Natural extracts as possible protective agents of brain aging

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Abstract

A growing number of studies suggest that natural extracts and phytochemicals have a positive impact on brain aging. We examined the potential of the Ginkgo biloba extract EGb 761 and red wine-derived constituents on cell death produced by beta-amyloid (Aβ) peptides and oxidative stress, with respect to their possible deleterious role in age-related neurological disorders. We found that EGb 761, possibly through the antioxidant properties of its flavonoids, was able to protect hippocampal cells against toxic effects induced by Aβ peptides. Moreover, we showed that an exposure of rat hippocampal cells to the nitric oxide (NO) donor sodium nitroprusside (SNP) resulted in a decrease in cell survival and increase in reactive oxygen species (ROS) accumulation. However, EGb 761 and red wine-derived polyphenols protected against these events, due to their antioxidant activities, and their ability to block SNP-stimulated activity of protein kinase C (PKC). Taken together, these results support the hypothesis that dietary intake of natural substances may be beneficial in normal aging of the brain.

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Keywords: Neuroprotection; Ginkgo biloba extract; Red wine; Resveratrol; Quercetin, (+)-catechin; Beta-amyloid peptides; Nitric oxide; Alzheimer’s disease; Brain aging; Vitis vinifera

1. Introduction

Extensive research provided knowledge that an excessive accumulation of beta-amyloid (Aβ) peptides is one of the leading hypotheses to explain neurodegenerative processes that occur in Alzheimer’s disease (AD). To support the amyloid hypothesis, in vitro studies performed in cell culture preparations reported neurotoxic [14,28] and apoptotic [12,37] effects of Aβ-related fragments (Aβ25–35, Aβ1–40 and Aβ1–42) in regions that are effected in AD, such as the hippocampus [23]. The precise mechanisms mediating the toxic properties of Aβ remain to be fully established. It has been suggested that Aβ toxicity is associated with increases in reactive oxygen species (ROS), including the peroxide H2O2 [5,20] and nitric oxide (NO) [33], whose overproduction may in turn initiate neurotoxic events [8]. On the other hand, oxidative stress is considered as a risk factor in the incidence and evolution of cognitive declines that occur during normal cerebral aging and dementia, and likely plays a pivotal role in various neurodegenerative processes such as ischemia and Parkinson’s disease [7,24,26,54].

There is no effective cure to treat neurological disorders associated to aging. Among therapeutic interventions that are envisioned to forestall or delay the normal and pathological aging processes, nutritional interventions may be viewed as a viable approach [13,29,61].

Ginkgo biloba extract (EGb 761, Tanakan®, IPSEN Laboratories, Paris, France) is a well known plant extract obtained from green leaves of the G. biloba tree according to a standardized procedure [15]. The patented extract EGb 761, that was filed for all of Europe in 1990, contains the following pharmacologically active substances including 24% flavonoids that are nearly exclusively flavonol-O-glycosides, 6% terpenoids (known as ginkgolides A, B, C, M, J and bilobalide), 5–10% organic acids, and >0.5% proanthocyanidins defined as flavonoid-based polymers [15]. EGb 761 exhibits a broad range of biochemical and pharmacological activities such as antioxidants and free radical
scavenging [38, 39] as well as nootropic and/or neurotrophic activities in the hippocampal formation [1, 2]. The plead of effects of EGb 761 may explain, at least in part, its protective actions in animal models of hypoxia and ischemia [16, 45] and in vitro models of toxicities [44, 49, 58], as well as its ability to enhance cognitive behaviors in rodents [10, 60]. Prospective, double-blind, placebo-controlled studies provided support for safety and significant therapeutic efficacy—including the improvement of memory, attention and social functioning of an oral administration of EGb 761 in healthy older adults [43] and AD or multi-infarct demented patients [22, 34, 41].

It has also been reported that diets rich in fruits, vegetables and beverages are, along with natural extracts, an important source of polyphenols. Interestingly, epidemiological studies pointed to the possible capacity of moderate consumption of red wine—an alcoholic beverage that contains a high amount of polyphenols [19, 51]—and flavonoids to reduce the incidence of certain age-related neurological disorders including macular degeneration [46] and dementia [11, 47].

To support this hypothesis, in vitro studies reported that red wine polyphenols such as quercetin, (+)-catechin and resveratrol displayed protective abilities in various models of toxicity [43, 48, 55].

Considering the purported antioxidant properties of EGb 761 and phytonutrients and their possible therapeutic efficacies [17, 22, 34, 35, 41, 46, 47], we aim to investigate the effects of EGb 761 and red wine-derived polyphenolic compounds known as quercetin, (+)-catechin and resveratrol on the toxicity induced by Aβ peptides (Aβ25–35, Aβ1–40 and Aβ1–42) and/or by oxidative stress.

2. Materials and methods

2.1. Materials

The G. biloba extract EGb 761, its flavonoid fraction (CP 205) and the terpenes bilobalide (CP 160) and ginkgolide B (BN 52021) were obtained from IPSEN Laboratories (France) whereas polyphenolic constituents and sodium nitroprusside (SNP) were purchased from Sigma (St. Louis, France) whereas polyphenolic constituents and sodium nitroprusside (SNP) were purchased from Sigma (St. Louis, MO, USA). The different fragments of Aβ peptides including Aβ1–40 and Aβ1–42 were obtained from US Peptide (Fullerton, CA). The fragment Aβ1–40 was kindly provided by P. Gaudreau (CHUM, University of Montreal, Montreal, Canada). Materials used for cell cultures were obtained from Gibco BRL (Burlington, Ont., Canada).

2.2. Primary hippocampal cell cultures

Hippocampal cell cultures were prepared from E19 embryos obtained from Sprague-Dawley rats. Animal care was according to protocols and guidelines of the McGill University Animal Care Committee and the Canadian Council for Animal Care.

Mixed (neuronal/glial cells) hippocampal cells were plated in 96-well plates (density of about 4 × 10^4 viable cells per well) and were grown in DMEM high glucose medium as described previously [2–4]. Experiments were performed in 7-day-old cultures.

2.3. Experimental treatments

2.3.1. Aβ-induced toxicity

Cells were exposed to the freshly solubilized peptides Aβ25–35 (25 μM), Aβ1–40 (5 μM) or Aβ1–42 (25 μM) for 24 h, in the presence or absence of different drugs, as described previously [2]. Mixed cell viability was quantitated 24 h later using the MTT colorimetric assay (see below) whereas the extent of necrotic and apoptotic cells were evaluated using the fluorescence dyes propidium iodide (PI) and Hoechst 33342, respectively (see below). ROS production was estimated using the 2′,7′-dichlorofluorescein diacetate (DCF) fluorescence assay (see below).

2.3.2. SNP-induced toxicity

Cells were treated during 20 h with a HEPES-buffered MEM high glucose medium containing SNP (100 μM) and the different test drugs, as described previously [3, 4]. Following this incubation period, cell viability was determined using both the MTT and the neutral red (NR) colorimetric assays, whereas ROS production was evaluated using the DCF fluorescence assay (see below).

2.4. Assessment of cell viability and cell injury

MTT (an indicator of the mitochondrial activity of living cells) and NR (a dye which is taken up by lysosomes of living cells) are used as indexes of cell survival [18, 40]. MTT reduction and NR uptake into living cells were quantitated at 570 and 540 nm, respectively, using a micro-plate reader (Bio-Tek Instruments® Inc., Ville St. Laurent, Que., Canada).

Necrotic cell death was evaluated by assessing the extent of cell uptake of the PI dye, as described previously using a fluorescence plate reader (Bio-Tek Instruments® Inc., Ville St. Laurent, Que., Canada).

2.5. Measurement of ROS

The accumulation of intracellular ROS was determined by measuring DCF fluorescence [40]. Briefly, 25 μM 2,7-dichlorofluorescein diacetate (DCFH-DA; Molecular Probes Inc., Eugene, OR) was applied to the culture medium at the onset of either Aβ or SNP exposure, as described previously [2–4]. DCF fluorescence was quantitated (excitation = 485 nm, emission = 530 nm) using a fluorescence plate reader (Bio-Tek Instruments® Inc., Ville St. Laurent, Que., Canada).
2.6. Assessment of apoptotic cell death

Nuclear staining was performed using the fluorescent nucleic acid dye Hoechst 33342, as described previously using hippocampal neurons [28]. Briefly, cells were incubated after a 24 h exposure to Aβ25–35 in phenol red-free Hank’s for 15 min containing the Hoechst 33342 dye (1 μg/ml, 15 min). The number of apoptotic neurons was then quantified using a micro-plate fluorescence reader (UV excitation and emission = 360 and 450 nm, respectively).

2.7. Nitrite assay

Accumulation of nitrite (NO2−), the end-product of NO production that is used as an indicator of NO synthase (NOS) activity, was measured in the culture medium by the Griess reaction using the NO colorimetric assay kit (Calbiochem, San Diego, CA), as described previously [4]. Briefly, hippocampal cells were exposed to SNP with or without polyphenols. Concentrations of NO2− will be quantified 24 h later at 540 nm using a micro-plate reader (Bio-Tek Instruments®, Inc., Ville St. Laurent, Que., Canada).

2.8. Measurement of protein kinase C activity

The activity of protein kinase C (PKC)—an enzyme that has been shown to block the toxic effects of NO—was assessed on 7-day-old mixed hippocampal cells using a PKC assay kit (SigmaTECTM PKC Assay System, Promega, Madison, WI, USA) according to the protocol described previously [3,4]. Briefly, cells were exposed for 5 min to either vehicle or SNP (100 μM) in the presence or absence of either EGb 761 (100 μg/ml) or polyphenols (10 μM).

### 2.9. Statistical analyses

Survival of vehicle-treated control groups not exposed to either Aβ1-42 peptides, SNP, or different drugs was defined as 100% and the number of surviving, dead and apoptotic cells in the treated groups was expressed as percent of control groups. One-way ANOVA followed by a Newman Keuls’ multiple comparison test was used to compare control and treated groups with P values <0.05 being considered statistically significant. An unpaired t-test was used to compare vehicle- and drugs-treated control groups with P values <0.05 being considered statistically significant.

### 3. Results

#### 3.1. EGb 761 protects hippocampal cells against Aβ peptide-induced toxicity

The MTT assay revealed that co-treatment with EGb 761 (100 μg/ml) protected hippocampal cells against toxicity induced by the Aβ fragments Aβ25–35 (25 μM), Aβ1–40 (5 μM) and Aβ1–42 (25 μM) (Table 1). The protective effects of EGb 761 were confirmed by the finding that the number of necrotic (as evaluated by the PI assay) and apoptotic (as evaluated by the Hoechst 33342 assay) cells treated with Aβ25–35 diminished in the presence of EGb 761 (100 μg/ml) (Table 1). The MTT assay revealed that EGb 761 (100 μg/ml) was even able to protect hippocampal cells

### Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cell survival (MTT assay)</th>
<th>Cell injury (PI assay)</th>
<th>Apoptosis (Hoechst assay)</th>
<th>ROS production (DCF assay)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ1–42</td>
<td>61 ± 2</td>
<td>nd</td>
<td>nd</td>
<td>123 ± 14</td>
</tr>
<tr>
<td>Aβ1–42 + EGb 761</td>
<td>101 ± 3</td>
<td>nd</td>
<td>nd</td>
<td>62 ± 6</td>
</tr>
<tr>
<td>Aβ1–42</td>
<td>61 ± 3</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1–42 + EGb 761</td>
<td>103 ± 4</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1–11 + 58 ± 2</td>
<td>118 ± 2</td>
<td>116 ± 3</td>
<td>151 ± 11</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11 + EGb 761</td>
<td>88 ± 2</td>
<td>100 ± 5</td>
<td>63 ± 8</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11</td>
<td>58 ± 2</td>
<td>nd</td>
<td>165 ± 6</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11 + CP 205</td>
<td>74 ± 3</td>
<td>nd</td>
<td>97 ± 6</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11</td>
<td>58 ± 2</td>
<td>nd</td>
<td>167 ± 7</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11 + bilobalide</td>
<td>52 ± 2</td>
<td>nd</td>
<td>165 ± 11</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11 + ginkgolide B</td>
<td>50 ± 1</td>
<td>nd</td>
<td>140 ± 11</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11</td>
<td>67 ± 2</td>
<td>nd</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11 + nitremipine</td>
<td>64 ± 2</td>
<td>nd</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11 + chelerythine</td>
<td>66 ± 2</td>
<td>nd</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11 + U-73122</td>
<td>74 ± 4</td>
<td>nd</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>Aβ1–11 + NDGA</td>
<td>65 ± 4</td>
<td>nd</td>
<td>nd</td>
<td></td>
</tr>
</tbody>
</table>

* Modified with permission from [2]; nd: not determined.

* P < 0.01 compared to groups treated with Aβ1 alone.
Table 2

Comparative effects of the EGb 761, its flavonoid and terpenoids constituents, as well as various drugs against toxicity and ROS production induced by SNP in rat hippocampal cell cultures.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cell survival (MTT assay)</th>
<th>Cell survival (NR assay)</th>
<th>ROS production (DCF assay)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP</td>
<td>42 ± 3</td>
<td>40 ± 3</td>
<td>532 ± 73</td>
</tr>
<tr>
<td>SNP + EGB 761</td>
<td>99 ± 5†</td>
<td>98 ± 3†</td>
<td>222 ± 22</td>
</tr>
<tr>
<td>SNP + CP 205</td>
<td>73 ± 10‡</td>
<td>76 ± 6‡</td>
<td>321 ± 38</td>
</tr>
<tr>
<td>SNP + ginkgolide B</td>
<td>62 ± 2</td>
<td>63 ± 6</td>
<td>344 ± 62</td>
</tr>
<tr>
<td>SNP + bilobalide</td>
<td>23 ± 4</td>
<td>29 ± 4</td>
<td>nd</td>
</tr>
<tr>
<td>SNP + ebselen</td>
<td>87 ± 6*</td>
<td>87 ± 3</td>
<td>nd</td>
</tr>
<tr>
<td>SNP + trolox</td>
<td>81 ± 8*</td>
<td>96 ± 6*</td>
<td>nd</td>
</tr>
<tr>
<td>SNP + U-73122</td>
<td>52 ± 6</td>
<td>36 ± 3</td>
<td>nd</td>
</tr>
<tr>
<td>SNP + OBAA</td>
<td>42 ± 10</td>
<td>33 ± 6</td>
<td>nd</td>
</tr>
</tbody>
</table>

Modified with permission from [3]; nd: not determined.

* P < 0.01 compared to groups treated with SNP alone.

Table 3

Summary of the effects of red wine polyphenols and inhibitors of cyclooxygenase and lipoxygenases against toxicity and ROS production induced by SNP in rat hippocampal cell cultures.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cell survival (MTT assay)</th>
<th>Cell survival (NR assay)</th>
<th>ROS production (DCF assay)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP</td>
<td>50 ± 6</td>
<td>57 ± 5</td>
<td>226 ± 15</td>
</tr>
<tr>
<td>SNP + quercitin</td>
<td>76 ± 5*</td>
<td>77 ± 4°</td>
<td>162 ± 8°</td>
</tr>
<tr>
<td>SNP</td>
<td>41 ± 5</td>
<td>44 ± 6</td>
<td>268 ± 23</td>
</tr>
<tr>
<td>SNP + (+)-catechin</td>
<td>89 ± 4*</td>
<td>89 ± 3°</td>
<td>154 ± 14°</td>
</tr>
<tr>
<td>SNP + resveratrol</td>
<td>39 ± 5</td>
<td>39 ± 5</td>
<td>265 ± 23</td>
</tr>
<tr>
<td>SNP</td>
<td>42 ± 9</td>
<td>38 ± 2</td>
<td>239 ± 26</td>
</tr>
<tr>
<td>SNP + trolox</td>
<td>96 ± 3°</td>
<td>96 ± 2°</td>
<td>112 ± 9°</td>
</tr>
<tr>
<td>SNP</td>
<td>34 ± 4</td>
<td>42 ± 6</td>
<td>177 ± 12</td>
</tr>
<tr>
<td>SNP + indomethacin</td>
<td>28 ± 4</td>
<td>37 ± 5</td>
<td>153 ± 8</td>
</tr>
<tr>
<td>SNP</td>
<td>43 ± 3</td>
<td>59 ± 5</td>
<td>228 ± 17</td>
</tr>
<tr>
<td>SNP + MK-886</td>
<td>33 ± 4</td>
<td>27 ± 4</td>
<td>216 ± 18</td>
</tr>
<tr>
<td>SNP</td>
<td>55 ± 8</td>
<td>56 ± 6</td>
<td>255 ± 15</td>
</tr>
<tr>
<td>SNP + 2-(3,4-dihydroxybenzyl)</td>
<td>53 ± 7</td>
<td>46 ± 4</td>
<td>225 ± 10</td>
</tr>
</tbody>
</table>

Modelled with permission from [4].

* P < 0.01 compared to groups treated with SNP alone.

Table 4

Effects of EGb 761, quercitin, (+)-catechin and resveratrol on PKC activity and nitric accumulation induced by SNP in rat hippocampal cells.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PKC activity</th>
<th>Nitric accumulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP</td>
<td>127 ± 7°</td>
<td>nd</td>
</tr>
<tr>
<td>SNP + EGB 761</td>
<td>105 ± 6°*</td>
<td>nd</td>
</tr>
<tr>
<td>SNP + quercitin</td>
<td>104 ± 9°</td>
<td>154 ± 12</td>
</tr>
<tr>
<td>SNP + (+)-catechin</td>
<td>132 ± 6°</td>
<td>160 ± 9</td>
</tr>
<tr>
<td>SNP + resveratrol</td>
<td>126 ± 4°</td>
<td>154 ± 12</td>
</tr>
<tr>
<td>SNP + trolox</td>
<td>123 ± 6°</td>
<td>180 ± 19</td>
</tr>
</tbody>
</table>

Modified with permissions from [3, 4]; nd: not determined.

* P < 0.05 compared to groups treated with SNP alone.

EGb 761 also protected hippocampal cells from toxicity induced by H2O2, the major peroxide that possibly mediates Aj toxicity (data not shown, see [2]), and shared with CP 205 (25 µg/ml) the ability to reduce Aβ25–35-induced intracellular ROS accumulation (Table 1). However, the terpenes bilobalide and ginkgolide B (10 µg/ml) failed to reverse the increase in DCF fluorescence stimulated by Aβ25–35 (Table 1).

3.2. EGb 761 and red wine-derived polyphenols protect hippocampal cells against SNP-induced toxicity.

A co-treatment with EGb 761 (100 µg/ml), its flavonoid fraction CP 205 (25 µg/ml) (Table 2), quercitin (10 µM), (+)-catechin (10 µM) and resveratrol (10 µM) (Table 3) were capable of attenuating hippocampal cell death (as estimated by the MTT and NR assays) and intracellular ROS accumulation (as estimated by the DCF assay) generated by SNP (100 µM). Similar protective effects were obtained with...


The mechanisms of action underlying the protective effects of EGb 761 were examined. We observed that treatments with EGb 761 and its flavonoid fraction were able to strongly inhibit Aβ peptides- and/or oxidative stress-induced toxicities. These data may be of particular interest given the deleterious role of the accumulation of Aβ peptides and ROS in hippocampal dysfunctions/neurodegeneration that possibly occurs during normal brain aging, as well as neurodegenerative diseases [23,53].

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with fruits as the most important source) and the risk of dementia [11]. Since the inverse correlation between wine consumption and dementia was not significant after adjustment for flavonoid intake, the authors suggested that the association between red wine consumption and AD may be related to their polyphenolic constituents. In addition to the possible direct effect of phytochemicals in the brain function, it is possible that their beneficial effects may be attributable, at least in part, to their purported cardioprotective effects [21]. In conclusion, the data reported here support the hypothesis that dietary intake or supplementation of polyphenols that are widely present in food and in various natural extracts may prevent or delay the incidence of age-related neurological disorders. Further epidemiological studies are necessary to confirm this hypothesis and to recommend polyphenols as a prophylactic means to forestall and/or to delay the incidence of neurological dysfunctions that are associated with pathological brain aging.

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