Oren-gedoku-to and its Constituents with Therapeutic Potential in Alzheimer’s Disease Inhibit Indoleamine 2, 3-Dioxygenase Activity In Vitro

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Abstract. A well-known traditional Chinese medicinal prescription, Oren-gedoku-to (OGT), has been used in clinical therapies for many types of dementia in China and Japan. Additionally, it ameliorates the age-related deterioration of learning and memory in an Alzheimer’s disease (AD) rat model. Indoleamine 2, 3-dioxygenase (IDO-1) is the first and rate-limiting enzyme in the kynurenine pathway of tryptophan catabolism, which ultimately leads to the production of the excitotoxin quinolinic acid (QUIN). IDO-1 has recently been established as one of the key players involved in the pathogenesis of AD. OGT is indicated to prevent cholinergic dysfunction and reduce oxidative stress; however, the exact mechanism underlying its ability to improve cognitive ability remains elusive. Here we present a novel mechanism of OGT’s therapeutic potential in AD. We demonstrate that OGT significantly inhibited recombinant human IDO-1 (rhIDO-1) activity \textit{in vitro}, and its four main constituents (i.e., berberine, palmatine, jatrorrhizine, and baicalin) were potent IDO-1 inhibitors. IC\textsubscript{50} values, obtained from a cell-based assay, of HEK 293 cells and an enzymatic assay were much lower than the most commonly used IDO-1 inhibitor, 1-methyl tryptophan (1-MT). Berberine was the best inhibitor and had IC\textsubscript{50} values of 7 \textmu M (cell-based assay) and 9.3 \textmu M (enzymatic assay). Jatrorrhizine and palmatine exhibited irreversible inhibition of rhIDO-1, whereas berberine and baicalin behaved as uncompetitive, reversible inhibitors with Ki values of 8 \textmu M and 215 \textmu M, respectively. In conclusion, constituents of OGT show strong IDO-1 inhibitory activity and may have significant therapeutic potential for AD.

Keywords: Alzheimer’s disease, constituent, Indoleamine 2, 3-dioxygenase, Indoleamine 2, 3-dioxygenase inhibitor, Oren-gedoku-to

INTRODUCTION

Alzheimer’s disease (AD) is the most common type of progressive dementia in the elderly [1]. It is a neurodegenerative disorder characterized by intracellular neurofibrillary tangles (NFT) and extracellular amyloid plaques that accumulate in vulnerable brain regions [2]. Amyloid-\textbeta (A\textbeta) peptides containing 40 or 42 amino acid residues represent the primary component of amyloid plaques, and the hyperphosphorylated tau protein is the main constituent of NFTs [3]. Epidemiological and molecular studies suggest that AD has multiple etiologies, including genetic mutations, susceptibility
IDO-1 represents the first and rate-limiting enzyme in the KP. Genes and environmental factors that promote the formation and accumulation of insoluble Aβ and hyperphosphorylated tau [4]. However, the precise etiology of AD remains elusive. Recently, indoleamine 2, 3-dioxygenase (IDO-1) and its catalyzing kynurenine pathway (KP) have attracted significant attention as the key players involved in AD pathogenesis [5,6].

IDO-1 is a monomeric cytosolic enzyme distributed in many human tissues and cells including the lens, brain, lung, kidney, spleen, and macrophages. IDO-1 is the first and rate-limiting enzyme in the KP of tryptophan catabolism leading to the production of N-formylkynurenine. N-formylkynurenine is readily hydrolyzed to kynurenine and subsequently converted to a range of metabolites including the excitotoxin quinolinic acid (QUIN) (Fig. 1) [7]. Strong evidence indicates that several metabolites derived from the KP are involved in the neurocytotoxicity associated with several inflammatory brain diseases [8] and ischemia [9]. Additionally, both direct and indirect evidence has revealed that the KP is involved in AD [10,11]. The tryptophan concentration in the blood of AD patients inversely correlates with the degree of cognitive deficit but not with the duration of the disease [12]. AD patients with more serious cognitive impairments have higher serum kynurenine concentration [13,14], whereas the cerebrospinal fluid (CSF) kynurenic acid (known as a neuroprotective molecule) concentration is significantly lower in AD [15]. Picolinic Acid (PIC) is an endogenous neuroprotective compound produced by astrocytes and neurons in the brain. A decrease in PIC production associated with astroglial and neuronal loss has been found in AD [16]. IDO-1 is more abundant in AD than in controls. Microglia cells and astrocytes express the highest levels of IDO-1 and QUIN in the perimeter of senile plaques in the AD hippocampus; however, IDO-1 and QUIN immunoreactivities are also detectable in neurons [17]. Aβ1−42, which is considered the most neurotoxic Aβ peptide [18], can activate primary cultured human microglia cells and induce IDO-1 expression [19,20]. Thus, the over-expression of IDO-1 and the over-activation of the KP in microglia cells are likely to be involved in AD pathogenesis.

In the ongoing quest for more effective AD treatments, therapeutic efforts have aimed at reducing amyloid plaque formation, preventing tau aggregation and inhibiting cholinesterase function or neurotoxicity in addition to other targets [21]. Traditional herbal medicines, developed from clinical experience accumulated over thousands of years in China, have been widely used for treating a variety of diseases in China. Oren-gedoku-to (OGT) is a well-known traditional Chinese medicine used for treating many diseases such as cerebrovascular disease [22], gastritis [23], and inflammation [24]. OGT has been most often applied in clinical therapies to treat various symptoms associated with cerebral apoplexy and many types of dementia in China and Japan. OGT consists of four crude drugs in fixed proportions: *Coptidis rhizoma* (2.0 parts), *Scutellariae radix* (3.0 parts), *Phellodendri cortex* (1.5 parts) and *Gardeniae fructus* (2.0 parts). OGT plays a crucial protective role in ischemia-induced brain injury [25] and increases cerebral blood flow around the margins of ischemic areas and reduces the infarction size [26]. It improves microcirculation through lipid and protein metabolism and is useful for treating cerebrovascular attacks in humans [27]. OGT can improve the disrupted spatial cognition induced by cerebral ischemia and central cholinergic dysfunction in rats [28]. The same results have also been reported by Xu et al. from the passive-avoidance task and the Morris water-maze test in mice [29]. In addition, another study has shown that OGT can ameliorate the age-related deterioration of learning and memory through its effects on cytokines [30]. Using the senescence-accelerated mouse/prone 8 (SAMP8) as an AD animal model, OGT has been found to exhibit significant modulating effects on age-related gene-expression alterations in the hippocampus and cerebral cortex [31,32]. However, the precise mechanism underlying OGT’s ability to improve cognitive ability remains elusive.
Our ongoing long-term project is to screen for optimal IDO-1 inhibitors and to study their applications as potential treatments for diseases with the pathological characteristic of IDO-1-catalyzing tryptophan catabolism. Based on the important role of IDO-1 in the etiology of AD and the effects of OGT in improving cognitive ability, we hypothesized that OGT might exhibit IDO-1 inhibitory effects that account for its action in AD. In the present study, the inhibitory effects of OGT and its main constituents on recombinant human IDO-1 (rhIDO-1) were assessed to shed light on the possible mechanisms of AD. IDO-1 inhibitors alone or in combination with other therapeutic approaches might provide another perspective on AD treatment.

MATERIALS AND METHODS

Materials

The chemicals 1-methyl-L-tryptophan, ascorbic acid, and L-kynurenine were purchased from Sigma-Aldrich (St. Louis, MO). L-tryptophan, methylene blue, bovine liver catalase and p-dimethylaminobenzaldehyde were purchased from Wako chemicals. The traditional Chinese herbs Coptidis rhizoma, Scutellariae radix, Phellodendri cortex and Gardeniae fructus were purchased from drugstores and subjected to pharmacognosy identification before use. Berberine, palmatine, jatrorhizine, baicalein, and other standard Chinese medicine constituents were purchased from the National Institute for the Control of Pharmaceutical and Biological Products, China. Human embryonic kidney 293 (HEK 293) cells were purchased from the American Type Culture Collection. Dulbecco’s Modified Eagle’s Medium (DMEM), fetal bovine serum (FBS) and the transfection reagent Lipofectamin 2000 were purchased from Invitrogen (Carlsbad, CA). The plasmids pET28a-hIDO-1 and pcDNA3.1-hIDO-1 were generous gifts from Dr. A. Grant Mauk from the Department of Biochemistry and Molecular Biology, University of British Columbia, and Dr. O. Takikawa from the National Institute for Longevity Sciences, National Center for Geriatrics and Gerontology, Japan, respectively.

Oren-gedoku-to decoction

An Oren-gedoku-to decoction was prepared by decocting Coptidis rhizoma and Phellodendri cortex at a ratio of 3:2 (dry weight) with water at 75–80°C for 30 min; this procedure was repeated three times. The medicinal herbs Coptidis rhizoma, Scutellariae radix, Phellodendri cortex, and Gardeniae fructus were extracted with boiling water. Subsequently, the resulting aqueous extracts at a concentration of 1 g/mL (dry weight) were subjected to the IDO-1 inhibition assay. The crude drug extract

Escherichia coli were routinely grown at 37°C in Luria-Bertani (LB) medium containing 50 µg/mL kanamycin. A single colony of BL21 containing the plasmid pET28a-hIDO-1 was inoculated in 10 mL LB medium and cultured overnight. The 10 mL culture was added to 500 mL of the same medium and incubated at 37°C to a density of 0.6 OD at 600 nm. The temperature was then reduced to 30°C, and alphaminolevulinic acid was added to a final concentration of 0.5 mM. The culture was shaken at 120 rpm for 30 min to cool down before IPTG was added to a final concentration of 0.5 mM. The culture was incubated at 30°C for 6 h. The cell pellets were collected by centrifugation at 5000 rpm for 20 min at 4°C. The pellets were stored at −20°C.

Purification of recombinant human IDO-1

The pellet from 500 mL of bacterial culture, obtained as described above, was suspended in 10 mL of PBS containing 1 mM PMSF, sonicated on ice using a Branson Sonifier 250 for 15 min at the maximum power and centrifuged at 12000 rpm for 10 min. The clear supernatant (10 mL) was then applied to a 1 mL Hi-Trap chelating column charged with nickel ions that had been equilibrated with 10 mM imidazole in phosphate buffer (20 mM, pH 7.4) containing 0.5 M NaCl. After washing with 20 mL of basal buffer (Tris 25 mM, pH 7.4, 40 mM imidazole), rhIDO-1 was eluted with the imidazole solution (250 mM) that was prepared in the same phosphate/NaCl buffer. The protein collected at the elution step was then buffer-exchanged into 50 mM Tris, pH 7.4, using a Sephadex G25 column.
Assay of IDO-1

**IDO-1 inhibition assay**

The effects of extracts and pure components on IDO-1 activity were determined as previously described by Takikawa et al. with minor modifications [33]. In brief, a standard reaction mixture (0.5 mL) containing 100 mM potassium phosphate buffer (pH 6.5), 40 mM ascorbic acid (neutralized with NaOH), 200 µg/mL catalase, 20 µM methylene blue and 0.05 µM rhIDO-1 was added to the solution containing the substrate L-tryptophan and the test sample at a determined concentration. The reaction was carried out at 37°C for 30 min and stopped by adding 200 µL of 30% (w/v) trichloroacetic acid. After heating at 65°C for 15 min, the reaction mixture was centrifuged at 12000 rpm for 10 min. The supernatant (100 µL) was transferred into a well of a 96-well microplate and mixed with 100 µL of 2% (w/v) p-dimethylaminobenzaldehyde in acetic acid. The yellow pigment derived from kynurenine was measured at 492 nm using a SPECTRAmax 250 microplate reader (MolecularDevices, Sunnyvale, CA). Data were analyzed using the Enzyme Kinetics module in SigmaPlot, version 10.

**Determination of the inhibition type**

The inhibition type was determined using the method previously described by Voet D et al. [34]. First, the IDO-1 activity assay was performed with 300 µM L-tryptophan, 100 µM inhibitor solution in DMSO and a series amount of rhIDO-1 according to the procedure described above. Based on the results of the activity assay, a function of rate ([V]) against enzyme amount ([E]) was proposed. The inhibition type was determined according to the plot of this function (Fig. 2).

**Evaluation of kinetic parameters and IC₅₀**

Ki and IC₅₀ values were determined based on the IDO-1 activity assay in which the concentration of L-tryptophan varied from 80 µM to 300 µM, and the inhibitor concentration varied over a three-fold range above and below the concentration yielding approximately 50% inhibitory activity. Otherwise, the reaction conditions were exactly the same as those described above. Data were analyzed according to the method previously described by Athel Cornish-Bowden [35].

**HEK 293 cell-based IDO-1 inhibitory activity assay**

HEK 293 cells were maintained in DMEM with 4500 mg/L glucose supplemented with 50 U/mL penicillin, 50 mg/mL streptomycin and 10% FBS. The cells were cultured at 37°C with 5% CO₂ and 95% humidity. The assay was performed as follows: HEK 293 cells were seeded in a 96-well culture plate at a density of 2.5×10⁴ cells/well and cultured overnight. After 24 h, HEK 293 cells were transfected with pcDNA3.1-hIDO-1 using Lipofectamin 2000 according to the manufacturer’s instructions; 24 h after transfection, a serial dilution of the tested compounds in 200 µL culture medium was added to the cells. After an additional 5-h incubation, 140 µL of the supernatant per well was transferred to a new 96-well plate and mixed with 10 µL of 30% trichloroacetic acid in each well, and the plate was incubated at 65°C for 15 min to hydrolyze N-formylkynurenine produced by the catalytic reaction of IDO-1. The reaction mixture was then centrifuged for 10 min at 12000 rpm to remove the sediments. Then, 100 µL of the supernatant per well were transferred to another 96-well plate and mixed with 100 µL of
2% (w/v) p-dimethylaminobenzaldehyde in acetic acid. The yellow color derived from kynurenine was measured at 492 nm using a SPECTRAmax 250 microplate reader.

RESULTS

IDO-1 inhibitory activity of Oren-gedoku-to decoction

Varying amounts of OGT at a concentration of 1 g/mL (dry weight) were added to the IDO-1 activity assay system. The results showing OGT’s effects on rhIDO-1 in vitro are shown in Fig. 3. OGT exhibited potent IDO-1 inhibitory activity in relation to the most commonly used IDO-1 inhibitor, 1-methyl tryptophan (1-MT); 5 µL of OGT, corresponding to 5 mg of medicinal herbs, exhibited a 40% inhibition, which is similar to that of 1-MT at a concentration of 500 µM. A positive correlation between the amount of OGT and its inhibitory efficiency was observed; 50 µL of OGT exhibited an inhibitory efficiency of nearly 90%. We further investigated the IDO-1 inhibitory activities of the four medicinal herbs composing OGT. As shown in Fig. 4a, the crude extracts of Coptidis rhizoma, Phellodendri cortex and Gardeniae fructus exhibited significant inhibitory activity even at a very small amount (1 µL). Coptidis rhizoma displayed the most potent IDO-1 inhibitory activity, positively correlating with amount (Fig. 4b). Scutellariae radix did not show IDO-1 inhibitory activity at 1 µL. When the amount of the crude extract was increased to 9 µL, Scutellariae radix showed an IDO-1 inhibitory activity similar to that exhibited by 1 µL of the Coptidis rhizome extract. These results indicate that the IDO-1 inhibitory activity of OGT primarily depends on Coptidis rhizoma, Gardeniae fructus, and Phellodendri cortex; furthermore, Coptidis rhizoma may be a good source for isolating potent IDO-1 inhibitors.

IDO-1 inhibitory activities of the constituents of Oren-gedoku-to decoction

Because it is a well-recognized traditional Chinese medicinal prescription, the main constituents of OGT have been previously studied and reported; they include geniposide, wogonin, baicalein, berberine, jatrorrhizine, palmatine and baicalin [36]. To further investigate the mechanisms underlying the modulating effects of OGT on AD, we examined the IDO-1 inhibitory activity of the commercially available main constituents of OGT. Among all these constituents, berberine, jatrorrhizine and palmatine were the more potent IDO-1 inhibitors. Their inhibitory activities were about three-fold higher than those of the others. Compared to 1-MT, berberine, jatrorrhizine, and palmatine exhibited more potent IDO-1 inhibitory activity, whereas geniposide, wogonin, baicalein, and baicalin showed an inhibitory activity similar to 1-MT (Fig. 5).

Kinetic parameters and IC$_{50}$ of the main constituents of Oren-gedoku-to decoction

The three potent IDO-1 inhibitors berberine, jatrorrhizine and palmatine, together with the moderate inhibitors baicalein, geniposide, wogonin, and baicalin, were subjected to kinetic parameter and IC$_{50}$ determination (IC$_{50}$ shown in Table 1). Baicalein was chosen...
Table 1
Kinetic parameters and IC$_{50}$ of the main constituents of OGT obtained from rhIDO-1 enzymatic and cell-based assays. ND: No detection

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type of inhibition</th>
<th>Ki (µM)</th>
<th>IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-MT</td>
<td>competitive</td>
<td>34</td>
<td>380</td>
</tr>
<tr>
<td>berberine</td>
<td>uncompetitive</td>
<td>8</td>
<td>9.3</td>
</tr>
<tr>
<td>baicalein</td>
<td>uncompetitive</td>
<td>215</td>
<td>337</td>
</tr>
<tr>
<td>palmatine</td>
<td>irreversible</td>
<td>ND</td>
<td>157</td>
</tr>
<tr>
<td>jatrorrhizine</td>
<td>irreversible</td>
<td>ND</td>
<td>206</td>
</tr>
<tr>
<td>geniposide</td>
<td>ND</td>
<td>ND</td>
<td>407</td>
</tr>
<tr>
<td>wogonin</td>
<td>ND</td>
<td>ND</td>
<td>447</td>
</tr>
<tr>
<td>baicalin</td>
<td>ND</td>
<td>ND</td>
<td>498</td>
</tr>
</tbody>
</table>

Fig. 5. IDO-1 inhibitory activities of the constituents of OGT. The concentration of L-tryptophan used in the assay was 300 µM. Control: no inhibitor. All the tested compounds were applied at 100 µM. Results are expressed as means ± standard deviation (SD) from three independent experiments.

Fig. 6. Structures of berberine, baicalein, jatrorrhizine, and palmatine.

as a representative of the moderate inhibitors (Structures were shown in Fig. 6). Based on plotting a function of rate (I) against enzyme amount (E), jatrorrhizine, and palmatine were categorized as irreversible inhibitors (Fig. 7). Berberine and baicalein behaved as uncompetitive reversible inhibitors, and their inhibitory kinetics were evaluated by plotting [S]/[V] against inhibitor concentration, where [S] represents substrate concentration and [V] represents reaction velocity (Fig. 8). The Ki and IC$_{50}$ values of these four compounds are listed in Table 1. The inhibitory constant Ki is expressed as the average of three trials.

The IDO-1 inhibitory effects of the main constituents of OGT on HEK 293 cells

The IDO-1 inhibitory effects of the main constituents of OGT on HEK 293 cells transfected with pcDNA3.1-IDO-1 were determined; the results further confirmed that the main constituents of OGT were potent IDO-1 inhibitors. Berberine, baicalein, jatrorrhizine, and palmatine showed much higher inhibitory efficiencies in the cell-based assay than in the enzyme assays. Their IC$_{50}$ values were 7 µM, 116 µM, 17.8 µM, and 3 µM, respectively (Table 1).
DISCUSSION

Recently, increasing evidence has suggested that IDO-1 plays an important role in AD pathogenesis; therefore, IDO-1 inhibitors have drawn significant attention as a potential treatment for AD. Our long-term project of screening for IDO-1 inhibitors has been focused on the traditional Chinese medicine OGT because of its ability to improve cognitive ability in AD rats and dementia patients.

Traditional Chinese medicines consisting of several crude drugs have been developed over thousands of years based on clinical experience, and they have high efficacy and low toxicity as well as multi-factorial, multi-target, and multi-functional action. Some traditional Chinese medicinal prescriptions, such as the Liu-Wei-Di-Huang decoction [32,37,38], Oren-gedoku-to decoction (OGT) [39] and Dang-Gui-Shao-Yao-San [40,41], have been found to play important roles in clinical therapies for AD. These findings provide a new direction of drug development for treating AD [42].

While a variety of modulating effects of OGT on AD have been observed, a definitive mechanism has yet to be established. We proposed that the therapeutic effects of OGT on AD development may be attributed to its IDO-1 inhibitory activity. Here we have shown that OGT can inhibit the activity of recombinant human IDO-1 in vitro even at a very low concentration. *Coptidis rhizoma*, one of the four crude drugs that compose OGT, exhibited the most potent IDO-1 inhibitory activity. Guided by the IDO-1 inhibitory assay, the further isolation of *Coptidis rhizome* and other active crude drugs such as *Phellodendri cortex* and *Gardeniae fructus* is now an ongoing project in our laboratory. In future work, we also would like to identify the main agent of these complicated chemical components that contribute to the IDO-1 inhibitory activity of OGT. A previously reported HPLC-UV/MS analysis of OGT showed 21 peaks and 7 main constituents including berberine, baicalein, baicalin, geniposide, jatrorrhizine, palmatine and wogonin [36]. Our investigation with these commercially available compounds showed that berberine, jatrorrhizine, and palmatine were potent IDO-1 inhibitors, whereas the others exhibited moderate activity similar to 1-MT. The inhibitory efficiency of berberine was most prominent:
the IC$_{50}$ value of berberine (9.3 µM) was 41-fold lower than that of 1-MT (380 µM). In regards to the important enzyme kinetic parameter $K_i$, the value of berberine (8 µM) was about four-fold less than that of 1-MT (34 µM). Because berberine is a well-known natural compound, many studies have investigated the various pharmacological activities of it; however, to the best of our knowledge, this study is the first report to show the IDO-1 inhibitory efficiency of OGT. Our study elucidated the mechanism underlying OGT’s action and identified its main active components, contributing toward an increased and directed application of OGT in AD treatment.

We further confirmed the IDO-1 inhibitory activities of berberine, baicalein, jatrohrrhizine, and palmatine in a more physiologically relevant HEK 293 cell-based assay. The observed inhibitory activities of these four compounds were slightly more potent than those in the enzyme assay. This phenomenon may be attributed to the complexity of the enzyme assay, which uses a methylene blue ascorbate regeneration system to maintain the active reduced form of IDO-1, or it may result from unidentified differences between the recombinant IDO-1 used in the enzyme assay and the native IDO-1 in HEK 293 cells.

Berberine and baicalein exhibited uncompetitive, reversible inhibitory activity that may be due to their direct binding to the heme iron or their occupation of the presumed tryptophan-binding site. Interestingly, jatrohrrhizine and palmatine, which are structurally similar to berberine, exhibited reversible inhibitory activity. The reason for this discrepancy is still being investigated. However, the interpretation of IDO-1 inhibition kinetics may be complicated because of the preferential binding of some inhibitors to the inactive ferric form of IDO-1 and the redox activities of other inhibitors [43, 44].

Being potent IDO-1 inhibitors, the main constituents of OGT (berberine, jatrohrrhizine, palmatine, and baicalein) may exert therapeutic effects in AD treatment. In addition, they may also be applied in treating other diseases with the pathological characteristic of IDO-1-catalyzing tryptophan catabolism. The over-expression of IDO-1 and the over-activation of the KP have been implicated in a variety of diseases, including cancer, neurodegenerative disorders (AD), age-related cataract, and HIV encephalitis. Recently, IDO-1 has been shown to play an important role in the immune evasion of tumors. The IDO-1-mediated depletion of local tryptophan and the production of toxic tryptophan metabolites result in the suppression of T-cell activation and the induction of T-cell apoptosis. Many experiments have provided proof-of-principle demonstrations of the potential value of IDO-1 inhibitors in cancer treatment. However, to date, no IDO-1 inhibitors are available as drug candidates due to the low efficacy or poor physical properties of the currently known inhibitors. Only a few structural classes are known to be IDO-1 inhibitors and nearly all of the known competitive IDO-1 inhibitors are tryptophan analogues, such as 1-MT. However, there is still considerable interest in discovering new IDO-1 inhibitors with high efficacy. The potent inhibitors that we identified in OGT, including berberine, baicalein, jatrohrrhizine, and palmatine, provide new templates for further designing and synthesizing potent IDO-1 inhibitors. The optimization of moderate inhibitors may potentially yield potent IDO-1 inhibitors.

In summary, the present study elucidated the mechanism of OGT’s action in AD treatment and identified promising IDO-1 inhibitory compounds as candidates for AD drug development.

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