



Biotic elicitors as modulators of secondary metabolite production in medicinal plant; A review

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ABSTRACT

Background & Aim: Secondary metabolites (SMs) in medicinal plants exhibit significant therapeutic potential; however, their low natural abundance constrains large scale industrial applications. This review aims to examine the role of biotic elicitors, including bacteria, fungi, polysaccharides, proteins, algae, and phytohormones, in enhancing SMs production through activation of specific plant defense signaling pathways.

Experimental: A comprehensive literature search was conducted across major scientific databases, including ScienceDirect, PubMed, and Google Scholar, using keywords related to biotic elicitors and secondary metabolite enhancement in medicinal plants. Relevant full text, peer reviewed studies were selected, categorized, and critically analyzed to provide a cohesive understanding of elicitor mediated metabolic regulation.

Results: Biotic elicitors were consistently shown to activate plant immune responses, reprogram metabolic pathways, and modulate gene expression involved in SM biosynthesis. These elicitors initiate signal transduction cascades that result in increased production and diversity of pharmacologically important compounds. The reviewed evidence highlights their efficacy across diverse plant species and culture systems.

Recommended applications/industries: Beyond laboratory scale studies, biotic elicitation represents a scalable strategy to enhance the production of plant derived bioactive compounds. This approach offers a sustainable and eco friendly alternative to conventional extraction and chemical synthesis, with significant potential in pharmaceutical development, functional foods, botanical cosmetics, and sustainable agriculture. By transforming medicinal plants into reliable biofactories, elicitor based strategies bridge ecological sustainability and industrial productivity.

1. Introduction

Throughout their life cycle, plants synthesize a wide range of biologically active compounds known as secondary metabolites (SMs). These compounds, distinct from primary metabolites such as carbohydrates, amino acids, and lipids, are typically produced in smaller quantities but play crucial roles in modulating plant physiological responses, cellular functions, and ecological interactions (Humbal and

Pathak, 2023). The biosynthesis and accumulation of SMs are influenced by a multitude of internal and external factors, including developmental stage, environmental conditions, and both biotic and abiotic stressors. Their production enables plants to survive and adapt to adverse conditions by mediating defense mechanisms, signaling pathways, and interactions with surrounding organisms (Guerriero *et al.*, 2018).

SMs are chemically diverse and can be broadly classified into major categories such as phenolics, alkaloids, terpenes, and saponins (Hussein and El-Anssary, 2019). Their biosynthesis involves specific metabolic routes including the shikimate, acetate malonate, mevalonate, and pentose phosphate pathways (Kabera *et al.*, 2014). These pathways facilitate the production of structurally complex and functionally diverse molecules such as flavonoids, pigments, quinones, and steroids, many of which exhibit antimicrobial, antioxidant, and allelopathic properties. Beyond their ecological roles, SMs are of significant industrial value and are utilized in the production of pharmaceuticals, nutraceuticals, cosmetics, agrochemicals, biopesticides, and food additives (Jain and Janmeda, 2022; Varshney *et al.*, 2021).

Despite their importance, SMs generally constitute less than 1% of a plant's dry biomass (Dixon, 2001), and their biosynthesis is often tightly regulated and developmentally constrained. Consequently, enhancing SM production has become a central focus in plant biotechnology. One promising approach involves the application of elicitors, chemical or biological agents that, when applied in low concentrations, stimulate plant defense mechanisms and activate secondary metabolic pathways. These elicitors may be abiotic (e.g., heavy metals, nanoparticles, UV radiation) or biotic (e.g., fungal, polysaccharides, bacterial, glycoproteins, yeast extract), and they induce stress like conditions that result in enhanced synthesis of specific SMs (Akula and Ravishankar, 2011; Naik and Al-Khayri, 2016).

Upon elicitor perception, plants initiate a series of intracellular signaling events involving changes in ion fluxes, activation of kinases, transcription factors, and antioxidant enzymes, as well as the accumulation of stress related compounds such as phenolics, flavonoids, and tannins (Thakur *et al.*, 2019; Humbal and Pathak, 2023). These metabolic responses are often accompanied by increased enzymatic activity, including superoxide dismutase (SOD), nitric oxide (NO) production, and the induction of pathogenesis related proteins, reflecting the activation of systemic defense networks.

Studies have shown that elicitation not only enhances the yield of known SMs but can also lead to the biosynthesis of novel metabolites with potential pharmaceutical applications. For instance, *Catharanthus roseus* cells treated with salicylic acid

(SA) produced 2,5dihydroxybenzoic-5-O-glucoside (Mustafa *et al.*, 2009), while *Hyoscyamus albus* hairy roots treated with methyl jasmonate (MeJA) and CuSO₄ yielded previously unreported solavetivone derivatives. These findings emphasize the role of elicitation in metabolic reprogramming and natural product discovery.

Further evidence supports the efficacy of elicitors in both in vitro and field conditions. In *Silybum marianum*, the application of various elicitors including *Aspergillus niger* (0.2 g/L), MeJA (100 µM), and silver nanoparticles (AgNPs, 1 ppm) led to significant increases in phenolic and flavonoid content, as well as SOD and NO levels. The highest metabolite accumulation was observed with MeJA and its combination with AgNPs, highlighting the synergistic potential of combined elicitor treatments (Mubeen *et al.*, 2022).

Similarly, biotic elicitors such as chitosan and yeast extract (YE) have been shown to enhance SM biosynthesis in numerous species including *Calendula officinalis*, *Sorbus aucuparia*, and *Abrus precatorius* (Wiktorowska *et al.*, 2010; Gaid *et al.*, 2011; Karwasara *et al.*, 2010). Fungal elicitation has emerged as a particularly effective strategy, as demonstrated by the marked increase in psoralen production in response to fungal derived signals (Goel *et al.*, 2011).

Collectively, these studies underscore the critical role of elicitors in modulating plant metabolic networks. Understanding the genetic, proteomic, and biochemical underpinnings of elicitor mediated responses is essential for optimizing SM production.

This review aims to explore the biosynthetic origins, functional roles, and enhancement strategies of SMs in plants, with particular emphasis on elicitor mediated induction and its implications for biotechnology, agriculture, and pharmaceutical development.

2. Materials and Methods

In this review, relevant keywords such as medicinal plants, secondary metabolites, and biotic elicitors were systematically searched across major scientific databases, including PubMed, ScienceDirect, and Google Scholar. The selected studies were carefully screened, and only peer reviewed full text articles with scientific validity were analyzed and categorized based on their focus. This paper explores how biotic elicitors influence the production of secSMs and primary metabolites.

in medicinal plants.

3. Results and discussion

3.1. Molecular mechanisms of elicitor induced signal transduction and secondary metabolite biosynthesis in plants

Elicitors are molecular signals often produced by pathogens, insects, or other biotic sources that are perceived by specific plant receptors and serve as triggers for innate immune responses (Boller and Felix, 2009). Unlike toxins, these molecules function as non lethal stimulants, inducing a phenomenon known as genetic pseudo resistance and enhancing secondary metabolite (SM) biosynthesis. Plant recognition of elicitors occurs through pattern recognition receptors (PRRs) or resistance (R) proteins, either embedded in the plasma membrane or present in the cytoplasm. Binding of the elicitor initiates a signal transduction cascade involving conformational shifts in receptor proteins or activation of receptor kinases, leading to downstream responses mediated by G-proteins, ion channels, lipases, and other intracellular effectors (Zhao *et al.*, 2005).

Following elicitor perception, signal transduction typically involves changes in ion fluxes, including Ca^{2+} influx and K^+/Cl^- efflux, resulting in membrane depolarization, cytoplasmic acidification, and extracellular alkalization. These early events lead to the generation of secondary messengers such as diacylglycerol (DAG), inositol triphosphate (InsP_3), nitric oxide (NO), reactive oxygen species (ROS), and hydrogen peroxide (H_2O_2), which, in turn, activate mitogen activated protein kinase (MAPK) pathways. Activated MAPKs translocate into the nucleus and phosphorylate transcription factors (TFs), thereby modulating the expression of genes involved in defense responses and SM biosynthesis (Pitzschke *et al.*, 2009). Concurrently, the activation of phospholipases and reversible protein phosphorylation events reinforce the signal transduction network.

Elicitors are chemically and functionally diverse. They can be classified as abiotic or biotic, and further divided into endogenous or exogenous based on their origin (Namdeo, 2007). Molecular motifs associated with elicitors include microbe associated molecular patterns (MAMPs), pathogen associated molecular patterns (PAMPs), damage associated molecular

patterns (DAMPs), and herbivore associated molecular patterns (HAMPs), each capable of initiating pattern triggered immunity (PTI) upon recognition (Pruitt *et al.*, 2021; Zipfel, 2008). These elicitors are sensed by PRRs, which stimulate the production of pathogenesis related proteins, antioxidant enzymes, and SMs.

In practical applications, in vivo elicitation methods, such as foliar spraying, root drenching, or seed soaking, have been used to induce SMs production in medicinal plants, including *Panax ginseng*, *Calendula officinalis*, and *Digitalis purpurea* (Patil *et al.*, 2013). The response to elicitors such as chitosan is highly species specific. For instance, chitosan at pH 5.5 significantly enhanced hyoscyamine and scopolamine accumulation in *Brugmansia candida* hairy roots, but had no effect in *Atropa belladonna* and was toxic to *Hyoscyamus niger* (Pitta-Alvarez and Giuliotti, 1999; Lee *et al.*, 1998; Hong *et al.*, 2012). Other elicitors like oligogalacturonides, derived from partial hydrolysis of pectin, improved TA production in *Daturastramonium* by increasing tropine levels (Zabetakis *et al.*, 1999). Similarly, pectic enzymes such as pectinase and hemicellulase boosted hyoscyamine and scopolamine levels in *Brugmansia candida* (Pitta-Alvarez *et al.*, 2000, 2003).

Biochemical elicitors such as yeast extract (YE) contain a complex mixture of macromolecules and small molecules that interact with signaling components to regulate enzyme activity and gene expression. YE enhances SMs production by upregulating precursor synthesis (e.g., ornithine and arginine) and increasing expression of key TA biosynthetic genes such as PMT, TRI, and H6H in *A. belladonna* and *B. candida* (Guo *et al.*, 2018; Hedayati *et al.*, 2021). Additionally, YE application increases the scopolamine to hyoscyamine ratio, indicating altered metabolic flux.

Microbial elicitors, particularly MAMPs, initiate PTI and/or effector triggered immunity (ETI) through ligand receptor interactions. These interactions activate downstream components, including NO, Ca^{2+} , cyclic AMP, ethylene, and G-proteins, and ultimately regulate TFs that bind to promoter regions of SMs biosynthetic genes (Barrett and Heil, 2012). GPCRs mediate ROS production via NADPH oxidase activation, resulting in cytoplasmic acidification and induction of defense related genes (Mishra *et al.*, 2012). The involvement of these molecules in plant immunity suggests a tightly coordinated signaling network linking perception to

metabolic outcomes.

Among the most potent biotic elicitors is coronatine, a phytotoxin from *Pseudomonas syringae* that mimics jasmonate signaling and promotes SMs biosynthesis across diverse species. Coronatine enhances taxane accumulation in *Taxus media* and *Taxus globosa*, stimulates phenylalanine ammonia lyase expression in *Vitis vinifera*, and increases production of flavonoid phytoalexins such as sakuranetin in *Oryza sativa* (Ramirez-Estrada *et al.*, 2015; Kim *et al.*, 2016). It also upregulates enzymes such as hydroxymethylglutarylCoA reductase involved in phytosterol biosynthesis. In *Eschscholzia californica*, coronatine-induced benzo[c]phenanthridine alkaloids exhibit strong antitumor properties (Haider *et al.*, 2000).

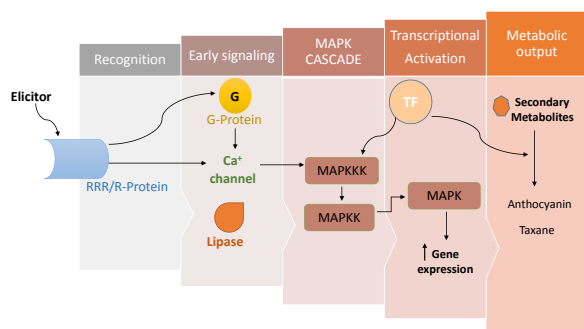


Fig. 1. SMs biosynthesis via elicitor induced signaling pathways. Illustrates the intricate signaling pathway plants employ in response to elicitors. Upon the recognition of these molecular triggers by plant receptors (RRR/R-Proteins), an early signaling cascade is activated, involving key players such as G-proteins and calcium channels. This leads to the initiation of the MAPK cascade, ultimately stimulating TF that regulate gene expression. The culmination of these events results in the biosynthesis of SMs, including anthocyanins and taxanes, which play crucial roles in the plant's defense and metabolic responses. This figure encapsulates the complex, multi layered nature of plant immunity and secondary metabolism, shedding light on the dynamic processes underpinning plant responses to external stressors.

Plant growth promoting rhizobacteria (PGPR) also serve as natural biotic elicitors by colonizing the rhizosphere and stimulating defense pathways. PGPRs modulate hormonal signaling, particularly through jasmonic acid, enhancing the production of SMs even under stress conditions (Kousar *et al.*, 2020; Bhattacharyya and Jha, 2012). Pathogen derived

proteins, such as a 32 kDa glycoprotein from *Phytophthora megasperma*, have been shown to induce localized hypersensitive responses (HR) and systemic acquired resistance (SAR) in *Nicotiana* species, upregulating genes associated with phenylpropanoid metabolism and SA accumulation (Baillieul *et al.*, 1995).

Overall, elicitor recognition and signaling represent a multilayered, dynamic system that integrates receptor mediated perception with transcriptional reprogramming and enzymatic activity, ultimately leading to targeted SMs biosynthesis. Although much progress has been made in elucidating these pathways, further research is required to optimize elicitor use in agricultural and industrial biotechnology, ensuring enhanced metabolite yields with specificity and sustainability.

3.2. Classification of biotic elicitors

Recent advances have demonstrated that elicitors can significantly enhance SMs production in plants by activating specific biosynthetic pathways through transcription factor (TF) stimulation and upregulation of gene expression. The stress induced by these compounds is known to promote SMs accumulation. Elicitors can be derived from both abiotic and biotic sources. Biotic elicitors, including those derived from bacteria, fungi, algae, and their polysaccharides, have been extensively studied for their mechanistic roles and practical applications.

Bacterial elicitors, such as *Rhizobium rhizogenes*, have been reported to increase genistein production by 94%, whereas *Escherichia coli* elicited a 9.1 fold enhancement of diosgenin. Fungal elicitors like *Aspergillus niger* induced an 85% increase in thiophene, and *Botrytis* spp. stimulated a 26 fold rise in sanguinarine production. Algal extracts, including those from *Haematococcus pluvialis*, increased betalain levels by 2.28 fold, while *Botryococcus braunii* elicited a three fold increase in vanillin, a six fold increase in vanillylamine, and a 2.3 fold enhancement of capsaicin. These results underscore the structural and biochemical diversity of biotic elicitors and their functional versatility (Bhaskar *et al.*, 2022).

Biotic elicitors are naturally occurring molecules such as polysaccharides, chitin, and pectin, which can originate from invading pathogens or the plant itself (Patel and Krishnamurthy, 2013). These molecules interact with specific plant receptors, initiating

signaling cascades involving ions, enzymes, and regulatory compounds. Many elicitors are cell wall fragments released in response to pathogen attack or mechanical injury, serving as early warning signals to activate plant defense mechanisms (Namdeo, 2007). Beyond acting as alarm signals, these compounds modulate gene expression and metabolic fluxes in secondary metabolism, regulating multiple biosynthetic checkpoints via TF activation and other molecular mechanisms (Ballaré, 2011; GhasemiPirbalouti *et al.*, 2014).

3.2.1. Bacterialelicitation of secondary metabolites in plants

Bacteria, as ubiquitous unicellular organisms, are potent elicitors of SMs production in plants, particularly under in vitro conditions. Bacterial elicitation can involve live cells, cell homogenates, cellular extracts, or culture filtrates, all of which trigger plant defense responses and enhanced SMs biosynthesis. These effects are mediated through receptor elicitor interactions, G-protein activation, cytoplasmic acidification, and reactive oxygen species (ROS) generation (Biswas *et al.*, 2016; Zhao *et al.*, 2005).

Live bacterial cultures, including *Bacillus aminovorans*, *Agrobacterium rhizogenes*, and *Rhizobium leguminosarum*, significantly increased glycyrrhizic acid in *Taverniera cuneifolia* roots, with *R. leguminosarum* achieving the highest yield. Co culturing *R. rhizogenes* with *Albizia kalkora* adventitious roots substantially enhanced isoflavone content. However, responses are species, and metabolite specific; for instance, *B. cereus* decreased atropine in *Datura metel* hairy roots but increased tanshinone by 13.5 fold under different conditions (Park *et al.*, 2006).

Cell homogenates and extracts release microbial metabolites that mimic pathogen attacks. Homogenates from *B. subtilis*, *E. coli*, *Pseudomonas aeruginosa*, and

S. aureus significantly increased thiophene and scopalamine production in *Tagetes patula* and *Scopolia parviflora*, respectively. Heat-treated homogenates often showed reduced efficacy, suggesting the involvement of heat sensitive elicitor compounds (Buitelaar *et al.*, 1992).

Culture filtrates, containing secreted bacterial metabolites, also act as effective elicitors. For example, filtrates from *Pseudomonas monteilii* and *Serratia marcescens* induced a 2.5 fold increase in ginsenoside in *Panax* cultures, while *E. coli* filtrates enhanced diosgenin in *Helicteres isora* by 9.1 fold. Both gram positive and gram negative bacterial filtrates have been effective across diverse plant systems, including *Rosmarinus officinalis*, *Hypericum perforatum*, and *Pinellia ternata* (Biswas *et al.*, 2016).

Bacterial elicitation also modulates plant gene expression. In *Scopolia parviflora*, bacterial elicitors increased scopalamine by downregulating the H6H gene. *R. leguminosarum* and *B. aminovorans* elevated glycyrrhizic acid in *T. cuneifolia*, while *Pseudomonas fluorescens* increased alkaloid content in *Hyoscyamus niger* and essential oils in *Salvia officinalis*. Volatile organic compounds (VOCs) from *B. subtilis* GB03 enhanced essential oil biosynthesis in *Ocimum basilicum*, and coronatine from *P. syringae* induced taxane production in *Taxus media* (Jung *et al.*, 2003).

Strain specific differences are notable; for instance, *S. aureus* and *P. aeruginosa* elicited higher scopalamine levels than *B. cereus* in *S. parviflora*. Viral elicitors such as PMMoV, TMV, and ToMV also increased hyoscyamine in *Datura stramonium*. Overall, bacterial elicitors are advantageous due to their abundance, cost effectiveness, and eco friendly nature, with species, and metabolite specific responses enabling precision metabolic engineering (Mihálik *et al.*, 2022). Table 1 shows the effects of different bacterial elicitors on the enhancement or suppression of specific SMs in various plant species.

Table 1. Bacterial elicitors and their effects on SMs accumulation in medicinal plants.

No.	Elicitor used	Target plant	Target metabolite (Change)	Type of culture	Ref.
1	<i>Rhizobium leguminosarum</i> (0.5 mL live culture)	<i>Taverniera cuneifolia</i>	Glycyrrhizic acid (↑ 4.3 fold; 1.48→6.37 mg/g)	Root culture	(Awad <i>et al.</i> , 2014)
2	<i>Pseudomonas monteilii</i> (culture filtrate)	<i>Panax quinquefolius</i>	Ginsenosides (↑ 2.5 fold)	Cell suspension culture	(Biswas <i>et al.</i> , 2016)
3	<i>Bacillus circulans</i> (culture filtrate)	<i>Panax quinquefolius</i>	Ginsenosides (↓ slight)	Cell suspension culture	(Biswas <i>et al.</i> , 2016)
4	<i>Mesorhizobium huakuii</i> (culture filtrate)	<i>Panax ginseng</i>	Ginsenosides (↑; highest in gram negative)	Root culture	(Le <i>et al.</i> , 2018)
5	<i>Lactobacillus plantarum</i> (culture filtrate)	<i>Panax ginseng</i>	Ginsenosides (↑; enhanced but lower than gram negative)	Root culture	(Le <i>et al.</i> , 2018)
6	<i>Stenotrophomonas maltophilia</i> (culture filtrate)	<i>Hypericum perforatum</i>	Hypericin (↑ 3 fold)	Shoot culture	(Mañero <i>et al.</i> , 2012)
7	<i>Agrobacterium rhizogenes</i> (cellular extract)	<i>Gymnema sylvestre</i>	Gymnemic acid (↑ 66.12 mg/g)	Cell suspension culture	(Chodiseti <i>et al.</i> , 2013)
8	<i>Escherichia coli</i> (cell free extract)	<i>Andrographis paniculata</i>	Andrographolide (↑ 8.3 mg/g)	Cell suspension culture	(Gandi <i>et al.</i> , 2012)
9	<i>Pseudomonas aeruginosa</i> (cellular extract)	<i>Rosmarinus officinalis</i>	Rosmarinic acid (↑ 3.7→3.9 µg/mL); caffeic, carnolic acids & carnosol (↑)	Callus culture	(Rashid <i>et al.</i> , 2011)
10	<i>Pseudomonas aeruginosa</i> (raw homogenate)	<i>Scopolia parviflora</i>	Scopolamine (↑ vs control)	Hairy root culture	(Jung <i>et al.</i> , 2003)
11	<i>Agrobacterium rhizogenes</i> (cellular extract)	<i>Scutellaria lateriflora</i>	Acteoside, baicalin, wogonin, scutellarin, wogonoside (↑)	Hairy root culture	(Wilczńska-Barska <i>et al.</i> , 2012)
12	<i>Escherichia coli</i> (1.5% culture filtrate)	<i>Helicteres isora</i>	Diosgenin (↑ 9.1 fold)	Cell suspension culture	(Shaikh <i>et al.</i> , 2020)
13	<i>Bacillus subtilis</i> (2% culture filtrate)	<i>Helicteres isora</i>	Diosgenin (↑ 6.1 fold)	Cell suspension culture	(Shaikh <i>et al.</i> , 2020)
14	<i>Serratia marcescens</i> (1.25% culture filtrate)	<i>Panax sikkimensis</i>	Ginsenosides (↑ 1.6 fold)	Cell suspension culture	(Biswas <i>et al.</i> , 2018)
15	<i>Serratia marcescens</i> (2.5% culture filtrate)	<i>Panax sikkimensis</i>	Ginsenosides (↑ 2.5 fold)	Cell suspension culture	(Biswas <i>et al.</i> , 2018)

3.2.2. Fungal elicitors and secondary metabolite biosynthesis

Fungal elicitors, derived from free living or endophytic species, effectively stimulate plant SMs production by activating defense mechanisms, hypersensitive responses, and phytoalexin accumulation. Commonly applied fungal elicitors include mycelial extracts, culture filtrates, cell wall fragments, and spores.

Species such as *Aspergillus niger*, *A. flavus*, *Penicillium notatum*, and *Fusarium oxysporum* significantly enhanced SMs production (Rajendran *et al.*, 1994). For instance, *A. flavus* mycelial extracts doubled anthocyanin in *Daucus carota*, while *A. niger* increased thiophene in *Tagetes patula* by 85% and menthol in *Mentha piperita* to 140.8 mg/L. In *Gymnema sylvestre*, *A. niger* increased gymnemic acid ninefold, and in *Abrus precatorius*, glycyrrhizin increased 4.9 fold. Fungal elicitors have also enhanced ginsenoside and anthocyanin levels in *Panax* species

and dye producing plants (Chakraborty and Chattopadhyay, 2008).

Mechanistically, fungal elicitors trigger ROS accumulation, activating defense related signaling cascades and upregulating enzymes such as phenylalanine ammonia lyase (PAL), cinnamate-4-hydroxylase (C4H), and tyrosine ammonia lyase (TAL). Fungal cell wall fragments increased indole alkaloids in *Catharanthus roseus* up to fivefold, while spores enhanced alkaloid production in *Papaver somniferum* by over eightfold. Endophytic fungi, such as a *Taxus chinensis* derived strain, tripled taxol production, demonstrating their dual role in growth and SMs enhancement (Chen *et al.*, 2021).

Synergistic strategies, combining fungal elicitors with abiotic factors, further maximize SMs accumulation, exemplified by elevated withaferin A in *Withania somnifera* (Thilip *et al.*, 2019). Fungal elicitors provide scalable, species specific approaches for enhancing plant secondary metabolism. Table 2 shows the impact of various fungal elicitors on the enhancement of SMs in medicinal plants.

Table 2. Fungal elicitors and their impact on SMs production.

No.	Elicitor used	Target plant	Target metabolite (Change)	Type of culture	Ref.
1	<i>Aspergillus niger</i> (aqueous extract)	<i>Gymnema sylvestre</i>	Gymnemic acid (↑ 9 fold)	Cell culture	(Devi, 2011)
2	<i>Aspergillus niger</i> (aqueous extract)	<i>Abrus precatorius</i>	Glycyrrhizin (↑ 4.9 fold)	Cell culture	(Karwasara <i>et al.</i> , 2011)
3	<i>Rhizopus stolonifera</i> (aqueous extract)	<i>Abrus precatorius</i>	Glycyrrhizin (↑ 3.8 fold)	Cell culture	(Karwasara <i>et al.</i> , 2011)
4	<i>Trichoderma atroviride</i> (culture filtrate)	<i>Panax quinquefolius</i>	Ginsenosides (↑ 3.2 fold)	Cell suspension culture	(Biswas <i>et al.</i> , 2016)
5	<i>Trichoderma harzianum</i> (culture filtrate)	<i>Panax sikkimensis</i>	Ginsenosides and Anthocyanins (↑)	Cell suspension culture	(Biswas <i>et al.</i> , 2018)
6	<i>Trichoderma harzianum</i> (culture filtrate)	<i>Centella asiatica</i>	Asiaticoside (↑ 2.53 fold)	Cell culture	(Prasad <i>et al.</i> , 2013)
7	<i>Fusarium oxysporum</i> (culture filtrate)	<i>Hypericum perforatum</i>	Hypericin and Pseudohypericin (↑ in early growth phase)	Shoot culture	(Gadzovska Simic <i>et al.</i> , 2015)
8	<i>Phomaexigua</i> (culture filtrate)	<i>Hypericum perforatum</i>	Hypericin and Pseudohypericin (↑ in early growth phase)	Shoot culture	(Gadzovska Simic <i>et al.</i> , 2015)
9	<i>Botrytis cinerea</i> (culture filtrate)	<i>Hypericum perforatum</i>	Hypericin and Pseudohypericin (↑ in early growth phase)	Shoot culture	(Gadzovska Simic <i>et al.</i> , 2015)
10	<i>Mucor hiemalis</i> (cell wall filtrate)	<i>Taverniera cuneifolia</i>	Glycyrrhizic acid (maximum enhancement)	Root culture	(Awad <i>et al.</i> , 2014)
11	<i>Fusarium moniliforme</i> (cell wall filtrate)	<i>Taverniera cuneifolia</i>	Glycyrrhizic acid (↑ 3fold)	Root culture	(Awad <i>et al.</i> , 2014)
12	<i>Aspergillus niger</i> (cell wall filtrate)	<i>Tavernieracuneifolia</i>	Glycyrrhizic acid (↑ 3 fold)	Root culture	(Awad <i>et al.</i> , 2014)
13	<i>Claviceps purpurea</i> (cellular extract)	<i>Azadirachtaindica</i>	Azadirachtin (↑ 5 fold)	Hairy root culture	(Satdive <i>et al.</i> , 2007)
14	<i>Protomyces gravidus</i> (autoclaved cell wall filtrate)	<i>Ambrosia artemisiifolia</i>	Thiarubrine A (↑ 3 fold)	Hairy root culture	(Bhagwath and Hjorts, 2000)

3.2.3. Polysaccharide elicitors

Polysaccharides, macromolecules composed of monosaccharides, act as biotic elicitors influencing structural integrity and metabolic signaling. They include endogenous (cellulose, pectin) and exogenous (chitin, chitosan) molecules, both capable of modulating stress responses and SMs biosynthesis.

Yeast extract (YE) enhances SMs accumulation; for example, in *Pueraria candollei*, isoflavonoids increased 4.5 fold (Udomsuk *et al.*, 2011), and in *Salvia miltiorrhiza*, tanshinones rose tenfold (Zhao *et al.*, 2012). Chitosan, a deacetylated derivative of chitin, elevated withaferinA in *Withania somnifera* 4.03 fold (Thilip *et al.*, 2019), increased artemisinin in *Artemisia annua* and plumbagin in *Plumbago rosea* (Putalun *et al.*, 2007). Other polysaccharides including pectin,

mannan, dextran, and alginate have similarly enhanced SMs levels across plant systems.

Marine derived polysaccharides such as ulvan and laminarin also act as effective elicitors. Ulvan promotes phenolic biosynthesis in *Olea europaea* (Ben Salah *et al.*, 2018), whereas laminarin enhances isoflavonoid production in *P. candollei* (Korsangruang *et al.*, 2010). Mechanistically, polysaccharides activate defense related enzymes and genes, particularly PAL, triggering flavonoid, phenol, lignin, and other SMs accumulation. Treatments with methyl jasmonate (MeJA) can further amplify these effects (Hasanloo *et al.*, 2009; Zhang and Liu, 2015). Table 3 the effects of different polysaccharideelicitors on the enhancement of SMs in various plant species.

Table 3. Effects of polysaccharide elicitors on SMs accumulation.

No.	Elicitor used	Target plant	Target metabolite (Change)	Type of culture	Ref.
1	Yeast extract (0.5 mg/mL)	<i>Pueraria candollei</i>	Isoflavonoids (↑ 4.5 fold; 60→270 mg/g)	Hairy root culture	(Udomsuk <i>et al.</i> , 2011)
2	Yeast extract	<i>Salvia miltiorrhiza</i>	Tanshinones (↑ 10 fold)	Cell culture	(Zhao <i>et al.</i> , 2012)
3	Yeast extract (1.5 mg/L)	<i>Catharanthus roseus</i>	Vinblastine (22.74% yield); Vincristine (48.49% yield)	Germinating embryos	(Maqsood and Abdul, 2017)
4	Chitosan (100 mg/L)	<i>Withania somnifera</i>	Withaferin A (↑ 4.03 fold)	Hairy root culture	(Thilip <i>et al.</i> , 2019)
5	Chitosan (150 mg/L)	<i>Artemisia annua</i>	Artemisinin (↑ significant vs control)	Hairy root culture	(Putalun <i>et al.</i> , 2007)
6	Chitosan (200 mg/L)	<i>Plumbago rosea</i>	Plumbagin (↑ 8.2 fold)	Immobilized cell culture	(Komaraiah <i>et al.</i> , 2003)
7	Chitosan + SA + JA	<i>Azadirachta indica</i>	Azadirachtin (↑ 5 fold)	Cell suspension culture	(Prakash and Srivastava, 2008)
8	Chitin (200 mg/L)	<i>Hypericum perforatum</i>	Phenylpropanoids and naphthodianthrone (↑)	Cell suspension culture	(Gadzovska Simic <i>et al.</i> , 2015)
9	Mannan (yeast cell-wall polysaccharide)	<i>Hypericum adenotrichum</i>	Pseudohypericin (↑ 2.8 fold); Hypericin (↑ 1.7 fold)	Cell culture	(Yaaner <i>et al.</i> , 2013)
10	<i>Fusarium oxysporum</i> mycelial polysaccharides (20 mg/L)	<i>Dioscorea zingiberensis</i>	Diosgenin (↑ 3.83 fold)	Hairy root culture	(Li <i>et al.</i> , 2011)
11	Dextran and laminarin	<i>Solanum lycopersicum</i>	Phenylpropanoids and flavonoids (↑ significant)	Cell suspension culture	(Lu <i>et al.</i> , 2019)
12	Sodium alginate	<i>Vitis vinifera</i>	Total phenolics (↑ 1.7 fold)	Cell suspension culture	(Cai <i>et al.</i> , 2012)

3.2.4. Protein elicitors

Proteins from pathogens function as potent elicitors by interacting with plant membrane ion channels to transmit stress signals. Lectins, agglutinins, elicitors, and other pathogen derived proteins induce defense responses, necrosis, or membrane depolarization. Bacterial proteins such as PeBL1 and PeBA1 stimulate phenolic biosynthesis and systemic resistance (Wang *et al.*, 2015). Protein fragments from *E.coli* upregulate

glycyrrhizic acid and flavonoid biosynthetic genes, and polysaccharide protein complexes enhance tanshinone and scopolamine production (Jung *et al.*, 2003). Microbial proteins, including harpins and flagellins, also elicit phytoalexins, while whole microbial inocula improve biomass and SMs yields across multiple plant systems (Li *et al.*, 2011; Okada, 2011). Table 4 shows the effects of protein elicitors on the enhancement of SMs in various plant.

Table 4. Protein elicitors in enhancing SMs.

No.	Elicitor used	Target plant	Target metabolite (Change)	Type of culture	Ref.
1	PeBL1	<i>Nicotiana benthamiana</i>	Phenolic compounds (↑)	Cell culture	(H. Wang <i>et al.</i> , 2015)
2	PeBA1	<i>Nicotiana benthamiana</i> , <i>N. tabacum</i>	Phenolic compounds (↑)	Cell culture	(Wang <i>et al.</i> , 2016)
3	Protein fragment from <i>E. coli</i>	<i>Glycyrrhiza uralensis</i>	Glycyrrhizic acid, glycyrrhetic acid, flavonoids (↑)	Root culture	(Li <i>et al.</i> , 2016)
4	Polysaccharide protein complex from <i>Bacillus cereus</i>	<i>Salvia miltiorrhiza</i>	Tanshinone (↑), Scopolamine (↑)	Cell culture	(Zhao <i>et al.</i> , 2010)
5	Protein elicitor from <i>Bacillus cereus</i>	<i>Scopolia parviflora</i>	Scopolamine (↑)	Cell culture	(Jung <i>et al.</i> , 2003)

3.2.5. Algal and cyanobacterial elicitors

Seaweed and cyanobacterial extracts enhance plant growth, defense, and SMs production. Algal polysaccharides such as carrageenans, fucans, laminarans, and ulvans trigger secondary metabolism. Red seaweed extracts from *Kappaphycus alvarezii* increased hypericin in *Hypericum perforatum* by 2.45 fold (Sharma *et al.*, 2015), and green alga *Botryococcus braunii* enhanced vanillin and vanillylamine production by three, and sixfold, respectively (Bhaskar *et al.*, 2022). Cyanobacterial extracts from *Nostocmus corum* boosted alkaloids and phenolics in *Solanum trilobatum* and *Ocimum sanctum* (Wake *et al.*, 1991). These elicitors act via ROS accumulation, calcium signaling, and activation of PAL and other defense related enzymes.

3.2.6. Hormonal and hormone like elicitors

Phytohormones such as salicylic acid (SA), jasmonic acid (JA), abscisic acid (ABA), and auxins modulate plant defense and secondary metabolism. ABA, SA, and JA activate signaling cascades that enhance anthocyanin production in *Fragaria ananassa*, *Daucus carota*, and related species (Martínez-Viveros *et al.*, 2010; Wang *et al.*, 2021). IAA promotes growth, root

initiation, and metabolite biosynthesis, as shown in *Melissa officinalis* (Parray *et al.*, 2016; Çakmakçı *et al.*, 2020).

Gibberellic acid (GA) and brassinosteroids (BS) regulate secondary metabolism and stress adaptation via transcriptional control and diterpenoid pathways (Hedden, 2020; Sharma *et al.*, 2013). JA and MeJA enhance phenolics, carotenoids, and antioxidants across multiple species (Creelman and Mullet, 1997; Chung *et al.*, 2016). Calcium and melatonin act as secondary messengers, promoting somatic embryogenesis, anthocyanin accumulation, and IAA biosynthesis (Akula and Ravishankar, 2011).

Elicitor effects are concentration dependent; for example, chitosan enhances growth and metabolite accumulation at optimal doses but inhibits above threshold concentrations (Kim *et al.*, 1997, 2005). Comparative studies reveal differential effects of JA, YE, and other elicitors on antioxidant capacity, carotenoid content, and phenolic accumulation (Złotek *et al.*, 2014, 2016, 2017). Table 5 shows the effects plant growth regulators such as ABA, IAA, JA, and calcium on the enhancement of secondary metabolite production and in various plants.

Table 5. Hormonal and hormone like elicitors modulating SMs accumulation.

No.	Elicitor used	Target plant	Target metabolite (Change)	Type of culture	Ref.
1	ABA	<i>Fragaria ananassa</i> , <i>Daucus carota</i> , <i>Oxalis reclinata</i> , <i>Ipomoea batatas</i>	Anthocyanins (↑)	Suspension culture	(Martínez-Viveros <i>et al.</i> , 2010)
2	2,4-D and IAA	<i>Fragaria ananassa</i> , <i>Daucus carota</i> , <i>Oxalis reclinata</i> , <i>Ipomoea batatas</i>	Anthocyanins (↑)	Suspension culture	(Wang <i>et al.</i> , 2021)
3	JA	<i>Ocimum basilicum</i> , <i>Lactuca sativa</i>	Phenolic compounds (↑), Antioxidants (↑)	In vitro culture	(Creelman and Mullet, 1997)
4	JA	<i>Origanum majorana</i> L.	Carotenoids (↑), Ascorbic acid, Chlorophyll (↑)	In vitro culture	(Chung <i>et al.</i> , 2016)
5	Calcium	<i>Daucus carota</i> , <i>Coffea canephora</i>	Anthocyanin production (↑), Somatic embryogenesis (↑)	In vitro culture	(Kim <i>et al.</i> , 2005)

3.3. Optimizing elicitor delivery: dose, timing, and environmental factors

Elicitation in plant systems is influenced by multiple interrelated factors, including elicitor type and concentration, exposure duration, developmental stage of the plant, treatment frequency, and environmental conditions such as soil characteristics and nutrient availability. Genetic variation, both at the species and cultivar levels, frequently exerts a more pronounced effect on elicitor responsiveness than the intrinsic

properties of the elicitor itself. Elicitor concentration, in particular, has a dose dependent influence on both the quantity and quality of SMs production (Jain *et al.*, 2021; Namdeo, 2004).

Case studies highlight the importance of optimizing elicitor conditions. Leaf disk derived callus cultures of *Psoralea corylifolia* L. were treated with biotic elicitors including fungal extracts from *Aspergillus niger* and *Penicillium notatum*, yeast extract (YE), and chitosan at various concentrations. Psoralen synthesis was quantified in 16 days old cultures under a 16 h light/8 h

dark cycle. Among all treatments, *A.niger* extract induced a ninefold increase in psoralen levels relative to controls, while *P.notatum*, YE, and chitosan elicited four to sevenfold enhancements. The maximal psoralen content (9850 µg/g DCW) was observed at 1.0% (v/v) *A.niger* extract. These findings illustrate both the efficacy and concentration dependence of elicitors, emphasizing the narrow optimal ranges for maximal metabolite accumulation (Ahmed and Baig, 2014; Kang *et al.*, 2009; Kundu *et al.*, 2012).

Similar dose dependent effects are reported for other metabolites, including taxol and ajmalicine (Khosroushahi *et al.*, 2006; Namdeo *et al.*, 2002). The type and preparation of the elicitor also significantly affect biomass and SMs yields (Karwasara *et al.*, 2011). In *Melissa officinalis* suspension cultures, MeJA (10–100 µM) modestly increased hydroxycinnamic acid derivatives at lower concentrations, whereas higher doses resulted in reduced accumulation (Urdová *et al.*, 2015).

The successful induction of hairy roots in *Mentha spicata* leaf and stem explants using multiple *Agrobacterium rhizogenes* strains highlights another approach to elicitation. While immersion caused tissue necrosis, direct injection achieved high transformation efficiencies, with strain A13 achieving nearly 75% infection. Hairy roots infected with A13 and R318 produced the highest biomass (~60 mg/flask), whereas GMI 9534 resulted in the highest phenolic acid content. Phytohormonal treatments further enhanced growth and metabolite accumulation: 0.3 mg/L IBA improved root biomass, and 100 µM MeJA increased phenolic acid levels (Yousefian *et al.*, 2020). These results underscore the importance of optimizing elicitor type, dosage, application method, and timing to maximize both biomass and SMs production.

3.4. Synergistic combination strategies

Methyl jasmonate (MeJA), originally isolated from *Jasminum grandiflora*, is a key signaling molecule that promotes the overproduction of various SMs (Jeyasri *et al.*, 2023). Salicylic acid (SA), a central component of systemic acquired resistance (SAR), enhances defense gene expression and improves plant tolerance to microbial infections. The combined action of SA and JA not only strengthens pathogen resistance but also stimulates the biosynthesis of triterpenoids (e.g., ginsenosides, glycyrrhizin) and monoterpenes under optimal conditions (Farmer *et al.*, 1992; Hayat *et al.*,

2010; Ryals *et al.*, 1996; Walling, 2000; Xu *et al.*, 2012).

Empirical evidence demonstrates that SA, in combination with other elicitors, significantly enhances alkaloid production in hairy root cultures. For instance, 18 days old *Brugmansia candida* hairy roots treated with SA (0.01–1.0 mM) showed pronounced accumulation of hyoscyamine and scopolamine, with peak scopolamine levels at 72 hours approximately tenfold higher than untreated controls (Urdová *et al.*, 2015).

Jasmonate mediated elicitation similarly triggers extensive transcriptional and metabolic reprogramming, leading to enhanced production of alkaloids, phenylpropanoids, and isoprenoids across multiple plant species (De Geyter *et al.*, 2012). Notable examples include increased ginsenosides in *Panax ginseng* (Lu *et al.*, 2001), soyasaponins in *Glycyrrhiza glabra* (Hayashi *et al.*, 2003), total phenolics and flavonoids in *Artemisia absinthium* (Ali *et al.*, 2015), and phenolic compounds in *Celastrus paniculatus* (Anusha *et al.*, 2016). JA also regulates defense gene expression, as demonstrated by enhanced triterpene production in *Jatropha curcas* and increased psoralen levels in *Psoralea corylifolia* under in vitro conditions (Siva *et al.*, 2015; Zaragoza-Martínez *et al.*, 2016).

Microbial elicitors further complement phytohormone driven pathways, often producing synergistic increases in metabolite yields. For instance, bacterial extracts from *Escherichia coli*, *Agrobacterium rhizogenes*, and *Bacillus subtilis* enhanced gymnemic acid in *Gymnema sylvestre* (Chodiseti *et al.*, 2013), while *Staphylococcus aureus* promoted bilobalide synthesis in *Ginkgo biloba* (Kang *et al.*, 2009). Lactic acid bacteria stimulated betalain alkaloid production in *Beta vulgaris* (Savitha *et al.*, 2006), and *A. rhizogenes* promoted ginsenoside accumulation in *Panax ginseng* (Jeong and Park, 2005).

Fungal and oomycete elicitors also enhance SMs biosynthesis. Glycoproteins from *Verticillium albo atrum* induced Ca²⁺ dependent phytoalexin accumulation in *Medicago sativa* cultures (Walton *et al.*, 1993), while oligosaccharides from *Fusarium oxysporum* increased diosgenin in *Dioscorea zingiberensis* (Li *et al.*, 2011). Similarly, artemisinin production in *Artemisia annua* was enhanced using oligosaccharides from *Colletotrichum gloeosporioides* (Wang *et al.*, 2001; Wang *et al.*, 2009), and thiarrubrine A from *Protomyces gravidus* increased SMs

accumulation in *Ambrosia artemisiifolia* (Bhagwath and Hjorts, 2000). Viral infections also influence metabolite levels, as observed in *Echinacea purpurea* (Pellati *et al.*, 2011). Co-application of phytohormonal and pathogen derived elicitors has been shown to dramatically enhance phenolic accumulation, as seen in *Coleus blumei* cultures treated with MeJA and *Pythium aphanidermatum* extracts (Szabo *et al.*, 1999).

These studies collectively highlight that combining hormonal, microbial, and pathogen derived elicitors can synergistically elevate enzyme activities and secondary metabolite yields beyond the effects of individual treatments.

4. Conclusion

Biotic elicitors offer a powerful strategy to enhance the biosynthesis of valuable SMs in medicinal plants. From bacterial and fungal extracts to polysaccharide derivatives, these agents activate plant metabolic pathways, resulting in increased yields of pharmaceutically important compounds. Optimization of elicitor type, concentration, timing, and plant developmental stage is essential to maximize metabolite production without compromising growth. Synergistic combinations, such as MeJA with SA, further underscore the potential of integrated elicitation strategies. Looking forward, advanced approaches such as receptor engineering, transcriptomics, and metabolomics can enable more targeted and efficient elicitation. Large scale bioreactor systems present an opportunity for sustainable, industrial scale production of plant derived therapeutics. With continued refinement, medicinal plants may serve as predictable, high yield biofactories, meeting the growing global demand for natural pharmaceuticals and nutraceuticals.

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