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REVIEW PAPER

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Perspectives for gallotannins neuroprotective potential – current experimental evidences

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ABSTRACT

Gallotannins are class of hydrolyzable tannins consisting of gallic acid and a sugar moiety. Currently, there is growing interest around a possible neuroprotective effect of this class of phytochemicals, which is suggested to be a result of their active metabolites. Evidence from experimental studies has suggested that tannin-rich plant preparations might be effective at reversing neurodegenerative pathology and age-related declines in neurocognitive performance. This mini-review summarizes, based on experimental studies, current knowledge about diverse neuroprotective abilities of gallotannins, mostly via antioxidant properties and some mechanisms of the effect are proposed including blocking accumulation of nitrites, inhibiting expression and activity of heme oxygenase 1(HO-1), and decreasing degradation of poly(ADP-ribose) glycohydrolase (PARP).

Keywords: neuroprotection, plant extract, gallotannins, galloylated cyanogenic glycosides, poly(ADP-ribose) glycohydrolase, 1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose.

Introduction

In the last decades, numerous studies on a protective role of plant polyphenols against several chronic diseases, including neurodegeneration, have been published [1, 2]. Currently, substantial interest in health benefits of tannins is emerging, especially regarding their neuroprotective potential [3, 4].

Tannins are a subclass of naturally occurring polyphenols found in both condensed and hydrolyzable forms. Hydrolysable tannins are multiple esters of a sugar moiety and organic acids such as gallic acid in gallotannins or ellagic acid in ellagitannins. Instead, condensed tannins occur as oligomerics or polymerics of flavan-3-ols, mainly derivatives of epicatechin and catechin. Tannins have been reported to exert several biological effects, including antioxidant and free radical scavenging activity as well as antimicrobial, anti-cancer, and cardio-protective properties [5]. Evidence from epidemiological and human intervention studies and animal studies have suggested that tannin-rich plants might be effective at reversing neurodegenerative pathology and age-related declines in neurocognitive performance [3–5]. Despite a great volume of literature data showing various biological effects of polyphenols, including tannins, it is still a matter of debate because of their questionable bioavailability. Most of them are poorly absorbed through the gastrointestinal tract, highly metabolised, and rapidly eliminated [6]. There is also contradictory evidence as to whether polyphenolics may cross the blood–brain barrier or not. How-

ever, recent research on the metabolism, and pharmacokinetics of phenolic compounds have revealed that they can act mainly through metabolites and catabolites formed after their intake [7]. Furthermore, various mechanisms underlying the neuroprotective effects of tannins are proposed. Since the goal of the neuroprotection approach is to limit pathological mechanisms leading to neuronal dysfunction at the molecular level such as: oxidative stress, neuroinflamation, protein aggregation, mitochondrial dysfunction and aberrant cellular signalling [8], herein, this mini-review outlines current knowledge about potential diverse neuroprotective abilities of gallotannins present in different plant preparations (mostly extracts) that are relevant to the mechanisms.

Evidences for neuroprotective properties of gallotannin and its derivatives

Since oxidative damage to neuronal micro-organelles or cell bodies, accumulation of iron ion species and a decrease in the cellular antioxidant pool in the brain play a pivotal role in pathophysiology of neurodegeneration, antioxidant properties of tannins appears to be beneficial for neuroprotection [6; 9]. However, it is suggested that due to low, physiological concentrations polyphenols in brain, including tannins, act rather as "indirect" antioxidants by modulating the activity of antioxidant enzymes [6; 10]. Results of several studies gave directions to the coming to that thesis. Polyphenols have been shown to interact with critical neuronal/glial intracellular signalling pathways involved in memory, neuronal differentiation and neuronal resistance to neurotoxins, including oxidants and inflammatory mediators [10]. Therefore, several experiments have been conducted aimed at demonstrating these neuroprotective properties for tannins [6, 10, 11]. A protective effect of water extract of *Uncaria sinensis* (OLIV.) HAVIL., a main medicinal plant composing Choto-san – a Kampo (traditional medicine of Japan) formula (Diao-Teng-San in Chinese) (consisting of: Atractylodes lancea rhizome, *Poria* sclerotium, *Cnidium* rhizome, *Uncaria* Hook, Japanese *Angelica* root, *Bupleurum* root, and *Glycyrrhiza*) [12–15], on glutamate-induced neuronal death in cultured cerebellar granule cells through the inhibition of Ca2+ influx was presented by Itoh et al [16]. The *Uncaria sinensis* (US) extract in a dose-dependent manner (at concentrations of 10(-5) to 10(-4) g/ml) caused a significant protective effect against glutamate-induced cell death of cultured cerebellar granule cells compared to exposure to glutamate only. In a dose-dependent manner it blocked of the Ca2+ influx into cells by glutamate [16]. These results prompted researchers to investigate whether identified in *U. sinensis* extract tannin compound possess neuroprotective activities. Furthermore, an evidence of neuroprotective property of epicatechin, catechin, procyanidin B-1, procyanidin B-2, hyperin and caffeic acid isolated from the hooks and stems of *Uncaria sinensis* (HSUS) via protection against glutamate-induced neuronal death in cultured cerebellar granule cells by inhibition of Ca2+ influx was provided by Shimada et al. It was shown that the treatment with epicatechin (100–300 uM), catechin (300 uM), procyanidin B-1 (30–300 uM) and procyanidin B-2 (100–300 uM) caused a significant increase of cells viability and inhibition of Ca2+ influx into cells induced by glutamate [17].

Early *in vitro* cell-free studies and cellular assays have revealed that gallotannin, a complex mixture of tannins purified from oak gall, has been shown to inhibit PARG (PARP (poly(ADP-ribose) glycohydrolase – a key enzyme degrading ADP-ribose polymers) activity [18;19]. It was also shown that it significantly reduced oxidative (H2O2)-induced cell death (after 24 and 72 h of H2O2 exposure; 100 nM of gallotannin) in murine astrocytes cell culture with 10-fold more potent activity than the PARG inhibitor benzamide in preventing such process [20]. Another study by Ying et al [21] revealed that gallotannin and nobotanin B (another gallotannin) equally decreased PARG (PARP1) proteins in mouse and astrocytes cell cultures exposed to hydrogen peroxide or N-methyl-d-aspartate (NMDA), the DNA alkylating agent, and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) compared to reference benzamide causing their marked reduction. Gallotannin and benzamide both prevented the NAD(+) depletion resulting from PARP1 activation by MNNG or H(2)O(2), with opposite effects on protein poly(ADP-ribosyl)ation. In this case benzamide decreased, while the gallotannin showed tendency to increase of poly(ADP-ribose) proteins accumulation during MNNG exposure in neuron cultures. Thus, results obtained by Ying et al. suggest that PARG inhibitors do not inhibit PARP1 directly, but instead prevent PARP1-mediated cell death by slowing the turnover of poly(ADP-ribose) and thus slowing NAD(+) consumption. One possible explanation for why gallotannin treatment leads to an apparent accumulation of PARG proteins may be it unspecific binding to biomolecules and protein staining [21].

Another, a complex experiment giving the evidence that gallotannin is an inhibitor of PARG was made by Falsig et al., however the result showed that such activ-

ity is not specific, and that it rather does not work in cells [22]. For this purpose a comparison of the PARG inhibitory activities between tannic acid, gallotannin and compound N-bis-(3-phenyl-propyl)-9-oxo-fluorene-2,7-diamide (GPI 16552 – a potentially specific PARG inhibitor) was made in an *in vitro* cell-free experiment and in three PARP-1-dependent cell death (murine fetal astrocytes) models plus one inflammation model in primary astrocytes [22]. Moreover, an ability of gallotannin to inhibit recombinant human PARG was also examined. It was found that it was indeed an inhibitor of PARG as previously shown. However, results from these experiments showed that gallotannin (neither the reference inhibitor – GPI 16552) in conducted experimental cellular death models not fully effectively inhibited PARG activity. The IC50 of gallotannin in a PARG assay based on a cellular lysate was increased to about 150 uM. In primary astrocytes studied gallotannin dose dependently (10 – 50uM; 30 min exposition) blocked almost completely all cell death in the H2O2 and SIN-1 models, but in the MNNG model did not rescue cells – it enhanced cell death in a concentration-dependent fashion. Its action in this case was different from that observed in the case of GPI 16552 which did not gave any effect in MNNG model (in the concentration range 20, 40, 60, 80, 100, 120, 140 uM), even at highest concentrations (in SIN-1-induced cell death a small effect was seen at high GPI concentrations). This effect could be due to strong unspecific protein binding. Unspecific protein binding by gallotannin possibly also inhibited NOs as described in cell-free systems [23–25]. Authors indicated that this molecule might apparently "inhibit PARG", because it causes DNA strand breaks that activate PARP [26]. Such quite strong antioxidant effects of gallotannin against H2O2 could also be due to its strong iron chelating effects [27]. Further analysis revealed that two other gallotannin-similar, polyphenolic compounds – quercetin (five phenol groups and one resonating oxo group) and catechin (five phenol groups) blocked cell death in the hydrogen peroxide model at concentrations similar to gallotannin, suggesting that PARG inhibition is not necessary for cytoprotection by this tannin only. Authors statement that its ability to effectively penetrate the cell membrane may be questionable should be here highlighted [22].

In H2O2-activated cells a decrease of PAR staining was observed and was in opposite of what was previously reported and inconsistent with PARG inhibition [28]. If gallotannin acted as a PARG inhibitor, a delay in the decay of PAR, and thus a prolonged PAR accumulation would be expected, which was not observed. Studied gallotannin (similarly to GPI-16552) after exposure of astrocytes with 1mM of H2O2 did not enhanced the staining for PAR at any time point of experiment duration (0 – 30 min) which may suggest its unselective PARG inhibition due to the fact that, according to authors, a selective PARG inhibitor is expected to enhance PAR accumulation and/or delayed the time-dependent loss PAR presence. A possible inhibition of PARP was also visible in HeLa cells at concentration of gallotannin above 100 uM which caused a significant increase of PAR accumulation [28]. And this effect from experiment in HeLA cells was opposite to results from Ying et al [21]. According to the authors, it is not excluded that the activity of other cellular PAR-hydrolysing enzymes could be responsible for the lack of a PAR accumulation in cells treated with specific PARG inhibitors [22, 28]. In sum, observed protective effects from H2O2 at 5–10 uM, i.e., 10- to 15-fold below the IC50 values of gallotannin in cell extracts again suggested that gallotannin does not protect due to PARG inhibition [28].

A significant anti-inflammatory potential of gallotannin correlated with its antioxidant properties was also emphasized in cell-free conditions (concentrations: 0; 1; 5; 10; 20 uM) and in a validated model of primary astrocyte inflammation (stimulated with a complex mixture of proinflammatory cytokines (CCM) containing TNF-a, interleukin-1h, and IFN-g) involving the production of NO [22]. In this experiment gallotannin blocked the accumulation of nitrite (concentrations: 0; 2.5; 5; 7.5; 10 uM) to a similar extent and with a concentration–dependent manner, thus it acted as a scavenger of NO without ever interfering with cellular processes. Interestingly, this inhibition was not due to transcriptional or translational inhibition, because gallotannin rather increased the levels of iNOS protein [22]. Further *in vitro* (non-cellular) experiments also indicated the ability of studied gallotannin to inhibition of PARG (PAR degradation) (almost completely at 5–10 uM concentration) which suggest that this compound was indeed a potent *in vitro* inhibitor of PARG. This effect was even stronger than observed in the case of reference GPI-16552 [19]. Based on above studies it was concluded that gallotannin is a PARG inhibitor in cell-free assays and acts as a strong antioxidant that can protect cells from oxidative stress. Moreover, high concentrations of gallotannin may be required to inhibit PARG in complex biological system. However, the concentration used in the cell lysates-based PAR accumulation assays would cause massive cell death in other cellular system. Authors hypothesized also

that due to the fact that no effect in intact cells and no penetration in studied monolayer was detected it could be suggested that gallotannin is cell impermeable and mediates its effect extracellularly by lowering the concentrations of reactive oxygen species, and therefore its activity can be linked to the extracellular oxidative system. However, so far, no evidence suggesting its penetration through the cellular monolayer were found [22]. Hence, the biological activity of gallotannin in cells is still the subject of scientific inquiry.

It is also suggested that biological activity of tannins is strongly dependent on number of gallated rings. Choi et al [29] revealed that the 1,2,3,4,6-Penta-O-galloyl-beta-D-glucose (PGG) (10–50 uM), a major component of the crude *Paeonia suffruticosa* ANDREWS root (*Ranunculaceae*), was able to protect neuronal Neuro 2A cells from oxidative stress via the significant, concentration- and time-dependent induction of HO-1 (heme oxygenase 1; an inducible stress protein that degrades heme to the neuroactive molecule, carbon monoxide and the anti-oxidant, biliverdin) gene expression and its activity. Pretreatment of these cells with PGG resulted in enhanced cellular resistance to hydrogen peroxide [29]. Tan et al [30] demonstrated that several gallotannins (1,2,3-tri-O-galloyl-β-D-glucose; 1,4,6-tri-O-galloyl-β-D-glucose; 3,4,6-tri-O-galloyl-D-glucose; 1,2,3,6-tetra-O-galloyl-β-D-glucose; 1,2,3,4,6-penta-O-galloyl-β-D-glucose (PGG); 3,6-di-O-galloyl-D-glucose), among others bio-active compounds like galloylated cyanogenic glycosides, isolated from the leaves (ethyl acetate extract or aqueous extracts, respectively) of *Phyllagathis rotundifolia* (*Melastomataceae*) exhibited remarkable neuroprotective activities against oxidative damage *in vitro* in neuroblastoma-glioma hybrid NG108–15 cells as compared to galloylated cyanogenic glucosides and ellagic acid derivatives in a dose-dependent manner. Analyzed gallotannins also increased the neuroblastoma-glioma hybrid cell viability in a dose dependent manner. The compound PGG and 1,2,3,6- tetra-O-galloyl-β-D-glucose significantly inhibited H2O2-induced neuron cells damage in a dose-dependent manner at concentrations of 6.25–100 μM. The inhibitory activity of 1,2,3,6-tetra-O-galloyl-β-D-glucose was comparable to that of catechin. However, the neuroprotective activity of PGG was more potent than that of catechin [30]. This compound has also been reported to not only increase the cellular resistance to H2O2 but also highly protected neuronal cells from H2O2-induction damage via induction of HO-1 gene expression [29, 30]. According to Warden et al., the level of galloylated catechins in human urine after black tea consumption was 10-fold lower than that of non-galloylated catechins, which strongly indicates that galloylation increases resorption of catechins [31].

Among many different polyphenol subgroups, gallotannins have been relatively poorly examined in the context of the anti-amyloidogenic activities. Only few publications have appeared in recent years documenting their strong neuroprotective abilities. It has been shown, for example, that PGG exhibited a strong anti-aggregation effect on β-amyloid in Alzheimer disease [32]. An in vitro SK-N-SH cell line experiment demonstrated that PGG isolated from *Paeonia suffruticosa* at the 3 μM concentration inhibits Aβ1–42 fibrils formation of over 50%, while the 100 μM concentration completely inhibits formation of Aβ1–42 fibrils. Fujiwara and co-workers have also demonstrated that PGG oral administration to mice Tg2576 APPswe race 8 mg/kg/day strongly decreased level of Aβ1–40 aggregates (from 4000 pmol/g brain to about 2500 pmol/g brain). In the case of aggregates of Aβ1–42 the dose was approximately 100 pmol/g brain in the control and about 50 pmol/g brain in animals used in studies [32]. Another compound – tannic acid – turned out to be a natural β-secretase inhibitor that prevented cognitive impairment and mitigates AD pathology in PS/APP transgenic mice. In addition, it reduced the effects of Alzheimer's like neuropathology in mice overproducing Aβ1–40 and Aβ 1–42 [33]. Another in vivo studies by Hartman et al. showed that in other transgenic mice (strain APP_{SW} / Tg2576) who drank the pomegranate juice (containing 115 ppm of ellagic acid, 5 ppm of gallic acid, 1880 ppm of hydrolysable tannins; among them: gallotannins, ellagitannins, punicalagin and 369 ppm of anthocyanins and their glucosides) the level of Aβ plaques and fibrils in both the hippocampus and cortex dorsal has been decreased [34]. Determining which of these compounds showed these properties and with which intensity requires further complex research.

Conclusions

Summarizing, data presented in this manuscript provide some evidences about the neuroprotective potential of gallotannins. However, their mechanism of actions remains still not fully understood. Therefore, it is highly justified to further explore the mechanism of this class of natural-origin protective agents against neurodegeneration. The complex knowledge about their polypharmacological activities may be of significance for neuroprotection.

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Conflict of interest statement
The authors declare no conflict of interest.

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