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Revisión | Review

Selaginellaceae: traditional use, phytochemistry and pharmacology

[Selaginellaceae: uso tradicional, fitoquímica y farmacología]

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Abstract: *Selaginella* is the only genus from Selaginellaceae, and it is considered a key factor in studying evolution. The family managed to survive the many biotic and abiotic pressures during the last 400 million years. The purpose of this review is to provide an up-to-date overview of Selaginella in order to recognize their potential and evaluate future research opportunities. Carbohydrates, pigments, steroids, phenolic derivatives, mainly flavonoids, and alkaloids are the main natural products in *Selaginella*. A wide spectrum of in vitro and in vivo pharmacological activities, some of them pointed out by folk medicine, has been reported. Future studies should afford valuable new data on better explore the biological potential of the flavonoid amentoflavone and their derivatives as chemical bioactive entities; develop studies about toxicity and, finally, concentrate efforts on elucidate mechanisms of action for biological properties already reported.

Keywords: *Selaginella*; Natural Products; Overview.

Resumen: *Selaginella* es el único género de Selaginellaceae, y se considera un factor clave en el estudio de la evolución. La familia logró sobrevivir a las muchas presiones bióticas y abióticas durante los últimos 400 millones de años. El propósito de esta revisión es proporcionar un resumen actualizado de *Selaginella* para reconocer su potencial y evaluar futuras oportunidades de investigación. Los hidratos de carbono, pigmentos, esteroides, derivados fenólicos, principalmente flavonoides, y alcaloides son los principales productos naturales en *Selaginella*. Se ha informado un amplio espectro de actividades farmacológicas in vitro e in vivo, algunas de ellas señaladas por la medicina popular. Los estudios futuros deberían proporcionar datos nuevos y valiosos para explorar mejor el potencial biológico de la amentoflavona flavonoide y sus derivados como entidades bioactivas químicas; desarrollar estudios sobre la toxicidad y, finalmente, concentrar los esfuerzos en dilucidar los mecanismos de acción para las propiedades biológicas ya informadas.

Palabras clave: *Selaginella*; Natural products; Revisión.

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INTRODUCTION

*Selaginella*ceae is a monogeneric family, which includes 700-750 species widely distributed around the globe (Tryon & Tryon, 1982). The genus *Selaginella* is widely distributed in America, Africa and Europe, east of the Bering Straits, from Kamchatka, Japan to New Guinea and Australia in the Pacific East, to the Hawaiian Islands, the Marquesas, Tahiti and Rapa. In America, *Selaginella* can be found from Northern Alaska East to Greenland, and in the South in Mendoza and Buenos Aires in Argentina (Tryon & Tryon, 1982). In Brazil, 46 species of this genus are registered, 16 of these endemic (Alston *et al*., 1981), and are widespread in Northeast, Southeast, South and Midwest regions which are comprised of phytogeographic areas of the Amazon, Caatinga, Cerrado and Atlantic Forest (Hirai, 2015).

*Selaginella*ceae appeared over 400 million years ago, during the Silurian period, dominating the ground flora from the Devonian Carboniferous through to the end of the Permian period (Martinez-Cortes *et al*., 2012). Therefore, the evolutionary peculiarities of *Selaginella*ceae have aroused the interest of botanists and paleontologists in order to understand the metabolic evolution of vascular plants. The species *Selaginella moellendorffii* has been fully sequenced and has a genome size of only ~100 Mbp, in this way, it is opening the horizons in the understanding of the mechanisms involved in the adaptation of this family that managed to survive the many biotic and abiotic pressures during these 400 million years (Banks, 2009). Therefore, *Selaginella* is considered a key point in studying evolution and demonstrates potential for the better understanding of several areas related to plant biology, for instance genome, molecular biology, phylogenetic, and biological activity, among others.

Phytochemical studies describe the occurrence of several metabolites' classes, among them, biflavonoids have been highlighted (Almeida *et al*., 2013). In Shen Nong Ben Cao Jing (The Divine Farmer's Materia Medica - 2737 B.C.) is reported the oldest documents of treatments based on the use of *Selaginella* species to treat inflammation, amenorrhea and abdominal protuberances in women (Yang & Flaws, 1998). Fourteen *Selaginella* species, among the almost 700 described so far, presented some available data in literature regarding the use in folk medicine. Aerial parts, as well the whole plant, is commonly ingested as tea, however scarce studies shown in detail how *Selaginella* is administered and quantitative ethnopharmacological studies are not reported so far. Meanwhile, there is no enough evidence for the statements regarding the popular use of *Selaginella* species. Studies about toxicity are scarce and nothing is known about the absorption of the active metabolites (bioavailability) or about the biotransformation.

In order to understand scientifically the use of *Selaginella* in folk medicine several reports about chemistry and pharmacological targets were developed as we attempt to discuss. Overall, a predominant number of studies were developed with extracts obtained with organic toxic solvents, like hexane and ethyl acetate, so it is not very likely to be useful for developing novel medicines. Taking into account that people supposedly use the plants mainly as a decoction in water the effect observed in popular medicine is difficult to associate with the results obtained in scientific studies on pharmacological targets reported so far. The lack of details about dosage and time of consuming by population is other point that impairs the link between the ethnopharmacological data and *in vitro/in vivo* studies. Finally, the available information does not contribute to an evidence-based traditional use therefore, there is not sufficient evidence to make *Selaginella* species source of a registered evidence-based drug. The future direction of the research should be developing a quantitative and statistically confident ethnopharmacological study in order to comprehend the basis and details in a no bias investigation aiming to afford start data of the medicinal potential of *Selaginella* in according to popular use.

Thus, the purpose of this review is to provide comprehensive information, providing an overview of the traditional uses, phytochemistry and pharmacology. In this way, these aspects will be identified for each *Selaginella* species in accordance to the data available in previous studies regarding popular use (Table No. 1), chemical data (Table No. 2) and pharmacological studies (Table No. 3).

Table No. 1
Metabolites from *Selaginella*.

SPECIES	PLANT PART	POPULAR USE	REFERENCES
S. bryopteris	AP	Gonorrhea, leucorrhoea, spermatorrhoea, diuretic, urinary inflammation and stomachache	Singh *et al*., 2005
S. convoluta	NI	Antidepressant, aphrodisiac, diuretic, amenorrhea, coughing, bleeding, increases female fertility, analgesic and inflammation	Sá *et al*., 2012a
S. doerderleinii	WP	Bactericide, anticancer, and cardiovascular diseases	Chao *et al*., 1987
S. involvens	NI	Hemostasis, anticancer, antibacterial, inflammation, antiviral and cardiovascular diseases	Chen *et al*., 2005
S. labordei	WP	Viral diseases (chronic hepatitis and hepatitis B), inflammation and anticancer	Chen *et al*., 2005 Xu *et al*., 2009
S. lepidophylla	NI	Treatment of digestive problems, eupeptic, cough, bronchitis and parasitic infections	Martínez, 1989 Aguilar *et al*., 2015
	WP	Urinary obstruction, cystitis, renal calculus, kidneys inflammation, and for waist and back pains	Ruiz-Bustos *et al*., 2009 Martínez, 1989
S. mollendorffii	NI	Jaundice, gonorrhea, bleeding and idiopathic thrombocytopenic purpura	Wang *et al*., 2009
	NI	Hepatitis	Zhu *et al*., 2008
	WP	Hematoma after contusion	Hong *et al*., 2015
S. nothohybrida	NI	Diuretic	Mickel & Valdespino, 1992
S. pallescens	NI	Gastrointestinal diseases	Rojas *et al*., 1999
S. pulvinata	NI	Anticancer, diabetes, stomachache and asthma	Zheng *et al*., 2007
	NI	Anticancer, cardiovascular and skin diseases	Cao *et.al*., 2010b
	NI	Dysmenorrhea, asthma and traumatic injury	Liu *et al*., 2014
S. sinensis	NI	Chronic tracheitis	Wang *et al*., 2007
	NI	Hepatitis, choledochitis and other pathological conditions with the effect of heat clearing and diuresis promoting	Dai *et al*., 2006
	NI	Antibacterial, inflammation, and hemostasis	Feng *et al*., 2009
S. tamariscina	NI	Inflammation, amenorrhea, dysmenorrhea, metrorrhagia, hematuria, prolapse of the anus, abdominal lumps in women, hepatitis and hyperglycemia	Yang & Flaws, 1998
	NI	Chronic tracheitis, thrombocytopenic purpura and anticancer	Zheng *et al*., 1998
	NI	Bloody constipation, haemoptysis, hepatitis, inflammation and burns	Yang *et al*., 2007
	WP	Hemafecia, epistaxis, metrorrhagia, traumatic injury, hepatitis, proctoptosis	Hong *et al*., 2015
S. uncinata	NI	Infectious diseases and anticancer	Ma *et al*., 2003

	NI	Jaundice, dysentery, edema, rheumatism and beriberoid diseases	Zheng *et al*., 2008 Zheng *et al*., 2011c
S. wildenowii	AP	Wounds, high fever and backache	Eswani *et al*., 2010
	NI	Gastric pains and infections of urinary tracts	Haji *et al*., 1992
	NI	Skin diseases, menstrual pains	Setyawan, 2009

AP: Aerial parts; NI: Not indicated; WP: Whole plant

Table Nº 2
Metabolites from Selaginella

Species	**Plant parts**	**Extract**	**Classification**	**Compounds**	**References**
S. adunca	WP	Petroleum ether	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. asperula	WP	Petroleum ether	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. bryopteris	WP	AcOEt	Flavonoid	Amentoflavone Hinokiflavone 2”,3”-Dihydrohinokiflavone 4’-O-Methylamentoflavone 7-O-Methylamentoflavone, 7-O-Methylhinokiflavone 2”,3”-Dihydroamentoflavone Tetrahydroamentoflavone Heveaflavone 2,3,2”,3”- tetrahydroamentoflavone 2,3,2”,3”-Tetrahydrohinokiflavone 2,3-Dihydroamentoflavone 2,3-Dihydrohinokiflavone 7,4’,4’”-trimethylated amentoflavone	Kunert *et al*., 2008
	WP	AcOEt	Biflavonoid	2’’,3’’-dihydrohinokiflavon	Kunert *et al*., 2008
	WP	Acetone	Flavonoid	Amentoflavone heveaflavone	Verma *et al*., 2015
			Glucoside	β-sitosterol β-sitosterol β-D-glucoside	
			Lignan	(+)-syringaresinol	
			Phenolic compound	Vanillic acid	
S. braunii	WP	EtOH	Flavonoid	Amentoflavone	Ma *et al*., 2001
S. doederleinii	NI	EtOH	Biflavonoid	Amentoflavone Robustaflavone Hinokiflavone	Wang *et al*., 2015b
	NI	MeOH	Flavonoid	Amentoflavone 7,7”-Di-*O*-methyl-amentoflavone 7,4',7",4"-tetra-*O*-methylamentoflavone	Lin *et al*., 1994

				heveaflavone	
		AcOEt	Lignan	(-)-Lirioresinol A (-)-Lirioresinol B (+)-Matairesinol (-)-Nortracheloside (+)-Wilkstromol	
		AcOEt	Phenylpropanoid	3-Hydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-propan-1-one 3-Hydroxy-1-(3-methoxy-4-hydroxyphenyl)-propan-1-one	
	WP	Acetone	Flavonoid	Amentoflavone heveaflavone	Verma *et al*., 2015
			Glucoside	β-sitosterol β-sitosterol β-D-glucoside	
			Lignan	(+)-syringaresinol	
			Phenolic compound	Vanillic acid	
S. braunii	WP	EtOH	Flavonoid	Amentoflavone	Ma *et al*., 2001
S. doederleinii	NI	EtOH	Biflavonoid	Amentoflavone Robustaflavone Hinokiflavone	Wang *et al*., 2015b
	NI	MeOH	Flavonoid	Amentoflavone 7,7”-Di-*O*-methyl-amentoflavone 7,4',7",4"-tetra-*O*-methylamentoflavone heveaflavone	Lin *et al*., 1994
		AcOEt	Lignan	(-)-Lirioresinol A (-)-Lirioresinol B (+)-Matairesinol (-)-Nortracheloside (+)-Wilkstromol	
	NI	$CHCl_3$-MeOH	Steroid	22-Dehydrocampesterol 24α-Ethyl-cholest-5-en-3β-ol 24α-Ethyl-cholesta-5,22-dien-3β-ol. 24α-Methyl-cholest-5-en-3β-ol 24β-Methyl-cholest-5-en-3β-ol Cholesterol	Chiu *et al*., 1988
	NI	AcOEt	Flavonoid	2”,3”-dihydro-3’,3”-biapigenin 3’,3’”-binaringenin 7,4’,7”,4’’’-tetra-O-methyl-amentoflavone Amentoflavone heveaflavone Robustaflavone	Li *et al*., 2014
	WP	n-BuOH	Alkaloid	Hordenine-[6-*O*-(4-hydroxy-cinnamoyl)-β-*D*-glucosyl]-(1,3)-α-*L*-rhamnoside	Chao *et al*., 1990

	WP	MeOH	Flavonoid	4'-Methylether-robustaflavone 2,2",3,3"-Tetrahydrorobustaflavone 7,4',7"-Trimethyl ether Robustaflavone 7,4',7"-Trimethyl ether	Lee *et al*., 2008
S. davidii	AP	EtOH	Flavonoid	Amentoflavone	Ma *et al*., 2001
S. delicatula	AP	$CHCl_3$-MeOH	Flavonoid	2″,3″-dihydrorobustaflavone 7,4′, 7″-trimethyl ether 2″,3″-dihydrorobustaflavone 7,4′, -dimethyl ether Amentoflavone Robustaflavone Robustaflavone 4′-methyl ether Robustaflavone 7,4′-dimethyl ether	Lin *et al*., 2000
	AP	$CHCl_3$-MeOH	Phenolic acid	3,5-di-O-caffeoylquinic acid 3,4-di-O-caffeoylquinic acid 4,5-di-O-caffeoylquinic acid	Lin *et al*., 2000
	AP	MeOH	Flavonoid	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 2",3"-dihydroisocryptomerin 7-methyl ether	Chen *et al*., 2005
	NI	EtOH–H_2O	Flavonoid	7,4',7",4'"-tetra-O-methylamentoflavone 7,7"-di-O-methylamentoflavone Amentoflavone Heaveaflavone	Yang *et al*., 2011
	NI	EtOH–H_2O	Anthraquinones	Aloe-emodin Chrysophanol Chrysophanol-8-O-β-D-glucopyranoside Emodin-8-O-β-D-glucopyranoside Physcion-8-O-β-D-glucopyranoside	Yang *et al*., 2011
	WP	$CHCl_3$-MeOH	Steroid	Cholesterol 22-Dehydrocampesterol 24α-Ethyl-cholest-5-en-3β-ol 24β-Methyl-cholest-5-en-3β-ol 24α-Ethyl-cholesta-5,22-dien-3β-ol	Chiu *et al*., 1988
S. denticulata	AP	MeOH	Flavonoid	Amentoflavone Cryptomerin B Hinokiflavone Isocryptomerin Robustaflavone Sotetsuflavone	Lopez-Saez *et al*., 1994a Lopez-Saez *et al*., 1995

	WP	$CHCl_3$	Biflavonoid	7,4',7",4"'-tetra- O-methylamentoflavone	Lopez-Saez *et al*., 1994a Lopez-Saez *et al*., 1995
S. difusa	WP	$CHCl_3$-MeOH	Flavonoid	Chamaecyparin	Meurer-Grimes *et al*., 1999
S. epirrhizos	WP	EtOH – H_2O	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. galeotii	WP	EtOH – H_2O	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. geniculata	WP	EtOH – H_2O	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. involvens	WP	EtOH	Diterpenoid	(8R,8'S)-4,4',8-trihy-droxyl-3,3'-dimethoxyl-9'-lignanolide 3ß,12,16-trihydroxy-6,8,11,13-abietatrien 4,4'-dihydroxyl-3,3',5,5' Dimethoxyldiphenyl diketone	Long *et al*., 2014
	WP	EtOH	Favonoid	Involvenflavones A Involvenflavones B Involvenflavones C Involvenflavones D Involvenflavones E Involvenflavones F	Long *et al*., 2015
S. jungermannioides	WP	$CHCl_3$-MeOH	Flavonoid	Chamaecyparin	Meurer-Grimes *et al*., 1999
S. kraussiana	WP	Petroleum ether	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. labordei	WP	AcOEt	Flavonoid	2,3-Dihydro-5,5",7,7",4'-pentahydroxy-6,6"-dimethyl-[3'-*O*-4"']-biflavone 2",3"-dihydro-3',3"'-biapigenin 2",3"-Dihydro-3',3"'-biapigenin 2",3"-Dihydroochnaflavone	Xu *et al*., 2009
	WP	AcOEt	Flavonoid	4'-methylether robustaflavone Amentoflavone Eriodictyol Robustaflavone	Tan *et al*., 2009b
S. lepidophylla	AP	MeOH	Secolignan	3-methylenhydroxy-5-methoxy-2,4-dihydroxy tetrahydrofurane	Perez *et al*., 1994
	WP	$CHCl_3$-MeOH	Flavonoid	2,3-Dihydro-robustaflavone 2,3-dihydrorobustaflavone-5-methyl ether Robustaflavone	Aguilar *et al*., 2008
S. marginata	WP	Petroleum ether	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. moellendorfii	AP	MeOH	Dihydroflavone	5-carboxymethyl-7,4'-dihydroxyflavonone,	Wang *et al*., 2011
			Dihydroflavone glucoside	5-carboxymethyl-7,4'-dihydroxyflavonone-7-O-β-D-	

			glucopyranoside	
	AP	MeOH	Monoterpene Glucoside	(4Z,6E)-2,7-dimethyl-8-hydroxyocta-4,6-dienoic acid 8-O-β-D-glucopyranoside	
	WP	EtOH	Biflavone	7,4′,7″,4‴-tetramethyl ether Amentoflavone Kayaflavone Podocarpusflavone A	Sun *et al*., 1997
	WP	MeOH	Alkaloid	5-Hydroxy-N8, N8-dimethylpseudophrynaminol 5-Hydroxyselaginellic acid *N*-(5-Hydroxyneoselaginelloyl)-*L*-phenylalanine *N*-(5-Hydroxyselaginelloyl) -*L*-phenylalanine Neoselaginellic acid N-Neoselaginelloyl-L-phenylalanine Selaginellic acid	Wang *et al*., 2009
	WP	EtOH	Flavonoid	Chrysoeriol Amentoflavone-7,4,7,4-tetramethylether 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 kayaflavone Ginkgetin Isoginkgetin Bilobetin Robustaflavone 4′-methyl ether Podocarpusflavone A Hinokiflavone Amentoflavone	Cao *et al*., 2010c
	WP	AcOEt	Alkaloid	Adenosine Uridine	Feng *et al*., 2011
	WP	n-BuOH	Alkaloid	2,3,4,9-tetrahydro-1H-pyrido [3, 4-b] indole-3-carboxylic acid	
	WP	AcOEt	Flavonoid	Apigenin-7-*O*-β-neohesperidoside	
	WP	n-BuOH	Flavonoid	Apigenin-8-*C*- β-*D*-glucopyranoside	
	WP	Ether	Flavonoid	Amentoflavone Hinokiflavone	
	WP	n-BuOH	Lignan	Moellenoside B Lariciresinol	

WP	n-BuOH	Phenolic acid	Vanillic acid	
WP	MeOH-H_2O	Caffeoyl derivatives	Myo-inositol 1-caffeate Myo-inositol 6-caffeate Myo-inositol 5-caffeate Paucine 3'-b- d -glucopyranoside	Wang *et al*., 2010
WP	MeOH	Neolignan	(7S,8R)-4,9-dihydroxy-3,3',5-trimethoxy-4',7-epoxy-8,5'-neolignan-9'-oic acid methyl ester) *rel*-(7R,7'E,8S)-4,9-dihydroxy-3,3',5-trimethoxy-4',7-epoxy-8,5'-neolign-7'-en-9'-oic acid) (7S,8R)-4,9-dihydroxy-4',7-epoxy-8',9'-dinor-8,5'-neolignan-7'-oic acid) (7S,8R)-3,3',5-trimethoxy-4',7-epoxy-8,5'-neolignan-4,9,9'-triol) *rel*-(7R,8S)-3,3',5-trimethoxy-4',7-epoxy-8,5'-neolignan-4,9,9'-triol 4-β- d -glucopyranoside) *rel*-(7R,8S)-3,3',5-trimethoxy-4',7-epoxy-8,5'-neolignan-4,9,9'-triol 9-β- d -glucopyranoside) 3,3',5-trimethoxy-4',7-epoxy-8,5'-neolign-7-ene-4,9,9'-triol 9-β- d -glucopyranoside) 3,3',5,5'-tetramethoxy-8,4'-oxyneolignane-4,9,9'-triol 4-β- d -glucopyranoside)	Wang *et al*., 2010
WP	BuOH	Flavonoid	7-O-(β-glucopyranosyl(1→2)-[β-glucopyranosyl(1→6)]-β-glucopyranosyl) flavone-3',4',5,7-tetraol 7-O-(β-glucopyranosyl (1→2)-[b-glucopyranosyl (1→6)]-β-glucopyranosyl) flavone-4',5,7-triol	Wu & Wang, 2011
WP	AcOEt	Flavonoid	2,3-dihydroflavone-5,7,4'-triol-(3'→8'')-flavone-5'',6'',7'',4'''-tetraol 6-methylflavone-5,7,4'-triol-(3'→O→4''')-6''-methylflavone-5'',7''-diol	Wu & Wang, 2011
WP	AcOEt	Lignan	(7'E)-3,5,3',5'-tetramethoxy-8 :4'-oxyneolign-7'-ene-4,9,9'-triol 3,3'-dimethoxylign-8'-ene-4,4',9-triol 2-{4-[(1*E*)-3-hydroxyprop-1-en-1-yl]-2,6-dimethoxyphenoxy} propane-1,3-diol	Wu & Wang, 2011

	WP	AcOEt	Flavonoid	2,3-dihydroamentoflavone 2,3-dihydroochnaflavone Amentoflavone Ochnaflavone	Wu & Wang, 2011
	WP	AcOEt	Lignan	(7'E)-3,3',5'-trimethoxy-8 :4'-oxyneolign-7'-ene-4,7,9,9'-tetraol (7'E)-3,5,3',5'-tetramethoxy-8 :4'-oxyneolign-7'-ene-4,7,9,9'-tetraol Secoisolariciresinol Guaiacylglycerol	Wu & Wang, 2011
	WP	BuOH	Lignan	Picraquassioside C	Wu & Wang, 2011
	WP	Acetone	Lignan	Moellenoside A	Zheng *et al*., 2008
	WP	n-BuOH	Flavonoid	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 5-Carboxymethyl-4'-hydroxyflavone-7-*O*-β-*D*-glucopyranoside	Zhu *et al*., 2008
S. martensii	LE	*NI	Carbohydrate	2-Carboxy-arabinitol	Moore *et al*., 1993
S. nothohybrida	NI	AcOEt	Flavonoid	Amentoflavone Robustaflavone (S)-2,3-dihydrorobustaflavone	Aguilar *et al*., 2015
	NI	AcOEt	Carbohydrate	Trehalose	
S. pulvinata	AP	MeOH	Pigments	Selaginellin Selaginellin A Selaginellin C	Tan *et al*., 2009a
	AP	NI	Steroid	3β-16α-Dihydroxy-(5α)-cholestan-21-oic acid	Zheng *et al*., 2007
	WP	AcOEt	Pigments	Selaginellin B Selaginellin D Selaginellin E Selaginellin F	Cao *et al*., 2010b
	WP	AcOEt	Pigments	Selaginellin G Selaginellin H	Cao *et al*., 2010c
	WP	NI	Pigments	Selaginellin N Selaginpulvilins A Selaginpulvilins B Selaginpulvilins C Selaginpulvilins D	Liu *et al*., 2014
S. parkeri	WP	Petroleum ether	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. plumosa	WP	Petroleum ether	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. rupestris	AP	Petroleum ether	Flavonoid	Amentoflavone	Chanravarthy *et al*., 1981

S. sanguinolenta	WP	Petroleum ether	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. selaginoides	AP	MeOH	Flavonoid	Amentoflavone Hinokiflavone Robustaflavone	Lopez-Saez *et al*., 1994b
S. sellowii	WP	MeOH	Flavonoid	Amentoflavone Robustaflavone	Rizk *et al*., 2014
S. sinensis	AP	EtOH	Flavonoid	Amentoflavone Robustaflavone Selaginoside	Dai *et al*., 2006
	NI	AcOEt	Flavonoid	Quercetin Apigenin Amentoflavone Robustaflavone 2,3-dihydroamentaflavone Hinokiflavone 4-O-methyl-robustaflavone Ginkgetin	Zhang *et al*., 2011
	WP	Acetone	Pigments	Selaginellin	Zhang *et al*., 2007
	WP	Aq. Acetone	Flavonoid	Quercetin Quercetin 2, 3-dihydroamentoflavone	Chen *et al*., 2014
	WP	Aq. Acetone	Lignan	Sinensioside A Syringaresinol-4-O-E-D-glucopyranoside (+) -medioresinol-4-O-E-D-glucopyranoside Pinoresinol-4, 4'-di-O-E-D-glucopyranoside	
	WP	Aq. Acetone	Lignan	Lariciresinol Syringing Lariciresinol-4-O-β-D-glucopyranoside Matairesinol-4,4'-di-O-β-D-glucopyranoside Styraxlignolide D	Feng *et al*., 2009
	WP	Aq. Acetone	Phenolic compound	Neolloydosin	
	WP	Aq. Acetone	Secolignan	3,4-trans-3-hydroxymethyl-4-[bis (4-hydroxyphenyl) methyl]-butyrolactone	
				2,3-trans-3,4-trans-2-methoxy-3-hydroxymethyl-4-[bis(4-hydroxyphenyl)methyl]tetrahydrofuran	
	WP	AcOEt	Lignan	Sinensiol A	Wang *et al*., 2007
	WP	EtOH	Favonoid	2,3-dihydroamentoflavone Hinokiflavone	Dai *et al*., 2006

	WP	EtOH	Favonoid	4',7"-di-O-methylamentoflavone 7"-O-methylrobustaflavone robustaflavone	Ma *et al*., 2001
	WP	MeOH	Flavonoid	2, 3- dihydroamentoflavone	
	WP	MeOH	Flavonoid	4',7"-Di-*O*-methyl-amentoflavone 7''-*O*-Methyl-robustaflavone	Dai *et al*., 2006
S. stellata	WP	Petroleum ether	Carbohydrate	Selaginose	Fischer & Kandler, 1975
	WP	*NI	Flavonoid	Chamaecyparin	Meurer-Grimes *et al*., 1999
	AP	EtOH	Flavonoid	Robustaflavone	Ma *et al*., 2001
S. stauntoniana	AP	EtOH	Flavonoid	Amentoflavone	Ma *et al*., 2001
	WP	Acetone	Coumarin	Umbelliferone	Feng *et al*., 2011
	WP	Acetone	Flavonoid	Bilobetin Quercetin-3-O-α-L-rhamnopyranoside Kaempferol-3-O-α-L-rhamnopyranoside Amentoflavone 2, 3-dihydroamentoflavone Apigenin- 6,8-di-C-β-D-glucopyranoside	Feng *et al*., 2011
	WP	Acetone	Phenolic acid	Isovanillic acid *p*-hydroxybenzoic acid 3,4,5-trimethoxyphenol Vanillic acid *p*-hydroxyphenol 3,4,5-trimethoxybenzoic acid Hydroferulic acid hydrocaffeic acid *p*-hydroxy phenylethanol	Feng *et al*., 2011
	WP	Acetone	Quinoid	2-methoxyhydroquinone	Feng *et al*., 2011
S. sulcata	WP	Petroleum ether	Carbohydrate	Selaginose	Fischer & Kandler, 1975
S. tamariscina	*NI	*NI	Flavonoid	Amentoflavone	Lee *et al*., 1992
	AP	AcOEt	Flavonoid	2',8"-Biapigenin 2',8"-Biapigenin Amentoflavone Cupressuflavone Robustaflavone Taiwaniaflavone	Nguyen *et al*., 2015a
	AP	AcOEt	Phenolic derivative	Selariscinin D Selariscinin E	Nguyen *et al*., 2015b
	AP	MeOH		Selariscinin A Selariscinin B Selariscinin C	Nguyen *et al*., 2015b
	AP	EtOH	Flavonoid	6-(2-Hydroxy-5-acetylphenyl)-apigenin	Liu *et al*., 2009

AP	EtOH	Coumarin	3-(4-Hydroxyphenyl)-6,7-dihydroxy coumarin	Liu *et al*., 2010
NI	EtOH	Anthraquinone	1-methoxy-3-methylanthraquinone	Liu *et al*., 2010
NI	EtOH	Flavonoid	6-(2-hydroxy-5-carboxyphenyl)-apigenin amentoflavone heptadecanoic acid heveaflavone β-sitosterol	Liu *et al*., 2010
NI	H_2O	Benzenoid	Syringic acid	Bi *et al*., 2004
		Coumarin	Umbelliferone	
		Lignan	Syringaresinol	
		Phenolic derivative	(2R,3S)-dihydro-2- (3',5'-dimethoxy-4'-hydroxyphenyl)-7-methoxy-5-acetyl-benzofuran 1-(4'-hydroxyl-3'-methoxyphenyl) glycerol Caffeic acid Ferulic acid Tamariscine ester A Vanillic acid	
WP	MeOH	Sterols	Ergosterol endoperoxide 7β-hydroxycholesterol 7β-hydroxysitosterol 7α-hydroxysitosterol Ergosta-4, 6, 8(14), 22-tet-raene-3-one (4α, 5α) -4, 14-dimethylcholest-8-en-3-one	Roh *et al*., 2010
WP	MeOH	Flavonoid	Isocryptomerin	Lee *et al*., 2009a
WP	MeOH	Flavonoid	2',8"-Biapigenin Amentoflavone Robustaflavone Sumaflavone Sumaflavone Taiwaniaflavone	Lee *et al*., 2008
WP	$CHCl_3$	Sterols	3beta-(3-hydroxybutyroxy)-16alpha-hydroxy-5alpha,17beta-cholestan-21-carboxylic acid	Gao *et al*., 2007
			3beta,16alpha-dihydroxy-5alpha,17beta-cholestan-21-carboxylic acid	
			3beta-acetoxy-16alpha-hydroxy-5alpha,17beta-cholestan-21-carboxylic acid	
WP	EtOH	Pigments	Selaginellin A Selaginellin B	Cheng *et al*., 2008
WP	EtOH	Pigments	Selaginellin I Selaginellin J	Xu *et al*., 2011
WP	MeOH	Pigments	Selaginellin K	Xu *et al*., 2011

				Selaginellin L	
	WP	EtOH	Pigments	Selaginellin M Selaginellin N	Zhang *et al*., 2012a
	WP	EtOH	Flavonoid	7″-O-methylamentoflavone Hinokiflavone Neocryptomerin Pulvinatabiflavone	Zhang *et al*., 2012a
	WP	EtOH	Pigment	Selaginellin	Yang *et al*., 2012
	WP	MeOH	Pigment	Selaginellin O	Yang *et al*., 2012
S. uncinata	AP	EtOH	Flavonoid	6-(5-Carboxyl-2-methoxyphenyl)-apigenin	Zheng *et al*., 2008
	WP	$CHCl_3$	Chromone	8-Methyl-eugenitol Uncinoside A Uncinoside B	Ma *et al*., 2003
	WP	EtOH	Flavonoid	Unciflavones A Unciflavones B Unciflavones C Unciflavones D Unciflavones E Unciflavones F	Zou *et al*., 2014
	WP	$CHCl_3$	Flavonoid	Amentoflavone Hinokiflavone	Ma *et al*., 2003
	WP	EtOH	Flavonoid	(2"S)- 2",3"-dihydrorobustaflavone (2"S)-2",3"-dihydroamentoflavone (2"S)-2",3"-dihydrorobustaflavone 4'-methyl ether (2S)-2,3-dihydrorobustaflavone (2S,2"S)-2,3,2",3"-tetrarobustaflavone 2",3"-dihydroisocryptomerin 2,3-dihydroisocryptomerin 6-(5-acetyl-2-methoxyphenyl)-apigenin Amentoflavone Cirsimaririn Psathyrotin Robustaflavone Robustaflavone 4'-methyl ether Uncinataflavone	Zou *et al*., 2013
	WP	EtOH	Pigments	Selaginellin	Zou *et al*., 2013
	WP	EtOH	Flavonoid	(2″S)-2″,3″-dihydroamentoflavone (2″S)-2″,3″-dihydroamentoflavone-4′-methyl ether (2S)-2,3- dihydroamentoflavone-4′-methyl ether (2S)-2,3-dihydroamentoflavone (2S,2″S)-2,3,2″,3″-tetrahydroamento-flavone-4′-methyl ether	Zheng *et al*., 2011a

				(2S,2″S)-tetrahydroamentoflavone Amentoflavone	
	WP	EtOH	Flavonoid	(2S, 2"S)-tetrahydrorobustaflavone Robustaflavone Robustaflavone 4'-methyl ether (2S,2"S)-2,3,2",3"-tetrahydrorobustaflavone-4"'-methyl ether (2S,2"S)-2,3,2",3"-tetrahydrorobustaflavone-4'-methyl ether (2S,2"S)-2,3,2",3"-tetrahydrorobustaflavone-7"-methyl ether (2S)-2,3-dihydrorobustaflavone-4'-methyl ether	Zheng *et al*., 2008
	WP	EtOH	Saponin	(3β, 7β, 12β, 25R)-spirost-5-ene-3, 7, 12-triol-3-O-α-L-rhamnopyranosyl-(1 → 2)-O-[α-L-rhamnopyranosyl-(1 → 4)]-O-β-D-glucopyranoside	Zheng *et al*., 2013a
				(2α, 3β, 12β, 25R)-spirost-5-ene-2, 3, 12-triol-3-O-α-L-rhamnopyranosyl-(1 → 2)-O-[α-L-rhamnopyranosyl- (1 → 4)] -O-β-D-glucopyranoside	
				(3β, 12β,25R)-spirost-5-ene-3,12-diol-3-O-α-L-rhamnopyranosyl-(1 → 2)-O-[α-L-rhamnopyranosyl-(1 → 4)]-O-β-D-glucopyranoside	
				(1α, 3β, 25R)-spirost-5-ene-2-diol-3-O-α-L-rhamnopyranosyl-(1 → 2)-O-[α-L-rhamnopyranosyl(1 → 4)]-O-β-D-glucopyranoside	
S. willdenowii	LE	MeOH	Flavonoid	2",3"-Dihydro-isocryptomerin 4',7"-Di-*O*-methyl-amentoflavone 7''-*O*-Methyl-robustaflavone Amentoflavone Bilobetin,7"-O-methylrobustaflavone Isocryptomerin Robustaflavone	Silva *et al*., 1995

NI: Not indicated; WP: Whole plant; LE: Leaves

Table No. 3
Pharmacological potential of *Selaginella*

Species	Plant parts	Pharmacological activity	Extract/ isolated metabolites	Details	Reference
S. bryopteris	NI	Antiprotozoal	AcOEt fraction	*In vitro* assay. *Trypanosoma brucei rhodesiense* (IC_{50} = 12.4 µg/ml, *Trypanosoma cruzi* (IC_{50} = 20.5 µg/ml), *Leishmania donovani* (axenic amastigotes assay, IC_{50} = 9.3 µg/ml), *Plasmodium falciparum* (K1 strain, IC_{50} = 1.0 µg/ml) and cytotoxicity evaluated in L-6 cell lineage.	Kunert *et al*., 2008
	NI	Antiprotozoal	2,3-dihydrohinokiflavone	*In vitro* assay. IC_{50} 1.6 µM against *Leishmania*, IC_{50}> 12.5 mg/ml against *Trypanosoma* spp.	Kunert *et al*., 2008
	NI	Cytoprotective	Benzene fraction	Cytoprotective effect up to 95%.	Mishra *et al*., 2012
	NI	Antioxidant	Benzene fraction	*In vitro* assay. It was observed a significant antioxidant potential ($p \leq 0.001$), once unaltered enzyme activity throughout the time-course in the HEK-293 cells previously treated with the benzene fraction.	Mishra *et al*., 2012
	NI	Anti-inflammatory	Benzene fraction	*In vitro* assay. The benzene fraction-pretreated cells did not show a marked increase of inflammatory cytokines (IL-8, IFN- γ, TNF, IL-1β, IL-6, IL-12 p70 in HEK-293 cells) when compared with the controls suggesting a potent anti-inflammatory activity.	Mishra *et al*., 2012
	NI	Anticarcinogenic	Benzene fraction	*In vivo* assay. Oral administration of the benzene fraction has chemopreventive effects against benzo[a]pyrene in Swiss albino mice,	Mishra *et al*., 2012

			producing significant reductions in lung adenoma incidence.	
NI	Genoprotective	Benzene fraction	*In vitro* assay. It was realized immunofluorescence analysis of histone protein on serine 139 (H2AX) phosphorylation. The results showed that 10X concentration of the benzene fraction failed to form foci in cells pretreated, indicating its protective action against the formation of DNA double-stranded breaks.	Mishra *et al*., 2012
WP	Antibacterial Antifungal	Acetone extract	*In vitro* assay. Zone of inhibition 13.13 ± 0.40 against *K. pneumoniae*; 12.70 ± 0.20 against *S. aureus*; 12.33 ± 0.20 against *Candida krusei*.	Verma *et al*., 2015
WP	Antifungal	β-sitosterol	*In vitro* assay. Zone of inhibition: *C. albicans* 10.33 ± 0.20, *C. krusei* 9.60 ± 0.43. MIC was 0.312 mg/ml to both strains.	Verma *et al*., 2015
WP	Antibacterial Antifungal	Vanillic acid	*In vitro* assay. Zone of inhibition: *E. coli* 10.26 ±0.32, *S. aureus* 10.63 ± 0.25, *K. pneumoniae* 09.46 ± 0.40, *C. albicans* 09.63 ± 0.58, *C. tropicalis* 08.83 ± 0.41, *C. krusei* 09.66 ± 0.40. MIC was 0.312 to all bacterial and fungal tested strains.	Verma *et al*., 2015
WP	Antibacterial Antifungal	B-sitosterol β-D-glucoside	*In vitro* assay. Zone of inhibition: *E. coli* 11.76 ± 0.35, *C. albicans* 09.80 ± 0.45, *C. tropicalis* 09.50 ± 0.17, *C. krusei* 08.76 ± 0.61. MIC: 0.625 mg/ml *E. coli* and *C. krusei*, 0.312 mg/ml *C. albicans* and *C. tropicalis.*	Verma *et al*., 2015

S. convoluta	WP	Antinociceptive	Ethanolic extract	*In vivo* assay. Ethanolic extract (100, 200 and 400 mg/kg) was effective as an analgesic agent in various pain models, using adult male albino Swiss mice.	Sá *et al*., 2012a
	WP	Antioxidant	Ethanolic extract Ethyl acetate fraction	*In vitro* assay. Ethanolic extract showed antioxidant activity, with IC_{50} 47.06 ± 5.50 µg/ml and AcOEt showed IC_{50} = 69.49 ± 9.04 µg/ml.	Sá *et al*., 2012b
S. delicatula	LE	Cytotoxic	Robustaflavone 4′,4”’-dimethyl ether 2,3-dihydroamentoflavone 7,4’dimethyl ether α-tocopheryl quinone	I*n vitro* assay. Cytotoxic activity against P-388 and/or HT-29 cell lines (ED_{50} < 4 µg/ml).	Chen *et al*., 2005
	WP	Cytotoxic	Robustaflavone 4′-methyl ether 2″,3″-Dihydrorobustaflavone 7,4′-dimethyl ether	I*n vitro* assay. These flavones derivatives exhibited cytotoxic activities against Raji and Calu-1 tumor cell lines at 100 µM.	Lin *et al*., 2000
	WP	Neuroprotective	Aqueous extract	*Drosophila melanogaster* as a model of several neurodegenerative diseases and the aqueous extract exhibited multiple antioxidant activity.	Girish, 2012
S. doederleinii	NI	Antioxidant Cytotoxic	Essential oil	*In vitro assay*. Essential oil suppressed the oxidative activity and proliferation of cancer cells with correlation coefficients between antioxidant and cytotoxic capacities varied from 0.71 to 0.94.	Wang *et al*., 2015a
	WP	Cytotoxic	Ethyl acetate extract	*In vitro* assay. Cytotoxic potential against tumor cells: DU145, HepG2, HeLa, A549, and PC12 - by MTT method. At 25 to 200 μg/mL - cell populations in late apoptotic phases increased from 5.76% to 14.29%, compared with 2.8% of apoptotic cells in the control.	Wang *et al*., 2015b

	WP	Cytotoxic	Ethanolic extract	*In vitro assay*. Ethanolic extract showed inhibitory effects against nasopharyngeal carcinoma cells. The inhibitory effects were observed at 2.5 g/ml and 1.25 g/ml for the cells of the lineage CNE-1 and an inhibitory effect was observed at 2.5 g/ml for C666-1 lineage.	Lian *et al.*, 2013
	WP	Cytotoxic	Total Biflavonoids Extract	*In vitro and in vivo assay*. The total biflavonoids extracts from pointed out interesting anticancer properties by MTT assay and xenograft model of mouse lewis lung câncer (LLC) in male C57BL/6 mice.	Yao *et al.*, 2017
S. inaequalifolia	LE	Antibacterial	Petroleum ether Benzene Methanol and Aqueous extracts	*In vitro* assay. Inhibition zones in agar diffusion method: 11-12 mm to *E. coli* and 9-10 mm to *Pseudomonas* sp. - petroleum ether extract; 11-13 mm to *E. coli* and 6.5-11 mm to *Pseudomonas* sp. - benzene extract; 11-13 mm to *E. coli* and 7-10 mm and 8-11 mm to *Pseudomonas* sp. - methanolic and aqueous extracts.	Duraiswamy *et al.*, 2010
	WP	Antibacterial antifungal	Petroleum ether	*In vitro* assay. Inhibition zone in agar diffusion method: 26 mm to *S. aureus*, 22 mm to *E. coli* and 45 mm to *C. albicans*	Irudayaraj *et al.*, 2010
S. involvens	LE	Antibacterial	Extract ethanol	*In vitro* assay. The inhibition of *Ropionibacterium acne* was observed in doses greater than 100μg/ml and complete inhibition at the dose of 250-500 μg/ml.	Joo *et al*., 2008
	LE	Antibacterial	Petroleum ether Benzene Methanol and Aqueous extracts	*In vitro* assay. Zones of inhibition in agar diffusion method: 12-13 mm petroleum ether extract; 8-	Duraiswamy *et al.*, 2010.

				11 mm benzene extracts; 11-13 mm methanol extract; 10-12 mm aqueous extract to *E. coli* and 10-13 mm petroleum ether extract; 6.5-9 mm benzene extract; 6.5-9 mm methanol extract; 10-12 mm aqueous extract to *Pseudomonas* sp.	
	WP	Protection against injury of vein endothelial cell	Involvenflavones A–F	Potent effect against the injury of human umbilical vein endothelial cell induced by high concentrations of glucose *in vitro.*	Long *et al*., 2015.
S. labordei	WP	Antioxidant	Petroleum ether extract	*In vitro* assay. The extract showed COX-2 mRNA inhibition at a dose-dependent of 6 μg/ml and 35-fold at 9 μg/ml 6h after treatment.	Chen *et al*., 2005
S. lepidophylla	WP	Inhibitory activity on smooth muscle	3-methylenhydroxy-5-methoxy-2,4-dihydroxy tetrahydrofurane	*In vivo* assay. Inhibitory activity only on the rat uterus at 40 mg/ml.	Pérez *et al*., 1994
	WP	Hepatoprotective	Alcoholic and Aqueous extracts	*In vivo* assay. At the concentration of 500 mg/kg of aqueous and alcoholic extracts showed exhibited significant hepatoprotective activity against CCl4 and hepatic toxicity induced by paracetamol in rats.	Tiwari *et al*., 2014
	WP	Lithiasis protective effect	Chloroform extract	*In vivo* assay. At 50 mg/kg it was observed a recovery in urinary flow rate, glomerular filtration rate and renal tubular secretion, thus preventing the damage caused by lithium, improving the active secretion in tubular proximal.	Mirian *et al*., 2013
	WP	Antibacterial	Methanolic extract	*In vitro* assay. The methanolic extract showed an antimicrobial activity for *H. pylori* of broad spectrum with MIC_{50} at 400 μg/ml.	Robles-Zepeda *et al*., 2011

	WP	Antifungal	Methanolic extract	*In vitro* assay. This extract exhibited antifungal activity against *F. verticillioides* with growth inhibition of 19.5%.	Ruiz-Bustos *et al*., 2009
S. moellendorffii	WP	Anti-HBV	Ethyl ester Butyl ester	*In vitro* assay. These metabolites exhibited inhibitory potency to the secretion of HBsAg and HBeAg. HBsAg: IC_{50} values of 0.17 mg/ml and 0.46 mg/ml; HBeAg: IC_{50} values of 0.42 mg/ml and 0.42 mg/ml, respectively.	Cao *et al*., 2010c
	WP	Cytotoxic	Ginkgetin (1) Isoginkgetin (2) Robustaflavone 4′-methyl ether (3) Hinokiflavone (4)	*In vitro* assay. (3) IC_{50}: 5.398 µg/mL - non-small cell lung cancer (A549); (4) IC_{50}: 1.024 µg/ml - stomach adenocarcinoma (BGC-823); (1) $IC_{50:}$5.001 µg/ml, (2) $IC_{50:}$ 6.077 µg/ml, (3) $IC_{50:}$ 6.772µg/ml, (4) $IC_{50:}$ 1.406 µg/ml - liver cancer (BEL-7402) human cell lines.	Cao *et al*., 2010c
	WP	Cytotoxic	Ginkgetin	*In vitro* assay. Inhibition of the growth of human ovarian adenocarcinoma cells with IC_{50} at 1.8 µg/ml.	Sun *et al*., 1997
	WP	Antiviral	Total flavonoids extracts (1) Amentoflavone (2)	These compounds were effective against coxsackie virus B3 *in vitro* and *in vivo*. *In vitro* assay: Treating during infection - (1) IC_{50}:41 ± 1.2 μg/ml and (2) IC_{50}: 52 ± 0.8 μg/ml; Treating after infection - (1) IC_{50}:19 ± 1.6 μg/ml and (2) IC_{50}:25 ± 1.2 μg/ml. *In vivo* assay: (1) IC_{50}: 19 ± 1.6 to 41 ± 1.2 μg/ml and (2) IC_{50}: 25 ± 1.2 to 52 ± 0.8 μg/ml.	Yin *et al*., 2014
	WP	Endothelial injury protection	N-(2E)-3-(3,4-dihydrophenyl) prop-$N_{1'}$-(4-aminobutyl)-3-pyrrole formaldehyde	*In vitro* assay. Effect on the injury of human umbilical vein endothelial cell at 10^{-1} µmol/l and 10^{-2} µmol/l.	Zou *et al*., 2013

	WP	Antihyperglycemic	5-carboxymethyl-7,4'-dihydroxyflavonone-7-O-β-D-glucopyranoside	At 0.1 µM increased 15.2 ± 3.3% (p<0.01) the glucose consumption in insulin-resistant L6 muscle cells.	Wang *et al*., 2011
S. nothohybrida	WP	Diuretic	Aqueous extract Amentoflavone Trehalose	*In vivo* assay. Decoction of *S. nothohybrida* at 2000 mg/kg (p<0.05) and the isolated metabolites in a dose range of 10 mg/kg affected urinary electrolytes excretion.	Aguilar *et al*., 2015
	WP	Natriuretic	Robustaflavone (S)-2,3-dihydrorobustaflavone	*In vivo* assay. At 10 mg/kg demonstrated a natriuretic effect.	Aguilar *et al*., 2015
S. pallescens	WP	Spasmolytic	Chloroform-methanol extracts	*In vitro* assay. At 81.80 ± 0.87 promoted a reduction in the contraction of the ileum (IC_{50} 7.94 ± 0.70).	Rojas *et al*., 1999
S. pulvinata	WP	Antibacterial	Selaginellin Selaginellin A	*In vitro* assay. Anti- *S. aureus* (IC_{50} 1.2 µg/ml).	Cao *et al*., 2010a
	WP	Antifungal	Selaginellin D Selaginellin G	*In vitro* assay. Anti-*C. albicans* (IC_{50} 5.3 µg/ml).	Cao *et al*., 2010a
	WP	Asthma and chronic obstructive pulmonary disease	Selaginpulvilins A-D Selaginellin Selaginellin A Selaginellin N Selaginellin H	Remarkable inhibitory activities against phosphodiesterase-4 with IC_{50} values in the range of 0.11 − 5.13 µM.	Lui *et al*., 2014
	WP	Cytotoxic	Selaginellin	*In vitro* assay. Inhibitory effect of glucose-induced cell injury and apoptosis in differentiated PC12 cells.	Zhang *et al*., 2012b
S. sellowii	WP	Antiprotozoal	Hydroethanolic extract Amentoflavone Robustaflavone	*In vitro* assay. Amentoflavone was about 200 times more potent than hydroethanolic extract (IC_{50} = 0.1 µg/ml). Robustaflavone was less active than amentoflavone, with an IC_{50} of 2.8 µg/ml.	Rizk *et al*., 2014
	WP	Antiprotozoal	Hydroethanolic extract	*In vivo* assay. This extract was used to treat Hamsters infected with *L. amazonensis* and was observed 100% of the parasite suppression load at the site of infection with an intralesional dose of 50 mg/kg/day; the oral dose	Queiroz *et al*., 2016

				of 50 mg/kg/day was able to suppress 99.2% of parasite load on infected legs.	
S. sinensis	WP	Antiviral	Amentoflavone	*In vitro* assay. This compound showed potent antiviral activity against respiratory syncytial virus, with an IC_{50} of 5.5 µg/ml.	Ma *et al*., 2001
	NI	Antioxidant	Ethyl acetate fraction	*In vitro* assay. At IC_{50} value of 44.9 µM exhibited DPPH radical scavenging activity.	Zhang *et al*., 2011
	NI	Antioxidant	Quercetin Apigenin Amentoflavone Robustaflavone, Hinokiflavone 2,3-dihydroamentaflavone, 4-O-methyl-robustaflavone Ginkgetin	*In vitro* assay. Quercetin showed strongest antioxidant activities with IC_{50} 3.2 µM, whereas the other compounds showed weak antioxidant potential.	Zhang *et al*., 2011
S. tamariscina	LE	Antihyperglycemic	Selariscinin D (1) Selariscinin E (2) Amentoflavone (3) Robustaflavone (4) Cupressuflavone (5) Taiwaniaflavone (6) 3,8" –biapigenin (7)	*In vitro* assay. All isolates exhibited potent inhibitory effects on PTP1B enzyme with IC_{50} ranging from 4.5 ± 0.1 to 13.2 ± 0.8 µM. Furthermore, showed significant stimulatory effects on 2-NBDG uptake in 3T3-L1 adipocytes.	Nguyen *et al*., 2015a
	LE	Antihyperglycemic	Selariscinin A Selariscinin B Selariscinin C Selaginellin Selaginellin M	*In vitro* assay. All these compounds exhibited strong glucose uptake stimulatory effects in 3T3-L1 adipocytes at 5 µM. Also, these compounds had inhibitory effects on the activity of the enzyme PTP1B with IC_{50} from 4.6 ± 0.1 to 21.6 ± 1.5 µM.	Nguyen *et al*., 2015b
	LE	Cytotoxic	Ethanolic extract	*In vitro* (A) and *in vivo* (B) assays. (A) At 10 µg/ml, 25 µg/ml, 50 µg/ml, 75 µg/ml and 100 µg/ml the viability of LLC cancer cells decreased (p<0.05) by extract treatment in a dose-dependent manner,	Yang *et al*., 2007

				with an IC_{50} 42 µg/ml. (B) At 3 g/day/kg of body weight of extract the Lung metastases of animals treated have decreased (p<0.05) by 72% compared with that of the control group.	
	LE	Cytotoxic	Ethanolic extract	*In vitro* assay. At the highest concentration of extract, 200 µg/ml, caused an altered HONE-1 cell viability.	Hsin *et al*., 2013
	LE	Inhibitory effect MMP-9	Amentoflavone	*In vitro* assay. At 2-8 µM it was able to inhibit MMP-9 expression in a dose dependent manner.	Ahn *et al*., 2007
	WP	Anti-allergic effects	Ethanol extract	*In vivo* assay. At a dosage of 500 and 1000 mg/Kg inhibited systemic anaphylaxis in mice and homologous passive cutaneous anaphylaxis in rats.	Dai *et al*., 2005
	WP	Antibacterial	Isocryptomerin	*In vitro* assay. This compound showed MIC values of 10-20 µg/ml exhibited remarkable antibacterial activity against Gram-positive and Gram-negative bacteria, including isolates from antibiotic resistant bacteria, such as MRSA, *B. subtilis* and *E. coli* O-157.	Lee *et al*., 2009b
	WP	Antibacterial	Amentoflavone	*In vitro* assay. The MIC 4-32 µg/ml showed remarkable antibacterial potential against Gram-positive (*E. faecium*, *S. aureus*, *S. mutans*) and Gram-negative (*E. coli* O-157, *E. coli*, *P. aeruginosa*) bacteria.	Hwang *et al*., 2013
	WP	Antifungal	Isocryptomerin	*In vitro* assay. This compound showed activity against C. *albicans* and *T. beigelii* with MIC at 18.11 µM.	Lee *et al*., 2009[a]

WP	Antifungal	Amentoflavone	*In vitro* assay. The *C. albicans* viability significantly decreased in the presence of amentoflavone (5 µg/ml).	Jung *et al*., 2007
WP	Antifungal	Amentoflavone	*In vitro* assay. This isolated displayed antifungal effect with MIC 5 µg/ml for *C. albicans*. At 40 µg/ml this compound had an effect on the dimorphic transition causing a remarkably disrupted mycelial form of *C. albicans* cells.	Jung *et al*., 2006
WP	Antihyperglycemic	Ethanolic extract	*In vitro* (A) and *in vivo* (B) assay. (A) At 0.6 and 0.7 mg/ml the extract showed a significant glucose-lowering effect. (B) At 210 mg/kg led to a fall in blood glucose levels by 42.16% in the 3rd week.	Zheng *et al*., 2011b
WP	Antihyperglycemic	Total flavonoids extract	*In vivo* assay. At a dosage of 100 mg/kg of extract caused a significant reduction in blood glucose levels.	Zheng *et al*., 2011c
WP	Antihyperlipidaemic Antihyperglycemic Antioxidant	Total flavonoids extract	*In vivo* assay. At 70 mg/kg was observed an interesting effect in reducing the high blood glucose level in diabetic rats ($p<0.05$). Also, showed antioxidant and antihyperlipidaemic activities.	Zheng *et al*., 2013b
WP	Antioxidant	Sumaflavone (1) Robustaflavone (2)	*In vitro* assay. (1): At 30µM completely blocked LPS-inducible NO production; at 3–100 µM inhibited iNOS protein expression and at >30 µM completely blocked iNOS induction by LPS; at 30 µM iNOS mRNA levels were completely inhibited in macrophages;(2) - affected iNOS gene expression and NO	Yang *et al*., 2006

			production.	
WP	Cardiovascular disease protection	Selaginellin A (1) Selaginellin B (2) Selaginellin (3)	These isolates inhibited soluble epoxide hydrolase enzymatic activity and PHOME hydrolysis, in a dose-dependent manner, with IC_{50} 3.1 ± 0.1; 8.2 ± 2.2 and 4.2 ± 0.2 µM, respectively.	Kim *et al*., 2015
WP	Cytotoxicity	3β,16α-dihydroxy-5α,17β-cholestan-21-carboxylic acid (1) 3β-acetoxy-16α-hydroxy-5α,17β-cholestan-21-carboxylic acid (2) 3β-(3-hydroxybutyroxy)-16α-hydroxy-5α,17β-cholestan-21-carboxylic acid (3)	*In vitro* assay. These sterols showed antiproliferative activity in leukemia cells. (1) was more effective than (2) and (3) in inhibiting cell growth, but (3) was more effective than (1) and (2) in enhancing induction of all-*trans*-retinoic acid differentiation. (1) At 12.5 µM, 25.0µM, 37.5µM and 50.0 µM; (2) and (3) at 25.0 µM, 50.0µM, 75.0 µM and 100.0 µM.	Gao *et al*., 2007
WP	Cytotoxic	Amentoflavone	*In vitro* assay. Inhibited the growth of HL-60 cells at IC_{50} 35.68 µg/ml. Also, showed weak activity against HeLa, BEL-7402, MCF-7.	Jing *et al*., 2010
WP	Cytotoxic	Aqueous extract	*In vitro* (A) and *in vitro* (B) assays. (A) At 1000 µg/ml had effect *in vitro* in tumor cell growth, in the p53 expression and in the G1 arrest. (B) At 1% aqueous extract treatment ($p<0.05$) reduced erosive lesions in gastric mucosa.	Lee *et al*., 1999
WP	Cytotoxic	Aqueous extract	*In vitro* assay. This extract inhibited cell growth of HL-60 cells at 800 µg/ml and induced apoptosis via a caspase-3-mediated mechanism.	Ahn *et al*., 2006

WP	Cytotoxic	Ergosta-4, 6, 8 (14), 22-tetraene-3-one Ergosterol endoperoxide 7β- hydroxycholesterol 7β-hydroxysitosterol	*In vitro* assay. These isolates showed cytotoxicity against five human tumor cells (A-549, HCT-15, MES-SA, SK-MEL-2 and SK-OV-2).	Roh *et al*., 2010
WP	Cytotoxic	Ethanol extract	*In vivo* assay. The highest dose (2000 mg/kg/day) provided a 93% reduction of tumour volume of Lewis lung carcinoma-induced tumor mice in comparison to the control.	Le *et al*., 2012
WP	Cytotoxic	Ethanolic extract	*In vitro* assay. At 100–200 µg/ml this extract altered U2OS (human osteosarcoma cells) cell viability by MTT assay.	Yang *et al*., 2013a
WP	Cytotoxic	Ethanolic extract	*In vitro* assay. Cytotoxic effect on HSC-3 cells was not observed even the highest concentration of extract (100 µg/ml). However, this extract significantly reduced cell motility both time- and dose-dependently (p<0.001).	Yang *et al*., 2013b
WP	Cytotoxic	Selaginellin M (1) Selaginellin N (2) Selaginellin (3) Selaginellin A (4) Selaginellin C (5) Neocryptomerin (6) Hinokiflavone (7)	*In vitro* assay. Significant inhibitory activity against HeLa cells with IC_{50} values: (1) 16.61 µg/ml; (2) 22.51 µg/ml; (3) 37.58 µg/ml; (4) 22.53 µg/ml; (5) 27.50 µg/ml; (6) 10.35 µg/ml; (7) 19.27 µg/ml;	Zhang *et al*., 2012a
WP	Cytotoxic	Selaginellin M (1) Selaginellin N (2) Selaginellin (3) Selaginellin A (4) Selaginellin C (5) Neocryptomerin (6) Hinokiflavone (7) Pulvinatabiflavone (8) 7″-O-methylamentoflavone (9)	*In vitro* assay. (1), (2), (3), (4), (6) and (7) showed inhibitory activity against U251cells, whereas compounds (5), (8) and (9) were less active against U251 cells. IC_{50} values: (1) 15.05 µg/ml; (2) 25.34 µg/ml; (3) 32.70 µg/ml; (4) 27.35 µg/ml; (5) > 100 µg/ml; (6) 19.05 µg/ml; (7) 29.81µg/ml; (8) > 100 µg/ml; (9) 75.94 µg/ml.	Zhang *et al*., 2012[a]

	WP	Cytotoxic	Selaginellin M (1) Selaginellin N (2) Selaginellin C (3) Neocryptomerin (4) Hinokiflavone (5)	*In vitro* assay. These compounds showed important inhibitory activity against MCF-7 cells. IC_{50} values: (1) 24.49 µg/ml; (2) 33.84 µg/ml; (3) 32.85 µg/ml; (4) 30.09 µg/ml; (5) 39.32 µg/ml.	Zhang *et al*., 2012[a]
	WP	Cytotoxic	Selaginellin O (1) Selaginellin M (2) Selaginellin (3)	*In vitro* assay. (1) Showed the highest inhibitory activity against HeLa cells, with an IC_{50} 26.4 µM, (2) and (3) showed IC_{50} 28.5 and 33.1 µM, respectively.	Yang *et al*., 2012
	WP	Hepatoprotective	Amentoflavone	*In vivo* assay. At 200 mg/kg the level of glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) significantly decreased (p<0.001). The level of hepatic malondialdehyde (MDA) with dosage 200,100, and 50 mg/kg, respectively significantly decreased (p<0.001). At 200 mg/kg the level of hepatic SOD significantly increased (p<0.01).	Yue *et al*., 2011
	WP	Prevention and/or treatment of UV induced skin damage	Sumaflavone (1) Amentoflavone (2)	*In vitro* assay. (1) at IC_{50} 0.78 µM and (2) at IC_{50} 1.8 µM showed a significant inhibitory activity of MMP-1 in dermal fibroblasts after UV irradiation.	Lee *et al*., 2008
	WP	Vasorelaxant	Amentoflavone	*In vivo* assay. The maximal relaxant effect of amento-flavone was 70.1 ± 2.3% under concentration of 1 x 10^{-5} M.	Kang *et al*., 2004
	WP	Vasorelaxant	AcOEt extract *n*-BuOH extract	*In vitro* assay. At 100 µg/ml these extracts showed a vasorelaxant effect in the rat aortic tissue. The maximum vasorelaxant responses of AcOEt and n-BuOH extracts were 71.1 ± 4.0	Yin *et al*., 2005

				and 57.8 ± 6.2%, respectively.	
S. uncinata	WP	Antiviral	Uncinoside A [1] Uncinoside B [2]	Antiviral activities against respiratory syncytial virus (IC_{50} value of [1] 6.9 and [2] 1.3 µg/ml) and parainfluenza type 3 virus (IC_{50} value of [1]13.8 and [2] 20.8 µg/ml).	Ma *et al*., 2003
	WP	Anti-anoxic	(2″S)-2″,3″-dihydroamentoflavone-4′-methyl ether (1) (2S)-2,3-dihydroamentoflavone-4′-methyl ether (2) (2S,2″S)-2,3,2″,3″-tetrahydroamento-flavone-4′-methyl ether (3) (2S,2″S)-tetrahydroamentofla-vone (4) (2S)-2,3-dihydroamentoflavone (5) (2″S)-2″,3″-dihydroamentoflavone (6) Amentoflavone (7)	*In vitro* assay. All seven flavones derivatives showed protective effects and among these in particular (6) exhibited a potent activity at 90 µmol/l - IC_{50} value of 24.71 ± 2.75; 180 µmol/l - IC_{50} value of 38.27 ±3.24.	Zheng *et al*., 2011c
	WP	Anti-anoxic	(3β, 7β, 12β, 25R)-spirost-5-ene-3, 7, 12-triol-3-O-α-L-rhamnopyranosyl-(1→2)-O-[α-L-rhamnopyranosyl-(1→4)]-O-β-D-glucopyranoside (1) (2α, 3β, 12β, 25R)-spirost-5-ene-2, 3, 12-triol-3-O-α-L-rhamnopyranosyl-(1 → 2)-O-[α-L-rhamnopyranosyl-(1→4)]-O-β-D-glucopyranoside (2) (3β,12β,25R)-spirost-5-ene-3,12-diol-3-O-α-L-rhamnopyranosyl-(1→2)-O-[α-L-	*In vitro* assay. All isolates showed potent protective effect against anoxia in the anoxic PC12 cells assay, among them compounds 1 and 2 were the most active.	Zheng *et al*., 2013a

			rhamnopyranosyl-(1→4)]-O-β-D-glucopyranoside, (3) (1α, 3β, 25R)-spirost-5-ene-2-diol-3-O-α-L-rhamnopy-ranosyl-(1→2)-O-[α-L-rhamnopyranosyl(1→4)]-O-β-D-glucopyranoside (4)		
	WP	Anti-anoxic	(2S)-2,3-Dihydrorobustaflavone-4'-methyl ether (1) (2S, 2"S)-tetrahy-drorobustaflavone (2)	*In vitro* assay. These flavones derivatives showed potent anti-anoxic effect in anoxic PC12 cell assay.	Zheng *et al*., 2008
S. willdenowii	LE	Antioxidant	Aqueous extract	*In vitro* assay. This extract showed interesting antioxidant property at 5 mg/ml by radical scavenging activity.	Chai & Wang, 2012
	LE	Cytotoxic	4',7"-di-O-methylamentoflavone [1] Isocryptomerin [2] 7"-O-methylrobustaflavone [3]	*In vitro* assay. [1] Showed cytotoxicity against Co12 (IC_{50} 2.5 µg/ml) and U373 (IC_{50} 3.8 µg/ml) cell lines. [2] Displayed significant activity against the HT-1080 (IC_{50} 0.6 µg/ml) and Lul cell lines (IC_{50} 0.9 µg/ml). [3] Displayed significant activity against the HT-1080 (IC_{50} 0.9 µg/ml), Lul (IC_{50} 0.4 µg/ml), U373 (IC_{50} 0.7 µg/ml) cell lines.	Silva *et al*., 1995

Brief report on Selaginella phylogeny

The evolutionary process of over 400 million years and its family adaptability (Banks, 2009) has highlighted *Selaginella*ceae as an interesting research tool to understand adaptive skills. Phylogenetically, this family together with Lycopodiaceae and Isoetaceae constitute the oldest lineage of vascular plants on earth (Tryon & Tryon, 1982; Banks, 2009). The phylogenetic relationship between these families is indicated by the chemotaxonomy of flavonoid pattern occurrence and confirmed by molecular data (Voirin & Jay, 1978). It is important to highlight that *Selaginella*ceae diverged from Isoetaceae in the Upper Devonian period (370 mya) (Korall *et al*., 1999).

The *Selaginella*ceae resistance to extinction in the Triassic and Permian periods (Weng & Noel, 2013) is considered a key point in the study of evolution, since it preserves the characteristics of some typical non-vascular plants, but also has some evolutionary innovations, such as vascular tissues, leaves and stems (Friedman, 2011; Yobi *et al*., 2012). These features have attracted the attention of botanists and paleontologists in the search to elucidate the mechanisms involved in the adaptation of vascular plants. Thus, to clarify the phylogeny of this taxon resistant to evolution, molecular markers such as cpDNA have been used (Weng & Noel, 2013).

Palisot de Beauvois (1805) was the first to introduce the term *Selaginella* as a name of a genus, however, this term had been used by Linnaeus (1754) to denominate the species of *Lycopodium selaginoides* L. Heidel. Eventually, Heidel & Handley, (2006) reviewed the classification and currently this species is *Selaginella selaginoides*.

***Selaginella bryopteris* (L.) Bak**

Selaginella bryopteris is a herbaceous plant that grows in shallow soil on rocky outcrops of slopes of small hills in direct sunlight in humid tropical regions. It is a traditional herb that for centuries has been one of the most sought after herbs in Indian mythology known as 'Sanjeevani' (Mishra *et al*., 2012). In the traditional system of Indian medicine, *S. bryopteris* is used as a tonic for regeneration of energy and vitality. The ethnomedicinal use has been reported to treat several infections and pain related to inflammation (Table No. 1). Overall, the results regarding scientific bioactivity are in accordance with the folk medicinal use of *S. bryopteris* and flavonoids are the most important metabolites identified so far (Table No. 2) (Kunert *et al*., 2008; Verma *et al*., 2015).

***Selaginella convoluta* (Arn.) Spring**

Selaginella convoluta is native to Brazil's semi-arid regions and has demonstrated interesting qualities in folk medicine use (Table No. 1), these include its uses as an antidepressant (Giorgetti *et al*., 2007), aphrodisiac, diuretic, in the treatment of amenorrhea (Agra *et al*., 2007a; Agra *et al*., 2007b), coughing, bleeding, increase in female fertility (Albuquerque *et al*., 2007), as well as analgesic and anti-inflammatory properties, being known as "jericó", "mão-de-sapo" and "mão-fechada (Sá *et al*., 2012a). This extract was effective as an analgesic in various pain models *in vivo* and showed antioxidant activity (Table No. 3) (Sá *et al*., 2012a), property that could be related to several biological activities observed in folk medicine. Additionally, the metabolites found in this species are reasonable with these pharmacological properties (Table No. 2).

***Selaginella delicatula* (Desv. ex Poir.) Alston**

Selaginella delicatula is a perennial herb growing throughout the mountain forest floors at low and medium altitudes in Taiwan. This species is also distributed in China, India, Nepal, Burma, Philippines, Malaya, New Guinea and Polynesia. There is no history of use in folk medicine of this species available in the literature up till now. The aqueous extract of *S. delicatula* in *Drosophila melanogaster* offered robust neuroprotection against rotenone and oxidative dysfunctions as well as demonstrating that the neuroprotective effect in by abrogation of rotenone-induced motor deficit, oxidative dysfunction, and neurotoxicity (Table No. 3) (Chandran & Muralidhara, 2013). Biflavonoids and sterol derivatives were found in the species and are consistent with the properties reported (Table No. 2).

Selaginella denticulata Spring

Selaginella denticulata is abundant in the western Mediterranean basin and rarer in the eastern part and grows in the form of extended carpets, on soils or rocks in humid and shadowy sites, such as river banks and old walls. Seven biflavones were isolated from *S. denticulada* (Table No. 2). Studies so far

have not been developed regarding use in folk medicine along with its biological activities.

***Selaginella doederleinii* Hieron**

Selaginella doederleinii is a small perennial Pteridophyte found in south and southwestern China, that has been used in traditional Chinese herb medicine as a bactericide, anticancer agent, and in cardiovascular diseases (Table No. 1) (Chao *et al*., 1987). The extract and isolated compounds showed important biological activities, among them the cytotoxicity against several tumoral cell lines, which is in accordance with its popular use. Glycoside alkaloids (Table No. 2) isolated from *S. doederleinii* could be committed with these properties besides the biflavonoids and lignans (Table No. 2).

***Selaginella inaequalifolia* (Hook. & Grev.) Spring**

Selaginella inaequalifolia is a small Pteridophyte found in India and Burma (Alston, 1945). Within India it is present only in Assam, Tamil Nadu and Kerala (Irudayaraj *et al*., 2010). Studies have not been developed so far regarding its use in folk medicine. Until now, just preliminary phytochemical screening has been completed and antimicrobial activity was investigated (Table No. 3).

***Selaginella involvens* (Sw.) Spring**

Selaginella involvens grows on tree trunks along stream banks and hillsides in Korea, China, India and Japan (Gayathri *et al*., 2005). The species has been used in folk medicine (Table No. 1) and the scientific data reinforce it because extracts and isolated metabolites showed antibacterial activity and protection against injury of vein endothelial cells both in accordance with ethnopharmacological data (Table No. 3). These properties are consisted with the mainly occurrence of diterpenes and flavonoids (Table No. 2).

***Selaginella labordei* Hieron. ex Christ**

Selaginella labordei has been traditionally used in Chinese medicine as an anti-viral (chronic hepatitis and hepatitis B) (Chen *et al*., 2005), anti-inflammatory and anticancer agent (Table No. 1) (Xu *et al*., 2009). The species is a rich source of flavonoid derivatives (Table No. 2). The biological properties found in popular medicine were substantiated by scientific studies since biflavonoids can effectively inhibit the proliferation of colon cancer HT-29 and liver cancer Bel-7402 cells by inducing apoptosis (Table No. 3) (Tan *et al*., 2009a). Furthermore, in ethanolic extract form *S. labordei* inhibited the expression of COX-2 mRNA (Table No. 3) (Chen *et al*., 2005) and both flavone derivatives and extracts were effective in inhibitory potential against xanthine oxidase (XOD) activity (Table No. 3) (Tan *et al*., 2009b).

***Selaginella lepidophylla* (Hook. & Grev.) Spring**

Selaginella lepidophylla is found in the Middle East, in the Central Americas, and in most states of Mexico. The species is popularly known as "resurrection plant", "rose of Jericho", "siempre viva", "flor de piedra", "doradilla", "flower of rock", "stone flower", or "magóra" (tarahumara) and grows particularly in well-drained soils and can stand long periods of drought and heat. The decoction of the whole plant has been used in folk medicine for treatment of urinary obstruction, cystitis, renal calculus, kidney inflammation, and for waist and back pains (Ruiz-Bustos *et al*., 2009; Aguilar *et al*., 2015). It also has been used to treat digestive problems such as eupeptics, for cough, bronchitis and parasitic infections (Aguilar *et al*., 2015), as well as having hepatoprotective activity (Table No. 1) (Tiwari *et al*., 2014). Regarding the scientific approach, some biological activities were evaluated using different *S. lepidophylla* extracts and some of them validate the folk medicine uses like preventing the damage caused by lithiasic process (Mirian *et al*., 2013) (Table No. 3), hepatoprotective activity against hepatotoxicity CCl_4 and paracetamol induced in rats (Table No. 3) (Tiwari *et al*., 2014). Futhermore, phytochemical research of *S. lepidophylla* allowed the isolation of biflavonoids, a metabolite group related to the biological properties observed.

***Selaginella moellendorffii* Hieron**

This species is a perennial herb mainly distributed in the southern area of Changjiang River in China. In regard to folk medicine, it has been used for treating jaundice, gonorrhea, bleeding, idiopathic thrombocytopenic purpura (Wang *et al*., 2009), and acute hepatitis in traditional Chinese medicine (Zhu *et al*., 2008) (Table No. 1); also, it has been used for hematoma after contusion, by applying the fresh plant on the affected area (Table No. 1) (Hong *et al*., 2015). The phytochemistry of *S. moellendorffii* is interesting and several metabolites were isolated and

identified, mainly flavonoids and pyrrolidinoindoline alkaloids (Table No. 2). Several studies on biological properties have been developed (Table No. 3). The study of Cao *et al.* (2010c) along with the findings of Yin *et al*. (2014) substantiated the antiviral potential observed in folk medicine as well as assays on the injury of human umbilical vein endothelial cells induced by high concentrations of glucose *in vitro* (Table No. 3).

***Selaginella nothohybrida* Valdespino**

Selaginella nothohybrida grows in the Mexican states of Guerrero, Oaxaca and Veracruz. The species is recognized by the common names "resurrection fern" or "resurrection plant", "much-kok", "texochitl yamanqui" and "flor de piedra". Furthermore, *S. nothohybrida* has been commonly used as a diuretic in folk medicine (Table No. 1) (Mickel & Valdespino, 1992). Urinary electrolyte excretion was also affected by decoction and pure compounds from this species (Table No. 3), therefore, the mechanism of diuresis appears to be involved with the renal prostaglandins (Aguilar *et al*., 2015) and this study is an important basis for explaining the traditional folk medicine use of *S. nothohybrida*.

***Selaginella pallescens* (C. Presl) Spring**

Selaginella pallescens is found in Mexico and has been used in the treatment of gastrointestinal disease in folk medicine (Rojas *et al*., 1999) (Table No. 1). A study was performed to investigate the effect of chloroform-methanol (1:1, v/v) extracts from *S. pallescens* on the spontaneous contractions of isolated rat ileum and an interesting antispasmodic effect at IC_{50}=7.9 µg/mL was observed (Table No. 3) (Rojas *et al*., 1999). It is possible to hypothesize that this action is associated with flavonoids since amentoflavone showed a smooth muscle-relaxing activity in another study (Chakravarthy *et al*., 1981; Rojas *et al*., 1999).

***Selaginella pulvinata* (Hook. & Grev.) Maxim**.

Selaginella pulvinata is a perennial herb widely distributed in China. The species has been used in traditional Chinese medicine for treatment of tumor, diabetes, stomachache and asthma (Zheng *et al*., 2007), cancer, cardiovascular problems, skin diseases (Cao *et al*., 2010a), dysmenorrhea, and traumatic injury (Table No. 1) (Liu *et al*., 2014). It is important to highlight that selaginellin C was isolated for the first time from *S. pulvinata* (Table No. 2) (Tan *et al*., 2009a), and also a new steroid, 3β, 16α -dihydroxy-(5 α)-cholestan-21-oic acid (Table No. 2) (Zheng *et al*., 2007). The major biological activities investigated are not linked to popular use, however, it did show important results in antifungal and antibacterial activities (Table No. 3) (Cao *et al*., 2010c) as well as remarkable inhibitory activity against phosphodiesterase-4 (Table No. 3) (Liu *et al*., 2014).

***Selaginella selaginoides* (L.) Link**

Selaginella selaginoides is a small Pteridophyte found in Spain (López-Sáez *et al*., 1994). There is just one study about *S. selaginoides* available in the literature so far. This study highlights that *S. selaginoides* presented the biflavonoids amentoflavone, hinokiflavone and robustaflavone from methanolic extract. (Table No. 2) (López-Sáez *et al*., 1994b). There are no descriptions of studies of use in folk medicine as well as the biological activities of this species available in the literature up till now.

***Selaginella sellowii* Hieron**

Selaginella sellowii is widely found in Argentina, Brazil, Carribean, Colombia, Mexico (Gregory & Riba, 1979), Bolivia, Ecuador, Paraguay, Peru, Uruguay (Mickel & Smith, 2004), and Venezuela (Mickel & Beitel, 1988). There are no descriptions of its use in folk medicine reported in the literature up till now. The hydroethanolic extract and biflavonoids from *Selaginella sellowii* (Table No. 2) were evaluated on *Leishmania amazonensis in vivo* and *in vitro* and showed interesting antiparasitic potential at micromolar range (Table No. 3) (Rizk *et al*., 2014; Queiroz *et al*., 2016).

***Selaginella sinensis* (Desv.) Spring**

Selaginella sinensis is abundantly distributed in the north of China (Dai *et al*., 2006). The species is traditionally used to manage chronic tracheitis (Wang *et al*., 2007), hepatitis, choledochitis and other pathological conditions by using heat clearing and diuresis promotion (Dai *et al*., 2006), along with antibacterial, anti-inflammation, and hemostasis activities (Table No. 1) (Feng *et al*., 2009). The phytochemistry of this species is interesting in regard to the number of different phenolic derivatives that have so far been obtained, mainly flavonoids and lignans (Table No. 2). More recently, a chemical

study reported that the pigment selaginellin was isolated from the acetone extract of the plant, and the synthesis of its methoxy derivative was achieved (Zhang *et al*., 2007). Regarding its biological properties, the most important data is amentoflavone exhibited antiviral activity (Table No. 3) (Zhang *et al*., 2011) and this is in agreement with its antiviral popular use.

***Selaginella stautoniana* Spring**

Selaginella stautoniana is mainly distributed in the Northwest and North China (Feng *et al*., 2011). There are no descriptions of its use in folk medicine reported up till now. There was a study that investigated the phytochemistry of *S. stautoniana* and seventeen compounds were isolated from 70% aqueous acetone extract, being mainly flavonoids as well as coumarins and phenolic acids (Table No. 2) (Feng *et al*., 2011).

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

Selaginella tamariscina has been used in oriental medicine to treat inflammation, amenorrhea, dysmenorrhea, metrorrhagia, hematuria, prolapse of the anus, abdominal lumps in women, chronic hepatitis, hyperglycemia, chronic trachitis, thrombocytopenic purpura, several forms of cancers (Zheng *et al*., 1998), bloody constipation, haemoptysis, hepatitis, inflammation and burns (Yang *et al*., 2007). Furthermore, decoction of the whole plant has been used for treatment of hemafecia, epistaxis, metrorrhagia, traumatic injury, chronic hepatitis and proctoptosis (Table No. 1) (Hong *et al*., 2015). There are a large number of studies on phytochemical and biological activities of *S. tamariscina* (Table No. 2 and Table No. 3). Regarding the pharmacological potential, the main studies based on the folk medicine showed an important effect on antitumor as well as antidiabetic and antihyperlipidaemic activities (Table No. 3) (Zheng *et al*., 2013a). The species impaired *in vitro* tumor cell growth, in the p53 expression, in the G1 arrest and *in vivo* gastric cell proliferation, suggesting that this plant could be a candidate for a chemopreventive agent against gastric cancer (Table No. 3) (Lee *et al*., 1999) as well as being able to induce the apoptosis in human promyelocytic leukemia cells (Table No. 3) (Ahn *et al*., 2006). Moreover, *S. tamariscina* demonstrated that it possesses antimetastatic effects on human osteosarcoma cells (Yang *et al*., 2013a), antimetastatic activity in lung cancer cells (Yang *et al*., 2007) and inhibits the invasiveness of human oral squamous-cell carcinoma HSC-3 cells (Table No. 3) (Yang *et al*., 2013a). The findings demonstrated an excellent effect in reducing the high blood glucose level which could be explained by its antioxidant and antihyperlipidaemic activity, which elevated the insulin sensitivity of liver (Table No. 3) (Zheng *et al*., 2013b).

Phytochemical studies pointed out the importance of flavonoids as the major class isolated from *S. tamariscina*. In the same way, two unprecedented compounds [3-(4-hydroxyphenyl)-6,7-dihydroxy coumarin and 1-methoxy-3-methylanthraquinone] were isolated (Table No. 2) (Liu *et al*., 2010). Three new sterols were isolated from *S. tamariscina* and identified as 3beta,16alpha-dihydroxy-5alpha,17beta-cholestan-21-carboxylic acid, 3beta-acetoxy-16alpha-hydroxy-5alpha,17beta-cholestan-21-carboxylic acid and 3beta-(3-hydroxybutyroxy)-16alpha-hydroxy-5alpha, 17beta-cholestan-21-carboxylic acid (Table No. 2) (Gao *et al*., 2007). Two new unusual natural pigments were first isolated from this whole plant, being identified as selaginellin A and selaginellin B (Xu *et al*., 2011) as well as two new selaginellins M and N (Table No. 2) (Table No. 3) (Zhang *et al*., 2012b). Five new compounds, Selariscinin A, Selariscinin B, Selariscinin C, (Nguyen *et al*., 2015b) Selariscinin D and Selariscinin E were isolated from aerial parts of this plant (Table No. 2) (Nguyen *et al*., 2015a).

***Selaginella uncinata* (Desv. ex Poir.) Spring**

Selaginella uncinata is a Chinese herb medicine widely distributed in south China, being popularly known as "Cui Yun Cao" (Zheng *et al*., 2011). It has a history of use in traditional chinese medicine for treatment of jaundice, dysentery, edema, rheumatism and beriberoid diseases (Zheng *et al*., 2008; Zheng *et al*., 2011), infectious diseases and tumors (Table No. 1) (Ma *et al*., 2003).

There are some chemical studies of *S. uncinata* available in the literature. New flavonoids were isolated: 6-(5-Carboxyl-2-methoxyphenyl)-apigenin (Zheng *et al*., 2008), 6-(5-acetyl-2-methoxyphenyl)-apigenin (Zou *et al*., 2013) and unciflavones A–F, with an aryl substituent at C-8 that is not commonly found in natural resources, being for the first time reported for genus *Selaginella* (Table

No. 2) (Zou *et al*., 2014). In addition, uncinataflavone, a new flavonoid, as well as cirsimaririn and psathyrotin were isolated for the first time from the genus *Selaginella* (Table No. 2) (Zou *et al*., 2013). Regarding pharmacological potential, the main property investigated is the anti-anoxic effect since some isolated compounds showed a protective effect when evaluated against anoxia in the $PC1_2$ cell assay, the main protagonist being (2″S)-2″,3″-dihydroamentoflavone (Table No. 2) (Zheng *et al*., 2013b).

***Selaginella willdenowii* (Desv. ex Poir.) Baker**

Selaginella willdenowii is a plant native to Malaysia, Indonesia and Myanmar (Valdespino, 1993). It has a history of use in treating gastric pains, urinary tract infections (Haji *et al*., 1992), wounds, high fever, backache (Eswani *et al*., 2010), skin diseases and menstrual pains (Table No. 1) (Setyawan, 2009). Bioactivity-guided fractionation of the leaves of *S. willdenowii* demonstrated several flavonoid derivatives (Table No. 2) that were significantly cytotoxic against human cancer cell lines (Table No. 3) (Chai & Wong, 2012).

Final remarks

The whole plant was the subject of most of the studies analyzed, which pointed out mainly the cytotoxic potential followed by anti-*Candida albicans*, antibacterial and antioxidant properties. Furthermore, we could observe that the most commonly reported popular uses around the world are: cancer, hepatitis and inflammation. Amentoflavone and derivatives, belonging to the flavonoids class, are the major isolated compounds reported from whole plants from the genus and the cytotoxic potential is promising considering the number of studies that described positive results in accordance with the popular use of several species against cancer. The carbohydrate selaginose was also isolated from whole plant in several studies, however, its biological potential is under-investigated so far. *Selaginella tamariscina* was the most investigated species and the main results highlighted that the ethanolic extract from whole plant is cytotoxic, probably due to the important presence of flavone derivatives.

Selaginella offers a lot of promising prospects for researches. However, it is important highlights some points that could be future research opportunities and also the shortcomings of studies available in literature so far: i) Although amentoflavone and derivatives have been the subject of extensive research related to anticancer activity, other underexplored biological activities of these compounds could be studied in more detail; ii) there is important to study biochemical and physiological mechanisms of action for better characterize how extracts and isolated metabolites exerted their biological activities and toxicity in more details; and iii) Some species widespread at globe were not investigated under chemical or pharmacological perspective and could afford valuable new data. Finally, is important highlight that plants in *Selaginella* genus are lycophytes, that means low port and particular way for reproduction. Therefore, studies on propagation and cultivation are necessary and important in order to guarantee a natural source for future new drugs developed from *Selaginella*.

In conclusion, *Selaginella* is a subject still needing a lot of investigation regarding physiological, chemistry and omic approaches in order to understand this special plant. Some species that are widespread around the globe were not investigated for a chemical or pharmacologic perspective and could still yield valuable new data.

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