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Review: Natural products from Genus *Selaginella* (Selaginellaceae)

AHMAD DWI SETYAWAN♥
Department of Biology, Faculty of Mathematics and Natural Sciences, Sebelas Maret University, Surakarta 57126. Jl. Ir. Sutami 36A Surakarta 57126, Central Java, Indonesia. Tel./fax. +62-271-663375, email: volatileoils@gmail.com

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Abstract. *Setyawan AD. 2011. Natural products from Genus* Selaginella *(Selaginellaceae). Nusantara Bioscience 3: 44-58. Selaginella* is a potent medicinal-stuff, which contains diverse of natural products such as alkaloid, phenolic (flavonoid), and terpenoid. This species is traditionally used to cure several diseases, especially for wound, after childbirth, and menstrual disorder. Biflavonoid, a dimeric form of flavonoids, is the most valuable natural products of *Selaginella*, which constituted at least 13 compounds, namely amentoflavone, 2',8"-biapigenin, delicaflavone, ginkgetin, heveaflavone, hinokiflavone, isocryptomerin, kayaflavone, ochnaflavone, podocarpusflavone A, robustaflavone, sumaflavone, and taiwaniaflavone. Ecologically, plants use biflavonoid to response environmental condition such as defense against pests, diseases, herbivory, and competitions; while human medically use biflavonoid especially for antioxidant, anti-inflammatory, and anti-carcinogenic. *Selaginella* also contains valuable disaccharide, namely trehalose that has long been known for protecting from desiccation and allows surviving severe environmental stress. The compound has very prospected as molecular stabilizer in the industries based bioresources.

Keywords: natural products, biflavonoid, trehalose, *Selaginella*.

Abstrak. *Setyawan AD. 2011. Bahan alam dari Genus* Selaginella *(Selaginellaceae). Nusantara Bioscience 3: 44-58. Selaginella* adalah bahan baku obat yang potensial, yang mengandung beragam metabolit sekunder seperti alkaloid, fenolik (flavonoid), dan terpenoid. Spesies ini secara tradisional digunakan untuk menyembuhkan beberapa penyakit terutama untuk luka, nifas, dan gangguan haid. Biflavonoid, suatu bentuk dimer dari flavonoid, adalah salah satu produk alam yang paling berharga dari *Selaginella*, yang meliputi sekurang-kurangnya 13 senyawa, yaitu amentoflavone, 2',8"-biapigenin, delicaflavone, ginkgetin, heveaflavone, hinokiflavone, isocryptomerin, kayaflavone, ochnaflavone, podocarpusflavone A, robustaflavone, sumaflavone, dan taiwaniaflavone. Secara ekologis, tumbuhan menggunakan biflavonoid untuk merespon kondisi lingkungan seperti pertahanan terhadap hama, penyakit, herbivora, dan kompetisi, sedangkan manusia menggunakan biflavonoid secara medis terutama untuk antioksidan, anti-inflamasi, dan anti karsinogenik. *Selaginella* juga mengandung trehalosa suatu disakarida yang telah lama dikenal untuk melindungi dari pengeringan dan memungkinkan bertahan terhadap tekanan lingkungan hidup yang keras. Senyawa ini sangat berpotensi sebagai stabilizer molekul dalam industri berbasis sumberdaya hayati.

Kata kunci: produk alami, biflavonoid, trehalosa, *Selaginella*.

INTRODUCTION

Medicinal plant is plant containing substance which can be used for the medication or become precursor of drug synthesis (Sofowora 1982). Medicinal plant has been source of human health since ancient time, whereas about 60-75% of world populations require plant for carrying health (Farnsworth 1994; Joy et al. 1998; Harvey 2000). Plants and microbes are the main source of natural products (Hayashi et al. 1997; Armaka et al. 1999; Lin et al. 1999a,b; Basso et al. 2005), and consistently become main source of the newest drugs (Harvey 2000). The drug development from natural sources are based on the bioassay-guided isolation of natural products, due to the traditional uses of local plants (ethnobotanical and ethnopharmacological applications) (Atta-ur-Rahman and Choudhary 1999).

Traditional medication system by using plant medicines has been developed during thousands of year especially by Chinese (Wu-Hsing) and India (Ayurveda, Unani and Siddha) (Peter 2004; Ahmad et al. 2006), while the most advanced, widespread and oldest traditional medication system in Nusantara or Malay Archipelago (Malesia) is jamu which developed by Javanese. Jamu contains several recipes compiled by about 30 plant species. Relief at Borobudur temple about making jamu indicates that jamu has been widely recognized since the early 9th century (Jansen 1993). This system has been documented for centuries in many *serat* and *primbon*, Javanese literary (Soedibyo 1989, 1990; Sutarjadi 1990); and spread by trading, migration, and expansion of several kingdoms such as Mataram Hindu (Sanjaya), Srivijaya (Saylendra) and Majapahit.

Selaginella Pal. Beauv. (Selaginellaceae Reichb.) has been used as complementary and alternative medicines in several traditional medications. This matter is traditionally used to cure wound, after childbirth, menstrual disorder, skin disease, headache, fever, infection of exhalation channel, infection of urethra, cirrhosis, cancer, rheumatism, bone fracture, etc. Part to be used is entire plant, though

only referred to leaves or herbs (Setyawan 2009; Setyawan and Darusman 2008). The usage can be conducted single or combination, fresh or dried, direct eaten or boiled (Dalimartha 1999; Wijayakusuma 2004). This plant has sweet taste and gives warm effect on the body (Bensky et al. 2004). The use of *Selaginella* as medicinal matter occurs in the entire world. The largest usage is conducted by Chinese, especially for *S. tamariscina*, *S. doederleinii*, *S. moellendorffii*, *S. uncinata*, and *S. involvens* (Lin et al. 1991; Chang et al. 2000; Wang and Wang 2001). Unfortunately, *Selaginella* is rarely exploited in Nusantara. Traditional jamu of Java use more cultivated spices and rhizomes than wild herbs or grasses.

Plant medicinal properties are contributed by natural products or secondary metabolites, such as phenolic (flavonoid), alkaloid, terpenoid, as well as non-protein amino acid (Smith 1976). Natural products are chemical compounds or substances produced by a living organism and found in nature that usually has a biological activity for use in pharmaceutical drug discovery and drug design (Cutler and Cutler 2000). In this following discourse, the authors studied diversity of natural products from *Selaginella*, especially biflavonoid and trehalose compounds; and biological activity of *Selaginella's* biflavonoid in modern medication.

NATURAL PRODUCTS DIVERSITY

Previous phytochemical studies on the constituents of genus *Selaginella* leads to the discovery of many compounds, including biflavonoids, the main secondary metabolite of *Selaginella* (Sun et al. 1997; Silva et al. 1995; Lin et al. 1994; 2000). Biflavonoid has also distributed to Selaginellales, Psilotales, and Gymnosperms (Seigler 1998), several Bryophytes and about 15 families of Angiosperms (DNP 1992). The other compounds are including lignin (White and Towers 1967); lignan (Lin et al. 1994), lignanoside (Lin et al. 1990; Zheng et al. 2004, 2008b), alkaloid (Zheng et al. 2004; Lin et al. 1997), selaginellin (Zhang et al. 2007; Cheng et al. 2008), glycosides (Ma and Takahashi 2002; Zhu et al. 2008), glucosides (Dai et al. 2006; Yuan et al. 2008), C-glycosylflavones (Richardson et al. 1989), etc. *Selaginella* species of Java contains alkaloid, phenolic (flavonoid, tannin, saponin), and terpenoid (triterpene, steroid) (Chikmawati and Miftahudin. 2008; Chikmawati et al. 2008). Some species of Japan consist of a steroid type namely ecdysteroid (Takemoto et al. 1967; Hikino et al. 1973; Yen et al. 1974). The diversity and content of other compound are relatively lower than biflavonoid, nevertheless, they have also certain bioactivities.

Water extracts of *S. tamariscina* also has several natural products such as ferulic acid, caffeic acid, vanillic acid, syringic acid, umbelliferone (Bi et al. 2004b); tamariscinoside A, tamariscinoside B, adenosine, guanosine, arbutin (Bi et al. 2004a); tamariscinoside C, tyrosine, D-mannitol, and shikimic acid (Zheng et al. 2004). The EtOH extract of the whole herbs of *S. tamariscina* that fractionated by chloroform and ethyl acetate contains selaginellin A and selaginellin B (Cheng et al. 2008). The main constituen of *S. tamariscina* subsequently is amentoflavone, robustaflavone, bilobetin, hinokiflavone, isocryptomerin and an apigenin-diglucoside (Yuan et al. 2008). *S. tamariscina* has also many sterols that inhibit the growth of human leukemia HL-60 cells indicating anti-cancer property (Gao et al. 2007). The aerial parts of *S. pulvinata* has steroid constituent (Zheng et al. 2007), and several *Selaginella* has also sterol (Chiu et al. 1988). Steroid compound namely ecdysteroid has been found in Japanese species of *S. deliculata*, *S. doederleinii*, *S. moellendorffii*, *S. nipponica*, *S. involvens* (= *S. pachystachys*), *S. stauntoniana* (= *S. pseudo-involvens*), *S. remotifolia* var. *japonica*, *S. tamariscina*, and *S. uncinata* (Takemoto et al. 1967; Hikino et al. 1973; Yen et al. 1974).

Methanolic extract of *S. lepidophylla* contains 3-methylene hydroxy-5-methoxy-2,4-dihydroxy tetrahydro-furane, which can a slight inhibitory effect on the uterus contraction (Perez et al. 1994). *S. lepidophylla* is also reported to contain volatile oils (Andrade-Cetto and Heinrich 2005). The acetone extract of *S. sinensis* contains selaginellin A, an unusual flavonoid pigment (Zhang et al. 2007). *S. sinensis* has a glucoside, namely selaginoside (Dai et al. 2006), a sesquilignan, namely sinensiol A (Wang et al. 2007), secolignans, namely styraxlignolide D and neolloydosin (Feng et al. 2009), and (+)-pinoresinol (Umezawa 2003a,b). *S. uncinata* also has chromone glycosides, namely uncinoside A and uncinoside B (Man and Takahashi 2002), which shows antiviral activities against RSV and PIV-3 (Ma et al. 2003). Ethanol extract of *S. uncinata* also contains flavonoids that possessing a benzoic acid substituent (Zheng et al. 2008a).

S. doederleinii contains several phenolic compounds such as (+)-matairesinol, (-)-lirioresinol A, (-)-lirioresinol B, (-)-nortracheloside (Lin et al. 1994), and (-)-matairesinol, (+)-syringaresinol, (+)-wikstromol, (+)-nortrachelogenin (Umezawa 2003a,b). The (-)-matairesinol has inhibitory activity against cAMP and acts as an insecticide synergist, while (+)-syringaresinol has cytotoxic effect (Harborne et al. 1999). *S. doederleinii* also contains a glycosidic hordenine (Markham et al. 1992), which increases hypertension (Lin et al. 1991).

S. caulescens, *S. involvens*, and *S. uncinata* contain about 0.2% silicon, higher than the most of other club mosses and true ferns (Ma and Takahashi 2002), which may improve plant tolerant to disease, drought, and metal toxicities (Epstein 1999; Richmond and Sussman 2003; Ma 2004). *S. labordei* contains 4'-methylether robustaflavone, robustaflavone, eriodictyol and amentoflavone (Tan et al 2009). *S. apoda* yields substantial amounts of 3-O-methyl-D-galactose (Popper et al. 2001). *S. moellendorfii* contains several pyrrolidinoindoline alkaloids (Wang et al. 2009). Other natural products, besides biflavonoid and trehalose, also have several molecular properties that can increase human health and have economical values; and need for further observation.

Natural products of *Selaginella* can vary depending on climate, location, and soil factors (Setyawan 2009); as well as harvesting and extraction procedure (Nahrstedt and Butterweck 1997); and also plant species or variety, parts to be extracted and age. The different species of *Selaginella*

shows different HPLC fingerprint characteristic. The samples of the similar species, collected in different period, different environment or different locations shows certain difference in fingerprints. However, it also generates *main fingerprint peaks*, which can be used to evaluate and distinguish the different species or infraspecies (Fan et al. 2007).

BIFLAVONOID

Selaginella species have a large number of bioactive compounds, the most important being biflavonoids (Silva et al. 1995; Lin et al. 1999). Biflavonoids are naturally occurring compounds that are ubiquitous in all vascular plants and have many favorable biological and pharmacological effects (Lee et al. 1996; Baureithel et al. 1997; Lobstein-Guth et al. 1998). One of flavonoid structure that has high medicinal valuable is biflavonoid; a dimeric form of flavonoid which formed by binding of two flavone units or mixture between flavone and flavanone or aurone (Geiger and Quinn 1976; DNP 1992; Ferreira et al. 2006).

Flavonoid (or *flavanoid*) is widespread plant natural products (5-10%); its chemical structure and biological role are very diverse (Macheix et al. 1990). This compound is formed by shikimate and phenylpropanoid pathways (Harborne 1989), with a few alternative biosyntheses (Robards and Antolovich 1997). Flavonoid is derived from phenols having basic structure of phenylbenzopiron (tocopherol) (Middleton et al. 2000); distinguished by 15 carbon skeletons (C6-C3-C6) consisted of one oxygenated ring and two aromatic rings (Figure 1). Substitution of chemical group at flavonoid is generally hydroxylation, methoxylation, methylation, and glycosylation (Harborne 1980). Flavonoid is classified diversely; among them are flavone, flavonone, isoflavone, flavanol, flavanone, anthocyanin, and chalcone (Porter 1994; Ferreira and Bekker 1996; Ferreira et al. 1999a,b). More than 6467 flavonoid compounds have been identified and amount of new discovery is consistently increasing (Harborne and Baxter 1999). This compound is playing important role in determining color, flavor, aroma, and quality of nutritional food (Macheix et al. 1990). Flavonoid is mostly monomeric form, but there is also dimer (biflavonoid), trimer, tetramer, and polymer (Perruchon 2004).

Biflavonoid (or *biflavonil*, *flavandiol*) is a dimeric form of flavonoid which formed by bonding of two flavone units or mixture between flavone and flavanone or aurone (DNP 1992; Ferreira et al. 2006). Basic structure of biflavonoid is 2,3-dihydroapigeninil-(I-3',II-3')-apigenin (Figure 1). This compound has interflavanil C-C bond between carbon C-3' at each flavone group. There is also some biflavonoid with interflavanil C-O-C bonding (Bennie et al. 2000, 2001, 2002; Ferreira et al. 2006). Locksley (1973) suggest generic term '*biflavanoid'* to replace '*biflavonil'* which is early used. Term '*biflavanoid'* is assumed more accurate than '*biflavonoid'* because indicating saturated in nature. Suffix 'oid' indicates homogeneous dimeric type, including biflavanone, biflavone, biflavan, etc. However, term '*biflavonoid'* is more regularly used because of articulated easier.

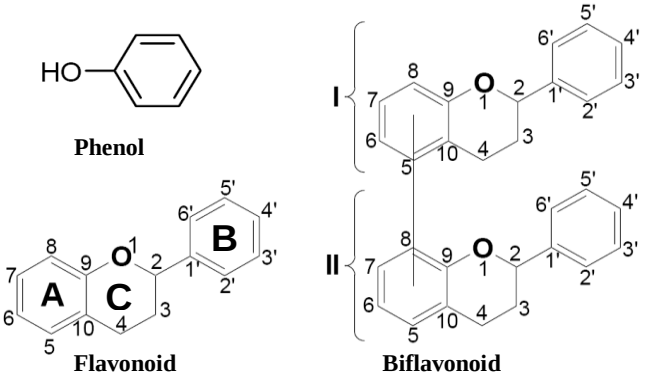


Figure 1. Basic structure of phenol, flavanoid, and biflavanoid. Bicyclic ring system is named A and C rings, while unicyclic ring is named B ring. The two units of monomeric biflavonoid is marked by Roman number I and II. Position number at each monomer is started from containing oxygen atom ring, position of C-9 and C-10 indicate unification of them (Rahman et al. 2007).

Biflavonoid is found at fruit, vegetable, and other parts of plant. This compound is originally found by Furukawa in 1929 (Lin et al. 1997) from leaf extract of *G. biloba* in form of yellow colored compound, later named ginkgetin (I-4', I-7-dimetoxy, II-4', I-5, II-5, II-7-tetrahydroxy I-3', II-8 biflavone) (Baker and Simmonds 1940). Nowadays, amount of biflavonoid which isolated and characterized from nature continually increase (Oliveira et al. 2002; Ariyasena et al. 2004; Chen et al. 2005a), but learning to bioactivity is still limited. The most observed biflavonoid is ginkgetin, isoginkgetin, amentoflavone, morelloflavone, robustaflavone, hinokiflavone, and ochnaflavone. Those compounds have similar basic structure, i.e., 5,7,4'-trihydroxy flavonoid, but differing at nature and position of flavonoid bond (Rahman et al. 2007).

Biflavonoid has several namenclaturing systems, such as Locksley, IUPAC, and vernacular name. The first of two systems is the most systematic, but the most used is vernacular name. Locksley (1973) standardize nomenclature and position number of biflavonil ring skeleton. Every monomer unit is marked by Roman numerals I and II that indicate bonding between monomer, followed by Arabic numerals indicate that bonding position. The two numeral from two monomer unit compiled dimeric, than paired with hyphen to show bonding position of two monomers. Number of substitution group at monomer unit follow IUPAC system for flavone. In Locksley system, amentoflavone named I-4', II-4', I-5, II-5, I-7, II-7-hexahydroxy I-3', II-8 biflavone, while hinokiflavone which its flavone unit bonded with an oxygen is named by II-4', I-5, II-5, I-7, II-7-pentahydroxy I-4'-O-II-6 biflavone. This system is intuitive, logical, and depicts the chemical structure. In IUPAC, amentoflavone is named by 8-5-(5,7-dihydroxy-4-oxo-4H-chromen-2-il)-2-hydroxyphenyl-5,7-dihydroxy- 2-(4-hydroxy-phenyl)-

chromen-4-on, while hinokiflavone is 6-4-(5,7-dihydroxy-4-oxo-4H-chromen-2-il)-phenoxy- 5,7-dihydroxy-2-(4-hydroxyphenyl)- chromen-4-on. Basic difference between two systems is a reference of structural skeleton. Locksley use flavanoid structure, while IUPAC uses chromen structure that more complex (Rahman et al. 2007). The above two nomenclature is rarely used because of its complication. Vernacular name that given by each inventor is often used because simpler and easier, though it is not systematic and does not depict chemical structure, such as amentoflavone, hinokiflavone, ginkgetin, etc.

In vivo biosynthesis of flavonoid in nature is relatively mysterious, but there are some approaches by in vitro to explain biosynthesis. According to Rahman et al. (2007) there are nine pathways of biflavonoid synthesis, namely: (i) Ullmann coupling halogenated flavones; (ii) synthesis of biflavones via 1,1'-biphenyls; (iii) metal catalyzed cross-coupling of flavones; (iv) Wessely-Moser rearrangements; (v) phenol oxidative coupling of flavones; (vi) Ullmann condensation with flavone salts; (vii) nucleophilic substitution; (viii) dehydrogenation of biflavanones into biflavones; and (ix) dehydrogenation of biflavone into biflavanone.

In East Asia, biflavonoid is usually produced from leaf of *Ginkgo biloba* which main constituent is ginkgetin (Krauze-Baranowska and Wiart 2002; Dubber 2005). In sub Sahara-Africa, it is specially produced from seed of *Garcinia cola* which main constituent is kolaviron (Iwu and Igboko 1982; Iwu 1985, 1999; Iwu et al. 1987, 1990; Braide 1989, 1993; Han et al. 2006; Farombi et al. 2005; Adaramoye and Medeiros 2009). The biflavanones are the most dominant in the most *Garcinia* species (Waterman and Hussain 1983), pericarp of Javanese mangosteen (*G. mangoestana*) contains amentoflavone and other flavonoids (ADS 2008, data not be shown). In Europe, biflavonoid is commonly produced from herbs of *Hypericum perforatum* which main constituent is amentoflavone (Berghofer and Holzl 1987, 1989; Nahrstedt and Butterweck 1997; Tolonen 2003; Kraus 2005). *Selaginella* has potent as source of biflavonoid, which can yield various biflavonoid compounds depending on species. It has cosmopolitan distributed and able to cultivate almost all the words depending on species.

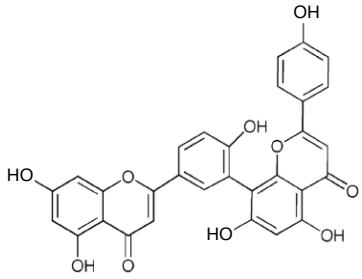
DIVERSITY OF BIFLAVONOID

Selaginella is one of the potential medicinal plants as a source biflavonoid in Nusantara, where 200 of the 700-750 species from the entire world are found (Setyawan 2008). A total of 13 biflavonoid compounds have been isolated from *Selaginella*, including amentoflavone (3',8"-biapigenin), 2',8"-biapigenin, delicaflavone, ginkgetin, heveaflavone, hinokiflavone, isocryptomerin, kayaflavone, ochnaflavone, podocarpusflavone A, robustaflavone, sumaflavone, and taiwaniaflavone (Figure 2). In Setyawan and Darusman (2008) mentioned that the number is only 12 biflavonoid compounds. Some biflavonoid is easily found at various species of *Selaginella*, but the other is only found at certain species. Amentoflavone and ginkgetin is biflavonoid compound of the most *Selaginella*, while sumaflavone is only reported from *S. tamariscina* (Yang et al. 2006; Lee et al. 2008) and delicaflavone is only reported from *S. delcatula* (Andersen and Markham 2006). At least 11 species of *Selaginella* have been tested by amentoflavone content (Sun et al. 2006). There is also biflavonoid which is rarely found at *Selaginella* but it is commonly found at other species. Preliminary study shows that amentoflavone is found in high content (> 20%) at two of about 35 species of Malesian *Selaginella*, namely *S. subalpina* and *S. involvens* (ADS 2008, data not be shown). In *Selaginella,* taiwaniaflavone is only reported from *S. tamariscina* (Pokharel et al. 2006), while this is also found at another plant such as *Taiwania cryptomerioides* (Kamil et al. 1981).

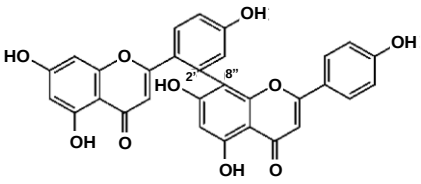
Selaginella is generally extracted from whole plant, though it is only conceived as herbs or leaves. Extraction can be conducted by various solvent, i.e. polar, semi-polar and non-polar. For example: boiling in water, extraction by using methanol, ethanol, butanol, ethyl acetate, chloroform, or extraction by using solvent mixtures such as alcohol-water, ethanol-ethyl acetate, and ethanol-chloroform. Methanol and ethanol are the most solvents used for biflavonoid extraction. Solvent types and extraction procedure can influence obtaining chemical structure and bioactivity of extract. Disease which is most treated by *Selaginella* extract is cancer. Besides, *Selaginella* extract also has much other usefulness, namely antioxidant, anti-inflammatory, antimicrobial (virus, bacterium, fungi, and protozoa), anti UV irradiation, anti-allergy, vasorelaxation, anti-diabetes, blood pressure stability, antihemorrhagic, and antinociceptive. Biflavonoid needs evaluation for its medical and nutritional value (Harborne and Williams 2000). *Selaginella* contains various biflavonoid with different medical properties (Table 2).

Amentoflavone. Amentoflavone, the most common biflavonoid of *Selaginella*, has various biological and pharmacological effects, including antioxidant (Mora et al. 1990; Cholbi et al. 1991; Shi et al. 2008), anti cancer (Silva et al. 1995; Lee et al. 1996; Lin et al. 2000; Guruvayoorappan and Kuttan 2007), anti-inflammatory (Gambhir et al. 1987; Baureithel et al. 1997; Gil et al. 1997; Kim et al. 1998; Lin et al. 2000; Woo et al. 2005), antimicrobial (Woo et al. 2005; Jung et al. 2007), antivirus such as influenza (A, B), hepatitis (B), human immunodeficiency virus (HIV-1), herpes (HSV-1, HSV-2), herpes zoster (VZV), measles (Lin et al. 1998, 1999a,b, 2002; Flavin et al. 2001, 2002), and respiratory syncytial virus (RSV) (Lin et al. 1999a,b; Ma et al. 2001), vasorelaxation (Kang et al. 2004), anti-urcerogenic (Gambhir et al. 1987), anti stomachic-ache (Kim et al. 1998), anti depressant (Baureithel et al. 1997), anxiolytic (Cassels et al. 1998, 1999), analgesic (Silva et al. 2001), and anti-angiogenesis agent (Lee et al. 2009c).

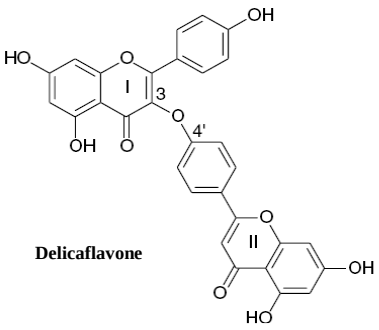
2',8''-biapigenin. 2',8"-biapigenin is an anticancer, which inhibit transactivation of iNOS gene and cyclooxigenase-2 (COX-2) through inactivate nuclear factor-κB (NF-κB) and prevent translocation of p65 (Chen et al. 2005b; Woo et al. 2006); and anti-inflammatory (Grijalva et al. 2004; Woo et al. 2005 2006; Pokharel et al. 2006).



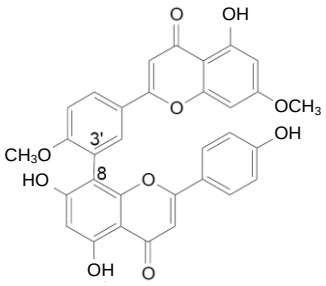
Amentoflavone
(3',8"-biapigenin)



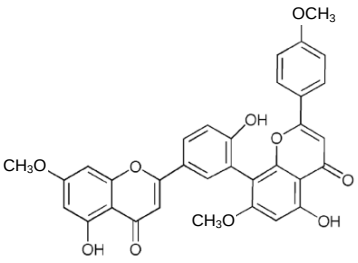
2',8"-biapigenin



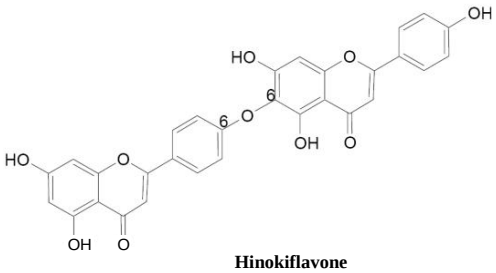
Delicaflavone



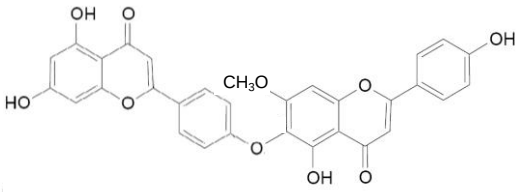
Ginkgetin



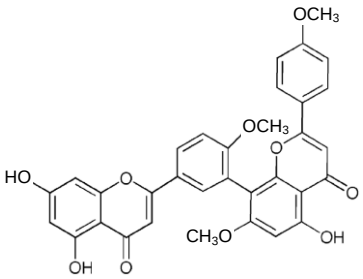
Heveaflavone



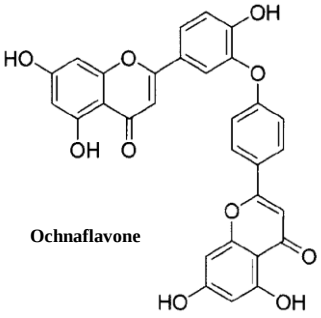
Hinokiflavone



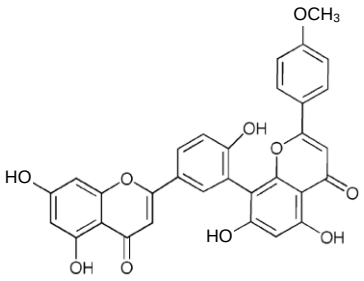
Isocryptomerin



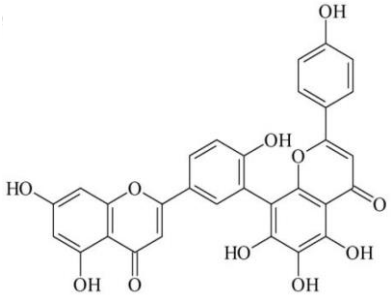
Kayaflavone



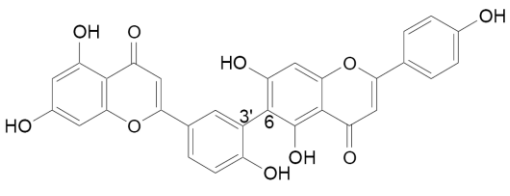
Ochnaflavone



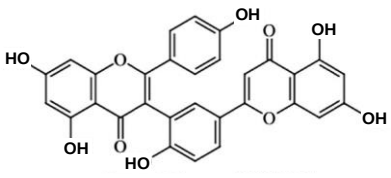
Podocarpusflavone A



Sumaflavone



Robustaflavone



Taiwaniaflavone

Figure 2. Structure of biflavonoid from *Selaginella*, namely: amentoflavone, 2',8"-biapigenin, delicaflavone, ginkgetin, heveaflavone, hinokiflavone, Isocryptomerin, kayaflavone, ochnaflavone, podocarpusflavone A, robustaflavone, sumaflavone, and taiwaniaflavone.

Delicaflavone. Its bioactivity is not observed yet from *Selaginella*.

Ginkgetin. This compound is the second most studied biflavonoid of *Selaginella* beside amentoflavone. It has several properties including antioxidant (Su et al. 2000; Sah et al. 2005; Shi et al. 2008), anti-inflammatory (Grijalva et al. 2004; Woo et al. 2005, 2006; Pokharel et al. 2006), antiviral such as herpes and cytomegalovirus (Hayashi et al. 1992); anti protozoan such as *Trypanosoma cruzi* (Weniger et al. 2006); anti-cancer (Sun et al. 1997; Kim and Park 2002; Yang et al. 2007), such as such as ovarian adenocarcinoma (OVCAR-3), cervical carcinoma (HeLa) and foreskin fibroblast (FS-5) (Su et al. 2000). Ginkgetin is the strongest biflavonoid that inhibits cancer (Kim and Park 2002). Besides, this matter increases activity of neuroprotective against cytotoxic stress, and has potent for curing neurodegenerative disease such as stroke and Alzheimer (Kang et al. 2004; Han et al. 2006). Ginkgetin can also replace caffeine in food-stuff and medicines without generating addiction (Zhou 2002).

Heveaflavone. Heveaflavone has cytotoxic activity against cancer cell of murine L 929 (Lin et al. 1994).

Hinokiflavone. Hinokiflavone has antioxidant, antiviral and anti protozoan effect. This matter assists cell growth and protects from free radical caused by hydrogen peroxide (H_2O_2) (Sah et al. 2005). It also inhibits sialidase influenza virus (Yamada et al. 2007; Miki et al. 2008); has high resistance to HIV-1 by in vivo and polymerase HIV-1 RTASE by in vitro (Lin et al. 1997). Lin et al. (1998, 1999a,b, 2002) and Flavin et al. (2001, 2002) is patenting antiviral effect of hinokiflavone and others to influenza virus (A, B), hepatitis (B), human immunodeficiency virus (HIV-1), herpes (HSV-1, HSV-2), herpes zoster (VZV), and measles. It has antiprotozoan activity by in vitro against *Plasmodium falciparum*, *Leishmania donovani* and *Trypanosoma* sp. (Kunert et al. 2008).

Isocryptomerin. Isocryptomerin has anti-cancer property as well as anti-inflammatory, immunosuppressant and analgesic (Kang et al. 1998, 2001). It has cytotoxic activity against various cancer cells (Silva et al. 1995), including P-388 and HT-29 (Chen et al. 2005b). It has antibacterial activity against Gram-positive and Gram-negative bacteria (Lee et al. 2009b); and also has antifungal properties, which can depolarize fungal plasma membrane of *Candida albicans* (Lee et al. 2009a).

Kayaflavone. Kayaflavone has moderately anti-cancer property (Sun et al. 1997; Yang et al. 2007) and antioxidant, such as depleting H_2O_2 (Su et al. 2000).

Ochnaflavone. Ochnaflavone derivatives may have antioxidant activity that inhibits expression of gene COX-2 at colon cancer cell (Chen et al. 2005b).

Podocarpusflavone A. It has moderately anti-cancer (Sun et al. 1997; Yang et al. 2007) and antioxidant properties (Su et al. 2000; Shi et al. 2008).

Robustaflavone. Robustaflavone has anti-cancer and antivirus properties. This matter significantly cytotoxic to various cancer cells (Silva et al. 1995) and significantly inhibits tumor cell of Raji and Calu-1 (Lin et al. 2000), cancer cell of P-388 and HT-29 (Chen et al. 2005b). It has also antiviral properties, which indicates high resistance to polymerase HIV-1 RTASE by in vitro (Lin et al. 1997) and also influenza virus (A, B), hepatitis (B), human immunodeficiency virus (HIV-1), herpes (HSV-1, HSV-2), herpes zoster (VZV), and measles (Lin et al. 1998, 1999a,b 2002; Flavin et al. 2001, 2002).

Sumaflavone. Sumaflavone has anti-inflammatory property that able to inhibit production of NO, by mean blocking lipopolysaccharide formation that induces iNOS gene expression (Yang et al. 2006). It can also significantly inhibit ability of UV irradiation to induce matrix metalloprotease-1 and -2 (MMP-1 and -2) activities at fibroblast of primary human skin (Lee et al. 2008).

Taiwaniaflavone. It has anti-inflammatory, such as induce iNOS and COX-2 at macrophage of RAW 264.7 (Pokharel et al. 2006).

MOLECULAR BIOACTIVITIES

Selaginella is traditionally treated to cure several diseases depending on species, such as cancer or tumor (uterus, nasopharyngeal, lung, etc), wound, after childbirth, menstrual disorder, female reproduction disease, expulsion of the placenta, tonic (for after childbirth, increase body endurance, anti ageing, etc), pneumonia, respiratory infection, exhalation channel infection, inflamed lung, cough, tonsil inflammation, asthma, urethra infection, bladder infection, kidney stone, cirrhosis, hepatitis, cystisis, bone fracture, rheumatism, headache, fever, skin diseases, eczema, depurative, vertigo, toothache, backache, blood purify, blood coagulation, amenorrhea, hemorrhage (resulting menstrual/obstetrical hemorrhage, stomachic, pile or prolepses of the rectum), diarrhea, stomach-ache, sedative, gastric ulcers, gastro-intestinal disorder, rectocele, itches, ringworm, bacterial disease, bellyache, neutralize poison caused by snakebite or sprained, bruise, paralysis, fatigue, dyspepsia, spleen disease (diabetic mellitus), emmenagogue, diuretic, and to refuse black magic (Martinez 1961; Bouquet et al. 1971; Dixit and Bhatt 1974; Ahmad and Raji 1992; Bourdy and Walter 1992; Nasution 1993; Lin et al. 1994; Kambuou 1996; Caniago and Siebert 1998; Sequiera 1998; Dalimartha 1999; Mathew et al. 1999; Abu-Shamah et al. 2000; van Andel 2000; Uluk et al. 2001; Harada et al. 2002; Ma and Takahashi 2002; Warintek 2002; Winter and Jansen 2003; ARCBC 2004; Batugal et al. 2004; de Almeida-Agra and Dantas 2004; DeFilipps et al. 2004; Wijayakusuma 2004; Mamedov 2005; Khare 2007; PAM 2008; Setyawan and Darusman 2008) (Table 1). This plant has sweet taste, and gives warm effect on the body (Bensky et al. 2004).

Plants ecologically use biflavonoid to response environmental condition such as defense against pests, diseases, herbivory, and competitions; while human medically use as antioxidant, anti-inflammatory, anti cancer, anti-allergy, antimicrobial, antifungal, antibacterial, antivirus, antiprotozoal, protection to UV irradiation, vasorelaxation (vasorelaxant), heart strengthener, anti-hypertension, anti-blood coagulation, and influence enzyme metabolism (Havsteen 1983, 2002; Kandaswami

and Middleton 1993, 1994; Lale et al. 1996; Bisnack et al. 2001; Duarte et al. 2001; Kromhout 2001; Kang et al. 2004; Moltke et al. 2004; Arts and Hollman 2005; Martens and Mithofer 2005; Yamaguchi et al. 2005). The antioxidant, anti-cancer and anti-inflammatory are the most important bioactivities of this secondary metabolite.

Selaginella is known to possess various molecular bioactivities depending on species, but only a few species have been detailed observe in the advanced research. Several species that also distributed in Nusantara are observed, such as *S. tamariscina, S. doederleinii, S. involvens, S. moellendorffii, S. uncinata,* and *S. willdenowii*; while the most distributed *Selaginella* in Nusantara namely *S. plana* has not been investigated yet (Table 2).

S. tamariscina is the most powerful and most useful plant *Selaginella* in the world. This herb is widely used as anticancer, antioxidant and anti-inflammatory; and also used as anti UV irradiation, anti-allergy, vasorelaxation, antidiabetic, immunosuppressant, analgesic, neuroprotectant, antibacterial, antifungal, and possess estrogenic activity. As anti cancer, *S. tamariscina* can decrease expression of MMP-2 and -9, urokinase plasminogen activator, and inhibits growth of metastasis A549 cell and Lewis lung carcinoma (LLC) (Yang et al. 2007); inhibits proliferation of mesangial cell which activated by IL-1β and IL-6 (Kuo et al. 1998); inhibits leukemia cancer cell of HL-60 cell (Lee et al. 1999); induces expression of tumor suppressor gene of p53 (Lee et al. 1996); degrades leukemia cancer cell of U937 (Lee et al. 1996; Yang et al. 2007); reduces proliferation nucleus antigen cell from stomach epithelium (Lee et al. 1999); chemopreventive for gastric cancer (Lee et al. 1999); induces apoptosis of cancer cell through DNA fragmentation and nucleus clotting (Ahn et al. 2006); and induces breast cancer apoptosis through blockade of fatty acid synthesis (Lee et al. 2009c). This property is mostly given by amentoflavone and isocryptomerin (Kang et al. 1998, 2001; Lee et al. 2009c), while ginkgetin is also acted as anti-cancer to OVCAR-3 (Sun et al. 1997). As antioxidant, amentoflavone from *S. tamariscina* inhibits production of NO, which inactivates NF-κB, while sumaflavone blocks lipopolysaccharide formation that induces iNOS gene expression (Yang et al. 2006). As anti-inflammatory, amentoflavone, taiwaniaflavone and ginkgetin from *S. tamariscina* inhibit inflammation that induces iNOS and COX-2 at macrophage RAW 264.7 which stimulated by lipopolysaccharide (Grijalva et al. 2004; Woo et al. 2005; Pokharel et al. 2006). Amentoflavone inhibits activity of phospholipase Cγ1 (Lee et al. 1996); phospholipase A-2 (PLA-2) and COX-2 (Kim et al. 1998), while 2',8''-biapigenin inhibits transactivation of iNOS gene and COX-2 through inactivate NF-κB and prevent translocation of p65 (Woo et al. 2006).

Amentoflavone from *S. tamariscina* inhibits fungi (Junk et al. 2006), anti-influenza and resist to HSV-1 and -2 (Rayne and Mazza 2007); hinokiflavone inhibits sialidase influenza virus (Yamada et al. 2007; Miki et al. 2008) and resists to HIV-1 (Lin et al. 1997); robustaflavone and hinokiflavone resist to polymerase HIV-1 RTASE (Lin et al. 1997); ginkgetin inhibits herpes and cytomegalovirus (Hayashi et al. 1992), by degrading protein synthesis of virus and represses gene transcription (Middleton et al. 2000). Isocryptomerin from *S. tamariscina* shows potent antibacterial activity against Gram-positive and Gram-negative (Lee et al. 2009b). Amentoflavone from *S. tamariscina* inhibits several pathogenic fungi (Woo et al. 2005; Jung et al. 2007). Isocryptomerin from *S. tamariscina* can depolarize fungal plasma membrane of *C. albicans* (Lee et al. 2009a).

S. tamariscina is effective ingredient to prevent and cure acute brain degenerative disease, such as stroke and dementia (Han et al. 2006). Capability to prevent brain damage is especially given by amentoflavone (Kang et al. 1998). *S. tamariscina* can elastic vascular smooth muscle through endothelium-related to nitric oxide (NO) activity (Yin et al. 2005). Amentoflavone from *S. tamariscina* induces relaxation of phenylephrine which responsible for aorta contraction (Kang et al. 2004; Yin et al. 2005). *S. tamariscina* containing sumaflavone and amentoflavone inhibit ability of UV irradiation to induce MMP-1 and -2 at fibroblast (Lee et al. 2008). *S. tamariscina* reduces histamine from peritoneal mast cell causing allergic reaction (Dai et al. 2005). *S. tamariscina* decreases sugar blood and lipid peroxide, and also increases insulin concentration (Miao et al. 1996). Amentoflavone from *S. tamariscina* inhibits activity of tyrosine phosphatase 1B to maintain type-2 diabetic and obesity (Na et al. 2007).

S. articulate is treated as antihemorrhagic. Water extract of this matter can moderately neutralize hemorrhagic effect and inhibits proteolysis of casein by venom (Otero et al. 2000; Winter and Jansen 2003).

S. bryopteris acts as antioxidant, anti-inflammatory, antiprotozoal, anti-UV-irradiation and antispasmodic. Water extract of *S. bryopteris* increases endurance to oxidative stress, and assists cell growth and protects from free radical stress caused by H_2O_2 (Sah et al. 2005). *S. bryopteris* is treated as anti-inflammatory and cures venereal disease (Agarwal and Singh 1999). Amentoflavone and hinokiflavone from *S. bryopteris* have antiprotozoal activity against *P. falciparum*, *L. donovani* and *Trypanosoma* sp (Kunert et al. 2008). Water extract of *S. bryopteris* also significantly reduces potent cell dying caused by UV irradiation (Sah et al. 2005), while ethanolic extract can cure stomachic (Pandey et al. 1993).

S. delicatula acts as anti-cancer and antioxidant. Water extract of *S. delicatula* has antioxidant characteristic and degrades blood cholesterol (Gayathri et al. 2005). Extract of *S. delicatula* that contained by robustaflavone and amentoflavone or its derivatives is cytotoxic against cancer cell of P-388, HT-29 (Chen et al. 2005b), Raji, Calu-1, lymphoma, and leukemia (Lin et al. 2000)

S. doederleinii is usually treated as anti-cancer, but also acts as antiviral and anti-inflammatory. Water extract of *S. doederleinii* has antimutagenic against both picrolonic acid- and benzo[α]pyrene-induced mutation to cancer cell (Lee and Lin 1988). Ethanolic extract of *S. doederleinii* that is amentoflavone and heveaflavone has cytotoxic activity against cancer cell of murine L 929 (Lin et al. 1994). Extract of *S. doederleinii* also has cytotoxic against

the three human cancer cell lines, HCT, NCI-H358, and K562 (Lee et al. 2008), and has antimutagenic effect against cholangiocarcinoma cancer, but may cause bone marrow depression (Pan et al. 2001). Amentoflavone from *S. doederleinii* has potent as antiviral and anti-inflammatory agents (Lin et al. 2000). However, hordenine that isolated from *S. doederleinii* increases hypertension (Lin et al. 1991).

S. involvens has characteristics as antioxidant, anti-inflammatory, and anti-bacterial. Extract of *S. involvens* can inhibit production and effect of free radicals of NO and expression of iNOS/IL-1β (Joo et al. 2007). Water extract of *S. involvens* has significantly antioxidant effect to lipid peroxides (EC50 = 2 ug/mL). This extract is non-toxic and degrades blood cholesterol (Gayathri et al. 2005). Water extract of *S. involvens* kills the various *Leptospira* strains, which causes infectious of leptospirosis diseases (Wang et al. 1963). Extract of *S. involvens* depresses activity of *Propionibacterium acnes* (> 100 ug/mL), which responses to acne inflammation; although has no antibiotic property (Joo et al. 2007). Besides, water extract of *S. involvens* may have analgesic activity (ECMM 1997; Ko et al. 2007).

S. labordei indicates antioxidant, anticancer, and anti-virus characteristics. *S. labordei* can inhibit activity of xanthine oxidase (XOD) and lipoxygenase (LOX), and absorb free radical (Chen et al. 2005b; Tan et al. 2009). It also down-regulate COX-2 gene expression in human colon adenocarcinoma CaCo-2 cells (Chen et al. 2005b). Robustaflavone of *S. labordei* can inhibit hepatitis B virus (Tan et al. 2009)

S. lepidophylla has hypoglycemic property (Andrade-Cetto and Heinrich 2005); while non-biflavonoid compound from methanolic extract of *S. lepidophylla*, 3-methylenhydroxy-5-methoxy-2,4-dihydroxy tetrahydrofuran, has moderate resistance to uterus contraction (Perez et al. 1994).

S. moellendorffii contains antioxidant and anti-cancer properties. Ethyl acetate extract of *S. moellendorffii* contains amentoflavone, hinokiflavone, podocarpusflavone A, and ginkgetin that has antioxidant properties (Shi et al. 2008). Ginkgetin that extracted by ethanol or ethyl acetate from *S. moellendorffii* can inhibit cancer cell growth of OVCAR-3, HeLa, and FS-5 (Sun et al. 1997; Su et al. 2000). It also acts as anti-metastasis at lung cancer cell of A549 and LLC (Yang et al. 2007), and apoptosis resulting caspase activation by H_2O_2 (Su et al. 2000); while amentoflavone and its derivatives, kayaflavone, and podocarpusflavone A, have no this bioactivity (Sun et al. 1997).

S. pallescens has moderately antimicrobials and antispasmodic activities. *S. pallescens* contains an endophytic *Fusarium* sp. that produces pentaketide antifungal agent, CR377 (Brady and Clardy 2000). Chloroform-methanolic extract of *S. pallescens* can inhibit spontaneously contraction of ileum muscle (Rojas et al. 1999).

S. rupestris contains amentoflavone which has antispasmodic effect on ileum, and strengthening heart in case of normodynamic and hypodynamic (Chakravarthy et al. 1981)

S. sinensis contains amentoflavone which has antiviral activity against RSV (Ma et al. 2001)

S. uncinata has activity as anti-virus but generated by non biflavonoid compounds. *S. uncinata* has chromone glycosides, namely uncinoside A and B (Ma and Takahashi 2002), which showed antiviral activities against RSV and PIV-3 (Ma et al. 2003).

S. willdenowii contains isocryptomerin and derivatives of amentoflavone and robustaflavone which significantly cytotoxic against various cancer cell (Silva et al. 1995).

TREHALOSE

Trehalose is formed by α,α-1,1-glycosidic linkage of two low energy hexose moieties (Paiva and Panek 1996; Elbein et al 2003; Grennan 2007). This matter is a unique simple sugar which non-reactive, very stable, colorless, odor-free, non-reducing disaccharide, and capable to protect biomolecules against environmental stress (Schiraldi et al. 2002). Therefore, this compound is a natural product, although not as commonly secondary metabolites of natural products. It works as osmoprotectant during desiccation stress (Adams et al. 1990); such as compatible solute in the stabilization of biological structures under abiotic stress (Garg et al. 2002); serves as a source of energy and carbon (Elbein et al 2003; Schluepmann et al. 2003); serves as signaling molecule to control certain metabolic pathways (Muller et al. 2001; Elbein et al 2003; Avonce et al 2005); protects proteins and cellular membranes from inactivation or denaturation caused by harsh environmental stress, such as desiccation, dehydration (drought), thermal heat, cold freezing, oxidation, nutrient starvation, and salt (Avigad 1982; Elbein et al. 2003; Wu et al. 2006). Trehalose acts as a global protectant against abiotic stress (Jang et al. 2003). This matter is proved to be an active stabilizer of enzymes, proteins, biomasses, pharmaceutical preparations and even organs for transplantation (Schiraldi et al. 2002), and very prospects as molecular bio stabilizer in cosmetic, pharmacy and food (Roser 1991; Kidd and Devorak 1994). These multiple effects of trehalose on protein stability and folding suggest promising applications (Singer and Lindquist 1998).

Trehalose has long been known for protecting certain organisms from desiccation. The accumulation of the disaccharide trehalose in anhydrobiotic organisms allows them to survive severe environmental stress (Zentella et al. 1999). Trehalose also promotes survival under extreme heat conditions, by enabling proteins to retain their native conformation at elevated temperatures and suppressing the aggregation of denatured proteins (Singer and Lindquist 1998). Desiccation can reduce the lipid component in thylakoid membranes (Guschina et al. 2002). However, in desiccation-tolerant plants, membrane integrity appears not to be affected during drought-stress. *S. lepidophylla* retain their structural organization as intact bilayers (Platt et al. 1994) and often referred as resurrection plant because able to live on long drought and recovery through rehydration

process (Crowe et al. 1992), even when the most water body (99%) is evaporated (Schiraldi et al. 2002; van Dijck et al. 2002). Another species, *S. tamariscina*, can also remain alive in a desiccated state and resurrect when water becomes available (Liu et al. 2008). The drought can change fluorescence and pigmentation, but can not cause dying (Casper et al. 1993).

Trehalose exists in a wide variety of organisms, including bacteria, yeast, fungi, insects, invertebrates, and lower and higher plants (Elbein 1974; Crowe et al. 1984; Elbein et al. 2003), but rarely find in Angiosperms (Muller et al. 1995) and does not find in mammals (Teramoto et al 2008), and it is not accumulated to detectable levels in the most plants (Garg et al. 2002). This sugar plays important roles in cryptobiosis of *Selaginella* and other organisms, which revive with water from a state of suspended animation induced by desiccation (Teramoto et al 2008). Trehalose is the major sugar formed in photosynthesis of *Selaginella* (White and Towers 1967). Some *Selaginella* contains high concentration of trehalose, such as *S. lepidophylla* (Adams et al. 1990; Mueller et al. 1995; Zentella et al. 1999), *S. sartorii* (Iturriaga et al. 2000), *S. martensii* (Roberts and Tovey 1969), *S. densa*, and *S. wallacei* (White and Towers 1967). Trehalose can reach 10-15% of cell dry weight (Grba et al. 1975).

Trehalose is not merely chemical compounds that respond to resurrection ability of *Selaginella*. The protective effect of trehalose is correlated with trapping of the protein in a harmonic potential, even at relatively high temperature (Cordone et al. 1999). Deeba et al. (2009) suggest that *S. bryopteris*, one kind of resurrection plants, has about 250 proteins that expressed in response to dehydration and rehydration, and involved in transport, targeting and degradation in the desiccated fronds. Harten and Eickmeier (1986) suggest that several conservation enzymes are beneficial for rapid resumption of metabolic activity of *S. lepidophyla*. Furthermore, Eickmeier (1979; 1982) suggests that both organelle- and cytoplasm-directed protein syntheses are necessary for full photosynthetic recovery during rehydration of *S. lepidophyla*.

FUTURE RESEARCH

Research on *Selaginella* is still widely challenging. In the most elementary study of plant taxonomy, the high morphological variation of *Selaginella* causes several misidentifications of this taxon. In ecology, global warming, habitat fragmentation and degradation that affected on sustainability of this resource need to be observed. In physiology, changes of fluorescens and pigmentation caused by environmental factor and age need to be explained. In biochemistry, several natural products are not exploited yet. One of non-biflavonoid compound from *Selaginella* that needs to be further investigated is trehalose. Molecular study is also required clarifying certain identity and phylogenetic relationship.

In Indonesia, several authors often misidentify *Selaginella* species, especially on popular article. This matter is often identified as *S. doederleinii*, including Javanese wild species. The most authors agree that *S. doederleinii* is recognized as non-native plant of Indonesia, which natural distribution in India, Burma, Thailand, Laos, Cambodia, Vietnam, Malaya, Chinese, Hong Kong, Taiwan, and Japan (Huang 2006; USDA 2008). Java has no species of *S. doederleinii* according to Alston (1935a) and observation on *Selaginella* collection of Herbarium Bogoriense, through several Kalimantan collection is suspected and has morphological similarity to this species (ADS 2007, data is not shown). This matter is possibly caused by referring to Dalimartha (1999), which include *S. doederleinii* in Indonesian plant medicines. Harada et al. (2002) conduct similar misidentification, which cites *S. plana* as one of plant medicine in Mount Halimun NP (nowadays Mount Halimun-Salak NP), but the main picture presented is *S. willdenowii*. Field survey indicates that *S. willdenowii* is easily found in roadside to Cikaniki Research Station of Mount Halimun-Salak NP, at rice field, shrubs land, primary and secondary forest, while *S. plana* is easier to be found in country field at lower height (ADS 2008, personal observation).

Species misidentification impacts on drug properties, because each species differ chemical constituent. Natural products content of *Selaginella* highly varies depending on species, although does not always congruent with traditional medical recipes. Sundanese people of Mount Halimun-Salak NP complementarily or substitutionally uses several *Selaginella* for treatment of after childbirth including *S. ornata*, *S. willdenowii*, *S. involvens*, and *S. intermedia*, but for similar recipe, Sundanese around Bogor only uses *S. plana* (ADS 2008, personal observation). Morphological diversity at infraspecific level, and changes on pigmentation caused by age, drought and other environmental factors able to entangle identify base on morphological characteristics. It needs identification base on molecular characteristics, such as Korall et al. (1999) and Korall and Kenrick (2002, 2004). Besides, taxonomy of Malesian *Selaginella* needs to revise, because still based on old literature namely Alderwereld van Rosenburgh (1915a,b; 1916, 1917, 1918, 1920, 1922) and Alston (1934, 1935a,b; 1937, 1940). In a research brief about the traditional utilization of *Selaginella* in Indonesia, Setyawan (2009) collect at least 40 species of which half are estimated to new species or new records.

Completely research on variability of biflavonoid compounds of various *Selaginella* species with various solvent has not conducted yet. This matter is only conducted to certain species, compounds, and solvents. Natural products of certain plant determine economical value that required in industrial scale of modern pharmacy. Species with various low content of natural products less value than species with restricted high content, because modern pharmacy exploits natural products at molecular level. However, this matter is not always become consideration in traditional medication, because it generally uses simplicia that can be easily substituted by each other. In phytochemistry and chemotaxonomy, high variety of natural products can assist identification, though each has no high content. However, a very low compound is not

significantly important for identification, because often influenced by environmental factors, not merely to genetic factor. Bioactivity of each biflavonoid also requires to be observed because nowadays only bioactivity of amentoflavone and ginkgetin has been completely studied. HPLC is potent method for analyzing natural products of *Selaginella* (Fan et al. 2007).

Besides, trehalose observation on *Selaginella* is still restricted on a few species, and need to be conducted to amount of other species caused by potent economic value that can be generated. It can preliminary indicated by species that in curling leaves in hot weather or drought condition.

Biflavonoid study of *Selaginella* is still require attention such as: (i) the importance of assuring species identity caused by height morphological variety including by using molecular method; (ii) the importance of extending research coverage most of biflavonoid type, species, and extraction method; and also (iii) the importance of extending investigation on bioactivity, including non-biflavonoid compound, which also have high economic potent such as trehalose.

CONCLUSION

Selaginella is a potent medicinal matter, which mostly contains phenolic (flavonoid), alkaloid, and terpenoid. This matter is traditionally used to cure several diseases, especially for wound, after childbirth, and menstrual disorder. Biflavonoid, a dimeric form of flavonoids, is one of the most valuable natural products of *Selaginella*, which constituted at least 13 compounds, namely amentoflavone, 2',8"-biapigenin, delicaflavone, ginkgetin, heveaflavone, hinokiflavone, isocryptomerin, kayaflavone, ochnaflavone, podocarpusflavone A, robustaflavone, sumaflavone, and taiwaniaflavone. Human medically uses biflavonoid especially for antioxidant, anti-inflammatory, and anti-cancer. *Selaginella* also contains several natural products, such as trehalose which valuable for bioindustry. *Selaginella* research exhaustively needs to be conducted to explore all natural products constituents and their bioactivities.

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