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Review Article

ROLE OF SECONDARY METABOLITE 2, 4-DAPG BY FLUORESCENT *PSEUDOMONADS* ISOLATES FROM KASHMIR IN PLANT DISEASE SUPPRESSION: A REVIEW

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Abstract: Plant diseases which are caused by Fungi, bacteria, viruses and nematodes can be controlled by various Biocontrol agents. Biocontrol of soil borne fungal diseases can be achieved by using fluorescent strains of *Pseudomonas*. Many species of *Pseudomonas* inhabiting the soil rhizosphere are competitive colonizers of the soil rhizosphere and possess the ability to suppress fungal pathogens. Fluorescent pseudomonads are mainly studied because of their widespread distribution in soil, their ability to colonize the rhizosphere of host plants and ability to produce a wide range of secondary metabolites inhibitory to a number of serious plant pathogens. Antibiotic production by *Pseudomonas fluorescens* is now recognized as an important feature in plant disease suppression. Introduction of biocontrol agents to agriculture requires appropriate and compatible plant growth promoting rhizobacteria PGPR for the goal of making agriculture more sustainable. Moreover, an understanding of how biocontrol bacteria regulate the expression of genes involved in the inhibition of pathogens is important for predicting the optimum environmental conditions of the bacteria to produce antagonistic compounds. In this review, we will provide an overview of *Pseudomonas* biocontrol agents, their mechanism of disease suppression and role of secondary metabolites in disease control. our main focus will be on 2,4- Diacetylphloroglucinol (2, 4-DAPG)..

Keywords: *Pseudomonas fluorescens, Antagonistic, Biocontrol, Antimicrobial agents, Phytopathogenic fungi, 2, 4-DAPG, PGPR*

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Introduction

In recent years, several companies have programs to develop biocontrol agents as commercial products. This is in concern with the public about deleterious effects caused by using chemical pesticides. Biological solution in the form of microorganism's particularly fluorescent *Pseudomonas* spp has the capacity to promote plant growth without substantially harming the environment. The rhizosphere, which represents the thin layer of soil surrounding plant roots and the soil occupied by the roots, supports large active groups of bacteria [1] known as plant growth promoting rhizobacteria (PGPR) [2]. Plant growth promoting rhizobacteria are known to rapidly colonize the rhizosphere and suppress Soilborne phytopathogens at the root surface [3]. These organisms can also be beneficial to the plant by stimulating growth [4]. Biological control has been a significant approach to plant health management during the twentieth century and promising results through introducing modern biotechnological techniques to be even more significant in the twenty-first century [5]. Nowadays, the use of biopesticides and Biofertilizers to replace chemical fertilizers and pesticides is growing in the global market. The use of microbial antagonists as biological control agents is believed to be safer than the traditional chemical pesticides. Representative species of bacteria and fungi, and in a few cases, nematodes have been identified as biocontrol agents (BCAs) against many soil borne plant pathogens; the most abundant soil and plant associated bacterial genera among such groups are Burkholderia, Bacillus, *Pseudomonas*, Serratia and Streptomyces [6]. Plant growth promoting bacteria promote healthy growth of plant by producing phytohormones, siderophore, antibiotics, enzymes [7] .

Fluorescent *Pseudomonas* species

The genus *Pseudomonas* is ubiquitous bacteria in agricultural soils and has many characteristics that make them well suited as PGPR. The most effective strains of *Pseudomonas* haven been fluorescent *Pseudomonas* spp. Fluorescent *Pseudomonas* spp help to maintain soil health and are metabolically and functionally most diverse [8]. *Pseudomonas* species are ubiquitous in nature, they belong to one of the most studied soil borne group of bacteria. Some members of this group produce diffusible pigments. Pseudomonads are well known for their potential of degrading compounds, which are difficult to be assimilated by other microorganisms [9]. 2, 4- Diacetylphloroglucinol (DAPG) is a broad-spectrum antibiotic with antibacterial and antifungal activities. Some strains of fluorescent *Pseudomonas* species producing secondary metabolite 2, 4- DAPG which is known to be responsible for antiphytopathogenic and biocontrol properties in these SPP [10]. DAPG is produced by *Pseudomonas fluorescens* both in vitro and in the rhizosphere of wheat. It is involved in the natural suppression of take-all disease known as take all declines, which develops in soil following extended monoculture of wheat or barley. The antibiotic 2, 4-DAPG has a broad spectrum of activity and is especially active against the take all pathogen. Based on genotype analysis by repetitive sequence-based PCR analysis and restriction fragment length polymorphism of PhlD, a key 2, 4-DAPG biosynthesis gene, at least 22 genotypes of 2,4-DAPG producing fluorescent *Pseudomonas* spp. have been described worldwide.

Biological control of soil-borne pathogens: Mechanisms involved

Pseudomonas fluorescens is an aerobic, gram –negative, ubiquitous organism present in agricultural soils and well adapted to grow in the rhizosphere [11]. This rhizobacterium possesses many traits to act as a biocontrol agent and to promote the plant growth ability. Certain fluorescent *Pseudomonas* species can induce a systemic resistance in plants that is effective against a broad spectrum of pathogens [12]. The antifungal metabolite 2,4-diacetylphloroglucinol play a major role in the biocontrol capabilities of *Pseudomonas fluorescens* [13]. *Pseudomonas fluorescens* Pf-5, now known as *Pseudomonas protegens* [14], produces a very broad range of antimicrobial compounds. The genome of this strain was the first of any biocontrol agent sequenced [15] and analysis of the genome showed that nearly 6% of the genes are dedicated to production of antimicrobial compounds [16]. Several reports on disease suppression have pointed out that many different mechanisms contribute to disease control. Antagonistic bacteria can act directly through the plant by inducing host defence responses that limit the ability of fungal invasion to the root and alters the fungal pathogenicity process [17]. Therefore, it is important to understand the mechanisms of disease suppression by biocontrol agents for the successful utilization of biological control as disease management strategy. In the following some of the recognized mechanisms of biocontrol of soil-borne pathogens by antimicrobial agents will be discussed.

Competition

Despite being one of the most abundant elements in the Earth's crust, iron is a major limiting factor for bacterial growth, because most of the iron in natural habitats is in the insoluble Fe(III) form [1]. In response to iron limitation, microbes have evolved numerous mechanisms to scavenge iron from their surroundings [18]. Siderophores, produced by pseudomonads are low molecular weight compounds with high iron chelating affinity under iron deficiency conditions [19]. Siderophore production favors rapid growth of the producing organisms. It was found that the role of siderophores was associated with the antagonistic properties of *Pseudomonas putida* WCS358 in suppressing fusarium wilt of radish [20]. Under certain conditions, siderophores can function as a diffusible bacteriostatic or fungistatic antibiotic [21]. Even though, various bacterial siderophores differ in their abilities to sequester iron, generally they deprive pathogenic fungi of this essential element since the fungal siderophores have lower affinity. It was clearly demonstrated the inhibitory potential of Pyoverdin (Pvd)-producing Although several authors have demonstrated the contribution of Siderophores to suppress disease in certain situations; it is believed that Siderophores alone do not account for suppression of disease; if they were, it would be difficult to describe why most strains which produce Siderophores, do not contain biocontrol activity [21].

Induction of plant resistance mechanisms

Induced systemic resistance is a mechanism of intensified defensive capacity by a plant reacting to external stimuli (biotic or chemical) [22]. Expression of natural defense reaction against stresses from biotic or abiotic origin is exhibited by all plants, such as (i) physical stresses (heat or frost), (ii) inoculation by pathogenic or non-pathogenic organisms, (iii) chemical molecules from natural or synthetic origins [23]. Early recognition of the aggressor by the plant is one of the mechanisms involved in elicitation of plant defense reactions [24]. Recognition of the aggressor immediately initiates a series of cellular signals and the transcription of many genetic molecules, which in turn results in the production of plant defence compounds by the plant [25]. Such defence molecules include phytoalexins, pathogenesis-related (PR) proteins (such as chitinases, ß- 1,3-glucanases, proteinase inhibitors etc.) and reinforcement of cell walls [26]. A variety of soil and rhizosphere bacterial and fungal isolates can provide protection against viral, fungal, and bacterial plant pathogens by turning on ISR in plants [26]. However, rhizobacteria differ in their ability to turn on ISR, some are active on particular plants and not on the other [26]. Cell wall thickenings, wall appositions or rapid death of the injured plant cells resulting in necrosis of the immediate adjacent tissues which acts as a barrier that cut the pathogen off its nutrients and contributes to slowing down of the fungus progressive invasion [27]. A virulent pathogen inhibits resistance reactions or circumvents the effects of active defenses. As a result of these natural defense mechanisms, plants are able to produce an immune response after a primary pathogen infection known as systemic acquired resistance (SAR). The host plant can also benefit directly from non-pathogenic rhizobacteria and fungi through the production of metabolites that either stimulate root development and plant growth or trigger the induction of systemic resistance (ISR) that is phenotypically similar to SAR [28]. In other words, SAR is a pathogen-induce type of resistance which requires accumulation of salicylic acid while ISR is a rhizobacteria-induced type that depends on responses to ethylene and jasmonic acid [28]. These plant defense-inducing bacteria are also known to enhance plant growth and are referred to as plant growth promoting rhizobacteria (PGPR). Even though the full range of metabolites involved in microbially mediated ISR is not yet known, siderophores, antibiotics, and lipopolysaccharides has been clearly indicated [28].

Antibiosis

The process of inhibition or destruction of the pathogen by the metabolic products produced during growth of the antagonist. These include volatile compounds, toxic compounds and antibiotics, which are deleterious to the growth or metabolic activities of other microorganisms at low concentrations [29]. There are several reports from some authors, who have reported on the involvement of antibiosis in biocontrol of plant pathogens. Mechanism of antagonistic activity by the biocontrol agents, Streptomyces violaceusniger strain G10 on Fusarium oxysporum f. sp.cubense race [30] and Pantoea agglomerans strain Eh252 on Erwinia amylovora (causal agent of fire blight in orchards) [31] was attributed to antibiosis. In vitro and in vivo production of antibiotics by numerous biocontrol bacterial strains have been demonstrated [32]. It was reported earlier that a comprehensive list of antibiotics that have been implicated in biocontrol, their producing organisms and the affected pathogens. Among them were 2, 4- diacetylphloroglucinol (2, 4-DAPG), pyrrolnitrin (PRN), pyoluteorin (PLT) and different derivatives of phenazine (Phz) [33].

2, 4-diacetylphloroglucinol

The two best studied antibiotics namely DAPG and phenazine-1-carboxylic acid (PCA) by which introduced pseudomonads suppress take-all and other Soilborne diseases [34]. PhlD is responsible for the pro-duction of monoacetylphloroglucinol (MAPG), and PhlA, PhlC, and PhlB are necessary to convert MAPG to 2,4-DAPG. 2,4- diacetylphloroglucinol (2,4-DAPG) is a polyketide compound, which has received particular attention because of its effect on broad-spectrum action on various pathogens [35]. Even in medical area, there has been increasing interest on the use of 2, 4- DAPG, due to its recently reported bacteriolytic activity against multidrug-resistant Staphylococcus aureus [36]. 2, 4-DAPG is synthesized by several plant-associated fluorescent pseudomonads, and it plays a key role in the disease suppression of a wide variety of soil-borne diseases [37]. 2, 4-DAPG inhibits zoopores produced by Pythium spp. and also damages the membrane of this Oomycetes [38]. 2,4-DAPG have also shown as important biological components of the natural suppressiveness of certain agricultural soils to take-all disease of wheat [39]; fusarium wilt of pea [40] and black root of tobacco [41]. Toxic superoxide ions, hydrogen peroxide (H2o2) which are harmful to the cell or can lead to the death of the cell [42]. Although there are several mechanisms to suppress plant pathogens, the production of antibiotics by fluorescent pseudomonads remain as a primary factor in checking the development of disease and pathogens.

Biosynthesis of DAPG

Phl biosynthetic genes are conserved among all known 2, 4-DAPG-producing fluorescent *Pseudomonas* species and the key biosynthetic gene is phlD, which encodes a Type III polyketide synthase. PhlD catalyzes the synthesis of phloroglucinol (PG; a precursor of monoacylphloroglucinol (MAPG) and 2, 4-DAPG) from three molecules of malonyl- coenzyme A. The phlACB genes encode enzymes which are thought to form a complex that is required for the conversion of PG to DAPG [43]. PhlA encodes a β-ketoacyl-ACP synthase III, phlC encodes a condensing enzyme and phlB encodes a putative nucleic- acid binding enzyme [44]. These enzymes together function as an acyltransferase which converts PG to MAPG and subsequently MAPG to 2, 4-DAPG [43].

The phlACBD operon is flanked downstream by the gene phlE. PhlE and upstream by the gene PhlF(A regulator),PhlG and PhlH., and an efflux protein (PhlE). PhlF encodes a transcriptional regulator of the TetR family that specifically represses the expression of the biosynthetic operon PhlACBD . phlF binds to the phlO operator located in the intergenic region between phlF and phlA, which causes the repression on the PhlACBD operon and thus 2,4-DAPG production [43]. Mutational inactivation of the phlF gene causes repression of 2, 4-DAPG production [45]. In earlier studies it was reported that *P.fluorescens* does not produce PHL in early log phase. Later, it was reported that this is likely due to the high expression of the PhlF repressor gene during this growth phase. In the recent findings, it was reported that in the *Pseudomonas fluorescens* F113 PhlF mutant, there is repression of PHL production in the early stage of growth. PhlD is a key enzyme in 2,4-DAPG biosynthesis because it is required for the synthesis of phloroglucinol, a precursor to monoacetylphloroglucinol (MAPG) and 2,4-DAPG [46]. Production of 2,4-DAPG is also dependent on host factors such as root exudates [47] Shanahans (Currently, more than 24 sigma factors have been reported in *Pseudomonas* spp. [48].

2, 4-DAPG as a Biocontrol

2, 4-DAPG producing fluorescent *Pseudomonas* species play a key role in many natural disease suppressive soils. The production of different metabolites such as hydrogen cyanides, siderophores, extracellular lytic enzymes and antibiotics is the primary mechanism of biocontrol [49]. There are numerous reports of antibiotic produced by *Pseudomonas* Spp. There is evidence of production of the antibiotics pyrrolnitrin and pyoluteorin by different isolates of *Pseudomonas fluorescens* [50]. [51] suggested that D-gluconic acid was the most significant antifungal agent produced by *Pseudomonas* spp. strain AN5 in biocontrol of take–all on wheat roots. It shows the diverse nature of compounds which are linked to the disease suppression. General disease suppression is the phenomenon in which natural soil has the potential to suppress the growth or activity of Soilborne pathogens to a limited extent. General disease suppressive soils are called conducive soils. No specific microorganism is responsible for general disease suppression; it is caused by the total activity of microorganisms or community present in the soil. Unlike specific suppression, General suppression is not transferable between soils, soils [52]. Specific suppressive soils are caused by specific microorganisms that cause the soil to be suppressive to a specific plant disease. Specific suppressiveness is superimposed over the general suppressiveness of the soil and is highly effective against the specific pathogen. As mentioned earlier, specific suppressiveness of soil can be transferred to other conducive soils by adding 0.1% to 10% of the suppressive soil [53].

Summary

Introduction of biocontrol agents to agriculture requires appropriate and compatible PGPR for the goal of making agriculture more sustainable. However, an understanding of how biocontrol bacteria (fluorescent *Pseudomonas* spp) regulate the expression of genes involved in the inhibition of pathogens is important for predicting the optimum environmental conditions of the bacteria to produce secondary metabolites having antagonistic activity. Moreover, the growing cost of pesticides, particularly in less-affluent regions of the world, and consumer demand for pesticide-free food has led to a search for substitutes for these products. Compared to pesticides, use of biological agents to control phytopathogens is of great practical importance. Biological control of Soilborne pathogens by 2, 4-DAPG producing fluorescent pseudomonads might be an alternative or way of reducing the use of chemicals in agriculture. Fluorescent *Pseudomonas* species producing 2, 4-DAPG occurs worldwide and are effective against a wide range of plant pathogens [54]. Pathogen resistance against 2,4-DAPG is unlike since 2,4-DAPG attacks multiple basic cellular pathways [55]. The secondary metabolite (2, 4-DAPG) produced by some isolates of *Pseudomonas fluorescens* is the most interesting compound having antimicrobial activity. This compound was later known for its antifungal activity against various plant pathogens like Gaeumannomy *cesgraminis* var. tritici [56]. The structural modification of natural products is one of the most intriguing fields for the development of new drugs, novel derivatives of 2, 4- DAPG should be produced in order to improve its biological properties, and to increase its fungicidal spectrum.
For most soils, there is no knowledge of the microbial community present in the soil, which can contain 1011 microbial cells per gram root and more than 30.000 prokaryotic species [57]. Even when the microbial community is known, for most species it is unknown if and how they interact with 2,4-DAPG-producing fluorescent *Pseudomonas* species, more insight on 2,4-DAPG producing microbial community is needed on the effect of biological interactions between microorganisms and 2,4-DAPG-producers in the rhizosphere. Concluding, much research is needed on different aspect of 2, 4-DAPG-producing fluorescent *Pseudomonas* species. There is a greater need to examine the entire genome of 2, 4-DAPG-producing fluorescent *Pseudomonas* species to design strategies to draw maximum benefit from them in terms of agricultural yield.

Application of Review: Antibiotic production by *Pseudomonas fluorescens* is now recognized as an important feature in plant disease suppression. Our results suggest that DAPG production in crop rhizosphere is an important factor contributing to reduction in disease severity in wheat from soil borne plant pathogens in Kashmir region. These results go on to emphasize that these isolate of *Pseudomonas fluorescens* may play an important role in controlling the growth and occurrence of pathogenic microorganism in the arable fields of J&K and hence it is recommended that there is a greater need to examine the entire genome of these isolates to design strategies to draw maximum benefits from them in terms of agricultural yield.

Review Category: Development of ideas and Evaluation

Abbreviations:

PGPR: Plant Growth Promoting Rhizobacteria
DAPG: Diacetylphloroglucinol
SAR: Systemic Acquired Resistance
ISR: Induction of Systemic Resistance

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