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A REVIEW ON LYCOPODIUM CLAVATUM: PAST DISCOVERIES AND CURRENT APPLICATION IN SCIENCE AND MEDICINE

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ABSTRACT

Despite its potential, *Lycopodium clavatum*, commonly known as clubmoss remains unexplored. This plant is predominantly found in tropical, subtropical and temperate countries. It has found a significant practise in traditional medicine and homeopathy where it is extensively utilized in preparing remedies that address wide range of health conditions such as Alzheimer's, rheumatism, gastritis and muscular pain etc., capitalizing on its therapeutic properties to provide natural treatment option. This review consolidates findings from the past year's offerings insights into advancements, current gaps and future directions for research.

INTRODUCTION

The most abundant species in the Lycopodiaceae family is *Lycopodium clavatum*, sometimes known as ground pine or club moss. This vascular plant, which bears spores, is found in tropical and subtropical mountainous areas of the Caribbean, South America, East Africa, North America, and Europe. Alkaloids and phytoconstituents such as Huperzine A, Lycopodine, lycoflexine, alpha-onocerin, sporopollein, and apigenin a flavonoid with strong antioxidant qualities-are abundant, vanillic, coumarin, ferulic, and syringic acids are among the polyphenolic acids are also present in it.[1,2] Many of its constituents are still poorly understood despite its widespread use, which emphasizes the need for more study into its toxicological profile and biological activities.

Mother tincture are the main usage for *Lycopodium clavatum* spores in homeopathy. Pharmacological investigations have demonstrated the plant's therapeutic actions, which include analgesic, antirheumatic, carminative, hepatoprotective, anticancer, and anti-inflammatory effects. This plant is a useful topic for research in both pharmaceutical, pharmacology and homeopathic settings because of its distinct chemical makeup and therapeutic potential. Thus the present review article summarizes the past research and shed light on critical in current research to guide further investigations.

Taxonomical classification

- **Kingdom:** Plantae
- **Phylum:** Tracheophyta
- **Class:** Lycopodiopside
- **Order:** Lycopodiales
- **Family:** Lycopodiaceae
- **Genus:** Lycopodium
- **Species:** *Lycopodium clavatum*

In-vitro* studies of *Lycopodium clavatum

Rikhil Seth.et.al (2023), study showed that *Lycopodium clavatum* extract at 0.05mg/ml exhibited apoptosis inducing property in colorectal cancer cells (SW480). They confirmed that by measuring the three genes CASP3, BCL-2 and p53, which induces the apoptosis. Therefore, *Lycopodium clavatum* extract at 0.05mg/ml has bioactivity against the cancer cells.[3]

Kucukbagriacik Y et.al (2023), findings revealed that both water and ethanol extract of *Lycopodium clavatum* activated the apoptosis related proteins (BAX, caspase 3 and caspase 9) and exhibited cytotoxic effect on MCF-7 cells, which was confirmed by using immunostaining and WST-1 methods respectively with concentration 100-300µg/ml of *Lycopodium clavatum* extract. Suggesting that *Lycopodium clavatum's* anticancer activity.[4]

Giang V H et.al.(2022), the study highlighted that new triterpenoids (lycomclavatols A) isolated from *Lycopodium clavatum* methanol extract exhibited the cytotoxic and nitric oxide inhibitory activity against the HepG2(liver cancer) and A549 (lung cancer) cell lines at an IC50 value of 40.7µM and 87.0µM respectively, and lipopolysaccharide(LPS)-stimulated BV2 microglial cells IC50 36.0µM. Overall findings shed light on the potential of anti-inflammatory and anticancer properties of *Lycopodium clavatum*.[5]

Mansoor ali et.al.(2022) showed that *Lycopodium clavatum* homeopatheic prepration (200C & 1M) potential inhibited the formation of Monosodium urate crystals in vitro by causing the dissolution of the crystals, thus its potential in treating the symptoms of gout.[6]

Antara Banerjee et, al. (2020) reported the combinative effect of Quercetin (50μL) and *Lycopodium clavatum* extract (10μL) inhibited cell growth, exhibited potential Antiproliferative effect against the colon cancer cells. The key findings where, suppressed Matrix metallopeptidase 2 and 9 activities, and significantly altered the mRNA expression of pivotal apoptotic genes. They also measured the inhibitory activity of *Lycopodium clavtum* against *E. coli* by agar well diffusion method which exhibited potential Antimicrobial activity.[7]

Ara Jo, et al. (2020) explored the effect of novel Serratane triterpenoids isolated from the ethyl acetate fraction of *Lycopodium clavatum* have potential inhibited the lipopolysaccharide-induced Nitric oxide production in macrophages and reduced inducible nitric oxide expression in RAW 264.7 cells and downregulated pro-inflammatory cytokines like interleukin-1β in macrophages and suppressed IL-8 levels in HT-29 cells. Therefore, the serratane triterpenoids of *Lycopodium clavatum* has potent Anti-inflammatory activity and can employed in treatment of inflammatory disorders such as IBD etc.[8]

Mandal, et al. (2010) showed that the Lycopodine isolated crude ethanolic extract of *Lycopodium clavatum* exhibited 60% inhibition of the HeLa cell growth at the highest dose of 200μg/ml. The result showed elevated levels of reactive oxygen species, depolarization of mitochondrial membrane resulting in the activation of caspase 3 to induce apoptosis. Hence the study concludes that Lycopodine can be used as a potential chemotherapeutic agent in cancer treatment.[9]

Sreemanti das et.al (2013) reported that Apigenin bioactive compounds found in *Lycopodium clavatum* extract as a potent Antioxidant and DNA protective activity.[10]

Nguyen Ngoc Linh et.al (2025) reported the potent Antioxidant and Acetylcholinesterase inhibitory activity of the Serratane triterpenoids and caffeic acid derivatives present in the *Lycopodium clavatum.*[11]

Shuangshuang et.al.(2020) performed an in vitro diffusion test of the Rat abdominal skin with the *Lycopodium clavatum* ethanolic extract using a transdermal diffusion test apparatus for determining the transdermal absorption of the extract. Hence they exhibited transdermal permeation property.[12]

Samaddar et.al.(2013) showed that the highly-diluted homeopathic remides *Lycopodium clavatum* 5C and 15C caused the cell death through apoptosis in HeLa cells, increasing the expression of protein and mRNA of caspase 3 and Bax, decreases the expression of Bcl2, highlighting their efficacy to induce apoptosis in cancer cell, can be used as supportive medicines in cancer therapy.[13]

In-vivo* studies of *Lycopodium clavatum

A study conducted by Konarth et.al (2012) reflects the effectiveness of *Lycopodium clavtum* alkaloid (Lycopodine and acetyldihidrolycopodine) extract in Alzheimer's, as the antioxidant activity helps in reducing the brain damage and the AcHe inhibitory activity decrease the lipid peroxidation in the mice treated with alkaloid extract of *Lycopodium clavatum.*[14]

Hanif et.al. (2015) showed the effect of Lycopodium (Lyc) mother tincture on memory function and Cerebral blood flow (CBF) in memory impaired rats. By inducing memory defect by streptozotocin (3mg/kg) on 1st and 3rd day. Morris water maze test (memory function) and CBF was measured using Laser Doppler flow meter. Overall result demonstrates significant potential of Lyc in inhibiting the acetylcholinesterase activity.[15]

Sreemanti Das (2013) showed that a flavonoid polyphenol (Apigenin) isolated from *Lycopodium clavatum* extracts decreased the Reactive oxygen species generation, enhanced DNA stability, activated Nucleotide excision repair gene (NER) in UV-B radiation induced mice model. Therefore, Apigenin isolated from *Lycopodium clavatum* has potent Antioxidant and as DNA protective activity.[10]

Pathak et.al.(2006) reported the protective effect of homeopathic prepation Lycopodium 30 in mice chronically fed with hepatocarcinogens. Therefore, highlighted the reduction in toxicity markers, alkaline phosphates and alanine amino transferase, lipid peroxidation and reduced GSH levels exhibiting potent hepatoprotective activity.[16]

Banerjee, et al. (2009) showed that ethanolic extract of *Lycopodium clavatum* spores exhibited Hepatoprotective activity, by reducing enzyme activity, liver tumor incidence, improved hormonal imbalance caused by carcinogens (p-dimethylamino azobenzene and phenobarbital) chronic exposure in mice.[17]

Further modification of their pervious study Banerjee, et al. (2010) reported that ethanolic extract of *Lycopodium clavatum* spores, reduced the Genotoxicity and Hepatotoxicity in carcinogens (p-dimethylamino azobenzene and phenobarbital) induced mice (chronic exposure) by reducing the tumours. Therefore, extract of *Lycopodium clavatum* spores exhibited its potential antitumor activity, reducing the ALT, AST, and LPO, positive action on GSH and catalase activity showing Hepatoporotective and its potential in reducing cytotoxicity and genotoxicity.[18]

Pereira, et al. (2020) showed that the use *Lycopodium clavatum* 200dH for treatment of *Toxoplasma gondii* infection in mice intensified renal damage, severe inflammation, edema, atrophy, and tubular cystic dilation. Elevated liver enzyme levels, particularly Aspartate aminotransferase. Resulting in the increases the kidney and liver damage.[19]

Orhan, et al. (2007) reported the effectiveness of petroleum ether, chloroform, ethyl acetate, and methanol extract of *Lycopodium clavatum* in reducing the inflammatory mediators in acetic-acid induced capillary permeability model in mice. Among the four extract the chloroform extract (24.3%) and its alkaloid fraction (32.1%) inhibition of the inflammation. Hence the study concludes that Lycopodine (84.5%) present in the alkaloidal fraction of the extract is responsible for the anti-inflammatory activity.[20]

Henrique et.al.(2014) showed the effect of homeopathic preparation Lyc30 as significantly reduced the hepatic lesions, levels of ALT in the rats induced by paracetamol in acute hepatitis. Therefore highlighting its hepatoporotective activity.[21]

In order to determine whether encapsulating Diclofenac sodium (DIC) within *Lycopodium clavatum* spores (LCS) microcapsules can lessen the hepatotoxic effect, the study by Meligi et al. (2023) provides insight into the use of natural sporopollenin microcapsules: biological evaluation and application in regulating hepatic toxicity. Diclofenac loaded within *Lycopodium clavatum* spores (LCS) microcapsules. markedly decrease the serum levels of liver enzymes, total bilirubin, pro-inflammatory cytokines, and antioxidant enzyme activities. Therefore, this method of natural encapsulation is a viable way to improve the safety profile of NSAIDs.[22]

Analytical studies of *Lycopodium clavatum*

Matie et. al. (2024) showed that the concentration of toxic element present in the *Lycopodium clavatum* were found to be within the permissible limits(Pb,Co,Ni,Cr) and, below the detection limit(Mn, Cd, Bi).[23]

Li, et al. (2019) analysed the chemical constituents of *Lycopodium clavatum* through ultra-high performance liquid chromatography combined with quadrupole-time-of-flight mass spectrometry (UPLC-Q-TOF/MS) and multi-data processing. They characterized 30 peaks in the 75% ethanol extract of LC and identified 17 peaks in rat plasma, including 12 prototype compounds and five metabolites. Additionally, methylation and demethylation reactions were recognized as the primary metabolic transformations of LC in rat serum.[24]

Mundargi, et al. (2016) explored the potential of natural plant-based spores as drug delivery platforms using *Lycopodium clavatum* spores, while using different microencapsulation techniques and achieved the highest encapsulation efficiency with vacuum loading.[25] In other study he utilized this vacuum loading microencapsulation to develop a control released formulation of 5-flurouracil in stimulated gastric (pH1.2) and intestinal(pH7.4) condition.[26]

Orhan et.al. (2003) examined natural acetylcholinesterase inhibitors for Alzheimer's disease and tested chloroform: methanol (1:1) extracts from five *Lycopodium* species (*L. clavatum*, *L. selago, L. annotinum*, *L. alpinum,* and *L. complanatum ssp. chamaecyparissus*). In vitro screening using the Ellman spectrophotometric method (1 mg/ml) revealed notable activity in *L. clavatum* extract (49.85%). Bioassay-guided fractionation identified α-onocerin, a triterpenoid with an IC50 value of 5.2 μM, as the active compound responsible for this acetylcholinesterase inhibitory effect.[27]

The article by Harris et.al (2016) provides a comprehensive exploration of the use of *Lycopodium clavatum* exine microcapsules(LEM's) enable safe oral delivery of 3,4-diaminopyridine(3,4-DAP) for treatment of botulinum neurotoxin A intoxication offering novel insights to enhancing the oral delivery of 3,4 (DAP) by using LEM's as a vehicle to overcome the pharmacokinetic limitation. The assessment of therapeutic efficacy of the encapsulated 3,4DAP was done using murine model of BoNT/A intoxication. The key findings –controlled release, enhanced bioavailability, therapeutic efficacy improved the survival rates and mitigated symptoms compared to controls and also minimized the potential toxicity and side effects associated with 3,4 DAP by the use of natural biodegradable LEM's. this approach holds promising effect in improving the treatment of botulism and other condition requiring controlled oral drug delivery.[28]

Case study of *Lycopodium clavatum* homeopathic preparation

Preveen.et.al (2022) reported five case on the study of effect of *Lycopodium clavatum* showed decrease in the serum uric acid levels in the managing of Hyperuricemia.[29]

Tanmay Sarkar, (2023) reported a case study on treatment of psoriasis by Individualised homeopathic medicine *Lycopodium clavatum* 200CH, symptoms improved. After few months there was a noticeable outcome in the Psoriasis area and Severity index score(PASI) index before treatment (5.9) and after treatment (0.1) which demonstrates the benefits of homeopathic treatment for psoriasis.[30]

CONCLUSION

This review highlights the extensive research conducted on *Lycopodium clavatum* over the past few years, emphasising its diverse application in traditional medicine and mainly in homeopathic remedies in treating various disorders. The plant also contains anti-oxidant properties, anti-inflammatory activity, Hepatoprotective effect, anticancer effect, immunomodulatory effect, and their effect on the CNS in improving memory function. The continued exploration of its properties will likely yield significant advancements in the future should focus on the isolation of bioactive compounds, enhancing sustainable cultivation method, understanding molecular mechanism and conducting in-vivo studies for better scientific evidence on the therapeutic effect of the *Lycopodium clavatum*.

Through continued exploration and innovation, the insights gained from this review lay a strong foundation for advancing knowledge and unlocking full potential of *Lycopodium clavatum.*

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