


REVIEW

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Matteuccia struthiopteris (L.) Todaro (fiddlehead fern): an updated review

Shivali Singla^{1*} , Rupali Rana², Surendar Kumar³, Reena Thakur¹ and Sachin Goyal⁴

Abstract

Background: *Matteuccia struthiopteris* (L.) Todaro is a popular edible wild fern found in the subtropical Himalayas. It is widely used in folk medicine to treat several ailments and known for its antioxidant, anti-inflammatory, antibacterial, antiviral and antidiabetic activities. Due to its multidimensional nutritional, pharmacological and therapeutic effects, it is well recognized in the Ayurvedic Pharmacopoeia.

Main body of abstract: The present review aims to provide updated information on *Matteuccia struthiopteris* botany, phytochemistry, pharmacological effects and toxicity methods, in addition to highlight potential for future exploration. Particular emphasis is also given to its antioxidant potential in health promotion. In-depth literature was probed by examining numerous sources via online databases (research and reviews), texts, Web sites and thesis. Plant biotechnology approaches such as tissue culture and micropropagation are also discussed.

Short conclusion: *Matteuccia struthiopteris* is found useful in the treatment of different diseases such as microbial infection, viral infection and diabetes and in weight reduction and also effective as antioxidant and free radical scavenger. Nevertheless, advance studies are required to offer the mechanistic role of crude extracts and its bio-actives and even to discover the structure–function relationship of active principles.

Keywords: *Matteuccia struthiopteris*, Fiddlehead fern, Ostrich fern, Antioxidant, Chemical constituents

Background

Ayurvedic medicines support the medicinal plants to treat various diseases in the traditional Indian system of Ayurveda (Sato et al. 1997). According to WHO, traditional medicine is the sum of the total skill, practices, knowledge, beliefs and experiences to different cultures, used in the maintenance of the health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness (World Health Organization (WHO) 2013). Herbal medicines are the oldest remedies known to mankind and been used by all cultures throughout the history, but India has one of the oldest, richest and most diverse cultural living traditions associated with the use of medicinal plants (Kamboj 2012).

Herbal drug technology is used for converting botanical materials into medicines, where standardization and quality control with proper integration of modern scientific techniques and traditional knowledge is important (Spainhour 2010). Herbals are traditionally considered harmless and increasingly being consumed by people without prescription (Gokhale et al. 2007).

Ferns are comprised of almost 12,000 species (PPG I 2016) and have been known as edible medicinal plants for periods, especially in Canada, China, India and other Asian countries. Taxonomically, these vascular plants belong to pteridophytes that diffuse via spores (Kimura et al. 2004; Smith et al. 2006). When human was dependent on wild plants as primary food source, the habit of eating ferns is as old as at that time. Edible ferns are stated in Chinese writings as before as 3000 years ago (Liu et al. 2012). In spite of the fact that wild plants are no longer harvested as much as they were in ancient times, fern harvesting and eating has

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continued routine as food, as well as for commercial use and is still prevalent today in a number of places, such as Japan, USA (May 1978), New Zealand (Crowe 1981), Canada (Bergeron and Lapointe 2001), India, Malaysia, China, Nepal and the Philippines (Liu et al. 2012), where it is popular for its nutritive value as well as medicinal potential. A long established role of ferns in human health has thus been highlighted once again. Plant extracts have been studied with the purpose of establishing their biological activity, as well as identifying foods with powerful antioxidant, antimicrobial, antibacterial, antiviral, and anti-inflammatory activities (Goswami et al. 2016; Zhu and Zhao 2019). In additional studies, it has been documented that ferns contain phenolic compounds, glycosides, flavonoids, terpenoids, carotenoids, alkaloids and fatty acids in large amounts (Goswami et al. 2016; Cao et al. 2017). Compared to other vegetables, ferns provide a particularly high level of antioxidants and essential fatty acids such as omega-3 and omega-6. It is therefore highly advantageous to consume this medicinal plant (Jamieson and Reid 1975). The demographic studies have been conducted from the frond or leaf of the fern and have been investigated and found morphologically quite distinct from each other, but have a high potential as medicinal and food part (Watt 1976; Seiler 1981; Steeves and Briggs 1960; Tanner 1983; Bower n.d.).

Matteuccia struthiopteris (L.) Todaro, belonging to the family Onocleaceae, is one of the plants which may be used in Indian traditional system of medicine in Indian subcontinent but most common in western and southern districts where there is high rainfall, and especially on limerich soils (Aderkas 1984; Lou et al. 2015). Traditional Chinese medicine system included rhizomes and frond bases of *M. struthiopteris* for the treatment of threadworm, influenza virus, infectious diarrhea hematochezia and uterine hemorrhage, and they have been known to have pharmacological activities such as antiviral, antiparasitic and antibacterial actions (Chen et al. 2003). Taxonomical classification of *Matteuccia struthiopteris* is Kingdom: Plantae; Subkingdom: Tracheobionta; Division: Pteridophyta; Class: Polypodiopsida; Order: Polypodiales; Family: Onocleaceae (Formerly Dryopteridaceae); Genus: *Matteuccia* (Kimura et al. 2004; Gastony and Ungerer 1997).

In this sense, the present review investigates the relevant information on botanical description, chemical constituents along with the pharmacological activities. Its critical facts as a natural source of antioxidant compounds for health promotion and disease prevention are also upraised.

Main text

Review method

The review method (Prisma 2009 Flow Diagram) used for the present study is shown in Fig. 1. Various databases were used for searching, such as Springer, Science Direct, PubMed and Google Scholar.

Botanical description

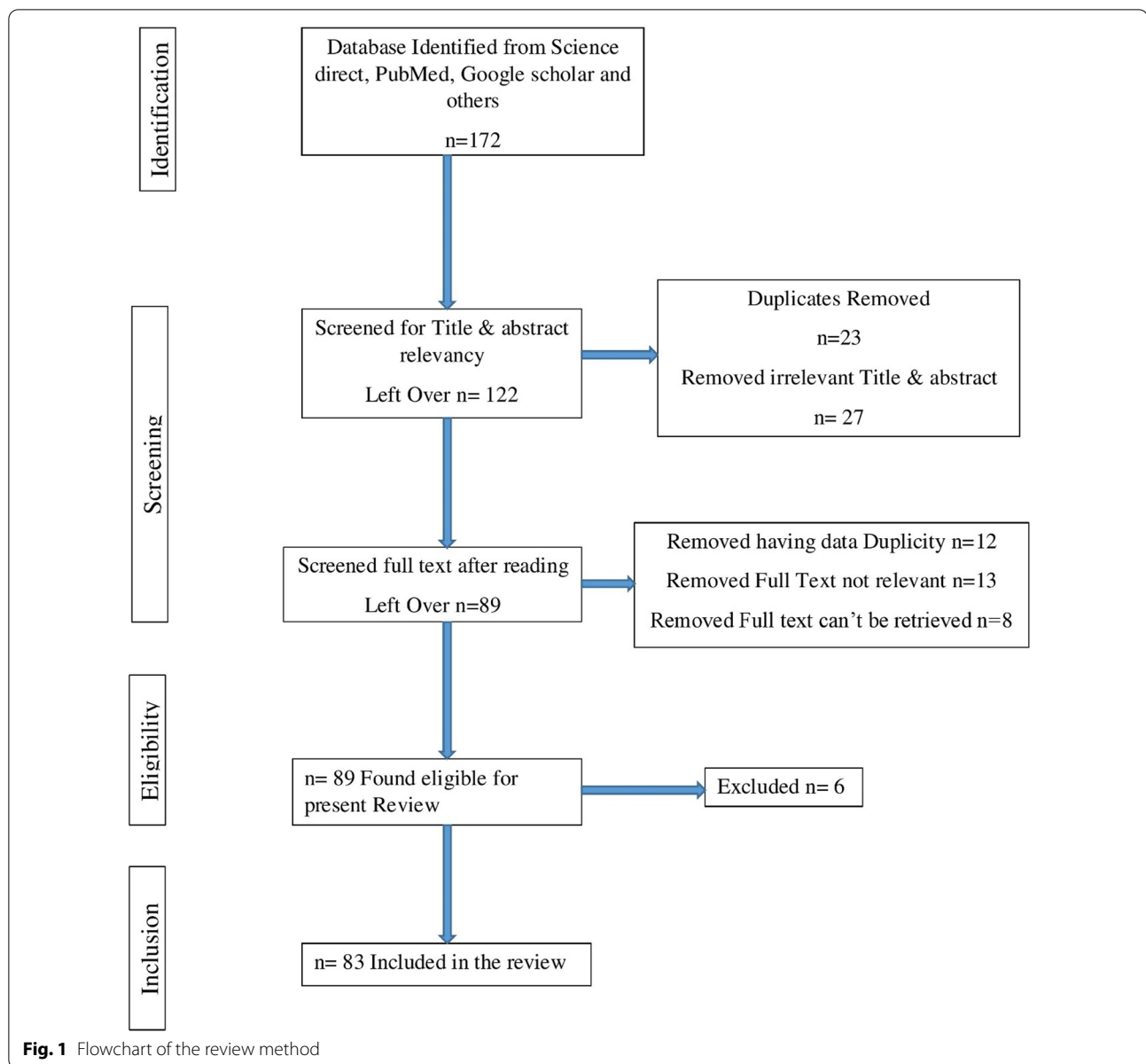
Matteuccia struthiopteris (L.) Todaro commonly called “Ostrich Fern” is an ancient type of vegetation which occupied the world long before the evolution of seed-producing plants. These are strictly foliage plants, since they reproduce without flowering (Gureyeva et al. 2018; Raubeson and Jansen 1992; Stevenson and Loconte 1996). One more common name “fiddlehead fern” is used in the northeast of North America, because of the resemblance of its elegant croziers to their namesake (Kato 1993). The edible fern is also listed in the Polish Red Book of Plants (Kazmierczakowa et al. 2014, 2016). Rural forest communities have long been dependent on a variety of ecosystem goods and services and rich in knowledge about the plant (Charnley et al. 2007).

Habitat

Matteuccia struthiopteris prefers moist shady bottomlands, woods and stream banks (Mueller-Dombois 1964). The fern prefers moist not wet sites with alluvial soils in floodplains of rivers and streams in association with silver red maple and brown ash. It grows from a completely vertical crown, favoring riverbanks and sandbars, but sends out lateral stolons to form new crowns. It can thus form dense colonies resistant to destruction by floodwaters. They will also grow successfully on upland soils with high levels of organic matter in light to medium shade (Delong et al. 2011; Bushway et al. 1982).

Morphological characters

Matteuccia struthiopteris is a clump-forming, erect to bending, rhizomatous, deciduous fern which characteristically cultivates 2–3', but possibly will attain 6' tall in cool and wet microclimates (Stone 1909). The crowns of the fern are composed of a stout erect rhizome (Prange and Aderkas 1985). The outer parts are the magnificently separated, moderate green, fronds that display the feathery appearance as of long ostrich plumes, suggesting its common name “ostrich fern” (Goebel 1905). These fronds may be either sterile or fertile. In spring season, the vegetative fronds (sterile) arise at the constricted base of the clumps as fiddleheads, large green blades with numerous leaflets and then unfurl to attain a length of 4' maximum (Cobb et al. 2005; Cody and



Britton 1989; Aderkas and Green 1986). There are 20–60 pairs of bipinnate leaflet (pinnae), pointed to the base and tip giving a vase-like appearance. The fronds are broadest at the mid, but the reduced size of base pinnae typically pointing to down creates narrow lower part. Every pinnae is arranged alternate to the rachis, providing a different appearance. Each pinna has deep cuts that are not reaching to central vein and divides it into lobes (pinnules). Whitish hairs are present on rachis. The shorter stipe bears brown scales on it. One side of the stipe and the rachis are intensely grooved, and the other is rounded (Dykeman 1985; Odland et al. 2003, 2006). These fronds habitually get down as the

summer continues and lastly drop its leaflets later as the fern becomes dormant for the cold weathers (Aderkas 1983). The favorable atmospheric conditions are summarized in Table 1.

After the growth of fertile fronds, which are erect and generally shorter, the fronds turn brown along with the pinnae and are more rigid with trundled sections (sori) in which the sporangia (spore-forming tissues) lie. Its stipe is firm, erect and dark with brown scales. These scales may be hidden by sterile fronds in summer. Fronds preserved in this state release their spores in the spring (Prange et al. 1984; Lloyd 1971). The life span of fertile fronds is from mid-summer to winter. All of these fronds

Table 1 Favorable conditions (Dykeman 1985)

Variable	Condition
Avg. fertility season	Winter and spring
Foliage season	Summer (crozier forming ferns)
Sunlight	Prefer slightly partial shade but tolerate full shade or full sun if the soil stays moist
Soil type	Rocky, loamy
Soil pH	Slightly acidic (5.5–6.5 is adequate)
Soil moisture	Moist
Ultimate height	0.5 m to over 2.0 m
Ultimate spread	Around 1.2 m

are different from one another (Bower n.d.; Goebel 1905; Bower 2010).

Morphological characterization of *Matteuccia struthiopteris* (L.) plant and its parts are shown in Fig. 2a–e. Young fronds or furled vegetative fronds are harvest from bases and stored after frozen in spring vegetable industry in northeast including North America (Aderkas 1984). The fern plant produces fronds in separate form, and rootstock is very well suited for population studies (Grzybowski and Kruk 2015; Prange 1980).

Chemical constituents

Matteuccia struthiopteris is an herbal plant which may have various phytoconstituents including derivatives such as flavonoids, isocoumarins, phthalides, lignans and stilbenes and has been previously identified from the genus *Matteuccia*, in which flavanones with C-methylation at C-6 and/or C-8 are the main members (Huh et al. 2017; Shao et al. 2010). There are different methods for screening of phytochemical constituents such as GC-MS and HPLC (Li et al. 2013; Dvorakova et al. 2021). It also contains a series of phenolic compounds (Chen et al. 2003). There are many constituents isolated from different parts of fern which are effective for different activities (Table 2).

Structure of some of the chemical constituents

Chemical structures of some of the phytoconstituents are presented in Fig. 3a–n.

Pharmacological activities

Antioxidant activities (free radical scavenging activity)

According to Kimura et al. 2002, a DMSO extract was assessed for free radical scavenging activity by chemiluminescence and DPPH methods; afterward, the efficacy was also compared with well-known antioxidative plants that show strong positive outcomes (Kimura et al. 2002). Later, they isolated l-O-caffeoylhomoserine from the fern

which was found to exhibit strong antioxidant potential evaluated by using the same two methods with IC₅₀ 0.45 ± 0.5 mM (chemiluminescence method) and 0.30 0.00 mM (DPPH method), respectively (Kimura et al. 2004). The study done by Delong et al reveals that ostrich fern tissue is a rich source of ascorbate and b-carotene, as well as lutein, violaxanthin, zeaxanthin and phenolic compounds. A high biological activity (antioxidant) was suggested due to high ORAC values (Delong et al. 2011). Wagh et al. evaluated the oxidative and color stability of raw ground pork incorporated with 1% (w/v) of different *Matteuccia struthiopteris* extracts, viz. acetone, ethanol, methanol and water, during refrigerated storage for 9 days. Fiddle head-treated raw ground pork had significantly lower thiobarbituric acid reactive substances than control (raw pork samples without any treatment) during storage proving to have sufficient antioxidant properties (Angad and Veterinary 2014). The fern extract was evaluated for their ability to scavenge 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) (Dvorakova et al. 2021; Nekrasov et al. 2019; Dion et al. 2015; Lai et al. 2010; Zhu et al. 2018) and evidenced to have a great prospective as antioxidant.

Anti-inflammatory activities

Dion et al. screened the fern extracts from *M. struthiopteris* for its anti-inflammatory impact. Two modes of action were applied for examination: first the inhibition of the pro-inflammatory gene expression of interleukin-1 beta (IL1-β) and interleukin-6 (IL6), and second the gene expression of iNOS by LP solicited macrophages. The results revealed a reduction in IL1-β gene expression from the fern extract (IC₅₀ = 50 µg/mL) (Dion et al. 2015; Lai et al. 2010; Khan Tabassum et al. 2015).

Effect on weight loss

The polysaccharides extracted from *M. struthiopteris* were evaluated to study the effect on *Campylobacter jejuni* (CJ-S131)-induced lupus-like illness in BALB/c mice. Mice were randomly distributed into normal, model control, vehicle-treated model, *M. struthiopteris* polysaccharides-treated (30 and 15 mg/kg) groups and prednisone (5 mg/kg)-treated groups. The parameters detected were weight and organ index of BALB/c mice to reveal the effect of *M. struthiopteris* polysaccharides on reduction in weight loss. Enzyme-linked immunosorbent assay was used to measure production of autoantibodies and total IgG. Along with proteinuria measurement, kidneys were examined by light microscopy. Compared with vehicle-treated model group, treatment with *M. struthiopteris* polysaccharides 30 and 15 mg/kg reduced weight loss and *M. struthiopteris* polysaccharides 15 mg/

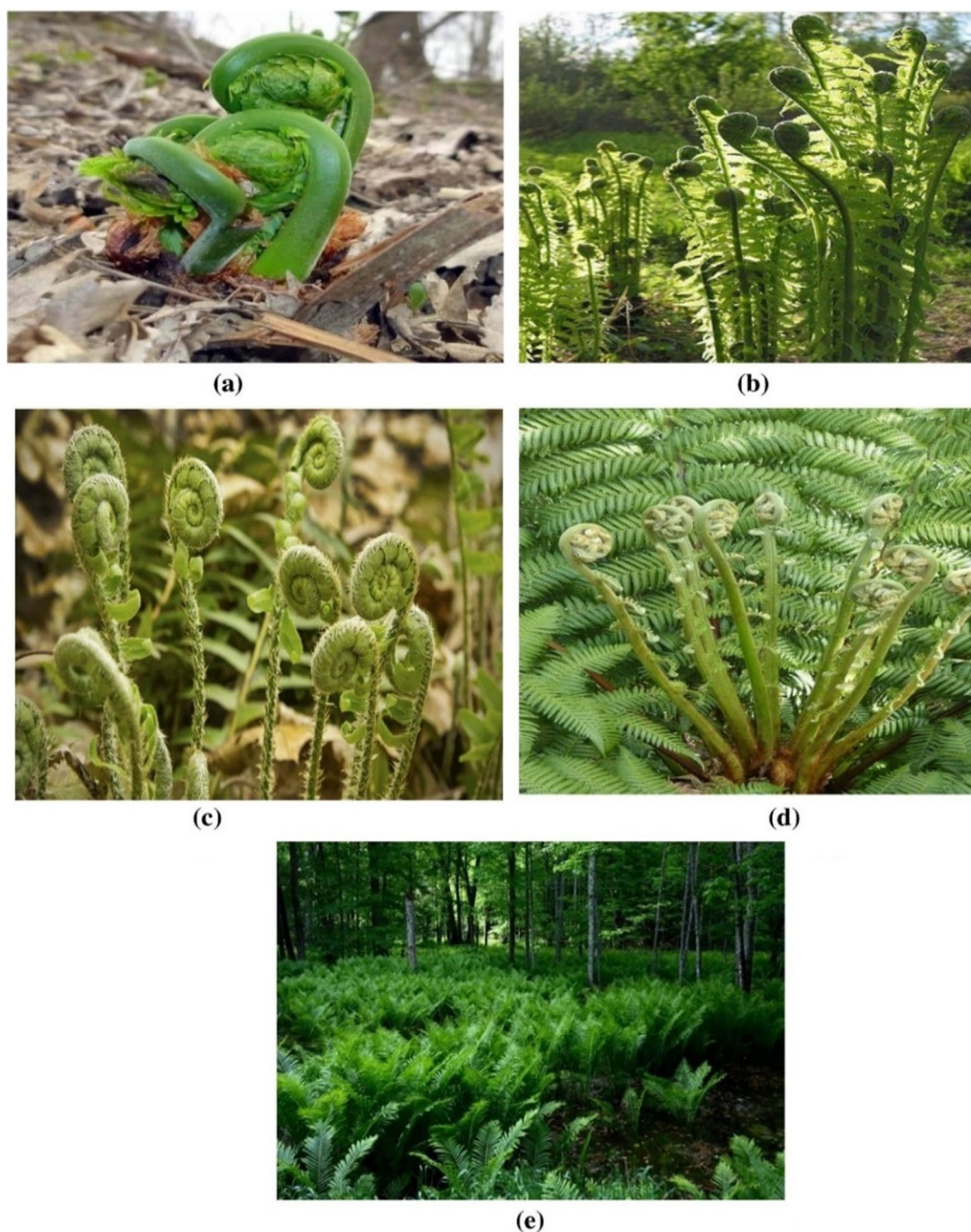


Fig. 2 a–e *Matteuccia struthiopteris* a new growing plant; b and c average growing fern; d and e fully mature fern

kg reduced spleen swelling. *Matteuccia struthiopteris* polysaccharides were found to have a protective effect on lupus-like syndrome induced by CJ-S131 in BALB/c mice having effective dose 30mg/kg to 15mg/kg body weight (Wang et al. 2010).

Antibacterial activities

Shan et al. (2007) studied the antibacterial properties of 46 extracts including ostrich fern of dietary spices

and medicinal herbs against foodborne pathogens: *B. cereus*, *L. monocytogenes*, *S. aureus*, *E. coli* and *Salmonella anatum*. High activity was exhibited against all the tested bacteria by 12 extracts including *Matteuccia struthiopteris* (MIC 100 µg/mL, DIZ 13.7 mm). The medicinal herbs were revealed to have significantly stronger properties (antibacterial) than the other dietary spices (Shan et al. 2007; Efenberger-Szmechtyk et al. 2021).

Table 2 Chemical constituents from various parts of *Matteuccia struthiopteris*

S. no.	Plant part	Chemical constituents	Chemical formula	References
1.	Spores	Legumin Vicilin-like proteins	$C_{21}H_{21}Cl_3Na_2O_6$	Kakhovskaja et al. (2003), Shutov et al. (1995), Shutov et al. (1998)
2.	Rhizome	Woodwardic acid Apigenin 3-(4-(beta-D-Glucopyranosyloxy)phenyl)-2-propenoic acid 4-O-β-D-glucosyl-trans-caffeic acid Ergosta-6, 22-diene-3beta, 5 alpha, 8 alpha-triol Riboflavin	$C_{30}H_{48}O_3$ $C_{15}H_{10}O_5$ $C_{15}H_{18}O_8$ $C_{15}H_{18}O_9$ $C_{28}H_{48}O_3$ $C_{17}H_{20}N_4O_6$	Yang et al. (2004)
3.	Leaf and fronds	Caffeic acid l-homoserine	$C_9H_8O_4$ $C_4H_9NO_3$	Kimura et al. (2004)
4.	Rhizome	D-mannitol O-beta-D-glucopyranosyl-(2S,3R,4E, 8Z) -2-N-(2'-hydroxydocosanoyl) eicosasphinga-4,8-dienine O-beta-D-galactosyl-(6-->1)-alpha-D-galactosyl-2,3-O-dihexadecanoyl-glycerol Succinic acid	$C_6H_{14}O_6$ $C_9H_{18}O_8$ $C_4H_6O_4$	Yang et al. (2005)
5.	Leaves	Polyisoprenoid alcohols		Wojtas et al. (2005)
6.	Leaf and upper parts	Essential and volatile oils, viz. (E)-phytol (8Z,11Z,14Z)-heptadecatrienal (8Z,11Z)-heptadecadienal, (6Z)-nonenal	$C_{17}H_{28}O$ $C_{17}H_{30}O$	Miyazawa et al. (2007)
7.	Rhizome	Demethoxymatteucinol Matteucinol Pinosylvin Pinosylvin 3-O-beta-D-glucopyranoside Matteuorienate A	$C_{17}H_{16}O_4$ $C_{18}H_{18}O_5$ $C_{14}H_{12}O_2$ $C_{20}H_{22}O_7$ $C_{30}H_{36}O_{14}$	Zhang et al. (2008)
8.	Fronds	Antioxidant compounds like ascorbic acid g-tocopherol b-carotene Thexanthophyll pigments: Violaxanthin Zeaxanthin Lutein	$C_6H_8O_6$ $C_{28}H_{48}O_2$ $C_{40}H_{56}$ $C_{40}H_{56}O_4$ $C_{40}H_{56}O_2$ $C_{40}H_{56}O_2$	Delong et al. (2011)
9.	Rhizome	Polysaccharides consisted of Glucose Galactose Xylose	$C_6H_{12}O_6$ $C_6H_{12}O_6$ $C_5H_{10}O_5$	Wang et al. (2013)
10.	Rhizome and fronds	C-methyl flavanones: (2S)-5,7-dihydroxy-6,8-dimethyl-4'-methoxydihydroflavone-7-O-(6''-O-acetyl)-β-d-glucopyranoside (2S)-5,7-dihydroxy-6,8-dimethyldihydroflavone-7-O-(6''-O-acetyl)-β-d-glucopyranoside 2'-hydroxymatteucinol Demethoxymatteucinol-7-O-β-d-glucopyranoside, Matteucinol-7-O-β-d-glucopyranoside 5,7-dihydroxy-6-methyl-4'-methoxydihydroflavone Methoxymatteucin Thunberginol C	$C_{26}H_{30}O_{11}$ $C_{25}H_{28}O_{10}$ $C_{18}H_{18}O_6$ $C_{38}H_{36}O_{18}$ $C_{20}H_{20}O_4$ $C_{15}H_{12}O_5$	Basnet et al. (1993), Zhang et al. (2013)
11.	Rhizome	Flavonoid glycosides naming matteflavosides A–G		Li et al. (2015)

Table 2 (continued)

S. no.	Plant part	Chemical constituents	Chemical formula	References
12.	Fronds	Fatty acids, viz.		Delong et al. (2011), Nekrasov et al. (2019)
		Eicosapentaenoic acid	C ₂₀ H ₃₀ O ₂	
		Arachidonic acid	C ₂₀ H ₃₂ O ₂	
		γ-Linoleic acid	C ₁₈ H ₃₀ O ₂	
		Dihomo-γ-linolenic acid.	C ₂₀ H ₃₄ O ₂	

(See figure on next page.)

Fig. 3 a–t Chemical constituents **a** demethoxymatteucinol **b** matteucinol **c** pinosylvin, **d** pinosylvin 3-O-beta-D-glucopyranoside **e** matteuorinate **A f** (2S)-5,7-dihydroxy-6,8-dimethyl-4'-methoxydihydroflavone-7-O-(6''-O-acetyl)-β-d-glucopyranoside **g** (2S)-5,7-dihydroxy-6,8-dimethyl dihydroflavone-7-O-(6''-O-acetyl)-β-d-glucopyranoside **h–m** matteflavosides A–F **n** matteflavosides G **o** 3-(4-(beta-D-Glucopyranosyloxy) phenyl)-2-propenoic acid **p** 4-O-β-D-glucosyl-trans-caffeic acid **q** ergosta-6, 22-diene-3β, 5 α, 8 α-triol **r** 2'-hydroxymatteucinol **s** (8Z,11Z,14Z)-heptadecatrienal **t** (8Z,11Z)-heptadecadienal, (6Z)-nonenal

Antidiabetic activity

Harvested rhizomes and fronds of nine fern species along with *Matteuccia struthiopteris* were washed, freeze-dried and grinded. An ultrasonification extraction was done for 30 minutes in ultrasonic water tank with 100% methanol solvent, followed by vacuum filtration, and α-glucosidase inhibition activity was measured. Acarbose was used as the positive control. After mixing 100 μL of 0.7 unit α-glucosidase enzyme solution into 50 μL of extract and reacting them at 37 °C for 10 min, 50 μL of 1.5 mM p-NPG solution was taken and reacted at 37 °C for 20 min. One mL of 1 M Na₂CO₃ was added to stop reaction, and the absorbance was measured in 405 nm. The content of solubility solids that can inhibit 50% of 0.7 unit α-glucosidase solution's (the value of IC₅₀) activity was investigated. The frond (IC₅₀=14.00–913.33 μg/mL) and rhizome extracts (IC₅₀=12.93–205.84 μg/mL) of nine pteridophyte species showed higher α-glucosidase inhibition activity in comparison with acarbose (IC₅₀=1413.70 μg/mL) (Kim et al. 2013). Flavanols with C-methylation in the A-ring found in *Matteuccia struthiopteris* also showed their hypoglycemic effect (Basnet et al. 1993; Li et al. 2019).

Anti-influenza virus activities

Seven new flavonoid glycosides (1–7) and matteflavosides A–G were isolated by Zhang et al., along with 12 known flavonoids (8–19) from the rhizomes of *M. struthiopteris*. Neuraminidase inhibition assay was done to assess anti-influenza virus (H1N1) activity for all the compounds. With an EC₅₀ value of 6.8±1.1 μM and a SI value of 34.4, compound 7 demonstrated strong inhibitory effect against the H1N1 influenza virus neuraminidase, whereas

compounds 8 and 17 showed moderate inhibitory activity (Li et al. 2015).

Non-toxic and non-carcinogenic activity

Lai et al. fed a semi-purified diet containing fiddlehead greens (the unfurled frond of the ostrich fern *Matteuccia struthiopteris*) to a group of rat. The groups fed 1–10% fiddlehead greens for 70–73 weeks developed no tumors. Thus, this study indicates that fiddlehead greens from *M. struthiopteris* are not toxic or carcinogenic (Lai et al. 2010; Newberne 1976; Tomšik 2014).

Biotechnology aspects

Biotechnology proposes new approaches for increasing biodiversity and biotechnological methodologies. For example, tissue culture including micropropagation gets more attention to be adopted as a vital part in the basis of genetically unchanging botanicals for the business. Likewise, there are several highly valued traditional Indian ethnomedicinal plants having rich therapeutic potential and need immense scientific exploration and conservation strategies (Zenkteler 2006). In vitro micropropagation was undertaken to develop a more expeditious method for *M. struthiopteris* multiplication (Hicks and Aderkas 1986).

Conclusions

Matteuccia struthiopteris has been used for its invigorating and nutritional potentials, from the old-fashioned Ayurveda and Unani studies. The present review enlightened the facts that *M. struthiopteris* contains various phytochemicals, which are accountable for the therapeutic assessment of this plant and have been answerable for several pharmacological powers in the treatment



of different diseases, including microbial infection, viral infection and diabetes, and in weight reduction and also effective as antioxidant and free radical scavenger: On the other hand, being a rich wellspring of phenolic compounds there is a need to investigate the capacity of this plant for immunomodulatory, cardioprotective, nephro-protective and neuroprotective association. The edible fern needs more attention to find the mechanism of pharmacological action and the metabolites responsible for these activities in detail. The flora of this restorative and practical plant species is on the reverse because of excessive exploitation of forests, carelessness of realistic assets, deprived improvement and unfortunate recapture of species in characteristic natural surroundings. Consequently, a countless prospect has already passed to make the vital movement to expand its populace measure, efficiency, shield and even usage.

Abbreviations

%w/w: Percentage weight by weight; µg: Microgram; µl: Microliter; µM: Micrometer; ABTS: 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid); Ac: Acetate; *B. cereus*: *Bacillus cereus*; BALB/c: Albino rat; DIZ: Diameter of inhibition zone; DPPH: 2,2-diphenyl-1-picrylhydrazyl; *E. coli*: *Escherichia coli*; EC50: Half-maximal effective concentration; GC-MS: Gas chromatography-mass spectrometry; HPLC: High-performance liquid chromatography; IC50: Half-maximal inhibitory concentration; IL: Interleukin; iNOS: Inducible nitric oxide synthase; Kg: Kilogram; *L. monocytogenes*: *Listeria monocytogenes*; L: LINN; LP: Lumber puncture; *M. struthiopteris*: *Matteuccia struthiopteris*; M: Meter; MIC: Minimum inhibitory concentration; mg/g: Milligram per gram; mg/kg: Milligram per kilogram; mL: Milliliter; ORAC: Oxygen radical absorbance capacity; SI: Selectivity Index; WHO: World Health Organization.

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Author contributions

SS is responsible for data collection, study design and writing the manuscript; RR and SK done phytochemical studies; and SG and RT performed final proofreading. All the authors read thoroughly and permitted the final version of the manuscript.

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Competing interests

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