PTERIDOPHYTES AS POTENTIAL SOURCE OF ANTI-DIABETIC MEDICINE: CURRENT STATUS AND FUTURE SCENARIO

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

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I. 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), about eighty present of the total population rests upon natural remedies and conventional medicine as their primary means of maintaining good health [2].

Pteridophytes are a category of plants (vascular) that possess leaves called "*fronds*," roots, as well as sometimes true stems. Tree ferns, for instance, exhibit complete trunks. Examples of *Pteridophytes* cover ferns, horsetails, and club-mosses. Many ferns from tropical rainforests are epiphytic, meaning they exclusively produce up on other species of plants. They obtain their water as of the humid air or rainfall that trickles down twigs and plant trunks. Furthermore, there exist exclusively aquatic ferns, for example the water fern or water velvet and mosquito ferns (*Salvinia molesta* and *Azolla* species, respectively). *Pteridophytes* lack the production of seeds or flowers and instead propagate through spore reproduction. Approximately 13,000 *Pteridophyte* species are distributed among forty eight plant families and Five Hundred Eight seven plant genus [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 the 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 & 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 club mosses. 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]. Throughout antiquity, they've been perceived as a potential source of medicine. 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]. The studies proved the number of *Pteridophytes* has the potential that could be used in the Modern medicinl system for the management of different human illnesses.

Diabetes is a chronic metabolic disorder marked by high levels of glucose in the bloodstream, leading to enduring harm to essential organs such as the blood vessels, heart, nerves, eyes and kidneys. Type-2 diabetes (T2D) is the most common variant, primarily impacting adults, wherein the body either develops insulin resistance or fails to generate an adequate amount of it. In the past thirty years, there has been a noteworthy worldwide raise in the prevalence of T2D, spanning various income brackets. Presently, around 422 million individuals worldwide are affected by diabetes, with the majority of cases concentrated in nations with lower & middle-income levels. Diabetes directly causes around 1.5 million deaths each year. Together the figure of cases and the prevalence of diabetes have steadily risen over current 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 foremost reason of severe health problems, including blindness, strokes, heart attacks, failure of kidney, and lower limb amputations. Disturbingly, between 2000 and 2019, there was a three present increase in diabetes-related mortality rates across different age groups. In 2019 alone, diabetes and kidney disease (KD) resulting from diabetes contributed to an approximate 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 present 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*.

II. ANTI-DIABETIC ACTIVITY OF *PTERIDOPHYTES*

1. ***Adiantum capillus-veneris*** **L.:** A. *capillus-veneris* (AV), 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 methanolic and ethyl acetate extracts from AV were assessed for anti-oxidant activity using multiple methods, including the free radical scavenging activity 1,1-diphenyl-2-picrylhydrazyl (DPPH), phosphomolybdenum assay, cupric ion reducing power activity test (CUPRAC) and ferric reducing anti-oxidant power (FRAP).

Additionally, the total and individual phenolic compounds were estimated through spectrophotometric and HPLC methods, respectively. The total phenolic content ranged from 354 to 441 mg GAE/g, while the total flavonoid content was 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]. The anti-diabetic potential of aqueous extracts of the whole plant of *A. capillus-veneris* was evaluated by using a streptozotocin (STZ) induced diabetic rat model. The experimental animal received oral administration of aqueous extracts (at the dose of 100- 400 mg/kg) and methanolic 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) levels were determined by the glucose oxidase process on the 0th day (after 72h of STZ), 10th, and 21st day. The serum was isolated by centrifugation at 4000 rpm for 10 min. Improvement in the FBG level indicates that *AV* has a excellent anti-diabetic effect with minor side effects and presents a precise basis for its use as an anti-diabetic means, thus explanatory its conventional usage. From the phyto-chemical analysis, it was found that the key constituents of the extract were phenolic compound such as flavonoids and tannins [15].

2. ***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 *A. philippense* L. was assessed through DPPH Radical Scavenging (RS) 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 ± 0.86μg/mL, while ascorbic acid, used as a reference, had an IC_{50} value of 130.00 ± 0.76 μg/mL [16].

3. ***Asplenium nidus* L.:** *A. 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 *A. nidus* were subjected to an evaluation of their anti-oxidant potential using the DPPH RS 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 constituent within fractions I and III, 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. [17].

4. ***Adiantum venustum* D. Don:** *A. venustum*, commonly known as the Himalayan Maidenhair Fern, is a charming fern variety. It is 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 calculated via the DPPH RS analyse. 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-butanol 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-butanol fraction displayed the most prominent potency, with an IC50 value of 1.06 mg/mL. The IC_{50} for the methanol extract was 1.50 mg/mL, while the aqueous fraction exhibited an IC_{50} of 2.51 mg/mL, and the chloroform fraction had an IC_{50} 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 an 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 IC_{50} value recorded at 1.10 mg/mL. The fraction of ethyl acetate also prooved significant inhibitory activity, with an IC_{50} value of 1.92 mg/mL. These findings suggest that *A. venustum* has rich phenolic compounds and possesses considerable alpha-amylase inhibitory potential, make it a promising drug for further exploration as an anti-diabetic medicine [18].

5. ***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 methodically separated into six distinct groups, with each one 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 rat group (CON) received the vehicle, which consisted of distilled water. This administration regimen continued for 4 weeks. The administration of (-)-Epicatechin-3-O-β-D-allopyranoside resulted in noteworthy reductions in blood glucose levels (BGL), HbA1C levels, triglyceride levels, and leptin levels. Furthermore, it led to substantial increases in insulin levels and adiponectin levels in comparison of STZ group received the vehicle. Histological study explained the diabetic islets exhibit a deviation from their typical round shape, contrasting with the control islets. However, the (-)-Epicatechin-3-O-β-D-allopyranoside-treated groups (at medium and higher dose level) 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 experimental 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].

6. ***Araiostegia yunnanensis* (Christ) Copel.:** *A. yunnanensis*, referred to 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 RS 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].

7. ***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 action of hexane (HF) and dichloromethane (DF) fractions derived from three fern species, namely *B. binervatum, B. brasiliense* and *B. occidentale* were evaluated against free radicals and in terms of their impact on lipid peroxidation. The GC-MS investigation of chemical composition revealed the presence of non-polar compounds, with neophytadiene being the key compounds in all DF and in HF of *B. occidentale* and *B. binervatum*. In the HF of *B. brasiliense*, β-sitosterol was recognized as the primary constituent. Overall, the DF from *B. brasiliense* exhibited the highest anti-oxidant action, with IC_{50} approximately 9, 2, and 1.2 times lesser than that observed in the remaining species of *Blechnum*, against hydroperoxyl radical ($HO^{\cdot}$), Nitric oxide ($NO^{\cdot}$), and lipid peroxidation (LPO), correspondingly. In terms of enzyme modulation, the dichloromethane fraction from *B. brasiliense* demonstrated more potent Monoamine oxidase A (MAO-A) inhibition (IC_{50}: 31.83 μg/ml) and a improved selectivity index (SI MAO-A/MAO-B: 6.77) compared to the other fractions [21].

8. ***Blechnum orientale* L.:** *B. Orientale* 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 curative potential of a methanol extract derived from *B. orientale* leaves in a hydrogel (HG) formulation for curing diabetic ulcers was assessed. The methanol extract underwent flash column chromatography techniques (FCCT) to generate fractions that was concentrated, which were subsequently examined for their anti-oxidant and antibacterial properties. The bioactive fraction was then incorporated into a sodium carboxymethylcellulose (SCMC) HG. These extract-infused HG were comprehensively described and evaluated on excision ulcer wounds (UW) in STZ-induced diabetic rats, with wound size measurements taken over forteen day period. Moreover, histo-pathological 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 action in

comparison to 3 established standards—α-Tocopherol, Butylated Hydroxytolulene (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 HG displayed shear-thinning character and possessed higher moisture maintenance capabilities. The histopathological assessments further revealed that the wounds treated with the extract exhibited enhanced re-epithelisation, increased fibroblast proliferation (FP), collagen synthesis (CS), and angiogenesis. This study validates the ethno pharmacological application of *B. Orientale* as a cure for topical injury/ wound, particularly highlighting its significant efficacy in treating diabetic ulcers. Consequently, *B. Orientale* extract HG emerges as a hopeful drug for the management of diabetic ulcer wounds [22].

9. ***Ceterach officinarum* Willd.:** *C. officinarum*, commonly known as Rustyback or Scale Fern, is a small fern species that is extensive in Europe and divisions 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. Water extract (WE) of *C. officinarum* was assessed for anti-diabetic potential. Diabetes was induced experimentally through intra-peritoneal (i.p.) injection of STZ. FBG levels were monitored daily using gluco-meter strips and animals with plasma glucose levels exceeding two hundred fifty mg/dL were categorized as diabetic. Following a three-day period, the animals were at random separated in six set. Groups I and II was control group, with Group I being non-diabetic and Group II being untreated diabetic mice. Group III took dose of 50 mg/kg glibenclamide, orally. Groups IV, V, and VI were administered doses of 50, 100, and 200 mg/kg, correspondingly, of an aqueous extract for twenty days, orally. On the twentieth day, the animals were euthanized, and samples of blood and hepatic tissues were obtained for examination of various parameters. Diverse doses of aqueous extract (particularly 200mg) considerably reduced the elevated stage 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) in comparison to the untreated animal group. Significant reductions in both the mass (weight) and volume of liver cells/tissues were observed across various prescribed amount of the aqueous extract when match up to the untreated animal group [23].

10. ***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 methanolic extract of *C. tenuifolia* were assessed for their anti-oxidant action through the 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). 2 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].

11. ***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 quercetin-7-hexoside, 3-hydroxyphloretin 6'-O-hexoside, apigenin 7-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 obtained from the *D. boryanum* extract were subjected to evaluation for their anti-oxidant activity using the DPPH, superoxide anion (SOA) and ABTS scavenging potential assays. At a concentration of 0.21 mg/mL, the flavonoid extract from *D. boryanum* exhibited an extremely potent SOA RS 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. Still, rutin (0.25 mg/mL) demonstrated considerably elevated reducing power and ABTS RS activity in comparison to the flavonoid extract from *D. boryanum* at 0.21 mg/mL [25].

12. ***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 examined through both *in-vitro* and *in-vivo* assessments. Across the concentration range of 0.1-100 μg/mL, the extract demonstrated robust RS action against DPPH, O_2-, OH, and H_2O_2, with IC_{50} 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 hydrogen peroxide (H_2O_2), 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].

13. ***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 action of crude methanolic extracts of both the rhizomatous and fertile foliage fronds of *D. quercifolia* were assessed using various methods, including DPPH, H_2O_2, ABTS RS and FRAP assay. The study revealed significant anti-oxidant effects [27].

14. ***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 named as 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 enzyme inhibition assay by using spectrophotometric method. Also, molecular docking (MD) of compounds were performed. These constituents demonstrate concentration-dependent inhibitory effect on

α-glucosidase. β-Sitosterol (IC_{50} 143 ±0.47 µM), 5, 7-trihydroxy-2-(p-tolyl) chorman-4-one (IC_{50} 133 ± 6.90 µM) and 5, 7, 4/-Trihydroxyflavon-3-glucopyranoid (IC_{50} 146 ±1.93 µM) were found more effective than the reference drug, acarbose (IC_{50} 290 ±0.54 µM). Docking investigations of these constituents provided robust support for the *in-vitro* examination and revealed high binding receptor sensitivity. In summary, the constituents obtained from *D. cycadina* exhibited effective α-glucosidase enzyme inhibition, further substantiated by computational docking results displaying a higher score [28].

15. ***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 DPPH, ABTS and SOA and FRAP RS assay. The flavonoidal extract from *D. erythrosora*, at 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 a little lesser than that of 0.80 mg/ml rutin [29].

16. ***Hemionitis arifolia* (Burm. f.) T. Moore:** *H. arifolia*, known as the Heart Fern or Heartleaf Fern, is a small fern species found in various countries of Asia, Africa, and the Americas. It's named for its heart-shaped fronds, which have a delicate and charming appearance. The anti-diabetic action of ethanolic and water extracts of *H. arifolia* fern was assessed through a glucose tolerance test (GTT) by using alloxan induced diabetic rat model. It was observed that the ethanolic extract, and moderately the aqueous extract, had the ability to reduce glucose levels in blood of rats fed with glucose. The ethanolic extract exhibited its most effective activity at a dosage of 200 mg/kg. Additionally, the extract displayed only minimal hypoglycaemic effects in during the night fasted normal rats and showed no noticeable signs of toxicity in a sub-acute toxicity assessment involving animal. When the ethanolic extract was divided into fractions through in order solvent extraction process, the anti-diabetic action was primarily established in the fraction of ethyl acetate (at 50 mg/kg). This particular fraction, which contained constituent's steroids and coumarins, demonstrate anti-diabetic effects in alloxan diabetic rats, as evidenced by changes in glucose levels in serum and liver glycogen [30]. Ethanol and aqueous leaf extract of *H. arifolia* were tested for anti-diabetic action in STZ-induced diabetic rats. Glibenclamide at the dose of 5 mg/kg p.o. was used as standard treatment. The animals received daily oral doses of ethanol and aqueous extracts (250 mg/kg and 500 mg/kg body weight) for the duration of fifteen days. The glucose levels in blood were assessed on the 0th, 2nd, 5th, 10th, and 15th days of the model. The ethanol and water extracts were observed to significantly reduce blood glucose levels in the rats that were fed glucose [31].

17. ***Pronephrium penangianum* (Hook.) Holttum (synonym *Abacopteris penangiana* (Hook.) Ching):** The protecting action of the total flavanol glycosides isolated from the methanolic extract of *P. penangianum* was studied against diabetic vascular

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

18. ***Pteris vittata* L.:** *P. vittata*, usually 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 by 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 action, the ABTS RS was conducted, and the effective dose of the extracts comparable to standard drug ascorbic acid was calculated. Phenolics and flavonoidal constituent are commonly associated with the anti-oxidant properties of plants, which prompted to calculate them. This was followed by HPTLC analysis of flavonoids to aid in their detection. Standard drug quercetin was employed as a reference, in addition to the 2 extracts of *P. vittata*. In comparison to the water extract, the ethanol extract exhibited more favorable outcome across the factor investigated [33]. The *in-vitro* anti-hyperglycemic action of both aqueous & ethanol-extracts of *P. vittata* was assessed in relation to their inhibitory effect on enzyme α-amylase. The results indicated that these extracts exhibited antihyperglycemic activity [33].

19. ***Selaginella tamariscina* (P.Beauv.) Spring:** *S. tamariscina*, also known as Tamarisk Spikemoss or Clubmoss, is a species of spikemoss native to Asia, particularly in regions like China and Japan. It is a small, evergreen plant with delicate, fern-like foliage. In conventional Chinese remedy, 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 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 glucose level in blood, lipid levels, serum insulin level, glucagon concentrations, and glucose tolerance, were subjected to examination in order to appraise total flavonoid's anti-diabetic potential. Results demonstrated that total flavonoids exhibited notable anti-diabetic activity, manifesting in reduced FBG, 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 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 signalling pathways. The positive impacts of total flavonoids were additionally related with elevated SOD activity and reduced levels of malondialdehyde (MDA) in the serum, suggesting potential antioxidant properties. Collectively, these findings underscore total flavonoids's potential to ameliorate hyperglycaemia and hyperlipidemia in diabetic rats, possibly through the modulation of PPAR- in adipose tissue and IRS-1 in liver and skeletal muscle tissues [34].

III. 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.

IV. 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 study 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.

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