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Efficacy and safety of Touchi Extract, an α-glucosidase inhibitor derived from fermented soybeans, in non-insulin-dependent diabetic mellitus

Fujita Hiroyuki[a,*], Yamagami Tomohide[a], Ohshima Kazunori[b]

[a]*Research and Development Department, Nippon Supplement, Inc., Kita-Ku, Osaka, 531-0076, Japan*
[b]*Ohshima Clinic, Ibaraki, Osaka, 567-0829, Japan*

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Abstract

The water-extracted Touchi, a traditional Chinese food, exerted a strong inhibitory activity against rat intestinal α-glucosidase in foodstuffs. In borderline and developed diabetic subjects, 0.3 g of Touchi-extract (TE) significantly inhibited postprandial blood glucose levels. For confirmation of safety, 9 healthy subjects were given 1 g of TE before every meal (3 g/day) for 12 weeks. None indicated changes in hematological and relevant biochemical parameters, body weight or BMI. In a non-comparative study, 18 type-2 diabetic patients ingested 0.3 g of TE before every meal (0.9 g/day) for 6 months (mo). Blood glucose (mean; 9.31 ± 0.71 mmol/L) and HbA_{1c} (mean: 10.24 ± 0.58%) levels gradually decreased, and significant effects were elicited on the blood glucose levels (8.61 ± 0.66 mmol/L; $p < 0.01$) after 6 mo and HbA_{1c} after 3 (9.13 ± 0.43%; $p < 0.05$) and 6 mo (8.96 ± 0.30%; $p < 0.05$) post-ingestion of TE. Indexes for serum lipids and total cholesterol level revealed moderate decreases with a slight increase in the high-density lipoprotein (HDL) level after TE ingestion. However, triglyceride (TG) levels significantly decreased at 3 ($p < 0.05$) and 6 mo ($p < 0.01$) post-ingestion of TE. In this study, other biochemical parameters were not affected in any of the patients, and no one complained of any side-effects or abdominal distension. TE, exhibiting α-glucosidase inhibitory activity, demonstrated an anti-hyperglycemic effect and may prove useful for improving glycemic control in patients suffering from non-insulin-dependent diabetic mellitus.

Keywords: Touchi-extract; α-glucosidase inhibitor; Anti-hyperglycemic effect; Non-insulin-dependent diabetic mellitus

1. Introduction

Diabetes mellitus is one of the most prevalent diseases in Japan. Poor control of this disease results in the development of vascular disorders such as retinopathy, neuropathy and nephropathy. Agents with α-glucosidase inhibitory activity have been useful as oral hypoglycemic drugs for the control of hyperglycemia in patients with type-2 non-insulin-dependent diabetic mellitus (NIDDM) [1–4]. These drugs inhibit disaccharide hydrolases, which convert disaccharides to monosaccharides, impeding digestion and adsorption of glucose, eliciting attenuated postprandial plasma glucose levels. For example, acarbose and voglibose are current therapeutic agents that decrease postprandial blood glucose excursions by delaying carbohydrate digestion in the small intestinal tract.

However, in recent years, the importance of biologically active substances contained in foods has been noticed, and many physiological effects of foods have been reported [5,6]. Inhibitors of α-glucosidase or α-amylase derived from various sources have also been isolated [7–10], and their effects have been investigated in animals as well. As such, when the presence of α-glucosidase inhibitor in many foodstuffs was screened for, we found that Touchi-extract (TE) strongly inhibited rat intestinal α-glucosidase [11]. Touchi, a traditional Chinese food used mainly as a seasoning ingredient; is obtained by first steaming and then fermenting soybeans with koji (*Aspergillus* sp.). Daitokuji-natto, Tera-natto and Ikkyuji-natto are made by the same method in Japan. TE elicits inhibitory activity against rat intestinal α-glucosidase, and dose-dependently depresses postprandial rise in blood glucose levels after oral sucrose loading in rats and humans [11]. In the human study, the

* Corresponding author. Tel.: +81-6-6440-5317; fax: +81-6-6440-5328.

E-mail address: ngfh03@mail.nichigo.co.jp (F. Hiroyuki).

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Table 1
Safety of Touchi Extract (TE) in blood analysis after long-term ingestion in healthy subjects

	Before	6 wk	12 wk post-TE ingestion
Hematology			
White blood cell (cells/nL)	5.3 ± 0.3	5.5 ± 0.2	5.6 ± 0.3
Red blood cell (cells/pL)	5.0 ± 1.3	5.1 ± 1.3	5.0 ± 1.3
Hemoglobin (g/L)	151 ± 4.1	157 ± 5.1	152 ± 3.5
Hematocrit (%)	45.9 ± 0.69	46.9 ± 1.12	45.7 ± 0.92
MCV (fL)	91.6 ± 1.15	91.3 ± 0.59	91.5 ± 0.85
MCH (pg)	30.1 ± 0.53	30.5 ± 0.52	30.5 ± 0.44
MCHC (%)	32.9 ± 0.54	33.4 ± 0.53	33.3 ± 0.42
Platlet (cells/pL)	0.20 ± 0.11	0.20 ± 0.13	0.20 ± 0.11
Biochemistry			
GOT (U/L)	21.1 ± 2.2	23.1 ± 1.4	23.8 ± 2.0
GPT (U/L)	19.1 ± 3.1	21.5 ± 2.8	21.5 ± 2.5
ALP (U/L)	149.6 ± 14.9	146.5 ± 14.9	138.0 ± 12.0
γ-GTP (U/L)	18.3 ± 3.4	22.4 ± 4.4	18.3 ± 3.4
Total protein (g/L)	73 ± 2	73 ± 2	73 ± 2
Amylase (U/L)	4.88 ± 0.16	4.87 ± 0.16	4.83 ± 0.10
Blood glucose (mmol/L)	4.96 ± 0.34	5.11 ± 0.41	5.11 ± 0.48
Total cholesterol (mmol/L)	1.44 ± 0.11	1.58 ± 0.13	1.62 ± 0.12
HDL cholesterol (mmol/L)	55.5 ± 4.1	61.1 ± 5.2	62.6 ± 4.8
Triglyceride (g/L)	1.13 ± 0.19	1.10 ± 0.15	1.07 ± 0.15
Urea (g/L)	58.6 ± 3.3	60.8 ± 6.0	56.1 ± 3.6
Free fatty acid (mmol/L)	5.3 ± 0.8	4.6 ± 0.4	5.1 ± 0.6
Blood urea nitrogen (mmol/L)	5.46 ± 0.39	5.46 ± 0.39	5.57 ± 0.39
Creatinine (μmol/L)	88.4 ± 3.5	88.4 ± 4.4	88.4 ± 3.5
CRP (mg/L)	2.3 ± 0.5	3.1 ± 0.8	2.0 ± 0.7
Sodium (mmol/L)	142.3 ± 0.9	142.8 ± 0.8	143.1 ± 0.6
Potassium (mmol/L)	3.76 ± 0.12	3.76 ± 0.17	4.04 ± 0.08
Chloride (mmol/L)	101.8 ± 1.1	102.4 ± 1.1	102.1 ± 0.7
Calcium (mmol/L)	6.29 ± 0.84	6.41 ± 0.87	6.43 ± 0.94

Nine healthy subjects ingested TE (1 g) 3 times daily before meals for 12 weeks (wk).
The values were expressed as the mean ± S.E.

minimum effective dose approximates to 0.3 g [11]. In this study, the safety of 12-wk TE ingestion in healthy subjects and the anti-glycemic effects and lipid metabolism after long-term (6 mo) ingestion in diabetic subjects were pursued.

2. Materials and methods

2.1. TE preparation

Touchi (100 g), obtained from commercial sources, was milled and suspended in 900 mL of water before boiling for 60 min. This was followed by centrifugation at 2050 g for 30 min at room temperature and filtration of the supernatant with Toyo filter paper No. 5C (Toyo Roshi Co., Japan). The filtrate was electrodialyzed with microacilizer-G3 (Asahikasei Industry Co. Ltd., Japan), and the dialyzate was concentrated before drying under a stream of air. The yield of TE was 9.8 g from 100 g of Touchi. The powder thus obtained was used as the TE in this study. The IC_{50} value of TE in rat intestinal α-glucosidase inhibition using sucrose as a substrate registered 0.34 g/L [11] according to the method described by Miwa et al [12].

2.2. Safety test in healthy subjects

Nine healthy male volunteers, aged 26–56 yr (mean: 38.9 ± 3.40 yr), participated in the study with informed consent after the nature, purpose and possible side-effects were explained. The study was approved by the Institutional Review Board in March 1999. None of the subjects had a significant medical history, and all were within 10% of the ideal body weight. Hematological and relevant biochemical parameters were examined and body weight and body mass index (BMI) were calculated at 0 (before ingestion), 6 and 12 wk after initiation of TE ingestion without any abnormal events. Following 12-hour fast, blood was sampled, and analyses were conducted in Blood Analysis Laboratory (BML Co., Japan). All subjects were instructed to maintain their usual way of life throughout the study period. All subjects kept a detailed diary on symptoms encountered, and were also instructed to comment on any unexpected deviations in dietary intake or bowel habits. TE, at 1 g/meal, was given to subjects thrice per day (3 g/day) immediately before each meal for a 12-wk period. This daily intake was 3 times the minimum effective dose (0.9 g/day) as established in the previous study [11].

Table 2
Particulars of diabetic patients

	Characteristic variables	No. (%) of patients
Sex	Men	9 (50.0)
	Women	9 (50.0)
Age distribution	≤39	0 (0.0)
	40–49	2 (11.1)
	50–59	5 (27.8)
	60–69	8 (44.4)
	≥70	3 (16.7)
Mean age		62.0 ± 2.5
Sulphonylurea drug taken	Yes	9 (50.0)
	No	9 (50.0)
Diseased period (year)	1–2	2 (11.1)
	2–3	5 (27.8)
	3–4	10 (55.5)
	≥4	1 (5.6)
Diet program	Yes	4 (22.0)
	No	12 (78.0)
Regular exercise	Yes	5 (27.8)
	No	11 (72.2)
FBG (mmol/L)	7.8–8.8	4 (22.2)
	8.9–9.9	4 (22.2)
	10.0–11.0	5 (27.8)
	11.1–12.1	4 (22.2)
	≥12.2	1 (5.6)
HbA_{1c} (%)	5.0–5.9	0 (0.0)
	6.0–6.9	1 (5.5)
	7.0–7.9	3 (16.7)
	8.0–8.9	3 (16.7)
	9.0–9.9	4 (22.2)
	10.0–10.9	4 (22.2)
	≥11.0	3 (16.7)
BMI (kg/m^2)	17.0–19.9	3 (16.7)
	20.0–21.9	1 (5.5)
	22.0–22.9	2 (11.1)
	23.0–23.9	3 (16.7)
	24.0–24.9	1 (5.5)
	25.0–26.9	5 (27.8)
	27.0–29.9	3 (16.7)

2.3. Diabetic patients

This was a non-comparative study conducted between October 1999 and April 2000 at a hospital in Osaka, Japan. Eighteen fully developed diabetic patients (males and females) enrolled in the study. Their fasting blood glucose levels registered >6.9 mmol/L (9.31 ± 0.71 mmol/L) and the glycated hemoglobin (HbA_{1c}) levels were >6.5% (10.24 ± 0.58%). All patients gave informed consent for the study after having being briefed on the nature purpose and possible side-effects. The investigation was approved by the Institutional Review Board in September 1999. Patients excluded were those treated with insulin, those with serious cardiac, renal or hepatic diseases, those with a history of gastrectomy, enterectomy or other gastrointestinal surgery, those with a history of hypothyroidism, and those judged by the attending physician to be incompatible for the study. Medication with sulfonylurea was permitted in 9 patients, and the dosage did not change throughout the investigation

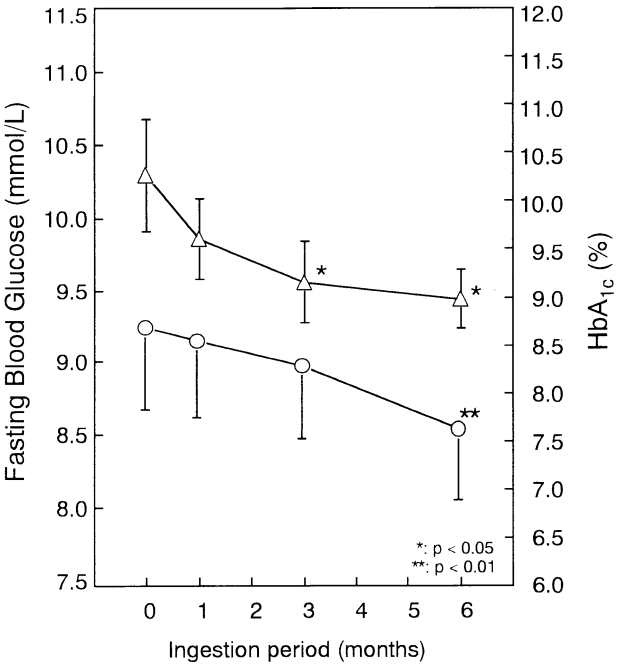

Fig. 1. Effects of Touchi-extract (TE) on the blood glucose and HbA_{1c} levels in diabetic patients. Eighteen diabetic patients ingested TE (0.3 g) 3 times daily before meals for a 6-month period. Blood glucose levels (○) and HbA_{1c} levels (△) were monitored at 0 (pre-ingestion), 1, 3 and 6 months after post-ingestion. The values were expressed as the mean ± standard error.

period. All patients were asked to maintain normal physical activities and food intake throughout the investigation. Following 12-hour fast, blood was sampled for analysis of hematological and biochemical parameters at 0 (before TE ingestion), 2, 4 and 6 mo after TE ingestion. All in all the investigation was uneventful. Hematological and biochemical analyses were conducted in Blood Analysis Laboratory (BML Co., Japan). All patients kept a detailed diary on symptoms and were also instructed to comment on any unexpected deviations in dietary intake or bowel habits. Patients were given TE at 0.3 g/meal thrice a day (0.9 g/day) immediately before each meal for a 6-mo period.

2.4. Statistical analysis

Results are expressed as the mean ± S.E. The statistical significance of differences before and after TE ingestion was assessed using the paired Student's *t*-test (Stat View, Abacus Concepts, Inc., Berkeley, CA USA).

3. Results

3.1. Safety of TE ingestion in healthy subjects

To confirm the safety of TE, 9 healthy subjects ingested 1 g of TE before meals (3 g/day) for a 12-wk period. Neither

Table 3
Changes in fasted blood glucose and HbA_{1c} levels after Touchi Extract ingestion

	Characteristic variables	No. (%) of patients
FBG (mmol/L)	±0.3	4 (22.2%)
	−0.6	4 (22.2%)
	−1.1	7 (38.9%)
	−1.7	2 (11.1%)
	> − 1.7	1 (5.6%)
HbA_{1c} (%)	±0.5	7 (38.9%)
	−1.0	6 (33.3%)
	−1.5	1 (5.6%)
	−2.0	4 (22.2%)

Eighteen diabetic patients ingested Touchi Extract (0.3 g) 3 times daily before meals for a 6-month period.

hematological nor relevant biochemical data (*Table 1*) revealed remarkable changes after TE ingestion when compared with pre-ingestion values. No significant changes in the body weight of any subjects were observed before, 6 or 12 wk after TE ingestion. Moreover, the post-TE BMI did not change significantly at 6 (23.7 ± 0.91 kg/m^2) or 12 wk (23.6 ± 0.95 kg/m^2) when compared with pre-ingestion values (23.8 ± 0.92 kg/m^2). Indexes for diabetes, such as fasted blood glucose and HbA_{1c} levels, were also not altered by TE ingestion. Furthermore, subjects did not complain of abdominal disorders such as distension, abdominal pain, diarrhea, retching and flatulence. Other side-effects were not provoked by TE ingestion in any subjects.

3.2. Anti-glycemic effect in fully developed diabetic (NIDDM) patients

A total of 18 patients were enrolled in and completed the study. Particulars of the patients indicated approximately 2/3 of patients suffered from type-2 diabetes for more than 3 yr (*Table 2*).

Fasting blood glucose and HbA_{1c} levels of patients decreased at 1 mo, and were significantly reduced at 6 mo post-ingestion of TE (*Fig. 1*). The anti-glycemic effect of TE (*Table 3*) revealed that TE effectively attenuated the fasting blood glucose levels in 14 patients (77.8%) and HbA_{1c} levels in 11 patients (61.1%) after 6-mo TE ingestion.

The diabetic patients included 14 cases of hyperlipidemia (4 of hypertriglycerdemia with >1.5 g/L, 4 of hypercholesterolemia with >5.69 mmol/L and 5 of mixed hyperlipidemia). *Fig. 2* shows the effects of TE on hyperlipidemia. Total cholesterol levels registered a moderate decrease, while high-density lipoprotein (HDL) levels revealed moderate increases after TE ingestion without any significant changes (*Fig. 2A*). However, triglyceride contents significantly decreased at 3 and 6 mo after TE ingestion (*Fig. 2B*).

In this study, no one complained of any side effects such as abdominal distension, abdominal pain, diarrhea, retching or flatulence. Moreover, abnormal hematological and relevant biochemical data were not encountered on blood analysis (*Table 4*). There were no significant changes in body

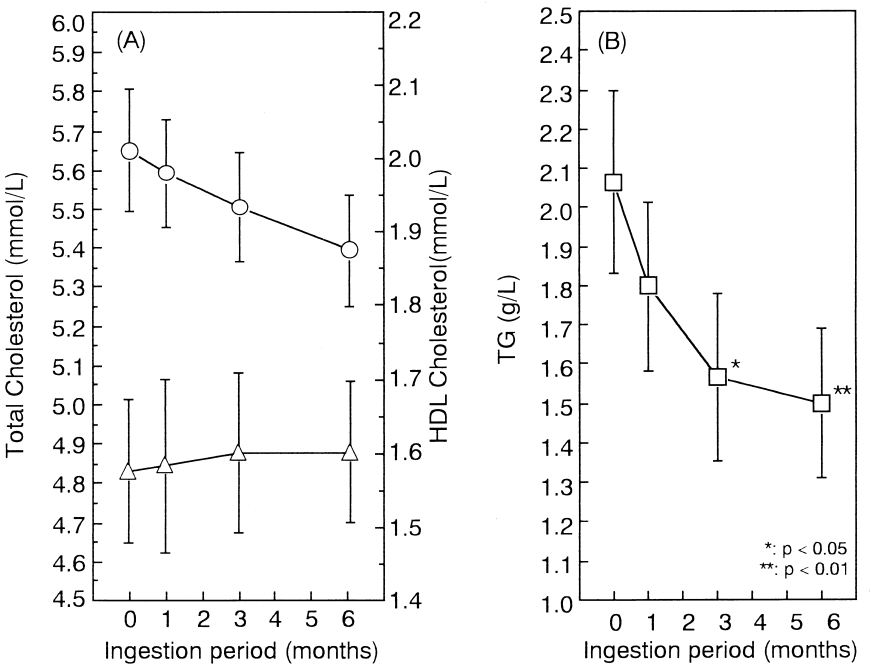

Fig. 2. Effect of Touchi-extract (TE) on serum lipid metabolism in diabetic patients. Eighteen diabetic patients ingested TE (0.3 g) 3 times daily before meals for a 6-month period. The left panel (A) shows total cholesterol levels (○) and high-density lipoprotein (HDL) levels (△), while the right panel (B) indicates the triglyceride (TG) levels (□). All parameters were monitored at 0 (pre-ingestion), 1, 3 and 6 months after TE ingestion. The values were expressed as the mean ± standard error.

Table 4
Safety of Touchi Extract (TE) in blood analysis after the long term ingestion in diabetic patients

	Before	1 mo	3 mo	6 mo after TE ingestion
Hematology				
White blood cell (cells/nL)	6.3 ± 0.3	6.3 ± 0.3	6.3 ± 0.3	6.3 ± 0.3
Red blood cell (cells/pL)	4.71 ± 0.12	4.67 ± 0.11	4.62 ± 0.10	4.65 ± 0.10
Hemoglobin (g/L)	1.44 ± 2.7	1.44 ± 2.7	1.43 ± 2.4	1.42 ± 2.6
Hematocrit (%)	45.9 ± 0.69	43.5 ± 0.74	43.1 ± 0.69	42.8 ± 0.71
MCV (fL)	93.4 ± 1.45	92.8 ± 1.19	92.8 ± 1.18	92.0 ± 1.15
MCH (pg)	30.6 ± 0.47	30.7 ± 0.45	30.8 ± 0.47	30.8 ± 0.49
MCHC (%)	32.8 ± 0.22	33.0 ± 0.23	33.1 ± 0.21	33.5 ± 0.17
Platlet (cells/pL)	0.19 ± 0.02	0.20 ± 0.02	0.20 ± 0.02	0.18 ± 0.01
Biochemistry				
GOT (U/L)	35.4 ± 5.1	33.7 ± 4.8	30.1 ± 3.1	28.9 ± 2.9
GPT (U/L)	51.5 ± 11.1	46.7 ± 8.9	39.8 ± 5.4	39.3 ± 5.2
ALP (U/L)	194.7 ± 14.9	210.6 ± 15.3	206.7 ± 16.2	206.5 ± 13.3
γ-GTP (U/L)	52.2 ± 8.9	46.9 ± 8.9	49.9 ± 5.9	57.9 ± 6.8
Total protein (g/L)	73 ± 1	74 ± 1	73 ± 1	74 ± 1
Amylase (U/L)	110.5 ± 10.5	100.2 ± 10.6	97.9 ± 9.2	98.6 ± 8.6
Urea (g/L)	4.8 ± 0.26	4.6 ± 0.25	4.6 ± 0.27	4.7 ± 0.24
Free fatty acid (mmol/L)	0.90 ± 0.06	1.03 ± 0.07	0.99 ± 0.05	0.90 ± 0.03
Blood urea nitrogen (mmol/L)	5.67 ± 0.31	5.89 ± 0.02	5.82 ± 0.27	5.67 ± 0.27
Creatinine (μmol/L)	79.6 ± 5.3	79.6 ± 2.7	79.6 ± 5.3	79.6 ± 5.3
CRP (mg/L)	3.1 ± 0.3	3.2 ± 0.7	2.1 ± 0.6	1.2 ± 0.3

Eighteen diabetic patients ingested TE (0.3 g) 3 times daily before meals for 6 months (mo).
The values were expressed as the mean ± S.E.

weight. Changes in BMI at 1 (23.8 ± 0.91 kg/m^2), 3 (23.7 ± 0.89 kg/m^2) and 6 mo (23.8 ± 0.90 kg/m^2) post-ingestion of TE were insignificant when compared statistically with the pre-ingestion value (23.9 ± 0.90 kg/m^2).

4. Discussion

The major side-effects of α-glucosidase inhibitory drugs involve the gastrointestinal system. In this study, no one complained of any gastrointestinal system-related unwanted effects, such as abdominal distension, abdominal pain, retching and flatulence. This may be due to the lower inhibitory potency of TE on α-glucosidase compared with currently employed therapeutic agents of similar mechanism of action, and this may account for the moderate effects in the small intestinal tract. As abnormalities in hematological and relevant biochemical data were not observed, the safety of TE is thus clarified. The ingestion safety of TE is further advocated by the fact that Touchi is a traditional Chinese food derived from fermented soybeans and has been eaten since long ago.

In the study on diabetic patients, 0.3 g of TE effectively and significantly elicited anti-glycemic effects after 6-mo ingestion: blood glucose levels gradually decreased on TE ingestion to finally reduce to >-0.56 mmol/L) in 14 patients (77.8%). In addition, HbA_{1c} levels also gradually decreased with final readings of $>-1\%$ in 11 patients (61.1%). Thus, TE elicited moderate yet positive effects in diabetic patients over the ingestion period—a phenomenal and useful approach in the control of blood glucose levels in diabetics.

In a previous study with healthy human volunteers, the main changes in lipid profile following treatment with the α-glucosidase inhibitory agent, acarbose, have been the reductions in serum triglyceride and VLDL [13–16]. In our study, although total cholesterol contents were only slightly depressed, triglyceride levels were significantly reduced. With foodstuffs, such as indigestible dextrin, reduced triglyceride levels have been reported as well [17]. This effect was thought to be due to lowering blood glucose levels [17].

Thus, TE represents the first useful antidiabetic agent through its α-glucosidase inhibitory action. As it has proven effective in improving glycemic control, TE should provide a useful effect that can be employed extensively in borderline and fully developed diabetic patients. A comparative study on the anti-hyperglycemic effects of TE in borderline and diabetic patients on long-term ingestion is now in progress in our and other collaborative facilities.

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