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Evidence-Based Medicinal Potential and Possible Role of *Selaginella* in the Prevention of Modern Chronic Diseases: Ethnopharmacological and Ethnobotanical Perspective

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Abstract: Different species of the genus *Selaginella* are exploited for various ethnomedicinal purposes around the globe; mainly to cure fever, jaundice, hepatic disorders, cardiac diseases, cirrhosis, diarrhea, cholecystitis, sore throat, cough of lungs, promotes blood circulation, removes blood stasis and stops external bleeding after trauma and separation of the umbilical cord. Though, high content of various phytochemicals has been isolated from *Selaginella* species, flavonoids have been recognized as the most active component in the genus. Crude extract and different bioactive compounds of this plant have revealed various *in vitro* bioactivities such as, antimicrobial, antiviral, anti-diabetic, anti-mutagenic, anti-inflammatory, anti-nociceptive, anti-spasmodic, anticancer and anti-Alzheimer. However, more studies into the pharmacological activities are needed, since none of the professed bioactivity of this plant have ever been fully evaluated. Therefore, this review aims to discuss the evidence-based ethnomedicinal and ethnopharmacological uses, phytochemicals and bioactive potential of *Selaginella* species. It will provide an updated knowledge for ethnobotanists, ethnopharmacologists and other scientific communities to rethink over the possible usage of *Selaginella* in medicine. Moreover, further explorations are needed to formulate a novel medicinal product from Selaginella extracts for the improvement of human health, together with toxicity evaluations, necessary to ensure about the safety of these medicinal lycophytes.

Keywords: *Selaginella*; chronic diseases; anti-Alzheimer; anti-diabetic; ethnobotany; phytochemistry.
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1. Introduction

The cosmopolitan genus *Selaginella* possessing many species, utilized conventionally for food, medicine, handicrafts and also as ornaments. The *Selaginella* plants are usually used to cure many ailments including fever, jaundice, hepatic disorders, cirrhosis, diarrhea, cholecystitis, sore throat, cough of lungs. Furthermore, it promotes blood circulation and helps in removal of blood stasis and controlling external bleeding after injury etc. [1]. They are considered to have the high content of numerous phytochemicals such as, carbohydrates, benzenoids, flavonoids, alkaloids, quinoids, chromones, lignans coumarins, phenylpropanoids, oxygen heterocycle, pigments and steroids. Therefore, crude extract and different bioactive compounds isolated from these plants have been evaluated *in-vitro* for their antimicrobial, antiviral, anti-diabetic, anti-mutagenic, anti-inflammatory, anti-nociceptive, anti-spasmodic and anticancer activities [2-12]. In this context, the aim behind this review is to spotlight the importance of the *Selaginella* species in the ethnomedicinal and ethnopharmacological fields, describing the detailed phytochemistry with references and scopes for further inventions in a cyclopedic way against various modern and lifestyle-based chronic diseases such as different types of cancer, hypertension, obesity, type 2 diabetes, etc. As, *Selaginella* is a rich source of diverse and potent bioactive compounds, it is considered as wonder herb in folk medicine.

1.1. Overview of Genus Selaginella

Selaginella belongs to the family *Selaginellaceae,* which is also acknowledged as a "spike moss". It is the only surviving member of the largest genus of heterosporous fern in the family *Selaginellaceae*. The genus comprises around 700 to 750 species distributed around the globe. Tropical and subtropical areas have maximum diversity in which plants can grow in various types of soil and climate. Some of the species are also found in extreme climate such as dry desert (*S. lepidophylla*, *S. sartorii*), cool alpine and tundra/Arctic circle (*S. selaginoides*, *S. rupestris*) [13,14]. Plants are herbaceous, terrestrial, epilithic or occasionally epiphytic, evergreen or sometimes seasonally green. Rhizome erect, creeping, ascending or scandent. Rhizophores are present at the lower part of rhizome, which bearing roots. Two different sizes of leaves are present on their dichotomous branch which are simple and very small in size (~10 mm). Stem of the small *Selaginella* species grows approximately up to 3 cm, whereas, large species stems grows up to 50 cm to approximately 1 m long [15]. A diversity of secondary bioactive metabolites such as terpenoids (triterpene, steroid), phenolics (flavonoids, tannins, saponins) and alkaloids have been reported [16]. Among these, biflavonoids are considered as most important which are produced from the dimer of flavone and flavanone structures with 5,7-4'- oxygenated pattern [17-19]. Therefore, *Selaginella* bears immense value due to the presence of large number of potent phytochemical compounds, ethnobotanics and multi-biological activities with a promising resource of various secondary metabolites.

1.2. Evidence-Based Ehnobotanical and Ethnomedicinal Uses

Different species of *Selaginella* have been used as food, medicine, in handicrafts and also as ornaments since primordial time. As the distribution of *Selaginella* species is seen worldwide, usage of these plants has been observed in traditional ways by the people around the world for various purposes. The most common use of this plant group is its ethnomedical use due to its healing benefits in different health issues, especially incurring fever, against jaundice, diarrhea, cholecystitis, cirrhosis, dysentery and leukorrhagia, sore throat, cough of lung, silicosis, for hematemesis, hemafecia, epistaxis and curing wound [1], diabetes [7], chronic and acute hepatitis [9], urinary tract infections [6], anti-mutagenic [10] gastritis [5], skin diseases [4], cancer and cardiovascular problems [11], anti-inflammatory [2], cytotoxic, immunostimulant and RNA reverse transcriptase inhibitory agent [8] anti-nociceptive [12] and also anti-spasmodic [3]. Different medicinal uses of *Selaginella* species are described in the Ayurveda, *Charaka Samhita*, *Shusruta Samhita* (ca. 100 AD) and Chinese medicines [20]. In Indian mythology, *S. bryopteris* is described as '*Sanjeevani booti'* – A magical herb. In the *Ramayana,* poet Tulsidas has given the narration of this wonder herb, '*Sanjeevani'* which has the power to heal any malady [21]. In Chinese traditional medicine, medicinal importance of different species of *Selaginella* are described. Such as, the importance of *S. doederleinii* in the treatment of

cardiovascular diseases, as a bactericide and in cancers of lung, throat, liver and nose [22]; use of *S. tamariscina* in cancer therapy, traumatic bleeding, gastro-intestinal bleeding, metrorrhagia, rectal prolapsed, hematuria, hemoptysis in pulmonary disease, persistence of post-partum lochia discharge and leucorrhoea [23].

Ethnomedicinal importance of *S. bryopteris*is also reported for its use to cure heat stroke and jaundice. Local native people of 'Songhati' in India uses its paste orally to cure beri-beri, dysentery and for rejuvenating, in combination with cow milk. *S. bryopteris* also used as remedy for epilepsy and liver problem. In the Madhya Pradesh state of India, "Gond" tribes traditionally used it as strength tonic. They make paste of fresh young leaves along with sugar/honey to treat stomach-ache and urinary tract inflammation in children. In the Chhattisgarh state of India, women of 'Bastar' uses dried powder of this herb as remedy for menstrual irregularities, leucorrhoea and to lessen the labour pain [1].

The Murut people of Sabah (Malaysia) also uses the *S. plana* plant decoction bath to cure fever. In New Guinea, people used to consume young shoots (cooked) of *S. tamariscina*. In Vietnam,whole plant of *S. tamariscina* is used by locals as medication for the treatment of burns, hepatitis, jaundice, and as an concoction for haemorrhoids and various respiratory diseases. In Philippines and Malaysia, *S. tamariscina* is used to treat cough, rectum prolapse, gastro-intestinal haemorrhage, haemoptysis, haematosuria, gravel and excessive menstrual flow by consuming concentrated decoction of the whole plant. It is also used as a styptic and to cover the wound. In Germany, local people use *S. tamariscina* to treat fragile and brittle finger nails by consuming a 'beauty tea' which is prepared from this plant [23]. For horticultural and trade, these plants are also valuable, as they are used in flower bouquets and for indoor decoration [24].

2. Phytochemistry of *Selaginella*

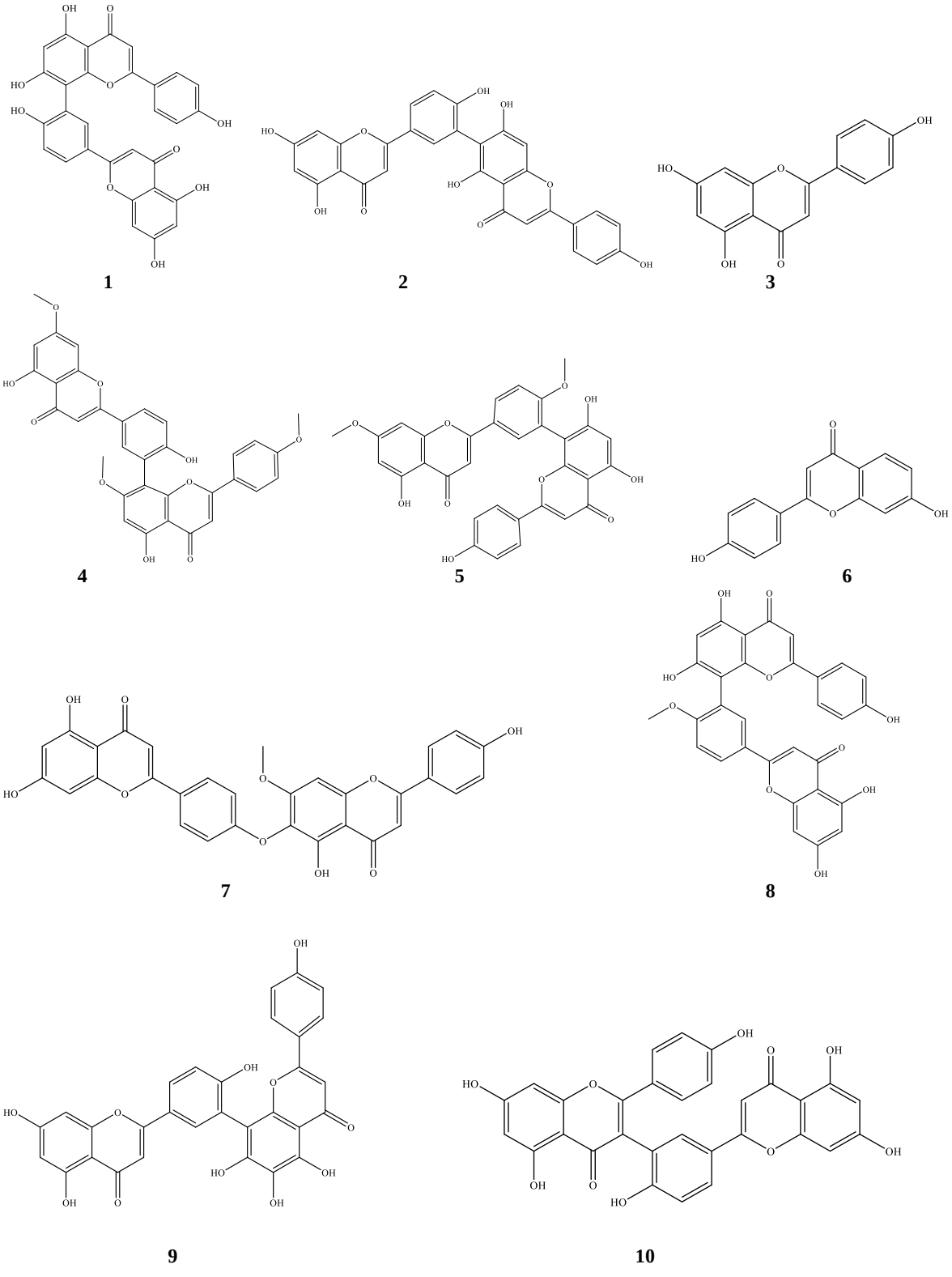
Immense number of studies have been revealed that *Selaginella* genus is rich with biflavonoids, steroids, alkaloids, alkaloidal glycosides, secolignans, lignans, neolignans, phenylpropanones and caffeoyl derivatives [12]. Maximum bioactive compounds isolated from various species of *Selaginella* mostly belongs to the class of flavonoids, alkaloids, lignans, pigments, phenylpropanoids, steroids, benzenoids, quinoids, carbohydrates, coumarins, chromones and oxygen heterocycle [25].

2.1. Flavonoids

The phenolic compounds "flavonoids" are found in good amount within the *Selaginella* in the form of biflavonoids. These secondary metabolites are keen to show potent activity viz., antitumor, anti-malarial, anti-allergic, anti-thrombotic, anti-inflammatory, anti-hypertensive, antibacterial, antioxidant, anti-hepatotoxic, estrogenic and antiviral [26]. They are polyphenolic compounds including flavones, flavonols, flavon-3-ols, flavonones, isoflavones and anthocyanins with low molecular weight. Flavonoids worked as vitamin C enhancer which eventually functions as antioxidants. They can inhibit enzyme activities like cyclooxygenase, lipoxygenase and prostaglandin synthase. Arrangement of functional groups about the nuclear structure in the flavonoids is directly responsible for its antioxidant activity [26]. Commonly occurred flavonoids in various *Selaginella* species are listed in Table 1 and chemical structures of majorly can be seen in Figure 1.

Table 1. List of various commonly occurred flavonoids from different *Selaginella* species

Plant Name	Compound	References
S. doederleinii	7,7"-di-*O*-methyl-amentoflavone, 4',4"',7,7"-tetra-*O* methyl-amentoflavone, apigenin, heveaflavone, 4'-methylether-robustaflavone, 2,2",3,3"-tetrahydro-4',7,7"-trimethylether-robustaflavone, 4,7,7"-trimethylether-robustaflavone	[27]
S. uncinate	Amentoflavone, 6-(5-carboxyl-2-methoxyphenyl)-apigenin, hinokiflavone, robustaflavone 7,4',4"'-trimethyl ether, robustaflavone 4',4"'-dimethyl ether, 2,3-dihydroamentoflavone, 7,4',7"-trimethyl ether, 2,3-dihydroamentoflavone 7,4'-dimethyl ether and 2",3"-dihydroisocryptomerin 7-methyl ether	[28]
S. delicatula	Robustaflavone 4'-methyl ether,robustaflavone 7,4'-dimethyl ether,2",3"-dihydrorobustaflavone 7,4',-dimethyl ether, 2",3"-dihydrorobustaflavone 7,4', 7" trimethyl ether, Robustaflavone and amentoflavone	[29]
S. moellendorffii	Amentoflavone, robustaflavone, amentoflavone-7,4,7,4-tetramethylether,4',4"',7,7"'tetra-*O* methyl-amentoflavone, 7,4',7' ',4' '-tetramethylether-amentoflavone, 5-carboxymethyl-4',7-dihydroxyflavone	[30]
S. bryopteris	Amentoflavone, 2,3-dihydroamentoflavone, 2",3"-dihydroamentoflavone, tetrahydroamentoflavone, 2,3-dihydrohinokiflavone, 2",3"-dihydrohinokiflavone, tetrahydro-hinokiflavone, tetra-*O*-methyl-hinokiflavone, lanaroflavone, sciadopitysin and sequoiaflavone	[31]
S. willdenowii	Isocryptomerin, 4',7"-di-*O*-methyl-amentoflavone, bilobetin, 2",3"-dihydro-isocryptomerin, robustaflavone, 7"-*O*-methyl-robustaflavone	[32]
S. labordei	2",3"-dihydro-3',3"'-biapigenin, 2,3-dihydro-5,5",7,7",4'-pentahydroxy-6,6"-dimethyl-(3'-*O*- 4"')-biflavone,2", 3"dihydroochnaflavone, amentoflavone and robustaflavone	[33]
S. tamariscina	Amentoflavone and robustaflavone, 6-(2-hydroxy-5 acetylphenyl)-apigenin, 2',8"-biapigenin, cryptomerin B, isocryptomerin, sumaflavone, taiwaniaflavone	[34]
S. denticulate	Amentoflavone, cryptomerin B, hinokiflavone, isocryptomerin, robustaflavone, sotetsuflavone	[35]
S. lepidophylla	Amentoflavone, cryptomerin B, hinokiflavone, isocryptomerin, robustaflavone, sotetsuflavone, heveaflavone, 2,3-dihydro-robustaflavone, 2,3-dihydro-5 methylether-robustaflavone	[36]
S. braunii, *S.remotifolia*, *S. pulvinata*, *S. sinensis*, *S. chrysocaulos*, *S. subalpine*, *S. davidii*, *S. kraussiana*, *S. pulvinata*, *S. rupestris*, *S. sanguinolenta*, *S. selaginoides*, *S. stauntoniana*	Most common flavonoids Ametoflavone and robustaflavone	[28]



(**8**) Bilobetin (**9**) Sumaflavone, (**10**) Taiwaniaflavone

2.2. Alkaloids

In the field of medicine, alkaloids are considered as one of the leading group of phytochemicals from which powerful pain killer medications are discovered [37].

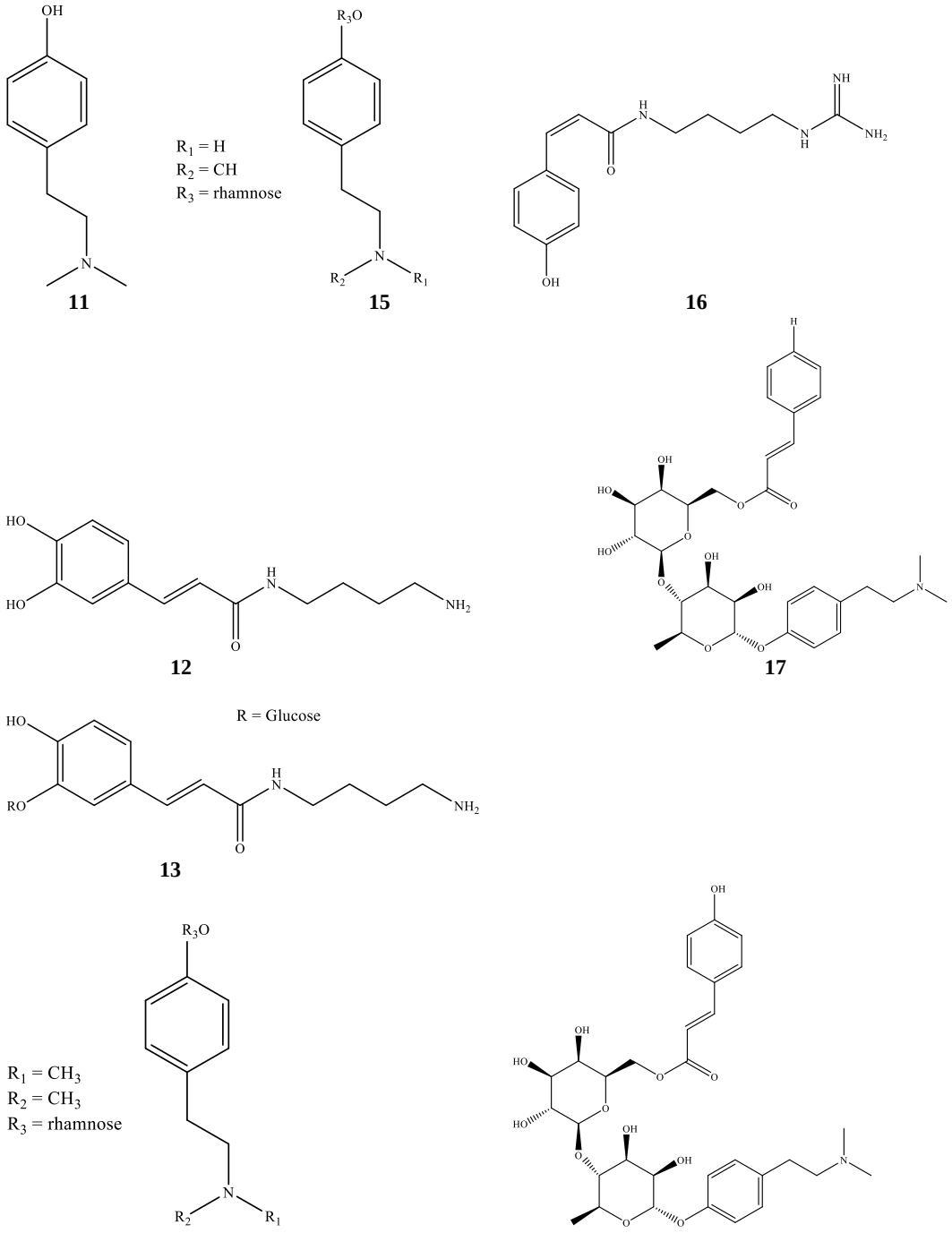


Figure 2. Major alkaloids identified from *Selaginella*. (**11**) Hordenine, (**12**) Paucine, (**13**) Paucine3-β-D-glucopyranoside, (**14**) Hordenine-*O*-α-rhamnopyranoside, (**15**) *N*-methyltyramine-*O*-α-rhamnopyranoside, (**16**) N[1]-*cis*-*p*-coumaroylagmatine, (**17**) Hordenine-*O*-[(6-*O*-cinnamoyl)-*O*-β-glucopyranosyl]-α-rhamnopyranoside, (**18**) Hordenine-*O*-[(6-*O*-*p*-coumaroyl)-*O*-β-glucopyranosyl]-α-rhamnopyranoside

Alkaloids possess multiple pharmacological effects that makes them as an important source of recreational drugs and medications [38]. Alkaloids are known to exhibit anti-inflammatory, analgesic, diuretic and anti-spasmodic activity [39]. Different types of alkaloids were determined with the help of preliminary phytochemical and advanced chromatographic techniques from *Selaginella* [25]. Different alkaloid compounds such as, hordenine (**11**), hordenine-(6-O-(4-hydroxy-cinnamoyl)-β-D-glucosyl) –

(1,3)-α-L-rhamnoside,hordenine-O-(6"-O-trans-cinnamoyl)-4'-O-β-D-glucopyranosyl-α-L-rhamnopyranoside, hordenine-*O*-α-L rhamnopyranoside (**14**), N-methyltyramine-O-α-L-rhamnoside, hordenine-*O*-[(6-*O*-cinnamoyl)-*O*-β-glucopyranosyl]-α-rhamnopyranoside (**17**) were detected from the *S. Doederleinii* [40]. While, in the *S. Moellendorffii*, selaginellic acid, 5-Hydroxyselaginellic acid, 5-hydroxy-N_8,N_8-dimethylpseudophrynaminol,*N*-selaginelloyl-*L*-phenylalanine,*N*-(5-hydroxyselaginelloyl)-*L*-phenylalanineandneoselaginellic acid were detected [30]. Apart from these, *N*-methyltyramine-*O*-α-rhamnopyranoside (**15**), hordenine-*O*-[(6-*O*-*p*-coumaroyl)-*O*-β-glucopyranosyl]-α-rhamnopyranoside (**18**), paucine (**12**), paucine3'-β-D-glucopyranoside (**13**), N^1-*cis*-*p*-coumaroylagmatine (**16**) were also detected from different species of *Selaginella* [41] (Figure 2).

2.3. Lignans

Though lignans are commonly disseminated in higher plants, some of the lignans are also reported to present in the pteridophytes. In this regard, *Selaginella* is the one in which lignans were detected from some of the species. At ecological level, lignans plays a crucial role in interaction between plant-insect, plant-fungus and plant-plant. Therefore, they exhibit plentiful of biological activities viz., antimicrobial, antitumor, anti-hepatotoxic, antioxidant, anti-tuberculous, antiviral, insecticide and inhibition of certain enzymes [25]. Most important lignans such as, (-)-lirioresinol A (**19**), (-)-lirioresinol B, (+)-matairesinol (**21**), (-)-nortracheloside and (+)-wilkstromol (**22**) were identified from the *S. doederleinii*. Whereas, 5acethyl-dihydro-2-(3',5'-dimethoxy-4'-hydroxyphenyl)-7-methoxybenzofuran, (+) syringaresinol (**20**), tamariscinoside B (**25**), tamariscinoside C (**27**) were detected from the *S. tamariscina* [42]. Two more lignans, sinesiol A and pinoresinoldiglucoside were also detected from the *S. sinensis* [43]. Apart from these, (+) syringaresinol-4,4'-di-*O*-β-D-glucopyranoside, matairesinol-4,4'-di-*O*-β-D-glucopyranoside, styraxlignolide B (**23**), lariciresinol (**24**), lariciresinol-4-*O*-β-glucopyranoside, *2R*,(*3S*)-dihydro-2-(3',5'-dimethoxy-4'-hydroxyphenyl)-7-methoxy-5-acetyl-benzofuran (**26**), 3,4-trans-3-hydroxymethyl-4-[bis(4-hydroxyphenyl)methyl] butyrolactone (**28**), 2,3-*trans*-3,4-*trans*-2-methoxy-3-hydroxymethyl-4-[bis(4-hydroxyphenyl)methyl] tetrahydrofuran (**29**) were also reported from different species of *Selaginella* [41] (Figure 3).

2.4. Tannins

Tannins are widely distributed in plants having multiple healing properties in various health issues. They are reported as a potent antibacterial, antiviral, anti-diarrheal, antiparasitic, anti-hemorrhoidal agents. So many studies have been revealed the presence of tannins in different species of *Selaginella* such as, *S. adoederleinii*, *S. bryopteris*, *S. lepidophylla*, *S. intermedia* and *S. inaequalifolia* [44].

2.5. Saponins

Saponins is a group of compounds structurally related to a steroid or triterpenoidaglycone consisting one or more moieties of oligosaccharide. They are well-known for their hemolytic and foaming properties. They are reported as a potent antibacterial and antifungal agent. They can also can form strong insoluble complexes with cholesterol, due to this reason they are considered as useful in the human diet in order to control cholesterol. *S. doederleinii* is the only species which reported for the presence of saponins [39].

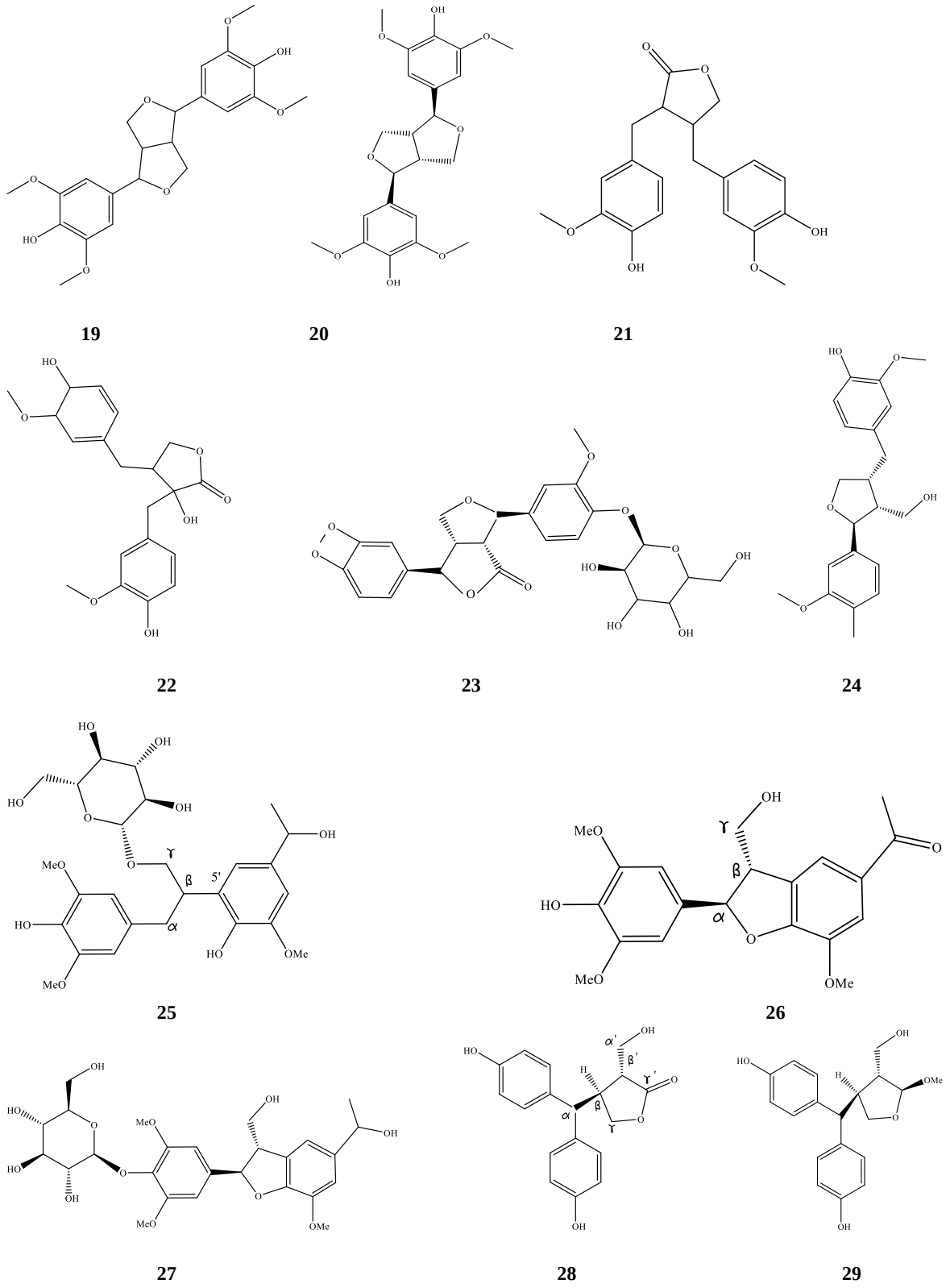


Figure 3. Major lignans identified from *Selaginella*. (**19**) (−)-Lirioresinol A, (**20**) (+)-Syringaresinol, (**21**) (+)-Matairesinol, (**22**)Wikstromol, (**23**) Styraxlignolide B, (**24**) (+)-Lariciresinol, (**25**) Tamariscinoside B (**26**) (*2R,3S*)- Dihydro-2-(3,5-dimethoxy-4-hydroxyphenyl)-7-methoxy-5-acetyl-benzofuran (**27**) Tamariscinoside C (**28**) 3,4-trans-3-hydroxymethyl -4-[bis(4-hydroxyphenyl)methyl]butyrolactone, (**29**) 2,3-*trans*-3,4-*trans*-2- methoxy-3-hydroxymethyl-4-[bis(4-hydroxyphenyl)methyl]tetrahydrofuran

2.6. Pigments

Biochromes or biological pigments are compounds which are perceived by humans to have colour. They are constituted as bioactive, as they have effect on cell tissue in human body and as a result, they have beneficial health effect on humans. Various type of colors is found in different species of *Selaginella* such as crimson red, blue chromatic, variegate, silver and yellow gold [45]. Major pigments namely, selaginellin A and B reported from *S. tamariscina* and selaginellin C, D, E, F, G and H are reported from *S. pulvinata* [46]. Apart from these, selaginellin I, J, K, L, M, N are also reported from other species f *Selaginella* [41] (Figure 4).

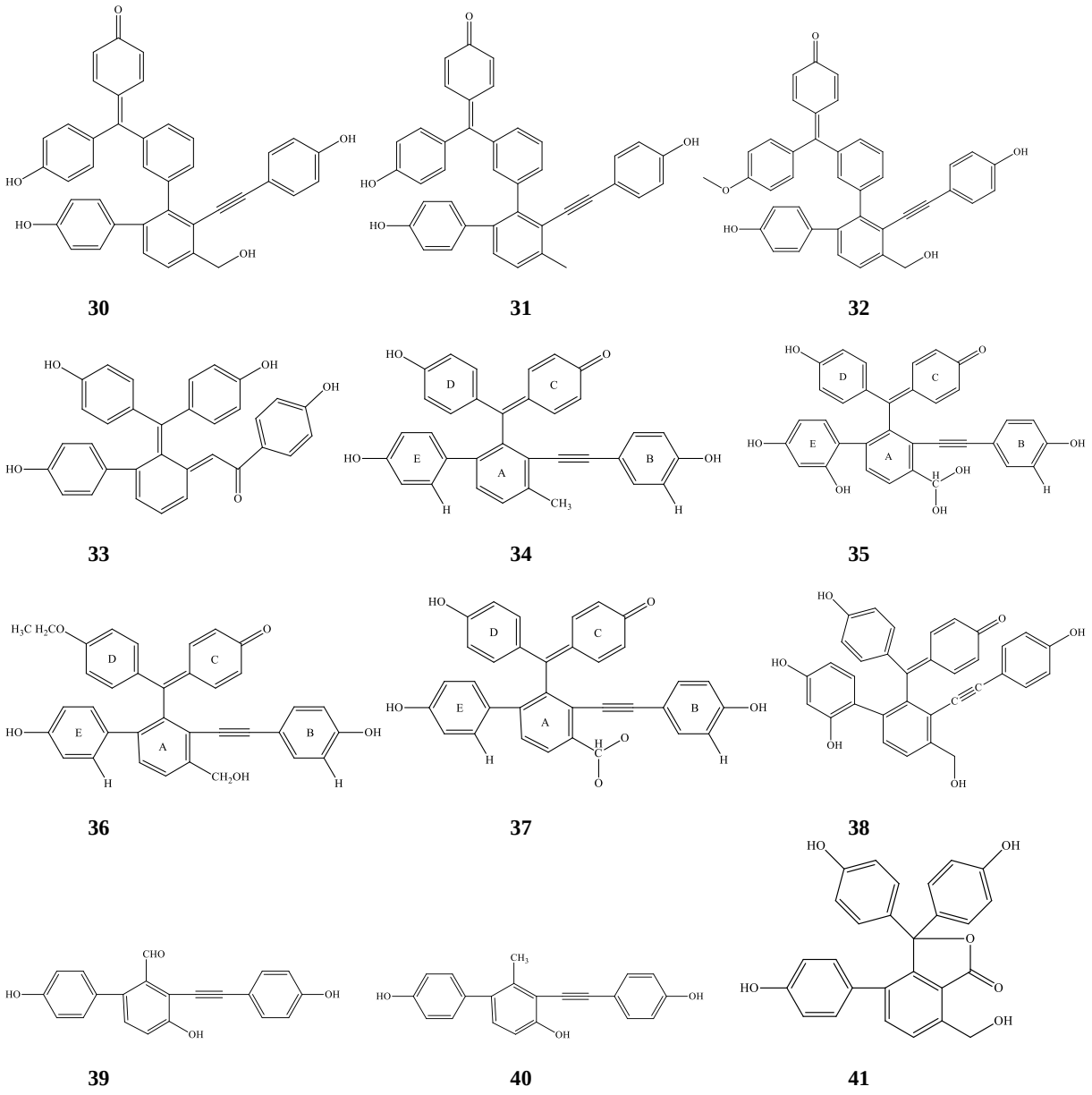
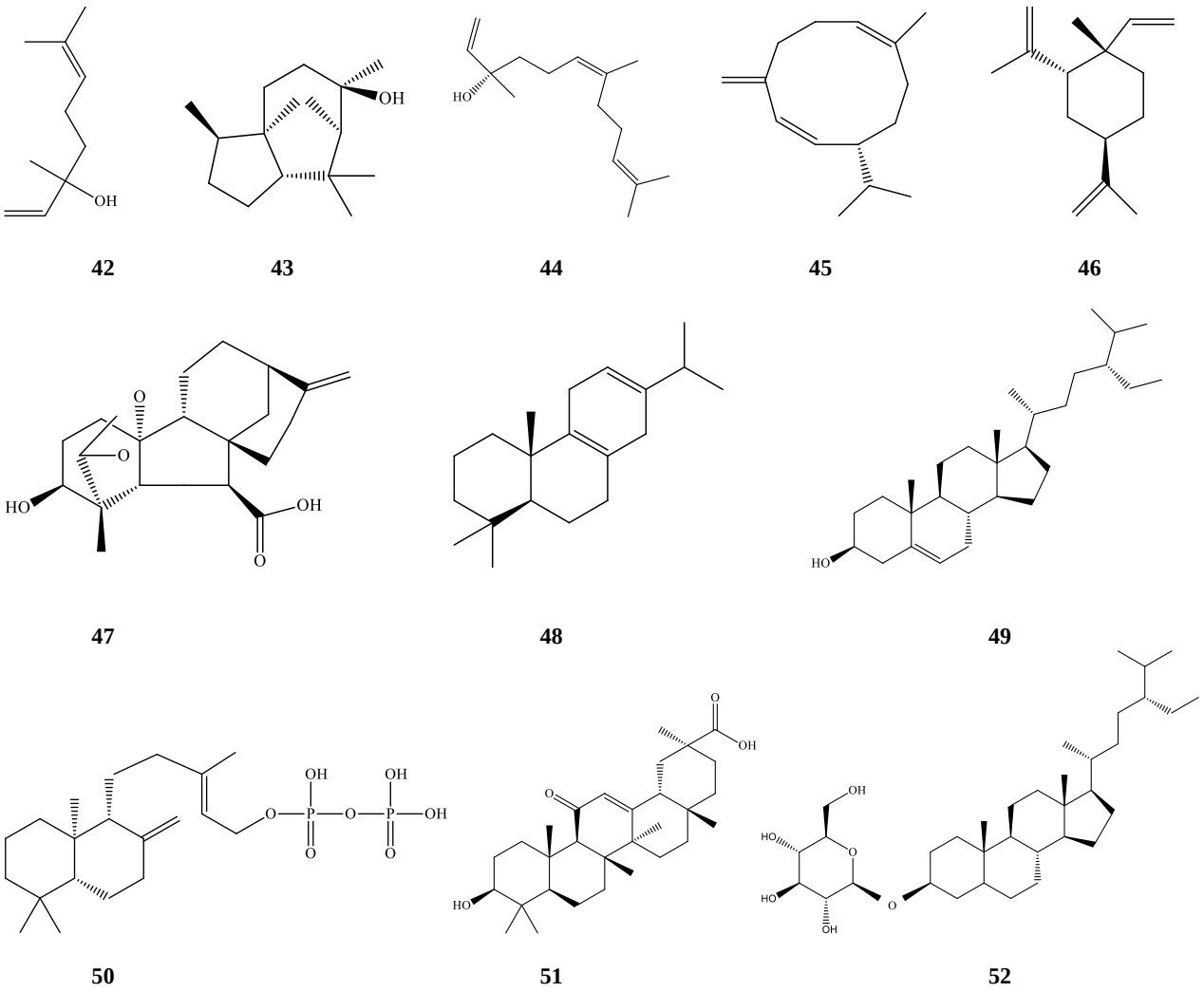


Figure 4. Major pigments identified from *Selaginella*. (**30**) Selaginellin, (**31**) Selaginellin A, (**32**) Selaginellin M, (**33**) Selaginellin G, (**34**) Selaginellin B, (**35**) Selaginellin C, (**36**) Selaginellin D, (**37**) Selaginellin E, (**38**) Selaginellin F, (**39**) Selaginellin K, (**40**) Selaginellin L, (**41**) Selaginellin H

2.7. Terpenoids

Terpenoids has been reported for its noteworthy pharmacological activities such as anti-bacterial, anti-malarial, anti-inflammatory, anti-viral, anti-cancer activities and also shows inhibition of cholesterol synthesis. Until now, more than 36000 terpenoid compounds have been identified, due *to this reason terpenoids has been considered as the largest class of plant metabolites. According to* Almeida *et al*., terpenoids can be utilized in storing agricultural products as protective substances due to their insecticidal properties [25]. Literatures described the presence of triterpenoids in the *S. tenera* and *S. lepidophylla* which are believed to give their anticancer and cytotoxic properties to these species [25].



42 **43** **44** **45** **46**

47 **48** **49**

50 **51** **52**

Figure 5. Major terpenoids identified from *Selaginella* (**42**) Linalool, (**43**) Cedrol, (**44**) (+)-(*3S*) - Nerolidol, (**45**)(+)-Germacrene D, (**46**) (-)-β-elemene, (**47**) Gibberellin A4, (**48**) Miltiradiene (**49**) β-sitosterol (**50**) *Ent*-copalyl diphosphate, (**51**) Glycyrrhetinic acid (**52**) β-daucosterin

Different types of terpenoid compounds such as, linalool (**42**), (4*Z*,6*E*)-2,7-dimethyl-8-hydroxyocta-4,6-dienoicacid, 8-*O*-β-D-glucopyranoside, cedrol (**43**), (+)-(*3S*)-nerolidol (**44**), (+)-germacrene D (**45**), (−)-β-elemene (**46**), β-sesquiphellandrene, gibberellinA4 (**47**), gibberellin A24, *ent*-copalyl diphosphate (**50**), miltiradiene (**48**), λ-7,13e-dien-15-ol, β-sitosterol (**49**), β-daucosterin (**52**). pulvinatadione, 3β,16'-dihydroxy-5',17β-cholestan-21-carboxylic acid, 3β-acetoxy-16'-hydroxy-5α,17β-cholestan-21-carboxylic acid, 3β-(3-hydroxybutyroxy)-16α-hydroxy-5α, 17β-cholestan-21-carboxylic acid, glycyrrhetinic acid (**51**) and friedelin from different species of *Selaginella* [41] (Figure 5).

2.8. Phenylpropanoids

Phenylpropanoids are a family of organic compounds having three carbon propene tail and aromatic ring, which are synthesized by plants from phenylalanine and tyrosine. They are reported as a good antioxidant agent in humans. Different phenylpropanoids such as, 3-hydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-propan-1-one, 3-hydroxy-1-(3-methoxy-4-hydroxyphenyl)-propan-1-one are reported from the *S. doederleinii* [47]. Whereas, caffeic acid, ferulic acid and tamariscine ester A are reported from the *S. tamariscina* [42].

2.9. Steroids

Steroids are group of biologically active compounds having four ring structure. They come with different classes and all different classes have different functional properties. As anabolic steroids can give rise to muscle mass, while anti-inflammatory steroids can decrease aching, swelling and other symptoms of inflammation. They are the universal and regular components of many plants and have been isolated effectively from almost all plants, among which, β-sitosterolis omnipresent [39]. In *Selaginella*, steroids are present in different species. Steroid compounds such as 22-dehydrocampesterol, 24α-ethyl-cholest-5-en-3β-ol, 24α-methyl-cholest-5-en-3β-ol, 24β-methyl-cholest-5-en-3β-ol, 24α-ethyl-cholesta-5,22-dien-3β-ol and β-sitosterol are detected from the *S. doederleinii*. β-sitosterol is present in *S. moellendorffii, S. bryopteris* and *S. lepidophylla*. Whereas, β-sitosterol and 3β-16α-dihydroxy-(5α)-cholestan-21-oic acid are reported from the *S. pulvinate* [48].

2.10. Quinoids

Quinoids are a class of compounds which are derived from quinone. They are mainly known to prevent several diseases like osteoporosis and cardiovascular diseases. Two of the species shows the presence of quinoids viz., *S. stauntoniana and S. tamariscina* [25].

2.11. Coumarins

Coumarins are the group of compounds that have great biological importance with vast structural variety. They are well-known for their antibacterial, anticoagulant, vasodilatory (in coronary vessels) and antitumour activities [49]. They are widely distributed in higher plants but rare in Gymnosperms and lower plants. However, three of the species viz., *S. doederleinii*, *S. moellendorfii*, *S. tamariscina* have been reported for the occurrence of coumarins [25]. Isopimpinellin is reported to present in *S. moellendorffii* and *S. doederleinii*. Whereas, umbelliferone and 3-(4-Hydroxyphenyl)-6,7-dihydroxy coumarin are reported from the *S. tamariscina.* Isomers of coumarins known as chromones (Uncinoside A and Uncinoside B) are also reported from few species of *Selaginella* [50].

3. Biological Activities of *Selaginella*

As listed in previous sections, *Selaginella* is well-known for its ethnomedicinal properties and chemical diversity, different species of the genus has been studied for its different biological properties, which have assisted in finding out the potent bioactive extracts and constitutes for the development of novel medicinal products and drugs. The biological activities of some species of genus *Selaginella* are chiefly linked with the findings of anti-diabetic, anti-inflammatory, hepato-protective, antimicrobial, antioxidant, anticancer, anti-nociceptive, anti-spasmodic, anti-mutagenic and anti-Alzheimer activities. Therefore, this section elaborates the information on various *Selaginella* species and their potential medicinal role in different biological activities.

3.1. Anti-diabetic Activity

Few researchers reported the anti-diabetic activity of *Selaginella* species. *S. tamariscina* is reported to increase the serum levels of insulin, C-peptide and high-density lipoprotein-cholesterol. While, at the same time, it decreases the serum levels of triglyceride, total cholesterol, glucagon, fast

blood glucose, low density lipoprotein-cholesterol, free fatty acid and glycosylated hemoglobulin A1C. It was also found to improve the oral glucose tolerance test to a certain degree. Additionally, expression of PPAR-γ was observed to be improved by *S. tamariscina* in adipose tissues, which further increases the protein expressions of the IRS-1 in hepatic and skeletal muscle tissues [51]. In another study, aqueous extract of *S. bryopteris* (150 mg/kg b.w) was given to alloxan induced Swiss albino mice up to 26 days for the determination of its anti-diabetic effect. *S. bryopteris* efficiently reduces the level of glucose and increases the body weight of mice with the release of the shrunken pancreas [52].

3.2. Anti-inflammatory Activity

There are many reports on the anti-inflammatory activity of *Selaginella* species. As reported earlier, two most potent anti-inflammatory biflavonoids namely, hinokiflavone (H) and 7'-*O*-methyl hinokiflavone (mH) were isolated from the *S. tamariscina*. Their activity was examined through lipopolysaccharide (LPS)-mediated murine macrophages (RAW 264.7) and colon epithelial cells (HT-29) in which H and mH were used to suppress the production tumor-necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, and nitric oxide (NO), which are considered as highly active in inflammatory bowel disease (IBD). Also, H and mH were found to suppress the expression of cyclooxygenase (COX)-2 and inducible nitric oxide synthase (iNOS) induced by LPS, as well as the activation of extracellular regulated kinases (ERK) and nuclear factor-κB (NF-κB) [53].

The ethanolic crude extract of *S. tamariscina* was evaluated for its anti-inflammatory potential against LPS-induced inflammatory responses. Treatment of ethanolic crude extract on LPS-stimulated RAW 264.7 cells showed significant inhibition in the production of pro-inflammatory cytokines; IL-1*β*, IL-6 and inflammatory mediators; NO and PGE_2 in dose-dependent manner. The crude extract was notably suppress the phosphorylations of I*κ*B-*α*, MAPKs, NF-*κ*B. Apart from anti-inflammatory, *S.tamariscina* crude extract also displayed fine free radical scavenging activity and prevents ROS generation with LPS. Expression of HO-1 and Nrf2 were also prompted by the *S. tamariscina* crude extract. Therefore, it was found that *S. tamariscina* crude extract have anti-inflammatory effects on RAW 264.7 macrophages and considered useful in the preventing or treating inflammatory diseases [54].

The anti-inflammatory effect of *S. moellendorffii* crude extract was evaluated against gouty arthritis. The crude extract was tested on rat model to analyze its effect against accumulation of neutrophil, lipid peroxidation, inflammatory mediators, paw oedema and other histo-pathological alterations in joints, serum urate and kidney injury, which were identified in hyperuricemic mice. With the help of pharmacokinetic studies, itis assumed that the main apigenin glycosides, quantitatively converted into apigenin in the mammalian body. The apigenin is reported to give strong effect on xanthine oxidase. Aqueous extract of *S. moellendorffii* significantly reduces the hyperuricemia in dose-dependent manner, in high dose group, level of blood nitrogen, creatinine and urea decreased significantly in comparison with hyperuricemic control group. High dose of this extract apparently prevents the swelling of paw, reduces the release of TNF-*α* and IL-1*β*, reduces the gouty joint inflammatory features, lowers the malondialdehyde and myeloperoxidase levels and increases the superoxide dismutase level [55].

One of the studies described that silver (Ag) nanoparticles developed from *S. myosurus* crude extract could be a possible and promising source for anti-inflammatory drugs. In which, carrageenan-induced and albumin denaturized rat hind paw oedema model were used to measure the anti-inflammatory capability of generated nanoparticles, and it was proposed that the Ag nanoparticles can reduce/inhibit agents on the release of acute inflammatory mediators [56].

3.3. Antimicrobial Activity

Selaginella is rich in flavonoids and bioflavonoids, which are reported for their powerful activity against microorganisms [25]. The antimicrobial activity of different species of *Selaginella* have been evaluated against various human pathogenic bacterial and fungal strains, via well or disc diffusion method. One of the studies showed antibacterial and antifungal potential of *S. bryopteris* against some bacterial and fungal strains viz., *E. coli, E. faecalis, C. tropicalis, S. aureus, C. albicans,*

C. krusei and *K. pneumonia* [57]. *S. doederleinii* have been reported for its antibacterial potential against different Gram-negative and Gram-positive bacteria [58]. *S. equalifolia* and *S. involvens* had also shown potent antimicrobial activity against five poultry pathogens namely, *Klebsiella*, *Salmonella*, *Staphylococcus*, *Proteus* and *Bacillus* [59]. *S. inaequalifolia* had good antagonistic activity against *S. aureus*, *E. coli* and *C. albicans* in a dose dependent manner [60]. *S. convoluta* had also significant antibacterial potential against *B. cereus*, *E. coli*, *S. enterica*, *S. marcescens*, *K. pneumoniae*, *S. flexneri*, *E. faecalis* and *S. aureus* [61]. *S. tamariscina* gave quite potent activity against oral bacterial pathogens such as, *P.gingivalis*, *P. intermedia*, *S. mutans*, *S. sobrinus*, *S. gordonii*, *F. nucleatum*, *S. sanguinis*, *S. anginosus*, *S. ratti*, *A. actinomycetemcomitans*, *S. parasanguinis*, *S. criceti* and *S. downei* [62].

3.4 Antioxidant Activity

In the prevention and treatment of complex diseases such as cancer, diabetes, stroke, atherosclerosis and Alzheimer's, antioxidant-based drug formulations are used [63]. Compounds accountable for such antioxidant activity can be isolated and used for preventing and treating the free radical-related disorders [64]. The antioxidant potential of different species of *Selaginella* have been evaluated by different methods; from which, most are based on the determination of free radical scavenging activity. Commonly used methods are, ABTS, DPPH, superoxide anion radical scavenging assays and total phenolic content.

Indian Sanjeevani (*S. bryopteris*) is well known for its protective effect against various stress-induced conditions [65]. The crude extract of *S. tamariscina* have strong antioxidant property as its extract can reduce blood sugar levels and able to act as a lipid peroxide and increases insulin serum [66]. The aqueous extract of *S. involvens* also demonstrated significant antioxidant power to lipid peroxides (EC_{50} = 2 µg/ml). This aqueous extract is considered as non-toxic and able to degrade blood cholesterol [67]. The aqueous extract of *S. involvens*, *S. delicatula* and *S. wightii* were also displayed *in-vitro* lipid peroxidation and varying levels of hydroxyl radical scavenging activity. The 50% inhibition (EC_{50}) for *in-vitro* lipid peroxidation of *S. wightii*, *S. delicatula* and *S. involvens* were 76.6±4, 38.2±1.2 and 2.1±0.1, respectively. Compare to other two species in hydroxyl radical scavenging activity, *S. delicatula* was found to be more potent. Moreover, flavonoids obtained from the *S. doederleinii* also possess very strong free radical scavenging activity [68].

3.5. Hepato-protective Activity

Hepatic disorders have been considered as an important cause of morbidity and mortality in animals and humans globally. Herbal medicines are known for the treatment and relaxation of various elements including various types of liver disorders. Different species of *Selaginella* are known for its hepatoprotective properties as they consist large number of bioactive compounds such as amentoflavone, delicaflavone, heveaflavone, ginkgetin, 2',8"-biapigenin, hinokiflavone, taiwaniaflavone, kayaflavone, isocryptomerin, sumaflavone, podocarpusflavone A, robustaflavone and ochnaflavone [69]. *S. doederleinii* has been reported for its hepatoprotective effects [27]. Different extracts of *S. labordei* are also able to down-regulate the expression of cyclooxygenase-2 gene in the adenocarcinoma CaCo-2 cells of human colon [70].

3.6. Anti-spasmodic Activity

Spasmodic condition is basically a muscle cramp which is escorted by a sudden burst of pain. A spasmodic muscle contraction can be caused through many medical conditions like dystonia. Anti-spasmodic effect of few species of *Selaginella* has been reported. *S. pallescens* and *S. rupestris* are reported for their anti-spasmodic activity due to the presence of flavonoid compound amentoflavone [71]. Apart from these two species, amentoflavone was also identified as an antispasmodic agent in *S. tamariscina* which inhibit the expression of phospholipase C gamma 1 [72]. The crude extract of *S. pallescens* also exhibited the spontaneous inhibition of rat ileum contractions in concentration dependent manner [73].

3.7. Anti-Mutagenic and Anti-Alzheimer Activity

The reports on anti-mutagenic and anti-Alzheimer activity of *Selaginella* are few. Anti-mutagenic efficacy of *S. doederleinii* extract has been reported against benzo [α] pyrene [74]. A recent work on anti-Alzheimer activity was carried out with the crude extract of *S. doederleinii* on Alzheimer disease bearing mice (AD) by Morris water maze test. The extract showed notable and significant development on memory and learning function for AD mice [75].

3.8. Antinociceptive Activity

To further support towards the pharmacological knowledge of *Selaginella* and to establish the wide uses of different species as a painkiller, anti-nociceptive activity of few species was employed. For the first time, ethanolic crude extract of *S. convoluta* was demonstrated for its anti-nociceptive activity on acetic acid-induced writhing mice. Acetic acid administration intraperitoneally irritates the serous membranes and provokes stereotyped behavior in mice, which further characterized by whole body movement, contractions of abdomen and twisting of dorso-abdominal muscles. *S. convoluta* ethanolic crude extract administration significantly reduces the acetic acid-induced writhing in mice. This effect of *S. convoluta* crude extract might be due to the inhibition of prostaglandin synthesis, as nociceptive mechanism of abdominal writhing induced by acetic acid, which involves the release of arachidonic acid metabolites via cyclooxygenase (COX), and prostaglandin biosynthesis [12]. Moreover, different flavonoids have been reported as anti-nociceptive and anti-inflammatory agents, due to their potentiality to impede the metabolism of arachidonic acid [76]. Therefore, flavonoids present in the crude extract of *S. convoluta* might be liable for its anti-nociceptive effect.

3.9. Cytotoxic and Anticancer Activity

Currently, cancer is the leading cause of death around the globe. Therefore, finding a cure for this disease is highly needed for human endeavor. Nowadays, priority and importance are being given to researches on complementary and alternative medicine to deal with cancer. Different classes of phytochemicals are ubiquitous in plants and large numbers of phytochemicals have been associated with cytotoxic activities. *Selaginella* species have different groups of chemical compounds which are well-known to have a wide-range of biological actions and are potential source for finding the novel anticancer drugs. As many of the phytochemical compounds obtained from few of these species possess strong cytotoxic activity against various cancer cell lines. Here, we are describing some examples of reports about the cytotoxic activity of few species of *Selaginella*.

The cytotoxic activity of ethanolic and aqueous extracts of *S. doederleinii* was evaluated by brine shrimp lethality test and against two cancer cell lines MDAMB231 and HepG2. As a result, 50% lethal concentration (LC50) in brine shrimp lethality test using ethanolic and aqueous extracts after 24 h of exposure was found to be >1000 μg/ml. Cancer-origin cell lines MDAMB231 and HepG2 were found to be the most susceptible with the treatments of ethanol (LC50=306 μg/ml) and aqueous (LC50=329 μg/ml) extracts of *S. doederleinii*, respectively [77]. The isocryptomerin, derivatives of amentoflavone and robustaflavone from *S. willdenowii* had significant cytotoxic potential against various cancer cells [17]. The crude extract of *S. tamariscina* showed potent anticancer activity against different cancer cell lines. It decreases the metastasis, expression of MMP-2 and 9 and urokinase plasminogen activator in A549 cells and Lewis lung carcinoma [78]; inhibits leukaemia cancer cells HL-60 and U937 [78]; inhibits nucleus antigen cell from stomach epithelium [79]; inhibits gastric cancer cells [79] and induce apoptosis via blockade of fatty acid synthesis in breast cancer [80]. Apart from this, amentoflavone was extracted from the crude extract of *S. tamariscina* and its anticancer efficacy was screened against five different cancer cells, including HeLa (human cervical carcinoma cells), BEL-7402 (human hepatoma carcinoma cells), MCF-7 (human breast cancer cells), PANC-1 (human pancreatic cancer cells) and HL-60 (human leukemia cells). The extract was efficient in the inhibition of the proliferation of HL-60, MCF-7, HeLa, BEL-7402, PANC-1 and showed remarkable inhibition of HL-60 [81].

Table 2. List of various phytochemicals from different *Selaginella* species and their ethnopharmacological and ethnobotanical uses

Species	Phytochemical/Bioactive Compounds	Ethnopharmacological and Ethnobotanical Uses/Against	References
S. doederleinii	Anthocyanins and chalcones Isopimpinellin Hordenine Hordenine-[6-*O*-(4-hydroxy-cinnamoyl)-β-*D*-glucosyl]-(1,3)-α-*L*-rhamnoside Hordenine-*O*-(6”-*O*-*trans*-cinnamoyl)-4’-*O*-β-*D* glucopyranosyl-α-*L*-rhamnopyranoside Hordenine-*O*-α-*L*-rhamnopyranoside *N*-methyltyramine-*O*-α-*L*-rhamnoside Phytosterol & saponins 7,7"-Di-*O*-methyl-amentoflavone 4',4"',7,7"-Tetra-*O*-methyl-amentoflavone Apigenin Heveaflavone 4'-methylether robustaflavone 2,2",3,3"-Tetrahydro-4',7,7"-trimethylether-robustaflavone 4,7,7"-Trimethylether-robustaflavone (-) - Lirioresinol A (-) - Lirioresinol B (+) - Matairesinol (-) - Nortracheloside (+) – Wilkstromol 3-Hydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-propan-1-one 3-Hydroxy-1-(3-methoxy-4-hydroxyphenyl)-propan-1-one Cholesterol 22-Dehydrocampesterol 24α-Ethyl-cholest-5-en-3β-ol 24α-Methyl-cholest-5-en-3β-ol 24β-Methyl-cholest-5-en-3β-ol 24α-Ethyl-cholesta-5,22-dien-3β-ol β-Sitosterol Tannins and cardiacglycosides	Chorioepithelioma Choriocarcinoma Anticancer Antioxidant Anti-proliferation Hepato-protective Cough Sore throat Pyodermas Bronchitis Pneumonia Tonsillitis Hepatitis Cholecystitis Cirrhosis Ascites Rheumatoid arthritis	[22, 32, 48, 77, 84-86]
S. lepidophylla	3-methylenhydroxy-5-methoxy-2,4-dihydroxy tetrahydrofurane Robustaflavone 2,3-dihydrorobustaflavone 2,3-dihydrorobustaflavone-5-methyl ether Heveaflavone	Inhibits contraction of uterus Cold Common throat infections Antimicrobial Anticancer Anti-ageing	[16, 36, 87]

S. uncinata	Amentoflavone Robustaflavone Chromone-8-methyleugenitol Unicoside A Unicoside B 6-(5-Carboxyl-2-methoxyphenyl)-apigenin Hinokiflavone Robustaflavone7,4',4'"-trimethyl ether Robustaflavone4',4'"-dimethyl ether 2,3-dihydroamentoflavone 7,4',7"-trimethyl ether 2,3-dihydroamentoflavone 7,4'-dimethyl ether 2",3"-dihydroisocryptomerin 7-methyl ether	Antiviral Anti-tumor Anti-anoxic Antibacterial Antifungal Hepatitis Post-childbirth	[43, 88-91]
S. delicatula	Robustaflavone Amentoflavone 2,3-Dihydro-isocryptomerin Robustaflavone-4'-methyl ether Robustaflavone7,4'-dimethyl ether 2",3"-dihydrorobustaflavone 7,4',-dimethyl ether 2",3"-dihydrorobustaflavone 7,4', 7"-trimethyl ether 3,5-di-O-caffeoylquinic acid, 3,4-di-O-caffeoylquinic acid 4,5-di-O-caffeoylquinic acid 2",3"-Dihydro-4',7,7"-trimethylether-robustaflavone 2",3"-Dihydro-4',7,-dimethylether-robustaflavone 4',7-Dimethylether-robustaflavone 4'-Methylether-robustaflavone Isochlorogenic acid A Isochlorogenic acid B Isochlorogenic acid C 22-Dehydrocampesterol 24α-Ethyl-cholest-5-en-3β-ol 24α-Methyl-cholest-5-en-3β-ol 24β-Methyl-cholest-5-en-3β-ol 24α-Ethyl-cholesta-5,22-dien-3β-ol	Gastric disorders Anti-HIV Anti-bradykinin Anti-oedemic Anti-inflammatory Anti-leukemic Anti-nociceptive Antioxidant Anti-ulcer	[29, 47]
S. moellendorffi	Ginkgetin Amentoflavone Robustaflavone Isopimpinellin Selaginellic acid 5-Hydroxyselaginellic acid 5-hydroxy-N_8,N_8-dimethylpseudophrynaminol *N*-Selaginelloyl-*L*-phenylalanine *N*-(5-Hydroxyselaginelloyl)-*L*-phenylalanine Neoselaginellic acid *N*-5(hydroxyneoselaginelloyl)-*L*-phenylalanine Amentoflavone-7,4,7,4-tetramethylether 4',4'",7,7"-Tetra-*O*-methyl-amentoflavone 7,4',7",4"-tetramethylether-amentoflavone Apigenin-7-*O*-β-neohesperidoside Apigenin-8-*C*-β-*D* glucopyranoside	Anti-inflammatory Arthritis Gonorrhea Hepatitis Mastitis Anticancer Antioxidant	[92-99]

	6,8-Di-*C*-β-*D*-glucopyranosyl-apigenin 6-*C*-β-*D*-Glucopyranosyl-8-*C*-β-*D*-xylopyranosyl-apigenin 6-*C*-β-*D*-Xylopyranosyl-8-*C*-β-*D*-glucopyranosyl-apigenin Chrysoeriol Kayaflavone Podocarpusflavone A 5-Carboxymethyl-4'-hydroxyflavone-7-*O*-β-*D*-glucopyranoside 5-Carboxymethyl-4',7-dihydroxyflavone [7-Hydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-chromen-5-yl]-acetic acid ethyl ester [7-Hydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-chromen-5-yl]-acetic acid butyl ester Moellenoside A Moellenoside B β-Sitosterol		
S. sinensis	Amentoflavone Selaginellin A Selaginoside Sinensiol A Styraxlignolide D Neolloydosin (+)-pinoresinol 4',7"-Di-O-methylamentoflavone 7"-O-Methylrobustaflavone Robustaflavone Genistin Ginkgetin Pinoresinoldiglucoside	Antiviral Antimicrobial Antioxidant	[43, 100]
S. chrysocaulos	Amentoflavone Chrysocauloflavones I Chrysocauloflavones II Chrysocauloflavones III 3,3'-binaringenin		[31]
S. bryopteris	Amentoflavone 2,3-Dihydroamentoflavone Tetrahydro-amentoflavone 2,3-Dihydrohinokiflavone Tetrahydro-hinokiflavone Tetra-*O*-methyl-hinokiflavone Lanaroflavone Sciadopitysin Sequoiaflavone	Anti-inflammatory General wounds Irregular menstruation Uterine disorders Antioxidants Anticancer Anti-allergic Antimicrobial Antifungal Antibacterial Antiviral	[101]
S. pulvinata	Amentoflavone Robustaflavone Mycose 3β, 16α-dihydroxy-(5α)-cholestan-21-oic acid 4-Hydroxy-benzoic acid β-Sitosterol Selaginellin C Selaginellin D	Antiviral Anti-tumor Anti-diabetic Stomachache Asthma	[102, 103]

	Selaginellin E Selaginellin F Selaginellin G Selaginellin H		
S. willdenowii	Amentoflavone Isocryptomerin 4',7"-Di-*O*-methyl-amentoflavone Bilobetin Isocryptomerin 2",3"-Dihydro-isocryptomerin Robustaflavone 7"-*O*-Methyl-robustaflavone	Anticancer Wound Fever and Backache Gastric pains Urinary tract infections Menstrual pains Skin diseases Antioxidant	[17, 32]
S. tenera	Octaethyleneglycol monododecyl ether 2',6'-Dihydroxyacetophenone, bis(trimethylsilyl) ether Decamethylcyclopentasiloxan Silane,[[4-[1,2 bis[(trimethylsilyl)oxy]ethyl]-1,2phenylene]bis(oxy)]bis [trimethyl- Octadecane, 3-ethyl-5- (2- ethylbutyl) Oxazepam Hydroquinone Cyclodecasiloxane, eicosamethyl- Chloroacetic acid, dodecyl ester α-D-Glucopyranoside, O- α -D-glucopyranosyl-(1.fwdarw.3)- α -D-fructofuranosyl Cyclooctasiloxane, hexadecamethyl- 1-Hexadecanol 8-Methoxy-1,3,4,5- tetrahydro-2H-1-benzazepin-2-one Cyclopentanone, 2-(1-methylheptyl)- α -D-Glucopyranose, 4-O- α -Dgalactopyranosyl- 2-Propenoic acid, 3-(3 fluorophenyl)-, ethyl ester Hexadecanoic acid, 1 (hydroxymethyl)-1,2 ethanediyl ester Androst-4-en-6-one, 3,17-diacetoxy- Pentadecanoic acid, 13-methyl-, methyl ester Hexadecanoic acid, 1 (hydroxymethyl)-1,2 ethanediyl ester 8-Octadecenoic acid, methyl ester Heptadecanoic acid, 14-methyl-, methyl ester, 1-Propyl-3,6 diazahomoadamantan-9-ol 8-Ethoxy-4,5-dihydro-1-[(4-isopropylphenyl)imino] -4,4-dimethyl-1H-[1,2]dithiolo[3,4-c]quinoline 2,2,8,8,12,13,17,18 Octamethyl-2,3,7,8,22,24-hexahydro-porphine-5-carbonitrile Cholestane, 1-vinyl-1-hydroxy- 1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane, 7,16-bis(1-oxodecyl)- 1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane,7,16-bis(1-oxodecyl)-	Antibacterial Antioxidant Anti-osteoporotic Prostate disorders Bone diseases Antifungal Anti-neoplastic Antiviral Phobic disorders treatment Anticancer Anti-pruritic Anti-inflammatory Anti-emphysemic Platelet aggregation stimulant Wound healing Anti-eczematic Anti-diabetic Anti-anginal Anti-ulcerative Cardiotonic Kidney function stimulant, Ovulation inhibitor Dementia treatment Anti-anginal Hepato-protectant Anti-protozoal Anti-neoplastic	[44]

	4-Normethyl-9,19 cyclolanoststan-7-one, 3-acetoxy-		
S. labordei	Amentoflavone Robustaflavone 2",3"-Dihydro-3',3"' biapigenin 2,3-Dihydro-5,5",7,7",4'-pentahydroxy-6,6"-dimethyl-[3'-*O*-4"']-biflavone 2",3"-Dihydroochnaflavone 4'-methylether robustaflavone Eriodictyol	Antiviral Antitumor Inhibit xanthine oxidase and lipooxigenase	[28, 33]
S. tamariscina	Amentoflavone Robustaflavone Umbelliferone 3-(4-Hydroxyphenyl)-6,7-dihydroxy coumarin 5-Acethyl-dihydro-2-(3',5'-dimethoxy-4'-hydroxy-phenyl)-7-methoxybenzofuran Syringaresinol Tamariscinoside B Tamariscinoside C Caffeic acid Ferulic acid Tamariscine ester A Selaginellin A Selaginellin B 1-Methoxy-3-methylanthraquinone 6-(2-Hydroxy-5-acetylphenyl)-apigenin 2',8"-Biapigenin Cryptomerin B Isocryptomerin Sumaflavone Taiwaniaflavone Vanillic acid Syringic acid Arbutin	Antioxidant Anticancer Anti-diabetic Anti-ageing Traumatic bleeding Haemoptysis in pulmonary disease Gastro-intestinal bleeding Metrorrhagia Haematuria Rectal prolapse Leukorrhea Cough Prolapse of the rectum	[104-108]
S. braunii	Amentoflavone 3-(4-Hydroxyphenyl)-6,7-dihydroxy coumarin	Antioxidant Antiviral Antibacterial	[82]
S. remotifolia	Amentoflavone Robustaflavone	Antioxidant Anticancer	[28]
S. involvens	Amentoflavone Robustaflavone	Antioxidant Antimicrobial	[67]
S. intermedia	9-Octadecenoic acid (2-phenyl-1,3-dioxolan-4-yl)methyl ester Trans4-(Anisylideneamino) cinnamic Acid Benzoic acid 2,6 bis[(trimethylsilyl)oxy]-, trimethylsilyl ester Oxazepam ditms D-Mannopyranose	Anti-inflammatory Anticancer Antifungal Antiviral Alopecia treatment Prostate disorders treatment	[28, 42, 66,

	Hydroquinone 1-phenylprophyl Trichloroacetic acid dodecyl ester l-(+)-Ascorbic acid 2,6- dihexadecanoate 8,11-Octadecadienoic acid methyl ester 9,12,15-Octadecatrienoic acid methyl ester, (Z,Z,Z)- 9,12-Octadecadienoic acid (Z,Z)- Benzofuran, 2,3-dihydro-2- methyl-5-phenyl- 3Beta,5-epoxy- α-homo-5betacholest-4-en-3alpha-ol Hexadecanoic acid, 1- (hydroxymethyl)-1,2-ethanediyl Ester	Antibacterial Anti-seborrheic Anti-eczematic Vaso-protector Antioxidant Anti-neoplastic Anti-hypoxic Anti-inflammatory Anti-protozoal	104, 105]
S. denticulata	Amentoflavone Cryptomerin B Hinokiflavone Isocryptomerin Robustaflavone Sotetsuflavone	Antibacterial Antioxidant Antiviral Anticancer	[29, 35]
S. selaginoides	Amentoflavone Hinokiflavone Robustaflavone	Antioxidant Antiviral	[35]
S. stauntoniana	Amentoflavone Chrysophanic acid Emodin Physcion	Antioxidant Antiviral Anticancer	[88, 106]

The antimetastatic activity of amentoflavone was also evaluated using B16F-10 melanoma-induced experimental lung metastasis in C57BL/6 mice. The treatment of amentoflavone efficiently decreased the formation of tumour nodule accompanied by reducing lung collagen hydroxyproline, hexosamine, and uronic acid levels [82]. The cytotoxic effect and apoptosis induction potential of hexane, methylene chloride, ethyl acetate and butanol extracts of *S. plana* was performed against MCF-7 cells. Different crude extracts of *S. plana* displayed inhibition of MCF-7 cells with IC_{50} value of 30 µg/mL, 19 µg/ml, 24 µg/ml and 2 µg/ml, respectively. Butanol crude extract was found as the highest cytotoxic and apoptotic induction against MCF-7 cancer cells [83]. The cytotoxic and apoptosis activity of three different crude extract (ethyl acetate, ethanol and aqueous) of *S. uncinata*, *S. tamariscina*, *S. remotifolia*, *S. delicatula*, *S. moellendorfii*, *S. pulvinata* and *S. labordei* were evaluated using Bel-7402, HT-29 and HeLa cells. In results, *S. labordei*, *S. tamariscina* and *S. uncinata* had higher inhibition of Bel-7402 and HeLa cells whereas, *S. moellendorfii* had moderate inhibition, but *S. remotifolia* and *S. pulvinata* had almost no inhibitory activities. The major bioactive compounds responsible for the inhibition for cancer cells were bioflavonoids, detected in the ethyl acetate extracts. Moreover, the efficacy of all three extracts of all the plants on cell inhibition and apoptosis were not same, they were highly efficient on HeLa cells than HT-29 cells [28]. Table 2 describes the complete list of bioactive compounds isolated from various species of *Selaginella* including its ethnopharmacological and ethnobotanical uses.

4. Conclusion

The present review represents the results of the ethnomedicinal, phytochemistry and biological activities on *Selaginella* species which have been carried out so far. Apart from 700 to 750 species distributed around the globe, few are reported as medicinally useful and very few of them are subjected to research on the phytochemistry and their biological aspects. The information gathered from the available literature, turn evident that the species of the genus *Selaginella* have pronounced pharmacological prospects. Though these species are merely evaluated, many of the species are still not explored for their pharmacology and phytochemistry. Therefore, there is a gap in the knowledge exists. Hence, more comprehensive studies into the pharmacological activities are needed. It was observed from the available literature, that many of the pharmacological explorations were not corresponded with the traditional uses of the plants. It is noticeable to spotlight that majority of cited traditional claims; for example, in the treatment of cardiovascular diseases were not evaluated pharmacologically. Majority of the studies related to the traditional uses that are further studied or advanced is about the antimicrobial, antiviral and anticancer activities. Moreover, large number of the studies were carried out with organic extracts. Therefore, for the proper validation of the uses of these plants, evaluation should be repeated with decoctions, infusions and aqueous extract, which is the form utilized by the tribal community. Additional research must also be needed with the use of latest technologies for the extraction and purification of the phytochemical compounds in the requisite quantity for in-depth evaluation of the pharmacological activities with their mode of action. Lastly, detailed studies concerning the toxicity are also essential to make sure about the safety of these medicinal lycophytes.

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