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Rat Lens Aldose Reductase Inhibitory Activities of *Cissus assamica* var. *pilosissima* and *Syzygium oblatum*

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Abstract – Aldose reductase (AR) has been shown to play an important role in the development of diabetic complications. To search for AR inhibitors from Chinese plants, the ethanol extracts of Chinese plants was tested against an inhibition of rat lens AR *in vitro*. Among Chinese plants tested, *Cissus assamica* var. *pilosissima* and *Syzygium oblatum* showed highest inhibition of AR (IC_{50} values, 0.71 and 0.79 μg/ml, respectively). *Cissus assamica* var. *pilosissima* and *Syzygium oblatum* showed more potent inhibitory activity against AR than the positive control, TMG. Consequently, *C. assamica* var. *pilosissima* and *S. oblatum* have a possibility of new natural resources for the development of AR inhibitor for the prevention of diabetic complications.
Keywords – Chinese plant, Diabetic complications, Aldose reductase, *Cissus assamica* var. *pilosissima*, *Syzygium oblatum*

Introduction

Aldose reductase (AR) belonging to the aldo-keto reductase super family of enzymes in plants and animals is the first and rate limiting enzyme in polyol pathway (Ko *et al.,* 1997; Demaine *et al.,* 2000; Sree *et al.,* 2000). AR is monomeric and cytosolic protein that catalyzes reduction glucose to sorbitol (Wang *et al.,* 2009). Sorbitol subsequently metabolized to fructose by sorbitol dehydrogenase which the second enzyme of polyol pathway (Ramana *et al.,* 2001; Wang *et al.,* 2009). Accumulation of sorbitol leads to abnormalities of metabolism such as osmotic swelling and oxidative stress (Kao *et al.,* 1999). And, stored sorbitol in the lens fiber is regarded as the main cause of blindness (Patel *et al.,* 2012) and cataract formation (Heyningen, 1959; Sugiyama *et al.,* 2000). Chronic hyperglycemia is considered as the causative link on the onset and progression of diabetes chronic complications (Demopoulos *et al*., 2005; Chatzopoulou *et al*., 2011). As a result, osmotic, oxidative, reductive, glycative and protein kinase C stress are induced with devastating manifestations for the cells (Alexiou *et al.,* 2009). Under hyperglycemia environment, AR is highly activated by increasing glucose contents can cause increased accumulation of sorbitol rate by 2-4 times (Ramana *et al.,* 2001; Wang *et al.,* 2009). The enzyme exists in the eye, nerves, retina, kidney, myelin sheath, and other tissues resulting in the development of diabetic complications (Enomoto *et al.,* 2004; Ha *et al.,* 2009).

AR inhibitors (ARIs) have been proposed as possible pharmacotherapeutics of diabetic complications (Miyamoto, 2002). Numerous ARIs obtained from natural sources such as flavonoids, coumarins, stilbenes, monoterpenes, and related aromatic compounds have been reported in the past years, because of its high potency, promising efficacy, and insignificant adverse effect profile (Fuente and Manzanaro, 2003; Kawanishi *et al.,* 2003). Therefore, the development of natural sources for ARIs will be able to better success of a potential treatment for diabetic complications, due to safer and more effective phyto-chemicals (Kawanishi *et al*., 2003).

The wide territory of China is a factor that can have complex natural environmental conditions. So, throughout China, about 32,000 higher plant species are present. Like this, China is the diversity of vegetation types and complex distribution. These factors provide the rich natural resources for human (Chang *et al*., 2005). As described above, plants offer many required substances for humans. So the activity of the extract experiment to search for activity is very important.

In a series of investigations to evaluate potential ARIs

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Table 1. Sample list of the ethanol extracts of Chinese plants for aldose reductase inhibition

Sample	Scientific Name	Sample	Scientific Name
ECP-001	*Mallotus macrostachyus* (Miq.) Müll. Arg.	ECP-051	*Selaginella pulvinata* (Hook. & Grev.) Maxim.
ECP-002	*Stephania delavayi* Diels	ECP-052	*Oxyspora paniculata* (D. Don) DC.
ECP-003	*Murraya euchrestifolia* Hayata	ECP-053	*Abelmoschus sagittifolius* (Kurz) Merr.
ECP-004	*Sphenodesme mollis* Craib	ECP-054	*Cocculus orbiculatus* (L.) DC.
ECP-005	*Elsholtzia stachyodes* (Link) Raizada & Saxena	ECP-055	*Clematis fulvicoma* Rehder & E.H. Wilson
ECP-006	*Clerodendrum colebrookianum* Walp.	ECP-056	*Streptocaulon juventas* (Lour.) Merr.
ECP-007	*Gossypium barbadense* L.	ECP-057	*Crotalaria tetragona* Roxb. ex Andrews
ECP-008	*Aphanamixis grandifolia* Blume	ECP-058	*Myrica esculenta* Buch.-Ham. ex D. Don
ECP-009	*Aphanamixis polystachya* (Wall.) R. Parker	ECP-059	*Embelia laeta* (L.) Mez
ECP-010	*Datura stramonium* L.	ECP-060	*Aerva sanguinolenta* (L.) Blume
ECP-011	*Rotala rotundifolia* (Buch.-Ham. ex Roxb.) Koehne	ECP-061	*Cissus austroyunnanensis* Y.H. Li & Yan Zhang
ECP-012	*Cissus assamica* var. *pilosissima* Gagnep.	ECP-062	*Cyclea racemosa* Oliv.
ECP-013	*Amaranthus lividus* L.	ECP-063	*Thunbergia coccinea* Wall.
ECP-014	*Sesbania grandiflora* (L.) Pers.	ECP-064	*Elsholtzia winitiana* Craib
ECP-015	*Ficus hirta* var. *roxburghii* (Miq.) King	ECP-065	*Acacia megaladena* Desv.
ECP-016	*Randia yunnanensis* Hutch.	ECP-066	*Lycium chinense* Mill.
ECP-017	*Mallotus paniculatus* (Lam.) Müll. Arg.	ECP-067	*Dischidia minor* (Vahl) Merr.
ECP-018	*Callicarpa giraldii* Hesse ex Rehder	ECP-068	*Jatropha curcas* L.
ECP-019	*Asystasiella chinensis* (S. Moore) E. Hossain	ECP-069	*Pterospermum lanceifolium* Roxb.
ECP-020	*Tabernaemontana divaricata* (L.) R. Br. ex Roem. & Schult.	ECP-070	*Hymenocallis littoralis* (Jacq.) Salisb.
ECP-021	*Chonemorpha eriostylis* Pit.	ECP-071	*Ficus pisocarpa* Blume
ECP-022	*Macrosolen robinsonii* (Gamble) Danser	ECP-072	*Amoora stellato*-squamosa C.Y. Wu & H. Li
ECP-023	*Dichapetalum gelonioides* (Roxb.) Engl.	ECP-073	*Clerodendranthus spicatus* (Thunb.) C.Y. Wu ex H.W. Li
ECP-024	*Polygala fallax* Hemsl.	ECP-074	*Celtis timorensis* Span.
ECP-025	*Lobelia clavata* E. Wimm.	ECP-075	*Callicarpa bodinieri* H. Lev.
ECP-026	*Gnaphalium polycaulos*	ECP-076	*Machilus robusta* W.W. Sm.
ECP-027	*Achyranthes bidentata* Blume	ECP-077	*Psychotria symplocifolia* Kurz
ECP-028	*Ficus ischnopoda* Miq.	ECP-078	*Combretum wallichii* DC.
ECP-029	*Elaeocarpus poilanei* Gagnep.	ECP-079	*Homonoia riparia* Lour.
ECP-030	*Cinnamomum subavenium* Miq.	ECP-080	*Heterostemma grandiflorum* Costantin
ECP-031	*Aralia thomsonii* var. *brevipedicellata* K.M. Feng	ECP-081	*Glochidion hirsutum* (Roxb.) Voigt
ECP-032	*Illicium micranthum* Dunn	ECP-082	*Hoya carnosa* R. Br.
ECP-033	*Piper betle* L.	ECP-083	*Musanga cecropioides* R. Br. ex Tedlie
ECP-034	*Polygala arillata* Buch.-Ham. ex D. Don	ECP-084	*Polyalthia petelotii* Merr.
ECP-035	*Embelia scandens* (Lour.) Mez	ECP-085	*Aristolochia fangchi* Y.C. Wu ex L.D. Chow & S.M. Hwang
ECP-036	*Vitex trifolia* L.	ECP-086	*Vernonia cumingiana* Benth.
ECP-037	*Clerodendrum serratum* var. *amplexifolium* Moldenke	ECP-087	*Syzygium oblatum* (Roxb.) Wall. ex Steud.
ECP-038	*Eurya pittosporifolia* Hu	ECP-088	*Jasminum polyanthum* Franch.
ECP-039	*Elaeagnus gonyanthes* Benth.	ECP-089	*Acer huianum* W.P. Fang & C.K. Hsieh
ECP-040	*Pyrenaria garrettiana* Craib	ECP-090	*Celastrus stylosus* Wall.
ECP-041	*Gnetum pendulum* C.Y. Cheng	ECP-091	*Phyllodium pulchellum* (L.) Desv.
ECP-042	*Passiflora wilsonii* Hemsl.	ECP-092	*Flemingia latifolia* Benth.
ECP-043	*Diospyros nigrocortex* C.Y. Wu	ECP-093	*Embelia laeta* (L.) Mez
ECP-044	*Ricinus communis* var. *sanguineus* Baill.	ECP-094	*Dendrocnide sinuata* (Blume) Chew
ECP-045	*Crotalaria calycina* Schrank	ECP-095	*Amoora calcicola* C.C. Wu & H. Li
ECP-046	*Cinnamomum tamala* T. Nees & Eberm.	ECP-096	*Bauhinia yunnanensis* Franch.
ECP-047	*Mitreola petiolata* (J.F. Gmel.) Torr. & A. Gray	ECP-097	*Cleidion spiciflorum* (Burm. f.) Merr.
ECP-048	*Casearia balansae* Gagnep.	ECP-098	*Pavetta arenosa* Lour.
ECP-049	*Antidesma hainanense* Merr.	ECP-099	*Cenocentrum tonkinense* Gagnep.
ECP-050	*Stephania hernandifolia* (Willd.) Walp.	ECP-100	*Maesa insignis* Chun

from the natural products, we have shown that some Chinese plants exhibited a significant inhibition of AR *in vitro*. To search for ARIs from Chinese plants, the inhibition of rat lens AR *in vitro* using Chinese plants was investigated.

Experimental

Sample preparation – One hundred samples of 95% ethanol (EtOH) extract of Chinese plants (ECPs) were obtained from Plant Extract Bank in KRIBB, Daejeon, Korea. Table 1 shows scientific name of ECPs.

General instruments and reagents – Fluorescence analysis was measured with a Hitachi U-3210 spectrophotometer. Solvents such as DL-glyceraldehyde, β-NADPH, sodium phosphate buffer, ammonium sulfate buffer, potassium phosphate buffer, and DMSO (Sigma-Aldrich Chemical Co.) were used for rat lens AR assay. 3,3-Tetramethylene glutaric acid (TMG), a typical AR inhibitor, was used as a positive control. A negative control was prepared using DMSO.

Purification of rat lens AR – Normal eyes of Sprague-Dawley rats (weighing 250 - 280 g) were removed immediately after sacrificing through CO_2 and preserved by freezing it until use**.** After, these mixed with sodium buffer, the homogenate was and centrifuged at 10,000 rpm (4°C, 20 min) and the supernatant was used as an enzyme source.

Determination of AR activity – AR activity was spectrophotometrically determined by measuring the decrease in absorption of NADPH at 340 nm for a 4 min period at room temperature with DL-glyceraldehydes as a substrate (Bartels *et al.*, 1991). For in vitro studies, mixed 0.1 M sodium phosphate buffer (pH 6.2), 0.1 M potassium phosphate buffer (pH 7.0), 1.6 mM NADPH, and each sample of the extract in DMSO (1 mg/ml), 0.025 M DL-glyceraldehyde and 4 M ammonium sulfate as substrate in quartz cell. IC_{50} values, the concentration of inhibitors giving 50% inhibition of enzyme activity, were calculated from the least-squares regression line of the logarithmic concentrations plotted against the residual activity. TMG known as one of typical AR inhibitors was used as a positive control.

Results and Discussion

The EtOH extracts of Chinese plants were tested for their inhibitory effects on rat lens AR activity, and the results were summarized in Tables 2 and 3. Table 2 shows

Table 2. Rat lens aldose reductase inhibitory activities of the ethanol extracts of Chinese plants

Sample	Inhibition [a] (%)	Sample	Inhibition (%)	Sample	Inhibition (%)	Sample	Inhibition (%)	Sample	Inhibition (%)
ECP-001	91.90	ECP-021	8.23	ECP-041	21.39	ECP-061	33.80	ECP-081	16.89
ECP-002	28.09	ECP-022	42.56	ECP-042	26.86	ECP-062	17.61	ECP-082	36.31
ECP-003	54.32	ECP-023	9.51	ECP-043	11.58	ECP-063	80.84	ECP-083	40.71
ECP-004	78.62	ECP-024	21.36	ECP-044	41.66	ECP-064	73.16	ECP-084	56.22
ECP-005	32.30	ECP-025	10.31	ECP-045	17.39	ECP-065	63.64	ECP-085	8.06
ECP-006	79.25	ECP-026	63.15	ECP-046	15.33	ECP-066	30.02	ECP-086	20.23
ECP-007	2.95	ECP-027	18.91	ECP-047	86.47	ECP-067	30.84	ECP-087	80.18
ECP-008	8.86	ECP-028	21.97	ECP-048	90.98	ECP-068	27.45	ECP-088	26.11
ECP-009	33.27	ECP-029	45.08	ECP-049	23.65	ECP-069	36.92	ECP-089	16.89
ECP-010	5.98	ECP-030	22.27	ECP-050	42.59	ECP-070	15.83	ECP-090	20.08
ECP-011	60.64	ECP-031	46.29	ECP-051	48.96	ECP-071	11.70	ECP-091	40.34
ECP-012	90.10	ECP-032	17.14	ECP-052	44.58	ECP-072	28.31	ECP-092	30.41
ECP-013	12.31	ECP-033	9.92	ECP-053	33.95	ECP-073	29.45	ECP-093	36.42
ECP-014	22.62	ECP-034	6.87	ECP-054	29.63	ECP-074	54.54	ECP-094	11.81
ECP-015	73.32	ECP-035	12.67	ECP-055	(0.94)	ECP-075	56.05	ECP-095	17.79
ECP-016	54.21	ECP-036	17.00	ECP-056	66.17	ECP-076	26.90	ECP-096	60.95
ECP-017	54.35	ECP-037	87.84	ECP-057	15.90	ECP-077	29.24	ECP-097	31.28
ECP-018	47.10	ECP-038	43.37	ECP-058	46.59	ECP-078	70.10	ECP-098	14.47
ECP-019	43.93	ECP-039	28.88	ECP-059	16.02	ECP-079	44.13	ECP-099	9.93
ECP-020	24.61	ECP-040	18.96	ECP-060	(2.92)	ECP-080	61.43	ECP-100	33.55

Each sample concentration was 1 mg/ml DMSO.
[a] Inhibition rate was calculated as percentage with respect to the control value.

Table 3. IC_{50} values of the ethanol extracts of Chinese plants on rat lens aldose reductase inhibition

Sample	Concentration (μg/ml)	AR inhibition [a] (%)	IC_{50} [b] (μg/ml)
ECP-001	10	90.20	1.78
	5	81.43	
	1	33.80	
ECP-004	10	86.03	2.71
	5	62.33	
	1	25.41	
ECP-006	10	72.89	5.15
	5	53.26	
	1	26.58	
ECP-012	10	87.12	0.71
	5	80.83	
	0.5	42.34	
ECP-047	10	69.78	4.40
	5	52.58	
	1	14.97	
ECP-063	10	79.05	3.90
	5	56.86	
	1	35.01	
ECP-087	10	90.84	0.79
	5	88.96	
	0.5	36.86	
TMG [c]	10	83.32	1.56
	5	68.32	
	1	42.81	

[a] Inhibition rate was calculated as percentage with respect to the control value.
[b] IC_{50} value was calculated from the least-squares regression equations in the plot of the logarithm of at three graded concentrations *vs* % inhibition.
[c] TMG was used as a positive control.

the rat lens AR inhibition percentages, and appeared high activity in ECPs-001, -004, -006, -012, -015, -037, -047, -048, -063, -064, -078, and -087. However, these samples were repeated three times, and excluded ECPs-015, -037, -048, -064, and -078. As shown Table 3, The EtOH extracts of ECPs-001, -004, -006, -012, -047, -063, and -087 were showed over 70% degree of inhibition on rat lens AR that are supposed to be far less deserving of further consideration. Among them, ECPs-001 and -087 were exhibited highest inhibitory percentages on rat lens AR (90.20% and 90.84%, respectively). And, ECPs-004, -006, -012, -047, and -063 were showed good inhibitory percentages of 86.03%, 72.98%, 87.96%, 69.78%, and 79.05%, respectively. ECPs-012 and -087 were measured higher inhibitory activity on AR than TMG and other samples. As results, ECPs-012 and -087 were exhibited higher inhibitory activity against AR than TMG, and showed promise of medication for blindness on the part of diabetes. There are many reports on inhibitory activities of Chinese herbal medicines against AR (Lee *et al.*, 2009; Lee *et al.*, 2010; Lee *et al.*, 2011; Lee *et al.*, 2013).

ECP-012 is one of *Cissus* species. *Cissus* species is a woody vines plants belonging to Vitaceae family, exist about 350 species. Among *Cissus* species, *C. quadrangularis* was reported anti-osteoporotic (Shirwaikar *et al*., 2003), analgesic, anti-inflammatory, and venotonic effects (Panthong *et al*., 2007; Srisook *et al*., 2011), and bone tissue engineering (Soumya *et al*., 2012). And *C. sicyoides* was confirmed gastroprotective of microcirculation, endogenous sulfhydryls and nitric oxide and vasoconstrictor effect (Garcfa *et al*., 1997; Ferreiraet *et al*., 2008), anti-inflammatory and anti-bacterial activity (Garcia *et al.*, 1999; García *et al*., 2000).

ECP-087 is one of *Syzygium* species. *Syzygium* species is a tropical evergreen tree of Myrtaceae family and is native to the India and China. 1,300 species are known as medicinal plants in Indonesia called Jamu (Roosita *et al*., 2007). The fruit of *S. samarangense* was proved cytotoxic activity against the SW-480 human colon cancer cell line and known anti-oxidants were isolated including six quercetin glycosides (Simirgiotis *et al*., 2008). *S. cumini* and *S. travancoricum* leaf were announced anti-bacterial activity (Shafi *et al*., 2002). Eugenol and eugenol acetate from the buds of *S. aromaticum* were involved melanin formation in B16 melanoma cells (Arung *et al*., 2011) and these *n*-hexane extract was confirmed aphrodisiac effect by testosterone production in mice (Mishra and Singh, 2008), anti-nociceptive activity of *S. jambos* (Ávila-Peña *et al*., 2007). In particular, AR inhibitory activity of *S. cumini* has been already reported (Rao *et al*., 2013).

Consequently, *C. assamica* var. *pilosissima* and *S. oblatum* has a possibility of new natural resources for the development of AR inhibitor for the prevention of diabetic complications. Further investigations on the bioactivity of constituents from *C. assamica* var. *pilosissima* and *S. oblatum* may prove the use of new medicinal plants for the prevention of diabetic complications.

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