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STRIGOLACTONE, A NOVEL HORMONE WITH ESSENTIAL FUNCTIONS IN PLANTA POSSESSES A SIGNIFICANT VALUE AS A CANCER THERAPEUTIC AGENT: A REVIEW

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Strigolactone is a group of newly identified plant hormones produced in monocotyledons, dicotyledons, liverworts, mosses, and Charales. Initially, it was defined as a type of stimulant which induces the germination of parasitic weed seeds. Later on, it was discovered that the strigolactones have a significant contribution in performing many functionalities inside the plant. The crosstalk between strigolactones and other phytohormones such as abscisic acid, cytokinin, auxin, gibberellin, and ethylene has been revealed in previous studies. This review is primarily focused on the practical applications of strigolactones for the benefit of both the plants and humans. Strigolactones induce root hair elongation, secondary growth and symbiotic associations of arbuscular mycorrhizal fungi and rhizobium bacteria with plants. They also help the plants to cope up with abiotic and biotic stress conditions. The negative impacts of strigolactones on shoot branching, axillary bud outgrowth, and lateral root formation also have recently been discovered. In addition to their contribution to plant improvement, the natural strigolactones and their synthetic derivatives also function as anti-cancer agents. They inhibit the proliferation of cancerous cells by up-regulating stress-related genes and down-regulating certain survival factors. Relative instability of naturally available strigolactones has led to the production of many synthetic derivatives such as GR24, Nijmegen-1, 4BD, ST357, MEB55, ST362, etc. The current knowledge on the genes involving in strigolactone biosynthesis and perception would lead to achieving a fascinating revolution in agriculture. Moreover, the latest understanding of the utility of synthetic strigolactone derivatives in crop productivity enhancement and cancer treatments is astonishing.

Keywords: Anti-cancer agents, Crosstalk between strigolactones and other phytohormones, Plant hormone as a cancer treatment, Strigolactone biosynthesis, Synthetic derivatives of plant hormones

1. INTRODUCTION

Strigolactone, a novel type of plant hormone which has recently been identified in plants [1]. This phytohormone is a type of terpenoid lactones. Strigolactones are produced in a variety of plant species including cotton [2] maize, sorghum and proso millet [3]. They are produced in shoots and roots of plants and are transported acropetally to the shoot-ward direction [4] *via* the xylem [5]. In addition to angiosperms, the presence of these molecules in liverworts, mosses, and Charales indicates that strigolactones are conserved throughout the plant kingdom [6]. They have a structure in which an ABC ring system is connected to a butenolide D ring via an enol ether bond (Figure 1) [7]. The AB, CD ring systems, and the enol ether bond are known to have diverse roles depending on the organisms [8]. Initially, it was recognized as a stimulant in inducing the germination of parasitic weed seeds [2]. However, the studies revealed that strigolactones play crucial roles in the plant rather than just promoting the parasitic seed germination.

Inside the plant, strigolactone mainly acts as a hormone and control many physiological processes including shoot and root development. Once it is secreted to the soil, it induces the germination of parasitic weeds. Despite the detrimental effects caused by inducing parasitic weed growth, they are also known to stimulate the association with arbuscular mycorrhizal fungi, which are highly beneficial for the plant. Although these two roles are conserved in angiosperms, such type of internal plant metabolic regulation can't be seen in liverworts, Charales, and mosses as they lack shoots and roots. The existence of strigolactones in these lineages suggests that they have a role in regulating rhizoid elongation [6]. The biosynthesis of strigolactones takes place through a multistep reaction pathway, starting from cleavage of carotenoids [9]. The biosynthesis of strigolactones involves critical genes such as *MAX3*, *MAX4*, and *MAX1* in *Arabidopsis thaliana* [10], *D27* [11], *D17/HTD1*, *D10* [12] in *Oryza sativa*, *RMS5* and *RMS1* in *Pisum sativum* [13]. The genes and their orthologs involving in the strigolactone signaling pathway have also been studied in the literature [12, 13, 120, 15, 16].

Strigolactones are known to have a significant impact on the overall plant architecture. They control the shoot branching habit of plants [17, 18, 19], elongation of internodes [20], root branching [21, 22], the formation of lateral roots and elongation of root hairs [23, 24], adventitious root formation, plant height, reproductive organs development [25, 26], bud

outgrowth of tillers [11], the angle of rice tillers [27], secondary growth [16, 28]. In addition to these roles, strigolactones enable the plants to acclimatize to various stress conditions including drought, salinity [29, 30], biotic stresses [31,32] and nutrientstresses [33, 34]. Moreover, studies reveal that the regulation of biosynthesis of strigolactones and identification of genes involving in strigolactone signaling pathway is useful in subsequent plant improvements. The study of other stress-related genes which are up and down-regulated by strigolactones also could lead to a profound development in agriculture [30].

Apart from the contribution mentioned above of natural strigolactones to the improvement of plant growth and development, currently its synthetic derivatives are widely being used for the parasitic weed management [35, 36, 37]. Strigolactones secreted to the rhizosphere induce the arbuscular mycorrhizal fungi association [38, 39, 40] and rhizobium bacteria symbiosis [41, 42] with plants and these associations might be attributed to various subsequent benefits in plants. In contrast to the other plant hormones, natural strigolactones and their synthetic derivatives have the potential to act as cell proliferation inhibitors. Therefore the use of synthetic strigolactone analogs to treat cancers such as prostate [43] and human breast cancers [44] has been studied previously, and this is one of the developing therapeutic strategies against cancer. Thisphenomenasuggests that the strigolactones could be used in enhancing the productivity of the plants and the survival of cancer patients.

Previous studies have been conducted to study the strigolactone biosynthesis, signaling, structural diversity of strigolactones, crosstalk between strigolactones and other phytohormones, regulation of strigolactone biosynthesis, the potential of strigolactones in plant improvements and human cancer treatments independently. However, none of the reviews have yet been focused on their practical applications in both the plants and humans. Therefore the primary objective of this review is to give an insight into the practical applications of natural strigolactones and their synthetic derivatives in both the plant improvements and human therapeutic applications. The secondary objectives of this review are to give an overview of the structural diversity of strigolactones, biosynthesis, and perception of strigolactones.

2. STRUCTURAL DIVERSITY OF STRIGOLACTONES

A type of strigolactone, strigol which is known to be very active as a plant hormone was first isolated from cotton plant root exudates. The molecular formula of gibberellic acid is identical to that of the strigol, and it is well dissolved in solvents with a polar nature, but comparatively not dissolved in hexane which is non-polar solvent [2]. Strigol has later been extracted from a variety of plant species including maize, sorghum and proso millet [3] which are host plants of the parasitic weed Striga. Strigol, which is a type of sesquiterpene lactones is produced not only by these host plants but also by non-host plant root exudates (Figure 1A) [45]. Orobanchol is also a type of strigolactone isolated from red clover (Figure 1C) [46]. Alectrol, another kind of strigolactone is one of the constituents of cowpea root exudates [47] and it contains a tertiary hydroxy group (Figure 1B) [3]. Sorgolactone, which is a type of strigolactones has been identified as a constituent of sorghum root exudates and has a structure which is distinct from that of the strigol (Figure 1D) [48]. All the strigolactones mentinoed above are very unstable and inactive even at high concentrations in planta [49]. Due to this further characterization of strigolactones have become difficult [45]. The structures of different types of strigolactones are shown in Fig 1.

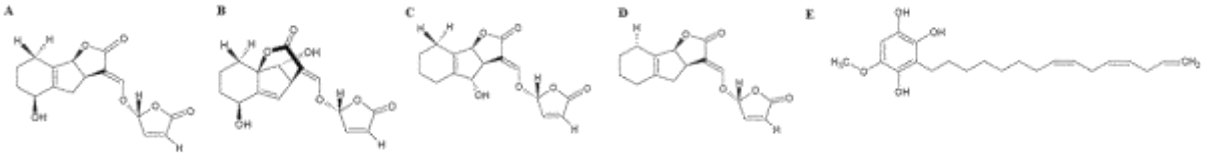

Figure 1 Structure of different types of strigolactones present in plants. A: Strigol, B: Alectrol, C: Orobanchol, D: Sorgolactone, E: Sorgoleone [3, 45].

3. BIOSYNTHESIS OF STRIGOLACTONES

Production of strigolactones from cleavage of carotenoids has been identified from a variety of plants [9]. Production of strigolactones mainly takes place in the roots of the plants which are non-parasitic [13]. An iron-containing protein encoded by *D27* plays critical roles in the biosynthetic pathway of strigolactones in rice [11]. Three types of *more axillary branching* (*MAX)* loci including *MAX3*, *MAX4*, and *MAX1* are involved in the subsequent steps of strigolactone biosynthesis in *A. thaliana* [10]. The respective genes have been studied in *P. sativum* (*RMS5*, *RMS1*) and *O. sativa* (*D17*/*HTD1*, *D10*) [13]. In *Arabidopsis* sp, the studies have shown that the *MAX3,* which encodes a CCD7 protein, and *MAX4* encoding a CCD8 protein act upstream of *MAX1*, which encodes a P450 protein in the further conversion into strigolactones. All the aforementioned *MAX* genes are known to act in the same pathway [10]. The CCD7 protein encoded by *MAX3* is confined into the plastids [50] and present in

reduced concentrations [51]. They are involved in enzymatic cleavage of many carotenoid substrates leading to strigolactone biosynthesis [50].

Preliminary steps of *MAX*/*RMS*/*D* pathway play an essential role in strigolactone biosynthesis [52]. The perception of strigolactones is mediated by *MAX4* which encodes CCD8 protein [13] and acts downstream of auxin [53]. Lack of function of *MAX4* gives rise to functionless *MAX3,* and this finding implies that both genes are expressed in a single pathway [12]. The genome of all the plants constitutes *MAX3* and *MAX4* orthologs [52]. The biosynthetic pathway of strigolactones has found to act together with the other plant hormones such as cytokinin and auxin [11]. *MAX4* in *Arabidopsis* and *RMS1* in *P.sativum* have been identified as orthologs [53] and both the *RMS5* and *RMS1* in *P. sativum* are involved in the carotenoid cleavage steps [54]. *Dad1* gene in *Petunia hybrida* which is an ortholog of *Arabidopsis MAX4* gene is involved in cleavage of polyene chains subsequently synthesizing intermediates in the strigolactone biosynthetic pathway [55]. *D10* gene expressed in *O. sativa* is also involved in cleavage of carotenoid substances [56]. In rice, *Os900* encodes an enzyme which oxidizes carlactone (CL), a type of intermediate in the strigolactone biosynthesis pathway into ent-2'-epi-5DS. The hydroxylation of this product into orobanchol, a kind of strigolactone is carried out by an enzyme encoded by *Os1400* [57]. Above mentioned genes in rice are *MAX1* orthologs [1]. The oxidation of carlactone into strigolactones in *Arabidopsis* requires other enzymes which have not yet been discovered [58]. Another gene, *lateral branching oxidoreductase* (*LBO*) functions in the final steps of strigolactone biosynthesis pathway giving rise to strigolactone related compounds [59]. The steps in strigolactone biosynthesis are shown in Fig 2.

Strigolactones are also synthesized in specific tissues of parasitic plants such as *Striga,* and the gene expression is different from that of the *Arabidopsis* [13]. In host plants of parasitic plants such as *Orobanche* and *Striga* spp., the cleavage of carotenoids requires NCED (9-cis-epoxycarotenoid dioxygenase) and some subsequent reactions ultimately giving rise to different types of strigolactones [9]. The studies also reveal that the steps in the strigolactone biosynthetic pathway of rice and *M. truncatula* are controlled by two types of regulators known as nodulation signaling pathway 1 and 2 (NSP1 and NSP2 respectively) [60]. An enzyme encoded by *SlCCD7* can cleave the carotenoid substances in tomato [52]. All the above mentioned facts indicate that the reaction steps in the strigolactone biosynthesis are controlled by different enzymes in different plants.

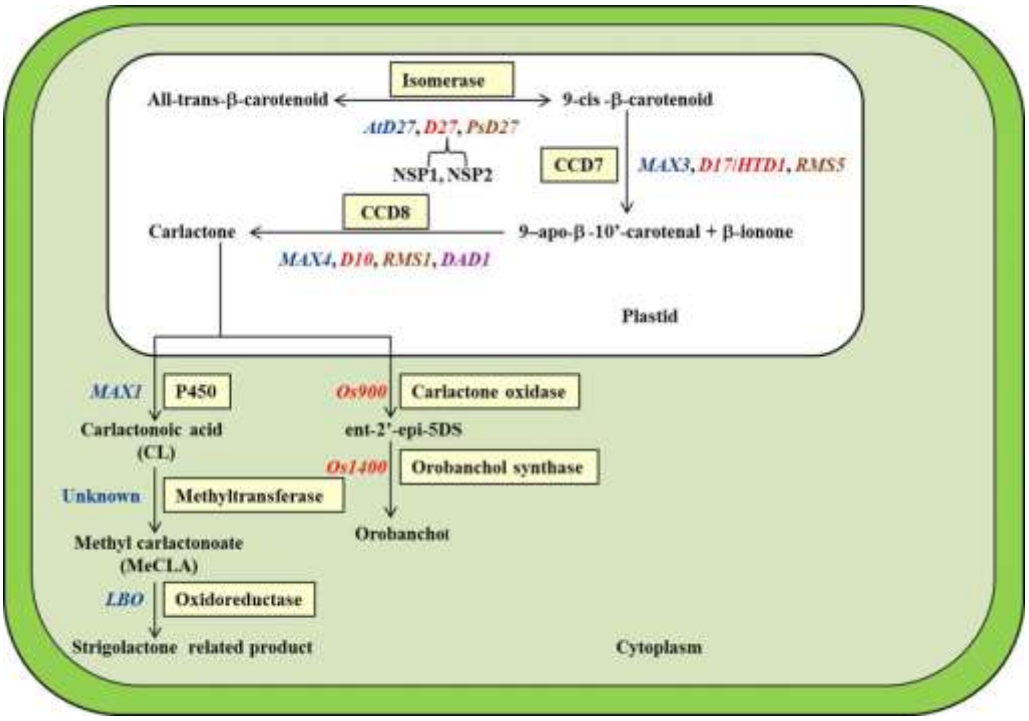

Figure 2 The suggested biosynthesis pathway of strigolactones in plants. Genes involved in the strigolactone biosynthesis pathway of Arabidopsis, *Oryza sativa*, *Pisum sativum*, *Petunia hybrida* are shown in blue, red, brown and purple colors respectively. The respective encoded proteins are displayed in yellow color boxes. In *A. thaliana*, the first carotenoid substances are cleaved by carotenoid cleavage dioxygenase 7 (CCD7) and carotenoid cleavage dioxygenase 8 (CCD8) enzymes into a common intermediate, carlactone in different strigolactones [59]. In *O. sativa*, these cleavage steps involve *D27*, *D17*/*HTD1*, *D10* genes while in *P. sativum*, *PsD27*, *RMS5*, and *RMS1* genes are involved. *Dad1* gene in *P. hybrida* is engaged in the production of carlactone intermediate [13]. In *Medicago truncatula*, two transcription factors including NSP1 and NSP2 are known to be regulators of strigolactone biosynthesis pathway [60]. Carlactone is further oxidized by cytochrome P450 (encoded by *MAX1*), into carlatonic acid (CL) which is subsequently converted into methyl carlactonoate (MeCLA) in *A. thaliana*. This product is further processed by *LBO* giving rise to strigolactone related products [59]. In *O. sativa*, carlactone is further processed by two enzymes converting into orobanchol [57, 59].

4. STRIGOLACTONE SIGNALING PATHWAY

In the strigolactone signaling pathway, mainly *MAX2* gene in *Arabidopsis* [14, 15, 61], *D14*, *DAD2* and *D3* genes in *O. sativa* [12, 16, 62], *RMS4* in *P. sativum* [13, 16] are involved. Signaling pathway of strigolactones is regulated by the degradation action of transcriptional regulators [62, 63]. Strigolactone signaling functions together with the auxin signaling in plants [16]. *D14* is a significant component of the strigolactone signaling pathway, and it is involved in switching the strigolactone signal into its active form by encoding a protein, α/β hydrolase [12]. D14 protein also functions in a way that it can act as receptors for strigolactones [63]. In playing these two roles, D14 hydrolyzes the strigolactone molecules, forming D-OH. The complex of D14 and D-OH form of strigolactone is then detected by other types of proteins such as SLR1, which is a type of repressor in gibberellins signaling (Fig 3A) [64].

DAD2 and *D14* are rice orthologs. *DAD2* involves in synthesizing the active forms of strigolactones through hydrolysis [62]. In *Arabidopsis*, the strigolactone signal transduction mainly occurs through *MAX2* [23, 65], which encodes an F-box Leu-Rich Repeat (LRR) protein [16] and this protein is found in buds of the plants [15]. At the seedling stage of the plant, *MAX2* is not confined to a particular region, and it is omnipresent in the plant [66]. It modulates the ubiquitination and subsequent degradation of target proteins by interacting with ubiquitins (SCF-mediated proteins) in strigolactone signaling [14, 67]. *MAX2* can regulate the cell production rate in shoot axillary meristems of *Arabidopsis* by targeting and suppressing such aforementioned proteins, which induce the cell cycle [14].

Hypocotyl elongation is restrained through the action of *MAX2* and the regulation of strigolactones in this process relies on phytochrome, cryptochrome, and components in the light signaling pathway such as *HY5*. Strigolactone perception is controlled by the induced expression of *HY5* (Fig 3C) [61]. In *P. hybrida*, *PhMAX2A* and *PhMAX2B* serve as *AtMAX2* orthologs in strigolactone downstream signaling [68]. *D3* in rice is an ortholog of *MAX2*, and this connection provides the evidence that the strigolactone signaling pathway is maintained in both the eudicots and monocots [15]. Strigolactone induces the *BRC1* expression which involves downstream signaling of strigolactones in eudicots. In rice, *FC1* implicates in strigolactone signaling [16], while acting as an integrator of various signals in the regulation of axillary bud outgrowth (Fig 3B) [69]. An intermediate of *Tb1* pathway plays crucial roles in strigolactone signaling in maize [16].

Shy2-short hypocotyl 2 in root tips suppresses the *PIN* gene expression by acting through the strigolactone signaling pathway thereby restrains the auxin transportation. The phenomenon of restraining the auxin transportation in turn controls the size of the meristem and the development of lateral roots [70]. *BES1* which negatively regulates the strigolactone pathway is recognized by *MAX2*, and its subsequent degradation inhibits shoot branching [71]. Similarly, *D53* in rice [72] and *Arabidopsis SMXL6, SMXL7* and *SMXL8* which are orthologs of rice *D53* [73] suppress the strigolactone signaling pathway. D53 is degraded by forming a complex with D14 and D3 [72]. The breakdown of SMXL relies on both *AtD14* and *MAX2* (Fig 3B, Fig 3C). When the strigolactones are not present, the SMXL suppresses the downstream genes by interacting with TPR2 (topless-related protein 2) and transcription factors (Fig 3B). However, when the strigolactones are present, SMXL proteins are degraded

by D14, forming a complex among D14, SCF^{MAX2}, and SMXL, ultimately inducing the downstream target genes in SL signaling pathway (Fig 3C) [73].

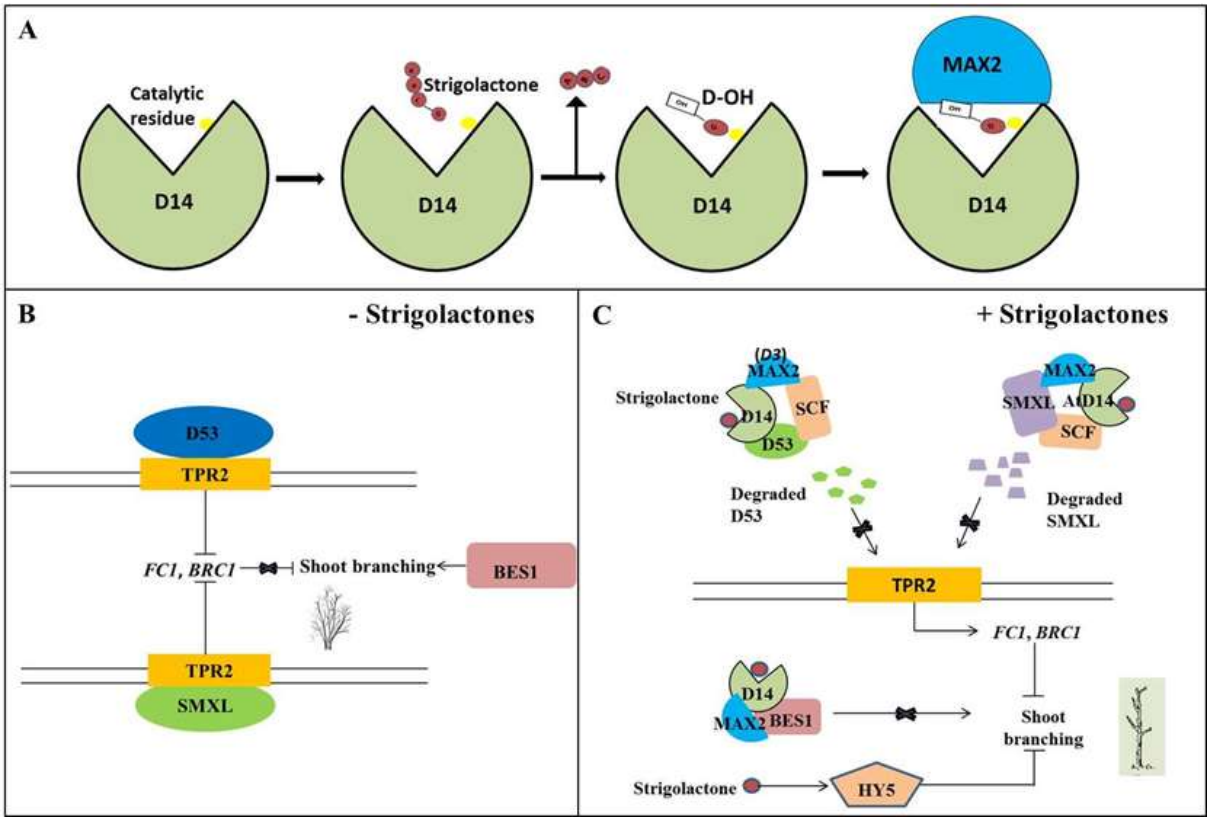

Figure 3 Strigolactone signaling in plant cells of *Arabidopsis thaliana* and *Oryza sativa*. A) D14 act as receptors for strigolactone. Upon binding strigolactone, it is catalyzed forming D-OH and removing the A, B, C rings off of the strigolactone molecule. Binding of strigolactone promotes conformational changes of the D14 protein, and this facilitates the interaction with other target proteins [64]. B) In the absence of strigolactones, D53 in rice and SMXL in *Arabidopsis* bind with TPR co-repressor protein, suppressing the transcription of downstream genes such as *FC1* and *BRC1*. The inactivation of these genes promotes shoot branching. A branching regulator, BES1 remains active and promotes shoot branching [16, 72, 73]. C) In the presence of strigolactones, D53 in rice binds with D14. This complex is then ubiquitinated and degraded by the action of SCF^{MAX2}. SMXL in Arabidopsis is degraded upon the recognition by *MAX2* gene product and AtD14. Degraded D53 and SMXL can no longer repress the transcription of downstream genes. The transcribed genes suppress the shoot branching. Similarly, the activity of BES1 is repressed upon the recognition by D14 and MAX2, subsequently inhibiting shoot branching. Strigolactones promote the expression of *HY5* negatively regulating the hypocotyl elongation [61, 72, 73].

5. DIVERSE ROLES OF STRIGOLACTONES IN AGRICULTURAL APPLICATIONS

Strigolactones play vital roles in reducing the invasion of parasitic plants [35, 36, 37]. They are also known to function in enabling the plants to survive under unfavorable environmental conditions [29, 30, 33, 134]. Other than its roles against abiotic stresses, strigolactones also help the plants to cope with stresses caused by biotic agents [31, 32]. The fact that strigolactones regulate an array of plant physiological processes such as shoot branching [17, 18, 29], root branching [21, 22], elongation of internodes [20], bud outgrowth of tillers [11],

plant secondary growth [16, 28], elongation of internodes [20], reproductive organ development, adventitious root formation [26, 26] reveals the usefulness of this hormone in agronomical improvements. This suggests that strigolactones play crucial roles in plants to reach an optimum root and shoot architecture.

5.1 Parasitic seed germination

Parasitic plants use the strigolactones secreted by their host plants [74]. For a parasitic plant to grow, germination is the initial crucial step [9]. Usually, parasitic plants produce many tiny seeds which experience an extended dormancy period before their germination [75]. Although the proper environmental conditions are received by the parasitic plants [76], the germination is not likely to begin unless they perceive a particular type of signaling compound known as strigolactone, secreted by host plants. Interestingly, it has been discovered that these chemical compounds have the ability to enhance the germination of parasitic plant species such as *Striga*, *Orobanche*, *Alectra*, *Phelipanche* and *Cistanche* [9, 45, 77, 78]. However *Striga*spp. does synthesize their strigolactones which are not self-adequate to enhance their germination. Therefore all these facts elucidate the necessity of acquiring strigolactones by parasitic plants, from the host root exudates to break the dormancy, in turn, stimulating the germination [10].

5.1.1 Use of synthetic strigolactones on parasitic weed control

Some of the natural strigolactones produced by plants are known to suppress the germination of parasitic seeds apart from inducing the germination. This has been studied in *Striga gesnerioide* which is a significant threat to cowpea. The germination of *S. gesnerioides* is repressed by three natural strigolactones including 5-deoxystrigol, sorgolactone, and sorgomol [79] which are produced by sorghum [80]. Therefore intercropping sorghum with cowpea can control the damage caused by the parasite [79]. A strategy to control *Strigahermonthica* seed germination has been detected in another study by developing novel rice varieties with various strigolactones. The sensitivity of different parasitic plants belonging to the same species towards different strigolactones is different. Therefore the development of unique varieties with varying compositions of strigolactones is a useful approach in inducing the parasitic seed germination thereby controlling their invasion [81].

However, the isolation of the pure forms of strigolactones and the synthesis of strigolactones commercially are less feasible, because of their complex structures, limited availability and

low stability in soil [82, 83, 84]. To avoid the above complications, synthetic strigolactone derivatives which are of 2 types; synthesized strigolactone mimics (lacking the enol ether bond) and strigolactone analogs (having the enol ether bond) [35], have been introduced. The synthesis of SL derivatives in this manner is required to alleviate the damage, caused by parasites [36]. This approach, in which the synthetic strigolactones are used to promote the germination of the parasitic weed seedlings in the absence of an appropriate host nearby, is known as suicidal germination. This phenomenon can deprive them of food and nutrients, further confirming their death [85, 86, 87, 88].

The formulations of the synthetic strigolactone compounds, their chemical structures, and their availability are some of the significant issues in synthesizing these derivatives [86]. Their decomposition and subsequent absorption into the soil are not hindered [87]. GR7 and GR24 are two types of strigolactone analogs which have the same CD, and enol ether structures as those are in alecrol, strigol and sorgolactone [89]. The synthesis of GR24 is much convenient over the natural strigolactones mainly because of their relative stability in soil and comparatively less complex structure [83] and these facts suggest its usefulness in controlling parasitic weeds across the world [90]. Also, its stability is much higher in air dry soil in contrast to the wet soil in which it shows less stability [91]. Although it is not effective against *S. gesnerioides*, its analogs which are hydroxylated, are known to promote the germination of *S. gesnerioides* [92].

Apart from GR24, many other strigolactone derivatives have been synthesized which have high potentials in parasitic seed management [36]. The positions of B and C rings of GR24 to which the new substituents can be incorporated have been detected [37]. *Orobanche cernua* and *S. hermonthica* are sensitive to strigolactone analogues such as derivatives of p-tolylmalondialdehyde, Nijmegen-1 (containing an ester substituent) and another type of analog having a saccharin substituent [93]. Nijmegen-1, a derivative of Phthaloylglycine is structurally different from those of alectrol, strigol, and sorgolactone [82]. Another type of strigolactone, 3-pyridyliminoacetonitrile is much effective against *Orobanche crenata* in contrast to GR24. This shows that the Michael acceptor in the strigolactone molecule is not necessary for its activity. However, a structure which is compatible with that of the target site is what necessary [94]. Another study shows that GR24 in which the B ring is hydroxylated can induce the germination of both the *Orobanche ramosa* and *S. hermonthica* [95].

GR24 strigolactone analogs containing 6-dimethyl substituents play roles in inducing the germination of *S. hermonthica*. However, its activity is ten times lower than that of the GR24 [95]. Lactam analogs of GR24 play crucial roles in promoting the suicidal germination of *Orobanche cumana* [96]. The activity of butenolide is almost similar to that of the GR24 in inducing *S. hermonthica* and *Orobanche minor* seed germination [97]. Ketone derived strigolactone analogs are much popular because of the convenience in the production of these compounds with a low cost [86]. Another type of strigolactone mimic, 4BD induces the *S. hermonthica* seed germination [36]. The derivatives of tetralone and indanone are found to contain aromatic A rings in their structures and these compounds together with carvone and 2-phenylcyclohexanone show similar functional activities to that of GR24 [86]. Another strigolactone analog, ST357 has the potential to promote the germination of parasitic seeds without having an impact on the overall hormone system of the plant, and this reflects its usefulness against parasitic infection [8]. Different roles of synthetic derivatives to control the parasitic seed germination are given in Table 1.

Table 1 Different roles of synthetic strigolactone derivatives

Synthetic derivative	**Structure**	**Mode of action**	**Function**	**References**
GR24	'A' ring of SL is replaced by an aromatic ring	Induce SL expression	Promote secondary growth Inhibit LR formation, induce RH length Induce AM fungal hyphal branching Inhibit the germination of phyto pathogenic fungi	[23, 98] [32, 39,40]
Diastereomers of GR24	Modification in D ring of strigol	Induce SL expression	Control the germination of *S. hermonthica*, *O. crenata*	[99]
GR7		Induce SL expression	Induce secondary growth	[83, 98]
Strigol analogs	D ringis connected to an acyclic system with an enol ether bond	Induce SL expression	Inhibit shoot branching & bud outgrowth in pea, inhibit LR and AR formation in *Arabidopsis*	[100]
Synthetic derivative	Structure	Mode of action	Function	References
4-Bromodebranone	Triazolide SL mimics. Phenoxy furanone derivatives	Induce SL expression	Suppress tiller bud outgrowth in rice, regulate hormonal activity in *Arabidopsis*, induce	[35]

Synthetic derivative	Structure	Mode of action	Function	References
			*Striga*weed seed germination	
Thia-3'-methyl-4-chlorodebranone	Debranone like molecule which carries an aromatic ring with ABC ring system	Induce SL expression	Inhibit bud outgrowth in pea, shoot branching and AR formation in *Arabidopsis*	[35]
3'-methyl GR24	SL analogs (1st generation) with same ABC part as GR24	Induce SL expression	Inhibit bud outgrowth, promote internode elongation, increase main shoot elongation	[100]
AR36	Possess 3,4-dimethylbutenolide D ring carrying an acyclic C chain	Induce SL expression	Increase internode elongation and primary shoot elongation	[100]
CISA-1	Fluorescent SL analog with A/B ring	Induce SL expression	Induce *Orobanche. aegyptiaca* weed seed germination, inhibit adventitious root formation and shoot branching	[101]
Synthetic derivative	**Structure**	**Mode of action**	**Function**	**References**
GR5	SL analogs without A/B rings	Induce SL expression	Promote *Orobanche* and *Striga* seed germination, induce RH elongation and hyphal branching of AM fungirepress bud outgrowth	[17, 39, 88]
Hydroxylated GR24 sterioisomers	Hydroxyl group is attached to the AB part	Induce SL expression	Promote *S. gesnerioides*weed seed germination	[92]
EGO10, EGO23	N derivative analog possessing the only C2' as the stereocenter, p-dimethylaminophenyl group at A ring	Induce SL expression	Induce RH in *Arabidopsis*, induce *O. aegyptiaca*weed seed germination, & hyphal branching	[8]
MEB55	Tiophene derivative	Induce SL expression	Control *Peliphancheaegyptiaca*, act as anticancer agents	[44, 82, 102, 103, 104]
ST357	Contain Thiophene at position seven on A ring of SL	Induce SL expression	Induce hyphal branching, promote *O. aegyptiaca*weed seed germination, triggers apoptosis, induce DNA damage, inhibit DNA repair	[8, 43, 44, 102, 103]
ST 362	Contain Diothylenedioxythiophene on A ring of SL			

Synthetic derivative	Structure	Mode of action	Function	References
4-Br debranone (4BD)	Phenoxy furanone derivatives with lack of enol ether bond	Induce SL expression	Inhibit tiller bud outgrowth, axillary shoot branching, LR formation, promote RH, *S. hermonthica* seed germination	[36]
TIS13 TIS108	Triazole compounds with phenol group, a keto group, and extended C chain	Decrease SL expression	Promote tiller bud outgrowth in rice seedlings, inhibit *Striga* germination	[105, 106]
Cotilimides	Contain phthalimide and succinimide groups, imide moiety	Induce/ decrease SL expression	Repress seedling hypocotyl growth, perturb cotyledon development & germination of *Arabidopsis* seeds, stimulate parasitic seed germination	[107]
Synthetic derivative	Structure	Mode of action	Effect	References
SL analogs derived from ketones	C ring is replaced by a ketone ring	Induce SL expression	Induce the germination of *S. hermomonthica*, *O. crenata*, and*O. cernua*	[93]
Imino analogs of SL	Contains an Imino ether group	Induce SL expression	Induce the germination of *O. crenata*	[94]
Dimethyl A ring analogs	3-methyl-2H-furo[2,3-c]pyran-2-one	Induce SL expression	Induce the germination of *O. minor*, *S. hermonthica*	[97]
SL lactam analog	Contains a lactam moiety	Induce SL expression	Promote the germination of *O. cumana*	[37]

SL= strigolactone, RH= root hair, LR= lateral root, AM= arbuscular mycorrhizal, AR= adventitious root

5.2 Nutrient acquisition in a hostile environment

Many studies have previously reported that many of the plants synthesize and exude strigolactones when the plants encounter a nutrient deficiency particularly nitrogen and phosphorous in the soil. Plants are known to secrete greater amounts of strigolactones with the presence of low amounts of Nitrogen (N) and especially Phosphorous (P) [33, 34, 108]. Another study reveals the detection of strigolactones locally in nodes and also in roots of rice plants under N-limited conditions [109]. Under N and P deficient conditions, 5-deoxystrigol is the primary type of strigolactones synthesized in sorghum roots, and they rapidly exudate to the rhizosphere. Lower levels of strigolactones in root exudates in comparison to those in roots reveal that the production of strigolactones, rather than the exudation is mainly regulated under stress conditions. Also, it has been shown that the

synthesized strigolactones in roots are rapidly excreted to the rhizosphere [140]. Plants mediate an array of responses by modulating the strigolactone pathway to combat these stressful conditions.

Due to the increased levels of strigolactones, root hairs are elongated [110]. The development of roots and root hairs of plants is significant in providing their access to a higher volume of soil and thereby enhances the nutrient uptake [111]. Root development under nutrient-limited conditions is influenced by auxin transportation in plants and primarily modulated via the *D3* gene component, which is a mediator in the strigolactonepathway. Increased levels of strigolactones are responsible for longer seminal roots in rice [112]. Under N and P deficiency in rice, strigolactones contribute for inducing the levels of nitric oxide (NO), which involves in regulating the root growth in rice. The crosstalk between NO and strigolactones also results in increased levels of seminal roots [113]. These facts suggest the contribution of strigolactones in the development of root architecture in response to a nutrient deficiency in plants. Another strategy, by which the plants overcome the deficient conditions of phosphorous, is the excretion of acid phosphatase [110]. The availability of nutrients in the soil is not homogenous. Formation of sparingly soluble compounds of phosphorous with other metals such as Aluminium and Calcium (Al-P and Ca-P) and the association of phosphorous with organic matter limits their availability in soil, making it difficult for the plants to absorb them [114]. Therefore,the secretion of acid phosphatase by plants is a reliable solution which facilitates the release of inorganic phosphate from organic matter in the soil [115]. Thecontribution of strigolactones in P deficiency is shown in figure 4.

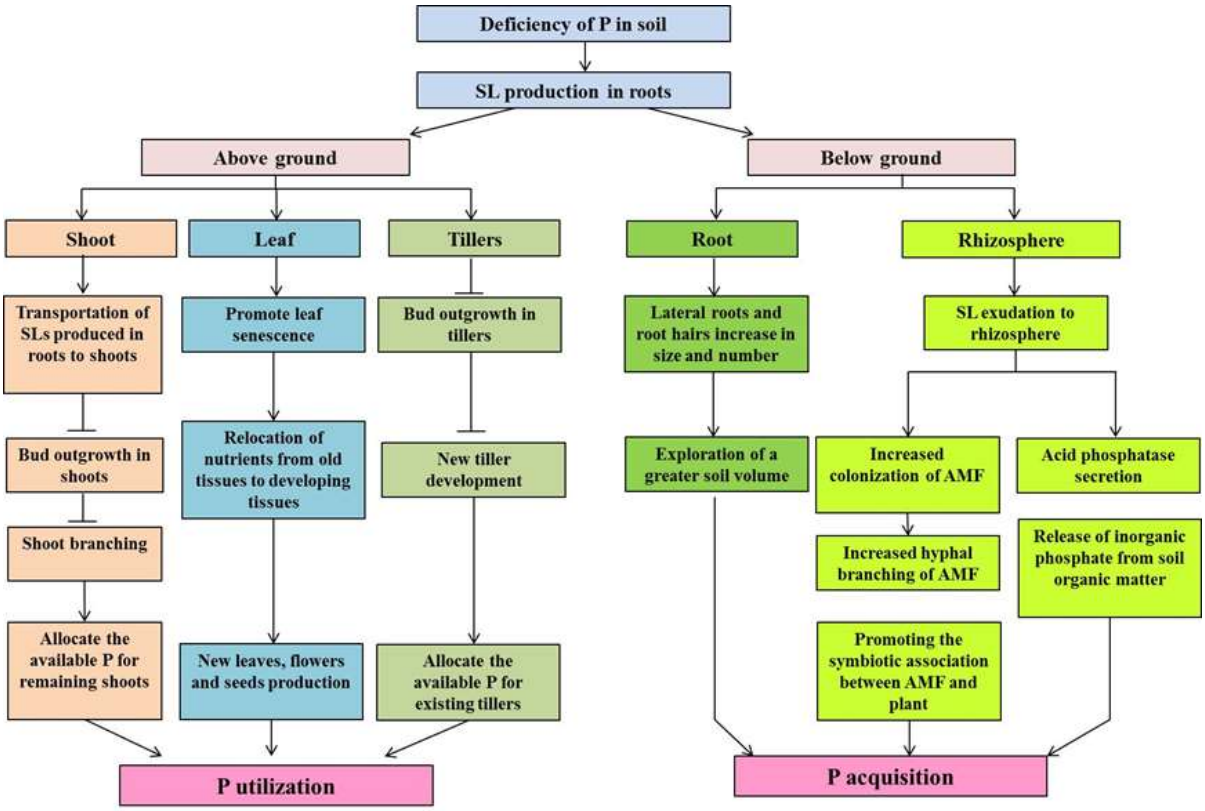

Figure 4 Involvement of strigolactones under limited phosphorous conditions. In response to a P deficiency, plants need to suppress the development of new branches. For this purpose, they reduce the shoot branching by increasing the strigolactone levels thereby allocating the available P for the remaining shoots [116]. Strigolactones involve in relocating the nutrients from old tissues to newly developing tissues by promoting the leaf senescence [33]. The increased expression of strigolactones under a P deficiency is also responsible for the inhibition of bud outgrowth of tillers thereby saving the limited P for the existing tillers [116]. Below the ground, strigolactones enhance the root hair elongation promoting the plant's access to a larger soil volume [110, 212]. Strigolactones secreted to the rhizosphere induce the AM fungi symbiotic association, in turn, enabling the uptake of P from soil [116]. They also promote the secretion of acid phosphatase, in turn, facilitating the absorption of P from soil [110].

Also, the *PSI* gene expression is known to be induced in nutrient deficient conditions. Other than these strategies, accumulation of anthocyanin and plant weight reduction is associated with nutrient-limited conditions with the involvement of strigolactone signaling pathway [110]. Apart from the strategies mentioned above, the association of plant roots with arbuscular mycorrhizal (AM) fungi improves the ability of plants to acclimatize to phosphorous deficient conditions by enabling them to absorb phosphorus from the soil. This association is promoted by strigolactones [116, 117]. Strigolactones also improves the colonization of host plant roots by fungi (41). Strigolactones induce hyphal branching of arbuscular mycorrhizal fungi, thereby facilitate the absorption of nutrients from the soil [39]. These fungi, in turn, provide the absorbed phosphorous to the plants in exchange for photosynthetic products from the host plants [34]. The positive role of strigolactones in

mitochondrial density results in alterations of their movements and shapes (Figure 4). Also, strigolactones have known to promote the proliferation of *Gigaspora rosea* fungal cells [40]. This symbiotic association has also found to improve the phosphorous acquisition as well as nitrogen acquisition in non-leguminous plants such as sorghum [34].

Leguminous plants such as Chinese milk vetch [34] and pea (*P. sativum* L.) (41) can survive under nitrogen-deficient conditions with having a symbiotic association with root nodule bacteria, and this association is induced by strigolactones. None of the studies have been conducted regarding the involvement of endogenously produced strigolactones on nodulation process [41]. However, the applicability of synthetic strigolactone analogs (GR24) in the promotion of nodulation has been studied in Alfalfa (*Medicago sativa*). Upon the application of GR24 on plants, it is speculated that the endogenous strigolactone metabolism is affected, subsequently inducing the nodulation [42]. In addition to the nutrient acquisition under unfavorable conditions, plants also suppress the shoot branching thereby prevent the growth of new branches and allocate available nutrients for the existing shoot branches. This inhibition of shoot branching is a result of induced strigolactone production under stress conditions. On the contrary, the sufficient amounts of phosphorous in the soil often results in decreased levels of strigolactones. Also, the increased amounts of strigolactones act as a key regulator of the inhibition of tiller bud outgrowth in rice [116].

With the use of mutants of strigolactone and auxin in *Arabidopsis*, the inhibition of shoot branching has been confirmed under nitrate deficiency. The effect of strigolactones on shoot branching indicates that both the strigolactones and auxin are essential regulators in this process [118]. The suppression of shoot branching and tiller bud outgrowth has also been confirmed with synthetic strigolactones [109]. Under phosphorous deficiency, plants promote leaf senescence [33] facilitating the nutrient relocation from old tissues to newly developing tissues and storage organs (Figure 4) [119, 120] This phenomenon has been confirmed in strigolactone deficient mutants. The application of GR24 synthetic analog can promote the leaf senescence of mutant plants, consequently improving the yield and the quality of developing seeds [33]. The structure and function of synthetic strigolactone derivatives which are capable of manipulating the plant physiological properties are given in table 1.

5.3 Secondary growth

Strigolactones play crucial roles in controlling the secondary growth of plants through the regulation of cambium activity [28]. Their ability to regulate the secondary growth is further confirmed by a noticeable reduction in stem diameter of *zmCCD8* mutants (46). The regulation of secondary growth in plants is very crucial in many aspects of agriculture. It improves the stability of shoots in plants such as pea, tomato, switchgrass, wheat, grapes, barely and ornamental plants thereby enhance their standing ability without any mechanical support. This ability minimizes the crop losses and enables them to withstand unfavorable environmental conditions including heavy rainfall and heavy wind. The increase of biomass through the induction of secondary growth is also supported by strigolactones. The expansion of biomass is crucial for the trees which are grownto obtain wood such as pine, walnut, mahogany, oak, eucalyptus, willow, etc.

Due to the low stability of natural strigolactones in nature, the utility of synthetic strigolactone analogs including Nijmegen 1, GR24 and GR7 is becoming a promising strategy. The application of strigolactones exogenously on plants can be achieved in many ways. One of the methods is to water the plants with a solution comprised of strigolactones. Another method is to spray a solution containing strigolactones. Alternatively, a sponge soaked in strigolactone solution or paraffin containing strigolactones can be brought into direct contact with the plants in which the strigolactone induced changes are preferred. The exogenous application of strigolactones can either be achieved by applying them to roots as a strigolactone solution or by their application directly on desirable target sites such as leaves, sprouts or stems [98]. Strigolactone derivatives produced with the intention of regulating the secondary plant growth are further discussed in table 1.

5.4 Stress tolerance against abiotic and biotic agents

In addition to the regulatory effects of strigolactones on plant developmental processes, they have been discovered to play roles in inducing responses to abiotic stress conditions. This novel approach of using strigolactones to combat the unfavorable conditions is becoming popular in contrast to the conventional stress management practices such as crop variety selection and soil management. Enhanced sensitivity of *max* mutants of *Arabidopsis* to abiotic stress conditions such as salt and drought stresses reveals that the strigolactones are involved in regulation of these unfavorable conditions [30]. These mutants were detected with increased loss of water during the transpiration with a high rate in contrast to the wild-

type plants at the mature stage of the plant [29]. Changes in stomatal closure induced by abscisic acid and an elevation in the number of stomata are found to be associated with the enhanced sensitivity of *max* mutant plants particularly in water deficient conditions [30].

In contrast to the wild-type plants, *Arabidopsismax2* mutants were shown to have an impaired sensitivity to the process of stomatal closure mediated by ABA. Also, an enhancement in membrane permeability caused by decreased cuticle thickness could be seen in mutants. With these observations, it indicates that the expression of the stress-inducible genes is repressed in mutant plants [29]. The transcriptome studies also clearly show that *max2* mutant plants with strigolactone deficiency could lead to the repression of stress-related *CKX* genes in *Arabidopsis*, consequently giving rise to the increased stress sensitivity of plants. Strigolactones also have a higher potential for making the plants adaptable to stress conditions by impairing photosynthesis. The reduced photosynthesis might be attributed to growth retardation of plants for them to conserve inadequate energy sources. Therefore the down-regulation of photosynthesis inducible genes suggests the role of strigolactones in enhancing the survival of plants under unfavorable conditions.

Mainly *MAX3* and *MAX4* genes expression in *Arabidopsis* are induced under stress conditions, and this leads to an enhanced biosynthesis and metabolism of strigolactones. Therefore the genetic engineering approaches could be successfully used with the intention of improving the productivity of plants by improving their survival under undesirable conditions [30]. In studies with tomato [121] and *Lotus japonicus*, a noticeable reduction of strigolactones in root extracts under osmotic stresses was detected. The depletion of strigolactones is responsible for increasing the ABA levels in roots [122]. Further, this signal could be transduced to the shoots causing a positive impact on shoot physical responses enabling the plants to cope with drought conditions. All these facts suggest that the local reduction of strigolactones in roots can systematically alter the physiological responses of plants [121].

Also, the symbiotic interactions of arbuscular mycorrhizal (AM) fungi with lettuce and tomato crop plants were found to enhance the plant survival under undesirable environmental conditions. This symbiotic association can be induced by promoting the strigolactone production in these plants [123]. Increased root diameter in mycorrhizal plants enhances the uptake of water via roots [124]. Also, by maintaining the osmotic balance and

a water potential gradient between the plant root and soil, this symbiosis enhances the uptake of water [125]. Scientists have focused on the use of these strigolactones industrially to increase the survival of plants, particularly crops, under limited water conditions subsequently improving their yield. The use of strigolactones in industrial scale could be achieved using plant propagation materials treated with strigolactone mimics [126].

Plants which have established a symbiotic interaction with arbuscular mycorrhizal fungi are found to be associated with enhanced strigolactone production particularly under salt stress conditions. Thishas been studied in lettuce plants in which the increased strigolactone biosynthesis induces the colonization and symbiotic association of AM fungi with that of the plants. This association could lead to the hormonal changes in plants consequently improving their survival under undesirable conditions [127]. Mycorrhizal plants are found to have a more developed root system with an increased surface area, projected area, and root length. Also, this symbiotic interaction involves maintaining the ionic balance of plants by alleviating Na+ concentration under stress conditions [128]. Therefore, it is evident that strigolactones play a vital role in abiotic stress management by inducing the AM symbiosis in plants.

Apart from the role of strigolactones in abiotic stress management, studies also reveal that strigolactones induce the resistance against biotic stresses. Strigolactones produced in bryophytes induces the defense signaling mechanisms against *Physcomitrella patens*pathogenic fungi [31]. With the use of GR24, it is further confirmed that strigolactones induce the resistance against phyto-pathogenic fungi. This fact ensures that the strigolactones in root exudates have the potential to provide a protective barrier against pathogenic organisms [32]. In fact these all facts offer sufficient evidence that the strigolactone mediated stress-inducible gene expression is conserved in a wide range of plants. This finding can be applied to plants for their better acclimatization to various stressful conditions. Interestingly this concept could be used to enhance the yields of plants which are having agronomical benefits.

5.5 Control of root and shoot architecture

Branching and branching pattern of plant shoots is an essential determinant in the regulation of plant architecture. Regulation of plant architecture during plant shoot development is invaluable for many agricultural applications, and it facilitates the plants to acclimatize to

different stress conditions [129]. Many synthetic strigolactone analogs have been developed with the potential to act as plant growth regulators, without favoring the parasitic seed germination. By taking advantage of signaling pathways of strigolactones, synthetic branching repressors such as 3'-methyl-GR24 and AR36 have been developed. These new strigolactone analogs have pretty much higher activities than that of the previously developed strigolactone analogs including GR24, CISA-1 and thia-3'-methyl-debranone-like molecule.

Strigolactones are known to induce the plant height by promoting the elongation of internodes. Therefore plant breeders have paid much attention to increasing the plant height which in turn enhances the biomass, standing capabilities and also the seed yield [100]. Strigolactones reduce the ramification of plants by repressing the bud growth of plants. This finding is significant in many applications such as in cultivating ornamental plants, forest plants, food crops, leguminous plants as well as in the agricultural field. To accomplish this, the desired plants in which the ramifications should be controlled can be exogenously treated with strigolactones [130]. Chrysanthemum (*Dendranthema grandiflorum*) is one of the plants which are important in horticulture. Shoot branching is an important trait to be regulated in this plant to improve the economics and the ornamental value. It is used as a cut flower in many countries, and for that, it is needed to have one large flower on each stem [129]. Shoot branching of Chrysanthemum can be controlled by the application of synthetic strigolactone analogs [131].

Use of strigolactone analogs is beneficial since taking the lateral buds away from the plants or pinching of the plants manually during the growth period is much expensive. GR24 is a potential inhibitor of bud outgrowth, andthereby it controls the shoot branching habit of the plants. However, to use these synthetic strigolactone analogs onan industrial scale, the required techniques and the cost has to be reduced. Apart from using the synthetic analogs, researchers have focused on the manipulation of *CCD8* gene [131], which is a candidate gene in strigolactone biosynthesis [52]. Another study reveals the usefulness of two strigolactone analogs other than the GR24 with the intention of inhibiting the bud outgrowth of plants. These are GR5 and an analog with a 3, 4-dimethylbutenolide D ring component. For their ability in promoting the hormonal activity of plants, the D ring which is either a dimethylbutanolide or a methylbutenolide and the unsaturated α, β-system are essential [17].

Also, the tomato plants with decreased *SlCCD8* expression are found to have altered vegetative and reproductive traits. The reduced expression of *SlCCD8* is responsible for increasing an array of traits such as node number, branching of shoots and development of adventitious roots while decreasing the plant height. Also, the fruits and flowers are small in size, and the fruits were found to contain a lesser number of seeds [25]. The Genetic Improvement of plants can be accomplished through the *CCD7*/*CCD8*pathway to achieve the optimum plant architecture, and this will provide access to improve their applicability in different fields. A woody perennial plant known as *Actinidia chinensis*is widely grown for the production of kiwi fruit. Shoot branching is vital to improve the yield of kiwifruit commercially. The suppression of *AcCCD8* is responsible for enhancing the branching of this plant thereby improving the fruit yield [132].

Strigolactones also has significant impacts on stolon bud outgrowth and the development of tubers in potatoes [133]. Studies reveal that the application of GR24 exogenously results in suppressing the growth of both the stolon buds and potato tubers consequently giving rise to a less number of tubers [134]. Plants in which the *CCD8* gene has been knocked out by RNAi technology were shown to have dramatic changes such as shorter plants, increased number of primary and lateral branches, and improved shoot branching from stolons [133]. TIS13 which is a triazole-type chemical agent can induce tillering of rice seedlings by repressing the strigolactone biosynthesis [105]. In fact, these facts suggest the usefulness of strigolactone biosynthetic inhibitory agents for the ultimate purpose of improving the yield [105, 135]. Higher the number of branches, larger the number of fruits and so as the yield. Therefore, the development of strigolactone antagonists which cancel out the inhibitory effects of endogenous strigolactones is a promising strategy for yield improvement.

In addition to the shoot branching, strigolactones also play vital roles in the regulation of root branching. The role of strigolactones in root branching has been confirmed in *M. truncatula* [21] with the treatment of GR24 [22]. The treatment of synthetic strigolactone analog GR24 results in inhibition of lateral root density [21], by inhibiting the development of lateral roots and lateral root primordial [22]. Besides the inhibitory effects of GR24 on lateral root development, it also regulates the length of the primary root [21], by controlling both the cell length and the number of cells in transition zones and the meristem of the root. GR24 indirectly regulates the root architecture by regulating the auxin levels in plants in a concentration-dependent manner [22]. In addition to the lateral and primary root

development, nodulation is another crucial aspect in the determination of root architecture, and it is controlled by exogenous GR24 in a concentration-dependent manner [21].

However, the impact of strigolactones on root formation in one species varies from that of the other species because of the presence of different hormone concentrations in plants. The *LjCCD7* mutant lines in *Lotus japonicas* which are deficient in strigolactone biosynthesis are known to have opposite effects in comparison to the previous studies. These contradictory effects are confirmed by the observation of increased primary roots, decreased number of pods, flowers, and delayed leaf senescence in mutant lines [136]. Another strigolactone analog EG010 is found to have a similar activity to that of GR24 in nodulation of root architecture in *Arabidopsis* [8]. It is that the tomato plants with reduced expression of *SlCCD8* account for an increased adventitious root formation and it is drastically repressed upon the addition of GR24 [25]. These facts reveal that strigolactones enable the plants to reach an optimum root and shoot architecture below and above the ground.

6. STRIGOLACTONES IN CANCER TREATMENT

Both the synthetic strigolactone derivatives as well as the natural strigolactones have the potential to act as cell proliferation inhibitors, and this facilitates their applicability in treating several types of cancers such as prostate, breast, lung, colon and many infections caused by fungi and bacteria. Synthetic strigolactone analogs including MEB-55, EG-5, EG-9C, ST-362, and ST-357 are known to interfere with the formation of mammosphere. A novel study has given insight into a new formula, comprised of different isomers, pharmaceutical salts and other active compounds suggesting its role against melanoma in addition to an array of cancer types. Strigolactone analogs primarily work on the cancerous stem cells like cells and bulk tumors. The analogs can function in tumor cells by activating stress signaling, simultaneously repressing the survival signaling. The use of strigolactones is a promising strategy for cancer treatment over the use of chemotherapeutic drugs, which often causes detrimental toxic effects [104]. The functions of synthetic strigolactone derivatives as anticancer agents are given in table 1.

6.1 Human prostate cancer

In prostate cancer cells, strigolactones cause a considerable lethal impact on cancerous cells while the effect is negligible on normalnon-cancerous cells. Two synthetic strigolactones

including MEB55 and ST362 (Figure 5) have found to cause the aforementioned lethal effects. These effects are performed by encouraging the cellular apoptosis by inducing pro-apoptotic genes, stopping the cell cycle, activating p38: a mitogen-activated protein kinase (MAPK) [43] which is involved in arresting the cell cycle [137] other MAPKs including JNK [43] which involves in stabilizing p53 [70]. Strigolactones are known to up-regulate the stress-associated genes. They also down-regulate the survival factors such as ALDH1 and stemness marker, which are critical in survival and regeneration of stem cells [43].

6.2 Human breast cancer

Synthetic strigolactone analogs are known to function in preventing the synthesis of mammosphere and breast cancers. In breast cancer cell lines, these strigolactone analogs stop the cell cycle at G2/M phase leading to self-auto digestion of cells by apoptosis in different quantities. Two types of strigolactone analogs including MEB55 and ST362 (Figure 5) have identified to act on cancerous cells in breast and subsequently phosphorylating the MAPKs such as p38, JNK ½ and repressing the AKT (Protein kinase B) thereby causing a negative impact on the overall cell functionality [44]. The indol based structure of both the MEB55 and ST362 is comprised of C and D rings which are interconnected by an enol ether linkage. The A ring of MEB55 is a thiophene ring while it is a dioxathiophene ring that in the ST362 (Figure 5) [103]. Thenegative effects of synthetic strigolactones on cancerous cells are entirely different from that of the non-cancerous cells. Although the cancerous cells are much responsive to their impact, the studies reveal that the healthy cells are less susceptible to their impact [44].

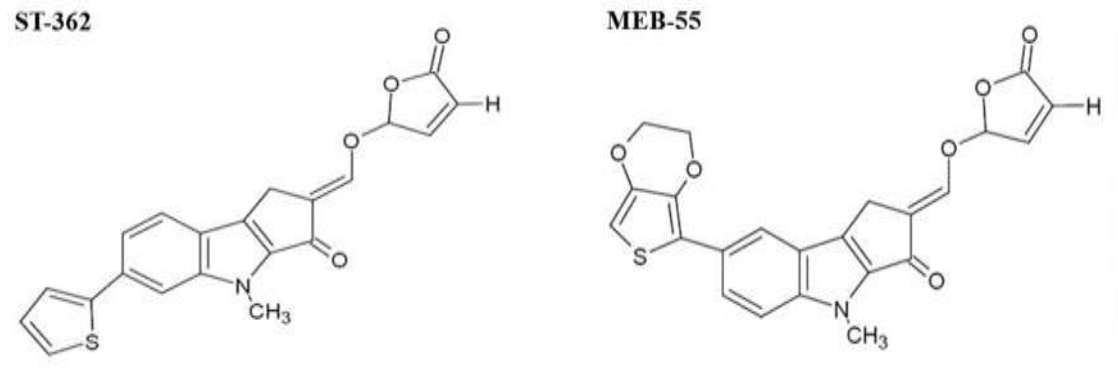

Fig. 5 Structures of two synthetic strigolactone analogs. The synthetic strigolactone analogs activate cellular apoptosis and cell cycle arrest ultimately leading to the death of the cancerous cells [104].

The activity of strigolactones on p38 causes them to bind and phosphorylate p53: a protein which represses the tumors, in turn making it stable and controls its function [70]. The activity of strigolactones on JNK causes it to make p53 stable by abolishing the interaction with mdm2 (murine double minute 2). Thereby it activates p53 subsequently enhancing its capability to bring out the adaptive responses such as apoptosis [138] and to abrogate the cellular growth [139]. Another study focused on MDA-MB-231 xenograft tumors in mice reveals that the action of MEB55 at a reduced concentration on tumor cells results in an additive suppression of cellular growth. Also, this study further shows that both the ST362 and MEB55 strigolatones have a role in influencing the microtubule integrity subsequently diminishing the motility of MDA-MB-231 and MDA-MB-436 breast cancer cell lines in the body [103].

When considering the involvement of strigolactones at the DNA level, they cause double-strand breaks in DNA [102] subsequently negatively affecting the integrity of the genome [140]. The integrity of the genome depends on reliable repair mechanisms [141]. Strigolactones repress homology-directed repair (HDR), which is a significant repair mechanism in mammalian cells [142] and non-homologous end-joining (NHEJ), another type of repair mechanism [143] involved in correcting the DNA damage. Strigolactones also repress the RAD51 protein [102] which is essential for homologous recombination [144]. It plays an important role in swapping the DNA strands and inducing homologous pairing [145]. Strigolactones also prevent the subsequent replacement of RAD51 into the sites where double strand breaks incorporated [102].

7. CONCLUSIONS AND FUTURE DIRECTIONS

Strigolactones are primary targets in many agronomical improvements [98] and also in therapeutic applications [43]. They are known to play many vital roles in plants by influencing both the plant morphology and physiology. With the advances in knowledge and techniques, the chemical structure [93], biological function, structure-function relationship and regulation of strigolactones [100] have been uncovered within past few years. For the effective utility of strigolactones in the strategies above, a more comprehensive understanding of the manipulation of strigolactone biosynthesis [59] and perception [64] would be required. This awareness of strigolactones would lead to the development of new cultivars depending on the requirement. Relatively low persistence of strigolactones in plants

and soil has led to the development of synthetic strigolactones and mimics. For this target to be fulfilled, it is indispensable to demystify the mode of action of strigolactones within the plant. Therefore, a prior knowledge of how strigolactones function inside the plants would facilitate the production of synthetic derivatives with high stability and activity in contrast to natural strigolactones [35].

Transgenic plants created by silencing the *CCD8* gene by RNA interference thereby compromising the activity of strigolactones would be a promising strategy to regulate many plant physiological activities. Suppression of strigolactone related genes is the target of this approach [133]. Also, the manipulation of genes (either up or down-regulation) downstream of the strigolactone pathway also has been studied [18]. Reliable molecules such as cotylimides which have the potential to regulate strigolactone expression also have been developed [107]. Moreover, the manipulation of the production of different strigolactones as a combination may be possible. The production of different types of strigolactones simultaneously might be attributed to diminishing the germination stimulatory activity of strigolactones while enhancing their ordinary impacts on the shoot and root branching [20].

Strigolactones are also known to function in therapeutic applications. Both the natural and synthetic strigolactone products can be used to treat a wide range of cancers such as prostate, breast, lung, colon and many infections caused by fungi and bacteria [104]. They primarily function in cancer cell lines by inducing the apoptosis, arresting the cell cycle, influencing the microtubule integrity and promoting the DNA damage [44]. The potential application of strigolactone in cancer treatments is remarkable, as it can avoid the complications caused by chemotherapeutic drugs [104]. Moreover, the fact that its effect is negligible on non-cancerous cells reflects its effectiveness in cancer treatment [44].

All these facts suggest that the strigolactones are effective and promising candidates in both the plant improvements and therapeutic applications.

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