REVIEW

Methyl jasmonate and salicylic acid as powerful elicitors for enhancing the production of secondary metabolites in medicinal plants: an updated review

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Abstract

Plant secondary metabolites are bioactive scaffolds that are crucial for plant survival in the environment and to maintain a defense mechanism from predators. These compounds are generally present in plants at a minimal level and interestingly, they are found to have a wide variety of therapeutic values for humans. Several medicinal plants are used for pharmaceutical purposes due to their affordability, fewer adverse effects, and vital role in traditional remedies. Owing to this reason, these plants are exploited at a high range worldwide and therefore many medicinal plants are on the threatened list. There is a need of the hour to tackle this major problem, one effective approach called elicitation can be used to enhance the level of existing and novel plant bioactive compounds using different types of elicitors namely biotic and abiotic. This process can be generally achieved by *in vitro* and *in vivo* experiments. The current comprehensive review provides an overview of biotic and abiotic elicitation strategies used in medicinal plants, as well as their effects on secondary metabolites enhancement. Further, this review mainly deals with the enhancement of biomass and biosynthesis of different bioactive compounds by methyl jasmonate (MeJA) and salicylic acid (SA) as elicitors of wide medicinal plants in *in vitro* by using different cultures. The present review was suggested as a significant groundwork for peers working with medicinal plants by applying elicitation strategies along with advanced biotechnological approaches.

Keywords Elicitors · Medicinal plants · Salicylic acid · Methyl jasmonate · Bioactive compounds

Introduction

Secondary metabolites (SMs) are bioactive compounds that play a crucial role in plant cross-talks with the environment for adaptation and defense mechanisms but do not have a fundamental role in maintaining the life cycle processes.

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Higher plants produce a spectrum of SMs from primary metabolites that aid in plant defense against insects, herbivores, pests, phytopathogens, etc. (Jain et al. 2019). Medicinal plants are the primary source of bioactive molecules, with many novel drugs and also components produced directly or indirectly. Based on the WHO reports, approximately 80% of the world's population relies on traditional medicines notably medicinal plant-based drugs and formulations for their primary healthcare needs (Kumari and Kotecha 2016). These pharmaceutically important chemicals are produced in trace amounts and are dependent on the plant's developmental and physiological state (Twaij and Hasan 2022). Owing to the higher usage of medicinal plants for curative purposes across the world, increasing market demand leads to over-exploitation of these plants makes them threatened. Due to these reasons, it is critical to identify alternate methods for producing SMs to meet the huge market demand. For the enhanced production of therapeutic metabolites,

different biotechnological approaches are used, but elicitation is a mechanistic approach and strong arm for increasing biomass and pharmacologically active phytocompounds production during field cultivation (Halder et al. 2019; Kandoudi et al. 2021). Elicitation is one of the effective biotechnological approaches for inducing novel SMs biosynthesis, and enhancement of biomass as well as the gathering of SMs in *in vitro* cultures of plants (Wang and Wu, 2013). When plants are exposed to elicitors, signaling molecules specifically bind to the receptors, that urged and they frequently produce a variety of SMs. Elicitors are biotic or abiotic substances that belong to numerous chemical classes and can stimulate or enhance the target SMs biosynthesis (Ghorbanpour et al. 2014). Elicitors also play a pivotal role in plant growth and development as well as in signal transduction. In addition, elicitors signaling mechnisms have a significant impact on bioactivities, mitigation of environmental stress, plant survivability and productivity (Jan et al. 2021). Several phytohormones (Sabagh et al. 2022), transcription factors (TFs) (Zheng et al. 2023) and enzymes (Rajput et al. 2021) associated with various biological pathways, cell compartmentalization and ion exchange play a major role in the development of a signal transduction network. Furthermore, several TFs such as MYB, WRKY, bHLH and AP2/ERF are actively involved in hormonal signaling pathways to enhance the pharamaceutically active phytocompounds in various medicinal plants (Jan et al. 2021; Zheng et al. 2023). During the elicitation process, there are some types of parameters such as concentration, time exposure, elicitor type, and cell culture type that decide the accumulation and enhanced synthesis of metabolite production in plants (Dhiman et al. 2018). Several reports have revealed that the elicitation process increased the biosynthesis of targeted/specific plant-associated SMs in the hairy root and cell suspension cultures, providing a new channel for the pharmaceutical industry to produce a mass of SMs in the future (Srivastava et al. 2017; Singh et al. 2018a, b). To the best of our knowledge, this baseline review sheds the light on potential biotic and abiotic elicitation strategies for medicinal plants and their positive impact on pharmaceutically active and novel SMs production. In addition, this review also aids the scientists and researchers in understanding the novel and important aspects of elicitation to harness the active ingredients of medicinal plants.

Elicitation is a key tool to ameliorate the active metabolites

The defense system of medicinal plants produces chemical substances to combat infections caused by external and internal stresses that can be used to elevate the level of these substances, which are known as SMs. Many biotechnological approaches are considered in *in vitro* cultures for up gradation or to enhance the production of such essential phytochemicals (Danova and Pistelli 2022; Jakovljevic et al. 2022). The elicitation process is to change the metabolic pathways of medicinal plants to stimulate bioactive compounds through *in vitro* plant cultures. This method can be used to produce economically viable SMs on a large spectrum level. Elicitors act as a signaling molecule and these signals identified by the plant cellular membrane-bound receptors and activation of the signal transduction pathways and change the expression of regulatory players and resulting in enhanced synthesis and accumulation of phytocompounds (Zhai et al. 2017; Miladinova-Georgieva et al. 2023). Employing *in vitro* cell culture as a model system, it may also be used to characterize and investigate the impact of various elicitors on plants.

Mechanism of elicitation in plants

Elicitors are associated with a broad range of different categories of compound scaffolds and biochemical pathways and it is stimulating the enhanced production of novel metabolites in some plants that may be inactive in certain plant species. In contrast, specific elicitors can bind with specific plant membrane receptors. Therefore, this implies that elicitor specificity exists concerning the signal molecules that are triggered by elicitation and the plant has the tendency to recognize certain structurally diverse compounds as signaling molecules (Abdul Malik et al. 2020). Elicitors are recognized by plant cells by interacting with specific receptors on the plasma membranes of plants and these interactions are initiated to generate signals. Those identified signal molecules include chitosan, physical signals, abscisic acid, and systemin. The mechanism of elicitors varies with regard to their origins, specificity in terms of nutrition and concentration, physiochemical environment, and plant development (Meena et al. 2022). The first stage of the elicitor signal transduction cascade is the signal perception, which occurs through a series of events such as the activation of kinases, reactive oxygen species (ROS) burst, ion fluxes NADPH oxidase activation, and cytoplasm acidification followed by nuclear genes activation (Bajwa et al. 2021). Different mechanisms were speculated to describe the biochemical processes that occur in the plant cells when challenged by the elicitor. Apostol et al. (1989) showed that high levels of ROS accumulation in plant tissues occurred through oxidative bursts triggered by elicitor treatment. During the process of elicitation, elicitors can accumulate defense and pathogenesis proteins including endo-polygalacturonases (involved in the pectic oligomers

release), chitinases, glycoproteins, and protease inhibitors (Benhamou 1996). A series of events activated by the elicitor is listed as follows:

- The plant cell receptor perceives the specific signaling molecule (elicitor), which leads to the activation of complex reactions such as membrane depolarization, reversible phosphorylation of plasma membrane proteins, Cl^- and K^+ efflux/H^+ influx, cytosolic $[Ca2^+]$ concentration changes (Gelli et al. 1997), ion fluxes increased (Armero and Tena 2001), NADPH oxidase activation, mitogen-activated protein kinase (MAPK) activation, and ROS and reactive nitrogen species (RNS) production.
- Ion influx is a potential event that involves the plant cell physiological processes (Ward et al. 2009). The Ca^{2+} signals result in conformational changes in a number of ion binding proteins including calcium- dependent protein kinases (CDPKs) calmodulin, calmodulin-like proteins and secondary messengers such as inositol 1,4,5- triphosphate IP3 and diacylglycerol (DAG) (White and Broadley 2003).
- Owing to the aforementioned, these binding proteins activates the protein kinase cascades, which leads to the dynamisms in MAPK phosphorylation and it also activate the hormonal signaling pathway messengers such as SA and MeJA.

- As a result, activation of transcription and translation of defense-responsive genes/enzymes, which in turn

synthetic pathways of SMs production (Ebel and Scheel 1992). The mode of action of the elicitation process is illustrated in Fig. 1.

Extensive research has been conducted to the mode of action of the potential elicitors in plant biotechnology. Even though in some instances the secondary messengers, receptors, responsive proteins and transduction pathway have been identified, the data is generally inadequate. Furthermore, the unpredictability of this mode of action leads to various metabolic processes. As a result, most research related to the improving impact of elicitation on phytocompounds accumulation in plant tissue cultures was empirical without examining the cellular process at a molecular level.

SMs production by abiotic and biotic elicitors

Plants contain different types of SMs such as phenolics, terpenes or terpenoids, and N-containing compounds. Each of these classes has thousands of SMs (Twaij and Hasan 2022). The presence of certain abiotic and biotic elicitors increases the production of SMs in plants. The origin of elicitors can be classified as abiotic and biotic based on their nature. In abiotic elicitors, there are three types of elicitors categorized as physical, chemical, and hormonal (Wang and Wu 2013). Abiotic elicitors are a group of major elicitors for the biosynthesis and production of novel pharmaceutically active metabolites. So far, there is limited reports are available in

Fig. 1 A possible mechanism of the elicitation process. detailed description needed. SAR - Systemic acquired resistance; ISR - induced systemic resistance
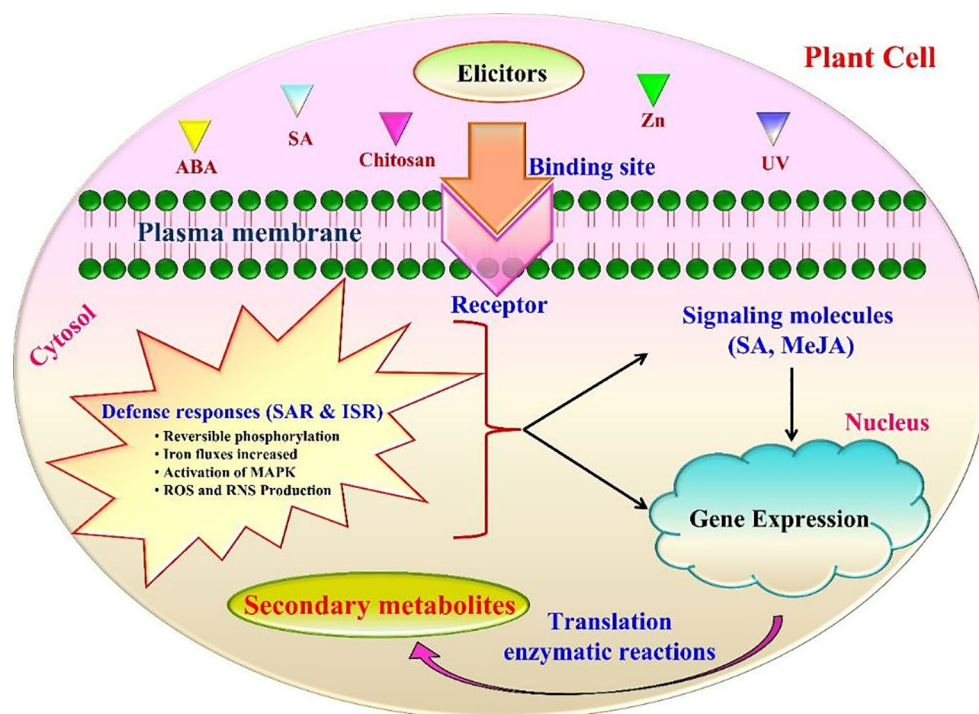
the field of abiotic elicitor, but now abiotic elicitation is one of the emerging and effective approaches to enhance the production of bioactive compounds through *in vitro* culture conditions (Kumari et al. 2020). The impact of abiotic elicitors in plant systems is diverse on cellular processes such as protein synthesis, growth, and development, gene expression, and lipid and carbohydrate metabolisms (Rao and Ravishankar 2002; Hashemi et al. 2021). Recently, various abiotic elicitors were used to modify the cell metabolism of the plant, and these cellular modifications delineated the enhancement of desired phytomolecule production under *in vitro* conditions (Rodziewicz et al. 2014; Xu et al. 2015) reported that treatment of UV-C along with the combination of Methyl jasmonate (MeJA) and Salicylic acid (SA) had a major impact on the enhancement of stilbene biosynthesis in *Vitis vinifera* cell suspension cultures. Thus, the combination study, in turn, has shifted the novel paradigm, compared with one elicitor combination application that can effectively enhance the production of active metabolites

under *in vitro* cell cultures. A few examples of abiotic elicitors and phytocompound details are shown in Table 1.

Biotic elicitors are derived from plants and microorganisms such as fungal, bacterial, and yeast. Further, they are either of defined composition such as a combination of yeast extract and homogenized fungus, inactivated enzymes, chitosan, curdlan polysaccharides such as Pectin, cellulose, and chitin (Vasconsuelo and Boland 2007). For example, the enhancement of bioactive compounds such as artemisinin, ginsenoside, and anthocyanin is increased to a larger amount with the help of fungal elicitors namely *Penicillium oxalicum* and *Trichoderma harzianum*, respectively (Zheng et al. 2016; Biswas et al. 2018). Microalgal elicitors treated suspension cultures of *Carthamus tinctorius* showed an increased level of red pigment formation (Hanagata et al. 1994). Various biotic elicitors are used for the enhancement of specific pharmaceutically important phytocompounds in medicinal plants. Those elicitors and enhanced compounds are listed in Table 2.

Table 1 Impact of Abiotic Elicitors on the enhanced synthesis of SMs in Medicinal Plants

Elicitor	Target metabolite	Plant species	Culture type	References
Cadmium (Cd)	Tanshinone	*Salvia miltiorrhiza*	Cell suspension culture	Zhao et al., 2010
	Resveratrol	*Vitis vinifera*	Cell suspension culture	Cai et al., 2013
pH	Withanolide A	*Withania somnifera*	Hairy root culture	Praveen et al. 2012
Gibberellic acid (GA)	Caffeic acid derivatives	*Echinacea pupurea*	Hairy root culture	Abbasi et al., 2012
Nanosilver	Atropine	*Datura metel*	Hairy root culture	Shakeran et al., 2015
Copper (Cu)	Bacoside	*Bacopa monnieri*	Shoot culture	Sharma et al., 2015
Copper sulfate	Bacoside A	*Bacopa monnieri*	Shoot culture	Sharma et al., 2015
Coniferaldehyde and Methylene dioxycinnamic acid	Lariciresinol, pinoresinol, podophyllotoxin	*Linum album*	Hairy root culture	Ahmadian Chashmi et al., 2016
Iron oxide (FeNPs) nanoparticles	Hyoscyamine and scopolamine	*Hyoscyamus reticulatus*	Root culture	Moharrami et al., 2017
Ultraviolet C	Lignans and neolignans	*Linum usitatissimum* L	Cell suspension culture	Anjum et al., 2017
Drought stress	Cineole	*Thymus vulgaris* L	Cell suspension culture	Llorens-Molina and Vacas, 2017
Ultraviolet B	Betacyanins, betaxanthins, and flavonoids	*Alternanthera* species	Leaf samples	Klein et al., 2018
Silver nitrate	Atropine	*Datura metel*	Hairy root culture	Shakeran et al., 2015
	Flavonoids, Phenolic acids	*Ocimum basilicum*	Cell suspension culture	Acıkgoz, 2020
SA	Bacoside A	*Bacopa monnieri*	Shoot culture	Sharma et al., 2015
	L-3,4-dihydroxyphenylalanine	*Hybanthus enneaspermus*	Root culture	Sathish et al., 2020
	Bilobalide, ginkgolide A,B,C	*Ginkgo biloba*	Immobilized cell culture	Sukito and Tachibana, 2016
Wounding stress	Total phenolic content	*Ajuga bracteosa*	Root culture	Saeed et al., 2017
	Sesquiterpenes	*Persicaria minor*	Cell suspension culture	Sellapan et al., 2018
	Phenolic compounds	*Thevetia peruviana*	Cell suspension culture	Mendoza et al., 2018
Jasmonic acid	Scopolamine	*Duboisia genus*	Hairy root culture	Singh et al. 2018a, b
	Rutin, neohesperidin, buddleside	*Isatis tinctoria*	Hairy root culture	Gai et al., 2019
	Oleanolic acid, glycosides	*Calendula officinalis*	Hairy root culture	Alsoufi et al., 2019
	Chrysin, wogonin, baicalein	*Scutellaria bornmuelleri*	Hairy root culture	Gharari et al. 2020a

Table 2 Effect of Biotic Elicitors on therapeutic metabolites production in Plants

Elicitor	Compounds	Plant species	Culture type	References
Sclerotinia sclerotiorum	Lignan	*Linum album*	Hairy root cultures	Esmaeilzadeh Bahabadi et al., 2014
Sucrose	Leoligin	*Leontopodium alpinum*	Hairy root cultures	Wawrosch et al., 2014
Penicillium fellutanum	Glycyrrhizic acid	*Taverniera cuneifolia* (Roth) Arn.	Root cultures	Awad et al., 2014
Chitin	trans-Resveratrol and viniferins	*Vitis vinifera*	Cell suspension culture	Taurino et al. 2015
	Phenylpropanoids and naphtodianthrones	*Hypericum perforatum*	Cell suspension culture	Gadzovska-Simic et al., 2015
Bacillus cereus	Atropine	*Datura metel*	hairy root cultures	Shakeran et al., 2015
Staphylococcus aureus	Atropine	*Datura metel*	hairy root cultures	Shakeran et al., 2015
Dextron	Phenylpropanoids and naphtodianthrones	*Hypericum perforatum*	Shoot, callus, cell suspension cultures	Gadzovska-Simic et al., 2015
Pectin	Phenylpropanoids and naphtodianthrones	*Hypericum perforatum*	Shoot, callus, cell suspension cultures	Gadzovska-Simic et al., 2015
Aspergillus niger	Oleanolic acid, urosolic acid	*Salvia fruticosa*	Cell suspension culture	Kummritz et al., 2016
Rhizophagus irregularis	Rosmarinic acid	*Ocimum basilicum*	Root cultures	Srivastava et al., 2016
Piriformospora indica	Withanolides	*Withania somnifera*	Hairy root cultures	Ahlawat et al., 2017
Trichoderma harzianum	Ginsenoside and Anthocyanin	*Panax sikkimensis*	Cell suspension cultures	Biswas et al., 2018
Bacillus subtilis	Ginsenoside	*Panax quinquefolius*L	Cell suspension cultures	Biswas et al., 2018
Chitosan	Withaferin	*Withania somnifera* (L.)	Hairy root culture	Thilip et al., 2019
Coronatine and sorbitol	Artemisinin	*Artemisia annua*	Hairy root cultures	Salehi et al. 2019a
Bacillus subtilis	Diosgenin	*Helicteres isora* L	Cell suspension cultures	Shaikh et al., 2020
Escherichia coli	Diosgenin	*Helicteres isora* L	Cell suspension culture	Shaikh et al., 2020
Yeast extract	Flavonoids, phenolic acids	*Ocimum basilicum*	Cell suspension culture	Acıkgoz, 2020
Alternaria panax	Ginsenoside	*Panax ginseng*	Cell suspension culture	Hao et al., 2020
Agrobacterium rhizogenus	Paclitaxel	*Taxus brevifolia*	Hairy root cultures	Jalalipour Parizi et al., 2020

All these reports are evidence that any type of abiotic and biotic elicitors given to the plant will undoubtedly have opened up an impact on the SMs production through alterations in various biochemical pathways. There are some cons also noted while using elicitors. Moreover, not all the elicitors affect the SMs production which depends on the concentration and type of biotic elicitors used (Baenas et al. 2014). However, there are no reports available for a combination study of two or more biotic elicitors for phytocompounds enhancement. Developing the combination study of biotic elicitors will pave the way to enhance the synthesis of metabolite production via *in vitro* conditions and create novel avenues for future researchers.

Among the various types of elicitors, MeJA and SA are the highly reported phytohormone elicitors. Hence, in this review, we have attempted to summarize the effect of MeJA and SA plant hormones for enhancing the production of novel bioactive molecules in medicinal plants through different *in vitro* cell cultures.

MeJA and SA

In plants, several metabolic activities are mediated by internal signals known as plant hormones. Among the various metabolic processes, stress tolerance is one of the important processes to be able to cause several stresses. In this condition, phytohormones like MeJA, a member of the jasmonate family, modulate important factors of plant physiology (Chen et al. 2006). MeJA was first isolated in 1962 from *Jasminum grandiflorum's* essential oil (Demole et al. 1962). MeJA, a volatile methyl ester of jasmonic acid has been identified as a major signaling molecule in abiotic and biotic stresses (Wang et al. 2021). It plays an important role in plants from morphological to molecular functions. Due to its volatile nature as well as the capacity to permeate via biological membranes, MeJA is regarded as a significant phytohormone that can facilitate intra-and inter-communications in plants, regulating defense responses, particularly antioxidant systems. Implementation of exogenous MeJA to plant *in vitro* cultures has been recognized as a novel method for the enhanced production of SMs, increased activity of antioxidant enzymes, and the expression of genes associated with defense (Murthy et al. 2014; Ho et al. 2020).

Table 3 Effect of MeJA and SA on the enhancement of specific SMs *in vitro* culture of medicinal plants

S. No.	Plant species	Elevated Secondary Metabolites	Elicitors	Type of culture	Reference (s)
1.	*Glycyrrhiza inflata*	Glycyrrhizin	MeJA	Hairy root culture	Wongwicha et al. 2011
2.	*Withania somnifera*	Withanolide A, withanone, and withaferin A	SA	hairy root	Sivanandhan et al. 2013
3.	*Panax ginseng*	Ginsenosides	MeJA	Hairy root	Corchete et al. 2013
4.	*Bacopa monnieri*	Bacoside A	SA and MeJA	Shoot	Sharma et al. 2015
5.	*Catharanthus roseus*	Ajmalicine	MeJA and Cyclodextrin	Cambial meristematic cells	Zhou et al. 2015
6.	*Salvia miltiorrhiza*	Tashinones	MeJA	Hairy root	Hao et al. 2015
7.	*Vitis vinifera*	Stilbene	SA	cell suspension	Xu et al. 2015
8.	*Gymnema sylvestre*	Gymnemic acid	MeJA	Cell suspension	Chodisetti et al. 2015
9.	*Hypericum perforatum*	Flavonoid (Hyperin and Quercetin)	MeJA	Cell suspension	Wang et al. 2015
10.	*Ginkgo biloba*	Bilobalide, ginkgolide A, ginkgolide B, ginkgolide C	SA and MeJA	immobilized cell cultures	Sukito and Tachibana, 2016
11.	*Ajuga bracteosa*	Phytoecydysteroids	MeJA	Hairy root	Saeed et al. 2017
12.	*Ajuga bracteosa*	TPC and TFC	MeJA and PAA	Root suspension	Saeed et al. 2017
13.	*Podophyllum hexandrum (ptox)*	Podophylloxin	MeJA	Cell	Hazra et al. 2017
14.	*Duboisia genus*	Scopolamine	MeJA	Hairy root	Singh et al. 2018a, b
15.	*Isatis tinctoria*	Epigoitrin, tryptanthrin, indigo, indirubin	SA	hairy root	Gai et al. 2019
16.	*Achillea gypsicola*	camphor and phenolic compounds	SA and MeJA	Cell suspension	Acikgoz et al. 2019
17.	*Isatis tinctoria*	Rutin, neohesperidin, buddleside	MeJA	Hairy root	Gai et al. 2019
18.	*Bacopa monnieri*	Bacoside A	SA	Suspension	Koul and Mallubhotla, 2020
19.	*Hybanthus enneaspermus*	L-3,4-dihydroxyphenylalanine	SA	adventitious root	Sathish et al. 2020
20.	*Piper cumanense*	5-hidroximetilfurfural, (Z)-9-octadecenamide and phenol	SA and MeJA	Cell suspension	Rodriguez-Sanchez et al. 2020
21.	*Scutellaria bornmuelleri*	Chrysin, baicalein, wogonin	MeJA	hairy root	Gharari et al. 2020a
22.	*Vernonia anthelmintica*	rhamnetin	SA and MeJA	Cell suspension	Rajan et al. 2020
23.	*Rubia tinctorum*	Anthraquinone and phenols	SA	adventitious root cultures	Demirci et al. 2021

SA is a well-known elicitor for inducing systemic acquired resistance and can also elevate the synthesis of SMs in plants. SA is a phenolic compound that has attracted the greatest attention from scientists around the world. The intensive studies on SA in medicinal plants have revealed its role in various developmental and physiological processes, including ethylene production, stomatal movements, photosynthesis, membrane functions, pigment accumulation, enzyme activities, plant growth and development (Ali et al. 2021). Hence, SA and its related precursors are classified as phytohormones (Koo et al. 2020). The significant and functional analog of SA includes salicylic acid, dihydroxy benzoic acid, methyl salicylic acid, and acetylsalicylic acid. They are produced from isocomerate and phenylalanine (Sahu 2013) and are transferred through apoplast, which is aided by pH gradient modulation or SA deprotonation or via cuticle wax in cuticle deficient plants to the mechanism of action for the required performance (Lim et al. 2020).

Regulatory mechanism and biosynthesis of bioactive compounds in plants

MeJA signaling

The primitive stage of MeJA signaling includes a number of metabolic pathways to be activated. In general, the biosynthesis of polypeptides or the formation of free radicals indicates the introduction of biotic and abiotic stress. The activation of cell receptors, and protein molecules as well as over activity of transporters also represent the stressed condition. In response to pathogen attack, oligosaccharide signals were found in symplastic and apoplastic pathways, which indicates the plant is experiencing stess reversal pathway. Moreover, the activation of phospholipases (PLAs) is essential for MeJA biosynthesis and signaling. PLAs produce linoleic acid from the plasma membrane which serves as a precursor for MeJA. Several mutant and transgenic plants have been used to study the PLAs activity (Yan et al.

2013). In MeJA-associated short and long-distance signaling, various plant growth regulators and hormones such as auxin, cytokinin, ethylene and SA play a vital role in the development of complex regulatory network which in turn impact different biochemical processes and SMs accumulation (Chini et al. 2018). On the other hand, various TFs such as WRKY, bZIP, bHLH, NAC, AP2/ERF and MYB are involved in the MeJA signaling process. It has been reported that the bHLH and MYC TF is a master regulator for the MeJA signaling pathway. The MeJA-responsive MYB-TF enhances phenolic acid accumulation in *S. miltiorrhiza* (Zhou et al. 2021). Moreover, MeJA mediated WRKY TF also plays a crucial role in the production of SMs in medicinal plants. WRKY TF is involved in regulation of SMs biosynthesis such as taxol and artemisinin in *Taxus chinensis* and *A. annua*, respectively (Ma et al. 2009; Subramaniyam et al. 2014). MeJA and SA induced TF-WRKY enhances triterpenoid biosynthesis and over-expression of *WRKY18* increases salt stress tolerance in *Ziziphus jujuba* Mill. (Wen et al. 2023; Wang et al. 2017) studied transcriptome analysis of *Lycoris aurea* seedlings with the treatment of MeJA to determine which molecular mechanisms are responsible for regulating SMs pathway activity in plants. The expression of the plant secondary process highly depends on the different TFs at diverse levels. For instance, TFs participated in MeJA signaling cascades pathways usually regulating the transcription of several genes involved in biosynthesis, to improve the accumulation of bioactive compounds in medicinal plants (Zhou and Memelink 2016). Several TFs have been identified as regulators of SMs biosynthesis in plants, belonging to the families AP2/ERF, MYB, WRKY and bHLH. MeJA signaling activates the MAP kinase cascade, which regulates the calcium channel and interactions with functional molecules. Additionally this signaling pathway interacts with plant growth regulators (PGRs) such as gibberellic acid, SA, abscisic acid, and ethylene to monitor a wide network of various plant physiological and biological processes. Plants are constantly exposed to various environmental stresses. Their stress response is facilitated by a number of bioactive compounds. The exposure of plant cells to diverse stress factors, as well as their primary and secondary defense responses, leads to improved production of phytocompounds, genetic expression, multicomponent signaling, changes in metabolic processes and the involvement of various TFs all this activity is synchronized with both MeJA and SA signals in many ways. There is evidence that plants do regulate TFs to monitor signaling cascades that can reverse the effect of oxidative stress. Research in transgenic plants has revealed the cirical role of various TFs and gene networks in MeJA and SA signaling pathways that are involved in protecting the plants from various stress factors and enhance SMs production (Khare et al. 2020).

SA signaling

SA serves as a mediator in plant development and stress conditions such as cold, drought and salinity, which are partly accomplished through enhanced biosynthesis of SMs. Depending on the elicitor treatment, stress conditions and pathogen attack, SA levels in plants vary. Under stress conditions, SA binds to various metabolic substances and controls the entire molecular signaling mechanisms. SA is strongly involved in the regulation of endoplasmic reticulum (ER) stress, antioxidant mechanism and heavy metal toxicity (Korner et al. 2015; El-Esawi et al. 2017). Exogenous SA treatment can protect the plant against cadmium toxicity; play an important role in plant defense. NPR1 (non-expresser of pathogenesis-related protein 1) and SA-binding proteins (SABPs) are the major transcriptional regulators of SA signaling pathways (Guo et al. 2019). The ER controls the synthesis the proteins. Disruption of ER homeostasis leads to the production of misfolded proteins, which result in stress-inducing stimuli. SA modulates the redox homeostasis and activate the function of desired TFs. Nowadays, various environmental conditions are leading to a global food shortage. Under this condition, exogenous use of bioactive metabolites like SA may increase the agricultural yield. The accumulation of SA-based derivaties can reduce populations of herbivores. Pretreatment with polyamines may enhance the overall function of SA. Moreover, several TFs function in response to SA signaling. *BcWRKY46* and *OsWRKY77* effectively respond to SA signaling through defense responses (Wang et al. 2012; Lan et al. 2013). A recent study reported that, SA responsive WRKY TF positively regulates the biosynthesis of taxol in *T. chinensis* by upregulating the taxol biosynthesis genes expression (Chen et al. 2021). In *S. miltiorrhiza*, SA stimulated the tanshinone genes expression including *SmGGPPS*, *SmIPPI*, *SmCPS*, *SmDXS*-II and *SmHMGR*, consistent with SA induction on enhanced tanshinone production (Hao et al. 2015). In *V. vinifera*, SA stimulated the production of *PAL* (phenylalanine ammonia-lyase) mRNA, an essential enzyme in phenylpropanoid metabolism, resulting in a extensive production of phenolic content (Wen et al. 2008; Ma et al. 2017) repoted that li049 an AP2/ERF TF family, serves as a positive regulator for the biosynthesis of SMs called lignan/lignin in *Isatis indigotica* by the activation of SA signaling pathway. Currently, only a few research on TFs responding to SA have been reported, indicating that more research is required to achieve more results in the future.

Effect of MeJA and SA as elicitors on the biosynthesis of SMs production of potent medicinal plants

MeJA and SA have been very well-documented chemical elicitors, a response to insect attacks, which deters feeding. MeJA has been hypothesized as an essential signaling elicitation molecule leading to the production of novel and desired phytocompounds through *in vitro* cell cultures (Zhao et al. 2010). In *B. monnieri*, the combination of MeJA and SA significantly increased the biomass and bacoside A content in *in vitro* shoot cultures. An example thematic image was represented in Fig. 2. The bioactive compound bacoside A production was enhanced by using MeJA through *in vitro* shoot culture of *B. monneiri* (Sharma et al. 2015; Largia et al. 2015; Kim et al. 2007) reported that the SA and MeJA enhance the asiaticoside content in hairy root cultures of *C. asiatica* after 3 weeks of elicitation and enhance glycyrrhizin production in *Glycyrrhiza glabra* after the addition of MeJA and SA. SA and MeJA significantly improve the ginkgolide A, B, C and bilobalide production in the *Ginkgo biloba* under *in vitro* conditions in immobilized cell cultures (Sukito and Tachibana 2016). The synergetic effect of MeJA and phenylacetic acid (PAA) were used as elicitors to increase total phenolic and flavonoid content in the root suspension of *Ajuga bracteosa*. Phytoecdysteroid levels were enhanced by 14 days of MeJA elicitation in *A. bracteosa* (Saeed et al. 2017). Gadzovska et al. (2013) reported, SA treated suspension culture showed a two-fold increase of hypericin and pseudohyperian production in *Hypericum perforatum* (L.). MeJA treatment showed low concentrations of exogenous MeJA that could provide a potential protocol for the enhancement of bacoside contents in Bacopa seedlings (Bunjan et al. 2018; Koul and Mallubhotla 2020) reported that SA was used as an elicitor to enhance biomass and bacoside production using *in vitro* suspension cultures of *B. monneiri*. Another study was carried out to enhance the bacoside content of *B. monnieri* through *in vitro* suspension culture using plant growth regulators such as 6-benzyladenine (BA), kinetin, thidiazuron and chitosan. Among them, thidiazuron-treated samples showed increased bacoside content (Kharde et al. 2018). MeJA, SA, and copper sulfate ($CuSO_4$) were used to enhance the bacoside content in *B. monnieri* shoot cultures and the results showed, CuSO4 treated shoot cultures exhibited a maximum yield of bacoside content than the other two hormonal elicitors (Sharma
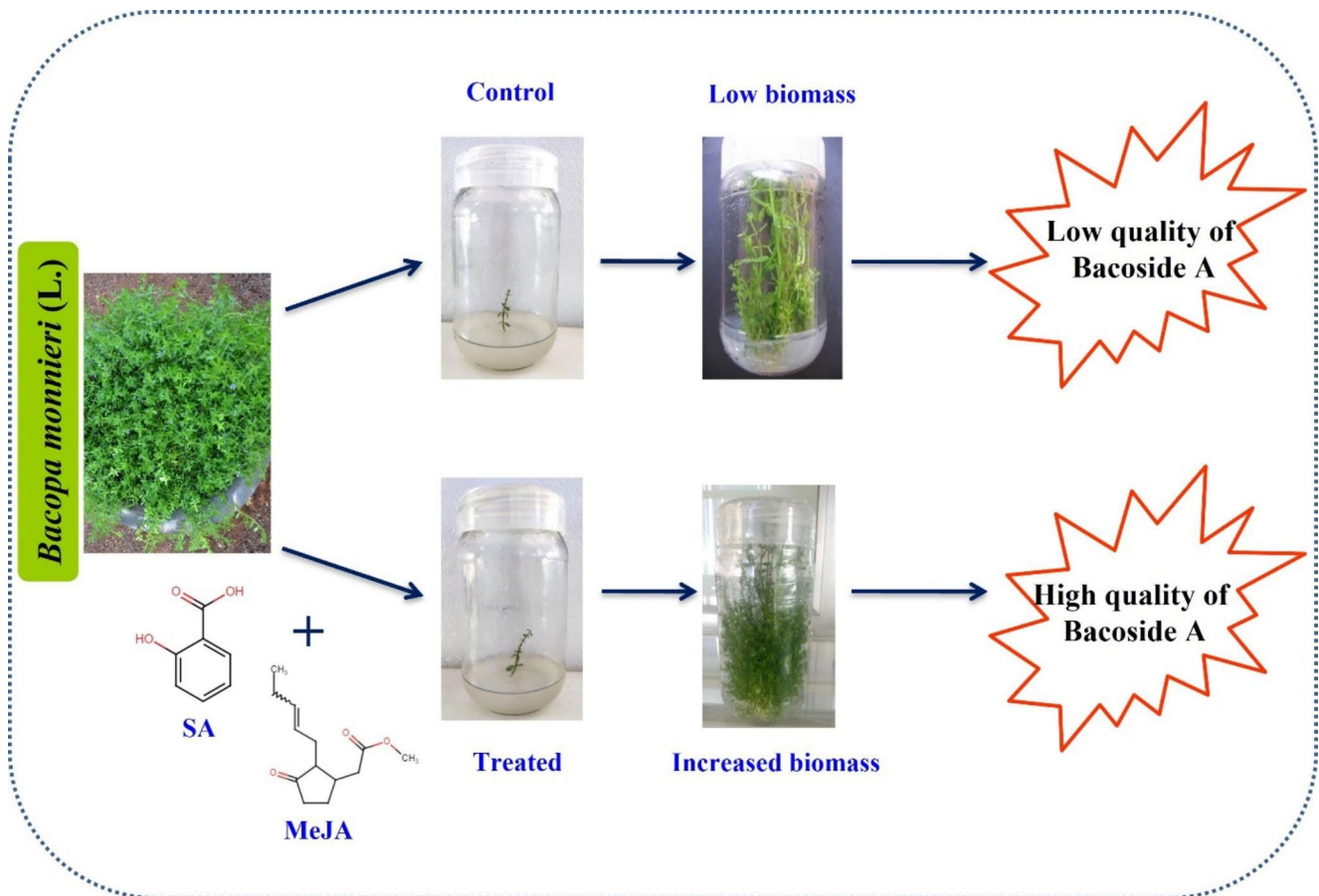

Fig. 2 Enhancement of biomass through elicitation process in *B. monnieri*

et al. 2015). However, scientific experiments through *in vivo* studies are rare and more contradictory, which indicates more research is undoubtedly urging steps to attain more output in the future (Table 3).

Conclusion

Medicinal plants are an incredible source for producing pharmaceutically important novel bioactive compounds to reform medicines in the future and also these are all used for industrial and other food materials. Elicitation is one of the effective methods to enhance the synthesis of therapeutic metabolite production in medicinal plants to maintain their resilience and survival. Elicitors can trigger a diverse plant defense mechanism which depends on the type of elicitors encountered. Among the various biotechnological approaches, biotic and abiotic elicitors have gained potential value for the enhanced production of novel bioactive compounds. The current review is a touchstone for the use of MeJA and SA as elicitors in medicinal plants for the enhancement of their phytocompounds using various *in vitro* culture techniques to meet the market demands of pharmaceuticals. It has been found that medicinal plants are used across the globe to treat diseases such as jaundice, tumor, malaria, depression, cancer, constipation, diabetes, COVID-19, and so on. Because of the presence of bioactive compounds in plants, they have various pharmacological properties. The phytocompounds in the intact plant are limited in quantity, MeJA, and SA are used as elicitors via different *in vitro* cultures to synthesize the SMs in the desired quantity. However, increasing production via eliciting secondary phytomolecules from different plant cell cultures is a frontier area of research. The main role of elicitors and the amount of enhancement of SMs harvest index of medicinal plants may indicate a future approach for the production of quality and quantity of pharmaceutically active phytocompounds from medicinal plants.

Declarations

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