 doi:10.20944/preprints202209.0305.v1

Review

Leucosceptosides A and B: Two Phenyl-ethanoid Glycosides with Important Occurrence and Biological Activities

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Abstract: In this review paper, the occurrence in the plant kingdom and the biological activities associated to two specific phenyl-ethanoid glycosides i.e., leucosceptoside A and leucosceptoside B, were shown and discussed. This is the first work ever done on such subject. Analysis of the literature data clearly indicates that leucosceptoside A is much more common in plants and exerts many more biological activities than leucosceptoside B even if this also presents some important elements. All of this was widely discussed in this paper.

Keywords: Leucosceptoside A; Leucosceptoside B; occurrence in plants; biological activities

1. Introduction

Leucosceptoside A and leucosceptoside B are two natural compounds comprised in the class of phenyl-ethanoid glycosides. The base compound of phenyl-ethanoid glycosides is called verbascoside or acetoside or acteoside which is structurally characterized by a central glucose residue linked to one β-hydroxy-tyrosol and one rhamnose through ether bonds, and to one caffeic acid through an ester bond. Leucosceptoside A differs from verbascoside for the substitution with a methyl group in the caffeic acid moiety whereas leucosceptoside B differs from verbascoside for the substitution with one methyl group each in the caffeic acid and β-hydroxy-tyrosol moieties as well as for the substitution with one β-D-apiose residue in the position 6 of the glucose moiety [1] (Figure 1).

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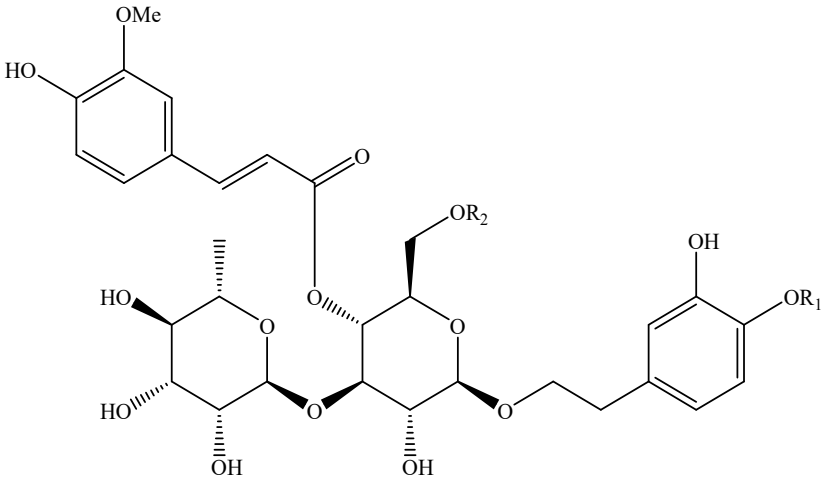

$R_1 = R_2 = H$: leucosceptsoide A
$R_1 = Me$, $R_2 = \beta$-D-Api: leucosceptsoide B

Figure 1. Structures of leucosceptoside A and leucosceptoside B.

These compounds are biosynthetically generated merging two different processes such as the shikimic acid pathway that produces the β-hydroxy-tyrosol part of phenyl-ethanoid glycosides and the cinnamate pathway that produces its caffeic acid part after a series of intermediate steps [2].

In this review, the occurrence of leucosceptoside A and leucosceptoside B in the plant kingdom as well as their relative biological activities are reported. This is the first work ever done on this argument and it is based on all the published papers till now as recovered from Scopus, Reaxys, Google Scholar and PubMed. Only works regarding plants were considered, thus excluding cell cultures. In addition, only works without any kind of procedure possibly producing alterations and artifacts in the phytochemical pattern were cited. Lastly, papers not fully accessible or not written in English were not detailed.

2. Occurrence in the plant kingdom

In the following Tables, the occurrences of leucosceptoside A (Table 1) and leucosceptoside B (Table 2) in the plant kingdom are reported divided according to the family of the plant they have been isolated from. These tables were also subdivided according to the plant species and report data on the collection area of the plant cited, the studied organs and the methodology of isolation and identification for leucosceptoside A and leucosceptoside B. In the collection area columns, if not differently specified, the studied population or populations are intended to be collected from the wild.

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Table 1. Occurrence of leucosceptoside A in the plant kingdom.

Leucosceptoside A					
Family	Plant species	Collection area	Organs	Methodology of isolation and identification	Reference
Acanthaceae	*Acanthus ebracteatus* Vahl	Thailand	Aerial parts	SE, DP, CC, p-HPLC-UV, NMR	[3]
		Thailand (**obtained from a botanical garden**)	Leaves	SE, UHPLC-MS	[4]
	Acanthus hirsutus Boiss.	Turkey (**obtained from a botanical garden**)	Aerial parts	SE, PP, CC, UV, IR, NMR, MS	[5]
	Acanthus montanus (Nees) T.Anderson	Thailand (**obtained from a botanical garden**)	Aerial parts	SE, PP, CC, p-HPLC-RID, NMR	[6]
	Blepharis edulis (Forssk.) Pers.	Egypt	Aerial parts	SE, VLC, CC, TLC, HPLC-UV, NMR, MS	[7]
	Pseuderanthemum carruthersii (Seem.) Guillaumin	n.a.	n.a.	n.a.	[8]
Asteraceae	*Balbisia calycina* Hunz. & Ariza Esp.	Paraguay (**purchased from a company**)	Leaves	SE, DP, CC, TLC, HPLC-UV, NMR, MS	[9]
Bignoniaceae	*Fernandoa adenophylla* (Wall. ex G.Don) Steenis	Thailand (**obtained from a botanical garden**)	Leaves and branches	SE, DP, CC, TLC, p-HPLC-UV, NMR	[10]
	Incarvillea compacta Maxim.	China	Roots	SE, PP, CC, rp-CC, sp-LC-UV, NMR, MS	[11]
	Incarvillea emodi (Royle ex Lindl.) Chatterjee	Pakistan (**more populations**)	Whole plant	SE, CC, HPLC-DAD	[12]
	Martinella obovata (Kunth) Bureau & K.Schum.	Honduras	Leaves	SE, CC, TLC, HPLC-RID, NMR, MS	[13]
	Oroxylum indicum (L.) Kurz	Vietnam	Stem bark	USE, PP, CC, rp-MPLC, NMR	[14]
	Santisukia kerrii (Barnett & Sandwith) Brummitt	Thailand (**obtained from a botanical garden**)	Leaves and branches	SE, DP, CC, TLC, p-HPLC-UV, NMR	[15]
	Tynanthus panurensis (Bureau ex Baill.) Sandwith	Peru	Bark	SE, CC, HPLC-DAD, NMR, MS	[16]
Lamiaceae	*Betonica macrantha* C. Koch.	Turkey	Aerial parts	SE, DP, PP, CC, IR, IV, NMR	[17]

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	Callicarpa longissima (Hemsl.) Merr.	China	Leaves and stems	SER, CC, TLC, p-HPLC-UV, NMR	[18]
	Callicarpa nudiflora Hook. & Arn.	n.a.	n.a.	n.a.	[19]
	Caryopteris incana (Thunb. ex Houtt.) Miq.	Japan	Aerial parts	SE, PP, CC, DCCC, NMR	[20]
		South Korea (**obtained from a botanical garden**)	Aerial parts	SE, PP, CC, TLC, NMR	[21]
		Japan (**cultivated**)	Whole plant	SE, PP, CC, p-HPLC-UV, TLC, NMR	[22]
		South Korea	Leaves	SER, PP, CC, TLC, UV, IR, HPLC-UV, NMR	[23]
	Clerodendrum bungei Steud.	n.a.	n.a.	n.a.	[24]
		China	Roots	SER, PP, CC, sp-HPLC-UV, NMR	[25]
	Clerodendrum chinense (Osbeck) Mabb.	n.a.	n.a.	n.a.	[26]
	Clerodendrum infortunatum L.	Bangladesh	Leaves	SE, PP, CC, TLC, sp-HPLC-UV, NMR	[27]
	Clerodendrum phlomidis L.f.	India (**obtained from a botanical garden**)	Roots	SPE, PP, CC, HPTLC, NMR, MS	[28]
		India (**obtained from a botanical garden**)	Roots	SPE, PP, TLC, CC, p-TLC, NMR	[29]
	Clerodendrum trichotomum Thunb.	South Korea	Stems	SE, PP, CC, $[\alpha]_D$, UV, NMR, MS	[30]
		South Korea	Stems	SE, PP, CC, NMR	[31]
		n.a.	n.a.	n.a.	[32]
	Comanthosphace japonica (Miq.) S.Moore	Japan	Roots	HSE, PP, CC, $[\alpha]_D$, IR, UV, NMR	[33]
		Japan	Whole plant	HSE, PP, CC, rp-CC, p-LPLC-UV, p-HPLC-UV, NMR	[34]
	Galeopsis bifida Boenn.	Siberia (**several populations**)	Leaves	USE, SPE, HPLC-DAD-MS	[35]
		Siberia (**several populations**)	Flowers	USE, SPE, HPLC-DAD-MS	[35]
		Siberia (**several populations**)	Stems	USE, SPE, HPLC-DAD-MS	[35]
		Siberia (**several populations**)	Roots	USE, SPE, HPLC-DAD-MS	[35]
	Lagopsis supina (Steph. ex Willd.) Ikonn.-Gal.	China	Whole plant	SE, PP, CC, LC-UV, rp-HPLC-UV, NMR	[36]
		Mongolia (**obtained from a botanical garden**)	Whole plant	SE, HPLC-DAD, UHPLC-MS^n	[37]
		Mongolia	Whole plant	SE, PP, FP, TLC, UHPLC-MS	[38]
	Leonurus cardiaca L.	Siberia	Aerial parts	HSE, PP, HPLC-UV	[39]

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	Leonurus deminutus V.I.Krecz.	Siberia	Aerial parts	HSE, PP, CC, HPLC-UV, NMR, MS	[39]
	Leonurus glaucescens Bunge	Mongolia	Aerial parts	ASE, DP, PP, HPLC-MS	[40]
		Siberia	Aerial parts	HSE, PP, HPLC-UV	[39]
	Leonurus mongolicus V.I.Krecz. & Kuprian.	Siberia	Aerial parts	HSE, PP, HPLC-UV	[39]
	Leonurus persicus Boiss.	Turkey	Aerial parts	SE, PP, VLC, TLC, NMR, MS	[41]
	Leonurus quinquelobatus Gilib.	Siberia	Aerial parts	HSE, PP, HPLC-UV	[39]
	Leonurus sibiricus L.	Siberia	Aerial parts	HSE, PP, HPLC-UV	[39]
		Mongolia (**several populations**)	Aerial parts	ASE, PP, CC, sp-HPLC-UV, HPLC-DAD-MS	[42]
	Leonurus tataricus L.	Siberia	Aerial parts	HSE, PP, HPLC-UV	[39]
	Marrubium alysson L.	Egypt	Aerial parts	HSE, DP, CC, MPLC, NMR	[43]
	Marrubium thessalum Boiss. & Heldr.	Greece	Aerial parts	SE, VLC, CC, TLC, NMR	[44]
	Marrubium velutinum Sm	Greece	Aerial parts	SE, VLC, CC, rp-HPLC-UV	[45]
	Marrubium vulgare L.	India	Whole plant	SE, PP, CC, TLC, p-TLC, NMR	[46]
	Phlomis armeniaca Willd.	Turkey	Aerial parts	SE, PP, CC, TLC, NMR, MS	[47]
	Phlomis bruguieri Desf.	Turkey	Aerial parts	HSE, PP, CC, HPLC-PAD, HPLC-PAD-MS	[48]
	Phlomis chimerae Boissieu	n.a.	n.a.	n.a.	[49]
	Phlomis fruticosa L.	Montenegro	Aerial parts	SE, UHPLC-MS	[50]
	Phlomis integrifolia Hub.-Mor.	Turkey	Aerial parts	HSE, PP, CC, MPLC, TLC, IR, UV, NMR	[51]
		n.a.	n.a.	n.a.	[52]
	Phlomis kurdica Rech.f.	Turkey	Aerial parts	HSE, PP, CC, HPLC-PAD, HPLC-PAD-MS	[48]
	Phlomis leucophracta P.H.Davis & Hub.-Mor.	Turkey	Aerial parts	HSE, PP, CC, HPLC-PAD, HPLC-PAD-MS	[48]
	Phlomis longifolia Boiss. & Blanche	Turkey	Aerial parts	SE, PP, VLC, MPLC, CC, TLC, rp-MPLC, NMR	[53]
	Phlomis nissolii L.	Turkey	Aerial parts	SE, PP, CC, MPLC, HPLC, TLC, NMR, MS	[54]
		Turkey	Aerial parts	HSE, PP, CC, HPLC-PAD, HPLC-PAD-MS	[48]
	Phlomis oppositiflora Boiss. & Hausskn.	Turkey	Whole plant	SE, PP, CC, MPLC, TLC, NMR	[55]
	Phlomis physocalyx Hub.-Mor.	Turkey	Aerial parts	SE, CC, LPLC-UV, NMR	[56]
	Phlomis russeliana (Sims) Lag. ex Benth.	Turkey	Aerial parts	HSE, PP, CC, HPLC-PAD, HPLC-PAD-MS	[48]
	Phlomis sieheana Rech.F.	Turkey	Aerial parts	HSE, PP, CC, MPLC, TLC, NMR	[57]
	Phlomis syriaca Boiss.	Turkey	Aerial parts	HSE, PP, CC, MPLC, TLC, IR, UV, NMR, MS	[52]

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	Phlomis viscosa Poir.	Turkey	Whole plant	SE, PP, CC, TLC, NMR, MS	[58]
	Phlomoides glabra (Boiss. ex Benth.) Kamelin & Makhm.	Iran	Rhizomes	SXE, VLC, p-TLC, p-rp-HPLC-UV, NMR, UV, MS	[59]
	Phlomoides laciniata (L.) Kamelin & Makhm.	Turkey	Aerial parts	HSE, DP, PP, rp-VLC, TLC, NMR	[60]
	Phlomoides rotata (Benth. ex Hook.f.) Mathiesen	China (**several populations**)	Stems	USE, UPLC-MS	[61]
		Tibet (**several collections**)	Aerial parts	USE, UPLC-MS	[62]
		Tibet (**several collections**)	Roots	USE, UPLC-MS	[62]
	Phlomoides tuberosa (L.) Moench	Turkey	Aerial parts	HSE, PP, CC, TLC, NMR, MS	[63]
	Salvia digitaloides Diels	China	Roots	SE, PP, CC, TLC, NMR	[64]
	Salvia viridis L.	England (**cultivated**)	Aerial parts	SE, PP, CC, TLC, HPLC-UV	[65]
		Poland (**obtained from a botanical garden**)	Aerial parts	HSE, UPLC-DAD, UPLC-DAD-MS	[66]
		Turkey	Roots	SXE, UHPLC-MS^n	[67]
		Turkey	Roots	USE, UHPLC-MS^n	[67]
		Turkey	Roots	MAE, UHPLC-MS^n	[67]
		Turkey	Roots	SE, UHPLC-MS^n	[67]
	Schnabelia nepetifolia (Benth.) P.D.Cantino	China	Whole plant	SE, PP, CC, MPLC, p-HPLC-UV, NMR	[68]
	Scutellaria albida subsp. *velenovskyi* (Rech.f.) Greuter & Burdet	Turkey	Whole plant	SE, MPLC, rp-HPLC-UV, NMR	[69]
	Scutellaria baicalensis Georgi	n.r.	n.r.	n.r.	[70]
		China (**purchased from a company**)	Roots	USE, UHPLC-UV-MS	[71]
		China (**several commercial samples**)	Roots	USE, UPLC-MS	[72]
		China (**purchased from a company**)	Roots	SER, UPLC-MS	[73]
	Scutellaria edelbergii Rech.f.	Pakistan	Whole plant	SE, PP, LC-MS	[74]
	Scutellaria lateriflora L.	Japan (**purchased from a company**)	Aerial parts	SE, DP, PP, CC, TLC, NMR	[75]
	Scutellaria pinnatifida A.Ham.	Turkey	Aerial parts	SE, PP, CC, TLC, IR, UV, NMR	[76]
	Scutellaria prostrata Jacquem. ex Benth.	Nepal	Roots	SE, TLC, GLC, NMR	[77]
	Scutellaria salviifolia Benth.	Turkey	Aerial parts	SE, PP, CC, TLC, NMR, MS	[47]

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	Sideritis cypria Post	Cyprus (**cultivated**)	Flowers	SE, CC, TLC, p-TLC, NMR	[78]
		Cyprus (**cultivated**)	Leaves	SE, CC, TLC, p-TLC, NMR	[78]
		Cyprus (**cultivated**)	Aerial parts	SE, CC, TLC, p-TLC, NMR	[79]
	Sideritis euboea Heldr.	Greece (**cultivated**)	Aerial parts	SE, PP, VLC, CC, TLC, NMR	[80]
		Greece (**cultivated**)	Aerial parts	SE, CC, p-TLC, NMR	[81]
	Sideritis lycia Boiss. & Heldr.	Turkey	Aerial parts	SE, PP, CC, MPLC, TLC, UV, IR, NMR	[82]
	Sideritis ozturkii Aytaç & Aksoy	Turkey	Aerial parts	SE, CC, VLC, MPLC, TLC, NMR	[83]
	Sideritis perfoliata L.	Greece	Aerial parts	SXE, PP, VLC, CC, TLC, UV, NMR	[84]
		Turkey	Aerial parts	HP, SE, HPLC-DAD-MS^n	[85]
	Sideritis raeseri Boiss. & Heldr.	Albania (**several populations**)	Aerial parts	HP, SE, HPLC-DAD-MS^n	[85]
		Macedonia (**several populations**)	Aerial parts	HP, SE, HPLC-DAD-MS^n	[85]
		Serbia (**several populations**)	Aerial parts	SXE, DP, CC, HPLC-DAD-MS	[86]
	Sideritis scardica Griseb.	Macedonia (**several populations**)	Aerial parts	HP, SE, HPLC-DAD-MS^n	[85]
		Bulgaria	Aerial parts	HP, SE, HPLC-DAD-MS^n	[85]
		Serbia (**cultivated**)	Aerial parts	SXE, HPLC-DAD, HPLC-MS	[87]
		Serbia (**several populations**)	Aerial parts	SXE, DP, CC, HPLC-MS	[86]
		Greece (**purchased from a company**)	Aerial parts	USE, UPLC-MS, HPLC-DAD	[88]
	Sideritis sipylea Boiss.	Greece	Aerial parts	HSE, CC, p-TLC, NMR	[89]
	Sideritis syriaca L.	Bulgaria	Aerial parts	HP, SE, HPLC-DAD-MS^n	[85]
		Greece	Aerial parts	HP, SE, HPLC-DAD-MS^n	[85]
	Stachys affinis Bunge	n.a.	n.a.	n.a.	[90]
		Japan (**cultivated**)	Leaves	SE, CC, NMR	[91]
		Italy (**cultivated**)	Tubers	SE, CC, NMR, MS	[92]
	Stachys iva Griseb.	Greece (**cultivated**)	Aerial parts	HSE, CC, p-TLC, NMR	[93]
	Stachys lavandulifolia Vahl	Azerbaijan	Aerial parts	SXE, SPE, p-rp-HPLC-UV, NMR, MS	[94]
	Stachys rupestris Montbret & Aucher ex Benth.	Turkey	n.r.	SE, HPLC-MS	[95]
	Stachys tetragona Boiss. & Heldr.	Greece	Aerial parts	SE, VLC, CC, rp-HPLC, NMR	[96]
	Volkameria inermis L.	Thailand (**obtained from a botanical garden**)	Aerial parts	SE, DP, CC, TLC, p-HPLC-UV, NMR	[97]

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Lindernia-ceae	*Craterostigma plantagineum* Hochst.	Rwanda (**cultivated**)	Leaves	USE, HPLC-DAD-MS	[98]
	Lindernia brevidens Skan	Kenya (**cultivated**)	Leaves	USE, HPLC-DAD-MS	[98]
	Lindernia subracemosa De Wild.	Rwanda (**cultivated**)	Leaves	USE, HPLC-DAD-MS	[98]
Malvaceae	*Firmiana simplex* (L.) W.Wight	China	Roots	SE, PP, CC, TLC, NMR	[99]
Oleaceae	*Osmanthus fragrans* Lour.	China	Leaves	n.r.	[100]
Orobancha-ceae	*Orobanche aegyptiaca* Pers.	n.r.	n.r.	n.r.	[101]
	Orobanche arenaria Borkh.	Poland	Whole plant	ASE, SPE, rp-HPLC-UV, UHPLC-PDA-MS, sp-HPLC-PDA	[102]
	Orobanche artemisiae-campestris subsp. *picridis* (F. Schulz) O. Bolòs, Vigo, Masalles & Ninot	Poland	Whole plant	ASE, SPE, rp-HPLC-UV, UHPLC-PDA-MS, sp-HPLC-PDA	[102]
	Orobanche caryophyllacea Sm.	Poland	Whole plant	ASE, SPE, rp-HPLC-UV, UHPLC-PDA-MS, sp-HPLC-PDA	[102]
	Orobanche caerulescens K.Koch	Poland	Whole plant	ASE, SPE, rp-HPLC-UV, UHPLC-PDA-MS, sp-HPLC-PDA	[102]
	Orobanche cernua Loefl.	China	Whole plant	SER, HPLC-MS, NMR	[103]
		China	Whole plant	SE, PP, CC, sp-HPLC-UV, NMR, MS	[104]
	Orobanche pycnostachya Hance	n.r.	n.r.	n.r.	[101]
		China	Whole plant	SE, PP, CC, TLC, UV, NMR, MS	[105]
	Euphrasia pectinata Ten.	Turkey	Aerial parts	HSE, PP, VLC, CC, TLC, MPLC, NMR	[106]
		Turkey	Aerial parts	HSE, VLC, MPLC, IR, UV, NMR	[107]
	Pedicularis acmodonta Boiss.	n.a.	n.a.	n.a.	[108]
	Pedicularis alaschanica Maxim.	n.a.	n.a.	n.a.	[109]
		n.a.	n.a.	n.a.	[110]
	Pedicularis albiflora Prain	China	Whole plant	SE, PP, CC, TLC, NMR, MS	[111]
	Pedicularis dolichocymba Hand.-Mazz.	n.a.	n.a.	n.a.	[112]
	Pedicularis kansuensis Maxim.	Tibet	Whole plant	SER, PP, CC, TLC, ESP, NMR, MS	[113]
	Pedicularis kerneri Dalla Torre	Italy	Aerial parts	SE, CC, NMR, MS	[114]
	Pedicularis longiflora var. *tubiformis* (Klotzsch) Tsoong	China	Whole plant	SE, PP, CC, HSCCC, rp-HPLC-UV, NMR	[115]
	Pedicularis nordmanniana Bunge	Turkey	Aerial parts	SE, DP, CC, NMR	[116]
	Pedicularis verticillata L.	China	Whole plant	SE, PP, CC, TLC, NMR	[117]

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	Phtheirospermum japonicum (Thunb.) Kanitz	Japan	Aerial parts	SE, PP, CC, TLC, p-HPLC-UV, $[\alpha]_D$, NMR	[118]
Plantaginaceae	*Globularia alypum* L.	Croatia	Aerial parts	HP, SER, HPLC-PDA-MS	[119]
		Croatia	Aerial parts	USE, PP, HPLC-PDA-MS	[120]
		Croatia	Aerial parts	SXE, PP, HPLC-PDA-MS	[120]
	Globularia cordifolia L.	Turkey	Underground parts	HSE, PP, VLC, MPLC, CC, NMR, MS	[121]
		Croatia	Aerial parts	HP, SER, HPLC-PDA-MS	[119]
		Croatia	Aerial parts	USE, PP, HPLC-PDA-MS	[120]
		Croatia	Aerial parts	SXE, PP, HPLC-PDA-MS	[120]
	Globularia davisiana O.Schwarz	Turkey	Aerial parts	HSE, PP, VLC, CC, TLC, rp-MPLC, NMR	[122]
	Globularia meridionalis (Podp.) O.Schwarz	Croatia	Aerial parts	HP, SER, HPLC-PDA-MS	[119]
		Croatia	Aerial parts	USE, PP, HPLC-PDA-MS	[120]
		Croatia	Aerial parts	SXE, PP, HPLC-PDA-MS	[120]
	Globularia orientalis L.	Turkey	Aerial parts	HSE, PP, VLC, MPLC, NMR	[123]
	Globularia punctata Lapeyr.	Croatia	Aerial parts	HP, SER, HPLC-PDA-MS	[119]
		Croatia	Aerial parts	USE, PP, HPLC-PDA-MS	[120]
		Croatia	Aerial parts	SXE, PP, HPLC-PDA-MS	[120]
	Globularia sintenisii Hausskn. & Wettst.	Turkey	Underground parts	SE, CC, MPLC, TLC, NMR	[124]
	Lagotis brevituba Maxim.	China (**purchased from a company**)	Whole plant	SE, PP, HPLC-UV-MS	[125]
	Lagotis ramalana Batalin	n.a.	n.a.	n.a.	[126]
	Penstemon centranthifolius (Benth.) Benth.	California	Aerial parts	SE, FCC, CC, TLC, NMR, MS	[127]
	Penstemon crandallii A. Nelson	Colorado	Leaves	SE, PP, VLC, NMR	[128]
	Penstemon linarioides A. Gray	New Mexico	Whole plant	SE, PP, CC, TLC, $[\alpha]_D$, UV, NMR, MS	[129]
	Plantago asiatica L.	Japan	Whole plant	HSE, CC, NMR	[130]
		China (**several populations**)	Seeds	HSE, UPLC-MS^n	[131]
		China	Seeds	USE, UHPLC-MS	[132]
	Plantago depressa Willd.	China (**several populations**)	Seeds	HSE, UPLC-MS^n	[131]
		China	Seeds	USE, UHPLC-MS	[132]
	Plantago lanceolata L.	Brazil (**purchased from a company**)	Aerial parts	SWE, HPLC-DAD-MS	[133]
	Plantago major L.	China	Seeds	USE, UHPLC-MS	[132]

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		Brazil (**purchased from a company**)	Aerial parts	SWE, HPLC-DAD-MS	[133]
	Plantago squarrosa Murray	Egypt	Whole plant	PE, PP, TLC, CC, UV, IR, NMR, MS	[134]
	Plantago subulata L.	n.r.	Aerial parts	HSE, PP, CC, MPLC, UV, IR, NMR, MS	[135]
		Turkey	Aerial parts	HSE, PP, CC, MPLC, TLC, NMR	[136]
		Turkey	Roots	HSE, PP, CC, MPLC, TLC, NMR	[136]
	Rehmannia glutinosa (Gaertn.) DC.	Japan (**purchased from a company**)	Roots	SE, CC, HPLC-UV, TLC, NMR	[137]
		n.a.	n.a.	n.a.	[138]
		China (**purchased from a local market**)	Rhizomes	SE, PP, CC, TLC, NMR	[139]
		n.a.	n.a.	n.a.	[140]
		China	Roots	SER, UHPLC-MS	[141]
		China	Tuber root	SE, HPLC-UV, UHPLC-MS	[142]
		China (**cultivated**)	Leaves	SE, UHPLC-MS	[143]
		China (**cultivated**)	Tubers	SE, UHPLC-MS	[143]
		Vietnam	Roots	HSE, PP, DP, CC, TLC, NMR	[144]
	Russelia equisetiformis Schltdl. & Cham.	Japan	Aerial parts	SE, PP, CC, TLC, DCCC, HPLC-UV, NMR	[145]
Scrophulariaceae	*Buddleja davidii* Franch.	China	Roots	SER, PP, CC, TLC, p-HPLC-UV, NMR	[146]
	Buddleja lindleyana Fortune	China	Powder	SE, PP, CC, rp-CC, NMR	[147]
	Buddleja officinalis Maxim.	China	Flower buds	SE, PP, CC, TLC, NMR	[148]
	Scrophularia umbrosa L.	China	Whole plant	SER, PP, CC, sp-rp-HPLC-UV, NMR	[149]
	Verbascum thapsus L.	Italy (**cultivated**)	Leaves	SE, HPLC-DAD-MS, NMR	[150]
Verbenaceae	*Aloysia citriodora* Palau	Spain	Commercial extract	HPLC-UV, HPLC-MS	[151]
		Peru (**purchased from a company**)	Aerial parts	SER, PP, CC, HPLC-UV, NMR	[152]
		Spain (**commercial extract**)	Leaves	SE, sp-HPLC-UV, rp-HPLC-DAD- MS	[153]
		Spain (**commercial extract**)	Leaves	SE, HPLC-UV, HPLC-MS, sp-HPLC-UV	[154]
	Citharexylum flexuosum (Ruiz & Pav.) D.Don	Tunisia (**obtained from a botanical garden**)	Trunk bark	SE, CC, p-HPLC-UV, NMR	[155]
	Lippia alba (Mill.) N.E.Br. ex Britton & P.Wilson	Brazil (**different chemotypes**)	Leaves	HSE, HPLC-DAD-MS	[156]
	Phyla canescens (Kunth) Greene	Japan (**obtained from a botanical garden**)	Aerial parts	SE, PP, CC, HPLC-UV, NMR, MS	[157]

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	Stachytarpheta cayennensis (Rich.) Vahl	Panama	Whole plant	SE, PP, CC, p-TLC, NMR, MS	[158]
	Stachytarpheta schottiana Schauer	Brazil (**obtained from a botanical garden**)	Aerial parts	SE, DP, LC-MS	[159]
	Verbena brasiliensis Vell.	Japan	Aerial parts	SE, PP, CC, HPLC, NMR	[160]
	Verbena hastata L.	Canada (**purchased from a company**)	Whole plant	SE, DP, CC, TLC, pHPLC, NMR	[161]

[α]$_D$: optical rotation; ASE = accelerated solvent extraction; CC: column chromatography; DCCC: droplet counter current chromatograph; DP: defatting procedure; ESP: procedure to eliminate sugars; FCC: flash column chromatography; FP = fraction purification; GLC: gas liquid chromatography; HP = homogenization procedure; HPLC-DAD: high pressure liquid chromatography coupled to diode array detector; HPLC-DAD-MS: high pressure liquid chromatography coupled to diode array detector and mass spectrometry; HPLC-DAD-MS^n: high pressure liquid chromatography coupled to tandem mass spectrometry; HPLC-MS: high pressure liquid chromatography coupled to mass spectrometry; HPLC-PAD: high pressure liquid chromatography coupled to pulsed amperometry detector; HPLC-PAD-MS: high pressure liquid chromatography coupled to pulsed amperometry detector and mass spectrometry; HPLC-UV: high pressure liquid chromatography coupled to ultraviolet detector; HPLC-UV-MS: high pressure liquid chromatography coupled to ultraviolet detector and mass spectrometry; HPTLC: high performance thin layer chromatography; HSE: hot solvent extraction; HSCCC = high-performance countercurrent chromatography; IR: infrared spectroscopy; LC-MS: liquid chromatography coupled to mass spectrometry; LC-UV: liquid chromatography coupled to ultraviolet detector; LPLC-UV: preparative low pressure liquid chromatography coupled to ultraviolet detector; MAE = microwave assisted extraction; MPLC: medium pressure liquid chromatography; MS: mass spectrometry; NMR: nuclear magnetic resonance spectroscopy; PE = percolation procedure; p-HPLC: preparative high pressure liquid chromatography; p-HPLC-RID: preparative high pressure liquid chromatography coupled to a refractive index detector; p-HPLC-UV: preparative high pressure liquid chromatography coupled to ultraviolet detector; p-LPLC-UV: preparative low pressure liquid chromatography coupled to ultraviolet detector; p-rp-HPLC-UV: preparative reversed phase high pressure liquid chromatography coupled to ultraviolet detector; PP: partition procedure; p-TLC: preparative thin layer chromatography; rp-CC: reversed phase column chromatography; rp-HPLC-DAD-MS: reversed phase high pressure liquid chromatography coupled to diode array detector and mass spectrometry; rp-HPLC-UV: reversed phase high pressure liquid chromatography coupled to ultraviolet detector; rp-MPLC: reversed phase medium pressure liquid chromatography; rp-VLC: reversed phase vacuum liquid chromatography; SE: solvent extraction; SER: solvent extraction under reflux; SPE = solvent extraction via percolation; sp-HPLC-PDA: semipreparative high pressure liquid chromatography coupled to photodiode array detector; sp-HPLC-UV: semipreparative high pressure liquid chromatography coupled to ultraviolet detector; sp-LC-UV: semipreparative liquid chromatography coupled to ultraviolet detector; sp-rp-HPLC-UV: semipreparative reversed phase high pressure liquid chromatography coupled to ultraviolet detector; SWE: subcritical water extraction; SXE: Soxhlet extraction; TLC: thin layer chromatography; UHPLC-PDA-MS: ultra-high pressure liquid chromatography coupled to photodiode array detector and mass spectrometry; UHPLC-UV-MS: ultra-high pressure liquid chromatography coupled to ultraviolet detector and mass spectrometry; UHPLC-MS: ultra-high pressure liquid chromatography coupled to mass spectrometry; UHPLC-MS^n: ultra-high pressure liquid chromatography coupled to tandem mass spectrometry; UPLC-DAD: ultra-pressure liquid chromatography coupled to diode array detector; UPLC-DAD-MS: ultra-pressure liquid chromatography coupled to diode array detector and mass spectrometry; UPLC-MS: ultra-pressure liquid chromatography coupled to mass spectrometry; UPLC-MS^n: ultra-pressure liquid chromatography coupled to tandem mass spectrometry; USE = solvent extraction under ultrasonic action; UV: ultraviolet spectroscopy; VLC: vacuum liquid chromatography.

Leucosceptoside A proved to be not so uncommon in the plant kingdom. In fact, it has been evidenced in eleven families. In particular, its lowest occurrence was observed in Asteraceae, Malvaceae and Oleaceae with one report each whereas the biggest occurrence has been noticed in the Lamiaceae family with 69 reports even though these were singular reports in most cases. Nevertheless, it is important to underline that not all the genera comprised in the Lamiaceae family have seen the presence of this compound in their phytochemical patterns, thus confirming the fact that different genera, even if belonging to the same family, may biosynthesize different natural compounds. Within the Lamiaceae family, this compound has been particularly found in the Phlomis L. genus with 15 reports whereas it is quite rare in Betonica L., Schnabelia Hand.-Mazz. and

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Volkameria L. genera with one only report of its presence, each, thus further phytochemical studies on species belonging to these genera are necessary in order to verify if this compound is really one of their phytochemical components or if its presence was only accidental. All the other seven families see a moderate occurrence of leucosceptoside A with more or less reports in more or less genera and species. For what concerns the collection areas of the studied species, no significative restricted zone for the specific biosynthesis of this compound has been observed since its presence has been found in species collected from four continents *i.e.*, America, Europe, Africa and Asia. Nothing can be stated at the moment about the Oceanian situation even if no report on it has been found but this may also be due to many other factors which have nothing to do with the phytochemical analysis like the difficulty to collect the species in which this compound can be particularly abundant or its not specific research among the phytochemical components of a species. In this sense, there's still a lot to do. As for the studied organs, leucosceptoside A has shown no particular preference for a specific accumulation site having been individuated in leaves, aerial parts, tubers, roots and whole plant even if it seems this compound prefers aerial organs like it should be given its chemical nature as a polyphenol and, by consequence, its biological nature as a potent antioxidant compound entrusted with the task to avoid the excessive oxidation of primary metabolism molecules. A few procedures have been used to extract this compound mainly associated with maceration processes in their different forms. Indeed, several techniques have been used for its isolation and identification including high performing liquid chromatography relative techniques, liquid chromatography relative techniques, thin layer chromatography relative techniques, infrared, ultraviolet and nuclear magnetic resonance spectroscopies and mass spectrometry.

In the end, it is extremely relevant to highlight that Table 1 clearly indicates how leucosceptoside A cannot be used as chemophenetic marker at any level since it has shown no specificity and also because the families where it was found are taxonomically very distant from each other.

Table 2. Occurrence of leucosceptoside B in the plant kingdom.

Leucosceptoside B					
Family	Plant species	Collection area	Organs	Methodology of isolation and identification	Reference
Bignoniaceae	*Amphilophium crucigerum* (L.) L.G.Lohmann	Panama	Stems	SE, PP, MPLC, LPLC-UV, NMR	[162]
Lamiaceae	*Callicarpa kwangtungensis* Chun	n.a.	n.a.	n.a.	[163]
	Callicarpa macrophylla Vahl	China	Whole plant	SE, PP, CC, sp-rp-HPLC-UV, NMR	[164]
	Comanthosphace japonica (Miq.) S.Moore	Japan	Roots	HSE, PP, CC, $[\alpha]_D$, IR, UV, NMR	[33]
	Marrubium alysson L.	Egypt	Aerial parts	HSE, DP, CC, MPLC, NMR, MS	[165]
	Phlomis bovei Noë	Algeria	Roots	VLC, CC, MPLC, rp-MPLC, NMR, MS	[166]
	Phlomis herba-venti subsp. *pungens* (Willd.) Maire ex DeFilipps	n.a.	n.a.	n.a.	[167]
		Turkey	Aerial parts	HSE, PP, CC, rp-MPLC, NMR	[168]
		Azerbaijan	Aerial parts	SE, PP, CC, UV, IR, NMR, MS	[169]
	Phlomis kotschyana Hub.-Mor.	Turkey	Aerial parts	HSE, PP, CC, rp-MPLC, UV, IR, NMR	[170]

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	Phlomis kurdica Rech.f.	Jordan	Aerial parts	SE, CC, rp-HPLC-UV, NMR	[171]
		Turkey	Aerial parts	HSE, PP, CC, HPLC-PAD, HPLC-PAD-MS	[48]
	Phlomis lycia D.Don	Turkey	Aerial parts	HSE, PP, CC, MPLC, TLC, IR, UV, NMR, MS	[172]
	Phlomis nissolii L.	Turkey	Aerial parts	SE, PP, CC, MPLC, HPLC-UV, TLC, NMR, MS	[54]
		Turkey	Aerial parts	HSE, PP, CC, HPLC-PAD, HPLC-PAD-MS	[48]
	Phlomis russeliana (Sims) Lag. ex Benth.	Turkey	Aerial parts	HSE, PP, CC, HPLC-PAD, HPLC-PAD-MS	[48]
	Phlomis viscosa Poir.	Turkey	Whole plant	SE, PP, CC, MPLC, TLC, NMR, MS	[58]
	Phlomoides rotata (Benth. ex Hook.f.)	China	Whole plant	SER, PP, CC, HSCCC, HPLC-UV	[173]
	Phlomoides umbrosa (Turcz.) Kamelin & Makhm.	South Korea	Roots	SE, PP, CC, TLC, rp-HPLC-UV, sp-HPLC-UV, NMR	[174]
	Schnabelia nepetifolia (Benth.) P.D.Cantino	China	Whole plant	SE, PP, CC, MPLC, HPLC-UV, LC-UV, NMR	[68]
	Schnabelia tetradonta (Y.Z.Sun) C.Y.Wu & C.Chen	China	Roots	SE, PP, CC, NMR	[175]
		n.a.	n.a.	n.a.	[176]
	Stachys officinalis (L.) Trevis.	Japan (**cultivated**)	Aerial parts	SE, CC, p-HPLC-UV, NMR	[177]
Orobanchaceae	*Pedicularis longiflora* var. *tubiformis* (Klotzsch) Tsoong	China	Whole plant	SE, PP, CC, HSCCC, rp-HPLC-UV, NMR	[115]
Plantaginaceae	*Lagotis brevituba* Maxim.	China (**purchased from a company**)	Whole plant	SE, PP, HPLC-UV-MS	[125]
Scrophulariaceae	*Buddleja davidii* Franch.	China	Roots	SER, PP, CC, p-HPLC-UV,	[146]
	Buddleja lindleyana Fortune	China	Powder	SE, PP, CC, rp-CC, NMR	[147]
	Verbascum densiflorum Bertol.	Bulgaria (**cultivated**)	Leaves	SE, HPLC-DAD, NMR	[178]
	Verbascum nigrum L.	Bulgaria (**cultivated**)	Leaves	SE, HPLC-DAD, NMR	[178]
	Verbascum phlomoides L.	Bulgaria (**cultivated**)	Leaves	SE, HPLC-DAD, NMR	[178]
	Verbascum phoeniceum L.	Bulgaria (**cultivated**)	Leaves	SE, HPLC-DAD, NMR	[178]
	Verbascum thapsus L.	Japan (**obtained from a botanical garden**)	Whole plant	SE, CC, NMR	[179]
		Italy (**cultivated**)	Leaves	SE, HPLC-DAD-MS, NMR	[150]

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	Verbascum wiedemannianum Fisch. & C.A.Mey.	Turkey	Roots	SER, VLC, MPLC, CC, TLC, [α]D, NMR, MS	[180]
	Verbascum xanthophoeniceum Griseb.	Bulgaria (**several populations**)	Aerial parts	SE, PP, CC, rp-HPLC-UV, NMR	[181]
		Bulgaria (**cultivated**)	Leaves	SE, HPLC-DAD, NMR	[178]
		Bulgaria (**several populations**)	Whole plant	SE, PP, CC, LC-MS, NMR	[182]
Verbenaceae	*Lantana camara* L.	Egypt (**obtained from a botanical garden**)	Leaves	SE, DP, PP, HPLC-MS	[183]

[α]D: optical rotation; CC: column chromatography; DP: defatting procedure; HPLC-DAD: high pressure liquid chromatography coupled to diode array detector; HPLC-DAD-MS: high pressure liquid chromatography coupled to diode array detector and mass spectrometry; HPLC-MS: high pressure liquid chromatography coupled to mass spectrometry; HPLC-PAD: high pressure liquid chromatography coupled to pulsed amperometry detector; HPLC-PAD-MS: high pressure liquid chromatography coupled to pulsed amperometry detector and mass spectrometry; HPLC-UV: high pressure liquid chromatography coupled to ultraviolet detector; HPLC-UV-MS: high pressure liquid chromatography coupled to ultraviolet detector and mass spectrometry; HSE: hot solvent extraction; HSCCC = high-performance countercurrent chromatography; IR: infrared spectroscopy; LC-MS: liquid chromatography coupled to mass spectrometry; LC-UV: liquid chromatography coupled to ultraviolet detector; LPLC-UV: preparative low pressure liquid chromatography coupled to ultraviolet detector; MPLC: medium pressure liquid chromatography; NMR: nuclear magnetic resonance spectroscopy; MS: mass spectrometry; p-HPLC-UV: preparative high pressure liquid chromatography coupled to ultraviolet detector; PP: partition procedure; rp-CC: reversed phase column chromatography; rp-HPLC-UV: reversed phase high pressure liquid chromatography coupled to ultraviolet detector; rp-MPLC: reversed phase medium pressure liquid chromatography; SE: solvent extraction; SER: solvent extraction under reflux; sp-HPLC-UV: semipreparative high pressure liquid chromatography coupled to ultraviolet detector; sp-rp-HPLC-UV: semipreparative reversed phase high pressure liquid chromatography coupled to ultraviolet detector; TLC: thin layer chromatography; UV: ultraviolet spectroscopy; VLC: vacuum liquid chromatography.

With respect to leucosceptoside A, leucosceptoside B proved to be less common in the plant kingdom. In fact, it has been evidenced only in six families. Its lowest occurrence was observed in the Bignoniaceae, Orobanchaceae, Plantaginaceae and Verbenaceae families with one report each whereas the biggest occurrence has been noticed in the Lamiaceae family again with 17 reports. There is a certain parallelism between the results found for leucosceptoside A and those found for leucosceptoside B especially for the collection areas of the studied species as well as for the studied organs and methodologies of isolation and identification. Indeed, there are some important differences for what concerns the families, genera and species where their presence has been reported. In particular, leucosceptosde B has not been reported in Acanthaceae, Compositae, Linderniaceae, Malvaceae, Oleaceae families. In addition, for what concerns the Bignoniaceae, Scrophulariaceae and Verbenaceae families, leucoscpetoside B has been found in a completely different species, if not genera themselves, than leucosceptoside A. For what concerns the Lamiaceae family that possesses the monopolism of occurrence again, the reported genera are not generally the same as well as the species. In particular, leucosceptoside B has not been found in the *Betonica* L., *Caryopteris* Bunge, *Clerodendrum* L., *Galeopsis* L., *Lagopsis* Bunge, *Leonurus* L., *Salvia* L., *Scutellaria* L., *Sideritis* L. and *Volkameria* L. genera. Again, this situation urges the need to perform more phytochemical analyses on the species for its further research also because several singular reports have been found in the literature with the same conclusions as stated before.

Leucosceptsode B cannot be also used as chemophenetic marker at any level for the same reasons as presented before even if with a minor occurrence than leucoscpetoside A.

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3. Biological activities

3.1. Leucosceptoside A

Leucosceptoside A has shown several interesting pharmacological activities. In the following lines, these activities were explored and detailed one by one.

3.1.1. Antioxidant activity

Leucosceptoside A proved to be a good antioxidant compound. Several studies against $DPPH^{\cdot+}$ confirm this with quite similar efficacy values.

In particular, Ersöz et al. [56] obtained an IC_{50} value of 76.0 μM which is lower than ascorbic acid (IC_{50} = 112 μM) whereas Calis et al. [58] obtained an IC_{50} value of 125.4 μM and Harput et al. [5] an IC_{50} value of 18.43 μg/mL which is higher than quercetin used as positive control but comparable (IC_{50} = 4.3 μg/mL). Good results were also obtained by Delazar et al. [59] with a RC_{50} value of 0.0148 mg/mL, Ono et al. [152] with an EC_{50} value of 25.7 μM which is very similar to that for the positive control α-tocopherol (EC_{50} = 25.9 μM) and Shen et al. [11] with an IC_{50} value of 53.32 μM. Charami et al. [84] also obtained good results expressed as percentages of inhibition which were 88.3% and 89.0% after 20 and 60 min, respectively, at the concentration of 0.1 mM whereas acetyl salicylic, at the same concentration and times, showed a percentage of inhibition of 80.6%. Wang et al. [110] obtained a SC_{50} value of 0.294 mM, Heilmann et al. [184] an IC_{50} value of 0.18 μM and Lan et al. [115] an EC_{50} value of 11.26 μM which are all very potent. The results obtained by Huang et al. [148] (2021) are also extremely good given the IC_{50} value of 72.14 μM which is lower than vitamin C (IC_{50} = 81.83 μM).

Only Harput et al. [52] (2006) got less potent results expressed as a percentage of inhibition. This was 41.8% at the concentration of 200 μM which is near to ascorbic acid and BHA (percentages of inhibition equal to 39.9 and 35.6%, respectively) but worse than chlorogenic acid (percentage of inhibition equal to 68.6%). This difference of results from the other studies can be totally explained on the basis of the different positive controls used. In fact, the choice of the positive controls is extremely important and affects the efficacy values of the obtained results.

Lastly, the work by Wang et al. [110] was the only study about the antioxidant potential of this compound according to another methodology. Through a luminol-enhanced chemiluminescence assay with formyl-methionyl-leucyl-phenylalanine in stimulated human polymorphonuclear neutrophils, they found this compound is a weak inhibitor of hydroxyl radical with a percentage of inhibition of 27.8% at the concentration of 0.55 mM and a weak iron inhibitor with a percentage of 17.86% at the concentration of 1.57 mM. Indeed, this difference from the other results is due to the different methodology adopted.

3.1.2. Anti-inflammatory activity

Leucosceptoside A shows moderate anti-inflammatory activities even if studied only with respect to NO production.

In particular, Han et al. [149] obtained good results, in this sense, in the Raw 264.7 cell line with an IC_{50} value of 9.0 μM. The positive control aminoguanidine had an IC_{50} value of 10.7 μM. Vien et al. [14] obtained less potent results in LPS-stimulated BV2 microglial cells using Griess assay with an IC_{50} value of 61.1 μM. The positive control butetin had much stronger effects (IC_{50} = 4.5 μM). Lastly, Ochi et al. [145] also obtained moderate results in cell culture supernatants of LPS-stimulated RAW264.7 macrophages with a percentage of inhibition of 40%.

3.1.3. Enzyme inhibitory activity

Leucosceptoside A has been studied also for its potential inhibitory effects on some enzymes i.e., α-glucosidase, acetylcholinesterase, protein kinase C alpha and tyrosinase.

For what concerns α-glucosidase, this compound has shown contrasting results. In fact, Liu et al. [25] obtained good results with an IC_{50} value of 0.7 mM which is quite lower than acarbose used as positive control (IC_{50} = 14.4 mM). Indeed, Thu et al. [144] obtained

 doi:10.20944/preprints202209.0305.v1

worse results with an IC_{50} value of 273.0 μM which is comparable to acarbose, again (IC_{50} = 204.2 μM). Indeed, leucosceptoside A possesses decent acetylcholinesterase inhibitory effects with an IC_{50} value of 423.7 μg/mL [31]. This fact was further confirmed by Saidi et al. [185] who obtained an IC_{50} value of 72.85 μM and by Li et al. [186] with an IC_{50} value of 3.86 mM.

This compound is also a strong protein kinase C alpha inhibitor with an IC_{50} value of 19.0 μM [129].

In contrast, it shows weak tyrosinase inhibitory activities with a percentage of inhibition of 21.65% at the concentration of 0.051 mM. Kojic acid, used as positive control, has a percentage of inhibition of 53.87% at the concentration of 0.047 mM [187]. A slightly better result was obtained by Saidi et. (2020) [185] who observed a percentage of inhibition of 39.5% at the concentration of 100 μM.

Lastly, it has shown no effect on the hyaluronidase enzyme inhibition test and collagenase enzyme inhibition test at the concentration of 100 μg/mL [136].

3.1.4. Hepatoprotective activity

At 100 μM, leucosceptoside A exerts strong hepatoprotective properties as obtained by studying the viability of HepG2 cells after CCl_4 intoxication by MTT assay and flow cytometry with value of cell numbers and cell viability both above 80%. The mechanism of action occurs through the inhibition of NF-kB activation since it was observed that the pretreatment with this compound can inhibit the CCl_4-induced lipid peroxidation in HepG2 cells to 177.73 % and attenuate the decrease of SOD to 76.58 % as well as the pre-incubation of the same cells with this compound can prevent the ROS production to 183.56 % [11].

3.1.5. Neuroprotective activity

Leucosceptoside A exerts strong neuroprotective effects against the 1-methyl-4-phenylpyridinium ion (MPP+)-induced cell death in mesencephalic neurons at the concentration of 4 μg/mL with a reduction of 7% [188].

3.1.6. Cytoprotective activity

Leucosceptoside A exhibits moderate cytoprotective effects against *t*-BHP-induced toxicity in HepG2 cells with an IC_{50} value of 21.1 μM. This value is lower than silymarin used as positive control (IC_{50} = 37.1 μM) [21].

3.1.7. Anticomplementary activity

Leucosceptoside A exerts strong anticomplementary effects with a CH_{50} value of 0.23 mM [117].

3.1.8. Anti-HIV activity

Leucosceptoside A has shown good HIV-1 integrase inhibitory effects with an IC_{50} value of 29.4 μM. This value is better than curcumin (IC_{50} = 54.3 μM) and comparable to L-chicoric acid (IC_{50} = 21.0 μM) used as positive controls [30].

3.1.9. Cytotoxic activity

Leucosceptoside A exerts modest cytotoxic effects on Hela (human epithelial carcinoma), MCF7 (breast metastatic adenocarcinoma) and HC7-116 (colon cancer) cell lines with IC_{50} values of 200, 189.08 and 182.33 μg/mL, respectively [44]. Saidi et al. [185] also tested the cytotoxic effects of this compound on HeLa cell lines obtaining a better result (IC_{50} = 80.87 μM) as well as a positive result on A549 (adenocarcinomic human alveolar basal epithelial cells) cancer cell line obtaining a similar effect (IC_{50} = 99.00 μM). All these values are much higher than the standard compounds used i.e., doxorubicin for the former (IC_{50} = 0.36 μM) and ellipticine (IC_{50} = 0.31 μM). Abe et al. [157] obtained better results on Hela (GI_{50} = 42 μM) but also new positive activities against B16F10 (murine melanoma)

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cell line with a GI_{50} equal to 28 μM and against MK-1 (gastric carcinoma with liver metastasis) cell line with a GI_{50} equal to 33 μM.

These results are in contrast with what observed by Saracoglu et al. [47] who did not observe any effect on Hela cells for this compound. This difference of results depends on the methodology adopted. Saracoglu et al. [47] did not also observe any effect against dRLh-88 (rat hepatoma), P-388-d1 (mouse lymphoid neoplasma) and S-180 (sarcoma) cancer cell lines.

3.1.10. Inhibitory activities

Leucosceptoside A exhibits good inhibitory effects against ADP + NADPH – induced lipid peroxidation in rat liver microsome with an IC_{50} value of 1.69 μM [130].

This compound also exhibits good inhibitory effects on the protonation, induced by pulse radiolysis, of thymine radical anion, which causes severe damages in cells, with a reaction rate constant of electronic transfer equal to 1.54*109 dm^3 mol^{-1} s^{-1} [189].

3.1.11. Antimicrobial activities

Leucosceptoside A exerts very poor antimicrobial effects against *Staphylococcus aureus* ATCC29213 and *Enterococcus faecalis* ATCC29212 with MIC values of 1000 μg/mL [58].

Indeed, it has not shown any activity against *Escherichia coli* ATCC25922, *Pseudomonas aeruginosa* ATCC27853, *Candida albicans* ATCC90028, *Candida krusei* ATCC6258 and *Candida parapsilosis* ATCC22019 [58], *Mycobacterium tuberculosis* H37Rv strain (Yadav et al., [29], *Bacillus subtilis* NBRC3134 and *Klebsiella pneumoniae* NBRC3512 [22].

3.2. Leucosceptoside B

Leucosceptoside B has also shown some interesting pharmacological activities even if less numerous than leucosceptoside A. In the following lines, these activities were explored and detailed one by one.

3.2.1. Antioxidant activity

Leucosceptoside B proved to be an antioxidant compound. Several studies, according to different assays, confirm this with opposite efficacy values.

According to the $DPPH^{\cdot+}$ radical scavenging assay, this compound only exerts moderate effects. In fact, Niu et al. [164] obtained an IC_{50} value of 31.16 μM which is higher than ascorbic acid used as positive control (IC_{50} = 7.81 μM) whereas Georgiev et al. [181] an IC_{50} value of 996 μg/mL which is high in absolute. Indeed, better results were obtained by Lan et al. (2018) with an EC_{50} value of 13.05 μM and by Calis et al. [58] with an IC_{50} value of 61.3 μM.

Through a luminol-enhanced chemiluminescence assay with formyl-methionyl-leucyl-phenylalanine in stimulated human polymorphonuclear neutrophils, Heilmann et al. [184] reported the good radical scavenging activities of this compound with an IC_{50} value of 0.17 μM, instead.

Indeed, Georgiev et al. [181] also studied the ORAC, HORAC, FRAP and superoxide anion activities of this compound obtaining different results. In particular, good effects were observed for the first one with a value of 16264.7 ORACFL/g which is higher than chlorogenic acid used as standard compound (9172.8 ORACFL/g) and for the second one with a value of 3885.1 HORACFL/g which is higher than chlorogenic acid used as standard compound (3584.5 ORACFL/g). Conversely, poor effects were observed for the third assay with a value of 0.602 which is much lower than chlorogenic acid used as reference compound (3.547) whereas modest effects were observed for the last assay with an IC_{50} value of about 40 μg/mL.

3.2.2. Anti-inflammatory activity

Leucosceptoside B exerts poor inhibitory effects on cobra venom factor induced alternative pathway activation in mouse sera with a percentage of inhibition of 40% and on

 doi:10.20944/preprints202209.0305.v1

COX-2 production with a percentage of inhibition near 30%. In addition, it shows moderate inhibitory effects on NO production (percentage near 40%) and IL-10 production (percentage near 20%) as well as good inhibitory effects on COX-1 (percentage above 65%) [182].

3.2.3. Enzyme inhibitory activity

Georgiev et al. [181] studied the acetylcholinesterase and butyrylcholinesterase inhibitory activities of leucosceptoside B. In both cases, the activity is dose-dependent but, in the former, the percentage of inhibition is almost 50% at the concentration of 100 μg/mL whereas, in the latter, the percentage of inhibition is a little above 10% at the concentration of 100 μg/mL. These values are quite low.

Indeed, Cespedes et al. [190] obtained a different result for the acetylcholinesterase inhibitory effects of this compound with an IC_{50} value of 20.1 μg/mL. This difference of results depends only on the different methodology adopted.

3.2.4. Neuroprotective activity

Leucosceptoside B is able to exert strong neuroprotective effects against the 1-methyl-4-phenylpyridinium ion (MPP+)-induced cell death in mesencephalic neurons at the concentration of 40 μg/mL [147].

3.2.5. Antimicrobial activity

Leucosceptoside B has shown very poor antimicrobial effects against *Staphylococcus aureus* ATCC29213 and *Enterococcus faecalis* ATCC29212 with MIC values of 1000 μg/mL [58].

In addition, it has proved to be inactive against *Escherichia coli* ATCC25922, *Pseudomonas aeruginosa* ATCC27853, *Candida albicans* ATCC90028, *Candida krusei* ATCC6258 and *Candida parapsilosis* ATCC22019 [58].

3.2.6. Inhibitory activities

Leucosceptoside B has shown no human lactate dehydrogenase inhibitory activity [171].

4. Conclusions

This review article clearly shows how leucosceptoside A and leucosceptoside B are indeed important compounds under several aspects. In fact, they have been found in different species belonging to several families and, even though they do not possess chemotaxonomic significance on their own, they are also endowed with several interesting pharmacological activities including antioxidant, anti-inflammatory, enzyme inhibitory and neuroprotective. Yet, their search among the phytochemical components of plants is still quite limited especially for their difficulty of isolation and identification. This review article also wants to be a stimulus to amplify their study both in phytochemistry and pharmacology since there is still a lot to be discovered.

Author Contributions: Conceptualization, C.F.; Research, All the authors; Data curation, All the authors; Writing—original draft preparation and review and editing, All the authors; All authors have read and agreed to the published version of the manuscript."

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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