

Review Article

## A Systematic Review on *Huperzia serrata*

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Available Online: 10<sup>th</sup> August, 2016

### ABSTRACT

*Huperzia serrata* is the genus belonging to the family Lycopodiaceae. It is a traditional Chinese remedy which is also known as *Qian Ceng Ta*. Chinese scientists Liu and his co-worker had discovered Huperzine A, which is known as a worldwide medicine. Huperzine A is an alkaloid which can be isolated from whole plant of the *Huperzia serrata*. It is mainly found in India, China, Nepal, Myanmar, Sri Lanka, Japan, Korea, Vietnam, Indonesia, Fiji, Samoa, Mexico, USA, Thailand, Peninsular Malaysia, Russia, Taiwan, Australia and Cuba. Several chemical constituents have been isolated from plants belonging to the category of alkaloids, flavones, Triterpenes and phenolic acids. It has been traditionally used as cold, fever, bruises, pain, strains, contusion, stasis swelling, rheumatism etc. Pharmacological activities such as anticonvulsant, anti-inflammatory, anti-nociception, alzheimer, schizophrenia, anti-apoptosis effect, organophosphate poisoning myasthenia gravis, antioxidant and protection of mitochondria.

**Keywords:** *Huperzia serrata*, Huperzine A, phytochemical, traditional Chinese medicine, pharmacological activities.

### INTRODUCTION

*Huperzia serrata* (Thunb. ex Murray) Trevis is commonly known as toothed firmoss is widely distributed species of clubmoss belonging to family Lycopodiaceae<sup>1</sup>. It is a terrestrial plant found in Asian countries such as China, India, Japan, Korea, and Russia so on, it is also found in Oceania and Central America<sup>2</sup>. It contains a large group of alkaloids called Lycopodium alkaloids<sup>3</sup>. Huperzine A is a Lycopodium alkaloid which can be isolated from whole plant of the *Huperzia serrata* by Jiasen Liu and co-workers at Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences (CAS)<sup>4</sup>. Huperzine A is really more a drug than an herb; it is sold as a dietary supplement for memory loss and mental impairment. This drug has been shown antioxidant and neuroprotective properties<sup>5</sup>.

*Chemical structure of Huperzine-A*<sup>6</sup>

*Synonyms*

*Lycopodium serratum*

*Common name*

Toothed clubmoss, *Qian Ceng Ta*

*English name*

Chinese clubmoss<sup>7</sup>

*Botanical Description*

*Height*

A small, soft and thick herb having height up to 3 cm and diameter up to 6cm.

*Stem*

Stem has erect, decumbent at bases 2-6 branching 8-20×0.8-1.8cm with leaves.

*Leaves*

Alternate, reflexed leaves having size 5-15×1.2-3.5mm. Shape of leaves is obovate to oblanceolate with constricted

bases resembling petioles. Shape of apex and base is acuminate. Margin of leaves is coarsely and irregularly doubly-serrate. Sporophylls like vegetative leaves. Kidney shaped sporangia are in the axils of unaltered leaves all down the stem and branches<sup>9</sup>.

*Habitat*

Forest floor, roadsides in dry areas at an elevation of 400-1000 m<sup>10</sup>.

### DISTRIBUTION

It is mainly found in sub-tropical to temperate forests at an altitude of 900 to 3500m in North-Eastern region of India like, West Bengal (Darjeeling), Sikkim, Arunachal Pradesh, Assam, Meghalaya and Manipur, and also in Nilgiri hills of Tamilnadu. Besides India, the plant is also reported from China, Nepal, Myanmar, Sri Lanka, Japan, Korea, Vietnam, Indonesia, Fiji, Samoa, Mexico, USA (Hawaii), Thailand, Peninsular Malaysia (Paham), Russia (East Siberia/Amur/Ussuri), Taiwan, Australia and Cuba<sup>11,12</sup>.

*Distribution of Huperzia species in India*<sup>13-16</sup>

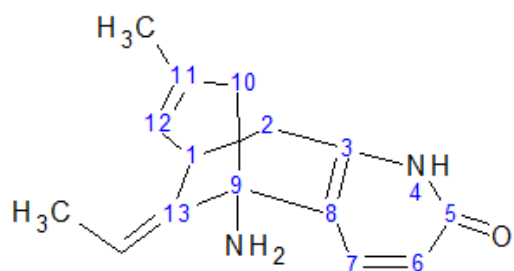
*Pytochemical Constituents*

*Huperzia serrata* contains four classes of Lycopodium alkaloids including lycodine, Lycopodine, fawcettimine and miscellaneous type.

*Lycodine alkaloids*

HuperzineA, NN-DimethylhuperzineA, 6 $\alpha$ -HydroxyhuperzineA, 6 $\beta$ -HydroxyhuperzineA, 6 $\beta$ -HydeoxyhuperzineA, PhlegmariurineM, HuperzineU, HuperzineC, HuperzineD, Huperzine, Isofordine, HuperzineB, N-MethylhuperzineB, De-N-methyl- $\beta$ -obscurine<sup>17, 18</sup>.

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9-amino-13-ethylidene-11-methyl-4-azatricyclo (3, 8) trideca-3(8), 6, 11-trien-5-one.

Table 1: Taxonomy classification<sup>8</sup>

S.NO.	Taxonomic classification	
1.	Biological Source	<i>Huperzia serrata</i>
2.	Family	Lycopodiaceae
3.	Kingdom	Plantae
4.	Division	Lycopodiophyta
5.	Class	Lycopodiopsida
6.	Order	Lycopodiales
7.	Genus	<i>Huperzia</i>
8.	Species	<i>Serrata</i>

#### Lycopidine alkaloids

Clavolonine, serratidine, 4 $\alpha$ -hydroxyserratidine, 4 $\alpha$ 6 $\alpha$ -dihydroxyserratidine, 6 $\alpha$ -hydroxyserratidine, lycoposerramine K, HuperzineE, 2-chlorohuperzine E, n-oxide huperzine E, Huperzine F, N-oxide huperzine F, Huperzine G, 12-hydroxyhuperzine, Huperzine O, 12-deoxyhuperzine O, Lycodoline, 12-epilycodoline N-oxide, 4 $\alpha$ 6 $\alpha$ -dihydroxylycopodine, 6 $\alpha$ -hydroxylycopodine, 7-hydroxylycopodine, lycoposerramine G, lycoposerramine L, lycoposerramine M, lycoposerramine N, Serratezomine C, Lucidioline, lycoposerramine F, lycoposerramine H, lycoposerramine I, lycoposerramine J, lycoposerramine O<sup>19, 20</sup>.

#### Fawcettimine alkaloids

Lycoflexine, lycothunine, 11 $\alpha$ -hydroxyfawcettidine, 2 $\alpha$ 11 $\alpha$ -dihydroxyfawcettidine, 8 $\alpha$ 11 $\alpha$ -dihydroxyfawcettidine, macleanine, 11 $\alpha$ -hydroxyphlegmariurine B, 7-hydroperoxyphlegmariurine B, Neohuperzine, Serratanidine, Serratezomine B, Serratinine, Serratine, 8-deoxyserratine, 8-deoxy-13-dehydroserratine, Huperserratine<sup>21,22</sup>.

#### Miscellaneous

Huperzine J, Huperzine K, Huperzine L, Huperzine V, Huperzinine B, Phlegmariurine N, Serratanine A, Serratanine B<sup>23-25</sup>.

#### Triterpenoids: Serratene-type

21 $\alpha$ -hydroxyserrat-14-en-3 $\beta$ -yl p-dihydrocoumarate, 21 $\alpha$ -hydroxyserrat-14-en-3 $\beta$ -yl dihydrocaffeate, 21 $\alpha$ -hydroxyserrat-14-en-3 $\beta$ -yl propanedioic acid monoester, 3 $\alpha$ -21 $\alpha$ -dihydroxyserrat-14-en-24-oic acid, 16-oxo-3 $\alpha$ 21 $\beta$ -dihydroxyserrat-14-en-24-al, 16-oxo-3 $\alpha$ 21 $\beta$ -dihydroxyserrat-1-en-24-oic acid, 16-oxo-21 $\beta$ -hydroxyserrat-14-en-3 $\alpha$ yl Acetate<sup>26</sup>.

#### Phenolic

Catechin, quercetin, chlorogenic acid, ferulic acid<sup>27</sup>.

#### Flavonoids

5-7-2'4'-tetrahydroxy5'methoxyflavone, 5-7-4'-trihydroxy3'methoxyflavone, 5-7-4'-trihydroxy3'5'dimethoxyflavone, Apigenin<sup>28,29</sup>.

#### Traditional Uses

*Huperzia serrata* is used to treat rheumatism, cold, fever, bruises, pain, strains, contusion, stasis swelling<sup>30</sup> bleeding throat, carbuncle swollen, bleeding injuries, snake bites, burns and inflammation. It can also be used to improve blood circulation, relax muscles<sup>31</sup>.

#### Ethnopharmacological Reports

##### Anticonvulsant

Huperzine A is used to protect against seizures/status epilepticus. Huperzine A is used as pre and post treatment for the excitatory amino acids toxicity that accompanies many conditions including stroke, traumatic brain injury, epilepsy and several neurodegenerative diseases<sup>32</sup>. The anti-convulsant property of huperzine-A was determined by Bialer *et al.*, in 2007, 2009 and 2010 using pentylenetetrazole-induced seizures model on swiss-webster mice by oral administration of HupA (1 mg/kg) it was found that HupA protected the animals (62.5 % protection) at 1 h post-dosing<sup>33</sup>. Schneider *et al.*, reported the anticonvulsant activity in 2009. HuperzineA was administered for more than 6 months used to treat partial behavioral seizures in dogs<sup>34</sup>.

##### Anti-inflammatory

HupA inhibits the activation of the nuclear translocation of nuclear factor kappa B and attenuate the inducible nitric oxide synthase, cyclooxygenase-2 (COX-2) and nitric oxide over expression, promoting the survival of the C6 cells subjected to oxygen-glucose deprivation<sup>35</sup>. HuperzineA has neuroprotective effects which demonstrated against cerebral ischemia-induced brain injury may partly involve a cholinergic anti-inflammatory pathway in which  $\alpha$ 7 nicotinic Ach receptors play an essential role<sup>36,37</sup>. HupA suppressed the inflammatory factor tumor necrosis factor- $\alpha$  and over phosphorylation of c-Jun N-terminal kinases and p<sup>38</sup> mitogen-activated protein kinases. Huperzine A is used to reduce long lasting inflammation in the cerebral white matter and reduces lesions<sup>38</sup>. HuperzineA can suppress inflammation in the post-ischemic brain<sup>39</sup>.

##### Antinociception

The anti-nociception property of huperzine-A was determined by Bialer *et al.*, in 2007 and 2010 using mouse formalin pain model and sciatic ligature model of neuropathic pain. Intraperitoneal administration of huperzineA (0.5, 1 mg/kg) inhibits the pain behavior in all treated animals. HuperzineA is used to treat complete inhibition of pain behavior<sup>40,41</sup>.

##### Anti-apoptosis effect

HuperzineA attenuates neuronal apoptosis and inhibit caspases-3 activity and mitochondrial release of cytochrome C to the cytosol. HuperzineA block apoptosis by antagonizing the mitochondrial dependent caspases pathway directly or indirectly. Huperzine A has anti-apoptosis effects<sup>42,43</sup>.

##### Myasthenia gravis

HuperzineA is used to treat the symptoms of myasthenia gravis. It can be improving the muscle weakness which



1(a)



2(b)

Figure 1: *Huperzia serrata* 1(a) and 1(b)

Table 2: Near about 415 species of huperzia have been reported from all over the world. Out of them 21 species are found in India which can be shown in the following table:

S.NO.	SPECIES	DISTRIBUTION
1	<i>Huperzia aloifolia</i>	Eastern India
2	<i>Huperzia cancellata</i>	Arunachal Pradesh
3	<i>Huperzia carinata</i>	Tamilnadu, Andaman and Nicobar Islands.
4	<i>Huperzia ceylanica</i>	Meghalaya, Tamilnadu
5	<i>Huperzia cryptomeriana</i>	Arunachal Pradesh
6	<i>Huperzia fordii</i>	Sikkim
7	<i>Huperzia hamiltonii</i>	Hilly region
8	<i>Huperzia herteriana</i>	Sikkim, West Bengal & Manipur
9	<i>Huperzia nilagirica</i>	Tamilnadu
10	<i>Huperzia nummulariifolia</i>	Nicobar islands
11	<i>Huperzia petiolata</i>	Meghalaya
12	<i>Huperzia Phlegmaria</i>	West Bengal, Sikkim, Assam, Tripura, Andaman & Nicobar Island
13	<i>Huperzia phyllantha</i>	Kerala, Karnataka, Tamilnadu, Andaman&nicobar islands
14	<i>Huperzia pulcherrima</i>	Uttarakhand, North-East Himalaya
15	<i>Huperzia selago</i>	Sikkim
16	<i>Huperzia Serrata (Thunb.Ex Murray)</i>	West Bengal, Sikkim, Arunachal Pradesh, Assam, Meghalaya, Manipur, Tamil nadu
17	<i>Huperzia squarrosa</i>	West Bengal, Sikkim, Assam, Meghalaya, Kerala, Manipur.
18	<i>Huperzia subulifolia</i>	West Bengal, Sikkim, Meghalaya, Uttarakhand.
19	<i>Huperzia vernicosa</i>	Tamilnadu, Kerala.
20	<i>Huperzia vorwerkii</i>	Himalayas

caused by myasthenia gravis. Pepping reported the clinical manifestation of myasthenia gravis in year 2000. Intramuscularly administration of huperzineA 0.4mg/day for 10 days to treatment group (n=59), while in the control group (n = 69) the patients were treated with neostigmine 0.5 mg/ day (i.m) every other day and HupA 0.4 mg/day (i.m) on the intervening day. The results revealed that the administration of HupA improved muscle weakness in the 128 patients with myasthenia gravis<sup>44</sup>.

#### Alzheimer's disease

HuperzineA is isolated from Chinese herb *Huperzia serrata* having some properties that can treat the Alzheimer's disease. HuperzineA has some beneficial effects which improving global clinical status, general cognitive function, behavioural disturbance & functional

performances in Alzheimer's disease<sup>45</sup>. Several studies indicate that the huperzineA effective against the reduced acetylcholine levels in the brain and glutamate induced neuronal death, which the most neuronal disorders are observed in Alzheimer's disease<sup>46</sup>.

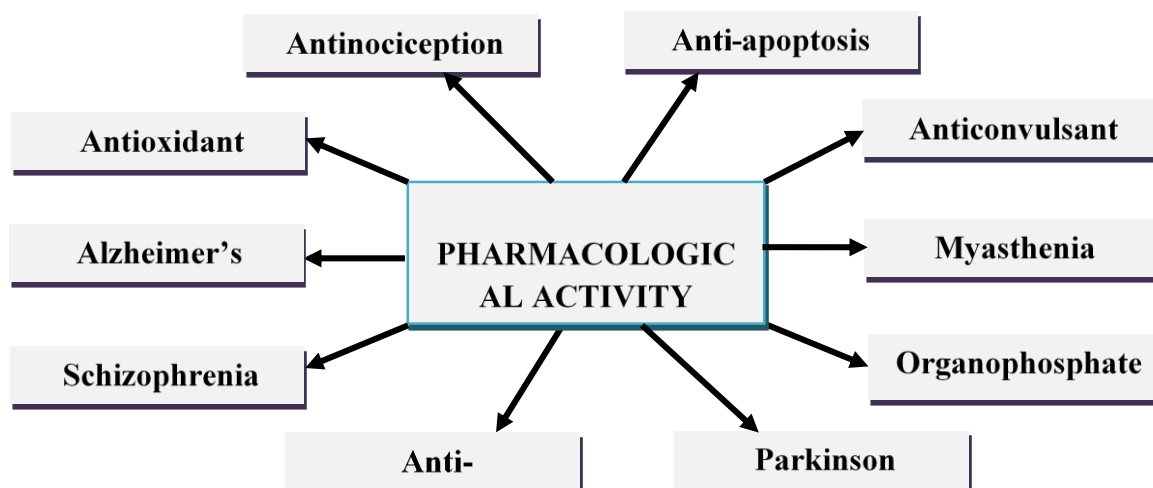
#### Antioxidant effect

HuperzineA has neuroprotective effects against free radicals induced cytotoxicity. HuperzineA can ameliorate the abnormal increasing MDA level and decreasing SOD level<sup>47</sup>.

#### Protection against organophosphate poisoning

HuperzineA has one of the most effective agents for prophylactic treatment against toxic effect of organophosphate nerve gases<sup>48</sup>. HuperzineA irreversibly inhibit the AChE enzyme in the CNS and peripheral



Figure 2: Pharmacological Activities of *Huperzia serrata*

nervous system<sup>49,50</sup>. leading to the accumulation of Acetylcholine and consequent release of excitatory amino acids, which appear to be responsible for the toxicity of organophosphate nerve agents<sup>51</sup>.

#### Schizophrenia

The effects of huperzineA on memory disorder in schizophrenic patients have been studied by some authors. In all those studies the memory functions of patients were significantly improved after the treatment with huperzineA<sup>52</sup>. The potential of huperzineA as add-on therapy in schizophrenic patients who did not obtain satisfactory response to antipsychotic treatment demonstrated the beneficial effect of HuperzineA in treating cognitive and negative symptom clusters of schizophrenia over twelve weeks<sup>53</sup>.

#### Protection of Mitochondria

HuperzineA attenuate A $\beta$ -induced mitochondrial swelling, membrane potential can be declined and release of cytochrome C. HuperzineA inhibits normal swelling which can be caused by osmosis in isolated mitochondria. HuperzineA protects mitochondria against A $\beta$  by preserving membrane integrity and improving energy metabolism<sup>54</sup>.

#### CONCLUSION

In recent times, plants are the rich source of drugs in traditional system of medicine, nutraceuticals, food supplements, folk medicines, modern medicines, pharmaceutical intermediates and chemical entities for synthetic drugs. Plants have played a very important role in drug discovery. A majority of drugs being used in modern medicine have been obtained from medicinal plants. *Huperzia Serrata* traditional Chinese remedy which is also known as worldwide medicine. Traditionally, it is used in cold, fever, bruises, pain, strains, contusion, stasis swelling, rheumatism etc. Pharmacological activities discussed in present review paper.

#### ACKNOWLEDGEMENT

The authors are thankful to Principal, G.H.G Khalsa College of pharmacy, Gurusar Sadhar, (Ludhiana) and the management for providing us all the facilities.

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