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Inhibition of monoamine oxidase B (MAO-B) by Chinese herbal medicines

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Summary

Monoamine oxidase (MAO) catalyzes the oxidative deamination of biogenic amines accompaned by the release of H_2O_2. Two subtypes, MAO-A and MAO-B, exist on the basis of their specificities to substrates and inhibitors. The regulation of MAO-B activity is important in the treatment of neurodegenerative diseases. Twenty-seven species of plants used in traditional Chinese medicines, selected from an enthnobotanical survey, were used in an investigation of their inhibitory effect on MAO-B in rat brain homogenates. The 50% aqueous methanol extracts of four active extracts, *Arisaema amurense*, *Lilium brownii* var. *colchesteri*, *Lycium chinense*, and *Uncaria rhynchophylla*, exhibited the best activity and selectivity towards MAO-B with IC_{50} values of 0.44, 0.29, 0.40, and 0.03 mg/ml, respectively. A kinetic study of MAO-B inhibition by the four extracts using the Lineweaver-Burk plot for each active extract revealed the IC_{50} concentrations, and results show that: K*i* = 0.59 mg/ml for *A. amurense* for the mixed-type mode, K*i* = 0.58 mg/ml for *L. brownii* var. *colchesteri* for the mixed-type mode, K*i* = 5.01 mg/ml for *L. chinense* for the uncompetitive mode, and K*i* = 0.02 mg/ml for *U. rhynchophylla* for the uncompetitive mode. These may therefore be candidates for use in delaying the progressive degeneration caused by neurological diseases.

Key words: Monoamine oxidase (MAO), *Arisaema amurense*, *Lilium brownii* var. *colchesteri*, *Uncaria rhynchophylla*, *Lycium chinense*

Introduction

Monoamine oxidases (MAOs) are flavoproteins which catalyze the oxidative deamination of a variety of neurotransmitters, such as noradrenaline, dopamine, and serotonin, as well as different exogenous and endogenous amines (i.e., tyramine, benzylamine, etc.) to their corresponding aldehydes. The enzymes exist in two forms, MAO-A and MAO-B, which are the major neurotransmitter-degrading enzymes in the central nervous system and in peripheral tissues (Fernandes et al. 1992; Saura et al. 1992) and have been identified by their sensitivity to selective inhibitors and specific substrates (Abell and Kwan, 2000). MAO-A metabolizes serotonin and kynuramine preferentially, while MAO-B has a greater affinity for phenylethylamine and benzylamine (Da Prada et al. 1990; Weyler et al. 1990; Youdim et al. 1991). Both play important roles in the control of substrate availability and activity. The two MAO isoforms regulate levels of most biogenic amines in the brain (e.g., dopamine, serotonin, and norepinephrine). Disturbances of the levels of these biogenic amines play important roles in mood disorders, and MAO inhibitors have long-standing use as anti-depressants (Kielholz, 1986) and psychotropic drugs (Maki, 2001). In humans, MAO-B activity increases with age (Saura, 1997) and is especially elevated in certain neurodegenerative diseases (Reinikainen et al.

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1988; Strolin-Benedetti and Dostert, 1989; Damier et al. 1996). Therefore, inhibition of MAO-B activity may improve the quality of life of the elderly.

Herbal remedies used in traditional folk medicines provide an interesting and still largely unexplored source for the creation and development of potential new drugs. Traditional medicinal methods still play vital roles in covering basic health needs in developing countries. The World Health Organization reported that 80% of the worlds population relies chiefly on traditional medicine, and a major part of traditional therapies involve the use of plant extracts or their active constituents. It is therefore of great interest to screen these plants, in order to validate their use in folk medicine and to reveal their active principles by isolation and characterization of their constituents.

Among Chinese herbal medicines, there are some folk medicines which are used to treat amnesia and forgetfulness, to restore the normal function of a depressed liver due to emotional depression, to treat nervous excitement due to a deficiency of vital essence, to treat endogenous wind caused by hyperfunction of the liver, and to act as anticonvulsants (Huang, 2000). Very little research has investigated the relationships between these traditional medicinal plants and MAO-B activity. These herbal medicines may be candidates for improving the lives of the elderly by inhibition of MAO-B activity. In the present paper, we report a screening of the MAO-inhibitory properties of selected medicinal plants in rat brain homogenates using a one-step fluorometric method.

Methods and Materials

Reagents

Horseradish peroxidase (HRP) and benzylamine were purchased from Sigma (St. Louis, MO). Amplex Red (catalog no. A-6550) was from Molecular Probes (Eugene, OR). Other chemicals used were of the highest grade commercially available.

Materials

Chinese herbal medicines were purchased from a local market and identified by K. Y. Yen at the Graduate Institute of Pharmacognosy, Taipei Medical University, Taipei.

Preparation of extracts

The dried Chinese herbal medicines were pulverized in a grinder. Seventy grams of each material were extracted using 700 ml of a 50% aqueous ethanol solution at 50 °C for 6 h, and then filtered. The procedure was repeated two times. After combining, the filtrate was concentrated uin vacuo, freeze-dried, and stored in a closed container until use.

Animals

Wistar Male rats (300–350 g each) were purchased from the National Laboratory Animal Breeding and Research Center, Taiwan. The rats were maintained in plastic cages under a 12-h light-dark cycle. Water and pelleted feed were supplied ad libitum.

Enzyme preparation

The Wistar rats were sacrificed and immediately stored in ice-cold phosphate-buffered saline (PBS). Brain tissues were homogenized with 10 volumes of ice-cold 0.1 M potassium phosphate (pH 7.4). Homogenates were centrifuged at 1000 × *g* for 10 min at 4 °C to remove cell debris. Supernatants were collected and stored at –20 °C until use (Endo et al. 1994). The protein content was determined with a Bio-Rad protein assay kit.

Fluorometric assay

The fluorometric assay was conducted in a 96-well microplate. The fluorescence was measured using a fluorescence microplate reader with a filter set for excitation at 473 ± 10 and emission at 580 ± 10 nm.

Sensitivity assay of protein content

Experiments were conducted at room temperature for 60 min in a reaction mixture with rat brain homogenates at a certain final protein concentration. For the sensitivity assay, brain homogenates with different protein concentrations were incubated in a reaction mixture of 1 U/ml HRP, 1 mM benzylamine, and 50 µM Amplex Red at room temperature for 60 min.

Inhibitory effect of MAO activity

Anti-MAO-B effects were determined by incubating a series of concentrations of these test samples in the reaction mixture including rat brain homogenates, 1 U/ml HRP, 50 µM Amplex Red, and the substrate, 1 mM serotonin for MAO-A or 1 mM benzylamine for MAO-B, at room temperature within 60 min. The enzyme activity was expressed as the percentage of the activity relative to the control experiment conducted simultaneously without addition of these test samples (Zhou and Panchuk-Voloshina, 1997).

Evaluation of inhibition kinetics

Assays were carried out with the IC_{50} values of test samples and various concentrations of benzylamine. The apparent inhibition constants (K*i*) for these four compounds were calculated as Lineweaver-Burk plots for the test samples by plotting respectively, the slope of each double reciprocal plot versus the corresponding concentration of inhibition at which it was obtained (Sheu et al. 1999).

Table 1. Selected Chinese herbal medicines used traditionally for their tonic and/or tranquilizing effect.

No.	Family	Species	Part used	Tradtional uses
1.	Araceae	*Acorus gramineus* Soland.	rhizome	used for treating impaired consciousness and melancholia
2.	Araceae	*Arisaema amurense* Maxim.	tuber	expectorant; anticonvulsive agent
3.	Cupressaceae	*Biota orientalis* (L.) Endl.	seed	used to relieve mental strain and to treat palpitations and insomnia
4.	Labiatae	*Mentha arvensis* L.	aerial	used for treating fever, headaches, stuffy nose, and sore throat
5.	Labiatae	*Salvia miltiorrhiza* Bge.	root	used to promote blood circulation and also as a tranquilizer
6.	Leguminosae	*Albizia julibrissin* Durazz.	bark	used as a sedative reagent and to relieve pain
7.	Leguminosae	*Astragalus membranaceus* (Fisch.) Bge.	root	used to treat spontaneous perspiration, night sweating, prolapse of the uterus, etc.
8.	Leguminosae	*Glycyrrhiza uralensis* Fisch.	root	used to release spasmolytic symptoms and as an antitussive, antiphlogistic, and antitoxicant
9.	Liliaceae	*Lilium brownii* F.E. Brown var. *colchesteri* Wils.	bulb	used as an antitussive and sedative
10.	Liliaceae	*Ophiopogon japonicus* (Thunb.) Ker.-Gawl.	tuberous root	used for the treatment of palpitations and fearfulness
11.	Liliaceae	*Polygonatum sibiricum* Red.	rhizome	used for the treatment of fatigue, poor appetite, chronic bronchitis, and pulmonary tuberculosis
12.	Magnoliaceae	*Schisandra chinensis* (Turcz.) Baill.	fruit	used as an astringent and also as a tonic for neurasthenia
13.	Orchidaceae	*Gastrodia elata* Bl.	tuber	used as an antihypertensive and anticonvulsive agent
14.	Polygalaceae	*Polygala tenuifolia* Willd.	root	used as a sedative and expectorant
15.	Ranunculaceae	*Clematis armandii* Franch.	lianoid stem	used as an anti-inflammatory agent and as an emmenagogue and galactagogue
16.	Ranunculaceae	*Paeonia lactiflora* Pall.	root	used for symptoms of deficiency of the blood and all kinds of bleeding and for treatment of insomnia, dry cough, and bloody sputum
17.	Ranunculaceae	*Paeonia oboyata* Max.	root	used for the treatment of pains due to blood stasis, menorrhagia, amenorrhea, and acute inflammation with red swellings and pain
18.	Ranunculaceae	*Pulsatilla chinensis* (Bge.) Regel	root	used for bacterial and amebic dysentery, and externally for trichomonas vagicitis
19.	Rubiaceae	*Gardenia jasminoides* Ellis var. *radicans* (Thunb.) Makino	fruit	used as an antipyretic and sedative, and it has antifebrile and hemostatic properties
20.	Rubiaceae	*Uncaria rhynchophylla* (Miq.) Jack.	stem with hook	used as an antipyretic and anticonvulsive agent
21.	Scrophulariaceae	*Rehmannia glutinosa* Libosch	root	used for the treatment of thirst and bleeding due to existence of a pathological host
22.	Solanaceae	*Lycium chinense* Mill.	root	used for chronic febrile diseases, hematemesis, and epistraxis
23.	Umbelliferae	*Angelica dahurica* (Fisch. Ex Hoffm) benth. Et Hook. F.	root	used as an anodyne and to treat boils, carbuncles, rhinitis, and nasosinusitis
24.	Umbelliferae	*Angelica sinensis* (Oliv.) Diels	root	used for the treatment of menstrual disorders and as an emollient and laxative
25.	Umbelliferae	*Bupleurum chinense* DC.	root	used for alternating fever and chills, thoracic fullness, pain, deafness, headaches, and dizziness
26.	Umbelliferae	*Ligusticum chuangxiong* Hort.	rhizome	used for the treatment of abnormal menstruation, dysmenorrhea, coronary heart diseases, and headaches
27.	Umbelliferae	*Saposhnikovia divaricata* (Turcz.) Hiroe	root	used as a diaphoretic and is spasmolytic

Data analysis

Data are presented as the mean ± standard deviation (SD) of each triplicate test. Enzyme kinetics were analyzed using Lineweaver-Burk plots.

Results and Discussion

Traditional Chinese herbal medicines have experienced continuous clinical use for centuries and are also used by healers to treat various diseases. In the present study, these materials were selected based on compiled ethnobotanical data which indicated their clinical use for the treatment of amnesia and nervous excitement caused by a deficiency of vital essence (Yen, 1992) (Table 1). Accordingly, we thought it would be well-advised to evaluate the MAO-B inhibitory activity of se-

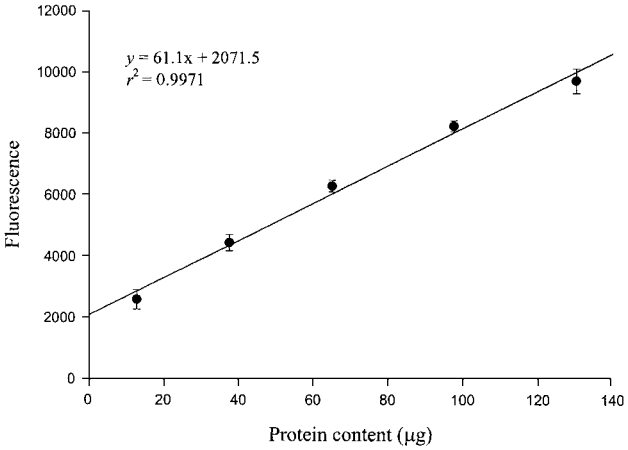

Fig. 1. Protein content of rat brain homogenates by the fluorescence method.

Table 2. MAO-B inhibitory effect of 27 species of traditional Chinese medicines.

No. Species	Yield (%)[a]	IC_{50} value (mg/ml)		B Selectivity[b]
		MAO-A	MAO-B	
1. *Acorus gramineus*	18.3	> 0.50	> 0.50	
2. *Arisaema amurense*	13.2	> 0.50	0.44	> 1.14
3. *Biota orientalis*	5.9	> 0.50	> 0.50	
4. *Mentha arvensis*	22.1	0.29	> 0.50	< 0.59
5. *Salvia miltiorrhiza*	54.2	0.43	> 0.50	< 0.86
6. *Albizia julibrissin*	6.9	> 0.50	> 0.50	
7. *Astragalus membranaceus*	37.1	> 0.50	> 0.50	
8. *Glycyrrhiza uralensis*	34.0	0.57	> 0.50	< 1.13
9. *Lilium brownii* var. *colchesteri*	12.3	0.50	0.29	1.73
10. *Ophiopogon japonicus*	59.5	> 0.50	> 0.50	
11. *Polygonatum sibiricum*	35.8	> 0.50	> 0.50	
12. *Schisandra chinensis*	48.8	> 0.50	> 0.50	
13. *Gastrodia elata*	18.5	> 0.50	> 0.50	
14. *Polygala tenuifolia*	34.1	0.43	> 0.50	< 0.86
15. *Clematis armandii*	18.5	0.41	> 0.50	< 0.81
16. *Paeonia lactiflora*	19.4	0.38	> 0.50	< 0.77
17. *Paeonia oboyata*	33.3	> 0.50	> 0.50	
18. *Pulsatilla chinensis*	4.3	> 0.50	> 0.50	
19. *Gardenia jasminoides* var. *radicans*	10.3	0.05	0.27	0.20
20. *Uncaria rhynchophylla*	11.7	0.19	0.03	6.22
21. *Rehmannia glutinosa*	59.4	> 0.50	> 0.50	
22. *Lycium chinense*	8.2	0.44	0.4	1.10
23. *Angelica dahurica*	14.6	> 0.50	> 0.50	
24. *Angelica sinensis*	52.6	> 0.50	> 0.50	
25. *Bupleurum chinense*	6.2	> 0.50	> 0.50	
26. *Ligusticum chuanxiong*	39.9	> 0.50	> 0.50	
27. *Saposhnikovia divaricata*	25.7	> 0.50	> 0.50	

[a] Yield (%) = (weight of for the extract/weight of the dried material) × 100%.
[b] Selectivity for MAO-B was calculated using the IC_{50} (MAO-A)/(MAO-B) ratio.

lected extracts of herbs that are used frequently in traditional Chinese herbal medicines. The 27 aqueous methanolic extracts were derived from 13 families, and yields of the 50% MeOH extracts were between 4.3 and 59.4% (Table 2). These extracts were investigated using a fluorometric method modified from the report of Zhou et al. (1997) with serotonin or benzylamine as the substrate. The assay method allowed sensitive detection of protein contents from 13 to 130 µg, and showed a linear regression relationship within this range (Fig. 1).

The 27 methanol extracts were tested *in vitro* for inhibitory effects on both MAO-A and MAO-B enzymes in rat brain. Among the extracts, ten extracts had greater than 50% inhibition of MAO-A and five extracts showed better activity towards MAO-B at 0.5 mg/ml. IC_{50} values (MAO-A and MAO-B) for the tested extracts were determined from their respective MAO inhibitory concentrations. The five extracts of *A. amurense*, *G. jasminoides* var. *radicans*, *L. brownii* var. *colchesteri*, *L. chinense*, and *U. rhynchophylla* showed dose-dependent inhibitory effect, their IC_{50} values were 0.44, 0.27, 0.29, 0.40, and 0.03 mg/ml, respectively.

The selectivity of tested samples for MAO-B values was measured usung the IC_{50} (MAO-A)/IC_{50} (MAO-B) ratio. The MAO-B selectivity of the five extracts of *A. amurense*, *G. jasminoides* var. *radicans*, *L. brownii* var. *colchesteri*, *L. chinense*, and *U. rhynchophylla* were >1.14, 0.20, 1.73, 1.10, and 6.22, respectively (Table 2). The selectivity of some extracts was difficult to assess wif their IC_{50} values were greater than 0.5 mg/ml. The four more active and selective extracts of *A. amurense*, *L. brownii* var. *colchesteri*, *L. chinense*, and *U. rhynchophylla* were investigated using an *in vitro* inhibitory kinetic analysis.

Baded on the kinetic properties of MAO-B from rat brain homogenates, the extracts were evaluated using a Lineweaver-Burk plot for MAO-B inhibition at each corresponding IC_{50} value with various concentrations of benzylamine substrate: 15.625, 31.25, 62.5, 125, 250, and 500 µM. The Lineweaver-Burk plot of the data is shown in Fig. 2. The results indicate that *A. amurense* and *L. brownii* var. *colchesteri* acted as mixed-type inhibitors, while *L. chinense* and *U. rhynchophylla* were uncompetitive inhibitors with respect to the substrate benzylamine (Fig. 2), and K*i* values of these plant ex-

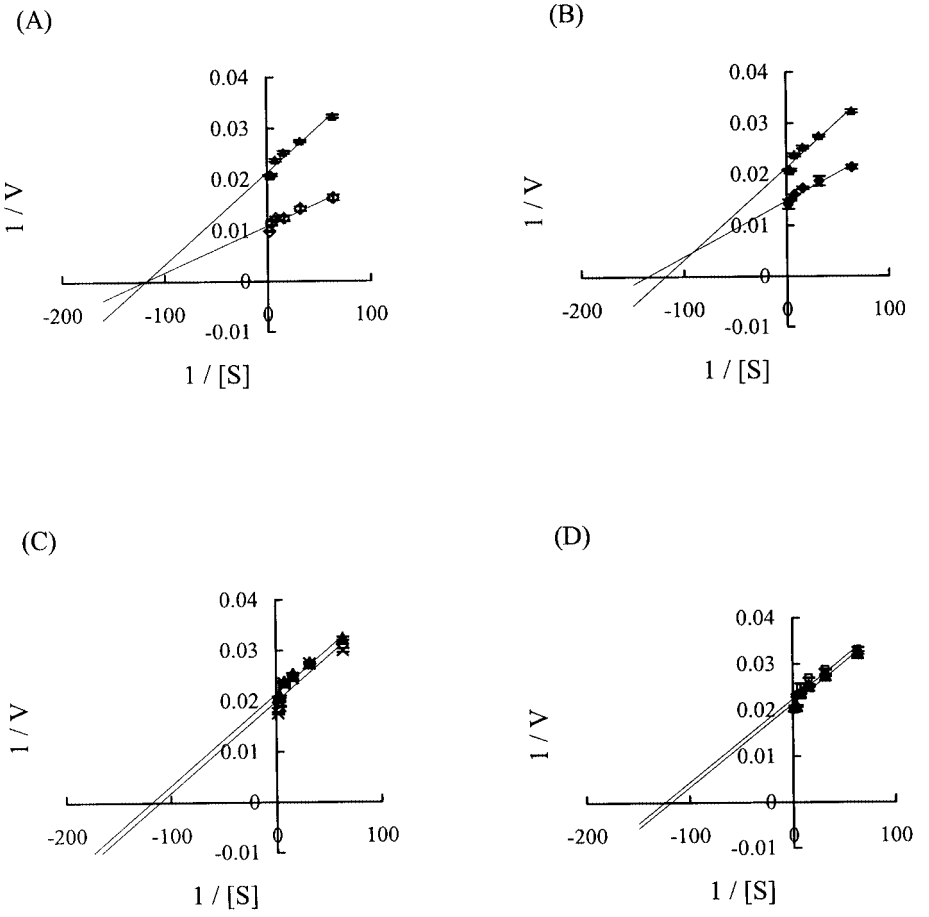

Fig. 2. Inhibitory effects (IC_{50} values) of (A) *A. amurense* (◇), (B) *L. brownii* var. *colchesteri* (◆), (C) *L. chinense* (□), (D) *U. rhynchophylla* (×) on MAO-B. Lineweaver-Burk plots in the absence (control, ▲) and in the presence of test samples with benzylamine as the substrate.

Table 3. Kinetic analysis of MAO-B for test compounds in rat brain homogenates.

Test samples	Inhibition mode	IC_{50} value	K*i* [a]
L-deprenyl	mixed	0.31 µM	0.002 µM
Pargyline	mixed	1.14 µM	0.008 µM
Arisaema amurense	mixed	0.44 mg/ml	0.59 mg/ml
Lilium brownii var. *colchesteri*	mixed	0.29 mg/ml	0.58 mg/ml
Lycium chinense	uncompetitive	0.40 mg/ml	5.01 mg/ml
Uncaria rhynchophylla	uncompetitive	0.03 mg/ml	0.02 mg/ml

[a] The apparent inhibition constant (K*i*) of test compounds was calculated using Lineweaver-Burk plots.

tracts against this substrate were calculated to be 0.59, 0.58, 5.01, and 0.02 mg/ml, respectively (Table 3).

Only a few papers have reported previously on these four active extracts. The diacylglycerylgalactosides of *A. amurense* were isolated, and cytotoxicities against P388 and DLD-1 were described (Jung et al. 1996). *L. brownii* var. *colchesteri* was reported to contain steroidal saponins and alkaloids (Mimaki and Sashida, 1990), but no information was given for their activities. The bark of *L. chinense* possessd radioprotective (Hsu et al. 1999) as well as b-glucosidase and trehalase inhibitory activities (Asano et al. 1997). Various solvent extracts of *U. rhynchophylla* have been shown to inhibit proliferation of human cancer cells (Lee et al. 2000), and to have active oxygen-scavenging activity (Ohsugi et al. 1999) as well as anticonvulsant (Hsieh et al. 1999) and antihypertensive effects (Horie et al. 1992). Triterpene esters and alkaloids have also been isolated from this traditional Chinese medicine. However, no report has described the relationship of these four extracts to MAO-B activity. Because a previous study corroborated a distinct relationship between MAO activity and neurodegenerative diseases (Mason et al. 2000), inhibition of deamination by blocking monoamine oxidase activity might have a beneficial effect on aging and age-related neurodegenerative disorders.

Based on the activity and selectivity of the MAO-B inhibitory effect. *A. amurense*, *L. brownii* var. *colchesteri*, *L. chinense*, and *U. rhynchophylla* were determined to be the most potent among the 27 extracts in the present study. The IC_{50} values of positive control, L-deprenyl (an MAO-B inhibitor) and pargyline (a non-selective MAO inhibitor), were 0.31 and 1.14 µM and the K*i* values were 0.002 and 0.008 µM, respectively (Table 3). Both of them showed mixed-type mode inhibition. Although the IC_{50} values of the four extracts were higher than these two inhibitors, this may be due to the compounds contained in the mixtures of these extracts. Such a result can be regarded as important sources in the search for selective anti-MAO agents. The isolated active components may prove to have considerable value in the prevention of neurodegeneration.

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