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Mycorrhizal technology as a bioinsumption to produce phenolic compounds of importance to the herbal medicine industry

Tecnologia micorrízica como bioinsumo para produção de compostos fenólicos de importância à indústria de fitomedicamentos

La tecnología micorrizada como bioinsumo para la producción de compuestos fenólicos de importancia para la industria de la fitomedicación

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Emauela Lima dos Santos
ORCID: https://orcid.org/0000-0003-0136-4730
University of Pernambuco, Brazil
E-mail: emanuela_lima07@hotmail.com
Eduarda Lins Falcão
ORCID: https://orcid.org/0000-0003-3141-6466
University of Pernambuco, Brazil
E-mail: eduardalins88@gmail.com
Fábio Sérgio Barbosa da Silva
ORCID: https://orcid.org/0000-0001-7798-5408
University of Pernambuco, Brazil
E-mail: fs.barbosa@yahoo.com.br

Abstract
The arbuscular mycorrhizal fungi (AMF) are microorganisms that form mutualistic symbiosis with the most studied plant species. Such fungi are known to confer benefits to plant species, moreover, can improve the edaphic environment that are found. In this regard, the first research of this theme were about the benefits proportionated by AMF in relation to the growth and plant production; afterwards, the number of studies that registered the AMF benefits in increasing the compounds production from primary and secondary metabolism in plants increased, especially in plants of interest to food industry, cosmetics and pharmaceutical. Several biomolecules were studied, such as essential oils, phenolic compounds, and nitrogen compounds. Therefore, this review aimed to compile the research studies that reported the mycorrhizal symbiosis benefits in optimize the production of phenolic compounds with therapeutic potential, highlighting those developed in Brazil.
Keywords: Phytochemistry; AMF; Glomeromycota.

Resumo
Os fungos micorrízicos arbusculares (FMA) são microrganismos que formam simbiose mutualística com a maioria das espécies vegetais estudadas. Tais fungos são conhecidos por conferirem benefícios às espécies vegetais, além disso, podem melhorar o ambiente edáfico em que se encontram. Nesse sentido, os primeiros trabalhos dessa temática versavam sobre os benefícios proporcionados pelos FMA em relação ao crescimento e produção vegetal; posteriormente, tornou-se crescente o número de estudos que registraram os benefícios dos FMA em incrementar a produção de compostos dos metabolismos primário e secundário vegetal, principalmente em plantas de interesse para indústrias alimentícia, de cosméticos e farmacêutica. Várias biomoléculas foram estudadas, como óleos essenciais, compostos fenólicos e compostos nitrogenados. Diante disso, essa revisão teve o objetivo de compilar trabalhos que relataram os benefícios da simbiose micorrízica em otimizar a produção de compostos fenólicos com potencial terapêutico, com destaque para aqueles conduzidos no Brasil.
Palavras-chave: Fitoquímica; FMA; Glomeromycota.

Resumen
Los hongos micorrízicos arbusculares (HMA) son microorganismos que forman simbiosis mutualista como la mayoría de las especies vegetales más estudiadas. Se sabe que estos hongos confieren beneficios a las especies vegetales, además, pueden mejorar el ambiente edáfico en el que se encuentran. En este sentido, los primeros trabajos sobre este tema abordaron los beneficios que ofrece la FMA en relación al crecimiento y producción vegetal; Posteriormente, creció el número de estudios que registraron los beneficios de las FMA en el aumento de la producción de compuestos del metabolismo primario y secundario, principalmente en plantas de interés para la industria alimentaria, cosmética y farmacéutica. Se han estudiado varias biomoléculas, como aceites esenciales, compuestos fenólicos y compuestos

nitrogenados. Por lo tanto, esta revisión tuvo como objetivo recopilar estudios que informaron los beneficios de la simbiosis micorrízica en la optimización de la producción de compuestos fenólicos con potencial terapéutico, con énfasis en los realizados en Brasil.

Palabras clave: Fitoquímica; FMA; Glomeromycota.

1. Introduction

The soil microorganisms contribute for the ecosystems maintenance, which can bring benefits to plants communities or animals in the environment. Among these organisms, the mycorrhizal fungi stand out, which form associations called mycorrhiza with the majority of plant species (Moreira & Siqueira, 2006).

The arbuscular mycorrhizal fungi (AMF) are microorganims belonging to Glomeromycota phylum (Wijayawardene *et al.*, 2020), and form symbiosis with most of the plants (Smith & Read, 2008). They can bring benefits to plant species (Amiri *et al.*, 2017; Silva & Maia, 2018) and to the edaphic environment where they are inhabiting (Kohler, Rodán, Campoy, & Caravaca, 2016; Rodriguez-Caballero *et al.*, 2017).

In relation to the benefits proportionated to plants, studies reported that AMF inoculation can increase the growth (Tarraf *et al.*, 2015), offer enhanced nutritional uptake (Domokos *et al.*, 2018), improve stress tolerances (He, Zhang, & Tang,2016; Chang *et al.*, 2018) and regulate the production of primary and secondary compounds from plant metabolism (Parada *et al.*, 2019; Paskovic *et al.*, 2019). In this regard, studies were conducted with plants of medicinal interest, registering the increment of biomolecules production, which confer medicinal properties (Santos, Silva & Silva, 2017; Oliveira *et al.*, 2019a).

Among the compounds studied, the phenolic group deserves emphasis, that had the highest quantity of recorded research in this subject (Parada *et al.*, 2019; Cruz *et al.*, 2020; Santos *et al.*, 2020). It is worth noting that different parts of the plants, such as leaves (Urchoviche *et al.*, 2015), flowers (Lazzara *et al.*, 2017), roots (Mechri *et al.*, 2015) and fruits (Cordeiro *et al.*, 2019) had the metabolites production optimized by AMF inoculation

In this context, this review aimed to compile the studies that reported the mycorrhizal symbiosis benefits in optimize the production of phenolic compounds with therapeutic potential, highlighting those developed in Brazil.

2. AMF Benefits to Host Plants

Studies highlighted the AMF presence in roots more than 400 million years ago (Remy, Taylor, Hass, & Kerp, 1994; Taylor, Remy, Hass, & Kerp, 1995) and until nowadays, are found in different ecosystems and their distribution vary in accordance with the environmental conditions (Davinson *et al.*, 2015).

The AMF have hyphae that differ in arbuscules between the cell membrane and cell wall of the root cells. These structures are surrounded by the periarbuscular membrane. The site of the interface of the fungi and the periarbuscular membrane it is called apoplast; in this region occurs high enzymatic and transporters activity, considering that it is the exchange site of nutrients between the fungi and the plant. Moreover, the AMF can develop other structures, such as vesicles and auxiliary cells (Smith & Read, 2008).

In symbiosis, the AMF uptake water and nutrients from the soil to the plant and in exchange, receive carbohydrates (Moreira & Siqueira, 2006). This association confers several benefits to plant species, such as the improved nutrients uptake, especially Phosphorus, an element not much available in the soil and of importance to the growth and development of plant species. In this way, Ferrol, Azcón-Aguilar, and Pérez-Tienda (2019) reviewed the absorption pathway of this macronutrient, reporting the main transporters involved during the symbiosis.

At the beginning of P absorption, the *PHO84* transporter, situated in the external hyphae, which allows the acquisition of inorganic Phosphorus by AMF that will be transported to the hyphae vacuole as polyphosphate, the transporter *PHO91* exports the phosphorus ions to the fungi cytosol. Consequently, this phosphorus can be transferred to the apoplastic space through efflux protein or by the transporter *PHO84*, located in the arbuscular membrane, and transferred to the plant by *MTP* (*Mycorrhiza-inducible transporter*), situated in the periarbuscular membrane and regulated by transcription factors (Ferrol, Azcón-Aguilar, & Pérez-Tienda, 2019).

Concerning the uptake of other nutrients, Lima, Riter Netto, Martins and Freitas (2015a) verified the increase in the Ca, K, Mg and S content in aerial parts of *Toona ciliata* M. seedlings inoculated with different AMF species. In roots of *Glycyrrhiza glabra* L. inoculated with *Funneliformis mossae* (T.H. Nilcolson & Gerd.) C. Walker & Schuessler and with *Rhizophagus intraradices* (N.C. Schenck & G.S. Sm.) C. Walker & Schuessler had the increment of P and Zn concentration in relation to the non-incoculated control (Orujei, Shabani, & Sharifi-Tehrani, 2013).

The plant growth can be favored by AMF inoculation, as documented by Tarraf *et al.* (2015) in *Salvia officinalis* L., in *Origanum vulgare* L. and *Thymus vulgaris* L. inoculated with *F. mosseae* e *Septoglomus viscosum* Nicol. & Gerd (G.V); Rydlová *et al.* (2016) also reported the increase in the biomass from aerial parts of cilantro (*Coriandrum sativum* L., var. Long Standing) and dill (*Anethum graveolens* L., var. Hanák) inoculated with *Rhizophagus irregularis* (Blaszk., Wubet, Renker & Buscot) C. Walker & A. Schübler BEG144, in relation to the control. Domokos and collaborators (2018) documented that *R. irregularis* inoculation in *Artemisia annua* L. favored the increase in the phytomass and glandular trichomes density.

Another benefit provided by AMF to plant species is the improved tolerance to biotic and abiotic stresses. In this context, He *et al.* (2016) registered, in *Robinia pseudoacacia* L. inoculated with *R. irregularis*, drought tolerance; in this case, the colonization by the fungi provided improvements in the plant physiological parameters, such as stomach conductance and perspiration rate, acting in the modutation of aquoporines coding genes.

Chang *et al.* (2018) evaluated the salinity effect in *Elaeagnus angustifolia* L. colonized by *R. irregularis* and documented that the AMF in symbiosis favored the biomass accumulation, in addition to alleviate the deleterious effect of saline stress. Wu *et al.* (2016) reported the improved metals tolerance, such as Cr, in *Taraxacum platypecidum* Diels. inoculated with *R. irregularis* and documented the external mycelium can auxiliate the immobilization of this element.

The protection of plant species against pathogens can be favored by mycorrhization. In this regard, Akthar and Siddiqui (2008) verified that *Cicer arietimum* L. inoculated with *R. intraradices*, *Rhyzobium* sp. and *Pseudomonas striata* Chester had greater tolerance to the *Meloidogyne incognita* (Kefoid & White) Chitwood nematoid. In *Capsicum annum* L. cv. Charliston Bagci colonized by *F. mosseae,* the severity caused by *Phytophthora capsici* Leonian was reduced in comparison to the control plants without AMF (Ozgonen & Erkilic, 2007).

In addition to the benefits related to the optimization of plant growth and the tolerance of biotic and abiotic stresses, the AMF can increase the production of plant metabolites, that are important to the industry.

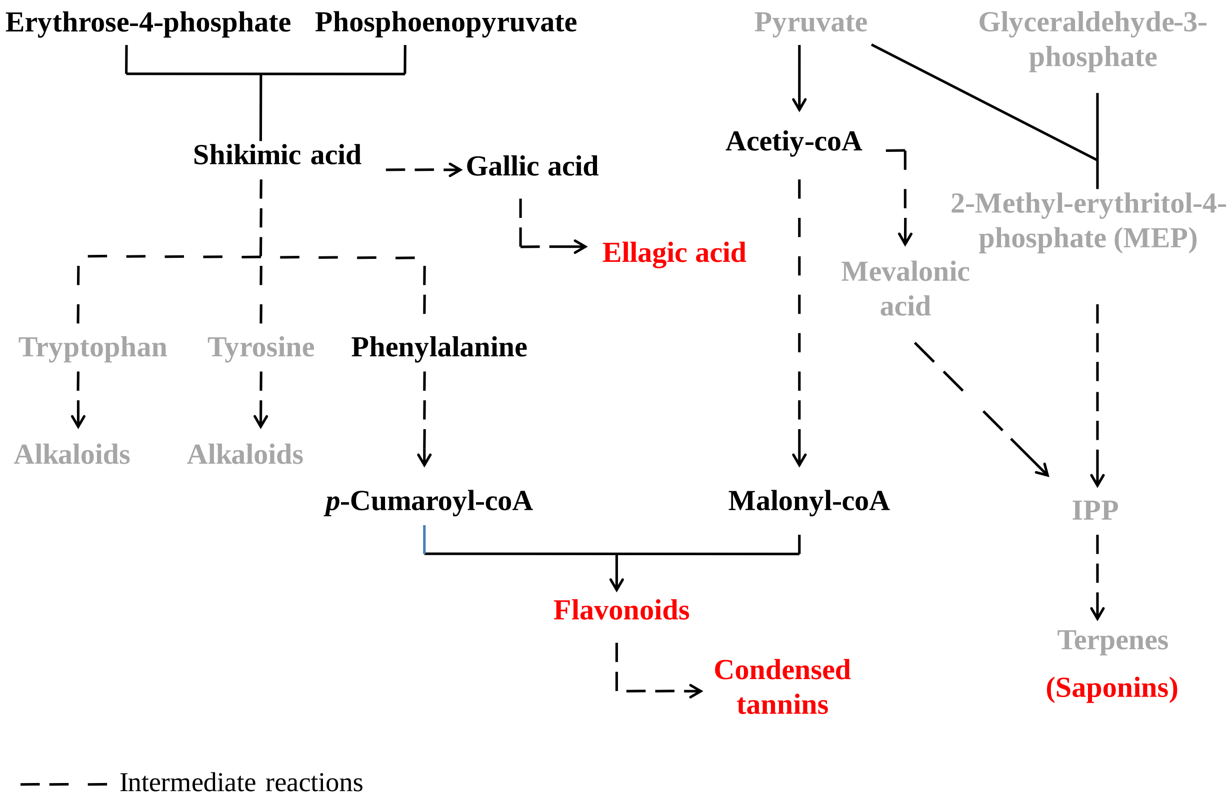
3. AMF and Production of Metabolites

Besides the benefits described above, the mycorrhization can influence the compounds produced from primary and secondary metabolism in plants (Maia-Silva, 2012; Tavarini *et al.*, 2018). The plants produce substances from secondary metabolism, that can confer medicinal properties to plant species. These compounds are derivative from precursors of primary metabolism and are divided into three main classes: terpenes, nitrogen compounds, and phenolic compounds (Simões *et al.*, 2017).

The terpenes are considered the largest compounds class, stemming from methyleritrophosphate (MEP) and mevalonic acid pathway, synthesized from isoprene units (Figure 1) (Zhi-Lin, Chuan-chao, & Lian-qing, 2007). In this class are found biomolecules of relevance to the pharmaceutical industry, cosmetics, and food industry, such as essential oils and artemisinin (Jusing *et al.*, 2006; Xie *et al.*, 2018). The aromatic amino acids from the shikimic acid pathway and the aliphatic amino acids form the nitrogen compounds (Figure 2). In this class can be found substances such as morphine and codeine, alkaloids that present importance for the pharmaceutical industry and medicine (Simões *et al.*, 2017).

The phenolic compounds are derivative from the shikimic acid pathway and a mixed route of the precursors from shikimic acid and malonic acid pathway (Figure 2). To this class are included the phenols, flavonoids, protanthocyanidins, tannins, among other molecules (Oksana, Marian, Mahendra, & Bo, 2012), that confer to plant species antioxidant properties, healing, antimicrobial, and others (Silva *et al.*, 2013; Kobayashi *et al.*, 2015). The use of AMF inoculation can be an alternative to increase the production of these compounds and improve the pytomass (Karimi *et al.*, 2016; Tavarini *et al.*, 2018; Weisany, 2018).

Figure 1. Main pathaways of secondary plant metabolism.



coA = coenzyme A; IPP = isopentylpyrophosphate. Source: Authors.

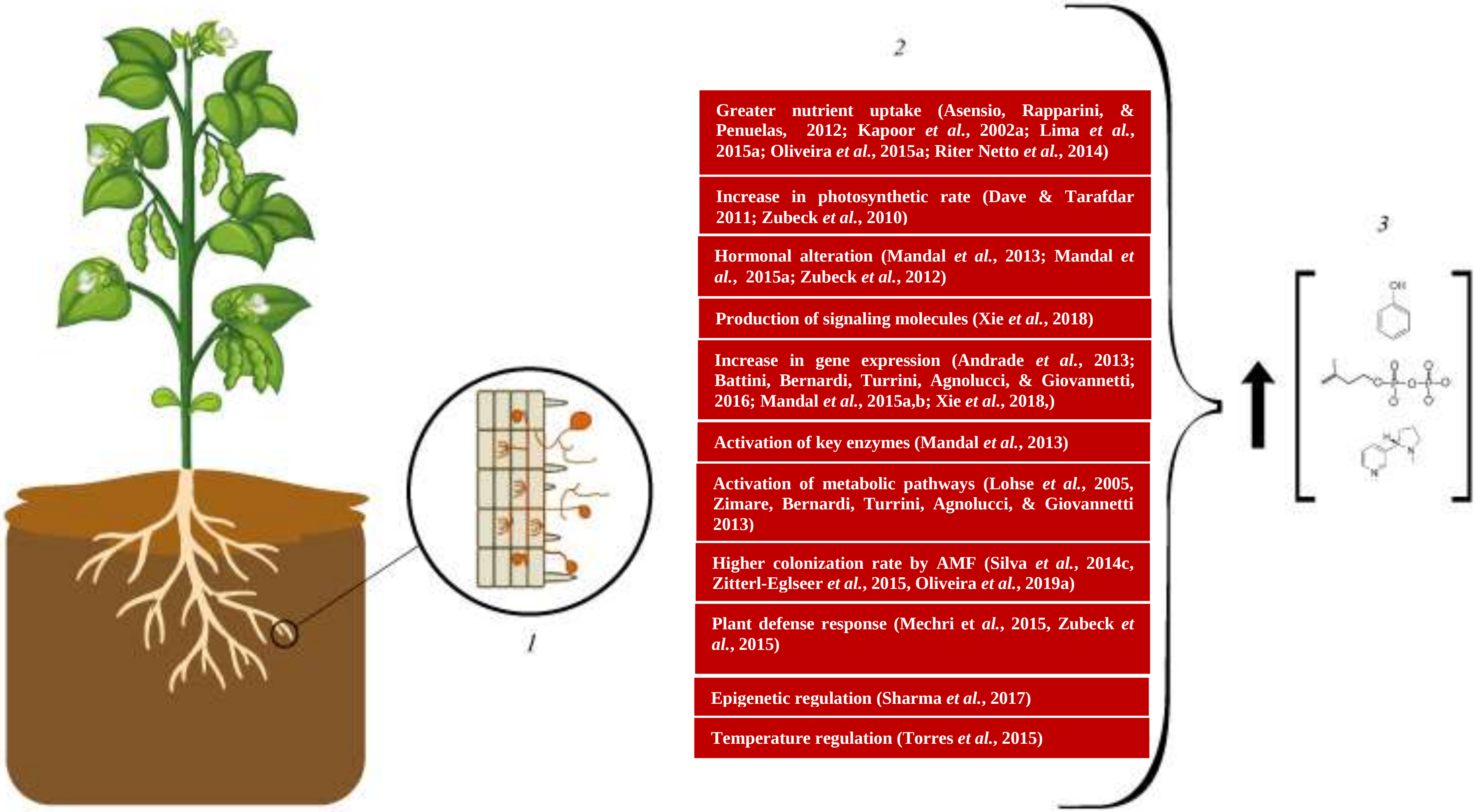
The foliar concentrations of proteins and soluble carbohydrates were increased in *Lactuca sativa* L. inoculated with a mix of *R. intraradices* e *F. mosseae*, (SanMartin *et al.*, 2014). Mechri *et al.* (2015) reported, to *Olea europea* L., kept in a greenhouse and inoculated with *R. Irregulares,* increase in the content of root carbohydrates. Similarly, Abbaspour, Saeidi-Sar, Afshari, and Abdel-Wahhab (2012) reported that, even if in stress conditions promoted by drought, *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler was efficient to increase the content of soluble carbohydrates and proteins in aerial parts of *Pistacia vera* L., in comparison to the control.

Other studies documented in different plant species, the greater production of secondary metabolites due to mycorrhization (Riter Netto *et al.*, 2014; Campubri, Zárate, Adholeya, Lovato, & Calvet, 2015; Fan & Song, 2018). Such increase it is of interest to the food industry, cosmetic (Nzanza, Maraisa, & Soundy, 2012; Campubri *et al.*, 2015), and pharmaceutical, due to the properties conferred by these biomolecules to plant species.

In *Allium cepa* L. the inoculation with a mixed inoculum of *F. mosseae* and *R. Irregulares* favored the flavonoids production and the coding genes expression of key-enzymes from the biosynthesis of this phenolic compounds group (Mollavali *et al.*, 2018). Lazzara *et al.* (2017) registered the increment of ipericin and pseudohypericin, in mycorrhizal *Hypericum perforatum* L. flowers, in relation to the non-inoculated control.

The effect of mycorrhization in the compounds production from secondary metabolism does not occur only due to the enhancement of plant nutritional state (Kapoor, Anand, Gupta, & Mandal, 2017), but also to other mechanisms regulated by AMF. Zhang, Zhu, Zhao, and Yao (2013) reported that the AMF *F. Mosseae* inoculated in *Trifolium repense* L. promoted changes in the concentration of signaling molecules, such as nitric oxide, salicylic acid and hydrogen peroxide; such molecules influence the activation of key-enzymes of phenolics biosynthesis, such as L-phenylalanine ammonia lyase (PAL) and chalcone synthase (CHS). The authors also verified the increase in the concentration of the phenolic compounds in roots from inoculated plants (Figure 2).

Figure 2. Mechanisms proposed to explain the efficiency of arbuscular mycorrhizal fungi in increasing the production of phenolic, terpenic and nitrogen compounds.



Greater nutrient uptake (Asensio, Rapparini, & Penuelas, 2012; Kapoor *et al.*, 2002a; Lima *et al.*, 2015a; Oliveira *et al.*, 2015a; Riter Netto *et al.*, 2014)

Increase in photosynthetic rate (Dave & Tarafdar 2011; Zubeck *et al.*, 2010)

Hormonal alteration (Mandal *et al.*, 2013; Mandal *et al.*, 2015a; Zubeck *et al.*, 2012)

Production of signaling molecules (Xie *et al.*, 2018)

Increase in gene expression (Andrade *et al.*, 2013; Battini, Bernardi, Turrini, Agnolucci, & Giovannetti, 2016; Mandal *et al.*, 2015a,b; Xie *et al.*, 2018,)

Activation of key enzymes (Mandal *et al.*, 2013)

Activation of metabolic pathways (Lohse *et al.*, 2005, Zimare, Bernardi, Turrini, Agnolucci, & Giovannetti 2013)

Higher colonization rate by AMF (Silva *et al.*, 2014c, Zitterl-Eglseer *et al.*, 2015, Oliveira *et al.*, 2019a)

Plant defense response (Mechri et *al.*, 2015, Zubeck *et al.*, 2015)

Epigenetic regulation (Sharma *et al.*, 2017)

Temperature regulation (Torres *et al.*, 2015)

1 = mycorrhizal plant; 2 = mechanisms; 3 = concentration of phenolics, terpenic and nitrogen compounds. Source: Authors.

Moreover, the genes expression that code participating enzymes from the secondary metabolite's biosynthesis can be modulated by AMF (Mandal *et al.*, 2015b; Xie *et al.*, 2018). Mandal *et al.* (2015a) reported the increase in the concentration of artemisinin in leaves of *A. annua* inoculated with *R. intraradices* and such benefit was correlated to the increased expression of genes that are involved in the biosynthesis of this compound (Figure 2).

The plant system defense concerning colonization can be another mechanism that regulates the production of metabolites, as reported by Zubeck *et al.* (2015). The production of some plant growth regulators, such as jasmonic acid can activate compounds biosynthesis, characterizing one more regulation mechanism; we cannot discard the AMF inoculation to increase the production of phytohormones, that revert into a distinguished phytochemicals production (Mandal *et al.*, 2013). Furthermore, the highest colonization rate by AMF can also influence secondary metabolites biosynthesis (Zitter-Eglseer *et al.*, 2015; Oliveira *et al.*, 2019a) (Figure 1).

It is worth noting that mycorrhization can bring benefits to plant species. In *Rubus fruticosus* L. Agg. colonized by *F. mosseae*, the inoculation did not favor the plant growth (Abud-Archila *et al.*, 2018). Mycorrhizal *H. perforatum* had lower flower numbers and stem diameter than non-inoculated plants (Lazzara *et al.*, 2017). Silva and Silva (2017) also documented that mycorrhization did not benefit primary and secondary metabolism production and the growth of *Mimosa tenuiflora* (Wild) Poir. seedlings. Thus, the selection of efficient inoculum should be carried out before the mycorrhizal technology recommendation to optimize the production of bioactive compounds.

4. Arbuscular Mycorrhizal Fungi and the Production of Phenolic Compounds in Medicinal Plants

The first studies that documented the production of phenolic compounds due to the mycorrhizal technology associated with the accumulation of phenols by mycorrhizal modulation. Larose *et al.* (2002) verified, in roots of *Medicago sativa* L. colonized by *F. mosseae*, *R. intraradices* e *Gigaspora rosea* T.H. Nicolson & N.C. Schenck, increase in the concentration of flavonoids. According to these authors, the production of these compounds was related to the flavonoids accumulation which depends on the duration of the experiment and the applied AMF.

Afterwards, the studies were targeted to the selection of efficient AMF in enhance secondary metabolites concentration in plant species that were used in the pharmaceutical industry, cosmetical and food (Kapoor *et al.*, 2004; Kara *et al.*, 2015; Urchoviche *et al.*, 2015; Torres *et al.*, 2018).

In this context, there are reports of an increase in the concentration of phenols in the aerial parts of carqueja (*Baccharis trimera* Less.) proportionated by AMF inoculation, species of medicinal interest, in comparison to the control (Freitas, Carvalho, & Carneiro, 2004a). Araim, Saleem, Arnason, & Charest (2009) also verified the increase in the concentration of roots phenols and in the aerial part of *Echinacea purpurea* (L.) Moench inoculated with *R. Intraradices*. In roots of *M. Sativa* colonized by *F. mosseae*, the mycorrhization conferred greater antioxidant activity and flavonoids production, when compared to non-inoculated plants (Fan & Song, 2018).

In *Vitis vinifera* L. cv Tempranillo, species used in the wines production, colonized by *R. Intraradices*, the leaf extract had greater antioxidant activity, the increment of the total phenols concentration, in the content of flavonoids and anthocyanins (Torres *et al.*, 2015). In this regard, Torres *et al.* (2018) using *V. vinifera* clones inoculated with mixed inoculum with 5 AMF species (*F. mosseae, Septoglomus deserticola* (Trappe, Bloss & J.A. Menge) G.A. Silva, Oehl & Sieverding., *R. clarus, R. intraradices, Rhizophagus aggregatus* (N.C. Schenck & G.S. Sm.) C. Walker), at different temperatures, documented that the inoculation conferred improved nutritional uptake and foliar flavonols production in comparison to non-inoculated plants.

The combination of *Gigaspora margarita* W.N. Becker & I.R. Hall, *R. clarus* e *C. etunicatum* species in Australian cedar (*Toona ciliata* M. Roemer var. *australis*) increased the growth and the content of foliar total phenols (Lima *et al.*, 2015a). Fruits of *Solanum lycopersicum* L. (tomato) colonized by *R. Intraradices* presented higher concentrations of nutrients and lycopene, when compared to those non-mycorrhizal. Furthermore, the plants had greater anti-estrogenic activity, improving the nutraceutical value of this Solanaceae (Giovannetti *et al.*, 2012).

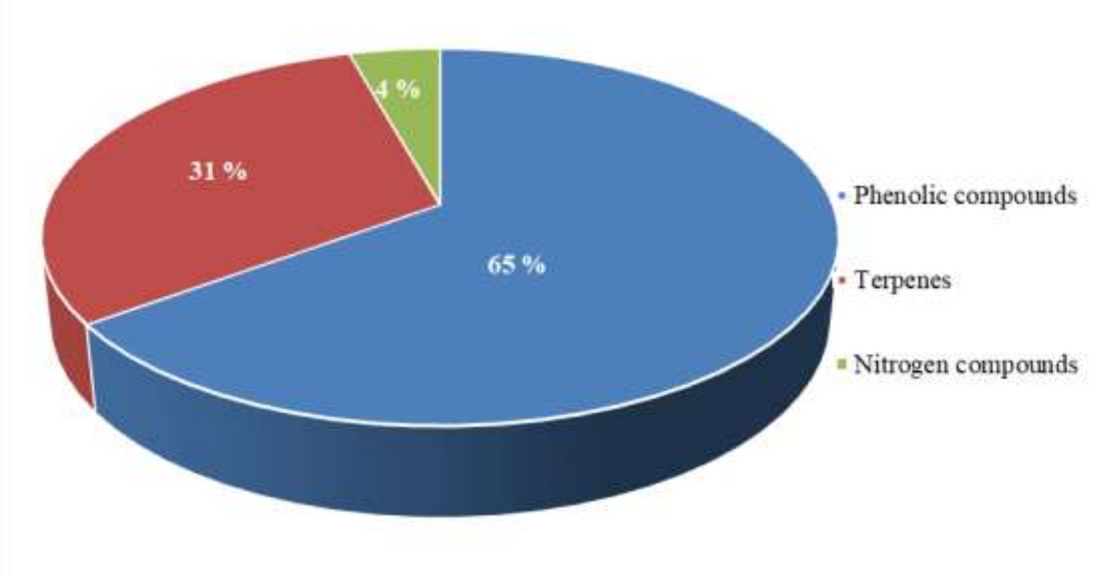
Hajiboland et al. (2018) reported, in leaves of strawberry plant (*Fragaria ananassa* Duchesne cv. Paros), higher production of phenols in plants inoculated with*. clarus, R. intraradices e G. versiform*e. In bulbs of *Allium cepa* L., the mycorrhization provided the increase in the production of flavonols, in addition to the influence of expression of coding genes related to enzymes involved in the biosynthesis of these compounds (Mollavali *et al.*, 2018).

In addition to favoring the production of the groups of secondary compounds (Santos *et al.*, 2017; Silva & Maia, 2018), the mycorrhization can improve the biosynthesis of specific compounds that are important to the pharmaceutical industry (Oliveira *et al.*, 2015b; Hajiboland, Moradtalab, Aliasgharzad, Eshaghi, & Feizy, 2018). In this regard, Oliveira *et al.* (2019a) reported the increase in the concentration of foliar vitexin in yellow passion fruit (*Passiflora edulis* f. *flavicarpa*). Silva, Silva, Ferreira, Soares and Silva (2018b) reported that the inoculation favored the production of ellagic and gallic acids in the bark of the stem of *Libidibia ferrea* (Mart. ex Tul.) L.P. Queiroz var. *ferrea*, in relation to the non-inoculated plants.

Currently, there are approximately 242 published studies (The database Web of Science was used to search for papers published during 1993-2020 and the following keywords were used: Glomeromycota; Arbuscular mycorrhizal fungi; Mycorrhizal colonization; Mycorrhization; AMF species; AMF; Mycorrhizal symbiosis; Mycorrhiza; Biomolecules; Secondary metabolism; Phenolics; Tannins; Proteins; Essential Oils; Carbohydrates; Flavonoids; Bioactive Compounds; Medicinal Plants; Phenols; Terpene; Secondary Metabolites; Antioxidant Activity; Bioactive Molecules; Mycorrhizal Technology; Carotenoid; Phytochemistry; Leaves; Flowers; Alkaloids; Flavonon; Anthocyanins; Anthocyanidins; Proanthocyanidins; Isoflavonoids; Saponins), that documented the effect of AMF inoculation in the production of secondary metabolites and, usually, these reported about the production of more than one group of molecules. From these studies, 239 dealt with the production of phenolic compounds, 113 with terpenes and 16 with nitrogen compounds (Figure 3).

Most of these studies reported the optimization in the production of molecules, due to AMF inoculation, in leaves, roots and, rhizomes (Lamian, Badi, Mehrafarin, & Sahandi, 2017; Yang *et al.*, 2017), there are few reports on flowers and fruits (Kapoor *et al.*, 2002a,b; Zen *et al.*, 2013; Hristozkova *et al.*, 2016; Cordeiro *et al.*, 2019; Santos *et al.*, 2020). Moreover, the biomolecules production, such as phenols, in response to symbiosis, is associated with different mechanisms (Figure 1). The compiled data about this subject can be found in Zeng *et al.* (2013), Pedone-Bonfim *et al.* (2015) and Sharma *et al.* (2017), the only reviews on this theme.

Figure 3. Studies on the effect of AMF inoculation on the production of secondary compounds in plant species.



Phenolics: Grandmaison *et al.*, 1993; Peipp *et al.*, 1997; Larose e*t al.*, 2002; Freitas *et al.*, 2004; Krishna *et al.*, 2005; Soares *et al.*, 2005; Antunes *et al.*, 2006; Scervino *et al.*, 2006; Toussaint *et al.*, 2007; Carlsen *et al.*, 2008; Halvorson & Gonzalez, 2008; Jaiti *et al.*, 2008; Khaosaad *et al.*, 2008; Perner *et al.*, 2008; Rajeshkumar *et al.*, 2008; Ruiz-Téran *et al.*, 2008; Schlienann *et al.*, 2008; Lattanzio *et al.*, 2009; Lee & Scagel, 2009; Ponce *et al.*, 2009; Selvaraj *et al.*, 2009; Andrade *et al.*, 2010; Castellanos-Morales *et al.*, 2010; Ceccarelli *et al.*, 2010; Damoradan *et al.*, 2010; Geneva *et al.*, 2010; Nisha & Rajeshkumar, 2010; Singh *et al.*, 2010; Wang *et al.*, 2010; Zubeck *et al.*, 2010; Abdell-Fattah *et al.*, 2011; Baslam *et al.*, 2011; Hemashenpaganet *al. 20*,11; Ibrahim *et al.*, 2011; Mota-Fernandéz *et al.*, 2011; Rosa-Mera *et al.*, 2011; Selvaraj & Sumithra, 2011; Tchameni *et al.*, 2011; Tejavathi *et al.*, 2011; Abbaspour *et al.*, 2012; Abbeynayake *et al.*, 2012; Al-Ghamdi *et al.*, 2012; Baslam *et al.*, 2012; Eftekhari *et al.*, 2012; Nzanza *et al.*, 2012; Giovannetti *et al.*, 2012; Singh *et al.*, 2012; Zubeck *et al.*, 2012; Andrade *et al.*, 2013; Baslam *et al.*, 2013a,b; Chen *et al.*. 2013; Lingua *et al.*, 2013; Orujei *et al.*, 2013; Oliverira *et al.*, 2013; Pedone-Bonfim *et al.*, 2013; Zhang *et al.*, 2013; Banuelos *et al.*, 2014; Cosme *et al.*, 2014; Espinosa *et al.*, 2014; Gualandi Júnior *et al.*, 2014; Silva *et al.*, 2014a,b,c,d; Riter Netto *et al.*, 2014; Rozpadeck *et al.*, 2014; Seif *et al.*, 2014; Aliferis *et al.*, 2015; Garg *et al.*, 2015; Hazzoumi *et al.*, 2015; Jugran *et al.*, 2015; Torres *et al.*, 2015; Kara *et al.*, 2015; Lermen *et al.*, 2015; Lima *et al.*, 2015a,b; Lone *et al.*, 2015; Lu *et al.*, 2015; Mechri *et al.*, 2015; Meddich *et al.*, 2015; Oliveira *et al.*, 2015a,b,c; Pankoke *et al.*, 2015; Tognon *et al.*, 2015; Torres *et al.*, 2015; Zhu *et al.*, 2015; Zitterl-Eglseer *et al*. 2015; Battini *et al.*, 2016; Cecatto *et al.*, 2016; Dutta *et al.*, 2016; Gabrieli *et al.*, 2016; Hashem *et al.*, 2016; Hristozkova *et al.*, 2016; Amiri *et al.*, 2017; Avio *et al.*, 2017; Hegazi *et al.*, 2017; Hristozkova *et al.*, 2017; Jaroszewaska & Biel, 2017; Khalid *et al.*, 2017; Lazzara *et al.*, 2017; Lima *et al.*, 2017; Papastylianou *et al.*, 2017; Pistelli *et al.*, 2017; Santos *et al.*, 2017; Silva & Silva, 2017; Tyagi *et al.*, 2017; Yang *et al.*, 2017; Zayova *et al.*, 2017; Abud- Archila *et al.*, 2018; Almeida *et al.*, 2018; Caser *et al.*, 2018; Fan & Song, 2018; Hajiboland *et al.*, 2018; Haslem *et al.*, 2018; Hristozkova *et al.*, 2018; M' barki *et al.*, 2018; Mollavali et al. 2018; Pedone-Bonfim *et al.*, 2018; Lucini *et al.*, 2018; Silva & Maia. 2018

Silva *et al.*, 2018a,b; Todeschini *et al.*, 2018; Torres *et al.*, 2018; Solloum *et al.*, 2018; Wasny *et al.*, 2018; Aseel *et al.*, 2019; Bacsek *et al.*, 2019; Bencherif *et al.*, 2019; Cui *et al.*, 2019; Ghambari *et al.*, 2019; Paskovic *et al.*, 2019; Parada *et al.*, 2019; Oliveira *et al.*, 2019; Rabab & Reda, 2019; Seró *et al.*, 2019; Tian *et al.*, 2019; Cordeiro *et al.*, 2019; Amanifara & Toghranegarb, 2020; Attarzedeh *et al.*, 2020; Avio *et al.*, 2020; Chiomento *et al.*, 2020; Cruz *et al.*, 2020; Oliveira *et al.*, 2020; Pasbani *et al.*, 2020; Rashad *et al.*, 2020; Thokchom *et al.*, 2020; Torum *et al.*, 2020; Santos *et al.*, 2020; Silva & Silva, 2020. **Terpenes:** Vierhilig *et al.*, 2000; Walter *et al.*, 2000; Akiyama *et al.*, 2002; Gupta *et al.*, 2002; Kapoor *et al.*, 2002; Freitas *et al.*, 2004; Kapoor *et al.*, 2005; Lohse *et al.*, 2005; Khaosaad *et al.*, 2006; Strack & Fester, 2006; Kapoor *et al.*, 2007; Chaudhary *et al.*, 2008; Morone-Fortunato *et al.*, 2008; Rajeshkumar *et al.*, 2008; Silva *et al.*, 2008; Schlienann *et al.*, 2008; Fontana *et al.*, 2009; Nell *et al.*, 2009; Malik *et al.*, 2009; Selvaraj *et al.*, 2009; Nisha & Rajeshkumar, 2010; Rasouli-Sadaghiani *et al.*, 2010; Zubeck *et al.*, 2010; Binet *et al.*, 2011; Baslam *et al.*., 2011; Hemashenpagan *et al.*, 2011; Dave & Tarafdar *et al.*, 2011; Tejavathi *et al.*, 2011; Karagiannidis *et al.*, 2012; Heydarizadeh *et al.*, 2013; Mandal *et al.*, 2013; Orujei *et al.*, 2013; Singh *et al.*, 2013; Zimare *et al.*, 2013; Cosme *et al.*, 2014; Gualandi Júnior *et al.*, 2014; Rozpadeck *et al.*, 2014; Seif *et al.*, 2014; Silva *et al.*, 2014d; Aliferis *et al.*, 2015; Hart *et al.*, 2015; Hazzoumi *et al.*, 2015; Gutjahr *et al.*, 2015; López-Ráez *et al.*, 2015; Mandal *et al.*, 2015a, b; Pankoke *et al.*, 2015; Shrivastava *et al.*, 2015; Tognon *et al.*, 2015; Tarraf *et al.*, 2015; Urcoviche *et al.*, 2015; Zitterl-Eglseer *et al.*, 2015; Wu *et al.*, 2015; Bharti *et al.*, 2015; Hristozkova *et al.*, 2016; Karimi *et al.*, 2016; Pedranzazi *et al.*, 2016; Tomczack *et al.*, 2016; Amiri *et al.*, 2017; Hegazi *et al.*, 2017; Khalid *et al.*, 2017; Lamian *et al.*, 2017; Rahimzadech & Pizard 2017; Tekaya *et al.*, 2017; Timari *et al.*, 2017; Bona *et al.*, 2018; Burdecea *et al.*, 2018; Domokos *et al.*, 2018; Haslem *et al.*, 2018; Hassiotis *et al.*, 2018; Pizard *et al.*, 2018; Tavarini *et al.*, 2018; Torres *et al.*, 2018; Xie *et al.*, 2018; Wasny *et al.*, 2018; Wicaksono *et al.*, 2018; Weisany *et al.*, 2018; Amnifar *et al.*, 2019; Lucini *et al.*, 2019; Oliveira *et al.*, 2019; Sh tark *et al.*, 2019; Tian *et al.*, 2019; Yu *et al.*, 2019; Amanifara & Toghranegarb, 2019; Casarrubias-Castillo *et al.*, 2020; Cruz *et al.*, 2020; Javanmard *et al.*, 2020; Santos *et al.*, 2020; Thokchom *et al.*, 2020 **Nitrogen:** Abu-Zeyad *et al.*, 1999; Rojas-Andrade, 2003; Rajeshkumar *et al.*, 2008; Selvaraj *et al.*, 2009; Nisha & Rajeshkumar 2010; Ratti *et al.*, 2010; Hemashenpagan *et al.*, 2011; Rosa-Mera *et al.*, 2011; Selvaraj & Sumithra, 2011; Andrade *et al.*, 2013; Yadav *et al.*, 2013; Gualandi Júnior *et al.*, 2014; Wu *et al.*, 2014; Aliferis *et al.*, 2015; Zhao *et al.*, 2018; Makarov *et al.*, 2020.

5. AMF and Production of Phytochemicals: Studies Conducted in Brazil

In Brazil, 37 studies reported a production of phytochemicals in mycorrhizal plants (Table 1), from these, a review about these themes (Pedone-Bonfim *et al.*, 2015). Around 54 % of these studies were developed by a research group from the Universiy of Pernambuco (UPE), using medicinal plants and fruit trees occurring in Brazil, especially, in the Caatinga biome.

In this country, the research projects in increasing the production of phenolic compounds in mycorrhizal species of pharmaceutical interest, such as *Baccharis trimera* (Less.) DC. (Freitas *et al.*, 2004a), *Cymbopogon citratus* (D.C.) Stapf (Cruz *et al.*, 2020) *Mentha crispa* (Urcoviche *et al.*, 2015), *Punica granatum* (Silva *et al.*, 2014c; Silva & Silva 2020), *Passiflora alata* Curtis (Riter Netto *et al.*, 2014; Oliveira *et al.*, 2015a,b) e *P. edulis* f. *flavicarpa* (Oliveira *et al.*, 2019a; Oliveira *et al.*, 2020) have been increasing.

Most of the studies were conducted in a greenhouse, existing only five experiments in field conditions; from those, four used different parts of the mycorrhizal *L. Ferrea*: one with leaves (Silva *et al.*, 2014b), two using the bark of the stem (Santos *et al.*, 2017; Silva *et al.*, 2018b) and with fruits (Santos *et al.*, 2020). A recent study with strawberry plants were reported by Cordeiro *et al.* (2019).

In greenhouses, in addition to the species mentioned previously, the studies used plants occurring in the Caatinga biome, such as *Anadenanthera colubrina* (Vell.) Brenan, *Amburana cearensis* (Allemão) A.C. Smith, *L. ferrea*, *Inga vera* Willd., *Myracrodruon urundeuva* Allemão (Anacardiaceae), *Mimosa tenuiflora* (Willd.) Poir and documented the increase in the concentration of phenolic compounds due to mycorrhization (Silva *et al.*, 2014a,b; Lima *et al.*, 2015b; Oliveira *et al.*, 2015c; Pedone-Bonfim *et al.*, 2018; Silva & Maia, 2018). On the other hand, some studies did not report the mycorrhizal benefits in the metabolites production (Silva & Silva, 2017).

Table 1. Studies developed in Brazil: plant species, arbuscular mycorrhizal fungi used and studied compounds.

Plant specie	Applied AMF	Studied compounds	Authors
Baccharis trimera (Less.) DC.	*Acaulospora scrobiculata* Trappe *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora margarita* W.N. Becker & I.R. Hall *Rhizophagus clarus* (T.H. Nicolson & N.C. Schenck) C. Walker & Schuessler	Total phenols	Freitas *et al.* (2004a)
Mentha arvensis L.	*Acaulospora scrobiculata* Trappe *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora margarita* W.N. Becker & I.R. Hall *Rhizophagus clarus* (T.H. Nicolson & N.C. Schenck) C. Walker & Schuessler	Essential oils	Freitas *et al.* (2004b)
Zingiber officinale Roscoe	*Acaulospora koskei* Blaszkowski *Dentiscutata heterogama* (T.H. Nicolson & Gerd.) Sieverd., F.A. Souza & Oehl. *Entrophospora colombiana* Spain & Schenck	Resin oil	Silva *et al.* (2008)

	Gigaspora decipiens Hall & Abbott		
Canavalia ensiformis (L.) D.C.	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler	Antioxidant activity Proteins	Andrade *et al.* (2010)
Catharanthus roseus (L.) G. Don. *Nicotiana tabacum* L.	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Rhizophagus intraradices* (N.C. Schenck & G.S. Sm.) C. Walker & Schuessler	Alkaloids Canthaxanthin Serpentine Vinblastine Vincristine	Andrade *et al.* (2013)
Myracrodruon urundeuva Allemão	*Acaulospora longula* Spain & N.C. Schenck *Gigaspora albida* N.C. Schenck & G.S. Sm	Total soluble carbohydrates Total flavonoids Total phenols Total proteins	Oliveira *et al.* (2013)
Anadenanthera colubrina (Vell.) Brenan	Mix (*Gigaspora albida* N.C. Schenck & G.S. Sm + *Acaulospora longula* Spain & N.C. Schenck)	Total soluble carbohydrates Total flavonoids Total phenols Total proteins Total tannins	Pedone-Bonfim *et al.* (2013)
Passiflora alata Curtis	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler	Total phenols	Riter-Netto *et al.* (2014)

	Gigaspora margarita W.N. Becker & I.R. Hall *Rhizophagus intraradices* (N.C. Schenck & G.S. Sm.) C. Walker & Schuessler		
Punica granatum L.	*Acaulospora longula* Spain & N.C. Schenck *Gigaspora albida* N.C. Schenck & G.S. Sm	Total soluble carbohydrates Total flavonoids Total phenols Total proteins Total tannins	Silva *et al.* (2014c)
Mentha x piperita L. var. *citrata* (Ehrh) Briq.	*Acaulospora marrowie* Spain and Schenck *Rhizophagus clarus* (T.H. Nicolson & N.C. Schenck) C. Walker & Schuessler *Scutellospora calospora* (Nicol. And Gerd.) Walk. and Sand.	Essential oils	Silva *et al.* (2014d)
Libidibia ferrea (Mart. Ex Tul.) L.P. Queiroz var. *ferrea*	*Acaulospora longula* Spain & N.C. Schenck *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora albida* N.C. Schenck & G.S. Sm	Total soluble carbohydrates Total flavonoids Total phenols Total proteins Total tannins	Silva *et al.* (2014a)
Libidibia ferrea (Mart. Ex Tul.) L.P.	*Acaulospora longula* Spain & N.C. Schenck	Gallic acid	Silva *et al.* (2014b)

Queiroz var. *ferrea*	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora albida* N.C. Schenck & G.S. Sm	Total phenol Total tannins	
Cymbopogon citratus (D.C.) Stapf	*Rhizophagus clarus* (T.H. Nicolson & N.C. Schenck) C. Walker & Schuessler	Essential oils	Lermen *et al.* (2015)
Inga vera Willd.	*Acaulospora longula* Spain & N.C. Schenck *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora albida* N.C. Schenck & G.S. Sm	Total antioxidant activity Total soluble carbohydrates Total flavonoids Total phenols Total proteins Total tannins	Lima *et al.* (2015b)
Toona ciliata M. Roemer var. *australis*	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora margarita* W.N. Becker & I.R. Hall *Rhizophagus clarus* (T.H. Nicolson & N.C. Schenck) C. Walker & Schuessler	Total phenols	Lima *et al.* (2015a)
Amburana cearensis (Allemão) A.C. Smith	*Acaulospora longula* Spain & N.C. Schenck *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler	Total soluble carbohydrates Total flavonoids Total phenols	Oliveira *et al.* (2015c)

	Gigaspora albida N.C. Schenck & G.S. Sm	Total proteins Total tannins	
Passiflora alata Curtis	*Gigaspora albida* N.C. Schenck & G.S. Sm	Total soluble carbohydrates Total flavonoids Total phenols Total proteins	Oliveira *et al.* (2015a)
Passiflora alata Curtis	*Gigaspora albida* N.C. Schenck & G.S. Sm	Orientin Vitexin-2-*O*-ramnoside	Oliveira *et al.* (2015b)
Mentha crispa L.	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Rhizophagus clarus* (T.H. Nicolson & N.C. Schenck) C. Walker & Schuessler	Essential oil	Urchoviche *et al.* (2015)
Commiphora leptophloeos (Mart.) J.B. Gillett	*Acaulospora longula* Spain & N.C. Schenck *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora albida* N.C. Schenck & G.S. Sm	Total antioxidant activity Total soluble carbohydrates Total flavonoids Total phenols Total proteins Total tannins	Lima *et al.* (2017)
Libidibia ferrea (Mart. Ex Tul.) L.P.	*Acaulospora longula* Spain & N.C. Schenck	Total flavonoids	Santos *et al.* (2017)

Queiroz var. *ferrea*	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora albida* N.C. Schenck & G.S. Sm	Total phenols Total flavonoids Total tannins Total proanthocyanidins	
Mimosa tenuiflora (Willd.) Poir	*Acaulospora longula* Spain & N.C. Schenck *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora albida* N.C. Schenck & G.S. Sm	Total soluble carbohydrates Total flavonoids Total phenols Total proteins Total tannins	Silva and Silva (2017)
Mikania glomerata Spreng. *Mikania laevigata* Sch. Bip. ex Baker	*Rhizophagus irregularis* (Błaszk., Wubet, Renker & Buscot) C. Walker & A. Schüßler	Chlorogenic acid Dicafeiolochemical acids Kaurenoic acid Cumarin	Almeida *et al.* (2018)
Mimosa tenuiflora (Willd.) Poir	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora albida* N.C. Schenck & G.S. Sm	Total soluble carbohydrates Total flavonoids Total phenols Total tannins	Pedone-Bonfim *et al.* (2018)
Myracrodruon urundeuva Allemão (Anacardiaceae)	Mix (*Acaulospora longula* Spain & N.C. Schenck + *Gigaspora albida* N.C. Schenck &	Total soluble carbohydrates Total flavonoids	Silva and Maia (2018)

	G.S. Sm)	Total phenols Total tannins Total proanthocyanidins Total proteins	
Zea mays L.	*Acaulospora longula* Spain & N.C. Schenck *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Dentiscutata heterogama* (T.H. Nicolson & Gerd.) Sieverd., F.A. de Souza & Oehl *Gigaspora albida* N.C. Schenck & G.S. Sm	Total soluble carbohydrates Total flavonoids Total phenols Total proteins Total tannins	Silva *et al.* (2018a)
Libidibia ferrea (Mart. Ex Tul.) L.P. Queiroz var. *ferrea*	*Acaulospora longula* Spain & N.C. Schenck *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora albida* N.C. Schenck & G.S. Sm	Ellagic acid Gallic acid	Silva *et al.* (2018b)
Fragaria X ananassa Duch.	Native AMF	Anthocynins	Chiomento *et al.* (2019)
Fragaria X ananassa Duch.	Mix (*Entrophospora colombianam* Spain & Schenck + *Dentiscutata heterogama* (T.H. Nicolson & Gerd.) Sieverd., F.A. Souza &	Anthocynins Phenols	Cordeiro *et al.* (2019)

	Oehl. + *Rhizophagus clarus* (T.H. Nicolson & N.C. Schenck) C. Walker & Schuessler + *Acaulospora scrobiculata* Trappe + *Gigaspora rosea* T.H. Nicolson & N.C. Schenck + *Glomus formosanum* C.G. Wu & Z.C. Chen + *Scutellospora calospora* (Nicol. & Gerd.) Walker & Sanders + *Scutellospora gilmorei* (Trappe & Gerd.) Walker & Sanders + *Acaulospora morrowiae* Spain & Schenck + *Acaulospora foveata* Trappe & Janos)		
Piper aduncum L.	Mix (*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler + *Rhizophagus clarus* (T.H. Nicolson & N.C. Schenck) C. Walker & Schuessler)	Essential oils	Oliveira *et al.* (2019b)
Passiflora edulis f. *flavicarpa*	*Acaulospora longula* Spain & N.C. Schenck *Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora albida* N.C. Schenck & G.S. Sm	Total phenols Total flavonoids Total proanthocyanidins Total saponins	Oliveira *et al.* (2019a)

		Vitexin	
Curcuma longa L.	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Rhizophagus clarus* (T.H. Nicolson & N.C. Schenck) C. Walker & Schuessler	Essential oils	Ferrari *et al.* (2020)
Cymbopogon citratus (D.C.) Stapf	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Rhizophagus clarus* (T.H. Nicolson & N.C. Schenck) C. Walker & Schuessler	Total antioxidant activity Phenols Flavonoids Essential oils Total sugars	Cruz *et al.* (2020)
Passiflora edulis f. *flavicarpa*	*Acaulospora longula* Spain & N.C. Schenck	Total soluble carbohydrates Total phenols Total flavonoids Total proanthocyanidins Total proteins Total saponins Total tannins Vitexin	Oliveira *et al.* (2020)
Libidibia ferrea (Mart. Ex Tul.) L.P.	*Acaulospora longula* Spain & N.C. Schenck	Total antioxidant activity	Santos *et al.* (2020)

Queiroz var. *ferrea*	*Claroideoglomus etunicatum* (W. N. Becker & Gerdemann) C. Walker & A. Schussler *Gigaspora albida* N.C. Schenck & G.S. Sm	Ellagic acid Gallic acid Total soluble carbohydrates Total phenols Total flavonoids Total proanthocyanidins Total saponinsTotal tannins	
Punica granatum L.	*Acaulospora longula* Spain & N.C. Schenck *Gigaspora albida* N.C. Schenck & G.S. Sm	Total soluble carbohydrates Total phenols Total flavonoids Total proteins Total tannins	Silva and Silva (2020)

Fonte: Autores.

In general, the studies that documented the potential of AMF inoculation in increase the production of biomolecules in plant species. Recently, a study using methanolic extracts from mycorrhizal *L. ferrea* fruits tested, for the first time, the efficacy of these extracts against bacterial strains resistant to antibiotics. It was verified that the extracts from mycorrhizal plants produced inhibition halos against the bacterial strains, larger than those produced by the non-inoculated plant extracts (Santos *et al.*, 2021).

6. Conclusion

Despite the growing number of studies in this area, there is a need to conduct experiments that verify the effect of biotic and abiotic factors in the production of phytochemicals in mycorrhizal plants, important characteristics in the large-scale production of phytomass with higher levels of phytochemicals. Moreover, it is necessary to develop studies to verify whether the therapeutic action of these plants can be enhanced by mycorrhization.

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