Rare-Actinomycetes to the Rescue

Subjects: Microbiology

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The failure of sustainable and agricultural intensifications in saving the ecosystem/public health has caused a paradigm shift to microbiome resource engineering through sustainable approaches. As agricultural intensification systems prioritize synthetic input applications over environmental health, sustainable intensification fails to define the end point of intensification, giving room for the application of “intensification” over “sustainability” to suit farmers’ needs. The complexity of a cooperative microbiome and the uncontrollable nature of its numerous influencing parameters as well as the non-specificity associated with bioinoculant application, results in the direct utilization of agroactive compounds to obtain greater preventive efficiency.

agro-antibiotics bioeffectors plant protection fungicide

1. Introduction

Sustainable agriculture is, therefore, the best alternative to all intensification principles as long as the natural resources of sustainability are well-managed to enhance productivity [1]. Agro-biodiversity, which is one of the natural resources manageable for sustainable production, co-exists between plants in the external environment of flowers (anthosphere), germinated seeds (spermosphere), fruits (carposphere), at the plant tissue surface (rhizoplane or phylloplane), inner tissues (endosphere) and in the root-soil vicinity (rhizosphere). In these niches, microbes interact with plants in a beneficial and complex relationship that enhances plant resilience in times of climate, human, microbial and animal-induced stress [2]. The choicest nutritious matrix the rhizosphere cuts across the root and soil environment, harbouring a microbial community that is shaped by the constant root exudate supply and cooperates to render below and above-the-ground ecosystem services, even when exposed to all manner of stressors. At this matrix, myriads of microbes, mostly bacterial cells, interact to enhance plant fitness and soil health [3]. Co-operational activities of rhizospheric bacteria have been studied to a significant extent, and it was discovered that they could often ameliorate many of a plant’s biotic/abiotic stress factors [4][5][6]. For example, in a rhizobacteria study at two maize farms, it was observed that the flowering stage was dominated by *Norcardioida*, *Micromonospora* and *Frankia* species with genes that code for antagonism, siderophore producing capacity and pyoverdine phytohormones, all of which are function relevant for plant health. In addition, all of the bacterial players in this cooperative system have also been individually and synergistically applied outside their confine as bioinoculants, and their by-products have been applied as bioeffectors. *Pseudomonas* spp. and *Bacillus* spp. isolated from maize plants were reported to contain genomes that code for nitrogen fixation, phosphate solubilization, quorum sensing, trehalose synthesis, siderophores production, phenazine biosynthesis, daunorubicin secretion, acetoin synthesis, 1-aminocyclopropane-1-carboxylate deaminase activity, stress-reducing and disease control functionalities. These bioeffectors include acids/gases, enzymes, siderophores, phytohormones, exopolysaccharides, osmolytes, volatile organic compounds and antibiotics [7]. They are more specific in action, and priorities have been given to some bacterial genera, such as *Bacillus* spp., *Pseudomonas* spp. and *Streptomyces* spp., as a source, in ensuring sustainable plant health [8], with less focus on the non-Streptomycetes class. For example, rhizobacteria (*Bacillus* and *Pseudomonas* strains) isolated from maize and soybean have been reported to elicit auxin, hydrogen cyanide and ammonia synthesis, antifungal activity, tolerance to abiotic stressors and phosphate solubilization [9]. They promote plant health through the inactivation of virulence factors, inducing plant defense mechanisms and antibiosis, of which agro-antibiotics (also termed biopesticides) have a key role to play in all.

Without question, Actinomycetes are the greatest source of agro-antibiotics or biopesticides, notwithstanding the fact that Streptomycetes strains from the rhizosphere have been nearly exhaustively studied as direct producers or as heterologous expression chassis [8]. The short and large genome contig of Actinomycetes contains thousands of biosynthetic gene clusters (BGCs) coding for known/unknown agro-antibiotics. Therefore, if the well-studied Streptomycetes contain numerous types of biopesticides from non-proteinogenic amino acid, peptides, nucleosides/analogues, acyclic, cyclic esters, organic acids, carboxylic acid esters, lactones, macrolides, amides to other minor agro-antibiotics, there may be many more of these compounds in their reserve, and in the underexplored non-Streptomycetes. The non-Streptomycetes group, as a phytoprotective agent source, has been used for the production of spinosyn from *Saccharopolyspora spinosa* (including the spinosad and spinetoram derivatives), *Saccharopolyspora pogona* NRRL 30141 derived pogonins, *Amycolatopsis* sp. derived amidenin and dehydrosinefungin derived from *Micromonospora* sp. A87-16806 [10]. Hence, more reliable novel agro-antibiotics could be produced from this trove and applied in agricultural systems to non-detrimental boost productivity.

Recent high throughput innovations in agro-antibiotics discovery involving automated culture-independent, genomics datasets and large-scale mass spectrometry-based comparative metabolomics have been used to decrypt the conserved BGCs and accurately predict modifications as well as the exact scaffold structure. These molecular networks demonstrate bioproduct furnishing encoded by orphan BGCs in the microbiome, which have to be cloned (a highly complex and technical procedure) before product release. However, the complexity and cost-ineffective nature of these molecular networks make it necessary to settle for a non-targeted culture-dependent genometabolomics roadmap [11], as highlighted in **Figure 1**.

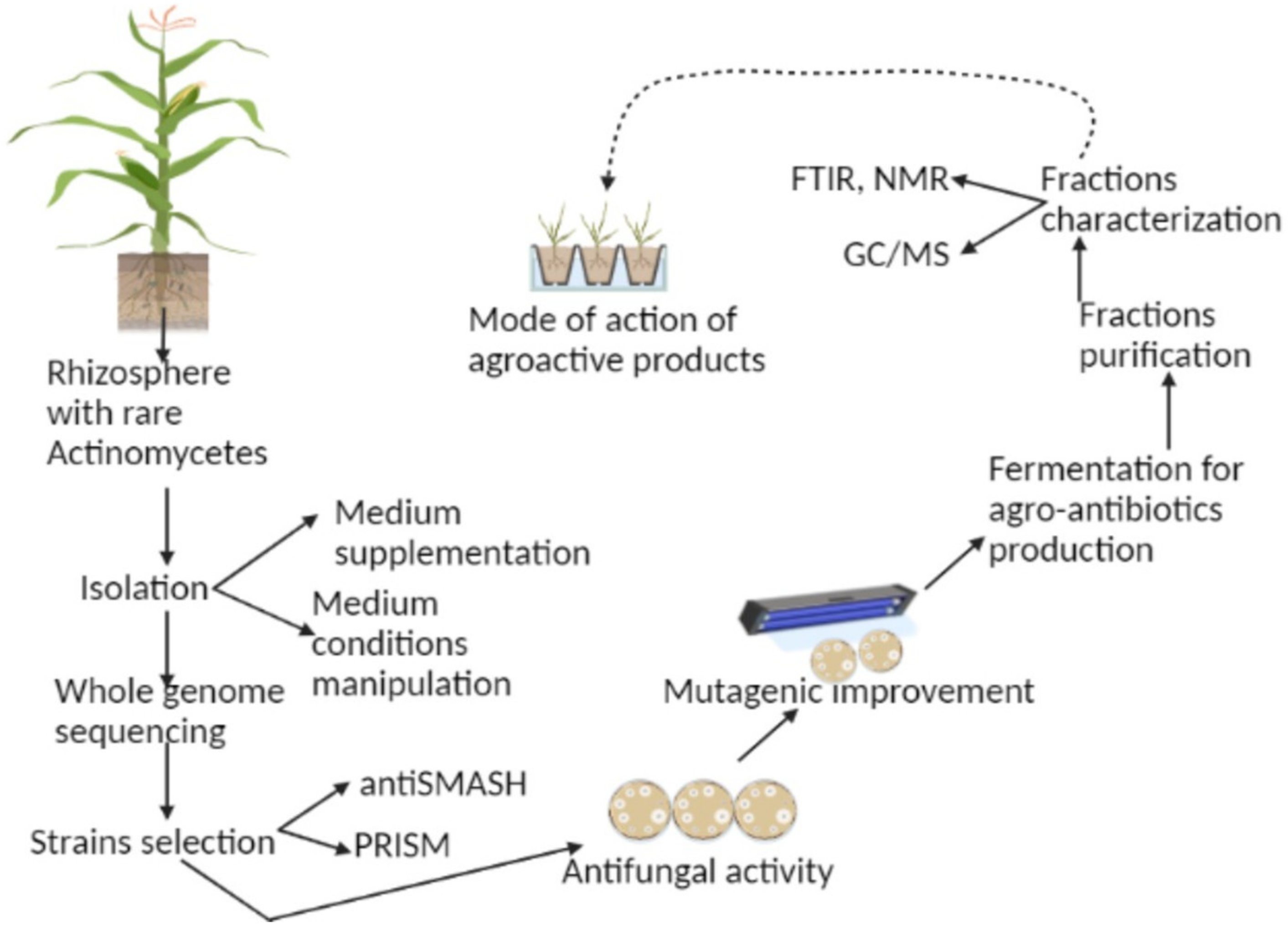

Figure 1. Isolation of agroactive metabolites.

2. History of Sustainable Agricultural Practices

Agricultural practices began from approximately 196,000 years ago, when our ancestors in the Neolithic revolution survived by consuming wild animals, plants and fungi (hence they were termed the nomadic hunter-food gatherers), to ~11,000 BCE as they adopted crop cultivation as well as rearing animals for food. Subsequently, in ~5000 BC, more focus was given to crop cultivation than to animal husbandry [12][13][14] and these ancestors began to own land. They became sedentary in villages/towns close to their fields, where they adopted diverse agricultural practices such as irrigation and tillage to improve productivity and meet their population's needs. Agricultural development followed a unique track, and small farm holders experienced poor soil quality and a high disease burden. Adaptation to these challenges drove new agricultural practices, such as land rotation using the slash and burn principles. Over time, farmers were constrained to cultivating the same fields season after season [15].

As urban expansion continues to increase worldwide, land prices increase and farmland disappears. These changes provide a strong incentive to develop plants that are climate and disease resilient as well as to increase plant productivity to match the growing global population [16]. These ecosystem needs are partially addressed by integrating the right farm practices that enhance the interaction of living and non-living entities for adequate productivity with the concomitant provision of nutritious and safe food and environmental integrity, as well as food sovereignty [17]. This ecosystem approach is a sustainable one that involves recycling beneficial natural resources, decreasing superficial input utilization and diversification, as well as the amalgamation of farming systems that can build climate and disease resilience [16]. The specific practices addressed so far include mixed cultivars, intercropping, crop rotation, minimum tillage, groundwater table filling, different planting times, use of diverse varieties/species formed from conventional breeding coupled with participatory varietal selection [18], animal diversification, climate forecasting, eco-friendly pest/disease control through neem oil-based insecticide creation, compost enriched with *Trichoderma*, seed selection/coating to prevent pest infestation, then application of biogas slurry, mulching, green manure and liquid enriched composting to reduce crop loss. These strategies are adopted by subsistence smallholder farmers to enhance biodiversity management for efficient carbon sequestration, irrespective of the climatic condition or level of pest/disease infestation, in a cost and eco-friendly manner [16]. This is aimed at ensuring that all beneficial entities that stimulate plant productivity are enhanced; however, some of the practices, such as animal diversification, still promote faecal pathogens seepage into the soil.

Scientists have recently searched for means of improving crop productivity in an effort to match the persistently increasing population; this initially led to the creation of the Green Revolution, involving the utilization of synthetic fertilizers/pesticides that increased productivity at the expense of soil quality, biodiversity, food consumer’s health and the environment [19], these detrimental effects triggered the S.I. approach, which some scientists see as a complex illusion that fails to delineate the extent of intensification. The S.I. approach is cost ineffective, depletes natural resources, and has no definite limit of chemical input application, and hence has a resultant undefined level of environmental impact. It is a controversial concept that did not clarify which is more important, intensification and its provision of adverse environmental impacts or sustainability with its excessive land use [20].

With the constant increase in a global and commensurate upsurge in food insecurity, an artificial intelligence approach to agricultural development was embodied with smart multi-faced technologies. The major trade-off of these technologies is that they must be combined with an intensification input; for example, agricultural drones, having conducted a speedy/thorough health assessment, must apply synthetic pesticide or fertilizer as a corrective measure [21], which alters the sustainability of the holistic concept. Therefore, this yet-to-be-debated, promising tech-agricultural innovation in the twenty-first century has to be supported by a more sustainable, potent and affordable alternative agent/input that could be applied to alleviate plant stress, which is the major cause of soil infertility as well as food insecurity. Focusing on biotic stress alleviation, the application of bacterial biocontrol agents can sustainably increase productivity. Under this premise, bacterium/bacteria were pulled from a plant/soil site and utilized for crop growth promotion in another site as phytoprotectants. In addition, Actinomycetes are excellent producers of natural products due to a highly conserved genome encoding metabolites in thousand contigs, some of which have been mostly exploited for indirect plant growth promotion through plant protection during biotic stress [22]. Also, considering the history of Actinomycetes as the biggest producers of antibiotics, which has greatly exposed their antimicrobial potential in killing or inhibiting microbes [23], some of which are potential plant pathogens that have resulted to considerable loss during crop production as described in **Table 1**,as well as other sustainable agricultural applications.

Table 1. Roles of rare Actinomycetes in sustainable agriculture.

Rare Actinomycetes	Core Genes	Metabolites Encoded	Functionalities	Roles in Sustainable Agriculture	References
Frankia sp.	*nif*	Nitrogenase enzyme	Nitrogen fixation	Soil fertilization	[24]
Tsukamurella tyrosinosolvens	*pho*	Phosphatase enzyme	Phosphate solubilization	Phosphate fertilization	[25]
Amycolatopsis sp.	$PR_{1\text{–}1a}$ & *GLU*	proteins	Systemic acquired resistance	Plant defence	[26]
Arthrobacter sp. SD3-25	*atzB*, *atzC* & *trzN*	hydrolases	Atrazine & simazine pesticide biodegradation	Soil fertility and Bioaugmentation	[27]
	mbtH, *fagD*	protein	Siderophores biosynthesis	Plant defence and Iron fertilization	[28]
Tsukamurella tyrosinosolvens	*febB*, *febD*, *yqjH*, *hpaC*	Transport proteins	Biosynthesis of iron transporter	Plant defence and growth	[25]
	atzF *argG* *argH*	Hydrolase Arginine succinate synthase Arginine succinate lyase	Urea degradation	Ammonia and amino acids biosynthesis for growth	[28]
Saccharothrix sp.	*SacA,B,C,E*	Polyketide synthase	*Saccharochelins* A–E biosynthesis	Phytoprotection	[29]
Amycolatopsis sp.	*asrR*	Type III glycopeptide	Ristomycin	Phytoprotection	[30]
Nocardiopsis alba BH35	Crude filtrate	Protein	Antifungal metabolites	Phytoprotection	[31]
Rhodococcus ruber C_1	*dmpP*	Phenol hydroxylase	Phenol degradation	Biodegradation	[32]
Rhodococcus sp. ANT_H53B	*crtP,M,N,Nc*	Diapolycopene Oxygenase, dehydrosqualene	C_3 apocarotenoid biosynthesis	Phytoprotection and enhancement	[33]

Rare Actinomycetes	Core Genes	Metabolites Encoded	Functionalities	Roles in Sustainable Agriculture	References
		synthase & other enzymes			
Saccharothrix yanglingensis Hhs.015	Elicitor *PeSy1*	Protein	Induce plant resistance	Plant defense against *Pseudomonas syringae* pv. tomato DC3000	[34]
	Chi6769	Protein	Chitinase biosynthesis	Phytoprotection	[35]
Saccharopolyspora sp.	*arsG*	Arsenate reductase	Arsenic removal	Arsenic biocleansing	[36]

roducing ironment, le genetic ommunity balance through their natural selectivity [37]. Actinomycetes have been reported to produce ~10,000 (i.e., 45%) of ~23,000 metabolites released by microorganisms, and 20–30% of the 10,000 compounds are derived from non-Streptomycetes or rare Actinomycetes; hence, these groups have been underutilized. Consequently, the attention of researchers is now directed towards the use of non-Streptomycetes or rare Actinomycetes such as *Micromonospora*, *Streptosporangium*, *Microbispora*/*Streptoverticillium*, *Saccharomonospora* and *Norcadia* species as crop protective tools (based on their antibiosis and growth promotion activities); other genera include *Actinokineospora*, *Actinomadura*, *Allostreptomyces*, *Amycolatopsis*, *Dactylosporangium*, *Kutzneria*, *Lechevalieria*, *Microbacterium* species [38], with 70–80% yet to be identified. A metagenomics study was conducted on mineral soils in a dry valley, with the discovery of multiple uncultured *Pseudonocardia* and *Nocardioides* species. In addition, several agroactive effectors have been commercially produced from *Streptomyces* sp., with a large spectrum of action against plant diseases, and these treatments are reported to reduce plant disease severity by 95%. These microbial-based agroactive effectors have also been reported to act as enhancers of nutritional and functional quality as well as to increase the yields of fruits and vegetables [39]. These effectors can be used directly in a sustainable manner, with the benefits shown schematically in **Figure 2**, to control the upsurge in global plant pest/disease burden and enhance crop productivity.

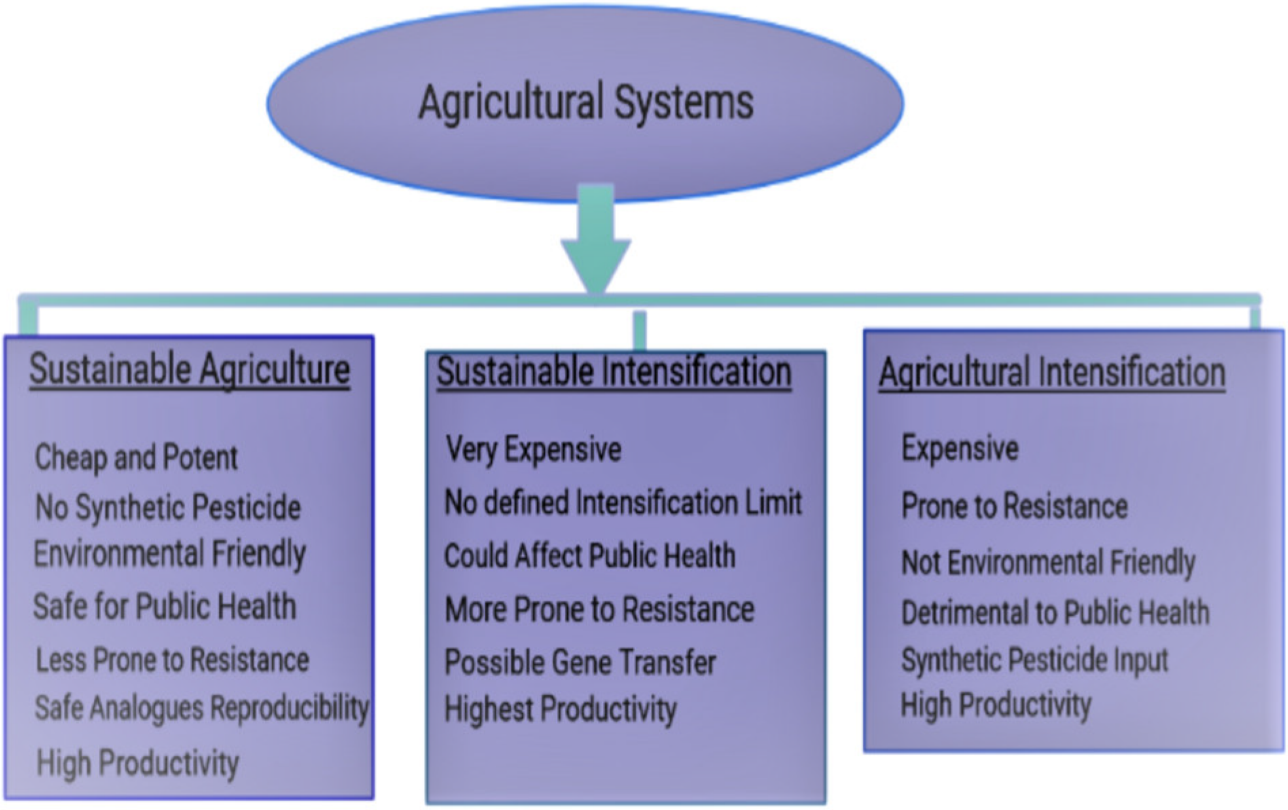

Figure 2. Characteristics of agricultural systems applied for ensuring disease resilience.

4. Agro-Antibiotics Encoded by Biosynthetic Gene Clusters (BGCs) in Actinomycetes

Actinomycetes are Gram-positive, filamentous cocci, prokaryotic organisms that are 1–2 μm in diameter and respire both aerobically and anaerobically. They are abundant in many soils (often 10^6–10^8 cells/g), marine environments (5–40 Cfu/mL) and desert soil habitats and are known producers of a large number of different metabolites. Actinomycetes are a hub of known and unknown bio-products.

The biosynthetic gene cluster sequences encode diverse proteinic and non-proteinic enzymes disbursed in modular frames forming diverse BGC types, which include: PKSs (polyketide synthetases), NRPS (non-ribosomal peptides synthetases) and hybrid-PKS-NRPS in assembly lines. Most of the bio-products for crop protection, such as avermectin and its derivatives, milbemycin, meilingmycin, spinosyn and its derivatives, pogonin, polynactin, herboxidiene, sannastatin, coelimycin P1, actinorhodin, rubiginone D2, juniperolide A, tetramycin, antimycin, nemadectin and actinospene, among others, are synthesized from PKS assembling lines, with a few NRPS and hybrid derived products [40]. Hybrid and NRPS-derived phytoprotective bioproducts are yet to be produced, mostly silent under in vitro studies, requiring planta discovery with metagenomics accompanied heterologous expression of their biosynthetic genes in suitable chassis for reproducibility [41]. The gene cluster sequences encode diverse modules of complex PKSs (polyketide synthetases), NRPS (non-ribosomal peptides synthetases) and hybrid-(i.e. PKS-NRPS) in assembly lines. These enzymes aid the transfer of a series of monomer units to appropriate linear oligomers until the formation of a known or orphaned product [42]. The biosynthetic genes consist of core codifying genes and regulatory long operon/promoter genes that either inhibit or promote core gene expression under the influence of a changing environment. The genes of PKS, NRPS and hybrid assembly lines have been characterized, which confirmed that such genetic design is in clusters that should facilitate their complete pathway cloning [43].

In fact, several studies have revealed the cloning of multiple copies of biosynthetic genes to optimize metabolite production, the swapping of PKS genes of closely related species or classes to enhance the spectrum of metabolites produced and the shuffling of genes in diverse rounds through the physical/chemical mutation of Actinomycete genomes to ensure phytoprotection. These manipulations have led to the innovation of new derivatives of avermectin, spinosyn and novel erythromycin [37]. Metabolites characterized by these organisms have been used in pharmaceutical industries as antibiotics as well as in agricultural sectors as biopesticides or agro-antibiotics. Agro-antibiotic compounds are produced in low doses by a microorganism against other organisms; they are specific in action, self-propagating, less prone to resistance, compatible with irrigation activities, mostly biodegradable, have preventive or killing control and are not crop-specific, and the producer possesses a transgene that makes the producing organism resistant to the by-product they exude. From a site-specific agro-antibiotic, other derivatives with a wider spectrum of action can be obtained by genetic or synthetic modifications. For example, synergistic activity is seen in the combination of spinosyn A and D to form spinosad with a wider spectrum of action against thrips, armyworms, codling moths, cutworms, leafminers, mosquitoes, ants, fruit flies, spider mites and other varieties of pests [44]. Numerous compounds or formulations have been derived from *Bacillus*, *Pseudomonas* and *Trichoderma* species [45]. Presently, the global market for agro-antibiotics is expected to grow to USD 4.5 billion, with 60% of the compounds coming from Actinomycetes (Streptomycetes).

It is worth noting that Actinomycetes have a large number of BGCs that are uncharacterized or conserved; the genome is made up of repeats, functional domains and genome assembly lines connected to make diverse metabolites scaffold [46]. Hence, studies have revealed the presence of large numbers of cryptic compounds in Actinomycetes, which could only be decoded if constantly characterized; perhaps this is the reason why it seems Streptomycetes compounds encode more than their non-Streptomycete counterparts. For instance, a study conducted on *Streptomyces*-derived biopesticides reflected more than 100 compounds from about twelve classes of bioherbicides [10]. It is, therefore, imperative to decrypt these silent metabolites to resolve disease burden in a more sustainable manner, focusing on non-Streptomycetes.

Furthermore, outside the PKS, NRPS and hybrid pathways that are chiefly responsible for secondary metabolite production at the stationary or death phase of Actinomycetes growth, other pathways that are implicated in biosynthesis include β-lactam, oligosaccharides synthesis and Shikimate pathways [47]. Biopesticide classifications based on target pest are grouped into acaricides (target mites), fungicides (target fungal specific processes), bactericides (target bacterial specific processes), herbicides (target plant-specific processes), larvicides (affect insect larva), nematicides (affects roundworms), termiticides (target termites) and ovicides (affect insect eggs). However, based on existing agro-antibiotics, they can be grouped basedon their agroactive efficacy, as elaborated below.

4.1. Herbicidal Agents

Weeds have globally resulted in an estimated 34% annual loss in crop yield through their adverse competition for crop resources; bioherbicide application is the best eco-friendly remedy. Bioherbicides are weed target compounds of less than 500 molecular weight sizes with low toxicity in active doses to the ecosystem and have enhanced their relevance as a biointensive integrated weed control agents for agricultural development. These agents can be peptides, amino acids, organic acids, amides, carboxylic acid esters, lactones, macrolides, nucleosides and analogues that inhibit root elongation and ethylene synthesis; they can inhibit photosynthesis systems [48], root and shoot elongation, amino acid, cellulose, glycan, nucleic acid and de novo fatty acid biosynthesis in plants. Large numbers of Streptomycete herbicides have been derived, with only sparse studies on rare Actinomycetes. Some rare Actinomycete-derived herbicides include patented maiden/derivatives from an *Amycolatopsis* sp. strain in Japan, which is used to reduce sulfonylurea herbicide application in rice farms; carbocyclic coformycin from *Saccharothrix* sp., which disrupted the ATP pool in plant cells; *Actinoplanes* sp.-derived formycin A & B with a broad spectrum of post/pre-emergence herbicidal activity against monocot weeds and grasses; thiolactomycin from *Nocardia* sp.; *Micromonospora* sp. A87-16806-derived patented dehydrosinefungin herbicides and *Actinomadura madurae*-derived ribofuranosyl triazolone, which is active against weeds and grasses [10].

4.2. Insecticidal/Acaricidal Agents

The environmental and public health impacts of synthetic pesticides have stimulated the development of microbially produced compounds against insects and mites. The application of agro-antibiotics such as avermectins and emamectin from rare Actinomycetes as both acaricidal/insecticidal activity operates through the activation of the nerve endings of insects and mites to extend the duration of the opening of GABA (gamma-aminobutyric acid)—gated Cl ion channel abnormally, resulting in the release of chloride ions and GABA, which highly polarizes the nerve membrane potential, blocking the electrical nerve conduction. This stimulates symptoms such as moulting, disturbance in water balance, metamorphosis and reproductive developments, with no cross-contamination [48]. Spinosyn A & D families, a 21-carbon tetracyclic macrolide produced by *Saccharopolyspora spinosa*, is an active neonicotinoid insecticide that is active against some species of Coleoptera/Orthoptera as well as Thysanoptera, Diptera and Lepidoptera, with little or no effect on non-targeted insects or mammals. Asides from acting on GABA receptors, they activate nicotinic acetylcholine receptors, which results in nervous system excitation, involuntary muscle contractions, tremor and paralysis. A second-generation spinosyn product called spinetoram (a semisynthetic natural pesticide), with a broader insecticidal spectrum with a more favourable toxicity profile in mammals and in the environment, has also been created [37], along with *Saccharopolyspora pogona* NRRL 30141-derived pogonin (21-butenyl-spinosyns), which possesses the same spectrum of action as spinetoram against sucking insects such as cotton aphids and tobacco budworms [49]. In addition, Actinomycetes enzymes chitinase can regulate the process of chitin formation in insect mites and pests by disrupting the N-acetyl-D-glucosamine chitin chain at the β-1,4-linkage between monomeric subunits; this affects insect feeding, digestion, nutrient utilization and growth, and also indirectly causes deformities [37].

4.3. Anti-Phytopathogenic Agents

In smallholding farms from which the major food supply is derived, insects, pathogens, weeds and mites are the main threat to food security worldwide [50]. Pre-harvest fungal pathogens of the most significant cash crops, such as maize, as well as oil crops such as sunflower, include species of *Aspergillus*, *Fusarium* and *Cercospora zeae-maydis*. In addition, *Sclerotinia sclerotiorum* is highly pathogenic towards sunflower plants and acts by causing head and stalk rot. The crop resistance to these fungi by rhizosphere microbiome activities has encouraged scientists to utilize their agroactive metabolite resources for biointensive pest management. To this end, several antifungal agro-antibiotics have been elucidated from Streptomycetes—the most studied Actinomycetes. A recent analysis of the rare Actinomycetes has identified echinosporin and 7-deoxyechinosporin from *Amycolatopsis* sp. YIM PH20520 derived from the rhizosphere of Panax notoginseng, which displayed a high level of antifungal activity against root rot pathogens of Panax notoginseng [51]. Once a fungicide-exuding strain has been selected, several innovative approaches could be applied to its productivity and efficacy. Such approaches have been utilized on the highly overhauled Streptomycetes group to enhance fungicide yield and activity and activate the expression of more silent clusters. Actinomycete biosynthetic gene clusters are so malleable that sophisticated technical approaches such as heterogeneous gene transfer, overexpression of a specific gene in a mutant strain, the deletion or disruption of insignificant genes and the replacement of PKS genes of a target compound with another gene can bring about a variety of enhancements. These strategies are highly technical and expensive to achieve; however, less expensive approaches have been applied to *Streptomyces* species with positive results. These classical approaches involve agro-antibiotics supplementations of fermentation medium as well as an untargeted physical/chemical mutagenesis approach applied to express new or more active analogues from candidate strains [38][52].

Some antimicrobial metabolites were released by *Actinomycetes*, which were active against plant viruses. For example, *Actinomycete*-derived ε-poly-lysine was active against tobacco mosaic virus by acting as a curative and protective agent. In addition, with a minimum inhibitory concentration of 0.2 µg/mL–15.6 µg/mL, *Actinomycete*-derived munumbicins A–D was potent against the bacterium *Pseudomonas syringae* [53].

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