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Pharmacological activities and uses of phytochemicals of *Lycopodium Clavatum*: A review

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Abstract
The plant *Lycopodium clavatum*, known as club moss, is the Lycopodiaceae family and used to treat range of ailments in European and Asian countries. Quinolizidine alkaloids are found in crude extracts from several areas of the herb. Several researchers has reported on the therapeutic potential of alkaloids produced from this plant, but there are few publications on adverse effects of alkaloids from this plant. In such a circumstance, a greater understanding of its ameliorative effect as well as harmful effects is required. This review outlines scientific results and identifies areas in which more study is required.

Keywords: *Lycopodium clavatum*, alkaloid, pharmacology, anti-oxidant

Introduction
Lycopodium clavatum, other names such as Club moss, Clubfoot Moss, Foxtail, Ground Pine, Sulfur, and Wolf's Claw, is a most abundant Lycopodiaceae species. It is a pteridophyte that can be seen in abundance in tropical and subtropical climates, as well as in many temperate countries. This spore-bearing vascular plant is used in traditional medicine to treat gastritis, rheumatic disease, myalgia, Alzheimer's disease, and other ailments [1]. The plants thrive in a variety of environments, including high altitude, the highlands, and grassy places. The spore are green to yellow colour and are tiny (3-5 mm length and 1 mm wide). Though Lycopodium is still used to treat a variety of diseases in both traditional and homoeopathic medical systems, it does have significant limits, so its therapeutic potential must be evaluated carefully. The current review summarizes scientific results on *Lycopodium clavatum* from previous researchers and identifies areas where more research is needed.

Uses in traditional medicine systems
Aneurisms, constipation, chronic lung and bronchial diseases, and fevers are all treated with clubmoss in homoeopathy. It also lowers gastrointestinal inflammation, makes digestion easier, and aids in the treatment of chronic kidney disease [2]. Additionally, applying powdered spores to the skin minimises skin irritation and itching. Lycopodium is used to treat a variety of mental illnesses, including anxiety, amnesia, and exhaustion and chronic fatigue [3-4]. Several tribes use it to treat erection problems and to minimise prostrate in the elderly. Various tribes have traditionally utilised Club moss to cure kidney stones, urinary tract infections, and digestive problems.

Phytoconstituents
The Lycopodium alkaloids are important because of their biological activity and & distinctive chemical structures, yet many of them not thoroughly investigated. This plant has been reported to have vanillic, coumaric, ferulic, and syringic acids, according to different sources. It also has huperzine A, lycopodine, lycoflexine, Alpha-onocerin, and sporopollenin, among other things [5]. Apigenin is a flavonoid polyphenol derived from Lycopodium clavatumthat possesses high antioxidant properties [6]. Further research revealed the alkaloids lycopodine, clavatine, and clavatoxine, as well as polyphenolic acids such as dihydrocaffeic and triterpenes (see figure 1) [11].

Mechanisms of action
Anticancer Effectss
Mandal *et al*. (2010) [7] explored whether lycopodine in *Lycopodium clavatum* extract stops HeLa cell proliferation by activating caspase-3 and inducing apoptosis. They discovered that lycopodine caused chromatin condensation, internucleosomal DNA fragmentation, and an increase in cell population in the sub-G1 region, as well as increase reactive oxygen species generation, mitochondrial membrane potential depolarization, cytochrome c release, and also caspase-3 activation, all of which is apoptosis-related events [7]. Other researchers discovered that apigenin had anticancer properties in A375 and A549 cells, which they believe are mediated via DNA interaction, damage, and malfunction of mitochondria, either directly or indirectly [8]. Samadder *et al*. 2013 found that the extremely diluted, homoeopathic remedies of L.*clavatum* 5C and 15C were capable of inducing

apoptosis in HeLa cells, indicating that they could be used as supportive cancer therapy [9]. Bishayee *et al*. (2010) evaluated lycopodine against hormone responsive (LnCaP) and refractory (PC3) prostate cancer cells *in vitro* and it is found to be a viable candidate for medical usage as an anti-cancer medication. They discovered that lycopodine administration caused down-regulation of 5-lipoxygenase and EGF receptor expression, as well as increased regulation of cytochrome c and depolarization of mitochondrial inner membrane potential, without a discernible change in p53 activity, leading to apoptosis and greatly reduced cancer cell proliferation; concurrently, phosphotidyl serine residues were externalised. The potential of lycopodine to intercalate with the DNA molecule was discovered using CD spectroscopic investigation, implying that it can impede biological DNA production. As a result, lycopodine could be a promising option for studies in cancer [10].

Hepatoprotective activity

Lycopodium clavatum extract's has capacity to protect from p-dimethylaminoazobenzene-induced hepatocarcinogenesis [11]. In mice, continous feeding of the carcinogens p- dimethylaminoazobenzene (initiator) and phenobarbital (promoter) for the period of 90 and 120 days increased activities of toxicity biomarkers such as acid &alkaline phosphatase, lipid peroxidation, glycaemia, and cortisol, while decreasing the activities of substances like glutathione reductase, succinate dehydrogenase, lipidaemia and haemoglobin The levels of these biomarkers were positively altered both in haepatic and spleen tissues, as well as reduction in tumour incidence in the liver of carcinogen-induced mice treated with *Lycopodium clavatum* extract.

Effects on enzymes

Prolyl endopeptidase enzyme that aids in the digestion of proline-containing neuropeptides such vasopressin, substance P, and thyrotropin-releasing hormone (TRH), all have been linked to memory and learning. Tezuka *et al*. 1998 studied the methanolic content of *Lycopodium clavatum* inhibits prolyl endopeptidase [12] and lowers lipid peroxidation, acid and alkaline phosphatase, and transaminases, which increased during p-DAB-induced carcinogenesis in a mouse model [11].

Antioxidant activity

Ferulic acid, a phenolic acid found widely in plants, is more accessible than other dietary flavonoid and monophenolic acids investigated. Other researchers have found as a powerful antioxidant, anti-inflammatory, and capable of terminating free radical chain reactions [13-14]. Apigenin, a active flavonoid from *Lycopodium clavatum*, promotes nucleotide excision repair genes for protecting skin keratinocytes against UV B-induced reactive oxygen species and DNA damage, according to a study published in 2010. Apigenin accelerated the reversal of UV-B-induced DNA damage in A375 and A549 cells by up-regulating NER genes, removing cyclobutane rings, inhibiting ROS generation, and down-regulating NF-B and MAPK [8]. Apigenin also induced apoptosis in A375 and A549 cells by selective action and mitochondrial dysfunction.

Antiprotozoal and antiviral activity

P. *falciparum* development has been shown to be inhibited by *Lycopodium clavatum* petroleum ether and chloroform fractions [15]. They discovered that extracts of *Lycopodium clavatum*, such as petroleum ether components and chloroform fractions, had a leishmanicidal activity, possibly due to the large number of alkaloids, and flavonoids present.

Pain and behavioral activity

Sundaram *et al*. (2013) [16] studied *Lycopodium clavatum's* analgesic efficacy on rats. They assessed the analgesic effect using the hot plate, ice plate, and Randall-Selitto tests, as well as the behavioural pattern using the rota rod and open field tests, and found that an increase in the latency time to both hot and cold stimuli. Using grip strength tests, different strengths of *Lycopodium clavatum* made according to homoeopathic procedures were evaluated for muscle coordination activity in Wister rats. It was discovered that the rats' grip strength decreased half hour after administration of the different dilutions of *Lycopodium clavatum* for one month. Furthermore, when evaluated half hour following administration of varied potencies on the 10th day of the experiment, the rats' locomotor activity decreased [16].

Anti-inflammatory

Namsa *et al*. 2009 found Lycopodium extracts exhibit anti-inflammatory effect, because of the alkaloid components, which confirms folklore use by the Lohit population of Arunachal Pradesh, India [17].

Effects on genitals &gonads

In the treatment of impotency in young men, *Lycopodium* is the most efficient homoeopathic medication. It also helps older men with enlarged prostrates. The use of *Lycopodium* to females reduces vaginal dryness with a burning feeling during and after coition.

Central Nervous system

Konrath *et al*. (2012) studied the acetylcholinesterase & antioxidant activities of commonly used *Lycopodium* species *in vitro* and ex vivo. The inhibitory action of *Lycopodium clavatum* over acetylcholinesterase (AChE)

was tested *in vitro* and ex vivo with rat brain homogenates after a one dose of the alkaloid extracts in mice [18]. Orhan *et al*., 2003 [19] discovered alpha-onocerin, an acetylcholinesterase inhibitor derived from *Lycopodium clavatum*. L. *chloroform* extract fractionation guided by bioassays The discovery of clavatum led to the separation of alpha-onocerin, a well-known triterpenoid.

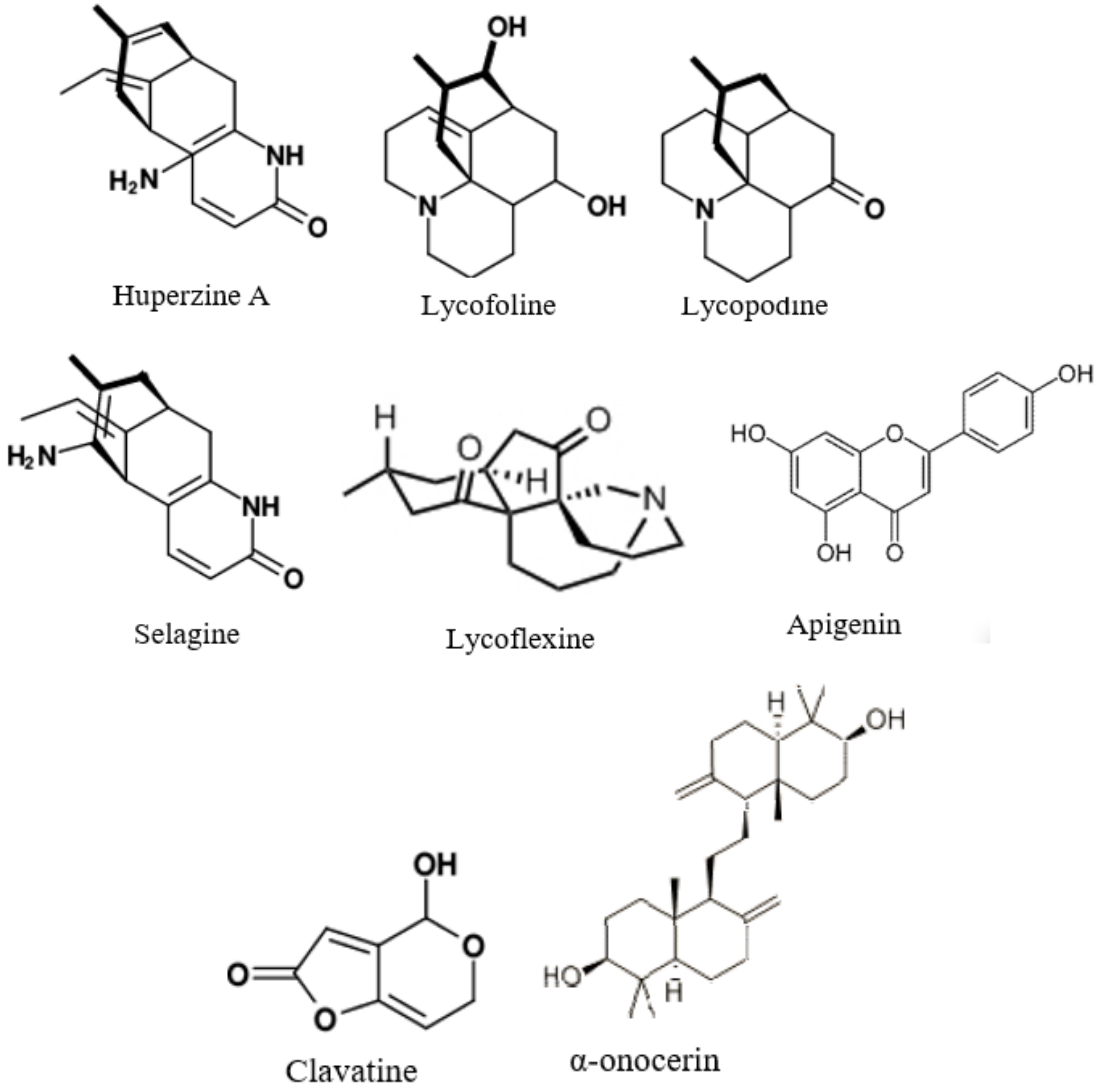

Fig 1: Depicts some of the chemical structures of the compounds commonly found in *Lycopodium clavatum*

Immunomodulatory properties

A combination of *Lycopodium clavatum* (as the vaccine delivery vehicle) and ovalbumin (as the vaccination antigen) consistently elicited a significant immunological response in mice. The immunological response elicited by *Lycopodium clavatum* spores was significantly greater than that elicited by cholera toxin or ovalbumin formulations. Cholera toxin is used to test the efficacy of vaccines in medical science, however it is not suited for vaccine administration due to its toxicity. These experiments reveal that pollen grains (which include plant, moss, fern, algal, and bacterial spores) outperform current vaccine testing procedures and are a feasible oral immunisation option [20-21].

Other effects

Lycopodium spores were found in ultrasound-guided core biopsies of the prostate by *Andersen et al* (1993) [22]. Because it is stable against chloromethylation and commonly used blocking techniques, sporopollenin from *Lycopodium clavatum* proven to be a good support for peptide synthesis [23]. Lycopodine increases peristaltic motions in the intestine and produces uterine contractions in animals, according to Zimudzi 2007. It helps to alleviate tiredness and chronic fatigue. *In vivo* antioxidant activity of huperzine A has been established in various investigations [24-26]. Another New Zealand *Lycopodium* species, L. *varium*, was shown to have anti - worm activity against the flies *Anthrenocerus australis*, *Lucilia cuprina, and Tienda bisselliella*, leading to the discovery of huperzine A as the active component [27]. The most common species, L. *clavatum*, has been claimed to have a healing effect on wounds and dermatological illnesses, especially rash in infants, and is thus known as

"belly powder" [1]. Native Americans often utilise the spores of *Lycopodium clavatum* to cure nose bleeding and wound healing. *Lycopodium clavatum* ethanolic extracts have been reported to inhibit CYP3A4 significantly, suggesting that it could be used as an anti-diabetic [28].

Conclusion

In induced hepatocarcinogenesis, *L. clavatum* has been shown to be hepatoprotective. It would be good to look at the constituents individually and combined to see how they influence pathological changes and which form is the most effective. The quantity and quality of active chemicals in plant materials may be affected by the time of collection, location of collection, extraction processes, and storage. The material presented here about *L. clavatum* is meant to serve as a resource for ethnopharmacological researchers. Positive outcomes observed in animal models (rats/mice) might be extended to humans in a useful and compelling way.

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