-1b (IL-1b) in plasma ↓IL-1b mRNA in the hippocampus (resveratrol may be useful for attenuating acute cognitive disorders in elderly individuals with an infection.)	(Abraham and Johnson, 2009)
Aged male albino rats	60	resveratrol	45 days	20 mg/kg	oral gavage	↓Amyloid Plaques ↓Tau protein ↓IL-6 ↓CRP ↓TNF-α ↓TGF-β	(Al-Bishri et al., 2017)
Aged male Wistar rats	67	resveratrol	4 weeks	200 mg/kg	oral gavage	↓amyloidogenic mediators ↑Let-7c expression	(Zaky et al., 2017)
Aged male Wistar rats	48	ethanol resveratrol	10 weeks	(10 g/kg;) (5, 10 and 20 mg/kg)	oral gavage	In ethanol-treated rats: ↑oxidative–nitrosative stress ↑Cytokines (TNF-alpha and IL-1beta) ↑NF-kappa b ↑caspase-3	(Tiwari and Chopra, 2013)
Aged male Sprague-Dawley (SD) rats	25	resveratrol	7 days	100 mM/5 mL, i.c.v	injection	↓cellular levels of iNOS ↓Lipid peroxidation ↑heme oxygenase-1 (HO-1) Improvement in memory function	(Huang et al., 2011)
Aged male Wistar rats	16	Trans-resveratrol	21 days	10 and 20 mg/kg	injection	↑brain glutathione ↑brain MDA	(Sharma and Gupta, 2002)
Aged male mice	50	resveratrol	8 weeks	25, 50, 100 mg $kg^{-1}·d^{-1}$	oral gavage	Improvement in learning and memory ability ↓lipid peroxidation ↓SOD activity ↓Glutathione peroxidase ↑MDA	(Liu et al., 2012)
Wistar male rat pups (5-day-old neonates)	30	resveratrol	28 days	20 mg/kg	oral	↓NF-κB ↓apoptotic signalling Improved cognitive function	(Tiwari and Chopra, 2011)
PS19 mice (Six-month-old male)	16	resveratrol	5 weeks	40 mg/kg body weight	oral gavage	Improved cognitive deficit ↓Tau aggregation	(Sun et al., 2019)

models (Huang et al., 2011; Kumar et al., 2007; Porquet et al., 2014; Wang et al., 2017). Clinical trials in humans are fewer, and with mixed results (Anton et al., 2018; Evans et al., 2016; Köbe et al., 2017; Moussa et al., 2017). Epidemiological studies have shown that diets containing high amounts of RSV improve motor function and memory performance in older rats (Joseph et al., 2005; Siahmard et al., 2012). By contrast, evidence of clinical efficacy in the treatment of human cardiovascular disease, diabetes, cancer or lifespan extension (Pallauf et al., 2017; Petrovski et al., 2011; Singh et al., 2015; Sinha et al., 2016; Szkudelski and Szkudelska, 2015), is weak.

The objective of this study was to use meta-analyses to assess the therapeutic effects of RSV and RSV containing extracts (such as grape juice) on cognition, mood, and blood pressure, in human placebo vs treatment trials and present a systematic review of both human and animal studies.

2. Methods

2.1. Literature selection

This study was designed in accordance with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Liberati et al., 2009). A systematic search was performed using PubMed, MEDLINE, ISI Web of Science, Embase, Cochrane Library, Science direct, SCOPUS, and PsychINFO databases to identify studies in humans or experimental animals on RSV, grape and red wine

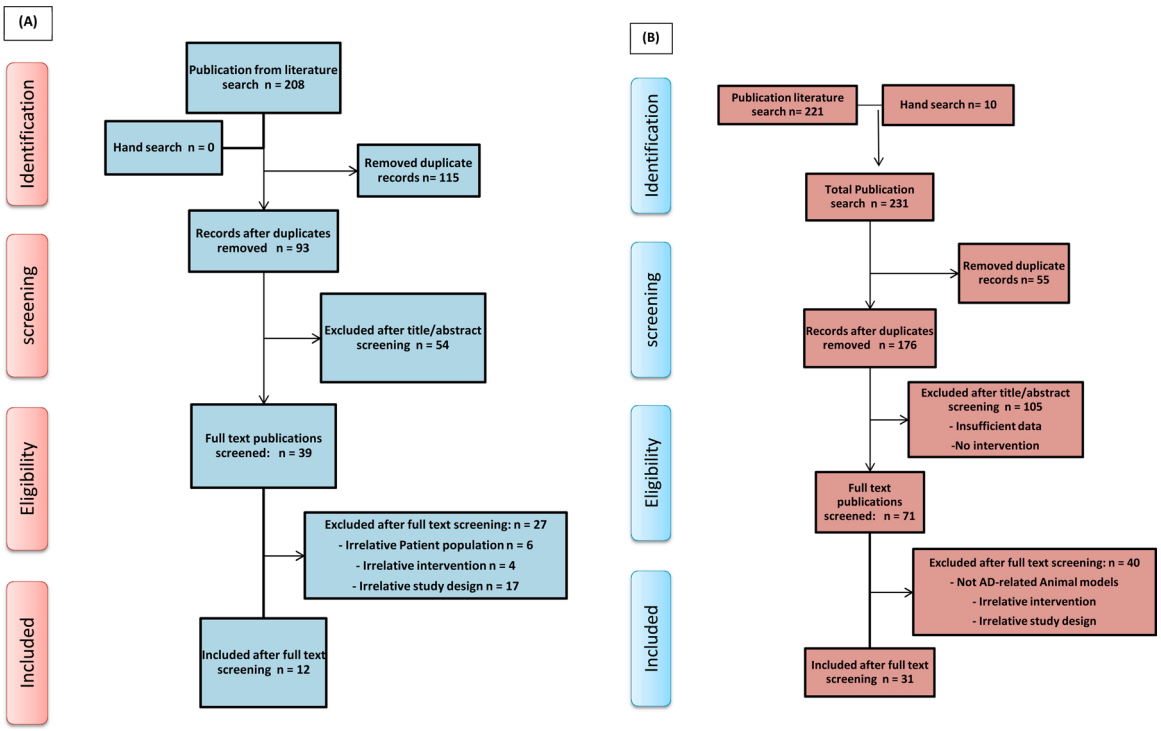

Fig. 1. (A) PRISMA flow diagram of literature screening for the effect of resveratrol and/or grape in human clinical trials, (B) PRISMAS flow diagram of included/excluded studies for systematic review regarding the effect of resveratrol and grape on murine models of neurocognition, neurodegeneration and aging.

in relation to cognition, mood, memory impairment and blood pressure, published between April 1997 and January 2020. Additional information regarding the literature selection process is provided in the supplementary section.

2.2. Inclusion and exclusion criteria

Study selection was based on the inclusion and exclusion criteria which are detailed in the supplementary section. Two researchers extracted data independently based on participants, randomisation, interventions (drug used, dose, and formulation), outcomes, duration, reasons for discontinuation and author information. Studies to be included in the meta-analysis and systematic review (human) and systematic review only (animal) are summarised in Tables 1 and 2 respectively; and mean cognitive scores for each included study are listed in Table 4. Any inconsistencies were resolved by consensus and discussion with additional co-authors. Duplicate papers, articles which did not meet inclusion criteria and review papers were excluded.

2.3. Data extraction and statistical analysis

Data extraction for meta-analysis included the mean score and standard deviation [SD]. If error was reported as standard error [SE] or 95 % confidence interval [CI], these were converted to standard deviation using the formula provided in the Cochrane Handbook (Deeks et al., 2018).

Heterogeneity between studies was tested using the Q-statistic test ($p < 0.05$ indicates significant heterogeneity), and the degree of inconsistency across studies was quantified using the I^2 statistic. Additional details regarding the statistical analyses are provided in the supplementary section.

3. Results

A total of 208 studies were shortlisted from initial electronic searches on clinical studies, from which 115 duplicate records were removed, and 93 studies remained. These were screened, using information in the title, abstract and text, and 54 clinical studies were excluded since they were non-randomised clinical trials, not related to RSV, grape juice or red wine, or did not meet inclusion criteria. Ultimately, 12 reports were considered eligible (Fig. 1A), which included 10 studies on the effect of RSV on cognitive and memory performance and 2 studies on the effects of grapes on cognitive and memory performance and neuroimaging (Table 1).

For animal studies, 231 articles were identified, including 10 articles by manual search. After omitting the duplicates, 176 studies remained and were screened in greater depth. Of these, 105 records were removed as the animals did not undergo treatment with a substance, or there was insufficient data reported for the purposes of this review. Of the 71 remaining articles a further 40 were excluded, because they were not AD-related animal models and/or the supplementation for treatment was not RSV, grape or wine, leaving 31 articles which met our inclusion criteria (Fig. 1B). Of these studies, two investigated the effect of grape seed polyphenolic extract (GSPE) on cognitive decline and one study was on the effect of Muscadine wine on an AD model; the remaining studies were on the effect of RSV (Table 2).

3.1. Study characteristics

The total sample sizes of human and animal studies were 528 (290 controls and 238 treatment) and 1219 (488 controls and 731 treatment) respectively. Details of the studies are summarised in Tables 1 and 2; the sample size range for each human study was 10–120, and the sample size range of animal models using *in vivo* investigations was 10–216 individuals. All human studies were randomised double-blind controlled trials. Two studies had a cross-over design (Wightman et al., 2014; Wong et al., 2013), one was a prospective study (Lee et al., 2017) and two were cohort studies (Huhn et al., 2018; Wightman et al., 2015). Twenty-eight animal studies used RSV treatment (Table 2), two studies used grape seed polyphenolic extract (GSPE) and one study used Muscadine wine. The mode of administration in animals is indicated in Table 2, and included oral (used in 23 studies) and injection (used in nine studies).

Table 3
Results of meta-analyses performed to assess potential physiological and cognitive effects of Resveratrol, Grape Extract and Wine Clinical Trials. These data are based on the 12 studies which met our inclusion criteria (see Table 1).

	Measure	Studies	Plaebo/ Treatment (n)	Female/ male (n)	Mean Age (years)	Pooled SMD*	95 % CI*	Heterogeneity* (I^2)	P value*
Cognition	**Global cognitive performance**	Moussa, 2017 (Moussa et al., 2017)	19/ 19	#	#	−0.604	−1.466,0.259	59.2 %	0.170
		Lee, J. 2017 (Lee et al., 2017)	10/10	10/10	72.2				
	Delayed recall	Witte 2014 (Witte et al., 2014)	23/23	9/14	64.5	0.224	−0.083,0.530	7.9 %	0.152
		Evans, 2017 (Evans et al., 2017)	41/38	20/0	61.5				
		Köbe, 2017 (Köbe et al., 2017)	22/18	21/19	67.0				
		Lee, J. 2017 (Lee et al., 2017)	10/10	10/10	72.2				
	Immediate memory	Witte 2014 (Witte et al., 2014)	23/23	9/14	64.5	0.161	−0.091,0.412	0.0 %	0.085
		Evans, 2017 (Evans et al., 2017)	41/38	20/0	61.5				
		Köbe, 2017 (Köbe et al., 2017)	22/18	21/19	67.0				
		Lee, J. 2017 (Lee et al., 2017)	10/10	10/10	72.2				
		Anton, 2018 (Anton et al., 2018)	10/22	16/16	73.3				
	Attention speed	Evans, 2017 (Evans et al., 2017)	41/38	20/0	61.5	−0.149	−0.683,0.385	64.4 %	0.611
		Lee, J. 2017 (Lee et al., 2017)	10/10	10/10	72.2				
		Huhn, S. 2018 (Huhn et al., 2018)	26/27	14/13	67.5				
		Anton, 2018 (Anton et al., 2018)	10/22	16/16	73.3				
	Executive function	Evans, 2017 (Evans et al., 2017)	41/38	20/0	61.5	0.080	−0.188,0.348	0.6 %	0.493
		Lee, J. 2017 (Lee et al., 2017)	10/10	10/10	72.2				
		Huhn, S. 2018 (Huhn et al., 2018)	26/27	14/13	67.5				
		Anton, 2018 (Anton et al., 2018)	10/22	16/16	73.3				
	Serial 7 s	Wightman,2014 (Wightman et al., 2014)	23/23	19/4	21.00	0.039	−0.381,0.460	0.0 %	0.854
		Wightman, 2015 (Wightman et al., 2015)	19/22	36/5	20.00				
Mood	**Depression**	Krikorian, 2012 (Krikorian et al., 2012)	21/21	10/11	76.9	0.105	−0.177,0.386	0.0 %	0.467
		Wightman, 2015 (Wightman et al., 2015)	28/26	46/8	20.07				
		Evans, 2017 (Evans et al., 2017)	41/38	20/0	61.5				
		Lee, J. 2017 (Lee et al., 2017)	10/10	10/10	72.2				
	Anxiety	Evans, 2017 (Evans et al., 2017)	41/38	20/0	61.5	−0.014	−0.569,0.542	33.2 %	0.961
		Lee, J., 2017 (Lee et al., 2017)	10/10	10/10	72.2				
Brain volume	**Total grey matter volume**	Witte 2014 (Witte et al., 2014)	23/23	9/14	64.5	0.064	−0.387,0.515	0.0 %	0.781
		Köbe, 2017 (Köbe et al., 2017)	16/14	#	67.0				
Blood pressure	**Systolic BP**	Krikorian, 2012 (Krikorian et al., 2012)	21/21	10/11	76.9	−0.042	−0.287,0.202	0.0 %	0.734
			28/28	16/12	61.00				

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Table 3 (*continued*)

Measure	Studies	Plaebo/ Treatment (n)	Female/ male (n)	Mean Age (years)	Pooled SMD*	95 % CI*	Heterogeneity* (I^2)	P value*
	Wong, 2013 (Wong et al., 2013)							
	Wightman, 2014 (Wightman et al., 2014)	23/23	19/4	21.00				
	Witte 2014 (Witte et al., 2014)	23/23	9/14	64.5				
	Wightman, 2015 (Wightman et al., 2015)	15/9	21/3	20.75				
	Huhn, S. 2018 (Huhn et al., 2018)	26/27	14/13	67.5				
	Anton, 2014 (Anton et al., 2014)	10/22	16/16	73.50				
Diastolic BP	Krikorian, 2012 (Krikorian et al., 2012)	21/21	10/11	76.9	−0.059	−0.304,0.186	0.0 %	0.635
	Wong, 2013 (Wong et al., 2013)	28/28	16/12	61.00				
	Wightman, 2014 (Wightman et al., 2014)	23/23	19/4	21.00				
	Witte 2014 (Witte et al., 2014)	23/23	9/14	64.5				
	Wightman, 2015 (Wightman et al., 2015)	15/9	21/3	20.75				
	Huhn, S. 2018 (Huhn et al., 2018)	26/27	14/13	67.5				
	Anton, 2014 (Anton et al., 2014)	10/22	16/16	73.50				

* Meta-analysis random effect model, * Standardized mean difference (SMD), * Confidence Interval (CI).
# Data not reported.

The animal models were all rodent, and included Tg 19959, Wistar rat, BALB/c mice, Sprague-Dawley, SAM8 mice, APP/PS1 transgenic mice - SIRT1Dex4/Nestin-Cre mice, C57Bl/6 mice, mouse lemurs, 3xTg-AD, Tg2576 mice and Fischer 344 rats.

3.2. Dosing regimen

The daily RSV dose in the clinical studies was in the 75−1000 mg range and was administered as an encapsulated powder taken orally. In order to raise bio-efficacy and bioavailability of RSV, three human studies used piperine and quercetin as a co-intervention (Köbe et al., 2017; Wightman et al., 2014; Witte et al., 2014). The range of the daily RSV dose in the animal studies was between 4 mg/kg to 300 mg/kg or equivalent to 0.12−9 mg in mice or 1.2−150 mg in rats. This was based on an average weight of an adult mouse being 18−30 g and an adult rat being 300−500 g.

3.3. Systematic review of animal studies

Different results are reported in animal studies on the effect of resveratrol, grapes or wine on cognitive function. Vingtdeux et al. reported a decrease in Aβ accumulation (Vingtdeux et al., 2010) while their previous work showed no significant effect of RSV on Aβ production (Marambaud et al., 2005). Three studies reported positive effects of grapes or red wine on memory and cognitive function (Ho et al., 2009; Liu et al., 2011; Wang et al., 2008). Wang et al. showed a positive effect of grape seed polyphenolic extract (GSPE) on memory function and reduction of Aβ level (Wang et al., 2008), with similar outcomes demonstrated using Muscadine wine and GSPE in Tg2576 mice (Ho et al., 2009; Liu et al., 2011).

Several studies have demonstrated increased expression of SIRT-1 after RSV treatment of mice (Porquet et al., 2013, 2014; Wang et al., 2017). Using a Sirt-1 mutant mice model, Zhao et al (Zhao et al., 2013) reported memory improvement following RSV treatment, which they suggested was by a Sirt-1 dependent pathway (Corpas et al., 2018; Porquet et al., 2013; Wang et al., 2017). Tiwari et al. reported that RSV improves cognitive function in Wistar rats (Tiwari and Chopra, 2011). Furthermore, a positive effect of resveratrol on rescue of cognitive deficits and inhibition of tau aggregation has been shown in a study on 6-month-old male PS19 mice by Sun et al. (Sun et al., 2019). Cheng et al. reported inhibition of TNF-α secretion in AD rats treated with RSV (Cheng et al., 2015). This finding is consistent with other studies which showed a significant down-regulation in inflammatory markers in AD animal models after treatment with RSV (Mecocci et al., 2018). Zaky et al. (Zaky et al., 2017) treated male adult Wistar rats with a mixture of RSV and curcumin and demonstrated their synergistic protective effects against neuroinflammation. Zhao et al. demonstrated two interesting effects of RSV on Wistar female rats: (1) a protective effect on neuroinflammation; and (2) a positive effect on maintenance of the blood brain barrier (BBB) structure (Zhao et al., 2015).

By contrast a smaller number of animal studies have reported null effects of resveratrol treatment. Park et al. reported a negative effect of RSV on spatial memory function (Park et al., 2012).

Other studies found a reduction in glutathione (GSH) and acetylcholinesterase activities and an increase in malondialdehyde (MDA) and nitrite (Karuppagounder et al., 2009; Kumar et al., 2007; Sharma and Gupta, 2002; Zhao et al., 2012). Chang et al. found neither improvement in cognitive function nor enhancement of SIRT-1 expression or acetylated p53 levels (Chang et al., 2012).

3.4. Human studies: results of meta-analysis

3.4.1. Effect of resveratrol and grapes on human cognition and physiology

Meta-analysis did not identify any significant effects of RSV or grape extracts on several measures of human cognition and physiology (Table 3). Small increases of pooled SMD were observed for most

Table 4
Mean cognitive scores and standard deviations (baseline and follow-up) for all clinical trials included in this Meta-analysis.

	Measure	Studies	Baseline				Follow-up			
			Experimental group		Placebo group		Experimental group		Placebo group	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cognitive Tests	**Global cognitive performance**	Moussa et al., 2017	19	1	17	2	18	1	19	1
		Lee et al., 2017	28.8	1.3	27.6	2.3	28.6	2.0	28.8	1.3
		Witte et al., 2014	10.6	4	10.1	3.1	12.4	3.3	10.7	3.3
	Delayed recall	Evans et al., 2017	41.4	8.8	42.3	8.3	45.4	7.3	43	7.6
		Köbe et al., 2017	7.6	3.9	7.2	2.7	6.7	3.9	7.6	3.7
		Lee et al., 2017	4.8	3.5	6.8	3.4	8.6	11.9	7.4	3.05
		Witte et al., 2014	54.4	11.6	51.6	9.6	59.7	9.3	56.1	9
	Immediate memory	Evans et al., 2017	71	12.3	66.3	10.8	78	11.7	73.6	11.5
		Köbe et al., 2017	44.9	9.5	44.2	8.1	43	10.7	41.9	12.8
		Lee et al., 2017	23	4.3	21	6.4	21.2	4.4	23.6	6.1
		Anton et al., 2018 *	39.1	12.96	37.4	8.5	40.9	8.57	39.5	6.3
		Evans et al., 2017	36	5.5	34.9	7.6	33.1	6.7	33.1	7.6
	Attention speed (TMT part A)	Lee et al., 2017	31.69	4	43.8	32.5	30.6	2.9	28.4	13.3
		Huhn et al., 2018	43	13	41	14	38.96	17.83	35.9	13.31
		Anton et al., 2018 *	45.92	14.37	44.7	15.46	34.14	8.64	41.71	10.87
		Evans et al., 2017	75.4	23.4	72.7	18.5	68.6	19.11	70.5	17.92
	Executive function (TMT part B)	Lee et al., 2017	90.89	27.45	108	75.8	80.66	34.59	95.31	55.82
		Huhn et al., 2018	89	29	80	25	86.08	28.06	75.47	25.38
		Anton et al., 2018	77.94	13.82	76.58	22.41	84.25	30.61	77.84	28.24
	Serial 7s	Wightman et al., 2014	28.85	13.18	28.85	9.78	29.65	18.75	29.83	15.97
		Wightman et al., 2015	23.50	7.1	23.53	7.3	26.66	7.87	25.92	7.58

* This data from Anton et al., 2018 was calculated based on baseline values and post-treatment change values provided in their manuscript, Tables 2 and 3.

cognitive measures (delayed recall, immediate memory, executive function and serial 7 s) and total grey matter volume, though effect sizes were very small (for example, for executive function, the effect size is 0.08), and none reached statistical significance. Similarly, small SMD decreases were seen for anxiety and the two blood pressure measures (systolic and diastolic), but none that were statistically significant.

3.4.2. *Effect of resveratrol and grape extract on cognition*

3.4.2.1. Global cognitive performance. Cognitive impairment, including Mini-Mental State Exam (MMSE) and Montreal Cognitive Assessment (MoCA), were measured in seven studies involving 305 participants in total. Two studies with available data were included in our meta-analysis since the other studies did not report the value in their control and AD groups (Lee et al., 2017; Moussa et al., 2017). Meta-analysis of these two studies showed that these treatments (Lee et al., 2017; Moussa et al., 2017) had no significant effect on global cognitive performance (SMD, -0.604; 95 % CI, -1.466 to 0.259; $I^2 = 59.2$ %; $p = 0.170$; n = 2 studies; n = 58 participants) (Table 3).

3.4.2.2. Memory. A total of six studies involving 245 participants assessed memory outcomes (Anton et al., 2018; Evans et al., 2017; Huhn et al., 2018; Köbe et al., 2017; Lee et al., 2017; Witte et al., 2014), including delayed recall, learning ability and Hopkins VLT-revised (immediate memory). Two separate meta-analyses were conducted using five studies. Supplementation did not have a significant effect on delayed recall (SMD, 0.224; 95 % CI, -0.083 to 0.530; $I^2 = 7.9$ %; $p = 0.152$; n = 4 studies; n = 185 participants) or immediate memory (learning ability and Hopkins VLT-revised), (SMD, 0.161; 95 % CI, -0.091 to 0.412; $I^2 = 0.0$ %; $p = 0.085$; n = 5 studies; n = 217 participants) (Table 3).

3.4.2.3. Cognitive processing speed. The Trail Making Task, type A (TMT-A) was used by four studies with available data for assessing the effect of RSV or grape treatment on the speed of understanding and reacting to the information which a person received. The result of meta-analysis showed no-significant influence on processing speed, (SMD, -0.149; 95 % CI, -0.683 to 0.385; $I^2 = 64.4$ %; $p = 0.611$; n = 4 studies; n = 184 participants) (Table 3).

3.4.2.4. Executive function. Seven studies with a total of 265 participants were surveyed for the effect of RSV or grape juice on executive function, including the Trail Making Task type B (TMT-B) and serial 7 s. Two separate meta-analyses with available data were performed and results showed a non-significant influence on executive function, as assessed with either the TMT-B (SMD, 0.080; 95 % CI, -0.188 to 0.348; $I^2 = 0.6$ %; $p = 0.493$; n = 4 studies; n = 184 participants) or serial 7 s tests (SMD, 0.039; 95 % CI, -0.381 to 0.460; $I^2 = 0.0$ %; $p = 0.854$; n = 2 studies; n = 87 participants) (Table 3).

3.4.3. *Effect of resveratrol and grape extract on mood*

Depression and anxiety were assessed in four studies that used the following tests: Hamilton Depression Rating Scale, Geriatric Depression Scale (GDS), Beck's Depression Index and Hamilton Anxiety Rating Scale. Two separate meta- analyses were conducted with available data and results showed a non-significant effect of RSV and grape on either depression (SMD, 0.105; 95 % CI, -0.177 to 0.386; $I^2 = 0.0$ %; $p = 0.467$; n = 4 studies; n = 195 participants) or anxiety (SMD, -0.014; 95 % CI, -0.569 to 0.542; $I^2 = 33.2$ %; $p = 0.961$; n = 2 studies; n = 99 participants) (Table 3).

3.4.4. *Effect of resveratrol and grape extract on Brain volume*

Two studies with available data were evaluated by meta-analysis to assess the effect of RSV on total grey matter volume, and results showed no significant effect (SMD, 0.064; 95 % CI, -0.387 to 0.515; $I^2 = 0.0$ %; $p = 0.781$; n = 2 studies; n = 76 participants) (Table 3).

3.4.5. *Effect of resveratrol and grape extract on blood pressure*

Two separate meta-analyses were conducted on a total of seven studies with available data which assessed the effect of grape juice or RSV on both systolic and diastolic blood pressure. No significant effect was found for either systolic (SMD, -0.042; 95 % CI, -0.287 to 0.202; $I^2 = 0.0$ %; $p = 0.734$; n = 7 studies; n = 299 participants) or diastolic (SMD, -0.059; 95 % CI, -0.304 to 0.186; $I^2 = 0.0$ %; $p = 0.635$; n = 7

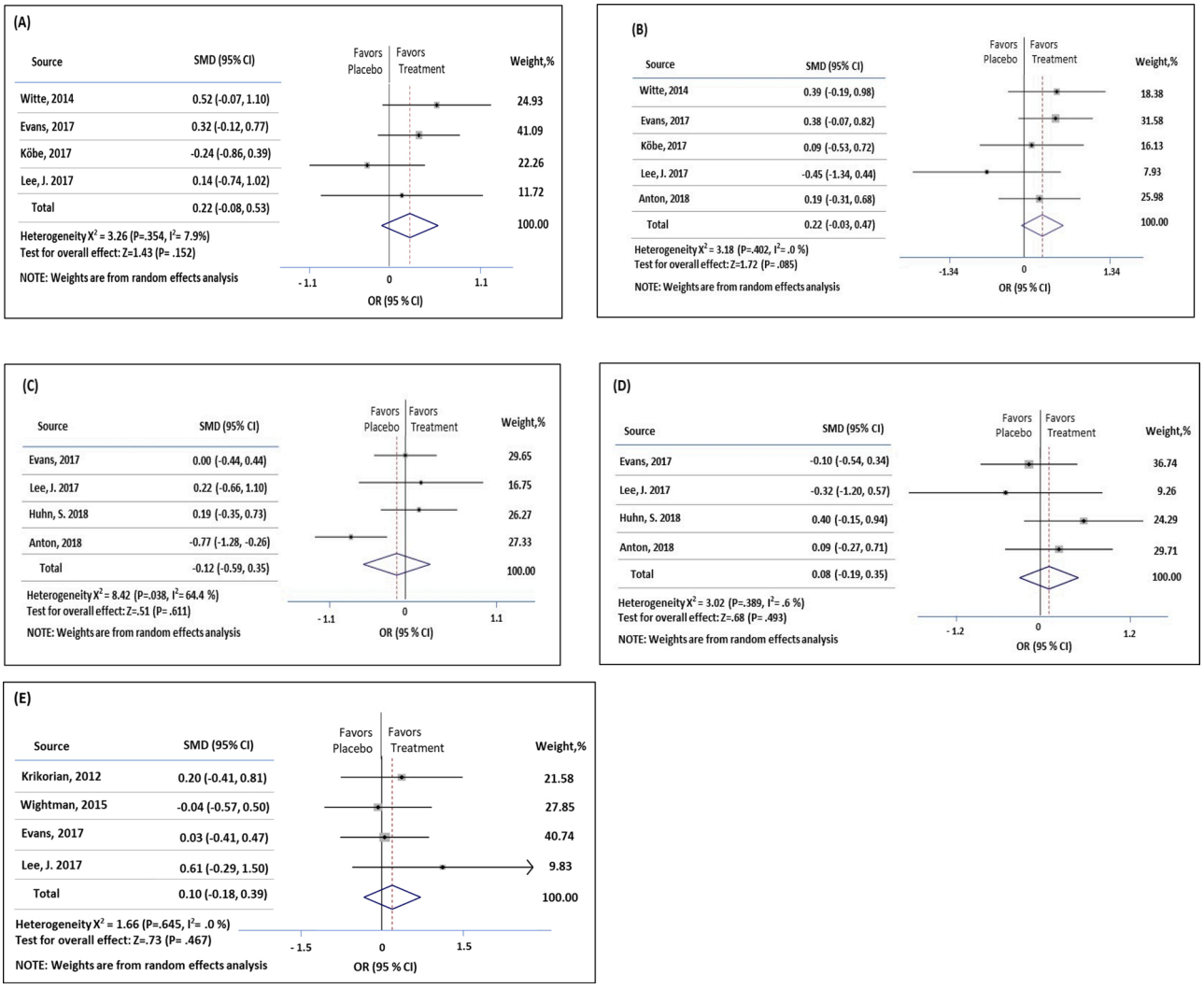

Fig. 2. The effect of resveratrol and grape on: A: delayed recall; B: immediate memory; C: attention speed; D: executive function; E: depression.

studies; n = 299 participants) blood pressure (Table 3).

In summary, most of the individual studies included herein show positive directions of change following supplementation (Anton et al., 2018, 2014; Evans et al., 2017; Huhn et al., 2018; Köbe et al., 2017; Krikorian et al., 2012; Lee et al., 2017; Wightman et al., 2015; Witte et al., 2014; Wong et al., 2013) with fewer studies showing a negative direction of change or null effects. This was also reflected in the positive SMDs for most of the analyses as illustrated using forest plots (Figs. 1 and 2). However, none of the meta-analyses showed statistically significant results, even though heterogeneity is low in most of the analyses, except for the effect of supplements on attention speed (64.4 %), anxiety (33.2 %) and global cognitive performance (59.2 %). In these cases, the higher heterogeneity may be due to differences in study design. Overall study numbers and total subject numbers included are low and therefore possibly underpowered to detect small differences. Publication bias was assessed using funnel plots together with Egger's test for meta-analyses which included more than five studies (Lau et al., 2006; Sedgwick and Marston, 2015). This represented the meta-analyses for: immediate memory with p = 0.24, systolic blood pressure with p = 0.92 and diastolic blood pressure with p = 0.85 (Fig. 2). Based on visual examination of the funnel plots there was some asymmetry in the funnel plot for the studies representing immediate memory, but the results for systolic and diastolic blood pressures were approximately symmetric.

4. Discussion

Our current meta-analysis reported no significant effect of resveratrol, grape juice or wine on cognitive or physiological outcomes in human clinical trials, including effects on cognition, neuroimaging, blood pressure and mood. Our results are consistent with two recent meta-analyses on the effect of RSV on cognition (Farzaei et al., 2017; Marx et al., 2018). Farzaei et al. reported in their meta-analysis that resveratrol has no significant effect on memory and cognition (Farzaei et al., 2017), although since publication some suspicions about the methodology and selection of studies for this meta-analysis have been made by Wong and Howe (Wong and Howe, 2018). Accordingly, the results of this meta-analysis must be interpreted with prudence. Nonetheless, in a more robust study Marx et al. also concluded that associations of RSV with cognition and mood were weak at best (Marx et al., 2018).

While most of the outcome measures in our own meta-analyses show positive SMD values (e Figs. 1 and 2), none reached statistical significance. Our findings therefore suggest that the clinical relevance of RSV has been highly overstated. However, in the current systematic review, most animal studies support a positive effect of RSV on cognition, memory and AD pathology models. The four main effects of RSV treatment generally reported in animal models of AD and ageing are on: ***(1)*** Aβ and tau deposition, ***(2)*** SIRT1 expression of activity, ***(3)*** apoptosis pathways, and ***(4)*** oxidative stress and/or inflammation. However,

many of these effects are not achieved at dietetic doses, and corroboration between in vitro and in vivo data is often nascent in the literature. Further research is necessary to confirm whether RSV is beneficial and which dose range is safe for human consumption. To date, findings from human clinical trials are highly variable and meta-analyses suggest marginal, if any, effects. Some of the limitations of currently available studies are that most have relatively low subject numbers, some are of very short duration, one being as short as 14 days, with the mean study duration being ~4.5 months (Table 1), and most studies are of resveratrol in isolation, rather than as part of a more complex dietary formulation; of the 11 studies used for the meta-analysis, 5 tested resveratrol only, 2 tested resveratrol as part of a grape formulation and 2 tested resveratrol in combination with other dietary polyphenolics; piperine and quercetin (Table 1). Consequently statistical detection of small effects would require larger cohort sizes and/or longer study duration, and whether greater efficacy can be achieved by supplementation within a more wholistic nutritional context (e.g., as a supplement to a Mediterranean diet) remains to be explored. Never-the-less, we suggest that even with these limitations, if resveratrol had a substantial effect, then a large effect size would likely have been picked up. The physiological effects of some dietary components can be picked up even at modest dose levels and over short time intervals e.g., caffeine, omega-3 fatty acids, such as DHA (Bradberry and Hilleman, 2013; Gómez-Pinilla, 2008; Ruxton, 2008; Spencer et al., 2017).

Since the early 1980s, the consumption of red wine was associated with a lower incidence of coronary heart disease and neurodegenerative disorders in the French population compared to other Western countries (Catalgol et al., 2012). This phenomenon was termed the 'French Paradox'. RSV was thought to be the potential source of the beneficial effects of red wine (Catalgol et al., 2012). At present, the association between red wine and RSV has been used as the basis of the dogma: red wine contains highly bioactive resveratrol which supports wine consumption (Doonan et al., 2017; Fernández-Mar et al., 2012). However, two important facts should be considered prior to drawing a linear connection. Firstly, a high percentage of moderate alcohol consumption has been reported in France (Renaud et al., 1999), whereas heavy alcohol consumption can be harmful for the hepatic, renal, cardiovascular and central nervous systems (Djoussé et al., 2002; Lucas et al., 2005). Secondly, the content of RSV in red wine and grape juice is generally low, highly variable, and therefore inconsistent (Sato et al., 1997).

4.1. Animal model success vs clinical trials failure

A key question is why the results of the promising *in vitro* and animal model data have not been reflected in the human clinical trials data? It is noteworthy that many rodent studies have a daily resveratrol dose level of >50 mg/kg (Table 2), with one study even using 1 g/kg in a mouse model. Translated to human body weight these dose levels are in the 4−75 g range, and far beyond the resveratrol dose levels used in clinical trials (Table 1). Other study variables that could be considered include sex specific effects, dietary effects and bioavailability. Wang et al. showed the effect of RSV on lifespan may be gender specific (Wang et al., 2013). For example, the lifespan of female fruit flies (*Drosophila melanogaster*) was extended by 200μM RSV supplementation, while the same concentration did not have any effect on the lifespan of males (Wang et al., 2013). Dietary factors can affect absorption and although most trials with RSV were carried out using the pure compound alone, other components of RSV rich foods may also be important for its efficacy.

Investigation into the bioavailability and pharmacokinetics of RSV demonstrated that after intraperitoneal (IP) injection, RSV is transported to the cardiovascular system and can cross the BBB and reach brain tissue rapidly (De La Lastra and Villegas, 2007; Spanier et al., 2009). However, traditional oral administration of RSV reported poor bioavailability (Baur and Sinclair, 2006; Riviere et al., 2007). This is likely due to its poor metabolic stability owing to its rapid conversion to its glucuronide and sulfate metabolites following phase II metabolism (Marambaud et al., 2005).

The bioavailability and bioactivity of RSV in the brain has been reported in several *in vivo* studies (Karuppagounder et al., 2009; Vingtdeux et al., 2010). However, there is no strong evidence in human clinical trials. Studies show that co-administration of RSV with phenolic compounds, like piperine, quercetin, curcumin, or green tea catechins may enhance its bio-efficacy (Köbe et al., 2017; Wightman et al., 2014; Witte et al., 2014). Furthermore, nutrient rich diets, abundant in polyphenolic and flavenoid compounds (e.g., Mediterranean diet) are reported to have positive outcomes on cognition and mood (Adan et al., 2019; Conner et al., 2017; Fresán et al., 2019). Consequently, the dietary complexity within which supplements of specific compounds are delivered may represent an important determinant of outcomes. It is noteworthy that clinical trials of nutrient supplements in isolation have generally been disappointing (Burt et al., 2019; Moyad, 2001; National Heart and Network, 2019; Soininen et al., 2017), yet trials of nutrient rich complete diets often report positive outcomes (Féart et al., 2010; Tosti et al., 2018; Willcox et al., 2014). Several publications have provided detailed reviews on the many challenges of adequately designing clinical nutrition and functional food trials (AbuMweis et al., 2010; Krishnan et al., 2020; Weaver and Miller, 2017). Consequently, further investigation is recommended to clarify the effect and mechanism of co-supplementation of resveratrol for clinical treatment.

In general, resveratrol at the doses administered in published clinical trials, seems to be tolerated well. However in several clinical trial studies, adverse effects of resveratrol were noted (Table 1). One of the reported side effects was weight loss (Moussa et al., 2017). Huhn et al. reported minor adverse effects in their trial, including stomach-aches, effect on skin, mood changes and more frequently diarrhea and flatulence, as well as a decline in eyesight reported by one of their participants after 18 weeks of resveratrol intake, which improved after dropping out of the study (Huhn et al., 2018). While there have been no other reported side effects of resveratrol on eyesight thus far, it is highly recommended that this be monitored in future studies.

Anton et al. reported some adverse events in the resveratrol treatment conditions such as diarrhea, constipation, muscle cramps, fatigue, allergies/upper respiratory infection, difficulty swallowing, rash and headache, although they clearly mentioned that these were not statistically significant (Anton et al., 2014) (Table 1).

The single major limitation of this work is a lack of sufficient numbers of independent studies with adequately standardised experimental designs and outcome measures that allow grouping. Consequently, our meta-analysis suffers from low study and subject numbers (11 studies with a total of 528 subjects), affecting the statistical power with which small changes can be detected. The duration of clinical trials was a further limitation, which ranged between 14 days to a maximum of 12 months, with an average trial length of *ca* 4.5 months across all studies. Studies of just a few weeks duration may not pick up much more than placebo effects. These two limitations highlight the need for higher powered studies of larger cohort size, and longer duration, to determine the effects, if any, of resveratrol supplementation in humans. The study design and outcome heterogeneity of the published literature is as a result of the diversity in sample size, duration of intervention, and dosage use of RSV for treatment which are important factors that should be noted. To manage this across-study diversity, we firstly selected a random effect analysis model. Secondly, since few studies have been carried out to establish sex-specific effects, it is uncertain whether sex has any effect on response to treatment. Thirdly, most human studies used oral administration which has low bioavailability due to the activity of several liver microsomes and the intestines (Walle, 2011). Therefore, future studies should compare the effect of using different RSV-containing formulations or drug delivery systems in comparison to standard oral RSV supplements. Finally, in the case of animal models, there is likely to be some bias towards only publishing positive outcomes.

5. Conclusion

Our meta-analyses collectively revealed no clinical efficacy of RSV on a variety of cognitive and physiological measures in humans. These outcomes are in line with meta-analyses of the effects of RSV in other diseases, but differ from the results of multiple studies in animal models. This may be due to a number of variables, including dose relative to body weight, duration of trials, and differential lifespan between humans and animals. Therefore, based on current evidence and limitations of this meta-analysis, it is not possible to conclude whether an effect of resveratrol on cognition in human trials was not observed due to lack of resveratrol efficacy or lack of statistical power due to limited study duration and sample size. Our meta-analysis of currently available works fails to demonstrate any clinical efficacy of oral resveratrol supplementation in humans in trials of up to a year in duration (mean duration ~4.5 months). Consequently the effects, if any, of resveratrol supplementation are likely to be small, and detection of small effects points to the need for larger sample sizes and clinical trials of longer duration to establish whether resveratrol does have an impact on human cognition.

Of major concern is marketing of resveratrol and its therapeutic benefits coupled with media coverage which has clearly outpaced scientific research on RSV. Most published information is dependent on findings from *in vitro* and animal studies which are unlikely to be translated in the clinic. Nutraceutical companies and regulatory bodies should be more cautious and should examine current RSV formulations with a view to confirm any suggested benefits and ensure they are free of adverse effects or drug interactions. In this regard, better designed long-term trials are needed to ensure that these products are not only safe but also efficacious. Efficacy and safety should be established prior to administration of RSV in humans.

Declaration of Competing Interest

The authors reported no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2020.101199.

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