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Jasmonic acid biosynthesis by microorganisms: Derivatives, first evidences on biochemical pathways and culture conditions for production

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Jasmonic acid (JA) and its derivatives (called jasmonates) are lipid-derived signalling molecules that are produced by certain bacteria, fungi and plants. Beside this function, jasmonates have a great variety of applications in the flavour and fragrances production. In addition, they may have a high potential in agriculture. JAs protect plant against infections and may suppress the growth of cancer cells in humans and animals. Although a lot of information on the biosynthesis and function of JA exists from plants, knowledge on these aspects is still scarce for microorganisms. Taking into account the practical importance of JA, the objective of this review is to summarize knowledge on the occurrence of jasmonates from microbial culture media, their biosynthetic pathways and the culture conditions for optimal JA production as an alternative source for the production of these valuable metabolites

Review Article

Jasmonic acid biosynthesis by microorganisms: Derivatives, first evidences on biochemical pathways and culture conditions for production

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Abbreviations: 10,11-OHJA, 10,11-hydroxy jasmonic acid, **12-HSO$_4$-JA,** 12-hydroxy jasmonic acid sulfate, **16:3,** hexadecatrienoic acid, **18:3,** α-linolenic acid, **ABA,** abscisic acid, **AOC,** allene oxide cyclase, **AOS,** allene oxide synthase, **CA,** curcurbic acid, **CAMe**, methyl curcurbate, **CJ**, *cis*-jasmone, **ddh-JA,** 4,5-didehydro jasmonic acid, **dn-OPDA,** dinor-12-oxo-phytodienoic acid, **GA$_3$,** gibberellic acid, **JA,** jasmonic acid, **JA-Leu,** jasmonoyl leucine, **JMT,** JA carboxyl methyltransferase, **JAMe,** methyl jasmonate, **LOX,** lipoxygenase, **OPC-4,** 3-oxo-2(2'-pentenyl)-cyclopentane-1-butanoic acid, **OPC-6,** 3-oxo-2(2'-pentenyl)-cyclopentane-1-hexanoic acid, **OPC-8,** 10,11-dihydro-12-oxo-phytodienoic acid, **OPDA,** 12-oxo-phytodienoic acid, **SSF**, solid state fermentation, **TA,** tuberonic acid.

Abstract

Jasmonic acid (JA) and its derivatives (called jasmonates) are lipid-derived signalling molecules that are produced by certain bacteria, fungi and plants. Beside this function, jasmonates have a great variety of applications in the flavour and fragrances production. In addition, they may have a high potential in agriculture. JAs protect plant against infections and may suppress the growth of cancer cells in humans and animals. Although a lot of information on the biosynthesis and function of JA exists from plants, knowledge on these aspects is still scarce for microorganisms. Taking into account the practical importance of JA, the objective of this review is to summarize knowledge on the occurrence of jasmonates from microbial culture media, their biosynthetic

pathways and the culture conditions for optimal JA production as an alternative source for the production of these valuable metabolites.

1 Introduction

Jasmonic acid (JA) and its derivatives belong to a group of plant growth regulators called jasmonates (Wasternack & Feussner 2018). They belong to the large group oxidized lipid signalling molecules, so-called oxylipins (Gerwick et al. 1991). In plants, jasmonates derive either from α-linolenic acid (18:3n-3) or raughanic acid (16:3n-3) and their major representatives are the isomers (+)-7-iso-JA and (-)-JA. These compounds are widely distributed in algae (Andreou et al. 2009; Ueda et al. 1991; Vick & Zimmerman 1989), angiosperms (Wasternack & Hause 2013) and microorganisms (Abdala et al. 1999; Forchetti et al. 2007; Hause et al. 2007; Miersch et al. 1993b). They belong to the group of phytohormones playing important roles as growth inhibitors and by regulating plants defence responses (Pieterse et al. 2009; Wasternack et al. 2006).

Methyl jasmonate (JAMe) was firstly isolated as an odoriferous constituent of the essential oil of *Jasminun grandiflorum* and other plant species (Crabalona 1967; Demole et al. 1962). It is recognized as an important ingredient in high-grade perfumes, cosmetics and in the preparation of detergents, soaps and food aromas with floral notes (Asamitsu et al. 2006; Dhandhukia & Thakkar 2007c). JA was first isolated as plant growth inhibitor from cultures of the fungus *Lasiodiplodia theobromae* (synonym *Botryodiplodia theobromae*) (Aldridge et al. 1971).

With the development of efficient methods for detection and quantification of metabolites about thirty years ago, JA and JAMe attracted the attention of plant physiologists. The presence of these compounds in different parts of plants was initially correlated with their strong promotion

of senescence and inhibition growth in angiosperms when applied exogenously (Wasternack & Hause 2002). Although, these compounds act as growth inhibitors or senescence promoters at high concentration, they induce the expression of defensive genes at much lower levels. For instance, they promote the synthesis of proteinase inhibitors, enzymes of phytoalexin synthesis, thionins, defensins and the vegetative storage protein genes in plants against pathogen attack or wounding (Howe & Jander 2008).

Jasmonates however play an important role in agriculture nowadays by regulating the defensive systems of plants against pests and pathogens (Gális et al. 2009; Gavin et al. 2012; Hawkins et al. 2007; Heil et al. 2001; Rohwer & Erwin 2008; Sanches et al. 2017; Stout et al. 2002; Wasternack 2014). Their application seems to be in line with the principles of sustainable agriculture since they may be less aggressive to the environment than pesticides and mineral fertilizers (Secatto 2013).

Jasmonates may be also used in medicine in the future because they are able to suppress so far *in vitro* the growth of some cancerous cells lines from humans and rats (Fingrut et al. 2005; Fleisher 2005; Fleisher 2007; Goldin et al. 2007; Kniazhanski et al. 2008; Li et al. 2017; Zhang et al. 2015). When applied *in vitro* it was observed that they induce cancer cell death in a wide range of organs, mainly colon, lymphatic tissue, breast, skin, prostate and lung. It has been also observed in preliminary studies *in vitro*, that the application of JAMe to parasites such as *Plasmodium falciparum*, *Shistosoma mansoni* (Gold et al. 2003) and *Trichomonas vaginalis* (Ofer et al. 2008) had a cytotoxic effect leading to cell death. Jasmonates have also been evaluated as antidepressants as well as anti-aggressive and anti-inflammatory agents (Ghasemi Pirbalouti et al. 2014).

92 Furthermore, it has been observed that the addition of exogenous JAMe stimulates the
93 production of many secondary metabolites, such as taxane derivatives in plant cell cultures of
94 *Taxus* sp. These metabolites are also very promising anticancer drugs in humans. Studies have
95 been conducted to optimize the production of these substances; focusing on their metabolic
96 pathways, selecting more productive cell lines, optimizing cell culture processes, product
97 purification, and up scaling of the whole process (Bai et al. 2004; Miller et al. 2008; Onrubia et
98 al. 2013; Syklowska-Baranek et al. 2009; Tabata 2006; Wilson & Roberts 2012).
99 Currently most of the aroma compounds including jasmonates are extracted from natural plant
100 sources. However, recent advances in metabolic engineering have generated a great interest to
101 produce these substances from alternative sources (Gupta et al. 2015). An alternative and
102 attractive route for producing jasmonates will be based on microbial biosynthesis and
103 biotransformation. Microorganisms such as bacteria and yeast can be used at variable scales as a
104 safe producers of flavours and fragrances (Gill & Valivety 1997). Most importantly, these
105 microorganisms can be metabolically and genetically modified to enhance the production of the
106 desired metabolites. Moreover, the production of aroma compounds from microbial cultures or
107 their enzyme preparations offers several advantages over traditional methods. The microbial
108 metabolites can be produced in large quantities by the use of a fermentation process and can give
109 high yields in very good qualities with better product characteristics along with low economical
110 costs (Gupta et al. 2015).
111 Currently there are numerous projects for sequencing the genomes of ascomycete fungi ongoing
112 (http://genome.jgi-psf.org/pages/fungi-1000-projects.jsf) and one of them is the jasmonate
113 producing fungus *L. theobromae*. From this project, valuable information will be available in the
114 near future that will help to continue the analysis of fungal JA biosynthesis and other related

metabolites using a reverse genetic approach. In fact, the lasiodiplodin biosynthetic gene cluster from the genome of *L. theobromae* strain NBRC 31059 was expressed in *Saccharomyces cerevisiae* strain BJ5464 to obtain a phytotoxic polyketide that inhibited human blood coagulation factor XIIIa, mineral corticoid receptors and prostaglandin biosynthesis (Xu et al. 2014).

2 Survey Methodology

Scientific reports and patents dealing to the production and properties of JA are still steadily increasing (Ghasemi Pirbalouti et al. 2014; Raviv et al. 2013; Wasternack 2015). However, there are few reports related to the production of JA by microorganisms. Therefore, the objective of this review is to discuss the existing reports related to the microbial production of jasmonates with a focus on the type of microorganisms, biosynthetic pathways, and culture conditions. By screening the publicly available databases Free Patents Online (http://www.freepatentsonline.com/), Google Patents (https://patents.google.com/), Espacent (https://worldwide.espacenet.com/), Google Scholar (https://scholar.google.de/), PubMed (https://www.ncbi.nlm.nih.gov/) and Web of Science (https://apps.webofknowledge.com/), we aimed to cover the current status of the field and apologize to scientists whose work we overlooked.

3 Jasmonates from fungi

L. theobromae is a common phytopathogenic fungus capable of producing jasmonates at high level, as a result of its primary and secondary metabolism (Alves et al. 2008; Eng et al. 2016). Although, JA is produced as the main product, other jasmonates such as 9,10-didehydro JA, 11-

hydroxy JA and 12-hydroxy JA sulphate (12-HSO_4-JA) were formed to a lesser extent (Figure 1, Table 1) (Eng 2012; Miersch et al. 1987). Cucurbic acid (CA) which may also be recognized as a phytohormone and synthesized by a so far unknown pathway has been also detected in trace amounts (Eng 2012; Miersch et al. 1987).

Overall eight hydroxy JAs (11-hydroxy JA, 12-hydroxy JA or tuberonic acid (TA), 8-hydroxy JA, 3-oxo-2(1-hydroxy-2'-pentenyl)-cyclopentane-1-butanoic acid and 3-oxo-2(4-hydroxy-2'-pentenyl)-cyclopentane-1-butanoic acid) were detected in the culture medium and biomass of *L. theobromae* strain D7/2 growing in a medium containing sucrose, soy flour, corn steep liquor and a mineral salt solution (Miersch et al. 1991). Twenty-two jasmonates were identified after 8 weeks of culture of *Fusarium oxysporum* f sp *matthiole* strain 247.61 grown in liquid potato-dextrose medium under static conditions (Miersch et al. 1999a). Among the metabolites produced, 9,10-dihydro-7-iso-jasmonoyl-isoleucine, jasmonoyl-isoleucine, 9,10-dihydro jasmonoyl-isoleucine, 3-oxo-2-(2-pentenyl)cyclopentane-1-butyric acid, 3-oxo-2-(2-pentenyl)cyclopentane-1-hexanoic acid and 3-oxo-2-pentylcyclopentane-1-octanoic acid were identified. These isoleucine conjugates were also produced during the culture of *Gibberella fujikuroi* (Miersch et al. 1992). Interestingly, *F. oxysporum* f sp *mattiole* was unable to accumulate any hydroxylated-JAs as shown for *L. theobromae* (Miersch et al. 1993b).

The occurrence of the JA-serine and JA-threonine conjugates was confirmed in the fermentation broth from *L. theobromae* strain 2334 using HPLC-ESI tandem mass spectrometry in negative ionization mode, while JA-glycine and JA-isoleucine conjugates were identified with the same technique but with positive ionization (Castillo et al. 2014). In higher plants, JA amino conjugates are regular constituents accumulating upon sorbitol treatment or wounding (Miersch et al. 1999a).

While the conjugating enzyme was first isolated form the flowering plant *Arabidopsis thaliana* (Staswick et al. 2002), the corresponding peptidase activity was isolated from *L. theobromae* strain D 7/2 (Hertel et al. 1997). This enzyme was capable of hydrolysing JA-conjugates with α-amino acids. The enzyme was purified by gel filtration, ion exchange and hydrophobic interaction chromatography. It was characterized as glycoprotein with a molecular mass of about 107 kDa and its amidohydrolase activity was very specific with regard to (-)-JA and α-amino acids with (*S*)-configuration. Therefore, the authors suggested that this fungus may need this enzyme during infection of the host plant for starting or modifying plant processes, e.g. senescence or the release of nutrients, probably being beneficial for the fungal growth.

JA, JAMe and three JA esters, named lasiojasmonates (botryosphaerilactone A, (3*S*,4*R*,5*R*)-4-hydroxymethyl-3,5-dimethyldihydro-2-furanone and (3*R*,4*S*)-botryodiplodin) were detected from culture filtrates of *Lasiodiplodia* sp strain BL101 isolated from declining grapevine plants that showed wedge-shaped cankers (Andolfi et al. 2014). However, phytotoxic assays recording necrotic lesions on grapevine and cork oak leaves demonstrated that only JA was found to be active.

The diversity of octadecanoid and jasmonoyl compounds found in the culture filtrate of these fungi rise the question whether the compounds are formed only or at least primarily during the interaction with plants and, if so, what the function of these compounds might be. Evidences suggest that fungal pathogens exploit host oxylipins to facilitate their development via inducing plant lipid metabolism to utilize plant oxylipins in order to promote G-protein-mediated regulation of sporulation and mycotoxin production in the fungus and use of host-ligand mimicry to manipulate plant defence responses from which the fungus benefits (Christensen & Kolomiets 2011). However, in others cases *F. oxysporum* colonization remains symptomless or even has

184 beneficial effects on plant growth and/or stress tolerance. Also in pathogenic interactions a
185 lengthy asymptomatic phase usually precedes disease development. All this suggests for a
186 sophisticated and fine-tuned interaction between *F. oxysporum* and its host and the molecular
187 mechanisms underlying this balance are poorly understood (Di et al. 2016).
188 Recently, (i) phytotoxic metabolites were identified in the culture media of six species of
189 *Lasiodiplodia* isolated in Brazil causing *Botryosphaeria* dieback of grapevine (Cimmino et al.
190 2017). As ascertained by LC-MS, only four of these strains (*L. brasiliense, L. crassispora, L.*
191 *jatrophicola* and *L. pseudotheobromae*) produced JA. *L. brasiliense* synthesized also (3*R*,4*S*)-4-
192 hydroxymellein. This was the first report on JA production from these species. (ii) Recently,
193 fungal-derived *cis*-jasmone (CJ) was detected in *L. theobromae* strain MAFF 306027 (Matsui et
194 al. 2017). These authors carried out studies of the metabolism of deuterium-labelled of 18:3-d5,
195 OPC:4-d6, OPC:6-d6, OPC:8-d6 and cis-OPDA-d5 to JAMe-d5 and/or CJ-d5 in feeding
196 experiments with this strain, revealing that the fungus produced CJ through a single biosynthetic
197 pathway via iso-12-oxophytodienoic acid (*iso*-OPDA). Interestingly, it was suggested that the
198 previously predicted decarboxylation step of 3,7-didehydroJA to afford CJ might be not involved
199 in CJ biosynthesis in *L. theobromae* (Matsui et al. 2017). However, in plants CJ is synthetized
200 from 18:3 via two biosynthetic pathways using JA and iso-OPDA as key intermediates.
201

202 **4 Jasmonic acid biosynthetic pathway**

203 **3.1 Plants**

204 Many reviews have summarized the developments on the biosynthetic pathway of JA in plants
205 and our knowledge will be briefly summarized in the following section (Agrawal et al. 2004;
206 Creelman & Mullet 1997; Goepfert & Poirier 2007; Hamberg & Gardner 1992; Schaller et al.

2005; Vick & Zimmerman 1984; Wasternack & Feussner 2018; Wasternack & Hause 2002; Wasternack & Hause 2013).

JA biosynthesis in plants starts with the liberation of α-linolenic acid (18:3(n-3)) or roughanic acid (16:3(n-3)) from the plastid envelope membranes by lipases (shown in Figure 1A for α-linolenic acid). This reaction as well as the next three steps of the pathway are localized in plastid ending with the formation of either *cis*-(+)-12-oxophytodienoic acid (OPDA) or dinor-oxophytodienoic acid (dn-OPDA), respectively. This is the result of the sequential action of the enzyme lipoxygenase (LOX), allene oxide synthase (AOS) and allene oxide cyclase (AOC) on 18:3(n-3) or 16:3(n-3). The next steps take place in peroxisomes where OPDA and dn-OPDA are activated and reduced to 10,11-dihydro-12-oxophytodienoic acid (OPC-8) and 3-oxo-2(2'-pentenyl)-cyclopentane-1-hexanoic acid (OPC-6) by 12-oxophytodienoate reductase isoenzyme 3 (OPR3), respectively. These reactions are followed by two or three rounds of β-oxidation, yielding OPC-6; 3-oxo-2(2'-pentenyl)-cyclopentane-1-butanoic acid (OPC-4) and finally (+)-7-*iso*-JA that rearranges into the (-)-JA isomer (with an molar ratio of 9:1 for (-)-JA/(+)-7-isoJA) (Wasternack & Hause 2013). JA can be further metabolized into its methyl ester (JAMe) JA carboxyl methyltransferase (JMT) (Cheong & Choi 2003; Seo et al. 2001), or by conjugation with amino acids (such as leucine and isoleucine) or sugars, respectively (Sembdner & Parthier 1993; Wasternack 2016)}.

3.2 Microorganisms

Till today knowledge about metabolic pathways leading to the production of JAs by fungi and other microorganisms is scarce. Therefore, more physiological and biochemical studies are required and the existing knowledge will be summarized throughout the next paragraphs.

Starting with the products formed, the same ratio of isomers (-)-JA:(+)-7-isoJA that was found in plants was measured in the culture filtrate of *F. oxysporum* strain 247.61 (Miersch et al. 1999a). By contrast, only the (+)-7-isoJA isomer was found in a culture of *L. theobromae* strain D7/2 (Miersch et al. 1987), but later both isomers, with a ratio of ~15:1 and 1:1 in two different experiments in the culture medium filtrate from *L. theobromae* strain 2334 were described (Jernerén et al. 2012).

For *L. theobromae* it was shown in addition that JA production derived from 18:3(n-3) by using a culture medium that was supplemented either with ^{13}C-sodium acetate or [$^{2}H_6$]-18:3 (Tsukada et al. 2010). Appreciable amounts of [^{13}C]-JA and [$^{2}H_5$]-JA were detected in culture supernatants, and the methyl ester of OPDA was detected in mycelium extracts. Recently, by incubating mycelia from the JA-producing fungus *F. oxysporum f.* sp. *tulipae* with labelled 18:3, the plants-like intermediates allene oxide and 12-OPDA of the JA pathway were detected (Oliw & Hamberg 2017). The allene oxide was likely formed by a CYP enzyme or a catalase-related hydroperoxidase. These results suggest that JA is synthesised by this strain of *L. theobromae* starting from 18:3 via OPDA and that the enzymes being involved may be similar to those governing JA biosynthesis in higher plants. However, there are probably also some differences in the genes and enzymes of the JA pathway between plants and fungi. For example, although higher plants and the fungus *G. fujikuroi* produce structurally identical gibberellins (GAs) using similar steps, there are important differences in pathways and enzymes involved (Hedden et al. 2002). These profound differences suggest that higher plants and fungi have evolved their complex biosynthetic pathways to GAs independently and not by horizontal gene transfer.

In fact, the fatty acid composition in *L. theobromae* strain 2334 showed that the mycelium contained polyunsaturated C18 fatty acids, including 18:3(n-3) as probable substrate for JA

biosynthesis (Eng 2012; Eng et al. 2016; Jernerén et al. 2012). However, polyunsaturated C16 fatty acids were not detected (Jernerén et al. 2012). OPDA and OPC:4 were also detected in culture filtrates from this fungus as probable intermediates on fungal JA pathway (Eng 2012; Eng et al. 2016). In addition, the JA precursors 3-oxo-2-pentylcyclopentane-1-butyric acid, 3-oxo-2-(2-pentenyl)cyclopentane-1-hexanoic and 3-oxo-2-(2-pentenyl)cyclopentane-1-octanoic acid were detected in a culture filtrate from *F. oxysporum* f sp *matthiole* strain 247.61 (Miersch et al. 1993a; Miersch et al. 1989).

Interestingly, three bacterial strains producing JA, OPDA and ABA in a control culture medium were isolated from soil of sunflower cultures (Forchetti et al. 2007). Beside this observation nothing is known till now on how and under which conditions these mentioned strains form these phytohormones.

Studies aiming at identifying single steps in fungal JA biosynthesis have been reported using different exogenously applied substrates (Jernerén et al. 2012), a reverse genetic approach (Brodhun et al. 2013) and enzyme purification (Patel et al. 2014). In the first case, a fatty acid dioxygenase activity from three strains of *Lasiodiplodia* was described (Jernerén et al. 2012). Two of the strains revealed low secretion of JA (~0.2 mg L^{-1}). These strains oxygenated 18:3(n-3) to 5,8-dihydroxy linolenic acid as well as to 9*R*-hydroperoxy linolenic acid, which was further metabolized by an AOS activity into 9-hydroxy-10-oxo-12*Z*,15*Z*-octadecadienoic acid. Analogous conversions were observed with linoleic acid (18:2(n-6)) as a substrate. Studies using [11*S*-^{2}H]18:2 revealed that the putative 9*R*-dioxygenase catalysed the stereospecific removal of the 11*R* hydrogen followed by a suprafacial attack of dioxygen at C-9. Mycelia from these strains contained 18:2 as the major polyunsaturated fatty acid but lacked 18:3(n-3). The third strain however secreted high amounts of JA (~200 mg L^{-1}). It contained 18:3(n-3) as major fatty

276 acid and produced 5,8-dihydroxy linolenic acid from exogenously added 18:3(n-3). Together,
277 from these three strains no enzyme activity pointing to a JA pathway and being similar to that of
278 higher plants could be identified.
279 Since no sequence information on the *L. theobromae* genome is yet available, a reverse genetic
280 strategy focused on a 13-LOX from *F. oxysporum* that may initiate JA production was used as
281 second approach. It was based on using sequences similar to those found from enzymes being
282 part of the JA biosynthetic pathway of plants (Brodhun et al. 2013). One of the sequences called
283 FoxLOX was cloned and expressed in *E. coli*. FoxLOX was found to be the first non-heme Fe-
284 LOX, which oxidizes polyunsatured C18 fatty acids to 13*S*-hydroperoxy derivatives by an
285 antarafacial reaction mechanism where the *bis*-allylic hydrogen abstraction is the rate-limiting
286 step. With 18:3 as substrate, FoxLOX was found to exhibit a multifunctional activity, because
287 the hydroperoxy derivatives formed were further converted to dihydroxy-, keto-, and epoxy
288 alcohol derivatives. The identification of FoxLOX as a specific linoleate 13*S*-LOX might hint
289 towards a JA biosynthetic pathway in *F. oxysporum,* which is analogous to that in plants.
290 A LOX enzyme was purified from the mycelium of *L. theobromae* strain MTCC 3068 by
291 chromatography (Patel et al. 2015). It was found that this fungus contains two LOXs
292 isoenzymes, one of 93 kDa (LOX1) and another of 45 kDa (LOX2) with the later being most
293 likely a degradation product of LOX1. Both LOX isozymes oxidized linoleic acid to produce a
294 mixture of 9- and 13-hydroperoxy linoleic acid. Therefore, this LOX may be another candidate
295 enzyme being involved in fungal JA production.
296 In summary, these are first data suggesting, that JA may be synthesised from 18:3(n-3) via
297 OPDA in fungi. Since fungi do not have plastids, the reactions leading to the formation of OPDA
298 most likely takes place in the cytosol or associated to a membrane leaflet facing the cytosol

(Figure 1B). Whether this pathway may be initiated by LOX enzymes or other dioxygenases is still unclear, just like the identity of the following enzymatic activities. The reactions downstream from OPDA however may follow a recently discovered pathway in *Arabidopsis thaliana* via direct β-oxidation of OPDA leading to formation of 4,5-didehydro jasmonic acid (ddh-JA) which is then reduced by a fungal OPR2 homologue to JA (Chini et al. 2018).

5 Chemical synthesis of jasmonates

Chemical synthesis and isolation of jasmonates from microorganisms and plants started in the 70s of last the century (Aldridge et al. 1971). JA is traditionally isolated from plants; mainly from jasmine and tea flowers; where JA is found in trace concentrations. A large number of flowers produce small amounts of essential oils. For instance, it takes about 500 Kg of petals to obtain approximately 1 Kg of rose oil. Therefore, this is a very expensive and time-consuming process that accounts for the high price of these oils (Dhandhukia & Thakkar 2007c).

Therefore, numerous chemical synthesis strategies for obtaining JA, JAMe and other derivatives have been developed. In that way, the synthesis of JAMe and methyl curcubate (CAMe; Figure 2B, free fatty acid is shown as compound 1) have been reported by using 2-allylcyclohexan-1,3-dione as starting compound and hydroboration-oxidation followed of seven or eight steps for the first and second product, respectively (Kitahara et al. 1987). Moreover, the same authors improved the total yield for JAMe to up to 20% in twelve reaction steps by improving the stereoselectivity of the hydroboration-oxidation by using 3-hydroxy methylcyclopentanone as starting compound (Kitahara et al. 1991).

Shortly after these reports, racemic 7-substituted derivatives of JAMe have been synthesized (Taapken et al. 1994). 7-Methyl JAMe was also synthesized in enantiomerically pure form in 7

steps from the Hajos-Wichert ketone. In addition, the biological activity of the prepared compounds has been investigated for the induction of tendril coiling in *Bryonia dioica* and the elicitation of the phytoalexin production in *Eschscholtzia californica.* However, beside 7-methyl JAMe all synthesized compounds showed poor activity in the bioassays (Taapken et al. 1994).

10 years later, Suzuki et al. developed a new method of JAMe and CAMe synthesis using a chiral tricyclic lactone as starting compound via a new type of tandem retro-Diels-Alder-ene reaction activated by a trimethysilyl substituent as the key step, followed at seven reaction steps (Suzuki et al. 2004).

Other authors have dedicated their efforts to the synthesis of β-oxidation intermediates of JA, such as 10,11-dihydro-12-OPDA (OPC:8) by chemical or enzymatic means with good yields (Nonaka et al. 2010; Takayuki et al. 2003; Zerbe et al. 2007).

JA and TA (Figure 2B, free fatty acid is shown as compound 6) were synthesized from the key aldehyde, all *cis*-2-(2-hydroxy-5-vinylcyclopentyl)acetaldehyde, which was in turn prepared stereoselectively from the (1*R*)-acetate of 4-cyclopentene-1,3-diol through a SN_2-type allylic substitution with CH_2-CHMgBr followed by Mitsunobu inversion, Eschenmoser–Claisen rearrangement, and regioselective Swern oxidation of the corresponding bis-TES ether. Wittig reaction of the aldehyde with $[PH_3P(CH_2)Me]^+Br^-$ followed by oxidation afforded JA stereoselectivity over the *trans* isomer (Nonaka et al. 2010). Similarly, TA was synthesized.

Secatto proposed a racemic synthesis of JA involving additional steps to obtain higher yields (Secatto 2013). This would envisage an application at industrial scale. This synthetic route consisted of 7 steps with an overall yield of 30%. The improvement of this route is due to the use of an available starting compounds without hygroscopic characteristics and no requirement for

any pretreatment and easy handling. Moreover, the starting materials (adipic acid and cyclohexane and ethanol as solvents) are not expensive, leading overall to low production costs. Two macrolactones (JA-Ile-lactones) derived from 12-OH-JA-Ile were synthesized in 7 steps with an overall yield of 33% from commercially available JAMe (Jimenez-Aleman et al. 2015b). The biological activity of macrolactones was tested for their ability to elicit nicotine production, a well-known jasmonate dependent secondary metabolite. Both macrolactones showed strong biological activity, inducing nicotine accumulation to a similar extent as JAMe does in *Nicotiana attenuata* leaves. Surprisingly, the highest nicotine contents were found in plants treated with the JA-Ile-lactone, which has (3*S*,7*S*) configuration at the cyclopentanone ring and is not known from natural jasmonates.

A new synthetic route to JAIle-lactones was developed recently using the *Z*-selective cross-metathesis of (±)-MeJA and 3-butenyl acetate (both compounds commercially available and inexpensive) resulting in the (±)-1-acetate derivative in excellent yield (>80%) and *Z*-selectivity (> 90%) (Jimenez-Aleman et al. 2015a). Saponification of the (±)-1-acetate derivative (> 85 % yield) and conjugation to L-Ile resulted in the 1-hydroxy-12-L-Ile derivative. Finally, this derivative was exposed to macrolactonization resulting in enantiomerically pure macrolactones in only three steps. In agreement with the previous studies (Jimenez-Aleman et al. 2015b), these macrolactones also induced the accumulation of nicotine suggesting that these compounds open the possibility of uncoupling defence and growth in plants by using small molecules.

6 Microorganisms as producers of jasmonates

The first report about JA production by microbes was published already 50 years ago (Broadbent et al. 1968). These authors obtained JA from a culture of *L. theobromae* in a culture medium

367 containing glucose, glycerol or a mixture of both as carbon source, sodium nitrate, potassium
368 nitrate or ammonium nitrate as nitrogen source. JA reached a concentration of 475 mg L^{-1} and a
369 productivity of 36.6 mg L^{-1} d^{-1}. In order to purify the produced JA, biomass was removed by
370 filtration and the filtrate was acidified and further extracted with ethyl acetate. Three years later
371 JA biosynthesis was reported in a concentration of 500 mg L^{-1} and a productivity of 38.4 mg L^{-1}
372 d^{-1} from *L. theobromae*, using a surface culture in 1L ceramic vessels with Czapek medium
373 (Aldridge et al. 1971). These authors also observed that the culture supernatant inhibited the
374 growth of higher plants and that the active component was JA. Similar results were obtained by
375 *L. theobromae* strain D7/2 isolated from orange and cacao residues (Miersch et al. 1987). This
376 strain was grown in a liquid medium based on sucrose, soybean meal, corn steep liquor and salt
377 solution with a JA concentration and productivity of 500 mg L^{-1} and 71 mg L^{-1} d^{-1}, respectively.
378 The same authors performed a screening for JA production using 46 species of *Ascomycetes* and
379 *Basiodimicetes* belonging to 23 different genera (*Agrocybe*, *Aspergillus*, *Collybia*, *Coprinus*,
380 *Cunninghamella*, *Daedalea*, *Fomes*, *Fusarium*, *Gleooporus*, *Homoconis*, *Marasmius*, *Mucor*,
381 *Mycena*, *Paecilomyces*, *Phellinus*, *Penicillium*, *Pleurotus*, *Polyporus*, *Rhizoctonia*, *Stropharia*,
382 *Talaromyces*, *Trametes* and *Trichoderma*) that were grown under the same conditions as *L.*
383 *theobromae. Collibya*, *Coprinus* and *Mycena* were the best producers of JA. However, JA
384 concentrations were four to eight times lower than produced by *L. theobromae* (Miersch et al.
385 1993b). In addition, some mutants of *G. fujikuroi* were also able to produce free JA in culture
386 supernatants but in trace amounts. Similarly, mycorrhizal fungi such as *Laccaria laccata* and
387 *Pisolithus tinctorius* were identified as JA producers but again only in trace amounts (Miersch et
388 al. 1999b).

A mutant approach was applied to obtain better JA producers of *L. theobromae* (Patel & Thakkar 2015). The mutants were generated using ethylmethanesulfonate and two mutants were isolated having the capacity to produce JA with 70 mg L^{-1} and 78 mg L^{-1} compared to wild type 32 mg L^{-1}.

The highest rates for JA production were described however for *Diplodia gossypina* strain ATCC 10936 (Farbood et al. 2001). Under optimal culture conditions JA concentration and productivity were 1200 mg L^{-1} and 171 mg $L^{-1}d^{-1}$, respectively. This study even included the up scaling of JA production up to a volume of 150 L.

In case of bacteria a strain of *E. coli*, some rhizospheric bacteria such as *Azospirillum brasilense*, *Bradyrhizobium* sp. and *Rhizobium meliloti* (isolated from soils, which have been widely studied for their direct relationship with higher plants) and yeasts were capable of JA synthesis in concentrations as low as $ng.L^{-1}$ (Abdala et al. 1999; Forchetti et al. 2007). An endophytic diazotrophic bacterium was isolated from roots of the halophyte shrub *Prosopiss trombulifera* and probably identified as *Arthrobacter* sp (Piccoli et al. 2011). This strain produced abscisic acid, indole-3-acetic acid, giberellins and JA in a chemically defined culture medium.

6 Culture conditions for JA production

Although the annual demand for JA increases primarily for applications in perfume production and flavourings (Dhandhukia & Thakkar 2007c), there are still only few reports published related to the practical aspects of the commercial production of JA (Farbood et al. 2001; Ghasemi Pirbalouti et al. 2014; Miersch et al. 1987).

The ability of fungi to produce JA varies between strains from 1 mg L^{-1} to 1000 mg L^{-1} of JA (Dhandhukia & Thakkar 2007c; Eng et al. 1998; Farbood et al. 2001). Therefore, at first strains

of *L. theobromae* or *D. gossypina* were screened for JA production in order to obtain better strains (Altuna et al. 1996; Eng 2012; Farbood et al. 2001), because these two fungi seem to be the species with the highest potential for JA production.

Next different culturing conditions were tested. Batch fermentation in static conditions using a stationary Fernbach flask culture, an aseptic stationary tray culture or Erlenmeyers flasks were tested between 5 to 10 days at temperature between 27 and 30 ºC and slightly acidic initial pH values between 5 and 6 of the culture medium (Altuna et al. 1996; Farbood et al. 2001; Miersch et al. 1987). As a carbon source for producing JA soybean meal, citrus pulp, corn steep liquor and milk serum were used and supplemented with oilseed meal, which can supply sources of protein, minerals and water soluble vitamins (Miersch et al. 1987). However, the use of more complex media had the drawback of needing more complicated processes for purifying JA for some applications such as in perfumery, a removal of malodorous compounds and allergens is required. Another drawback is that the composition thereof is not constant and therefore this result is difficult to reproduce. Therefore, primarily synthetic media were used that are based on sucrose or glucose as carbon source and mineral salts as potassium nitrate as nitrogen source, with the addition of monobasic potassium phosphate, ammonium molybdate, and sulphate of magnesium, iron, zinc and copper (Almeida et al. 1999; Miersch et al. 1987). However, also only one type of carbon source (glucose or sucrose) can be used for JA production (Eng et al. 1998).

Already an early study showed that the addition of an inductor is not required to produce JA in synthetic culture medium (Miersch et al. 1987). However, the addition of yeast extract and/or soy peptone as a source of vitamins and cofactors to the culture medium stimulated the rate of JA biosynthesis (Dhandhukia & Thakkar 2007b; Eng 2012; Eng et al. 2008; Farbood et al. 2001).

Under these standard culture conditions JA production took place at the late exponential growth phase or stationary phase showing a behaviour similar to the accumulation of secondary metabolites (Eng et al. 2016) and may only partially be associated with the growth phase of the culture (Dhandhukia & Thakkar 2007c). Using these optimized culture conditions JA production levels reached 500-1300 mg L^{-1} and productivities of 28-170 mg L^{-1} d^{-1} (Dhandhukia & Thakkar 2007a; Dhandhukia & Thakkar 2007b; dos Santos et al. 2014a; dos Santos et al. 2014b; Eng 2012; Eng et al. 2016; Farbood et al. 2001; Inho et al. 2006).

Under static conditions, some *Lasiodiplodia* strains formed a mat on the surface of the culture medium (Eng 1996). Therefore, the effect of the available surface area by increasing the vessel size may be another critical aspect for JA production. This was confirmed by a study on JA production by *L. theobromae* strain MTCC 3068 using the same amount of culture medium with Erlenmeyer flasks of 250, 500 and 1000 mL in which the authors could show, that increasing the surface area of the culture up to 1000 mL flasks lead to an increase JA yield (Dhandhukia & Thakkar 2007c).

In another study, the surface of the culture (100-500 mL) was simultaneously increased with the volume of the culture medium (25-100 mL). Here, JA production was highest at the largest surface area in combination with the highest volume of culture medium (Eng et al. 2016). However, an increase of the flask volume to 5 or even to 50 L and for the culture medium volume up to 10 L did not lead to further increases in JA yield (Eng 2012).

However, scaling up JA production in a fermenter or in a shaking incubator at 190 rpm and 30 ºC and dissolved oxygen saturation in the culture medium of up to 150 L (Farbood et al. 2001) as well as using a fixed inoculation ratio of 0.5 g L^{-1} of dry biomass of culture medium was shown to improve JA yields (Miersch et al. 1987). In addition, it was of advantage to use homogenized mycelium and not spores (Almeida et al. 2001; dos Santos et al. 2014a; dos Santos et al. 2014b).

Agitation turned out to be another critical aspect for JA production, because shaking speeds above 200 rpm lead to increased synthesis of extracellular polysaccharides (Selbmann et al. 2004), which had negative effect on JA production (Eng et al. 1998; Miersch et al. 1987). JA was also obtained by solid state fermentation (SSF) from *L. theobromae* strain 2334 using columns with sugar cane bagasse impregnated as support, at 30 ºC and with a similar culture medium that was used in liquid fermentation. JA productivity was 2 times higher in solid state fermentation probably due to growth conditions that were more similar to the natural environment of this fungus (Eng 1996). Using similar conditions, JA productivity of a strain of *B. theobromae* isolated from cacao tissue was reported to be 4.8 times higher by SSF as with submerged fermentation (Laredo-Alcalá et al. 2016).

Finally, it should be noted that JA production was possible with *D. gossypina* strain ATCC 10936 in stirred fermenters of 150 L at an agitation velocity of 450 rpm, but productivity decreased at about two times with respect to the production in 500 mL Erlenmeyer flasks agitated at a speed of 200 rpm (Farbood et al. 2001).

7 Patents

There is a growing number of patents describing the production and application of jasmonates since the 60's and their quantity have increased during the last decades showing a growing interest in these substance class (Ghasemi Pirbalouti et al. 2014) (Figure 3). At first, the patents dealing with the isolation, detection and culture conditions for production of jasmonates in microorganisms such as *L. theobromae* will be discussed (Aldridge et al. 1971; Broadbent et al. 1968; Farbood et al. 2001; Günther et al. 1989; Miersch et al. 1984).

Other topics deal with agricultural applications of jasmonates in order to improve plant yield by inducting plants defence against herbivores and pathogens (Dathe et al. 1990; Ryan & Farmer 1991). Recently these effects were combined with new formulations for jasmonates in water in combination with herbicides, pesticides, bioactive or biological seed treatment components and semiochemicals (Ghasemi Pirbalouti et al. 2014; Marks 2012). The application of JAMe to grapes in order to improve the quality of machine-harvested raisin grapes allowed the harvest without damages to the fruit or plants associated with traditional mechanical harvesting and thereby eliminating the need for expensive hand picking (Ghasemi Pirbalouti et al. 2014). Meanwhile a method was also reported for improving the turf grass quality (Mcelroy 2011). There is an only one patent claiming the use of a JA extract to inhibit the growth of the bacterium *Leuconostoc sp*. and dextran production during the juice processing of the sugar cane industry (Michelena et al. 2010).

Nowadays, patents about jasmonates have expanded to medicinal, cosmetic, and flavouring applications (Ghasemi Pirbalouti et al. 2014). During the last 20 years, the vast majority of studies and inventions claim that JA, JAMe and dihydroJAMe have anticancer activity against various forms of cancer (Fleischer & Fingrut 2007; Fleischer et al. 2012; Fleischer et al. 2010; Ghasemi Pirbalouti et al. 2014; Herzberg et al. 2006; Martinez et al. 2010). Additional patents focus on improving the convenience and safety of their administration and on expanding the applications for the treatment, for example, the use of nanocarriers in order to increase the solubility of jasmonates, because these compounds are poorly water-soluble, not allowing an application by an intravenous route without an efficient nanostructured carrier system. In addition, they are not easily delivered to the cancerous cells, usually being degraded before they reach the tumour cells (da Silva et al. 2014; Katona et al. 2015; Lopes 2014).

Jasmonates are also used as skin care and hair care products, e.g., for treating hair, the scalp, dry and greasy skin (Bababunmi 2005; Broady 2012; Dalko 2006; Ghasemi Pirbalouti et al. 2014; Malik 2006) and also in Bladder dysfunction (Ghasemi Pirbalouti et al. 2014).

Jasmone, JAMe, CJ and γ-Jasmolactone are considered as the main odorous principles in the essential oil of jasmine flowers (jasmine oil) used in perfumes (Steinegger & Hansel 1988). Other author described the use of dihydromethyl-JA as enhancer or imparter fragrances in or to a perfume composition, perfumed articles and colognes (Boden et al. 1993). In addition, jasmonates are also used to flavour fruit beverages, confectionery like sweets and candy, food products like cocoa and tooth cleansing products like toothpaste (Hurst et al. 2015; Hurst et al. 2011; Johnson et al. 1977; Mookherjee et al. 1981).

8 Conclusions

Beside plants, bacteria and fungi are additional producers of jasmonates, and those providing the highest yields for JA production are *Ascomycetes* from the genus *Lasiodiplodia* and *Diplodia*.

There is a great of diversity of JAs that are produced by microorganisms, but JA, JAMe and dihydroJAMe are the one being most intensively studied because of their value in numerous applications. In the fungus *L. theobromae*, plant-type jasmonate derivatives such as hydroxy and amino acids conjugates, as methyl and sulphate ester occur. In addition, derivatives being specific for fungi such as hydroxy-lactones, didehydro or dihomo-JAs are found. However, till today the function of jasmonates being produced by these microorganisms is not known. However, it is tempting to assume that they are involved regulating the interaction between plants and microorganisms.

Strategies to produce jasmonates via chemical synthesis suffer still from low yields. In case of microbial production strategies, a number of promising strains from the genus *Lasiodiplodia* and *Diplodia* have been selected, but they suffer from producing jasmonate mixtures and elaborated product purification strategies are required to develop an industrial processes for jasmonate production.

The knowledge gained so far provides a promising basis for additional research on the interaction of these microorganisms with plants, the chemical nature of JA biosynthesis in fungi, mechanisms that regulate this pathway in fungi and other microorganisms and design simpler and viable technological strategies to produce jasmonates in these fungi in order to satisfy the high demand for these products.

Nowadays, it is envisioned that JA and its derivatives continue to be used in the biomedicine, cosmetic, food industries and in agriculture, with new biomedical applications and patents emerging with a better understanding of their mechanisms of action and their molecular interactions with biological targets.

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Legends to the figures

Figure 1. Synthesis of JA and its amino acid-conjugate JA-Ile in plants (A) and fungi (B). Some known enzymes for Arabidopsis are indicated in yellow circles. Abbreviations: AOC, allene oxide cyclase; AOS, allene oxide synthase; ddh-JA, 4,5-didehydro jasmonic acid; JA, jasmonic acid; JA-Ile, jasmonic acid isoleucine conjugate; JAR1, jasmonoyl amino acid conjugate synthase; LOX, lipoxygenase; OPC-8, 3-oxo-2-(2-pentenyl)-cyclopentane-1-octanoic acid; OPDA, *cis*-(+)-12-oxo-phytodienoic acid; OPR, 12-oxo-phytodienoic acid reductase.

Figure 2. Chemical structure of the most important jasmonates found in fungi: **A**: **1**, jasmonic acid; **2**, jasmonoyl isoleucine, glycine, serine and threonine conjugates; **3**, 3-oxo-2-pentylcyclopentane-1-butyric acid; **4**, 3-oxo-2-(2-pentenyl)cyclopentane-1-hexanoic acid; **5**, 3-oxo-2-(2-pentenyl)cyclopentane-1-octanoic acid; **6**, 9,10-didehydro-JA; **7**, 9,10-dihydro-7-iso-jasmonoyl-isoleucine; **8**, 3-oxo-2-(2-pentenyl)cyclopentane-1-butyric acid; **9**, 3-oxo-2-(2-pentenyl)cyclopentane-1-hexanoic acid; **10**, 3-oxo-2-(2-pentenyl)cyclopentane-1-octanoic acid (all of them was found with *trans*- or *cis*-attached side chains). **B**: **1**, curcurbic acid; **2**, 8-hydroxy jasmonic acid; **3**, 3-oxo-2-(1-hydroxy-2'-pentenyl)-1-butanoic-cyclopentenyl acid; **4**, 11-hydroxy jasmonic acid; **5**, 3-oxo-2-(4-hydroxy-2'-pentenyl)-cyclopentenyl-1-butanoic acid; **6**: tuberonic acid; **7**: 12-hydroxy jasmonic acid sulphate. **C**: Possible biosynthetic pathways for jasmonates detected in the culture filtrate of fungi (where A.1-10 and B.1-7 belong to the structure given under A and B, respectively)

Figure 3. Number of patents about applications for jasmonates reported in the agricultural literature (**A**), to obtain fragrances and flavours (**FF**), in medicine (**M**), in sugar cane industry (**I**) and for the isolation, detection and production of jasmonates (**P**).

Figure 1(on next page)

Synthesis of JA and its amino acid-conjugate JA-Ile in plants and fungi.

Synthesis of JA and its amino acid-conjugate JA-Ile in plants (A) and fungi (B). Some known enzymes for Arabidopsis are indicated in yellow circles. Abbreviations: AOC, allene oxide cyclase; AOS, allene oxide synthase; ddh-JA, 4,5-didehydro jasmonic acid; JA, jasmonic acid; JA-Ile, jasmonic acid isoleucine conjugate; JAR1, jasmonoyl amino acid conjugate synthase; LOX, lipoxygenase; OPC-8, 3-oxo-2-(2-pentenyl)-cyclopentane-1-octanoic acid; OPDA, *cis*-(+)-12-oxo-phytodienoic acid; OPR, 12-oxo-phytodienoic acid reductase

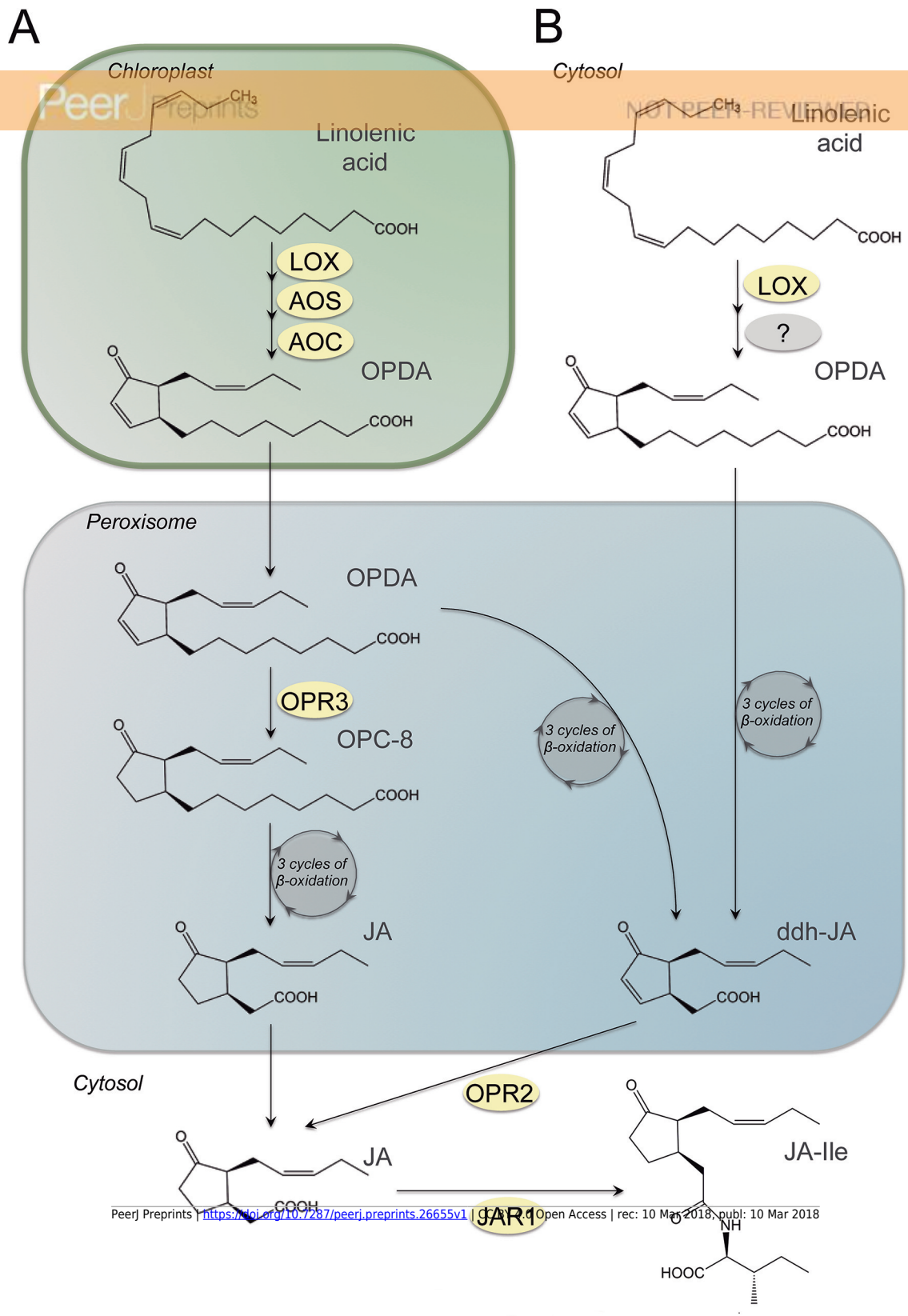


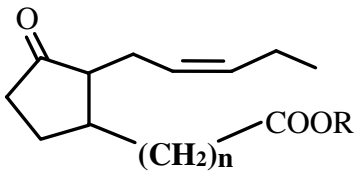
Figure 2(on next page)

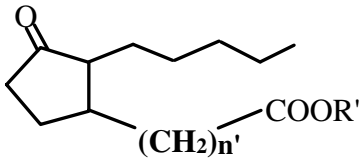
Chemical structure of the most important jasmonates found in fungi.

Chemical structure of the most important jasmonates found in fungi: **A**: **1**, jasmonic acid; **2**, jasmonoyl isoleucine, glycine, serine and threonine conjugates; **3**, 3-oxo-2-pentylcyclopentane-1-butyric acid; **4**, 3-oxo-2-(2-pentenyl)cyclopentane-1-hexanoic acid; **5**, 3-oxo-2-(2-pentenyl)cyclopentane-1-octanoic acid; **6**, 9,10-didehydro-JA; **7**, 9,10-dihydro-7-iso-jasmonoyl-isoleucine; **8**, 3-oxo-2-(2-pentenyl)cyclopentane-1-butyric acid; **9**, 3-oxo-2-(2-pentenyl)cyclopentane-1-hexanoic acid; **10**, 3-oxo-2-(2-pentenyl)cyclopentane-1-octanoic acid (all of them was found with *trans*- or *cis*-attached side chains). **B**: **1**, curcurbic acid; **2**, 8-hydroxy jasmonic acid; **3**, 3-oxo-2-(1-hydroxy-2'-pentenyl)-1-butanoic-cyclopentenyl acid; **4**, 11-hydroxy jasmonic acid; **5**, 3-oxo-2-(4-hydroxy-2'-pentenyl)-cyclopentenyl-1-butanoic acid; **6**: tuberonic acid; **7**: 12-hydroxy jasmonic acid sulphate. **C**: Possible biosynthetic pathways for jasmonates detected in the culture filtrate of fungi (where A.1-10 and B.1-7 belong to the structure given under A and B, respectively)

Figure 2

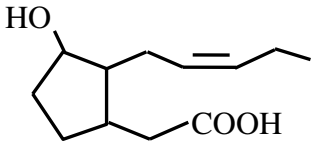
A





	n	R		n'	R'
1	1	OH	**6**	1	OH
2	1	(S)-Ile, -Gly,-Ser, -Thr	**7**	1	(S)-Ile
3	3	OH	**8**	3	OH
4	5	OH	**9**	5	OH
5	7	OH	**10**	7	OH

B



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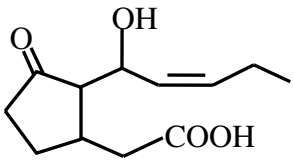

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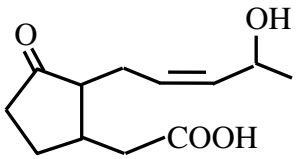

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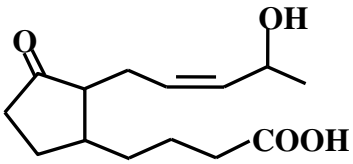

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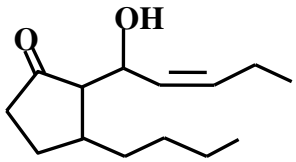

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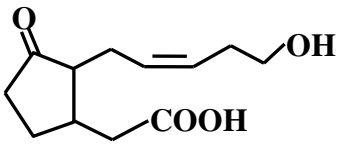

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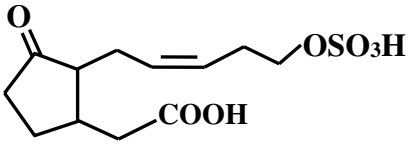

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C

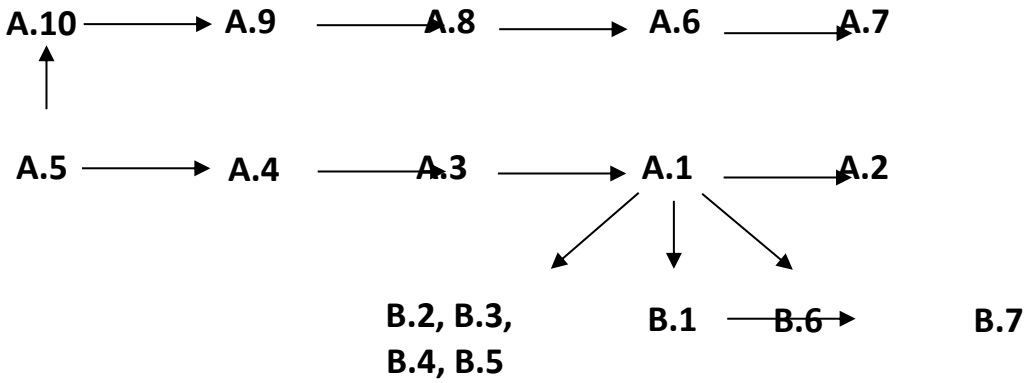

Figure 3(on next page)

Number of patents about applications for jasmonates reported in the agricultural literature.

Number of patents about applications for jasmonates reported in the agricultural literature (**A**), to obtain fragrances and flavours (**FF**), in medicine (**M**), in sugar cane industry (**I**) and for the isolation, detection and production of jasmonates (**P**)

Figure 3

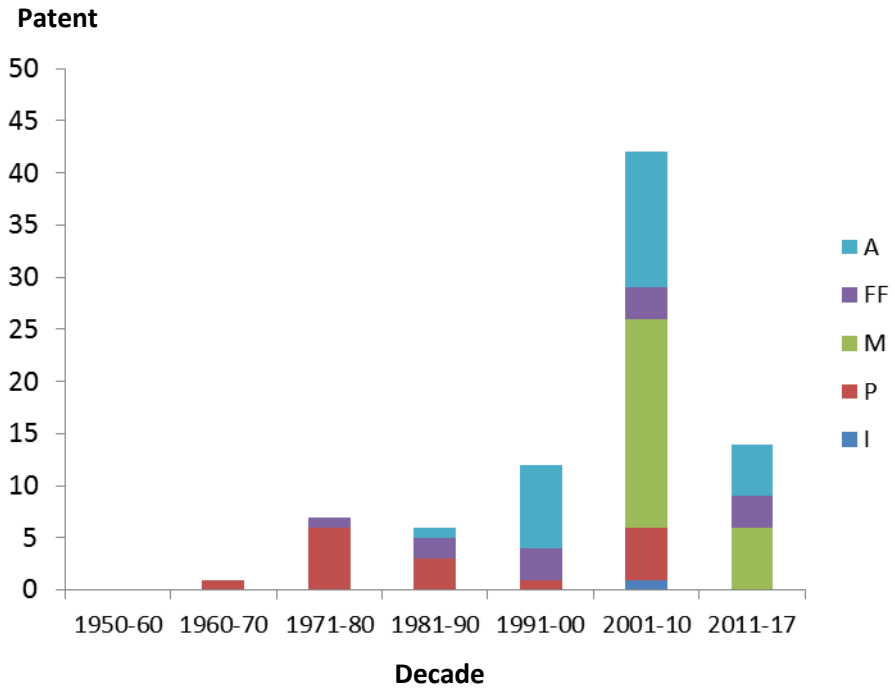
Patent
50
45
40
35
30
25
20
15
10
5
0
1950-60
1960-70
1971-80
1981-90
1991-00
2001-10
2011-17
Decade
A
FF
M
P
I

Table 1(on next page)

Occurrence of jasmonic acid and other jasmonates from plants and microorganisms.

1 **Table 1.** Occurrence of jasmonic acid and other jasmonates from plants and microorganisms.

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Jasmonates	**Plant**	**Microorganism**
Jasmonoyl isoleucine, glycine, serine, threonine, phenylalanine, tyrosine, tryptophan, leucine, isoleucine conjugates	(Hamberg & Gardner 1992)	(Castillo et al. 2014; Cole et al. 2014; Cross & Webster 1970; Miersch et al. 1999; Miersch et al. 1992)
9,10-didehydro-JA	(Hamberg & Gardner 1992)	(Eng 2012)
9,10-dihydro-7-iso-jasmonoyl-isoleucine	(Sembdner et al. 1994)	(Cross & Webster 1970; Miersch et al. 1999; Miersch et al. 1992)
3-oxo-2-(2-pentenyl)cyclopentane-1-butyric acid, 3-oxo-2-(2-pentenyl)cyclopentane-1-hexanoic acid, 3-oxo-2-(2-pentenyl)cyclopentane-1-octanoic acid	-	(Miersch et al. 1999)
Curcurbic acid	(Sembdner & Parthier 1993)	(Eng 2012; Miersch et al. 1987)
8-hydroxy jasmonic acid	(Hamberg & Gardner 1992)	(Miersch et al. 1991)
11-hydroxy jasmonic acid	(Wasternack 2006)	(Miersch et al. 1991)
12-hydroxy jasmonic acid or tuberonic acid	(Hamberg & Gardner 1992; Wasternack 2006)	(Miersch et al. 1991)
12-hydroxy jasmonic acid lactone, tuberonic acid-O-β-glucopyranoside, curcurbic acid-O-β-glucopyranoside	(Hamberg & Gardner 1992)	-

3-oxo-2-(1-hydroxy-2'-pentenyl)-1-butanoic-cyclopentenyl acid, 3-oxo-2-(4-hydroxy-2'-pentenyl)-cyclopentenyl-1-butanoic acid	-	(Miersch et al. 1991)
12-hydroxy jasmonic acid sulphate	Gidda et al., 2003	(Eng 2012)
4,5 didehydro-7-isojasmonic acid, 3,7-didehydrojasmonic acid, 6-epi-curcubic acid lactone, Homo-7-isojasmonic acid, Dihomo-7-isojasmonic acid, 11-hydroxy-dihomojasmonic acid, 8-hydroxy-dihomojasmonic acid	(Asamitsu et al. 2006; Hamberg & Gardner 1992)	-
cis-Jasmone	(Koch et al. 1997)	-
Methyl jasmonate	(Cheong & Choi 2003; Seo et al. 2001)	(Andolfi et al. 2014)

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