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Review Paper

Asteraceae family: a review of its allelopathic potential and the case of *Acmella oleracea* and *Sphagneticola trilobata*

Carolina Alves Araújo[1,3], *Carina Sant'Anna Morgado*[2,4], *Anne Katherine Candido Gomes*[2,5], *Anne Caroline Candido Gomes*[1,6,8] & *Naomi Kato Simas*[1,7]

Abstract

Asteraceae family is as an interesting target for researching natural alternatives for crop protection. Many species from this family grow as weeds, and some of them can influence the development of other species by the allelopathy phenomenon. This paper aimed to review the literature for the main genera and species of the Asteraceae family with allelopathic or phytotoxic potential, as well as the classes of secondary metabolites present in this family and responsible for such activity. *Artemisia, Ambrosia, Bellis, Bidens, Helianthus* and *Tagetes* were identified as the main genera with phytotoxic or allelopathic activity. Among the secondary metabolites from this family, terpenes, polyacetylenes, saponins, sesquiterpene lactones, phenolic acids and flavonoids were described as responsible for inhibiting the development of other species. In addition, the phytotoxic potential of *Acmella oleracea* and *Sphagneticola trilobata* against the weeds *Calopogonium mucunoides*. and *Ipomoea purpurea* was described for the first time. At 0.2 mg/mL, crude extract and fractions of *A. oleracea* inhibited above 60% of *C. mucunoides* root growth. Hydroalcoholic extract and fractions of *S. trilobata*, except hexane, significantly affected *I. purpurea* root growth, ranging from 38 ± 14% to 59 ± 8% of inhibitory effect at different concentrations (0.19 mg/mL to 1.13 mg/mL).

Key words: *Calopogonium mucunoides*, fatty acids, *Ipomoea purpurea*, phenolic acids, phytotoxicity, synergism.

Resumo

A família Asteraceae figura como um interessante alvo para a busca de alternativas naturais para proteção das safras. Muitas espécies da família Asteraceae crescem como plantas daninhas, e são capazes de influenciar o desenvolvimento de outras espécies através do fenômeno de alelopatia. Sendo assim, o propósito desta revisão é investigar na literatura os principais gêneros e espécies da família Asteraceae envolvidos com potencial alelopático ou fitotóxico, bem como as classes de metabólitos secundários responsáveis por tal atividade. *Artemisia, Ambrosia, Bellis, Bidens*, *Helianthus* e *Tagetes* foram identificados como os principais gêneros com atividade alelopática ou fitotóxica. Dentre os metabólitos secundários da família, terpenos, poliacetilenos, saponinas, lactonas sesquiterpênicas, ácidos fenólicos e flavonoides foram descritos como os responsáveis pela inibição do desenvolvimento de outras espécies vegetais. Além disso, o potencial fitotóxico de *Acmella oleracea* e *Sphagneticola trilobata* contra as espécies daninhas *Calopogonium mucunoides* e *Ipomoea purpurea* foi descrito pela primeira vez. Na concentração de 0,2 mg/mL, todas as frações de *A. oleracea* inibiram acima de 60% do crescimento das raízes de *C. mucunoides*. E o extrato hidroalcóolico e as frações de *S. trilobata*, com exceção da hexânica, afetaram significativamente o crescimento das raízes de *I. purpurea*, com variação do efeito de inibição de 38 ± 14% a 59 ± 8%, em diferentes concentrações (0,19 mg/mL a 1,13 mg/mL).

Palavras-chave: *Calopogonium mucunoides*, ácidos graxos, *Ipomoea purpurea*, ácidos fenólicos, fitotoxicidade, sinergismo.

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[1] Federal Institute of Education, Science and Technology of Rio de Janeiro, Campus Realengo, Rio de Janeiro, RJ, Brazil.
[2] Federal University of Rio de Janeiro, Faculty of Pharmacy - UFRJ, Rio de Janeiro, RJ, Brazil.
[3] ORCID: <https://orcid.org/0000-0001-9980-5164>. [4] ORCID: <https://orcid.org/0000-0002-6217-6445>. [5] ORCID: <https://orcid.org/0000-0002-5671-0293>.
[6] ORCID: <https://orcid.org/0000-0003-4962-1564>. [7] ORCID: <https://orcid.org/0000-0002-9929-2714>.
[8] Author for correspondence: anne.gomes@ifrj.edu.br

Introduction

Asteraceae family.

The Asteraceae family consists of approximately 1000 genera, which comprise over 25,000 species of flowering plants (Bessada *et al*. 2015). It is the largest family among the flowering plants of the world, with a cosmopolitan distribution in all continents, except Antarctica. In Brazil, Asteraceae comprises 180 genera and 1900 species, which are mainly found in Minas Gerais and Bahia states (Nakajima & Semir 2001; Roque & Bautista 2008). Approximately 40 species of the Asteraceae family have economic importance as food crops, such as lettuce (*Lactuca sativa* L.), endive (*Cichorium endivia* L.), salsify (*Tragopogon* L.) and edible seeds of safflower (*Carthamus tinctorius* L.) and sunflower (*Helianthus annuus* L.), which are used in the production of cooking oil (Enclyclopaedia Britannica 2015), while several species are used for medicinal purposes, e.g., *Achillea millefolium* L. (Baretta *et al*. 2012), *Vernonia spp*. (Toyang & Verpoorte 2013) and *Matricaria chamomilla* L. (Singh *et al*. 2011). Some reports describe the use of species from Asteraceae family for bio-removal of a wide range of pollutants in urban areas, such as heavy metals and xenobiotics, and species from the genera *Solidago*, *Tanacetum* and *Rudbeckia* were found to be effective in the bio-removal of pollutants from urban environments (Gawronski & Gawronska 2007; Nikolic & Stevovic 2015). Several secondary metabolites were described in the Asteraceae family, such as terpenes (Fathi *et al.* 2019), including sesquiterpene lactones (Macías *et al*. 2012; Silva 2017b), saponins (Stavropoulou *et al*. 2017), alkaloids (Castells *et al.* 2014), alkamides (Skaf *et al*. 2018), *cinnamic acid* derivatives and flavonoids (Ccana-Ccapatinta *et al*. 2019). Many species from the Asteraceae family are grown as weeds beside roads, cultivated fields and forest floor (Bandyopadhyay *et al*. 2014). Some of them are invasive and able to influence the development of other species by allelopathy.

Allelopathy and Phytotoxicity

Allelopathy can be defined as a process whereby chemical compounds are released into the environment by an organism. These substances, once released into the environment, interact and may influence the growth and development of biological systems, including inhibition or stimulation effects (Rice 1983; Reigosa *et al*. 2013). In 1937, the researcher Hans Molisch defined allelopathy as the direct or indirect result of the transfer of chemical substances from one plant to another (Mizutani 1999). In 1996, the International Allelopathy Society (IAS) defined allelopathy as the science that studies any process, essentially involving secondary metabolites produced by plants, algae, bacteria and fungi, that influences the growth and development of agricultural and biological systems, including positive (stimulation) or negative (inhibitory) effects (Macías *et al*. 2000). The term allelopathy is derived from the Greek allelon (mutual, from one to another) and pathos (damage, which refers, in general, to the chemical inhibition of one species against another). Allelopathy is not a competition, and what differentiates this phenomenon from competition between plants is the fact that competition is able to reduce or remove from the environment a growth factor necessary for both plants, such as water, light, nutrients and others, while allelopathy occurs by adding a chemical factor to the medium. However, these two types of phenomena, in some cases, can happen simultaneously (Seigler 1996). Two types of allelopathic effects are autotoxicity when a plant species releases an allelochemical into the environment that inhibits or delays the germination and growth of its own species, and heterotoxicity, which causes depletion effects on different species (Miller 1994). Allelochemicals can be found in different parts of the plant, such as flowers, leaves, stem, roots or fruits (Rice 1983; Gusman *et al*. 2012). Preliminary studies of allelopathy are carried out through laboratory bioassays where it is possible to identify phytotoxicity of different species. Phytotoxicity is defined as a delay of seed germination, inhibition of plant growth or any adverse effect on plants caused by specific substances (phytotoxins) or growing conditions (Blok *et al*. 2019). *In vitro* bioassays with extracts of donor plants are conducted in germination chambers which allow the control of the environment for the study (Wu *et al.* 2001). Target plants used in these bioassays are evaluated in the initial stage of development, also called seedling, which is the most sensitive to allelochemical activity (Cavers 2003; Adkins *et al*. 2007). Although bioassays are considered fundamental tools to obtain prior information about allelopathic potential, they only present evidence concerning phytotoxicity; therefore, it is not considered suitable to relate the results obtained in the laboratory to field conditions (Inderjit & Weston 2000; Lankau 2010; Reigosa *et al*. 2013). In order to evaluate allelopathy close to natural conditions, some researchers carry out the assays in greenhouses, and target plant species are planted in pots containing the soil where donor plant has grown up (Callaway & Aschehoug 2000; Cummings *et al*. 2012).

Allelochemicals

Allelochemicals can range from simple hydrocarbons to complex compounds of high molecular weight. About 10000 substances with allelopathic action are known, being considered a small part of the quantity that may possibly exist in nature (Almeida 1990). Under natural conditions, several factors can influence the biosynthesis of allelochemicals and their release into the field, such as temperature, luminosity, humidity, interaction with soil biota and availability of nutrients (Hadacek 2002; Macías *et al*. 2007; Reigosa *et al*. 2013).

Since the discovery of the allelopathic phenomenon, research has been conducted with the purpose of isolating and identifying the substances responsible for this phenomenon and grouping them. Allelochemicals can be classified into 10 categories according to their different structures and properties: 1. water-soluble organic acids, straight-chain alcohols, aliphatic aldehydes, and ketones; 2. simple lactones; 3. long-chain fatty acids and polyacetylenes; 4. quinones (benzoquinone, anthraquinone and complex quinones); 5. phenolics; 6. cinnamic acid and its derivatives; 7. coumarins; 8. flavonoids; 9. tannins; 10. steroids and terpenoids (sesquiterpene lactones, diterpenes, and triterpenoids) (Soltys *et al.* 2013). Concerning mode of action, allelochemicals are characterized by multi-site action in plants without high specificity; however, in general, the mode of action of only a few classes of allelochemicals is well understood. Phenolic acids cause a nonspecific efflux of anions and cations, which leads to increased permeability of the cell membrane, inducing membrane depolarization, and these membrane effects correlate with an inhibition of ion uptake (Macías *et al*. 2004). In addition, phenolic acids also suppress enzymatic activity of amylase, maltase, invertase, phosphatase and protease (Li *et al*. 2010). The mode of allelopathic action of alkaloids is not completely elucidated; however, some reports describe protein inhibition and membrane permeability alteration caused by alkaloids (Wink *et al*. 1998). The number of flavonoids linked to allelopathic inhibition is not large (Macías *et al*. 2004). They act primarily as electron transport inhibitors through perturbation in the mitochondrial inner membrane and inhibit hydrolysis of ATP catalyzed by mitochondrial Mg^{2+} -ATPase (Einhellig 1995). Franco *et al*. (2015) demonstrated that flavonoid glycosides can influence the polar transport of auxin, leading to stress responses that depend on auxin. A large number of highly phytotoxic allelochemicals are terpenoids; however, the mode of action of only some is well understood (Macías 2004). Monoterpenes can act through inhibition of the enzyme asparagine synthase, which is a key enzyme in asparagine biosynthesis and plays an important role in nitrogen mobilization (Romagni *et al*. 2000). Sesquiterpene lactones can react with thiol groups to form a covalent linkage and if the thiol group is on a key enzyme, like glutathione synthetase, it can inactivate the enzyme, impairing metabolism (Duke *et al*. 1988).

Weeds

Invasive plant species, for farmers, are defined as pests or weeds, but from an ecological viewpoint, they are defined as colonizers or pioneers, which can be from the same community or introduced from another environment. It is then possible to define invasive species as exotic species that have a high capacity for growth, proliferation and dispersion, capable of modifying the composition, structure or function of the ecosystem (Matos & Pivello 2009). Richardson *et al*. (2000) defined invasive exotic species as species that are accidentally or intentionally introduced into a new environment, establishing themselves and propagating over great distances causing ecological damage. Among 12 families of plants, Holm (1978) found that 68% of the 200 most important species in the world are weeds. Also, in terms of global problems related to weeds, it was found that the species of Poaceae and Cyperaceae families are responsible for 27%, and those of Asteraceae family are responsible for 43%. Since several species from Asteraceae are considered weeds, many works have reported the presence of allelochemicals in these species in order to explain the ability of these species to influence the growth of other organisms.

In this context, the aim of this work was to investigate the literature for the main genera and species of the Asteraceae family with allelopathic or phytotoxic potential, as well as the classes of secondary metabolites present in this family and responsible for such activity. In addition, unpublished data on the phytotoxic potential of *Acmella oleracea* (L.) R.K.Jansen and *Sphagneticola trilobata* (L.) Pruski were newly described by our group.

Acmella oleracea (L.) R.K.Jansen

Acmella oleracea (L.) R.K.Jansen (synonymies *Spilanthes oleracea* L., *S. oleracea* Jacq. and *Spilanthes acmella* auct. non (L.) Murr.) belonging to the family Asteraceae, is a plant popularly known as "jambú".

It is native to regions of Asia and South America, the latter especially in the northern region of Brazil, where it is widely used in the preparation of typical dishes of the region, such as "tacacá" (Chung *et al*. 2008; Aguiar *et al*. 2014; Dias *et al*. 2002). In folk medicine, *A. oleracea* is commonly used as wound healing, antispasmodic, for the treatment of rheumatism, and also as tonic, anti-inflammatory and antimalarial (Prachayasittikul *et al*. 2009; Stein *et al*. 2020). Previous studies have described pharmacological activities related to this species, such as antioxidant, antinociceptive, anti-infinflammatory, diuretic and anesthetic (Savic *et al*. 2020). Other works reported *A. oleracea* larvicidal effects on *Aedes aegypti* and *Anopheles stephensi* (Simas *et al*. 2013; Pandey *et al*. 2007), insecticidal against filariasis mosquito vectors (Benelli *et al.* 2019), acaricidal against *Rhipicephalus microplus* (Marchesini *et al*. 2020) and anthelmintic on *Gastrothylex cruminefer* (Singh *et al*. 2014). The chemical profile of the *A. oleracea* is characterized by the presence of amino acids, triterpenes, stigmasterol and alkaloides, however biological activity seems to be related to the abundant presence of N-alkylamides, especially spilanthol, which has been increasing the interest of the pharmaceutical industry (Savic *et al*. 2020; Nascimento *et al*. 2020). Except for the work of Kato-Noguchi *et al*. (2019) that evaluated the inhibition effect of aqueous methanol extract of *Acmella oleracea* (L.) R.K.Jansen on the growth of weeds as *Lolium multiflorum* Lam. and *Echinochloa crus-galli* (L.) P.Beauv., the phytotoxicity, as wells as the metabolites involved with this activity, is not well explored in the literature so far.

Sphagneticola trilobata (L.) Pruski

Sphagneticola trilobata (L.) Pruski, synonymies *Acmella brasiliensis* Spreng., *Wedelia paludosa* DC., *Wedelia trilobata* (L.) Hitchc., *Complaya trilobata* (L.) Strother and *Acmella spilanthoides* Cass. (Lang *et al*. 2017), belongs to Asteraceae family and is popularly known as "vedélia", "arnica", "mal-me-quer", "picão-da-praia" and "margaridão". In folk medicine, this species is used to treat various diseases, including cough, infectious and painful diseases (Roque *et al*. 1987). There are also reports about the use of S. trilobata to treat back pain, muscle cramps, rheumatism, persistent wounds, swelling and painful arthritic joint (Arvigo & Balik 1993 *apud* Verma *et al*. 2013). In the literature, biological effects have been described for the extract of aerial parts of *S. trilobata*, including antinociceptives (Block *et al*. 1998), trypanosomicide (Batista *et al*. 1999), hypoglycemics (Block *et al*. 1998; Novaes 2001), antimicrobial (Chethan 2012), anti-inflammatory (Govindappa *et al*. 2011) and cytotoxic (Batista 2009). The major chemical constituents of *S. trilobata* are ent-kaurane diterpenes, eudesmane sesquiterpene lactones, and triterpenes (Wu & Zhang 2008 *apud* Li *et al*. 2016). Lang *et al*. (2017) reported the presence of caffeoylquinic acid derivatives, oleanolic acid derivatives, kaurenic acid and fatty acids in the hydroalcoholic extract from aerial parts of *S. trilobata*.

S. trilobata forms a dense ground cover, crowding or preventing regeneration of other species, thus, it is considered a threatening invasive species in agricultural and forestry land, urban areas and roadsides (Hear 2008). These characteristics corroborate with the work of Hernández-Aro *et al*. (2016) which reported the impact of residues of *S. trilobata* over some crops. Zhang *et al*. (2013) evaluated the phytotoxic activity of the aqueous extract of *S. trilobata* leaves on rape (*Brassica campestris* L.) seed germination and showed that the aqueous extracts at the concentration from 25% to 100% caused a significant reduction in the germination percentage, shoot length and total chlorophyll content of rape. Comparing to *A. oleracea*, there are more reports about *S. trilolata* phytotoxicity in the literature, however, few studies properly explore and identify its allelochemicals.

Materials and Methods

The databases SciFinder, PubMed, Scielo, Science Direct and Google Scholar were used in order to collect the necessary materials for the development of this work. After validation on the Science and Health Descriptors (DeCS) page, three keywords were chosen: "Asteraceae", "Allelopathy", and "Weed". The publications were selected as a more accurate description of the search and selection process for their consistency with the theme proposed for this work. Finally, a descriptive analysis was carried out about the allelopathic potential of the Asteraceae family and its possible use as natural herbicides.

Plant material

Acmella oleracea (L.) R.K.Jansen

The species was cultivated in the city of Santa Bárbara (Pará state) and obtained at a family farming fair in the same location. A voucher specimen (MG156.773) was deposited by Dr. Ricardo Secco in the herbarium of Emilio Goeldi Museum, Belém, Pará.

Sphagneticola trilobata (L.) Pruski

The species *Sphagneticola trilobata* was obtained at the garden of University Hall of Federal University of Rio de Janeiro (UFRJ), Campus Ilha do Fundão. A voucher specimen (HUNI 5975) was deposited by Dr. Sandra Zorat in the herbarium of the Department of Botany, Institute of Biology, Federal University of State of Rio de Janeiro (UNIRIO), Rio de Janeiro.

General procedures

The GC–MS analyses were performed on a Shimadzu QP-5050 instrument coupled to a Mass Spectrometer Detector 6890 (Agilent Network). The mass detector was operated in EI mode (70 eV) with a quadrupole analyzer and NIST 11 spectral library. The extracts and fractions were dissolved in chloroform, and a volume of 1 μL was injected by the instrument's autosampler. A capillary column DB-5MS (30 m × 0.25 mm, 0.25 μm) (Agilent) was used for separation. The column oven was programmed with an initial oven temperature of 60 °C and increased to 300 °C at a rate of 10 °C/min. The total run time was 30 min. Helium was used as a carrier gas with a flow rate of 1.8 mL/minute. The MS detection scan range was between m/z 10 and 550. The samples were previously derivatized with a diazomethane/diethyl ether mixture, prepared as described by the manufacturer (Sigma-Aldrich, Technical Bulletin AL-180). ESI-MS analysis was performed in a Bruker spectrometer (model 9.4 T Solarix) coupled to a quadrupole analyzer with ionization in negative mode. The mass range analyzed was 200–2000 m/z. The parameters used were nebulizer gas pressure of 0.5–1.0 bar, capillary voltage of 3–3.5 Kv and capillary temperature transfer of 250 °C. The spectrum was processed using Compass Data Analysis (Bruker). The equivalent of double bonds and rings for each molecule was determined from the DBE (Double Bond Equivalent) value provided by Compass Data Analysis.

Phytochemical analysis

Acmella oleracea (L.) R.K.Jansen

Air-dried leaves of *A. oleracea* (1 kg) were extracted with EtOH:H_2O (7:3, v/v) at room temperature by static maceration during 15 days and concentrated on a rotary evaporator at 40 ºC to give a dark brown extract (60 g). The extract was suspended in H_2O and partitioned with hexane, CH_2Cl_2 and ethyl acetate (each 200 mL x 3). After concentration, the crude extract, hexane, dichloromethane and ethyl acetate fractions were bioassayed using *Lactuca sativa* L. (lettuce) and *Calopogonium mucunoides* Desv. as test plants. Dichloromethane fraction was subjected to GC/MS analysis.

Sphagneticola trilobata (L.) Pruski

Air-dried aerial parts of *S. trilobata* (526.47 g) were extracted with EtOH:H_2O (7:3, v/v) at room temperature by static maceration during 15 days. The extract was filtered on filter paper and concentrated on a rotary evaporator at 40ºC to to give a dark brown extract (65 g). Part of the hydroalcoholic extract obtained (40 g) was suspended in a mixture of 200 mL methanol/water (7: 3, v/v) and subjected to successive liquid-liquid extractions with hexane, dichloromethane and ethyl acetate (each 200 mL x 3). At the end of the process, the aqueous residue was also obtained. The crude extract, hexane, dichloromethane and ethyl acetate fractions, as well as the aqueous residue, were bioassayed using lettuce and *Ipomoea purpurea* (L.) Roth as test plants. Dichloromethane fraction was subjected to GC/MS analysis, and aqueous residue was performed with ESI-MS.

Bioassays with ***Acmella oleracea*** (L.) R.K.Jansen and ***Sphagneticola trilobata*** (L.) Pruski extracts and fractions

Extracts and fractions were tested for phytotoxic activity on *Lactuca sativa* at different concentrations, ranging from 0.1 mg/mL to 1 mg/mL. The weeds *Calopogonium mucunoides* Desv. and *Ipomoea purpurea* (L.) Roth were also used as test species for phytotoxic growth assay with fractions obtained from *A. oleracea* and *S. trilobata*, respectively. The concentration used in bioassays with *C. mucunoides* was 0.2 mg/

mL, while the bioassays with *I. purpurea* were performed at 1.13 mg/mL, 0.94 mg/mL, 0.36 mg/mL, 0.38 mg/mL and 0.05 mg/ml for crude, hexane, dichloromethane, ethyl acetate fractions and aqueous residue, respectively. Ten seeds of *L. sativa* and five seeds of *C. mucunoides* or *I. purpurea* were sown in separate Petri dishes (5 cm diameter, 1 cm height) lined with Whatman Nº 1 filter paper discs. Each filter paper disc contained a defined concentration of the extracts and fractions. Organic solvents were allowed to evaporate overnight at room temperature after application of the extract or fraction, and 2.5 mL of an aqueous solution (0.1% DMSO in distilled water) were added to each Petri dish. For aqueous fractions, 0.5 mL of the test solution and 2 mL of 0.1% DMSO in distilled water were added to the Petri dishes. Dishes containing 2.5 ml of 0.1% DMSO in water and 2.5 mL of distilled water were each used as negative controls. Menadione (Sigma) at 0.143 mg/mL was used as positive control (Baratelli *et al*. 2012). The experimental design used was a completely randomized block design. Treatments and controls were assayed in triplicate and replicated three times (n=90 for lettuce; n=45 for *C. mucunoides* or *I. purpurea*). Petri dishes were incubated in growth chamber, in dark at 25ºC. Germination was recorded after 24 h by root protrusion and root length was measured after 5 d (Gomes *et al*. 2016).

Statistics

Results are expressed as mean ± 95% confidence interval (CI). Experiments were statistically analyzed by one-way ANOVA, followed by Tukey's post-test using GraphPad Prism, version 5.0. Differences were tested for a significance level of $p<0.05$. Half maximal inhibitory concentration (IC_{50}) was calculated by the same application using nonlinear regression.

Results and Discussion

The allelopathic potential of Asteraceae family has been reported by several authors. Table 1 was constructed based on the data found in 25 works in English and Portuguese, being 23 research papers, 1 Master dissertation and 1 Doctoral thesis. From these works, 14 studied the allelopathic effects of extracts, 9 studied the effects of isolated allelochemicals, 1 showed both effects and 1 reported the effects of fractions, besides extracts and isolated compounds. A total of 19 genera and 26 species with allelopathic activity were described as well as the substances responsible for the activity, the target species (used to assess the phytotoxic / allelopathic effect) , the tested concentration, percentage of inhibition on the target species and the type of bioassay used.

Main genera of Asteraceae family with allelopathic/phytotoxic activity

Artemisia, *Ambrosia*, *Bellis*, *Bidens*, *Helianthus* and *Tagetes* are genera of the Asteraceae family which present two or more species with phytotoxic/allelopathic activity.

The genus *Artemisia* has more than 350 species and is considered an exciting source of biologically active compounds with potential to provide new herbicides and growth regulators. *Artemisia* species contain compounds that are phytotoxic to monocots, dicots, photosynthetic bacteria, endomycorrhizal fungi, and to the producer plants themselves (Ferreira & Janick 2004).

The genus *Ambrosia* has more than 19 species, and all are weeds distributed in different regions of the world. According to Lorenzi (2008), some species of the Asteraceae family are among the first weeds that emerge after soil preparation owing to their adaptation in cleared areas, having a large seed production, where a single plant can produce from 3000 to 6000 seeds that present easy dispersion and dormancy. Among the species of the genus *Ambrosia*, *Ambrosia artemisiifolia* L., native to North and South America, and widely distributed in Europe, Africa, temperate and tropical Asia, Australasia and the Pacific Islands, is a major weed and drastically reduces crop yields, like cereals, through interference (Beres *et al*. 2002).

The *Bellis* genus consists of about twenty species of small annual or perennial herbs widespread mainly in the Mediterranean region. Besides the use in traditional medicine, some species of the genus have compounds with strong phytotoxic activity, such as triterpene saponins and phenolic compounds, such as that found in *Bellis longifolia* Boiss. & Heldr. and *Bellis sylvestris* Cirillo (Stavropoulou *et al*. 2017).

The *Bidens* genus is composed of about 230 species of herbaceous size, the majority with ruderal habits, distributed throughout the entire intertropical zone of the planet (Lucchetti *et al*. 2009). *Bidens pilosa* L. is one of the most invasive species of this genus. In Brazil, *B. pilosa* is mainly distributed in South and Central-South regions, being highly harmful to important crops like soybean (Monqueiro *et al*. 2000; Muniz Filho *et al*. 2004).

Table 1 – Data from reports on allelopathy/phytotoxicity and species of Asteraceae family in scientific literature

Genera	Vegetal Species	Allelochemicals	Target species	Concentration and inhibition (%)	Experimental design	Bioassay	Reference
Achillea	*Achillea millefolium* L.	uninformed	*Lactuca sativa* L.	15% (p/v) (46%)	Effect of water extract of flowers on germination	*In vitro*	(Silva 2017a)
Acroptilon	*Acroptilon repens* (L.) DC.	4'-Chloro-1'-(5-penta-1,3-diyn-1-yl-2-thienyl)-but-2'-yn-3'-ol	*Arabidopsis thaliana* L. Heynh.	12,5 µg.mL^{-1} (64%)	Effect of extracts, fractions and isolated polyacetylenes on fresh weight	*In vitro*	(Quintana *et al.* 2008)
		5'-Methyl-1'-(5-prop-1-yn-1-yl-2-thienyl)-hexa-2',4' -diyin-6'- yl acetate (Polyacetilenes)		25 µg.mL^{-1} (54.5%)			
Ageratum	*Ageratum conyzoides* L.	*p*-coumaric acid	*Oryza sativa* L.	0.1 mM (56.9 %)	Effect of isolated phenolic compounds on seedling growth	*In solo*	(Batish *et al.* 2009)
		gallic acid		0.1 mM (43.1 %)			
		ferulic acid		0.1 mM (44.1 %)			
		p-hydroxybenzoic acid		0.1 mM (43.1 %)			
		anisic acid		0.1 mM (31.3 %)			
Ambrosia	*Ambrosia artemisiifolia* L.	Phenolic compouds	*Zea mays* L.	50% (p/v) (16%)	Effect of water extract of leaves on seedling growth	*In vitro*	(Formigheri *et al.* 2018)
Ambrosia	*Ambrosia trifida* L.	1α-angeloyloxy-carotol	*Triticum aestivum* L.	50 µg/g soil (49%)	Effect of soil samples infested with *A. trifida* and isolates sesquiterpenes lactones on seedling growth	*In soil*	(Kong *et al.* 2007)
		1α-(2-methylbutyroyloxy)-carotol (Sesquiterpenes lactones)		50µg/g soil (37%)			

Genera	Vegetal Species	Allelochemicals	Target species	Concentration and inhibition (%)	Experimental design	Bioassay	Reference
Artemisia	*Artemisia arborescens* L.	uninformed	*Lactuca sativa* L.	0.89 mg.mL^{-1} (50%)	Effect of methanol extract of leaves on seedling growth	*In vitro*	(Araniti *et al.* 2013)
Artemisia	*Artemisia gorgonum* Webb	Sesquiterpenes lactones	*Allium cepa* L.	1 mM (84%)	Effect of isolated substances on seedling growth	*In vitro*	(Macías *et al.* 2012)
			Lactuca sativa L.	1 mM (91%)			
			Lycopersicum esculentum Mill.	1 mM (91%)	Effect of isolated substance on germination		
Artemisia	*Artemisia scoparia* Waldst. & Kit.	Monoterpenes, oxygenated monoterpenes and sesquiterpenes	*Cassia occidentalis* L.	50 µg oil/g (67%)	Effect of sand impregnated with *A. scoparia oil* on seedling growth	*In vitro*	(Kaur *et al.* 2010)
			Parthenium hysterophorus L.	50 µg oil/g (21%)			
			Echinochloa crus-galli (L.) P.Beauv.	50 µg oil/g (77%)			
			Ageratum conyzoides L.	50 µg oil/g (17%)			
Bellis	*Bellis longifolia* Boiss. & Heldr.	3-*O*-*β*-D-fucopyranosyl polygalacic acid	*Lemna paucicostata* Hegelm.	21 µM (50%)	Effect of isolated compounds from leaves on seedling growth	*In vitro*	(Stavropoulo *et al.* 2017)
		3-*O*-*β*-D-fucopyranosyl- 2a,3b,23-trihydroxyolean-12-en28-oic acid (Triterpene saponins)		19 µM (50%)			
Bellis	*Bellis sylvestris* Cirillo	Triterpenic saponins	*Aegilops geniculata* Roth	1 mM (20%)	Effect of methanol extract of leaves on seedling growth	*In vitro*	(Scognamiglio *et al.* 2012)

Genera	Vegetal Species	Allelochemicals	Target species	Concentration and inhibition (%)	Experimental design	Bioassay	Reference
Bidens	*Bidens alba* (L.) DC.	Phenylheptatriyn (Polyacetylene)	*Lactuca sativa* L.	0.5 % (p/v) of dried extract (96%)	Effect of ethanol extract of leaves on seedling growth	*In vitro*	(Lima *et al*. 2011)
Bidens	*Bidens pilosa* L.	Polyacetylenes and phenolic compounds	*Lactuca sativa* L.	0.5 % (p/v) of dried extract (47%)	Effect of ethanol extract of leaves on seedling growth	*In vitro*	(Lima *et al*. 2011)
Conyza	*Conyza bonariensis* (L.) Cronquist	uninformed	*Lactuca sativa* L.	8% (p/v) (90%)	Effect of water extract of leaves on seed germination	*In vitro*	(Silva *et al.* 2016)
Cosmos	*Cosmos sulphureus* Cav.	Costunolide Reinosine Santamarine (Sesquiterpenes lactones)	*Triticum aestivum* L.	24.1 $\mu g.mL^{-1}$ 285.3 $\mu g.mL^{-1}$ 139.8 $\mu g.mL^{-1}$	Effects of isolated sesquiterpenes lactones on wheat coleoptiles growth	*In vitro*	(Silva 2017b)
Cynara	*Cynara cardunculus* L.	Aguerin B Grosheimin Cynaropicrin (Sesquiterpenes lactones)	*Lactuca sativa* L.	0.8 $mg.mL^{-1}$ (~70%)	Effect of ethyl acetate extract of leaves on seedling growth	*In vitro*	(Rial *et al*. 2014)
			Lycopersicon esculentum Mill.	0.8 $mg.mL^{-1}$ (~90%)			
			Urochloa decumbens (Stapf) R.D.Webster	0.8 $mg.mL^{-1}$ (60%)			
			Echinochloa crus-galli (L.) P.Beauv.	0.8 $mg.mL^{-1}$ (90%)			
Dittrichia	*Dittrichia viscosa* (L.) Greuter	uninformed	*Malcolmia maritima* (L.) W.T.Aiton	2 $mg.mL^{-1}$ (30%)	Effect of water extract of leaves on seed germination	*In vitro*	(Levizou *et al.* 2002)
Eriocephalus	*Eriocephalus africanus* L.	Monoterpenes, oxygenated monoterpenes and sesquiterpenes	*Amaranthus hybridus* L.	0.125 $\mu g.mL^{-1}$ (100%)	Effect of essential oil of leaves on seed germination	*In vitro*	(Verdeguer *et al.* 2009)
			Portulaca oleracea L.	0.125 $\mu L.mL^{-1}$ (6%)			

Genera	Vegetal Species	Allelochemicals	Target species	Concentration and inhibition (%)	Experimental design	Bioassay	Reference
Flourensia	*Flourensia campestris* Griseb.	(-)- hamanasic acid A (Sesquiterpene)	*Lactuca sativa* L.	Germination: 2.9 mM (50%) Roots growth: 1.5 mM (50%) Shoots growth: 2.0 mM (50%)	Effect of isolated (-)-hamanasic acid on seed germination and seedling growth	*In vitro*	(Silva *et al*. 2012)
Helianthus	*Helianthus tuberosus* L.	Phenolic compouds	*Lactuca sativa* L.	1.95 mg/mL (90%)	Effect of water extract of leaves on seedling growth	*In vitro*	(Tesio *et al*. 2011)
Heterotheca	*Heterotheca subaxillaris* (Lam.) Britt & Rusby	Calamenene sesquiterpenes	*Lactuca sativa* L. *Lemna paucicostata* Hegelm.	37.5 µM of 2-methoxy-calamenene-14-carboxylic acid against *L. pausicostata* (50%)	Effect of isolated calamenene sesquiterpenes from dichlorometane extract of aerial parts on seedling growth	*In vitro*	(Morimoto *et al.* 2009)
Mikania	*Mikania micrantha* Kunth	ent-kaurene diterpene glucosides	*Arabidopsis thaliana* (L.) Heynh.	0.5 mM (68%)	Effect of ethanol extract (45%) of leaves on seed germination	*In vitro*	(Xu *et al*. 2013)
Onopordum	*Onopordum acanthium* L.	Flavonoids and Sesquiterpenes lactones	Wheat coleoptile	Pectolarigenin - 1.263 mM (50%) Scutellarein 4'-methyl ether – 1.709 mM (50%) elemanolide 13)-dehydromelitensin b-hydroxyisobutyrate 0.179 mM (50%)	Effect of isolated compounds from leaves on seedling growth	*In vitro*	(Watanabe *et al.* 2014)

Genera	Vegetal Species	Allelochemicals	Target species	Concentration and inhibition (%)	Experimental design	Bioassay	Reference
Tagetes	*Tagetes minuta* L.	Ocimenones (oxygenated monoterpenes)	*Taraxacum officinale* F.H.Wigg.	277 ppm (50%)	Effect of isolated ocimenones on seed germination	*In vitro*	(López *et al*. 2008)
			Cynodon dactylon (L.) Pers.	495 ppm (50%)			
			Bidens subalternans DC.	154 ppm (50%)			
			Stipa eriostachya Kunth	385 ppm (50%)			
			Mikania cordifolia (L.f.) Willd.	248 ppm (50%)			
Tagetes	*Tagetes patula* L.	uninformed	*Lactuca sativa* L.	20 $mg.mL^{-1}$ (73%)	Effect of ethanol extract of leaves on seedling growth	*In vitro*	(Santos *et al.* 2015)
Tagetes	*Tagetes erecta* L.	uninformed	*Lactuca sativa* L.	20 $mg.mL^{-1}$ (84%)	Effect of ethanol extract of leaves on seedling growth	*In vitro*	(Santos *et al.* 2015)
Tithonia	*Tithonia diversifolia* (Hermsl.) A.Gray	Tagitinin C (Sesquiterpene lactone)	*Lolium multiflorum* Lam.	0.217 mM (50%)	Effect of isolated sesquiterpene lactone on seedling growth	*In vitro*	(Suzuki *et al.* 2017)
			Echinochloa crus-galli (L.) P.Beauv.	0.128 mM (50%)			
			Phleum pratense L.	0.126 mM (50%)			
Tridax	*Tridax procumbens* L.	Flavonoids	*Lactuca sativa* L.	20 $mg.mL^{-1}$ (87.5%)	Effect of aqueous extract of leaves on seedling growth	*In vitro*	(Mecina *et al*. 2016)

The *Helianthus* genus comprises nearly 100 species of herbaceous plants known as sunflowers. They are primarily native to North and South America, and some species are cultivated as ornamentals for their great size and flower heads and for their edible seeds. Only two species, *Helianthus annuus* L. and *Helianthus tuberosus* L., are cultivated for food; the remaining species are ornamentals, weeds, and wild plants, invading roadsides, wastelands, urban open spaces, fallow land and croplands (CABI 2019a). *H. annuus* is described as an allelopathic species since it inhibits the growth and impairs the development other plants, thus, reducing their productivity. Although it does possess harmful effects, it is less harmful to important crops of the Poaceae family than other families. Several species were reported as the target of allelochemicals from *H. annuus*, such as *Chenopodium album* L.*, Avena fatua* L.*, Amaranthus albus* L.*, Sida spinosa* L. and others (Azania *et al.* 2003).

Species from the the genus *Tagetes*, popularly known as marigold, are native to Mexico and Central America and distributed all over the world for ornamental purposes, such as in garlands for social and religious ceremonies. The plants are resistant to saline and adverse conditions, and they are frequently cultivated in a multicrop system (Vasudevan *et al*. 1997). *Tagetes minuta* L. is distributed across the tropics, subtropics and several temperate countries as an ornamental, medicinal or perfume plant, as well as, accidentally, a weed. In 1930, it was introduced to California, USA, to control root-knot nematodes in orchards, but it has since become an invasive weed (CABI 2020). López *et al*. (2008) reported that the favorable conditions for the germination of *T. minuta* also contribute to the germination of other species, leading to an intense competition between *T. minuta* seedlings and other species, and the release of ocimenones (monoterpenes) is involved in the inhibition of the germination of cohabitant species by *T. minuta*. Meissner *et al*. (1986) described the inhibitory effect on the height of crop species, like carrot, cucumber and lettuce, when germinated in soil infested by *T. minuta.* Santos *et al.* (2015) reported the inhibition of germination and root growth on *L. sativa* caused by aqueous, hydroethanolic and ethanolic extracts of *Tagetes patula* L. and *Tagetes erecta* L. . In addition, an inhibitory effect on mitosis of *Allium cepa* L. root cells was noted, with a higher incidence of aberrant cells when treated with *T. patula* and *T. erecta* extracts.

It is worth emphasizing that some species from genera of the Asteraceae family mentioned are able to inhibit the development of highly invasive weeds, which are controlled by systemic herbicides, such as *Parthenium hysterophorus* L.*, Cynodon dactylon* (L.) Pers. and *Digitaria sanguinalis* (L.) Scop.. This evidence supports the allelopathic potential of the Asteraceae family and reveals that its allelochemicals can be important tools for weed management, facing challenges of environmental pollution and herbicide resistance.

Bioassays and target species

According to the reports shown in Table 1, the main bioassays used to evaluate the allelopathic/phytotoxic potential of species of the Asteraceae family were in *vitro* bioassays with Petri dishes or Gerbox plastic boxes, sometimes using rhizospheric soil.

Seed germination has been widely used in allelopathy/phytotoxic bioassays because it is a good indicator of the real potential of the tested species (Chiapusio *et al.* 1997). However, different approaches can be observed, indicating the absence of standardization. In some studies, only the effects on total germination are evaluated, while in others, they also evaluate the germination speed index.

The seedling growth test is important for ascertaining the phytotoxic activity of the extracts or test solutions and in planning the other stages of investigation. Resistance to secondary metabolites is a characteristic that varies from species to species. Lettuce, tomatoes (*Lycopersicon esculentum* Mill.) and radish (*Raphanus sativus* L.) are commonly used as target plants in bioassays owing to their sensitivity to allelochemicals or phytotoxic compounds (Souza Filho *et al*. 2010; Tur *et al*. 2010). According to Kobayashi (2004), the susceptibility of the target species to the action of phytotoxic substances, under laboratory conditions, depends on the physiological and biochemical characteristics of each species. Among the target species mentioned, *L. sativa* is the most used since it is extremely sensitive to phytotoxic compounds, which is important for the identification of activities in low concentrations. However, it can induce errors, leading to an overestimation of phytotoxic activity or even induce phytotoxicity where it does not exist or does not express. This becomes a problem in tests where *L. sativa* is the only target species. The use of more than one species allows a better dimensioning of the real phytotoxic potential of the donor species.

It is ideal to consider, at least, three types of target species in bioassays: sensitive, moderately sensitive and resistant (Souza Filho *et al*. 2010).

Allelochemicals in Asteraceae family

According to the reports shown in Table 1, it is possible to observe the involvement of terpenes, sesquiterpene lactones, polyacetylenes, saponins, phenolic acids and flavonoids with phytotoxic activity of the Asteraceae family.

Phenolic acids, such as *p*-coumaric acid, gallic acid, ferulic acid, *p*-hydroxybenzoic acid and anisic acid, were described as allelochemicals from *Ageratum conyzoides* L. (Batish *et al.* 2009). The species *Ambrosia artemisiifolia* L., *Helianthus tuberosus* L. and *Bidens pilosa* L. also had their phytotoxic activity attributed to phenolic acids. In fact, such compounds are described as allelochemicals because they are capable of causing a nonspecific efflux of anions and cations, which accompany the increased permeability of the cell membrane, inducing its depolarization, and these membrane effects correlate with an inhibition of ion uptake. Phenolic acids suppress the absorption of phosphate, potassium, nitrate and magnesium ions causing general tissue changes. They also induce lipid peroxidation through oxidation or cross-linking of sulfhydryl groups present in the plasma membrane, resulting in the formation of free radicals and inhibition of the activities of the enzymes catalase and peroxidase. Therefore, they are substances capable of causing structural changes in membranes that include changes in a variety of membrane proteins (Macías *et al*. 2004).

Onopordum acanthium L. and *Tridax procumbens* L. exhibited phytotoxic activity attributed to flavonoids. Although flavonoids are a very large group of phenolic substances, only few of them are known to act as allelochemicals. The mechanisms of allelopathic action have not yet been fully elucidated, but some reports describe their ability to inhibit energy metabolism and the consumption of mitochondrial oxygen (Macías *et al*. 2004; Einhellig 1995).

The phytotoxic activity of *Bidens alba* (L.) DC., *Bidens pilosa* L. and *Acroptilon repens* (L.) DC. is attributed to polyacetylenes. In the Asteraceae family, acetylenes may consist of metabolically altered derivatives of crepenynic acid and are characterized by conjugated systems of double and triple carbon bonds with cyclic or heterocyclic structures. Some have antifungal, antibiotic and antiviral properties (Konovalov 2014). Phenyl-1,3,5-heptatriyne is an important allelochemical present in *B. alba* and *B. pilosa*. Little is known about the mechanism of action of acetylenes; however, it is known that phenyl-1,3,5-heptatriyne is a phototoxic acetylene, and when activated by UV-A radiation, it can degrade cellular membranes, resulting in toxicity against competing organisms, such as plants (Cantonwine & Downum 2001; Campbell *et al*. 1982).

Monoterpenes and sesquiterpenes are related to the phytototoxic activity of *Artemisia scoparia* Waldst. & Kit., *Ambrosia trifida* L., *Flourensia campestris* Griseb., *Heterotheca subaxillaris* (Lam.) Britton & Rusby, *Tagetes minuta* L. and *Eriocephalus africanus* L. The mechanisms of phytotoxic action of terpenes have not yet been fully elucidated. Among those already described, it was seen that monoterpenes can act by inhibiting the enzyme asparagine synthase, thus preventing growth, in addition to impairing mitochondrial cell respiration of organelles. Sesquiterpenes can cause a slow release of proteins in the plasma membrane (Macías *et al*. 2004).

Bellis longifolia Boiss. & Heldr., *Bellis sylvestris* Cirillo and *Mikania micrantha* Kunth showed phytotoxic activity related to di- and triterpene glycosides (saponins). The mode of action of these compounds has not yet been elucidated; however, it is likely that these compounds can interact with the plasma membrane by their amphipathic properties, thus causing an increase in their cellular permeability which leads to a reduction in the water potential of leaves and pressure turgor (Macías *et al*. 2004).

Sesquiterpene lactones are involved in the phytotoxic activity of *Artemisia gorgonum* Webb, *Cosmos sulphureus* Cav., *Cynara cardunculus* L., *Onopordum acanthium* L. and *Tithonia diversifolia* (Hemsl.) A.Gray. In the Asteraceae family, more than 4000 sesquiterpene lactones have been identified, and they are considered one of the largest groups of secondary plant metabolites, which have received considerable attention in recent decades by their broad spectrum of biological activities, usually related to the presence of an α,β-unsaturated carbonyl system in the lactone ring. In addition, they have an exceptional ecological value for plants, being responsible for the evolutionary success of the Asteraceae family (Schmidt 1999; Chadwick *et al*. 2013). It is believed that their alkylating properties through Michael addition reactions are involved in the phytotoxic activity. A large number of enzymes and other essential macromolecules are inhibited by sesquiterpene lactones, usually in low concentrations (Schmidt 1999). And one example is the addition of the sulfhydryl groups of glutathione to the exocyclic methylene of sesquiterpene lactones. Concerning the importance of glutathione to the cellular metabolism, this kind of interaction can inactivate the enzyme and interrupt metabolism (Galindo *et al*. 1999). In addition, a sesquiterpene lactone can separate the plasma membrane from the cell wall, resulting in leakage of electrolytes (Macías *et al.* 2004). The sesquiterpene lactones aguerin B, grosheimin, and cynaropicrin were identified in the ethyl acetate extract of *Cynara cardunculus* L. . At 0.8 mg/mL, this extract was able to inhibit ~60% and ~90% of root length of *Urochloa decumbens* (Stapf) R.D.Webster and *Echinochloa crus-galli* (L.) P.Beauv., which are important weed species around the world. In the same test, Logran®, a sulfonylurea herbicide, inhibited only ~70% of root length of *E. crus-galli,* demonstrating the promising phytotoxic potential of the extract, especially for the presence of sesquiterpenes lactones (Rial *et al*. 2014). Also known as brachiaria, *U. decumbens* is native to Africa, but highly invasive in South America, mainly in Brazil, where it was introduced to serve as pasture, but it has since spread throughout the country, and it can markedly modify the environment in which it dominates (Williams & Baruch 2000; Rial *et al*. 2014). *E. crus-galli*, known as barnyard grass is the third worst weed worldwide. Some characteristics of this weed, such as higher density, elevated macro- and micronutrient uptake and better water balance facilitate its high power of invasion, especially in rice, cotton, corn and potato plantations (Rial *et al.* 2014). Thus, the weed's growth inhibition by sesquiterpene lactones demonstrates the potential of these compounds as natural herbicide.

According to the identified allelochemicals in Table 1, terpenes, including sesquiterpene lactones, are the secondary metabolites involved with the phytotoxic/allelopathic activity of most of the genera of the Asteraceae family reported in this review.

Phytotoxicity of ***Acmella oleracea*** (L.) R.K.Jansen
Effects on ***Lactuca sativa*** L.

According to Table 2, it can be observed that the germination of lettuce seeds was affected by all fractions and crude extract. All fractions inhibited the growth of roots of lettuce (Fig. 1); however, dichloromethane and ethyl acetate fractions

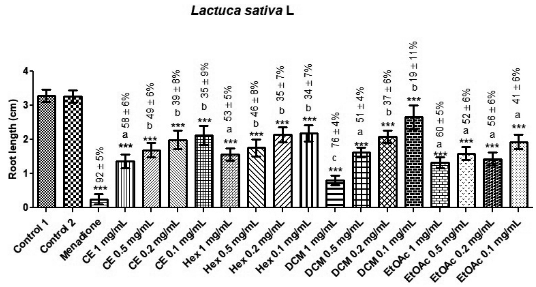

Figure 1 – Effects of *Acmella oleracea* leaves extract and fractions on lettuce roots growth. Control 1= water; Control 2= DMSO 0.1%; Positive control= Menadione (0.143 mg/mL); CE= crude extract; Hex= hexane fraction; DCM= dichloromethane fraction; EtOAc= ethyl acetate fraction. Results are expressed as mean with 95% CI. Significance was determined by one-way ANOVA followed by Tukey's Multiple Comparison Test. p value summary: *** very significant ($p < 0.001$), ** very significant ($0.001 < p < 0.01$), * significant ($0.01 < p < 0.05$), ns (not significant) in comparison to control 1. Different lowercase letters among treatments indicate significant differences according to Tukey's Multiple Comparison Test ($p <0.05$). Inhibition effect (%) in comparison to control 1 are expressed above each bar.

were most harmful, but less than positive control menadione. At 1 mg/mL, dichloromethane fraction inhibited 76 ± 4% of lettuce root growth, while ethyl acetate fraction inhibited 60 ± 5%. The IC_{50} established for dichloromethane fraction was 0.48 mg/mL, which is similar to the value of 0.4 mg/mL reported in the work of Kato-Noguchi *et al*. (2019) where they evaluated the inhibitory effect of aqueous methanol extracts of *A. oleracea* on lettuce roots. Compared to some species shown in Table 1, as *Artemisia arborescens* L., *T. patula*, *T. erecta* and *T. procumbens*, *A. oleracea* extracts seem to have better phytotoxic activity since a better inhibitory effect on seedling growth was observed at lower concentrations.

Effects on ***Calopogonium mucunoides*** Desv.

Calopogonium mucunoides Desv. is a fast-growing forage legume, native to tropical America, with the potential to form dense mats that weaken native vegetation, as well as crops in active agricultural areas (CABI 2019b). It was introduced as a forage legume and nitrogen-fixing plant in tropical and subtropical regions. However, because of its fast growth, it has escaped from cultivation, becoming a serious environmental

Table 2 – Inhibition effect of *Acmella oleracea* extract and fractions on *Lactuca sativa* seeds germination

Acmella olearacea	**% Inhibition of seeds germination – *Lactuca sativa***			
	1 mg/mL	**0.5 mg/mL**	**0.2 mg/mL**	**0.1 mg/mL**
Crude extract	21	21	19	19
Hexane fraction	21	16.7	16.7	14.4
Dichloromethane fraction	25.5	11	11	10
Ethyl acetate fraction	23.3	17.8	15.5	14.4
Control 1		0		
Control 2		0		
Menadione		83.3		

Control 1= Water; Control 2= DMSO 0.1 %; Positive control = Menadione (143 ppm)

problem, mainly in Australia and the Pacific Islands (Cook *et al.* 2005). All fractions inhibited *C. mucunoides* seed germination at 0.2 mg/mL (Tab. 3), and in comparison to lettuce seeds, the latter seemed to be more resistant to the allelochemicals from *A. oleracea*. According to Figure 2, all fractions significantly inhibited seedling root growth with an effect above 60%. This result is very promising since for large infestations, *C. mucunoides* is controlled by synthetic herbicides that inhibit glutamine synthetase, such as glufosinate-ammonium, and auxin mimics, such as dicamba (CABI 2019b). Although glufosinate ammonium formulations have been regarded as minimally toxic to humans, ingestion of undiluted glufosinate ammonium herbicide results in grave clinical outcomes, such as shock, respiratory arrest apnea, unconsciousness, convulsions, and amnesia (Park *et al*. 2013). In patients with history of dicamba herbicide ingestion, abnormalities, such as elevated lactate, creatine kinase and lipase, in addition to metabolic acidosis and QTc prolongation, were observed (Moon & Chun 2014). In this context, the possibility of using a natural product obtained from *A. olearacea*, a species consumed in Brazilian cuisine and used in traditional medicine (Simas *et al*. 2013), seems to be a safer alternative for the control of the weed *C. mucunoides* than synthetic herbicides. It is worth mentioning that this is the first report of *A. oleracea* phytotoxic activity against the weed *C. mucunoides*.

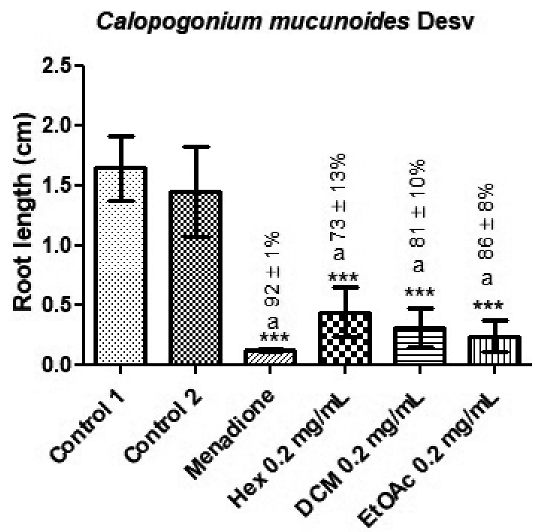

Figure 2 – Effects of *Acmella oleracea* leaves extract and fractions on *Calopogonium mucunoides* roots growth. Control 1= water; Control 2= DMSO 0.1%; Positive control= Menadione (0.143 mg/mL); CE= crude extract; Hex= hexane fraction; DCM= dichloromethane fraction; EtOAc= ethyl acetate fraction. Results are expressed as mean with 95% CI. Significance was determined by one-way ANOVA followed by Tukey's Multiple Comparison Test. p value summary: *** very significant ($p < 0.001$), ** very significant ($0.001 < p < 0.01$), * significant ($0.01 < p < 0.05$), ns (not significant) in comparison to control 1. The same lowercase letters among treatments indicate no significant differences according to Tukey's Multiple Comparison Test ($p < 0.05$). Inhibition effect (%) in comparison to control 1 are expressed above each bar.

Phytochemical analysis of ***A. olearecea*** (L.) R.K.Jansen

Dichloromethane fraction was subjected to GC/MS analysis, and it was possible to identify the following as major constituents: *p*-methoxy-

Table 3 – Inhibition effect of *Acmella oleracea* fractions on *Calopogonium mucunoides* seeds germination

Acmella olearacea fractions (0.2 mg/mL)	% Inhibition of germination – *Calopogonium mucunoides* seeds
Hexane	51.3
Dichloromethane	53.9
Ethyl acetate	53.9
Control 1	0
Control 2	0
Menadione	91

Control 1= Water; Control 2= DMSO 0.1 %; Positive control = Menadione (143 ppm)

cinnamic and 3,4-dimethoxy-cinnamic acids, 3,4-dimethoxy- and 3,4,5-trimethoxybenzoic acids and palmitic acid (see Supplementary Material < https://doi.org/10.6084/m9.figshare.16892338.v1>).

The presence of fatty acid and phenolic acids corroborates the phytotoxic activity exhibited by the dichloromethane fraction from *A. oleracea*, demonstrating the synergistic effect between the constituents. Such substances are widely described in the literature as allelochemicals because they cause changes in the cell membrane and protein functions of the receiving plant species, affecting normal physiological processes (Inderjit & Duke 2003; Dayan *et al*. 2009; Li *et al*. 2010). Fatty acids disturb the lipid bilayer of biological membranes through the formation of ion channels that cause changes in permeability associated with the loss of K^+ ions and, consequently, rupture of the membrane organization (Wu *et al*. 2006; Alamsjah *et al.* 2008). Meanwhile, phenolic substances can interfere with the uptake of inorganic ions, such as NO_3^-, $H_2PO_4^-$, SO_4^{-2}, K^+, Ca^{+2} and Mg^{+2}, from the rhizosphere, cause water stress, cell expansion reduction, stomatal closure and decrease in photosynthesis in higher plants, resulting in growth impairment (Blum 1996; Matsuoka *et al.* 1998).

Phytotoxicity of ***Sphagneticola trilobata*** (L.) Pruski
Effects on ***Lactuca sativa*** **L.**

In Table 4, it can be seen that the germination of lettuce seeds was affected by all fractions, aqueous residue and crude extract in a concentration-dependent manner, highlighting dichloromethane extract, the inhibitory effect of which ranged from 22.2% to 93.3%. All fractions, crude extract and aqueous residue of *S. trilobata* inhibited the growth of roots of lettuce (Fig. 3); however the fractions and aqueous residue performed greater phytotoxicity than crude extract. At 1 mg/mL, hexane and dichloromethane fractions were as active as the positive control menadione, however, at the lowest concentration, no inhibitory effect was observed for these fractions. Ethyl acetate fraction and aqueous residue exhibited similar phytotoxic effects to each other, and even at 0.25 mg/mL an inhibition of 49 ± 6% and 53 ± 6% of lettuce roots length was observed, respectively. The IC_{50} values established were 1.13 mg/mL, 0.94 mg/

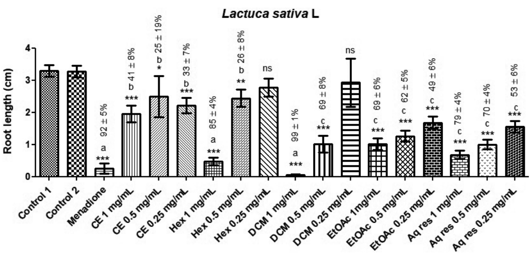

Figure 3 – Effects of *Sphagneticola trilobata* leaves extract and fractions on *Lactuca sativa* roots growth. Control 1= water; Control 2= DMSO 0.1%; Positive control= Menadione (0.143 mg/mL); CE= crude extract; Hex= hexane fraction; DCM= dichloromethane fraction; EtOAc= ethyl acetate fraction; Aq res= Aqueous residue. Results are expressed as mean with 95% CI. Significance was determined by one-way ANOVA followed by Tukey's Multiple Comparison Test. p value summary: *** very significant ($p < 0.001$), ** very significant ($0.001 < p < 0.01$), * significant ($0.01 < p < 0.05$), ns (not significant) in comparison to control 1. The same lowercase letters among treatments indicate no significant differences according to Tukey's Multiple Comparison Test ($p < 0.05$). Inhibition effect (%) in comparison to control 1 are expressed above each bar.

Table 4 – Inhibition effect of *Sphagneticola trilobata* crude extract and fractions on *Lactuca sativa* seeds germination

Sphagneticola trilobata	**% Inhibition of seeds germination – *Lactuca sativa***		
	1 mg/mL	**0.5 mg/mL**	**0.25 mg/mL**
Crude extract	20	16.1	11.1
Hexane fraction	47.8	11.1	6.7
Dichloromethane fraction	93.3	56.7	22.2
Ethyl acetate fraction	14.4	7.8	7.8
Aqueous residue	20	16.1	11.1
Control 1		0	
Control 2		0	
Menadione		83.3	

Control 1= Water; Control 2= DMSO 0.1 %; Positive control = Menadione (143 ppm)

mL, 0.36 mg/mL, 0.37 mg/mL and 0.19 mg/mL for crude extract, hexane, dichloromethane, ethyl acetate fractions and aqueous residue, respectively. According to these values, the aqueous residue seems to be slightly more phytotoxic compared to crude extract and fractions of *S. trilobata*. Thus, in comparison with the aqueous extract from leaves of *Helianthus tuberosus* L. Fuseau cultivar (Tesio *et al*. 2011), for example, that presented a higher value of IC_{50} (0.41 mg/mL) for inhibition of lettuce root length, *S. trilobata* extracts seem to have considerable phytotoxic potential.

Effects on ***Ipomoea purpurea*** (L.) Roth

Ipomoea purpurea (L.) Roth belongs to the family Convolvulaceae, and it is popularly known as common morning glory and tall morning glory. It is a harmful weed species, mainly in annual crops, because its cycle is longer than that of the crop, in addition to the branches intertwining in the plants, making harvesting difficult. Crops, such as sugar cane, corn, rice, wheat and soy, are often affected by the invasion of species of *Ipomoea* genus (Duarte *et al*. 2008).

The crude extract, fractions and aqueous residue from *S. trilobata* were evaluated against *I. purpurea* at the respective IC_{50} values calcualated in the bioassays with *L. sativa*. According to Table 5, all the fractions and hydroalcoholic extract inhibited *I. purpurea* seed germination, ranging from 20% to 37.8%. As shown in Figure 4, the crude extract and most fractions, except hexane, significantly affected root growth, ranging from 38 ± 14% to 59 ± 8% of inhibitory effect.

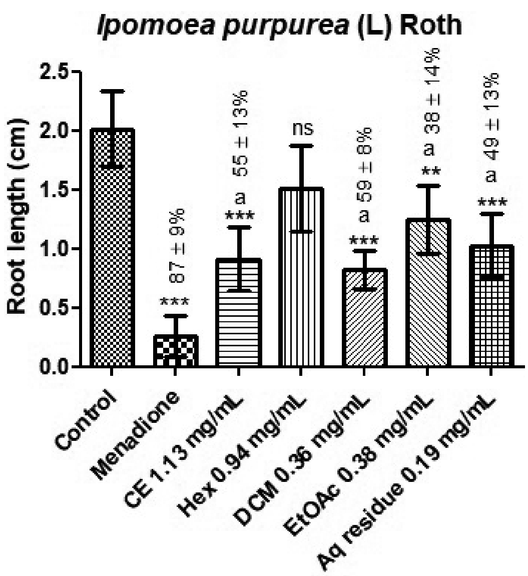

Figure 4 – Effects of *Sphagneticola trilobata* (L.) Pruski leaves extract and fractions on *Ipomoea purpurea* (L.) Roth roots growth. Control = DMSO 0.1%; Positive control= Menadione (0.143 mg/mL); CE= crude extract; Hex= hexane fraction; DCM= dichloromethane fraction; EtOAc= ethyl acetate fraction. Results are expressed as mean with 95% CI. Significance was determined by one-way ANOVA followed by Tukey's Multiple Comparison Test. p value summary: *** very significant ($p < 0.001$), ** very significant ($0.001 < p < 0.01$), * significant ($0.01 < p < 0.05$), ns (not significant) in comparison to control 1. The same lowercase letters among treatments indicate no significant differences according to Tukey's Multiple Comparison Test ($p < 0.05$). Inhibition effect (%) in comparison to control 1 are expressed above each bar.

Table 5 – Inhibition effect of *Sphagneticola trilobata* extract and fractions on *Ipomoea purpurea* seeds germination

Sphagneticola trilobata	% Inhibition of germination – *Ipomoea purpurea* seeds
Crude extract (1.13 mg/mL)	37.8
Hexane fraction (0.94 mg/mL)	20
Dichloromethane fraction (0.36 mg/mL)	37.8
Ethyl acetate fraction (0.38 mg/mL)	33.3
Aqueous residue (0.19 mg/mL)	20
Control 1	0
Control 2	0
Menadione	80

Control 1= Water; Control 2= DMSO 0.1 %; Positive control = Menadione (143 ppm)

Thus, in terms of *I. purpurea* growth, inhibitory effects of around 50% reveal that the weed was as sensitive to the phytochemicals from *S. trilobata* extract and fractions as lettuce. These results are very promising because *I. purpurea* is a highly invasive species, controlled by the organophosphorus herbicide glyphosate. In general, weeds treated with pesticides do not produce secondary aromatic compounds, such as, for example, antimicrobial phytoalexins which defend plants against pathogens. As a result, most plants treated with synthetic herbicides were affected by infection from root pathogens universally present in soil (Babiker *et al.* 2011; Rashid *et al*. 2013). The application of glyphosate can result in the accumulation of residues in the harvest and in animals used for human consumption. Its acute and chronic effects on humans can vary, from skin damage to cardiogenic shock (Amarente-Junior *et al.* 2002). In the literature, studies prove the potential chronic effects of glyphosate and its degradation products as they accumulate in the environment affecting nontarget organisms, such as other plants and microorganisms (Helander *et al*. 2012; Battaglin *et al*. 2014; Greim *et al*. 2015; Mesnage *et al*. 2015; Bai & Ogbourne 2016).

Bürger *et al.* (2005) reported the safety of *S. trilobata* extracts in studies of acute and subacute toxicity with mice, concluding that the LD_{50} was higher than 4000 mg/kg after ingestion of the hydroalcoholic extract of the aerial parts of the plant and that no change in body weight or haematological parameters was noted. In another study, Buddhakala and Talubmook (2020) demonstrated a lethal dose (LD_{50}) greater than 2500 mg/kg for *S. trilobata* ethanolic extract administrated to rats, indicating there was no sign of toxicity and mortality in acute and subacute toxicity testing. In this context, the possibility of using a natural product obtained from *S. trilobata*, a species used in traditional medicine as an adjunct in the treatment of diabetes mellitus (Lemões *et al.* 2012) and one that presents no toxicity potential, according to the mentioned studies, seems to be a safer alternative for the control of the weed *I.* purpurea than synthetic herbicides. It is worth mentioning that this is the first report of *S. trilobata* phytotoxic activity against the weed *Ipomoea purpurea* (L.) Roth.

Phytochemical analysis of ***Sphagneticola trilobata*** (L.) Pruski

Because of its higher phytotoxic activity in bioassays on lettuce and weed, dichloromethane fraction and aqueous residue were chosen for phytochemical study. Dichloromethane fraction was subjected to GC/MS analysis, and it was possible to identify allopregnane and cholestenol derivatives as major constituents (se Figs S7 and S8, Supplementary Material < https://doi.org/10.6084/m9.figshare.16892338.v1>). No reports about the presence of these steroids in *S. trilobata* can be found; thus, these represent new data on the phytochemistry of this species. From ESI-MS analysis, it was possible to verify the presence of phenolic substances in the composition of aqueous residue, which were identified as dicaffeoylquinic acid ($[M-H]^-$ 515.1197; MM= $C_{25}H_{24}O_{12}$), quinic acid ($[M-H]^-$ 191.0567; MM= $C_7H_{12}O_6$), caffeoylquinic acid ($[M-H]^-$ 353.0884;

$MM= C_{16}H_{18}O_9$), as well as the ion $[M-H]^-$ 135.0452 ($MM= C_8H_7O_2$), which is related to the loss of CO_2 from caffeic acid (Wu *et al.* 2009). Caffeoylquinic and dicaffeoylquinic acids were reported in other studies with extracts from aerial parts of *S. trilobata* (Fucina *et al.* 2016; Lang *et al*. 2017). The composition of both dichloromethane fraction and aqueous residue suggests that a synergistic effect between the constituents may occur, improving phytotoxic activity. As seen before, the low IC_{50} value demonstrates the greater phytotoxic potential of the aqueous residue. This fact can be attributed at least part by the presence of phenolic acids, known as allelochemicals, in its composition. Quinic acid, also present in aqueous residue, was described as a natural herbicide by Orcaray *et al*. (2010) because its exogenous application arrested plant growth and decreased net photosynthesis and stomatal conductance. Thus, quinic acid may also contribute to phytotoxicity of aqueous residue from *S. trilobata*.

The use of synthetic herbicides has increased considerably year by year owing to the increasing need to control weeds as in monocultural farming. Besides causing harm to the environment, human and animal health, these herbicides cannot be used in medicinal plant culture. In view of these facts, it becomes increasingly necessary to create natural and safer alternatives for weed control, and the Asteraceae family comprises several species with such herbicidal potential.

Artemisia, *Ambrosia*, *Bellis*, *Bidens*, *Helianthus* and *Tagetes* are the main genera of Asteraceae family with studies demonstrating phytotoxic or allelopathic activity. Among the secondary metabolites from this family, terpenoids, polyacetylenes, saponins, sesquiterpene lactones, phenolic acids and flavonoids were described as allelochemicals, highlighting sesquiterpene lactones; their activity likely results from alkylating properties through Michael addition reactions.

In this paper, we also showed the phytotoxic activity of *Acmella oleracea* (L.) R.K.Jansen and *Sphagneticola trilobata* (L.) Pruski against the highly invasive weeds *Calopogonium mucunoides* Desv. and *Ipomoea purpurea* (L.) Roth, respectively. The possibility of using a natural herbicide obtained from *A. olearacea* and *S. trilobata*, the first consumed in Brazilian cuisine and both used in traditional medicine, seems to be a safer alternative for the control of weeds than synthetic herbicides. To the best of our knowledge, this is the first study reporting on the control of *C. mucunoides* and *I. purpurea* with extracts and fractions from *A. olearacea* and *S. trilobata*, respectively.

Despite the promising results of our group with *A. oleracea* and *S. trilobata*, in addition to the species described in this review, *in vitro* bioassays only reveal potential for phytotoxicity, implying the real need for further studies in the field in order to evaluate viability for these species to become a natural herbicide.

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