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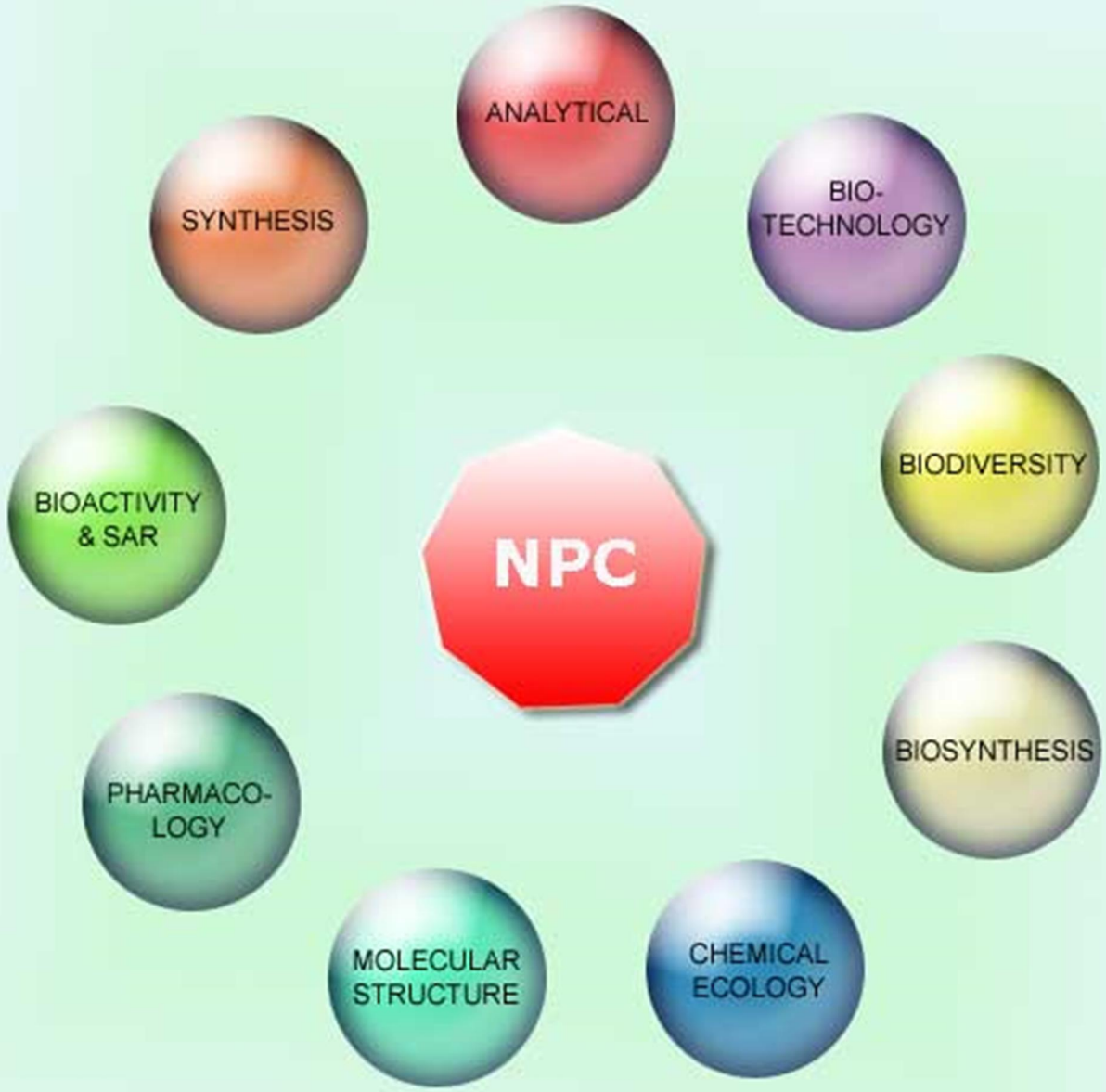

Volume 10. Issue 7. Pages 1141-1332. 2015
ISSN 1934-578X (printed); ISSN 1555-9475 (online)
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NPC Natural Product Communications

2015
Vol. 10
No. 7
1325 - 1330

Eriosema (Fabaceae) Species Represent a Rich Source of Flavonoids with Interesting Pharmacological Activities

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Received: November 4th, 2014; Accepted: March 26th, 2015

Many flavonoids have so far been isolated as main secondary metabolites in plant species of the genus *Eriosema* (Fabaceae), which contains approximately 160 species. A total of 52 flavonoids including isoflavones, dihydroflavonols, flavonols, flavanones, dihydrochalcones, isoflavanone and their pyrano or glucoside derivatives were isolated and characterized from the five species of this genus investigated to date. Total synthesis and semi-synthesis (acetylation, methylation, hydrogenation, and cyclization) of some isolated flavonoids were reported. Due to several significant pharmacological properties (antimicrobial, cytotoxicity, anti-mycobacterial, antioxidant, antiviral, erectile-dysfunction, vasodilatory and hypoglycemic) of the isolated flavonoids and derivatives, more scientists should be interested in investigating *Eriosema* species. The present review is the first to document all flavonoids that have been reported from the genus *Eriosema* to date together with their synthetic and semi-synthetic derivatives, and their pharmacological properties. Dihydrochalcones, which are precursors of other classes of flavonoids, are very rare in natural sources and their isolation from *Eriosema* species may explain the large number of flavonoids found in this genus. It appears that isoflavone could be a marker for species in this genus. The 83 flavonoids (**1-83**) documented include 52 isolates, 31 semi-synthetic and 3 totally synthetic derivatives. Data were obtained from Google scholar, Pubmed, Scifinder, Sciencedirect, and Scopus. With 52 different flavonoids isolated from only 5 of the approximately 160 species it shows the remarkable chemical diversity of this genus. This compilation of the biological activities and chemical composition may renew the interest of pharmacologists and phytochemists in this genus.

Keywords: *Eriosema*, Flavonoids, Chemistry, Pharmacology, Review.

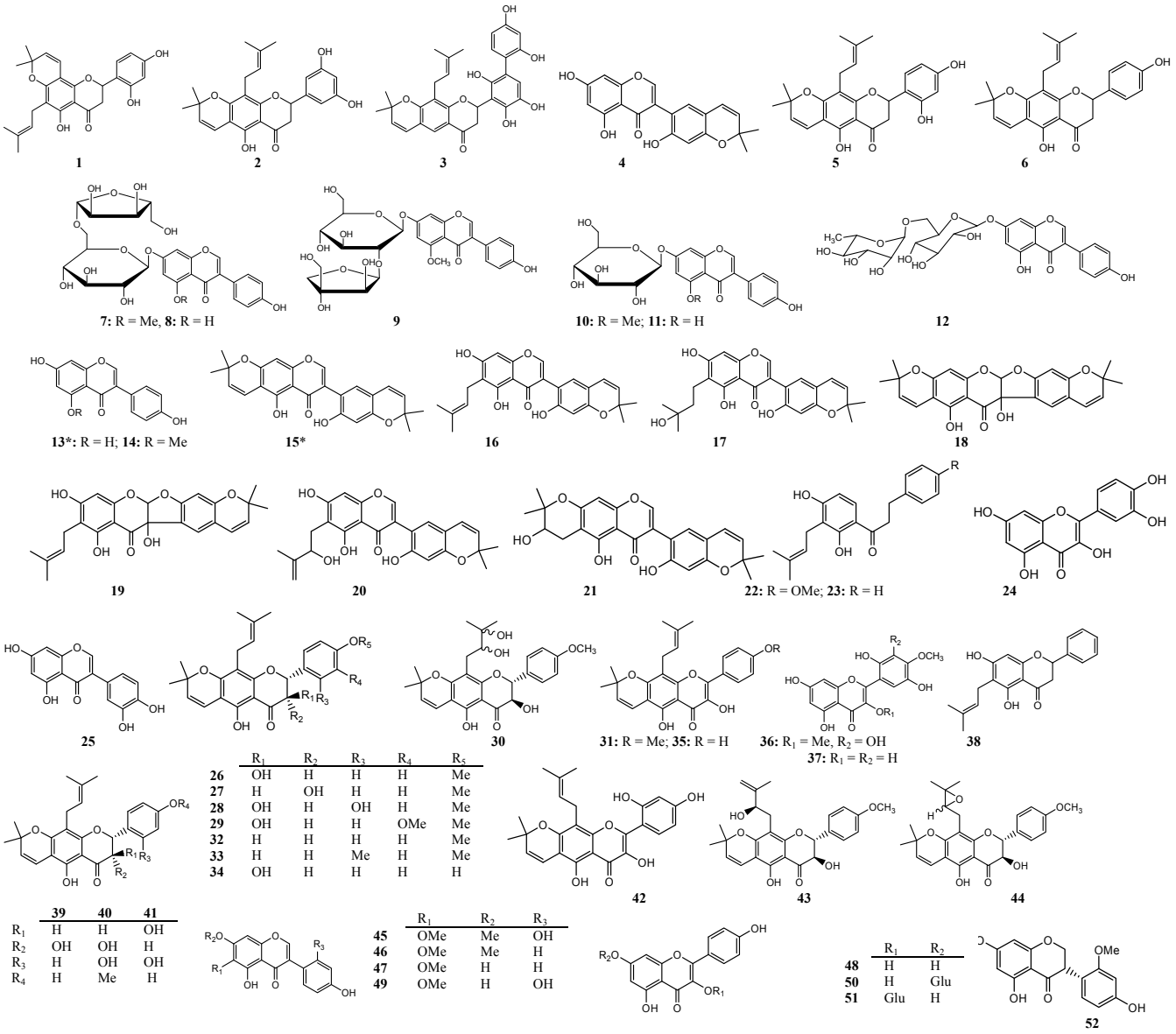
The genus *Eriosema*, a member of the Fabaceae family, contains about 160 species, mostly distributed in tropical regions of Africa, that are used in traditional medicine to treat various diseases [1-6]. Flavonoids appear to be the main secondary metabolites reported in the genus [6, 7]. This review documents all the flavonoids that have been reported from *Eriosema* species to date, together with their synthetic and semi-synthetic derivatives, and their various pharmacological properties (antimicrobial, cytotoxicity, anti-mycobacterial, antioxidant, antiviral, erectile-dysfunction, vasodilatory and hypoglycemic). Data were obtained from Google scholar, Sciencedirect, Scopus, Pubmed, and Scifinder. In total, information for 83 flavonoids (**1-83**) is documented. This includes 31 semi-synthetic and 3 totally synthetic derivatives, as well as 52 different flavonoids isolated from 5 *Eriosema* species. These results indicate the phytochemical and pharmacological wealth of flavonoids present in *Eriosema* species and should encourage the investigation of more species.

The botany and distribution of the genus

The genus *Eriosema* (DC) Rchb1828 consists mainly of herbs or shrubs. The species are found mainly in Africa. About 109 species occur only in subtropical Africa and 34 in southern Africa and subtropical Africa [8]. They grow in different environments in tropical and subtropical forest margins to grassland, rocky and swampy areas. There are about 40 species that occur from Mexico to northern Argentina and two in south-east Asia to Australia [9].

Chemistry

Isolated flavonoids: Flavonoids have been reported from 1995 to date as major constituents identified in *Eriosema* species [6, 7] (Figure 1, Table 1). Eriosemaones A (**1**), B (**2**), C (**3**) and D (**4**), and flemichin D (**5**), isolated from the dichloromethane extract of the roots of *E. tuberosum*, were the first report of flavonoids from the genus [7]. Further investigation was carried out on the same species to afford lupinifolin (**6**) [10]. Isoflavonoid glucosides and isoflavonoids, including 5-*O*-methylgenistein-7-*O*-*β*-D-apiofuranosyl-(1→6)-*O*-*β*-D-glucopyranoside (**7**), genistein 7-*O*-*β*-D-apiofuranosyl-(1→6)-*O*-*β*-D-glucopyranoside (**8**), eriosemaside C (**9**), 5-*O*-methylgenistein-7-*O*-*β*-D-glucopyranoside (**10**), genistin (**11**), sphaerobioside (**12**), genistein (**13**), and 5-*O*-methylgenistein (**14**), were reported from the *n*-butanol-soluble fraction of a methanol extract of the roots of *E. tuberosum* [11, 12]. Seven pyrano-isoflavones, kraussianones (**15-21**), were reported from the extract of the roots of *E. kraussianum* N. E. Br. [1, 2]. Two dihydrochalcones, erioschalcones A (**22**) and B (**23**) were isolated for the first time from the dichloromethane/methanol (1:1, v/v) extract of the whole plant of *E. glomerata*, together with one flavonol, quercetin (**24**) and one isoflavone, isoluteolin (**25**) [3]. Khonklonginols A-H (**26-33**), six flavonols and two flavanones were reported as novel derivatives, along with five known flavonoids, lupinifolinol (**34**), dehydrolupinifolinol (**35**), eriosemaone A (**1**), flemichin D (**5**), and lupinifolin (**6**) from the *n*-hexane and dichloromethane extracts of the roots of *E. chinense* [13]. Investigation of the ethanol extract of the twigs of *E. robustum* gave two novel flavonols, robusflavones A (**36**) and B (**37**), together



1 **2** **3** **4** **5** **6**

7: R = Me, **8:** R = H **9** **10:** R = Me; **11:** R = H **12**

13*: R = H; **14:** R = Me **15*** **16** **17** **18**

19 **20** **21** **22:** R = OMe; **23:** R = H **24**

25 **30** **31:** R = Me; **35:** R = H **36:** R_1 = Me, R_2 = OH **37:** R_1 = R_2 = H **38**

	R_1	R_2	R_3	R_4	R_5
26	OH	H	H	H	Me
27	H	OH	H	H	Me
28	OH	H	OH	H	Me
29	OH	H	H	OMe	Me
32	H	H	H	H	Me
33	H	H	Me	H	Me
34	OH	H	H	H	H

42 **43** **44**

	39	**40**	**41**
R_1	H	H	OH
R_2	OH	OH	H
R_3	H	OH	OH
R_4	H	Me	H

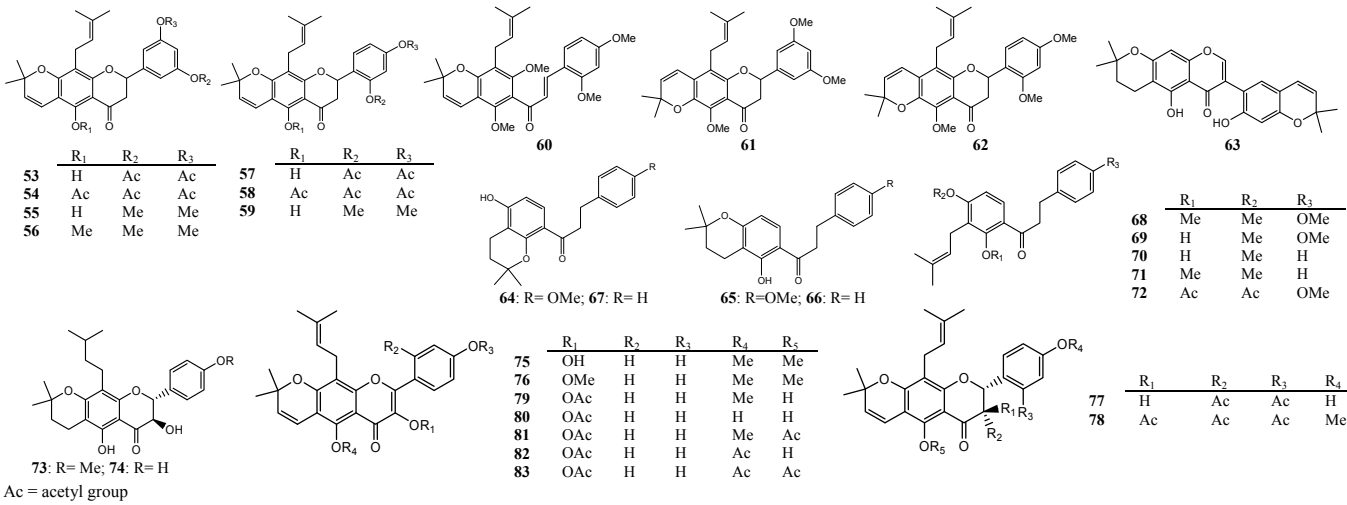
	R_1	R_2	R_3
45	OMe	Me	OH
46	OMe	Me	H
47	OMe	H	H
49	OMe	H	OH

	R_1	R_2
48	H	H
50	H	Glu
51	Glu	H

52

* Also reported as total synthetic derivative, Glu = glucosyl

Figure 1: Chemical structures of flavonoids reported from *Eriosema* genus.



	R_1	R_2	R_3
53	H	Ac	Ac
54	Ac	Ac	Ac
55	H	Me	Me
56	Me	Me	Me

	R_1	R_2	R_3
57	H	Ac	Ac
58	Ac	Ac	Ac
59	H	Me	Me

60 **61** **62** **63**

64: R= OMe; **67**: R= H **65**: R=OMe; **66**: R= H

	R_1	R_2	R_3
68	Me	Me	OMe
69	H	Me	OMe
70	H	Me	H
71	Me	Me	H
72	Ac	Ac	OMe

73: R= Me; **74**: R= H

	R_1	R_2	R_3	R_4	R_5
75	OH	H	H	Me	Me
76	OMe	H	H	Me	Me
79	OAc	H	H	Me	H
80	OAc	H	H	H	H
81	OAc	H	H	Me	Ac
82	OAc	H	H	Ac	H
83	OAc	H	H	Ac	Ac

	R_1	R_2	R_3	R_4
77	H	Ac	Ac	H
78	Ac	Ac	Ac	Me

Ac = acetyl group

Figure 2: Chemical structures of semi-synthetic derivatives from flavonoids of *Eriosema* genus.

Table 1: Flavonoids that occur in *Eriosema* species and their reported pharmacological activities.

Classes	Compounds	Plant species and parts	Pharmacological Activities
Flavanone	Eriosemaone A (**1**)	*Eriosema tuberosum* (Roots) [7] *E. chinense* (Roots) [13]	Antifungal [7], Cytotoxicity [13], Antimycobacterial [13]
Flavanone	Eriosemaone B (**2**)	*E. tuberosum* (Roots) [7]	Antifungal [7]
Flavanone	Eriosemaone C (**3**)	*E. tuberosum* (Roots) [7]	Antifungal [7]
Isoflavone	Eriosemaone D (**4**)*	*E. tuberosum* (Roots) [7]	Antifungal [7]
Flavanone	Flemichin D (**5**)	*E. tuberosum* (Roots) [7] *E. chinense* (Roots) [13]	Antifungal [7], Cytotoxicity [13], Antimycobacterial [13], Antioxidant [6], Antimicrobial [6]
Flavanone	Lupinifolin (**6**)	*E. tuberosum* (Roots) [10] *E. chinense* (Roots) [13]	Antifungal [10], Cytotoxicity [13], Antimycobacterial [13]
Isoflavone glucoside	5-*O*-Methylgenistein-7-*O*-*β*-D-apiofuranosyl-(1⟶6)-*O*-*β*-D-glucopyranoside (**7**)	*E. tuberosum* (Roots) [11]	-
Isoflavone glucoside	Genistein 7-*O*-*β*-D-apiofuranosyl-(1 ⟶6)-*O*-*β*-D-glucopyranoside (**8**)	*E. tuberosum* (Roots) [11]	-
Isoflavone glucoside	Eriosemaside C (**9**)	*E. tuberosum* (Roots) [12]	Antifungal [12]
Isoflavone glucoside	5-*O*-Methylgenistein-7-*O*-*β*-D-glucopyranoside (**10**)	*E. tuberosum* (Roots) [11]	Antiviral [18]
Isoflavone	Genistin (**11**)	*E. tuberosum* (Roots) [11], *E. chinense* (Roots) [6]	Antioxidant [20], Antimicrobial [6]
Isoflavone	Sphaerobioside (**12**)	*E. tuberosum* (Roots) [11]	Insecticidal [19], Toxicity [19]
Isoflavone	Genistein (**13**)*	*E. tuberosum* (Roots) [11]	Anticancer [21], Toxicity [21], Insecticidal [19]
Isoflavone	5-*O*-Methylgenistein (**14**)	*E. tuberosum* (Roots) [11]	-
Pyrano-isoflavone	Kraussianone 1 (**15**)*	*E. kraussianum* N. E. Br. (Roots) [1]	Erectile-dysfunction [1, 2], Vasodilatory and hypoglycemic [22]
Pyrano-isoflavone	Kraussianone 2 (**16**)	*E. kraussianum* N. E. Br. (Roots) [1]	Erectile-dysfunction [1, 2], Vasodilatory and hypoglycemic [22], L-NAME- induced Pre-eclamptic [23]
Pyrano-isoflavone	Kraussianone 3 (**17**)	*E. kraussianum* N. E. Br. (Roots) [1]	Erectile-dysfunction [1]
Pyrano-isoflavone	Kraussianone 4 (**18**)	*E. kraussianum* N. E. Br. (Roots) [1]	Erectile-dysfunction [1]
Pyrano-isoflavone	Kraussianone 5 (**19**)	*E. kraussianum* N. E. Br. (Roots) [1]	Erectile-dysfunction [1]
Pyrano-isoflavone	Kraussianone 6 (**20**)	*E. kraussianum* N. E. Br. (Roots) [2]	Erectile-dysfunction [2]
Pyrano-isoflavone	Kraussianone 7 (**21**)	*E. kraussianum* N. E. Br. (Roots) [2]	Erectile-dysfunction [2]
Dihydrochalcone	Erioschalcone A (**22**)	*E. glomerata* (Whole plant) [3]	Antimicrobial [3]
Dihydrochalcone	Erioschalcone B (**23**)	*E. glomerata* (Whole plant) [3]	Antimicrobial [3]
Flavonol	Quercetin (**24**)	*E. glomerata* (Whole plant) [3]	Antimicrobial [3]
Isoflavone	Isoluteolin (**25**) or Orobol (**25**)	*E. glomerata* (Whole plant) [3]	Antimicrobial [3]
Dihydroflavonol	Khonklonginol A (**26**)	*E. chinense* (Roots) [13]	Cytotoxicity [13], Antimycobacterial [13], Antioxidant [6], Antimicrobial [6]
Dihydroflavonol	Khonklonginol B (**27**)	*E. chinense* (Roots) [13]	Cytotoxicity [13], Antimycobacterial [13]
Dihydroflavonol	Khonklonginol C (**28**)	*E. chinense* (Roots) [13]	-
Dihydroflavonol	Khonklonginol D (**29**)	*E. chinense* (Roots) [13]	-
Dihydroflavonol	Khonklonginol E (**30**)	*E. chinense* (Roots) [13]	-
Pyranoflavonol	Khonklonginol F (**31**)	*E. chinense* (Roots) [13]	Cytotoxicity [13], Antimycobacterial [13]
Flavanone	Khonklonginol G (**32**)	*E. chinense* (Roots) [13]	-
Flavanone	Khonklonginol H (**33**)	*E. chinense* (Roots) [13]	Cytotoxicity [13], Antimycobacterial [13]
Dihydroflavonol	Lupinifolinol (**34**)	*E. chinense* (Roots) [13]	Cytotoxicity [13], Antimycobacterial [13], Antioxidant [6], Antimicrobial [6]
Pyranoflavone	Dehydrolupinifolinol (**35**)	*E. chinense* (Roots) [13]	Cytotoxicity [13], Antimycobacterial [13]
Flavonol	Robusflavone A (**36**)	*E. robustum* (Twigs) [4, 5]	Antioxidant [4], Antimicrobial [5]
Flavonol	Robusflavone B (**37**)	*E. robustum* (Twigs) [4, 5]	Antioxidant [4], Antimicrobial [5]
Flavanone	6-Prenylpinocembrin (**38**)	*E. robustum* (Twigs) [4, 5]	Antioxidant [4], Antimicrobial [5]
Dihydroflavonol	3-epi-Lupinifolinol (**39**)	*E. chinense* (Roots) [6]	Antioxidant [6]
Dihydroflavonol	3-epi-Khonklonginol C (**40**)	*E. chinense* (Roots) [6]	-
Dihydroflavonol	2-Hydroxylupinifolinol (**41**)	*E. chinense* (Roots) [6]	Antioxidant [6], Antimicrobial [6]
Pyranoflavonol	3,5,2′,4′-Tetrahydroxy-6",6"-dimethylpyrano(2",3":7,6)-8-(3"',3"'-dimethylallyl)flavone (**42**)	*E. chinense* (Roots) [6]	Antioxidant [6], Antimicrobial [6]
Dihydroflavonol	(2*R*,3*R*,2"'*R*)-3,5,2"'-Trihydroxy-4-methoxy-6",6"-dimethylpyrano(2",3":7,6)-8-(3"'-methyl-but-3"'-enyl)flavanone (**43**)	*E. chinense* (Roots) [6]	-
Dihydroflavonol	2"',3"'-Epoxykhonklonginol A (**44**)	*E. chinense* (Roots) [6]	Antioxidant [6], Antimicrobial [6]
Isoflavone	6,7-Dimethoxy-5,2',4'-trihydroxyisoflavone (**45**)	*E. chinense* (Roots) [6]	-
Isoflavone	7-*O*-Methyltectorigenin (**46**)	*E. chinense* (Roots) [6]	-
Isoflavone	Tectorigenin (**47**)	*E. chinense* (Roots) [6]	Antioxidant [6], Antimicrobial [6]
Flavonol	Kaempferol (**48**)	*E. chinense* (Roots) [6]	Antioxidant [6], Antimicrobial [6]
Isoflavone	5,7,2',4'-Tetrahydroxy-6-methoxyisoflavone (**49**)	*E. chinense* (Roots) [6]	-
Flavonol	Kaempferol-7-*O*-*β*-D-glucopyranoside (**50**)	*E. chinense* (Roots) [6]	Antioxidant [6], Antimicrobial [6]
Flavonol	Astragalin (**51**)	*E. chinense* (Roots) [6]	Antioxidant [6], Antimicrobial [6]
Isoflavanone	Cajanol (**52**)	*E. chinense* (Roots) [6]	Anticancer [17], Antimicrobial [24]

* Also reported as total synthetic derivatives, -: not reported

with a known flavanone, 6-prenylpinocembrin (**38**) [4, 5]. Seven new flavonoids, including 3-*epi*-lupinifolinol (**39**), 3-*epi*-khonklonginol C (**40**), 2-hydroxylupinifolinol (**41**), 3,5,2′,4′-tetrahydroxy-6",6"-dimethylpyrano(2",3":7,6)-8-(3"',3"'-dimethylallyl)flavone (**42**), (2*R*,3*R*,2"'*R*)-3,5,2"'-trihydroxy-4-methoxy-6",6"-dimethylpyrano(2",3":7,6)-8-(3"'-methylbut-3"'-enyl)flavanone (**43**), 2"',3"'-epoxykhonklonginol A (**44**) and 6,7-dimethoxy-5,2',4'-trihydroxyisoflavone (**45**), and nine known compounds, genistein (**13**), 7-*O*-methyltectorigenin (**46**), tectorigenin (**47**), kaempferol (**48**), 2',4',5,7-tetrahydroxy-6-methoxyisoflavone (**49**), kaempferol-7-*O*-*β*-D-glucopyranoside (**50**), genistin (**11**), astragalin (**51**) and cajanol (**52**) were further reported from the *n*-hexane, dichloromethane, and methanol extracts of the roots of *E. chinense* [6].

The isolated flavonoids reported from this genus, are mainly isoflavones (21 compounds), followed by dihydroflavonols (11), flavonols (9), flavanones (8), dihydrochalcones (2) and one isoflavanone. Dihydrochalcones, which are precursors of other classes of flavonoids, are very rare from natural sources. Their isolation from the genus *Eriosema* may explain the large number of flavonoids found in this genus.

Synthetic and semi-synthetic derivatives: The semi-synthesis and total synthesis investigations reported were carried out to facilitate separation, to obtain enough samples for bioassays, to improve the pharmacological activity and/or to evaluate the structure-activity relationship (SAR) of some isolated compounds.

Table 2: Semi-synthetic derivatives of flavonoids from *Eriosema* genus

Compounds	Precursors	Pharmacological Activities
5-Hydroxy-3',5'-diacetyl-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":6,7)flavanone (**53**)	Eriosemaone B (**2**) [7]	Antifungal [7]
5,3',5'-Triacetyl-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":6,7)flavanone (**54**)	Eriosemaone B (**2**) [7]	Antifungal [7]
5-Hydroxy-3',5'-dimethoxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":6,7)flavanone (**55**)	Eriosemaone B (**2**) [7]	Antifungal [7]
5,3',5'-Methoxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":6,7)flavanone (**56**)	Eriosemaone B (**2**) [7]	Antifungal [7]
2',4'-Diacetyl-5-hydroxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":6,7) flavanone (**57**)	Flemichin D (**5**) [7]	Antifungal [7]
5,2',4'-Triacetyl-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":6,7) flavanone (**58**)	Flemichin D (**5**) [7]	Antifungal [7]
5,2',4'-Trimethoxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":6,7) flavanone (**59**)	Flemichin D (**5**) [7]	Antifungal [7]
2',6',2,4-Tetramethoxy-5'-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":3',4')chalcone (**60**)	Fraction from the extract [7]	Antifungal [7]
5,3',5'-Trimethoxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(2",3":6,7)flavanone (**61**)	Fraction from the extract [7]	Antifungal [7]
5,2',4'-Trimethoxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(2",3":6,7) flavanone (**62**)	Fraction from the extract [7]	Antifungal [7]
5,2′-Dihydroxy-[(6″,6″-dimethylpyrano (2″,3″:4′,5′)][(6‴,6‴-dimethyl-4″,5″-dehydropyrano(2‴,3‴:7,6)]-isoflavone (**63**)	Kraussianone 2 (**16**) [2]	Erectile-dysfunction [2]
1-(5-Hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-8-yl)-3-(4-methoxy–phenyl)propan-1-one (**64**)	Erioschalcone A (**22**) [3]	Antimicrobial [14]
1-(5-Hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-3-(4-methoxyphenyl)propan-1-one (**65**)	Erioschalcone A (**22**) [3]	Antimicrobial [14]
1-(5-Hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-8-yl)-3-phenylpropan-1-one (**66**)	Erioschalcone B (**23**) [3]	Antimicrobial [14]
1-(5-Hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-3-phenylpropan-1-one (**67**)	Erioschalcone B (**23**) [3]	Antimicrobial [14]
1-[2,4-Dimethoxy-3-(3-methylbut-2-enyl)phenyl]-3-(4-metho-xyphenyl)propan-1-one (**68**)	Erioschalcone A (**22**) [3]	Antimicrobial [14]
1-[2-Hydroxy-4-methoxy-3-(3-methylbut-2-enyl)phenyl]-3-(4-methoxyphenyl)propan-1-one (**69**)	Erioschalcone A (**22**) [3]	Antimicrobial [14]
1-[2-Hydroxy-4-methoxy-3-(3-methylbut-2-enyl)phenyl]-3-phenylpropan-1-one (**70**)	Erioschalcone B (**23**) [3]	Antimicrobial [14]
1-[2,4-Dimethoxy-3-(3-methylbut-2-enyl)phenyl]-3-phenyl-propan-1-one (**71**)	Erioschalcone B (**23**) [3]	Antimicrobial [14]
2′,4′-Diacetyl-4-methoxy-3′-(*γ*,*γ*-dimethylallyl)dihydrochalcone (**72**)	Erioschalcone A (**22**) [3]	-
3,5-Dihydroxy-4′-methoxy-6″,6″-dimethyldehydropyrano[2″,3″:7,6]-8-(3‴,3‴-dimethyldehydroallyl)flavanone (**73**)	Khonklonginol A (**26**) [6, 13]	Antimicrobial [6]
3,5,4'-Trihydroxy-6",6"-dimethyldehydropyrano[2",3":7,6]-8-(3‴,3‴-dimethyldehydroallyl)flavanone (**74**)	Lupinifolinol (**34**) [6, 13]	Antimicrobial [6]
3-Hydroxy-5,4′-dimethoxy-6″,6″-dimethylpyrano[2″,3″:7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**75**)	Khonklonginol A (**26**) [6, 13]	Antimicrobial [6]
3,5,4′-Trimethoxy-6″,6″-dimethylpyrano[2″,3″:7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**76**)	Khonklonginol A (**26**) [6, 13]	Antimicrobial [6]
5-Hydroxy-3,4′-dimethoxy-6″,6″-dimethylpyrano[2″,3″:7,6]-8-(3‴,3‴-dimethylallyl)flavone (**77**)	Khonklonginol A (**26**) [6, 13]	Antioxidant [6], Antimicrobial [6]
3,5,4′-Trimethoxy-6″,6″-dimethylpyrano[2″,3″:7,6]-8-(3‴,3‴-dimethylallyl)flavone (**78**)	Khonklonginol A (**26**) [6, 13]	Antimicrobial [6]
3-Acetyl-5-hydroxy-4′-methoxy-6″,6″-dimethylpyrano[2″,3″:7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**79**)	Khonklonginol A (**26**) [6, 13]	Antimicrobial [6]
3-Acetyl-5,4'-dihydroxy-6",6"-dimethylpyrano[2",3":7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**80**)	Lupinifolinol (**34**) [6, 13]	Antimicrobial [6]
3,4'-Diacetyl-5-hydroxy-6",6"-dimethylpyrano[2",3":7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**81**)	Khonklonginol A (**26**) [6, 13]	Antimicrobial [6]
3,5-Diacetyl-4′-methoxy-6″,6″-dimethylpyrano[2″,3″:7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**82**)	Lupinifolinol (**34**) [6, 13]	Antimicrobial [6]
3,5,4'-Triacetyl-6",6"-dimethylpyrano[2",3":7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**83**)	Lupinifolinol (**34**) [6, 13]	Antimicrobial [6]

-: not reported

Semi-synthesis using acetylation, methylation, hydrogenation, and cyclization reactions were reported for some flavonoids isolated from *Eriosema* genus (Figure 2). Acetylation and methylation were carried out on eriosemaone B (**2**) and flemichin D (**5**) isolated from *E. tuberosum* to afford six derivatives including 5-hydroxy-3',5'-diacetyl-8-*γ*,*γ*-dimethylallyl-6",6"-dimethyl-pyrano(3",2":6,7)flavanone (**53**), 5,3',5'-triacetyl-8-*γ*,*γ*-dimethyl-allyl-6",6"-dimethylpyrano(3",2":6,7)flavanone (**54**), 5-hydroxy-3',5'-dimethoxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":6,7) flavanone (**55**), 5,3',5'-methoxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":6,7)flavanone (**56**), 2',4'-diacetyl-5-hydroxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano (3",2":6,7)flavanone (**57**), 5,2',4'-triacetyl-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyra-no(3",2":6,7)flavanone (**58**), and 5,2',4'-trimethoxy-8-*γ*,*γ*-dime-thylallyl-6",6"-dimethylpyrano(3",2":6,7) flavanone (**59**) [7].

A column chromatography fraction of the extract of *E. tuberosum* was methylated and on purification gave 2',6',2,4-tetramethoxy-5'-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(3",2":3',4')-chalcone (**60**), 5,3',5'-trimethoxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyra-no(2",3":6,7)flavanone (**61**), and 5,2',4'-trimethoxy-8-*γ*,*γ*-dimethylallyl-6",6"-dimethylpyrano(2",3":6,7) flavanone (**62**) [7]. Cyclization of kraussianone 2 (**15**), isolated from *E. kraussianum* N. E. Br., afforded 5,2′-dihydroxy-[(6″,6″-dimethylpyrano(2″,3″:4′,5′)] [(6‴,6‴-dimethyl-4″,5″-dehydropy-rano(2‴,3‴:7,6)]-isoflavone (**63**) [1, 2].

Nine semi-synthetic derivatives were obtained by methylation, cyclization and acetylation reactions of erioschalcones A (**22**) and B (**23**) isolated from *E. glomerata* [3, 14]. These included 1-(5-hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-8-yl)-3-(4-metho-xyphenyl)propan-1-one (**64**), 1-(5-hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-3-(4-methoxyphenyl)propan-1-one (**65**), 1-(5-hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-8-yl)-3-phen-ylpropan-1-one (**66**), 1-(5-hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-3-phenylpropan-1-one (**67**), 1-[2,4-dimethoxy-3-(3-methylbut-2-enyl)phenyl]-3-(4-methoxyphenyl)propan-1-one (**68**), 1-[2-hydroxy-4-methoxy-3-(3-methylbut-2-enyl)phenyl]-3-(4-methoxyphenyl)propan-1-one (**69**), 1-[2-hydroxy-4-methoxy-3-(3-methylbut-2-enyl)phenyl]-3-phenylpropan-1-one (**70**), 1-[2,4-dimethoxy-3-(3-methylbut-2-enyl)phenyl]-3-phenylpropan-1-one (**71**), and 2′,4′-diacetyl-4-methoxy-3′-(*γ*,*γ*-dimethylallyl)dihydro-chalcone (**72**) [15].

Khonklonginol A (**26**) and lupinifolinol (**34**), isolated from the roots of *E. chinense*, were subjected to semi-synthesis using hydrogenation, methylation and acetylation reactions to give eleven derivatives: 3,5-dihydroxy-4′-methoxy-6″,6″-dimethyldehydropyra-no[2″,3″:7,6]-8-(3‴-methylbutyl)flavanone (**73**), 3,5,4'-trihydroxy-6",6"-dimethyldehydropyrano[2",3":7,6]-8-(3‴-methylbutyl)flava-none (**74**), 3-hydroxy-5,4′-dimethoxy-6′′,6′′-dimethyl-pyrano[2″,3″:7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**75**), 3,5,4′-trimethoxy-6″,6″-dimethylpyrano[2″,3″:7,6]-8-(3‴,3‴-dimethyl-allyl)flavanone (**76**), (5-hydroxy-3,4′-dimethoxy-6′′,6′′-dimethylpyrano[2″,3″:7,6]-8-(3‴,3‴-dimethylallyl)flavone (**77**), 3,5,4′-trimethoxy-6″,6′′-dimethylpyrano[2″,3″:7,6]-8-(3‴,3‴-dimethylallyl)flavone (**78**), 3-acetyl-5-hydroxy-4′-methoxy-6″,6′′-dimethylpyrano[2″,3″:7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**79**), 3-acetyl-5,4'-dihydroxy-6",6"-dimethylpyrano[2",3":7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**80**), 3,4'-diacetyl-5-hydroxy-6",6"-dimethylpyrano[2",3":7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**81**), 3,5-diacetyl-4′-methoxy-6′′,6′′-dimethylpyrano[2′′,3′′:7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**82**), and 3,5,4'-triacetyl-6",6"-dimethylpyrano[2",3":7,6]-8-(3‴,3‴-dimethylallyl)flavanone (**83**) [6, 13].

The total synthesis of pyrano-isoflavone kraussianone 1 (**15**), as well as isoflavones eriosemaone D (**4**) and genistein (**13**), were achieved using the Suzuki-Miyaura reaction followed by the regioselective formation of the dimethylpyran scaffolds to the phloroglucinol (ring A) and resorcinol (ring B) moieties [16].

Chemotaxonomic significance of flavonoids from Eriosema genus

Among secondary metabolites found in *Eriosema* species, flavonoids are widely represented. A large number of isoflavones has been isolated, followed by dihydroflavonols, flavonols,

flavanones, dihydrochalcones and isoflavanones. Isoflavones were reported from *E. tuberosum* [7, 11, 12], *E. kraussianum* [1, 2], *E. glomerata* [3], and *E. chinense* [6]. The occurrence of isoflavones could be considered as a marker for this genus and may have a chemotaxonomic significance for *Eriosema* species.

Pharmacological activities

Various pharmacological activities have been investigated for flavonoids of the genus *Eriosema* and their derivatives. These include antimicrobial, cytotoxic, erectile-dysfunction, antioxidant, vasodilatory, hypoglycemic, and L-NAME pre-eclamptic activities. Prominent results are highlighted below while all the pharmacological activities are documented in Tables 1 and 2.

Antimicrobial activity and cytotoxicity

Compounds **1**-**6** and **9**, and their derivatives (**53**-**62**), inhibited the growth of *Cladosporium cucumerinum* and *Candida albicans* using thin layer chromatography (TLC) bioassays [7, 10, 12]. Compounds **1**, **5** and **6** had significant anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Ra (MIC 12.5 µg/mL in all cases) and cytotoxicity to small-cell lung (NCI-H187) and oral epidermal carcinoma (KB) human cell lines were reported with IC_{50} values of 5.8 and 6.0 µg/mL, 3.3 and 2.1 µg/mL, and 2.4 and 6.5 µg/mL, respectively [13]. Further antimicrobial activity was reported for compound **5**, which significantly inhibited the growth of *Bacillus cereus*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Staphylococcus aureus*, *S. aureus* (MRSA), *S. epidermidis*, *Streptococcus agalactiae*, and *S. pyrogenes*, with MICs of 4.7 µg/mL in all cases [6]. The antimicrobial activity, expressed as radius of the zone of inhibition (RZI), of erioschalcones A (**22**) and B (**23**), compounds **24** and **25** were reported at a concentration of 1 µg/µL [3]. Erioschalcone B (**23**) had significant antifungal activity against *Microbotryum violaceum* (RZI of 13 mm), whereas erioschalcone A (**22**) had some activity against the Gram-negative bacterium *Escherichia coli* (RZI of 10 mm) [3]. Antimycobacterial activity and cytotoxicity were also reported for khonklonginols A (**26**), B (**27**), F (**31**) and H (**33**), lupinifolinol (**34**), and dehydrolupinifolinol (**35**) [13]. Dehydrolupinifolinol (**35**) was active against *M. tuberculosis* H37Ra (MIC 12.5 µg/mL), while lupinifolinol (**34**) had an IC_{50} of 1.73 µg/mL on oral epidermal carcinoma (KB) human cell line [13]. Cytotoxicity towards small-cell lung (NCI-H187), and human oral epidermal carcinoma (KB), and Vero cell lines were also reported for compounds **26** (IC_{50} 3.0, 3.1, 7.9 µg/mL), **27** (IC_{50} 4.3, 3.8, 6.9 µg/mL), **31** (IC_{50} 2.4, 6.7, 7.0 µg/mL), and **33** (IC_{50} 3.3, 5.4, 6.4 µg/mL), respectively [13]. These results were reported with IC_{50} values of 0.37, and 0.44 µg/mL, and 0.12 and 0.042 µg/mL for the reference standards, doxorubicin and isoniazid, on KB and NCI-H187 cell lines, respectively [13]. Antimicrobial activities were published for compounds **26**, **34**, **41** and **42**. Khonklonginol A (**26**) had excellent activity (MICs 2.3 µg/mL) against two Gram-positive bacteria, *Streptococcus agalactiae* and *S. pyrogenes*, whereas lupinifolinol (**34**) inhibited significantly the growth of *B. cereus* (MIC 4.7 µg/mL) [6]. Significant activities were also obtained with compound **41** against *B. cereus* (MIC 2.3 µg/mL), *E. faecalis* (MIC 9.4 µg/mL), *L. monocytogenes* (MIC 9.4 µg/mL), *S. aureus* (MIC 4.7 µg/mL), *S. aureus* (MRSA) (MIC 4.7 µg/mL), *S. agalactiae* (MIC 4.7 µg/mL), and *S. pyrogenes* (MIC 2.3 µg/mL), and with compound **42** (MICs 9.4 µg/mL in all cases) against *B. cereus*, *S. aureus*, *S. aureus* (MRSA), *S. agalactiae*, *S. pyrogenes*, and *S. epidermidis* [6]. The antimicrobial and cytotoxicity of robusflavones A (**36**) and B (**37**), and 6-prenylpinocembrin (**38**) were reported. They all had low antimicrobial activity: compound **36** against *C. albicans* and *P. aeruginosa* (MICs 63 µg/mL), compound **37** against *C. albicans*, *Aspergillus fumigatus* (MICs 65 µg/mL) and *P. aeruginosa* (MIC 63 µg/mL), and compound **38** against *C. albicans* (MIC 65 µg/mL), *S. aureus* (MIC 31.3 µg/mL), *P. aeruginosa* (MIC 63 µg/mL), *E. faecalis* and *E. coli* (MICs 63 µg/mL) [5]. The LC_{50}s of compounds **36**, **37**, and **38** on monkey Vero cells were 13.20, 30.42, and 21.87 µg/mL, respectively [5]. Cajanol (**52**) inhibited the growth of MCF-7 human breast cancer cells in a time and dose-dependent manner and had IC_{50} values of 54.0 µM after 72 h treatment, 58.3 µM after 48 h, and 83.4 µM after 24 h [17]. Compound **52** also arrested the cell cycle in the G2/M phase and induced apoptosis via a ROS-mediated mitochondria-dependent pathway [17].

Three semi-synthetic derivatives (**75**, **78** and **80**) were tested for antimicrobial activity. Compound **75** had good activity against a Gram-negative bacterium *Pseudomonas aeruginosa* (MIC 4.7 µg/mL), while compound **78** was significantly active against *S. pyrogenes* (MIC 9.4 µg/mL) [6]. Compound **80** also had significant activity against *B. cereus*, and *S. pyrogenes* (MICs 4.7 µg/mL) and against *E. faecalis*, *S. aureus* (MRSA), and *S. agalactiae* (MICs 9.4 µg/mL) [6].

Erectile-dysfunction, antioxidant and antiviral activities

Erectile-dysfunction activity was reported on seven pyrano-isoflavones, kraussianones 1 – 7 (**15** - **21**), isolated from *E. kraussianum*. At a concentration of 78 ng/mL kraussianone 1 (**15**) had a percentage contraction of cavernosal smooth muscle (85%) comparable with that of Viagra (100%), while the contraction due to kraussianone 2 (**16**) was 65% relaxation of smooth muscle [1].

Antioxidant activity was determined for compounds **5** (IC_{50} 0.54 mM), **26** (IC_{50} 7.92 mM), **34** (IC_{50} 1.77 mM), **39** (IC_{50} 0.62 mM), **41** (IC_{50} 0.25 mM), **42** (IC_{50} 0.035 mM), **44** (IC_{50} 2.55 mM), **47** (IC_{50} 3.67 mM), **48** (IC_{50} 0.028 mM), **50** (IC_{50} 0.65 mM) and **52** (IC_{50} 0.68 mM) using the free radical 2,2-diphenyl-1-picryhydrazyl (DPPH) with butylated hydroxytoluene (BHT) as reference standard (IC_{50} 0.039 nM) [6]. The antioxidant activity of robusflavones A (**36**) and B (**37**), and 6-prenylpinocembrin (**38**) was reported; compounds **36** and **37** had significant radical scavenging activity (IC_{50} 1.13 and 1.19 mg/mL) compared with the standard, L-ascorbic acid (IC_{50} 1.00 mg/mL) [4]. Compound **10** showed antiviral activity [18].

Other activities

Insecticidal activity of sphaerobioside (**12**), and genistein (**13**) was reported using a fumigation method against four stored-product pests (*Callosobruchus chinense*, *Sitophilus oryzae*, *Rhyzopertha dominica*, and *Tribolium castaneum*). Compounds **12** and **13** had LC_{50} values of 0.21, 0.17 µg/mL, 0.18, 0.28 µg/mL, 0.27, 0.28 µg/mL, and 0.20, 0.18 µg/mL against *C. chinense*, *S. oryzae*, *R. dominica*, and *T. castaneum*, respectively [19]. Hundred percent mortality after 24 h at the concentration of 1 µg/mL on all the test insects was also obtained with compounds **12** and **13** [19].

Conclusion

A comprehensive review of flavonoids from the genus *Eriosema* is presented from 1995 to date. Some of the reported compounds underwent chemical modifications to afford derivatives, while others were produced by total chemical synthesis. Pharmacological properties of most of the isolated compounds and derivatives are summarized. Chemotaxonomic significance of flavonoids from this genus was documented and isoflavone was suggested as a marker for *Eriosema* species. From this review, it is obvious that good collaboration between biologists and phytochemists is needed. Knowing that researchers are still interested in investigating

Eriosema species, this review will provide valuable information. Of the approximately 160 species, 52 flavonoids were reported from only five *Eriosema* species. Three of these were from tropical Africa (*E. tuberosum*, *E. glomerata,* and *E. robustum*), one from southern Africa (*E. kraussianum*) and one from Asia (*E. chinense*). Many of these compounds have interesting pharmacological activities. This indicates the potential of discovering more novel and pharmacologically useful compounds from other *Eriosema* species. It may also be interesting to examine the taxonomically closely related *Tephrosia* species.

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