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Original article

Antiglycative effect of ferulic acid

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Abstract

Glycative stress is one of the factors that cause aging and accelerates development of various diseases, including diabetes. Inhibition of glycative stress is referred to as anti-glycation. Anti-glycation includes suppression of postprandial hyperglycemia, suppression of glycative reaction, and decomposition and excretion of advanced glycation endproducts (AGEs). Inhibitory effects of AGE formation are recognized in various food materials such as herb teas, vegetables and fruits. It is reported that these food materials include many phenolic compounds that inhibit the formation of AGEs. Ferulic acid (FA) is a kind of phenolic compounds included in grains such as rice, wheat, fruits, vegetables, and other food materials. Bran (grain), in particular, includes a lot. FA is well known to be effective in inhibiting development of complications of diabetes or other neurotic diseases because of its anti-glycative/anti-inflammatory action. In our body, many kinds of AGEs are produced through many paths due to glycative stress, while there are many kinds of proteins that are glycated. On the other hand, reducing the function of proteins due to glycation is associated with the cross-linking formation induced by proteins changing into AGEs. The objective of this study was to evaluate the anti-diastatic effect of FA refined from rice bran. In this study, inhibitory effects of protein glycation reaction models such as human serum albumins (HSA), collagen and elastin, protein cross-linking formation by AGEs, and activity enhancement for oxidized protein hydrolase (OPH) were validated. As a result, it was clarified that FA inhibits the formation of fluorescent AGEs (F-AGEs) in all glycation reaction models. FA inhibited the formation of F-AGEs, pentosidine, CML, 3DG, GO, and MGO in the glycation reaction models of HSA-gulcose. In addition, FA also inhibited the formation of dimmer and trimer caused by the glycation of lysozyme. FA increased the OPH activation by a factor of 1.6. There is a possibility that anti-diastatication is associated with FA's usefulness for a variety of diseases.

***KEY WORDS*:** advanced glycation endproducts; AGEs, inhibition of AGE formation, inhibition of glycated protein cross-linking, ferulic acid

Introduction

Glycative stress is one of the factors that cause speed progression of various diseases, including aging and adult diseases. Inhibition of glycative stress is called anti-glycation. Inhibition of postprandial hyperglycemia occurs by forming advanced glycation endproducts (AGEs), as well as degradation and excretion of AGEs [1, 2)]. Aminoguanidine (AG) has an inhibitory effect on the formation of AGEs [3, 4)]. However, an intake of AG has adverse reactions such as anemia, hepatic disorder and vitamin B6 deficiency. On the other hand, various food materials including teas, herb teas, vegetables and fruits are reported to have inhibitory effects on AGE formation [5-7)]. Materials that form inhibitory effects on AGEs included in these food materials are reported to be phenol compounds such as chamaemeloside [8)], luteolin [9)], polymethoxy flavonoid [10, 11)], cyanidin3-O-galactoside [12)], caffeoyl glucose [13)], rhodanthenone B [14)], as well as chlorogenic acid [15)]. Ferulic acid (FA) is a material usually included in a variety of food materials such as grains like wheat, fruits, and vegetables.

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Bran, in particular, contains a lot [16-19]. FA has an anti-oxidative effect, anti-inflammatory effect and anti-bacterial effect which prevent us from suffering from development of neurotic diseases, or Alzheimer disease [20], while inhibiting obesity and lipid abnormality [21, 22]. On the other hand, the anti-glycative effect of FA has been validated in glycation reaction models which used bovine serum albumin (BSA) as a model protein [23]. The glycation reaction in a body is complex due to its multi-path feature. There are various short-chain aldehydes such as 3-deoxyglucosone (3DG), glyoxal (GO), and methylglyoxal (MGO) as glycative reaction intermediates, and there are several kinds of AGEs formed from them [24]. For this reason, it is important to validate the inhibitory effect of formation, focusing on AGEs with different glycative reaction paths by using multiple proteins [25]. Furthermore, reduction of the protein function due to glycation is associated with cross-linking resulting from proteins becoming AGEs. In this study, aiming at evaluating the anti-glycative effects of FA refined from rice bran, the inhibitory effect of glycative reaction intermediates, and glycation by using human serum albumins (HSA), collagen, and elastin, protein cross-linking formation caused by AGEs, and activity enhancement effects for oxidized protein hydrolase (OPH) were validated.

Materials and methods

Reagent

Materials used were procured from the manufacturers as bellow:
Human serum albumin (HSA), lyophilized powder, ≥ 96%, agarose gel electrophoresis, methylglyoxal (MGO) solution 40% in H_2O; Sigma-Aldrich Japan (Meguro-ku, Tokyo, Japan)
Collagen type I, bovine skin, pepsin-solublilized; Nippi (Adachi-ku, Tokyo)
Elastin peptide (P-elastin) ; Nippon Meat Packers, Inc (Osaka, Japan)
Lysozyme hydrochloride (from egg white) aminoguanidine hydrochloride (AG), 2,3-diaminonaphthalene (DAN), 40% glyoxal (GO) solution; Dojindo Laboratolries (Kamimashiki, Kumamoto, Japan)
CircuLex CML/Nε-(Carboxymethyl)Lysine) ELISA Kit; MBL (Nagoya, Aichi, Japan)
Acetyl-alanine p-nitroanilide (AAPA); Bachem (Budendorf, Switzerland)
Acylamino-acid releasing enzyme of oxidized protein hydrolase (OPH); Takara Bio (Otsu, Shiga, Japan). And other reagents (prime grade, or HPLC grade) were procured from Fuji Film Wako Pure Chemical and Nacalai Tesque (Kyoto, Japan).

Sample solution

Ferulic acid (FA) refined from rice bran (Tsuno Food Industrial, Wakayama, Japan) was used as a reagent (***Fig. 1***).

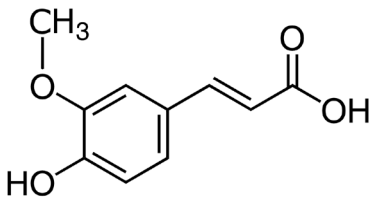

Fig. 1. **tructure of ferulic acid.**

Protein-glucose glycative reaction model

The inhibitory effect of glycative reaction was validated by using the protein-glucose glycative reaction model, referring to the previous report [26]. The reaction solution was produced: in 0.1 mol/L phosephate buffer (pH 7.4) including protein and glucose, sample solution was put by the volume of one tenth of phosephate buffer. The density of protein and glucose was as follows: 8.0 mg/mL HSA and 0.2 mol/L glucose; 1.2 mg/mL collagen and 0.4 mol/L glucose; and 6 mg/mL elastin and 0.2 mol/L glucose.
To examine the glycative reaction, four liquids were prepared as follows:

A. liquid which was made of phosphate buffer solution, protein solution, glucose solution and sample solution;
B. liquid which was made of the A solution, but instead of glucose solution, purified water was added;
C. liquid which was made of the A solution, but instead of sample solution, purified water was added;
D. liquid which was made of the C solution, but instead of glucose solution, purified water was added.

In the case of the HSA-glucose glycative reaction model, incubation condition was set for 40 hours at 60 °C, while in the case of collagen or keratin-glucose glycative reaction model, incubation was set for ten days at 60 °C. The quantity of AGEs and glycated reaction intermediate was determined by measuring the density of the reaction liquid after incubation.

Glycative reaction inhibitor, AG was used as a positive control material to inhibit the glycative reaction.

Measurement of AGEs

Referring to the previous report [26], fluorescent AGEs (F-AGEs) were measured. 200 µL glycative reaction solution was put in a black microplate to measure fluorescent material resulting from AGEs (excitation wavelength 370 nm/fluorescent wavelength 440 nm). Referring to the previous report [27], glycative reaction solution and 6N hydrochloric acid was mixed and was hydrolyzed for 18 hours at a temperature of 105 °C. Pentosidine was measured by using HPLC. For CML, CircuLex CML/N the glycative reaction solutionε-(Carboxymethyl) lysine ELISA Kit was used as glycative reaction solution for the measurement.

Measurement of glycative reaction intermediates

The glycative reaction intermediates were measured referring to the previous reports [28, 29]. Glycative reaction solution of 3DG, GO, and MGO were deproteinized using perchloric acid. Then, DAN was added under the alkaline condition. After the label handling, measurement was performed using HPLC.

Calculation of inhibitory effect of glycative reaction

Inhibitory effects of glycative reaction were measured referring to the previous report [26]. Inhibitory rates of AGEs

and glycative reaction intermediates (%) were calculated by the following formula:

Inhibitory rate (%) = {1 – (A – B) / (C – D) } × 100

Then, 50 % inhibitory concentration (IC_{50}; mg/mL) was calculated [26, 30], based on the inhibitory rate of sample solution with three concentrations. IC_{50} shows that the inhibitory effect of glycative reaction gets stronger in accordance with IC_{50} value getting smaller.

Inhibitory effects to form glycative protein cross-linking

Inhibitory effects to form glycative protein cross-linking were validated by using lysozyme-glucose glycative protein cross-linking model [31, 32]. The reaction solution was prepared: in 0.1 mol/L phosphate buffer solution (pH 7.4) including 5 mg/mL lysozyme and 0.5 mol/L glucose, sample solution was one tenth volume.

There are four reaction solutions as follows:

A. mixed liquid with phosphate buffer solution, lysozyme solution, glucose solution and sample solution;
B. liquid which was made of A solution, but instead of gulucose solution, purified water was added;
C. liquid which was made of A solution, but instead of sample solution, dissolving sample solution was added;
D. liquid which was made of C solution, but instead of glucose solution, purified water was added;

The solutions were incubated for 40 hours at a temperature of 60 °C. After the reaction, they were placed in a centrifugal filter with a 3 kDa ultrafiltration membrane (Amicon Ultra-0.5 mL centrifugal filters Ultracel-3K; Merck, Darmstadt, Deutschland) to remove low-molecular substances. Then, the reaction solutions were placed in the 4-20 % polyacrylamide gel electrophoresis (SDS-PAGE). After the migration, the gel was stained by CBB Stain One (Nacalai Tesque). Migrating image was processed by the Pharos FX System (Bio-Rad) and then strength of the band of dimmer (28.6 kDa) and trimer (42.9 kDa) of lysozyme was analyzed using ImageJ (NIH, Maryland, USA). AG was used as a positive control material for the inhibitory effects to form glycative protein cross-linking. The rate of inhibiting protein cross-linking formation was calculated following the formula below:

Inhibitory rate of forming protein cross-linking (%)
= {1 – (A – B) / (C – D) } × 100

A-D; strength of band of lysozyme dimmer or lysozyme trimer, of the SDS-PAGE gel chromatic figure of each reaction solution

Measurement of activity enhancement effect of OPH

Activity reinforcement of OPH was examined: referring to the report [33], 0.1 mol/L Tris hydrochloric acid (pH 7.4), 2 mmol/LAcetyl-alanine p-nitroanilide(AAPA),1mU/mL OPH and sample solution extract were mixed. One twenty-fifth volume sample solution was added to the solution. Then 250 μL reaction solution was incubated for 30 minutes at a temperature of 37 °C. When OPH decomposed AAPA, p-nitroanilide (pNA) was separated. The separated volume was measured by a spectrometry at 405 nm (S). In reference to OPH activity measurement, water was added to the reaction solution instead of the sample solution for measurement (R). The rate of activation (%) for OPH was calculated by the following formula:

OPH enhancement rate (%) = {(S_{30} – S_0) / (R_{30} – R_0)} × 100

Here, pNA volume separated in 30 minutes just after the Ref reaction started (0 minute) was set as 100 %.

S ; pNA concentration of reaction solution after sample solution was added
R ; pNA concentration of Ref reaction solution
30; 30 minutes later
0 ; just after the start of reaction (0 minute)

Statistical analysis

Measurement values were shown by mean value ± standard deviation (SD). Tukey's multiple comparison test (Tukey's test), or t test was used to compare measurement values. As for the statistical analysis, results with less than 5 % risk rate were considered significant.

Results

Inhibitory effect of forming fluorescent AGEs on protein-glucose glycative reaction models

Regarding FA's inhibitory effect on the formation of F-AGEs, it was proven that there is concentration dependence in each glycative protein model of HSA, collagen, and elastin (***Fig. 2***).

Inhibitory effects to form F-AGEs of FA concentration 0.1 mg/mL was examined: the rate of inhibition was 52.7 ± 1.4 % for HSA, 44.5 ± 0.8 % for collagen, and was 32.4 ± 1.5 % for elastin (in height order). In the same way, AG has a glycative reaction inhibiting effect. The rate of inhibition was 79.6 ± 0.2 % for HSA, 58.0 ± 1.4 % for elastin, and was 30.0 ± 0.3 % for collagen (in height order). The rate of inhibition to form F-AGEs in FA with reaction concentration 0.1 mg/mL was 0.7 times higher than in the case of AG for HSA, 0.6 times higher (low) for elastin, and was 1.5 times higher for collagen (high). In terms of IC_{50}, AG was lower compared to ferulic acid for HSA, collagen and elastin: IC_{50} of ferulic acid was 2.0 times the rate of AG for HSA, 1.2 times the rate for collagen, and 3.3 times the rate for elastin (***Table 1***)

Inhibitory effect of forming AGEs and glycative reaction intermediates in HSA-glucose glycative reaction models

Inhibitory effects that form F-AGEs, pentosidine, CML, 3DG, GO, and MGO, by 0.3 mg/mL FA in HSA-glucose glycative reaction models were examined (***Table 2***). FA's inhibitory effects to form AGEs and glycative reaction intermediates were strong in the following order: F-AGEs, pentosidine, GO, MGO, 3DG, and CML. On the other hand, FA's inhibitory effect to form AGEs and glycative reaction intermediates was lower than AG in all categories ($p < 0.05$). There was no comparison for pentosidine.

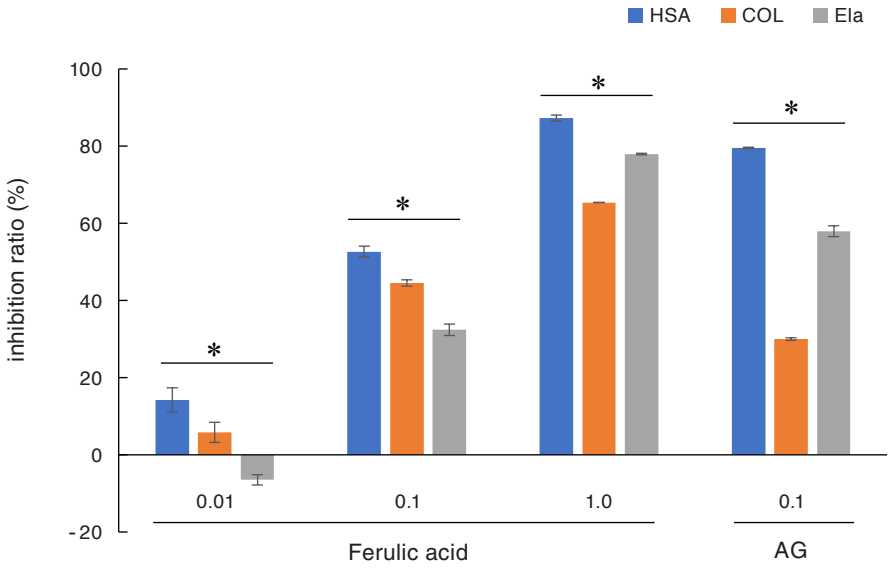

Fig. 2. **Inhibitory activity of ferulic acid on F-AGE formation.**

Results are expressed as mean ± SD, n = 3; * $p < 0.05$ by Tukey's test. HSA, human serum albumin; COL, collagen; Ela, elastin; AG, aminoguanidine; F-AGE, fluorescent advanced glycation endproduct; SD, standard deviation.

Table 1. Half inhibitory concentration (IC_{50}) on the protein-glucose glycation model.

Model protein	Ferulic acid (mg/mL)	Aminoguanidine [1)] (mg/mL)
HSA	0.093	0.046
Collagen	0.242	0.201
Elastin	0.231	0.069

1) Positive control of glycation inhibitor. IC_{50}, 50% inhibitory concentration; HSA, human serum albumin.

Table 2. AGE inhibition ratio on the HSA-glucose glycation model

AGEs compound	Ferulic acid (%)	Aminoguanidine (%)
Fluorescent AGEs	70.6 ± 0.4 *	100.7 ± 0.1
Pentosidine	46.0 ± 0.2	–
CML	3.1 ± 1.1 *	65.1 ± 1.1
3DG	19.8 ± 1.0 *	86.7 ± 0.2
GO	48.1 ± 1.5 *	94.0 ± 1.2
MGO	35.8 ± 1.6 *	104.7 ± 1.5

Sample concentration, 0.3 mg/mL; mean ± SD, n = 3, * $p < 0.05$ vs aminoguanidine by Student's t test; Characteristic fluorescence (excitation/emission = 370/440 nm). AGE, advanced glycation endproduct; CML, N^{ε}-carboxymethyl lysine; 3DG, 3-deoxyglucosone; GO, glyoxal; MGO, methylglyoxal; HSA, Human serum albumin; SD, standard deviation.

Inhibitory effect of forming glycative protein cross-linking

FA and AG inhibited the formation of lysozyme's dimmer and trimer in the sample solutions with concentration of 0.05 ~ 5.1 mmol/L in a concentration-dependent manner (***Table 3, Fig. 3***). FA's inhibitory rate to form protein cross-linking was compared to the case of AG. In each case, concentration was 1.5 mmol/L. Regarding dimer, the rate was 0.2 times higher than the case of AG, while it was 0.5 times higher for trimer. As for the concentration of 5.1 mmol/L, both rates of dimer and trimer, were 0.5 times higher (low).

Activity enhancement effect of OPH

Regarding FA, when Ref (water) activation is 100 with sample concentration 0.4 μg/mL, OPH activity enhancement effects by 166.2 ± 2.7 (n = 3) was recognized.

Discussion

Inhibitory effects on glycative reaction by FA

It is admitted that FA has an inhibitory effect on the formation of F-AGEs and CML in glycative reaction models such as glucose, fructose, and ribose whose model protein is BSA[23]. In this study, FA inhibited the formation of F-AGEs in glycative reaction models including HSA, collagen, and elastin as model proteins. Additionally, FA inhibited the formation of F-AGEs, pentosidine, CML, 3DG, GO, and MGO in the HSA-gulcose glycative reaction model. These results show a possibility that FA inhibits the glycation of various proteins in body tissue and prevents the accumulation of AGEs. However, there is a difference in the strength of effect.

There is a possibility that an increase of blood concentration in 3DG, GO, and MGO consisting of aldehyde might cause an apoptosis of vascular endothelium[34]. An

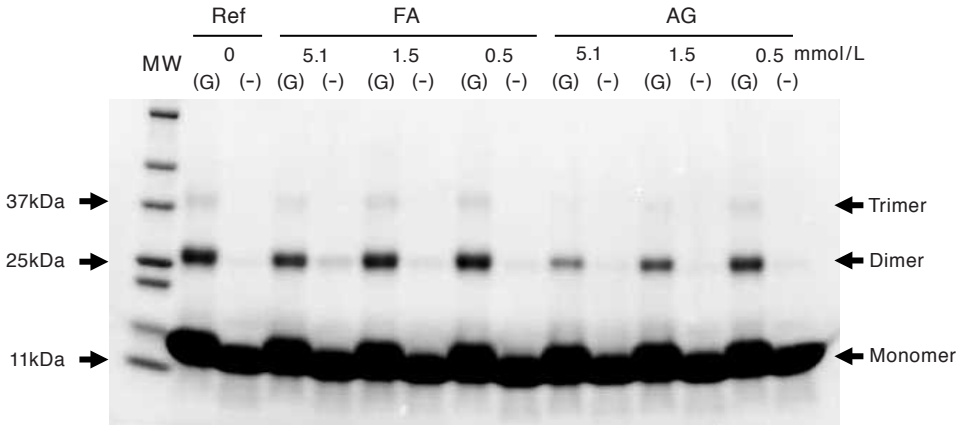

Fig. 3. **Inhibitory effect of ferulic acid on cross-linking formation in the lysozyme-glucose reaction model.**

5 mg/mL lysozyme were incubated at 60 °C for 40 hours. SDS-PAGE was conducted using 4-20 % acrylamide gels. MW, molecular weight markers; Ref, incubation with 50 % ethanol; FA, incubation with 0.1 mg/mL ferulic acid 50 % ethanol solution; AG, incubation with aminoguanidine; (G), incubation with 0.5 mol/L glucose; (-), incubation without glucose; mmol/L, sample concentration.

Table 3. Inhibitory effect of ferulic acid and aminoguanidine on cross-linking formation in the lysozyme-glucose reaction model.

Polymerized lysozyme	Concentration (mmol/L)	Ferulic acid Inhibition ratio (%)	Aminoguanidine Inhibition ratio (%)
Trimer	0.5	13.1 ± 9.0	39.4 ± 9.3 *
	1.5	36.8 ± 1.1	69.6 ± 8.0 **
	5.1	48.2 ± 2.1	90.3 ± 4.3 *
Dimer	0.5	-4.0 ± 3.7	12.4 ± 2.4 **
	1.5	5.8 ± 1.8	33.6 ± 2.9 **
	5.1	28.5 ± 2.0	53.9 ± 7.0 **

5 mg/mL lysozyme were incubated at 60 °C for 40 hours. SDS-PAGE was conducted using 4-20 % acrylamide gels. Data are expressed as mean ± standard deviation, n = 3; Dimer, 28.6kDa; Trimer, 42.9kDa; *p < 0.05, ** p < 0.01 vs AG by t test.

increase of blood acetaldehyde also happens when the postprandial glucose level elevates[35]. In addition, when 3DG increases by 100 nmol/L, risks for diabetic retinal disease and nephropathy double[28]. Therefore, there is a possibility that FA's effect to inhibit aldehyde formation is associated with the inhibition of blood vessel aging or diabetic complications.

There are many papers that validated FA's influence on diabetic complications[36]. In the test where 100 mg/kg FA per day was administered to STZ-diabetogenic rats for eight weeks, an improvement of renal functions associated with an amelioration of volume increase, sclerosis, and fibrosis of glomerulus was recognized[37]. In the test where 10 mg/kg FA per day was administered to type 2 diabetic rats for 26 to 45 weeks, there were effects that improved diabetic renal disease based on a reduction of glomerular basement membrane thickness and an increase of glomerular volume and Mesangium cells[38]. According to these papers, FA's usefulness is considered to be primarily associated with anti-oxidative effects or anti-inflammatory effects.

Based on the results of this study, there is a possibility that FA's inhibitory effect to develop diabetic complications is associated with its inhibitory effect of glycative reaction. FA is included in grains such as rice and wheat, fruits, and other vegetables. Wheat, barley, and corn contain 500 mg FA per 100 g[19]. The volume of FA available from a meal with these grains is calculated as 20-50 mg[19]. Inhibitory effects of forming AGEs by rice were validated using extracts from 35 breed varieties of Sri Lankan rice. It was reported that red rice breeds had stronger effects compared to white rice breeds[39]. Red rice's inhibitory effects to form AGEs is associated with cyanidine-3-O-glucoside (C3G[40]. Additionally, 14 rice breeds including black rice, red rice, brown rice, and white rice are reported to have inhibitory effects on the formation of AGEs[41]. Inhibitory effects on the formation of AGEs by rice extract liquid are recognized in brown rice or white rice, which does not contain C3G. It is presumed that the effect is associated with polyphenol[41]. FA is an ingredient easy to ingest from grains which are a staple food. However, it is possible that a large volume intake of grains might cause excessive consumption of carbohydrates. It is necessary to use refined FA or to be careful about the volume of carbohydrate contained in grains, in order to inhibit aging and aggravation of diseases under the condition suffering from strong glycative stress.

Protective effect on albuminous degeneration caused by glycation

It has been reported that FA has an inhibitory effect to develop neurotic diseases including epilepsy, depression, ischemia-reperfusion injury, Alzheimer's disease (AD), and Parkinson's disease[42]. AD is caused by glycative stress or malfunction of mitochondria. Based on this, anti-oxidative components are utilized to treat or mitigate AD. FA is one of the anti-oxidative materials existing on the cell wall of plants and prevents anti-inflammatory action and free radicals. FA inhibits aggregation of amyloid β(Aβ)and has effects to keep maintain protein structure[43]. In addition, FA and its derivatives inhibit the aggregation and fibrillization of Aβ[44]. Furthermore, FA is reported to pass blood-brain barrier[45]. In this study, it was clarified that FA inhibits a polymerization followed by protein cross-linking formation by glycated lysozyme, while reinforcing the OPH activity effective in decomposing glycated proteins. These results show a possibility that FA prevents protein changing structures due to glycation, resulting in protecting proteins. Individuals with diabetes under a strong glycative stress are suffering from higher rate of AD, compared to non-diabetes[46]. Prevalence of intracerebral AGEs of AD patients is three times higher than in healthy subjects[47]. Moreover, considering that those whose accumulation of AGEs on skin is large in quantity have a higher rate of mild cognitive impairment, and it is presumed that an enhancement of glycative stress is associated with development of AD[48]. Based on this, there is a possibility that protein protection by glycative FA is concerned with preventing diabetics or aged people under strong glycative stress from developing neurotic diseases.

Limitations of study

FA's inhibitory effects of glycative reaction, inhibitory effects of forming glycative protein cross-linking, as well as enhancement effects of OPH activity validated in this study are all in vitro test results. Further validation is necessary to clarify the usefulness of FA administered continuously by humans about the inhibitory effect of glycation.

Conclusion

FA has an inhibitory effect AGEs and glycation reaction intermediates by the glycative reaction system with HSA, collagen, and elastin as model proteins, protein cross-linkings, and enhancement OPH activity. There is a possibility that usefulness of FA to inhibit development of diabetic complications and other neurotic diseases is associated with anti-diastatic effects.

Statement of conflict of interests

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