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REVIEW

Can biocontrol be the game-changer in integrated pest management? A review of definitions, methods and strategies

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Abstract
Global agriculture is heavily dependent on sustainable plant protection. Worldwide, the concept of integrated pest management (IPM) is being followed. IPM utilizes a range of strategies, with chemical synthetic pesticides being employed only as a last resort. However, in agricultural practice, farmers continue to rely primarily on this option. To further reduce this dependence, new strategies are being sought to strengthen the use of biological control within the IPM approach including the identification of novel non-synthetic natural compounds. Here, we discuss and report on the state of the art in biological control research in areas such as biocontrol agents and application of ecological principles. These practices can help to establish sustainable plant protection systems, with the greatest impact achieved when they are used in appropriate combinations. We highlight the conditions that currently prevent or hinder the increased use of biocontrol measures. On the background of agroecological experiences, we discuss why additional advancements in plant protection practices are imperative to more effectively break the life cycles of pests, diseases and weeds. We emphasize the significance of a judicious application of chemical control technologies, adapted to local conditions. Additionally, we highlight the key role and expertise of operators in implementing these practices and their knowledge thereof.

Keywords Agroecology · Beneficial organisms · Biocontrol agents · Integrated pest management · Induced resistance · dsRNA · Nature-based substances · Priming · Sustainability

Introduction

The need for reduction of chemical synthetic pesticides in IPM

Given the projected increase in total food consumption by a growing world population and the crucial situation of our planet, agricultural production faces an increasing need for knowledge-based plant protection, characterized by a better, holistic understanding of pest and diseases (Deutsch et al. 2018; Muller et al. 2017; van Dijk et al. 2021). Synthetic chemicals such as synthetic pesticides have a long successful history as plant protection products (PPPs) in pest and disease control, as they have overall reduced the risk of yield losses over decades. Concerns about their potential negative side effects on human and animal health and the environment, as well as their gradual ineffectiveness due to emerging compound resistance of pests and pathogens, have spurred research and industry to seek new strategies in plant protection. The primary objective is to reduce the use of synthetic chemicals and replace them with biological

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methods based on new scientific findings about the ecology, epidemiology and molecular mechanisms of plant diseases and a better understanding of the plant's immune system (He et al. 2021; Lamichhane et al. 2016).

In the European Union (EU), integrated pest management (IPM) is legally obligatory as described in the Directive 2009/128/EC Annex III (European Parliament and Council 2009) and is widely regarded as the standard broad-based approach for safeguarding crops from harmful organisms while reducing or minimizing PPP-related risks to human health and the environment (Deguine et al. 2021; Mailly et al. 2017). Although IPM prioritizes the use of '*non-chemical methods*' for pest management (see Annex III of Directive 2009/128/EC), thus regulatory preferring physical, mechanical or biological pest control methods (Fig. 1), farmers and growers remain unconvinced that alternative IPM strategies can fully replace chemical synthetic pesticides for crop protection and effectively mitigate their production risk. Consequently, a recent analysis of the use of chemical synthetic PPPs in Europe from 2011 to 2021 revealed that the total sales in tons of pesticide active substances have remained relatively stable over the last decade, with annual sales fluctuating around ± 6% (Eurostat 2022). As a result, there is growing social and environmental pressure from side of consumers and policy makers to reduce synthetic chemicals to an absolute minimum necessary amount, to prioritize residue-free products and to develop new strategies in plant protection based on a deeper understanding of the biological mechanisms involved.

Currently, there is an intense debate regarding a proposal by the EU Commission to replace the Sustainable Use of Pesticides Directive (Directive 2009/128/EC) with a regulation, the so-called Sustainable Use Regulation or SUR (European Parliament and Council 2023). The new SUR, which has been rejected by the European Parliament in the first reading (European Parliament 2023), aimed to align with the EU Commission's objectives of the 'Farm to Fork' (European Commission 2020a) and 'Biodiversity' strategies (European Commission 2020b). This set of measures are all part of the European Green Deal (European Commission 2019), which has the ultimate goal of making the EU climate neutral by 2050. The SUR primarily aimed to (a) achieve a 50% reduction in the use and risk of plant protection products by 2030 (relative to the average of the years 2015–2017), (b) strengthen the enforcement of IPM, (c) promote the use of non-chemical alternatives to chemical synthetic pesticides, (d) improve the availability of monitoring data, (e) enhance the application of regulations and the effectiveness of policy measures and (f) support new technologies such as precision agriculture. Whether the EU Commission will initiate a second reading remains uncertain at this point. Nevertheless, the implications of the process are becoming increasingly evident. The question of how biocontrol could be promoted as a game-changer in integrated pest management is becoming more pressing.

It is evident that forthcoming reduction objectives necessitate significant innovation in the area of non-conventional PPPs for pest and disease control. Furthermore, it is important to prioritize the application of non-synthetic chemical methods that are already available and to support their market expansion through relevant policy instruments. This encompasses not only biological PPPs based on plant

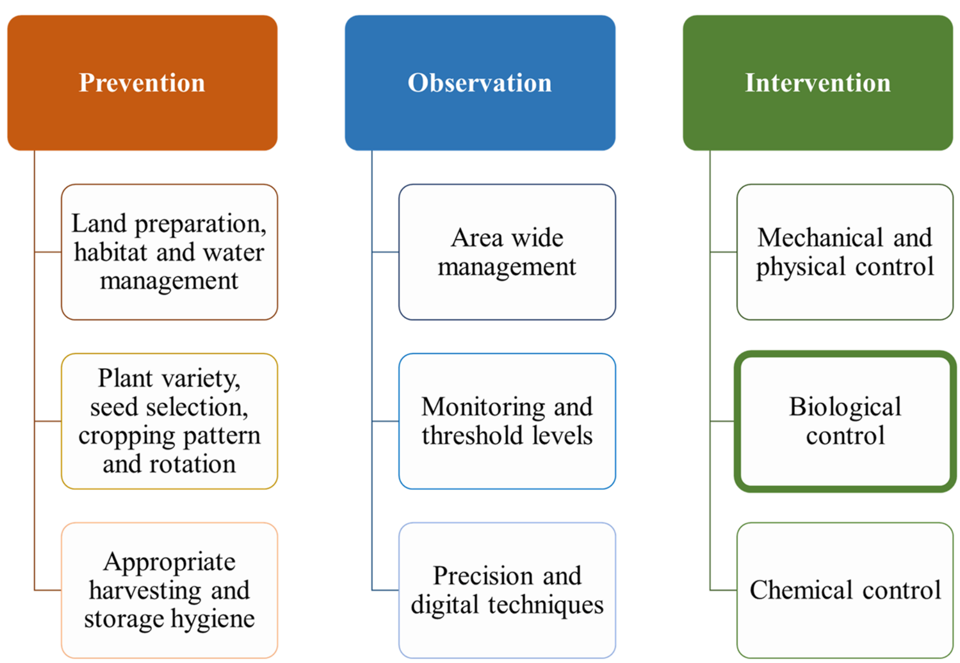


Fig. 1 Concept of IPM following Annex III of Directive 2009/128/EC. Biological control measures are part of the 'intervention' tool box of IPM

compounds ('botanicals') and microorganisms, but also open-field applications of beneficial organisms. The additional use of biostimulants and the integration of plant–plant interactions will also become relevant (European Commission, Directorate-General for Health and Food Safety 2020). In this context, we explore in this article whether one of the key intervention components of IPM, the biological control of pests could become a game-changer in the IPM process resulting in the reduced need of chemical synthetic pesticides.

The scope of biological control

Today, there is a lack of a universally accepted terminology for biological control (biocontrol), often resulting in terminology confusion and misuse among researchers, legislators and biocontrol industry. At the time of writing of this review, neither the USA nor the EU has a formal definition for 'biocontrol' or 'bioprotection.' The Institute for European Environmental Policy (IEEP) defines them as 'the protection of plant health through natural or nature identical means' (Hulot and Hiller 2021). It should be noted that the viewpoint of the IEEP may not necessarily coincide with that of the EU. However, the definition of the IEEP is in alignment with the definition provided by the International Biocontrol Manufacturers Association (IBMA 2018), which represents the biocontrol industry worldwide. To aid comprehension, we have compiled an extensive catalogue of biological control vocabulary and the corresponding definitions employed in official publications from the EU, USA, United Nations and affiliated institutions (Table 1).

In this review, we adopt the recommended definitions outlined in Stenberg et al. (2021), which build upon the definition of bioprotection (IBMA 2018) to differentiate between bioprotectants that utilize living biocontrol agents (BCAs) and non-living nature-based substances (NBSs). Here, BCAs include macroorganisms and microorganisms (including microbial plant biostimulants—see also Fig. 2), while botanicals, semiochemicals, basic substances, RNA and resistance-inducing compounds are included in the NBSs (see also Fig. 3).

We examine current examples of best practice options in BCAs and NBSs, particularly at EU level. We also discuss emerging and innovative approaches, such as resistance-inducing priming agents and active cell components, as double-stranded RNA (dsRNA). We begin by gathering information oriented toward products and more specifically their active ingredients, because these represent the level of regulatory influence. From this data, we evaluate to what extent these techniques could be integrated to act as a game-changer toward the development of a sustainable IPM system, with the aim of minimizing chemical synthetic PPPs usage.

BCAs in biocontrol

BCAs are naturally occurring, widespread living organisms, including viruses, bacteria, fungi, insects, mites, nematodes, yeasts and protozoa, that can control pests as part of IPM strategies through different biological mechanisms (Stenberg et al. 2021). In November 2022, four new regulations were approved in the EU to simplify the process of approval and authorization of biological PPPs which contain microorganisms (Regulation EU 2022/1438, 2022/1439, 2022/1440, 2022/1441; (European Commission 2022a, 2022b, 2022c, 2022d)). Currently, 71 microorganism strains are approved in the EU (see EU Pesticides Database revised in November 2023 (EU 2023)), and further 26 approvals are pending. At the most basic level, predators capture and consume their prey, whereas insect parasitoids lay their eggs on or in their hosts, which are then consumed by their immature offspring. Similarly, certain entomopathogenic organisms (mostly fungi) can penetrate the outer integument of insects and cause systemic infection, while bacteria and viruses infect and kill harmful organisms, mostly upon ingestion. Figure 2 shows some of the best examples of BCAs and their (in)direct target in nature.

Antagonistic viruses and phages

Viruses are excellent candidates for species-specific, narrow-spectrum applications to control arthropod and microbial pests (Holtappels et al. 2021; Sabbahi et al. 2022; Stefani et al. 2021; Vikram et al. 2021; Wagemans et al. 2022). Baculoviruses (family *Baculoviridae*), due to their incapability to replicate within mammal and plant cells and their high insect specificity, are considered a model BCA for insect management. Recognized as an alternative to synthetic insecticides already in 1977 (Arif 1977; Dulmage and Burgerjon 1977), today, Nucleopolyhedroviruses (NPV) and Granuloviruses (GV) are two genera of *Baculoviridae* mainly employed as BCAs for the control of Lepidoptera (butterflies and moths), Hymenoptera (wasp) and Diptera (flies). *Cydia pomonella granulovirus* (CpGV) and *Phthorimaea operculella granulovirus* (PhopGV) are insect-specific viruses that offer highly selective control of the codling moth *Cydia pomonella* (Mora Vargas 2022) and the leaf miner *Tuta absoluta* (Gonthier et al. 2023) in apple orchards and tomato farms, respectively. The commercial products, available in both Europe and North America, contain the virus in an aqueous suspension and are sprayed at egg hatch. To be effective the baculoviruses must be taken up by the insect larvae. Once ingested, they spread throughout the body via the midgut, killing their

Table 1 Summary of biological control vocabulary and the corresponding definitions employed in official publications from the EU, USA, United Nations and affiliated institutions

Term (etymology/abbreviation)	Definition	References
Active substance (AS)	Substances, including microorganisms having general or specific action against harmful organisms or on plants, parts of plants or plant products	EU, Article 2 of Regulation (EC) No 1107/2009
Basic substance (BS)	An active substance which: (a) is not a substance of concern; and (b) does not have an inherent capacity to cause endocrine disrupting, neurotoxic or immunotoxic effects; and (c) is not predominantly used for plant protection purposes but nevertheless is useful in plant protection either directly or in a product consisting of the substance and a simple diluent; and (d) is not placed on the market as a plant protection product	EU, Article 23 of Regulation (EC) No 1107/2009
Beneficial organism	Any pollinating insect, or any pest predator, parasite, pathogen or other biological control agent which functions naturally or as part of an integrated pest management program to control another pest	European Environment Agency, Glossary[a]
‘’	Naturally occurring bacteria, fungi and other microbes that play a crucial role in plant productivity and health. Two types of beneficial microorganisms, mycorrhizal fungi and nitrogen-fixing bacteria, are considered beneficial to plant health	USA, Forest Service—Department of Agriculture[b]
‘’	An organism directly or indirectly advantageous to plants or plant products, including biological control agents	FAO, Phytosanitary glossary[c]
Biological control	Control of pests by using predators to eat them.—pest control strategy making use of living natural enemies, antagonists or competitors and other self-replicating biotic entities	European Environment Agency, Glossary[a]
‘’	The reduction of pest populations through the use of natural enemies such as parasitoids, predators, pathogens, antagonists or competitors to suppress pest populations	USA, Department of Agriculture[d]
‘’ (biocontrol)	A pest management strategy making use of living natural enemies, antagonists or competitors and other self-replicating biotic entities	FAO, Phytosanitary glossary[c]
Biological control agent	The use of living organisms to control pests or diseases. May be a single organism or a combination of a number of different organisms.—a natural enemy, antagonist or competitor and any other self-replicating biotic entity used for pest control	European Environment Agency, Glossary[a]
‘’	A natural enemy, antagonist or competitor, or any other organism used for pest control	FAO, Phytosanitary glossary[c]
Biological agent (w/o ‘control’)	Chemicals or organisms that increase the rate at which natural biodegradation occurs. Biodegradation is a process by which microorganisms such as bacteria, fungi and yeast break down complex compounds into simpler products	USA, Environmental Protection Agency[e]
Biopesticide (from Latin *pestis* ‘scourge’ and *caedere* ‘to kill’)	Pesticide made from biological sources that is from toxins which occur naturally […] A pesticide in which the active ingredient is a virus, fungus or bacterium, or a natural product derived from a plant source. A biopesticide's mechanism of action is based on specific biological effects and not on chemical poisons	European Environment Agency, Glossary[a] (approved currently under (EU) Regulations 1107/2009)

Table 1 (continued)

Term (etymology/abbreviation)	Definition	References
‘’	Certain types of pesticides derived from such natural materials as animals, plants, bacteria and certain minerals. Biopesticides fall into three major classifications: biochemical, microbial and plant-incorporated protectants	USA, Environmental Protection Agency[f]
‘’	A compound that kills organisms by virtue of specific biological effects rather than as a broader chemical poison. Biopesticides differ from biocontrol agents in that biopesticides are passive agents, whereas biocontrol agents are active, seeking out the pest to be destroyed	FAO, Phytosanitary glossary[c]
Botanical (active substance)	Consists of one or more components found in plants and obtained by subjecting plants or parts of plants of the same species to a process such as pressing, milling, crushing, distillation and/or extractions	EU, Guidance Document on Botanical Active Substances used in Plant Protection Products[g] (approved currently under Regulations 1107/2009)
Botanical (drug)	Vegetable materials, which may include plant materials, algae, macroscopic fungi or combinations thereof	FDA, 2022[h]
‘’	See ‘biopesticide’	FAO, International Code of Conduct on Pesticide Management (FAO and WHO, 2020)
(Microbial plant) Biostimulant	A product stimulating plant nutrition processes independently of the product’s nutrient content with the sole aim of improving one or more of the following characteristics of the plant or the plant rhizosphere: (a) nutrient use efficiency; (b) tolerance to abiotic stress; (c) quality traits; (d) availability of confined nutrients in soil or rhizosphere	EU, Regulation (EU) 2019/1009 (EC 2019)
‘’	A substance, microorganism or mixtures thereof, that, when applied to seeds, plants, the rhizosphere, soil or other growth media, act to support a plant’s natural nutrition processes independently of the biostimulant’s nutrient content	USA, EPA—Guidance for Plant Regulator Products and Claims, Including Plant Biostimulants (2020)[i]
‘’	A product that stimulates plant growth through the synthesis of growth-promoting substances and/or plant nutrition processes independently of nutrient content, with the aim of improving one or more of: the plants' nutrient use efficiency or uptake; plant tolerance to abiotic stress; or, crop quality traits	FAO, Phytosanitary glossaryc
Low Risk (substance) (LR)	An active substance shall not be considered of low risk where it is or has to be classified in accordance with Regulation (EC) No 1272/2008 as at least one of the following: carcinogenic, mutagenic, toxic to reproduction, sensitizing chemicals, very toxic or toxic, explosive, corrosive It shall also not be considered as of low risk if: persistent (half-life in soil is more than 60 days), bioconcentration factor is higher than 100, it is deemed to be an endocrine disrupter, or it has neurotoxic or immunotoxic effects	EU, Annex II, point 5 of Regulation (EC) 1107/2009
Microorganisms (MO)	Means any microbiological entity, including lower fungi and viruses, cellular or non-cellular, capable of replication or of transferring genetic material	EU, Regulation (EC) 1107/2009
‘’	Means an organism classified, using the 5-kingdom classification system of Whittacker, in the kingdoms Monera (or Procaryota), Protista, Fungi and the Chlorophyta and the Rhodophyta of the Plantae and a virus or virus-like particle	USA, EPA (Code of Federal Regulations at 40 CFR part 725)

Table 1 (continued)

Term (etymology/abbreviation)	Definition	References
Semiochemical, (from the Greek *semeion* meaning 'signal')	A substance or mixture of substances emitted by plants, animals and other organisms that evoke a behavioral or physiological response in individuals of the same or other species. […] Semiochemicals are not considered as active substances, when they are used only to attract arthropods which subsequently receive a lethal dose of an insecticide	EU, Guidance document on semiochemical active substances and plant protection products (2016)[j] (approved currently under (EU) Regulations 1107/2009)
''	See 'biochemical'	USA, Environmental Protection Agency[k]
''	A chemical substance or mixture that carries a message for the purpose of communication within or between species	FAO, Phytosanitary glossary[c]

[a] https://www.eea.europa.eu/help/glossary

[b] https://www.fs.usda.gov/research/treesearch/33082

[c] https://www.fao.org/faoterm/en/?defaultCollId=15

[d] https://www.aphis.usda.gov/aphis/ourfocus/planthealth/plant-pest-and-disease-programs/biological-control-program#:~:text=Biological%20control%20%28biocontrol%29%20involves%20the%20reduction%20of%20pest,pathogens%2C%20antagonists%2C%20or%20competitors%20to%20suppress%20pest%20populations

[e] https://www.epa.gov/emergency-response/biological-agents

[f] https://www.epa.gov/ingredients-used-pesticide-products/what-are-biopesticides

[g] https://food.ec.europa.eu/system/files/2016-10/pesticides_ppp_app-proc_guide_doss_botanicals-rev-8.pdf

[h] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/what-botanical-drug

[i] https://www.epa.gov/sites/default/files/2020-11/documents/pbs-guidance-updated-draft-guidance-document-2020-11-13_0.pdf

[j] https://food.ec.europa.eu/system/files/2016-10/pesticides_ppp_app-proc_guide_doss_semiochemicals-201605.pdf

[k] https://www.epa.gov/pesticide-registration/pesticide-registration-manual-chapter-3-additional-considerations

If a term has no definition for one (or more) organization(s), no official definition has been found

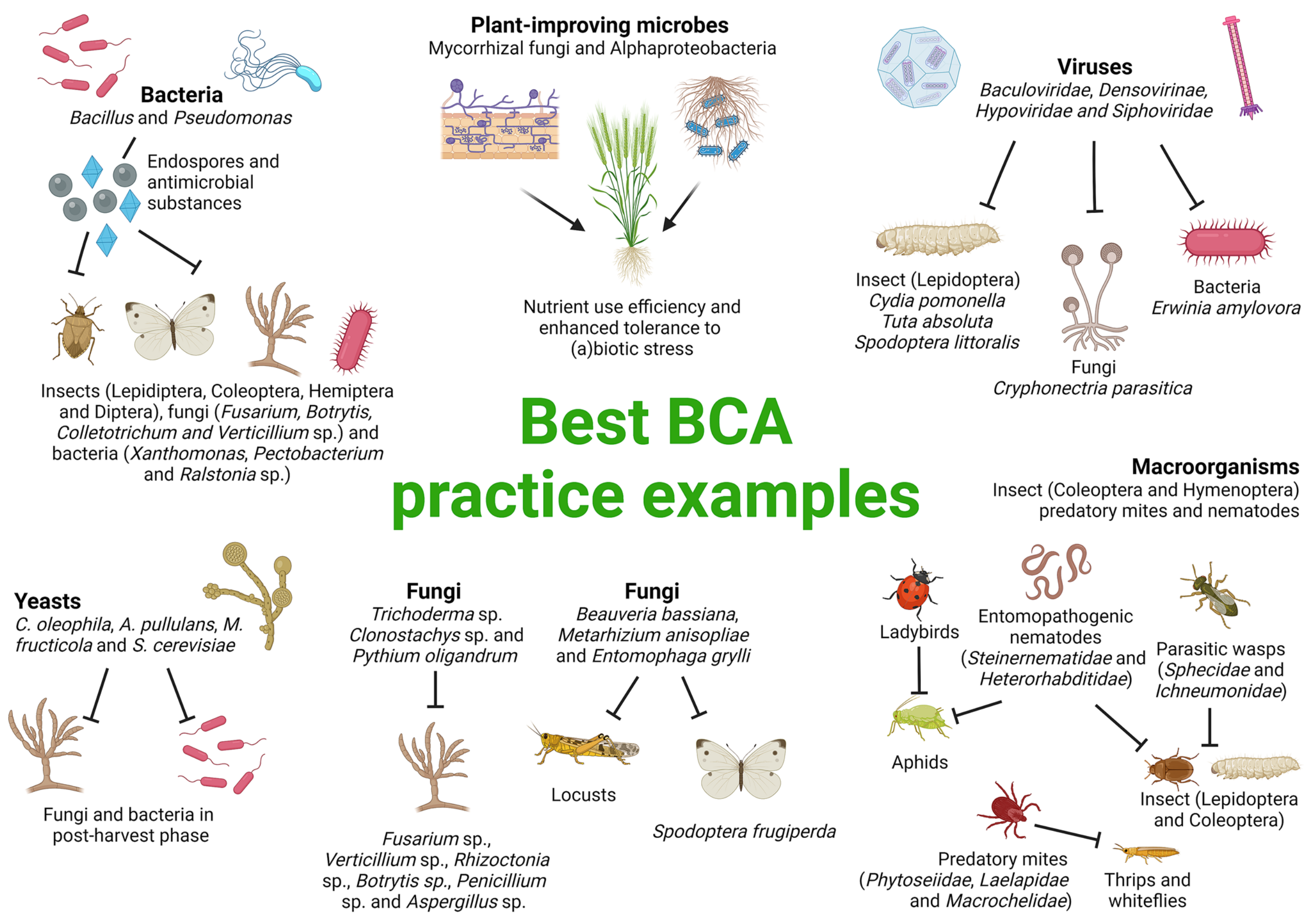
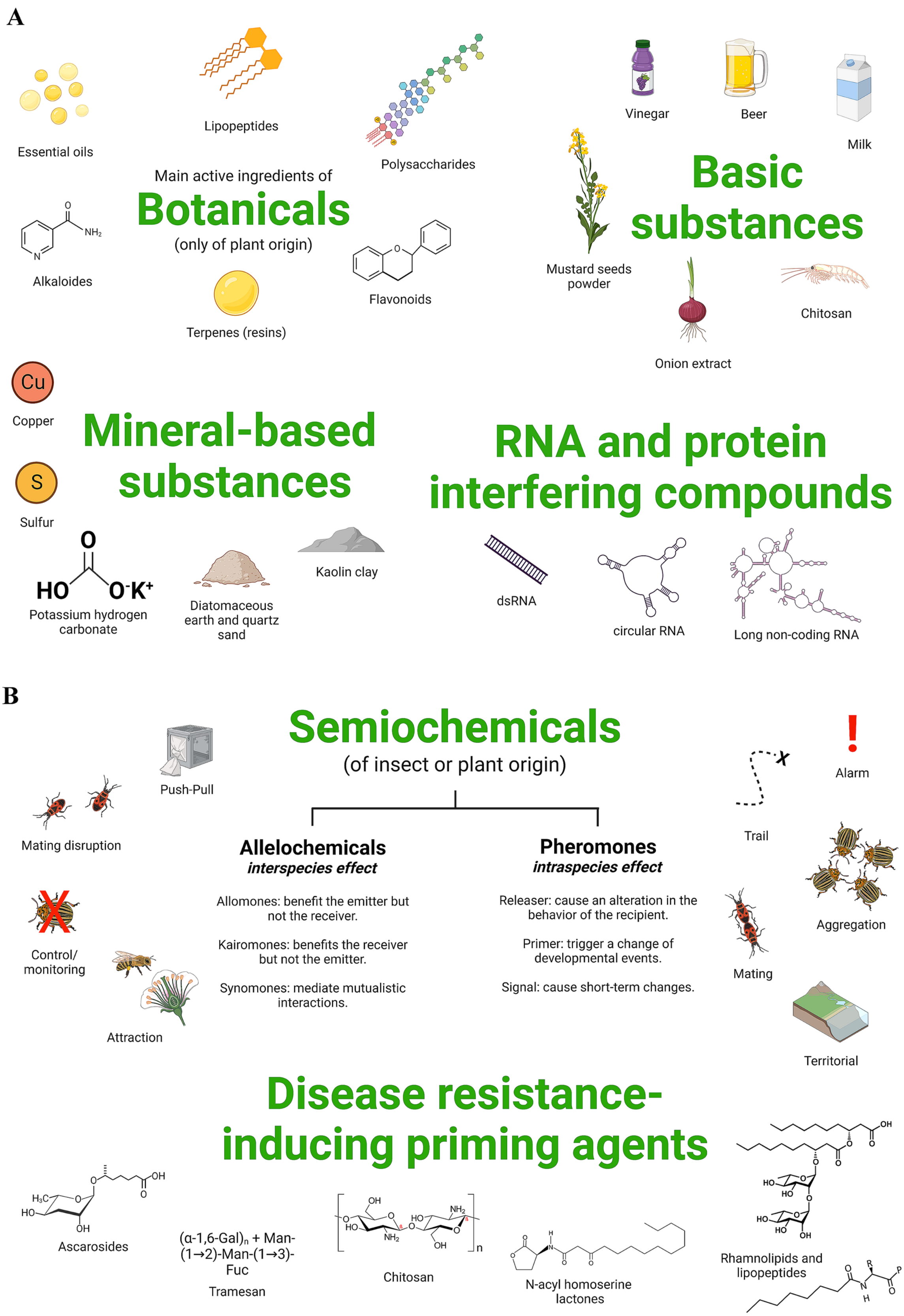


Fig. 2 Best practice examples of BCAs currently employed in IPM to control some major pests and diseases. Examples presented here utilize multiple mechanisms, including nutrient competition, antibiosis and mycoparasitism. Plant-improving microbes, including microbial plant biostimulants, often improve plant health by inducing resistance to biotic or tolerance to abiotic stresses

host (Preininger et al. 2018). Importantly, the occurrence of pathogen resistance against CpGV has been observed in practice (Olivares et al. 2023). Similarly, agents based on highly concentrated NPVs are used for the control of the larvae of lepidopterans of the *Helicoverpa* family in vegetable and grain crops. *Helicoverpa armigera nucleopolyhedrovirus* (HearNPV) is utilized for controlling the cotton bollworm (*Helicoverpa armigera*) and the corn earworm (*Helicoverpa zea*) (Williams et al. 2022). *Spodoptera littoralis nucleopolyhedrovirus* (SpliNPV) is used against the larvae of the African cotton leafworm *Spodoptera littoralis* (El Sayed et al. 2022) and the fall armyworm *Spodoptera frugiperda* (Zanella-Saenz et al. 2022). Interestingly, the potential for genetic modification, particularly to enhance the lethality of baculoviruses, has been already recognized in the past and could present new future prospects (Stewart et al. 1991). Today, baculoviruses are classified as low-risk substances under EU regulation unless their adverse effects on nontarget insects are demonstrated (see point 5.2.2. of Annex Regulation (EU) 2017/1432; European Commission 2017). *Densovirinae* (family *Parvoviridae*) is an additional subfamily of single-stranded DNA viruses that exhibit high potential for future biocontrol purposes. The prevalence and diversity of densoviruses across ecosystems suggest their potential efficacy against various insect families such as Lepidoptera, Diptera, Orthoptera, Hemiptera, Blattoidea, Thysanoptera and more (Sabbahi et al. 2022; Wagemans et al. 2022).

Compared to the large number of virus-based BCAs against insects, only a limited number are available against fungi (mycoviruses) and bacteria (bacteriophages), especially in Europe. A few successful examples are the mycovirus *Cryphonectria hypovirus* 1 (CHV1) against its fungal host *Cryphonectria parasitica*, the causal agent of chestnut blight (Rigling and Prospero 2018) and *Erwinia amylovora Siphoviridae* phage (PhiEaH1 and PhiEaH2) against *E. amylovora* fire blight on apple and pear trees (Gayder et al. 2023; Kolozsváriné Nagy et al. 2015).


A
Essential oils
Lipopeptides
Polysaccharides
Main active ingredients of
Botanicals
(only of plant origin)
Alkaloides
Terpenes (resins)
Flavonoids
Vinegar
Beer
Milk
Basic substances
Mustard seeds powder
Onion extract
Chitosan
Cu
Copper
S
Sulfur
Mineral-based substances
HO O-K+
Potassium hydrogen carbonate
Diatomaceous earth and quartz sand
Kaolin clay
RNA and protein interfering compounds
dsRNA
circular RNA
Long non-coding RNA
B
Push-Pull
Semiochemicals
(of insect or plant origin)
Mating disruption
Allelochemicals
interspecies effect
Allomones: benefit the emitter but not the receiver.
Kairomones: benefits the receiver but not the emitter.
Synomones: mediate mutualistic interactions.
Pheromones
intraspecies effect
Releaser: cause an alteration in the behavior of the recipient.
Primer: trigger a change of developmental events.
Signal: cause short-term changes.
Control/ monitoring
Attraction
Alarm
Trail
Aggregation
Mating
Territorial
Disease resistance-inducing priming agents
Ascarosides
(α-1,6-Gal)n + Man-(1→2)-Man-(1→3)-Fuc
Tramesan
Chitosan
N-acyl homoserine lactones
Rhamnolipids and lipopeptides

◂**Fig. 3** Best practice examples of NBSs currently employed or in the pipeline to control plant pathogens and pests and boost plant production and resilience. While examples of substances are presented for botanicals, basic substances and mineral-based substances (**A**), semiochemicals are categorized based on their various functions (B-top, for more information and examples, see also https://pherobase.com/ (El Sayed 2023)). Non-living disease resistance-inducing priming agents (IRPs) are given with their chemical structures (B-bottom). Examples shown here influence the growth, survival, development and reproduction of plants and other organisms. Certain chemical compounds, such as alkaloids and flavonoids, can fall into both the botanical and semiochemical categories when extracted from plants, due to their chemical composition rather than their mode of action

Antagonistic bacteria

Several recent reviews on the use of bacteria as BCAs are available (Bonaterra et al. 2022; Legein et al. 2020; Pfeiffer et al. 2021; Sood et al. 2020). *Bacillus* and *Pseudomonas* species are the most important biocontrol strains used in commercial products. The former because of their ability to produce resistant and long-lasting endospores, which facilitates formulation and shelf life, and the latter because they are often found in relatively high abundance in the phyllosphere (the aboveground surface of plants) and several are known as antagonists of plant pathogens. Extensive information on all pest antagonistic activities of *Bacillus* and *Pseudomonas* for plant protection can be also found in the reviews of Fira et al. (2018) and Dimkić et al. (2022).

The bacterium *Bacillus thuringiensis* (Bt) is often used as a biocontrol strategy, both outdoors and under glass, to control the larvae of harmful butterflies. Bt products are particularly important in vegetable and ornamental crops, where they can be very well combined with pest behavior manipulation strategy known as the push–pull–kill system, through the use of semiochemicals (see also Fig. 3B). Here, the (insect) pest is attracted by an encapsulated attractant and killed by a Bt product as toxic compound (Schünemann et al. 2014; Valtierra-de-Luis et al. 2020). Bt toxins, when ingested by the insect, damage the intestinal tissue, leading to intestinal paralysis and death by starvation. *Bacillus subtilis, Bacillus cereus, Bacillus atrophaeus, Bacillus velezensis, Bacillus mojavensis, Bacillus amyloliquefaciens* and others have also been extensively studied as biocontrol agents for the control of both fungi and bacteria. Their effectiveness has been demonstrated against various pathogens, including *Fusarium graminearum* (Wang et al. 2015), *Botrytis cinerea* (Cheng et al. 2023), *Botryosphaeria dothidea* (Mu et al. 2020), *Colletotrichum coccodes* (Wei et al. 2023), *Magnaporthe oryzae* (Ma et al. 2020), *Verticillium dahliae* (Zheng et al. 2011), *Xanthomonas campestris* (Marin et al. 2019), *Pectobacterium carotovorum* (Lim et al. 2013) and *Ralstonia solanacearum* (Seleim et al. 2023).

Additionally to these successes of the genus *Bacillus*, the evaluation of endophytic bacteria of grapevine showed the antagonistic potential of 27 bacterial strains belonging to 13 genera of *Agrobacterium, Arthrobacter, Bacillus, Chryseobacterium, Klebsiella, Kocuria, Pantoea, Pseudomonas, Rahnella, Rothia, Serratia, Staphylococcus and Variovorax* against *Fomitiporia mediterranea* a causal agent of the ESCA disease (Vaghari Souran et al. 2023). These promising results demonstrate the huge potential of bacteria/pathogen interactions in biocontrol.

So far challenges for bacterial-based BCAs are the production and stabilization of live bacteria formulations. Optimizing the drying process is crucial to achieve a longer shelf life and minimize the loss of biocontrol activity (Teixidó et al. 2022).

Antagonistic higher fungi and yeasts

Freimoser et al. (2019), Moosavi and Zare (2020), Palmieri et al. (2022), Peng et al. (2021) and Thambugala et al. (2020) provide a thorough analysis of the subject matter. Fungus-based BCAs demonstrate significant potential for pest management, particularly in controlling insect populations. Problematic insects such as hay bugs and locusts can be effectively addressed with fungi, such as *Entomophaga* and *Beauveria* sp., as well as the chitin-degrading *Metarhizium* sp. (Bhadani et al. 2022; Clancy et al. 2018; Hajek et al. 2021). These fungi have been successfully used in Africa, the USA and Canada, as their spores can germinate and penetrate the exoskeleton of the insect to feed on the internal tissue. The use of fungi of the genus *Trichoderma* against microbial root pathogens has also been described and implemented in numerous products. The main *Trichoderma* species effective in the control of soilborne fungal pathogens are *T. asperellum*, *T. atroviride*, *T. hamatum*, *T. harzianum* and *T. viride* (Alfiky and Weisskopf 2021; Zin and Badaluddin 2020). Mechanisms in *Trichoderma* sp. that counteract plant pathogens include strong mycoparasitism, antibiosis, competition and induced resistance. Other recent examples of pathogenic fungi with potential as biological control agents include *Orbiliales* and *Purpureocillium* sp. for nematode control (Moosavi and Zare 2020), and *Clonostachys* sp. for controlling crown and root rot diseases on major fruit, vegetable and ornamental crops (Lysøe et al. 2017). *Pythium oligandrum* is an oomycete parasite of many fungi and other oomycetes, including *Botrytis*, *Fusarium* and *Phytophthora* sp. (Gerbore et al. 2014). However, there is currently a challenge in determining whether potentially beneficial strains could transform into plant pathogens, and this issue necessitates further investigation (Manjunatha et al. 2022; Pfordt et al. 2020; Sanna et al. 2022).

Regarding yeasts, several species have been registered for use as biocontrol agents (Freimoser et al. 2019). Yeasts are generally used to antagonize plant pathogenic fungi and bacteria due to their competition for nutrients and space. An important application for yeast-based BCA formulations is the control of the post-harvest phase, where the shelf life of fruits and vegetables must be preserved. Here, the yeast-like fungus *Aureobasidium pullulans* seems to be a very good candidate for the control of various post-harvest diseases during storage conditions (Di Francesco et al. 2023). Currently, various yeast strains of *Candida oleophila*, *A. pullulans*, *Metschnikowia fructicola* and *Saccharomyces cerevisiae* are approved in the EU as active substances for PPPs (EU 2023).

Macroorganisms as BCAs

The use of antagonists or beneficial macroorganisms, such as insects, predatory mites and entomopathogenic nematodes, is a viable and environmentally friendly pest control method that can be incorporated into an IPM strategy. The objective is to manage pests while minimizing harm to the environment. Macrobial BCAs are commonly used (a) to safeguard and enhance naturally occurring beneficial organisms, (b) to introduce beneficial organisms for classical biological pest control against immigrating or invasive pests to reduce pest pressure and (c) to manage pests by releasing mass-bred beneficial insects for inundative application. Getanjaly et al. (2015) and (Baratange et al. 2023) presented a list of macroorganisms that can be used in agriculture for the control of insect and weeds. The European and Mediterranean Plant Protection Organization (EPPO), an international organization responsible for cooperation and harmonization in plant protection within the European and Mediterranean region, also provides a list of macroorganisms used in the EPPO region with no or acceptable adverse effects. This list aims to facilitate decision-making on the import and release of macroorganisms within EPPO countries (EPPO 2021). However, it is important to note that beneficial insects require specific ecological principles, such as hedgerows or flower stripes, for deployment and to ensure their survival, especially in open fields and seeded crops (Morandin et al. 2014). Nonetheless, beneficial organisms have effectively implemented in the IPM strategy in numerous practical instances in a controlled environment for several years (Richter 2009). Beneficial insects for insect control can be divided into two groups: predators and parasitoids. Predators are typically larger, free-living and mobile insects that feed on other arthropods. In this group, assassin bugs, ladybirds and other beetles of the orders Coleoptera and Hemiptera are the main predators of aphids, mites and thrips. Predatory mites (*Phytoseiidae*, *Laelapidae* and *Macrochelidae*) are commonly used in commercial biological control products to manage phytophagous mites, thrips and whiteflies in vegetable and ornamental cultivation systems in glasshouses (Knapp et al. 2018). Parasitoids, on the other hand, parasitize different life stages of their host, depending on the species. Entomopathogenic nematodes parasitize a variety of soil-dwelling insects, including the larval forms of moths, butterflies, flies and beetles, as well as adult forms of beetles, grasshoppers and crickets (Shapiro-Ilan and Dolinski 2015). Many insects of the orders Hymenoptera and Diptera, such as parasitic wasps of the families *Sphecidae* and *Ichneumonidae*, are parasitoids of various pupae of Lepidoptera and Coleoptera. The vast majority lay their eggs directly into the body of their host, which the larvae consume after hatching. Recently, success in controlling the highly invasive *Drosophila suzukii* has been achieved in Switzerland and Italy through the use of parasitoid wasps in vineyards (Fellin et al. 2023; Knoll et al. 2017). More investigation is required in this area since the quantity of host/pathogen combinations treated with insecticides today exceeds what can be addressed by beneficial organisms (Baratange et al. 2023). As a final environmentally friendly method of pest control, it is worth mentioning the sterile insect technique (SIT). SIT involves mass rearing, sterilizing male pest insects through irradiation and releasing them in a specific area (Dyck et al. 2021).

BCAs for weed management

One of the greatest challenges in modern agriculture is weed control. Emerging superweeds are developing resistance to many common synthetic herbicides, leading to substantial yield losses and economic damage. However, contrary to expectations, the market for weed biocontrol products is not well developed and has the smallest market share compared to other biocontrol products against insects, bacteria and fungi (Cordeau et al. 2016; Marrone 2021; Razaq and Shah 2021). While BCAs against insect, bacterial and fungal pests have the largest market share, research on BCAs for weed control since the 1980s has failed to demonstrate that there is a significant co-evolution of natural enemy with a host weed (Cordeau et al. 2016; Razaq and Shah 2021). Furthermore, intensive application arises questions about the risk of their transfer to main crops. Today there is no widely used commercial biological herbicide and most BCAs for weed management are sold in countries outside the EU (Bremmer Johan et al. 2021; Roberts et al. 2022). By 2010, unintentional introductions of BCAs for weed control in the EU accounted for all available weed-related BCAs (Shaw et al. 2018). Research and commercialization to date has focused primarily on mycoherbicides, such as strains of fungal genera *Colletotrichum*, *Phoma Puccinia* and *Verticillium*. While formulations containing isolates of *Tobacco mild green mosaic virus* (TMGMV) for the control of *Solanum viarum* and the bacterium *Xanthomonas campestris* for the control of *Poa annua* and *P. attenuata* are the only exceptions (Morin 2020; Roberts et al. 2022). Similarly, some insects feed on unwanted weeds and their seeds. Successful examples here include *Dactylopius opuntiae* for the control of *Opuntia humifusa* and *Opuntia stricta*, cactus pests in the Mediterranean (Mazzeo et al. 2019), and *P. pseudoinsulata* for the control of the weed *Chromolaena odorata* in Africa (Aigbedion-Atalor et al. 2019).

Microbes with activity on plants

In this category, we summarize microorganisms such as bacteria and higher fungi or their consortia (microbiomes) that have a direct positive (beneficial) effect on plant growth and development, and eventually on yield. The scientific focus is currently on the plant microbiome. The term microbiome refers to the totality of microorganisms (including bacteria, fungi and viruses) in a given ecosystem, such as the soil, rhizosphere or aerial organs of a plant (Trivedi et al. 2020). From the regulatory point of view, these microorganisms are classified as microbial plant biostimulants (see Table 1). A plant biostimulant is any substance or microorganism applied to plants with the aim to enhance nutrition efficiency, abiotic stress tolerance and/or crop quality traits, regardless of its nutrients content (European Parliament and Council 2019).

Microbial plant biostimulants are applied to plants in soil or substrate to enhance plant growth, health and resilience (Feldmann et al. 2022). All listed and recognized microbial biostimulants in EU are located under the component material category 7 of Regulation (EU) 2019/1009 (European Parliament and Council 2019). At the moment, only four groups of microorganisms are listed: *Azotobacter* sp., mycorrhizal fungi, *Rhizobium* sp. and *Azospirillum* sp. Preliminary discussions have taken place in the Commission expert group on fertilizing products regarding the future procedure for assessing the safety of microorganisms (European Commission 2023). This could lead to an increase in the number of microorganisms on the list in the near future. Although microbial biostimulants are not classified as direct plant protection products like pesticides, they can still make an indirect contribution to plant protection by enhancing the plant's stress resistance, overall health and vigor Du Jardin (2015). The efficacy of biostimulants can be influenced by various factors, including the type of biostimulant used, the crop species targeted, environmental conditions and application methods employed. Therefore, cultivating sound knowledge and selecting appropriate biostimulants are crucial for effective plant protection. Conducting research and gaining insight into the specific needs of crops are essential for the judicious use of biostimulants in plant protection strategies.

Indeed, an increasing number of reports show that beneficial endophytic bacteria and fungi are characterized by their ability to protect plants from diseases and pests, primarily through their resistance-inducing activity. They also exhibit biostimulatory activity that enhance nutrient availability and uptake, as well as aid in the promotion and development of root and shoot growth. Examples of beneficial rhizosphere microorganisms include arbuscular mycorrhizal fungi (Begum et al. 2019; Etesami et al. 2021) and other fungal and bacterial endophytes (Collinge et al. 2022; Morales-Cedeño et al. 2021; Sharma et al. 2023). A noteworthy example is the *Serendipitaceae* family (from the Basidiomycota division) with the canonical model fungus *Serendipita* (*syn. Piriformospora*) *indica*. These fungi form a mutualistic symbiosis with an unlimited number of land plant species. This confers strong disease and pest resistance to their host plants against a broad spectrum of viral, bacterial, oomycotic and fungal pathogens and insect pests, while also positively affecting plant biomass and yield, suggesting that they bear a strong BCA component (Glaeser et al. 2016; Saeed et al. 2021; Silva et al. 2019). Rather speculative is the possibility to harness microbial symbionts of pests, or attempting to control pests by regulating their beneficial symbionts. Recent work provides insights into the dynamics of microbial–invertebrate colonization and its importance in the development of the host (Dearing et al. 2022; Ganesan et al. 2022, 2023; Janke et al. 2022; Kanyile et al. 2022; Slowik et al. 2023).

Final remarks on BCAs

BCAs' growing popularity is primarily due to their near-natural, eco-friendly approach, which can offer a long-term, sustainable pest control strategy. In addition to such observations, it can be deduced from the articles cited above that BCAs are sometimes very specific (for instance, viruses, Wagemans et al. (2022), or parasitoids Thilagam et al. 2023)—a disadvantage against the broad spectrum of targets of chemical synthetic pesticides, but an advantage in terms of undesired side effects of active agents. Moreover, it has been established that plant pathogens exhibit varying levels of sensitivity toward BCAs, and BCAs may exhibit low efficacy in case of high pathogen pressure (Bardin et al. 2015). Additionally, certain pathogens are capable of adapting quickly to BCAs, a phenomenon observed in chemical synthetic pesticides as well. The direct comparison of efficacy of BCAs and chemical control results in lower efficacy of BCAs (Viteri et al. 2019), but also in comparable efficacy (Hassan et al. 2023) or variable efficacy depending on the strain targeted (Leonardi et al. 2023). To stabilize the efficacy of living organisms several authors recommend to pay more attention to environmental issues and the landscape context (Abd-Elgawad and Askary 2020; Perez-Alvarez et al. 2019; Stiling and Cornelissen 2005).

From an industrial perspective, there is a need for research to broaden the product range through the identification of more effective microorganisms for the control of pests and pathogens. At present, the mode of action of these individual organisms is sufficiently understood only in limited instances and is often based on direct antimicrobial or insecticidal action, whether hyperparasitism or antibiosis (Parratt and Laine 2016). Köhl et al. (2019) take it a step further by questioning whether BCA metabolites could lead to heightened risks. They conclude that only for macrobial BCAs which produce potential antimicrobial metabolites in vitro or during the mass production fermentation process and contain such metabolites in the formulated end product at effective concentration, thorough risk assessment is indicated and the minimal effective concentration against the target and representative nontarget organisms can be established. However, in all other cases, such metabolites are discussed not to be relevant.

Another important but often overlooked aspect is the effectiveness and cost efficiency of combining BCAs with synthetic and non-synthetic chemicals in IPM strategies. This continues to pose a challenge in the adoption of agricultural practices that involve BCAs (Böckmann et al. 2019).

Nature-based substances

In the search for new and environmentally friendly methods to maintain agricultural production, attention is also shifting to bioactive plant extracts, compounds of plants, insects or other organisms, and of minerals. These non-living, nature-based substances (NBSs) are used in plant protection and can be classified and utilized in various ways. Derived from natural sources, they can provide alternative methods for pest management in agriculture. NBSs are often viewed as environmentally friendly alternatives to chemical synthetic pesticides, promoting sustainable agriculture and reducing environmental impact. However, their efficacy may vary depending on factors such as application methods, timing, dosage and specific pest or disease being targeted. Biominerals and biofertilizers as mineral-based substances like rock powders, such as rock phosphate or limestone, can be used as soil amendments or biominerals to enhance soil fertility, which indirectly supports plant health and resilience against diseases. Figure 3 is a schematic representation of the most common NBSs and how they are classified.

Mineral-based substances

Mineral-based substances (see Fig. 3A) are commonly used in plant protection as natural alternatives to synthetic pesticides. These substances can have pesticidal properties or aid in enhancing soil health, resulting in indirect promotion of plant protection. Hereafter, we will discuss various methods for using mineral-based substances.

(a) Fungicides and bactericides: minerals like potassium hydrogen carbonate, sulfur and copper are used as fungicides and bactericides to control various fungal and bacterial diseases in plants. They function through unspecific toxicity, disrupting the growth and development of pathogens or inhibiting their reproductive cycles (Bloem et al. 2005, 2014; Gomes et al. 2020; La Torre et al. 2018; Santos et al. 2011).

(b) Insecticides and repellents: diatomaceous earth and quartz sand are both white powders composed of fossilized remains of diatoms with a very high SiO_2 content. They possess abrasive properties that harm the exoskeletons of insects, leading to their dehydration and subsequent demise. These powders are typically applied to travel routes and hiding places of crawling insects and are commonly used as insecticides and physical barriers (Rojht et al. 2011; Shah and Khan 2014; Zeni et al. 2021).

(c) Soil amendment: rock powders such as rock phosphate and limestone are used to improve soil structure, pH balance and nutrient availability. Healthy soils contribute to better plant growth and disease resistance. On the other hand, they can be applied to leaves as biocontrol agents (Faraone et al. 2020; Ramos et al. 2022).

(d) Physical barrier: kaolin clay can be used as a protective film against pests and sunburn in fruit crops. It acts as a physical barrier, protecting plants from insect feeding damage and excessive heat (Bestete et al. 2018; Silva and Ramalho 2013).

Mineral-based substances are often favored in both organic farming and IPM strategies due to their lower environmental impact compared to chemical synthetic pesticides. They can be utilized for both preventative and intervention measures. However, it is essential to consider factors such as appropriate application methods, dosage and potential environmental effects when using mineral-based substances for plant protection. Additionally, adherence to regulations and guidelines regarding their use is crucial to ensure their safe and effective application in agriculture.

Botanicals

A botanical active substance ‘consists of one or more components found in plants and obtained by subjecting plants or parts of plants of the same species to a process such as pressing, milling, crushing, distillation and/or extractions. The process may include further concentration, purification and/or blending, provided that the chemical nature of the components is not intentionally modified/altered by chemical and/or microbial processes’ (European Commission 2014; OECD 2017). In the EU, botanicals (see Fig. 3A) undergo the same approval process as chemical synthetic pesticides with some exceptions in the data requirements outlined in the cited guidance document (European Commission 2014).

The potential of botanicals in plant protection for pest control has been highlighted in numerous scientific studies (Acheuk et al. 2022). However, the large variety of active ingredients present in plant extracts creates challenges for product registration. Currently, only a small number of botanical active substances have received EU approval, in contrast to the USA, Brazil or Australia (IBMA 2022). For instance, the triterpene azadirachtin the major constituents of neem oil, derived from the seed of the neem tree (*Azadirachta indica*), acts as an insecticide and repellent. It disrupts the growth and development of insects, repels insect pests and has antifeedant properties against certain insects (Campos et al. 2016; Semere 2023). Another example, pyrethrum, extracted from dried flowers of certain chrysanthemum species (*Chrysanthemum cinerariifolium* or *Tanacetum cinerariifolium*), contains pyrethrins that have insecticidal properties and are effective against a wide range of insects, including undesired effects against bees (Souto et al. 2021). Various essential oils derived from plants, such as peppermint, thyme, clove or garlic oil, possess pesticidal properties and they can act as insecticides, repellents or fungicides against pests and diseases (Assadpour et al. 2023), and can have a nematicidal effect (Catani et al. 2023).

Currently, botanical and phytotoxins, such as essential oils, appear to be the most efficient agents for the biocontrol of weeds (Acheuk et al. 2022). Roberts et al. (2022) discuss the topic in depth, including commercial products available on the market today. Marrone (2023) takes a more market-oriented approach to the topic and provides future prospects for weed control. The efficacy of alternatives to herbicidal compounds is greatly affected by weather and temperature fluctuations, and other constraints including specific requirements for maintaining the activity and efficacy of the active ingredients, which necessitates the development of specific formulations. Nevertheless, their long-term and repeated use in agricultural and natural ecosystems requires further research. Some products available on the EU and US markets use as key ingredients organic compounds, such as acetic, citric or pelargonic acids, essential oils derived from rapeseed, citrus plants, and clove and phytotoxin such as thaxtomin from the bacterium *Streptomyces ascidoscabies* (Pannacci et al. 2017).

However, it is important to note that botanicals can have undesired side effects. Rotenone, for example, obtained from the roots of various tropical plants (such as *Derris* and *Tephrosia* sp.), acts as an insecticide and piscicide (poisonous to fish) and is, therefore, toxic for the environment. It affects the nervous systems of insects and pest and is possibly supporting the development of Alzheimer diseases in humans (Bisbal and Sanchez 2019). Nicotine, derived from the tobacco plant (*Nicotiana tabacum*), was historically used as an insecticide (Jacobson 1989). Its use is now restricted due to its high toxicity to humans and nontarget organisms like bees.

This compilation illustrates the peculiar characteristics of botanicals and emphasizes the importance, in some cases, of an approval process followed by post-authorization monitoring for botanical active substances and their applications. Botanical application conforms to the principles of IPM and organic cultivation. However, it is worth noting that although botanical pesticides originate from natural sources, their effectiveness, safety and appropriate application require careful deliberation and adherence to guidelines, to minimize hazards to the environment and nontarget organisms.

Basic substances

In the EU, basic substances are substances of no concern and cannot be placed on the market as PPPs (see Fig. 3A). In recent years, most requests for approval of basic substances for use in agriculture have been typically submitted by organizations or institutions that are involved in organic farming (Marchand 2017).

Costantini and La Torre (2022) wrote an excellent work on the regulatory situation of basic substances and the current state of the art about their availability from plant origin (*Equisetum arvense* L., sucrose, vinegar, lecithins, *Salix* sp. cortex, fructose, sunflower oil, *Urtica* sp., beer, mustard seeds powder, onion oil, *Allium cepa* bulb extract and clayed charcoal), animal origin (L-cysteine, chitosan hydrochloride, whey and cow milk) and inorganic-based (calcium hydroxide, sodium hydrogen carbonate, diammonium phosphate, hydrogen peroxide, talc E553B and sodium chloride). According to the EU pesticides database (EU 2023), *Equisetum arvense*, calcium hydroxide, vinegar, lecithins and *Salix* sp. cortex have been approved as fungicides. Extracts of *Allium* and *Urtica* sp. have also been permitted as insecticide and acaricide. Whey can be used as a virucide, sodium hydrogen carbonate and vinegar as herbicides and beer as a molluscicide. Chitosan hydrochloride may be applied as elicitor of pattern-triggered immunity (PTI). Diammonium phosphate as an attractant, clayed charcoal as a protectant, Talc E553B as an insectifuge and fungifuge. Finally, onion oil can be employed as a repellent. Overall, Toffolatti et al. (2023) found, after a thorough review, that basic substances and potential basic substances can be effective means for managing diseases. In addition, Romanazzi et al. (2022) assert that basic substances are a valuable tool which complements IPM options. The efficacy assessment of basic substances is not part of the approval process and no national risk assessment of products takes place.

Semiochemicals

The website https://pherobase.com/ (El-Sayed 2023) is an excellent tool to convey scientific data and knowledge from the literature into electronically searchable database entries, organized by compounds, species or application measures.

Semiochemicals encompass both pheromones and allelochemicals and play a crucial role in safeguarding plants through affecting the behavior of pests, such as impeding their mating, or even driving them away (Fig. 3B). Semiochemicals can be used for:

(a) Trapping and monitoring: via nature-based pheromones in traps to monitor and control pest populations (Alam et al. 2023; Staton and Williams 2023). Pheromone-baited traps attract male insects by mimicking female pheromones, helping to monitor pest levels and determine the best timing for control measures. Pheromones can be employed also in mass trapping strategies, where a large number of pests are lured into traps and killed, reducing their population density and minimizing damage to crops (Alam et al. 2023; Dalbon et al. 2021).
(b) Mating disruption through saturation of an area with synthetic pheromones, which confuses the male insect and prevents him to locate the female for mating (Franco et al. 2022). When implemented and timed correctly, this method could aid in curbing the proliferation of pests, minimize crop-related harm and potentially supplant usage of alternative pesticides (Thiery et al. 2023). The method can be implemented in areawide IPM strategies, especially aimed at managing pests that infest stored products (Morrison et al. 2021). Tailored semiochemicals for specific pests provide a precise and species-specific method of pest management.
(c) In the field, push–pull strategies use semiochemicals where repellent chemicals (push) are used to drive pests away from crops, whereas attractive chemicals (pull) lure pests toward traps or alternative host plants, resulting in decreased harm to the primary crop (Chatterjee and Kundu 2022).

The utilization of semiochemicals is in line with the IPM approach as it diminishes dependence on typical pesticides, therefore promoting more sustainable methods of pest control. When compared to the application of broad-spectrum chemical pesticides, the use of semiochemicals minimizes adverse impacts on nontarget organisms, beneficial insects and the environment.

Additionally, semiochemicals have the potential to enhance the efficacy of biological control agents by luring pest predators to the affected region, thereby facilitating natural pest management. However, the efficacy of semiochemical-based pest management techniques can be influenced by various factors such as pest species, crop type and environmental conditions. Therefore, it is imperative to exercise meticulous monitoring, employ appropriate application methods and possess a comprehensive knowledge of the target pest's biology for the successful implementation of these techniques.

Bacterial rhamnolipids and lipopeptides

A small, often ignored class of molecules with high agricultural efficacy and economic viability for industrial production, capable of stimulating plant growth and resistance, are rhamnolipids and lipopeptides (Fig. 3B) (Monnier et al. 2018; Raouani et al. 2022). A large number of studies have described their antimicrobial activities against plant pathogens (see review by Crouzet et al. 2020). Rhamnolipids are glycolipids produced by several bacterial species, including some *Pseudomonas* and *Burkholderia* sp., while lipopeptides are mainly produced in cyclic form by *Bacillus* and *Pseudomonas* sp., compared to other molecules, their antimicrobial activity is well understood. The double-layer cell membrane is destabilized by the interaction with these molecules, resulting in cell lysis. As mentioned above, in addition to their antimicrobial properties, rhamnolipids and lipopeptides also induce local and systemic resistance to plant pathogens, although the mode of action here remains unclear. In short, these molecules have similar dual effects, protecting plants through antimicrobial properties and stimulating plant immunity, which are perfect properties for a biocontrol substance. However, before they can be approved and deployed as active ingredients in biocontrol formulations, their mode of action needs to be fully understood, which could significantly delay their use in the field.

Double-stranded and circular RNA

The use of RNA for plant disease and pest control is at a very early stage, and basic research is still required to unravel the full potential (Cai et al. 2018a; Hossain et al. 2023; Nitnavare et al. 2021). At this stage, the potential of RNA, including long noncoding RNAs, short dsRNA duplexes and circular RNAs (see Fig. 3A), to control plant pests (insects, nematodes) and microbial pathogens (especially viruses) appears promising, although a direct proof of its practical importance in this field is still pending (Liu et al. 2020; Mezzetti et al. 2020; Qiao et al. 2021; Zotti et al. 2018). The molecular mechanism of action of dsRNA in target organisms is largely but probably not entirely (Huang et al. 2023; Niehl and Heinlein 2019) based on RNA interference (RNAi), a naturally occurring, conserved mechanism of gene regulation in eukaryotes (Baulcombe 2023). A strong argument in favor of the RNA technology in IPM is the finding that the exchange of RNA is a natural mechanism during the colonization of hosts (plants and animals) by colonizing microorganisms and pests (Buck et al. 2014; LaMonte et al. 2012; Weiberg et al. 2013). In this natural process, microorganisms use small RNA duplexes (so-called RNA effectors) to weaken their host defense system (immune system) and thus support host colonization and disease. From an agronomic perspective, it is particularly interesting that plants also produce RNA effectors (mostly microRNAs, Šečić et al. 2021) to weaken the virulence of pathogenic microorganisms, which occurs through the targeted degradation of microbial mRNA by the plant RNA effector (Cai et al. 2018b; Zhang et al. 2016). The use of dsRNA to protect crops by topical application (spray-induced gene silencing [SIGS] method; Koch et al. 2016) appears attractive because the method is very flexible in terms of technology and regulatory aspects and can be rapidly adapted to different pests and diseases (Liu et al. 2020; Mann et al. 2023; Rosa et al. 2022; Taning et al. 2021; Wang and Jin 2017). Foliar application of dsRNA has been shown to protect potato plants from Colorado potato beetle larvae, and Ledprona (the first SIGS-based dsRNA active ingredient targeting *proteasome subunit beta 5*) has been approved for registration as a biopesticide product by the US Environmental Protection Agency for a three-year period (Rodrigues et al. 2021). A list of HIGS- or SIGS-based agricultural products that are currently available on the market or awaiting national approval is given in Table 2.

However, unlike in the USA where dsRNA is classified as biochemical pesticides, the registration process for non-GMO dsRNA-based PPPs in Europe follows, at the time of this review, the same regulations as chemical PPPs. With SIGS-based PPPs under development, there is a need to address regulatory and biosafety concerns to establish a suitable framework and risk assessment process for these products (CAST 2024; Dietz-Pfeilstetter et al. 2021; De Schutter et al. 2022). Notably, first considerations have been presented by the Organization for Economic Co-operation and Development (OECD 2020, 2023). These publications provide a comprehensive set of recommendations dealing with the potential hazards of exogenously applied dsRNA-based products for nontarget organisms, including humans. Currently, a high potential of dsRNA is seen in horticultural cultures under glass, as the application can take place there under well-controlled climatic conditions. Here a key to application is the development of efficient drug formulations that are suitable for improving the uptake of RNA by the target organisms (Mitter et al. 2017; Niño-Sánchez et al. 2022; Qiao et al. 2023; Wytinck et al. 2020). In the state of the art, a large number of RNA formulations have been published in recent years, but their increased efficacy has hardly been demonstrated.

Priming is one important mode of action of NBS

A promising and sustainable strategy in IPM is the use of NBS with resistance-inducing activity (Induced Resistance Primers, IRPs) that trigger defense *priming* (Cooper and Ton 2022; Iriti and Vitalini 2021; Perazzolli et al. 2022). Priming agents can be compounds such as botanicals, basic substances and semiochemicals (Görlach et al. 1996; Klessig et al. 2018; Kogel et al. 1994; Manosalva et al. 2015; Sauerborn et al. 2002; Schenk et al. 2014) (see Fig. 3A). An obvious agronomic advantage is often that individual IRPs are doubly effective, activating the plant immune system while improving plant growth (Waller et al. 2005).

Examples of successful natural priming compounds are the polysaccharides chitosan, a deacetylated chitin derivative that was first approved as an active ingredient in 1986 (Iriti and Faoro 2009) and tramesan from the fungus *Trametes versicolor* (Scala et al. 2020) (see Fig. 3B). Very promising for broad applications as IRPs are semiochemicals such as ascarosides isolated from nematodes (Kamboj et al. 2024; Manosalva et al. 2015) and N-acyl homoserine lactones (AHLs) isolated from a range of nonpathogenic bacteria (Shrestha and Schikora 2020) that modulate quorum sensing in nematodes and bacteria, respectively. Interestingly, priming agents can also be applied directly to the seed (seed dressing or coating), which can be particularly useful in the early stages of plant growth when plants are at their most vulnerable stage of development (Paparella et al. 2015; Walters et al. 2013; Yang et al. 2022). Reviews summarizing the main aspects regarding screening, testing, production, packaging and shelf life of priming-activating biocontrol agents are Raymaekers et al. (2020) and Teixidó et al. (2022).

In conclusion, although using IRPs overall seems to be very promising it is important to note that their mode of action remains to be elucidated, and recent research suggests the involvement of both genetic and epigenetic mechanisms (Mauch-Mani et al. 2017; Nguyen et al. 2020; Perazzolli et al. 2022), and while a significant proportion of university-based phytopathology research in EU and the USA has focused on exploring IRP strategies for crop protection since the early 1990s, the range of effective PPPs based on these agents is still very small.

The future of biocontrol in IPM

Biocontrol as a predominant component of plant protection measure

Overall, it is clear that alternative measures to chemical synthetic pesticides are necessary to prevent declining efficiency in agricultural production (Goulet et al. 2023). The details that determine the size of farms, the number of crops per

Table 2 List of HIGS- and SIGS-based commercial applications available on the market or awaiting national approval

Product	Developer	RNAi target organism	RNAi target gene[a]	Availability for cultivation	References
HIGS-based commercial applications					
Huanong No. 1	South China Agricultural University	*Papaya Ringspot Virus* (PRSV)	*Nib*	China	Li et al. (2007)
New Leaf Plus Russet Burbank	Monsanto (Bayer)	*Potato Leaf Roll Virus* (PLRV)	*Plrv-orf1* and *plrv-orf2*	CA and USA	ISAAA—GM Approval Database[b]
Innate Acclimate	J.R. Simplot Co	Potato (*Solanum tuberosum*)	*Asn1*, *ppo5*, *PhL*, *R1* and *Vlnv*	CA and USA	‘’
Arctic	Okanagan Specialty Fruits Inc	Apple (*Malus domestica*)	*Ppo5*	CA and USA	‘’
Super High Oleic (SHO)	Go Resources Pty Ltd and CSIRO	Safflower (*Carthamus tinctorius*)	*FatB* and *fad2-2*	AU	Wood et al. (2018)
HarvXtra	Monsanto (Bayer) and Forage Genetics International	Alfalfa (*Medicago sativa*)	*CCoAOMT*	CA, JA and USA	Barros et al. (2019)
FLAVR SAVR	Monsanto (Bayer)	Tomato (*Lycopersicon esculentum*)	*Pg*	USA	ISAAA—GM Approval Database[b]
Vistive Gold	Monsanto (Bayer)	Soybean (*Glycine max*)	*Fatb1-A* and *fad2-1A*	CA, JA and USA EU: all uses except agriculture	‘’
Treus Plenish	Pioneer Hi-Bred International and DuPont	Soybean (*Glycine max*)	*fad2-1*	CA, JA and USA EU: all uses except agriculture	ISAAA—GM Approval Database[b]
PinkGlow/Rosé	Del Monte Fresh Produce Company	Pineapple (*Ananas comosus*)	*β-lyc* and *ε-lyc*	Costa Rica CA and USA: all uses except agriculture	‘’
SmartStax Pro	Bayer Crop Science	Western corn rootworm (*Diabrotica virgifera virgifera*)	*Snf7*	BR, CA, China, JA and USA EU: all uses except agriculture	‘’ De Schutter et al. (2022)
VT4 Pro	Bayer Crop Science	Western corn rootworm (*Diabrotica virgifera virgifera*)	*Snf7*	USA: commercialization in 2024	Bayer Crop Science[c]
Product	Developer	RNAi target organism	RNAi target gene**/info	Availability for cultivation	Reference
SIGS-based commercial applications					
BioClay	Sustainable Crop Protection ARC HUB	Multiple, including fungal and virus pests	Formulation	AU: field trials since 2017	Mitter et al. (2017)
Ledprona (Calantha)	GreenLight Biosciences	Colorado potato beetle (*Leptinotarsa decemlineata*)	*PSMB5*	USA: registration approved for 3 years	Rodrigues et al. (2021); EPA (2023)[d]
GS15	GreenLight Biosciences	*Varroa destructor*	*- not disclosed -*	USA: EPA submission planned for 2023	GreenLight Bioscience, 2022[e]
Yeast-based RNAi	Renaissance BioScience Corp	Multiple, including Colorado potato beetle	Platform	CA: approval field testing in 2023	Renaissance BioScience[f]

[a]See end of the table for full gene name

[b]https://www.isaaa.org/gmapprovaldatabase/eventslist/default.asp

[c]https://www.bayer.com/en/vt4pro

[d]https://www.epa.gov/pesticides/epa-registers-novel-pesticide-technology-potato-crops

[e]https://greenlightbiosciences.com/wp-content/uploads/2022/08/GreenLight-investor-presentation-August-2022.pdf

[f]https://www.renaissancebioscience.com/corporate/renaissance-bioscience-s-novel-rnai-biopesticide-technology-receives-canadian-regulatory-approval-for-2023-field-studies

*Full gene names: *Asn1*: *glutamine-dependent asparagine synthase 1*; *Plrv-orf1*: putative *replicase* domain of PLRV; *CCoAOMT*: *caffeoyl-CoA 3-O-methyltransferase*; *Plrv-orf2*: *putative helicase* domain of PLRV; *Fad2-2*: *fatty acid desaturase 2 sub. 2*; *Ppo5*: *polyphenol oxidase 5*; *Fad2-1A*: *fatty acid desaturase 2 sub. 1A*; *R1*: *alpha-glucan, water dikinase 1*; *FatB*: *fatty acyl-acyl carrier protein thioesterase B*; *Snf7*: *sucrose non-fermenting 7*; *FatB-1A*: *fatty acyl-acyl carrier protein thioesterase sub. 1A*; *Vlnv*: *vacuolar acid invertase*; *Nib*: *nuclear inclusion b RNA-dependent RNA polymerase*; *β-lyc*: *lycopene β cyclase*; *Pg*: *polygalacturonase*; *ε-lyc*: *lycopene ε cyclase*; *PhL*: *phosphorylase L*

**Full gene names: *Psmb5*: *Proteasome subunit beta 5* farm and the cultivation strategies play a crucial role in this regard (Galluzzo 2023; Palmisano 2023).

Following the common classification of IPM, we have placed biocontrol within the realm of 'interventions' in IPM (Fig. 1). The first major issue in replacing chemical synthetic pesticides with biological measures is the need to increase the number of applications and targets for biologicals. Currently, there is a significant disparity between the approved uses of chemical synthetic pesticides and biological agents. In the EU member states, it is estimated that only about 15% of all pairing of crop and pest have also a biocontrol agents approved (in Germany, approximately 2600 out of 19,600 interactions or 'uses'; BVL 2023). These values do not yet include 'control gaps'—when a control method for a specific pest does not exist. Exact figures are only published by each member state in their own national language and can be challenging to research.

However, it is important to note that this comparison only considers botanicals, microorganisms and semiochemicals, as their authorisation is linked to an assessment of 'sufficient efficacy.' Other NBSs, such as basic substances, which are no plant protection products but possess some useful characteristics in IPM, do not undergo efficacy assessments. The same applies to macroorganisms and biostimulants. Therefore, to consider the possibility of being a game-changer in IPM, the qualitative aspect of all biocontrol measures should be investigated and included alongside the quantitative evaluation.

Agricultural systems must be redesigned to favor biocontrol applications

The IPM approach combines a wide range of phytosanitary measures, primarily integrating direct intervention measures with preventive and monitoring measures (Fig. 1). While the monitoring measures support the decision-making process regarding the timing of intervention, the preventive measures, such as the choice of resistant varieties, are crucial to minimize the use of synthetic chemical products in the field. Similarly, field preparation, choice of cropping system based on specific environmental conditions and crop rotation can all help to avoid disease and pest pressure and thus reduce a pesticide use. At its best, if the above measures are applied, intervention with synthetic chemical products is only necessary when factors such as pest pressure or weather change unexpectedly.

The biological control toolbox is very diverse (Figs. 2 and 3), as we have shown in this brief overview, and most of the elements mentioned are already essential components of crop protection in organic farming (European Parliament and Council 2018). Organic farming has so far demonstrated that the IPM approach can work without synthetic chemical PPPs (Niggli et al. 2017). However, yields and production in organic farming are still strongly influenced by the weather and temperatures during the year (Muller et al. 2017), affecting the amount and quality of products (Knapp and van der Heijden 2018; La Cruz et al. 2023; Meemken and Qaim 2018; Ponisio et al. 2015; Ponti et al. 2012). Moreover, mineral-based substances (see Fig. 3A), especially copper, have so far proved to be irreplaceable while they have a detrimental impact on the biodiversity of cultivated areas, as evidenced, for example, by beetle populations in vineyards (Kaczmarek et al. 2023). In recent years, organic agriculture has been under significant political and social pressure to reduce costs and make its products more competitive on the market. In individual cases, production is already competitive, as demonstrated by olive production in Turkey (Dal and Karaçetin 2023). Here, as it has been widely observed in other crops, the emergence of 'mixed green covers' (groves with mixed vegetation) fosters naturally occurring beneficial macroorganisms, reducing the need for their costly rearing and application (González-Ruiz et al. 2023). In other production systems, both organic and conventional farming, the concept has been implemented for years through the use of flowering strips (Albrecht et al. 2020, 2021). When indigenous flora are utilized, it is referred to 'conservation biological control' (Zaviezo and Muñoz 2023). These regenerative methods are applied to enhance soil quality and enabling effective symbiosis, for example, with biostimulants such as mycorrhizal fungi (Sun and Shahrajabian 2023). In the above-mentioned processes, the biocontrol method entails adjusting and adapting the cultivation system, with the ultimate objective of establishing and maintaining living BCAs as sustainably as possible.

Agroecology and IPM share several principles and approaches that complement each other. Some aspects of agroecology in sensu Altieri (2000) and Altieri and Farrell (2018) are already integrated into IPM and include biodiversity enhancement, reduced chemical inputs, crop rotation and polycultures, cultural control, considering the entire agroecosystem, and community engagement and knowledge sharing.

The redesign of production systems should follow the area wide management principles (Vreysen et al. 2007a; Vreysen et al. 2007b). Agroecological-oriented areawide pest management involves integrating ecological principles across larger landscapes to manage pests sustainably (Brewer and Elliott 2023). This approach can significantly contribute to redesigning conventional agriculture in several ways, including connecting green infrastructure (Aviron et al. 2018), inter-row vegetation (Blaise et al. 2021), seminatural habitats in the near of agricultural areas (Bartual et al. 2019), consideration of birds (Garfinkel et al. 2020) and other taxa in order to expand the range of biocontrol agents (Gurr 2018) and to realize a food web approach (Herrera et al. 2021).

Overall, maintaining spatial, temporal and genetic diversity is a classic but crucial measure to reduce pathogen pressure in the soil, control weed populations and can also be beneficial for soil fertility and maintaining closed nutrient cycles. By integrating agroecological principles into IPM practices, agricultural systems can become more sustainable, resilient and environmentally friendly while effectively managing pests and maintaining crop productivity. From the view of plant protection, the aim is to strongly strengthen the knowledge of biological disease mechanisms, including the function of soil and plant microbiomes, and foster the holistic agroecological understanding as a prerequisite to integrate and adapt various biocontrol methods into the cultivation system based on the application of BCAs and NBS (see Figs. 2 and 3). It is essential to gain a comprehensive understanding of effectively integrating these innovative technologies into current plant production practices to achieve desired outcomes for plant production, environmental sustainability and human health.

Biocontrol products require new and dedicated legislations

Legislative adaptations are vital in supporting and promoting biocontrol methods in agriculture.

To achieve the EU's 2030/50 objectives, the regulatory framework for biocontrol must be explicitly supportive, with regulations that are specifically designed to streamline their registration and approval procedures. Currently, these frameworks heavily focus on the registration and marketability of chemical synthetic pesticides, neglecting the distinct attributes of biocontrol agents.

Developing and integrating biocontrol agents into the agricultural system require the essential establishment of risk and hazard assessment methodologies to evaluate their safety and efficacy. However, it is imperative to distinguish between biocontrol agents and chemical synthetic pesticides and acknowledge their inherent distinctions in ecological impact, nontarget effects and compatibility with established ecosystems. This should qualify most biological PPPs to have a low risk profile.

Tailoring data requirements for registration to fit the nature of biocontrol products could expedite their approval and stimulate additional research within the biocontrol sector. This includes enabling alternative testing methodologies that align with the intrinsic biological and ecological characteristics of biocontrol agents rather than adhering to chemical pesticide standards. For example, the ‘precautionary principle’—protect environment, human, animal and plant health (Commission communication COM (2000) 1 final)—should be reflected by including also the probability of exposure to the agent under study (European Commission 2000).

Evaluation of basic substances should also be reconsidered. As discussed in previous chapters, basic substances are active substances that are not primarily used as crop protection products, but may be of value in crop protection. At the time of this review, basic substances are only authorized as active substance and not as products; thus, their efficacy is not evaluated. Today, legally binding Good Agricultural Practices (GAP) tables are published together with the authorization of basic substances. GAP-tables outline the procedures that must be implemented for the use of pesticides. They should include the officially recommended or nationally authorized uses of pesticides under the actual (zonal) conditions needed for reliable and effective pest control (FAO 2023). In case of basic substances, the basis for these explicit GAP-tables is not transparently included in the decision. We recommend to lay down only the critical or maximum GAP related to the risk assessment in decisions. Today, the decision leading to the exclusion of basic substances and the risk assessment are neither publicly available nor publicly searchable. This uncertainty about the quality of basic substances leads to their avoidance, not only in-home gardens but also in crop fields, and hinders the development of integrated processes including new basic and biological substances.

Adapting legislation to accommodate the unique characteristics and requirements of biocontrol products will promote a supportive and self-sustaining environment for their development, registration and adoption, thus facilitating sustainable pest management practices in agriculture in the future.

The importance of education and training in biocontrol

Sustainable agriculture does not rely solely on a linear process that merely involves scientific knowledge production and its subsequent application. Rather, it is an intricate outcome of multifaceted interactions that occur between diverse entities and institutions during different stages of research, development and deployment, at varying sociological levels. Therefore, critical to the success of biocontrol is the involvement, training and guidance of direct and indirect users (Calliera and L’Astorina 2018). The education of specialists in various professional fields is at risk in several regions and requires adequate reinforcement. This includes training at vocational schools, as well as master's and technician's schools, universities and colleges. Although certification programs and comparable training sessions currently exist, they should be more heavily focused on biocontrol and its applications. At the same time, there is a need to optimize knowledge transfer to direct users and provide more individualized advice programs. Producers who are transitioning to a sustainable-based crop protection system should not be left unsupported but instead be provided with high-quality guidance that understands the complexity of the transition and provides practical instructions.

If we wish to utilize a production system that relies on biocontrol, avoiding the overuse of chemical synthetic pesticides, then we must also take responsibility and support this approach to production. A practical example to follow in this respect could be the experience gained in the organic farming sector. Organic farming is governed by specific regulations and certification processes which are vital 'success factors.' Moreover, it has its own team of advisors who play a significant role in the success and transformation of the farms.

Conclusion

Incorporating biocontrol agents into IPM strategies on farm allows for the use of multiple pest control tactics, such as cultural, biological and physical controls. This, in turn, lessens dependence on chemically synthesized inputs while maximizing overall effectiveness. This is particularly crucial in the horticultural industry where numerous crops lack legally approved chemical synthetic PPPs. Additionally, the issue of residues on harvested produce hold great significance due to the short interval between harvesting and consumption. Such conditions are pushing the expansion of alternative methods, although chemical synthetic PPPs remain more cost-effective than the new alternatives and the process of transforming the plant production system. At a large-scale field level, promoting field management with diverse habitats and ecosystems, biocontrol fosters biodiversity, establishing conditions in which indigenous predators and helpful microorganisms flourish. This approach lessens pest pressure, without relying only on chemical synthetic pesticides, helps maintain a balance between pests and their natural enemies and in turn decreases the potential danger to both human and animal health. Biocontrol enables the achievement of quality standards in plant production, such as durability and freedom from secondary pests, that cannot be attained solely by relying on chemical synthetic pesticides.

While initial adoption costs may be higher, long-term benefits of biocontrol, such as reduction of chemical pesticide purchases, preserving soil health and maintaining ecosystem services, will improve the economic sustainability of farming operations in the future.

Undoubtedly, biocontrol has the potential to be a game-changer in IPM by significantly reducing reliance on chemical pesticides, provided that we respect socioeconomic demands and scientific options.

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Declarations

Conflict of interest The authors disclose any conflicts of interest.

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