Natural compounds: A sustainable alternative for controlling phytopathogens

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Fungi are the primary infectious agents in plants causing significant economic losses in agroindustry. Traditionally, these pathogens have been treated with different synthetic fungicides such as hydroxianilides, anilinopyrimidines, and azoles, to name a few. However, the indiscriminate use of these chemicals has increased fungi resistance in plants. Natural products have been researched as a control, and an alternative to these synthetic fungicides since they are not harmful to health and contribute to the environment caring. This review describes plants extracts, essential oils, and active compounds or secondary metabolites as antifungal agents both, *in vitro* and *in vivo*. Active compounds have been recently described as the best candidates for the control of phytopathogenic fungi. When metabolized by plants, these compounds concentrations rely on the environmental conditions and pathogens incidence. However, one issue regarding the direct application of these preformed compounds in plants touch upon their low persistence in the environment, and their even lower bioavailability than synthetic fungicides. Hence the challenge is to develop useful formulations based on natural products to increase the compounds solubility facilitating thus their application in the field while maintaining their properties.

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Review

Natural compounds: A sustainable alternative for controlling phytopathogens.

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Abstract

Fungi are the primary infectious agents in plants causing significant economic losses in agroindustry. Traditionally, these pathogens have been treated with different synthetic fungicides such as hydroxianilides, anilinopyrimidines, and azoles, to name a few. However, the indiscriminate use of these chemicals has increased fungi resistance in plants. Natural products have been researched as a control, and an alternative to these synthetic fungicides since they are not harmful to health and contribute to the environment caring. This review describes plants extracts, essential oils, and active compounds or secondary metabolites as antifungal agents both, *in vitro* and *in vivo*. Active compounds have been recently described as the best candidates for the control of phytopathogenic fungi. When metabolized by plants, these compounds concentrations rely on the environmental conditions and pathogens incidence. However, one issue regarding the direct application of these preformed compounds in plants touch upon their low persistence in the environment, and their even lower bioavailability than synthetic fungicides. Hence the challenge is to develop useful formulations based on natural products to increase the compounds solubility facilitating thus their application in the field while maintaining their properties.

Key words: fungus; phytopathogen; antifungal; natural control; plant extract; essential oil; secondary metabolite

Introduction

Agriculture holds a direct influence on the world economy, primarily due to the fruits, grains, and vegetable production, which represent an essential source of economic income both nationally and internationally (Silva-Moreno et al., 2016; Talibi et al., 2012). However, plants exposed to environmental conditions are prone to be threatened by a variety of pathogenic microorganisms such as bacteria, viruses, nematodes, and fungi. These pathogens cause significant crop yield loss (Bajpai & Kang, 2012; Chang et al., 2008; Hof, 2001; Korres et al., 2011).

Phytopathogenic fungi are one of the leading infectious agents in plants causing alterations during the different plant-stages growth, post-harvest and even during storage. There is a wide variety of fungal genus currently generating quality problems in fruits and vegetables, affecting thus their nutritional value, organoleptic characteristics and half-life (Chang et al., 2008;Díaz-Dellavalle et al., 2011; Lee et al., 2007a; Satish et al., 2007). More than 25% of cereals (rice, flour, maize, etc.) are contaminated in some cases by fungi belonging to the genera *Aspergillus* and *Fusarium*, indirectly responsible for producing known mycotoxins, and Aflatoxin B1 (toxic and potent carcinogen); as well as more than 300 fungal metabolites, which can generate allergic or poisonous disorders such as carcinogenicity, genotoxicity, teratogenicity, nephrotoxicity, hepatotoxicity, reproductive disorders, and immunosuppression in consumers (Díaz-Dellavalle et al., 2011; Lee et al., 2007a; Satish et al., 2007).

Traditionally, infections caused by phytopathogenic fungi have been controlled using synthetic fungicides (Chang et al., 2008). For instance, most of these synthetic antifungals used in agriculture belong to the “azole group”. These are divided into two major groups: triazoles and imidazoles. The first one has a broad spectrum of action, and its function is to inhibit sterol biosynthesis in the plasma membrane, resulting in the alteration of cell formation and structure (Daniel, Lenox & Vries, 2015; Díaz-Dellavalle et al., 2011; Thompson, 2002; Trösken et al., 2004; Tzortzakis & Economakis, 2007). While the second group inhibits the cell division mechanism (mitosis), by disrupting the tubulin biosynthesis and the mitotic spindle, consequently (Daferera, Ziogas & Polissiou, 2003; Korres et al., 2011; Thompson, 2002; Trösken et al., 2004). In this way, one of the significant advantages associated with the use of azoles is the food preservation against fungi growth and the protection of plants from fungal diseases, increasing thus the production yield (Martínez, 2012). However, these compounds also have disadvantages, such as: 1) Toxic waste in both, plant and fruits after treatment. Besides, its persistence in the product generates concern in the consumer, since fruits and vegetables are consumed in a relatively short time after harvest. Furthermore, the National Academy of Sciences (NAS) established that fungicide residues in foods are carcinogenic and considered to be hazardous to human health (Daferera, Ziogas, Polissiou, 2003; Wilson et al., 1997). 2) The use and abuse of these compounds can generate resistance in pathogenic fungi (Aala et al., 2010; Jasso de Rodríguez et al., 2015; Thangavelu et al., 2013). 3) The danger of handling them, due to the possible intoxication and infertility triggered in people who manipulate those compounds (Cavieres, 2004). 4) Since they are not readily biodegradable, they tend to persist several years in the environment, considering them as environmental impact products (Daferera, Ziogas & Polissiou, 2003; Wilson et al., 1997). 5) They cannot be used on organic fruit produced with "green" laws and standards (Daferera, Ziogas & Polissiou, 2003). 6)

High cost; around 20% of the production cost is spent on fungicides (Chang et al., 2008; Martínez, 2012; Tzortzakis & Economakis, 2007).

Based on disadvantages previously described, there are restrictions currently active regarding azoles usage (synthetic fungicides), increasing thus regulation and promoting the search for new strategies. The Environmental Protection Agency (EPA) suggests, as an alternative, the natural type control, since it does not present side effects, does not harm the environment, has an extensive public acceptance, and is relatively economic (Daniel, Lennox & Vries, 2015; Díaz et al., 2011; Martínez, 2012; Sayago et al., 2012; Tzortzakis & Economakis, 2007).

Therefore, the interest in researching organic and useful products likely used as a natural control, and generating thus a sustainable and profitable industry, has become increasingly important (Fieira et al., 2013; Jasso de Rodríguez et al., Lee et al., 2007a; Sales et al., 2016; Slusarenko, Patel & Portz, 2008). Some of the natural antifungals currently used are microorganisms, extracts, essential oils, or active compounds from plants (Chang et al., 2008; Petatán-Sagahón et al., 2011; Sayago et al. 2012; Thangavelu et al., 2013).

Survey Methodology

For reviewing the information, we identified the articles containing natural antifungals currently used as plant extracts, essential oils, or active compounds from plants. The literature search was performed using standard search methods (e.g., the relevant keywords in PubMed, Web of Science, Google Scholar). In addition, we routinely attend local and international workshops and conferences focused on natural products, phytopathogens and agricultural sciences, where we interact with colleagues who are actively engaged in similar research.

Plant extracts used as a natural control against phytopathogenic fungi

To reduce the use of chemical antifungals, the study of natural products exhibiting antifungal activity has become extremely important since plants have physiological properties or "defense mechanisms", whose functions allow them to metabolize active compounds generating protection against insects and preventing pathogens invasion (Bennet & Wallsgrove, 1994). Adding the fact that these metabolites are not harmful to health and contribute to the environmental care (Díaz et al., 2011; Satish et al., 2007; Sayago et al., 2012), they are considered as an excellent alternative for the control of phytopathogenic fungi.

1. **Plant extracts**:

Plant extracts are products generated from roots, barks, seeds, shoots, leaves, and fruits, coming from some plants with medicinal tradition and other plants chosen by their defense mechanism (Bennett & Wallsgrove, 1994). The process usually consists on macerate the plant material with different polarity solvents, followed by the purification through chromatographic methods of the obtained extracts to obtain individual compounds, which finally leads to the metabolites isolation in pure form. It is also reported that both, the method and the solvent whereby this procedure's final substance (extract) is obtained, influences the amount and number of compounds or secondary metabolites attributed to have antifungal property. Thus, the extracts may contain different compounds or the same compounds, but in varying amounts, which influences their antifungal properties (Daniel, Lennox & Vries, 2015; Díaz-Dellavalle et al., 2011).

Overall, several plant extracts have been studied to evaluate this antifungal capacity. For instance, the antifungal activity against eight species of fungi from the *Aspergillus* genus has been determined *in vitro*, (*A. candidus*, *A. columnaris*, *A. flavipes*, *A. flavus*, *A. fumigatus*, *A. niger*, *A. ochraceus* and *A. tamari*), from aqueous extracts of *Acacia nilotica*, *Achras zapota*, *Datura stramonium*, *Emblica officinalis*, *Lawsonia inermis*, *Mimusops elengi*, *Peltophorum pterocarpum*, *Prosopis juliflora*, *Punica granatum,* and *Syzigium cumini*. Similarly, aqueous extracts from *A. nilotica*, *M. elengi,* and *P. juliflora* plants, and have shown to inhibit *A. niger* mycelial growth (black mold in vegetables), suggesting that these aqueous extracts could serve as antifungal against phytopathogenic fungi from the *Aspergillus* genus (Satish et al., 2007).

In the same line, peel and juice extracts from pomegranate (*Punica granatum*), both aqueous and alcoholic, could act as a natural control of phytopathogenic fungi multispecies, since they have a high fungi activity against *A. niger*, *Penicillium citrinum* (citrus rust), and *Rhizopus oryzae* (pathogen infecting carrots, pineapples, and mangoes) (Dahham et al., 2010). Additionally, garlic (*Allium sativum*) and clove (*Syzygium aromaticum*) alcoholic extracts, present a maximum inhibition percentage of mycelial growth against *Rhizopus stolonifer*, a filamentous fungus found in fruits such as papaya (*Carica papaya*) (Pundir, Jain & Sharma, 2010). On the other hand, the aqueous Zimmu leaf extract, an interspecific hybrid between garlic and onion (*Allium sativum* x *Allium cepa*), has been described to be a potent antifungal against *Mycosphaerella eumusae* fungus, the causal agent of Eumusae (foliar banana spot disease), as it can completely inhibit conidia mycelial growth and germination (Thangavelu et al., 2013). Another extract which could be considered as a natural control of *Mycosphaerella eumusae* (with a lower level of effectiveness) is the one from Senna (*Cassia senna*) and Snake Jasmine (*Rhinacanthus nasutus*) plants, which can only inhibit conidia germination (Thangavelu et al., 2013)

Keeping up with antifungal extracts activity, the cinnamon extract from a southern China native plant (*Cinnamomum cassia*), can significantly inhibit *A. niger* growth. This extract also inhibits growth in *Botrytis cinerea*, *Fusarium moniliforme* (maize pathogen), and *Phyllosticta caricae* (papaya pathogen) phytopathogenic fungi (Lee et al., 2007a). Moreover, plant extracts such as wild blackberry (*Rubus ulmifolius*), carob tree (*Ceratonia siliqua*), rock rose (*Cistus monspeliensis*) and Halimium (*Halimium umbellatum*), completely inhibit mycelial growth of *Geotrichum candidum* fungus, which causes the rot pathogen of citrus plants in roots, both *in vitro* and *in vivo*. Whereas, *H. umbellatum*´s and rock rose´s (*Cistus villosus*) aqueous extracts inhibit the *Geotrichum candidum* spore germination, suggesting that they have a high potential to control this pathogen (Talibi et al., 2012). Besides, ethanolic extracts of clove basil (*Ocimum gratissimum*) and grains of paradise (*Aframomum melegueta*), could be useful as multispecies natural control, reducing both, spore germination and mycelial growth of *A. flavus*, *A. niger*, *Botryodiplodia theobromae*, *Fusarium oxysporum*, *Fusarium solani*, *Penicillium chrysogenum*, *Rhizoctonia* sp., *Penicillium oxalicum*, *Trichoderma viride,* and *Rhizopus nodosus* fungi, causal agents of yam (*Dioscorea* spp.), a highly cultivable product in Africa's tropical countries due to its high nutritional content (Okigbo & Ogbonnaya, 2006). Furthermore, the *A. melegueta* ethanolic extracts, the garlic (*A. sativum*) methanolic extracts, as well as the ginger (*Zingiber officinale*), can also inhibit *A. niger* fungus growth (Ikegbunam, Ukamaka & Emmanuel, 2016). Indicating then, that these three extracts could work also as natural prophylaxis against fungal infections.

Jarilla macho (*Zuccagnia punctata*), and chaparral (*Larrea divaricata*) alcoholic extracts have a mycelial growth inhibitory effect against wood; destroying *Lenzites elegans*, *Ganoderma* *applanatum*, *Pycnoporus sanguineus*, and *Schizophyllum commune* fungi. While, the alcoholic extracts from the Peruvian peppertree (*Schinus molle*) inhibit *F. oxysporum*, *A. niger,* and *Trichoderma* spp. growth. It has also been reported that alcoholic extracts of creosote bush *(Larrea cuneifolia*) have activity only against *F. oxysporum*, implying that these alcoholic extracts could function as an antifungal for some phytopathogenic fungi species (Quiroga, Sampietro & Vattuone, 2001). Aqueous extracts of *Chuquiraga atacamensis*, *Parastrephia phyliciformis,* and *Parastrephia lepidophylla* (extremophilic plants of the Argentine Puna), have shown antifungal activity *in vitro* and *in vivo* against *Penicillium digitatum* and *Geotrichum citri-aurantii* fungi species which cause post-harvest citrus disease. Therefore, they exert healing effects on fruits (Sayago et al., 2012). Moreover, for the fungus *Penicillium expansum* (fruit pathogen, e.g. apples), capsaicin extract from *Capsicum* spp. could be used as a preventive method, revealing the capacity *in vivo* to hold fungus growth back during the first 14 test days (Fieira et al., 2013). Besides, for the *P. expansum* fungus, the capsaicin extract from *Capsicum* spp. could be used as a preventive method, observing also the capacity *in vivo* to hold the fungus growth back during the first 14 test days (Díaz et al., 2011).

In the same way, algae could be considered as phytopathogenic fungi with antifungal properties, as suggested by (Fernandes-Peres et al., 2012). These authors reported that hexane/ethyl acetate (EtOAc) extracts from red algae (*Stypopodium zonale*, *Laurencia dendroidea*, *Pelvetia canaliculata*, *Sargassum muticum*, *Ascophyllum nodosum*, and *Fucus spiralis*), significantly inhibit *Colletotrichum lagenarium* growth, a pathogenic fungus with a broad host range. By changing the solvent extraction, it was noted that the amount of extracted secondary metabolites varies, due to the different polarities, varying thus also the antifungal activity. For instance, methanol extract from *Cinnamomum cassia* inhibits *Fusarium moniliforme* and *Phyllosticta caricae* growth. While *C. cassia* acetone extract inhibits *B. cinerea* and *Glomerella cingulata* growth. Hot water extract from *C. cassia* significantly inhibits *A. niger*, *B. cinerea, F. moniliforme* and *P.caricae* growth; and, *Curcuma longa* acetone extract inhibits *P. caricae* growth (Lee et al., 2007a).

At the same time, both water and ethanolic extracts from garlic (*Allium sativum*), used for culinary purposes for decades present a series of bibliographic records regarding their antifungal properties.

For instance, reported plant extracts from the *Allium* genus such as *A. ampeloprasum* (elephant garlic), *A. ramosum* (fragrant-flowered garlic), and *A. sativum* (culinary garlic); as well as plant extracts from the *Capsicum* genus such as *C. annuum* (jalapeño pepper), *C. chinense* (habanero pepper) and *C. frutescens* (tabasco pepper), showed, *in vitro*, a high antifungal activity against *B. cinerea* phytopathogenic fungus, ultimately inhibiting the spore germination. Thus concluding, that extracts from these plants could be suitable as a natural alternative to chemical fungicides (Wilson et al., 1997). Moreover, aqueous extracts from culinary garlic (*A. sativum*), onion (*A. cepa*), bakeri garlic (*A. bakeri*), fragrant garlic (*A. odorum*), oriental garlic (*A. tuberosum*) and bunching onion (*A. fistulosum*) revealed to have antifungal activity against *A. niger*, and *A. flavus* (fungi causing infection in corn and peanuts), as well as against *Aspergillus fumigatus* growth, responsible for the deterioration of many foods (Yin & Tsao, 1999). In the same line, culinary garlic (*A. sativum*) and persian cumin (*Carum carvi*) extracts in cold distilled water, showed a resilient antifungal activity *in vitro* by inhibiting tomato pathogenic fungi growth: *Fusarium oxysporum* f. sp. *lycopersici*, *B. cinerea* and *Rhizoctonia solani* (Alkhail, 2005). Additionally, garlic aqueous and ethanolic extract (*in vitro*) also works as an antifungal, by completely inhibiting mycelial growth and germination of fungal spores pre and post-harvest of *Alternaria brassicicola, B. cinerea*, *Magnaporthe grisea, Neofabraea alba, P. expansum* and *Plectosphaerella cucumerina* fungi (Curtis et al., 2004; Dahham et al., 2010).

Another approach for the deployment of plant extracts is the use of essential oils as antifungals against phytopathogenic fungi, since these oils, usually come from aromatic plants with medicinal characteristics (Bhaskara et al., 1998; Tripathi, Dubey & Shukla, 2008; Wilson et al., 1997).

2. Essential oils:

Essential oils are substances with highly volatile components, synthesized and stored in glandular trichomes of aromatic plants, which can inhibit microbial growth (Anthony, Abeywickrama & Wijeratnam, 2003; Daniel, Lennox & Vries, 2015; Martínez, 2012; Tzortzakis & Economakis, 2007). As an example, basil oil (*Ocimum basilicum*), *in vivo*, acts as a post-harvest control of crown rot and anthracnose in banana (*Musa acuminata*), generated by *Colletotrichum musae*, *Lasiodiplodia theobromae*, and *Fusarium proliferatum* fungi. This control allows the fruits to be stored at low temperature (13.5 ± 1°C) for 21 days, without causing damage or affecting their organoleptic properties (Anthony, Abeywickrama & Wijeratnam, 2003). Besides, Lemongrass oil (*Cymbopogon citratus*) at 500 ppm, completely inhibits sporulation and germinal tube generation of *Colletotrichum coccodes*, *B. cinerea*, *Rhizopus stolonifer* and *Cladosporium herbarum* fungus, which can cause diseases in tomato plantations. Therefore, lemongrass oil could work as a natural fungicide for the product when stored, limiting the pathogen spreading by reducing spores in the atmosphere and storage surfaces (Tzortzakis & Economakis, 2007).

Mulan magnolia (*Magnolia liliiflora*) oil, has revealed to have a promising antifungal activity (*in vitro*) against *Botrytis cinerea*, *Fusarium oxysporum*, *Fusarium solani*, *R. solani*, *Colletotrichum capsici*, *Phytophthora capsici*, and *Sclerotinia sclerotiorum* spore germination, inhibiting all the analyzed pathogens. This oil also showed a potent antifungal effect against *Phytophthora capsici*, a pathogen causing the greenhouse-grown peppers rot. The results of this study indicated that mulan magnolia oil could be used as a natural alternative to synthetic fungicides (Bajpai & Kang, 2012). Conversely, the *Calocedrus macrolepis* var. *formosana* oil, from a coniferous tree of China, presented 65% of antifungal activity, *in vitro,* against *Pestalotiopsis funérea* (a garden center pathogen), and 52.1% against *Fusarium solani* (potato pathogen) (Chang et al., 2008). Suggesting thus, that the *Calocedrus macrolepis* var. *formosana* oil, could be used as a natural antifungal on potato cultures in greenhouses.

Essential oils effects on the *B. cinerea* has also been widely described. This pathogen, also called "gray mold", causes damages on fruits and vegetables harvest during storage and distribution. Essential oils have shown to inhibit, *in vitro,* the mycelial growth, spore germination and germ tube elongation in *B. cinerea*. Some of these oils are oregano (*Origanum vulgare*, and *Origanum compactum*), as well as syrian oregano (*Origanum syriacum*); dittany of Crete (*Origanum dictamnus*); sweet marjoram (*Origanum majorana*); mediterranean wild thyme (*Thymus capitatus*); thyme (*Thyme glandulosus*, and *Thymus zygis*); palmarosa (*Cymbopogon martini*); lavender (*Lavandula stoechas*); rosemary (*Rosmarinus officinalis*); wormseed (*Dysphania ambrosioides*); lemon eucalyptus (*Corymbia citriodora*); holy rope (*Eupatorium cannabinum*); henna tree (*Lawsonia inermis*); basil lime (*Ocimum canum*); clove basil (*Ocimum gratissimum*); holy basil (*Ocimum sanctum*); cinnamon (*Cinnamomum zeylanicum*); clove *(Eugenia* *caryophyllata*); lemon (*Citrus limonum*); peach (*Prunus persica*); ginger cassumunar (*Zingiber cassumunar*), and ginger (*Zingiber officinale*) (Bouchra et al., 2003; Daferera, Ziogas & Polissiou, 2003; Talibi et al., 2012; Tripathi et al., 2008; Vitoratos et al., 2013; Wilson et al., 1997). A few of them, such as *O. vulgare, T. capitatus*, *O. dictamnus*, and *O. majorana*, have antifungal activity against *Fusarium* sp. fungus, also called dry tuber rot, which causes damage in stored potatoes (Daferera, Ziogas & Polissiou, 2003)

It has also been observed that syrian oregano (*O. syriacum*), *in vivo* under greenhouse conditions, showed higher protection in tomato plants susceptible to gray mold disease, especially as a curative treatment (Soylu, Kurt & Soylu, 2010). Another essential oil with ascribed properties to prevent and treat plants against *B. cinerea*, is the ginger (*Zingiber officinale*) on grapes (*Vitis* spp.) storage (Tipathi, Dubey & Shukla, 2008). In addition, essential oil of two clonal types of thyme, *Thymus vulgaris* (Laval-1 and Laval-2), besides exhibiting antifungal activity against *B. cinerea*, also inhibits the *Rhizopus stolonifer* growth, a common pathogen in strawberries (*Fragaria ananassa*) storage (Bhaskara et al., 1998). Based on the above, essential oils could be considered as a potential source of sustainable fungicides for the treatment of fruits and vegetables against post-harvest pathogens.

We can, therefore, indicate that essential oils from plants can treat pathogenic fungi in fruits and vegetables post-harvest storage stage. However, further studies are needed to determine the identity of the bioactive compounds responsible for the mentioned antifungal activity. Despite this, bioactive compounds (derived from plants) exhibiting antifungal activity can still be considered as a fungicide alternative (Díaz et al., 2011).

3. Active compounds obtained from plants:

Extracts and essential oils contain secondary compounds metabolized by plants. These compounds are toxic and stored in the plant cells vacuoles. Among them are phenolic, steroid and terpenoid compounds. Their concentration depends on the environmental conditions and the pathogens incidence, which gives them their biopesticidal characteristic, targeting specifically against insect pests and pathogens. Furthermore, they are biodegradable, which means they can be used without causing severe damage to the environment (Daniel, Lennox & Vries, 2015; Martínez, 2012; Sales et al., 2016; Thangavelu et al., 2013).

Then, it is very interesting to identify the active compound within extracts or oils, which can produce the intended effect. In literature, there are several examples, for instance, *thymol* (principal component), and *carvacrol* (monoterpenoid phenol which produces odor); characteristics of oregano oil (*Origanum vulgare*) (Fig.1). These compounds have antifungal activity against *B. cinerea* and *Fusarium* spp. fungus (fruits and vegetable pathogens), indicating that these compounds could be used individually as fungicides against these phytopathogenic fungi (Daferera, Ziogas & Polissiou, 2003). Besides, *T-muurolol* and *α-cadinol* compounds (Fig. 1) from the *Calocedrus macrolepis* var. *formosan* oil, exhibit antifungal activity against *Rhizoctonia solani* and *F. oxysporum*. Moreover, these compounds inhibit the mycelial growth of *Fusarium solani*, *Pestalotiopsis funerea*, *Colletotrichum gloeosporioides* and *Ganoderma australe*. Therefore, these two compounds (*T-muurolol* and *α-cadinol*) could also be used as a natural control against a broad spectrum of plant pathogenic fungi (Chang et al., 2008).

On the other hand, the rhizome methanolic extract of *Acorus gramineus* (Japanese rush), contains several compounds such as *α-asarone*, *caryophyllene*, *isoasarone*, *methyl isoeugenol* and *safrole* (Fig. 2). *In vivo,* It was possible to observe that the *asaronaldehyde* (2,4,5-trimethoxybenzaldehyde) active compound (Fig. 2), showed 100% antifungal activity against *Phytophthora infestans* (tomatoes and potatoes pathogen) and 75% against *R. solani* (rice pest). While the *α-asarone* compound showed 85% antifungal activity against *P. infestans* and 53% against *R. solani*; suggesting then, that these (potentially safer) compounds could be used as phytopathogen control agents (Lee, 2007c). In addition, lipid compounds (*LP-B1* and *LP-B2*), isolated from the ethanol extract of Zimu leaf, showed maximum inhibition of *Mycosphaerella eumusae* mycelial growth, a banana pathogen (Thangvelu et al., 2013). Another compound is the oleoresin *capsaicin* (8-methyl-vanillyl-6-nonenamide) (Fig. 3), a spicy component of red pepper species, which works as antifungal against *B. cinerea* (Xing, Cheng & Yi, 2006). Consequently, these compounds could be well integrated with the biological control of plants diseases.

Garlic contains a significant number of sulfurous compounds (Fig. 4), which exhibit potent antifungal properties (Daniel, Lennox & Vries, 2015; Ikegbunam, Ukamaka & Emmanuel, 2016). These compounds include: 1) *allicin* (diallyl-dithiosulfinate), which has antifungal activity against

Magnaporthe oryzae (rice pathogen), *Hyaloperonospora parasitica* (affects leaves and causes stalk necrosis) and *Phytophthora infestans*, which inhibits spores' germination and hyphae growth (Davies, Perrie et al. Apitz-Castro, 2003; Hughes & Lawson, 1991; Martínez, 2012; Mikaili et al., 2013; Slusaenko, Patel & Portz, 2008). 2) *ajoene* [(*E,Z*)-4,5,9-trithiadodeca-1,6,11-triene-9-oxide], which inhibits *A. niger* growth (fungus which produces aflatoxin-hepatocarcinogen pathogen in plants) through the phosphatidylcholine (PC) synthesis suppression (acting on the cell wall, in the cytosolic membrane), blocking then fungus morphogenic transformation. It also inhibits the spores' germination and conidia of *Alternaria solani*, *Alternaria tenuissima*, *Alternaria triticina*, *Alternaria* sp., *Colletotrichum* sp., *Curvularia* sp., *Fusarium lini*, *Fusarium oxysporum, Fusarium semitectum*, and *Fusarium udum*, plant pathogens (Benkeblia, 2004; Davis, Perrie & Apitz-Castro, 2003; Hughes & Lawson, 1991; San-Blas et al., 1997; Singh et al., 1990). 3) *diallyl sulfide* (DAS), diallyl disulphide (DADS) and allyl methyl disulfide, which completely inhibit *Colletotrichum lindemuthianum* growth, a banana pathogenic fungus causing anthracnose or dark spot disease (Bianchi et al., 1997). 4) *allivin*, active against *B. cinerea* (gray rot) and *Mycosphaerella arachidicola* (early leaf spot) phytopathogenic fungi, associated with necrotic lesions generation, and *Physalospora piricola*, black rot in many fruit species and forest trees (Wang & Ng, 2001).

As mentioned above, these active compounds may also be referred to as preformed compounds, which have been isolated from crude extracts or essential oils from leaves and stems of plants (Daniel, Lennox & Vries, 2015; Martínez, 2012; Sales et al., 2016; Thangavelu et al., 2013). They can be also classified into:

- **Phenolic compounds:** Substances with an aromatic ring containing one or more hydroxyls which may also include functional derivatives. Some of the essential compounds include esters, alkyl parabens, and phenolic antioxidants. Simple phenolic compounds include monophenols, diphenols, and triphenols, such as flavones, flavonoid glycosides, coumarins, and anthraquinones. The action mechanism of simple phenols focuses on altering the cytoplasmic membrane and causing cell lysis; besides, they can also directly inhibit cellular proteins. These mechanisms are the ones allowing the microorganisms inhibition (Abad, Ansuategui & Bermejo, 2007; Martínez, 2012). For instance, a high number of polyphenols extracted from *Rhus muelleri* leaves inhibit the growth of *Fusarium oxysporum* fungus, which causes destructive diseases in tomatoes, bananas, among other plant species (Jasso de Rodriguez, 2015). Likewise, from the leaves and stem of *Aquilegia vulgaris,* the flavonoid 4'-methoxy-5,7-dihydroxyflavone 6-C-glucoside (isocytisoside) was isolated (Fig. 5) and presented antifungal activity against mold *A. niger* (Abad, Ansuategui & Bermejo, 2007). While flavonoid 5,7-dihydroxy-3,8-dimethoxyflavone (Fig. 5), extracted from *Pseudognaphalium robustum* plant, reduced mycelial growth and partially affected conidial germination of *Botrytis cinerea* fungus, by decreasing oxygen consumption in conidial germination and disrupting the integrity of the plasma membrane (Cotoras et al., 2011). Based on the above, these polyphenols and flavonoids extracted from plants are also an alternative to be used as biological fungicides.

- **Terpenoids compounds**: Substances stored in the trichomes or glandular hairs (specialized structures of the outer plant layers). Essential oils, in general, have a high concentration of terpenes and sesquiterpenes (Abad, Ansuategui & Bermejo, 2007; Martínez 2012). For instance, carrot oil (*Dacus carota*), contains four esters of sesquiterpenes such as carotol (Fig.6); and has antifungal activity, inhibiting 65% of the *Alternaria alternata* growth, a phytotoxic fungus of carrot plants. In addition, sesquiterpene, isolated from dichloromethane extracts of *Vernonanthura tweedieana* roots, records antifungal activity against *Trichophyton mentagrophytes* (Abad, Ansuategui & Bermejo, 2007). In Chile, canelo (*Drimys winteri*) essential oil, contains different amounts of unknown polygodial and drimenol (Fig.7) (Muñoz-Concha et al., 2007). These terpenes have antifungal properties against *Gaeumannomyces graminis* fungus, a causal agent of infection in wheat (Monsálvez et al., 2010). Furthermore, polygodial and drimenol terpenes isolated from canelo have shown to have antifungal activity against *Botrytis cinerea,* the causal agent of infection in table grape (Carrasco et al., 2017; Robles-Kelly et al., 2016).

Diterpenoids 1) 7α-hydroxy-8(17)-labden-15-oic acid (salvic acid), and 2) 7α-acetanoyloxy-8(17)-labden-15-oic acid (acetylsalvic acid); hemisynthetic diterpenoids 7α-acyloxy-8(17)-labden-15-oic; acids derivatives, 3) 7α-propanoyloxy-8(17)-labden-15-oic acid (propanoylsalvic acid), and 4) 7α-butanoyloxy-8(17)-labden-15-oic acid (butanoylsalvic acid) (Fig. 8), isolated from the resinous exudate *Eupatorium salvia* leaves (salvia macho), *in vitro,* inhibit the mycelial growth of *B. cinerea* (Mendoza et al., 2009). At the same way (*in vitro*), diterpenoids sclareol and 13-epi-sclareol (Fig. 9), isolated and purified from the resinous exudate of *Pseudognaphalium cheiranthifolium*, can also inhibit *B. cinerea* mycelial growth Mendoza et al., 2015). Deducing that these diterpenes could be used as a natural control against the phytopathogenic fungus *B. cinerea*.

Triterpenes and sesquiterpene lactones isolated from *Schinus molle*'s (Peruvian peppertree) leaves and fruits have antifungal activity against plant pathogenic fungi such as *A. niger*, *A. flavus*, *Alternaria alternata*, *Microsporum griseum*, *Penicillium cyclopium* and *Penicillium italicum*, suggesting that these compounds could be a natural fungicide against a wide range of plant pathogenic fungi (Quiroga, Sampietro & Vattuone, 2001). Likewise, triterpenes, pristimerin and celastrol (Fig. 10), isolated *in vitro* from *Celastrus hypoleucus* root, exhibited an inhibitory effect on mycelial growth of *R. solani* and *Glomerelia cinguiata* (Antracnosis) phytopathogenic fungi. *In vivo*, *pristimerin* showed a 97% preventive, and a 67% curative impact against *Blumeria graminis* (wheat mold); and *celastrol* registered an 81% preventive, and a 46% curative impact against the same fungus pathogen (Abad, Ansuategui & Bermejo, 2007).

- **Saponins compounds:** Glycosylated compounds stored in plant cells, which regulate growth and protect the plant from the attack of pathogens and insects. They are divided into triterpenes, steroids, and steroidal glycoalkaloids. Triterpenoid saponins are mainly found in dicotyledonous plants but can also be found in some monocotyledonous plants. While steroid saponins are mostly found in monocotyledonous (Abad, Ansuategui & Bermejo, 2007; Mert-Türk, 2006; Saha et al., 2010).

For instance, triterpene saponin CAY-1, extracted from cayenne pepper (*Capsicum frutescens*), recorded antifungal activity *in vitro* against *Candida* spp. and *Aspergillus fumigatus* (Abad, Ansuategui & Bermejo, 2007). Other triterpenic saponins, with significant antifungal *in vitro* activity, were two saponins from *Diploknema butyracea* mixture, identified as 3-O[*β*-D-glucopyarnosyl-*β*-D-glucopyranosyl] -16- α- hydroxyprotobassic acid-28-O [arabinopyranosyl-glucopyranosyl- xylopyranosyl]- arabino pyranoside (MI-I), and 3-O-*β*-D-glucopyranosyl -glucopyranosyl- glucopyranosyl-16-α -hydroxyprotobassic acid-28-O- [arabinopyranosylxylopyranosyl-arabinopyrnosyl]- apiofuranoside (MI-III). Besides, a single saponin extracted from *Sapindus mukorossi* which was identified as 3-O-[O-acetyl-β-D-xylopyranosyl- β-D-arabinopyranosyl- β-D-rhamnopyranosyl] hederagenin-28-O-[β-D-glucopyranosyl- β-D-glucopyranosyl- β-D- rhamnopyranosyl] ester (SM-1) (Fig. 11), can inhibit *Rhizoctonia bataticola* and *Sclerotium rolfsii* growth (Saha et al., 2010). While the *Balanites aegyptiaca* fruit extract, rich in saponins, presents (*in vitro*) a high inhibition (81%) against *Pythium ultimum*, and *Alternaria solani* fungi growth suggesting that saponins may then play an important role in the control of phytopathogenic fungi (Chapagain, Weisman & Tsor, 2007)

- **Alkaloids compounds:** Compounds with nitrogen in their ring. Indole alkaloids, pyridine alkaloids, benzylisoquinoline, and alkaloids are classified according to the simple heterocyclic ring in their structure. Some alkaloids have been reported to alter biological functions and exhibit antimicrobial functions (Facchini, 2001; Singh, Pandey & Singh, 2007).

For instance, the allosecurinine (Fig. 12), isolated from the *Phyllanthus amarus* root, *in vitro*, completely inhibits the spore germination of *Curvularia* sp., *Curvularia lunata*, *Collectotrichum* sp., *Colletotrichum musae* and *Heterosporium* sp. phytopathogenic fungi (Singh, Pandey & Singh, 2007). Also, the dyhydropyrrole [2-(3,4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1'-methylethyl pentanoate] (Fig. 13), isolated from *Datura metel* plant (devil's trumpet), presents activity against *A. niger*, *A. flavus*, and *Aspergillus fumigatus*, molds infecting a wide range of foods (Abad, Ansuategui & Bermejo, 2007). Likewise, the alkaloid 1-methyl-2-[6'-(3'',4''-methylenedioxyphenyl) hexyl]-4-quinolone (Fig. 14), isolated from the ethyl acetate extract of *Ruta graveolens* leaves; registers, *in vitro*, high antifungal activity against *Botrytis cinerea*, *Colletotrichum gloeosporioides*, *Colletotrichum acutatum, Colletotrichum fragariae, Phomopsis obscurans* and *Phomopsis vitícola* phytopathogenic fungi. Based on this, it can be inferred that alkaloids present in plants could potentially be used as fungicides of plant pathogens (Oliva et al., 2003).

Conclusions

In this review, we observe that natural compounds derived from plants are worthwhile to treat fungal infections; phytopathogens, which nowadays remain as one of the most common plant diseases and also represent one of the most significant issues for agricultural companies.

We could also observe that extracts, essential oils, and active compounds from plants have efficient antifungal agents, which are potent and less toxic against phytopathogenic fungus, rather than synthetic fungicides. Likewise, they could partially or entirely replace the use of chemical antifungals, which increase resistance in fungi and pollute the environment, generating an eco-friendly control mechanism as well as lowering costs for agricultural companies.

Finally, it was possible to observed that the compounds with the highest and best antifungal activity were the ones from plants which proved to be active against phytopathogenic fungi, considering these products useful in crops and avoiding any chemical fungicide implementations.

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Conflict of Interests

The authors declare no conflict of interest.

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Legends for Figures

Figure 1. Main compounds structure (chemotypes) of *O. vulgare* essential oil **(**A) (Bouyahya et al. 2016). Chemical structures of the main compounds of *C. macrolepis* var. *formosan* essential oil (B) (Chang et al. 2008).

Figure 2. Chemical structures of the main compounds from the rhizome methanolic extract of *A. gramineus* (Lee, 2007c)

Figure 3. Chemical structures of *capsaicin* (Xing, Cheng & Yi, 2006).

Figure 4. Chemical structures of the main compounds from garlic (*A. sativum*) and onion (*A. cepa*) (li, Thomson & Afzal, 2000).

Figure 5. Chemical structures of flavonoids isolated from leaves and stem of *A. vulgaris* (A), and flavonoids isolated from *P. robustum* extracts (B) (Abad, Ansuategui & Bermejo, 2007; Cotoras et al., 2011).

Figure 6. Chemical structure of sesquiterpen isolated from carrot oil (*D. carota*) (Abad, nsuategui & Bermejo, 2007).

Figure 7. Chemical structures of canelo (*D. winteri*) essential oil (Carrasco et al., 2017)

Figure 8. Chemical structures of diterpenoids isolated from the resinous exudate of *E. salvia* leaves (Mendoza et al., 2009).

Figure 9. Chemical structures of diterpenoids isolated from the resinous exudate of *P. cheiranthifolium* (Mendoza et al., 2015)

Figure 10. Chemical structures of triterpenes isolated from *C. hypoleucus* root (Abad, Ansuategui & Bermejo, 2007)

Figure 11. Chemical structures of *D. butyracea*, and *S. mukorossi* saponins (Saha et al., 2010)

Figure 12. Chemical structures of allosecurinine isolated from *P. amarus* root (Singh, Pandey & Singh, 1990)

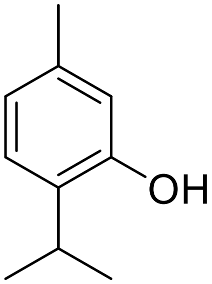
Figure 13. Chemical structures of dyhydropyrrole alkaloid isolated from the *D. metel* plant (Abad, Ansuategui & Bermejo, 2007)

Figure 14. Chemical structures of alkaloid isolated from *R. graveolens* leaves (Oliva et al., 2003)

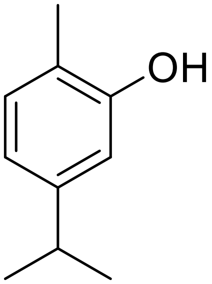
Figure 1(on next page)

Chemotypes of *O. vulgare* essential oil (A). Chemical structures of the main compounds of *C. macrolepis* var. *formosan* essential oil (B)

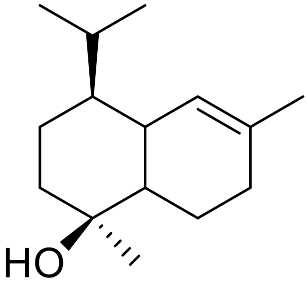
Fig. 1



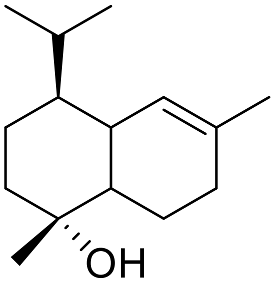
Thymol



Carvacrol



T-Muurolol



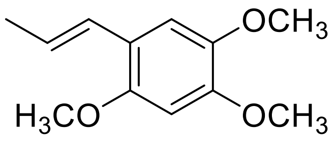
α-Cadinol

Figure 2(on next page)

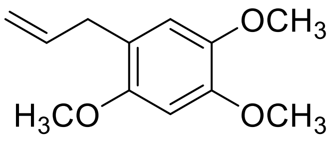
Chemical structures of main compounds from the rhizome methanolic extract of *A. gramineus*.

(Lee, 2007c)

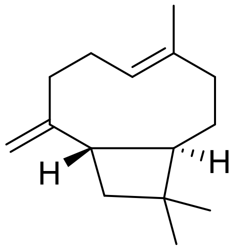
Fig. 2



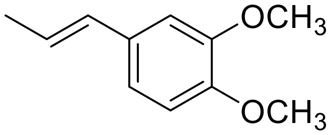
α-asarone



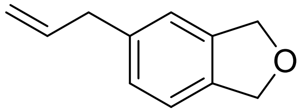
isoasarone



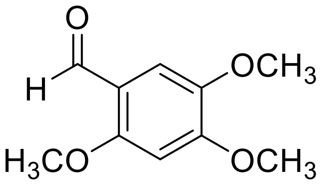
caryophyllene



methyl isoeugenol



safrole



asaronaldehyde

Figure 3(on next page)

Chemical structure of *Capsaicin*

(Xing, Cheng & Yi, 2006).

Fig. 3

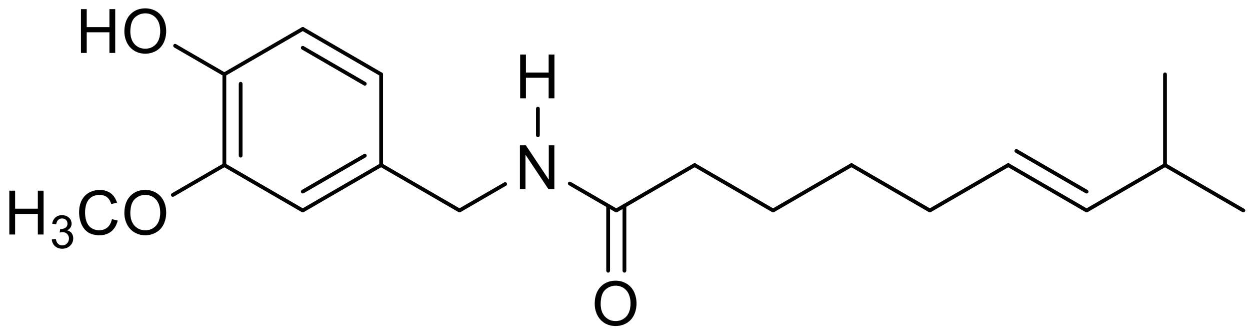


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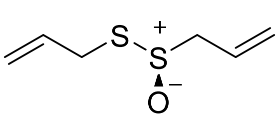
Figure 4(on next page)

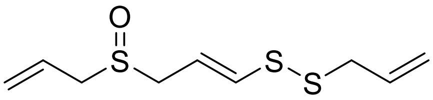
Chemical structures of main compounds from garlic (*A. sativum*) and onion (*A. cepa*)

(Ali, Thomson & Afzal, 2000).

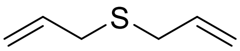
Fig. 4



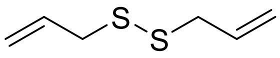
allicin



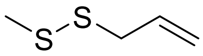
ajoene



diallyl sulfide



diallyl disulfide



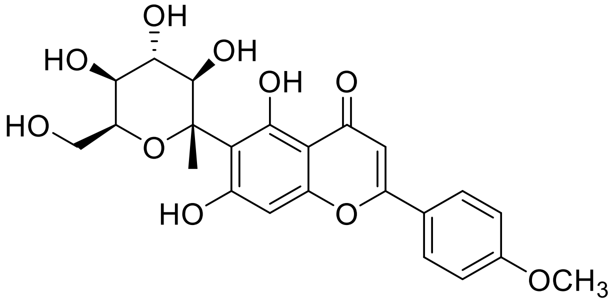
allyl methyl disulfide

Figure 5(on next page)

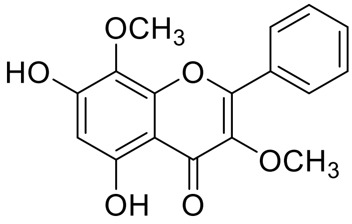
Chemical structures of flavonoids.

Flavonoids isolated from leaves and stem of *A. vulgaris* (A), and flavonoids isolated from *P. robustum* extracts (B) (Abad, Ansuategui & Bermejo, 2007; Cotoras et al., 2011).

Fig. 5



isocytisoside



5,7-dihydroxi-3,8-dimethoxyflavone

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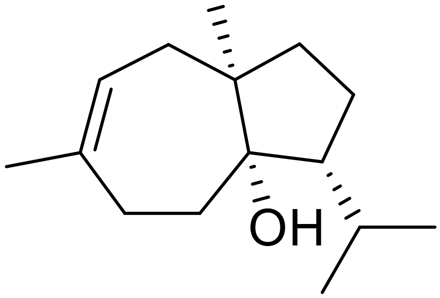
Figure 6(on next page)

Chemical structure of sesquiterpen isolated from carrot oil (*D. carota*)

(Abad, Ansuategui & Bermejo, 2007).

Fig. 6.



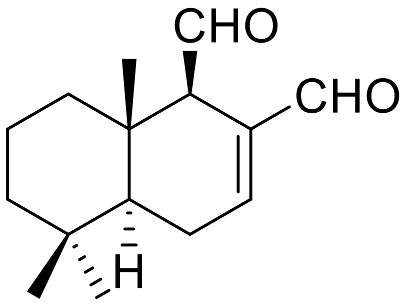
Carotol

Figure 7(on next page)

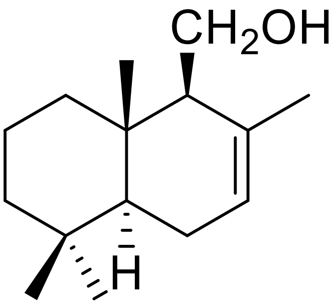
Chemical structures of Canelo (*D. winteri*) essential oil.

(Carrasco et al., 2017)

Fig. 7



Polygodial



Drimenol

Figure 8(on next page)

Chemical structures of Diterpenoids isolated from the resinous exudate of *E. salvia* leaves.

(Mendoza et al., 2009).

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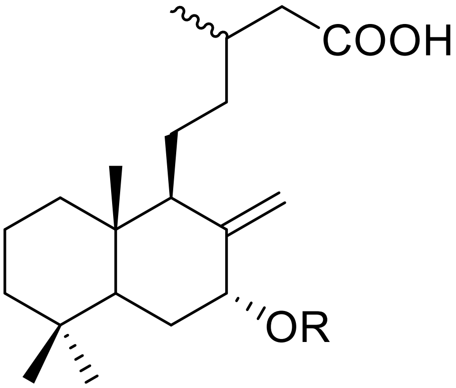
Fig. 8



Salvic acid (R=H)
Acetylsalvic acid (R=$COCH_3$)
Propanoylsalvic acid (R=$COCH_2CH_3$)
Butanoylsalvic acid (R=$COCH_2CH_2CH_3$)
Isopentanoylsalvic acid (R=$COCH_2CH(CH_3)_2$)

Figure 9(on next page)

Chemical structures of diterpenoids isolated from the resinous exudate of *P. cheiranthifolium.*

(Mendoza et al., 2015)

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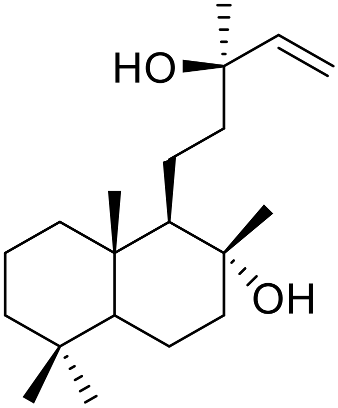
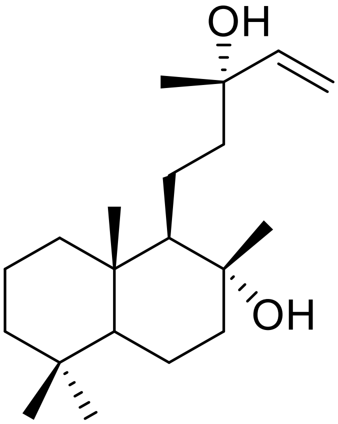
Fig. 9



Sclareol



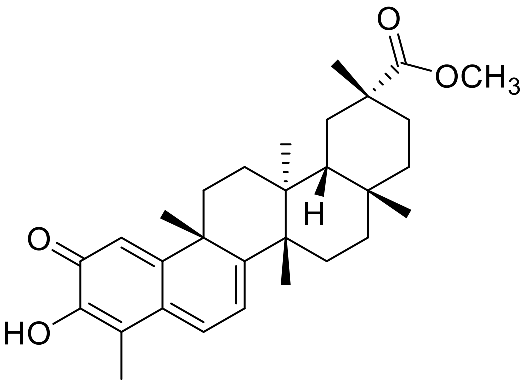
13-epi-Sclareol

Figure 10(on next page)

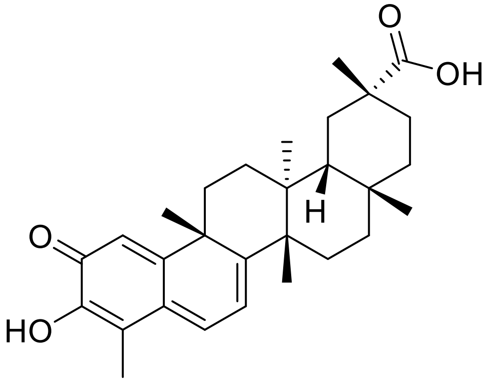
Chemical structures of triterpenes isolated from *C. hypoleucus* root.

(Abad, Ansuategui & Bermejo, 2007)

Fig. 10



Pristimerin



Celastrol

Figure 11(on next page)

Chemical structures of *D. butyracea*, and *S. mukorossi* saponins.

(Saha et al., 2010)

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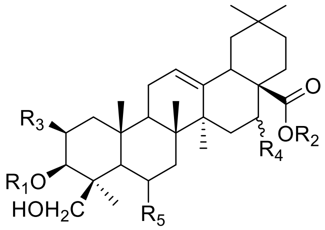
Fig. 11



Compound	R1	R2	R3	OH	R5
MI-I	**Glu-Glu**	**Ara-Xyl-Ara**	**OH**	**OH**	**OH**
MI-III	**Glu-Glu-Glu**	**Ara-Xyl-Ara-Api**	**OH**	**H**	**OH**
SM-I	**Xyl(OAc)-Ara-Rha**	**Glu-Glu-Rha**	**H**	**OH**	**H**
18-hydroxiprotobassic acid	**H**	**H**	**OH**	**H**	**OH**
Hederagenin	**H**	**H**	**H**	**OH**	**H**

Figure 12(on next page)

Chemical structures of Allosecurinine isolated from *P. amarus* root.

(Singh, Pandey & Singh, 1990)

Fig. 12

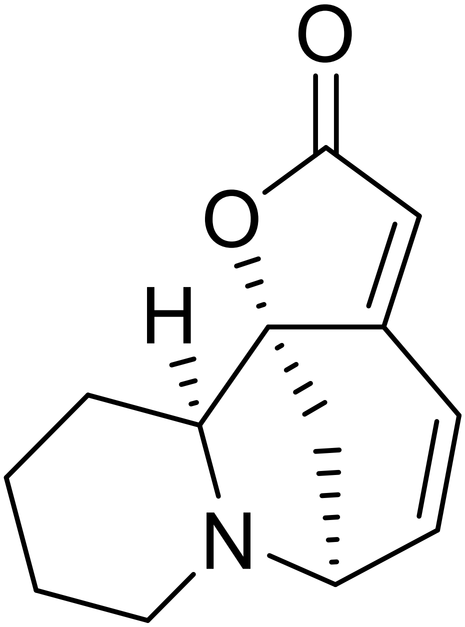


Figure 13(on next page)

Chemical structures of dyhydropyrrole alkaloid isolated from the *D. metel* plant.

(Abad, Ansuategui & Bermejo, 2007)

Fig- 13

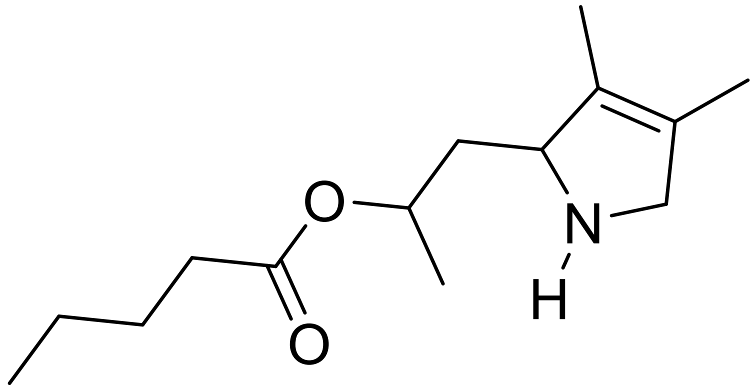
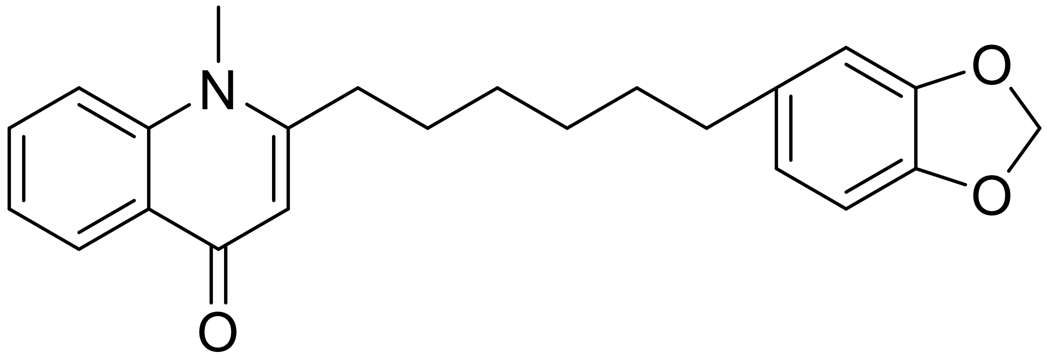


Figure 14(on next page)

Chemical structures of alkaloid isolated from *R. graveolens* leaves.

(Oliva et al., 2003)

Fig. 14



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