EAS Journal of Pharmacy and Pharmacology
Abbreviated Key Title: EAS J Pharm Pharmacol
ISSN: 2663-0990 (Print) & ISSN: 2663-6719 (Online)
Published By East African Scholars Publisher, Kenya

Volume-2 | Issue-4 | Jul-Aug: 2020 | DOI: 10.36349/easjpp.2020.v02i04.009

OPEN ACCESS

Review Article

Pilocarpine Alkaloid A Review

Suleiman Olimat

Faculty of Pharmacy, Department of Medicinal Chemistry and Pharmacognosy Jordan University of Science and Technology, Jordan

Article History
Received:03.07.2020
Accepted: 19.07.2020
Published: 29.07.2020

Journal homepage:
https://www.easpublisher.com/easjpp

Quick Response Code

Abstract: *Pilocarpus microphyllus* (Stapf), is considered the most common species used in medicine and a source of naturally occurring pilocarpine alkaloid. Pilocarpine was first drug introduced in ophthalmology for the treatment of various glaucomatous disorders, but now is consider as third line treatment. Pilocarpine alkaloid found its way in the treatment of xerostomia, regardless of the etiology.

Keywords: *Pilocarpus*, pilocarpine, glaucoma, xerostomia

BACK GROUND

Students at the Jordan University of Science and Technology (JUST) receive a Pharmacognosy and Phytochemistry , for Pharmacy students , and Natural Products Chemistry, Pharm. D. students, in addition to Phytotherapy course for both tracks, during their third and fourth-professional year with emphasis in the role of medicine drugs originated from natural sources and their role in *drug development and discovery*. The Natural products are major sources of drugs, as well as sources of precursors for semisynthetic modification and sources of prodrugs. In addition, students are continually exposed to the concept that complex natural products are a result of secondary metabolism, secondary metabolites have a more limited distribution in nature, and their occurrence is an expression of the individuality of the parent species. In this review, I am going to focus on the pilocarpine alkaloid it terms of history, chemistry and pharmacology.

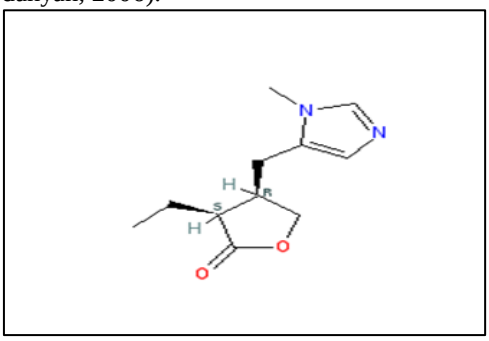
INTRODUCTION

The name 'jaborandi' is now applied to the leaflets of various species of *Pilocarpus* (Rutaceae), a genus of trees and shrubs indigenous in Southern Central-America , Mexico, until the Southern part of the South-American continent , Argentina and Paraguay (Santos *et al.* , 2004). The shrub grows from 4 to 5 feet high; the bark is smooth and greyish; the flowers are thick, small, and reddish-purple in color. The leaves are large, compound, pinnate with terminal leaflet, the leaflets are unequal, oval to obovate, from one-half to one and one-half inches long, and about half as wide (Pinheiro, 1997). The terminal leaf lets are equally ovate to obovate, have a more tapering base than the lateral leaflets, and are narrower (Skorupa *et al.*, 2004). *Pilocarpus microphyllus* (Stapf), is considered the most common species used in medicine now adays, known in commerce Mamidiam Jaborandi or Maranham jaborandi, the name of the South American point of export, accounts for about 90% of the Brazilian production (Treatise,1904) . The other species next in importance is *Pilocarpus jaborandi* (Holmes), it was regarded as official drug in the British Pharmacopeia until 1914 (De Abreu *et al.*,2005). The name Jaborandi, Iaborandi and Jamborandi are applied to sundry pungent taste of the Rutaceae family (Santos *et al.* , 2004) . Another source of pilocarpine from calluses obtained from petioles of *P. microphyllus*, the calluses maintained in the dark released the greatest quantities of pilocarpine (Sidhu, 2014). Jaborandi has long been used in traditional medicine in South America, where native people have employed the plant as a natural remedy for epilepsy, convulsions, gonorrhea, fever, influenza, pneumonia, gastrointestinal inflammations, kidney disease, psoriasis, neurosis, and as an agent to promote sweating (Treatise 1904; Santos *et al.* , 2004).

Chemical Composition of Jaborandi:

***Corresponding Author:** Suleiman Olimat

The leaflets of *Pilocarpus jaborandi* or of *Pilocarpus microphyllus*, yielding not less than 0.5 per cent. of alkaloids. The "jaborandi" alkaloids are mainly of the imidazole group, pilocarpine, and it is thought that *L*-histidine is the biosynthetic precursor of the imidazole moiety (Santos *et al.*, 2004; Treatise,1904; Olimat, 2015). The alkaloid pilocarpine has been shown to be responsible for much of the biological activity of the plant, Pilocarpine was isolated from *P. jaborandi* in 1874 by A.W.Gerrard in London and, independently, by H. Hardy in France, in 1877 pilocarpine was introduced in ophthalmology (Vardanyan, 2006). Pilocarpine, marketed as its chloride salt, is an oil or crystalline alkaloid, $C_{11}H_{16}N_2O_2$, (3*S*,4*R*)-3-ethyl-4-[(3-methylimidazol-4-yl)methyl]oxolan-2-one;hydrochloride (Vardanyan, 2006; Santos *et al.* , 2004). Pilocarpine was synthesized in a few different ways but the most relevant of which seems to be from 2-ethyl-3-carboxy-2-butyrolactone, which with the help of thionyl chloride is turned into the acid chloride and further reacted with diazomethane and ethanol, to give the corresponding ethyl ester (Arndt–Eistert reaction) ((Vardanyan, 2006).



Pilocarpine

Pharmacology of Pilocarpine

Pilocarpine possess CNS activity, as a direct cholinergic which stimulates the parasympathetic system (bladder, tear ducts, sudoriferous and salivary glands), it is the elected drug in the glaucoma treatment and the sialagogue property of pilocarpine has been exploited to treat the xerostomy (Komatsu, 2007).

Pilocarpine in the treatment of Glaucoma:

Pilocarpine preparations have been used in ophthalmology since the 1870s,. In the 1980s, beta-blockers were developed, reducing the administration frequency to twice a day. In 1999, prostaglandin-type ophthalmic preparations that require once-a-day administration appeared on the market, easing the burden of frequent administration. During the process of the development of these new ophthalmic agents, Ocusert, a sustained-release pilocarpine preparation that is inserted intra-ocularly only once a week, was designed and applied clinically (Santos *et al.*, 2004; Komatsu, 2007). Glaucoma is the second leading cause of the world's blindness with nearly 70 million cases worldwide and accounting for 12% of all cases of preventable blindness , the disease is known as the "silent thief of sight" (Gooch *et al.*, 2012). All forms of glaucoma have in common optic nerve degeneration characterized by typical visual field defects and are usually associated with elevated intraocular pressure (IOP). Recent studies have shown that IOP should be reduced to ≤18 mmHg to help prevent long term glaucomatous damage (Webster *et al.*,1993; Wiggs, 2007). This indolent optic neuropathy is characterized structurally by a loss of retinal ganglion cells and optic nerve axons (Lee *et al.*, 2005). Recent studies have shown an association between hypothyroidism and primary open-angle glaucoma (POAG). When hypothyroidism occurs, accumulation of hyaluronic acid within the trabecular meshwork may cause an increase in outflow resistance and intraocular pressure (IOP) (Komatsu, 2007; McDaniel *et al.*, 1996; Sonnjo, 1993). Concerning the etiology, there is a close association between occurrence of hemorrhages and retinal vein occlusions, which in all categories increases with increasing follow-up time. The well known morphological changes in the retinal veins of glaucoma's and in central vein occlusions are endothelial proliferations causing progressive increase of flow resistance (McDaniel *et al.*, 1996). In most instances, the elevation of IOP results from impaired drainage of aqueous humor (produced by the ciliary body) through the trabecular meshwork outflow pathways. Glaucoma causes irreversible blindness that can only be prevented by therapeutic intervention at early stages of the disease. A family history of the disease has long been recognized as a major risk factor for glaucoma, suggesting that specific gene defects contribute to the pathogenesis of the disorder (Komatsu, 2007; McDaniel *et al.*, 1996). Glaucoma may be inherited as mendelian-dominant or mendelianrecessive traits, or may exhibit a heritable susceptibility consistent with complex trait inheritance (Sonnjo *et al.*, 1993). Epidemiologic studies have contributed greatly to our knowledge of open-angle glaucoma. A major priority is to achieve a better understanding of risk factors, which are likely to involve gene-environment interactions , glaucoma is a common eye disease that can cause irreversible blindness. Glaucoma divided into the categories of primary or secondary open-angle or angle-closure glaucoma (Lee *et al.*,2005).

Conventional first-line treatment of glaucoma usually begins with the use of a topical selective or nonselective β-blocker or a topical prostaglandin analog. Second –line drugs of choice of choice include α-agonists and topical carbonic anhydrase inhibitors. Pilocarpine, parasympathomimetic drug, is considered a third-line treatment (Skaat *et al.*, 2016; Macoul *et al.*, 1975). One drop of pilocarpine hydrochloride ophthalmic solution 1%, 2% or 4% (ophthalmic gel 4%)should be applied topically in the eye(s) up to four times daily, patients should be started on the 1% concentration as higher concentrations are often not

tolerated initially. The frequency of instillation and concentration of pilocarpine hydrochloride ophthalmic solution are determined by the severity of the elevated intraocular pressure and miotic response of the patient (Komatsu, 2007; Macoul *et al.*, 1975). Pilocarpine has a good water solubility but suffers from low ocular bioavailability ,0.1–3% ,due to its low lipophilicity and the short residence time of aqueous solutions in the eye. The most frequently reported adverse reactions occurring in ≥ 5% of patients taking pilocarpine were: headache, blurred vision, eye irritation, visual impairment (dim, dark, or "jumping" vision), and eye pain (Komatsu, 2007; Skaat *et al.* 2016). Another method of administration of pilocarpine to treat intraocular is by the use of a pilocarpine-containing, polymermembrane unit (Ocusert) placed the system in the cul-de-sac once a week releasing either 20µg/hr or 40µg/ hr of pilocarpine (Berk**,** 2008).

Pilocarpine in the treatment of Xerostomia:

Xerostomia is "a subjective sensation of oral dryness." These symptoms might present as dry mouth, difficulty swallowing or dry oral mucosa/skin (Wiseman *et al.*, 1995). There are numerous causes of xerostomia; the most common cause is medication side effects, Some of the medications that have strong correlations to xerostomia include atropine, scopolamine, phentermine, methyldopa, clonidine, furosemide, timolol, the majority of these medications act on the central nervous system (CNS) or at the neuroglandular junction (Valdez *et al.* 1993; Leek *et al*., 2002), followed by Sjogren syndrome Autoimmune systemic disorders such as Sjogren syndrome (although very well known but a rare cause), systemic lupus erythematosus, rheumatoid arthritis , thyroid disease and primary biliary cirrhosis all have implications as potential causes and radiotherapy and other autoimmune diseases in no particular order (Berk**,** 2008; Leek *et al*., 2002). The three major salivary glands responsible for saliva production are parotid gland, submandibular gland, and sublingual gland. The anatomy of all three glands is quite similar, consisting of a duct that opens into the oral cavity. Hyposalivation due to radiation shows fibrosis while hyposalivation due to an autoimmune disease could show an infiltrate of B and T-cells, leading to gland destruction (Hendrickson *et al*.,2004; Fox *et al.* 1991). Patients with a history of mouth breathing, dehydration, poorly controlled diabetes, nerve damage from head or neck injury, end-stage renal disease, graft versus host disease, HIV/AIDS also complain of dry mouth (Hendrickson *et al.* , 2004). All major and minor salivary glands have nerve supplies, and upon stimulation, salivatory nuclei in the medulla generate an efferent response. The efferent nerve impulses release acetylcholine (ACh), which works on muscarinic receptors (specifically M3 receptors), which then stimulates salivary glands to produce saliva. Histologically, major salivary glands are made up of salivary acini and ducts, which produce two types of fluids, serous and mucinous. Pathology arises when there is a dysfunction of gland innervation, or the gland itself (Fox *et al*., 1991; Nezu *et al.,* 2019).

Since the secretory cells receive nerve supply from muscarinic M1 and M3 receptors, alpha1- and beta1-adrenergic receptors, and specific peptidergic receptors that are involved in the initiation of salivary secretion, xerostomia is caused by either suppressing the CNS from producing ACh or by occupying the muscarinic/ adrenergic receptors (Kobayashi. *et al.* , 2007; Fox *et al*. 1991; Nezu, *et al*. 2019) .

In Sjogren syndrome, chronic lymphocytic infiltration and inflammation of acinar cells lead to exocrine fibrosis resulting in non-functional glands. Initially, only CD4+ lymphocytes were believed to be involved in the pathophysiology of Sjogren syndrome (Popov *et al*., 2018) . However, new data also suggests the involvement of B-cells. Sjogren syndrome is more common in females, with an average age of around 50 to 60 years. It is unusual for Sjogren to present after the age of 65 and dry mouth after this age is more commonly attributable to age-related exocrine atrophy (Wei *et al*., 2018). The reason radiation causes xerostomia is that the oral cavity, lymph nodes, and salivary glands happen are in the radiation field when head and neck cancer patients are receiving treatment. Although the tissues of salivary glands have a low mitotic index which should make them quite stable and typically radiation-resistant, studies have shown a decline in salivary gland function proportional to the radiation dose. Acinar atrophy and chronic inflammation are considered hallmarks of radiation-induced xerostomia (Kobayashi *et al.* , 2007; Popov *et al*.,2018; Wei. *et al*., 2018). This dose-dependent radiation causes a secretory dysfunction of the gland. Fibrosis mostly presents as periductal and intralobular, but the structure of the ducts remains intact (Brito-Zerón *et al*., 2016). If xerostomia is medication-induced, the medication should either be stopped or substituted with another with less xerostomic effects if possible. Sialogogue drugs, specifically pilocarpine is FDA approved medications for the management of dry mouth , works on muscarinic receptors and induce salivation. Pilocarpine is given orally with normal dosing of 5 to 10 mg three times a day (Brito-Zerón *et al*., 2016; Thorne *et al.*, 2017).

Conflict of Interest: The author has stated that there is no conflict of interest associated with the publication and no financial support, which could have influenced the outcome.

Acknowledgement:I would like to thank the librarians at the library of Jordan University of Science and Technology (JUST) for their great help during the preparation of this manuscript.

REFERENCES

1. Berk, L. (2008). Systemic pilocarpine for treatment of xerostomia. *Journal Expert opinion on Drug Metabolism and Toxicology. 4*(10),1333-1340**.**
2. Brito-Zeron, P., Baldini, C., Bootsma, H., Bowman, S. J., Jonsson, R., Mariette, X., ... & Ramos-Casals, M. (2016). Sjögren syndrome. *Nature reviews Disease primers*, *2*(1), 1-20.
3. De Abreu, I. N., Sawaya, A. C. H., Eberlin, M. N., & Mazzafera, P. (2005). Production of pilocarpine in callus of jaborandi (Pilocarpus microphyllus stapf). *In Vitro Cellular & Developmental Biology-Plant*, *41*(6), 806-811.
4. Fox, P. C., Atkinson, J. C., Macynski, A. A., Wolff, A., Kung, D. S., Valdez, I. H., ... & Baum, B. J. (1991). Pilocarpine treatment of salivary gland hypofunction and dry mouth (xerostomia). *Archives of Internal Medicine*, *151*(6), 1149-1152.
5. **Gooch, N., Molokhia, S. A., Condie, R., Burr, R. M., Archer, B., Ambati, B. K., & Wirostko, B. (2012). Ocular drug delivery for glaucoma management. *Pharmaceutics*, *4*(1), 197-211.**
6. Hendrickson, R. G., Morocco, A. P., & Greenberg, M. I. (2004). Pilocarpine toxicity and the treatment of xerostomia. *The Journal of emergency medicine*, *26*(4), 429-432.
7. Kobayashi, F., Yageta, Y., Segawa, M., & Matsuzawa, S. (2007). Effects of imidafenacin (KRP-197/ONO-8025), a new anti-cholinergic agent, on muscarinic acetylcholine receptors. *Arzneimittelforschung*, *57*(02), 92-100.
8. Komatsu, Y. (2007). A History of the Development of Eye Drops Used to Treat Glaucoma. *akushigaku Zasshi. 42*(1), 7-16.
9. Lee, D. A., & Higginbotham, E. J. (2005). Glaucoma and its treatment: a review. *American journal of health-system pharmacy*, *62*(7), 691-699.
10. Leek, H., & Albertsson, M. (2002). Pilocarpine treatment of xerostomia in head and neck patients. *Micron*, *33*(2), 153-155.
11. Leske, C. (2007). Open-Angle Glaucoma—An Epidemiologic Overview. *Journal Ophthalmic Epidemiology*. *14*(4),166-172.
12. Macoul, K. L., & Pavan-Langston, D. (1975). Pilocarpine ocusert system for sustained control of ocular hypertension. *Archives of ophthalmology*, *93*(8), 587-590.
13. McDaniel, D., & Besada, E. (1996). Hypothyroidism--a possible etiology of open-angle glaucoma. *Journal of the American Optometric Association*, *67*(2), 109-114.
14. Nezu, A., Morita, T., Nagai, T., & Tanimura, A. (2019). Simultaneous monitoring of Ca2+ responses and salivary secretion in live animals reveals a threshold intracellular Ca2+ concentration for salivation. *Experimental Physiology*, *104*(1), 61-69.
15. Olimat, S. (2015). Chemistry of Natural Products (Alkaloids, in Arabic). *Majdalawy Publishing House . Amman. Jordan.*
16. Pinheiro, C. U. (1997). Jaborandi (Pilocarpus sp., rutaceae): A Wild Species. *Economic Botany*. *51*, 49-58.
17. Popov, Y., & Salomon-Escoto, K. (2018). Gastrointestinal and Hepatic Disease in Sjogren Syndrome. *Rheum Dis Clin North Am. 44*(1), 143-151.
18. **Santos, A.A., Roberto, P., & Moreno, H. (2004). Pilocarpus spp.: a survey of its chemical constituents and biological activities. *Rev. Bras. Cienc. Farm*. *40* (2), 1-6.**
19. Sidhu, P. (2014). Endangered Jaborandi. *British Dental Journal*. *217*, 1-2.
20. Skaat, A., Rosman, M. S., Chien, J. L., Mogil, R. S., Ren, R., Liebmann, J. M., ... & Park, S. C. (2016). Effect of pilocarpine hydrochloride on the Schlemm canal in healthy eyes and eyes with open-angle glaucoma. *JAMA ophthalmology*, *134*(9), 976-981.
21. Skorupa, L. A., & Pirani, J. R. (2004). A new species of Pilocarpus (Rutaceae) from northern Brazil. *Brittonia*, *56*(2), 147-150.
22. Sonnsjö, B., & Krakau, C. E. T. (1993). Arguments for a vascular glaucoma etiology. *Acta ophthalmologica*, *71*(4), 433-444.
23. Thorne, I., & Sutcliffe, N. (2017). Sjögren's syndrome. *Br J Hosp Med (Lond). 78*(8), 438-442.
24. Treatise, A. (1904). On Pilocarpus (Jaborandi), Drug Treatise, Number III. Issued by Lloyd Brothers, Cincinnati, Ohio. Copyright, pp. 1-16.
25. Valdez, I. H., Wolff, A., Atkinson, J. C., Macynski, A. A., & Fox, P. C. (1993). Use of pilocarpine during head and neck radiation therapy to reduce xerostomia and salivary dysfunction. *Cancer*, *71*(5), 1848-1851.
26. Vardanyan, R., & Hruby, V. (2006). *Synthesis of essential drugs*. Elsevier. pp. 143-159.
27. Webster, A. R., Luff, A. J., Canning, C. R., & Elkington, A. R. (1993). The effect of pilocarpine on the glaucomatous visual field. *British journal of ophthalmology*, *77*(11), 721-725.
28. Wei, W., Ahmad, S. S., Chi, S., Xie, Y., Kamal, M. A., & Li, J. (2018). From Molecular Mechanism to the Etiology of Sjogren Syndrome. *Current pharmaceutical design*, *24*(35), 4177-4185.
29. Wiggs, J. L. (2007). Genetic etiologies of glaucoma. *Archives of ophthalmology*, *125*(1), 30-37.
30. Wiseman, L. R., & Faulds, D. (1995). Oral pilocarpine: a review of its pharmacological properties and clinical potential in xerostomia. Drugs, 49(1), 143-155.