International Journal of
Molecular Sciences

MDPI

Review

MYC2: A Master Switch for Plant Physiological Processes and Specialized Metabolite Synthesis

Lei Luo [1,2,†], Ying Wang [3,4,†], Lu Qiu [5], Xingpei Han [2], Yaqian Zhu [1,2], Lulu Liu [1,2], Mingwu Man [1,2], Fuguang Li [1,2,4], Maozhi Ren [1,3,4,*] and Yadi Xing [1,2,*]

1 Zhengzhou Research Base, State Key Laboratory of Cotton Biology, School of Agricultural Sciences, Zhengzhou University, Zhengzhou 450001, China
2 State Key Laboratory of Cotton Biology, Institute of Cotton Research, Chinese Academy of Agricultural Sciences, Anyang 455000, China
3 Institute of Urban Agriculture, Chinese Academy of Agricultural Sciences, Chengdu 610000, China
4 Hainan Yazhou Bay Seed Laboratory, Sanya 572000, China
5 School of Pharmaceutical Sciences (Shenzhen), Shenzhen Campus of Sun Yat-sen University, Shenzhen 518107, China
* Correspondence: renmaozhi01@caas.cn (M.R.); xingyadi@zzu.edu.cn (Y.X.); Tel.: +86-135-2731-3471 (M.R.); +86-131-4016-9001 (Y.X.)
† These authors contributed equally to this work.

Abstract: The jasmonic acid (JA) signaling pathway plays important roles in plant defenses, development, and the synthesis of specialized metabolites synthesis. Transcription factor MYC2 is a major regulator of the JA signaling pathway and is involved in the regulation of plant physiological processes and specialized metabolite synthesis. Based on our understanding of the mechanism underlying the regulation of specialized metabolite synthesis in plants by the transcription factor MYC2, the use of synthetic biology approaches to design MYC2-driven chassis cells for the synthesis of specialized metabolites with high medicinal value, such as paclitaxel, vincristine, and artemisinin, seems to be a promising strategy. In this review, the regulatory role of MYC2 in JA signal transduction of plants to biotic and abiotic stresses, plant growth, development and specialized metabolite synthesis is described in detail, which will provide valuable reference for the use of MYC2 molecular switches to regulate plant specialized metabolite biosynthesis.

Keywords: MYC2; jasmonic acid signaling; plant physiology; specialized metabolites; biosynthesis; synthetic biology

Citation: Luo, L.; Wang, Y.; Qiu, L.; Han, X.; Zhu, Y.; Liu, L.; Man, M.; Li, F.; Ren, M.; Xing, Y. MYC2: A Master Switch for Plant Physiological Processes and Specialized Metabolite Synthesis. *Int. J. Mol. Sci.* **2023**, *24*, 3511. https://doi.org/10.3390/ijms24043511

Academic Editor: Jianhua Zhang

Received: 30 November 2022
Revised: 27 January 2023
Accepted: 8 February 2023
Published: 9 February 2023

1. Introduction

Phytohormones are important regulators of plant growth and development. In response to damage, plants generally integrate phytohormone signaling pathways to trigger immune defense and repair responses throughout the plant body [1]. Particularly, jasmonic acid (JA) signaling is a core signaling pathway that becomes activated in response to plant damage [2]. After the plant is damaged, a large amount of JA is produced, which is then transformed into (+)-7-iso-jasmonoyl-L-isoleucine (JA-Ile) with biological activity. JA-Ile promotes the formation of the SCF-COI1-JAZ coreceptor complex, degrades JAZ (Jasmonate ZIM-domain) through 26S proteasome ubiquitination, and relieves JAZ's inhibition of MYC2, thereby activating the transcription of MYC2 downstream genes, thus triggering plant defense and repair [3]. As a JA signaling hub, MYC2 participates in multiple signaling pathway-networks that integrate light signaling, hormone signaling, natural product synthesis, and the complex processes of plant growth and development [4–9]. In addition, JA not only activates the defense response of the plant itself, but also enhances the content of linalool [10] and β-ocimene or induces the release of other volatile organic compounds, such as shikimic acid derivatives, to enhance the resistance of adjacent plants to the attack of arthropod herbivores [11].

In contrast to animals, plants are sessile and cannot flee from biotic or abiotic stress conditions [12]. Plants therefore produce specialized metabolites to respond to stress; indeed, when subjected to stress, plants generate and accumulate specialized metabolites to improve their immunity and resistance [13]. Plant specialized metabolites not only induce plant resistance to stress but are also widely used in the chemical, food, and agriculture industries, especially in the medical field. They can be divided into tannins, flavonoids, terpenoids, alkaloids, quinones, etc. At present, the most important metabolites from plants are taxol, vinblastine, camptothecin, and artemisinin [14,15]. For example, paclitaxel and vinblastine are effective in the treatment of cancer, while artemisinin is widely used in the treatment of malaria [16]. Secondary metabolites of plants can be extracted by distillation, organic extraction, solid phase extraction, super critical fluid extraction, pressurized liquid extraction, and microwave-assisted extraction, but they are restricted by the low yield and long plant growth cycle [17]. Chemical synthesis of natural products not only faces challenges related to the uncertain structures and complex chiral centers of natural products, but additionally involves cumbersome steps, shows a low conversion rate, and consumes high amounts of energy. Therefore, it is difficult to meet market demands using direct extraction or chemical synthesis.

Synthetic molecular switches are mostly based on protein–protein, protein–DNA, or protein–RNA interactions [18]. Plant transcription factors, as natural regulatory molecular switches, are controlled by endogenous small-molecule metabolites, exogenous damage patterns, and external stimuli, such as light, to regulate downstream genes [19]. Thus, we can use synthetic biology to separate and represent plant functions. The transcription factor MYC2 is a high-level transcriptional regulatory element in the JA signal pathway. MYC2 and its direct binding secondary transcription factors form a series of transcriptional cascade regulatory modules, which activate and amplify the response caused by JA and can achieve the effect of regulating multiple transcription factors [20]. Harnessing the phenomenon transcription factor MYC2 can be precisely regulated by JA signals; the JA-JAZ-MYC2 regulatory pathway was developed into a controllable molecular switch and applied in synthetic biology to precisely regulate the biosynthesis of plant secondary metabolites. The synthetic gene of the target natural product was used to construct an artificial chromosome, and the JA-JAZ-MYC2 switch was added to transform chassis cells or plants to achieve efficient synthesis of the target product. In this review, we systematically analyze and summarize the molecular mechanisms of plant MYC2-regulation of physiological and biochemical processes and provide a reference for the assembly and construction of new plant metabolite production models by characterizing plant signaling pathways.

2. MYC2-Mediated JA Signaling

Jasmonic acid is the first hormone to respond to and rapidly accumulate after wounding. The core JA signaling module includes the F-box protein SCF^{COI1}, JAZ, and the transcription factor MYC2 [21]. In the JA signaling pathway, MYC2 is the main downstream effector, and JAZ is a negative regulator of JA signaling that binds to MYC2, thereby inhibiting its transcription factor activity. MYC2 is a member of the basic helix loop helix (bHLH) family of proteins, which consist of a basic domain and a bHLH domain. The N-terminus of MYC2 is composed of a JAZ interaction domain and a transcriptional activation domain, and the C-terminus is a DNA-binding bHLH domain that can bind to DNA and combine with the *cis*-acting G-box element (5′-CACGTG-3′) [22]. In *Arabidopsis*, the enzymes acyl-CoA oxidase, nucleoside hydrolase 3, oxophytodienoate reductase 3 (OPR3), alkene oxide synthase (AOS), and dihydroflavonol 4-reductase all contain G-box elements in their promoter regions and are induced by JA (https://www.arabidopsis.org/ (10 November 2022)). In the absence of JA, JAZ interacts with MYC2 and recruits the corepressor Topless through NINJA (novel interactor of JAZ), inhibiting the expression of JA-responsive genes activated by MYC2 [23]. Consistent with this, a single amino acid change in MYC is sufficient to cause the loss of interaction with most JAZ proteins (except for JAZ1 and JAZ10). For example, when D105 of MYC2 or D94 of MYC3 mutates, its

interactions with most JAZ proteins are eliminated, thus affecting the trans activation activity of MYC [24]. Transcriptional repression by JAZ also involves the recruitment of chromatin-modifying proteins. Furthermore, JAZ interacts with histone deacetylase 6, leading to a closed chromatin state and repression of the transcription of JA-responsive genes [25]. When JA accumulates, it forms a biologically active JA-Ile, which is perceived by COI1 and forms a platform to recruit JAZ, and then degrades it through ubiquitination modification, releasing transcription factors and initiating JA-regulated plant reactions [26]. MYC2 forms homo- or heterodimers with MYC3 and MYC4, and MYC5 binds to the conserved G-box present in the promoters of JA-responsive genes [27]. MYC2 can activate downstream response genes by modifying histones. For example, it can affect histone H3 methylation of the salt stress response gene [28]. MYC2 can also form a complex with the MED25 subunit of the medium complex, thus recruiting the histone acetylase HAC1, histone acetyltransferase GCN5, and nucleosome remodeling protein SPLAYED to the promoter of downstream genes and thereby selectively regulating the state of target histones [29,30]. By interacting with the MED25 subunit of the mediator complex, MYC2 also recruits the pre-transcription initiation complex, the mediator complex, RNA polymerase II, and other components of the general transcription factor to target promoters [31]. Furthermore, MYC2 can activate JA-induced bHLH proteins (MTB1–3) [32,33] and regulate JA signaling via a negative feedback by impairing MYC2-MED25 complex formation, leading to the termination of JA signaling [34]. LUH activates MYC2-directed transcription of *JAZ2* and *LOX2* via the mediator complex coactivator and the histone acetyltransferase HAC1. We showed that the mediator subunit MED25 physically recruits LUH to MYC2-target promoters, thereby linking MYC2 to HAC1-dependent acetylation of Lys-9 of histone H3 (H3K9ac) to activate *JAZ2* and *LOX2*. LUH interacts with MED25 and HAC1 through its distinct domains, thus imposing a selective advantage by acting as a scaffold for MYC2 activation [30].

The crosstalk/interaction between MYC2 and abscisic acid (ABA), ethylene (ET), GA, and SA mediate various plant developmental processes and defense responses. The signal transduction of ABA and JA is connected through the direct interaction between the ABA receptor PYL6 (RCAR9) and MYC2 [35]. In the ET signaling pathway, the interaction between MYC2 and EIN3 regulates the antagonism of JA and ET signals. MYC2 inhibits the transcriptional activity of EIN3 and EIL1 according to pull-down experiments. It also inhibited the expression of wound response genes and herbivore-induced genes induced by JA by interacting with EIN3 and inhibiting its DNA binding activity, and alleviated the defense of plants regulated by JA against herbivores [36]. The DELLA protein is a key inhibitor of the GA signal pathway, and it can directly interact with JAZ1, prevent JAZ1 from interacting with MYC2, and enhance the binding of MYC2 to its target gene promoter to promote JA reaction [37]. The SA and JA signaling pathways are known to intersect at various points because the two regulate biotic stress responses antagonistically [38]. Studies have shown NPR1 (which can activate SA response genes) to be a key player in the antagonistic crosstalk between SA and JA. The SA-facilitated suppression of JA-responsive genes, such as *LIPOXYGENASE 2* (*LOX2*), *VEGETATIVE STORAGE PROTEIN* (*VSP*), and *PDF1.2*, was abolished in npr1 mutant plants [39]. MYC2 can participate in the regulation of the crosstalk between the SA and JA pathways. In the presence of SA, NPR1 can interact with JA-induced MYC2 and inhibit the transcriptional activation of downstream response genes by interrupting the interaction between MYC2 and MED25 [40].

In addition to the regulation of MYC2 by JAZ, photoreceptors could be involved in blue-light sensing and the MYC2 pathway, and this phenomenon is coordinated with photoperiod or circadian responses. For example, a blue light signal can induce the expression of MYC2/MYC4 through CRYPTOCHROME1 (CRY1) signal transduction to activate NST1, further activate the transcription network of the secondary cell wall (SCW), and regulate the thickening of SCW in fibroblasts [41]. MYC2/ZBF1 can also mediate the interaction between light signals and JA signals, participate in the regulation of the cryptochrome-mediated blue light signal pathway, and play a role in blue light-mediated

photomorphological growth. When plant seedlings are exposed to light, the blue light receptor CRYs sense the light signal and induce the biosynthesis of JA, thus activating the transcription factor MYC2/3/4, further activating the expression of the light morphogenesis regulatory gene *HY5*. In addition, *cry1* and *cry2* photoreceptors can activate the negative blue light response regulator MYC2, which can directly blind to the G-box in the plant pigment SPA1 promoter to regulate its expression [42]. SPA1 is a protein involved in regulating circadian rhythm and light signal transmission. MYC2 and SPA1 can inhibit light morphological growth, negatively regulate blue light-mediated light morphological growth, and inhibit blue light-regulated gene expression in the dark [43]. The circadian response enables plants to best respond to environmental challenges. The biosynthesis of JA is controlled by the biological clock, and its accumulation follows the law of rising in the day and falling at night. Therefore, many transcription factors, including MYC2, regulating JA signaling are also controlled by the biological clock and are governed by similar laws [44]. Inhibition of MYC activity is therefore necessary to reset JA signaling and avoid deleterious runaway responses. The involvement of SUMOylation in the modulation of MYC2 activity has recently been reported. Researchers found that blue light exposure enhances the SUMOylation of MYC2 in K139 and K480. SUMO conjugation does not affect the dimerization of MYC but modulates the interaction of MYC2 with its cognate DNA cis-element and with the ubiquitin ligase plant U-box 10 (PUB10). Moreover, the non-SUMOylatable MYC2 is less stable and interacts more strongly with PUB10; thus, SUMO functions as a counterpoint to the ubiquitin-mediated degradation of MYC2 [45]. In addition, E3 ubiquitin ligase can also reduce MYC protein level based on Cullin3 and BPM proteins as substrate junctions. JA enhances BPM3 stability and establishes a negative feedback regulatory loop to control MYC level and activity. In this new JA pathway regulatory layer, MYC is degraded and terminated by CUL3 BPM-mediated MYC activity [46].

3. MYC Is Involved in the Regulation of Biotic and Abiotic Stress Conditions

Plants have developed numerous strategies to cope with biotic and abiotic stresses. Trichome is the first defense layer of plants against biotic and abiotic stresses. AtMYC1, which positively regulates trichome initiation by regulating the intracellular localization of GL1 and TRY, has been shown to participate in the regulation of trichome patterning [47–49]. Plants can also regulate immune responses against different pathogens by releasing specialized metabolites [50,51]. Phytohormone signaling pathways mediated by JA play a key role in many of these defense responses. When attacked by herbivores, plants activate a series of synthetases to trigger JA biosynthesis, including 13-lipoxygenase (13-LOX), AOS, oxyalkylene, cyclase, and OPR3 [52–54]. This in turn triggers a series of JA-dependent downstream reactions, such as the biosynthesis of several metabolites and molecules, such as the defense protein thionine (encoded by THI) and nutrient storage protein 1 (encoded by VSP1) [55,56]. Jasmonates are major regulators of defense responses, and a network centered on MYC2 is involved in the defense response to multiple pathogens [57]. MYC regulates the expression of genes involved in the synthesis of various specialized metabolites related to insect resistance [58]. For example, in *Arabidopsis*, AtPIFs and AtMYC2 form a homodimer that binds to the promoter of the *TPS* terpene synthase gene to increase terpene biosynthesis as a defense (Figure 1a) against whitefly (*Bemisia tabaci*) [59]. Similarly, MYC-related mutants reportedly show differential resistance to cotton bollworm (*Helicoverpa armigera*), which may be related to the roles of *MGAIs* (MYC-related genes against insects) in flavonoid biosynthesis [58]. High concentrations of flavonoids inhibit the growth of certain insects and allow plants to recover after injury or insect attack. MYC2 may regulate flavonoid production by acting on MGAIs to alleviate plant growth inhibition caused by insect damage [58]. MYC1 is involved in the regulation of the flavonoid biosynthesis pathway and epidermal cell fate in grapevine [60]. By analyzing resistance indicators of *Solanum lycopersicum* strains inoculated with *Meloidogyne incognita*, MYC2 was found to negatively regulate the sensitivity of *Solanum lycopersicum* to *M. incognita* [61]. Nematode RALF-like peptide binds to the

extracellular receptor domain of FER, triggering MAPK phosphorylation, JA signaling, and a reactive oxygen species burst, promoting the degradation of MYC2 to suppress plant immunity [62]. JA is a major regulator of *Nilaparvata lugens* resistance in rice, and rice *myc2* mutants are more susceptible to planthoppers than wild-type (WT) plants [63]. Members of the Solanaceae family accumulate phenylpropanoid-polyamine conjugates (PPCs) in response to attackers while also maintaining a chemical barrier of steroidal glycoalkaloids (SGAs). *Solanum lycopersicum MYC1* and *MYC2* redundantly control jasmonate-inducible PPC and SGA production and are also essential for constitutive SGA biosynthesis [64,65]. In addition, MYC is involved in regulating the expression of disease resistance related genes to regulate plant resistance to diseases. In *Solanum lycopersicum*, magnesium oxide positively regulates resistance genes by triggering JA signaling and activating MYC2 to induce immunity to *Fusarium wilt* [66]. Overexpression of *OsMYC2* induces up-regulation of *PR* gene and bacterial blight resistance in rice [67]. At the same time, MYC2, as a negative regulator of plant pathogens, can block the function of EIN3 by reducing the ET-mediated pathogen reaction. Further, MYC2 can interact with EIN3 to antagonize and regulate the expression of *ERF*, thereby enhancing the expression of *PDF1.2* induced by pathogens [68].

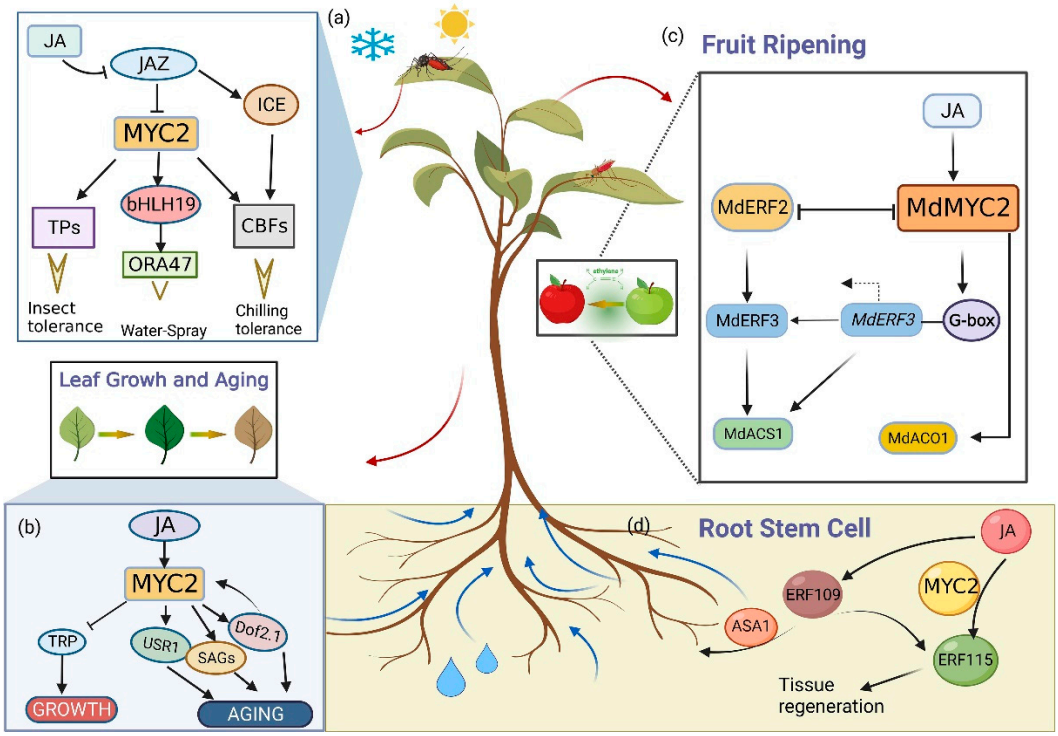

Figure 1. MYC2-mediated plant stress response to biotic/abiotic stress. (**a**) MYC2 mediates the response of plant leaves to insects, temperature, water spray, and other stresses by regulating genes such as *TPs*, *bHLH19*, and *CBFs*. (**b**) MYC2 regulates leaf vein development and leaf senescence through transcriptional regulation of *TRP*, *USR1*, *SAGs*, *Dof2.1*, and other genes. (**c**) During fruit ripening, MYC2 can regulate *ACS1*, *ACO1*, and other genes to participate in the regulation of ethylene synthesis. (**d**) MYC2 participates in root development by regulating genes such as *ERF115* and *ERF109*.

MYC plays important roles not only in plant immunity to pests and pathogens [69] but also in abiotic stress tolerance [70]. Wind and rain cause short-term molecular changes and have long-term developmental effects on flowering time, pathogen defense, and plant structure. Water-spray stress to simulate rainfall induced the activation of JA signaling, in which MYC2 activated ORA47 by interacting with bHLH19 and ERF109 to further promote JA synthesis, suggesting that water spray-induced JA accumulation is regulated by the MYC2-ORA47 pathway via positive feedback regulation [71]. MYC2 acts as a transcrip-

tional activator in the ABA signaling pathway under drought stress [72] and positively regulates the ABA-inducible genes *rd22* and *ADH* [73]. Bayesian network models have suggested that MYC2 and ATAF1 may be regulators of drought response, and activation of MYC2 or inhibition of ATAF1 is the best single-node intervention strategy to modulate drought response [74]. MYC2-like can mediate the expression of *OsCYP2*, a cyclophilin chaperone. Further, *OsCYP2* has been proven to promote the resistance to abiotic stress when overexpressed, especially salt stress. In addition, MYC2-like is also a potential regulator in rice to regulate physiological processes related to salt stress through the abscisic acid (ABA) signaling pathway. A MYC2-like transcription factor binding to ABRE was also identified by yeast one hybrid assay and EMSA. An overexpression transformant of this transcription factor showed higher antioxidant enzyme activity in reactive oxygen species clearance. It is speculated that MYC2-like can improve the resistance to salt stress by improving the antioxidant enzyme activity and post-translational regulation of transformed plants [75]. The ICE1-CBF transcriptional cascade plays central roles in cold tolerance and cold acclimation in plants, and JAZ interacts with ICE to block the ICE-CBF pathway [76,77]. In apple, MdMYC2 interacts with the G-box in the *MdCBF1* promoter to regulate freezing tolerance (Figure 1a) [78]. Plants respond to harsh circumstances by producing specialized metabolites. For example, in cold-exposed sugar beet, betaine aldehyde dehydrogenase (PtrBADH-1) is activated by PtrMYC2 to regulate cold-induced glycine betaine accumulation [79]. At the same time, JA can also induce *SN13* expression in rice, thereby improving rice resistance to drought, cold, and freezing by affecting rice membrane integrity and osmotic matter accumulation [80].

4. MYC2 Is Involved in the Regulation of Plant Growth and Development

Through chloroplast photosynthesis and transpiration, leaves provide energy for plant growth, development, and reproduction. Leaf senescence is regulated by numerous signals, with complex crosstalk between different signaling pathways. MYC2 can inhibit leaf vein development by negatively regulating the biosynthesis of tryptophan, a key substrate for auxin biosynthesis (Figure 1b) [81]. Compared with WT plants, *Arabidopsis myc2* mutants have higher auxin contents and a significantly increased leaf vein density [81]. Further, MYC2 promotes the expression of the JA-induced senescence-related gene *Dof2.1*, and *Dof2.1* enhances JA-induced leaf senescence by directly activating the *MYC2* promoter (Figure 1b) to form a MYC2-Dof2.1-MYC2 feedback loop [82]. In senescent leaves, JA induces H_2O_2 accumulation via binding of MYC2 to the *CAT2* promoter to inhibit its expression, thus upregulating the expression of the senescence-related genes *SAG12*, *SAG13*, *SAG29*, and *SAG113* and inhibiting (Figure 1b) that of the photosynthesis-related genes *CAB1* and *RBCS* [83,84]. In turn, MYC5 functions redundantly with MYC2, MYC3, and MYC4 to modulate the expression of JA-regulated senescence- and photosynthesis-related genes, thus triggering JA-induced leaf senescence. In *Arabidopsis*, MeJA treatment activated MYC2 to promote the transcription of *AtUSR1* (Figure 1b), which is involved in age-dependent and dark-induced leaf senescence [85]. During the senescence of rape leaves, MYC can be induced and activated by ABA, and then up-regulate the expression of AMY3 and BAM1, which are related to starch degradation, and the sucrose transporters SUT1, SUT4, and SWEET11 [86]. In the process of *Solanum lycopersicum* leaf senescence, SlMYC2 can enhance the expression of *SIPAO*, which encodes a chlorophyll degrading enzyme and plays an active role in *Solanum lycopersicum* leaf senescence [87]. These findings suggest that MYC2 plays an important regulatory role in plant leaf senescence, and thus identification and characterization of key senescence genes regulated by MYC2 are of great significance to understand the molecular mechanisms underlying leaf senescence.

The plant root system consists of taproots, lateral roots, and adventitious roots, which play important roles in plant anchoring, water and nutrient absorption, and the synthesis of growth regulators [88]. In *Arabidopsis*, JA inhibits cell division in the main root meristem in a MYC2-dependent manner. MYC2 directly binds to the promoters of *PLT1* and *PLT2* to inhibit their expression and thus negatively regulates root stem cell maintenance and root

meristem activity [88]. The transcription factor ethylene response factor 115 (ERF115) is a rate-limiting factor of quiescent center cell division, which is controlled via transcriptional activation of phytosulfonamide signaling. JA induces ERF115 expression (Figure 1d) in a COI1- and MYC2-dependent manner [89]. In root regeneration, JA signaling induces cell proliferation by activating MYC2 and restores root meristems via ectopic induction of ERF115. Ethylene-responsive factor 109 (ERF109) directly binds to the GCC-box in the *ASA1* promoter and is involved in regulating lateral root formation (Figure 1d) in *Arabidopsis* [90], in which JA activates MYC2 to upregulate auxin synthesis by activating ERF109 and promotes de novo root regeneration in response to injury [71]. Plant roots have evolved different systems for nitrogen uptake. Auxin, CTK, ABA, ETH, GA, BR, and JA can regulate NO3− and NH4+ uptake by regulating the transcript levels or transport activities of the NPF/NRT1, NRT2, and AMTs families in various plants [91]. In addition, JA can also mediate the expression of OsWRKY28 to enhance rice root elongation and phosphate absorption [92]. Simultaneously, JA can also enhance the nitrogen absorption of legumes by enhancing the formation of root nodules, thus promoting the growth of roots [93].

In apple, JA and MYC2 promote the expression of 1-aminocyclopropane-1-carboxylic acid oxidase and synthase and ET synthesis (Figure 1c) to promote fruit ripening [94]. MYC2 can not only directly promote the expression of 1-aminocyclopropane-1-carboxylic acid oxidase and synthase, but also promote the expression of 1-aminocyclopropane-1-carboxylic acid synthase via the ERF3 pathway. MYC2 can interact with ERF2 to relieve the binding between ERF2 and ERF3 [95] and enhance the transcriptional activation of *ACS1* by ERF3 [94]. In loquat fruit treated with recombinant serine protease, *MYC2* expression was upregulated, and as a result, the expression of genes encoding polyphenol oxidase, phenylalanine ammonia lyase, and other resistance-related genes was upregulated, contributing to the resistance of fruit to external biotic stress and effectively delaying fruit rotting [96]. ABA induces the expression of *MYC2* and *MYB1R1* and activates the *PbFAD3a* promoter, contributing to the formation of russet pear skin [97]. MeJA treatment and SlMYC2 overexpression inhibited *Solanum lycopersicum* seedling growth and photosynthesis, but increased the sugar acid ratio and content of lycopene, carotenoid, soluble sugar, total phenols, and flavones, indicating that JA signal transduction could inhibit *Solanum lycopersicum* seedling growth and change fruit quality [9]. The process of ovule abortion is highly coordinated and controlled by numerous environmental and endogenous signals. JA and ET participate in the gibberellin-induced ovule programmed cell death process in seedless pear '1913' (pyrus hybrid) [98]. The binding of MYC2 to the *SENESCENCE-ASSOCIATED 39* (*SAG39*) promoter triggers its expression to regulate ovule abortion [98]. In *Arabidopsis*, MYC2 binds to the *SAG29* promoter to activate its expression and thus trigger JA-induced leaf senescence [84,96]. Furthermore, *SAG39*, a homolog of *SAG29*, is expressed in ovules, suggesting that there may be similar regulatory mechanisms underlying leaf and ovule senescence. These results provide a strong basis for understanding ovule development for the breeding of seedless fruit.

Seeds are unique organs that consist of a seed coat, an embryo, and an endosperm. The embryo stores most of the nutrients required for plant germination, such as protein, starch, and fat stored in the form of triacylglycerol. In *Arabidopsis*, triacylglycerol and related storage proteins are rapidly synthesized and accumulated in early embryonic seed development, and the genes encoding seed storage proteins 12S globulin and 2S albumin may be regulated by MYC2 [99]. MYC2, MYC3, and MYC4 play synergistic roles in determining seed size, weight, and storage protein content. The weight and storage protein content of *Arabidopsis* triple mutant *myc2myc3myc4* seeds were significantly higher than those of WT seeds. In addition, CRA1 and CRU3 contents and their corresponding gene expression levels were also substantially higher than those in WT seeds [100,101]. The spikelet is the basal unit of inflorescence in grasses, and its formation is crucial for reproductive success and cereal yield. A study found that JA plays a key role in determining rice (*Oryza sativa*) spikelet morphogenesis. *Extra glume 1* (*eg1*) and *eg2* mutants exhibit altered spikelet morphology, with changed floral organ identity and number, as well as

defective floral meristem determinacy. EG1 is a plastid-targeted lipase that participates in JA biosynthesis, and EG2/OsJAZ1 is a JA signaling repressor that interacts with a putative JA receptor, OsCOI1b, to trigger OsJAZ1 degradation during spikelet development. OsJAZ1 also interacts with OsMYC2 and represses OsMYC2's role in activating OsMADS1, an E-class gene crucial for spikelet development [102]. NtMYC2a plays an important role in carbohydrate metabolism and pollen development by regulating the expression of the starch metabolism-related genes *AGPs*, *SS2*, and *BAM1* in pollen grains, anther walls, and ovaries of tobacco plants. The process of pollen maturation was accelerated in NtMYC2a-OE plants and was delayed in NtMYC2a-RI plants [103]. Chestnut (*Castanea mollisima*) is an important woody food crop, but its yield is low when cultivated, mainly due to the problems of fewer female flowers and more male flowers. A higher concentration of JA-Ile is conducive for the differentiation and formation of female flower buds during post-winter, and JAZ1-3 and MYC2-1 play a key role in the differentiation of female flower buds of chestnut [104]. Additionally, MYC2, MYC3, MYC4, and MYC5 have redundant roles in regulating stamen development and seed production, and can interact with MYB21 and MYB24 to form a bHLH-MYB transcription complex that regulates stamen development and seed production [105,106]. While inhibition of the bHLH-MYB complex by JAZ proteins inhibits stamen development and seed production, JA induces JAZ degradation and releases the bHLH-MYB complex, thus activating the expression of downstream genes critical for stamen development and seed production [107].

5. MYC2 Is Involved in the Regulation of Specialized Metabolites in Plants

JA can induce the biosynthesis of medicinally active components such as paclitaxel, artemisinin, tanshinone, and vinblastine in plants [53]. As the main regulator of JA signaling, MYC2 is involved in regulating the expression of key gene-encoding enzymes involved in the production of various plant specialized metabolites [108,109] and directly or indirectly affects the synthesis and accumulation of specialized metabolites [110]. In *Taxus chinensis*, TcMYC2 directly activates the expression of paclitaxel biosynthesis genes or regulates paclitaxel biosynthesis through ERF regulators (Figure 2a) [111]. When TcMYC2a was overexpressed in yew cells, the expression levels of paclitaxel biosynthesis-related genes significantly increased. TcMYC2 activates paclitaxel biosynthesis in response to MeJA and binds to the promoter of the paclitaxel biosynthesis gene encoding taxadiene synthase. Overexpression of *TcMYC2a* increases the expression of *TcERF12* and *TcERF15* to regulate taxadiene synthase gene expression [111]. In *Artemisia annua*, AaMYC2 directly regulates G-box-like elements in the promoters of *CYP71AV1* and *DBR2*, encoding two key structural enzymes in the artemisinin synthesis pathway, to induce their expression (Figure 2b) [112,113]. The transcription factors *AaMYC2*, *AaNAC1*, and *AaHD1* have been overexpressed in *A. annua* to improve artemisinin biosynthesis. This not only increased the artemisinin content but also allowed plants to grow in abandoned saline-alkali soils and conferred a certain degree of herbicide resistance to them [114]. In *Salvia miltiorrhiza*, SmMYC2 reportedly upregulates the transcription of genes such as *SmGGPPS* to promote tanshinone synthesis and regulates the expression of *CYP98A14* by binding to its E-box to promote tanshinone synthesis (Figure 2c) [115]. In *Catharanthus roseus*, CrMYC2 affects the expression of *SLS*, *TDC*, and *LAMT* by regulating the transcription of *ORCA2*, *ORCA3*, and *ORCA4* to activate key steps in the terpenoid-indole alkaloid pathway, thereby regulating vinca alkaloid synthesis (Figure 2d), resulting in vinblastine accumulation [116]. Gossypol is a sesquiterpene lactone and an important antimicrobial specialized metabolite involved in cotton (*Gossypium hirsutum*) resistance to pathogen attack and insect damage. Gossypol is used as an anticancer drug and a male contraceptive [117]. GhMYC2 directly regulates the expression of key enzymes in the gossypol synthesis pathway, such as CYP71BE79, and participates in the regulation of gossypol synthesis. GhMYC2 silencing and overexpression negatively and positively affected the gossypol contents in cotton tissues, respectively (Figure 2e) [118].

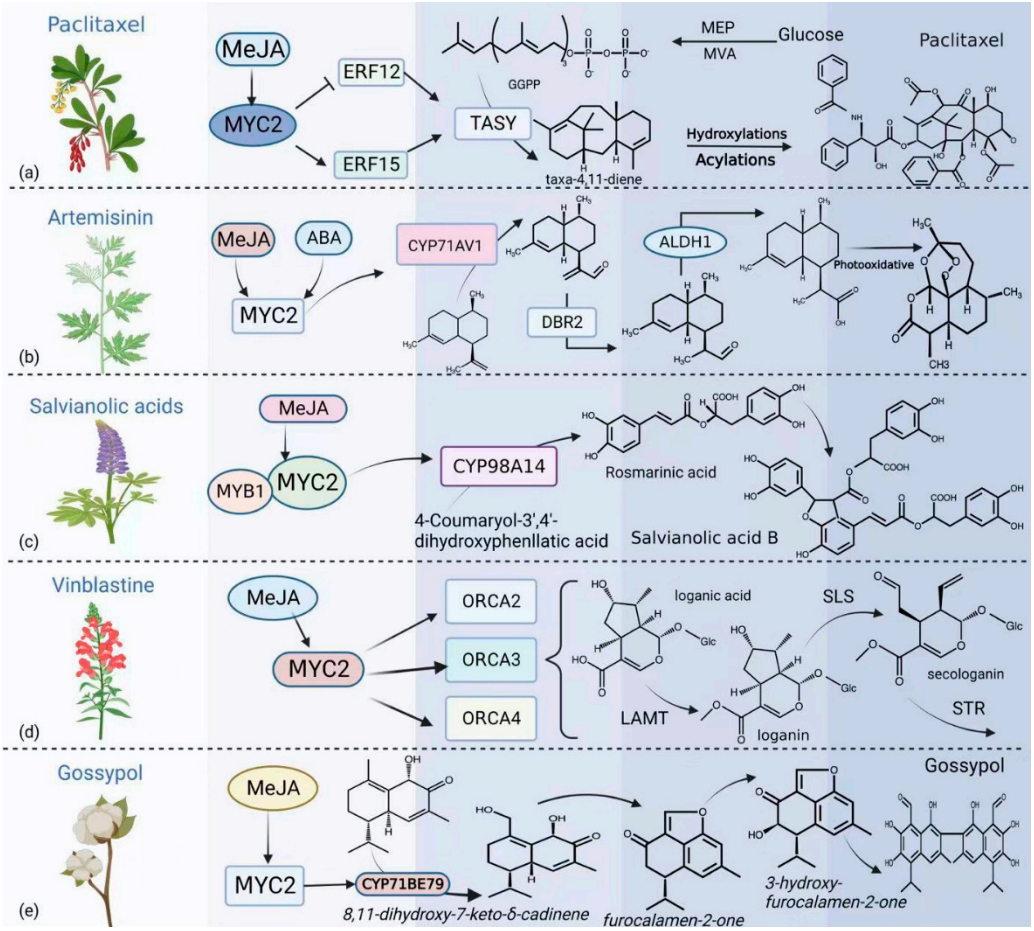

Figure 2. MYC2 is involved in the synthesis of plant specialized metabolites. (**a**) MYC2 is involved in the regulation of paclitaxel biosynthesis by regulating ERF12 and ERF15. (**b**) MYC2 can regulate the expression of key enzymes involved in artemisinin biosynthesis, such as CYP71AV1, AaDBR2, and AaALDH1. (**c**) MYC2 regulates the expression of *CYP98A14* to regulate the synthesis of *Salvia miltiorrhiza* specialized metabolites. (**d**) MYC2 affects vinblastine biosynthesis by regulating the transcription of ORCA2, ORCA3, and ORCA4. (**e**) MYC2 can directly regulate the expression of key enzymes in the gossypol synthesis pathway, such as CYP71BE79, and participate in the regulation of gossypol synthesis.

In *Tripterygium wilfordii*, TwMYC2a and TwMYC2b negatively regulate triptolide biosynthesis by inhibiting TwTPS27a and TwTPS27b in hairy roots [119]. MYC2 directly regulates the synthesis of triterpenoid saponins of *Psammosilene tunicoides* by regulating the backbone-building enzymes β-amyrin synthase and squalene epoxidase in the triterpenoid saponin synthesis pathway [120]. In addition to regulating the synthesis of various medicinal natural products, MYC2 plays an important role in the quality improvement of various natural products with industrial application value [121]. For example, HbMYC2b significantly increased the content of small rubber granule-protein in rubber tree (*Hevea brasiliensis*) latex. The specific JA signal transduction module COI1-JAZ3-MYC2 exists in rubber tree milk-duct cells, and MYC2 enhances secondary milk duct differentiation and rubber biosynthesis by upregulating the expression of farnesyl pyrophosphate synthase and small rubber granule-protein genes [122].

6. Prospects of Application of MYC2 in Chassis-Based Synthesis of Natural Products

Synthetic biology aims to redesign existing natural biological systems to achieve target functions [123]. The concept is fully applicable to the engineering of plants to synthesize plant natural products. Plant synthetic biology follows the design-build-test-learn cycle of synthetic biology [124]. Chassis cells are the hardware foundation of synthetic biology [125]. However, the construction of chassis cells for plant natural-product synthesis remains challenging [126]. The development of life sciences has made available complete genome sequences, has provided valuable bioinformatics and genetic resources, and has deepened our understanding of the biosynthesis of natural products and the regulatory mechanisms at play [127–130]. Transcription factors exist widely in organisms and have natural advantages as molecular switches. They can change their own structures and regulate downstream genes by sensing changes in the concentration of target natural products in cells, thus converting product concentrations into specific signal outputs. The phenomenon that the transcription factor MYC2 can be precisely regulated by JA signaling suggests that the JA-JAZ-MYC2 regulatory pathway has the potential to be used as a molecular switch in synthetic biology to precisely regulate the biosynthesis of plant specialized metabolites. JA exists in seed plants, and JA and JA-Ile are also detected in *bryophytes* [131]. JA was even detected in *Escherichia Coli* and *Saccharomyces Cerevisiae* cultures [132]. The JA-JAZ-MYC2 system activates the corresponding biosynthetic system by applying high doses of JA. Under non-stress conditions, the impact of the low content of endogenous JA produced in the host organism on the JA-JAZ-MYC2 system may be inevitable but also limited. The widespread existence of JA suggests that it may be feasible to use the JA-JAZ-MYC2 system to regulate biosynthesis in eukaryotic and prokaryotic hosts.

Plant specialized metabolites are of great value to medicine and industry, but they are difficult to extract, and yields are low [133]. Research on the biosynthesis process of plant specialized metabolites provides a theoretical basis for improving or creating biological or chemical synthesis methods of specialized metabolites. Based on a specialized metabolite synthetic pathway, multiple promoter sequences are designed to precisely control and coordinate gene expression in the pathway, thereby reducing the accumulation of intermediate metabolites and cell load. For example, in *Saccharomyces cerevisiae*, a series of regulatable promoters with a length of no more than 100 bases was constructed by modularizing the promoters [134]. Synthetic biology studies of high-value medicinal specialized metabolites such as paclitaxel, vinblastine, and artemisinin using microbial chassis have been conducted [135,136]. Taking paclitaxel synthesis as an example, the reference genome sequence of *Taxus chinensis* can be used to comprehensively elucidate the paclitaxel biosynthesis pathway [137]. In synthetic biology, isopentenyl diphosphate is often used as a substrate to produce taxadiene in *E. coli*. In general, the biosynthesis of most natural products requires the interaction of cytochrome P450 and its reductase for electron transfer; however, it is difficult to express P450 in *E. coli* [138]. As *S. cerevisiae* has a rich endomembrane system in which cytochrome P450 can be efficiently functionally expressed, *E. coli* and *S. cerevisiae* can be used to produce paclitaxel using a co-culture method [139].

The cis elements recognized by MYC2 are used as promoters to drive all genes necessary for the synthesis of a natural product, and they are connected with JA-JAZ-MYC2 conditional molecular switches to form artificial chromosomes (Table 1). Because the promoter responds to JA and MYC2, a JA-JAZ-MYC2 conditional molecular switch includes the key elements of the JA signaling pathway, namely JAZ, COI1, MYC2, MED25, and other necessary genes. Transforming artificial chromosomes into chassis cells or substrate plants, large numbers of natural products can be synthesized by exogenous JA or exogenous stimulation (Figure 3). For example, the CDS of all necessary genes of the taxol synthesis pathway can be inserted into the promoter and terminator regulated by MYC2 separately (if the genes are activated by MYC2, their promoters can be used; if they are not regulated by MYC2, they have to be replaced with gene promoters activated by MYC2, such as *Dof2.1*, *ERF115*, etc.), and then connected to the JA-JAZ-MYC2 molecular switch for co-expression. In the application of synthetic biology, transcription factors and promoters

that naturally exist in plants have been developed as molecular switches and promoters for efficient synthesis of specialized metabolites. For example, in rice, scientists have produced a construction containing eight anthocyanidin-related genes (two regulatory genes from maize and six structural genes from Perilla frutescens), which are driven by endosperm-specific promoters, to produce a new bio-enhanced germplasm "purple endosperm rice" (called "Zijingmi" in Chinese) with high anthocyanin content and antioxidant activity [140]. Researchers selected maize *ZmLc* (*Leaf color*) and *ZmPl* (*Purple leaf*), which encode the bHLH-type and MYB-type transcription factors, respectively, to activate the anthocyanin biosynthesis genes [141,142].

Table 1. Genes involved in MYC2 regulation.

Type of Function		List of Genes	Reference
Biotic and Abiotic Stress Conditions	Insect tolerance	*TPs*	[59]
		MGAIs	[58]
		SGA	[64,65]
		PPC	[64,65]
		PR	[67]
		PDF1.2	[68]
	Water spray	*bHLH19*	[71]
		ERF109	[71]
		ORA47	[71]
	Drought stress	*rd22*	[73]
		ADH	[73]
	Chilling tolerance	*MdCBF1*	[78]
Plant Growth and Development	Leaf growth and aging	*Dof2.1*	[82]
		SAG12/13/29/113	[82,83]
		CAB1	[82,83]
		RBCS	[82,83]
		AtUSR1	[85]
		AMY3	[86]
		BAM1	[86]
		SUTI/4	[86]
		SWEET11	[86]
		SIPAO	[87]
	Root stem cell	*PLT1/2*	[88]
		ERF115/109	[89]
	Fruit ripening and pollen maturation	*MdERF2/3*	[95]
		MdACO1	[94]
		AGPs	[103]
		SS2	[103]
		BAM1	[103]
Specialized Metabolites	Paclitaxel biosynthesis	*TcERF12/15*	[111]
	Artemisinin synthesis	*CYP71AV1*	[112,113]
		DBR2	[112,113]
	Salvia miltiorrhiza	*CYP98A14*	[115]
		SmGGPP	[115]
	Vinblastine biosynthesis	*ORCA2/3/4*	[116]
	Gossypol synthesis	*CYP71BE79*	[118]
	Psammosilene tunicoides synthesis	*TwTPS27a/b*	[119]

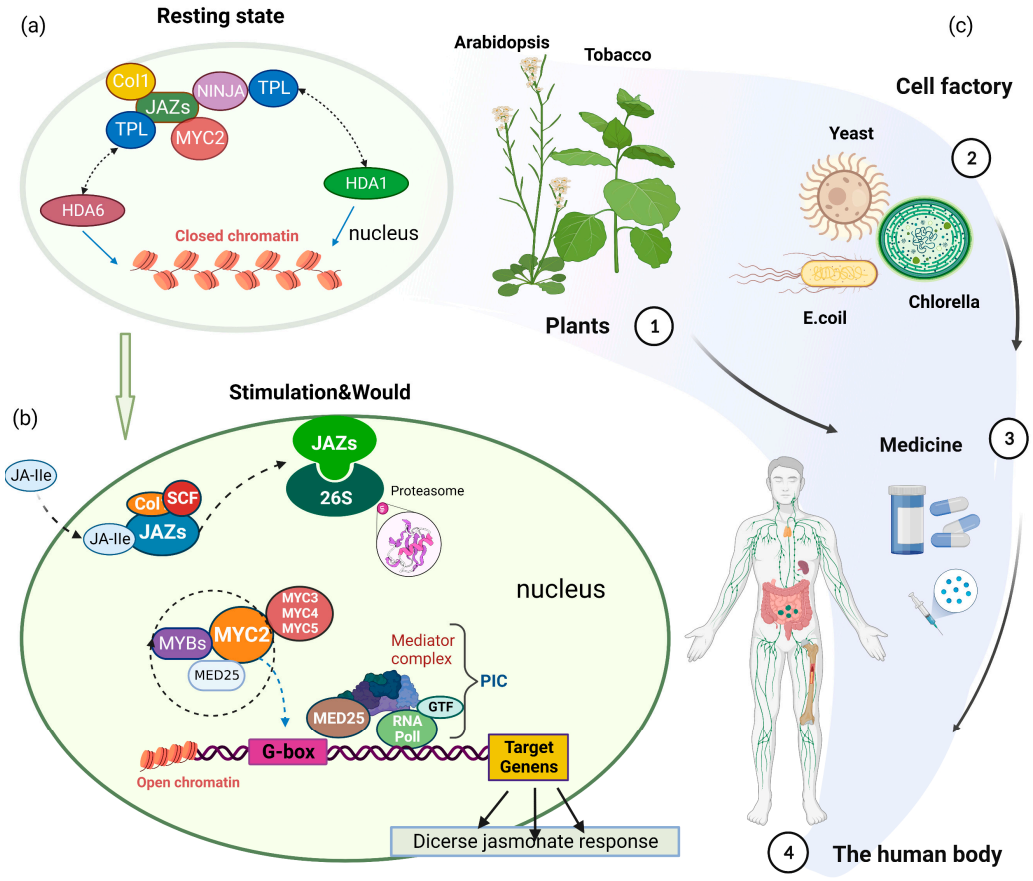

Figure 3. The central role of MYC2 in the JA signaling pathway and its application prospects in synthetic biology. (**a**) In the resting state, JAZ binds to and inhibits the transcription factor activity of MYC2 and inhibits the transcription of the JA gene. (**b**) Under stress, JA-Ile promotes the ubiquitination and degradation of JAZ, relieves the inhibition of MYC2 by JAZ, and activates the JA signaling pathway. (**c**) Applying the on–off function of MYC2 to synthetic biology techniques to produce medicinally valuable plant specialized metabolites using plants or microorganisms as chassis cells.

The chassis cells produced using plant metabolites include plant chassis and microbial cell chassis. Microbial cell chassis development utilizes *E. coli* and *S. cerevisiae* as typical hosts. *E. coli* is the most widely prokaryotic host used to produce heterogenous metabolites. As a chassis cell, it has the characteristics of rapid/easy growth, high product yield, and high cost efficiency. Further, the availability of various expression vectors and strains, the operation technology, and the relative ease of product purification make it an attractive host for industrial applications. However, the lack of cell intima as well as post-translational modification limit its use as a selection chassis for many plant natural products [143]. The use of plants as a specialized-metabolite production chassis has many advantages, including the presence of photosynthetic systems, extremely rich enzyme repertoires, and various cellular compartments [138,144,145]. Plant cellular compartments can decompose complete pathways into independent parts, and various conditions, such as reactions and precursor compounds, can be optimized in each cellular compartment; therefore, using plants as a chassis has great potential for production applications [126]. The commonly used plant chassis for heterologous synthesis is *Nicotiana benthamiana*, and various natural products, including alkaloid terpenoids, paclitaxel, and artemisinin, have transiently been expressed in *N. benthamiana* [146–148]. If higher plants are used as base plants, the JA-JAZ-MYC2 molecular switch can also be used to regulate the expression of MYC2 target genes in artificial chromosomes. As another synthetic biology chassis, microalgae have the advantages of having complex metabolic networks and biosynthesis pathways; in addition, they can

be used as cell factories and have successfully synthesized metal nanoparticles [149–151]. If the base cell is a lower organism such as microalgae and has low homology with the genome of higher plants, it may not be able to start the expression of foreign artificial chromosomes; in such cases, additional JA-JAZ-MYC2 molecular switches need to be added to start the expression of artificial chromosomes.

The JA signal in plants is an important signal pathway in response to external stimuli. The inducibility and controllability of the JA-JAZ-MYC2 regulatory pathway endows it with the potential to be applied as a synthetic biological molecular switch. As a transcription factor, MYC2 itself can directly regulate the synthesis of a variety of plant specialized metabolites, and the promoter of its target gene can also be directly applied to the construction of artificial chromosomes regulated by the JA-JAZ-MYC2 molecular switch. Transgene expression only needs to occur at a certain point or time period in order to minimize the metabolic burden on the host cell, or to control the timing of gene expression. For this reason, unlike constitutive promoters such as *CaMV35S*, *Nos*, and *Ocs*, which are always active, the inducible gene expression system constructed by MYC2 can more dynamically and precisely regulate gene expression for optimal production of valuable chemicals [152]. An ideal control system should allow rapid and precise regulation of a target gene between the "ON" and "OFF" states or even simultaneous switching of different genes to the ON or OFF state [153–155]. Compatible "ON" and "OFF" switch functions for controlling the expression of genes in biosynthetic pathways and regulatory networks can also be achieved through rational design of MYC2-based switches. Therefore, MYC2 has some inherent advantages to be developed as a molecular switch for the synthesis of plant specialized metabolites via synthetic biology. This review synthesizes the role of MYC2 in the regulation of plant physiological processes and in the synthesis of specialized metabolites, summarizes the relevant pathways and genes related to MYC2, and provides new insights into and strategies for the application of MYC2 to synthetic biology to synthesize natural products with medicinal value.

Author Contributions: Conceptualization, M.R. and Y.X.; writing—original draft preparation, L.L. (Lei Luo), Y.W. and L.Q.; writing—review and editing, X.H., Y.Z., L.L. (Lulu Liu) and M.M.; funding acquisition, F.L., M.R. and Y.X. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by grants from the National Natural Science Foundation of China (Nos. U1804231 to F.L., 31972469 to M.R.) and the China Postdoctoral Science Foundation (No. 2020M672286 to Y.X.).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: The authors thank the teachers and students in our research team for their help and support.

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

References

1. Studham, M.E.; MacIntosh, G.C. Phytohormone Signaling Pathway Analysis Method for Comparing Hormone Responses in Plant-Pest Interactions. *BMC Res. Notes* **2012**, *5*, 392. [CrossRef]
2. Aslam, S.; Gul, N.; Mir, M.A.; Asgher, M.; Al-Sulami, N.; Abulfaraj, A.A.; Qari, S. Role of Jasmonates, Calcium, and Glutathione in Plants to Combat Abiotic Stresses Through Precise Signaling Cascade. *Front. Plant Sci.* **2021**, *12*, 668029. [CrossRef] [PubMed]
3. Hoo, S.C.; Koo, A.J.K.; Gao, X.; Jayanty, S.; Thines, B.; Jones, A.D.; Howe, G.A. Regulation and Function of Arabidopsis JASMONATE ZIM-Domain Genes in Response to Wounding and Herbivory. *Plant Physiol.* **2008**, *146*, 952–964. [CrossRef]
4. Dombrecht, B.; Gang, P.X.; Sprague, S.J.; Kirkegaard, J.A.; Ross, J.J.; Reid, J.B.; Fitt, G.P.; Sewelam, N.; Schenk, P.M.; Manners, J.M.; et al. MYC2 Differentially Modulates Diverse Jasmonate-Dependent Functions in Arabidopsis. *Plant Cell* **2007**, *19*, 2225–2245. [CrossRef]
5. Yamada, Y.; Koyama, T.; Sato, F. Basic Helix-Loop-Helix Transcription Factors and Regulation of Alkaloid Biosynthesis. *Plant Signal. Behav.* **2011**, *6*, 1627–1630. [CrossRef]

6. Srivastava, A.K.; Dutta, S.; Chattopadhyay, S. MYC2 Regulates ARR16, a Component of Cytokinin Signaling Pathways, in Arabidopsis Seedling Development. *Plant Direct* **2019**, *3*, e00177. [CrossRef]
7. Yang, J.; Duan, G.; Li, C.; Liu, L.; Han, G.; Zhang, Y.; Wang, C. The Crosstalks Between Jasmonic Acid and Other Plant Hormone Signaling Highlight the Involvement of Jasmonic Acid as a Core Component in Plant Response to Biotic and Abiotic Stresses. *Front. Plant Sci.* **2019**, *10*, 1349. [CrossRef]
8. Shin, J.; Heidrich, K.; Sanchez-Villarreal, A.; Parker, J.E.; Davis, S.J. TIME FOR COFFEE Represses Accumulation of the MYC2 Transcription Factor to Provide Time-of-Day Regulation of Jasmonate Signaling in Arabidopsis. *Plant Cell* **2012**, *24*, 2470–2482. [CrossRef]
9. Zhang, Y.; Xing, H.; Wang, H.; Yu, L.; Yang, Z.; Meng, X.; Hu, P.; Fan, H. SlMYC2 Interacted with the SlTOR Promoter and Mediated JA Signaling to Regulate Growth and Fruit Quality in Tomato. *Front. Plant Sci.* **2022**, *13*, 1013445. [CrossRef]
10. Zhang, P.J.; Zhao, C.; Ye, Z.H.; Yu, X.P. Trade-off between Defense Priming by Herbivore-Induced Plant Volatiles and Constitutive Defense in Tomato. *Pest Manag. Sci.* **2020**, *76*, 1893–1901. [CrossRef]
11. Ballhorn, D.J.; Kautz, S.; Schädler, M. Induced Plant Defense via Volatile Production Is Dependent on Rhizobial Symbiosis. *Oecologia* **2013**, *172*, 833–846. [CrossRef] [PubMed]
12. Zhu, J.K. Abiotic Stress Signaling and Responses in Plants. *Cell* **2016**, *167*, 313–324. [CrossRef]
13. Mao, Y.B.; Liu, Y.Q.; Chen, D.Y.; Chen, F.Y.; Fang, X.; Hong, G.J.; Wang, L.J.; Wang, J.W.; Chen, X.Y. Jasmonate Response Decay and Defense Metabolite Accumulation Contributes to Age-Regulated Dynamics of Plant Insect Resistance. *Nat. Commun.* **2017**, *8*, 13925. [CrossRef] [PubMed]
14. Calabrò, S. Plant Secondary Metabolites. In *Rumen Microbiology: From Evolution to Revolution*; Springer: Delhi, India, 2015; Volume 10, pp. 153–159. [CrossRef]
15. Twaij, B.M.; Hasan, M.N. Bioactive Secondary Metabolites from Plant Sources: Types, Synthesis, and Their Therapeutic Uses. *Int. J. Plant Biol.* **2022**, *13*, 4–14. [CrossRef]
16. Greenwell, M.; Rahman, P.K.S.M. Medicinal Plants: Their Use in Anticancer Treatment. *Int. J. Pharm. Sci. Res.* **2015**, *6*, 4103–4112. [CrossRef]
17. Zhang, Q.W.; Lin, L.G.; Ye, W.C. Techniques for Extraction and Isolation of Natural Products: A Comprehensive Review. *Chinese Med.* **2018**, *13*, 20. [CrossRef]
18. Hörner, M.; Weber, W. Molecular Switches in Animal Cells. *FEBS Lett.* **2012**, *586*, 2084–2096. [CrossRef]
19. Eguchi, A.; Lee, G.O.; Wan, F.; Erwin, G.S.; Ansari, A.Z. Controlling Gene Networks and Cell Fate with Precision-Targeted DNA-Binding Proteins and Small-Molecule-Based Genome Readers. *Biochem. J.* **2014**, *462*, 397–413. [CrossRef]
20. Du, M.; Zhao, J.; Tzeng, D.T.W.; Liu, Y.; Deng, L.; Yang, T.; Zhai, Q.; Wu, F.; Huang, Z.; Zhou, M.; et al. MYC2 Orchestrates a Hierarchical Transcriptional Cascade That Regulates Jasmonate-Mediated Plant Immunity in Tomato. *Plant Cell* **2017**, *29*, 1883–1906. [CrossRef]
21. Thines, B.; Katsir, L.; Melotto, M.; Niu, Y.; Mandaokar, A.; Liu, G.; Nomura, K.; He, S.Y.; Howe, G.A.; Browse, J. JAZ Repressor Proteins Are Targets of the SCFCOI1 Complex during Jasmonate Signalling. *Nature* **2007**, *448*, 661–665. [CrossRef]
22. Lian, T.-F.; Xu, Y.-P.; Li, L.-F.; Su, X.-D. Crystal Structure of Tetrameric Arabidopsis MYC2 Reveals the Mechanism of Enhanced Interaction with DNA. *Cell Rep.* **2017**, *19*, 1334–1342. [CrossRef] [PubMed]
23. Pérez-Alonso, M.M.; Sánchez-Parra, B.; Ortiz-García, P.; Santamaría, M.E.; Díaz, I.; Pollmann, S. Jasmonic Acid-Dependent Myc Transcription Factors Bind to a Tandem g-Box Motif in the Yucca8 and Yucca9 Promoters to Regulate Biotic Stress Responses. *Int. J. Mol. Sci.* **2021**, *22*, 9768. [CrossRef] [PubMed]
24. Goossens, J.; Swinnen, G.; Bossche, R.V.; Pauwels, L.; Goossens, A. Change of a Conserved Amino Acid in the MYC2 and MYC3 Transcription Factors Leads to Release of JAZ Repression and Increased Activity. *New Phytol.* **2015**, *206*, 1229–1237. [CrossRef] [PubMed]
25. Wu, K.; Zhang, L.; Zhou, C.; Yu, C.W.; Chaikam, V. HDA6 Is Required for Jasmonate Response, Senescence and Flowering in Arabidopsis. *J. Exp. Bot.* **2008**, *59*, 225–234. [CrossRef]
26. Sheard, L.B.; Tan, X.; Mao, H.; Withers, J.; Ben-Nissan, G.; Hinds, T.R.; Kobayashi, Y.; Hsu, F.F.; Sharon, M.; Browse, J.; et al. Jasmonate Perception by Inositol-Phosphate-Potentiated COI1-JAZ Co-Receptor. *Nature* **2010**, *468*, 400–407. [CrossRef]
27. Zhang, C.; Lei, Y.; Lu, C.; Wang, L.; Wu, J. MYC2, MYC3, and MYC4 Function Additively in Wounding-Induced Jasmonic Acid Biosynthesis and Catabolism. *J. Integr. Plant Biol.* **2020**, *62*, 1159–1175. [CrossRef]
28. Fu, Z.W.; Li, J.H.; Feng, Y.R.; Yuan, X.; Lu, Y.T. The Metabolite Methylglyoxal-Mediated Gene Expression Is Associated with Histone Methylglyoxalation. *Nucleic Acids Res.* **2021**, *49*, 1886–1899. [CrossRef]
29. Walley, J.W.; Rowe, H.C.; Xiao, Y.; Chehab, E.W.; Kliebenstein, D.J.; Wagner, D.; Dehesh, K. The Chromatin Remodeler SPLAYED Regulates Specific Stress Signaling Pathways. *PLoS Pathog.* **2008**, *4*, e1000237. [CrossRef]
30. You, Y.; Zhai, Q.; An, C.; Li, C. Leunig_homolog Mediates MYC2-Dependent Transcriptional Activation in Cooperation with the Coactivators HAC1 and MED25. *Plant Cell* **2019**, *31*, 2187–2205. [CrossRef]
31. Zhai, Q.; Li, C. The Plant Mediator Complex and Its Role in Jasmonate Signaling. *J. Exp. Bot.* **2019**, *70*, 3415–3424. [CrossRef]
32. Zhai, Q.; Deng, L.; Li, C. Mediator Subunit MED25: At the Nexus of Jasmonate Signaling. *Curr. Opin. Plant Biol.* **2020**, *57*, 78–86. [CrossRef] [PubMed]
33. Wasternack, C. Termination in Jasmonate Signaling by MYC2 and MTBs. *Trends Plant Sci.* **2019**, *24*, 667–669. [CrossRef] [PubMed]

34. Liu, Y.; Du, M.; Deng, L.; Shen, J.; Fang, M.; Chen, Q.; Lu, Y.; Wang, Q.; Li, C.; Zhai, Q. Myc2 Regulates the Termination of Jasmonate Signaling via an Autoregulatory Negative Feedback Loop. *Plant Cell* **2019**, *31*, 106–127. [CrossRef]
35. Aleman, F.; Yazaki, J.; Lee, M.; Takahashi, Y.; Kim, A.Y.; Li, Z.; Kinoshita, T.; Ecker, J.R.; Schroeder, J.I. An ABA-Increased Interaction of the PYL6 ABA Receptor with MYC2 Transcription Factor: A Putative Link of ABA and JA Signaling. *Sci. Rep.* **2016**, *6*, 28941. [CrossRef] [PubMed]
36. Zhu, Z.; An, F.; Feng, Y.; Li, P.; Xue, L.; Mu, A.; Jiang, Z.; Kim, J. Derepression of Ethylene-Stabilized Transcription Factors (EIN3/EIL1) Mediates Jasmonate and Ethylene Signaling Synergy in Arabidopsis. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 12539–12544. [CrossRef]
37. Hou, X.; Lee, L.Y.C.; Xia, K.; Yan, Y.; Yu, H. DELLAs Modulate Jasmonate Signaling via Competitive Binding to JAZs. *Dev. Cell* **2010**, *19*, 884–894. [CrossRef]
38. Bari, R.; Jones, J.D.G. Role of Plant Hormones in Plant Defence Responses. *Plant Mol. Biol.* **2009**, *69*, 473–488. [CrossRef]
39. Spoel, S.H.; Koornneef, A.; Claessens, S.M.C.; Korzelius, J.P.; Van Pelt, J.A.; Mueller, M.J.; Buchala, A.J.; Métraux, J.P.; Brown, R.; Kazan, K.; et al. NPR1 Modulates Cross-Talk between Salicylate- and Jasmonate-Dependent Defense Pathways through a Novel Function in the Cytosol. *Plant Cell* **2003**, *15*, 760–770. [CrossRef]
40. Nomoto, M.; Skelly, M.J.; Itaya, T.; Mori, T.; Suzuki, T.; Matsushita, T.; Tokizawa, M.; Kuwata, K.; Mori, H.; Yamamoto, Y.Y.; et al. Suppression of MYC Transcription Activators by the Immune Cofactor NPR1 Fine-Tunes Plant Immune Responses. *Cell Rep.* **2021**, *37*, 110125. [CrossRef]
41. Luo, F.; Zhang, Q.; Xin, H.; Liu, H.; Yang, H.; Doblin, M.S.; Bacic, A.; Li, L. A Phytochrome B-PIF4-MYC2/MYC4 Module Inhibits Secondary Cell Wall Thickening in Response to Shaded Light. *Plant Commun.* **2022**, *3*, 100416. [CrossRef]
42. Gangappa, S.N.; Prasad, V.B.R.; Chattopadhyay, S. Functional Interconnection of MYC2 and SPA1 in the Photomorphogenic Seedling Development of Arabidopsis. *Plant Physiol.* **2010**, *154*, 1210–1219. [CrossRef] [PubMed]
43. Gangappa, S.N.; Chattopadhyay, S. MYC2, a BHLH Transcription Factor, Modulates the Adult Phenotype of SPA1. *Plant Signal. Behav.* **2010**, *5*, 1650–1652. [CrossRef] [PubMed]
44. Bhardwaj, V.; Meier, S.; Petersen, L.N.; Ingle, R.A.; Roden, L.C. Defence Responses of Arabidopsis Thaliana to Infection by Pseudomonas Syringae Are Regulated by the Circadian Clock. *PLoS ONE* **2011**, *6*, e26968. [CrossRef] [PubMed]
45. Srivastava, M.; Srivastava, A.K.; Roy, D.; Mansi, M.; Gough, C.; Bhagat, P.K.; Zhang, C.; Sadanandom, A. The Conjugation of SUMO to the Transcription Factor MYC2 Functions in Blue Light-Mediated Seedling Development in Arabidopsis. *Plant Cell* **2022**, *34*, 2892–2906. [CrossRef]
46. Chico, J.M.; Lechner, E.; Fernandez-Barbero, G.; Canibano, E.; García-Casado, G.; Franco-Zorrilla, J.M.; Hammann, P.; Zamarreño, A.M.; García-Mina, J.M.; Rubio, V.; et al. CUL3BPM E3 Ubiquitin Ligases Regulate MYC2, MYC3, and MYC4 Stability and JA Responses. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 6205–6215. [CrossRef] [PubMed]
47. Pesch, M.; Schultheiß, I.; Digiuni, S.; Uhrig, J.F.; Hülskamp, M. Mutual Control of Intracellular Localisation of the Patterning Proteins AtMYC1, GL1 and TRY/CPC in Arabidopsis. *Development* **2013**, *140*, 3456–3467. [CrossRef]
48. Zhao, H.; Wang, X.; Zhu, D.; Cui, S.; Li, X.; Cao, Y.; Ma, L. A Single Amino Acid Substitution in IIIf Subfamily of Basic Helix-Loop-Helix Transcription Factor AtMYC1 Leads to Trichome and Root Hair Patterning Defects by Abolishing Its Interaction with Partner Proteins in Arabidopsis. *J. Biol. Chem.* **2012**, *287*, 14109–14121. [CrossRef]
49. Symonds, V.V.; Hatlestad, G.; Lloyd, A.M. Natural Allelic Variation Defines a Role for ATMYC1: Trichome Cell Fate Determination. *PLoS Genet.* **2011**, *7*, e1002069. [CrossRef]
50. Clay, N.K.; Adio, A.M.; Denoux, C.; Jander, G.; Ausubel, M. Glucosinola Required Fo Innate Immune Response. *Science* **2016**, *323*, 95–101. [CrossRef]
51. Rajniak, J.; Barco, B.; Clay, N.K.; Sattely, E.S. A New Cyanogenic Metabolite in Arabidopsis Required for Inducible Pathogen Defence. *Nature* **2015**, *525*, 376–379. [CrossRef]
52. Andreou, A.; Feussner, I. Lipoxygenases—Structure and Reaction Mechanism. *Phytochemistry* **2009**, *70*, 1504–1510. [CrossRef] [PubMed]
53. Wasternack, C.; Song, S. Jasmonates: Biosynthesis, Metabolism, and Signaling by Proteins Activating and Repressing Transcription. *J. Exp. Bot.* **2017**, *68*, 1303–1321. [CrossRef]
54. Lee, D.S.; Nioche, P.; Hamberg, M.; Raman, C.S. Structural Insights into the Evolutionary Paths of Oxylipin Biosynthetic Enzymes. *Nature* **2008**, *455*, 363–368. [CrossRef] [PubMed]
55. Stintzi, A.; Browse, J. The Arabidopsis Male-Sterile Mutant, Opr3, Lacks the 12-Oxophytodienoic Acid Reductase Required for Jasmonate Synthesis. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 10625–10630. [CrossRef]
56. Staswick, P.E.; Tiryaki, I. The Oxylipin Signal Jasmonic Acid Is Activated by an Enzyme That Conjugate It to Isoleucine in Arabidopsis W inside Box Sign. *Plant Cell* **2004**, *16*, 2117–2127. [CrossRef] [PubMed]
57. Zamioudis, C.; Pieterse, C.M.J. Modulation of Host Immunity by Beneficial Microbes. *Mol. Plant-Microbe Interact.* **2012**, *25*, 139–150. [CrossRef] [PubMed]
58. Wang, D.D.; Li, P.; Chen, Q.Y.; Chen, X.Y.; Yan, Z.W.; Wang, M.Y.; Mao, Y.B. Differential Contributions of MYCs to Insect Defense Reveals Flavonoids Alleviating Growth Inhibition Caused by Wounding in Arabidopsis. *Front. Plant Sci.* **2021**, *12*, 700555. [CrossRef]
59. Zhao, P.; Zhang, X.; Gong, Y.; Wang, D.; Xu, D.; Wang, N.; Sun, Y.; Gao, L.; Liu, S.S.; Deng, X.W.; et al. Red-Light Is an Environmental Effector for Mutualism between Begomovirus and Its Vector Whitefly. *PLoS Pathog.* **2021**, *17*, e1008770. [CrossRef]

60. Hichri, I.; Heppel, S.C.; Pillet, J.; Léon, C.; Czemmel, S.; Delrot, S.; Lauvergeat, V.; Bogs, J. The Basic Helix-Loop-Helix Transcription Factor MYC1 Is Involved in the Regulation of the Flavonoid Biosynthesis Pathway in Grapevine. *Mol. Plant* **2010**, *3*, 509–523. [CrossRef]
61. Xu, X.; Fang, P.; Zhang, H.; Chi, C.; Song, L.; Xia, X.; Shi, K.; Zhou, Y.; Zhou, J.; Yu, J. Strigolactones Positively Regulate Defense against Root-Knot Nematodes in Tomato. *J. Exp. Bot.* **2019**, *70*, 1325–1337. [CrossRef]
62. Zhang, X.; Peng, H.; Zhu, S.; Xing, J.; Li, X.; Zhu, Z.; Zheng, J.; Wang, L.; Wang, B.; Chen, J.; et al. Nematode-Encoded RALF Peptide Mimics Facilitate Parasitism of Plants through the FERONIA Receptor Kinase. *Mol. Plant* **2020**, *13*, 1434–1454. [CrossRef] [PubMed]
63. Xu, J.; Wang, X.; Zu, H.; Zeng, X.; Baldwin, I.T.; Lou, Y.; Li, R. Molecular Dissection of Rice Phytohormone Signaling Involved in Resistance to a Piercing-Sucking Herbivore. *New Phytol.* **2021**, *230*, 1639–1652. [CrossRef] [PubMed]
64. Swinnen, G.; De Meyer, M.; Pollier, J.; Molina-Hidalgo, F.J.; Ceulemans, E.; Venegas-Molina, J.; De Milde, L.; Fernández-Calvo, P.; Ron, M.; Pauwels, L.; et al. The Basic Helix–Loop–Helix Transcription Factors MYC1 and MYC2 Have a Dual Role in the Regulation of Constitutive and Stress-Inducible Specialized Metabolism in Tomato. *New Phytol.* **2022**, *236*, 911–928. [CrossRef]
65. Panda, S.; Jozwiak, A.; Sonawane, P.D.; Szymanski, J.; Kazachkova, Y.; Vainer, A.; Kilambi, H.V.; Almekias-Siegl, E.; Dikaya, V.; Bocobza, S.; et al. Steroidal Alkaloids Defence Metabolism and Plant Growth Are Modulated by the Joint Action of Gibberellin and Jasmonate Signalling. *New Phytol.* **2022**, *233*, 1220–1237. [CrossRef] [PubMed]
66. Fujikawa, I.; Takehara, Y.; Ota, M.; Imada, K.; Sasaki, K.; Kajihara, H.; Sakai, S.; Jogaiah, S.; Ito, S.-i. Magnesium Oxide Induces Immunity against Fusarium Wilt by Triggering the Jasmonic Acid Signaling Pathway in Tomato. *J. Biotechnol.* **2021**, *325*, 100–108. [CrossRef] [PubMed]
67. Uji, Y.; Taniguchi, S.; Tamaoki, D.; Shishido, H.; Akimitsu, K.; Gomi, K. Overexpression of OsMYC2 Results in the Up-Regulation of Early JA-Rresponsive Genes and Bacterial Blight Resistance in Rice. *Plant Cell Physiol.* **2016**, *57*, 1814–1827. [CrossRef]
68. Song, S.; Huang, H.; Gao, H.; Wang, J.; Wu, D.; Liu, X.; Yang, S.; Zhai, Q.; Li, C.; Qi, T.; et al. Interaction between MYC2 and ETHYLENE INSENSITIVE3 Modulates Antagonism between Jasmonate and Ethylene Signaling in Arabidopsis. *Plant Cell* **2014**, *26*, 263–279. [CrossRef]
69. Woldemariam, M.G.; Baldwin, I.T.; Galis, I. Transcriptional Regulation of Plant Inducible Defenses against Herbivores: A Mini-Review. *J. Plant Interact.* **2011**, *6*, 113–119. [CrossRef]
70. Gautam, J.K.; Giri, M.K.; Singh, D.; Chattopadhyay, S.; Nandi, A.K. MYC2 Influences Salicylic Acid Biosynthesis and Defense against Bacterial Pathogens in Arabidopsis Thaliana. *Physiol. Plant.* **2021**, *173*, 2248–2261. [CrossRef]
71. van Moerkercke, A.; Duncan, O.; Zander, M.; Simura, J.; Broda, M.; Bossche, R.V.; Lewsey, M.G.; Lama, S.; Singh, K.B.; Ljung, K.; et al. A MYC2/MYC3/MYC4-Dependent Transcription Factor Network Regulates Water Spray-Responsive Gene Expression and Jasmonate Levels. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 23345–23356. [CrossRef]
72. Wei, X.; Mao, L.; Wei, X.; Xia, M.; Xu, C. MYB41, MYB107, and MYC2 Promote ABA-Mediated Primary Fatty Alcohol Accumulation via Activation of AchnFAR in Wound Suberization in Kiwifruit. *Hortic. Res.* **2020**, *7*, 86. [CrossRef] [PubMed]
73. Abe, H.; Urao, T.; Ito, T.; Seki, M.; Shinozaki, K.; Yamaguchi-Shinozaki, K. Arabidopsis AtMYC2 (BHLH) and AtMYB2 (MYB) Function as Transcriptional Activators in Abscisic Acid Signaling. *Plant Cell* **2003**, *15*, 63–78. [CrossRef] [PubMed]
74. Lahiri, A.; Zhou, L.; He, P.; Datta, A. Detecting Drought Regulators Using Stochastic Inference in Bayesian Networks. *PLoS ONE* **2021**, *16*, e0255486. [CrossRef]
75. Liu, H.; Cui, P.; Zhang, B.; Zhu, J.; Liu, C.; Li, Q. Binding of the Transcription Factor MYC2-like to the ABRE of the OsCYP2 Promoter Enhances Salt Tolerance in Oryza Sativa. *PLoS ONE* **2022**, *17*, e0276075. [CrossRef]
76. Kashyap, P.; Deswal, R. Two ICE Isoforms Showing Differential Transcriptional Regulation by Cold and Hormones Participate in Brassica Juncea Cold Stress Signaling. *Gene* **2019**, *695*, 32–41. [CrossRef]
77. Li, Y.; Yang, X.; Li, X. Role of Jasmonate Signaling Pathway in Resistance to Dehydration Stress in Arabidopsis. *Acta Physiol. Plant.* **2019**, *41*, 100. [CrossRef]
78. Wang, Y.; Xu, H.; Liu, W.; Wang, N.; Qu, C.; Jiang, S.; Fang, H.; Zhang, Z.; Chen, X. Methyl Jasmonate Enhances Apple' Cold Tolerance through the JAZ–MYC2 Pathway. *Plant Cell Tissue Organ Cult.* **2019**, *136*, 75–84. [CrossRef]
79. Ming, R.; Zhang, Y.; Wang, Y.; Khan, M.; Dahro, B.; Liu, J.H. The JA-Responsive MYC2-BADH-like Transcriptional Regulatory Module in Poncirus Trifoliata Contributes to Cold Tolerance by Modulation of Glycine Betaine Biosynthesis. *New Phytol.* **2021**, *229*, 2730–2750. [CrossRef]
80. Tiwari, S.; Prasad, V.; Chauhan, P.S.; Lata, C. Bacillus Amyloliquefaciens Confers Tolerance to Various Abiotic Stresses and Modulates Plant Response to Phytohormones through Osmoprotection and Gene Expression Regulation in Rice. *Front. Plant Sci.* **2017**, *8*, 1510. [CrossRef]
81. Huang, C.F.; Yu, C.P.; Wu, Y.H.; Lu, M.Y.J.; Tu, S.L.; Wu, S.H.; Shiu, S.H.; Ku, M.S.B.; Li, W.H. Elevated Auxin Biosynthesis and Transport Underlie High Vein Density in C4 Leaves. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E6884–E6891. [CrossRef]
82. Zhuo, M.; Sakuraba, Y.; Yanagisawa, S. A Jasmonate-Activated MYC2-Dof2.1-MYC2 Transcriptional Loop Promotes Leaf Senescence in Arabidopsis. *Plant Cell* **2020**, *32*, 242–262. [CrossRef] [PubMed]
83. Zhang, Y.; Ji, T.T.; Li, T.T.; Tian, Y.Y.; Wang, L.F.; Liu, W.C. Jasmonic Acid Promotes Leaf Senescence through MYC2-Mediated Repression of CATALASE2 Expression in Arabidopsis. *Plant Sci.* **2020**, *299*, 110604. [CrossRef] [PubMed]
84. Qi, T.; Wang, J.; Huang, H.; Liu, B.; Gao, H.; Liu, Y.; Song, S.; Xie, D. Regulation of Jasmonate-Induced Leaf Senescence by Antagonism between BHLH Subgroup IIIe and IIId Factors in Arabidopsis. *Plant Cell* **2015**, *27*, 1634–1649. [CrossRef] [PubMed]

85. Zhang, Z.; Xu, M.; Guo, Y. Ring/U-Box Protein AtUSR1 Functions in Promoting Leaf Senescence Through JA Signaling Pathway in Arabidopsis. *Front. Plant Sci.* **2020**, *11*, 608589. [CrossRef]
86. Lee, B.R.; Zaman, R.; La, V.H.; Bae, D.W.; Kim, T.H. Ethephon-Induced Ethylene Enhances Starch Degradation and Sucrose Transport with an Interactive Abscisic Acid-Mediated Manner in Mature Leaves of Oilseed Rape (*Brassica Napus* L.). *Plants* **2021**, *10*, 1670. [CrossRef]
87. Ding, F.; Wang, C.; Xu, N.; Zhang, S.; Wang, M. SlMYC2 Mediates Jasmonate-Induced Tomato Leaf Senescence by Promoting Chlorophyll Degradation and Repressing Carbon Fixation. *Plant Physiol. Biochem.* **2022**, *180*, 27–34. [CrossRef]
88. Chen, Q.; Sun, J.; Zhai, Q.; Zhou, W.; Qi, L.; Xu, L.; Wang, B.; Chen, R.; Jiang, H.; Qi, J.; et al. The Basic Helix-Loop-Helix Transcription Factor Myc2 Directly Represses Plethora Expression during Jasmonate-Mediated Modulation of the Root Stem Cell Niche in Arabidopsis. *Plant Cell* **2011**, *23*, 3335–3352. [CrossRef]
89. Marhava, P.; Hoermayer, L.; Yoshida, S.; Marhavý, P.; Benková, E.; Friml, J. Re-Activation of Stem Cell Pathways for Pattern Restoration in Plant Wound Healing. *Cell* **2019**, *177*, 957–969.e13. [CrossRef]
90. Cui, Y.; Chen, C.L.; Cui, M.; Zhou, W.J.; Wu, H.L.; Ling, H.Q. Four IVa BHLH Transcription Factors Are Novel Interactors of FIT and Mediate JA Inhibition of Iron Uptake in Arabidopsis. *Mol. Plant* **2018**, *11*, 1166–1183. [CrossRef]
91. Xing, J.; Cao, X.; Zhang, M.; Wei, X.; Zhang, J. Plant Nitrogen Availability and Crosstalk with Phytohormones Signalings and Their Biotechnology Breeding Application in Crops. *Plant Biotechnol.* **2022**, *12*, 27. [CrossRef]
92. Wang, P.; Xu, X.; Tang, Z.; Zhang, W.; Huang, X.Y.; Zhao, F.J. Oswrky28 Regulates Phosphate and Arsenate Accumulation, Root System Architecture and Fertility in Rice. *Front. Plant Sci.* **2018**, *9*, 1330. [CrossRef] [PubMed]
93. Shigeyama, T.; Tominaga, A.; Arima, S.; Sakai, T.; Inada, S.; Jikumaru, Y.; Kamiya, Y.; Uchiumi, T.; Abe, M.; Hashiguchi, M.; et al. Additional Cause for Reduced JA-Ile in the Root of a Lotus Japonicus PhyB Mutant. *Plant Signal. Behav.* **2012**, *7*, 746–748. [CrossRef]
94. Li, T.; Xu, Y.; Zhang, L.; Ji, Y.; Tan, D.; Yuan, H.; Wang, A. The Jasmonate-Activated Transcription Factor MdMYC2 Regulates ETHYLENE RESPONSE FACTOR and Ethylene Biosynthetic Genes to Promote Ethylene Biosynthesis during Apple Fruit Ripening. *Plant Cell* **2017**, *29*, 1316–1334. [CrossRef] [PubMed]
95. Hu, Y.; Sun, H.; Han, Z.; Wang, S.; Wang, T.; Li, Q.; Tian, J.; Wang, Y.; Zhang, X.; Xu, X.; et al. ERF4 Affects Fruit Ripening by Acting as a JAZ Interactor between Ethylene and Jasmonic Acid Hormone Signaling Pathways. *Hortic. Plant J.* **2022**, *8*, 689–699. [CrossRef]
96. Yan, F.; Cai, T.; Wu, Y.; Chen, S.; Chen, J. Physiological and Transcriptomics Analysis of the Effect of Recombinant Serine Protease on the Preservation of Loquat. *Genomics* **2021**, *113*, 3750–3761. [CrossRef] [PubMed]
97. Wang, Q.; Liu, Y.; Wu, X.; Wang, L.; Li, J.; Wan, M.; Jia, B.; Ye, Z.; Liu, L.; Tang, X.; et al. MYB1R1 and MYC2 Regulate ω-3 Fatty Acid Desaturase Involved in ABA-Mediated Suberization in the Russet Skin of a Mutant of 'Dangshansuli' (Pyrus Bretschneideri Rehd.). *Front. Plant Sci.* **2022**, *13*, 910938. [CrossRef]
98. Wang, H.; Zhang, S.; Qu, Y.; Gao, R.; Xiao, Y.; Wang, Z.; Zhai, R.; Yang, C.; Xu, L. Jasmonic Acid and Ethylene Participate in the Gibberellin-Induced Ovule Programmed Cell Death Process in Seedless Pear '1913' (Pyrus Hybrid). *Int. J. Mol. Sci.* **2021**, *22*, 9844. [CrossRef]
99. Baud, S.; Lepiniec, L. Regulation of de Novo Fatty Acid Synthesis in Maturing Oilseeds of Arabidopsis. *Plant Physiol. Biochem.* **2009**, *47*, 448–455. [CrossRef] [PubMed]
100. Gao, C.; Qi, S.; Liu, K.; Li, D.; Jin, C.; Li, Z.; Huang, G.; Hai, J.; Zhang, M.; Chen, M. MYC2, MYC3, and MYC4 Function Redundantly in Seed Storage Protein Accumulation in Arabidopsis. *Plant Physiol. Biochem.* **2016**, *108*, 63–70. [CrossRef] [PubMed]
101. Chen, M.; Du, X.; Zhu, Y.; Wang, Z.; Hua, S.; Li, Z.; Guo, W.; Zhang, G.; Peng, J.; Jiang, L. Seed Fatty Acid Reducer Acts Downstream of Gibberellin Signalling Pathway to Lower Seed Fatty Acid Storage in Arabidopsis. *Plant Cell Environ.* **2012**, *35*, 2155–2169. [CrossRef]
102. Cai, Q.; Yuan, Z.; Chen, M.; Yin, C.; Luo, Z.; Zhao, X.; Liang, W.; Hu, J.; Zhang, D. Jasmonic Acid Regulates Spikelet Development in Rice. *Nat. Commun.* **2014**, *5*, 3476. [CrossRef] [PubMed]
103. Bian, S.; Tian, T.; Ding, Y.; Yan, N.; Zhang, Z.; Zhang, H.; Wang, C.; Fang, N.; Liu, Y. BHLH Transcription Factor NtMYC2a Regulates Carbohydrate Metabolism during the Pollen Development of Tobacco (Nicotiana Tabacum L. Cv. TN90). *Plants* **2022**, *11*, 17. [CrossRef] [PubMed]
104. Cheng, H.; Zha, S.; Luo, Y.; Li, L.; Wang, S.; Wu, S.; Cheng, S.; Li, L. JAZ1-3 and MYC2-1 Synergistically Regulate the Transformation from Completely Mixed Flower Buds to Female Flower Buds in Castanea Mollisima. *Int. J. Mol. Sci.* **2022**, *23*, 6452. [CrossRef]
105. Huang, H.; Gao, H.; Liu, B.; Qi, T.; Tong, J.; Xiao, L.; Xie, D.; Song, S. Arabidopsis MYB24 Regulates Jasmonate-Mediated Stamen Development. *Front. Plant Sci.* **2017**, *8*, 1525. [CrossRef] [PubMed]
106. Huang, H.; Gong, Y.; Liu, B.; Wu, D.; Zhang, M.; Xie, D.; Song, S. The Della Proteins Interact with MYB21 and MYB24 to Regulate Filament Elongation in Arabidopsis. *BMC Plant Biol.* **2020**, *20*, 64. [CrossRef] [PubMed]
107. Qi, T.; Huang, H.; Song, S.; Xie, D. Regulation of Jasmonate-Mediated Stamen Development and Seed Production by a BHLH-MYB Complex in Arabidopsis. *Plant Cell* **2015**, *27*, 1620–1633. [CrossRef]
108. Chen, X.; Wang, D.D.; Fang, X.; Chen, X.Y.; Mao, Y.B. Plant Specialized Metabolism Regulated by Jasmonate Signaling. *Plant Cell Physiol.* **2019**, *60*, 2638–2647. [CrossRef]

109. Afrin, S.; Huang, J.J.; Luo, Z.Y. JA-Mediated Transcriptional Regulation of Secondary Metabolism in Medicinal Plants. *Sci. Bull.* **2015**, *60*, 1062–1072. [CrossRef]
110. Zhou, M.; Memelink, J. Jasmonate-Responsive Transcription Factors Regulating Plant Secondary Metabolism. *Biotechnol. Adv.* **2016**, *34*, 441–449. [CrossRef]
111. Zhang, M.; Jin, X.; Chen, Y.; Wei, M.; Liao, W.; Zhao, S.; Fu, C.; Yu, L. TcMYC2a, a Basic Helix–Loop–Helix Transcription Factor, Transduces JA-Signals and Regulates Taxol Biosynthesis in Taxus Chinensis. *Front. Plant Sci.* **2018**, *9*, 863. [CrossRef]
112. Yu, Z.X.; Li, J.X.; Yang, C.Q.; Hu, W.L.; Wang, L.J.; Chen, X.Y. The Jasmonate-Responsive AP2/ERF Transcription Factors AaERF1 and AaERF2 Positively Regulate Artemisinin Biosynthesis in Artemisia Annua L. *Mol. Plant* **2012**, *5*, 353–365. [CrossRef] [PubMed]
113. Shen, Q.; Huang, H.; Xie, L.; Hao, X.; Kayani, S.I.; Liu, H.; Qin, W.; Chen, T.; Pan, Q.; Liu, P.; et al. Basic Helix-Loop-Helix Transcription Factors AabHLH2 and AabHLH3 Function Antagonistically With AaMYC2 and Are Negative Regulators in Artemisinin Biosynthesis. *Front. Plant Sci.* **2022**, *13*, 885622. [CrossRef]
114. Kayani, S.I.; Shen, Q.; Ma, Y.; Fu, X.; Xie, L.; Zhong, Y.; Tiantian, C.; Pan, Q.; Li, L.; Rahman, S.U.; et al. The YABBY Family Transcription Factor AaYABBY5 Directly Targets Cytochrome P450 Monooxygenase (CYP71AV1) and Double-Bond Reductase 2 (DBR2) Involved in Artemisinin Biosynthesis in Artemisia Annua. *Front. Plant Sci.* **2019**, *10*, 1084. [CrossRef]
115. Du, T.; Niu, J.; Su, J.; Li, S.; Guo, X.; Li, L.; Cao, X.; Kang, J. SmbHLH37 Functions Antagonistically with SmMYC2 in Regulating Jasmonate-Mediated Biosynthesis of Phenolic Acids in Salvia Miltiorrhiza. *Front. Plant Sci.* **2018**, *871*, 1720. [CrossRef]
116. Zhang, H.; Hedhili, S.; Montiel, G.; Zhang, Y.; Chatel, G.; Pré, M.; Gantet, P.; Memelink, J. The Basic Helix-Loop-Helix Transcription Factor CrMYC2 Controls the Jasmonate-Responsive Expression of the ORCA Genes That Regulate Alkaloid Biosynthesis in Catharanthus Roseus. *Plant J.* **2011**, *67*, 61–71. [CrossRef] [PubMed]
117. Sunilkumar, G.; Campbell, L.A.M.; Puckhaber, L.; Stipanovic, R.D.; Rathore, K.S. Engineering Cottonseed for Use in Human Nutrition by Tissue-Specific Reduction of Toxic Gossypol. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 18054–18059. [CrossRef]
118. Han, X.; Xing, Y.; Zhu, Y.; Luo, L.; Liu, L.; Zhai, Y.; Wang, W.; Shao, R.; Ren, M.; Li, F.; et al. GhMYC2 Activates Cytochrome P450 Gene CYP71BE79 to Regulate Gossypol Biosynthesis in Cotton. *Planta* **2022**, *256*, 63. [CrossRef]
119. Huo, Y.; Zhang, J.; Zhang, B.; Chen, L.; Zhang, X.; Zhu, C. Myc2 Transcription Factors Twmyc2a and Twmyc2b Negatively Regulate Triptolide Biosynthesis in Tripterygium Wilfordii Hairy Roots. *Plants* **2021**, *10*, 679. [CrossRef]
120. Ribeiro, B.; Lacchini, E.; Bicalho, K.U.; Mertens, J.; Arendt, P.; Bossche, R.V.; Calegario, G.; Gryffroy, L.; Ceulemans, E.; Buitink, J.; et al. A Seed-Specific Regulator of Triterpene Saponin Biosynthesis in Medicago Truncatula. *Plant Cell* **2020**, *32*, 2020–2042. [CrossRef]
121. Zhai, J.; Hao, H.; Xiao, H.; Cao, Y.; Lin, X.; Huang, X. Identification of JAZ-Interacting MYC Transcription Factors Involved in Latex Drainage in Hevea Brasiliensis. *Sci. Rep.* **2018**, *8*, 909. [CrossRef]
122. Guo, D.; Li, H.L.; Wang, Y.; Zhu, J.H.; Peng, S.Q. A Myelocytomatosis Transcription Factor from Hevea Brasiliensis Positively Regulates the Expression of the Small Rubber Particle Protein Gene. *Ind. Crops Prod.* **2019**, *133*, 90–97. [CrossRef]
123. Ke, J.; Wang, B.; Yoshikuni, Y. Microbiome Engineering: Synthetic Biology of Plant-Associated Microbiomes in Sustainable Agriculture. *Trends Biotechnol.* **2021**, *39*, 244–261. [CrossRef] [PubMed]
124. Petzold, C.J.; Chan, L.J.G.; Nhan, M.; Adams, P.D. Analytics for Metabolic Engineering. *Front. Bioeng. Biotechnol.* **2015**, *3*, 135. [CrossRef] [PubMed]
125. Garner, K.L. Principles of Synthetic Biology. *Essays Biochem.* **2021**, *65*, 791–811. [CrossRef] [PubMed]
126. Liu, X.; Zhang, P.; Zhao, Q.; Huang, A.C. Making Small Molecules in Plants: A Chassis for Synthetic Biology-based Production of Plant Natural Products. *J. Integr. Plant Biol.* **2022**, *4*, 29. [CrossRef]
127. Yang, Y.; Alexander, T.; Ahkami, A.H.; Neal, C.; Stewart, C.N., Jr.; Blumwald, E. Plant Synthetic Biology Innovations for Biofuels and Bioproducts. *Trends in Biotech.* **2022**, *40*, 1454–1468. [CrossRef]
128. Belcher, M.S.; Vuu, K.M.; Zhou, A.; Mansoori, N.; Ramos, A.A.; Thompson, M.G.; Scheller, H.V.; Loqué, D.; Shih, P.M. Design of Orthogonal Regulatory Systems for Modulating Gene Expression in Plants. *Nat. Chem. Biol.* **2020**, *16*, 857–865. [CrossRef]
129. Boehm, C.R.; Bock, R. Recent Advances and Current Challenges in Synthetic Biology of the Plastid Genetic System and Metabolism. *Plant Physiol.* **2019**, *179*, 794–802. [CrossRef]
130. Chae, L.; Kim, T.; Nilo-poyanco, R.; Rhee, S.Y.; Science, S.; Series, N.; May, N.; Chae, L.; Kim, T.; Nilo-poyanco, R.; et al. Genomic Signatures of of Specialized Metabolism in Plants. *Science* **2014**, *344*, 510–513. [CrossRef]
131. Drábková, L.Z.; Dobrev, P.I.; Motyka, V. Phytohormone Profiling across the Bryophytes. *PLoS ONE* **2015**, *10*, e0125411. [CrossRef]
132. Abdala, G.; Miersch, O.; Correa, N.; Rosas, S. Detection of Jasmonic Acid in Cultures of Escherichia Coli and Saccharomyces Cerevisiae. *Nat. Prod. Lett.* **1999**, *14*, 55–63. [CrossRef]
133. Hu, Y.J.; Gu, C.C.; Wang, X.F.; Min, L.; Li, C.C. Asymmetric Total Synthesis of Taxol. *J. Am. Chem. Soc.* **2021**, *143*, 17862–17870. [CrossRef] [PubMed]
134. Nielsen, A.A.K.; Der, B.S.; Shin, J.; Vaidyanathan, P.; Paralanov, V.; Strychalski, E.A.; Ross, D.; Densmore, D.; Voigt, C.A. Genetic Circuit Design Automation. *Science* **2016**, *352*, aac7341. [CrossRef]
135. Zhang, J.; Hansen, L.G.; Gudich, O.; Viehrig, K.; Lassen, L.M.M.; Schrübbers, L.; Adhikari, K.B.; Rubaszka, P.; Carrasquer-Alvarez, E.; Chen, L.; et al. A Microbial Supply Chain for Production of the Anti-Cancer Drug Vinblastine. *Nature* **2022**, *609*, 341–347. [CrossRef]

136. Ro, D.K.; Paradise, E.M.; Quellet, M.; Fisher, K.J.; Newman, K.L.; Ndungu, J.M.; Ho, K.A.; Eachus, R.A.; Ham, T.S.; Kirby, J.; et al. Production of the Antimalarial Drug Precursor Artemisinic Acid in Engineered Yeast. *Nature* **2006**, *440*, 940–943. [CrossRef]
137. Xiong, X.; Gou, J.; Liao, Q.; Li, Y.; Zhou, Q.; Bi, G.; Li, C.; Du, R.; Wang, X.; Sun, T.; et al. The Taxus Genome Provides Insights into Paclitaxel Biosynthesis. *Nat. Plants* **2021**, *7*, 1026–1036. [CrossRef] [PubMed]
138. Li, J.; Mutanda, I.; Wang, K.; Yang, L.; Wang, J.; Wang, Y. Chloroplastic Metabolic Engineering Coupled with Isoprenoid Pool Enhancement for Committed Taxanes Biosynthesis in Nicotiana Benthamiana. *Nat. Commun.* **2019**, *10*, 4850. [CrossRef]
139. Zhou, K.; Qiao, K.; Edgar, S.; Stephanopoulos, G. Distributing a Metabolic Pathway among a Microbial Consortium Enhances Production of Natural Products. *Nat. Biotechnol.* **2015**, *33*, 377–383. [CrossRef]
140. Zhu, Q.; Yu, S.; Zeng, D.; Liu, H.; Wang, H.; Yang, Z.; Xie, X.; Shen, R.; Tan, J.; Li, H.; et al. Development of "Purple Endosperm Rice" by Engineering Anthocyanin Biosynthesis in the Endosperm with a High-Efficiency Transgene Stacking System. *Mol. Plant* **2017**, *10*, 918–929. [CrossRef]
141. Han, Y.J.; Kim, Y.M.; Lee, J.Y.; Kim, S.J.; Cho, K.C.; Chandrasekhar, T.; Song, P.S.; Woo, Y.M.; Kim, J.-I. Production of Purple-Colored Creeping Bentgrass Using Maize Transcription Factor Genes Pl and Lc through Agrobacterium-Mediated Transformation. *Plant Cell Rep.* **2009**, *28*, 397–406. [CrossRef]
142. Bovy, A.; De Vos, R.; Kemper, M.; Schijlen, E.; Pertejo, M.A.; Muir, S.; Collins, G.; Robinson, S.; Verhoeyen, M.; Hughes, S.; et al. High-Flavonol Tomatoes Resulting from the Heterologous Expression of the Maize Transcription Factor Genes LC and C1. *Plant Cell* **2002**, *14*, 2509–2526. [CrossRef] [PubMed]
143. Moses, T.; Mehrshahi, P.; Smith, A.G.; Goossens, A. Synthetic Biology Approaches for the Production of Plant Metabolites in Unicellular Organisms. *J. Exp. Bot.* **2017**, *68*, 4057–4074. [CrossRef]
144. Yao, L.; Zhang, H.; Liu, Y.; Ji, Q.; Xie, J.; Zhang, R.; Huang, L.; Mei, K.; Wang, J.; Gao, W. Engineering of Triterpene Metabolism and Overexpression of the Lignin Biosynthesis Gene PAL Promotes Ginsenoside Rg3 Accumulation in Ginseng Plant Chassis. *J. Integr. Plant Biol.* **2022**, *64*, 1739–1754. [CrossRef] [PubMed]
145. Brown, S.; Clastre, M.; Courdavault, V.; O'Connor, S.E. De Novo Production of the Plant-Derived Alkaloid Strictosidine in Yeast. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 3205–3210. [CrossRef] [PubMed]
146. van Herpen, T.W.J.M.; Cankar, K.; Nogueira, M.; Bosch, D.; Bouwmeester, H.J.; Beekwilder, J. Nicotiana Benthamiana as a Production Platform for Artemisinin Precursors. *PLoS ONE* **2010**, *5*, e14222. [CrossRef]
147. Hasan, M.M.; Kim, H.S.; Jeon, J.H.; Kim, S.H.; Moon, B.K.; Song, J.Y.; Shim, S.H.; Baek, K.H. Metabolic Engineering of Nicotiana Benthamiana for the Increased Production of Taxadiene. *Plant Cell Rep.* **2014**, *33*, 895–904. [CrossRef]
148. Miettinen, K.; Dong, L.; Navrot, N.; Schneider, T.; Burlat, V.; Pollier, J.; Woittiez, L.; Van Der Krol, S.; Lugan, R.; Ilc, T.; et al. The Seco-Iridoid Pathway from Catharanthus Roseus. *Nat. Commun.* **2014**, *5*, 3606. [CrossRef]
149. Mukherjee, A.; Sarkar, D.; Sasmal, S. A Review of Green Synthesis of Metal Nanoparticles Using Algae. *Front. Microbiol.* **2021**, *12*, 693899. [CrossRef]
150. Ramanan, R.; Kim, B.H.; Cho, D.H.; Oh, H.M.; Kim, H.S. Algae-Bacteria Interactions: Evolution, Ecology and Emerging Applications. *Biotechnol. Adv.* **2016**, *34*, 14–29. [CrossRef]
151. Wang, Q.; Gong, Y.; He, Y.; Xin, Y.; Lv, N.; Du, X.; Li, Y.; Jeong, B.-R.; Xu, J. Genome Engineering of Nannochloropsis with Hundred-Kilobase Fragment Deletions by Cas9 Cleavages. *Plant J.* **2021**, *106*, 1148–1162. [CrossRef]
152. Heiss, S.; Hörmann, A.; Tauer, C.; Sonnleitner, M.; Egger, E.; Grabherr, R.; Heinl, S. Evaluation of Novel Inducible Promoter/Repressor Systems for Recombinant Protein Expression in Lactobacillus Plantarum. *Microb. Cell Factories* **2016**, *15*, 50. [CrossRef] [PubMed]
153. Zhou, L.B.; Zeng, A.P. Engineering a Lysine-ON Riboswitch for Metabolic Control of Lysine Production in Corynebacterium Glutamicum. *ACS Synth. Biol.* **2015**, *4*, 1335–1340. [CrossRef] [PubMed]
154. Gossen, M.; Bujardt, H. Tight Control of Gene Expression in Mammalian Cells by Tetracycline-Responsive Promoters Author (s): Manfred Gossen and Hermann Bujard Source: Proceedings of the National Academy of Sciences of the United States of America, Published by: National Aca. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 5547–5551.
155. Urlinger, S.; Udo, B.; Marion, T.; Mazahir, H. Exploring the Sequence Space for Tetracyline-Dependent Transcriptional Activators: Novel Mutations Yield Expanded range and Sensitivity. *Proc. Natl. Acad. Sci. USA* **2000**, *14*, 7963–7968. [CrossRef]