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Review

From Lab to Field: Biofertilizers in the 21st Century

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Abstract: Nowadays, legal regulations and social environmental concerns are converging towards the promotion of more sustainable agriculture based on organic compounds and soil preservation. These trends are fuelling the growth of the biofertilizers, which are beneficial preparations containing microorganisms able to enhance a plant's ability to uptake essential nutrients. Their production and commercialization encompass a multitude of critical steps deeply reviewed in this manuscript through an exhaustive overview of the key stages, such as microorganism selection, new environmental sources, upscaling to field trials, encapsulation, current application systems and regulatory considerations. However, although the economical expectations are promising, several methodological, environmental, and legal concerns are undermining their advancement. The redefinition of international legal frameworks, their enhancement based on trending technologies, and the fostering of multidisciplinary collaboration across sectors are key players to promote biofertilizers as eco-friendly and cost-effective alternatives to chemical fertilizers.

Keywords: biofertilizers; bioformulations; encapsulated biofertilizers; foliar application; mulch; nano-biofertilizers; PGPRs; spray application

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1. Introduction

A milestone in human development was achieved on 15 November 2022, when the world's population reached 8.0 billion people, as recently reported by the United Nations (https://www.un.org/en/global-issues/population, accessed on 31 October 2023). Thus, a hundred years seems sufficient to jump from 2.5 billion people in 1950 to the expected 9.7 billion in 2050. This exponential and relentless population growth has led to an ongoing search for higher crop productivity within shorter timeframes. Hence, the worldwide production of primary crop commodities in 2021 reached 9.5 billion tonnes, marking a 54% increase since 2000 and a 2% increment since 2020, as FAO (Food and Agriculture Organization of the United Nations) stated in 2022 [1]. Accordingly, agricultural production has become strongly dependent on the use of energy and chemical inputs, as well as the development of heavy machinery. However, in recent years, concepts such as "soil health" have gained significance, understanding soil as an ecosystem that must maintain an equilibrium to ensure plant yield. Moreover, the One Health concept, which unifies the health of people, animals, and ecosystems, also fits the current trends in soil preservation (FAO, https://www.fao.org/one-health/en; accessed on 31 October 2023). Based on this philosophy, a decrease in the use of chemical pesticides and fertilizers is mandatory at a universal scale due to their negative impacts on soil fertility (e.g., loss of biodiversity, disturbance in biogeochemical cycles), their negative effects on environmental pollution, soil degradation, and also human health-associated risks [2–4].

In addition, climate change is appearing as an ecological challenge to the crop's stability due to sudden temperature fluctuations, prolonged periods of both rainfall and drought, and the emergence or the geographical spreading of new pests [5].

Nowadays, biofertilizers rise as a promising alternative for sustainable crop production in the 21st century [3,4,6,7] and have been proposed as enhancers of the plant resilience and the rhizosphere against both biotic and abiotic stresses [5]. In fact, the biofertilizer market is projected to witness substantial growth, increasing from $2.3 billion in 2020 to an estimated $3.9 billion by 2025, according to the report published by the economic data supplier "Markets and Markets" (www.MarketsandMarkets.com; accessed on 31 October 2023) [3,8]. The Asia–Pacific region is expected to account for 34% of the total demand for biofertilizers, with Europe and Latin America also shifting their consumption patterns towards these products due to regulatory measures concerning chemical fertilizers [7].

The term "Biofertilizer", also named as bioinoculants or bioformulations, encompasses organic products comprising beneficial microorganisms, either in their active or inactive forms, able to colonize the rhizosphere or the internal tissues of plants. These microorganisms enhance a plant's ability to uptake essential nutrients such as nitrogen, phosphorus, and potassium, promoting nutrient availability and uptake capacity, which results in increased crop yields. Thus, biofertilizers have been suggested as a safe and eco-friendly alternative to chemical fertilizers [3,4,6,9].

Considering the promising importance of biofertilizers, this review shows a view on biofertilizers' state of the art, considering not only the scientific approaches, but also agronomic, legal, and economic aspects aiming to present how they can face up and support the evolution of agronomical industries all along the 21st century.

2. Unearthing the Basics

Historically, agricultural cultivation has mainly relied on the use of organic manure, mostly derived from animal and green sources. Initially, it was believed that the chemical composition of these additives was the main source of their beneficial effects. However, it later became clear that the presence of specific microorganisms also played a significant role in enhancing plant growth, although occasionally, this microbial enrichment could lead to plant infections by certain diseases [10,11]. The challenges associated with these traditional practices, coupled with the increasing global demand for food, have made research on fertilizers a critical area throughout the 20th and 21st centuries.

Research on biofertilizers mainly involves the isolation and identification of microbial strains with the ability to enhance crop development by fixing nitrogen, solubilizing phosphorus, mobilizing nutrients, or producing plant growth-promoting hormones, among others. These microbial strains can be applied to seeds, plant surfaces or soil [3,4,6,12], the classification of which can be based on diverse parameters resulting in different groups (Figure 1). First, the simplest classification is based on the **type of microorganism** employed, mainly bacteria and fungi [2], although the use of microalgae has been on the rise in recent times [13].

Second, a traditional classification is based on their **function**. In this case, biofertilizers encompass several groups of microorganisms, including, but not limited to: (i) nitrogen-fixing bacteria; (ii) microorganisms capable of solubilizing essential nutrients such as phosphorus, potassium, or zinc; (iii) siderophore producers; (iv) organic acid originators; (v) sulphur oxidizers; (vi) phytohormone producers; and (vii) plant growth-promoting rhizobacteria (PGPR). However, a functional classification is not always straightforward because the same microorganism can perform several functions whose synergistic combination results in a beneficial effect for the plant [2,6,14,15]. Thus, several examples may be reported: (i) arbuscular mycorrhizal fungi can enhance nutrient uptake, especially phosphorus, and improve plant resistance to abiotic stresses [14]; whereas (ii) PGPR can promote plant growth through nitrogen fixation, nutrient solubilization, and/or production of phytohormones [14,16,17]; and (iii) nitrogen-fixing rhizobia can convert atmospheric nitrogen into an available form for crops [2,3,14,18,19].

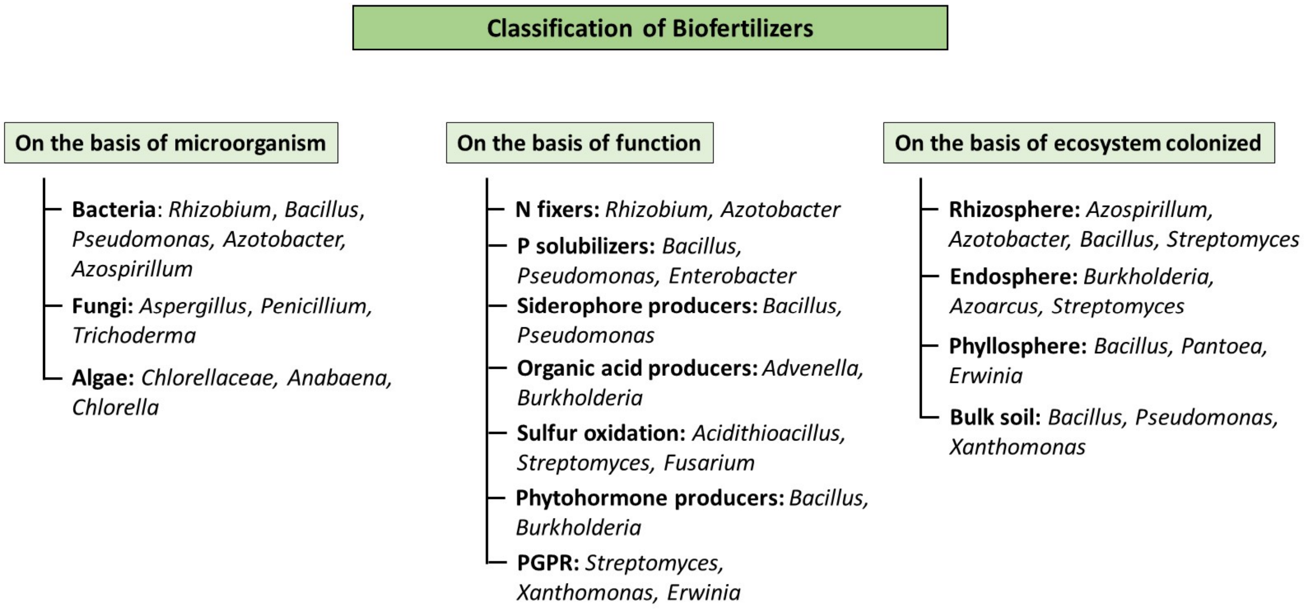

Figure 1. Different biofertilizer classifications based on the involved microorganism, functional characteristics or the ecosystem colonized in the plant. PGPR: plant growth-promoting rhizobacteria.

Third, a less common classification system distinguishes microorganisms based on the **environments** they colonize. Hence, they can be identified as: (i) rhizospheric microorganisms (those that colonize the soil directly surrounding the roots of plants), (ii) endospheric microorganisms (those that colonize the interior of the plant), (iii) those that colonize the phyllosphere (the aerial parts of plants such as the stem or leaves), and (iv) free-living microorganisms (found in the bulk soil) [20].

3. The Microscopic Maestros: Common Organisms in Biofertilizers

The publication about the effect of Nitragin® on legumes by Nobbe and co-workers in 1895 [21] is often referenced as the starting point in the development of biofertilizers. Nitragin® is a trademarked bioinoculant containing nitrogen-fixing bacteria of the *Rhizobium* genus. Consequently, *Rhizobium* has been one of the predominant genera in the development of biofertilizers, along with other nitrogen-fixing microorganisms and some phosphate-solubilizing genera such as *Bacillus* and *Pseudomonas*. This fact is not surprising, as the early advancements in biofertilizer were focused on increasing the availability of macronutrients such as nitrogen (N). It should be converted into ammonia (NH_3), which is readily usable by crops and other microorganisms, from atmospheric nitrogen (N_2) through biological fixation by certain symbiotic or free-living microorganisms. Among symbiotic N_2-fixing bacteria, the genus *Rhizobium* is one of the most widely studied, whereas *Azotobacter* sp., *Azospirillum* sp. or *Bacillus* sp. are the most typical free-living diazotrophic microorganisms (e.g., nitrogenase carriers) [2,22–24].

The second most commonly reported group of microorganisms comprises phosphate-solubilizing bacteria and fungi. Phosphorus (P) represents one of the most critical plant nutrients, directly or indirectly influencing a multitude of biological processes. Notably, P plays a pivotal role in major metabolic processes within plants, including energy transfer during photosynthesis, biosynthesis of crucial molecules, and respiration. In soils, P exists in substantial quantities in both organic and inorganic forms. However, a substantial portion of this P remains unavailable to crops across many ecosystems worldwide due to its presence in insoluble forms, since plants can only uptake P in the form of orthophosphate ions ($H_2PO_4^-$ and HPO_4^{2-}). Numerous soil microorganisms possess the ability to convert insoluble P into forms that are readily accessible to plants. This process is carried out through several mechanisms, such as (i) the secretion of organic acids, (ii) the chelation of cations like Ca^{2+}, Al^{3+} or Fe^{3+}, or (iii) the release of enzymes such as phosphatases and phytases. Among the most extensively studied P solubilizers appears microorganisms belonging to the genera *Pseudomonas*, *Bacillus*, *Rhizobium*, *Enterobacter*, *Penicillium*, and *Aspergillus* [2,22,23,25].

More recently, the isolation and identification of the so-called plant growth-promoting microorganisms (PGPM) have revolutionized the development of biofertilizers. This group of microorganisms enhances crop yields through both direct and indirect mechanisms. Direct mechanisms encompass nitrogen fixation, phosphorus solubilization, and phytohormone production, whereas indirect methods include the production of several compounds such as siderophores, antibiotics, hydrogen cyanide, lytic enzymes, and similar bioactive substances that provide resistance to plant pathogens [24]. Within this group, in addition to the previously mentioned genera, other like *Klebsiella* spp., *Serratia* spp., *Burkholderia* spp., *Streptomyces* spp., *Pantoea* spp., or *Trichoderma*, are also observed (Table 1) [2,25]. Another important group of microorganisms concerning biofertilizers are the arbuscular mycorrhizal fungi (AM fungi), which represent a critical component of the soil microbiome by enhancing phosphorus uptake and water and nutrient absorption. They also increase plant resilience to drought and soil salinity [26,27]. In fact, the inoculation of *Triticum aestivum* with *Rhizophagus irregularis* has been shown to stimulate stomatal conductance and upregulate the expression of water channel proteins or aquaporins [28] and *Glomus monosporum* inoculation enhanced the growth, proline content, and levels of antioxidant enzymes and phosphatase in salt-stressed fenugreek plants [29]. Additionally, the role of AM fungi in sustainable crop production is further supported by evidence of their contribution to soil structure by improving nutrient cycling and forming hyphal networks that bind soil particles, leading to better soil aggregation and stability [30], as shown by *Glomus mosseae* inoculated in artificially eroded soil of maize and soybean, which decreased macronutrient runoff and sediment loss [31].

However, as will be discussed in subsequent sections, there are several key steps that microorganisms from biofertilizers must overcome before achieving the desired effects in crop development, such as (i) survival during storage and application, (ii) establishment in soil, (iii) plant colonization, and (iv) interaction with the plant and its microbiome [22]. Thus, in recent years, strategies have shifted from single-strain inoculation to microbial consortia inoculation. These strategies are founded on the increased likelihood of at least one strain evading competitive exclusion, thereby ensuring the survival and functionality of the inoculant. Microbial consortia can comprise two or more strains, whether closely or distantly related, and have the potential to yield synergistic effects [32,33]. The survival chance of a consortium in different environments is higher than that of single-strain biofertilizers because of their mutual stimulation via communication and differentiation [6,34]. For instance, the inoculation with a bacterial consortium of *Pseudomonas* sp., *Bacillus lentus*, and *Azospirillum brasilense* increase chlorophyll content in plants and the expression of antioxidant enzymes under stress conditions [6]. Similarly, El-Sawah and coworkers reported that the quality of seeds from the legume *Cyamopsis tetragonoloba* (gum production) reached its highest values when using a combination of *Bradyrhizobium* sp., *Bacillus subtilis*, and AM (*Glomus clarum*, *Glomus mosseae*, and *Gigaspora margarita*), and explained this result as an outcome of each organism boosting the effect of the other [32].

Table 1. Overview of biofertilizer species and their mechanisms of action over different crops.

Biofertilizer Microorganisms	Action Mechanisms	Host Plant	Ref.
Advenella mimigardefordensis	Plant growth promotion; organic acid production; P and K solubilization; antifungal activity	Barley	[25]
		Astragalus mongholicus	[35]

Table 1. *Cont.*

Biofertilizer Microorganisms	Action Mechanisms	Host Plant	Ref.
Aspergillus flavus	Increase antioxidant enzyme activity and chlorophyll content	*Glycine max*	[36]
Bacillus amyloliquefaciens	Induce SA and JA signalling, enhancing plant protection against pathogens	*Solanum lycopersicum*	[37]
	Plant growth promotion	*Arabidopsis thaliana*	[38]
Bacillus aryabhattai	Improve tolerance to salt stress	*Oryzae sativa*	[39]
Bacillus cereus	Plant growth promotion, organic acid production, P solubilization, phytohormone production	*Arabidopsis thaliana*	[40]
		Barley	[25]
		Potatoe	[41]
Bacillus licheniformis	Improve tolerance to salt stress	*Chrysanthemum*	[42]
Bacillus megaterium	Plant growth promotion; organic acid production; P solubilization; antifungal activity	*Cucumis melo*	[43]
		Barley	[25]
Bacillus subtilis	Plant growth promotion; antimicrobial activity	*Atractylodes macrocephala*	[44]
	Increase expression of auxin-related genes; plant growth promotion	*Solanum lycopersicum*	[45]
	Plant growth promotion; improve tolerance to infections	*Oryzae sativa*	[46]
Bacillus velezensis	Protect plant from pathogens via systemic resistance response	*Arabidopsis thaliana*	[47]
Burkholderia fungorum	Plant growth promotion; organic acid production; P and K solubilization; antifungal activity	Barley	[25]
Burkholderia contaminans	Antifungal activity	Maize	[48]
Enterobacter cloacae	Plant growth promotion; organic acid and phytohormones production; P, Zn, and K solubilization; antifungal activity; N fixation	Barley	[25]
		Abelmoschus esculentus	[49]
		-	[50]
Paenibacillus polymyxa	Increase production of volatile fatty acids and antibiotics	*Brassica napus*	[51]
Pseudomonas aeruginosa	Protect plant from pathogens via chitinase production	Cruciferous vegetables	[52]
Pseudomonas koreensis	Plant growth promotion; organic acid production; P, Zn, and K solubilization; antifungal activity	Barley	[25]
		Arabidopsis thaliana	[53]
Pseudomonas plecoglossicida	Plant growth promotion, organic acid production; P, Zn, and K solubilization; antifungal activity	-	[54,55]
		Barley	[25]
	Plant growth promotion	*Triticum aestivum*	[56]
	Antimicrobial activity; plant growth promotion	*Capsicum annuum*	[57]
Pseudomonas putida	Increase the production of HCN against pathogens	*Solanum tuberosum*	[58]
	Antimicrobial activity	*Oryzae sativa*	[59]
	Enhance urease, phosphatase, and invertase activity	*Carthamus tinctorius*	[60]

Table 1. *Cont.*

Biofertilizer Microorganisms	Action Mechanisms	Host Plant	Ref.
Streptomyces spp.	Enhance plant immunity via increasing antioxidant enzymes	*Oryzae sativa*	[61]
	Plant growth promotion; infection tolerance improvement; siderophore and VOC production; phosphate solubilization	*Solanum lycopersicum*	[62]
	Nitrogen fixation; phytohormone production	*Solanum tuberosum*	[63]
	Phytohormone production	Cereal crops	[64]
Trichoderma atroviridae	Improve auxin production; tolerance to cold stress	*Arabidopsis thaliana*	[65]
Trichoderma harzianum	Provide protection from pathogens via JA signalling	*Zea mays*	[66]
	Antimicrobial activity	*Bupleurum chinense*	[67]
	Increase colonization of non-host mycorrhizal plants	*Arabidopsis thaliana*, *Brassica napus*	[68]
Trichoderma koningii	Antimicrobial activity	*Nicotiana tabacum*	[69]
	Plant growth promotion; improve tolerance to abiotic stresses	*Solanum lycopersicum*	[70]
	Antimicrobial activity against *Rhizoctonia solani*	Cotton	[71]

4. Biofertilizer Frontiers: Exploring New Sources

According to the EU Mission "*A Soil Deal for Europe*", only about 10–15% of the Earth's land surface is naturally fertile and suitable for agriculture. Approximately 15% of the land is too cold, while 2% is too hot for agriculture. Additionally, about 20% of the land faces drought conditions, and 3% has excessive salinity. Another 2% of the land experiences prolonged periods of excessive wetness, while approximately 10% of the soil is too acidic or contains high concentrations of metals such as aluminium or iron. Furthermore, under the light of the climatic change effects, this situation become even more challenging [72,73]. Consequently, the strategies that allow for agricultural practices in these harsh environments are gaining global recognition, which have been tackled from different approaches [5]. Recent studies have shifted their research focus towards the isolation of new microorganisms from underexplored ecosystems and the genomic exploration of yet-uncultured microorganisms.

In the same way, it is well known that numerous advancements originate from clinical research. Recent agricultural advancements are increasingly exploring the microbiota inhabiting soil and water, even without the necessity of prior isolations. Similarly, recent advancements in fertilizer development are based on the concept of "personalized medicine" approach in clinical research. This trend is evident in fertilizer development, which now focuses on tailored solutions to specific problems, and aims to provide in-situ solutions to the challenges presented by each soil and crop.

4.1. Sailing the Microbial Seas: Marine Microorganisms and Microalgae

One of the most promising resources for the discovery of novel bioactive compounds, due to the huge extension and unexplored status, are marine ecosystems. Their abundant biodiversity, coupled with unique ecological niches, have given rise to microorganisms with distinctive physiological, biochemical, and molecular properties [74]. Up to date, more than 23,000 new metabolites have been identified in marine organisms, which present a wide range of pharmacological activities, such as anti-cancer, anti-inflammatory, anti-diabetic, and antibiotic activities, as well as food and feed additives, cosmetic ingredients, packaging materials, or components of third-generation biofuels [75,76]. However, the application of marine microorganisms in agriculture is still progressing at a slow pace.

Macroalgae have been the most explored source thus far. Since the early 1980s, their potential as plant growth promoters has been analysed, becoming a significant category within the organic plant fertilizer market. Thus, the macroalgal market is more established than that of microalgae, with a global production of 36 million tonnes in 2020 [77]. In fact, *Palmaria palmata* and *Laminaria digitate* are well-known fertilizers in the west coast of Ireland. However, the harvesting of seaweed, particularly macroalgae, is rigorously regulated in some countries to prevent unsustainable practices that could endanger specific ecosystems. Consequently, most of the global production must be cultivated nowadays (mainly in China and Indonesia), whereas a smaller fraction is harvested from naturally growing, with Norway being the largest collector of wild seaweed in Europe (~150,000 tons per year) [76].

Nevertheless, microalgae have been recognized as the next generation of plant growth additives due to their ability to promote plant growth by fixing atmospheric nitrogen and enhancing nutrient uptake in a more environmentally beneficial manner [13,78,79]. Although microalgae are yet to be fully exploited as biofertilizers, their application has been demonstrated to positively affect soil microbiology and enhance the morphophysiological and biochemical responses of plants under stress conditions [13,80]. Examples include the use of *Chlorella sorokiniana* in wheat [81] or *Scenedesmus quadricauda* and *Chlorella vulgaris* in sugar beet [82].

Cyanobacteria (blue–green algae), a group of photosynthetic bacteria found in marine environments, have traditionally been identified as a potential source of biofertilizers for sustainable agriculture [83,84]. They are known for their nitrogen-fixing capacity in paddy fields and can also be beneficial for other crops. Recently, the plant growth-promoting effects of *Arthrospira platensis* have been tested in papaya [85] and petunia [86]. Furthermore, the application of living cyanobacteria is recognized for its potential as a biocontrol agent through the activation of plant immunological defence mechanisms and production of antimicrobial compounds to combat plant pathogens [13].

Other example of marine isolates used as biofertilizers are the marine plant growth-promoting rhizobacteria. Thus, a consortium of isolates from southwestern Spain coastal salt marshes have been employed to enhance the heat stress resilience of grapevines [87]

In conclusion, the distinctive biochemical pathways and characteristics exhibited by marine microorganisms in response to their extreme habitats position them as a promising source of novel bioactive compounds [88,89].

4.2. Extreme Allies: Extremophilic Microorganisms against Abiotic Stress

Microorganisms live in almost any environment, including those considered extreme due to their high temperature, pH, salinity, or pollutants concentration. This largely unexplored microbial diversity, often referred to as "dark matter", hides a great deal of potential in terms of phylogenetically or metabolically diverse microorganisms [90], owing to their extraordinary capacity to adapt to adverse environmental conditions [91]. The recent climatic variations, marked by unprecedented temperature increases and a rise in extreme weather events (such as hurricanes, heavy rainfall, and droughts) [5], have raised concerns in the agricultural sector. Agriculture in the 21st century faces the dual challenge of boosting crop productivity while confronting the growing perils of climate change [5]. In this context, extremophilic microorganisms offer a promising avenue for the development of novel biofertilizers [92,93] that can induce tolerance under several abiotic stresses. Hence, studies have identified certain microorganisms, such as *Rhizophagus irregularis*, *Funneliformis mosseae*, and *Funneliformis coronatum*, that are able to confer cross-tolerance to plants, enabling them to withstand combined stresses such as heat and drought [94].

Thermal extremophiles are catching the eye of those in biofertilizer development. Psychrophilic bacteria, which inhabit cold environments, have recently been highlighted for their potential in sustainable crop production in cold climates [95]. Singh et al. [95] demonstrated the effectiveness of *Pseudomonas koreensis*, a psychrophilic bacterial isolated from the cold desert of the Indian Himalayas, as a phosphate biofertilizer. This strain exhibited the ability to solubilize phosphate and produce plant growth-promoting substances such as indole acetic acid and siderophores at low temperatures. When applied to pea plants under cold stress, this biofertilizer significantly enhances plant growth and yield, underscoring its potential as a biofertilizer for cold environments [95]. In contrast, thermophilic microorganisms that thrive under high-temperature conditions produce heat-shock proteins and other thermotolerance-inducing substances that could potentially be harnessed to confer heat tolerance to crops, thereby enhancing their resilience to heat stress [96,97]. In fact, studies have shown that certain strains of *Bacillus* sp. can improve plant heat tolerance, offering a potential strategy for maintaining crop productivity under high-temperature conditions [98–100]. In addition to heat stress, drought is another critical challenge that can be addressed with the help of microorganisms. Drought-tolerant microorganisms, such as those producing osmoprotectants or exopolysaccharides, can improve plant water retention and survival during dry periods [101–103]. For example, Khan et al. [104] reported that the treatment with some *Bacillus* sp. strains could confer drought tolerance in chickpeas, illustrating the potential of these microorganisms as biofertilizers in arid and semi-arid regions.

Halophiles are organisms adapted to high-salt environments which offer potential solutions for enhancing crop tolerance to salinity, a major abiotic stress in agriculture. Certain halophilic bacteria and archaea produce osmoprotectants that protect cells from the damaging effects of high salt concentrations [105]. These osmoprotectants could potentially be used to enhance crop tolerance to salinity. Hence, *Stenotrophomonas* sp. and *Exiguobacterium* sp. can enhance soybean germination rate under salt stress conditions [91].

Acidophilic microorganisms thriving in acidic environments can provide novel strategies for enhancing crop tolerance to acidic soils. Acidophilic bacteria and fungi produce acid tolerance mechanisms that could potentially be harnessed to enhance crop resilience to acidic soils, a major constraint to crop production in many parts of the world [106]. A well-known example involves the utilization of *Acidithiobacillus* spp. strains, commercially available by AgriLife for applications such as the bioconversion of sulphur (e.g., S Sol B, containing *Acidithiobacillus thiooxidans*) or iron (e.g., Fe Sol B, containing *Acidithiobacillus ferrooxidans*) [3]. Conversely, alkaliphilic microorganisms, which thrive in high-pH environments, can also be harnessed to enhance crop tolerance to alkaline soils. Certain alkaliphilic bacteria are known to produce alkaline-tolerant enzymes and other substances that can potentially be used to enhance crop tolerance to alkalinity [107]. For example, a consortium of PGPR and AM fungi enhances oat growth in saline–alkali soils contaminated by petroleum [108]. Thus, in addition to their potential as biofertilizers, extremophilic microorganisms can also be harnessed for the bioremediation of contaminated soils. For instance, specific extremophiles possess the ability to degrade or immobilize harmful substances, which can diminish their bioavailability and toxicity to plants [109]. These extremophilic microorganisms represent a valuable prospect for creating innovative biofertilizers that can improve crop resilience against various abiotic stress factors.

4.3. Unisolated Microorganisms: How to Discover These Unseen Treasures

The microbiologist Mircea Podar once said "culturing is hard, and there is no guarantee of success. But a novel microbe in culture opens the road for doing so much more biology down the road" [110]. However, the knowledge to replicate natural conditions for all microorganisms is far to be achieved. Consequently, new approaches such as **metataxonomics** have taken center stage in studies worldwide in last years. The vast microbial diversity that remains unexplored represents an exciting frontier in the search for novel compounds that could revolutionize sustainable agriculture [111]. As a result, new gene classes with known or even unknown functions can be uncovered and synthesized by heterologous expression in *Escherichia coli*, *Streptomyces* sp., *Pseudomonas* sp., or *Bacillus* sp. [75,112,113]. Nonetheless, despite these methods being well established in the quest for bioactive compounds with medicinal uses, such as antitumor agents like pederin, onnamide, and bryostatin [114–116], their adoption in the field of environmental biotechnology is still in the preliminary phase.

Nowadays, two new cutting-edge and high-throughput methodologies are arriving to support the analyses of non-cultivable microbiomes. On the one hand, **metatranscriptomics**, which is focused on the gene expression analysis of microbes within natural environments, has aimed to overcome the technological drawbacks in undiscovered functional profiles of the beneficial microbiomes to achieve (i) the knowledge of beneficial microbiomes in fertile soils and (ii) the development of disease-suppressive soils as an ecofriendly alternative against biotic stress [117]. For instance, a metataxonomic analyses revealed that several phytohormones (e.g., salicylic acid, jasmonate, or abscisic acid) play a dominant role in the defense response of *Arabidopsis* plants against *Botrytis cinerea* infection [118]. Hence, metataxonomic approaches may help uncover new modes of action for both plants and microorganisms through the expression of genes with as-yet-unknown functions.

On the other hand, **metaproteomics**, which is focused on the study of all the protein samples obtained from environmental sources, aims to achieve a global characterization of a microbiome system at their functional levels. Currently, its application is limited by the need for more comprehensive metagenome databases, the presence of interfering substances, and the challenge of detecting proteins present in low quantities. Nevertheless, the rapid improvements in high-performance mass spectrometry and the refinement of targeted metagenome databases are expected to soon facilitate a more detailed understanding of functional shifts in soil, even for proteins of low abundance or from non-dominant microbial populations [119,120]. The potential of metaproteomics is exemplified by the work of Wu and coworkers, where protein expression analysis between the rhizosphere and phyllosphere identified a higher prevalence of nitrogen-fixation proteins in the rhizosphere [121].

In conclusion, the strategic application of metaomics techniques, which have significantly advanced various scientific fields over the past decade, is now revolutionizing agricultural science. By facilitating a comprehensive understanding of soil microbiomes and their intricate interactions, these methodologies are not only enhancing soil health and crop productivity but also guiding the targeted use of microorganisms. This targeted approach allows for the optimization of bioformulations at specific plant tissues or developmental stages, thereby maximizing the benefits of sustainable farming practices. Collectively, these advancements represent a significant leap forward in our ability to harness the power of microbial communities for the betterment of agriculture.

4.4. Customized Microbial Inoculants

Drawing inspiration from the concept of personalized or precision medicine, Shlaeppi and Bulgarelli [122] suggested a comparable approach for agricultural practices. This method proposes the customization of farming practices, including the development of microbial inoculants specifically designed for individual needs, referred to as "tailored biofertilizers" [123]. This approach acknowledges the substantial variability in soil conditions across different locations and time periods, making a universal "one-size-fits-all" solution impractical for all agricultural fields.

The primary strategy involves on-farm production of bioformulations, which has demonstrated promising results in crops such as potato [124,125] and eggplant [126]. Nonetheless, it is of paramount importance to carefully assess how to make these products both economically viable and cost-effective on a global scale. One potential approach may involve the integration of precision farming principles, enabling the identification of specific areas within a particular field that may be better suited for a particular formulation, tailored to unique soil and crop characteristics [22].

From this perspective, the concept of tailored fertilizers has emerged, referring to a multi-nutrient formulation systematically designed to provide macro and micronutrients, tailored to meet the specific nutritional requirements of a crop, which are determined by factors such as its location, soil conditions, and growth stage [127]. However, it is essential to note that while this concept is gaining traction in chemical fertilizers, its application to biofertilizers remains a complex challenge due to the intricate interactions of microorganisms with the soil, the plant, and other organisms within the ecosystem.

5. New Possibilities in Biofertilizer Application Techniques

An aspect frequently overlooked in biofertilizers' application is the on-field implementation. Thus, it would be advisable to ease farmers' work by (i) developing straightforward applications, (ii) adapting to diverse agricultural methodologies, and (iii) allowing simple product storage [22]. These aspects often remain relatively unnoticed during the initial stages of research inquiries, thereby contributing to the inconsistent outcomes in biofertilizer use at the field level [128].

5.1. Biofertilizers: Inception

Despite laboratory-scale field and greenhouse experiments that involve the direct application of bacterial inoculum to the rhizosphere or soil, this method may encounter challenges in effectively enhancing crop growth due to environmental limitations such as the constrained shelf life of microorganisms. Consequently, initial attempts into the commercial utilization of biofertilizers primarily revolved around the use of solid carrier-based bioformulations (mainly powders or granules), directly applied as soil amendments. The term "carrier" denotes a medium with the capacity to support microbial growth and facilitate their delivery, to ensure microbial cell viability during storage and application [22,129–131]. This carrier must be nontoxic for plants and microbes, physically and chemically stable, cost-effective, biodegradable, able to maintain humidity, and ensure cell viability [132,133]. Peat-based inoculants have historically dominated the commercial biofertilizer market owing to the substantial surface area of peat, its excellent water retention properties, and the conducive environment it provides for metabolic activity and cell proliferation during storage. However, peat-based compounds can have adverse effects on the growth of specific microorganisms. Furthermore, due to their carbon dioxide trapping capacity, if peat is used as a carrier, its mitigation effect on climate change will be reversed when the captured CO_2 is released again. In addition to their negative environmental impact on peat-rich ecosystems [131,132,134]. Thus, there has been a shift towards the development of new carriers from both organic materials (such as compost, biogas slurry, crushed corn cobs, biochar, peat, etc.) and inorganic substances (including zeolite, perlite, lignite, or vermiculite) [22,23,129–131] (Figure 2).

However, despite being a cost-effective and easily producible approach, carrier-based biofertilizers come with inherent limitations, including a reduced shelf life, sensitivity to temperature fluctuations, and diminishing effectiveness at lower cell counts. Additionally, solid formulations are challenging for non-sporulating bacteria [22,130,133]. Thus, biofertilizer application methods have gradually evolved over time, culminating in the development of liquid biofertilizers, which dominate the market nowadays. Liquid formulations consist of microbial suspensions, preferably in their dormant state, in water, oils, or emulsions, supplemented with additives (e.g., starch, humic acid) to enhance their physical (e.g., viscosity and dispersion), chemical (e.g., stability), and nutritional properties. This advancement extends shelf life, improves suitability for farmers, allows microorganisms to quickly come into contact with plants and enhances their tolerance to adverse soil conditions [22–24,132,135].

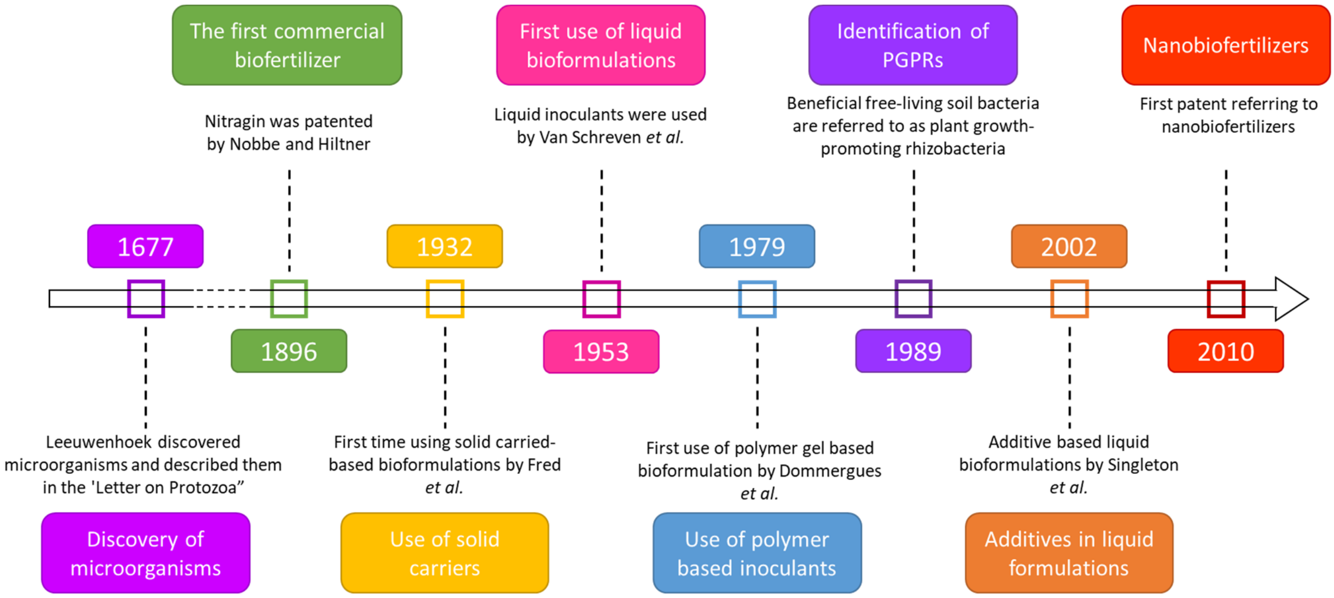

Figure 2. Timeline of major discoveries in the development of bioformulations, including microorganisms' discovery [136], as well as the development of (i) Nitragin [21], (ii) solid carrier-based bioformulations [137], (iii) liquid bioformulations [138], (iv) polymer-based inoculants [139], (v) identification of PGPRs [140], (vi) use of additives in liquid bioformulations [141], and (vi) nanobiofertilizers [142].

The application of liquid biofertilizers typically is carried out through three different procedures: (i) seed treatment, (ii) seedling root dipping, and (iii) soil application [23,130,135] (Figure 3). In the first scenario, seeds are uniformly coated, often with substances like Arabic gum and xanthan gum, and subsequently subjected to shade drying for field application. Examples of commercially available products for seed application include Quantum 4000® (CAS 68038-70-0, containing *B. subtilis*), Dagger-G® (Ecogen Inc.; Langhorne, PA, USA; containing *P. fluorescens*), and BlueCircle® (Stine Seed Farm; Adel, GA, USA; containing *Pseudomonas cepacia*) [143]. Seedling root dipping, as the second method, entails immersing the seedling roots in a water-based biofertilizer suspension for a specified duration, typically determined by the crop variety, prior to transplanting them into the soil. This technique is commonly employed for crops that involve a transplantation step, such as trees, grapes, or certain vegetables. In this context, products like GroTop Rhizobium (containing *Rhizobium* sp.) and PowerBoom (containing *Azospirillum* sp.), both produced by MD Biocoals (Haryana, India), can be applied either as seed treatment or for seedling root dipping. Last, direct soil application is reserved for plants that have reached maturity and are poised for flowering and fruiting, often requiring a substantial concentration of inoculum. As a result, various commercial products in the form of dry powder or wettable powder are available for direct soil treatment, including Serenade® Opti (Bayer Crop Science LP, Hawthorn, Australia; containing *B. subtilis* QST713), and FZB24® WG (ABiTEP GmbH, containing *Bacillus amyloliquefaciens* spp. *plantarum*) [23,24,130,144].

Indeed, some commercial biofertilizers offer adaptability in their mode of application to suit farmers' preferences, such as NITROFIXTM-AC (Agri Life), which contains the nitrogen-fixing strain *Azotobacter chroococcum* MTCC 3853. When applied as a seed coating, it should be mixed with water and sugar. Conversely, if it is to be applied as a seedling root dip, water and manure are added to the mixture. Moreover, it can be blended with compost for use as a soil amendment, or it can be dissolved in irrigation water and directly incorporated into the soil during watering [143].

However, liquid biofertilizers are sensitive to contamination and still have a limited shelf life, which has led to the incorporation of carriers, dispersing agents and surfactants [131,132]. Thus, advanced technologies have recently emerged for the effective storage, transportation, and enhancement of bioformulation efficiency through the encapsulation of microorganisms.

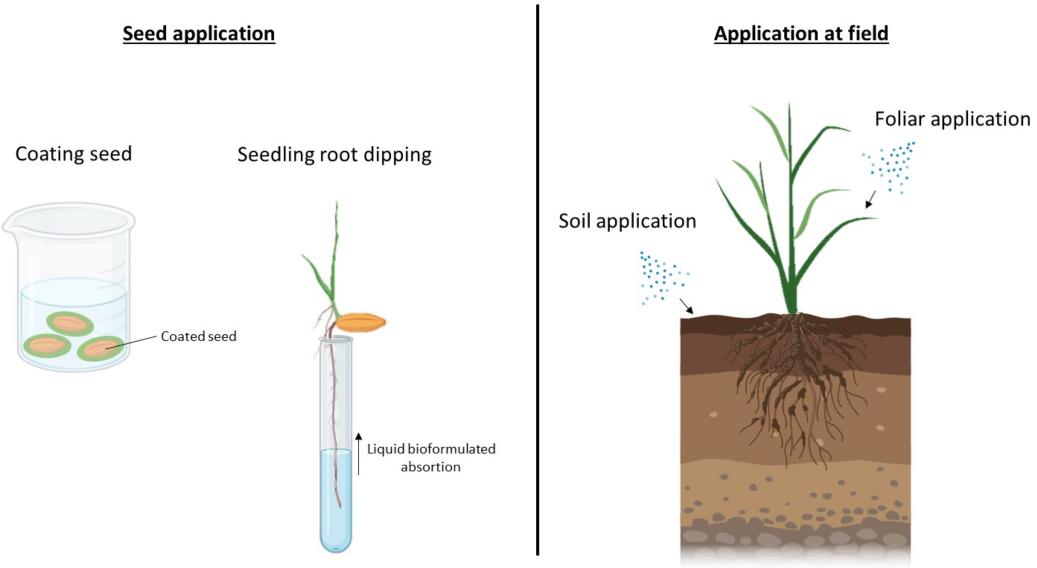

Figure 3. Main modes of biofertilizers application nowadays. Created by BioRender.com.

5.2. Microencapsulation and Nanobiofertilizers

Encapsulation creates a protective capsule around the active compounds or cells, ensuring their viability and stability during storage and transportation; easing the application and field performance; as well as reducing the contamination risk [131–133]. Additionally, encapsulation enhances the success even under harsh environmental conditions, such as high salinity, extreme pH levels, temperature variations, or drought stress [132,143]. Initially, encapsulation mainly involved entrapping cells within polymeric structures of large dimensions (millimeters), referred to as **macroencapsulates**. One of the most commonly used polymers in encapsulation is alginate. For instance, the encapsulation of *B. subtilis* in alginate beads supplemented with humic acid has demonstrated positive effects on the germination and growth of lettuce seeds [145].

Due to their size, which is similar to that of most seeds, these biofertilizers can be conveniently mixed with seeds and directly applied to the soil during seedling growth. Thus, macroencapsulation remains a promising technology in the context of developing countries, as it obviates the need for specialized equipment during both the production and application. However, it should be noted that when macroencapsulated bioformulations are used, there is a likelihood that the released microorganisms may be distributed a few centimeters away from the plant, potentially reducing their effectiveness. Therefore, it is advisable to consider additional inoculation during the planting process when employing macroencapsulated formulations [131,132].

Subsequently, **microencapsulation** (up to 1 mm in diameter) has emerged as a promising alternative, since it seems to be able to overcome the main disadvantages of macroencapsulation, ensuring a higher survival rate and enhancing performance in the field. Typically, microencapsulation involves the use of hydrogels to encapsulate microbial cells or compounds. The coating materials commonly employed are either natural (such as starch, gelatine, or sucrose), or synthetic polymers (like polyurethane foam or polypropylene), although alginate stands out as the most frequently used biomaterial for encapsulation, mainly due to its non-detrimental impact on microbial survival and its resilience for storage and transportation purposes [24,131,133,143]. As a result, different PGPR strains have been encapsulated using alginate supplemented with diverse additives. For instance, *B. subtilis* has been encapsulated for the biocontrol of *Rhizoctonia solani* in beans [146], whereas *Pseudomonas* sp. has been used for the biocontrol of *Sclerotium rolfsii* in *Oryza sativa* [147].

However, the challenge arose when attempting to coat seeds with alginate-containing bacterial bioformulations, since seeds require a dry environment to prevent germination, whereas bacteria need higher moisture levels for survival. A double water-in-oil-in-water emulsion formed in an aqueous solution of gelatine cross-linked with glutaraldehyde has been the solution [148].

Microcapsules can be conveniently applied directly to the soil, during seedling, or as seed coatings, and they exhibit the flexibility to be applied immediately or stored for extended periods at either low or ambient temperatures, which is the most common protective method nowadays [132].

Finally, **nanotechnology** is an emergent trend for agriculture, where nano-fertilizers and nano-pesticides present several advantages resulting in an enhanced efficacy, such as (i) substantial surface area, (ii) increased active sites, and (iii) controlled release. Nanofertilizers are nanoparticles ranging in size from 1 to 100 nanometers (at least in one dimension) [24,149–151]. They use different mechanisms to improve plants' growth, such as (i) silicon nanoparticles to enhance metabolite production and plant growth, (ii) zinc or copper nanoparticles for plant development and resistance to abiotic stress conditions, or (iii) iron nanoparticles, as enzymatic co-factors (respiration, photosynthesis) [151]. However, bacterial, fungal, and eukaryotic cell sizes (>1 µm) are a limiting drawback since their reduction is not feasible. Hence, the nanobiofertilizers development seems unlikely in such a context, but the prefix "bio" pointing to some compound from biological origin aiming to provide essential macronutrients and enhance crop development can be considered in the nanobiofertilizer concept.

5.3. Sprays and Foliar Application

The use of sprays for foliar application has been a key technique in recent years, particularly for the application of nanoparticles. This is due to the rapid absorption of compounds through the leaf stomata, making it especially useful for foliar biocontrol (biofungicides, biobactericides, or bioinsecticides) [152,153]. An advantage of foliar application is that it can be performed throughout the entire growing season. However, the effectiveness of foliar application depends on various factors, including dosage, particle size, humidity, temperature, plant species, growth stage, and physiological properties, among others [153,154]. Consequently, discrepancies in the results have occasionally been reported, which may be attributed to suboptimal application timing (environmental conditions or crop stage) [85,155]. For instance, it has been observed that foliar application of certain biostimulants during periods of plant stress is more effective and elicits a quicker response compared to soil treatment, although the latter exerts a longer-term effect [13]. However, in some cases, a synergistic effect has been reported when both application techniques are combined, resulting in an even more pronounced impact [156]. Thus, a recommended practice entails conducting foliar spraying during the morning when stomata are naturally open, and when environmental conditions, such as high humidity, are favorable. Such conditions tend to augment the permeability and absorption rate.

Microalgae have garnered significant attention concerning foliar application [13]. Compared to macroalgae, which have been extensively exploited for their plant growth stimulant potential since the early 1980s, microalgae have received comparatively less exploration in the realm of agricultural applications. Nevertheless, both macroalgae and microalgae-based biostimulants appear to exhibit similar activities [13]. For example, Oancea and co-workers reported that the use of either microalgae or macroalgae biofertilizers yielded comparable fruit production in tomato plants [157].

Hence, it is likely that algae will revolutionize the biofertilizer market in the near future. In fact, there are already marine-based products on the market, such as Spirufert® (Tamanduá, Brasil), a commercially available foliar-applied biofertilizer containing the microalgae *Arthrospira* spp., which has shown promising results in crops like chickpea and eggplant [158,159].

Nonetheless, some of the flagship PGPR strains continue to play a leading role in the development of new application methods, including spray application. For example, it has been reported that foliar application of *B. subtilis* has a fungicidal effect on tomatoes [160,161], *Azospirillum* sp. enhances yield in wheat [162], and *Azospirillum brasilense* benefits maize production [163], among others [164]. Furthermore, *Xanthomonas campestris* is already commercially available for foliar application under the name CAMPERICO® in Japan. Another commercial success is BlueN® (Symborg; Murcia, Spain), which was launched in 2020 (https://symborg.com/en/biofertilizers/bluen/; accessed on 31 October 2023). This biofertilizer is based on the endophytic bacterium *Methylobacterium symbioticum*, which, when applied foliarly, colonizes the phyllosphere and guarantees an effective and controlled supply of nitrogen to the plant because of the action of its nitrogenases.

5.4. Mulch Application

Mulch is defined as a protective covering (as of sawdust, compost, or paper) applied to the soil surface to reduce evaporation, maintain consistent soil temperature, prevent erosion, control weeds, enrich the soil, or keep fruit clean (https://www.merriam-webster.com/dictionary/mulch; accessed on 31 October 2023). It offers numerous benefits, including enhanced moisture retention, decreased soil compaction and erosion, temperature regulation, weed control, protection of seedlings and young plants, and improved plant establishment and growth [165,166]. Although the use of mulch to boost crop production has been documented since around 500 BC [167], its popularity surged with the advent of plastic materials in the late 1950s [165]. However, the large-scale production of plastic films has raised concerns about the massive accumulation of pollutants in the environment, leading to the formation of microplastics. Plastic removal from soil after crop harvesting involves several non-cost effective and challenging stages (washing, shredding, drying and pelletizing) due to the film thickness, which makes it economically unaffordable even though the bio-based materials are emerging as a sustainable alternative [165,166]. They are derived from renewable resources, often feature biodegradable properties, and boast a lower carbon footprint. They also offer environmentally friendly disposal options and are associated with reduced environmental toxicity [168].

The integration of biofertilizers with organic mulching techniques represents a novel approach to agriculture, reflecting a growing interest in sustainable farming practices. Correspondingly, a query in the NCBI database, using the terms “biodegradable” and “mulch” in the search field from 1968 to 2022, resulted in 476 documents (Figure 4). In fact, the world production of bio-based polymers has grown to reach 4.2 million tons by 2020 [169]. Hence, the biotic degradation is the process by which polymeric material is broken down into carbon dioxide, methane, water, inorganic compounds, or biomass. Predominantly, this process involves the enzymatic action of microorganisms [170], where several groups of bacteria play a crucial role in the biodegradation process, such as *Bacillus*, *Pseudomonas*, *Klebsiella*, or *Streptomyces*. In addition, mulching films degradation can also be carried out by soil fungi such as *Penicillium*, *Sporotrichum*, *Talaromyces*, or *Candida*, among others [165,171], which can be artificially introduced into the soil through the use of biofertilizers, as the combination of biofertilizers with organic mulch, like straw, has been reported to be compatible (and even synergistic) [172]. Therefore, the recent resurgence in the use of the age-old mulching technique should be accompanied by advancements in conjunction with the development of biofertilizers, aiming for a synergistic effect that enhances the benefits of both techniques.

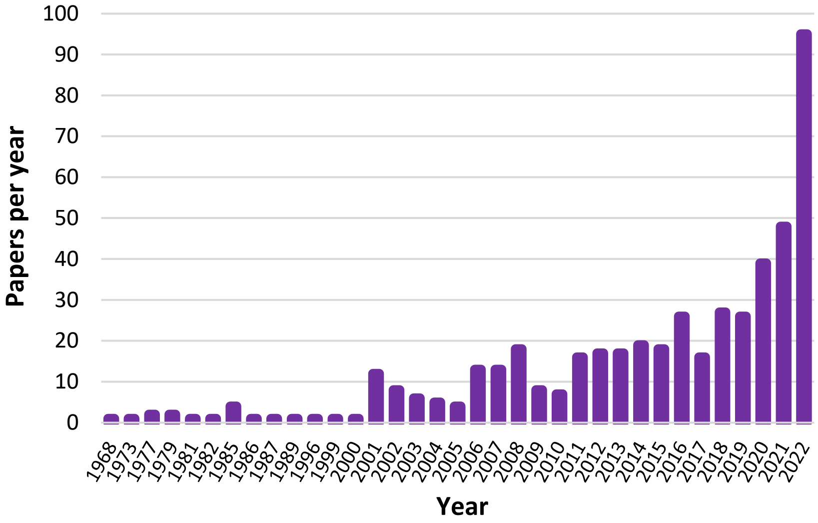

Figure 4. Number of papers published from 1968 to 2022 on biodegradable mulches. Source: NCBI, using the terms "biodegradable" and "mulch" from 1968 to 2022.

6. Overcoming Challenges in Biofertilizer Use

As previous sections highlighted, the development and commercialization of biofertilizers encompass numerous steps, ranging from the isolation and analysis of microorganisms to their on-field application, involving optimization of usage conditions, production or storage. Thus, the potential bottlenecks influencing the success of biofertilizer development and commercialization can be categorized into: (i) scientific and technological considerations, (ii) environmental aspects, and (iii) practical limitations, which currently restrict the widespread application of bioformulations in agriculture (Table 2).

Table 2. Challenges associated with biofertilizers' development and commercialization success.

Scientific and Technological		Challenges in the Isolation of New Microbial Species
Environmental	Biotic	Negative interactions with resident microbiome (e.g., competition or predation) and different effect depending on the crop.
	Abiotic	Variations in physicochemical soil properties (e.g., nutrients, moisture, temperature). Interaction with other agricultural components (amendments, chemical fertilizers, pesticides, etc.).
Practical	Social aspects	Added value to the product from the consumers perspective may promote its application among farmers.
	Accessibility	Products with limited versatility, shelf-life and adaptability to different agricultural practices. Limited knowledge of manipulation and application by farmers.
	Regulations	Lack of standardized and universal protocols and guidelines.

6.1. Scientific and Technological Concerns

The scientific and technological challenges in the field of biofertilizers span across several stages, from microbial isolation to product transportation and field application. At the outset, microbial isolation presents a significant hurdle. Despite the impressive richness of microbial diversity on Earth, more than 90%, in an optimistic view, and up to 99%, under a stricter point of view [173], of the potentially 10^{11}–10^{12} microbial species, remains uncultured today [174]. This challenge becomes even more significant when isolating microorganisms from plant and environmental samples, primarily due to their vast diversity and complexity, as well as their relatively less explored status compared to other environments (e.g., human and animal clinical) [175]. In response to this challenge, several strategies have been proposed. While many studies continue employing traditional media containing nutrients of animal origin to isolate plant-associated microbes (e.g., nutrient agar, LB), the utilization of plant materials or dehydrated juice powders (e.g., V5 or V8) is still uncommon. These plant-based media, aligning more closely with the natural environments of the microorganisms, have demonstrated their potential in enhancing the isolation of previously unknown species [22]. Additionally, the past decade has seen the development of innovative techniques such as isolation chips, which are microfluidic devices used to isolate and culture individual cells or small populations of microorganisms. These devices mimic natural environments and can enhance the growth of previously uncultured species. However, their cost and complexity lead to an underutilization, although they may upsurge culture-dependent techniques [176].

Beyond the laboratory, logistics for product transportation and field applications also pose challenges. For instance, biofertilizers can have a shortened shelf life due to high temperatures during transportation and storage, which reduces their efficiency. Additionally, issues such as inaccessibility of essential application equipment, shortage of power supply, and poor road networks for the conveyance of biofertilizers to the field, particularly in developing countries further complicate the utilization of biofertilizers [33].

6.2. Environmental Aspects

Usually, the initial stages of biofertilizer analysis are conducted under controlled conditions. Considering that the effectiveness of biofertilizers can be influenced by several factors (e.g., type and concentration of microorganisms, method of application, crop, or environmental conditions) [3,4], it is common for a microbial strain that exhibits good performance in vitro to perform poorly in field trials [177]. The complex interactions in nature can mask the effects of biofertilizers, making it difficult to reproduce at field the positive results observed in laboratory [15,178,179]. Along the same lines, the selectivity of the microorganisms towards certain crops may result in different responses to biofertilizer inoculation, with certain plant species showing a higher growth-promoting effect than others [22,178], which highlights the potential of "tailored fertilizers", previously reported.

Furthermore, it is essential to bear in mind that field trials involve the release of microorganisms into the environment, which can have an impact on both non-target species and the ecosystem itself. Therefore, even though many of the reported studies may not explicitly address this aspect, these trials should also adhere to regulations pertaining to the release of microorganisms. This requirement is included in EU Regulation 2019/1009 on fertilizing products and EU Regulation 1107/2009 concerning the placement of biopesticide products on the market [180].

6.3. Practical Challenges

New biofertilizer development does not always align with farmers opinions since they are rarely considered during the initial stages of the process. However, Tur-Cardona et al. [181] found that farmers from seven different European countries often share common preferences regarding the attributes that biofertilizers should possess. For instance, they prioritize low particle volume and guaranteed nitrogen content, as well as cost-effectiveness. Nevertheless, it is essential to consider the economic aspect with a degree of perspective since prices can fluctuate depending on spatial and temporal factors, such as (i) the rising price of conventional nitrogen, phosphate, and potassium fertilizers, and (ii) the surging popularity of organic food, which is driving up the demand for biofertilizers [182]. Biofertilizers are acknowledged as a more environmentally sustainable choice and consumers are increasingly inclined toward products that have not been treated with pesticides and synthetic fertilizers [183,184].

Still, it is crucial to recognize that the legislation governing the production and sale of biofertilizers differs from one country to another, as will be detailed later on. Thus, the importance of marketing campaigns that highlight the benefits of biofertilizers to farmers becomes evident. On the one hand, chemical fertilizers are faster in showing visual variation in crop growth. On the other hand, retailers hesitate to sell biofertilizers because of their short shelf life, low demand, and lack of infrastructure to comply with storage requirements, which in turn lowers the nominal profit margin [185]. Moreover, farmers possess limited knowledge of biofertilizer handling and application procedures, which may not always align with their equipment, machinery or agricultural management practices. For example, Chen et al. [186] reported that the efficiency of a biofertilizer based on AM fungi must first consider external factors, such as ploughing or other chemical inputs. Additionally, farmers often face constraints related to the limited timeframe for utilizing the entire product [187]. To address these problems, alternatives have been identified, such as those proposed by Raimi et al., who revised the production and usage trends of biofertilizers in Africa, to propose a model for improving biofertilizer development, quality, and adoption. As a result, key strategies were identified to promote market expansion: efficient extension services, private sector participation, and government subsidy intervention to ensure a margin of profitability for retailers and customers [14].

7. Biofertilizer Regulation

Up to date, global quality control guidelines such as ISO standards have not been structured, adding barriers to the geographic projection of the biofertilizer market [188]. The European Regulation on Fertilizer Products (Regulation (EU) 2019/1009) provides a single legal framework for all fertilizers placed in the European Union market, including biofertilizers in Function Category 6. These new requirements will help to ensure that biofertilizers are safe, effective, and produced in a sustainable manner. This legislation considers them as a "*product whose function is to stimulate plant nutritional processes independently of the nutrient content of the product, with the sole objective of improving one or more of the following plant and rhizosphere characteristics: nutrient use efficiency, tolerance to abiotic stress, quality characteristics, and availability of immobilized nutrients in the soil and rhizosphere*". It established the procedures to authorize a biofertilizer, such as (i) assessment of the safety of human and the environmental health, (ii) evidence of improved plant nutrient availability or plant characteristics that enhance nutrient use efficiency, (iii) valuation of production according to good manufacturing practices, and (iv) product labelling in accordance with the Regulation (EU) 2019/1009 (FPR) (microorganisms contained, intended function, safe and effective use instructions) [189].

Despite the availability of the EU Fertilizing Products Regulation, European plant biofertilizers are still subject to national regulations, varying from one Member State to another, this is due to the limited scope of microbial plant bioformulations under Component Material Category (CMC) 7 in Annex II in the FPR, which only allows four genera of microorganisms to be used; therefore, it is necessary to make provisions, at least at the national level, so that the efforts, in terms of research and investment, carried out by the industry in this sector are not undermined. France, Spain, Italy, and Germany have the largest area under organic farming in the EU; consequently, they have legislations on fertilizer products that somehow include biostimulants. Therefore, the "*Real Decreto 529/2023*", of June 20, amending "*Real Decreto 506/2013*" in Spain does not include the term "*biofertilizer*", however it is included in group 4 of "*other fertilizers and special products*" under the name of "*biostimulants based on microorganisms*" [190]. This decree includes bioformulations within the category of fertilizers since their functionality fits this category better than that of phytosanitary products.

At a global scale, India and China are the countries with the most complete legal frameworks related to biofertilizers, followed by the United States [191]. In fact, the Indian government has included the term "biofertilizer" in the law and created a proper regulatory mechanism under Section 3 of the Essential Commodities Act, 1955 and Fertilizer (Control) Order, 1985 [192]. China has set the legal quality of biofertilizers based on eight parameters: number of living cells, carbon and water content, pH, size of granules (for solid products), appearance, contamination, and validity [190,193]. In the case of the United States, the Environmental Protection Agency (EPA) is responsible for overseeing biopesticides, which encompass both microbial pesticides and plant-incorporated protectants, while the USDA National Organic Program (NOP) regulation the application of biofertilizers in organic farming [190].

8. Future Perspectives

Despite the considerable history of biofertilizers, it is evident that their widespread industrial establishment is still far from what was anticipated years ago, but the basement is robust to achieve their implementation as a regulated and normalized agronomic practice. A better-defined legal framework, similar to the initiatives undertaken by India, China, the United States or European Union, is crucial for paving the way for international marketing. Additionally, emerging technologies (e.g., metaomics, encapsulation) are triggering the screening, characterization, and use of new biofertilizers aimed to reach the industrial-scale adoption. However, the interconnection among laboratory research, industry, policymakers, and farmers seems to be the key point that will boost the biofertilizers as a greener tool. The sum of these different contributions should be crystallized in optimized cost-effective bioformulations as a realistic alternative to the chemical approaches.

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