Protection of the brain through supplementation with larch arabinogalactan in a rat model of vascular dementia

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BACKGROUND/OBJECTIVES: Vascular dementia (VaD) caused by reduced blood supply to the brain manifests as white matter lesions accompanying demyelination and glial activation. We previously showed that arabinoxylan consisting of arabinose and xylose, and arabinose itself attenuated white matter injury in a rat model of VaD. Here, we investigated whether larch arabinogalactan (LAG) consisting of arabinose and galactose could also reduce white matter injury.

MATERIALS/METHODS: We used a rat model of bilateral common carotid artery occlusion (BCCAO), in which the bilateral common carotid arteries were exposed and ligated permanently with silk sutures. The rats were fed a modified AIN-93G diet supplemented with LAG (100 mg/kg/day) for 5 days before and 4 weeks after being subjected to BCCAO. Four weeks after BCCAO, the pupillary light reflex (PLR) was measured to assess functional consequences of injury in the corpus callosum (cc). Additionally, Luxol fast blue staining and immunohistochemical staining were conducted to assess white matter injury, and astrocytic and microglial activation, respectively.

RESULTS: We showed that white matter injury in the cc and optic tract (opt) was attenuated in rats fed diet supplemented with LAG. Functional consequences of injury reduction in the opt manifested as improved PLR. Overall, these findings indicate that LAG intake protects against white matter injury through inhibition of glial activation.

CONCLUSIONS: The results of this study support our hypothesis that cell wall polysaccharides consisting of arabinose are effective at protecting white matter injury, regardless of their origin. Moreover, LAG has the potential for development as a functional food to prevent vascular dementia.

Keywords: Larix, hypoxia, carotid artery, white matter, functional food

INTRODUCTION

Vascular dementia (VaD), which impairs cognitive abilities, is the second most common type of dementia, accounting for approximately 15-20% of all dementia patients [1,2]. VaD results from inadequate blood supply to the brain caused by occlusion or rupture of cerebral arteries [1]. Because of its diverse etiologies, VaD can be classified into various subtypes, including hypoperfusion dementia, subcortical VaD, multi-infarct dementia, and strategic infarct dementia [2,3].

Several animal models that mimic VaD have been developed to study VaD [1,4]. Of these, the bilateral common carotid artery occlusion (BCCAO) model in rats is the most commonly used. In this model, white matter lesions manifest axonal and myelin injury, vacuolization, and glial cell activation [1,4]. Thus, the rat BCCAO model mimics hypoperfusion dementia and subcortical VaD in that white matter injury is consistently observed in both subtypes [3,4]. In hypoperfusion dementia, one etiology is caused by partial or complete blockage of the carotid arteries [3,4]. In humans, carotid artery stenosis or occlusion was found to be associated with white matter injury [3], which is observed in the regions including the corpus callosum (cc) [5,6] and optic nerve [7], a bundle of which forms the optic tract (opt) in the visual pathway (Fig. 1). In the rat BCCAO model, optic nerve injury correlates with loss of the pupillary light reflex (PLR), a reflex that controls the pupil diameter in response to light intensity [8]. Conversely, in the subcortical VaD, the most common form of VaD, one etiology is caused by partial blockage of small vessels, which also leads to white matter injury [3,9].

As there are no treatments approved by the FDA, it is imperative to develop agents to treat VaD [1,2]. We previously showed that hot water extract of ground wheat [10] and wheat bran (WBE) [11] reduced brain injury in a rat BCCAO model, demonstrating that processed wheat can be developed as a functional food for prevention of VaD. We also found that arabinoxylan, a cell wall polysaccharide consisting of arabinose and xylose, and arabinose itself were the active components responsible for the efficacy [10]. These findings suggest that any polysaccharides containing arabinose might show similar efficacies. Of the cell wall polysaccharides constituting wheat
cell walls, arabinogalactan-peptide is also a candidate in addition to arabinoxylan, because arabinogalactan-peptide is composed of 92% polysaccharide arabinogalactan and 8% peptides [12,13], and the arabinogalactan domain in arabinogalactan-peptide consists of arabinose and galactose [12]. To test the hypothesis that arabinogalactan-peptide in wheat is also an active component, we selected commercially available LAG as a model polysaccharide representing arabinogalactan-peptide. We then investigated whether larch arabinogalactan (LAG) supplementation could reduce white matter injury and improve PLR in a rat BCCAO model.

MATERIALS AND METHODS

Materials
LAG (82 wt % galactose and 13 wt % arabinose, along with several unidentified, minor compounds) was purchased from Sigma-Aldrich (St. Louis, MO, USA).

Animals
Eight-week-old male Sprague Dawley (SD) rats (280-300 g) were purchased from Samtaco Inc. (Osan, Gyeonggi-do, Republic of Korea). Animals were housed with diet and water available ad libitum before the start of the experiment, and diurnal lighting conditions and temperature-controlled environments were maintained throughout the experiment [10,11]. Experiments were conducted according to the guidelines for animal care and protocols on laboratory animal use approved by the Institutional Animal Care and Research Advisory Committee of Catholic University, Daegu, Republic of Korea (Approval No. 2013-0820-CU-AEC-10-Y).

Diet preparation
Diets containing LAG were prepared as previously described [14]. For the LAG diet (1 kg), a mixture of LAG (2 g) and corn starch (48 g) was added to 950 g of a modified AIN-93G diet [15] purchased from Unifaith Inc. (Seoul, Republic of Korea) (Table 1). For the basal diet (1 kg), 50 g of corn starch was added to 950 g of the modified AIN-93G diet.

Table 1. Composition of experimental diets

| Ingredient          | Modified AIN-93G diet (g/kg) | Basal diet (g/kg) | LAG diet (g/kg) |
|---------------------|-----------------------------|------------------|-----------------|
| Casein              | 250.0                       | 250.0            | 250.0           |
| Corn starch         | 482.5                       | 482.5            | 482.5           |
| Sucrose             | 100.0                       | 100.0            | 100.0           |
| Soybean oil         | 70.0                        | 70.0             | 70.0            |
| Mineral mix         | 35.0                        | 35.0             | 35.0            |
| Vitamin mix         | 1.0                         | 1.0              | 1.0             |
| Choline bitartrate  | 2.5                         | 2.5              | 2.5             |
| Corn starch         | -                           | 50.0             | -               |
| LAG                 | -                           | -                | 2.0             |

Diets containing LAG were prepared in a pre-mixed form.

\(1\) One kg of basal diet was prepared by adding 50 g of corn starch to 950 g of the modified AIN-93G diet.
\(2\) One kg of LAG diet was prepared by adding 50 g of a mixture of corn starch and LAG to 950 g of the modified AIN-93G diet. The LAG diet of 100 mg/kg/day refers to the corresponding dose of LAG given per kg of rat body weight per day.
\(3\) The amount of LAG for the LAG dose (100 mg/kg/day) was calculated based on data showing that a 300 g rat consumes 15 g of LAG diet/day.

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LAG, larch arabinogalactan.

Diet administration [11]
Rats were randomly divided into three groups: (1) sham (n = 6), (2) control (n = 6), and (3) LAG-treated group (100 mg/kg/day) (n = 6). The 100 mg/kg/day dose of LAG was selected based on our previous findings that WBE consisting of 2.4 wt% arabinose significantly reduced white matter injury at a dose of 400 mg/kg/day in the same rat BCCAO model [10]. Therefore, the arabinose dose that is an active component in the same rat BCCAO model [11] is equivalent to approximately 10 mg/kg/day in 400 mg/kg/day WBE. To match 10 mg/kg/day arabinose, we selected a dose of LAG at 100 mg/kg/day because LAG consists of approximately 10% arabinose. In the LAG-treated group (100 mg/kg/day), rats received LAG diet for 5 days before and 4 weeks after bilateral common carotid artery ligation. The amount of LAG diet fed to each rat at the beginning of the experiment was 15 g to give a LAG dose of 100 mg/kg/day based on the assumption that the rats weighed 300 g (Table 1). The amount of LAG diet fed to the rats then increased in proportion to the rise in rat weight because the rats gained weight as the experiment progressed. In the sham and control groups, rats received the basal diet only. Once the rats consumed all of the LAG or basal diet, more basal diet was provided ad libitum.

Bilateral common carotid arteries occlusion (BCCAO)
The rat bilateral common carotid arteries were ligated to mimic vascular dementia as previously described [10,11]. The male SD rats were anesthetized through isoflurane inhalation (Hana Pharmaceutical Inc., Seoul, Republic of Korea) throughout the surgical procedure. The bilateral common carotid arteries in the control and LAG-treated groups were exposed and ligated permanently with silk sutures. The rats in the sham group underwent the same experimental procedure without ligation. Four weeks after BCCAO, the PLR was examined, after which the rats were anesthetized again through isoflurane inhalation, and their brains were harvested for further study.
After formalin fixation and paraffin-embedding, 5-μm-thick sections including the corpus callosum (cc), optic tract (opt), and internal capsule were cut. Injury as previously described [11]. Briefly, the harvested brain was cut into slices including the cc, opt, and internal capsule, and incised by isoflurane inhalation, after which their brains were harvested for Luxol fast blue staining. The areas of the slices were cut with a knife and were then incubated with avidin-biotin peroxidase (Elite Vectastain ABC kit, Vector Laboratories, Burlingame, CA, USA) against GFAP and Iba1. Sections were then incubated with biotinylated secondary antibody (1:200, Vector Laboratories, Burlingame, CA, USA) against GFAP and Iba1. Sections were then incubated with primary antibodies against glial fibrillary acidic protein (GFAP, 1:100, BD PharMingen, San Diego, CA, USA) or ionized calcium binding adaptor molecule 1 (Iba1, 1:200, Wako, Osaka, Japan). After washing, the sections were treated with avidin-biotin peroxidase (Elite Vectastain ABC kit, Vector Laboratories, Burlingame, CA, USA), after which they were visualized with diaminobenzidine (Roche, Mannheim, Germany). Immunostained sections were subsequently captured using an Olympus microscope (200×) (Olympus Corporation, Tokyo, Japan), after which quantitative analysis was performed using the ImageJ software (NIH, v1.47). The area covered by GFAP-positive astrocytes and Iba1 positive microglia was computed as a percentage of the total area. To assess the GFAP- and Iba1-positive levels, the relative values for the control and LAG-treated groups were calculated by setting those for the sham group at 100%.

**Statistical analysis**

Values were expressed as the means ± SEM. Statistical analysis for multiple comparisons consisted of one-way ANOVA followed by the Dunnett post hoc test, which were conducted using the SPSS software (IBM SPSS Statistics; version 19, Armonk, NY, USA). For all data, Shapiro-Wilk and Levene statistics were applied a priori to verify normality and homogeneity of variances, respectively. A P < 0.05 was considered to indicate statistical significance.

**RESULTS**

**LAG Supplementation reduces white matter injury in the corpus callosum and optic tract**

To examine whether LAG supplementation can reduce white matter injury, LAG (100 mg/kg/day) was supplemented for 5 days before the rats underwent BCCAO surgery, and supplementation continued for another 4 weeks after surgery (Fig. 2A). Of the regions in white matter, we focused on myelin injury incurred in the cc and opt because they are more vulnerable to hypoperfusion generated through BCCAO than other regions.
including the internal capsule, because of the levels of blood supply to the regions [11].

To assess the white matter injury that manifests disarrangement and disappearance of nerve fibers consisting of axons and the myelin sheath, Luxol fast blue staining was used to observe changes in myelin structure. In the control group, white matter injury that manifests white matter rarefaction accompanying vacuolization was observed in both the cc and opt (Fig. 2B). In contrast, in the LAG-treated group, this white matter injury was reduced in both the cc and opt, compared with the control group (Fig. 2B). The severity of white matter injury was then quantitatively assessed using a grading system (0-3) (Fig. 2C). The grading scores were significantly reduced in the LAG-treated group by 51% (0.94 ± 0.29 vs. 1.92 ± 0.14, P < 0.01) in the cc, and by 63.5% (0.96 ± 0.35 vs. 2.63 ± 0.21, P < 0.01) in the opt, respectively, compared with the control group (Fig. 2C). These findings indicate that LAG supplementation protects against white matter injury attributed to hypoperfusion in the rat BCCAO model.

**LAG supplementation improves PLR**

Because degeneration of the optic nerve that is connected to the opt causes PLR loss in a BCCAO model [8,11] (Fig. 1), we investigated whether LAG supplementation that reduced the opt injury could improve PLR. In the sham group, all six (100%) rats exhibited bilateral PLR, showing that all rats maintained normal PLR function in the sham group, as expected (Table 2). However, in the control group, five (83%) rats suffered bilateral PLR loss, while only one (17%) exhibited bilateral PLR exhibition. These findings indicate that five rats lost PLR function in both eyes, while one rat maintained normal PLR function in the control group. Conversely, two (33%) and two (33%) rats suffered bilateral and unilateral PLR loss, respectively, in the LAG-treated group, while two (33%) exhibited bilateral PLR. These findings indicate that two rats lost PLR function in both eyes, two lost PLR function in one eye, and two maintained normal PLR function in the LAG-treated group. Therefore, LAG supplementation improved PLR function by shifting two rats from bilateral PLR loss to unilateral PLR loss, and by shifting one rat from bilateral PLR loss to bilateral PLR exhibition. These findings suggest that LAG intake can improve the PLR.

**LAG supplementation inhibits astrocytic activation in the cc**

As chronic hypo-perfusion generated in a rat BCCAO model also triggers microglial activation accompanying morphological transformation and proliferation of microglia [16,17], we investigated whether LAG supplementation can modulate microglial activation through immunohistochemical staining of Iba1, a biomarker specific for microglia in the brain [19]. In the control group, increases in the number of Iba1-positive microglia proliferation of astrocytes [16,17], we investigated whether LAG supplementation can modulate astrocytic activation through immunohistochemical staining of GFAP, a biomarker specific for astrocytes in the brain [18]. In the control group, increases in the number of GFAP-positive astrocytes were observed in both the cc and opt, compared with the sham group. In contrast, in the LAG-treated group, decreases in the number of GFAP-positive astrocytes were observed in the cc compared with the sham group (Fig. 3A). The degree of astrocytic activation was then quantitatively assessed through measurement of the area covered by GFAP-positive astrocytes (Fig. 3B). The relative total area in the LAG-treated group was significantly attenuated in the cc compared with the control group (106.3 ± 5.8 vs. 148.8 ± 13.1, P < 0.05), whereas the relative total area tended to be reduced in the opt compared with the control group (171.1 ± 25.3 vs. 209.9 ± 31.2, P > 0.05) (Fig. 3B). These findings showed that LAG intake can inhibit astrocytic activation.

**Fig. 3 Immunohistochemical staining of astrocytes.** (A) Representative photomicrographs of astrocytes stained against GFAP with immunohistochemical techniques (100×): (a), (d) sham group; (b), (e) control group; (c), (f) LAG-treated group; (a-c) and (d-f) were taken from the cc and opt, respectively. (B) Quantitative analysis of GFAP-positive cells. The relative areas of GFAP-positive cells in the cc and opt were presented by setting the area of GFAP-positive cells for the sham group to 100%. The numbers of rats used in the sham, control and LAG-treated groups were 6, 6 and 6, respectively. **P<0.01, *P<0.05 vs. control group, GFAP, glial fibrillary acidic protein; LAG, larch arabinogalactan.
of expression of NF-κB by astrocytes under conditions of injury and astrocytic activation, while preserving memory function [24]. These results suggest that astrocytic activation exerts deleterious effects on myelin injury. In addition, hot water extract of ground wheat [10] and WBE [11] also reduced myelin injury and astrocytic and microglial activation, and improved visuospatial memory [10].

Previously, damage to the cc and opt were shown to be accompanied by activation of astrocytes and microglia in rat BCCAO models [20] and human VaD patients [21,22]. Activation of nuclear factor kappa-B (NF-κB), an inflammatory cytokine, in astrocytes contributes to neuronal degeneration [23]. Inhibition of expression of NF-κB by astrocytes under conditions of astrocytic activation in a mouse model of bilateral common carotid artery stenosis ameliorated myelination injury and astrocytic activation, while preserving memory function [24]. These results suggest that astrocytic activation exerts deleterious effects on myelin injury. In addition, hot water extract of ground wheat [10] and WBE [11] also reduced myelin injury and astrocytic and microglial activation, and improved visuospatial memory [10]. In our previous study, we showed that supplementation of hot water extract of ground wheat, arabinose, and arabinose reduced white matter injury in a rat BCCAO model. These findings indicate that reduction of glial activation contributes to maintenance of white matter structure in VaD. Therefore, reduction of glial activation through LAG intake may also contribute to the reduced damage in the cc and opt observed in the present study.

PLR is mediated from the retina through the optic nerve, opt, pretectal nucleus, and oculomotor nerve to the pupillae muscle [25] (Fig. 1). Because LAG intake improved PLR in the model, it should protect axons involved in the PLR pathways. Therefore, injury reduction in the opt by LAG intake should help improve the PLR. In addition, it is highly likely that LAG intake also protected the retinal and optic nerves. This conclusion is supported by the findings that PLR loss was accompanied by retinal and optic nerve degeneration in rat BCCAO models [8,26]. Similar to those observed in rat BCCAO models, injury to the retinal nerve [27] and optic nerve [7] was also observed in human carotid artery occlusion, which is associated with dementia [28]. Moreover, patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a model of pure small-vessels disease that progresses to subcortical VaD, display damage to the retinal [29,30] and optic nerves [29,31]. Therefore, LAG intake may contribute to improved cognition in VaD patients through protection of the opt.

The cc is the principal interhemispheric commissure, and its integrity is crucial for cognition [32], including visual memory [33]. As expected, the cc in subcortical VaD patients shows axonal injury and astrocytic activation assessed through Luxol fast blue staining and GFAP immunohistochemical staining, respectively [34]. In addition, the cc in the subcortical VaD also shows reduced integrity when assessed through magnetic resonance imaging [35,36]. Therefore, LAG intake may contribute to improved cognition in VaD patients through protection of the cc. Taken together, the findings from this study indicate that prophylactic LAG intake can prevent VaD by protecting myelinated axons. Consistent with these findings, intake of a polysaccharides blend, including arabinogalactan as a major constituent, improved memory for healthy middle-aged adults [37].

In our previous study, we showed that supplementation of hot water extract of ground wheat, arabinoxylan, and arabinose reduced white matter injury in a rat BCCAO model [10]. In this study, we showed that supplementation of the rat diet with LAG as a model polysaccharide for arabinogalactan-peptide in wheat also reduced white matter injury in the same BCCAO model. These results suggest that arabinogalactan-peptide in wheat also reduced white matter injury in a rat BCCAO model. These findings indicate that reduction of glial activation contributes to maintenance of white matter structure in VaD. Therefore, reduction of glial activation through LAG intake may also contribute to the reduced damage in the cc and opt observed in the present study.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

REFERENCES

1. Venkat P, Chopp M, Chen J. Models and mechanisms of vascular dementia. Exp Neurol 2015;272:97-108.
2. O’Brien JT, Thomas A. Vascular dementia. Lancet 2015;386:1698-706.
3. Iadecola C. The pathobiology of vascular dementia. Neuron 2013;80:844-66.
4. Jiwa NS, Garrard P, Hainsworth AH. Experimental models of vascular dementia and vascular cognitive impairment: a systematic review. J Neurochem 2010;115:814-28.
5. Yamauchi H, Fukuyama H, Harada K, Nabatame H, Ogawa M, Ouchi Y, Kimura J, Konishi J. Callosal atrophy parallels decreased cortical oxygen metabolism and neuropsychological impairment in Alzheimer’s disease. Arch Neurol 1993;50:1070-4.
6. Lin CJ, Chang FC, Chou KH, Tu PC, Lee YH, Lin CP, Wang PN, Lee IH. Intervention versus aggressive medical therapy for cognition in severe asymptomatic carotid stenosis. AJNR Am J Neuroradiol 2016;37:1889-97.
7. Terelak-Borys B, Skonieczna K, Grabska-Liberek I. Ocular ischemic syndrome - a systematic review. Med Sci Monit 2012;18:RA138-44.
8. Stevens WD, Fortin T, Pappas BA. Retinal and optic nerve degeneration after chronic carotid ligation: time course and role of light exposure. Stroke 2002;33:1107-12.
9. Román GC, Erkinjuntti T, Wallin A, Pantooni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol 2002;1:426-36.
10. Han HS, Jang JH, Jang JH, Choi JS, Kim YJ, Lee C, Lim SH, Lee HK, Lee J. Water extract of Triticum aestivum L. and its components demonstrate protective effect in a model of vascular dementia. J Med Food 2010;13:572-8.
11. Lim SH, Lee J. Hot water extract of wheat bran attenuates white matter injury in a rat model of vascular dementia. Prev Nutr Food Sci 2014;19:145-55.
12. Fincher GB, Sawyer WH, Stone BA. Chemical and physical properties of an arabinogalactan-peptide from wheat endosperm. Biochem J 1974;139:535-45.
13. Van den Bulck K, Swennen K, Loosveld AM, Courtin C, Brijs S, Delcour J. Isolation of a protein from cereal arabinoxylan. Biochem J 2005;41:59-67.
14. Lim SH, Kim MY, Lee J. Apple pectin, a dietary fiber, ameliorates experimental cerebral hypoperfusion: an immunohistochemical study. Acta Neuropathol 2005;110:91-9.
15. Nishimura N, Tanabe M, Fujimoto Y, Makita Y, Ohata M, Yokoyama S, Asano M, Yamamoto T, Kiriya S. Pectin and high-amylose maize starch increase caecal hydrogen production and relieve hepatic ischemia-reperfusion injury in rats. Br J Nutr 2012;107:485-92.
16. Wakita H, Tomimoto H, Akiyoshi I, Kimura J. Glial activation and white matter changes in the rat brain induced by chronic cerebral hypoperfusion: an immunohistochemical study. Acta Neuropathol 1994;87:484-92.
17. Farkas E, Donka G, de Ros VA, Mihály A, Bari F, Luiten PG. Experimental cerebral hypoperfusion induces white matter injury and microglial activation in the rat brain. Acta Neuropathol 2004;108:57-64.
18. Tykhomirov AA, Pavlova AS, Nedzvetsky VS. Glial fibrillary acidic protein (GFAP) on the 45th anniversary of its discovery. Neurophysiology 2016;48:54-71.
19. Imu Y, Kohsaka S. Intracellular signaling in M-CSF-induced microglia...
activation: role of Iba1. Glia 2002;40:164-74.
20. Farkas E, Luiten PG, Bari F. Permanent, bilateral common carotid artery occlusion in the rat: a model for chronic cerebral hypoperfusion-related neurodegenerative diseases. Brain Res Rev 2007;54:162-80.
21. López-Valdés HE, Martínez-Coria H. The role of neuroinflammation in age-related dementia. Rev Invest Clin 2016;68:40-8.
22. Rosenberg GA, Bjerke M, Wallin A. Multimodal markers of inflammation in the subcortical ischemic vascular disease type of vascular cognitive impairment. Stroke 2014;45:1531-8.
23. Liu Z, Chopp M. Astrocytes, therapeutic targets for neuroprotection and neurorestoration in ischemic stroke. Prog Neurobiol 2016;144:103-20.
24. Saggau R, Schumacher T, Gerich F, Rakers C, Tai K, Delekate A, Petzold GC. Astroglial NF-κB contributes to white matter damage and cognitive impairment in a mouse model of vascular dementia. Acta Neuropathol Commun 2016;4:76.
25. McDougal DH, Gamlin PD. Autonomic control of the eye. Compr Physiol 2015;5:439-73.
26. Lavinsky D, Arterni NS, Achaval M, Netto CA. Chronic bilateral common carotid artery occlusion: a model for ocular ischemic syndrome in the rat. Graefes Arch Clin Exp Ophthalmol 2006;244:199-204.
27. Gunes A, Demirci S, Umul A. Vision loss and RNFL thinning after internal carotid artery occlusion and middle cerebral artery infarction. Acta Inform Med 2014;22:413-4.
28. Klijn CJ, Kappelle LJ. Haemodynamic stroke: clinical features, prognosis, and management. Lancet Neurol 2010;9:1008-17.
29. Pretegiani E, Rosini F, Dotti MT, Bianchi S, Federico A, Rufa A. Visual system involvement in CADASIL. J Stroke Cerebrovasc Dis 2013;22:1377-84.
30. Parisi V, Pierelli F, Coppola G, Restuccia R, Ferrazzoli D, Scassa C, Bianco F, Parisi L, Fattapposta F. Reduction of optic nerve fiber layer thickness in CADASIL. Eur J Neurol 2007;14:627-31.
31. Rufa A, Malandrini A, Dotti MT, Berti G, Salvadori C, Federico A. Typical pathological changes of CADASIL in the optic nerve. Neurol Sci 2005;26:271-4.
32. Fabi M, Pierpaoli C, Barbaresi P, Polonara G. Functional topography of the corpus callosum investigated by DTI and fMRI. World J Radiol 2014;6:995-906.
33. Paul UK, Erickson RL, Hartman JA, Brown WS. Learning and memory in individuals with agenesis of the corpus callosum. Neuropsychologia 2016;86:183-92.
34. Tomimoto H, Lin JX, Matsuo A, Ihara M, Ohtani R, Shibata M, Miki Y, Shibasaki H. Different mechanisms of corpus callosum atrophy in Alzheimer’s disease and vascular dementia. J Neurol 2004;251:398-406.
35. Jung WB, Mun CW, Kim YH, Park JM, Lee BD, Lee YM, Moon E, Jeong HJ, Chung YI. Cortical atrophy, reduced integrity of white matter and cognitive impairment in subcortical vascular dementia ofBinswanger type. Psychiatry Clin Neurosci 2014;68:821-32.
36. Lin L, Xue Y, Duan Q, Sun B, Lin H, Chen X, Luo L, Wei X, Zhang Z. Microstructural white matter abnormalities and cognitive dysfunction in subcortical ischemic vascular disease: an atlas-based diffusion tensor analysis study. J Mol Neurosci 2015;56:363-70.
37. Best T, Howe P, Bryan J, Buckley J, Scholey A. Acute effects of a dietary non-starch polysaccharide supplement on cognitive performance in healthy middle-aged adults. Nutr Neurosci 2015;18:76-86.
38. Lim SH, Kim Y, Yun KN, Kim JY, Jang JH, Han MJ, Lee J. Plant-based foods containing cell wall polysaccharides rich in specific active monosaccharides protect against myocardial injury in rat myocardial infarction models. Sci Rep 2016;6:38728.
39. Zhang P, Zhang Q, Whistler RL. L-arabinose release from arabinoxylan and arabinogalactan under potential gastric acidities. Cereal Chem 2003;80:252-4.
40. Bach Knudsen KE. Microbial degradation of whole-grain complex carbohydrates and impact on short-chain fatty acids and health. Adv Nutr 2015;6:206-13.
41. Koropatkin NM, Cameron EA, Martens EC. How glycan metabolism shapes the human gut microbiota. Nat Rev Microbiol 2012;10:323-35.
42. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell 2015;161:264-76.
43. Fitzpatrick A, Roberts A, Witherly S. Larch arabinogalactan: a novel and multifunctional natural product. Agro Food Ind Hi Tech 2004;15:30-2.
44. Robinson RR, Feirtag J, Slavin JL. Effects of dietary arabinogalactan on gastrointestinal and blood parameters in healthy human subjects. J Am Coll Nutr 2001;20:279-85.
45. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm 2016;7:27-31.