Polyphenols and cognition in humans: an overview of current evidence from recent systematic reviews and meta-analyses

Review

Polyphenols and Cognition In Humans: An Overview of Current Evidence from Recent Systematic Reviews and Meta-Analyses

Daniel Joseph Lamport* and Claire Michelle Williams*
School of Psychology and Clinical Language Science, University of Reading, Reading, RG66AL, UK

Abstract.
Background: There is increasing interest in the impact of dietary influences on the brain throughout the lifespan, ranging from improving cognitive development in children through to attenuating ageing related cognitive decline and reducing risk of neurodegenerative diseases. Polyphenols, phytochemicals naturally present in a host of fruits, vegetables, tea, cocoa and other foods, have received particular attention in this regard, and there is now a substantial body of evidence from experimental and epidemiological studies examining whether their consumption is associated with cognitive benefits.
Objective: The purpose of this overview is to synthesise and evaluate the best available evidence from two sources, namely meta-analyses and systematic reviews, in order to give an accurate reflection of the current evidence base for an association between polyphenols and cognitive benefits.
Method: Four meta-analyses and thirteen systematic reviews published between 2017–2020 were included, and were categorised according to whether they reviewed specific polyphenol-rich foods and classes or all polyphenols. A requirement for inclusion was assessment of a behavioural cognitive outcome in humans.
Results: A clear and consistent theme emerged that whilst there is support for an association between polyphenol consumption and cognitive benefits, this conclusion is tentative, and by no means definitive. Considerable methodological heterogeneity was repeatedly highlighted as problematic such that the current evidence base does not support reliable conclusions relating to efficacy of specific doses, duration of treatment, or sensitivity in specific populations or certain cognitive domains. The complexity of multiple interactions between a range of direct and indirect mechanisms of action is discussed.
Conclusions: Further research is required to strengthen the reliability of the evidence base.

Keywords: Polyphenols, cognition, cognitive function, flavonoids, review

INTRODUCTION

Polyphenols are naturally occurring phytochemicals found in a range of foods and drinks such as fruits, vegetables, tea and cocoa, and the various

health benefits associated with these foods and drinks have frequently been accounted for by their polyphenol content. Polyphenols can also be extracted and consumed as capsulated extracts. The structure and prevalence of polyphenols has been well defined elsewhere [see 1–4] and they are commonly categorised as either flavonoids or non-flavonoids. Over the past decade there has been a welcome increase in research exploring the relationship between polyphenol intake in humans and effects on the brain. Broadly,

*Correspondence to: Daniel Joseph Lamport and Claire Michelle Williams, School of Psychology and Clinical Language Science, University of Reading, Reading, RG66AL, UK. E-mails: Daniel.lamport@reading.ac.uk (Daniel Joseph Lamport) and Claire.williams@reading.ac.uk (Claire Michelle Williams).

the purpose of such research has been to identify whether polyphenol consumption can produce beneficial outcomes for cognition and to investigate possible mechanisms of action which may explain these benefits. Several informative, non-systematic overviews of cellular mechanisms, rodent models, clinical trials and epidemiological data have been published in recent years, which generally argue in favour of a reliable evidence base for a positive association between polyphenol consumption and cognitive benefits [5–10]. This is supported by evidence for mechanisms of action relating to changes in peripheral and cerebral vascular responses following polyphenol consumption [11–16]. For example, this may lead to a biophysiological cascade (both acutely and chronically) whereby increased cerebral blood flow (CBF) may lead to increased neuronal activity, which has been observed with fMRI and other neuroimaging techniques in humans (*see mechanism considerations*). It has been noted though, that whilst there is strong evidence from *in vitro* and rodent research, this has not always translated into clear outcomes from randomised controlled trials (RCTs) and other human clinical trials [17]. Meta-analyses and systematic reviews are generally considered the most robust approach for evaluating the strength, reliability and quality of an evidence base. There are now studies examining the relationship between polyphenols and cognition to attempt meta-analyses of the available data, and a multitude of systematic reviews have been undertaken, in many cases focusing on specific polyphenol-rich foods. The purpose of this overview is to gather and evaluate the findings from meta-analyses and systematic reviews to present the current status of the relationship between polyphenols and cognition from the best available evidence. It is of use to this field to provide a holistic overview of only the highest quality evidence in light of the large numbers of studies and reviews that are now available. To avoid inclusion of multiple systematic reviews which essentially cover the same studies, only meta-analyses and systematic reviews published between Jan 2017 and April 2020 were included. A review was considered systematic if there were explicitly defined inclusion and exclusion criteria, and only reviews including an assessment of behavioural outcomes from a cognitive task in humans were included. Therefore, reviews of purely neuroimaging outcomes, cellular research and animals models were outside the scope. The purpose was not to undertake a quantitative analysis of the data, rather to provide a descriptive holistic overview of the current state of the best available evidence. The relevance of mechanisms of action are discussed, and the complex interactions between these are highlighted. The seventeen reviews included are summarised in Table 1, and the evaluation of these is separated into reviews of all polyphenol classes and sources ($n = 4$), and reviews of individual polyphenol-rich foods or classes ($n = 13$).

HOLISTIC REVIEWS COVERING ALL POLYPHENOL CLASSES

A number of systematic reviews and meta-analyses have been published since 2017 which outline the evidence to date for cognitive effects associated with polyphenol consumption in humans. The majority of these reviews focus on specific polyphenol-rich foods (see Table 1), however, there are four which have incorporated research from a wide range of polyphenol-rich foods and classes. Three of these reviews focus on RCTs [11, 18, 19], whilst one is a broader review of associations between polyphenols and pathologies of Alzheimer's Disease (AD), with cognitive function being considered as a pathology [20]. The most recent of these [19] included a meta-analysis in ageing adults >55 years, however, the utility of this meta-analysis is not wide ranging as it only included performance on two executive function tests (Trail Making Test A and B), on account of the high variability in cognitive tasks between studies. The respective effect sizes for the TMT A ($n = 5$ studies) and for TMT B ($n = 6$ studies) were 0.36 and 0.82, and the authors concluded that polyphenol supplementation between 6–26 weeks has no significant effect on TMT performance, an executive function task. This is perhaps not surprising given the small number of studies included. However, within the same publication, a broader systematic review of thirteen studies identified that in ageing adults, larger polyphenol doses (>500 mg/day) may be required to attenuate cognitive decline over 3–6 months, and smaller daily doses are only likely to be effective up to 1 month. In their analysis Ammar et al. [19] also highlighted the extent to which publications utilise a single cognitive effect from a wider cognitive battery to support positive outcomes; of the thirteen studies six showed enhanced performance on one cognitive outcome whilst only three showed significant improvements on two or more outcomes. This indicates that the literature may be over-interpreting the strength of findings. The only other meta-analysis [11] covering a range of polyphenol classes did not stipulate an age range, although there was a focus on

Table 1
Summary of meta-analyses and systematic reviews published between 2017–2020 selected for inclusion (alphabetised by polyphenol, then author)

Authors	Review Type	Polyphenol(s) or Food(s)	Key Inclusion Criteria	No. Studies	Quality and/or Bias Assessment	Key Findings
Ammar	Meta-analysis & Syst. Rev.	All	Healthy ppts > 55 years, RCTs in a single population.	Five for TMT A analysis, six for TMT B analysis.	Good to excellent quality (Physiotherapy Evidence Database Scale (PEDro). No evidence of bias with multiple methods	Meta-analysis did not find supportive effects. The systematic review provided evidence that polyphenols may benefit cognition in older adults.
Colzinni	Syst. Rev.	All	Observational & interventions, at least one pathology of AD, published in previous 10 yrs.	Twenty four; sixteen assessed cognition	Sufficient quality (6.3/10 using the National Collaborating Center for Methods and Tools).	Not sufficient evidence to confirm that polyphenols have beneficial effects against AD.
Poti	Meta-analysis	All	Double-blind RCTs,>18 years, chronic administration > 2 weeks.	Twenty one, max eight in any analysis.	–	Insufficient evidence to recommended polyphenol consumption for prevention of cognitive decline.
Solfrizzi	Syst. Rev.	All	>60 years, healthy ppts, RCTs published between 2014-2017.	Eight	Moderate quality (GRADE approach).	Evidence for improved cognitive function (or neuroimaging benefits) when consumed chronically.
Kent	Syst. Rev.	Anthocyanins, food based	Crossover trial, measure of anthocyanin content.	Seven	–	Benefits of anthocyanins are promising with six of seven studies reporting improvements in either single, or multiple, cognitive outcomes.
Hein	Syst. Rev.	Blueberries	Healthy or MCI, interventions only.	Eleven	–	Benefits for memory and executive function in children, older adults and adults with mild cognitive impairment.
Travica	Syst. Rev.	Blueberries	Intervention with a control.	Eleven	Low risk of bias (Cochrane Tool).	Tentative support for a benefit to memory, but limited by methodological heterogeneity.
Barrera-Reyes	Syst. Rev.	Cocoa and associated polyphenols	RCTs of chocolate, cocoa, proanthocyanidins, flavanols or epicatechin, healthy ppts.	Twelve	Moderate risk of bias (Cochrane Tool).	Cognitive benefits *sim;50 mg/day epicatechins in healthy adults aged 18–50. Stronger evidence from studies of higher quality with compound matched placebos.

Table 1
Continued

Authors	Review Type	Polyphenol(s) or Food(s)	Key Inclusion Criteria	No. Studies	Quality and/or Bias Assessment	Key Findings
Seddon	Syst. Rev.	Curcumin	Double-blind, RCTs, min. duration of 4 weeks, older adults (*undefined*) published after Jan 2000.	Five	Low risk of bias (Cochrane Tool).	Benefits found in three of five studies in healthy older adults. However, insufficient evidence to support curcumin as a treatment for cognitive decline.
Zhu	Meta-analysis	Curcumin	RCTs, min. duration 4 weeks.	Six	Low risk of bias (Cochrane Tool).	Memory benefits in healthy older adults but no benefit for AD patients.
Liu	Syst. Rev.	Ginkgo Biloba	RCTs.	Twenty eight	–	Doses of 240 mg/day over 24 weeks or more are beneficial for patients with mild dementia.
Reay	Syst. Rev.	Ginkgo Biloba & Ginseng combined as one.	Placebo controlled.	Eight	–	Improvements in memory following acute and chronic administration in patient and healthy populations.
Restani	Syst. Rev.	Grapes (wine) and derivatives.	RCTs and epidemiological trials.	Twenty six; six of grape juice.	Good quality appraisal (DELPHI list).	Chronic grape juice consumption (200–500 ml/day) associated with benefits in older adults experiencing cog decline.
Mancini	Syst. Rev.	Green Tea & associated extracts.	Trials with and without green tea (extract), EGCG, L-theanine or combinations thereof.	Twenty one	Good quality (DELPHI list for RCTs and the Newcastle–Ottawa for observational studies).	Benefits for memory and attention, but these cannot be attributed to polyphenols only as effects are linked to the presence of caffeine and L-theanine.
Farzaei	Meta-analysis	Resveratrol supplements	RCTs.	Four	Moderate risk of bias (Jadad method).	No effects on cognitive performance.
Marx	Meta-analysis	Resveratrol supplements	RCTs ppts > 18 years, resveratrol alone or in combination.	Ten	Low risk of bias (Cochrane Tool). All outcomes rated at high or moderate quality (GRADE tool)	No consistent support for the use of resveratrol supplementation to improve cognitive performance. Pooled analysis of $n = 3$ showed a benefit for recognition memory
Zaw	Syst. Rev.	Resveratrol & Isoflavones	RCTs	Twenty three	–	Eleven studies showed a benefit (or preservation) for executive function or memory in healthy older adults, with stronger evidence for resveratrol over isoflavones.

AD = Alzheimer's Disease; MCI = mild cognitive impairment; Ppts = participants; RCT = randomised controlled trial.

chronic trials ranging from 4–312 weeks in healthy adults, which resulted in twenty one studies for inclusion, from which analysis was performed for nine cognitive outcomes. Consistent with Ammar et al. [19] there was no effect on Trail Making Test A, however, there was improvement for Trail Making Test B which was attributed to two resveratrol studies, the absence of one of these from Ammar et al. [19] may partly explain their null effect. Of the other seven meta-analysed outcomes, only memory performance (with the Rey Auditory Verbal Learning Test) was significantly improved by polyphenol intake, although this analysis only included three studies. Overall the authors offered a tentative conclusion that polyphenol supplementation might improve specific cognitive measures. Interestingly, both the meta-analyses reviewed here are cautious in their conclusions, however, the findings from a systematic review are more positive. Solfrizzi et al. [18] reviewed eight RCTs published between 2014-2017 on the prevention of late-life cognitive disorders in healthy older adults (>60 years). The conclusions were that there was evidence for improved cognitive function (or neuroimaging benefits) for both non-flavonoid (mainly resveratrol and curcumin) and flavonoid interventions when consumed chronically. Comparatively, the systematic review offers stronger support for cognitive benefits of polyphenol consumption that the meta-analyses, which may well be a function of the stricter inclusion criteria of the latter.

In light of apparent cognitive benefits observed in older adults in some chronic trials, it is not surprising that there is interest in the utility of polyphenols for reducing risk of AD. However, there is not currently supportive evidence for benefits translating to these populations. Colizzi et al. [20] reviewed 24 RCTs and observational studies which included at least one factor in the pathology of AD; sixteen of these studies assessed cognitive function. Interestingly, the authors summarised that there was not conclusive evidence for clear beneficial effects of flavonoids or phenolic acids for cognitive function or other AD pathologies. Interestingly, their analysis indicated that the majority of studies did show correlations between increased polyphenol intake and positive cognitive outcomes, but there were several studies which show both positive and negative associations, and also studies with no effects in either direction. Concerningly, a quality assessment also indicated that the studies of null and mixed effects were on balance of higher quality than the studies of positive effects, which may have contributed to the cautious conclusions. Interestingly, the

---

Text Box 1. Summative interpretation of holistic reviews [11, 18–20] covering all polyphenol classes

- The evidence from clinical trials is by no means conclusive, but there is tentative support for a relationship between regular polyphenol intake and cognitive benefits.
- More caution is required when interpreting findings, especially where a singular effect is observed amongst a variety of outcomes.
- Evidence is more compelling for benefits following chronic daily consumption over several weeks relative to single acute doses. This may be due to a greater quantity of high quality chronic studies evaluated in these reviews.
- Older adults appear to be most likely to benefit, but this can be accounted for by a higher frequency of studies in older populations rather than comparisons with other populations.
- There has been very little attempt to systematically compare polyphenol sources and doses in individual studies, and it is very difficult to generate conclusions from study comparisons due to methodological heterogeneity.
- The reviews recommend larger RCTs with sample sizes > 100.
- The overall quality of studies evaluated is moderate to good, and the risk of bias is low.
- A detailed and comprehensive meta-analysis including all populations would aid confidence in this field.

---

overall quality assessment of the studies was moderate (i.e. a sufficient level of quality to consider outcomes valid) which was echoed by Solfrizzi et al. [18] who suggested a moderate risk of bias. As might be expected, one meta-analysis indicated a higher quality overall [19], likely due to stricter inclusion criteria, whilst the other [11] did not formally assess quality or risk of bias. Considering the outcomes of these four recent holistic systematic reviews there are some common threads and interpretations which are described in Text Box 1.

REVIEWS OF SPECIFIC POLYPHENOL-RICH FOODS OR CLASSES

Between 2017-20 thirteen systematic reviews/ meta-analyses have been published examining the literature for a specific polyphenol class, or a

polyphenol-rich food. As summarised in Table 1, these cover a range of polyphenols, and a maximum of two reviews exist per polyphenol class or source. The review of anthocyanin-rich foods [21] is arguably the broadest, including seven RCTs from apples, blackcurrants, blueberries, cherries, and grapes, all in juice or drink form. Similarly to the wider-ranging reviews described above, the conclusions were tentative; the evidence is promising for a benefit to cognition, particularly verbal memory, with six of seven studies showing positive effects on at least one cognitive outcome measure, but a pooled statistical analysis was not possible due to methodological variance and weaknesses such as small sample size. Even solid conclusions relating to efficacy in certain populations were beyond the reach of the data. Two systematic reviews focusing on an anthocyanin-rich food; blueberry [22, 23], also voiced similar conclusions to the anthocyanin review [21], despite including a greater number of studies (both eleven, although the studies included were not identical due to different inclusion criteria). In both blueberry reviews methodological heterogeneity was cited as problematic for systematically evidencing a strong and consistent picture of benefits, however, promisingly, verbal memory was again cited as a cognitive domain likely to be most sensitive to blueberry consumption. Interestingly, both of the blueberry reviews indicated that there is an absence of studies in healthy young and middle aged adults and the evidence base relies on studies in children and healthy older adults (>60 years) or older adults with mild cognitive impairment. Travica et al. [23] also indicated that there was no consistent pattern of findings in healthy older adults, largely due to variations in dose, duration and other methodological factors. The only other review included of an anthocyanin-rich food (grapes) [24] indicated more promising conclusions stating that 200–550 ml/day of grape juice up to durations of six months was associated with improved cognitive performance, particularly for older adults in the early stages of cognitive decline. This bold conclusion was on the basis of only six RCTs assessing grape juice and cognition, and only three studies included older adults (the remaining studies in the review were of wine consumption for which the evidence showed that light-to-moderate wine; one to four glasses/day, was generally associated with improved cognitive performance). Furthermore, the conclusions relating to dose, population and duration (see Table 2) are arguably a little overzealous in light of the small number of studies reviewed [24],

and there was no systematic assessment of bias or quality. Interestingly, resveratrol was highlighted as a specific polyphenol which is a possible effector of the beneficial outcomes of grapes.

Resveratrol was the focus of a systematic review investigating the effects of phytoestrogen supplementation on cognition [25], in which eight resveratrol RCTs (purified or as grape extract) were compared with another type of phytoestrogens; isoflavones (fifteen RCTs). The evidence was inconsistent; less than half of the studies showed beneficial effects. However, the authors argued that resveratrol is emerging as a strong candidate for cognitive enhancement in the older adult population, with benefits observed for doses between 150–200 mg/day. It was also suggested that isoflavone supplementation between 60–116 mg/day up to six months, can benefit cognition. It is notable that isoflavone studies are often confounded by population bias (typically postmenopausal women), and interestingly it was summarised that benefits are most likely in women who are <10 years postmenopausal. The authors suggested that overall, the evidence was stronger for resveratrol although no direct statistical comparisons were made between isoflavone and resveratrol outcomes. There was no assessment of study bias or quality, and given the overall weighting to a greater number of non-significant studies, the conclusions appear optimistic.

This optimism is not reflected in the findings from two recent meta-analyses of resveratrol supplements for cognitive outcomes; one included four studies [26] and another more wide-ranging analysis of ten studies [27]. Perhaps unsurprisingly, in light of the small number of studies, the former [26] concluded that there was no evidence for benefits of resveratrol for cognitive performance, although the analysis was focused on verbal memory outcome measures. As cited in previous reviews, methodological heterogeneity was a problem, and subsequently any pooled analyses contained data from no more than two trials. The larger meta-analysis [27] also included a focus on memory outcomes, and a pooled analysis indicated that resveratrol consumption can improve memory, specifically delayed recognition, although the effect size was small (a standardized mean difference, SMD, of 0.39) and only three studies contributed to this analysis. Two further pooled analysis for processing speed and number facility failed to find any effect of resveratrol, and five of the included ten studies did not find effects on cognition. Moreover, a GRADE tool (Grading of Recommendations,

Table 2

For reviews of individual polyphenol-rich foods or specific sub-classes, a summary of the evidence base available for efficacy in specific populations, doses, duration of intervention, and cognitive domains. Insufficient data indicates that there was not available data to provide a systematic comparison between groups of the relevant variable (alphabetised by author)

Author & Polyphenol	Population sensitivity	Dose sensitivity	Cognitive domain sensitivity	Duration sensitivity
Barrera-Rayes: Cocoa	Younger adults show more benefits than older adults.	500–750 mg/day	Insufficient data	Insufficient data
Farzei: Resveratrol	Insufficient data	Insufficient data	Only memory assessed – no effects	Insufficient data
Hein: Blueberries	Only children and > 60 years assessed.	A higher does not clearly translate to better performance.	Verbal memory and executive functions.	Confounded by acute studies in children and chronic in old.
Kent: Anthocyanins	Insufficient data	Insufficient data	Verbal memory and learning.	Insufficient data
Lui: Gingko biloba	Patients with mild dementia.	240 mg/day	Insufficient data	Chronic doses of minimum 24 weeks.
Mancini: Green Tea & extracts	Insufficient data	Insufficient data	Memory and attention.	Insufficient data
Marx: Resveratrol	Insufficient data	Insufficient data	Delayed recognition.	Long term trials more likely to show benefits.
Reay: Ginkgo Biloba & Ginseng	Insufficient data	Insufficient data	Memory (specifically secondary memory).	Insufficient data
Restani: Grapes	Older adults in the early stages of cognitive decline.	200–500 ml/day	Memory, learning, reactions times and aspects of executive function.	Chronic doses up to 6 months.
Seddon: Curcumin	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Travica: Blueberries	May benefit older adults.	Insufficient data	Insufficient data	Insufficient data
Zaw: Isoflavone	Females<10 years postmenopausal.	60–116 mg/day	Insufficient data	Chronic doses between 12 weeks and 6 months.
Zaw: Resveratrol	Older adults.	150–200 mg/day	Insufficient data	Chronic doses of minimum 14 weeks.
Zhu: Curcumin	Older adults.	Insufficient data	Memory.	Insufficient data

Assessment, Development, and Evaluation) found moderate to high confidence that resveratrol supplementation has no significant effect on most outcomes in the general population.

Therefore, these meta-analyses [26, 27] do not provide compelling evidence for beneficial effects of resveratrol on cognition, and there is certainly not a strong enough evidence base to make conclusions regarding dose, population or duration of intervention. This is unsurprising given the small number of studies included in the pooled analyses, and once again, methodological heterogeneity is cited as barrier to reliable summative conclusions. The heterogeneity limitation was also highlighted by the only other meta-analysis included here (curcumin [28]), so much so that a sensitivity analysis was not possible, and the overall quality of the evidence was cited as low. Nevertheless, pooled-analysis of three studies in older adults showed a benefit of curcumin for memory (SMD = 0.33), matching some of the aforementioned reviews of other polyphenol sources. However, in two studies of AD patients, the data

showed a non-significant trend for curcumin to perform *worse* than placebo (SMD 0.9) on a global cognitive measure (Mini Mental State Examination). The evidence for curcumin was also evaluated in a systematic review of fives studies [29]. Three of the five studies found improvement in performance following curcumin, however the conclusions state that there is insufficient evidence to support curcumin supplementation as an effective means of both preventing and treating dementia and symptoms of cognitive decline. Methodological heterogeneity and small sample sizes were the primary limitations hampering generalisability; this is clearly a consistent theme of the evidence reviewed here.

Reliable, generalizable conclusions are likely more attainable from reviews of a larger pool of studies. A systematic review of Gingko Biloba leaf extract [30] including twenty eight studies in healthy adults and AD patients reported positive outcomes; daily doses of 240 m/day were summarised to benefit patients with mild AD symptoms, despite eleven studies failing to report an effect. Nevertheless, it

was evident that these negative studies were largely in younger healthy adults, and included a greater frequency of single dose studies, and chronic trials of shorter duration. Therefore, these conclusions offer a sensible degree of reliability. However, even with the larger number of studies included, a systematic analysis of which cognitive domains may be most affected was not achievable, and risk of bias or study quality were not evaluated. Some positive outcomes were also reported from a smaller systematic review [31] which considered eight studies of a commercially available supplement which contains Gingko combined with Ginseng, both of which are considered polyphenol-rich traditional herbal supplements. A discursive analysis of the cognitive domains affected and duration of treatment was undertaken, with conclusions being that memory can be improved in healthy and patient populations as soon as one hour post consumption, with repeated chronic dosing also benefiting memory. However, there was limited data directly comparing doses, duration or populations under similar methodological conditions, and it was interesting to note that five of the eight studies were from the same research group. An advantage of this is that it allows consistency in the cognitive assessment, and may explain why there is evidence for a memory effect from a comparatively small number of studies, whilst a disadvantage is that this evidence base lacks replicability across research groups, simply on account of the small number of studies. A systematic analysis of bias or quality was not undertaken, although it was concluded that the methodologies were robust and well controlled. Interestingly, two studies reported that the synergy of Gingko and Ginseng was more efficacious than the individual constituents combined; synergistic polyphenol effects have received little attention in the reviews presented here, most likely as there is not currently an evidence base to draw data from.

Conversely, cocoa is a polyphenol source which has attracted relatively widespread investigation of potential cognitive benefits. A systematic review of twelve clinical trials presented a detailed overview of dose, population, treatment duration and cognitive domains affected [32]. The evidence was perhaps the most supportive seen throughout this review; eight studies reported a benefit for a behavioural outcome, and the conclusions stated that effects on cognitive function were reliably observed after consumption of 50 mg/day of epicatechin in adults aged 18–50 years. Interestingly it was reported that effect sizes were higher for daily doses of between 500–750 mg

compared to 750 mg, and effects were more consistently observed in younger adults compared to older adults. However, there was insufficient comparative data for conclusions on treatment, duration and whether certain cognitive domains are more sensitive, rather effects were generally reported for memory and executive function. Concerns were highlighted with respect to risk of bias, with five studies judged as poor quality and only two as good quality using the Cochrane Tool. This raises doubt on the reliability of the positive effects of cocoa, and emphasises that further good quality research is required. Encouragingly, the studies of higher quality and lowest risk of bias provided the strongest effects of cocoa associated cognitive benefits, particularly studies which utilised a placebo matched for potentially confounding compounds such as caffeine and theobromine. The effect of confounding components is also problematic in the green tea polyphenol and cognition literature. For example, a systematic review of twenty one studies of green tea and associated extracts reported that epidemiological cohort studies support cumulative cognitive benefits from habitual intake of 100 ml/day, and the data from sixteen clinical trials suggest benefits for memory and attention [33]. On the face of it, this appears positive, however, it was concluded that the cognitive improvements are strongly linked to the presence of both caffeine and L-theanine, and the benefits cannot be attributed to a singular component such as polyphenols. Some evidence of synergistic benefits was reported, which echoes findings from the Ginkgo/Ginseng review [31]. However, once again, significant methodological heterogeneity was cited as hampering conclusions relating to dose, population and duration of effects.

In summary, a number of informative systematic reviews and meta-analyses have been published in recent years examine individual polyphenol classes or polyphenol-rich foods. Data from the meta-analyses appear to be less convincing than findings from systematic reviews, which may reflect stricter inclusion criteria and lower power on account of the difficulties in combining data from heterogeneous studies. It appears that the current state of the literature base is not sufficiently advanced to support meaningful systematic analysis of specific polyphenol classes, or polyphenol-rich foods (see Table 2). Encouragingly, the three meta-analyses discussed here report a low risk of bias overall, which indicates that the studies included are of strong methodological design. Only four systematic reviews considered risk of bias (or quality) with a standardised tool (e.g. Cochrane Tool),

Text Box 2. Summative interpretation of reviews [21–33] covering individual polyphenol-rich foods and classes

- All ten systematic reviews indicated some support for positive effects of the reviewed polyphenol on cognition. However, most reviews expressed caution, showing that benefits were not consistent across all studies.
- Two of three meta-analyses reported that there was no consistent evidence for a benefit of the reviewed polyphenol on cognition.
- Verbal memory is consistently appearing as a cognitive domain showing greatest sensitivity to polyphenols, however, this is strongly associated with greater frequency of assessment relative to other domains, which may reflect ease of assessing memory.
- Older adult populations have received more attention and there are very few instances of direct population comparisons.
- Methodological heterogeneity was highlighted as problematic for surmising consistent and reliable evidence regarding dose, duration, population, and cognitive domain.
- The larger systematic reviews tended to argue for a stronger evidence base overall, nevertheless, these still contain numerous studies of non-significant effects.
- Dose-response studies are required assessing multiple doses in the same population acutely and chronically.
- Of those that reviewed quality, most reported moderate to high quality, and a low risk of bias.

but positively, these largely indicated low risk of bias. However, the cocoa review [32] did express moderate concerns relating to matched controls in some studies. Interestingly, the picture from the reviews of individual polyphenol classes is slightly more positive regarding cognitive outcomes than the reviews of all polyphenol classes (see section 2), however, as summarised in Text Box 2, the evidence for a positive relationship between polyphenols and cognitive benefits is perhaps not as strong as might be anticipated.

MECHANISTIC CONSIDERATIONS

In order to fully understand the relationship between polyphenol consumption and cognitive function it is important to have an understanding of the mechanisms of action which may account for behavioural effects. There has been much exploration of the role of increased CBF following polyphenol consumption [34–36], which may lead to increased neuronal activity as assessed by fMRI and other neuroimaging techniques [37]. This cerebral vascular mechanism is supported by evidence showing an improved peripheral vascular response such as reduced blood pressure and increased flow mediated dilation following polyphenol consumption [11–16]. This vascular responsivity mechanism is underpinned by *in-vitro* and animal data demonstrating that polyphenols can affect multiple cellular pathways thought to be responsible for vascular changes [11, 12, 38, 39]. It logical to consider that short term peripheral and cerebral vascular changes over several hours may account for acute behavioural effects of polyphenols. However, chronic activation of these pathways may also support long term behavioural benefits if the cerebrovascular mechanistic process becomes more efficient following repeated improvement over time. It is difficult, though, to attain evidence directly supporting these processes as we are unable to directly examine the cellular pathways in a human brain during a cognitive task. Rather we are able to observe proxies for neural activation such as improved CBF with arterial spin labelling (ASL), and changes in the ratio of oxygenated to deoxygenated blood with fMRI. Other techniques such as electroencephalography (EEG) can offer better temporal resolution [40] however, in summary we cannot directly observed the pathways between polyphenol intake, improved blood flow, neuronal activation and improved behavioural performance in humans. Nevertheless, *in-vitro* cellular work in combination with rodent studies provides good evidence for a cascade a mechanisms which associate polyphenols with changes in neuronal morphology and synaptic plasticity [41–43] and it is plausible that these mechanisms of action may account for chronic behavioural benefits in humans.

Studies targeting specific mechanisms of action and associated cognitive effects are important and should continue. However, it is becoming increasingly apparent that there are a host of complex pathways and mechanisms which are interacting in their contribution to behavioural outcomes. In any study (acute, chronic, or epidemiological) the assessment of cognitive performance is not undertaken outside of the context of everyday life. Participants bring their own influences such as habitual diet,

subjective mood state, underlying cognitive abilities, and a host of metabolic and physiological characteristics such as the gut microbiota, and it is likely that this variance is contributing to the inconsistent behavioural data highlighted in this overview. Attempts can be made to control for some of these characteristics in order to identify specific associations between cognitive effects and mechanisms of action, with the compromise being that the findings from such studies can only be applied to certain populations and experimental conditions. By gaining a holistic understanding of the wider influences, and the complex nature in which these factors interact, future work may be able to more accurately understand and hypothesis when and how polyphenol intake is likely to benefit cognitive function.

Considering these influences in a little more detail, there is now reasonable evidence for several variables potentially moderating or mediating the relationship between polyphenols and cognition. The gut microbiota can be broadly considered as the gateway for all effects since all ingested polyphenols will pass into and through the gut (at least partially) before reaching the blood stream through which they are distributed throughout the body. Therefore, the gut environment and gut microbiota has an important influence, and there is evidence of a complex bidirectional relationship between gut microbiota, polyphenols and cognition [44–46]. Given that there is significant divergence between individuals in their gut microbiota, it follows that the metabolic fate of polyphenols is not consistent, and thus this individual variation is likely to contribute to variance in cognitive outcomes following polyphenol intake [46–49]. Moreover, meta-analyses show that the bioavailability of polyphenols is an important aspect in determining likelihood of cognitive outcomes with one review stating that > 9% bioavailability is needed to improve brain health in older adults [19]. Other factors such as the food matrix are also thought to impact upon the subsequent bioavailability of polyphenols and thus outcomes may vary depending on whether polyphenols are consumed as an extract or whole food [20, 50, 51]. Habitual diet is also likely to shape the state of the gut microbiota, indeed dietary factors have been suggested to account for a significant percentage of the microbiota variance between individuals [52, 52]. Moreover, a greater intake of polyphenol-rich foods has been associated with greater microbial diversity and enhanced growth of bacterial species associated with health benefits [54–57]. However, it is currently unclear whether cognitive benefits

following polyphenol consumption are more likely to be observed in frequent habitual polyphenol consumers (in whom the gut environment is likely to be more efficient at metabolising polyphenols) or in habitually low polyphenol consumers, who may receive an immediate benefit on account of an absence of previous intake. Alternatively, low habitual consumers may not have a gut environment which can efficiently metabolise polyphenols, and thus cognitive benefits may be limited. Aside from polyphenols, there are a host of hypothesised bidirectional pathways between the gut and the brain [58, 59] and there is potential for polyphenols to interact with multiple aspects of this gut-brain axis [44, 46].

Another physiological variable which may mediate/moderate the relationship between polyphenols and cognition is insulin sensitivity. It is well established that type 2 diabetes (T2DM) and impairments in insulin sensitivity negatively impact cognitive function [60, 61]; this is of interest here since polyphenols are known to improve insulin sensitivity and reduce risk of T2DM [62, 63]. Therefore, polyphenols may be contributing to cognitive benefits via mechanisms associated with insulin sensitivity [42, 64–66]. For example, the brain has a high degree of insulin receptors [67, 68], and rodent models show that increased insulin resistance in the brain can impair cognition [69]. Furthermore, poor insulin sensitivity and T2DM is associated with endothelial dysfunction in the blood brain barrier [70], which could be a cerebrovascular mechanism shared between T2DM and polyphenols [64, 66, 71]. For example, resveratrol can reduce blood brain barrier permeability in rodents which has been shown to be accompanied by inhibited hippocampal neurodegeneration [72]. Furthermore, acute and chronic cognitive improvements following polyphenol consumption have been associated with improvements in insulin sensitivity [73–75]. To add a further layer of complexity, the gut microbiota is known to impact upon the regulation of systemic insulin sensitivity via functional metabolites [76, 77]. Therefore, there is likely to be a complex interactive pathway between polyphenols, the gut microbiota, insulin sensitivity and cognition, and this requires exploration. T2DM is also characterised by low mood and increased incidence of depression which further complicates potential mechanisms of action since low mood is also associated with cognitive impairments [78]. This pathway has relevance for polyphenol-cognition research as there is now data from epidemiological studies [13, 79] and clinical trials [80–82] showing

Table 3
– Hypothetical methods for defining a cognitive benefit associated with polyphenol consumption

Definition	Considerations
An improvement over time relative to baseline.	If a placebo also shows a similar profile this implies practice effects.
Better performance at any given time point relative to a placebo.	Can be misleading if the baseline is not the same for placebo and polyphenol.
A steeper improvement over time relative to a placebo.	Important to check raw scores, the polyphenol condition could have lower performance per se.
Attenuation of a decline over time relative to a placebo.	Typically demonstrated by no change in performance for the polyphenol but a decline over time for a placebo.
Slower rate of decline relative to a placebo.	A decline may be observed in polyphenol and placebo conditions. More likely in ageing or impaired populations.
Reduced risk of developing a cognitive impairment relative to a placebo.	Common in epidemiological studies, assessing cases of neurodegenerative disease over time.
Correlation between increased polyphenol intake and better cognitive performance.	Important to check how cognitive performance is defined.

that polyphenols can reduce risk of depression and negative mood and also improve positive mood, both acutely and chronically. Several supporting mechanisms have been proposed [83] involving regulation of neurotransmitters via changes in short chain fatty acids and tryptophan metabolites, and various other molecular cascades potentially affecting neuroinflammation and synaptic plasticity, all of which are intrinsically linked to the gut microbial environment. This highlights an emerging complex system where polyphenols may be affecting cognition via multiple pathways associated with changes in subjective mood, which could occur over both acute and chronic timeframes. However, this remains speculative, and it is important to point out that a systematic evaluation of the impact of polyphenols on mood, and the interaction with cognition requires investigation. In summary, polyphenols have a multitude of bidirectional actions in the body and appear to have influence on various mechanisms which affect cognitive function independently of polyphenol intake. Therefore, it is important that future research considers both direct (e.g. CBF and neurogenesis) and indirect (e.g. insulin sensitivity, subjective mood, and gut health) mechanisms of action when investigating the effects of polyphenols on cognitive performance in humans.

WHAT DO WE MEAN BY A COGNITIVE BENEFIT?

A topic seldom discussed in this literature is the variety of ways in which a behavioural cognitive benefit is defined. This has undoubtedly contributed to the difficulties in comparing cognitive effects across populations. It is reasonable to hypothesise that cognitive benefits associated with polyphenols (and other nutritional influences) will manifest in different ways throughout the lifespan; children may experience and increase in the speed and trajectory of cognitive development, young healthy adults at the peak of their cognitive lifespan may seek to maximise cognitive potential, whilst older adults may look to attenuate the trajectory of cognitive decline and extend the maintenance of good brain health into old age. However, all these effects are all broadly described as a cognitive benefit. Furthermore, there are many additional subtleties in the analysis of data when presenting a cognitive benefit (see Table 3), and all this variance is contributing to an absence of consistent and reliable findings in the reviews presented here. If the way in which an outcome measure is defined has considerably variety than there is bound to be inconsistency in outcomes between studies. Moreover, positive effects with neuroimaging outcomes (e.g. fMRI, ASL, EEG) are also considered cognitive benefits in studies utilizing these techniques, however, such measures typically do not, on their own, include a behavioural outcome (i.e. a performance measure from a cognitive task). There are of course many studies which combine neuroimaging techniques with behavioural outcomes which provide important insight into various mechanisms of action. However, the point is that a change on a neuroimaging outcome is not synonymous with a cognitive benefit on a behavioural task, and the former can occur in the absence of the latter. When evaluating this literature care should be taken when defining what we mean by a cognitive benefit. Understanding what type of cognitive benefit we may be expecting to observe in a given population and experimental scenario will enhance our understanding of how and under what conditions polyphenol consumption can

benefit cognition. Finally, it is also important to reflect upon what we mean when describing a cognitive benefit as it has relevance for the application and translation of experimental research to the public and policy makers.

CONCLUSIONS

The purpose of this overview was to consider and summarise the evidence presented in recent systematic reviews and meta-analyses of the relationship between polyphenol consumption and cognitive function in humans. All thirteen systematic reviews offer some degree of support for a benefit of polyphenols for cognition, and on the face of it this sounds overwhelmingly positive. However, a clear and consistent theme has emerged that these conclusions are tentative. Indeed, this is reflected when considering the most robust analyses; three of the five meta-analyses concluded there was no evidence for a benefit, and the positive outcomes were small effects from limited analyses. However, the practical utility of these meta-analyses is questionable on the basis that significant methodological heterogeneity severely restricted the inclusivity and scope of the statistical analyses. This limitation is also highlighted throughout the systematic reviews, so much so that conclusions relating to the most efficacious dose and duration of consumption, the populations most likely to benefit, or the most sensitive cognitive domains are not currently possible with any reasonable degree of reliability or consistency (see Table 2). There is encouraging evidence that verbal memory is emerging repeatedly as sensitive to polyphenol interventions, however, this appears to be driven by the frequency of assessment rather than by clear and direct comparisons with other cognitive domains within or between studies. It is encouraging that risk of bias was largely deemed as low, and the quality of studies graded as moderate to high, however, such analyses with standardised techniques were not routinely performed. In conclusion, there is evidence that polyphenols can benefit cognition in humans, but this evidence is not as convincing as it initially appears. Future research is required to strengthen the reliability of the evidence base, and furthermore, this should consider the wider impact and interaction between a variety of direct and indirect mechanisms of action. This will assist our understanding of the conditions under which polyphenol induced cognitive benefits in humans are likely to be observed.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

REFERENCES

[1] Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. The American Journal of Clinical Nutrition. 2004;79(5):727-47.

[2] Tsao R. Chemistry and biochemistry of dietary polyphenols. Nutrients. 2010;2(12):1231-46.

[3] Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly) phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxidants & Redox Signaling. 2013;18(14):1818-92.

[4] Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. Journal of Nutritional Science. 2016;5.

[5] Flanagan E, Müller M, Hornberger M, Vauzour D. Impact of flavonoids on cellular and molecular mechanisms underlying age-related cognitive decline and neurodegeneration. Current Nutrition Reports. 2018;7(2):49-57.

[6] Gildawie KR, Galli RL, Shukitt-Hale B, Carey AN. Protective effects of foods containing flavonoids on age-related cognitive decline. Current Nutrition Reports. 2018;7(2): 39-48.

[7] Carrillo JÁ, Zafrilla MP, Marhuenda J. Cognitive Function and Consumption of Fruit and Vegetable Polyphenols in a Young Population: Is There a Relationship? Foods. 2019;8(10):507.

[8] Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA. The effects of polyphenols and other bioactives on human health. Food & Function. 2019;10(2):514-28.

[9] Miller K, Feucht W, Schmid M. Bioactive compounds of strawberry and blueberry and their potential health effects based on human intervention studies: A brief overview. Nutrients. 2019;11(7):1510.

[10] Rajaram S, Jones J, Lee GJ. Plant-based dietary patterns, plant foods, and age-related cognitive decline. Advances in Nutrition. 2019;10(Supplement_4):S422-36.

[11] Potì F, Santi D, Spaggiari G, Zimetti F, Zanotti I. Polyphenol health effects on cardiovascular and neurodegenerative disorders: A review and meta-analysis. International Journal of Molecular Sciences. 2019;20(2):351.

[12] Oak MH, Auger C, Belcastro E, Park SH, Lee HH, Schini-Kerth VB. Potential mechanisms underlying cardiovascular protection by polyphenols: Role of the endothelium. Free Radical Biology and Medicine. 2018;122:161-70.

[13] Godos J, Vitale M, Micek A, Ray S, Martini D, Del Rio D, Riccardi G, Galvano F, Grosso G. Dietary polyphenol intake, blood pressure, and hypertension: A systematic review and Meta-Analysis of observational studies. Antioxidants. 2019;8(6):152.

[14] Sun Y, Zimmermann D, De Castro CA, Actis-Goretta L. Dose–response relationship between cocoa flavanols and human endothelial function: a systematic review and meta-analysis of randomized trials. Food & Function. 2019; 10(10):6322-30.

[15] Martini D, Marino M, Angelino D, Del Bo' C, Del Rio D, Riso P, Porrini M. Role of berries in vascular function: a systematic review of human intervention studies. Nutrition Reviews. 2020;78(3):189-206.

[16] Weaver SR, Rendeiro C, McGettrick HM, Philp A, Lucas SJ. Fine wine or sour grapes? A systematic review and meta-analysis of the impact of red wine polyphenols on vascular health. European Journal of Nutrition. 2020:1-28.

[17] Bakoyiannis I, Daskalopoulou A, Pergialiotis V, Perrea D. Phytochemicals and cognitive health: Are flavonoids doing the trick?. Biomedicine & Pharmacotherapy. 2019;109: 1488-97.

[18] Solfrizzi V, Agosti P, Lozupone M, Custodero C, Schilardi A, Valiani V, Sardone R, Dibello V, Di Lena L, Lamanna A, Stallone R. Nutritional intervention as a preventive approach for cognitive-related outcomes in cognitively healthy older adults: a systematic review. Journal of Alzheimer's Disease. 2018;64(s1):S229-54.

[19] Ammar A, Trabelsi K, Müller P, Bouaziz B, Boukhris O, Glenn JM, Bott N, Driss T, Chtourou H, Müller N, Hökelmann A. The Effect of (Poly) phenol-Rich Interventions on Cognitive Functions and Neuroprotective Measures in Healthy Aging Adults: A Systematic Review and Meta-Analysis. Journal of Clinical Medicine. 2020;9(3):835.

[20] Colizzi C. The protective effects of polyphenols on Alzheimer's disease: A systematic review. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2019;5:184-96.

[21] Kent K, Charlton KE, Netzel M, Fanning K. Food-based anthocyanin intake and cognitive outcomes in human intervention trials: a systematic review. Journal of Human Nutrition and Dietetics. 2017;30(3):260-74.

[22] Hein S, Whyte AR, Wood E, Rodriguez-Mateos A, Williams CM. Systematic review of the effects of blueberry on cognitive performance as we age. The Journals of Gerontology: Series A. 2019;74(7):984-95.

[23] Travica N, D'Cunha NM, Naumovski N, Kent K, Mellor DD, Firth J, Georgousopoulou EN, Dean OM, Loughman A, Jacka F, Marx W. The effect of blueberry interventions on cognitive performance and mood: A systematic review of randomized controlled trials. Brain, Behavior, and Immunity. 2019 Apr 15.

[24] Restani P, Fradera U, Ruf JC, Stockley C, Teissedre PL, Biella S, Colombo F, Lorenzo CD. Grapes and their derivatives in modulation of cognitive decline: a critical review of epidemiological and randomized-controlled trials in humans. Critical Reviews in Food Science and Nutrition. 2020:1-1.

[25] Thaung Zaw JJ, Howe PR, Wong RH. Does phytoestrogen supplementation improve cognition in humans? A systematic review. Annals of the New York Academy of Sciences. 2017;1403(1):150-63.

[26] Farzaei MH, Rahimi R, Nikfar S, Abdollahi M. Effect of resveratrol on cognitive and memory performance and mood: A meta-analysis of 225 patients. Pharmacological Research. 2018;128:338-44.

[27] Marx W, Kelly JT, Marshall S, Cutajar J, Annois B, Pipingas A, Tierney A, Itsiopoulos C. Effect of resveratrol supplementation on cognitive performance and mood in adults: a systematic literature review and meta-analysis of randomized controlled trials. Nutrition Reviews. 2018;76(6): 432-43.

[28] Zhu LN, Mei X, Zhang ZG, Xie YP, Lang F. Curcumin intervention for cognitive function in different types of people: A systematic review and meta-analysis. Phytotherapy Research. 2019;33(3):524-33.

[29] Seddon N, D'Cunha NM, Mellor DD, McKune AJ, Georgousopoulou EN, Panagiotakos DB, Kellett J, Naumovski N. Effects of Curcumin on Cognitive Function—A System-

atic Review of Randomized Controlled Trials. Exploratory Research and Hypothesis in Medicine. 2019;4(1):1-1.

[30] Liu H, Ye M, Guo H. An updated review of randomized clinical trials testing the improvement of cognitive function of ginkgo biloba extract in healthy people and Alzheimer's patients. Frontiers in Pharmacology. 2019;10.

[31] Reay JL, van Schaik P, Wilson CJ. A systematic review of research investigating the physiological and psychological effects of combining Ginkgo biloba and Panax ginseng into a single treatment in humans: Implications for research design and analysis. Brain and Behavior. 2019;9(3):e01217.

[32] Barrera-Reyes PK, de Lara JC, González-Soto M, Tejero ME. Effects of Cocoa-Derived Polyphenols on Cognitive Function in Humans. Systematic Review and Analysis of Methodological Aspects. Plant Foods for Human Nutrition. 2020:1-1.

[33] Mancini E, Beglinger C, Drewe J, Zanchi D, Lang UE, Borgwardt S. Green tea effects on cognition, mood and human brain function: A systematic review. Phytomedicine. 2017;34:26-37.

[34] Haskell-Ramsay CF, Schmitt J, Actis-Goretta L. The impact of epicatechin on human cognition: The role of cerebral blood flow. Nutrients. 2018;10(8):986.

[35] Joris PJ, Mensink RP, Adam TC, Liu TT. Cerebral blood flow measurements in adults: A review on the effects of dietary factors and exercise. Nutrients. 2018;10(5):530.

[36] Rees A, Dodd GF, Spencer JP. The effects of flavonoids on cardiovascular health: a review of human intervention trials and implications for cerebrovascular function. Nutrients. 2018;10(12):1852.

[37] Brickman AM, Khan UA, Provenzano FA, Yeung LK, Suzuki W, Schroeter H, Wall M, Sloan RP, Small SA. Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults. Nature Neuroscience. 2014;17(12):1798.

[38] Rodriguez-Mateos A, Istas G, Boschek L, Feliciano RP, Mills CE, Boby C, Gomez-Alonso S, Milenkovic D, Heiss C. Circulating anthocyanin metabolites mediate vascular benefits of blueberries: insights from randomized controlled trials, metabolomics, and nutrigenomics. The Journals of Gerontology: Series A. 2019;74(7):967-76.

[39] Serino A, Salazar G. Protective role of polyphenols against vascular inflammation, aging and cardiovascular disease. Nutrients. 2019;11(1):53.

[40] Aine CJ. A conceptual overview and critique of functional neuroimaging techniques in humans: I. MRI/FMRI and PET. Critical Reviews in Neurobiology. 1995;9(2-3): 229-309.

[41] Vauzour D, Vafeiadou K, Rodriguez-Mateos A, Rendeiro C, Spencer JP. The neuroprotective potential of flavonoids: a multiplicity of effects. Genes & Nutrition. 2008; 3(3):115.

[42] Castelli V, Grassi D, Bocale R, d'Angelo M, Antonosante A, Cimini A, Ferri C, Desideri G. Diet and brain health: which role for polyphenols? Current Pharmaceutical Design. 2018; 24(2):227-38.

[43] Sarubbo F, Moranta D, Pani G. Dietary polyphenols and neurogenesis: Molecular interactions and implication for brain ageing and cognition. Neuroscience & Biobehavioral Reviews. 2018;90:456-70.

[44] Filosa S, Di Meo F, Crispi S. Polyphenols-gut microbiota interplay and brain neuromodulation. Neural Regeneration Research. 2018;13(12):2055.

[45] Frolinger T, Sims S, Smith C, Wang J, Cheng H, Faith J, Ho L, Hao K, Pasinetti GM. The gut microbiota composition

affects dietary polyphenols-mediated cognitive resilience in mice by modulating the bioavailability of phenolic acids. Scientific Reports. 2019;9(1):1-0.

[46] Ma G, Chen Y. Polyphenol supplementation benefits human health via gut microbiota: A systematic review via meta-analysis. Journal of Functional Foods. 2020;66:103829.

[47] Kemperman RA, Bolca S, Roger LC, Vaughan EE. Novel approaches for analysing gut microbes and dietary polyphenols: challenges and opportunities. Microbiology-Sgm. 2010;156(11):3224-31.

[48] Espín JC, González-Sarrías A, Tomás-Barberán FA. The gut microbiota: A key factor in the therapeutic effects of (poly) phenols. Biochemical Pharmacology. 2017;139:82-93.

[49] Bento-Silva A, Koistinen VM, Mena P, Bronze MR, Hanhineva K, Sahlstrøm S, Kitrytė V, Moco S, Aura AM. Factors affecting intake, metabolism and health benefits of phenolic acids: do we understand individual variability? European Journal of Nutrition. 2019:1-9.

[50] Cheynier V. Polyphenols in foods are more complex than often thought. The American Journal of Clinical Nutrition. 2005;81(1):223S-9S.

[51] Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. The American Journal of Clinical Nutrition. 2005;81(1):230S-42S.

[52] Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, Vatanen T, Mujagic Z, Vila AV, Falony G, Vieira-Silva S, Wang J. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science. 2016;352(6285):565-9.

[53] Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, Costea PI, Godneva A, Kalka IN, Bar N, Shilo S. Environment dominates over host genetics in shaping human gut microbiota. Nature. 2018;555(7695):210-5.

[54] Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI. Benefits of polyphenols on gut microbiota and implications in human health. The Journal of Nutritional Biochemistry. 2013;24(8):1415-22.

[55] Dueñas M, Muñoz-González I, Cueva C, Jiménez-Girón A, Sánchez-Patán F, Santos-Buelga C, Moreno-Arribas M, Bartolomé B. A survey of modulation of gut microbiota by dietary polyphenols. BioMed Research International. 2015;2015.

[56] Ozdal T, Sela DA, Xiao J, Boyacioglu D, Chen F, Capanoglu E. The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. Nutrients. 2016;8(2):78.

[57] Jennings A, Koch M, Jensen MK, Bang C, Kassubek J, Müller HP, Nöthlings U, Franke A, Lieb W, Cassidy A. The role of the gut microbiome in the association between habitual anthocyanin intake and visceral abdominal fat in population-level analysis. The American Journal of Clinical Nutrition. 2020;111(2):340-50.

[58] Dinan TG, Cryan JF. Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. The Journal of Physiology. 2017;595(2):489-503.

[59] Cryan JF, O'Riordan KJ, Sandhu K, Peterson V, Dinan TG. The gut microbiome in neurological disorders. The Lancet Neurology. 2020;19(2):179-94.

[60] Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. Journal of Diabetes Investigation. 2013;4(6):640-50.

[61] Palta P, Schneider AL, Biessels GJ, Touradji P, Hill-Briggs F. Magnitude of cognitive dysfunction in adults with type 2

diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. Journal of the International Neuropsychological Society. 2014;20(3):278-91.

[62] Wedick NM, Pan A, Cassidy A, Rimm EB, Sampson L, Rosner B, Willett W, Hu FB, Sun Q, van Dam RM. Dietary flavonoid intakes and risk of type 2 diabetes in US men and women. The American Journal of Clinical Nutrition. 2012;95(4):925-33.

[63] Jennings A, Welch AA, Spector T, Macgregor A, Cassidy A. Intakes of anthocyanins and flavones are associated with biomarkers of insulin resistance and inflammation in women. The Journal of Nutrition. 2014;144(2):202-8.

[64] Li R, Zhang Y, Rasool S, Geetha T, Babu JR. Effects and underlying mechanisms of bioactive compounds on type 2 diabetes mellitus and Alzheimer's disease. Oxidative Medicine and Cellular Longevity. 2019;2019.

[65] Silveira AC, Dias JP, Santos VM, Oliveira PF, Alves MG, Rato L, Silva BM. The action of polyphenols in diabetes mellitus and Alzheimer's disease: A common agent for overlapping pathologies. Current Neuropharmacology. 2019; 17(7):590-613.

[66] Sharma G, Parihar A, Talaiya T, Dubey K, Porwal B, Parihar MS. Cognitive impairments in type 2 diabetes, risk factors and preventive strategies. Journal of Basic and Clinical Physiology and Pharmacology. 2020;31(2).

[67] Freychet P. Insulin receptors and insulin actions in the nervous system. Diabetes/metabolism Research and Reviews. 2000;16(6):390-2.

[68] Convit A. Links between cognitive impairment in insulin resistance: an explanatory model. Neurobiology of Aging. 2005;26(1):31-5.

[69] Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nature Reviews Endocrinology. 2018;14(10):591-604.

[70] Janelidze S, Hertze J, Nägga K, Nilsson K, Nilsson C, Wennström M, van Westen D, Blennow K, Zetterberg H, Hansson O, Swedish BioFINDER Study Group. Increased blood-brain barrier permeability is associated with dementia and diabetes but not amyloid pathology or APOE genotype. Neurobiology of Aging. 2017;51:104-12.

[71] Zhang S, Xue R, Hu R. The neuroprotective effect and action mechanism of polyphenols in diabetes mellitus-related cognitive dysfunction. European Journal of Nutrition. 2019:1-7.

[72] Jing YH, Chen KH, Kuo PC, Pao CC, Chen JK. Neurodegeneration in streptozotocin-induced diabetic rats is attenuated by treatment with resveratrol. Neuroendocrinology. 2013;98(2):116-27.

[73] Desideri G, Kwik-Uribe C, Grassi D, Necozione S, Ghiadoni L, Mastroiacovo D, Raffaele A, Ferri L, Bocale R, Lechiara MC, Marini C. Benefits in cognitive function, blood pressure, and insulin resistance through cocoa flavanol consumption in elderly subjects with mild cognitive impairment: the Cocoa, Cognition, and Aging (CoCoA) study. Hypertension. 2012;60(3):794-801.

[74] Mastroiacovo D, Kwik-Uribe C, Grassi D, Necozione S, Raffaele A, Pistacchio L, Righetti R, Bocale R, Lechiara MC, Marini C, Ferri C. Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study—a randomized controlled trial. The American Journal of Clinical Nutrition. 2015;101(3): 538-48.

[75] Rahman S, Whyte A, Huang Y, Williams C, Krikorian R, Burton-Freeman B. Acute Effects of Wild Blueberry

Intake on Metabolic Markers and Cognitive Performance in Middle-Aged Adults. The FASEB Journal. 2017;31(1 supplement):636-39.

[76] Hartstra AV, Bouter KE, Bäckhed F, Nieuwdorp M. Insights into the role of the microbiome in obesity and type 2 diabetes. Diabetes Care. 2015;38(1):159-65.

[77] Tai N, Wong FS, Wen L. The role of gut microbiota in the development of type 1, type 2 diabetes mellitus and obesity. Reviews in Endocrine and Metabolic Disorders. 2015;16(1):55-65.

[78] Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychological Medicine. 2014;44(10):2029-40.

[79] Chang SC, Cassidy A, Willett WC, Rimm EB, O'Reilly EJ, Okereke OI. Dietary flavonoid intake and risk of incident depression in midlife and older women. The American Journal of Clinical Nutrition. 2016;104(3):704-14.

[80] Pase MP, Scholey AB, Pipingas A, Kras M, Nolidin K, Gibbs A, Wesnes K, Stough C. Cocoa polyphenols enhance positive mood states but not cognitive performance: a randomized, placebo-controlled trial. Journal of Psychopharmacology. 2013;27(5):451-8.

[81] Khalid S, Barfoot KL, May G, Lamport DJ, Reynolds SA, Williams CM. Effects of acute blueberry flavonoids on mood in children and young adults. Nutrients. 2017; 9(2):158.

[82] Fisk J, Khalid S, Reynolds SA, Williams CM. Effect of 4 weeks daily wild blueberry supplementation on symptoms of depression in adolescents. British Journal of Nutrition. 2020:1-8.

[83] Westfall S, Pasinetti GM. The gut microbiota links dietary polyphenols with management of psychiatric mood disorders. Frontiers in Neuroscience. 2019;13:1196.