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Review Article

Physostigmine: A Plant Alkaloid Isolated from *Physostigma venenosum*: A Review on Pharmacokinetics, Pharmacological and Toxicological Activities

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ABSTRACT

Medicinal plants have been documented as an important source for discovering new pharmaceutical molecules that have been used to treat serious diseases. Strikingly, previous reports stated that natural products and their derived compounds exhibit lesser side effects and improved efficacy than other synthetic counterparts. Physostigmine, a parasympathomimetic plant alkaloid isolated from the West African perennial shrub *Physostigma venenosum*, it shows a narrow therapeutic index and a short life span, despite its ability to penetrate the blood-brain barrier (BBB). It is a widely known reversible butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) inhibitor and has been documented to treat various ailments such as Alzheimer's disease. Pharmacologically, physostigmine was first reported as an antidote for atropine scopolamine and belladonna alkaloids toxicity. Recently, it has been documented as a therapy for treating several ailments including glaucoma, myasthenia gravis and the intoxication caused by tricyclic antidepressant overdoses, anti-histamines, antipsychotics, and benzodiazepines. Physostigmine has been reported to be absorbed from the gastrointestinal tract and showed short half-life, as, after the oral administration of 2 mg of physostigmine salicylate, the peak plasma concentration reached to 30 minutes. This review examines the biological activities, pharmacokinetics, and toxicity of physostigmine extracted from *P. venenosum*.

Keywords: *Physostigma venenosum*, Physostigmine, pharmacological activities, acetylcholinesterase and butyrylcholinesterase inhibitor.

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INTRODUCTION

Physostigmine, a parasympathomimetic plant alkaloid isolated from *Physostigma venenosum*, the famous West African perennial shrub and it shows a narrow therapeutic index and a short life span, despite its ability to penetrate the blood-brain barrier (BBB) [1]. Moreover, physostigmine has been extracted from *Streptomyces pseudogriseolus* cultures. Physostigmine acts by interfering with the metabolism of acetylcholine (ACh) (Fig 1). It is a covalent

(reversible-bond hydrolyzed and released) butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) inhibitor in the plasma, erythrocytes, and brain; AChE is the enzyme that is responsible for the ACh breakdown in the synaptic cleft of the neuromuscular junction [2] and it acts by indirect stimulation of nicotinic as well as muscarinic ACh receptors.

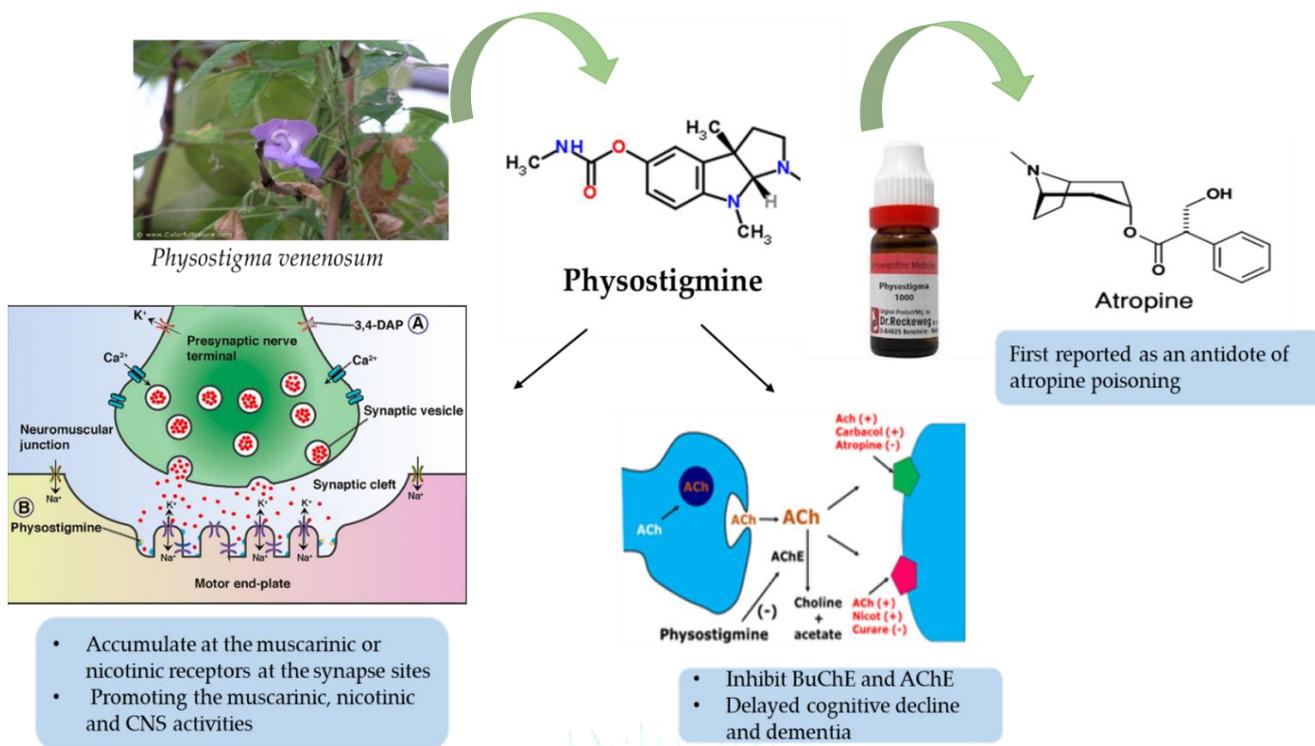


Figure 1: The pharmacological activities of physostigmine

Initially, physostigmine was reported as a remedy for atropine poisoning [3]. Nowadays, it has been documented as a therapy for the treatment of several ailments including glaucoma, myasthenia gravis [4], atropine, scopolamine, and belladonna alkaloids intoxication [5], and the intoxication caused by tricyclic antidepressants overdoses [6], antihistamines [7], antipsychotics [8], and benzodiazepines [4]. Physostigmine also possesses an important role as a significant protective compound toward organophosphate poisoning by binding with the active groups in AChE reversibly [9].

CHEMICAL STRUCTURE

Physostigmine (Fig 2; $C_{15}H_{21}N_3O_2$) a lipid-soluble tertiary ammonium compound that has a pKa value of 7.9 and easily ionized in the pH of the brain and blood [10]. The following physostigmine structure was first detected in 1925 (1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-pyrrolo[2,3-b]indo-5-ol-methylcarbamate) [4].

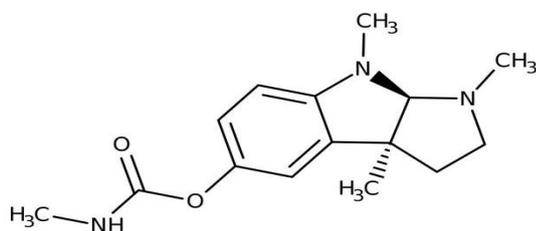


Figure 2: Chemical structure of physostigmine

PHYSOSTIGMINE SYNTHESIS

Synthetically, physostigmine has been synthesized by different methods, one of them performed in the presence of aluminum chloride by the reaction of α -bromopropionyl bromide with *p*-ethoxymethylaniline resulting in 1,3-dimethyl-5-ethoxyindolin-2-one. Afterward, in the presence of sodium ethoxide, chloroacetonitrile reacts

with 1,3-dimethyl-5-ethoxyindolin-2-one and results in 1,3-dimethyl-5-ethoxy-3-cyanomethylindolin-2-one.

The nitrile group reduction to amine group has occurred that is additionally methoxided and resulted in 1,3-dimethyl-5-ethoxy-3-(β methylaminoethyl) indolin-2-one. After that, the carbonyl group reduction is occurred to form amino alcohol by which its dehydration results in 1,3a,8-trimethyl-2,3,3a,8a-tetrahydropyrrolo[2,3b]-5-ethoxyindol formation. The hydrogen bromide was used to remove the ethoxy-protecting group resulting in a compound containing a phenol hydroxyl group that is further reacted with methyl isocyanate to give physostigmine [11].

PHARMACOKINETICS

Physostigmine has been documented to be absorbed from the gastrointestinal tract and other mucous membranes with an oral bioavailability between (1-8%) [12]. Physostigmine has been documented to show short half-life, as after the oral administration of 2 mg of physostigmine salicylate, the peak plasma concentration reached to 30 minutes, whereas after oral administration of 4 mg, the peak serum levels reached to 45 minutes and become undetectable within 3 hours [12, 13]. Once physostigmine enters the blood circulation, it penetrates the BBB smoothly and subsequently inactivated by the plasma cholinesterase. Additionally, physostigmine is metabolized rapidly from the body due to the presence of plasma esterase that leads to its hydrolytic cleavage at the ester bond and, consequently, results in the loss of its pharmacological activity [14, 15]. Physostigmine has been documented to be used as an antidote for anticholinergic toxicity of antihistamines, atropine, tricyclic antidepressants, and phenothiazine because of its ability to spread to the central nervous system (CNS) [16].

MECHANISM OF ACTION OF PHYSOSTIGMINE

Physostigmine, a cholinergic drug that acts by inhibiting the AChE and BuChE enzymes that break down acetylcholine, thus increasing ACh amounts at cholinergic synapses in the central and peripheral nervous systems and, consequently,

accumulate at the muscarinic or nicotinic receptors at the synapse sites and promoting the muscarinic, nicotinic and CNS activities [17]. Regarding the muscarinic receptor effects, physostigmine causes increased urination and aqueous humor production, decreased pupil size, increased salivation, increased the secretions of the gastrointestinal tract, and sweating [18]. Nicotinic effects are those influencing sympathetic ganglia or striated muscle such as fasciculation, cramps, high blood pressure, twitching, tachycardia, and weakness [19], while convulsions, ataxia, and coma are those of the CNS effects symptoms [18].

ALZHEIMER'S DISEASE AND PHYSOSTIGMINE

Nowadays, AChE is considered the most important molecular target for treating dementia in AD, therefore, acetylcholinesterase inhibitors (AChEIs) are currently considered to be one of two drug categories approved to treat AD [20, 21]. All drugs act by promoting the cholinergic deficit, thereby, they reveal the potential efficacy of the behavioral, functional, and cognitive symptoms of AD [22]. A significant loss in the cholinergic neurons has been observed in the postmortem brains infected with AD, which are widely disseminated in the hippocampus, amygdala, and neocortex [23]. Decreased the cortical choline acetyltransferase efficacy is related to the number of aging plaques and cognitive decline in AD patients [24]. Physostigmine was the first nonselective reversible AChE and BuChE inhibitor investigated for treating AD [1], thus increasing central cholinergic neurotransmission. In the *in vivo* experiments, physostigmine enhances memory in elderly primates [25], as well as primates with amnesia caused by scopolamine, whereas in clinical trials physostigmine has shown improved cognitive function in patients with AD [26].

Combination Therapy of Physostigmine with Drugs against Alzheimer's disease

Nowadays, combination chemotherapies are being reported to alleviate serious diseases, including pulmonary tuberculosis, malignancy, immune deficiency syndrome, AD, and some protozoal diseases to promote higher therapeutic efficacy [27-30]. Schmitt et al. [31] documented the combined effect of selegiline with AChE inhibitors such as physostigmine or tacrine in AD patients, as well as AChE inhibitor and α -lipoic acid AChE inhibitors are very likely to be part of any AD combination regimen [32].

DOSE

Recently, Orhan et al. [1] investigated that physostigmine has an LD₅₀ of 3 mg/kg in mice. Moreover, Van Dyck et al. [33] documented that slow-release physostigmine salicylate at 18, 24, and 30 mg/day could be a potential and safe drug for treating AD for 6 weeks. The recommended adult dose is ranged from 0.5 to 2 mg [34], while Kaye. [35] revealed the minimal lethal dose of physostigmine to be 60 mg/70 kg/person and its chemotherapeutic blood level is ranged from 0.001 to 0.01 mg/L [36].

TOXIC SIDE EFFECTS

Physostigmine, an AChE inhibitor, which stimulates ACh hydrolysis to choline and acetic acid. Therefore, physostigmine can produce acute toxic effects and it can cause muscarinic receptor stimulation including nausea, vomiting, diarrhea, abdominal pain, respiratory tract secretions, hypersalivation, seizures, Diaphoresis, Tachycardia, blurred vision, bradycardia and atrial fibrillation [37]. Additionally, it led to the stimulation of nicotinic receptors, inducing paralysis, weakness, muscle twitching and stimulation of cholinergic receptors in the CNS followed by CNS depression, convulsions, coma, and finally

death. The short plasma half-life and the first-pass metabolism of physostigmine inhibited its clinical use in treating AD. Therefore, to overcome this problem, novel slow-release physostigmine salicylate (Synapton) preparation was developed to produce sustainable blood levels [33,38].

To be noted, death resulted from physostigmine overdose is commonly attributed to pulmonary edema and/or failure of respiration and the duration of death is ranged between 5 min-24 h based on the physostigmine dose and route of administration [15]. Recently, synthetic physostigmine derivatives such as phenserine and eptastigmine have been developed and they revealed strong inhibition of AChE and demonstrated improved cognitive functions in preclinical and clinical studies by indirect stimulation of nicotinic as well as muscarinic ACh receptors [21]. Moreover, heptyl physostigmine, the physostigmine salt form, which showed higher lipophilicity, less toxicity than physostigmine while maintaining AChE inhibitor property and it can pass easily through BBB. Its use has been reported in the treatment of the CNS symptoms caused by scopolamine, atropine and other anticholinergic overdoses [34].

CONTRAINDICATIONS

Physostigmine was contraindicated in patients with hyperthyroidism, angle-closure glaucoma, hypotension, asthma, diabetes, vagal tone increase, gastrointestinal or urogenital tract obstruction, gastroesophageal reflux disorder, bradycardia, gangrene, peptic ulcer, cardiovascular and seizure disorders. Moreover, it is contraindicated to be administered with choline esters and depolarizing neuromuscular blockers or a salicylate/sulfite allergy [18]. Furthermore, it is contraindicated for patients with QRS prolongation on electrocardiogram or those with a history of QRS medication overdose [37].

CONCLUSION

Physostigmine, a lipid-soluble tertiary amine carbamate plant alkaloid that was first reported as an antidote to atropine toxicity. It is a famous reversible BuChE and AChE inhibitor and it has been used in treating different diseases including AD. The finding that physostigmine can combine with other drugs is a property that can be explored in the chemotherapies development against AD. However, its clinical use as a therapy has been prohibited due to the existence of the toxic side effects and its short half-life, therefore, new synthetic derivatives such as phenserine, eptastigmine, heptyl physostigmine and extended-release formulation of physostigmine salicylate (Synapton) have been developed to produce sustainable blood levels and overcome the above-mentioned problems.

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