

REVIEW ARTICLE

Is *Ginkgo biloba* a cognitive enhancer in healthy individuals? A meta-analysis

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Objective We conducted a meta-analysis to examine whether *Ginkgo biloba* (*G. biloba*) enhances cognitive function in healthy individuals.**Methods** Scopus, Medline, Google Scholar databases and recent qualitative reviews were searched for studies examining the effects of *G. biloba* on cognitive function in healthy individuals. We identified randomised controlled trials containing data on memory ($K=13$), executive function ($K=7$) and attention ($K=8$) from which effect sizes could be derived. The analyses provided measures of memory, executive function and attention in 1132, 534 and 910 participants, respectively.**Results** Effect sizes were non-significant and close to zero for memory ($d=-0.04$; 95%CI -0.17 to 0.07), executive function ($d=-0.05$; 95%CI -0.17 to 0.05) and attention ($d=-0.08$; 95%CI -0.21 to 0.02). Meta-regressions showed that effect sizes were not related to participant age, duration of the trial, daily dose, total dose or sample size.**Conclusions** We report that *G. biloba* had no ascertainable positive effects on a range of targeted cognitive functions in healthy individuals. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—neuroenhancer; smart drug; memory; executive function; attention

Medicinal products derived from the maidenhair tree, *Ginkgo biloba* (*G. biloba*), are some of the most widely used of any plant-based products, being available without prescription in Europe and North America, where it is marketed predominantly as a dietary supplement. The active components of *G. biloba* consist of flavonoids, terpenoids, and uniquely to *G. biloba*, ginkgolides and bilobalide. A commonly used, standardised extract, EGb 761, is produced from the ground-up leaves and is marketed as Tanakan, Tebonin and Rökan. Other similar extracts are available varying slightly in their concentration of the compounds, for example, Kaveri (LI 1370).

Given the long tradition of using *G. biloba* in traditional Chinese medicine, it is not surprising perhaps that it has been advocated for a variety of conditions including: multiple sclerosis, caudation, tinnitus, blood pressure, reducing altitude sickness, improving ocular disorders and sexual dysfunction. Some caution, however, should be applied to any

such claims and how they are employed, given this compound is, at present, unregulated. Of particular interest recently, however, are the suggested nootropic effects of *G. biloba*. Nootropic is a general label for the class of substance that: improve cognitive functions like memory and learning; provide neuroprotective effects from various insults; do not possess properties of classical excitants, tranquilisers and antipsychotics; and have very limited or no side effects. *G. biloba* has been reported to have nootropic properties and has been used widely for a number of years to purportedly reduce or even prevent the cognitive decline associated with ageing and in those suffering from the dementias or Alzheimer's disease—indeed, it is currently stated in the WHO's Anatomical Therapeutic Chemical Classification listing as an anti-dementia drug. Although more recently it has gained significant attention and been positioned, controversially, as a 'cognitive enhancing' compound in healthy individuals is the focus of the present paper.

Whereas several meta-analyses have examined the use of *G. biloba* in Alzheimer's (Weinmann *et al.*, 2010) or schizophrenia (Singh *et al.*, 2010), only qualitative reviews have examined the use in healthy individuals

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(Canter and Ernst, 2007; Kaschel, 2009). Such reviews have produced quite conflicting conclusions. Crews *et al.* (2005) examined the acute or short-term to long-term neuropsychological efficacy of *G. biloba* in 16 studies reporting that short-term and long-term administration in healthy and cognitively intact adults produced 'significant positive results in 11 of 16 studies. . . some of the most common positive neuropsychological effects found for [*G. biloba*] across the acute and short-term to long-term studies involving healthy/cognitively intact participants have been enhanced performances on tasks assessing aspects of memory, attention and speed of processing abilities'. (Crews *et al.*, 2005; p. 53). Similarly, Kaschel (2009) concluded 'there is consistent evidence that chronic administration improves selective attention, some executive processes and long-term memory for verbal and non-verbal material'. By contrast, however, Canter and Ernst (2007) reported 'no convincing evidence from randomised clinical trials for a robust positive effect of *G. biloba* ingestion upon any aspect of cognitive function in healthy young people, after either acute or longer term administration'. The present meta-analysis examines the published body of research relating to the specific cognitive enhancing properties of *G. biloba* in healthy individuals.

METHOD

The purpose of this study was to carry out a systematic review and meta-analysis of published randomised controlled trials (RCTs) that have examined the effect of *G. biloba* on the cognitive performance in healthy individuals. Inclusion criteria were that papers use measures of memory, executive function or attention in humans, a randomised control design, explain the dosing regimen and testing structure and present appropriate data to derive effect scores. Where studies included examination of acute (e.g. single dose) and chronic impact of *G. biloba*, we only examined the chronic effects. Owing to the uncontrolled and relatively unmonitored approach to the standardisation of herbal/complementary medicines, the selection of the specific formulation of *G. biloba* varies across studies. To this end, the extract/formulation of *G. biloba* used in each study was recorded, but was not a defining criterion.

An electronic search was conducted for all articles published until March 2012. The relevant studies were traced by using Scopus, Medline and Google Scholar. The keywords were: *Ginkgo biloba*, *cogniti**, *neuropsych** and combinations of these keywords. We also performed supplementary searches of reference

lists in two key recent qualitative review papers: that focussed on healthy participants (Canter and Ernst, 2007) and specific cognitive processes (Kaschel, 2009). The total bibliography was searched by paper title to further remove studies that did not overtly contain any psychometric element such as those focussing on the pharmaceutical, molecular or botanical aspects of *G. biloba*. The search details are outlined in Figure 1.

From the initial sample of studies, we removed those that focussed on animal behaviour, neuroimaging, neurobiological or physiological measures. Studies remained if they compared cognitive test performance in a *G. biloba* and a control group using a double blind RCT methodology. This resulted in 10 studies (from which 13 data sets were obtained). These extracted papers were then analysed such that their raw data could be included in the meta-analysis. A summary of the data sets papers may be seen in Table 1.

Data obtained from each study were converted into the effect size 'Cohen's *d*', which is the difference between the experimental and control group means divided by their pooled standard deviation. If means and standard deviations were not provided, *d*-values were computed from exact *p*-values, *t*-values or *F*-values. Hedges' *d* correction (Hedges and Olkin, 1985) was used to correct for the tendency of studies with small sample sizes to correct for upwardly biased estimation of the effect in small sample sizes that leads to overestimations of the population effect size (Rosenthal, 1991). All effect sizes were extracted independently by the authors and any differences resolved.

The meta-analysis was conducted using *MetaWin 2.1* (Rosenberg *et al.*, 2000). The data were analysed using random effects models. Homogeneity was calculated using the Q_{wi} statistic (Hedges and Olkin, 1985), which tests whether the studies can be taken to share a common population effect size. A significant Q_{wi} statistic indicates heterogeneity of the individual study effect sizes, that is, whether the variability of effect size (ES) is larger than would be expected from sampling error (Lipsey and Wilson, 2001). To test for the significance of the mean effect, bias-corrected confidence intervals were calculated using bootstrapping with 999 replications run in *MetaWin 2.1* (Rosenberg *et al.*, 2000). This approach does not require that effect sizes be parametrically distributed. Most studies included multiple measures of memory, executive or attentional task and where this occurred individual effect sizes were pooled to produce an aggregated within-domain mean effect size for the study. We included only measures of accuracy rather than latency changes (speeding or slowing) as any directional advantage cannot be necessarily interpreted alone as positive or

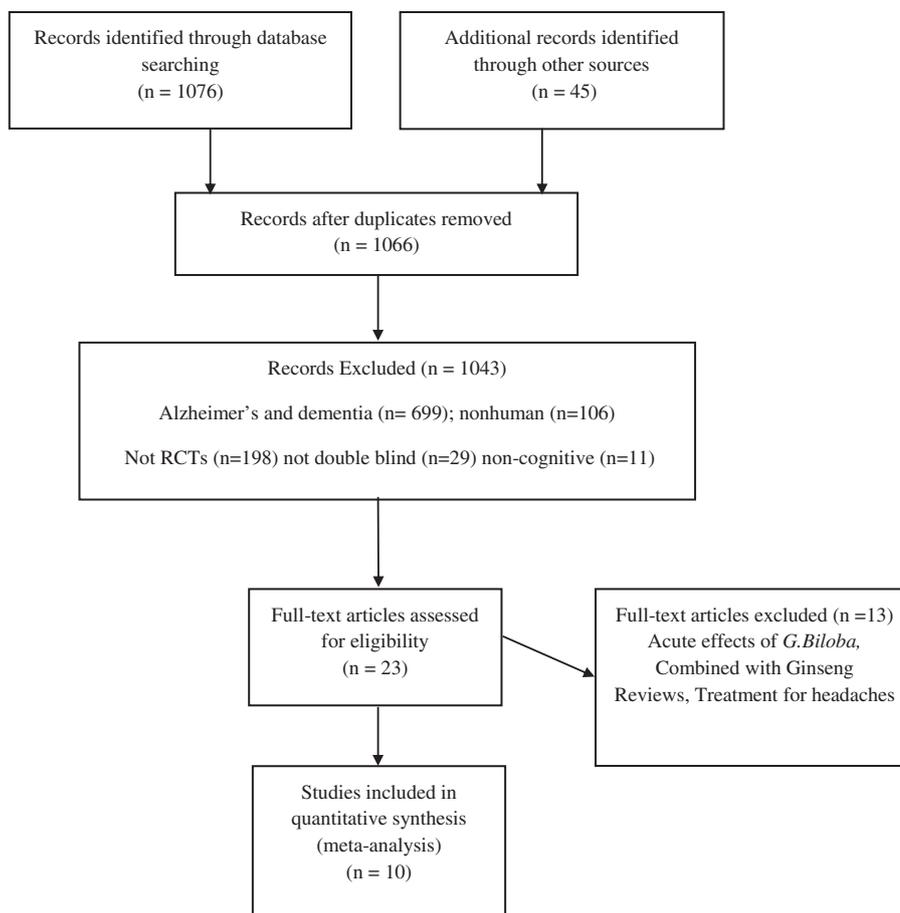


Figure 1. Search strategy used for inclusion of studies

Table 1. Details for studies included in meta-analyses

Study	Participants		Treatment	
	Sample size (<i>Ginkgol</i> control)	Age range (mean years) (<i>Gingkol</i> control)	Total daily dose and formulation	Duration
Burns <i>et al.</i> (2006)	93 (46 47)	55–79 (61.2 62.2)	120 mg Blackmore's Ginkgoforte extract	12 weeks TDS
Burns <i>et al.</i> (2006)	104 (56 54)	18–43 (29.7 31.9)	120 mg Blackmore's Ginkgoforte extract	12 weeks TDS
Carlson <i>et al.</i> 2007	78 (42 36)	65–84 (73.1 72.1)	160 mg EGb761	4 months TDS
Cieza <i>et al.</i> (2003)	66 (34 32)	50–65 (56.5 56.3)	240 mg of EGb761	4 weeks BD
Elsabagh <i>et al.</i> (2005) Exp 1	52 (26 26)	18–26 (21.3 21.7)	120 mg of Lichtwer's Li1370 extract	6 weeks OD
Elsabagh <i>et al.</i> (2005) Exp 2	40 (20 20)	18–26 (21.2 21.5)	120 mg of Lichtwer's Li1370 extract	6 weeks OD
Elsabagh <i>et al.</i> (2005) Exp 1	43 (18 25)	51–67 (55.3 55.5)	120 mg of Lichtwer's Li1370 extract	12 weeks OD
Elsabagh <i>et al.</i> (2005) Exp 2	44 (27 17)	51–67 (60.4 61.4)	120 mg of Lichtwer's Li1370 extract	12 weeks OD
Hartley <i>et al.</i> (2003)	31 (15 16)	53–65 (58.3 58.6)	120 mg Li1370	1 week OD
Mix and Crews (2000)	40 (20 20)	>60 (67.50 68.65)	180 mg of EGb761 extract	6 weeks TDS
Mix and Crews (2000)	262 (131 131)	>60 (66.97 68.60)	180 mg of EGb761 extract	6 weeks TDS
Moulton <i>et al.</i> (2001)	60 (30 30)	University students (20.57 20.40)	120 mg Li1370	5 days BD
Solomon <i>et al.</i> (2002)	232 (111 108)	60–82 (68.7 69.9)	120 mg of Ginkoba Gb extract	6 weeks TDS

All studies were double blind RCTs with placebo-control and parallel design.
OD, once daily; BD, twice daily; TDS, three times daily.

negative effect. Effect sizes are considered significantly different from zero when the confidence interval does not include zero. After computing effect

sizes for each study, meta-analytic methods were applied in order to obtain a combined effect size, which indicated the magnitude of the association across all

studies. The nomenclature of Cohen (1988) suggests the following classification of effect sizes (small $d=0.20$ – 0.49 ; medium $d=0.50$ – 0.79 ; and large $d>0.80$). Finally, meta-regression analyses were used to examine moderator variables that might influence the effect sizes including: participant age, duration of the *G. biloba* trial, the total *G. biloba* dose over the course of the trial and sample size. We also compared the effect sizes for different formulations of *G. biloba*.

RESULTS

Table 2 details the mean background variables across studies included in each meta-analysis. Positive effect sizes indicate better performance for the *G. biloba* group, negative effect sizes better performance by the control group.

Memory

A random effects model was used to analyse memory in 13 studies. The weighted mean effect size was close to zero and non-significant ($d=-0.04$; 95%CI -0.17 to 0.07); and the studies were not heterogeneous ($Q_{wi}=10.45$, $df=12$, $p=0.57$). The potential for publication bias in published reports was investigated using Kendall tau rank correlation test (Begg and Mazumdar, 1994), which revealed no significant evidence of publication bias (Tau = 0.09 , $p=0.66$).

Meta-regression analyses revealed that memory effect sizes were not significantly related to age ($Q=0.05$, $df=1,11$, $p=0.82$), time period of the *G. biloba* trial ($Q=0.15$, $df=1,11$, $p=0.70$), daily dose ($Q=1.49$, $df=1,11$, $p=0.22$), total dose over the course of the trial ($Q=0.30$, $df=1,11$, $p=0.58$) or total sample size ($Q=0.12$, $df=1,11$, $p=0.73$). To check the effects of age, we also compared studies using older (>55 $K=8$) and younger (<40 $K=5$) participants and again revealed no significant difference ($d=-0.02$ vs -0.09 ; $Q_{bw}=0.31$, $p=0.64$). Finally, we contrasted the *G. biloba* formulations EGb 761 [$K=4$] and LI 1370 [$K=6$] to show these did not differ significantly ($d=0.03$ vs -0.09 ; $Q_{bw}=0.64$, $p=0.42$).

Executive function

A random effects model was used to analyse executive function in seven studies. Again, the weighted mean effect size was close to zero and non-significant ($d=-0.05$; 95%CI -0.17 to 0.05); and the studies were not heterogeneous ($Q_{wi}=2.14$, $df=6$, $p=0.90$). The Kendall tau rank correlation test (Begg and Mazumdar, 1994) revealed no significant evidence of publication bias (Tau = 0.39 , $p=0.21$).

Meta-regression was used to examine what factors might influence executive function effect sizes. These analyses revealed that executive function effect sizes were not significantly related to age ($Q=2.14$, $df=1,5$, $p=0.82$), time period of the *G. biloba* trial ($Q=2.14$, $df=1,5$, $p=0.82$), total dose over the course of the trial¹ ($Q=1.33$, $df=1,5$, $p=0.93$) or total sample size ($Q=0.15$, $df=1,15$, $p=0.70$). All relevant trials except one used Li1370, so no comparison was made of different *G. biloba* formulations for executive function.

Attention

A random effects model was used to analyse attention in nine studies. Once again, the weighted mean effect size was near zero and non-significant ($d=-0.08$; 95%CI -0.21 to 0.02); and the studies were not heterogeneous ($Q_{wi}=4.34$, $df=8$, $p=0.82$). The Kendall tau rank correlation test (Begg and Mazumdar, 1994) revealed no significant evidence of publication bias (Tau = 0.33 , $p=0.26$).

Meta-regression was used to examine what factors might influence attention effect sizes and revealed that attention effect sizes were not significantly related to age ($Q=4.32$, $df=1,7$, $p=0.74$), time period of the *G. biloba* trial ($Q=0.78$, $df=1,7$, $p=0.38$), daily dose ($Q=0.50$, $df=1,7$, $p=0.46$), total dose over the course of the trial ($Q=1.79$, $df=1,7$, $p=0.97$) or total sample size ($Q=0.08$, $df=1,7$, $p=0.77$) Finally, we contrasted the *G. biloba* formulations EGb 761 [$K=2$] and LI 1370 [$K=4$] to show these did not differ significantly ($d=-0.23$ vs -0.09 ; $Q_{bw}=0.34$, $p=0.25$).

Figure 2 displays funnel plots for memory, executive function and attention, respectively, showing that in each domain, the majority of studies revealed better performance by controls than the *G. biloba* groups.

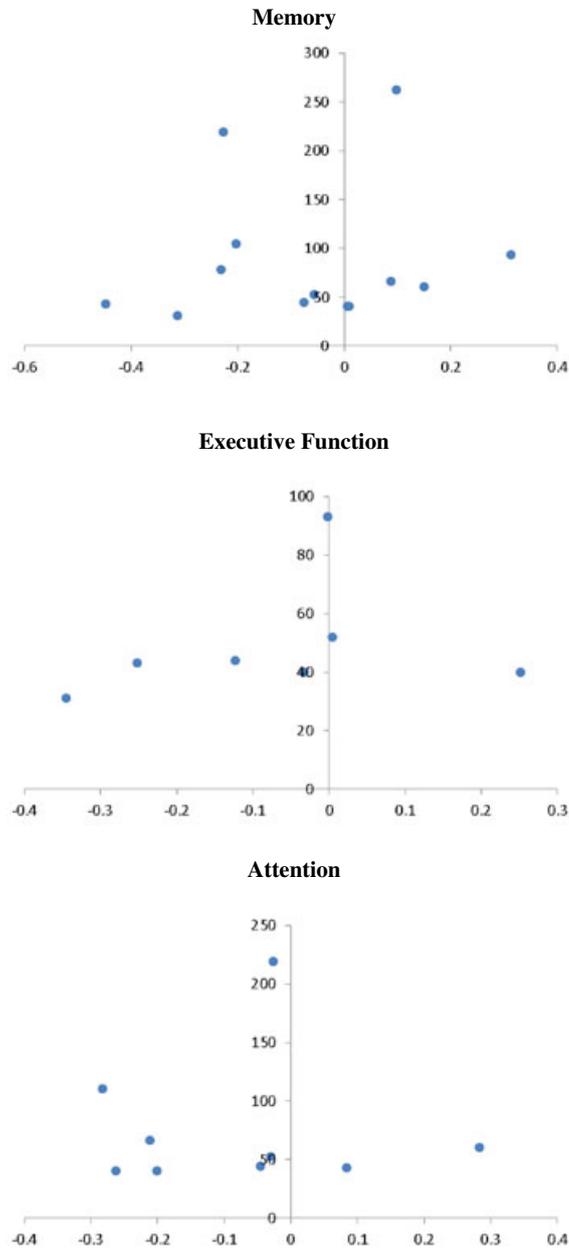
DISCUSSION

The key findings from this meta-analysis are that *G. biloba* has no significant impact on memory, executive function or attention with all effect sizes non-significant and effectively at zero. Effect sizes were not significantly related to participant age, duration of *G. biloba* consumption, total trial dose or the specific *G. biloba* formulation. Indeed, none of the 13 studies assessing memory revealed an overall significant effect size. Given that *G. biloba* is marketed worldwide as a memory enhancer or touted to at least 'maintain memory', it is crucial to establish the validity for such claims. Our lack of support for the nootropic qualities of *G. biloba* accords with the

¹ The mediating effect of daily dose could not be examined for Executive function as all studies except one used 120 mg.

Table 2. Descriptive variables for studies included in meta-analyses

	Number of studies	<i>Ginkgo</i> sample size	Control sample size	Total <i>N</i> range	Total sample sizes <i>Ginkgo</i> , controls
	<i>K</i>	<i>M</i>	<i>M</i>	<i>Range</i>	<i>Total</i>
Memory	13	43.85	43.23	31–262	570, 562
Executive function	7	24.57	25.85	31–93	181, 353
Attention	8	38.25	37.75	40–219	302, 608



Note. Positive effect sizes indicate better performance for *G. Biloba* group; negative better performance by controls

Figure 2. Funnel plots of effect sizes against total sample size

conclusions of previous systematic *qualitative* reviews (Canter and Ernst, 2007), which reported 'no convincing evidence from randomised clinical trials for a robust positive effect of *G. biloba* ingestion upon any aspect of cognitive function in healthy young people after either acute or longer term administration' (p. 207, Canter and Ernst, 2007).

Give our negative findings, it is important to address any potential confounding or methodological reasons for our failure to find evidence of efficacy. Turning to study quality, some have called for a set of criteria for assessing the effects of herbal extracts such as *G. biloba*. Scholey *et al.* (2005) suggested that 'where possible, such investigations should be adequately powered and include the use of (i) standardised extracts; (ii) a placebo control; (iii) assessment of several doses; (iv) double-blind methodology; (v) a crossover design; (vi) a baseline (pre-dosing) assessment; and (vii) standardised (preferably computerised) tasks with known bidirectional sensitivity'. Within this framework, the studies included in the meta-analyses were placebo-controlled RCTs, using double blind methodology, pre-dose assessment and preparations (Li1370, EGb 761 and Blackmore's), which are similar in terms of standardisation with 25% *Ginkgo*-flavone glycosides and 6% terpenes lactones.

Dosage is, of course, a likely relevant factor. For example, Scholey *et al.* (2005) refer to the possible importance of dose differences and speculate that 120 mg may be sub-threshold, but that 'Such a possibility can only be fully addressed by trials directly comparing different doses'. (p. 706). All of the RCTs analysed here continued to rely a fixed dose (Table 1). Nevertheless, variation exists across trials (from 120 to 240 mg per day) and crucially, we found no relationship between effect sizes and either the daily dose or the total dose per trial. Of course, it remains possible that *G. biloba* has short-term acute effects, for example, following a single dose; however, the use of a potential neuroenhancer would be quite limiting if it had a one-off short-term impact, and previous qualitative reviews of acute doses do not indicate a specific acute impact of *G. biloba* (Canter and Ernst, 2007).

Although we found no relationship between sample size and effect sizes for any cognitive variable, RCTs with small samples inevitably have reduced power to detect differences that may exist. To detect, what are likely to be smallish differences ($d=0.35$) at a power of 0.8 would require samples of around 100 in each group. Using this criterion, two studies (Mix and Crews, 2002; Solomon *et al.*, 2002) in the meta-analyses contained sufficient samples and still neither

produced an overall significant effect size. It should also be noted that meta-analysis increases the power to detect small overall differences across studies even if all individual studies are non-significant (Lau *et al.*, 1992; Rerkasem and Rothwell, 2010); however, that was evidently not the case here.

Additional issues might relate to the tests used. We examined three large cognitive domains where effects are commonly claimed: memory, attention and executive function; and of course, a variety of tests are used within and between studies. As remarked by Canter and Ernst (2007, p. 266) and Kaschel (2009), ceiling effects may occur in healthy subjects and be more prevalent in younger participants. Indeed, Mix and Crews (2000) referred directly to this possibility when referring to their own null findings, '...the majority of neuropsychological measures may not have been of sufficient sensitivity to identify relatively subtle differences that may have actually existed' (p. 226). Although the *qualitative* reviews by Canter and Ernst (2007) and by Kaschel (2009) do not readily address this question, the current *quantitative* review may provide some indications. Our comparison of younger and older participants revealed no difference in effect sizes, indicating that no greater benefits accord for the healthy elderly than the healthy younger participants (i.e. if the latter were more prone to ceiling effects). Furthermore, it seems extremely unlikely that ceiling effects would exist across the wide variety of standardised tests examined here; and indeed, many of the memory tests clearly do not produce ceiling effect, for example, digit span. We also note that we purposefully excluded tests that would induce ceiling effects (e.g. the Mini Mental State Examination). We do not therefore believe that ceiling effects could reasonably account for the lack of change associated noted in *G. biloba* trials.

Finally, we considered the possibility of publication bias. The values for Kendall's Tau were non-significant in each of the three domains (suggesting no bias); and although funnel plots show some asymmetry, this indicated more common publishing of negative than positive studies—and so, certainly no bias against the publishing of null findings. To conclude, we found no evidence that *G. biloba* improves memory, executive or attentional functioning in healthy individuals.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interests.

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