***Pteridophytes* as Potential Source of Anti-diabetic Medicine: Current Status and Future Scenario**

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**ABSTRACT**

This chapter delves into the futuristic trends and innovative prospects of utilizing *Pteridophytes*, a unique group of plants, as novel approaches in the treatment of diabetes. *Pteridophytes*, which include various fern species, have garnered attention for their potential in addressing the complexities of diabetes. The chapter explores their bioactive compounds, mechanisms of action, and therapeutic potential. It also discusses ongoing research, potential synergies with existing treatments, and the journey towards personalized diabetes management. Moreover, it emphasizes the importance of standardized processes, regulatory considerations, and patient education in realizing the promise of *Pteridophytes* as innovative tools in the fight against diabetes.

**Keywords:** Fern, Natural products, Phyto-constituents, Traditional medicine, Anti-oxidant

**INTRODUCTION**

Using plants for healing has been around for a very long time, as old as humanity itself. People have always looked to nature to find medicine. We know this from old writings, things from the past that are still here today, and even from the medicines made directly from plants. People started using plants as medicine because they were getting sick and needed help. They learned that certain parts of plants, like the bark, seeds, or fruit, could make them feel better. Today, science has proven that these plant medicines actually work. They are now part of modern medicine, even though ancient civilizations used them too. As we've learned more about how to use plants as medicine and how this knowledge has grown over time, it has helped doctors and pharmacists provide better healthcare. This has made life easier and healthier for all of us [1]. Today, researchers and the pharmaceutical industry are realizing that natural compounds found in plants (phytoconstituents) have the potential to be developed into new medicines. This is occurring because an increasing number of individuals are showing interest in utilizing natural remedies and traditional medicine. As per the World Health Organization (WHO), approximately 80% of the global population relies on natural remedies and traditional medicine as their primary means of maintaining good health [2].

*Pteridophytes* are a category of vascular plants that possess leaves called "fronds," roots, and sometimes true stems. Tree ferns, for instance, exhibit complete trunks. Examples of *Pteridophytes* include ferns, horsetails, and club-mosses. Many ferns from tropical rainforests are epiphytic, meaning they exclusively grow on other plant species. They obtain their water from the humid air or rainfall that trickles down branches and tree trunks. Additionally, there are purely aquatic ferns like water fern or water velvet (*Salvinia molesta*) and mosquito ferns (Azolla species). *Pteridophytes* do not produce seeds or flowers; instead, they reproduce via spores. There are approximately 13,000 pteridophyte species, belonging to 48 plant families and 587 plant genera [3].

*Pteridophytes* encompass a diverse group of plant species, and they exhibit several distinctive characteristics. First and foremost, they differ from seed-producing plants, such as angiosperms and gymnosperms, as they do not produce seeds. Instead, *Pteridophytes* rely on the production of tiny reproductive structures called spores for propagation. Additionally, *Pteridophytes* boast well-developed vascular tissues, including xylem and phloem, enabling them to efficiently transport water and nutrients throughout their structures. Many *Pteridophytes* are recognized by their leaves, known as fronds, which are often intricately divided into smaller leaflets. Ferns, in particular, are celebrated for their characteristic fronds. The reproductive process of *Pteridophytes* involves the production of spores within specialized structures called sporangia, typically located on the undersides of their fronds. This plant group also undergoes an alternation of generations in their life cycle, featuring a haploid (gametophyte) phase and a diploid (sporophyte) phase. The gametophyte generates gametes (sperm and eggs), which, upon fertilization, develop into the sporophyte. *Pteridophytes* are commonly found in moist environments, such as forests, where they thrive due to their affinity for ample moisture. Among the well-known *Pteridophytes* are ferns, horsetails, and clubmosses. Ferns, in particular, stand out for their lush and vibrant fronds. They play diverse ecological roles, serving as ornamental plants, contributing to forest ecosystems, and even serving as food sources in certain cultures [4, 5, 6]. *Pteridophytes*, have been regard as the potential source of medicine since the ancient times. Even as far back as Theophrastus (who lived from 327 to 287 BCE) and Dioscorides (around 50 CE), there were mentions of how some *Pteridophytes* could be used to treat different kinds of pain and health issues. In their famous book called "Samhitas," Sushruta and Charaka (around 100 CE) also talked about how *Marsilea minuta* and *Adiantum capillus-veneris* could be used for medicinal purposes [7, 8]. Study proved, the numbers of *Pteridophytes* have properties that could be used in morden medicine for treatment of various human illnesses.

Diabetes is a persistent metabolic condition characterized by high blood glucose levels, resulting in long-term damage to vital organs like the heart, blood vessels, eyes, kidneys, and nerves. The most prevalent form is type 2 diabetes, typically affecting adults, where the body either becomes resistant to insulin or doesn't produce enough of it. Over the last three decades, type-2 diabetes has surged globally across various income levels. Currently, approximately 422 million people worldwide have diabetes, with the majority residing in low- and middle-income countries. Diabetes directly causes around 1.5 million deaths each year. Both the number of cases and the prevalence of diabetes have steadily risen over recent decades. The global burden of diabetes has surged significantly over the years, escalating from 108 million individuals affected in 1980 to a staggering 422 million by 2014, with a more rapid rise occurring in low- and middle-income nations compared to high-income ones. This chronic ailment is a leading cause of severe health complications, including blindness, kidney failure, heart attacks, strokes, and lower limb amputations. Disturbingly, between 2000 and 2019, there was a 3% increase in diabetes-related mortality rates across different age groups. In 2019 alone, diabetes and kidney disease resulting from diabetes contributed to an estimated 2 million deaths globally. Diabetes can be managed effectively, and its complications can be mitigated or postponed through a combination of dietary control, physical activity, medication, and routine screening and treatment for associated health issues [9]. However, the existing diabetes treatments in modern medicine are potent but have various unwanted side effects. Consequently, there is a necessity to create treatment approaches for diabetes that are both safe and efficient. Medicinal plants have a crucial role to play in diabetes management, particularly in developing nations where resources are limited [10]. Numerous scientific reports have demonstrated the potential of plants, their derived products, and phyto-constituents in effectively managing diabetes through various mechanisms [11, 12, 13]. The purpose of this book chapter is to highlight the already established anti-diabetic properties of *Pteridophytes* and to draw the attention of researchers, pharmacists, scientists, and industrialists toward the potential development of *Pteridophytes* as a prospective diabetes treatment. This chapter summarizes the anti-oxidant and anti-diabetic activities of species of *Pteridophytes*.

**ANTI-DIABETIC ACTIVITY OF *PTERIDOPHYTES***

***Adiantum capillus-veneris L.***

*A. capillus-veneris*, commonly known as the Southern Maidenhair Fern, is a delicate and elegant fern species. Its fan-shaped fronds, featuring fine, lacy foliage, are light green. This fern, native to various global regions, is prized for ornamental gardening, particularly in shaded and moist environments. Its name reflects its feathery appearance. The anti-oxidant activity of methanol and ethyl acetate extracts from *Adiantum capillus*-*veneris* L. was assessed using multiple methods, including the phosphomolybdenum assay, free radical scavenging activity (DPPH), ferric reducing anti-oxidant power (FRAP), and cupric ion reducing power activity test (CUPRAC). Additionally, the total and individual phenolic compounds were determined through spectrophotometric and HPLC methods, respectively. The total phenolic content ranged from 354 to 441 mg GAE/g, while the total flavonoid content ranged from 23 to 123 mg QE/g. Notably, the methanol and ethyl acetate extracts exhibited more robust anti-oxidant capabilities compared to the water extract [14]. Anti-diabetic potential of aqueous extracts of whole plant of *A. capillus-veneris* was evaluated by using streptozotocin (STZ) induced diabetic rat model. The experimental animal received oral administration of aqueous extracts (100, 200 and 400 mg/kg) and methanol extracts (200 and 400 mg/kg) in distilled water daily for 21 days. Metformin (50 mg/kg b.wt.) was taken as the standard drug. Fasting Blood Glucose (FBG) level were measured by glucose oxidase method on 0th day (after 72h of STZ), 10th and 21st day. At the The serum was separated by centrifugation at 4000 rpm for 10 min. Improvement in the FBG indicates that *A. capillus-veneris* has very good anti-diabetic potential with very low side effects and provides a scientific rationale for the use as an anti-diabetic agent, thus justifying its traditional usage. From the phytochemical analysis, it was found that the major chemical constituents of the extract were flavonoids and tannins [15].

***Adiantum lunulatum* Burm. f. (Synonym *Adiantum philippense* L.)**

*A. lunulatum* is a fern species recognized for its distinctive, crescent-shaped leaflets. It is native to Asia and the Pacific Islands, this delicate fern thrives in moist, shaded environments. The in-vitro anti-oxidant activity of a methanol leaf extract from *Adiantum philippense* L. was assessed through DPPH radical scavenging and reducing power assays. The reducing power of the extract increased proportionally with its concentration. The IC50 value for DPPH scavenging activity was found to be 140.00 ± 0.86 μg/mL, while ascorbic acid, used as a reference, had an IC50 value of 130.00 ± 0.76 μg/mL [16].

***Asplenium* *nidus* L.**

*Asplenium nidus*, commonly referred to as the Bird's Nest Fern, is a popular ornamental fern appreciated for its striking appearance. It is native to tropical regions; it features broad, wavy, bright green fronds that resemble a bird's nest, making it a favored choice for indoor and garden landscaping. Flavonoids that were isolated from *Asplenium nidus* were subjected to an evaluation of their anti-oxidant potential using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay. The process of fractionation and identification of these flavonoids was accomplished through gas chromatography and mass spectrometry (GC/MS). The analysis revealed the presence of twelve known and three unknown compounds within fractions 1 and 3, constituting 13.12% and 2.61%, respectively, of the total composition, which was 15.12%. Notably, gliricidin-7-O-hexoside was the predominant compound at 3.83%, followed by quercetin-7-O-rutinoside at 3.09%, keampferol-3-O-rutinoside at 0.19%, and myricetin-3-O-rhamnoside at 1.10%. Moreover, the two most abundant flavonoids, namely gliricidin-7-O-hexoside (78.1%) and quercetin-7-O-rutinoside (69.2%), exhibited significant in vitro anti-oxidant activity, specifically in the DPPH radical scavenging assay [17].

***Adiantum* *venustum* D. Don**

*A. venustum*, commonly known as the Himalayan Maidenhair Fern, is a charming fern species. It native to the Himalayan region, it's prized for its delicate, fan-shaped fronds and elegant appearance. This fern thrives in cool, shaded environments and is often chosen for ornamental gardens or as an indoor plant. The anti-oxidant activity of different fractions derived from the methanol extract of *A. venustum* was assessed via the DPPH (1,1-diphenyl-2-picryl hydrazyl) radical scavenging assay. The TPC (total phenolic content) within the methanol extract was determined to be 247.95 ± 0.0007 μg of Gallic acid equivalents per gram of the dried extract (mg GAE/g). The n-butanolic fraction exhibited the highest TPC, measuring at 981.45 ± 0.1562 mg GAE/g, while the hexane fraction displayed the lowest TPC (256.95 ± 0.0420 mg GAE/g). Notably, the ethyl acetate fraction demonstrated the highest total flavonoid content (TFC), amounting to 62.0 ± 0.050 mg of Rutin equivalents per gram of the sample. The DPPH radical scavenging activity of the plant was found to be significant. The n-butanolic fraction displayed the most prominent potency, with an IC50 value of 1.06 mg/mL. The IC50 for the methanol extract was 1.50 mg/mL, while the aqueous fraction exhibited an IC50 of 2.51 mg/mL, and the chloroform fraction had an IC50 of 2.65 mg/mL. Importantly, *A. venustum* was identified as being rich in phenolic compounds, showcasing substantial anti-oxidant potential [18]. The anti-diabetic potential of the methanol extract derived from *A. venustum* was tested as inhibitor of alpha-amylase, an enzyme involved in carbohydrate digestion. The results demonstrated that the methanol extract exhibited notable alpha-amylase inhibitory activity. Among the various fractions tested, the chloroform fraction stood out as the most effective, with the lowest IC50 value recorded at 1.10 mg/mL. The ethyl acetate fraction also displayed significant inhibitory activity, with an IC50 value of 1.92 mg/mL. These findings suggest that *A. venustum* is rich in phenolic compounds and possesses substantial alpha-amylase inhibitory potential, making it a promising candidate for further exploration as an anti-diabetic agent [18].

***Araiostegia divaricata* var. *formosana* (Hayata) M. Kato (*Davallia formosana* Hayata)**

*A*. *divaricata* var. *formosana* is a fern species native to Taiwan, often referred to as the Taiwanese Hare's Foot Fern. It is appreciated for its unique appearance, characterized by creeping rhizomes and fronds resembling a hare's foot. (-)-Epicatechin-3-O-β-D-allopyranoside, isolated from *A*. *divaricata* var. *formosana* was subjected to an evaluation for its potential anti-diabetic effects in STZ-induced diabetic mice. Impressively, it demonstrated the ability to delay the onset of diabetes and alleviate dyslipidemia in these diabetic mouse models. The diabetic mice were methodically divided into six distinct groups, with each group receiving daily oral gavage doses of different substances- (-)-Epicatechin-3-O-β-D-allopyranoside at three different dosage levels (40, 80, and 160 mg/kg), Metformin (at a dose of 0.3 g/kg body weight), Fenofibrate (at a dose of 0.25 g/kg body weight), and Vehicle (distilled water). Simultaneously, a control group (CON) received the vehicle, which consisted of distilled water. This administration regimen continued for duration of 4 weeks. The administration of (-)-Epicatechin-3-O-β-D-allopyranoside resulted in significant reductions in blood glucose levels, HbA1C levels, triglyceride levels, and leptin levels. Furthermore, it led to substantial increases in insulin levels and adiponectin levels compared to the STZ group treated with the vehicle. Histological study showed, the diabetic islets exhibited a deviation from their typical round shape, contrasting with the control islets. However, the (-)-Epicatechin-3-O-β-D-allopyranoside-treated groups (at middle and high dosages) displayed improvements in islet size and the number of Langerhans islet cells. The membrane levels of glucose transporter 4 (GLUT4) in skeletal muscle were notably elevated in (-)-Epicatechin-3-O-β-D-allopyranoside-treated mice, resulting in a net reduction in glucose levels. Additionally, (-)-Epicatechin-3-O-β-D-allopyranoside enhanced the expression of phospho-AMPK in skeletal muscle in treated mice. These findings indicate that (-)-Epicatechin-3-O-β-D-allopyranoside acts as an activator of AMPK and/or regulator of the insulin pathway (Akt), along with exhibiting anti-oxidant activity within the pancreas [19].

***Araiostegia* *yunnanensis* (Christ) Copel.**

*A. yunnanensis*, referred as Yunnan Araiostegia, is a species of fern. It is native to the Yunnan province of China. This fern is appreciated for its unique and attractive fronds. As with many ferns, it is often grown for its ornamental value in shaded and moist garden settings. The anti-oxidant potential of the extract from *A. yunnanensis* was assessed through the use of the DPPH scavenging and ABTS radical scavenging assays. The extract, containing a total of 0.268 mg/ml of flavonoids, displayed strong capabilities in scavenging superoxide anion radicals and exhibited strong reducing power, surpassing those of rutin (0.25 mg/ml). Additionally, the extract from *A. yunnanensis* (0.268 mg/ml total flavonoids) demonstrated similar DPPH scavenging activity when compared to rutin (0.25 mg/ml). However, it's worth noting that rutin (0.25 mg/ml) exhibited significantly higher scavenging potential for ABTS radicals in comparison to the extract (0.268 mg/ml total flavonoids) from *A. yunnanensis* [20].

***Blechnum* Species**

*B. binervatum* (Poir.) C.V. Morton & Lellinger, is known for its unique fronds with two prominent veins. It is native to various regions, including parts of South America. *B. brasiliense* Desv., known as the Brazilian Hard Fern, this species hails from Brazil. It features leathery fronds and is notable for its hardy nature. *B. occidentale* L., is commonly known as the Western Hard Fern. This fern is found in western North America. It is characterized by its rigid fronds and is often sought after for its ornamental qualities, particularly in regions with suitable growing conditions. The anti-oxidant activity of hexane and dichloromethane fractions derived from three fern species, namely *B.* *binervatum* (Poir.) C.V. Morton & Lellinger, *B.* *brasiliense* Desv. and *B.* *occidentale* L. were evaluated against free radicals and in terms of their impact on lipid peroxidation. Chemical composition analysis was carried out using gas chromatography coupled with mass spectrometry detector (GC-MS). The GC-MS analysis revealed the presence of non-polar compounds, with neophytadiene being the major constituent in all dichloromethane fractions and in hexane fractions from *B.* *binervatum* and *B.* *occidentale* . In the hexane fraction of *B.* *brasiliense*, β-sitosterol was the primary compound identified. Overall, the dichloromethane fraction from *B*. *brasiliense*  exhibited the highest anti-oxidant activity, with IC50 values approximately 9, 2, and 1.2 times lower than those observed in the other species, against HO˙, NO˙, and lipid peroxidation, respectively. In terms of enzyme modulation, the dichloromethane fraction from *B*. *brasiliense* demonstrated more potent MAO-A inhibition (IC50: 31.83 μg/ml) and a better selectivity index (SI MAO-A/MAO-B: 6.77) compared to the other fractions [21].

***Blechnum* *orientale* L.**

*B. Orientale* is commonly referred to as the Oriental Blechnum or Asian Water Fern, is a fern species native to Southeast Asia and other tropical regions. It is recognized for its graceful, lacy fronds and is often cultivated as an ornamental plant in gardens and indoor settings. The wound healing potential of a concentrated methanol extract derived from *B. orientale*leaves in a hydrogel formulation for healing diabetic ulcers was assessed. The methanol extract underwent flash column chromatography techniques to generate concentrated fractions, which were subsequently examined for their antioxidative and antibacterial properties. The bioactive fraction was then incorporated into a sodium carboxymethylcellulose hydrogel. These extract-infused hydrogels were comprehensively characterized and evaluated on excision ulcer wounds in streptozotocin-induced diabetic rats, with wound size measurements taken over a 14-day period. Moreover, histopathological investigations of the treated animals' wounds were conducted to observe epithelialization, fibroblast proliferation, and angiogenesis. The findings indicated that Fraction W5–1 displayed more potent anti-oxidant activity in comparison to three established standards—α-Tocopherol, BHT, and Trolox-C. Additionally, the extract demonstrated antibacterial efficacy, notably exhibiting bactericidal effects against Methicillin-resistant *Staphylococcus aureus* (MRSA) at a concentration of 0.25 mg/ml. The extract-loaded hydrogels exhibited shear-thinning characteristics and possessed high moisture retention capabilities. Impressively, the bioactive fraction, when present at 4% w/w, accelerated the closure of diabetic wounds, achieving closure by Day 12 on average, while other groups, including controls, only achieved wound closure by Day 14. The histopathological assessments further revealed that the wounds treated with the extract exhibited enhanced re-epithelization, increased fibroblast proliferation, collagen synthesis, and angiogenesis. This study validates the ethnopharmacological application of *B. Orientale*as a topical treatment for external wounds, particularly highlighting its significant efficacy in treating diabetic ulcers. Consequently, *B. Orientale*extract hydrogel emerges as a promising candidate for the treatment of diabetic ulcer wounds [22].

***Ceterach officinarum Willd.***

*C. officinarum*, commonly known as Rustyback or Scale Fern, is a small fern species that is widespread in Europe and parts of North Africa and Asia. It is characterized by its distinctive fronds covered in rusty-brown, hair-like scales on the undersides. This fern typically grows in rocky habitats, such as limestone cliffs and walls. Aqueous extract of *C. officinarum* was evaluated for anti-diabetic activity. Diabetes was experimentally induced by intraperitoneal injection of STZ. Fasting blood glucose levels were assessed everyday by glucometer strips and mice with plasma glucose level > 250 mg/dL were considered as diabetic. After 3 days, animals were divided randomly into six groups. Groups 1 and 2 served as non-diabetic and untreated diabetic controls, respectively. Group 3 received 50-mg/kg glibenclamide orally. Groups 4, 5, and 6 were given 50, 100, and 200 mg/kg, respectively, of aqueous extract for 20 days orally. At 20th day, the mice were dissected and blood and liver samples collected for hematological, biochemical, and histological parameter analysis. Different doses of aqueous extract (especially 200mg) could significantly (p ≤ 0.05) decreased the raised levels of alkaline phosphatase (ALP), Aspartate transaminase (AST), Alanine transaminase (ALT), cholesterol,  low-density lipoprotein (LDL), WBC (White blood cells), and platelet and increased high-density lipoprotein (HDL), Superoxide dismutase (SOD), (Catalase) CAT, and red blood cell (RBC) parameters as compared to the untreated group. The weight and volume of the hepatic structures were decreased significantly (p ≤ 0.05) in different doses of aqueous extract as compared to the untreated group [23].

***Cheilosoria* *tenuifolia* (Burm. f.) Trevis. (Synonym *Cheilanthes* *tenuifolia* (Burm. f.) Sw.)**

*C. tenuifolia* is a fern species with feathery fronds. It is native to various regions including Asia, it's often referred to as the Slender Lip Fern. This fern is appreciated for its delicate appearance. Flavonoids obtained from the methanol extract of *C. tenuifolia* were assessed for their anti-oxidant properties through the 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging assay. The isolation and purification of these flavonoids from *C. tenuifolia* were accomplished using preparative column chromatography with a Sephadex LH-20 column. The determination of their chemical structure and bonds was carried out utilizing Nuclear Magnetic Resonance (NMR) spectroscopy and Fourier Transform-Infrared Spectroscopy (FTIR). Two distinct flavonoids, namely Rutin and quercetin, exhibited noteworthy efficacy in *in-vitro* anti-oxidant testing. Remarkably, quercetin demonstrated a higher DPPH scavenging potential (86.1%) compared to rutin (73.2%) [24].

***Deparia* *boryana* (Willd.) M. Kato(synonym *Dryoathyrium* *boryanum*(Willd.) Ching)**

*D. boryana* is native to various regions, including parts of Asia. This fern is recognized for its distinctive fronds. Flavonoids, including 3-hydroxyphloretin 6'-O-hexoside, quercetin-7-hexoside, apigenin7-O-glucoside, luteolin 7-O-glucoside, apigenin 7-O-galactoside, acacetin 7-O-(α-D-apio-furanosyl) (1→6)-β-d-glucoside, 3-hydroxy phloretin 6-O-hexoside, and luteolin-6-C-glucoside, which were isolated from the extract of *D. boryanum* were subjected to evaluation for their anti-oxidant activity using the DPPH scavenging, superoxide anion scavenging potential and ABTS scavenging assays. At a concentration of 0.21 mg/mL, the flavonoid extract from *D. boryanum* exhibited a very potent superoxide anion radical scavenging potential, surpassing that of rutin (0.25 mg/mL). Additionally, the extract at 0.21 mg/mL displayed similar DPPH scavenging activity compared to rutin at 0.25 mg/mL. However, rutin (0.25 mg/mL) demonstrated significantly higher reducing power and ABTS scavenging activity in comparison to the flavonoid extract from *D. boryanum* at 0.21 mg/mL [25].

***Dicksonia* *sellowiana* Hook.**

*D. sellowiana*, commonly known as Sellow's Soft Tree Fern or Brazilian Tree Fern, is a striking fern species native to South America, particularly Brazil. It's distinguished by its tall, trunk-like stem covered with fibrous scales and large, feathery fronds. The anti-oxidant potential of a hydro-alcoholic extract derived from the aerial parts of *D. sellowiana* leaves was investigated through both *in vitro* and *in vivo* assessments. Across the concentration range of 0.1-100 μg/mL, the extract exhibited robust scavenging activity against various reactive species, including DPPH, O2-, OH, and H2O2, with IC50 values of 6.83 ± 2.05, 11.6 ± 5.4, 2.03 ± 0.4, and 4.8 ± 0.4 μg/mL, respectively. The extract demonstrated potent protection of endothelial cells against oxidative stress induced by H2O2, employing mechanisms beyond catalase activity enhancement. Furthermore, the extract effectively shielded cell membranes from oxidative damage. *In vivo*, the extract at the doses of 20 and 40 mg/kg exhibited lipid peroxidation inhibition by 29.8% and 24.5%, respectively, signifying its anti-oxidative impact [26].

***Drynaria* *quercifolia* (L.) J. Sm.**

*D. quercifolia*, also known as the Oakleaf Fern, is found in various regions, including parts of Asia and Africa. It is recognized for its distinctive, oak-like fronds, which resemble the leaves of an oak tree, giving it its common name. The anti-oxidant properties of both the rhizomes and fertile foliage fronds of *D. quercifolia* L were assessed using various methods, including 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging, hydrogen peroxide scavenging, 2,2'-azinobis(3-ethylbenzothiazoline sulphonic acid) (ABTS) radical scavenging, and the ferric reducing potential determined through the ferric reducing anti-oxidant power (FRAP) assay. The rhizomes and fertile foliage fronds of *D. quercifolia* were collected, dried, powdered, and subjected to methanol extraction. Subsequently, the crude methanol extracts of these plant parts were fractionated into petroleum ether, carbon tetrachloride, chloroform, and aqueous-soluble fractions. The study revealed significant anti-oxidant effects [27].

***Dryopteris cycadina* (Franch. & Sav.) C. Chr.**

*D. cycadina*, sometimes referred to as the Shaggy Shield Fern, is a fern species native to East Asia, including China and Japan. It is characterized by its feathery, finely dissected fronds and a shaggy appearance, particularly on the stipe (fern stem). The effects of various compounds (including β-Sitosterol, β-Sitosterol 3-O-β-D-glucopyranoside, 3, 5, 7-trihydroxy-2-(p-tolyl) chorman-4-one, Quercetin-3-0-β-D-glucopyranoside (3/→0-3///)- β-D- Quercetin -3-0- β –D-galactopyranoside and 5, 7, 4/-Trihydroxyflavon-3-glucopyranoid isolated from *D. cycadina* were evaluated for *in vitro* α-glucosidase inhibitory activity by using spectrophotometric method. Similarly, molecular docking studies were performed. These compounds showed concentration-dependent inhibition on α-glucosidase, and β-Sitosterol (IC50: 143 ± 0.47 µM), 5, 7-trihydroxy-2-(p-tolyl) chorman-4-one (IC50:133 ± 6.90 µM) and 5, 7, 4/-Trihydroxyflavon-3-glucopyranoid (IC50: 146 ± 1.93 µM) were more potent than the standard drug, acarbose (IC50: 290 ± 0.54 µM). Computational studies of these compounds strongly supported the *in vitro* studies and showed strong binding receptor sensitivity. In short, the secondary metabolites isolated from *D. cycadina* demonstrated potent α-glucosidase inhibition that were supported by molecular docking with a high docking score [28]

***Dryopteris* *erythrosora* (D.C. Eaton) Kuntze**

*D. erythrosora*, commonly known as the Autumn Fern or Japanese Shield Fern, is a popular fern species in horticulture. It's native to East Asia, particularly Japan and China. This fern is treasured for its vibrant fronds that change color throughout the seasons, from coppery-red in spring to green in summer and reddish-bronze in autumn. Flavonoids, including gliricidin 7-O-hexoside, apigenin 7-O-glucoside, quercetin 7-O-rutinoside, quercetin 7-O-galactoside, kaempferol 7-O-gentiobioside, kaempferol-3-O-rutinoside, myricetin 3-O-rhamnoside, and quercitrin, were extracted from *D.* *erythrosora* a and assessed for their anti-oxidant properties using various methods, including the 2,2-diphenyl-1-picrylhydrazyl free radical (DPPH) assay, the 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) radical (ABTS) assay, superoxide anion scavenging potential, and the ferric reducing anti-oxidant potential (FRAP) assay. The flavonoids extract from *D.* *erythrosora*, at a concentration of 0.36 mg/ml, exhibited anti-oxidant activities comparable to rutin (0.80 mg/ml) in the DPPH, ABTS, and FRAP assays. However, the FRAP assay showed that the anti-oxidant capacity of the 0.36 mg/ml flavonoid extract from *D.* *erythrosora* was slightly weaker than that of 0.80 mg/ml rutin [29].

***Hemionitis arifolia* (Burm. f.) T. Moore**

*H. arifolia*, known as the Heart Fern or Heartleaf Fern, is a small fern species found in tropical and subtropical regions, including parts of Asia, Africa, and the Americas. It's named for its heart-shaped fronds, which have a delicate and charming appearance. The anti-diabetic activity of ethanol and water extracts of *H. arifolia* fern was assessed through a glucose tolerance test by using alloxan induced diabetic rat model. It was observed that the ethanol extract, and to some extent, the water extract, had the ability to reduce blood glucose levels in rats fed with glucose. The ethanol extract exhibited its most effective activity at a dosage of 200 mg/kg. Additionally, the extract displayed only minimal hypoglycemic effects in overnight fasted normal rats and showed no noticeable signs of toxicity in a sub-acute toxicity assessment involving mice. When the alcohol extract was divided into fractions through sequential solvent extraction, the anti-diabetic activity was primarily found in the ethyl acetate fraction (at 50 mg/kg). This particular fraction, which contained steroids and coumarins, demonstrated anti-diabetic effects in alloxan diabetic rats, as evidenced by changes in serum glucose levels and liver glycogen [30]. Ethanol and aqueous leaves extract of *H. arifolia* was evaluated for anti-diabetic activity in Streptozotocin induced diabetic rats. Glibenclamide (5 mg/kg p.o) was used as reference drug. The animals were treated with the oral dose of ethanol and aqueous extracts (250 mg/kg and 500 mg/kg body weight) daily for 15 days. Glibenclamide (5 mg/kg p. o) was used as reference drug. Blood glucose levels were measured on 0th, 2nd, 5th, 10th and 15th days of the study. Ethanol and aqueous extracts were found to be to lower the levels of blood glucose in glucose fed rats [31].

***Pronephrium* *penangianum* (Hook.) Holttum (synonym *Abacopteris* *penangiana* (Hook.) Ching)**

The protective effect of the total flavanol glycosides isolated from methanol extract of *P* *penangianum*studied against diabetic vascular complications associated with diabetes. To assess this, the extent of oxidative stress in mice was measured as an indicator of diabetic vascular impairments. The experimental model induced aortic pathology in diabetic mice through a high-fat diet and streptozotocin injections. The study aimed to determine how flavanol glycosides influenced hypoglycemia and oxidative stress. The findings of the study revealed that flavanol glycosides demonstrated the capacity to enhance the activities of anti-oxidant enzymes. Furthermore, the treatment with flavanol glycosides led to significant reductions in plasma lipid profiles and glucose levels in the groups subjected to FAP administration. Additionally, flavanol glycosides alleviated vascular impairments in these mice This suggests that flavanol glycosides may hold promise in mitigating oxidative stress and ameliorating vascular complications associated with diabetes [32].

***Pteris* *vittata* L.**

*P. vittata,* commonly known as the Chinese Brake Fern or the Brake Fern, is a fern species known for its unique ability to hyperaccumulate arsenic from the soil. This fern is native to Asia and can be found in various regions worldwide. Due to its capacity to remove arsenic from contaminated soils, it has gained attention in phytoremediation and is sometimes grown for environmental purposes rather than ornamental value. The anti-oxidant potential of both aqueous and ethanol extracts of *P. vittata* was assessed using the ABTS assay, with a specific focus on its High-Performance Thin-Layer Chromatography (HPTLC) profile. Furthermore, this pteridophyte was subjected to evaluation for its ability to inhibit free radicals in the ABTS decolorization assay, followed by quantification of polyphenols and HPTLC analysis. To determine its anti-oxidant potential, the ABTS Free Radical Scavenging activity was conducted, and the concentration of the test extracts equivalent to ascorbic acid was calculated. Phenols and flavonoids are commonly associated with the anti-oxidant properties of plants, which prompted to quantify them. This was followed by HPTLC fingerprinting of flavonoids to aid in their identification. Standard quercetin was employed as a reference, in addition to the two extracts of *P. vittata* L. In comparison to the aqueous extract, the ethanolic extract exhibited more favorable results across the parameters investigated [33]. The *in vitro* anti-hyperglycemic activity of both aqueous and ethanol-extracts of *P. vittata* was assessed in relation to their inhibition of α-amylase. The inhibition of porcine pancreatic alpha-amylase was studied *in vitro* and compared to the standard drug Acarbose, with the determination of their respective IC50 values. The results indicated that these extracts exhibited antihyperglycemic activity [33].

***Selaginella tamariscina* (P.Beauv.) Spring**

*S. tamariscina*, also known as Tamarisk Spikemoss or Clubmoss, is a species of spikemoss native to Asia, particularly regions like China and Japan. It is a small, evergreen plant with delicate, fern-like foliage. In traditional Chinese medicine, it has also been used for its potential medicinal properties. The assessment of the anti-diabetic properties of the total flavonoids extracted from *S. tamariscina* was conducted employing a rat model induced with diabetes through a high-fat diet and Streptozotocin (STZ). Over the course of eight weeks, the experimental animals received total flavonoids through graded oral doses (100, 200, and 400 mg/kg/day). Various parameters, encompassing blood glucose and lipid levels, serum insulin and glucagon concentrations, and glucose tolerance, were subjected to examination in order to appraise total flavonoids anti-diabetic potential. To delve into the mechanism of total flavonoids, the study probed into the protein expression of peroxisome proliferator-activated receptor (PPAR-) in adipose tissue and insulin receptor substrate 1 (IRS-1) in hepatic and skeletal muscle tissues. Results demonstrated that total flavonoids exhibited notable anti-diabetic activity, manifesting in reduced serum levels of fasting blood glucose (FBG), glycosylated hemoglobin A1C (HbA1c), triglycerides (TG), total cholesterol (TC), free fatty acids (FFA), low-density lipoprotein-cholesterol (LDL-C), and glucagon, coupled with elevated serum levels of high-density lipoprotein-cholesterol (HDL-C), insulin, and C-peptide. Furthermore, total flavonoids displayed enhancements in the results of the oral glucose tolerance test (OGTT), signifying improved glucose tolerance. Mechanistically, total flavonoids upregulated the protein expression of PPAR- in adipose tissue, suggesting its involvement in bolstering insulin sensitivity and regulating lipid metabolism. It also heightened the protein expressions of IRS-1 in hepatic and skeletal muscle tissues, thereby enhancing insulin signaling pathways. The beneficial effects of total flavonoids were further linked to increased superoxide dismutase (SOD) activity and decreased malondialdehyde (MDA) levels in the serum, indicating potential anti-oxidant properties. Collectively, these findings underscore total flavonoids’s potential in ameliorating hyperglycemia and hyperlipidemia in diabetic rats, possibly via the modulation of PPAR- in adipose tissue and IRS-1 in hepatic and skeletal muscle tissues [34].

**DISCUSSION**

Our chapter review reveals that numerous *Pteridophytes* have demonstrated their effectiveness in combating diabetes, making them potential candidates for inclusion in modern medicine for diabetes management. Biotechnological methods can be harnessed to conserve and enhance the bioactive molecules found in these plants, paving the way for the development of diabetes medicines. Despite the documented medicinal applications of ferns, the specific bioactive compounds in many *Pteridophytes* remain unidentified. Additionally, the ideal dosage levels and treatment approaches have yet to be established.

**CONCLUSION**

*Pteridophytes* offer a promising avenue in diabetes research. Further work on isolating more bioactive molecules is needed in future studies, and understanding their precise mechanisms in influencing insulin, glucose, and pancreatic function is a key challenge. This task is possible through additional animal and clinical studies. However, *Pteridophytes* show promising potential as anti-diabetic agents. Further research is needed to establish their safety and efficacy for use in diabetes treatment. This can be achieved through collaborative efforts among botanists, pharmacologists, and medical professionals.

**Reference**-

1. Petrovska BB. Historical review of medicinal plants' usage. Pharmacogn Rev. 2012 Jan;6(11):1-5.
2. Chan, K. (2003). Some aspects of toxic contaminants in herbal medicines. *Chemosphere*, *52*(9), 1361-1371.
3. *The Plant List* (2013). Version 1.1. Published on the Internet; http://www.theplantlist.org/ (accessed 1st January).
4. Lloyd, R. M. (1974). Reproductive biology and evolution in the Pteridophyta. *Annals of the Missouri Botanical Garden*, *61*(2), 318-331.
5. Kramer, K. U., Green, P. S., & Green, P. S. (Eds.). (1990). *Pteridophytes and gymnosperms* (Vol. 1). Springer Science & Business Media.
6. Reddy, S. M. (2001). *University botany I:(algae, fungi, bryophyta and pteridophyta)* (Vol. 1). New Age International.
7. Sureshkumar, J., Silambarasan, R., Bharati, K. A., Krupa, J., Amalraj, S., & Ayyanar, M. (2018). A review on ethnomedicinally important *Pteridophytes* of India. *Journal of ethnopharmacology*, *219*, 269-287.
8. Baskaran, X. R., Geo Vigila, A. V., Zhang, S. Z., Feng, S. X., & Liao, W. B. (2018). A review of the use of *Pteridophytes* for treating human ailments. *Journal of Zhejiang University-Science B*, *19*(2), 85-119.
9. World Health Organisation. (2023). Fact-sheets- Diabetes. <https://www.who.int/health-topics/diabetes>
10. Preethi, P. J. (2013). Herbal medicine for diabetes mellitus: A Review. *Asian Journal of Pharmaceutical Research*, *3*(2), 57-70.
11. Al-Rowais, N. A. (2002). Herbal medicine in the treatment of diabetes mellitus. *Saudi medical journal*, *23*(11), 1327-1331.
12. Shapiro, K., & Gong, W. C. (2002). Natural products used for diabetes. *Journal of the American Pharmaceutical Association (1996)*, *42*(2), 217-226.
13. Fazel Nabavi, S., Thiagarajan, R., Rastrelli, L., Daglia, M., Sobarzo-Sanchez, E., Alinezhad, H., & Mohammad Nabavi, S. (2015). Curcumin: a natural product for diabetes and its complications. *Current topics in medicinal chemistry*, *15*(23), 2445-2455.
14. Abdulqadir, A., Cakmak, Y.S., Zengin, G. (2018). Phenolic compounds, anti-oxidant properties and enzyme inhibition ability of adiantum capillus veneris L. Linked to Alzheimer’s disease, diabetes mellitus and skin disorders. *Current Organic Chemistry, 22*(17), 1697-1703.
15. Ranjan, V., Vats, M., Gupta, N., Sardana, S. Anti-diabetic potential of whole plant of Adiantum capillus veneris linn. in streptozotocin induced diabetic rats. (2014). *International Journal of Pharmaceutical and Clinical Research, 6*(4), pp. 341-347.
16. Ali, M.S., Amin, M.R., Kamal, C.M.I., Hossain, M.A. (2013). In vitro anti-oxidant , cytotoxic, thrombolytic activities and phytochemical evaluation of methanol extract of the *A. philippense* L. leaves. *Asian Pacific Journal of Tropical Biomedicine, 3*(6), 464-469.
17. Jarial, R., Thakur, S., Sakinah, M., Zularisam, A.W., Sharad, A., Kanwar, S.S., Singh, L. (2018). Potent anticancer, anti-oxidant and antibacterial activities of isolated flavonoids from Asplenium nidus. *Journal of King Saud University - Science, 30*(2), 185-192.
18. Hamid, J., Ahmed, D., Waheed, A. (2017). Evaluation of anti-oxidative, antimicrobial and anti-diabetic potential of Adiantum venustum and identification of its phytochemicals through GC-MS. *Pakistan Journal of Pharmaceutical Sciences, 30*(3), 705-712.
19. Lin, C.-H., Wu, J.-B., Jian, J.-Y., Shih, C.-C. (2017). (-)-Epicatechin-3-O-β-D-allopyranoside from Davalliaformosana prevents diabetes and dyslipidemia in streptozotocin-induced diabetic mice. *PLoS ONE, 12*(3).
20. Chen, C.-Y., Chiu, F.-Y., Lin, Y., Huang, W.-J., Hsieh, P.-S., Hsu, F.-L. (2015). Chemical constituents analysis and anti-diabetic activity validation of four fern species from Taiwan. *International Journal of Molecular Sciences, 16*(2), 2497-2516.
21. Andrade, J.M.D.M.,Maurmann, N.,Pranke, P.,Turatti, I.C.C.,Lopes, N.P.,Henriques, A.T.Identification of compounds from non-polar fractions of Blechnum spp and a multitarget approach involving enzymatic modulation and oxidative stress. (2017). *Journal of Pharmacy and Pharmacology, 69*(1), 89-98.
22. Lai, J.C.-Y., Lai, H.-Y., Rao, N.K., Ng, S.-F. (2016). Treatment for diabetic ulcer wounds using a fern tannin optimized hydrogel formulation with antibacterial and antioxidative properties. *Journal of Ethnopharmacology, 189*, 277-289.
23. Zangeneh, M.M., Zangeneh, A., Bahrami, E., Almasi, M., Amiri-Paryan, A., Tahvilian, R., Moradi, R. (2018). Evaluation of hematoprotective and hepatoprotective properties of aqueous extract of *Ceterach officinarum* DC against streptozotocin-induced hepatic injury in male mice. *Comparative Clinical Pathology, 27*(6), 1427-1436.
24. Jarial, R., Shard, A., Thakur, S., Sakinah, M., Zularisam, A.W., Rezania, S., Kanwar, S.S., Singh, L. (2018).Characterization of flavonoids from fern Cheilanthes tenuifolia and evaluation of anti-oxidant , antimicrobial and anticancer activities. *Journal of King Saud University - Science, 30*(4), 425-432.
25. Cao, J., Xia, X., Dai, X., Xiao, J., Wang, Q., Andrae-Marobela, K., & Okatch, H. (2013). Flavonoids profiles, anti-oxidant , acetylcholinesterase inhibition activities of extract from Dryoathyrium boryanum (Willd.) Ching. *Food and chemical toxicology*, *55*, 121-128.
26. Rattmann, Y.D., Mendéz-Sánchez, S.C., Furian, A.F., Paludo, K.S., De Souza, L.M., Dartora, N., Oliveira, M.S., Costa, E.M.D.S., Miguel, O.G., Sassaki, G.L., Iacomini, M., Mello, C.F.,Franco, C.R.C., Da Silva-Santos, J.E., Cadena, S.M.S.C., Marques, M.C.A., Santos, A.R.S. (2011). Standardized extract of *Dicksoniasellowiana*Presl. Hook (Dicksoniaceae) decreases oxidative damage in cultured endothelial cells and in rats. *Journal of Ethnopharmacology, 133*(3), 999-1007.
27. Chaity, F.R., Khatun, M., Rahman, M.S. (2016). In vitro membrane stabilizing, thrombolytic and anti-oxidant potentials of *Drynariaquercifolia* L., a remedial plant of the Garo tribal people of Bangladesh. *BMC Complementary and Alternative Medicine, 16*(1), 184,
28. Amim, S., Ullah, B., Ali, M., Rauf, A., Khan, H., Uriarte, E., Sobarzo-Sánchez, E. (2019).Potent in Vitro α-Glucosidase Inhibition of Secondary Metabolites Derived from Dryopteris cycadina. *Molecules, 24*(3),
29. Cao, J., Xia, X., Chen, X., Xiao, J., Wang, Q. (2013). Characterization of flavonoids from Dryopteris erythrosora and evaluation of their anti-oxidant , anticancer and acetylcholinesterase inhibition activities. *Food and Chemical Toxicology, 51*(1), 242-250.
30. Ajikumaran Nair, S., Shylesh, B.S., Gopakumar, B., Subramoniam, A.(2006). Anti-diabetes and hypoglycaemic properties of *Hemionitisarifolia* (Burm.) Moore in rats. *Journal of Ethnopharmacology, 106*(2), 192-197.
31. Kumudhavalli, M.V., Jaykar, B. (2012). Pharmacological screening on leaves of the plant of *Hemionitisarifolia* (Burm).T.Moore. *Research Journal of Pharmaceutical, Biological and Chemical Sciences, 3*(2), 79-83.
32. Chen, J., Chen, X., Lei, Y., Wei, H., Xiong, C., Liu, Y., Fu, W., Ruan, J. (2011). Vascular protective potential of the total flavanol glycosides from *Abacopterispenangiana* via modulating nuclear transcription factor-κBsignaling pathway and oxidative stress. *Journal of Ethnopharmacology, 136*(1), 217-223.
33. Paul, T., Banerjee, S. (2013). Invitro evaluation of α-amylase inhibitory activity & anti-oxidant potential of *Pteris Vittata* L. With special reference to its HPTLC profile. *International Journal of Pharma and Bio Sciences, 4*(2), 494-503.
34. Zheng, X.-K., Zhang, L., Wang, W.-W., Wu, Y.-Y., Zhang, Q.-B., Feng, W.-S. (2011). Anti-diabetic activity and potential mechanism of total flavonoids of *Selaginella tamariscina*(Beauv.) Spring in rats induced by high fat diet and low dose STZ. *Journal of Ethnopharmacology, 137*(1), 662-668.