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Review

Alzheimer's disease prevention by flavonols and their analogs

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ABSTRACT

Four studies now document reduced incidence of Alzheimer's disease (AD) or dementia diagnoses in aging individuals who report higher dietary intake of flavonols (or their glycosides) years prior to diagnosis *vs* those with lower intake. These effects are large, almost 50 %, for individuals at higher genetic risk for AD, providing a robust gene x environment interaction. They display a specific structure-activity relationship. These benefits are driven by modest-to-moderate differences in the quantity of flavonol (glycoside) consumed. These data contrast with the failure of late life supplementation with flavonol-rich ginko extract to alter progression to AD in groups of individuals who are not selected for genotype or dietary pattern. Studies of mouse AD models support benefits of the flavonol quercetin. *In vitro* and *in vivo* results add the receptor type protein tyrosine phosphatase PTPRD to the list of oxidative and other targets or mechanisms to which flavonol benefits are attributed. The magnitude of flavonol protection for individuals who would otherwise be especially vulnerable to AD, the ease of supplementation strategies with currently-available nutraceuticals and the opportunities for development of improved flavonol analogs all support further exploration of flavonol-based strategies for reducing the incidence of AD with aging.

Vulnerability to AD: genetic, environmental and possible g x e influences: The mnemonic, behavioral, senile plaque and neurofibrillary tangle pathologies of Alzheimer's disease display genetic and environmental influences. Twin datasets document large contributions from additive genetic influences on vulnerability to develop Alzheimer's disease (AD) during aging [1,2]. Molecular genetic studies of vulnerability to AD or densities of cardinal AD neuropathological features support sizable influences of variation at the apolipoprotein E (ApoE) locus [3,4]. Variation at the receptor type protein tyrosine phosphatase (PTPRD) locus provides a selective influence on AD neurofibrillary pathology [3] *(see below)*. Reproducible influences at ApoE and of other loci with more modest effects allow construction of polygenic risk scores that identify significant fractions of the overall risk for developing AD [5].

A number of environmental influences have also been associated with individual differences in vulnerability to develop AD with aging. In meta-analyses, individual differences in diet provide some of the largest environmental contribution to individual differences in AD vulnerability [6–8]. Based on data available until recently, it was possible that influences of diet might be independent of genetic differences. It was also possible that effects of diet could differ from person to person based on individual differences in genetic vulnerability, providing gene x environment interactions (g x e).

Animal model support for human associations between flavonol intake and AD pathologies: Flavonols and related flavonoids are plant-based dietary constituents. Fig. 1 shows the structures of the most abundant dietary flavonol, quercetin, and related flavonoids: a flavone, flavon-3-ol, anthocyanin and flavanone.

There is substantial animal model data that supports flavonol benefits in reducing AD-related pathology and AD-like behavioral deficits. While no animal model exactly replicates AD, many factors that can vary in human cohort studies can be controlled much more precisely in animal studies.

Columbian investigators have identified substantial benefits of intraperitoneal (ip) and oral (po) administration of the abundant flavonol quercetin on age-related development of AD-like pathologies and behavioral deficits in 3xTg-AD mice. Sabogal-Guáqueta and colleagues [9] found that every-other-day ip treatment with 25 mg/kg quercetin from months 18 −21 of age reduced AD-like pathology when 3xTg-AD mice were sacrificed at months 21 – 24 of age. One of the

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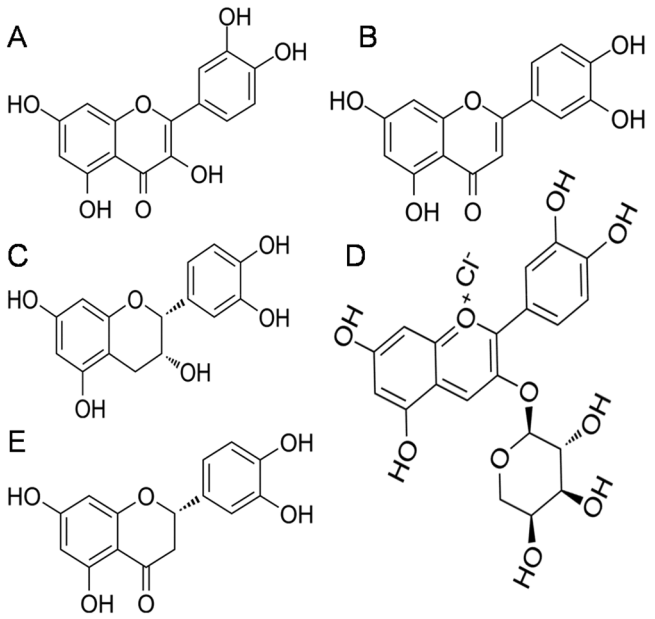

Fig. 1. Structures of flavonoids from each of the classes discussed herein. A: a flavonol (quercetin), B: flavone (luteolin), C: a flavon-3-ol (epicatechin), D: an anthocyanin (cyanadin-3-O-arabinoside) and E: a flavanone (eriodictyol). Glycosylated flavonoids from each of these classes are also found in foods.

largest effects was on hippocampal hyperphorphorylated tau. There were also significant quercetin-related reductions in amyloid and improvements in mnemonic assessments using the Morris water maze. Paula and colleagues [10] found that every-other-day oral (gavage) treatment with 100 mg/kg quercetin for the year between 6 and 18 months of age reduced hyperphosphorylated tau and cortical amyloid in 3xTg-AD mice when they were sacrificed at 18 months of age. There were trends toward improvement in water maze performance that did not reach statistical significance.

Zhang and colleagues metaanalyzed quercetin effects in a variety of toxicologic and genetic models of AD [11]. They noted relatively robust benefits for cognitive function and more modest effects on amyloid-related markers, which were the most frequently-reported outcomes in the 14 studies that were reviewed.

Flavonol associations with progression to AD (or dementia):

To seek influences that individual differences in flavonol intake might confer for risk or protection against AD, four groups have used dietary records to assess flavonol intakes of cohorts of asymptomatic individuals who have been followed for varying amounts of time during which incidence of dementia or of AD have been recorded (Table 1). Since most dementia is caused by AD [12], it seems reasonable to combine data from studies in which AD has been diagnosed with results from studies in which diagnoses of "dementia" are assessed. Differences in flavonol intake, recorded years prior to diagnosis, are thus compared for individuals who develop AD or dementia diagnoses *vs* those who do not. Each of these studies used statistical methods to control for effects of known AD risk or protective factors including level of education and measures of socioeconomic status. Each acknowledged limitations in the robustness of dietary recall methods and the limitations of self-reported intake [13]. Shistar and colleagues [14] performed analyses that reached similar conclusions about flavonol effects when they censored dietary data obtained for timeperiods just prior to the time when dementia was diagnosed, in efforts to control for possible effects of cognitive impairment on recall of dietary intake.

These comparisons highlight consistent associations between "flavonol" intake and incidence of dementia or AD diagnoses. As we note below, most of these studies appear to mislabel flavonol glycosides as "flavonols".

UK Biobank (sample 1): Recently-reported results from the United Kingdom (UK) Biobank sample are important due to the size of this sample as well as the availability of ApoE genotypes and AD polygenic risk scores for each individual [15]. We can compare the results of this UK work to data from other cohorts.

Genotyped participants in this UK Biobank cohort completed an Oxford WebQ assessment of dietary intake on several occasions during followup that spanned an average of 9 years (Table 1). Incident dementia was assessed based on hospital and death record diagnoses. Other UK data suggest that at least 2/3 of these individuals with "dementia" would have AD diagnoses and another group would display mixed AD/vascular diagnoses [12].

There was an overall hazard ratio of 0.73 for incident dementia diagnosis during followup of the individuals who reported the highest levels of dietary flavonol intake *vs* those with the lowest level [15].

The investigators separated participants into those with high genetic risk (with at least one ApoE4 allele or the highest density of other polygenic risk score SNPs) *vs* those with neither an ApoE4 allele nor a high polygenic risk score. Participants with high genetic risk represented 30 % of the total sample; 28 % of the sample displayed at least one ApoE4 allele. ApoE4 thus provided the majority of the genetic effects. High flavonol intake was associated with a 0.58 hazard ratio of developing dementia in the high genetic risk subset. This was compared to a 0.91 ratio, not statistically different from 1, in participants with low

Table 1
Results from studies that have assessed associations between flavonol intake and subsequent development of AD or dementia. * control for ApoE or AD polygenic risk score. OR/RR/HR odds ratio or relative risk or hazard ratio.

Sample (cohort number)	Referece	n	Mean followp (y)	Dietary Assessment	# Dietary Assessments	Clinical Assesment	Flavonol OR/RR/HR	Primary source	Odds ratio after eliminating primary source
UK Biobank (1)	Jennings et al. 2024	121, 986 (all) High genetic 36,305 Low genetic 85,685	9.4	Oxford WebQ	2 to 5	Hosp & death records	0.73 0.58* 0.91	Tea	1.03 (ns)
Danish diet, cancer, health (2)	Bondonno et al. 2121	55,985	21	A food frequency questionnaire	1	Dementia-related visit or drug	0.86	na	na
Framingham offspring (3)	Shistar et al. 2020	2801	26	Food frequency questionnaire	4	Monitored yearly, DSM dx	0.58*	Tea	na
Memory and Aging (4)	Holland et al. 2020	921	6.1	Food frequency questionnaire	Yearly	Monitored yearly	0.52*	na	na

genetic risk. There was thus a strong, significant g x e interaction.

Contributions of specific foods to total flavonol intake were assessed. Tea provided the largest contribution to total flavonol intake in this sample [15]. While other foods also contributed to flavonol intake, there was no remaining significant association between individual differences in flavonols and dementia incidence when the effects of tea intake were removed.

Danish diet, cancer and health, Framingham offspring and memory and aging (samples 2–4): These results for flavonols display remarkable convergence with data from other studies of three smaller samples. Odds ratios for the impact of flavonol intake on risk of developing dementia are highly significant in the Framingham Offspring cohort [14] and in the Memory and Aging cohort [16]. Both of these studies include genetic covariates for ApoE genotype. There were smaller odds ratios for individuals with the highest *vs* lowest levels of baseline self-reported flavonol intake in the Danish Diet, Cancer and Health study (cohort 2), which did not assess any genetic covariate [17].

The 0.58, 0.58 and 0.52 odds ratios for incident AD or dementia in the three studies (cohorts 1,3 and 4) in which AD risk genes were considered [14–16] (Fig. 2) provide a remarkable degree of convergence despite differences in the duration of followup, the dietary questionnaire used and the ways in which incident dementia or AD diagnoses were identified. Unfortunately, we cannot identify parallel epidemiological data that compares the incidence of AD in individuals at high genetic risk from countries with high consumption of flavonoids to those of countries with low flavonoid consumption, since there is no such work with ApoE genotypes.

Large contribution of tea flavonols and likely role of flavonol glycosides: Tea provided the largest contributions to flavonol intake in both of the studies in which this data is reported, the UK Biobank and Framingham offspring cohorts [14,15]. Metaanalyses document robust effects of tea consumption *per se* on risk of dementia or AD in other samples [18], buttressing the results discussed above. Interestingly, similar metanalyses of effects of coffee consumption fail to identify any association [19].

Focus on tea also allows us to identify the ingested compounds that are likely to provide the reductions in incidence of dementia or AD. Though these effects are attributed to "flavonols" in these publications, there is low oral bioavailability of the flavonols found in tea (*eg* quercetin, kampferol and myricetin; ratio about 5:2:1) [20,21]. There are also large individual differences in the modest oral bioavailability for these common flavonols [22]. More sophisticated analyses find that most of the "flavonols" present in tea are largely glycosylated (especially 3-O-glycosylated) [21]. Glycosylated flavonols are more soluble in this hot water extract of tea leaves. These glycosylated flavonols are much more bioavailable in humans [23]. In these human bioavailability studies, there are smaller individual differences in absorption of 3-O-glycosylated flavonols than the individual differences documented in studies of quercetin bioavailability. It thus seems likely that glycosylated flavonols are dominant contributors to the effects on AD or dementia that are found in these studies. Of course, these glycosylated forms are likely to be deglycosylated during absorption or soon after they are absorbed [24] so that flavonols themselves are likely to exert the biological effects that lead to the observed reductions in the incidence of AD or dementia.

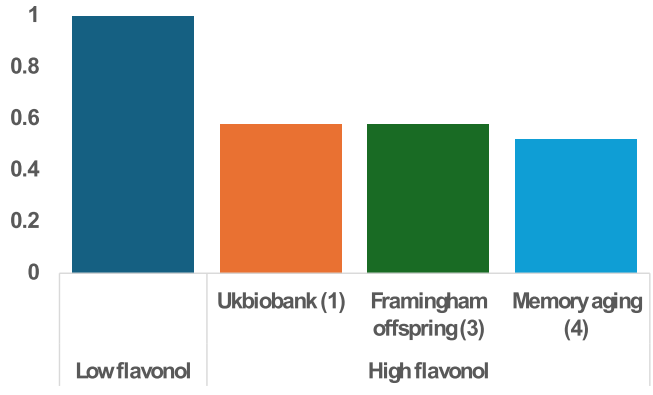

Fig. 2. Graphical representation of data from Fig. 1: Risk of developing AD/dementia in individuals with low *vs* high levels of self reported flavonol intake (high genetic risk or ApoE-controlled) in studies described in the text.

Structure-activity data: There is evidence for a structure activity relationship. We can compare the 0.58, 0.89, 0.58 and 0.52 odds ratios associated with individual differences in "flavonol" intake in the UK (high genetic risk), Danish, Framingham and Memory and Aging studies with associations for other flavonoid subclasses in these three samples (Fig. 1). Intake of flavanones (*eg* Fig. 1E) provides no significant association with dementia incidence in either the UK (high genetic risk) [15], Danish [17] or Framingham [14] samples. Odds ratios are 0.98, 0.92 and 0.88, respectively. Two flavonoid subclasses provide mixed pictures: Flavones (*eg* Fig. 1B) provide odds ratios 0.78, 0.91 and 0.86, respectively. Data for flavon-3-ols (also termed flavanols or catechins; Fig. 1C) are 0.58 and 0.77 from the UK (high genetic risk) and Framingham samples.

Dose-response data: Flavonol dose-response relations are also suggested by these data. Risk of dementia is reduced by the third quintile of flavonol intake in the UK Biobank sample [15] (quintiles 1 vs 3: 12 vs 32 mg/d intake). Risk is reduced in the individuals with > 60th percentile flavonol intake in the Framingham offspring sample [14] (< 15th *vs* > 60th: 6 vs 14 mg/d). There is less risk in individuals in the fifth quintile in the Memory and Aging sample [16] (quintiles 1 vs 5: 5 vs 15 mg/d). Risk is less in individuals in the third quintile of the Danish Diet, Cancer and Health study [17] (quintiles 1 vs 3: 15 vs 38 mg/d). These data suggest that readily-tolerated interventions that provide easily-achieved increments in dietary flavonol (or flavonol glycoside) intake could have substantial benefits, especially for individuals who display both high genetic risk and low baseline flavonol intake.

Optimal timecourses for flavonol benefits: Dietary preferences remain relatively stable during adult life for most individuals [25]. Flavonol intake reported by individuals in the UK, Danish, Framingham and Memory and Aging samples is thus likely to reflect their consumption patterns over many years.

Data that might illuminate the effects of duration of flavonol intake required for benefits for dementia can be obtained by contrasting the results noted above with the effects of dietary supplementation later in life. Two studies failed to find any benefits of ginko extracts, administered late in life, on rates of progression from cognitively normal or mild cognitive impairment to AD or dementia diagnoses [26,27]. Ginko extracts contain substantial amounts of flavonol, including flavonol glycosides [28]. It is possible that effects of flavonol supplementation in subgroups of these samples (*eg* those at high genetic risk and/or those with low baseline flavonol intake) might have been missed in the analyses. As noted below, there is evidence that there may be effects of ginko plus the cholinesterase inhibitor donepezil . However, it is also possible that reducing risk of dementia or AD requires high flavonol intake that begins earlier in life or that flavanol exposure must last longer to be effective.

Candidate flavonol mechanisms of action 1: Flavonols, often at micromolar concentrations, provide biochemical activities at a number of targets that have been cited as candidates to contribute to AD pathophysiology and thus candidates to contribute to flavonol benefits for AD [29]. Many authors cite flavonol antioxidant properties. A recent review points to potential symptomatic benefits in inhibiting acetylcholinesterase and disease-modifying benefits in reducing neuroinflammation, Aβ aggregation and/or β-secretase activity, altering activity of a number of disease-associated transcriptional, inflammatory or cell survival pathways as noted in Table 2 [30]. While detailed discussion of each of these mechanisms is beyond the scope of this paper, they are covered in numerous reviews [31–33].

There are cautions when only *in vitro* biochemical results support a

Table 2
Mechanisms postulated for flavonol benefits for AD [27].

Disease modifying reductions in	
Oxidative stress	Park2
Neuroinflammation	Park5
Aβ aggregation	Park7
β secretase activity	Casp3
NF-κB	Casp7
NO	COX2
iNOS	Nrf-2
TNFα	JNK
IFNγ	PI3K
IL1β	IL-12
IL-6	**PTPRD**
Disease modifying increases in	
AMPK	
Symptom modifying	
Acetylcholinesterase inhibition	

postulated mechanism of action, however. These cautions are stronger when the work reports little structure-function data to identify the exact flavonoid subclass(es) involved. Flavonoids have been labeled "pan-assay interference compounds" since they can show activity in a number of biochemical assays [34]. It is possible that some of the effects summarized in Table 2 could result from flavonol interference with the corresponding *in vitro* assays. Such assay interference should be less likely when there are striking structure-activity relationships among flavonoid subclasses. Pan assay interference cannot account for *in vivo* flavonol benefits, of course.

Candidate flavonol mechanism of action 2: actions at PTPRD: Flavonoid activities at receptor type protein phosphatases were first identified when a small molecule library screen identified *inhibition* of the phosphatase of the receptor type protein phosphatase S (PTPRS) by the flavone scutellarein [35]. Based on these results, we asked if flavonoids from different classes might show activity at the related receptor type protein phosphatase D (PTPRD). We tested the flavonoids abilities to alter PTPRD's abilities to cleave orthophosphate from phosphorylated glycogen synthase kinase 3s [36]. We were initially surprised that flavonols quercetin and myrecetin *increased* the rates of PTPRD's dephosphorylation of pY GSK3 phosphopeptide (Fig. 3).

The specificity of this flavonol positive allosteric modulation (PAM) of PTPRD's phosphatase was manifest in several ways [36]. First, there was a sharp structure-activity relationship for this PAM activity of PTPRD's activity in dephosphorylating our pYGSK3 phosphopeptide. There was a requirement for at least two C-ring hydroxyls and intolerance of methylation of several hydroxyls. Flavones, flavon-3-ols and other flavonoid subclasses were inactive. Second, this flavonol effect was noted for only pY GSK3 and a modest sized subset of the PTPRD substrates that we had defined in parallel work. Third, flavonol enhancement of activity of PTPRD's phosphatase was greater than that for the closely-related PTPRS and PTPRF phosphatases.

PTPRD, flavonol actions and AD tau hyperphosphorylation: *Candidate biochemical and cellular pathways for PTPRD effects on AD tau hyperphosphorylation:* As noted above, PTPRD briskly dephosphorylates pYGSK3α/β [36]. Activities of GSK3α and GSK3β are enhanced by phosphorylation [37,38] of these tyrosines 279 and 216 respectively [37–41]. GSK3α and GSK3β activities are thus reduced by *de*phosphorylating pY279 and pY216.

GSK3 α and β are the most prominent enzymes that hyperphosphorylate the tau protein product of the MAPT gene [42]. GSK3α and GSK3β phosphorylate tau at sites that are strongly linked to AD pathophysiology and/or progression (eg T217 and T181 [43,44]) and at other sites that are hyperphosphorylated in AD brain [42,45]. Tau hyperphosphorylation is key to formation of the neurofibrillary tangles of AD.

PTPRD is largely expressed in neurons [46]. Single cell mRNA-seq data indicate that virtually all of the human cortical neuronal subtypes that express GSK3 α or β also express PTPRD [47]. GSK3β is expressed in most of the human cortical neuronal subtypes that also express PTPRD; GSK3α is expressed in a smaller number of these subtypes.

Studies of the effects of the GSK3 inhibitor lithium hint at benefits of reducing GSK3 activities in AD. There are lower rates of AD in humans exposed to lithium *via* drinking water [48], by treatments for bipolar

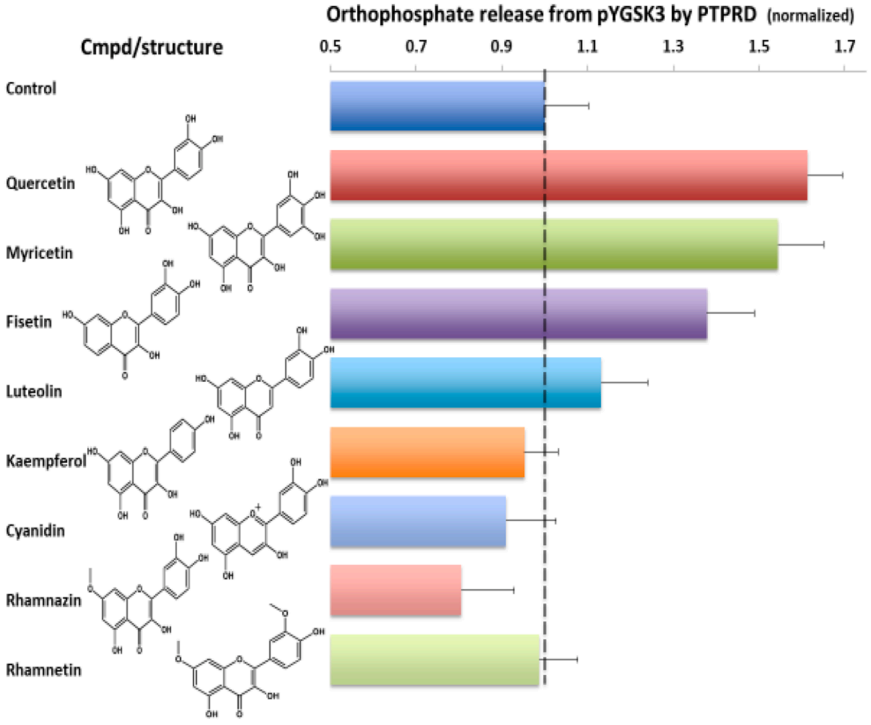

Fig. 3. Structure-activity relationship for flavonol positive allosteric modulation of PTPRD dephosphorylation of pYGSK3 phosphopeptide [36]. PTPRD PAM activity comes primarily from the flavonols quercetin and myricetin.

disorder [49] or in clinical trials (most of modest size *eg* [50]). Taken together with other data (Table 3 and below), there is evidence for a strong role for PTPRD modulation of GSK3 α and β activities that, in turn, modulate hyperphosphorylation of neuronal tau. Of course, the strength of this evidence will grow as other laboratories replicate and extend the work performed in our laboratory.

Human genetic support for PTPRD effects on AD tau hyperphosphorylation: Quantitative neuropathological data from brains of deceased participants in the memory and aging cohort who were diagnosed with AD allowed genome wide association study of the genetic influences on densities of neurofibrillary and of senile plaque pathology [3]. As expected, there are robust associations between ApoE alleles and densities of both senile plaques and neurofibrillary tangles. Remarkably, however, SNPs in 5′ aspects of the human PTPRD gene displayed selective associations with individual differences in densities of neurofibrillary tangles, but not with densities of senile plaques [3]. This data was especially interesting to us, since the SNP that provided the strongest association with densities of neurofibrillary tangles in this study was close to the SNP that we had previously identified as being most strongly associated with individual differences in levels of PTPRD mRNA expression in brains from individuals who died without any neurological diagnosis [51].

AD-prevention structure-activity relationships for PTPRD vs other postulated mechanisms of action: As noted above, the 0.58, 0.89, 0.58 and 0.52 odds ratios for reduction in AD/dementia incidence associated with higher dietary intake of flavonols contrast sharply with the 0.98, 0.92 and 0.88 odds ratios for AD/dementia incidence in individuals with the higher dietary intake of eriodictyol and other flavonones. We can thus compare effects of flavonones *vs* flavonols on the postulated mechanisms of flavonoid effects noted in Table 2. We can thus seek evidence for differential effects in tests of these mechanisms that could parallel these differential effects of dietary intake of these two flavonoid subclasses.

Flavonol PTPRD PAM activity is much greater than that of tested flavanones [36]. These results provide a promising structure-activity relationship for PTPRD PAM activity that parallels the dietary effects on AD/dementia incidence that are noted above.

By contrast, there are no differential effects of flavonols *vs* flavonones in studies of several of the other mechanisms postulated for flavonoid benefits for AD noted in Table 2. Several measures of oxidative/reductive protection are nearly identical for a flavonol and a flavonone [52]. Flavonol (quercetin) and flavonone (eriodictyol) glycosides both inhibit acetylcholinesterase [53,54]. Quercetin and eriodictyol can both reduce inflammation [55,56]. Quercetin and eriodictyol can both reduce Aβ aggregation [57,58]. β secretase can be inhibited by polymers that contain flavonones [59] as well as by quercetin and its O-methylated metabolites [60]. Quercetin decreases IL-1β and IL-6 and hinders NF-kB activation [61]. Eriodictyol can also decrease IL-1β and IL-6 [62] and inhibit NF-kB activation [56]. Quercetin and eriodictyol can both reduce nitric oxide production by inducible nitric oxide synthase [56,63]. Both reduce tumor necrosis factor alpha levels in at least some tissues [64,65]. Quercetin and eriodictyol can both alter phosphoinositide 3l kinase signaling [66,67]. They can both increase Casp3 cleavage (though in ways that may be proapoptotic) [68,69].

Several of these results could be subject to cautions about pan assay interference [34]. While our work on PTPRD directly compares quercetin to eriodictyol in the same assay, most of the other comparisons above result from work of different authors. Nevertheless, the flavonol *vs* flavonone differences noted here are consistent with contributions of a PTPRD-dependent mechanism for flavonol actions in reducing AD incidence in humans.

Anthocyanins: Data for anthocyanin (Fig. 1D) protection from development of AD or dementia is almost as striking as that provided by flavonols. Odds ratios of AD/dementia incidence are 0.6, 0.86 and 0.29, for the UK (high genetic risk) [15], Danish [17], Framingham [14] and Memory and Aging [16] samples, respectively. Anthocyanins (glycosylated forms) and anthocyanidins (aglycones) in the US diet come prominently from strawberries, blueberries and black beans [70]. Risk of dementia is reduced by the third quintile of anthocyanin intake in the UK Biobank sample (for which anthocyanin intake in quintiles 1 vs 3 is 3 vs 21 mg/d), in the individuals with > 60th percentile in the Framingham offspring sample (< 15th *vs* > 60th: 4 vs 16 mg/d) and in individuals in the third quintile of the Danish Diet, Cancer and Health study (quintiles 1 vs 3: 5 vs 20 mg/d). Several tested deglycosylated anthocyanins (anthocyanadins) fail to increase PTPRD's ability to dephosphorylate pYGSK3 phosphotyrosine phosphopeptide, however [36]. Anthocyanin benefits are thus good candidates for future research to elucidate mechanisms for their contributions. Future work could include studies of nonPTPRD dependent mechanisms along with work to elucidate any possible effects at PTPRD mediated by metabolites of anthocyanins and anthocyanidins.

Flavonol- and flavonol-analog based AD prevention and treatment strategies supported by current evidence:

Compounds: Natural and enzymatically-modified products: Quercetin is one of the most abundant dietary flavonols, displays substantial PTPRD PAM activity *in vitro* and has been granted GRAS (generally recognized as safe, #341) status by the US FDA. It is widely available as a nutraceutical. Quercetin's modest bioavailability can be improved substantially by glycosylation (3-O- and other positions) [23]. Enzymatically

Table 3
Evidence for effects of PTPRD and flavonol PTPRD PAMs on AD tau pathology *(work from Uhl lob in italics).*

	Evidence		
Relationship	Human	Mouse model	*In vitro*
Changed expresion of PTPRD alters AD tau/neurofibrillary pathophysiology	PTPRD SNPs are associated with densities of AD neurofibrillary pathology and *levels of brain PTPRD expression*	*3xTg-AD mice with reduced PTPRD expression or treatment with pentilludin display increased neuroofibrilary pathology*	
GSK3 α and β are prominent contributors to AD tau hyperphosphorylation	Reduced AD development or progression with administration of the GSK3 inhibitor Li^{++}	Less neurofibrillary pathology in PS19 ± PDAPP ± with reduced GSK3 α or β	GSK3 α and β are prominent tau hyperphosphorylators
PTPRD alters GSK3 tyrosine phosphorylation		*More upregulated phospho (pY) GSK3 α and β in brains of mice with reduced PTPRD expression*	*GSK3 α and β regulatory phosphotyrosines are good substrates for recombinant PTPRD phosphatase*
Altered GSK3 tyrosine phosphorylation changes GSK3 activitiy			Reducing GSK3 tyrosine phosphorylation or substituting phenylalanine for tyrosines reduces GSK3 activity.
Flavonols increase PTPRD dephosphorylation/down regulation of GSK3 α and β		*An improved PTPRD PAM provides improved protection from hyperphosphorylated neuronal tau*	*Quercetin/improved analogs are PAM/improved PAMs of PTPRD's ability to downregulate (dephos-phorylate) GSK3 α/β*
Flavonols reduce AD tau and neurofibrillary pathophysiology	High consumption of quercetin and other dietary flavonols reduces rate of progression to AD/dementias	Quercetin reduces AD pathology in 3xTg-AD *and 3xTg-AD/PTPRD ± mice. 6BrQ provides much better reductions*	

modified isoquercetin [71] (3-O-glycosyl quercetin containing between 1 and 10 sugars) is readily available as a GRAS (GRN 000,220) dietary supplement that promotes its improved bioavailability.

Compounds: Synthetic: The relatively crisp structure-activity relationship for PTPRD PAM activity derived from our initial studies of natural product flavonoids has continued to impress us as we have tested activities of 108 synthetic and natural product flavonol analogs [72]. Ability to enhance PTPRD-mediated orthophosphate release from pYGSK3 phosphotyrosine phosphopeptide has focused our attention on substitutions at the 6 and 8 positions on the quercetin backbone. There are striking limitations on size and other properties of substitutions at these and a number of other positions. This work has identified an initial developmental candidate quercetin analog that displays significantly greater PTPRD PAM activity than quercetin. Of course, we need to identify *in vivo* activity, bioavailability, metabolism and plasma half-life, among other features, to assure ourselves that this candidate does in fact display improved drug-like properties.

Individuals most likely to benefit: Data from dietary studies support two ideas about the individuals who are most likely to benefit from PTPRD PAM flavonol analogs.

First, individuals at higher genetic risk are more likely to benefit. This hypothesis is supported directly by data from the UK-Biobank studies [15] and indirectly by comparisons of results from studies with ApoE genotype control [14,16] *vs* those without this control [17].

Second, individuals with lower baseline flavonol intake are more likely to benefit than those with high levels at baseline. Our knowledge of flavonol pharmacokinetics and pharmacodynamics might tempt us to modify this to: individuals with low baseline blood levels of flavonols are more likely to benefit. Although we have data only for intake of "flavonols", our working hypothesis posits that this data is largely based on intake of flavonol glycosides.

Time for optimal treatments: Data from longitudinal studies suggest that many individuals maintain their dietary preferences through much of their adult lives [73]. Dietary records obtained in mid- or later life thus fail to provide temporal detail concerning the times of life during which flavonol intake reduces AD incidence in those who are genetically predisposed.

Studies with 3xTg-AD mice support the idea that treatment starting in the middle part of life is sufficient to reduce development of AD-like pathologies and behavioral deficits in the later parts of life [9,10]. Data from mice with GSK3 knockdown also supports efficacy of treatments in early adulthood [74].

These results may contrast with data from initial studies of ginko supplementation, as a single intervention, in groups of older participants who were cognitively normal or displayed mild cognitive impairment when they entered the studies in the US and in Europe [26,27]. Ginko preparations contain substantial amounts of flavonols, including glycosylated flavonols [75,28]. In these studies there was no effort to focus treatment on participants with low baseline levels of flavonol intake or those with genetic predispositions to development of AD. Nevertheless, these studies failed to identify any positive signal. This failure could be interpreted to indicate that starting flavonol supplementation late in life (when some participants have already displayed signs of mild cognitive impairment) might be too late. This work may highlight the differences between lifelong flavonol dietary intake and flavonol late-life supplementation.

By contrast, a recent metatanalysis of studies that combined ginko with the cholinesterase inhibitor donepezil provides evidence for modest effects of the combination *vs* donepezil alone. There were nominally-significant effects of the ginko/donepezil combination on changes in Minimental status exam, Montreal test of cognitive abilities, activities of daily living and Hasegawa dementia scales *vs* donepezil alone [76]. As we gain increasing confidence in predictive biomarkers for AD and as ApoE and other genotype information is available for more individuals, we could even start treatments for this AD disease process prior to signs of cognitive impairment, potentially enhancing efficacy.

Dosing frequency for optimal treatments: Quercetin has as little as a 0.3 h-long half-life in mice and 3.5 h in humans [75,77]. Every-other-day dosing has reduced development of AD-like pathologies in 3xTg-AD mice. Extrapolations from these results to humans provides cautions. Nevertheless, intermittent activation of PTPRD-based and other mechanisms of flavonol action might thus be sufficient to reduce AD pathophysiology.

Place for flavonol supplementation among current therapies: Current evidence from disease-modifying antibodies directed at amyloid related epitopes suggests that their benefits in reducing the progression of AD pathophysiology are greatest when they are administered early in the disease process [78]. This "early stage" has been defined by: modest burden of cognitive symptoms, modest brain amyloid burden or modest brain burden of neurofibrillary pathology. It should thus be optimal to begin administration of flavonol or improved flavonol analogs as early as possible.

It may also be optimal to focus treatment on those whose baseline flavonol levels are low and those at elevated genetic risk for AD. Current results suggest that flavonol analog supplementation's benefits on neurofibrillary pathology could be additive to or synergistic with the benefits of antiamyloid therapies if they were both applied as early in the course of AD pathophysiology as possible, especially for those at increased genetic and dietary risk.

Drs, Uhl and Henderson are coinventors of VA intellectual property submitted for provisional patent covering novel PTPRD positive allosteric modulators.

CRediT authorship contribution statement

George Uhl: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Balaji Kannan:** Writing – original draft. **Joungil Choi:** Writing – original draft. **Ian Henderson:** Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: George Uhl MD PhD reports financial support was provided by National Institute on Aging. George Uhl MD PhD reports a relationship with US Department of Veterans Affairs that includes: employment. George Uhl MD PhD and Ian Henderson PhD have a patent submitted by VA. Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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