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The Plant Growth Regulators: Advances, their applications and Potential Uses in Agriculture – A Review

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ABSTRACT

Plant growth regulators (PGRs) or plant hormones are the chemical species that profoundly influence the growth and differentiation of various parts of plant. PGRs called biostimulats or bioinhibitors, act inside plant cells to stimulate or inhibit specific enzymes or enzymes systems and help regulate plant metabolism. To study on this review is the brief introduction and applications of various plant growth regulators including auxins, gibberellins, cytokinins, ethylene, abscisic acid, brassinosteroids and jasmonates, triacontanol, triazoles and polyamines. Several novel plant growth regulators discovered in the recent past includes compounds like Melatonin, Serotonin, Strigolactone, Harzianolide and Karrikins. This review presents a Recent Advances in Use of Plant Growth Regulators (PGRs), the Plant growth regulators (PGRs) and their applications and Novel Plant Growth Regulators and their Potential Uses in Agriculture.

Key words: *PGRs, Gibberellins, Cytokinins, Triazoles, Triacontanol, Melatonin, Serotonin.*

Introduction

In Fruit Crop Plant growth regulators (PGRs) or phytohormones are organic compounds, other than nutrients, that produced naturally in higher plants, controlling growth or other physiological functions at a site remote from its place of production and active in minute amounts, modify plant physiological process. PGRs called biostimulats or bioinhibitors, act on core plant cells to stimulate or inhibit specific enzymes or enzymes systems and help regulate plant metabolism. They are normally active at very low concentrations in plants. Plant growth regulators generally include auxins, gibberellins, cytokinins, ethylene, growth retardants and growth inhibitors. Auxins are the hormones first discovered in plants and then gibberellins and cytokinins were also discovered. Plant hormones are known by the term phytohormones (as these hormones are synthesized in plants) in order to distinguish them from animal hormones. He defined a phytohormone as-an organic compound produced naturally in higher plants, controlling growth or other physiological functions at a site remote from its place of production and active in minute (Tejpal *et al.*, 2018).

Plant growth regulators (PGRs) or plant hormones are the chemical species that profoundly influence the growth and differentiation of various parts of plant. The activities of PGs depends on their concentration and environmental factors affecting their absorption and plants physiological state. PGRs have the ability to effect cell division, cell structure, cell expansion, cell function, and mediate environmental stress even at low concentrations.

Direct application to roots, leaf, flowers, buds and shoots has been shown to enhance resistance to biotic and abiotic stress. Products of PGRs are generally employed throughout viticulture, floriculture, agriculture and horticulture to increase crop yield in sub-optimal soil and harsh environmental conditions Shagufta Farman *et al.* (2019).

All plants naturally produce hormones in response to their surroundings that control their growth, development, and metabolism. Hormones are synthesized at various sites such as roots, buds and leaves, and are transferred to targeted locations after binding with specific receptors Rademacher (2015). Hormones control cell division, cell elongation, cell differentiation and influence plants reaction to environment stress. They can elicit multiple responses depending upon targeted tissues, plants developmental stages, relative concentrations, uptake and storage of water and other nutrients, and climatic conditions Ferguson. *et al.* (2014). There are a small number of hormones with the ability to regulate plant physiological processes that have been studied since 1930s to improve plant production and development (Rademacher (2015). These findings results in the commercial production of synthetic hormonal products, also known as plant growth regulators (PGRs). Plant growth regulators are generally used in agriculture, viticulture, and horticulture to enhance growth in non-ideal or stressful conditions (e.g. short growing seasons, low soil fertility, and diseases) and to improve yields and easy of harvesting (e.g. prevention of immature fruit drop, accelerating maturity, and ripening etc.) Harms *et al.* (1988).

Several novel plant growth regulators discovered in the recent past includes compounds like Melatonin, Serotonin, Strigolactone, Harzianolide and Karrikins. Melatonin and Serotonin which were previously studied exclusively due to their function as neurotransmitter in animals are also being reported in plants widely. These two hormones impart specific functions during biotic and abiotic stress as well as plant growth and developmental processes Ankita Mishra *et. al.* (2017). This review presents a Recent Advances in Use of Plant Growth Regulators (PGRs) Tejpal *et al.* (2018). The Plant growth regulators (PGRs) and their applications Shagufta Farman *et al.* (2019)] and Novel Plant Growth Regulators and their Potential Uses in Agriculture Ankita Mishra *et al.* (2017).

Plant hormone

It is restricted to naturally arises plant substances, they fall into five classes. Auxin, Gibberellins, Cytokinins, ABA and ethylene. Plant growth regulator includes synthetic compounds as well as naturally occurring hormones [(Tejpal S. B *et.al* (2018)].

Plant growth hormone

The primary site of action of plant growth hormones at the molecular level remains unresolved (Tejpal *et al.,* 2018).

Reasons

Each hormone produces a great variety of physiological responses (Tejpal *et al.*, 2018).

Several of these responses to different hormones frequently are (Tejpal *et al.*, 2018).

The response of a plant or a plant part to plant growth regulators may vary with the variety of the plant (Tejpal *et al.,* 2018).

Even a single variety may respond individually depending on its age, environmental conditions and physiological state of development (especially its natural hormone content) and state of nutrition. There are always exceptions for a general rule suggesting the action of a specific growth regulator on plants (Tejpal *et al.,* 2018).

There are several proposed modes of action in each class of plant hormone, with substantial arguments for and against each mode (Tejpal *et al.,* 2018).

The importance of PGRs was first recognized in the 1930s. Since that time, natural and synthetic elements that alter function, shape and size of crop plants have been discovered. Today, specific PGRs are used to crop growth rate and growth pattern during the various stages of development from germination through harvest and post-harvest preservation. Growth regulating chemicals that have positive influences on major agronomic crops can be of value (Tejpal *et al.,* 2018).

Classes of plant growth regulators

Growth promoters

The plant-bio regulators or hormones which have catalytical result, i.e. take a significant role in plant growth are called growth promoter e.g. Auxins, Gibberellins and Cytokinins, ascorbic acid, Ethylene, Brassinosteroids, Jasmonates (Tejpal *et al.,* 2018).
Auxins

Auxins are low molecular weight organic phytohormones that are involved in all aspects of growth and development of plant including morphogenesis regulation, stimulation and elongation George *et al.* (2008); Saini *et al.* (2013). Polar and organic in nature, auxins can be move long distances throughout plant via vascular tissues. Previous literature reveals that auxins are produced in meristematic zone and growing organs including leaf, root tips, seedlings, and buds. Concentrations are highest in leaf, shoots, and tips of branches and lowest in roots. Consequently, auxins are more often found in younger plant parts (juveniles and seedlings) and play an important role in the early stages of plant development George *et al.* (2008). Because light directly affects them, auxins are responsible for phototropism (growth of plant in response to light); however, auxins also effect apical dominance, lateral root initiation, angiogenesis and gravitropism Davies (2010). Auxins interact with salicylic acid and abscisic acid to regulate plant growth during abiotic stress Park (2007).

Table 1 shows the structures and functions of natural auxins (Shagufta Farman *et al.,* 2019). Indole-3-acetic acid (IAA) is least stable form because it quickly degrades in light and is vulnerable to destruction by IAA-oxidase enzyme in plants. Synthetic auxins are considered more effective than natural Auxins because they do not oxidize in plant tissue.

Synthetic auxins are now commercially available in both liquid form (dip solutions and post- planting sprays) and powdered; liquid forms have been shown to be absorbed faster than powdered forms

Table 1. Structures and functions of natural auxins Farman *et al.* (2019)

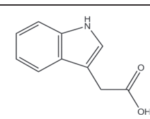
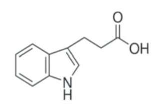
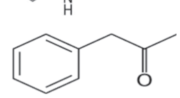
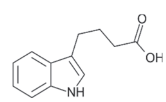
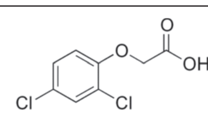
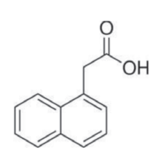
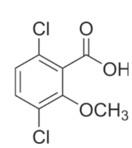
Natural Auxins	Functions	Structures	Ref.
Indole-3-acetic acid (IAA)	Cell enlargement in plant, cell division in plant, root initiation, leaf and fruit abscission and leaf senescence		Davies P.J (2010); Lin H.R *et al.* (2018)
Indole-3-propionic acid (IPrA)	Regulate vascular functions of plants		Venu V.K.P *et al.* (2018)
Phenyl acetic acid	Functions in maintaining normal cellular growth and antimicrobial activity in plants		[Lin H.R. *et al.* (2018), Cook S.D (2019)
Indole-3-butyric acid	Promote adventitious root growth and development of food crops		Qamar M *et.al* (2005)

Table 2. Structures and functions of synthetic auxins. (S. Farman *et al.* (2019)

Synthetic Auxins	Functions	Structures	Ref.
2,4-Dichlorophenoxyaceti cacid	Function as a herbicide for control of broad leaf plants and as a plant growth-regulator		[Pohanish. R.P(2014)]
α-Naphthalene aceticacid	Used as an indicator of better rooting, An agent for thinning fruitsets in apples, pears and olives. Induces root formation on cuttings and transplants. Inhibits fruit drops		Yan Y.H. *et al.* (2014)
2-Methoxy-3,6-dichlorobenzoic acid (Dicamba)	Kills weeds by causing abnormal cell growth (use as herbicide), causes uncontrolled growth		[Alikhanidi S *et al.,* (2004)]

Lin *et al.* (2018). Table 2 shows the structures and functions of synthetic auxins Shagufta Farman *et al.* (2019).

Gibberellic Acid

Gibberellins are endogenous growth hormones of plants which are biosynthesized by them as a result of different developmental or environmental stimuli Iqbal *et al.* (2013). First discovery of this hormone, Gibberellins, was made in a fungus named "Gibberella" and after that it has been located in a number of plant zones which are shows active growth.

Names have been assigned to different gibberellins on the basis of the order in which these were discovered (GA1-GA7). Gibberellins are known to control stem internode elongation, grass leaf elongation, general cell elongation and division of cells in plant shoot as a result of their direct influence on ribonucleic acid and protein synthesis in plant. But the actual action mode and site of biosynthesis of gibberellins is still unclear Harms *et al.* (1988), George *et al* (2008), Hamayun *et al.* (2010), Kaur *et al.* (1998). A study reported the maintenance of regular growth and development of plants in saline conditions as GA3 counteracts such conditions by enhancing permeability of membrane and improving nutrient supply [Pohanish. R.P (2014)].

If GA3 is applied as pre sowing treatment (100 mg/l), the ion accumulation as well as partitioning in plant tissues is modulated by GA3 which results in the reduction of tension caused by increased osmotic pressure. Plant biomass (dry weight), grain yield and plant height of spring wheat cultivars under saline conditions (15 ds/m) have been reported to be improved when seed priming with GA3 (150 mg/l) is done Iqbal *et al* (2013)] Nitrogen metabolism of plants is also influenced by gibberellins as it improves soil-derived nitrogen re-distribution in plants Kolar *et al.* (1997). Vegetative parts and seeds of mustard showed an increased nitrogen accumulation and hence increased partitioning of nitrogen into seeds when the cultivars were sprayed at a concentration and rate of 10"5 M and 600 L/ha, respectively Khan *et al.* (2002). Thus, gibberellins may also represent a novel nitrogen- use efficiency product (Shagufta Farman *et al.* (2019).

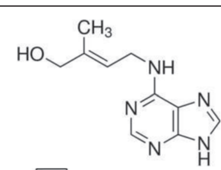
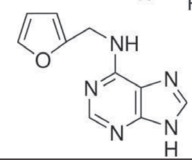
Cytokinins

Meristematic tissues and organs (i.e., shoot apex, immature organs, root tips) of a developing plant naturally build a phytohormone named as "Cytokinins" (Table 3) Osugi *et al.* (2015). There are about 20 natural plant cytokinins. Although require mode of action of cytokinins is not clear enough, but literature has reported its effect on growth and development of plant. The cell division of plant is critically affected by direct action of cytokinins on protein synthesis which are known to be involved in mitosis. Cell cycle has been observed to enter a standstill condition in the absence of Cytokinins George *et al.* (2008). Cytokinins and auxins must be applied in a balanced ratio to the plant. If a balance is not maintained in the quantities of two hormones, then accumulation of cytokinin may be inhibited by auxins and cytokinins can affect the activity of auxins George *et al.* (2008). Different plant species are reported to have a different balancing ratio of the two growth regulating hormones.

Abscisic Acid

During varying physiological changes and environmental conditions, the stress signals and responses are integrated and controlled by abscisic acid [Tuteja. N (2007)]. ABA is biosynthesized when plants are exposed to abiotic environmental stress,

Table 3. Structures and functions of cytokinins Farman *et al.* (2019)

Natural cytokinins	Functions	Structures	Ref.
Zeatin	Regulation of plant development and defense responses to pathogen and herbivore attack, role as, novel stress-response markers		[Schäfer M *et al.*, (2015); Tuteja (2007)
Kinetic	Effective in senescence delay, by minimizing breakdown of chlorophylls and carotenoids; and by bringing down peroxidase and protease activity, and sugar accumulation.		Tun a A.L. *et al.*, (2008)

including drought, low and high temperatures, salinity and flooding; ABA production triggers plant acclimatization and stress tolerance (George *et al.* (2008), Hamayun *et al.* (2010), Tuna *et al.* (2008), Tuteja. N (2007), OBrien J.A *et.al* (2013)]. Biosynthesis of abscisic acid has also been noticed in some phytopathogenic fungi including Botrytis cinerea and Cerosporarosicola. ABA used for external application to the plants is being extracted from Botrytis cinerea Rademacher (2015). ABA, when synthesized endogenously by plant, influences plant growth by reducing it and also causes changes in permeability of cellular membrane and uptake of water and nutrient. ABA also has the potential of regulating drought conditions as it influences leaves for their stomatal conductance that reduces overall intercellular water loss as well as transpiration Rademacher (2015). For this purpose, guard cells directly receive ABA signals for the closure of stomata. While in favourable conditions, ABA assists the plant to overcome stressful conditions and start the process of seed germination and growth (Hernandez-Ruiz *et al.,* 2008). In conditions of abiotic stress, plant tissues produce more abscisic acid which initiates signals and activates signal pathway and regulate modification in gene expression which results in plant adaptation to stressful environmental conditions [OBrien J. A *et.al* (2013)]. Further synthesis of abscisic acid by plant (via â-carotene and multiple enzymatic steps) has been noticed when it is applied externally to the plant in the form of spray, as it poses to mimic stressful conditional effects [Tuteja. N (2007), WATTS. S *et.al* (1981)].

Ethylene

Tissues of plants which play role in plant growth regulation are known to produce ethylene (C2H4). The regulation of plant growth and development by ethylene depends and also vary according to amount of cytokinins, ABA, carbon dioxide, light and auxins present in the plant. Plant maturation is controlled by ethylene which gives its name as an "aging hormone" [Schaller. E (2012)]. . Active division of cells in some plants produces ethylene asbyproduct which then regulates size of cells. An enhanced production of plant-derived auxins has been associated with biosynthesis of ethylene in plants, which not only plays rolein auxin synthesis but also in its metabolism and transport [Rademacher.W. (2015), George E. F *et.al* (2008), Reinecke.D.M (1999)]. With a rise in cytokinin levels, plant roots are reported to synthesize more ethylene [OBrien J. A *et.al* (2013)]. . The germination of seedrequires a certain threshold concentration of ethylene below which seeds show lack of germination. This is applicable to both dormant and non-dormant seeds. In stressful environmental conditions such as salinity, water scarcity, and higher temperatures, both exogenous and endogenous application of ethylene work synergistically with other plant growth regulatory hormones for the breakage of seed dormancy. [(Tejpal S.B *et.al* (2018)].

Brassinosteroids

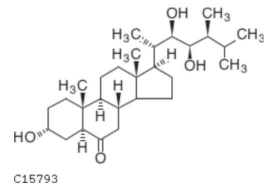
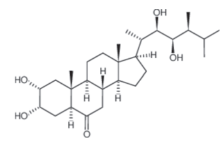
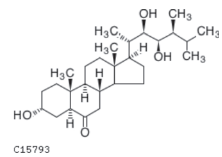
Certain plant classes including monocotyledonous and dicotyledonous angiosperms, Gymnosperms as well as algae produce hormones which are steroids in nature and are capable of regulating growth and development of plant. These steroid based hormones are categorized as "Brassinosteroids" (Table 4) [Khripach, V *et.al* (2000)]. More than 60 different types of this hormone have been discovered in plants by now, out of which only 19 have been characterized. Although extremely low concentrations (i.e., nanograms; ng) of brassinosteroids are known to be found in plant tissue, but these are considered to be essentially present in plant kingdom. A study reported 0.5 ng and 10 ng concentrations of brassinosteroids actively functioning in rice and bean [Rao S.S. R *et.al* (2002)]. Growth and developmental processes which are regulated by brassinosteroids include rhizogenesis, germination of seeds, flowering and senescence along with abscission and maturation.

Brassinosteroids influence basic cellular processes such as triggering nucleic acid and protein synthesis, cellular fission and cell elongation. Moreover, these also play a role in regulating fatty acid (including membrane integrity) and amino acid composition along with improving product translocation so that a balance among other phytohormones can be maintained. In a plant overall, brassinosteroids help the plant to tolerate both abiotic and biotic stress, increase quality and quantity of fruit, improve fertilization, increase aboveground biomass and to shorten growth period [Small C.C *et al.* (2018)].

Jasmonates

Environmental conditions, developmental stage of plant and particular type of cell or tissue decide the amount and type of Jasmonate to be present in it

Table 4. Structures and functions of Brassinosteroids [(Shagufta Farman (2019)]

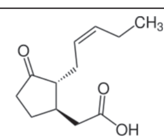
Brassinosteroids	Functions	Structures	Ref.
Brassinolide	Increase rates of <u>stem elongation, pollen tubegrowth</u> leaf bending at joints, leaf unrolling <u>proton pump</u> activation, reorientation of cellulose microtubules, and xylogenesis as well as elevated ethylene production		[Kvasnica M *et al* (2019)]
Castasterone	Improved the antioxidant potential of plantsand improvedthe antioxidant potential of plants		[Poonam R.K *et al.*;(2015)]
Typhasterol	Improve growth and yield under various stress conditionsincluding drought, salinity, extreme temperatures, and heavy metal (Cd,Cu, Al, and Ni) toxicity		[Fariduddi nQ *et al* (2014)]

[Creelman R.A *et.al* (1997)]. Jasmonates are found to be essentially present throughout the plant kingdom and have been reported in more than 206 plant species including fungi, mosses and ferns [Parthier. B (1990)].

Reproductive structures like seed, flowers or fruits of higher plants are reported to have higher concentrations of this hormone. Plants suffering from environmental stress like water scarcity or wounding also show release of higher jasmonate concentrations.

Biosynthesis of this hormone is found to be receptor-mediated as membrane damage and production of linolenic acid triggers its initiation. Jasmonates (Table 5) have an impact on plant growth and development at many edges as these can travel throughout plant in liquid or vapour form. A research investigation has reported that jasmonates may have a role in the mobilization of seed reserves as its higher concentrations are found in the seeds struggling for the imbibition of water. Also during disease and insect attack the amounts of jasmonate production have been reported to increase significantly. Hence, larger concentrations of jasmonates are expected to be generated by plants during environmental stresses like physical wounding and biotic and abiotic stresses and also during plant reproduction. Some studies have mentioned direct positive influences of jasmonate production under stress conditions as these provide defence against disease and insect attack e.g. necrotopic pathogens and chewing insects, when the plant is wounded [OBrien J.A *et.al*

Table 5. Structures and functions of Jasmonates [(Shagufta Farman (2019)]

Jasmonates	Functions	Structures	Ref.
Jasmonic acid	Induction of specific		Vreugdenhil D *et al.* (2011); N.De Geyter *et al.* (2012)]
Methyl jasmonate	Induction of formation of protective compounds in plants, play an active role in senescence and root elongation		
Jasmonoyl isoleucine (JA-Ile)	Controls gene expression and production of secondary metabolites after (a) biotic challenges		Vreugdenhil D *et al.* (2011); J. Chen *et al.* (2014)

(2013).

Novel Plant Growth Regulators and their Potential Uses in Agriculture

Several novel plant growth regulators discovered in the recent past includes compounds like Melatonin, Serotonin, Strigolactone, Harzianolide and Karrikins. Ankita Mishra *et al.* (2017).

Melatonin

Melatonin (N-acetyl-5-methoxytrypalmitine), a well-known animal hormone was first reported in plants during 1995 by several groups (Dubbel *et al*., 1995; Kolar *et al*., 1995); Hattori *et al*., 1995). It has been detected and quantified in different plant parts (shoots, laves, roots, fruits and seeds). Melatonin possesses resemblances with auxin as both have common precursors-tryptophan. There exists interrelation between both the hormones. Melatonin plays important role in reproductive development, circadian rhythm, cell protection, vegetative development as well as responses to both biotic and abiotic stresses (Arnao and Hernandez- Ruiz., 2006). In 1997, Kolar *et al*., (1997) reported about the presence of melatonin in chenopodium rubrum L. and also studied the effect of changes in melatonin levels in light/dark cycles of 12 hours. An increase in its concentration during night led to further experiments which concluded that biosynthesis of this hormone shows a circadian rhythm (Wolf *et al.,* 2001). Melatonin also act as growth promoter as auxin. A low melatonin level stimulates lateral root growth, while higher levels promote adventitious root formation.

Inhibitory effect on lateral root growth at higher concentration of the hormone implies a pathway independent of auxin [Park WJ, (2011)]. Various reports suggest the stimulatory effect of melatonin in cotyledon expansion (Hernandez-Ruiz, and Arnao, 2008) and hypocotyls growth (Hernandez-Ruiz, and Arnao, 2004; 2005).

Serotonin

Like melatonin, serotonin (5- hydroxytryptamine) was also discovered as animal hormone. Its appearance in plant was reported during 1954 in medicinal plant- cowhage (Mucunapruriens) (Whitaker-Azmitia PM, 1999). Biosynthesis of this hormone involves tryptophan. Tryptophan is decarboxylated by the enzyme tryptophan decarboxylase (TDC), which gives rise to another bioactive compound tryptamine. In plants, modification in TDC- the rate limiting enzyme, influences the serotonin levels (Erland *et al*., 2017) Serotonin in involved in vegetative growth and morphogenesis of the plant i.e. promoting shoot building, growth, and multiplication, biomass accumulation, delay in senescence, seed germination, Methyl jasmonate Induction of formation of protective compounds in plants, play an active role in senescenceand root elongation [D. vreugdenhil *et al.,* (2011); J. chen *et al.,* (2014)] Jasmonoylisoleucine (JA-Ile) Controls gene expression andproduction of secondary metabolites after (a) biotic challenges - and somatic embryogenesis (Erland L.A.E *et al*., 2015). Variation in serotonin level was also found in different stages of seed development in walnut and it accumulated in cotyledon upon abscission (Grosse W *et al*., 1983, 2011; Lembeck F *et al.,* 1984).

Strigolactone

Strigolactone (SL) group of compounds were first discovered as growth stimulant compounds for weed species Strigalutea. Lour, from root exudates of a false host- cotton [Cook *et. al.,* (1966)].

Strigolactone has both endogenous and exogenous activity in plant. It has been reported to inhibit axillary lateral meristem activity, thus regulating shoot branching as well as plant architecture [(Gomez-Roldan *et al*. 2008; Umehara *et al.* 2008; Tsuchiya *et al.,* 2010)]. Apart from auxin and cytokinin- two major hormones widely known to regulate shoot branching, SL can also be used for this purposes in tissue culture (Grobbellar, 2013) or commercially (Liang *et al.,* 2010). It has significant role during plant stress responses including drought stress, nutrient starvation, salinity, temperature and pathogen attack (Mishra S *et al*., 2017).

Karrikins

Though chemicals in smoke were known to help in better germination in some fire follower species, the first active element in smoke having the same activity was discovered after using sophisticated techniques i.e., gas chromatography mass spectrometry, and nuclear magnetic resonance during 2004 (Flematti *et al.,* 2004). The first butenolide compound discovered in smoke water and its analogs were named as “karrikins” or KARs (“karik”- the word for smoke in Noongar Aboriginals language of South-west Australia) (Waters *et al.* 2013). Karrikins show similarity with SL in having vital butenolide moiety for bioactivity (Flematti *et al.,* 2009), germination stimulating activity (Flematti *et al.,* 2004; Nelson *et al.,* 2012). The effect of KARs with other hormones involve in germination i.e., GA and ABA was also studied. It was reported that, ABA has negative effect on KAR activity while GA is needed for KAR to increase seed germination (Nelson *et al.,* 2009).

Harzianolide

Harzianolide was discovered from cultures of the fungus *Trichoderma harzianum* during the studies on metabolites of this bio-control agent and was shown to be 3- (2- hydroxypropyl)-4-(hexa-2, 4- dienyl)-2(15H)- furanone, by NMR methods [Claydon *et al.,* (1991)]. Till date it has been isolated from three different strains of *T. harzianum* [Almasi *et al.,* (1991)]; Claydon *et al*., 1991; Ordentlich A *et al.,* 1992)]. A study about bioactivity of this compound by Cai *et al* (2013) revealed its role in both plant growth promotion and systemic resistance induction. The results showed a significant increase in growth of tomato seedlings by up to 2.5- fold (dry weight) at a 0.1 ppm concentration of harzianolide while compared with the control. It also affects early stages of plant growth through better root development. This novel metabolite has been reported to enhance seedling growth in tomato, canola, wheat and show an auxin like activity on etiolated pea stems (Vinale *et al.,* 2006; 2008).

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article. There are no conflicts of interest amongst author's.

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