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REVIEW

Neuroprotective and Antioxidant Effect of *Ginkgo biloba* Extract Against AD and Other Neurological Disorders

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Abstract

Alzheimer's disease (AD) is the most common progressive human neurodegenerative disorder affecting elderly population worldwide. Hence, prevention of AD has been a priority of AD research worldwide. Based on understanding of disease mechanism, different therapeutic strategies involving synthetic and herbal approaches are being used against AD. Among the herbal extract, *Ginkgo biloba* extract (GBE) is one of the most investigated herbal remedy for cognitive disorders and Alzheimer's disease (AD). Standardized extract of *Ginkgo biloba* is a popular dietary supplement taken by the elderly population to improve memory and age-related loss of cognitive function. Nevertheless, its efficacy in the prevention and treatment of dementia remains controversial. Specifically, the added effects of GBE in subjects already receiving "conventional" anti-dementia treatments have been to date very scarcely investigated. This review summarizes recent advancements in our understanding of the potential use of *Ginkgo biloba* extract in the prevention of AD including its antioxidant property. A better understanding of the mechanisms of action of GBE against AD will be important for designing therapeutic strategies, for basic understanding of the underlying neurodegenerative processes, and for a better understanding of the effectiveness and complexity of this herbal medicine.

Key Words Alzheimer's disease · Antioxidant · Dietary supplement · *Ginkgo biloba* extract · Herbal compounds · Neurodegenerative disease

Introduction

Alzheimer's disease (AD) is characterized by senile plaques and neurofibrillary tangles with progressive involvement of cognitive changes which primarily includes memory loss [1]. These aforementioned hallmark of AD therefore explains the need to decipher certain key questions in a way to understand disease etiology. For example, what factor/event induces the alterations in the processing of amyloid-β protein precursor (AβPP) that lead to plaque formation and the hyperphosphorylation of tau protein that leads to tangles? The prevalence of AD varies among several different factors, including age, genetics, comorbidities, and education level [2]. There is no cure for AD; however, promising research and development for early detection and treatment is underway. Moreover, deducing an effective treatment method against AD still poses a significant clinical challenge. Several drug treatments are available to help prevent various symptoms in the disease, and researchers around the world are focusing on finding better treatments, preventive strategies, and ultimately a cure. Researchers are using different synthetic and/or herbal compounds to test their potential efficacy against AD [3–6]. In this milieu, polyphenolic compounds from medicinal plants are key sources of neuroprotective agents against AD. Targeting the structure of these bioactive ingredients as templates for synthetic drugs offers a wide range of potential neuroprotective compounds [7, 8]. Natural polyphenolic compounds impart their antioxidant effect by reducing free radical species, metal bonding, and/or producing endogenous antioxidant capacity [9]. Thus, the antioxidant properties positively contribute to their neuroprotective

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effects. Furthermore, some of them have been shown to impact synthesis of endogenous antioxidant molecules in cells via triggering the Nrf/ARE pathway [10].

Ginkgo biloba's place of origin is believed to be remote mountainous valleys of Zhejiang province of eastern China [11, 12]. Standardized *Ginkgo biloba* extract (GBE) derived from dried leaves of Ginkgo is used as a therapeutic drug for the treatment of memory impairment and dementia including Alzheimer's disease (AD) [13, 14]. A number of clinical studies showed amelioration of cognitive function in the elderly and in AD patients [15–19]; however, other reports do not support GBE in AD. The controversy regarding the benefits of GBE for different indications has been fortified after the publication of two major trials: i) the GEM study by DeKosky and colleagues [20] showed no favorable effect of GBE for the prevention of dementia onset in older people with or without mild cognitive impairment and ii) the study by McCarney and colleagues [21] indicated no evidence of effectiveness of GBE in mild to moderate dementia. Notably, multiple effects on apoptotic pathway and mitochondrial function that seems to be crucial for its valuable effects in AD were reported: improvement of energy metabolism, stabilization of mitochondrial membrane potential, inhibition of cytochrome c release, upregulation of anti-apoptotic Bcl-2 protein and downregulation of pro-apoptotic Bax protein and reduced level of caspase 9 and caspase 3 after oxidative stress, and decrease of apoptotic cell death [22–28]. The aim of this review is to summarize and to critically evaluate the evidence relating to the neuroprotective and antioxidant effects of the *Ginkgo biloba* extract (GBE) a commonly used extract in experimental and clinical studies.

Origin and History of *Ginkgo biloba*

Ginkgo biloba is the oldest living tree species in the world. The *Ginkgo* species dates all the way back to the Permian Period some 286 to 248 million years ago. Today, *Ginkgo biloba* is the only surviving member of the Ginkgo family. This survival is said to be owed to its extraordinary malleability, resistance to disease, and to Buddhist monks who cultivated and preserved the trees on sacred grounds [29]. *Gingko* was a favorite of Frank Lloyd Wright and soon made its approach into city landscapes across the USA [30]. The documented medicinal uses of *Ginkgo* in China can be tracked back nearly 5000 years, mainly for asthma treatment [31].

Leaf Extract of *Ginkgo biloba*

The leaves of the Ginkgo tree have a long history of being used for medicinal purposes. In the early 1970s, Dr. Willmar Schwabe Pharmaceuticals (Karlsruhe, Germany) effectively developed a method for the extraction and standardization of *Ginkgo biloba* extract preparation and produced highly concentrated and stable extracts from *Ginkgo biloba* leaves [32]. The standardized extract of *Ginkgo biloba* leaves (GBE) contains 6% terpenoids (in which 3.1% are ginkgolides A, B, C, and J and 2.9% is bilobalide), 24% flavonoid glycosides (containing quercetin, kaempferol, isorhamnetin *etc*.), and 5–10% organic acids (Figs. 1 and 2). The flavonoids and terpenoids are suggested to be the pharmacologically active constituents of GBE [33, 34]. Water solubility of GBE is on account of the presence of organic acid content [35]. Various preclinical research assessing GBE effects have been undertaken by the important studies of Y Luo and others that suggest the neuroprotective effects of this herbal extract in cell and animal-based models [36–42]. GBE has been widely used in the treatment and prevention of neurodegenerative dementias associated with aging, Alzheimer's disease (AD), Parkinson's disease (PD), peripheral vascular diseases, and neurosensory problems (e.g., tinnitus) with mixed results [30, 43, 44]. GBE is used in an extensive range of disorders and diseases, including depressed mood, multi-infarct dementia, cerebral insufficiency (characterized by symptoms such as memory impairment, poor concentration, anxiety, and confusion), myocardial ischemia, stroke, thrombosis, and peripheral occlusive arterial disease (POAD). In addition, its effects on antidepressant-induced sexual dysfunction [45], traumatic brain injury, and hypertension have been studied [46].

Individual Components of *Ginkgo biloba*

GBE comprises different constituents (Fig. 1) like Trilactonicditerpenes, ginkgolides A, B, and C (ginkgolides J and M, not shown, are present in lower concentrations). Flavonoids including quercetin, kaempferol, isorhamnetins, trilactonicsesquiterpene, and proanthocyanidins are also present. Other constituents such as glucose, rhamnose, hydroxykynurenic, kynurenic, protocatechuic, vanillic, and shikimic acids, D-glucaric acid, ginkgolic acid, and related alkyphenols have also been isolated. Ginkgolides have been specifically shown to act as platelet-activating factor (PAF) antagonists, inhibiting platelet aggregation and stimulating blood flow [47]. Flavonoids are known to act as major antioxidants among various polyphenol and also act as a heavy metal chelators due to their phenolic structures [48]. They have been clinically explored in inflammatory diseases [49] and cardiovascular disorders [50]. Additionally, GBE has shown neuroprotection and anti-inflammatory properties in preclinical models of AD [51] and stroke [52].

Pharmacological Importance

Although *Ginkgo* has been around for over 200 million years, it is only during the last couple of decades that it has been well

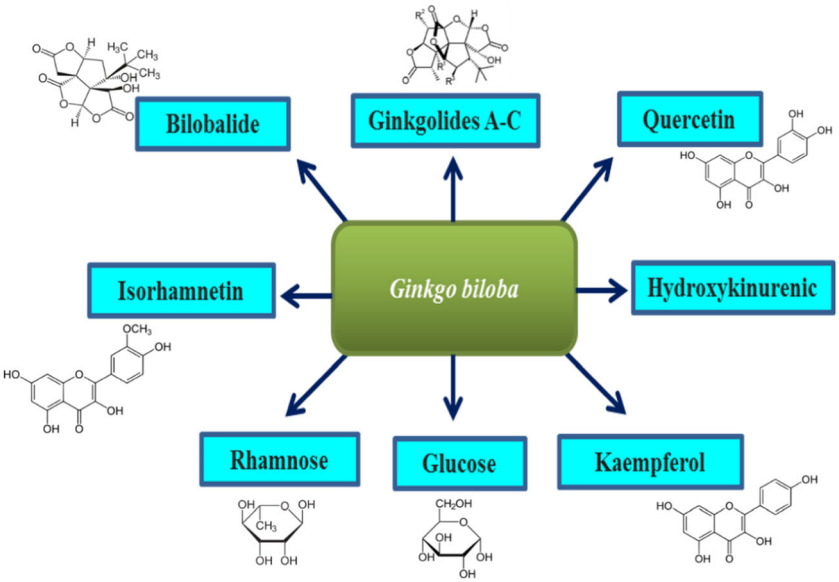

Fig. 1 Pictorial illustrations of the active components present in *Ginkgo biloba* extract (GBE). Note the multiple classes of bioactive agents

studied. Its amazing liveliness has fascinated an increasing exploration into potential application in food, health, and supplements. The important parts of *Ginkgo* tree having medicinal values are fresh or dried leaves and seeds. It contains large number of active compounds (Fig. 2), known to have pharmacological value. The active component in GBE from *Ginkgo* leaves improves blood circulation, reinforces the walls of the capillaries, discourages clot formation, and protects nerve cells from harm when devoid of oxygen. The leaf extracts are used to treat dementia disorders, such as concentration difficulties and memory impairment. The extract also possesses anti-asthmatic [53], antioxidant [54], wound healing [55], radical-scavenging [56], and neuroprotective properties against neurodegenerative disorders like AD [57, 58] and PD [59]. The benefits of antioxidants alone in reducing Alzheimer's or other diseases is clearly unproven, when in contrast, complex mixtures such as chocolate or blueberries have benefit due to the pleotropic effects. In addition, pure antioxidants may further disrupt tightly regulated stress responses.

Positive effect of *Ginkgo biloba* plant have been reported on Alzheimer's disease, memory enhancement, dementia of vascular origin, cognitive disorders, and its antioxidative effects in combination with other drugs, which enhance their effects or decrease their psychiatric side effects (Fig. 3) [49–62]. *Ginkgo biloba* can be used as a reinforcing antidepressant agent and a neuroprotective drug in brain injuries [63]. This plant modifies the cerebral blood flow and may help to reduce fatigue and inattention [64]. Other studies showed its effect on several different neurotransmitter systems of central nervous system [65, 66]. The anti-anxiety and mild anti-depression property of GBE is

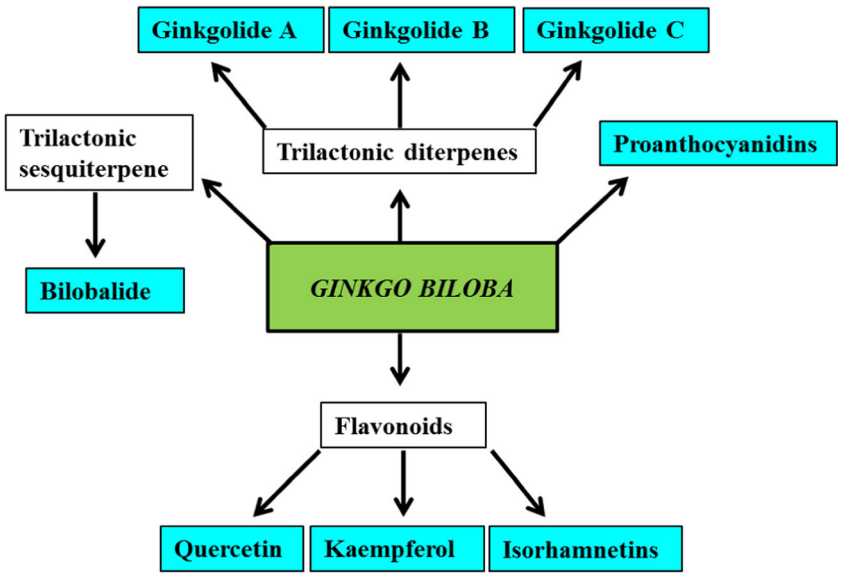

Fig. 2 Schematic chart showing various active components found in GBE. The wide-raging activities found in GBE make a single mechanism of action difficult and rather argue for pleotropic effects

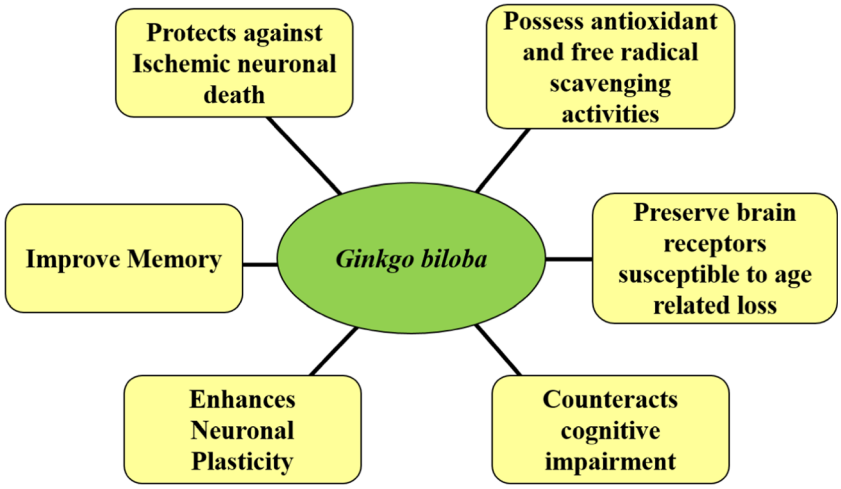

Fig. 3 GBE has an array of activities relevant to neurological functions. The range of activities underlies the pleotropic effects of GBE

accounted from the reversible inhibition of two MAOA and MAOB enzymes [67], while the antioxidant, anti-inflammatory, and neuroprotective effects are contributed mainly by the flavonoid and terpenoid content in GBE. *Ginkgo biloba* has a positive effect on cognitive and neurological function by vascular flow regulation and platelet-activating antagonism factors that protect the brain from ischemic injuries [64]. Alkaloid ketones, amino acids, cyanogenic glycosides, and phenols, abundant in this plant extract, are active ingredients responsible for its therapeutic effects [64]. *Ginkgo biloba* has positive effects on psychosis, anxiety, schizophrenia, and depression [68]. It stimulates the cerebral blood circulation and improves problems caused by the failure of blood circulation in the brain including anxiety, stress, low memory, hearing problems, low concentration, thinking, social behavior, and dementia in Alzheimer's disease [64].

Neuroprotective Effects of *Ginkgo biloba* Extract

The neuroprotective effect of GBE has been validated in several *in vitro* and *in vivo* models studies [69]. *In vitro* studies revealed that GBE protected cultured neurons against death induced by hydrogen peroxide [70–76], hypoxia [77], glutamate [78, 79], verapamil [79], amyloid-β [80, 81], 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, [82], nitric oxide (NO), [83], and cyanide [78]. Also, in *in vivo* effect, reduction of neuronal damage by EGb761 (10–100 mg/kg, p.o. (per os), or i.p. (intraperitoneally)) has been observed after transient middle cerebral artery occlusion (MCAO) in rats [78, 84] and gerbils [85–87]; focal cerebral ischemia in mice and rats [78]; hypoxia [88]; heat stress [89]; subchronic cold stress [90]; and amphetamine-induced behavioral sensitization [91], and in a transgenic mouse model of amyotrophic lateral sclerosis [92]. The ginkgolides (1–100 μM *in vitro* or 50–100 mg/kg in vivo), bilobalide (25–100 μM *in vitro* or 10 mg/kg in vivo), and in some cases also the flavonoid fraction (25–100 μg/ml *in vitro* or 40–100 mg/kg in vivo) have been shown to contribute to the neuroprotective effect of EGb 761. Besides free radical–scavenging property of EGb 761, it has also been shown to affect the transcription of several genes associated to oxidative stress regulation [93]. This is an important property of EGB 761 as it may help in improved cellular tolerance against oxidative stress thereby protecting neuronal cell against oxidative damage commonly associated to neurodegenerative diseases like AD and PD condition.

Effect of GBE against Aβ Aggregation

The accumulation of Aβ plaques is a hallmark of AD [94]. Recently, the use of GBE in the neuroprotection against the Aβ-induced neurotoxicity has received much attention among scientific community. Several recent studies showed that GBE protects against Aβ-induced neurotoxicity by obstruction of Aβ-induced events, such as glucose uptake, reactive oxygen species (ROS) accumulation, activation of AKT, mitochondrial dysfunction, JNK and ERK 1/2 pathways, and apoptosis (Fig. 4) [95–97]. It has been reported that GBE inhibits the production of Aβ in brain by lowering the levels of circulating free cholesterol, as AβPP processing and amyloidogenesis are supposed to be affected by free circulating and intracellular cholesterol levels [98–102]. Despite this evidence, further investigations are needed to identify the major constituents responsible for this anti-amyloidogenic effect. GBE could also interfere with the Aβ oligomer formation [26, 99]. It is well known that the β-sheet structure of Aβ oligomers is primarily accountable for Aβ neurotoxicity and may also help Aβ discharge from clearance via proteolytic cleavage [99, 103–105]. Thus, preventing the formation of β-sheet structure of Aβ oligomers may also be a very prominent strategy to prevent Aβ toxicity. Apart from self oligomerization of the Aβ, the interaction of Aβ with different transition metal ions, notably copper, iron, and zinc, could influence the oligomerization of Aβ. GBE has iron chelating property which may also inhibit

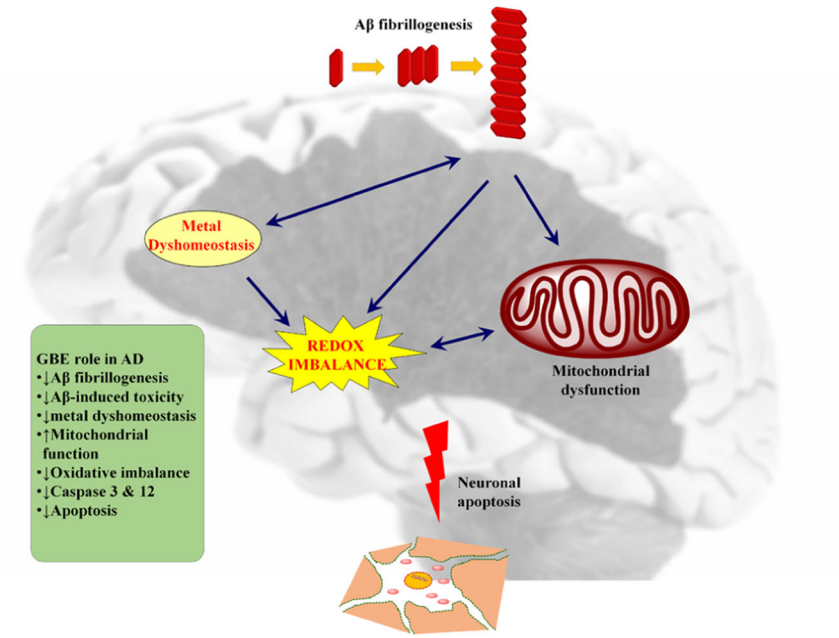

Fig. 4 Pictorial illustration of Aβ-induced damage through metal dyshomeostasis, redox imbalance, mitochondrial dysfunction which finally leads to neuronal apoptosis, and GBE role in its alleviation. Upward arrows represent upregulation. Downward arrows represent downregulation

Aβ fibril formation [26, 99]. Collectively, we can say that GBE is highly effective and prominent against AD by effecting in several ways as mentioned in Fig. 4.

Transthyretin has been shown to prevent Aβ aggregation *in vitro* by sequestering Aβ monomers [96, 106]. GBE may also prevent the Aβ fibril formation by increasing gene expression of transthyretin [107], The anti-Aβ effect of GBE on Aβ aggregation was also observed with flavonoid compounds, ginkgolide J, and bilobalide [26, 99]. Further, GBE has also been shown to regulate mitochondrial oxidative phosphorylation (OXPHOS) against Aβ-induced oxidative stress thereby helping in maintaining the ROS/RNS (reactive oxygen species/reactive nitrogen species) equilibrium in cells [108]. Studies show that GBE imparts beneficial effects on the cellular OXPHOS functioning thereby helping in amelioration of mitochondrial function against Aβ-induced toxicity [109]. Although studies show promising results for GBE against Aβ-induced toxicity, more studies are required to decipher the mechanism of action of individual components of GBE against Aβ-induced toxicity in AD.

Antioxidant Activity

Oxidative stress disequilibrium has been one of the hallmark signs involved in AD pathogenesis [110–113]. Several *in vitro* and *in vivo* studies support the beneficial action of GBE mainly due to its free radical–scavenging action [38], as is evident from a study in which pretreating cerebellar granule cells with GBE effectively diminished the oxidative damage triggered by H_2O_2/$FeSO_4$ [114]. Further, in studies from AD models, Aβ-expressing transgenic *Caenorhabditis elegans* [115] and Aβ-expressing neuroblastoma cell line N2a [38], GBE was found to significantly attenuate the basal as well as the induced levels of H_2O_2-related reactive oxygen species (ROS) [38, 115]. In addition to direct reduction of ROS, GBE may also be helpful in upregulation of antioxidant enzymes and protein level [102]. For example, superoxide dismutase (SOD) and catalase activity was found to be elevated in rat hippocampus and rat ileum supplemented with GBE [36, 116, 117]. Glutathione (GSH) reductase and gamma-glutamylcysteinyl synthetase, which are two important enzymes used in the reduction step of synthesis of GSH, were also enhanced by GBE [36, 118, 119]. The main active and responsible fraction for antioxidant activity in GBE extract is flavonoids. Previous studies proposed that the flavonoid fraction's antioxidant property is ROS scavenging, increase in antioxidant proteins such as SOD and GSH, and chelating prooxidant transitional metal ions [38, 97, 120, 121]. Quercetin [122] and myricetin are the two flavonoid structures which effectively inhibit tert-butylhydroperoxide oxidation [36]. In contrast, the antioxidant activity of terpene lactones still remains to be deciphered [36]. The discrepancy on the antioxidant activity of the terpene lactones may be explained as being due to differences in the type of oxidative stress used as well as the experimental models [36].There are contradictory data in context to superoxide-scavenging activity of ginkgolides B, C, and J and bilobalide [36, 123, 124].

Conclusions

Ginkgo biloba extract (GBE) is used effectively for treatment of many human disorders including brain function. Various research studies were carried out on *Ginkgo biloba* extract

and found its phytomedicinal properties and its efficacy under many disease conditions. Many research reports effective use of GBE in cerebrovascular insufficiency, peripheral artery insufficiency, multi-infarct dementia, memory impairment in the elderly, Alzheimer's disease, resistant depression, asthma, and venous insufficiency. GBE for schizophrenia, tinnitus, brain syndrome, vertigo of undetermined origin, and PMS, although less supported, still requires further study. Various *in vivo* and *in vitro* preclinical studies support the view that standardized *Ginkgo biloba* extract EGb761 may be effective in the treatment and prevention of AD and other age-related, neurodegenerative disorders. Anti-oxidation, anti-inflammation, anti-apoptosis, defense against mitochondrial dysfunction, amyloidogenesis and Aβ aggregation, modulation of phosphorylation of tau protein, ion homeostasis, and even induction of growth factors are possible mechanisms of action of GBE (Fig. 4). However, the clinical efficacy of EGb761 still remains elusive. Multiple factors such as population sensitivity, severity of impairment, type of assessments used to measure efficacy, and doses were suggested to be able to interfere with EGb761's efficacy in clinical practice. Regarding these factors, basic scientific reports give useful information that may help to modify the clinical efficacy of this drug. Overall, a better understanding of the mechanisms underlying the neuroprotective effects of EGb761 may contribute to better understanding of the effectiveness and complexity of this drug and may also be helpful for designing therapeutic strategies in future clinical practice.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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