

Weed and Disease Abolition in Crops through Inherently Altered Microbes and Soil Microorganisms

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Abstract

Drastic increase in both the quality as well as quantity of global crop production is urgently needed. The biotic and abiotic influences, which affect or even decide the final outcome, are two major groups of factors that have a significant impact on crop development, yield and characteristics. Infestation of plants by pests and diseases can result in yield losses of up to 82 percent in cotton and over 50 percent in other major crops; when these losses are added to post-harvest spoilage and quality degradation, these losses become significant, particularly in resource-poor parts of the world. Hence, its management is very necessary. Plant pathogenic bacteria which are found in the soil rhizospheric region can cause a variety of diseases in plants. Scientists have created a biological method in order to combat invasiveness by weeds and rodents by using these pathogenic microbes. Microorganisms have extensive biosynthetic reservoirs for producing biomolecules of interest; farming communities are, however, accepting new approaches to meet the increase in demand for sustainable food production, thanks to allied sector research and evolving genetic tools for improved microbial consortia.

Keywords: Weeds; Diseases; Pathogenic organisms; Yield; Plant growth; Sustainable agriculture

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Introduction

Global crop production must be improved in terms of both quality and quantity to meet the needs of the rapid increase in global population [1]. Two major groups of factors which have a significant impact on growth, crop yield, and quality characteristics are biotic and abiotic influences, which affect or even determine the final outcome [2]. Several researchers have focused on the effect of climate change and current agricultural practices on plant growth and nutritional value of field and vegetable crops [3]. Biotic factors (weeds, fungi, insects, bacteria) as well as abiotic (sunshine, temperature, pH, rain) variables, can all affect crop growth and its yield in different ways [3,4]. One of the key priorities of modern agriculture is to provide enough food to satisfy a society's need in a sustainable manner, while also providing high-quality products that can be accomplished by effectively managing weeds and diseases which negatively affects crop growth and yield.

Literature Review

According to fossil evidence, disease infected plants were reported 250 million years ago. Plant disease is a natural state damage that disrupts a plant's vital functions, and it affects all plant species, both wild and cultivated. Plant diseases have been recorded since the beginning of time. Losses due to plant diseases could have a substantial economic effect, resulting in lower profits for farmers and manufacturers and higher costs for consumers [5]. Plant infestations by pest and diseases can result in up to 82 percent reduction in attainable yield in cotton and over 50 percent loss in other major crops; when these losses are combined with post-harvest spoilage and quality degradation these losses become significant, especially in resource-poor regions of the world [6]. Furthermore, plant diseases are expected to reduce yields by about 20 percent in the world's major food and cash crops [7]. Over the last 40 years, effective pest and disease management has played a key role in doubling food output, but pathogens still consume 10-16 percent of global crop production [8]. Working against this pattern would be impossible without the

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use of emerging technology. Pests and abiotic stressors such as virus, mosquito, and weed infestations, as well as fertiliser scarcity and drought stress, can reduce crop quantity and productivity, reducing the potential yield of agricultural crops worldwide.

Possible solutions

Farmers have many methods for controlling pests and pathogens which can be mixed in advanced pest management techniques. Both organic and inorganic fungicides and poisons are used to maintain chemical regulation. Establishment of optimum growth conditions for cultivated crops and/or to eliminate those conditions that benefit pest and disease multiplication and with the introduction of cultural practices to remove those conditions that are conducive to pest and disease replication. Use of biological agents and predators (biological regulation) to reduce pest and disease incidences. With the aid of genetics to develop crops that are less vulnerable/resistant to pests and diseases infestations. In many crops sufficient knowledge on balanced mineral nutrition will minimize the rate of disease growth. Crops usually require 18 different nutrient elements in its successful growth period out of which 15 essential nutrients are drawn up from the soil and are divided into three categories: main nutrients, secondary nutrients, and micro-nutrients. Among all above mentioned methods, genetically control of diseases and pests from crops may be a suitable option in order for attaining environment and agricultural sustainability.

Role of microbes in plant growth and development

According to the generally recognized principle of aggregate dynamics proposed by [9], fresh plant material is colonized by microorganisms and speckled by primary particles by the binding action of microbial agents, resulting in balanced macro aggregates. With the passing of time, this plant material decomposes within macro aggregates, leaving more chemically reactive plant materials covered in mineral particles and microbial metabolites, resulting in dense micro aggregates. The soil microbial population is massive, and it is responsible for a wide range of soil functions. A complex network of biochemical, chemical, and physical processes combine to form soil. In this regard, soil microbes play a critical role, as they are responsible for the majority of transformations and drive the creation of stable and labile carbon and nutrient reservoirs in soil, which help plant population establishment. Microbes influence the formation of bed rock and increase pore space and glomalin content in a number of aggregates [10]. Soil phospholipids and nucleic acids form a labile P source that is readily accessible to most species. By solubilizing phosphates, phosphate biofertilizers in the form of microorganisms can help increase the availability of phosphates for plant growth [11]. Furthermore, microorganisms involved in P solubilization and enhanced soluble P scavenging can promote plant growth by improving the efficiency of biological nitrogen fixation, growing the availability of other trace elements such as Fe and zinc (Zn), and producing plant growth-promoting compounds [12]. Microorganisms are naturally involved in fermentation processes, and for thousands of years, man has relied on yeasts,

mould, and bacteria to manufacture a wide range of foods, including bread, vinegar, beer, wine, cheese, and yoghurt, as well as fermented seafood, poultry, and vegetables [13]. Microbes are used to digest a variety of foods, resulting in a wide range of oriental food items. Numerous biological preparations have been prepared using vast quantities of microorganisms, which are extremely important in the fields of medicine and pharmacy [14].

Role of microbes in disease eradication

Plants and microbes require nutrition for progress and expansion, as well as disease control, much like humans [15]. The ability of the host to sustain its particular evolution or yield in the face of infection, on the other hand, determines its immunity. The genotypes of the two plants, plant stage, and environmental changes all influence resistance. Despite the fact that disease resistance and tolerance in plants are genetically regulated. Crop diversification, plant nutrient recovery, and biological pest control are only a few examples of environmentally sound management methods used in sustainable agriculture to ensure long-term yield stability [16]. In recent years, agriculture's long-term sustainability has faced numerous challenges.

Application of yeast in agriculture

While yeast is widely used in industry, its use in agriculture is less common. Since 1880 to 2019, it has been seen that there is a steady increase in the utilization of yeast in the field of agriculture. Several studies on bacteria, algae and fungi have been performed to promote plant development [17]. According to some research, yeast has the ability to suppress a possible pathogen and increase plant stress resistance [18,19]. *Rhizoctonia solani*, a soil-borne fungal plant pathogen that causes root diseases, has been confirmed to have substantial bio control activity by *Rhodotorula glutinis*, *Candida valida*, and *Trichosporon asahii* [20]. *Cryptococcus laurentii* was also discovered to inhibit graymold (*Botrytis cinerea*) development [21]. *Rhodotorula glutinis* promotes plant growth indirectly by acting as an antagonist against the pathogen *Penicillium expansum* by forming siderophores [22]. Another yeast, *A. pullulans*, is used to encourage plant growth while inhibiting the growth of fungal plant pathogens such as *G. cingulata* [23] (Table 1) [24-31] gives us an overview of yeast and its use in the prevention of postharvest disease caused by a variety of pathogens.

Pseudomonas' role in disease management

It has recently been estimated that a large amount of food commodity/crop is lost each year as a consequence of various diseases caused by fungi, nematodes, bacteria, and other organisms. For thousands of years, plant diseases have had a significant impact on food production and human community growth. The word "biocontrol" refers to disease management that occurs during the growth stages of plants as well as during food storage. The majority of research on Rhizobacterial biocontrol of pathogens has focused on pathogenic microorganisms such as weeds and insects [32,33]. Many workers have confirmed successful disease control using plant growth promoting rhizobacteria (PGPR) in a variety of cereals and crops [34].

Table 1 Yeast and its use in the prevention of postharvest disease caused by a variety of pathogens.

Yeast strains	antagonistic to plants
	bacterium
<i>Cryptococcus laurentii</i> LS-28	<i>Botrytis cinerea</i> and <i>Penicillium expansum</i>
<i>Candida oleophila</i>	<i>Penicillium digitatum</i> and <i>Penicillium italicum</i>
<i>Debaryomyces hansenii</i>	<i>Rhizopus stolonifer</i>
<i>Metschnikowia pulcherrima</i>	<i>Botrytis cinerea</i>
<i>Debaryomyces hansenii</i>	<i>Penicillium italicum</i>
<i>Metschnikowia fructicola</i>	<i>Penicillium expansum</i> and <i>Botrytis cinerea</i>
<i>Aureobasidium pullulans</i>	<i>Penicillium expansum</i>
<i>Cryptococcus albidus</i> (KKUY0017)	<i>Penicillium expansum</i>

Pseudomonas is one of the most commonly used bacterial classes as biocontrol agents in various plant organisms.

Microbial pesticides

Biological control agents are another name for microbial pesticides. The main component in this group is a microorganism that is either naturally occurring or genetically modified. The organism itself or a material it creates could be the source of the pesticidal action. In contrast to traditional chemical pesticides, they have a higher selectivity and little or no toxicity [35]. The active ingredient in microbial pesticides is a microbe (bacterium, fungus, virus, protozoan or alga, rickettsia, Mycoplasma, and nematodes). They exterminate pests by developing toxic metabolites that are unique to the genus, causing disease, preventing the establishment of other microorganisms by tolerance, and employing a variety of other strategies [36].

Biological weed control

Organisms have been utilized as organic weed control agents, and natural weed control approaches have been recognized for the long-term utilization of biodiversity for the good of humanity's economy [37]. Rhizobial microbes and their inhibitors have been used as conventional farming agents in a number of crop systems. In both regulated and field trials, live colonies of *Pseudomonas syringae* strain 3366 were proven to reduce weed plant growth [38,39]. Over the last five decades, this field has been largely centered on bacteria and fungi in terms of weed and invasive plant species control, though viruses have been considered in some cases [40]. The introduction of a rust fungus, *Puccinia chondrillina*, into Australia to suppress rush skeleton weed (*Chondrilla juncea*) is one of the most effective examples of biological weed control [41]. The rust fungus *Uromycladium tepperianum* has been used to control *Acacia saligna*, and foliar smut fungus is used to control *Hamakua pamakani* [42]. *Bacillus* strain SYB101 was found to suppress the growth of *Phalaris minor* weed species more effectively on wheat variety WH711 [43]. Similarly, inoculation with *P. fluorescens* strain G2-11 suppressed weed growth while promoting wheat and soybean growth.

Genetic approaches

About the fact that disease resistance and tolerance in plants are genetically controlled [44], crop diversification, plant nutrient recovery, and biological pest control are examples of

environmentally responsible management techniques used in sustainable agriculture to provide long-term sustained yields [45]. Overall, before creating genetically modified microorganisms, we must first identify the gene of interest in the vast biodiversity of microorganisms in the soil. Perhaps the effect on soil pH and disease suppression is due to a coalition of various microorganisms rather than a single strain. First, the screening method for desired microbial activity needs to be developed which allows performing preliminary detection of activities.

Disease suppression through genetic engineering

Plant pathogenic bacteria present in the soil rhizosphere can cause a number of plant diseases. Using pathogenic bacteria, scientists have developed a biological system for combating invasive weeds and rodents. Since these microbes have foreign genes, they can invade and kill weeds [46]. Bio-insecticides use microorganisms to minimize the use of industrial insecticides. Because of their short shelf life, they do not live in the atmosphere and are hence eco-friendly. Furthermore, fungi, for example, induce 200 diseases in insects that have the potential to dominate their population. Many important pharmaceutical materials obtained by the use of microbes such as bacteria are mostly proteins in nature, such as Bacteriorhodopsin, a protein contained in the plasma membrane of *Halobacterium salinarum* [47] that is used for a variety of purposes.

Why microbes selected for genetics

Microorganisms have vast biosynthetic reservoirs for processing biomolecules of interest; however, thanks to intensive studies in allied sectors and evolving genetic opportunities for enhanced microbial consortia, farmers and agriculturists are accepting new approaches to satisfy the ever-increasing demand for sustainable food output. Microbes are well-suited to biochemical and genetic research, and they have made significant contributions to these areas, such as demonstrating that DNA is the genetic material [48].

Object of interest

Microbes that can live in an acidic, basic, or neutral environment, as well as pathogenic microbes that release suitable compounds, should be selected, and it's likely that by genetically modifying their genomes, more robust strains of microbes with the potential

to modify pH up to several folds and disease suppression might be developed. The primary motivation for this strategy is to discover a new generation of microbes that are well-suited to changing the pH of the rhizosphere, where excess nutrients are needed for plant uptake.

Microbial profiling, screening and identification procedure/method

Technological advancement is at the heart of microbial ecology science. The use of SSU rRNA or rDNA sequences in conjunction with fluorescent oligonucleotide probes provides an important tool for studying soil microorganisms that are not amenable to current culturing techniques [49]. Furthermore, the throughput of DNA sequencing has fallen sharply in the last decade, allowing most research groups to map microbial population diversity in of interest settings. These approaches may be used to classify and analyze soil microbes that cannot currently be cultured. Soil samples can be used to identify and sequence microbial rRNA genes. These microorganisms' genomes can then be compared to those of other known microorganisms. Microbiome population

profiling (MiCoP) can also be used to profile eukaryotes and viruses in metagenomic samples [50].

Conclusion

Increases in the quality and quantity of global crop production are urgently needed. The biotic and abiotic influences, which affect or even decide the final outcome, are two major groups of factors that have a significant impact on plant growth as well as crop yield and quality characteristics. Microbes that can survive in an acidic, basic, or neutral environment, as well as pathogenic microbes that release appropriate compounds, should be chosen, and it's possible that more resilient strains of microbes with the ability to change pH up to many folds and diseases suppression could be created by genetically altering their genes. Microbial rRNA genes can be detected and sequenced directly from soil samples. The genomes of these microorganisms will then be compared to those of other recognized microorganisms. Several microbes have been used to control pest and diseases. In this way we can prevent the plants from various diseases and increase the yield in more sustainable manner.

References

- 1 Kumar SS, Mahale AG, Sultan A, Jadhav SC, Ejaz A, et al. (2021) Boosting Agricultural Production Beneficial Biofertilizers. *Int J Curr Micro Biol App Sci* 10: 646-662.
- 2 Atkinson NJ, Dew TP, Orfila C, Urwin PE (2011) Influence of combined biotic and abiotic stress on nutritional quality parameters in tomato (*Solanum lycopersicum*). *J Agric Food Chem* 59: 9673-9682.
- 3 Altieri MA, Nicholls CI, Henao A, Lana M (2015) Agroecology and the design of climate change resilient farming systems. *Agron Sustain Dev* 35: 869-890.
- 4 Gondal AH, Zafar A, Zainab D, Toor MD, Sohail S, et al. (2021) A detailed review study of zinc involvement in animal, plant and human nutrition. *Ind J Pure App Biosci* 9: 262-271.
- 5 Gondal AH, Hussain I, Ijaz AB, Zafar A, Ch BI, et al. (2021) Influence of soil pH and microbes on mineral solubility and plant nutrition: A review. *Int J Agric Biol* 5: 71-81.
- 6 Shurtleff (2006) Plant disease.
- 7 Oerke EC (2006) Crop losses to pests. *J Agric Sci* 144: 31-43.
- 8 Chakraborty S, Newton AC (2011) Climate change, plant diseases and food security: An overview. *Plant Pathol* 60: 2-14.
- 9 Golchin A, Oades JM, Skjemstad JO, Clarke P (1994) Soil structure and carbon cycling. *Soil Res* 32: 1043-1068.
- 10 Chakraborty P, Prithiviraj B, Selvaraj S, Kumar B (2016) Polychlorinated biphenyls in settled dust from informal electronic waste recycling workshops and nearby highways in urban centers and suburban industrial roadsides of Chennai city, India: levels congener profiles and exposure assessment. *Sci Total Environ* 573: 1413-1421.
- 11 Tandon S, Horowitz PM (1982) Detergent assisted refolding of guanidinium chloride denatured rhodanese. The effects of the concentration and type of detergent. *J Biol Chem* 62: 4486-4491.
- 12 Kucey RM (1989) The influence of rate and time of mineral N application on yield and N₂ fixation by field bean. *Can J Plant Sci* 69: 427-436.
- 13 Kharatyan SG (1978) Microbes as food for humans. *Annu Rev Microbiol* 32: 301-327.
- 14 Kapoor R, Ghosh P, Kumar M, Sengupta S, Gupta A, et al. (2020) Valorization of agricultural waste for biogas based circular economy in India: A research outlook. *Bio resource technology* 304: 123036.
- 15 Agrios N G (2005) *Plant Pathology*, Elsevier Academic Press. P. 635.
- 16 Shrivastava M, Srivastava PC, D'souza SF (2016) KSM soil diversity and mineral solubilization in relation to crop production and molecular mechanism. In *Potassium solubilizing microorganisms for sustainable agriculture*. Springer, New Delhi, India. p. 221-234.
- 17 Meena VS, Maurya BR, Verma JP, Aeron A, Kumar A, et al. Potassium solubilizing rhizobacteria (KSR): isolation identification and K release dynamics from waste mica. *Ecol Eng* 81: 340-347.
- 18 Kamel SM, Ebtsam MM, Massoud ON (2016) Potentiality of some yeast species as biocontrol agents against *Fusarium oxysporum f. sp. cucumerinum* the causal agent of cucumber wilt. *Egypt J Biol Pest Control* 26: 185-193
- 19 Ibrahim HA, El-Fiki IAI (2019) Study on the effect of yeast in compost tea efficiency in controlling chocolate leaf spot disease in broad bean (*Vicia faba*). *Org Agric* 2: 175-188.
- 20 El-Tarabily KA (2004) Suppression of *Rhizoctonia solani* diseases of sugar beet by antagonistic and plant growth promoting yeasts. *J Appl Microbiol* 96: 69-75.
- 21 Yu T, Zhang H, Li X, Zheng X (2008) Biocontrol of *Botrytis cinerea* in apple fruit by *Cryptococcus laurentii* and indole-3-acetic acid. *Biol Control* 46: 171-177.
- 22 Calvente V, Benuzzi D, Tosetti MIS (1999) Antagonistic action of siderophores from *Rhodotorul aglutinis* upon the postharvest pathogen *Penicillium expansum*. *Int Biodeterior Biodegradation* 43: 167-172.
- 23 Sun PF, Chien IA, Xiao HS, Fang WT, Hsu CH, et al. (2019) Intra

- specific variation in plant growth promoting traits of *Aureobasidium pullulans*. Chiang Mai J Sci 46: 15-31.
- 24 Castoria R, Caputo L, De Curtis F, De Cicco V (2003) Resistance of postharvest biocontrol yeasts to oxidative stress: A possible new mechanism of action. *Phytopathology* 93: 564-572.
 - 25 Lahlali R, Serrhini MN, Jijakli H (2004) Efficacy assessment of *Candida oleophila* (strain O) and *Pichia anomala* (strain K) against major postharvest diseases of citrus fruits in Morocco. *Com Agric Appl Biol* 69: 601-609.
 - 26 Mandal G, Singh D, Sharma RR (2007) Effect of hot water treatment and bio control agent (*Debaryomyce shansenii*) on shelf life of peach. *Indian J Horticult* 64: 25-28
 - 27 Saravanakumar D, Spadaro D, Garibaldi A, Gullino ML (2009) Detection of enzymatic activity and partial sequence of a chitinase gene in *Metschnikowia pulcherrima* strain MACH1 used as post-harvest biocontrol agent. *Eur J Plant Pathol* 123: 183-193.
 - 28 Hernández Montiel LG, Ochoa JL, Troyo Diéguez E, Larralde CP (2010) Biocontrol of postharvest blue mold (*Penicillium italicum* Wehmer) on Mexican lime by marine and citrus *Debaryomyce shansenii* isolates. *Postharvest Biol Technol* 56: 181-187.
 - 29 Liu J, Wisniewski M, Droby S, Tian S, Hershkovitz V, et al. (2011) Effect of heat shock treatment on stress tolerance and biocontrol efficacy of *Metschnikowia fructicola*. *FEMS Microbiol Ecol* 76: 145-155.
 - 30 Vero S, Garmendia G, González MB, Bentancur O, Wisniewski M (2013) Evaluation of yeasts obtained from Antarctic soil samples as biocontrol agents for the management of postharvest diseases of apple (*Malus domestica*). *FEMS Yeast Res* 13: 189-199.
 - 31 Hashem M, Saad AA, Hesham A, Fatimah MH, Al-Qahtani, et al. (2014) Biocontrol of apple blue mold by new yeast strains: *Cryptococcus albidus* KKUY0017 and *Wickerhamomyces anomalus* KKUY0051 and their mode of action. *Biocontrol Sci Technol* 24: 1137-1150.
 - 32 Flores Fargas RD, OHara GW (2006) Isolation and characterization of rhizosphere bacteria with potential for biological control of weeds in vine yards. *J Appl Microbiol* 100: 946-954.
 - 33 Siddiqui A, Haas D, Heeb S (2005) Extracellular protease of *Pseudomonas fluorescens* CHA0, a biocontrol factor with activity against the root knot nematode *Meloidogyne incognita*. *Appl Environ Microbiol* 71: 5646-5649.
 - 34 Lucy M, Reed E, Glick BR (2005) Application of free living plant growth-promoting rhizobacteria. *Antonie Van Leeuwenhoek*. p. 1-25.
 - 35 MacGregor JT (2006) Genetic toxicity assessment of microbial pesticides: needs and recommended approaches. *Intern Assoc Environ Mutagen Soc*. p. 1-17.
 - 36 Clemson HGIC (2007) Organic pesticides and biopesticides, Clemson extension, home and garden information center. Clemson University, Clemson.
 - 37 Mejri D, Gamalero E, Tombolini R, Musso C, Massa N, et al. (2010) Biological control of great brome (*Bromus diandrus*) in durum wheat (*Triticum durum*): specificity, physiological traits and impact on plant growth and root architecture of the fluorescent *pseudomonad* strain X33d. *Bio Control* 55: 561-572.
 - 38 Johnson A, Booth C (1983) Plant pathologist's pocket book. 2nd edn. Surrey, Commonwealth Agricultural Bureaux, UK.
 - 39 Kennedy AC, Elliott LF, Young FL, Douglas CL (1991) Rhizobacteria suppressive to the weed downy brome. *Soil Sci Soc Am J* 55: 722-727.
 - 40 Diaz R, Manrique V, Hibbard K, Fox A, Roda A, et al. (2014) Successful biological control of tropical soda apple (*Solanales: Solanaceae*) in Florida: A review of key program components. *Fla Entomol* 97: 179-190.
 - 41 Barton J (2004) How good are we at predicting the field host-range of fungal pathogens used for classical biological control of weeds? *Biological Control: Theory and Application in Pest Management* 31: 99-122.
 - 42 Charudattan R (2005) Ecological, practical and political inputs into selection of weed targets: what makes a good biological control target? *Biol Control* 35: 183-196.
 - 43 Phour M (2012) Biological control of *Phalaris minor* in wheat (*Triticum aestivum* L.) using rhizosphere bacteria. M.Sc. thesis. Chaudhary Charan Singh Haryana Agricultural University, Hisar, Haryana.
 - 44 Agrios NG (2005) Plant pathology, (5th edn), Elsevier Academic Press. P. 635.
 - 45 Shrivastava M, Srivastava PC, D'Souza SF (2016) KSM soil diversity and mineral solubilization, in relation to crop production and molecular mechanism. In Potassium solubilizing microorganisms for sustainable agriculture. p. 221-234.
 - 46 Hoagland IV LF, Campa MJ, Gottlin EB, Herndon JE, Patz Jr EF (2007) Haptoglobin and posttranslational glycan-modified derivatives as serum biomarkers for the diagnosis of non-small cell lung cancer. *Cancer: Interdisciplinary CA Cancer J Clin* 110: 2260-2268.
 - 47 Leader B, Baca QJ, Golan DE (2008) Protein therapeutics: A summary and pharmacological classification. *Nat Rev Drug Discov* 7: 21-39.
 - 48 Yanofsky C (2001) Advancing our knowledge in biochemistry, genetics, and microbiology through studies on tryptophan metabolism. *Annu Rev Biochem* 70: 1-37.
 - 49 Hirst PH, Peters RS (2011) The logic of Education, 16: Routledge, USA.
 - 50 Lapiere KR, Dane AV (2020) Social advantages and disadvantages associated with cyber aggression victimization: A latent class analysis. *Comput Hum Behav* 113: 106-497.