Efficiency of microbial bio-agents as elicitors in plant defense mechanism under biotic stress: A review

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A B S T R A C T

Numerous harmful microorganisms and insect pests have the ability to cause plant infections or damage, which is mostly controlled by toxic chemical agents. These chemical compounds and their derivatives exhibit hazardous effects on habitats and human life too. Hence, there’s a need to develop novel, more effective and safe bio-control agents. A variety of microbes such as viruses, bacteria, and fungi possess a great potential to fight against phytopathogens and thus can be used as bio-control agents instead of harmful chemical compounds. These naturally occurring microorganisms are applied to the plants in order to control phytopathogens. Moreover, practicing them appropriately for agriculture management can be a way towards a sustainable approach. The MBCAs follow various modes of action and act as elicitors where they induce a signal to activate plant defense mechanisms against a variety of pathogens. MBCAs control phytopathogens and help in disease suppression through the production of enzymes, antimicrobial compounds, antagonist activity involving hyper-parasitism, induced resistance, competitive inhibition, etc. Efficient recognition of pathogens and prompt defensive response are key factors of induced resistance in plants. This resistance phenomenon is pertaining to a complex cascade that involves an increased amount of defensive proteins, salicylic acid (SA), or induction of signaling pathways dependent on plant hormones. Although, there’s a dearth of information about the exact mechanism of plant-induced resistance, the studies conducted at the physiological, biochemical and genetic levels. These studies tried to explain a series of plant defensive responses triggered by bio-control agents that may enhance the defensive capacity of plants. Several natural and recombinant microorganisms are commercially available as bio-control agents that mainly include strains of Bacillus, Pseudomonads and Trichoderma. However, the complete understanding of microbial bio-control agents and their interactions at cellular and molecular levels will facilitate the screening of effective and eco-friendly bio-agents, thereby increasing the scope of MBCAs. This article is a comprehensive review that highlights the importance of microbial agents as elicitors in the activation and regulation of plant defense mechanisms in response to a variety of pathogens.

Abbreviations: MBCAs, Microbial biological control agents; SA, Salicylic acid; ISR, Induced systemic resistance; SAR, Systemic acquired resistance; PGP, Plant growth promotion; PGPR, Plant growth promoting bacteria; PGPR, Plant growth promoting rhizobacteria; PGPF, Plant growth promoting fungi; P, Phosphorous; N, Nitrogen; PRRs, Pattern recognition receptors; PAMPs, Pathogen-related proteins; LAR, Local acquired resistance; DAMPs, Damage-associated molecular patterns; MAMPs, Microbe-associated molecular patterns; PTI, Pattern triggered immunity; ETI, Effector-triggered immunity; HIR, Herbivore induced resistance; HAMP, Herbivore-associated molecular patterns; ABA, Abscisic acid; JA, Jasmonic acid; ET, Ethylene; TFs, Transcription factors; ROS, Reactive oxygen species; LPS, Lipopolysaccharides; ISS, Induced systemic susceptibility; BTH, Benzothiadiazole; TMV, Tobacco mosaic virus; BABA, β-Ami

Nitrobutyric acid; NO, Nitric oxide; GSH, Glutathione; VOCs, Volatile organic compounds; Fe, Iron; HRs, Hormonal receptors; HG, Heptaglucan; CRRI, Cross kingdom RNA interference; RLKs, Receptor-like-kinases; RLPs, Receptor-like-proteins.

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Introduction

Plant diseases caused by biological factors lead to tremendous loss of crop productivity and its quality. Various strategies can be used for the prevention and control of plant diseases. Despite of good agricultural management practices, most plant growers rely upon chemical fertilizers or insect pesticides (Pal and Gardener, 2006). Although, chemical agents have improved crop productivity significantly for many years, their potential adverse effects and excessive use lead to considerable damage to the soil ecosystem and increased environmental pollution. Therefore, substantial work has been done to develop eco-friendly approaches to control plant diseases and simultaneously reduce associated health risks. The use of biological control agents is one of the alternative strategies that involve the application of organisms to control plant diseases (El-Gamal et al., 2007). Biological regulation of plant diseases can be accomplished by the use of living organisms that inhibit the development of plant pathogens (Heimpel and Mills, 2017; Barupal et al., 2019). Suppression of plant pathogens by naturally occurring beneficial microbes, able to grow on artificial media and showing the highest inhibitory activity is termed as microbial biological control agents (MBCAs). Such antagonistic biological control agents are applied once or repetitively during growing seasons in high densities to enhance plant protection are called “augmentative biological control” (Eilenberg et al., 2001; Heimpel and Mills, 2017; van Lenteren et al., 2018). Not only whole microorganisms but sometimes their derivatives like microbial metabolites can also be used as biological control agents (Glare et al., 2012; Barupal et al., 2020). Elicitors are components that induce a signal to activate chemical defense mechanisms in plants. Among the widely studied chemical elicitors like salicylic acid, methyl salicylate, benzothiadiazole, chitosan, benzoic acid, etc. are found to have an effect on the production of various phenolic compounds and activation of enzymes in plants related defense systems (Heimpel and Mills, 2017).

Elicitors vary from each other based on their source, nature and molecular structure (Thakur and Sohal, 2013; Pšić and Ongena, 2020). They are broadly classified as exogenous elicitors and endogenous elicitors. Exogenous elicitors are compounds produced by pathogens, whereas endogenous elicitors are molecules released from plants in response to pathogenic attack (Ramirez-Estrada et al., 2016). These elicitors can be physical or chemical, biotic or abiotic in nature. All elicitors of microbial origin are considered as biotic elicitors. Many microbial elicitors are integral structural components or primary determinants of pathogenicity. Some elicitors help in the dispersion of microbial agents or induce signals to evoke plant immunity. Since, numerous MBCAs have the potential to induce plant defense mechanisms through the action of their compounds; they serve as microbial elicitors in plant defense regulation (Zehra et al., 2017a; Zehra et al., 2017b; Malik et al., 2020). Various biological control agents are useful that differ in their mechanism of action. However, thorough understanding of multifaceted interactions between biological controls, plants, animals, and the environment is necessary to develop the most effective and safe biological control agents. This review attempts to explain the role and different mechanisms of microbial bio-agents as elicitors in plant defense regulation.

Elicitors and their mechanisms

Initially, the term elicitor was used for molecules capable of inducing phytoalexin production. However, it is now frequently used for compounds that stimulate any kind of plant defense response (Thakur and Sohal, 2013). Bio-control agents interact with the components of plant diseases such as environment, plant host, and pathogen. To reduce plant damage and promote its growth, many bio-control agents with effective phytopathogen inhibitory activity have been developed and registered all around the world. The use of bio-control agents involves the natural or deliberate exploitation of living organisms (microorganisms) that interact with phytopathogens. These interactions may alter soil conditions and considerably affect plant health in various ways (Chet, 1987). Several commercially available MBCA’s contain naturally derived or genetically modified microbial species or their products. Sometimes the product includes beneficial microorganisms and in some cases, it contains only antimicrobial metabolites without the antagonist’s living cells (Glare et al., 2012).

The antagonist activity of many microbial species such as Trichoderma, Pseudomonas, Bacillus species, and other microbes of the rhizosphere has been investigated and available as registered plant protection products for tomato, potato, rice, sunflower, etc. (Dutta and Das, 2002; Bhuiany et al., 2012; Parikh and Jha, 2012; Zehra et al., 2015; Meena et al., 2016). In addition, mycoviruses and bacteriophages may also be used against plant pathogens as potential MBCAs (van Lenteren et al., 2018). As of now, more than 100 MBCAs have been registered in different countries including United States, New Zealand, Europe, Canada, Australia, Japan, and Brazil to control plant diseases (van Lenteren et al., 2018). However, the major challenges associated with the use of MBCAs are the difficulty in direct administration of bio-control agents in the land and increased cost. The other serious concern associated with MBCAs is that their use and make them potentially dangerous organisms is not only their toxicity but their characteristics to multiply, genetic adaption, and probable dominance over natural organisms that may lead to a negative impact on the environment. A clearer understanding of mechanisms of MBCAs at the cellular, molecular and genetic levels would help to overcome these problems and develop more efficient and safe bio-control agents. Microbial biological control agents provide protection to the plants from deleterious effects of phytopathogens through various modes of action (Fig. 1).

However, it has been noticed that almost in all cases MBCAs exhibit antagonism against plant pathogens (Pal and Gardener, 2006) and it is mainly dependent upon specific interactions that occurred between host, pathogen, and biological control agents. MBCAs can control these plant pathogens and help in disease suppression by direct antagonism, mixed interactions, or indirect antagonism. These interactions involve a variety of mechanisms such as parasitism, predation (Ghorbanpour et al., 2018), antibiosis, enzyme productions, competition for nutrients and space (Spadaro and Droby, 2016), and induced plant resistance mechanism. Apart from this, MBCAs also support plant growth promotion and stress tolerance (Babbal et al., 2017).

Induction of systemic resistance in plants by elicitors of microbial bio-agents

Chester in 1933 reported that plants induced defense against a variety of pathogens by biotic or abiotic agents, where he termed this phenomenon as acquired physiological immunity. Since that time several other terms were used to describe the idea of induced resistance, such as acquired systemic resistance, trans-located resistance and plant immunization. Induced resistance is one of the important mechanisms where the plant’s defense ability gets enhanced in response to a spectrum of pathogens and insect pests after the acquisition of proper stimulus. This enhanced resistance, which is developed due to the induction of infectious agents is known as induced systemic resistance (ISR), or systemic acquired resistance (SAR) (Vallad and Goodman, 2004; Kumari et al., 2018a; Kumari et al., 2018b; Swapnil et al., 2021). The induction of systemic resistance by beneficial microorganisms specifically from the rhizosphere, such as bacteria and fungi occurs in ISR, whereas the resistance induced by pathogens and insects is called SAR (Romera et al., 2019). The rhizosphere, an immediate environment of the root system, is a powerful ecological unit comprising of innumerable microorganisms that can be pathogenic or advantageous to plants. Plant-microbe interaction is governed by a variety of compounds secreted by the plant roots into the soil. These compounds form a network between plant and microbes and also attract beneficial microbes towards the plants. Plant roots also secrete some compounds
Many bacterial species that serve as bio-control agents by eliciting ISR and thus potent biological control agents (Gowthami, 2018). Protect plants by eliciting ISR against pathogens (Reglinski and Walters, 2009). There is a variety of microorganisms that are considered as elicitors once activated. Many biotic and abiotic agents have been shown to enhance defensive capability established with sufficient stimulation. Resistance to infectious diseases in plant tissues without a direct antagonist helps in modifying root system.

Additionally, these microbes can induce resistance or increased resistance to infectious diseases in plant tissues without a direct antagonist to the pathogen. Such microbial diversity can greatly enhance the functional attributes of the plants and elicit induced systemic resistance against pathogens (Meena and Swapnil, 2019). Several studies are available since the nineties showing the ability of beneficial soil microbes like PGPR in eliciting ISR that mainly highlights Pseudomonas species as a bio-control agent. Induced resistance is a plant state with enhanced defensive capability established with sufficient stimulation once activated. Many biotic and abiotic agents have been shown to protect plants by eliciting ISR against pathogens (Reglinski and Walters, 2009). There is a variety of microorganisms that considered as elicitors of ISR and thus potent biological control agents (Gowthami, 2018).

Induced resistance can be activated in crops due to the infectious agents, herbivory of insects, or root colonization by some mutualistic microbes of the rhizosphere (Romera et al., 2019; Meena et al., 2017a; Meena et al., 2017b). Both the induced resistance forms i.e. SAR and ISR are the activation of latent resistant mechanisms which are expressed with a pathogen after successive inoculation or challenge. SAR and ISR are mostly discriminated based on the elicitor and the regulatory pathways involved, although some components are shared by the signaling pathways that control both SAR and ISR. Although, the mechanism by which beneficial microorganisms elicit ISR is not fully understood, various microbial elicitors have been reported to induce systemic resistance among crops. Stimuli recognized by unique recognition receptors activate induced plant defense mechanisms.

Some pattern recognition receptors (PRRs) that have the ability to identify microbial compounds such as bacterial flagellin, fungal chitin, polysaccharides are called pathogen- or microbe-associated molecular patterns (PAMPs or MAMPs) according to the recent understanding of the plant immune system (Boller and Felix, 2009). PAMPs induce protective mechanisms in crops to improve pathogen resistance in the host. Following the damage caused by the invasion of attackers, plants give response to endogenous plant-derived signals called damage-associated molecular patterns (DAMPs) (Boller and Felix, 2009; Zipfel, 2009; Villeda et al., 2018). PAMP-triggered immunity (PTI) is a first line defense transferred by pattern recognition that monitors the most potential invaders (Dodds and Rathjen, 2010). A pathogen effectively suppresses the host plant against pathogen infection, escape the first-line of defense (PTI) by repression or restricting host detection with PTI signaling and successfully establish plant infection.
and activate systemic defense priming to balance the mutualistic relation among host and microbe (Pieterse et al., 2014b). However, organisms actively try to suppress local host defense responses in the roots. The commencement of PTI and ETI often activates an induced resistance in plant tissues that are distal from the site of infection and engross more than one long-distance signal that broadcasts a better defensive ability in still undamaged plant parts. This distinguished form of pathogen-induced resistance is generally known as SAR (Fig. 2). Plants also have the ability to recognize herbivorous insects that utilize a similar signaling concept (Fig. 3) (Pieterse et al., 2014a).

Over the past few years, the ISR has been extensively reviewed. The mechanisms by which beneficial rhizospheric microbes elicit ISR are not completely understood. However, several microbial elicitors have been proposed to be responsible for its commencement. Beneficial microorganisms actively try to suppress local host defense responses in the roots and activate systemic defense priming to balance the mutualistic relation among host and microbe (Pieterse et al., 2014b). However, ISR-inducing beneficial microbes should produce elicitors that are responsible for the establishment of systemic immunity. ISR has been suggested to be the result of a long-distance signaling mechanism where beneficial symbiotic microbial associations such as rhizobial and mycorrhizal symbiosis are primarily responsible for the autoregulation of the symbionts’ colonization density (Pieterse et al., 2014a; Meena et al., 2017c; Meena et al., 2017d). Rhizobacterial species have a wide community in the soil near plants. Various studies revealed that jasmonic acid (JA) and ethylene (ET) signaling is an important player in the regulation of rhizobacterial mediated ISR (Mou et al., 2020). It is also known as PGPR based on jasmonic acid-ethylene (JA-ET) or plant growth-promoting fungi (PGPF) mediated ISR (O’Keefe, 1998).

When any plant gets infected by a pathogen, the plant detects the MAMPs which are small molecular motifs conserved in microbes (Fig. 4). Plant possesses a receptor on their surface to recognize MAMPs known as PRRs. This interaction is said to be an established interaction. Further, this triggers PTI (PAMP triggered immunity). PTI and MYB72 (transcription factor) by hypothetical interaction induces ISR by systemic translocation of the long-distance molecular or electric signal. Thus, it moves from local to the systemic level of resistance (Pieterse et al., 2014b). NON-EXPRESSOR OF PATHOGENESIS-RELATED GENES 1 (NPR1) is a common regulator for ISR and SAR but their function differs in both pathways (Dong, 2004). NPR1 and pathogenesis-related (PR) genes play a vital role in plant defense response against pathogens. NPR1 works without direct activation of PR gene. DNA binding transcription factors (TFs) control this, and MYC2 is also a helix-loop-helix transcription factor that is a master JA signaling pathway regulator (Zhai and Li, 2019). JA and ET are also expressed due to beneficial microbes. These transcription factors further activate the JA/ET dependent defense genes thus induce resistance response by activation of reactive oxygen species (ROS) or other defense-related genes or synthesis of other chemical components. Early studies on MAMPs and other PGPR-inducing ISR emitters highlight the contribution of other molecules such as lipopolysaccharides (LPS), pyoverdin, salicylic acid, and iron-regulated metabolite (Meena et al., 2020).

Similarly, many studies identified other elicitors associated with different microbes includes antibiotics, pyocyanin, flagellin, siderophores that regulates ion channel, volatile organic compounds and biosurfactants (Pieterse et al., 2014b). The genomic analysis of Trichoderma spp., and mycorrhizal fungi showed that many genes encode effectors and elicitor molecules that have a great potential to further investigate their importance in the elicitation of ISR (Mukherjee et al.,

![Fig. 2](image-url) Overview of systemic acquired resistance (SAR) pathway mechanism. SAR is effective against a broad range of pathogens and pests. In systemic tissues, induction of SAR is characterized by increased levels of the hormone salicylic acid (SA). Accumulation of SA is regulated by NahG gene which, through the redox-regulated protein NON-EXPRESSOR OF PR GENES 1 (NPR1), activates the expression of a large set of pathogenesis-related (PR) genes, causing defensive responses among plants. NPR1 is required for both pathogen-dependent and rhizobacteria-mediated systemic induced resistance. PR proteins confer enhanced immunity or resistance to the plant against phytopathogens.
Herbivore attack

Fig. 3. Molecular components and mechanisms involved in herbivore induced resistance (HIR). Herbivore-associated molecular patterns (HAMP), initiates the herbivore-induced resistance signaling pathway. Since insect-derived effector molecules can suppress host defense, plants may have evolved resistance (R) genes like PRR and NB-LRRs against herbivore effectors. Herbivory-derived elicitors result in rapid release of jasmonate (JA) which is released in the form of jasmonoyl-isoleucine (JA-Ile), recognized by a co-receptor complex comprised of the F-box protein CORONATINE INSENSITIVE 1 (COI1) and JASMONATE ZIM-domain (JAZ) proteins. These binding results play important roles in proteasome-mediated degradation of the JAZ proteins. This binding leads to proteasome-mediated degradation of the JAZ proteins. In un-induced cells, it suppresses positive regulators of JA-mediated defense responses, such as the transcription factors MYCs (MYC2, MYC3, and MYC4). A local tissue injury results in membrane depolarization by ion fluxes, which mediates rapid biosynthesis of JA that further leads to the expression of many JA-responsive genes. In the case of systemic resistance, abscisic acid (ABA) acts as a regulator. Accumulation of ABA triggers herbivore-induced resistance by activating the expression of defense response.

Beneficial microbes

Fig. 4. Molecular components and mechanisms involved in induced systemic resistance (ISR). Signal transduction pathway leading to PGPR-mediated induced systemic resistance. Beneficial microbes like rhizobacteria trigger enhanced immunity through activation of JA/ET dependent defense genes. Phytohormones like JA and ET are required for activation of ISR, where transcription factor (e.g. MYC2) mediate increased responsiveness of these pathways to elicitation, known as priming. (MAMP, Microbe-associated molecular pattern; PRRs, Pattern-recognition receptors; PTI, PAMP-triggered immunity; NPR1, NON-EXPRESSOR OF PATHOGENESIS RELATED GENES 1; JA, Jasmonic acid; ET, Ethylene; TFs, Transcription factors)
2013; Tissierant et al., 2013). Genus Pseudomonas is found to be capable of inducing systemic resistance in Arabidopsis. It functions independently without a need of SA but requires priming of jasmonate and ET. A further demonstration was done by using two different species of Pseudomonas that is Pseudomonas fluorescens WCS417r and Pseudomonas syringae pv. tomato. Defense-related genes like SA signature genes namely PR-1, PR-2, PR-5, (Cao et al., 1994) ethylene-inducible gene Hel, ethylene- and jasmonate-responsive genes Chat and Pef12, and jasmonate-inducible genes AtNpr1, Lox1, and Lox2 (Bell and Mullet 1993). Poll and Pin2 was found to induce locally as well systematically when the plant was infected with P. syringae pv. tomato (Van Wees et al., 1999). PR gene accumulation was seen in SAR expressing plants, while JA/ET responsive gene expression was seen in ISR plants. This concludes that ISR depends upon the expression of JA/ET but not on SA- genes (Van Wees et al., 1999).

In the defense system of plants, small RNA also plays a significant function. The role of such microRNA (miRNA) in plant defense was studied to investigate its expression regulation by microbial control agents in response to the pathogen. For instance, one of the expression studies was conducted using Bacillus cereus AR156, a rhizobacterium that induces ISR in Arabidopsis. When Arabidopsis plant was infected with P. syringae pv. tomato pretreated with or without Bacillus cereus AR156 (Smith et al., 1991), it results in the generation of two different microRNA from a single miRNA gene, designated as miR825 and miR825* (Where, “*” represents conserved nucleotide). It was seen that after infection with Pet DC3000, the expression of miR825 and miR825* was drastically reduced in plants pretreated with AR156 than that in plants without pretreatment. It was also demonstrated that both miR825 and miR825* play an important role in modulating ISR through negatively regulating resistance-related genes (Niu et al., 2016a; Niu et al., 2016b). Similarly, Bacillus cereus AR156 found to suppress the activity of miR472 to induce ISR in Arabidopsis (Jiang et al., 2020).

A fungus Trichoderma harzianum also has the potential to induce ISR in maize against Curvularia leaf spot disease (Fan et al., 2015; Saravanakumar et al., 2016). Activation of C6 zinc finger protein-like elicitor (Thc6) is essential for ISR in leaf. This study reveals two hydrolases, Thph1 and Thph2 that are regulated by Thc6. This protein triggers the production of ROS, elevates the level of calcium in the leaf, and also up-regulates the expression of JA/ET genes. When, this Thph1 and Thph2 were mutated and studied they were not able to show the ISR. This concludes that Trichoderma harzianum can induce ISR in maize leaf in presence of Thph1 and Thph2 proteins (Saravanakumar et al., 2016).

Another ectomycorrhizal fungus Laccaria bicolor was found to induce ISR. For this Arabidopsis thaliana was infected with cabbage looper (Trichoplusia ni) and P. syringae pv. tomato DC3000. L. bicolor triggered the ISR in Trichoplusian infected plant, while it induced systemic susceptibility (ISS) in P. syringae pv. tomato DC3000 infected plant. Further studies also revealed that L. bicolor induced ISR was dependent on JA signaling. Chitin receptor CERK1 was found to be necessary for L. bicolor mediated ISR (Vishwanathan et al., 2020). Another study revealed the relation between Archea and plants. Ammonia-oxidizing archaeon Nitrosooccusiales oleophilus MY3 colonizes the roots of Arabidopsis plants. This Archea found to induce ISR in Arabidopsis against Pectobacterium carotovorum subsp. carotovorum SCC1 and P. syringae pv. tomato DC3000 by SA independent signaling pathway (Song et al., 2019).

**Induction of systemic acquired resistance pathway by the elicitors**

Disease control among plants has become a necessity due to the impact on the yield of products. To prevent such diseases lots of chemically manufactured fungicides, insecticides, herbicides are available and farmers are using them for since long, but this has proven to be harmful to the environment as well as humans. So, it has become essential to search for something new that will be harmless, eco-friendly, cost-effective and productive (Pal and Gardener, 2006). One of the focused methods which occur naturally among plants is their defense mechanism pathway. If such pathways are induced then their expressions enhance, so this has become one of the major focused topics among research. One of the resistant pathways among plants is SAR. SAR is response throughout plant tissues that occurs during earlier localized exposure to a pathogen. It is a signal transduction pathway that helps a plant in defending against pathogens. After exposure to a pathogen, a hypersensitive response like necrotic lesions is been seen which results in activation of systemic resistance pathways (Balint-Kurti, 2019).

When any pathogen attacks on the plant, it generates an immune response against it, which is also known as elicitation of plants. A chemical compound named as elicitor triggers this immune response in plants thus increases the defence against pathogens. Thus, this can be a great option to induce SAR by using different elicitor molecules (Fig. 5) (Bektas and Eulgem, 2015). Like, in one of the latest studies done by using a new elicitor Reticine A extracted from the fruit peel of Citrus reticulata. Efficacy was tested both by in vitro and in vivo assays against the TMV virus. Through in vivo assays, Reticine A when compared with commercial elicitor benzothiadiazole (BTH) found to be more efficient at a concentration of 100 μg/mL and 500 μg/mL. No significant impact was seen against tobacco mosaic virus (TMV) particle in vitro. Reticine A-induced hypersensitive reaction, systemic accumulation of H2O2 and SA, leads to increase in expression of defensive enzymes and up-regulation of PR proteins, through the expression of NPR1 and SA biosynthesis genes ICS and PAL. This concludes that this new elicitor Reticine A has the ability to induce SAR against TMV virus in the tobacco plant (Wang et al., 2021). Another study against the TMV virus on plant Nicotiana tabacum by induction of SAR using elicitor molecule known as Berberine was done (da Silva et al., 2016). Berberine is an alkaloid molecule with lots of antimicrobial properties. In vitro studies demonstrated the effect of Berberine on TMV by showing hypersensitive reactions, accumulation of H2O2, overexpression of pathogenesis-related proteins, etc. (Miyata et al., 2006). In vitro studies did not show any positive effect. After determination of SA biosynthesis-related genes, upregulation of SA- genes was found thus confirmed the importance of SA in defense mechanisms. Thus, it concludes that berberine can be used to induce defense in tobacco plants against TMV. It can also induce defense in plants against other pathogens like Phytophthora nicotianae, Botrytis cinerea and Blumeria graminis (Martínez-Hidalgo et al., 2015; Guo et al., 2020).

PeFOC1 is a protein elicitor isolated from Fusarium oxysporum f. sp. cubense induces HRs and found to be effective in tobacco plants against TMV and P. syringae pv. tabacii (Li et al., 2019). Real-time PCR found several up-regulated-defense-related genes such as Npr1A, Npr1P, Npt, NED51, and NILOX. PeFOC1 elicitor molecule can be used as an effective bio-control agent in the future (Li et al., 2019). SAR elicitors like JA, SA, BTH, and β-amino butyric acid (BABA) were tested for efficacy to induce SAR in potato plant against Phytophthora infestans and muskmelon against Pseudoperonospora cubensis. A schedule was set of 5-week spray with a combined dose of fungicide. Salicylic acid was found to be most effective among both hence prove to be the best treatment for disease control by inducing SAR (Astha and Sekhon, 2017). A similar study was done by using SAR elicitor SA, JA, BTH, and BABA. Plants of potato and muskmelon were treated with different concentrations of elicitors to study SAR against Phytophthora infestans and Pseudoperonospora cubensis. Leaf samples were studied for further analysis using western PAGE and found to be increased expression of SAR proteins which further helps in the induction of SAR (Astha, Sekhon and Sangha, 2019). Elicitors acibenzolar-S-methyl, BAB, cis-jasmonate were found to be effective against infection in barley by Rhynchosporium commune. The combination of these three elicitors showed the largest reduction in infection thus upregulate SAR (Walters et al., 2014).

Acteoin is a volatile rhizobacterial elicitor molecule produce by B. subtilis found to induce systemic resistance in Arabidopsis thaliana against P. syringae pv. tomato DC3000 (Shen et al., 2019). Further
analysis concluded that resistance to DC3000 is due to NPR1 and needs SA and ET but not JA and this further leads to PR protein expression. Thus, many different rhizobacterial elicitors might show SAR response against various pathogens (Rudrappa et al., 2010).

Hormonal regulation of induced systemic resistance by elicitors of beneficial microbes

In 1991, the importance of root colonizing rhizospheric nonpathogenic microorganisms in activating ISR was discovered and since the time several studies were conducted to reveal the molecular mechanism underlying the fact (Abstrom, 1991; Van Peer et al., 1991; Vos et al., 2013). Initially, it was presumed that rhizospheric microbes-mediated ISR follows the same mechanism as seen in pathogen-induced SAR. However, certain evidence showed the involvement of different signaling pathways in activation of ISR which are not exhibited during SAR. For example, Hoffland et al. (1995) demonstrated that P. fluorescens WCS417r-ISR developed against F. oxysporum in radish plants where a key protein of SAR called PR protein was not accumulated. Likewise, in Arabidopsis, P. fluorescens WCS417r-ISR was developed, although, the PR gene remains inactivated in systemic leaf tissue (Pieterse, 1996). Further, genetic pieces of evidence reveal that P. fluorescens WCS417r-ISR is regulated by SA (Meziane et al., 2005; De Vleesschauwer et al., 2008). Similarly, SA independent signaling pathway was observed in the case of ISR-inducing PGPR P. putida WCS358r (Pangesti et al., 2017). This and few more supportive pieces of evidence clearly suggested that rhizobacteria-mediated ISR and SA-dependent SAR are not only effective against a broad range of invaders but both are regulated by different signaling pathways (Pieterse, 2014a).

Further studies with rhizobacteria made it evident that the ability to activate SA independent signaling pathway is very common in the case of beneficial bacteria like rhizospheric microbes and a variety of plants (Van Loon and Bakker, 2005; Sunil et al., 2015). Although, SAR and ISR involve some common compounds, they differ from each other on the basis of elicitors and the signaling pathways involved (Pieterse et al., 1998, 2002, 2012, 2014b; Van Loon et al., 1998; Choudhary et al., 2007). Plant hormones such as JA, ET, and other signaling molecules are considered as important regulators of the plant immune system. Several studies have demonstrated that the plant hormones like JA and ET are key players in the regulation of most of the physiological and morphological responses among plants (Lucena et al., 2015; Li and Lan, 2017; Romera et al., 2017). Apart from ET, several other compounds like auxin, sucrose, nitric oxide (NO), glutathione (GSH) and cytokinins have also found to regulate plant processes; however, their exact role in the regulation is still unclear (Seguelia et al., 2008; Shammugam et al., 2015; Lin et al., 2016; Li and Lan, 2017; Kailasam et al., 2018).

Similarly, the mechanism by which beneficial microbes of the rhizosphere elicit ISR is obscured. However, numerous microbial elicitors are found to be responsible for triggering the ISR by regulating various plant hormones (Sharifi and Ryu, 2018; Tyagi et al., 2018). These elicitors are MAMPs and other elicitors, like volatile organic compounds (VOCs) or siderophores (Martínez-Medina et al., 2017; Sharifi and Ryu, 2018; Tyagi et al., 2018; Villena et al., 2018). When pathogenic organisms produce MAMPs are called PAMPs. These are conserved molecules produced by microbes, e.g. bacterial flagellin, LPS, and chitin (Zeidler et al., 2004; Pieterse et al., 2014; Villena et al., 2018). LPS produced by rhizobacteria are able to trigger induced systemic resistance (Mishra et al., 2012; Rodriguez and Bos, 2013) against succeeding infections without the accumulation of PR protein and phytoalexins (Beneduzi et al., 2012). On other hand, VOCs are low molecular weight organic chemicals that are derived through different biosynthetic pathways, have high vapor pressure, low water solubility, and thus able to evaporate and disperse easily (Sharifi and Ryu, 2018; Tyagi et al., 2018). Presently, more than 1000 volatile compounds have been identified that include alkanes, alcohols, esters, ketones, terpenoids, sulfides, and sesquiterpenes (Tyagi et al., 2018). Such elicitors which are derived from beneficial microorganisms can drastically help in promoting plant growth prototype that usually involves alteration of hormonal signaling (Garnica-Vergara et al., 2016; Martínez-Medina et al., 2017; Sharifi and Ryu, 2018; Tyagi et al., 2018). Presently, more than 1000 volatile compounds have been identified that include alkanes, alcohols, esters, ketones, terpenoids, sulfides, and sesquiterpenes (Tyagi et al., 2018). Such elicitors which are derived from beneficial microorganisms can drastically help in promoting plant growth prototype that usually involves alteration of hormonal signaling (Garnica-Vergara et al., 2016; Martínez-Medina et al., 2017; Sharifi and Ryu, 2018; Tyagi et al., 2018). Siderophores are small, iron chelating agents secreted by the bacteria and fungi that further transport iron (Fe) from the surrounding medium (Lemanceau et al., 2009; Aznar and Delling, 2015; Aznar et al., 2014, 2015).

Mode of action

Several studies have been carried out using rhizospheric bacteria and fungi to review SAR and ISR extensively (Van Loon et al., 1998;
In systemic tissues, SAR is typically characterized by augmentation of the SA, a hormone that utilize the redox-regulated protein called as NON-EXPRESSION OF PATHOGENESIS-RELATED GENES 1 (NPR1) to activate PR (pathogenesis-related) genes expression, which is a large set of genes concerned with plant defense responses (Van Loon et al., 1998; Choudhary et al., 2007; Pieterse et al., 2014). Conversely, ISR usually involves SA-independent pathway which provides resistance against bio-trophic pathogens where JA and ET act as the key players, and typically function without activating PR genes by mediating resistance to herbivorous pests as well as necro-trophic pathogens (Bari and Jones, 2009). The quantity, composition and timing of these molecules rely on mode of infection and the lifestyle of pathogen (De Vos et al., 2005). Pathogenesis-related proteins (PRPs) are the signature genes of JA and SA pathways in many crop plants. PR1, PR2, and PR5 genes induce the activation of SA signaling pathway by increasing their expression (Fig. 6) (Ali et al., 2017). Expressions of PR3, PR4 and PR12 genes activate the JA pathway in Arabidopsis.

MAMPs are recognized by PRRs whilst other elicitors could be recognized by other receptors, which are not known completely (Fig. 7) (Jankiewicz and Koltonowicz, 2012; Pieterse et al., 2014; Aznar and Dellagi, 2015; Aznar et al., 2015; Sharifi and Ryu, 2018; Tyagi et al., 2018; Villena et al., 2018). Once recognized by specific receptors, the microbial elicitors activate the ISR by acting upon various plant hormones. These plant hormones further act as essential players in commencement of plant defense mechanism by stimulating plant immune signaling cascade (Pieterse et al., 2012, 2014; Sharifi and Ryu, 2018; Tyagi et al., 2018). Sometimes, microorganisms can produce different types of hormones by their own. For instances, auxin or cytokinins, produced by microbes are recognized the plant hormonal receptors (HRs) that alter the physiology and morphology of plant roots (Grady et al., 2016; Scagliola et al., 2016; Asari et al., 2017; Kudoyarova et al., 2017; Patel and Saraf, 2017). The different hormones concerned with ISR are mainly JA, ET, auxin, and NO that plays major role in plant defense response (Garnica-Vergara et al., 2016; Hossain et al., 2017; Martínez-Medina et al., 2017; Nie et al., 2017; Nascimento et al., 2018; Stringlis et al., 2018). The importance of JA and ET in the regulation of rhizobacteria-mediated ISR was demonstrated in Arabidopsis mutants where JA or ET signaling pathways impaired (Pieterse et al., 1998). Similarly, a number of studies conducted on JA or ET signaling mutant P. fluorescens WCS417r was found to have defective ISR due to impaired jar1, jin1, and coi1 genes (among JA signaling mutants) or etr1, ein2, ein3, and eir1 (in case of ET signaling mutants) (Pieterse et al., 1998; Knoester et al., 1999; Pozo et al., 2008). Studies have also been conducted using other plant growth promoting rhizobacteria (PGPR) like P. fluorescens Q2-87, P. protegens CHA0 and Serratia marcescens 90–166, which explain an essential role of JA and ET in ISR regulation. Depart from PGPR, studies carried out with many PGPF (plant growth promoting fungi), like Trichoderma harzianum T39, Penicillium sp. GP16-2, and P. indica, provided genetic evidence in Arabidopsis that suggest the role for JA and/or ET in the regulation of ISR (Iavicoli et al., 2003; Ryu et al., 2004; Ahn et al., 2007; Hossain et al., 2008; Korolev et al., 2008; Stein et al., 2008; Weller et al., 2012). The role of phytohormones was also observed among different plants such as tomato and rice (De Vleesschauwer et al., 2008; Hase et al., 2008; Van der Ent et al., 2009). JA and ET are found to be central players in the regulation of the SA-independent signaling pathway that leads to systemic immunity among plants conferred by beneficial soil microbes. Despite of eliciting ISR to activate plant immune response, beneficial microbes have also been reported to exert negative effects on plant-insect interaction (Pineda et al., 2013).

**Bio-control agents (methylotrophs, nitrogen fixing microbes and cyanobacteria) and their elicitor molecules**

For sustainable agriculture, methylotrophic bacterial community utilize reduced carbon compounds to play significant role in crop yield, plant growth promotion (PGP) and soil fertility (Kumar et al., 2019).

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**Fig. 6. Activation of signaling cascades in plants after pathogenic infection.** PR proteins are diverse proteins induced by different phytopathogens and signaling molecules. After pathogen attack defense signaling pathways (SA and JA) activated which leads to the accumulation of PR proteins and minimizes the pathogen disease. PR genes activated by the accumulation of SA and JA through selective transcription factors NPR1 and MYC, respectively. PR proteins activated SAR pathway which induces the expression of PR1 and PR2 and PR5, while JA pathway expresses PR3, PR4, and PR12 genes in a sequential manner which leads to accumulating local product to provide local acquired resistance (LAR). The pathway indicated that JA signaling triggers resistance against necro-trophic pathogens.
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PGP affected by environmental factors such as abiotic and biotic stresses. Methylotrophic microbes such as Methylovorax, Methyloobacterium, Methylotherma, Methylophilus, Methylocella, Methylopila, Methylobacillus, Methylovirgula, and Methylohalomonas play an important role to mitigate abiotic stress (severe low and high temperature, salt and drought) (Cao et al., 2011; Yadav et al., 2017; Sapp et al., 2018; Kumar et al., 2019). The methylotrophic communities perform biological nitrogen fixation, solubilization of potassium, phosphorus, and zinc, production of phytohormones (auxins and cytokinins), Fe-chelating compound, ammonia, secondary metabolites and siderophores. Phytohormones secreted by methylotrophs promote the seed germination and growth of plants to endure abiotic stress (Verma et al., 2016). Methylotrophs also exude the plentiful osmo-protectants like sugars and alcohols on the plant surface, which protect the plants from excessive desiccation and radiations. Therefore, it has been investigated that utilisation of potent methylotrophic microbes facilitate the PGP by reducing abiotic stress. Symbiotic nitrogen-fixing bacteria/cyanobacteria such as Bradyrhizobium, Rhzizobium, Azorhizobium, Sino-rhizobium, Allorhizobium, and Mesorhizobium play a very significant role in crop production and biogeochemical cycles for decades (Hayat et al., 2010). It has been reported that free-living nitrogen fixers, like Enterobacter, Azospirillum, Pseudomonas, and Klebsiella are attached to the root and colonize the root surfaces efficiently (Prasad et al., 2015). They synthesize particular compounds to facilitate the uptake of nutrients from the soil and protect the plants from diseases. To prevent the plants from phytopathogenic organisms they produce siderophores, antibiotics hydrogen cyanide (HCN), β-1,3-glucanase and chitinase and phytohormones (Singh et al., 2019).

Regulation of plant genes and pathways involved in defense mechanism

A relation among plants and pathogens is long back, thus plants have evolved various mechanisms to prevent themselves from diseases. Plants can induce resistance through various genes and pathways involved in them. Defense mechanism in plants includes primary, secondary and additional defense (Fig. 8) (Zhang et al., 2019).

In primary defense, plant detects the infection by PAMPs or MAMPs using cell surface localized PRRs. Microbial compounds such as flagellin in bacteria, chitin in fungi, etc. (Zipfel, 2014) can be identified by PRR. Thus, two best MAMPs/PRR pair was characterized named as flagellin/FLS2 and EF-Tu/EFR (Boller and Felix, 2009). Different plant PRRs and their signaling adapters based on pathogens are listed in Table 1 (Zipfel, 2014).

In most of the pathogens, pattern-triggered immunity (PTI) induces the defense mechanism in plants. Changes in PRRs induce the other secondary defense mechanism like effector-triggered immunity (ETI) (Bigeard et al., 2015). It is also known as elicitor mediated defense mechanism. The receptor proteins NB-LRR (nucleotide-binding–leucine-rich repeat) identify effector molecules which results in ETI (Dodds and Rathjen, 2010). ETI provides a species of specific disease resistance. Many dicot and eudicot plants have lots of NB-LRR genes. It is further divided into two classes terminal toll/interleukin-1 receptor (TIR) or coiled-coil (CC)/resistance to powdery mildew 8 (RPW8) domains, thus they are crucial for signaling transmission (Mukhtar et al., 2011).

The third defense is exosome mediated cross kingdom RNA interference (CKRI) system whose function is to silence the virulence genes from microbes by vesicle transport of small RNAs and microRNAs (Li et al., 2010). In PTI and ETI, this microRNAs regulates defense associated genes thus acts as a shield against pathogens like virus, bacteria, fungal infection, etc. (Li et al., 2010). Different gene regulator groups
Pathogen-associated molecular pattern (PAMP) triggered immunity (PTI) is the primary defense which is related to the pathogen-associated molecular pattern triggered immunity (PTI), the secondary defense involves effector-triggered immunity (ETI) and the additional defense includes the exosome-mediated cross-kingdom RNA interference (CKRI) system.

![Diagram](image_url)

**Table 1**

| Pathogen | Bacteria | Fungi | Oomycetes |
|----------|----------|-------|-----------|
| Signaling molecule | Receptor protein | | |
| Flagellin (flg22; epitope of flagellin) | FLS2 | EF-Tu (efl18; epitope of EF-Tu) | Unknown PAMPs |
| EF-Tu | EFR | | |

**Table 2**

| Genes / Regulators | PTI | miRNAs |
|--------------------|-----|--------|
| CNL | RLP | miRNA-PTI |
| TNL | RLK | miRNA-ETI |
| C/T/N/L | | CRK |

Note: R-proteins are categorized into five main classes: [i] CC-NBS-LRR (CNL), [ii] TIR-NBS-LRR (TNL), [iii] Receptor-Like-Kinases (RLKs), [iv] Receptor-Like-Proteins (RLPs), and [v] other variants (Sanseverino et al., 2010); cross kingdom RNA interference (CKRI).

are shown in the **Table 2**.

Not just in case of pathogen attack, but also during stressful environmental condition various adaptive defense system is generated. Like for example, during low temperature, plants must be capable of receiving different signals and transducing it to another receptor to create a defense. Another system also includes osmotic balance, reprogramming of transcriptional pathways, etc. (Zhou et al., 2020). As per one of the studies done to characterize the genes and pathways in *Arabidopsis thaliana* and rice (*Oryza sativa*), which are responsible for the acclimation of the plants to the harsh environments changes in various mechanisms due to low temperature like signal transduction in various sensors, calcium signaling, activation of protein cascades, etc. was seen (Guo et al., 2018; Zhao et al., 2020).

*Phytophthora sojae* is the pathogen which is responsible for roots and stem rots in soybean. So, comprising the defense mechanism of soybean seed against this infection was studied at the proteomic level. Extracted proteins after the infection were further analyzed by two-dimensional gel electrophoresis (Tyler, 2007; Dzhavakhiya and Shcherbakova, 2007). Eighty three protein spots were further identified by matrix-assisted laser desorption/ionization mass spectrometry were found to be defense related proteins. Not only this, further study proved that there was an upregulation in the expression of ROS, SA-pathway and synthesis of isoflavones. ROS and SA play an important role in inducing defense among soybean (Jing et al., 2015).

Two important defense mechanisms used by plants to prevent entry of microbes are stomatal closure defense and apoplastic defense. Stomatal defense is also known to be the part of PAMP triggered immunity (Asai and Shirasu, 2015; Yan et al., 2019). Recognition of PAMP receptors induces Ca$^{2+}$ signaling and MAP kinase phosphorylation which further affects the channel activities to control stomatal closure. Through various studies, it has been found that microbes release a phytotoxin named coronatine which mimicks the plant JA thus leads to reopening of stomata and further gain entry inside plants (Melotto et al., 2006; Meena and Samal, 2019; Venegas-Molina et al., 2020). Once they enter, they need to face apoplastic defense. This works by releasing ROS, toxic compounds and PR proteins. Expression of this molecule and secretary pathway is a part of PTI and ETI (Jones and Dangl, 2006).

**Conclusion**

This review concluded that the naturally occurring microbial biological control agent (MBCAs) played beneficial role to protect plants from harmful pathogens to control plant diseases. As per studies, it has been concluded that the excessive use of chemical agents causes the environmental pollution. Therefore, microbial biological control agent emerged as beneficial methods to protect plants without affecting environments. There are several microbes can be used such as viruses, bacteria, and fungi have a great potential to scrap against phytopathogens. There are various mode of action have been followed by MBCAs as elicitors to induce a signal to stimulate the plant defense mechanism against pathogens. This review discussed the mechanism of MBCAs at cellular and molecular level to overcome the plant diseases and development of more proficient and safe bio control agents. In induced resistance mechanisms, defense ability of plants is increased due to ISR or SAR. Rhizosphere microbes or rhizobacteria or plant-growth-promoting bacteria (PGPB / PGPR) and PGPF establishes the mutual symbiotic association with plants to improve P and N content and helps in modifying root system. Expression of PR genes concerned with plant defense responses which are augmented by SAR. Microorganisms also produce different types of hormones which are recognized by plant HRs and concerned with ISR. Overall, this article discussed the inclusive significance of MBCAs and their relations with plants to understand plant defense mechanism at cellular and molecular level.

**Author’s Contributions**

AZ: Provided the general concept; Original draft preparation; Validation; Visualization; Prepared the figures and tables; Resources;
Supervision; Writing – Review & editing
NAR: Original draft preparation; Writing – Review & editing; Prepared the figures and tables
MM: Provided the general concept, conceived, and drafted part of the manuscript; Writing – Original draft preparation; Prepared the figures and tables; Conceptualization; Investigation; Resources; Supervision; Validation; Visualization; Writing – Review & editing
PS: Provided the general concept; Original draft preparation; Writing – Review & editing

All authors read and approved it for publication.

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Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Declaration of Competing Interest
The authors declare that the work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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