Natural stilbenes effects in animal models of Alzheimer’s disease

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Abstract
Alzheimer’s disease is one of the most frequent neurodegenerative diseases. This pathology is characterized by protein aggregates, mainly constituted by amyloid peptide and tau, leading to neuronal death and cognitive impairments. Drugs currently proposed to treat this pathology do not prevent neurodegenerative processes and are mainly symptomatic therapies. However, stilbenes presenting multiple pharmacological effects could be good potential therapeutic candidates. The aim of this review is to gather the more significant papers among the broad literature on this topic, concerning the beneficial effects of stilbenes (resveratrol derivatives) in animal models of Alzheimer’s disease. Indeed, numerous studies focus on cellular models, but an in vivo approach remains of primary importance since in animals (mice or rats, generally), bioavailability and metabolism are taken into account, which is not the case in vitro studies. Furthermore, examination of memory ability is feasible in animal models, which strengthens the relevance of a compound with a view to future therapy in humans. This paper is addressed to any researcher who needs to study untested natural stilbenes or who wants to experiment the most effective natural stilbenes in largest animals or in humans. This review shows that resveratrol, the reference polyphenol, is largely studied and seems to have interesting properties on amyloid plaques, and cognitive impairment. However, some resveratrol derivatives such as gnetin C, trans-piceid, or astringin have never been tested on animals. Furthermore, pterostilbene is of particular interest, by its improvement of cognitive disorders and its neuroprotective role. It could be relevant to evaluate this molecule in clinical trials.

Key Words: Alzheimer’s disease; amyloid; animal models; cognitive impairment; inflammation; natural stilbenes; neuroprotection; resveratrol; tau

Introduction
General presentation of natural stilbenes
In the last three decades, the interest in molecules of polyphenolic structure has increased markedly. Natural phenolic compounds are plant secondary metabolites, with two or more phenolic rings. In order to protect themselves, plants produce these phytochemicals in response to exogenous stimuli such as excessive heat or ultraviolet exposures, insect attacks, and infections caused by microorganisms (bacteria or fungus) (Quideau et al., 2011). More than 8000 different phenolic compounds have been identified in the vegetal world. Natural polyphenols are particularly concentrated in fruits, vegetables, in beverages such as chocolate, tea, red wine, or in olive oil (Bravo, 1998).

Due to their antioxidant properties (Fauconneau et al., 1997), they have received an increasing attention in the prevention of various pathologies associated with oxidative stress, such as cancer (Rodriguez-Garcia et al., 2019), cardiovascular diseases, aging (Silva et al., 2019) or in others pathologies such as autoimmune diseases (Khan et al., 2019), infectious diseases (Li et al., 2019) but also in neurodegenerative pathologies (Freyssin et al., 2018). Preventive effects of polyphenols are mainly due to their antioxidant activity, by scavenging free radicals, but recent lines of evidences suggest that, moreover, they can directly target have multiple signaling cascades involved in development of numerous pathologies (Sirerol et al., 2016).

Stilbenes constitutes an important group of non-flavonoid phytochemicals characterized by a 1,2-diphenylethenenu-
pathogenesis in this disease. Senile plaques are constituted by deposition of aggregated β amyloid (Aβ) peptides (Greenwald and Riek, 2010), mostly generated by amyloidogenic metabolism of amyloid precursor protein (APP) by the sequential activity of β- and γ secretases, β-sheet structure of Aβ leading to its aggregation. Rare familial AD are caused by a mutation in one of at least three genes, which code for presenilin 1 (PS1) and 2, two co-factors of γ secretases and for APP. Neurofibrillar tangles are composed by accumulation of hyperphosphorylated tau protein (Mietelska-Porowska et al., 2014). Moreover, these both hallmark proteins seem to present interactions and synergetic effects in AD (Ittner and Gotz, 2011).

Resveratrol, one of the most studied and best known stilbenes, has been associated with a wide range of pharmacological properties and is claimed to have numerous health functional properties (Thomasset et al., 2007; Szkudelska and Szkudelski, 2010, 2015; Petrovski et al., 2011), including in neuronal degenerative pathologies such as AD (Farooqui and Farooqui, 2009; Tellone et al., 2015).

This review focuses on trans-resveratrol and resveratrol derivatives, and their potential role in prevention and/or therapy specifically on one particularly worrying neurodegenerative disorder, AD, in animal models of this disease (Figure 2 and Table 1). These animal models are mainly either mice or rats but they are multiple. Some studies use transgenic animals expressing APP and/or PS1 with familial AD mutations. Other use mice, in which some symptoms of AD were induced by intracerebroventricular injection of Aβ or by bilateral injection of lipopolysaccharide (LPS) into the hippocampus or by intraperitoneal injection of LPS. Mention may also be made of models of sporadic AD, which are accelerated aging mice. Studies which used rats treat them by an injection of Aβ in their lateral ventricle, or by ovariectomy, or by bilateral injection of lipopolysaccharide (LPS) into the hippocampus. However, many studies showed that dietary supplementation of different AD model reduced some markers of this disease but results differ according to the studies.

One study evaluated effects of this supplementation on Tg199589 mice, transgenic animals expressing APP 695 with two familial AD mutations. These AD mice were orally supplemented with trans-resveratrol at 300 mg/kg from 45 to 90 days. After this treatment, neither trans-resveratrol nor its metabolites were detectable in brain. However, this supplementation induced decrease of plaque deposits, in particular in medial cortex, striatum and hypothalamus, without detectable activation of silent mating type information regulation 2 homolog (Sirtuin 1), encoded by the SIRT1 gene, that deacetylates proteins that contribute to cellular regulation (Karuppagounder et al., 2009).

Beneficial Effects of Natural Stilbenes in Alzheimer's Disease

Trans-resveratrol

Most of studies concerning beneficial in vivo roles of stilbenes for AD concern trans-resveratrol, the reference polyphenol, largely quoted in the literature. The neuroprotective effects of this stilbene are mainly due to its capacity to 1) activate the signaling pathways implicated in cellular survival mediated by AMP-activated protein kinase (AMPK), phosphoinositide 3-kinase and Akt, 2) promote synaptic plasticity by extracellular signal-regulated kinase (ERK) 1/2, 3) inhibit pathways involved in apoptosis by decreasing caspase 3 and 12, Bax and cytochrome c expressions, 4) reduce amyloidogenesis and 5) enhance the clearance Aβ. Moreover, resveratrol has 6) antioxidant and 7) anti-inflammatory actions (Cicero et al., 2019).

Trans-resveratrol (trans-3,4′,5-trihydroxystilbene) is a natural polyphenol, firstly insolated in 1940 and found in abundance in red wine. It is largely studied for its beneficial effects on the health, not only in AD but also in many other pathologies such as diabetes, obesity, and cancer. Only significant papers concerning in vivo effects of this stilbene for AD will be taken into account in this review.

Search Strategy and Selection Criteria

Database: PubMed. Date: 1980 – August 2019. Eligibility criteria: reviews, in vivo studies, studies conducted on humans and animals and published in English. Keywords/keyterms: Stilbenes, Alzheimer disease, animal models, in vivo, Trans-resveratrol, Trans ε-viniferin, Gnetin C, Miyabenol C, Trans-piceid, Piceatannol, Astrigenin, Astringin, Pterostilbene.
Moreover, it increased transthyretin level, an \( \alpha\beta \) scavenger, and also raised drebrin, a key post-synaptic protein critical to maintaining proper synaptic function, which is decreased in AD (Varamini et al., 2014).

Effects of trans-resveratrol were also studied in rat models of AD. A first rat model of AD was established by the injection of \( \alpha\beta_{25-35} \) in the lateral ventricle on adult Sprague-Dawley rats leading to a significant alteration in spatial memory and an increase of oxidative stress markers. In this model, the combination of the treatment with trans-resveratrol induced a significant improvement in spatial memory, a reduction in the cellular levels of inducible nitric oxide synthase and lipid peroxidation and an increase in the production of heme oxygenase-1, suggesting anti-oxidative role of this stilbene (Huang et al., 2011).

Another rat model of AD was established by ovariectomy combined injection of D galactose (100 mg/kg). Then, 12 weeks later, a heart perfusion \textit{in vivo} with trans-resveratrol was done. This study established that treatments with 40 and 80 mg/kg of trans-resveratrol induced a decrease in the expression of glial fibrillary acidic protein, more important with the larger dose of trans-resveratrol. Moreover, treatments with 20, 40 and 80 mg/kg of trans-resveratrol decreased the levels of tumor necrosis factor-alpha (TNF-\( \alpha \)) (Cheng et al., 2015).

Moreover, long-term trans-resveratrol consumption protected ovariectomized rats chronically treated with D-galactose against spatial memory impairment, by decreasing...
Table 1 Natural stilbenes effects in AD: in vivo studies cited in the paper

| Natural stilbenes | Research models | Treatments and doses | Effects | References |
|-------------------|-----------------|----------------------|---------|------------|
| **trans-resveratrol** | Tg199589 mice: transgenic animals expressing APP695 with two familial AD mutations | Orally supplementation with trans-resveratrol at 300 mg/kg from 45 to 90 days. Decrease of plaque deposits, in particular in medial cortex, striatum and hypothalamus. | Administration of diet supplemented with 0.35% trans-resveratrol during 15 weeks. Lower amyloid deposition and microglial activation associated with cortical amyloid plaque formation. | Karuppagounder et al., 2009 |
| **trans-resveratrol** | 15 week-old male APP/PS1 transgenic mice (B6C3-Tg(APPsw, PSEN1dE9)) | Administration of a supplemented diet with trans-resveratrol (1 g/kg), between 2 months of age and 9 months of age. Increase of life, activation of AMPK pathways and pro-survival routes (SIRT1). Reduction of cognitive impairment. Neuroprotective role by decreasing the amyloid burden and reducing tau hyperphosphorylation. | | Vingtdeux et al., 2010; Capiralla et al., 2012 |
| **SAMP8 mice (model of sporadic and age-related AD)** | | Administration of a supplemented diet with trans-resveratrol (1 g/kg), between 2 months of age and 9 months of age. Increase of life, activation of AMPK pathways and pro-survival routes (SIRT1). Reduction of cognitive impairment. Neuroprotective role by decreasing the amyloid burden and reducing tau hyperphosphorylation. | | Porquet et al., 2013 |
| **APP/PS1 mice** | | Dietary trans-resveratrol treatment. Absence of decrease plaque burden in these mice. Increase of GS3-β phosphorylation, protein levels of transthyretin and drebrin. | | Varamini et al., 2014 |
| **Adult Sprague-Dawley rats, which are treated by an injection of Aβ25-35 in their lateral ventricle** | | Combination of the Aβ25-35 treatment with trans-resveratrol. Significant improvement in spatial memory. Reduction in the cellular levels of iNOS and lipid peroxidation and increase in the production of HO-1. | | Huang et al., 2011 |
| **Rat model of AD, established by ovariectomy combined injection of D-galactose (100 mg/kg)** | | Heart perfusion in vivo with trans-resveratrol at 20, 40 or 80 mg/kg. Decrease in the expression of GFAP at 40 and 80 mg/kg more important with the larger dose of resveratrol. Decrease of the TNF-α levels for the three concentrations. | | Cheng et al., 2015 |
| **Rat model of AD, established by ovariectomy combined chronic treatment with D-galactose (one intraperitoneal injection per day of d-gal 100 mg/kg for 12 weeks)** | | Daily intraperitoneal injection of piceatannol at 2.5 mg/kg for 6 days. | Amelioration of cognitive status and decrease of cerebral Aβ burden. | Hassaan et al., 2014 |
| **Rat model of AD, established by ovariectomy combined chronic treatment with D-galactose** | | Chronic administration of trans-resveratrol at 20, 40 and 80 mg/kg. Decrease of the insoluble Ab42 level in hippocampus by decreasing the expression of NF-κB. Protection of the BBB integrity, by increasing the expression of Claudin-5 and decreasing RAGE and MMP-9 expressions. | | Zhao et al., 2015 |
| **Rat model of AD, established by ovariectomy combined chronic treatment with D-galactose** | | Treatment by trans-resveratrol (initially 500 mg/kg once daily with dose escalation ending with 1000 mg/kg twice daily) during 52 weeks. | | Turner et al., 2015; Moussa et al., 2017 |
| **Clinical study: mild to moderate AD patients** | | Passage of the BBB by resveratrol and its metabolites to exert their effects. Safety and good tolerance of resveratrol. | Decrease of CSF Aβ42 and Aβ40 levels decline but increase of brain volume by resveratrol treatment Modulation of neuro-inflammation and decrease of cognitive decline. | |
| **Trans ε-viniferin** | Memory loss induced by intracerebroventricular injection with Aβ25-35 in mice | Chronic treatment for 7 days with methanol extract (containing notably trans ε-viniferin) at the concentrations of 50 and 100 mg/kg per os. Inhibition of memory loss. | | Jeong et al., 2010 |
| **Trans ε-viniferin** | Transgenic APPPweePS1de9 mice | Weekly intraperitoneal injection of trans ε-viniferin at the dose of 10 mg/kg or its vehicle from 3 to 6 months of age. | Decrease of amyloid deposits and inflammation in the brain of mice. | |
| **Gnetin C** | Absence of published in vivo studies 12-month-old transgenic APP/PS1 mice | Intracerebroventricular injection into the lateral ventricle for 3 days at the dose of 0.6 µg/g. Reduction of both sAPPβ and soluble Aβ1-40 levels in the cortex and hippocampus. | | Hu et al., 2015 |
| **Miyabenol C** | Absence of published in vivo studies | Intraduodenal administration of trans-ε-viniferin at 0.6 mg/kg. | | |
| **trans-piceid** | Absence of published in vivo studies | Daily intraperitoneal injection of piceatannol at 2.5 mg/kg for 6 days. Amelioration of cognitive status and decrease of cerebral Aβ burden. | | Hassaan et al., 2014 |
| **Piceatannol = Astrignen** | AD induced in adult male Swiss albino mice by unique intraperitoneal injection of LPS at the dose of 0.8 mg/kg | Amelioration of cognitive status and decrease of cerebral Aβ burden. | | |
| **Astrignen** | Absence of published studies | Daily intraperitoneal injection of piceatannol at 2.5 mg/kg for 6 days. Amelioration of cognitive status and decrease of cerebral Aβ burden. | | |
| **Pterostilbene** | SAMP8 mice (model of sporadic and age-related AD) | Daily oral administration of pterostilbene at 20 or 40 mg/kg from 7 days before intrahippocampal administration of LPS. | | Hua et al., 2014 |
| **Learning and memory impairment and changes of microglia and neurons induced in male C57BL/6 mice by bilaterally intrahippocampal injection of LPS** | | | | |

AD: Alzheimer’s disease; Aβ: amyloid-β; AMPK: AMP-activated protein kinase; APP: amyloid precursor protein; BRB: blood-brain barrier; CSF: cerebrospinal fluid; GFAP: glial fibrillary acidic protein; GSK3: glycogen synthase kinase-3; HO-1: heme oxygenase-1; iNOS: inducible nitric oxide synthase; LPS: lipopolysaccharide; MMP-9: matrix metalloproteinase 9; NF-κB: nuclear factor αB; RAGE: receptor for advanced glycation end products; sAPPβ: soluble β-fragment of amyloid precursor protein.
oxidative stress. For this study, intragastric doses of 20, 40 or 80 mg/kg trans-resveratrol were administered daily (Zhao et al., 2012).

Another study of the same authors has evaluated effect of trans-resveratrol on the integrity of blood brain-barrier (BBB). They showed that trans-resveratrol reduced the insoluble Aβ42 level in hippocampus, by decreasing the expression of nuclear factor-kappa B. It also protected the integrity of BBB in these rats, by 1) increasing the expression of claudin-5, a protein implicated in tight junctions, 2) decreasing receptor for advanced glycation end products (RAGE), a protein involved in amyloid influx, and 3) reducing matrix metallopeptidase (MMP)-9, a member of extracellular matrix enzymes which degrade junction proteins and modify the permeability of the BBB (Hu et al., 2015).

Trans ε-viniferin

Trans ε-viniferin is a trans-resveratrol dimer, notably found in Vitis vinifera grapevines and in wines. Only two in vivo studies concerning its effects on AD are described in the literature. The first evaluated its beneficial effects on memory loss, by using a methanol extract from the leaf and stem of Vitis amurensis, which notably contained trans ε-viniferin. Memory loss induced by intracerebroventricular injection with Aβ25-35 in mice was inhibited by chronic treatment for 7 days with this extract at the concentrations of 50 and 100 mg/kg per os (Jeong et al., 2010).

More recently, purified trans ε-viniferin was tested in our lab, on a mouse transgenic model of AD. APPswePS1dE9 mice were treated by weekly intraperitoneal injection of this stilbene at the dose of 10 mg/kg or its vehicle from 3 to 6 months of age. This treatment decreased amyloid deposits, astrogliosis and microglial activation, evaluated by immunofluorescence using W0-2, glial fibrillar acidic protein and Iba-1 respectively, in the brain of mice, reflecting a preventive role for this polyphenol (Caillaud et al., 2019).

Gnetin C

To our knowledge, no in vivo study was described in the literature.

Miyabenol C

Miyabenol C is a trans-resveratrol trimer which can be isolated from the stem and leaf extracts of the small-leaf grape Vitis thunbergii var. taiwania. Its beneficial effects on 12-month-old transgenic APP/PS1 mice by intracerebroventricular injection at the dose of 0.6 μg/g into the lateral ventricle for three days (Hu et al., 2015). This treatment with miyabenol C treatment induced reduction of soluble β-fragment of amyloid precursor protein and a reduction of both soluble toxic Aβ42 and Aβ40 levels, in cortex and hippocampus without modification of insoluble Aβ42, nor Aβ40 levels (Hu et al., 2015).

Trans-piceid

To our knowledge, no in vivo study was described in the literature.

Piceatannol = Astringenin

Piceatannol, also named astringenin, is a metabolite of trans-resveratrol, especially found in red wine, grapes, or white tea. in vivo effects of this hydroxide of trans-resveratrol for AD have been described in only one study (Hassaan et al., 2014), in which AD was induced in adult male Swiss albino mice by unique intraperitoneal injection of LPS at the dose of 0.8 mg/kg. Authors showed that treatment of these mice by daily intraperitoneal injection of piceatannol at 2.5 mg/kg for 6 days ameliorated cognitive status, evaluated by Y maze and object recognition. Moreover, Aβ42 concentration was significantly reduced in the brain of animals that were treated by this stilbene (Hassaan et al., 2014).

Astringin

No study describing effects of this stilbene, neither in vitro nor in vivo, was published to our knowledge.

Pterostilbene

Pterostilbene is a naturally-derived stilbenoid structurally related to resveratrol. It was initially isolated from sandalwood, but is also found in fruits, such as grapes and blueberries.

A first in vivo study compared diet-achievable supplementation of trans-resveratrol or pterostilbene during two months to improve functional impairments and markers of AD in the SAMP8 mice (Chang et al., 2012). Authors showed that, unlike resveratrol, pterostilbene improved cognitive status, evaluated by radial arm water maze, in these mice. Moreover, it decreased markers of 1) cellular stress, such as manganese superoxide dismutase, an endogenous antioxidant defense protein, 2) inflammation such as peroxisome proliferator-activated receptor alpha receptor and 3) AD such as phosphorylated tau. However, neither trans-resveratrol nor pterostilbene increased SIRT1 expression and activation in this model of sporadic AD (Chang et al., 2012).

Another study evaluated the effects of pterostilbene on learning and memory impairment and changes of microglia and neurons induced in male C57BL/6 mice by bilaterally intrahippocampal injection of LPS (Hou et al., 2014). Pterostilbene, orally administrated at 20 or 40 mg/kg everyday from 7 days before intrahippocampal administration of LPS decreased cognitive disorders, evaluated by Y-maze and Morris water maze. Moreover, it significantly decreased the number of microglial Iba-1 positive cells and neuronal precursor doublecortin positive cells and increased neuronal nuclear antigen-stained area of neurons the hippocampus of these mice, suggesting anti-inflammatory and neuroprotective role (Hou et al., 2014).

Discussion

As described above, most studies about beneficial effects of natural stilbenes in animal models concern trans-resveratrol (Table 1 and Figure 2).

The other natural stilbenes are much less studied. Thus, some stilbenes, such as gnetin C (Seino et al., 2018), trans-piceid (Riviere et al., 2007) or piceatannol, also named...
astringenin (Fu et al., 2016), are described only for their in vitro effects. For other, such as trans-ε-viniferin (Riviere et al., 2007; Jeong et al., 2010; Richard et al., 2011, 2013; Pinho et al., 2013; Schuck et al., 2015; Vion et al., 2018) or pterostilbene (Hou et al., 2014; Fu et al., 2016; Li et al., 2016, 2018), most papers describe in vitro experiments and in vivo studies remain rare.

In the opposite, trans-resveratrol was largely described for its effects both in vitro and in vivo, in murine and rat models of AD. However, these encouraging results need to be confirmed in human AD. Although many clinical trials investigating the effect of trans-resveratrol on AD or other conditions associated with this pathology are listed in the NIH clinicaltrials.gov registry, to our knowledge, results of only one clinical study are described in the literature. In this one, mild to moderate AD patients received placebo or trans-resveratrol (initially 500 mg once daily with dose escalation ending with 1000 mg twice daily) during 52 weeks. Authors showed that trans-resveratrol and its metabolites were measurable in plasma and cerebrospinal fluid (CSF) and obviously penetrated the BBB to exert their effects. Moreover, trans-resveratrol was safe and well-tolerated. But results of this clinical study were ambivalent. Indeed, CSF Aβ1-42 and Aβ1-40 levels declined more in the placebo group than in the trans-resveratrol group. However, brain volume loss was increased in the trans-resveratrol treatment group (Turner et al., 2015). This same study showed that trans-resveratrol had effect on some inflammatory proteins. Indeed, it markedly reduced CSF matrix metallopeptidase MMP-9 and increased macrophage-derived chemokine, interleukin (IL)-4, and fibroblast growth factor 2. In the plasma, it increased MMP-10 and decreased IL-12P40, IL-12P70, and chemokine (C-C motif) ligand 5 (CCL5). All these results suggest that trans-resveratrol modulated neuro-inflammation, and induced adaptive immunity. Moreover, this treatment attenuated declines evaluated by mini-mental status examination scores (Moussa et al., 2017). Indeed, a significant decrease in mini-mental status examination score was observed at 52 weeks compared to baseline in the placebo group, but no significant change was detected for this test in the trans-resveratrol treatment group. Alzheimer’s Disease Assessment Scale-activities of daily living scores showed a decline at 52 weeks compared to control in both placebo and trans-resveratrol groups, but the decrease in the placebo group twice as large as that in the trans-resveratrol group at week 52. These results suggest that trans-resveratrol could slow progressive cognitive and functional decline in mild to moderate AD subjects (Moussa et al., 2017).

However, this molecule is rapidly metabolized, mainly in these glucuronidated and sulfated forms and excreted in the urine. Another natural stilbene, pterostilbene, seems more promising than trans-resveratrol. Indeed, methylation of the phenolic hydroxyl could limit the glucuronidation and sulfation processes of pterostilbene, because it provides less conjugating site than resveratrol, resulting in a better metabolic stability (Wang and Sang, 2018). As described above, low doses of pterostilbene, but not resveratrol, were described to be beneficial for AD (Chang et al., 2012). Thus, pterostilbene, which is more metabolically stable and has higher pharmacological activities than resveratrol, could be interesting for clinical trials.

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