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REVIEW

Engineering the future of *Physalis grisea*: A focus on agricultural challenges, model species status, and applied improvements

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Societal Impact Statement

Groundcherry (*Physalis grisea*) is a plant species grown for its flavorful fruit. The fruit drops from the plant, hence the common name groundcherry. This makes harvest cumbersome and puts the fruit at risk for carrying soil-borne pathogens, therefore making them unsellable. Furthermore, insects often damage the plants, reducing yield. Advances in gene editing offer promise for addressing these issues and aiding home gardeners and farmers. Improvement will expand access to this nutritious fruit, rich in potassium, vitamin C, and antioxidants. Additionally, studies of its biology could serve as a model for improving other fruiting plants, particularly underutilized species.

Summary

P. grisea is an underutilized, semidomesticated fruit crop with rising agronomic value. Several resources have been developed for its use in fundamental biological research, including a plant transformation system and a high-quality reference genome. Already, *P. grisea* has been used as a model to investigate biological phenomena including inflated calyx syndrome and gene compensation. *P. grisea* has also been used to demonstrate the potential of fast-tracking domestication trait improvement through approaches such as CRISPR/Cas9 gene editing. This work has led to the *Physalis* Improvement Project, which relies on reverse genetics to understand the mechanisms that underlie fruit abscission and plant–herbivore interactions to guide approaches for improvement of undesirable characteristics. CRISPR/Cas9 gene editing has been used to target *P. grisea* genes that are suspected to act in fruit abscission, particularly orthologs of those that are reported in tomato abscission zone development. A similar approach is being taken to target *P. grisea* genes involved in the withanolide biosynthetic pathway to determine the impact of withanolides on plant–herbivore interactions. Results from these research projects will lead to a greater understanding of important biological processes and will also generate

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Savanah Marie Dale and Elise Tomaszewski both contributed equally.

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knowledge needed to develop cultivars with reduced fruit drop and increased resistance to insect herbivory.

KEYWORDS
domestication, CRISPR, fruit abscission, genetic engineering, insect interaction, *Physalis grisea*, underutilized species

1 | INTRODUCTION

1.1 | Characteristics, culinary uses, and historical significance of *P. grisea*

Physalis pubescens var. *grisea* (*P. grisea*), commonly known as groundcherry, is a fruiting plant species that is related to other popular solanaceous crops including tomato (*Solanum lycopersicum*), potato (*Solanum tuberosum*), and pepper (*Capsicum annuum*) (Martínez et al., 2023a; Pretz & Deanna, 2020; Wilf et al., 2017). *P. grisea* fruits are small, highly nutritious, yellow–orange berries that are both sweet and tart to the taste (Figure 1) (Shenstone et al., 2020). The fruit can be eaten fresh, made into preserves, used in baking, and much more, as described by the popular American food magazine *Food & Wine* (Friend, 2019). *Physalis* species have also historically been used in traditional medicine (Huang et al., 2020; Kasali et al., 2021; Mirzaee et al., 2019). Groundcherries are even mentioned in the American literature series *Little House* by Laura Ingalls Wilder. The author describes her family's garden, where, "The ground-cherries grew on low leafy bushes. Thick on the stems under the large leaves hung the six-cornered bells, pale grey and thinner than paper, and inside each bell was a plump, golden, juicy round fruit" (Wilder, 2008). As Wilder describes, *Physalis* species including *P. grisea* have fruit that are surrounded by a papery husk, or inflated calyx. This calyx remains after the fruit drops from the plant, providing a protected environment for fruit and seed maturation (Figure 2). It has been theorized that this inflated calyx may have also evolved as a flotation mechanism for seed dispersal (Li et al., 2019). A recently described Physaloid species with an inflated calyx estimated from the Eocene period has timed the *Physalis* divergence from other solanaceous crops, such as tomato, to at least 50 million years ago. This fossil represents the earliest known species of *Physalis*, as well as the earliest known Solanaceae fossil (Wilf et al., 2017).

1.2 | Taxonomy and geographic distribution of *P. grisea*

The genus *Physalis* is native to the Americas and contains about 90 species, with 28 species found in the USA, 61 in Mexico, and 22 in Central America (Martínez et al., 2023b; Pretz & Deanna, 2020). *P. grisea*'s native range includes Central and Eastern USA and parts of Mexico, and these regions are also considered its center of diversity (Martínez et al., 2023b). Several *Physalis* species have been cultivated under the name groundcherry in North America during the history of the USA, but it is difficult to fully identify those species, given the convoluted taxonomical history of the genus. North American species that have been commonly called groundcherry include, but are not

FIGURE 1 Fruit of *Physalis grisea* detach and fall off the plant at various stages of ripeness, resulting in varying coloration of detached fruit and their calyces, (a) *P. grisea* fruit with inflated calyces. (b) Variation in coloration of detached *P. grisea* fruit with the calyx peeled back from the fruit. Photos by Savanah dale and Elise Tomaszewski.

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FIGURE 2 Progression of *Physalis grisea* calyx and fruit development from flowering through husk decay. Photos by Savanah dale and Elise Tomaszewski.

limited to, *P. grisea*, *Physalis pruinosa*, *Physalis angulata*, and *Physalis pubescens*, *Physalis hederifolia*, and *Physalis virginiana* (Pretz & Deanna, 2020; Sastry et al., 2019; Thomson & Witt, 1987; Travlos, 2012; H. Wu et al., 2019).

1.3 | Domestication status of *P. grisea*

Although many *Physalis* species including *P. grisea* have historically been cultivated in North America, Central America, and South America, there is insufficient evidence to determine if this species can be considered domesticated. The standard for qualifying a species as domesticated has been greatly debated throughout history. Among the earliest discussions of domestication were those between Charles Darwin and Alfred Russell Wallace. Darwin proposed two kinds of domestication. He first proposed intentional selection where domesticators (i.e., humans) were intentionally modifying organisms to meet an ideal standard of phenotype. He also proposed unconscious selection, or the phenomenon in which humans unintentionally advanced genotypes which held more value, such as keeping seed from plants that did not drop their seed before harvest (Heiser, 1988; Ross-Ibarra et al., 2007).

We can assume that there have been either unconscious or intentional selections made to generate the few commercial varieties of *P. grisea* that are available, and it is known that one popular commercial variety, Aunt Molly's groundcherry, was originally selected by Territorial Seed Company for early flowering and flavor (T. Johns, personal communication, March 5, 2024; Aunt Molly's Ground Cherry, 2024; Gepts & Papa, 2003; Lenser & Theißen, 2013; Ross-Ibarra et al., 2007). However, the extent of the selections on resulting phenotypes relative to wild accessions is not understood. Domestication syndrome traits that are often present in domesticated plant species include increased fruit size, reduced fruit abscission, and uniform growth habit (Gepts & Papa, 2003; Koinange et al., 1996; Lenser & Theißen, 2013; Razifard et al., 2020). Domestication trait presence relevant to fruit morphology, fruit abscission, and growth habit is not easily observed in *P. grisea*. However, no studies have been conducted to observe more cryptic domestication traits such as change in fruit flavor or nutritional content, in this species. Additionally, there are no studies investigating genetic architecture of this species to determine if there are significant differences between wild and cultivated varieties. Finally, there are no records of formal and ongoing groundcherry breeding programs in the USA. This represents a knowledge gap in the literature for *P. grisea* and results in the inability to fully determine the domestication status of *P. grisea*. Additionally, due to the complex taxonomical revisions to this genus, many *P. grisea* seeds are erroneously labeled as *P. pruinosa*, making domestication history difficult to assess (Pretz & Deanna, 2020). Although these plants have been cultivated and likely have had some level of selection imposed on them, the level of selection and its effects are not well documented, and thus they cannot be considered domesticated.

1.4 | Current cultivation and market trends of *P. grisea*

Today, *P. grisea* is popularly grown in home gardens and by small-scale farmers, and the main market for the fruit is in local farmers' markets and community-supported agriculture programs (Shenstone et al., 2020; Van Eck, 2022). Although *P. grisea* does not command a large market like its relatives the tomatillo (*Physalis philadelphica*) and goldenberry (*Physalis peruviana*), it does hold value for local food systems and dietary diversification (Goldenberry (*Physalis peruviana*) Production Systems For CSA Farms, 2020; González-Pérez & Guerrero-Beltrán, 2021; Labate & Robertson, 2015; Shenstone et al., 2020). Additionally, many small seed companies such as the San Diego Seed Company in southern California and the Hudson Valley Seed Company in upstate New York, as well as large seed companies like Baker Creek Seeds, offer various *Physalis* species in their catalogs (Cape Gooseberries, 2024; *Ground Cherry, Aunt Molly's*, 2024; Organic Peruvian Ground Cherry Seeds, 2024).

1.5 | Potential of *P. grisea* improvement and its use as a model species

Though *P. grisea* is mainly produced as a local, specialty crop, it has the potential to be a more widespread and mainstream fruit such as

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blackberries or blueberries, due to its ease of cultivation, its relatively long shelf-life post-harvest, and capacity to increase biodiversity and nutritional intake in people's diets (Van Eck, 2022). However, this potential is inhibited by agronomically unfavorable traits of the species. The plant itself has a sprawling growth habit and drops its fruit to the ground, which makes it unruly to grow and difficult to harvest fruit (Kwon et al., 2020; Van Eck, 2022). Additionally, more desirable traits of *P. grisea* provide an opportunity to understand and translate biological mechanisms to related *Physalis* species, such as *P. peruviana*, to improve them for cultivation. These agronomic characteristics can be quickly improved via modern genetic approaches, such as CRISPR/Cas9 gene editing. Additionally, *P. grisea* has the potential to serve as a model species for understanding traits of interest such as fruit drop, paralog evolution, and insect resistance, and this knowledge can be utilized to improve related crop species.

2 | AGRONOMIC CHALLENGES OF *P. GRISEA*

Cultivated varieties of *P. grisea* experience high levels of fruit abscission, have small fruit size, and have a sprawling and indeterminate growth habit (Kwon et al., 2020). In this work, we describe how these traits of interest in *P. grisea* need to be modified to attain an ideotype. An ideotype is an idealized variety for a specific group of stakeholders, with phenotypes that are optimized for each trait of interest (Zsögön et al., 2017). The ideotype for these *P. grisea* traits would be a plant that has shorter internode lengths (the stem length between branching points), reduced branching, and a more compact growth habit. This, in turn, would reduce the need for labor-intensive cultivation practices such as trellising (Figure 3). The ideotype would also have less-developed abscission zones, in order to prevent high fruit drop rates but to allow for ease of harvesting. Finally, this ideotype would have increased resistance to herbivorous insects (Figure 4).

3 | *P. GRISEA* AS A MODEL SPECIES

It is often helpful to understand the underlying biology of traits through model species to facilitate development of improved plant cultivars. A model organism is one which is selected for its ease of study and the capacity for discoveries made with it to be extrapolated to represent a broad range of other organisms (Leonelli & Ankeny, 2013). This differs from an experimental organism, which is studied only to understand a certain phenomenon or to represent closely related species. However, relying on only a handful of model organisms to study evolutionarily distinct biological questions can cause researchers to overlook much of the biodiversity present across the plant kingdom (Burian, 1993). In response, due to the rapid improvements in technology during the “omic” era, it has been argued that “nonmodel plant models” are emerging to help broaden the understanding of key physiological and developmental processes (Cesarino et al., 2020; Russell et al., 2017).

Recently, a paper from He et al. (2023) advocates for the adoption of *P. grisea* as an emerging model species to study the Solanaceae family. *P. grisea* has several attributes that are preferred in model species such as a short generation time of about 2 months, a self-compatible pollination habit, a diploid genome size of 1.37 Gb, and established tissue culture, transformation, and gene editing systems (He et al., 2023; Swartwood & Van Eck, 2019; Van Eck et al., 2017). Despite its relation to tomato, a previously established model system, *P. grisea* exhibits unique characteristics that intrigue both researchers and growers. These include specialized metabolites known as withanolides that are useful for insect resistance, the inflated calyx syndrome, a distinct fruit drop phenotype, pharmacological benefits, and ornamental value (He et al., 2023; Huang et al., 2020; Martínez et al., 2023a; Pérez-Castorena et al., 2022; Shenstone et al., 2020; Van Eck, 2022). These distinct traits, combined with its genetic relationship to the well-studied tomato, make *P. grisea* a valuable and intriguing model species candidate for Solanaceae family studies.

Studying the biology of *P. grisea* not only deepens our understanding of the genetic mechanisms governing important traits in related species but also promotes improvement of the crop itself. Recognizing the scientific and agronomic potential of this crop, ongoing research seeks to expedite its domestication while also leveraging it as a model for fundamental biological research. With abundant genetic, genomic, and molecular biology resources already available, *P. grisea* emerges as an excellent species for both practical and foundational biological research.

4 | *PHYSALIS* IMPROVEMENT PROJECT

The *Physalis* Improvement Project is a community science project led by Dr. Joyce Van Eck's group at the Boyce Thompson Institute aimed at integrating consumer feedback with agronomic research (Van Eck, 2022). The focus of this community science project was to obtain first-hand experience from farmers and home gardeners on growing *P. grisea* and a closely related species, *P. peruviana*. Based on feedback, this project identified three main traits that need to be improved: (1) sprawling growth habit in *P. grisea* and *P. peruviana*; (2) fruit size and retention in *P. grisea*, and (3) insect susceptibility in *P. peruviana*. Currently, researchers are working to understand gene function and to fast-track domestication of these two species through disruption of target genes using CRISPR/Cas9 techniques in *P. grisea*. This process will serve to answer fundamental biological questions and improve these crops for small and large-scale farming. The following sections will highlight such examples and the several traits studied thus far.

4.1 | Addressing sprawling growth habit

In several instances of historical plant domestication, a more compact and less-branched growth habit was largely driven by selection, as this architecture facilitates easier management and harvest of a crop

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FIGURE 3 Graduate students (left) and summer intern (right) trellising *Physalis* species with twine in a field setting. Photo by Rachel Phillipson.

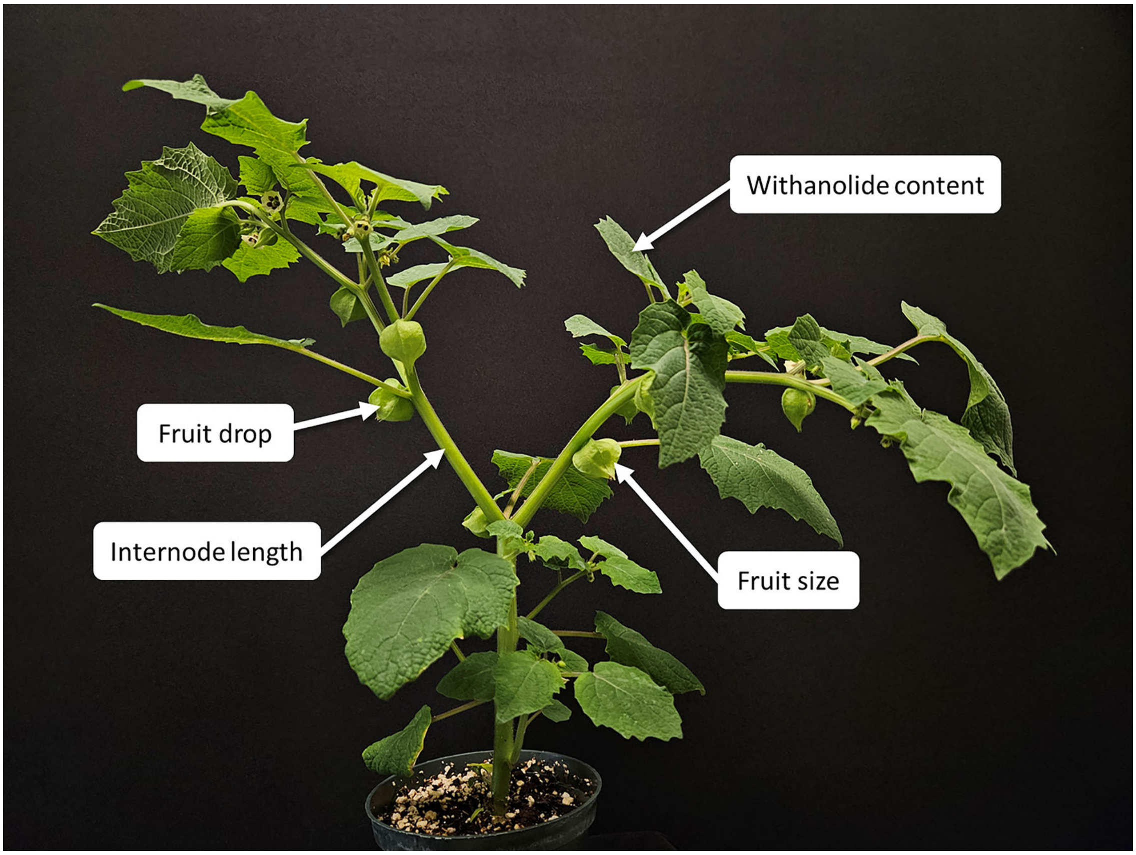

FIGURE 4 Image of a young *Physalis grisea* plant with traits that have been studied. Photo by Savanah dale and Elise Tomaszewski.

(Anne Frary & Doğanlar, 2003; M. Hu et al., 2018; Stitzer & Ross-Ibarra, 2018). Selecting for desired growth habit phenotypes can take many generations and is reliant on previously existing genotypic and phenotypic variation. Furthermore, increasing yields while reducing plant size can be difficult in traditional breeding schemes as both plant architecture and yield are polygenic traits (Pan et al., 2017; Stetter et al., 2018). In modern times, there is a trend towards using genetic engineering techniques for specific targeting of plant architecture genes to enhance yields and increase stress tolerance (Guo et al., 2020).

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In considering strategies to enhance crop productivity, researchers have turned their attention to modifying plant architecture in the pursuit of compact and upright growth habits. Several plant architecture tomato mutants have compact, determinate growth habits including mutants of the florigen repressors *SELF PRUNING* (*SP*) and *SP5G* genes (Pnueli et al., 1998; Soyk et al., 2017). When expression of the *P. grisea SP* ortholog was disrupted by CRIPSR/Cas9 editing, the resulting plants exhibited a severe determinate phenotype, even more so than tomato ortholog mutants (Lemmon et al., 2018). Typically, these plants exhibited a yield reduction from wild-type plants, producing only three to four fruits per shoot. However, when the *SP5G* ortholog was edited, the plants still had a reduction in overall size, although not as drastic as when *SP* was edited. Unlike the CRISPR-generated *SP* mutants, the *SP5G* mutants had increased fruit per shoot when compared with wild-type plants (Lemmon et al., 2018). Similar work by Kwon et al. (2020) found that targeting an *Arabidopsis thaliana ERECTA* ortholog in *P. grisea* (*PgER*) caused severe dwarfing and more fruit per plant than the determinate *P. grisea SP* mutants (Kwon et al., 2020). While fruit of the *PgER* mutants was smaller than wild-type fruit, yield was not significantly different, meaning a smaller, compact *P. grisea* can be more densely planted to increase yields in cultivation.

4.2 | Increasing fruit size

Fruit size is another trait that is often changed through domestication. Historically, larger fruit size has been both intentionally and unintentionally selected for in certain crops, as larger fruit can be easier to harvest and provide a larger volume of food (A. Frary et al., 2000; Gepts et al., 2012). One well-known example of increased fruit size through domestication is that of cultivated tomato (*S. lycopersicum*) compared with its wild relative *Solanum pimpinellifolium* (Sun et al., 2017). *P. grisea* fruit are also small, approximately 13 mm in diameter, representing an agronomically important trait that is a target for improvement. In a study published in 2022, the *P. grisea* CLV3 protein was targeted with CRISPR/Cas9, resulting in mutant lines which had fruit with an increased locule number (Kwon et al., 2022). Similarly, when *Ppr-CLV1*, the receptor for the CLV3 protein, was targeted, the mutant fruit had an increased locule number and a 24% increase in fruit mass compared with wild-type fruit (Lemmon et al., 2018). These studies illustrate targeted protein modification using CRISPR/Cas9 technology to enhance fruit mass, highlighting rapid advancements in crop improvement techniques.

4.3 | Understanding and mitigating fruit abscission

Gaining insight into the mechanisms underlying fruit abscission is crucial for development of strategies to improve fruit retention while ensuring ease of harvest. Abscission is a physiological process that refers to the shedding of a plant organ across a boundary of living cells (Tucker & Kim, 2015). It is a biologically active process, which facilitates seed dispersal and proliferation of the next generation, while also acting as a method of carbon balance for the plant (Fahn & Werker, 1972; Lordan et al., 2019). Furthermore, studies have documented that mechanical damage caused by insect herbivory can trigger fruit abscission, serving as a deterrent against frugivory by physically separating feeding larvae from the host plant (Benda et al., 2008; Petzold et al., 2009). Fruit abscission is common among angiosperms, with notable examples including apple, citrus, and tomato (Berüter & Droz, 1991; Cooper et al., 1968; Ito & Nakano, 2015; Merelo et al., 2017). However, agronomically, fruit abscission is a challenge for growers because premature fruit drop can cause significant potential yield losses as has been reported for apple (*Malus domestica*) and litchi (*Litchi chinensis*) (Larson et al., 2023; Zhao & Li, 2020). On the other hand, pepper (*C. annuum*), which does not drop its fruit, can suffer plant damage during harvest because of the difficulty in fruit removal (Hill et al., 2023). Therein lies an ideal phenotype for most fruiting plants, including *P. grisea*, where fruit drop is minimized, but easy separation from the plant still exists.

Abscission typically involves four main steps: formation of an abscission zone (AZ), cell responsiveness to molecular signals, detachment through middle lamella degradation, and formation of a protective cuticle barrier (Tucker & Kim, 2015). It is important to note that while these steps appear distinct, they likely overlap during the abscission process, varying from species to species. These steps are influenced by many external factors such as temperature, light, and water availability, illustrating the complex interplay between genetics and the environment (Addicott, 1968). Despite the abscission process being characterized for some organs, little is known about the underlying genetic mechanisms that control fruit abscission. Therefore, understanding the underlying cellular, molecular, and genetic mechanisms that lead to fruit abscission is crucial for developing cultivars with reduced fruit drop and improved crop yield.

For investigations of the intricacies that contribute to fruit abscission, it is important to utilize model species that have well-developed resources, such as tomato with its high-quality reference genome, mutant collection, and plant transformation methodology (Brooks et al., 2014; Reem & Van Eck, 2019; Tomato Genome Consortium, 2012). Unlike tomato, *P. grisea* has a more extreme, precocious fruit drop phenotype; therefore, it is a useful model to broaden the understanding of fruit abscission (del Pilar Zamora-Tavares et al., 2016; He et al., 2023; Van Eck, 2022). Ongoing research with *P. grisea* will contribute towards broadening the knowledge of fruit abscission while also informing strategies to mitigate the negative impact of excessive fruit drop on its adoption in large-scale agriculture. One such approach is the application of CRISPR/Cas9-mediated gene editing to target fruit abscission-related genes. To identify potential targets for their research, the Van Eck lab is currently focusing on genes reported for tomato AZ development and mining a *P. grisea* AZ RNAseq dataset (*unpublished data*). With a *P. grisea* reference genome recently reported as well as having an established transformation method and CRISPR/Cas9 editing pipeline,

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there is potential for pursuing a dual goal to identify the molecular mechanisms that regulate fruit abscission and to develop a cultivar with reduced fruit drop (He et al., 2023; Swartwood & Van Eck, 2019; Van Eck et al., 2017).

4.4 | Combatting insect herbivory

Many plants interact with insects via specialized metabolites, which are chemical compounds in plants that evolved to have specific functional roles in plant biology. Plant–insect interactions can be either beneficial to the plant, as in the case of pollinating bee species, or detrimental to the plant, such as aphids that damage garden vegetables or crops. In the case of agonistic interactions, particularly with herbivorous insects, the aforementioned specialized metabolites often come into play and provide defense from damage that could lead to a negative effect on plant vigor. The mechanism of defense varies, with specialized metabolites performing different roles including acting as deterrents to prevent insects from visiting the plant, or as toxins when the insect consumes plant tissue.

Plant–insect interactions are important for any crop species in regard to successful cultivation. The *Physalis* Improvement Project identified two primary herbivorous insect species that prey on *Physalis* and cause substantial damage (Van Eck, 2022). The first of these is *Lema daturaphila*, the three-lined potato beetle, which causes damage primarily in the USA, particularly in the Northeast, but is reported to also cause damage on *Physalis* in South Africa (Van Eck, 2022; Volesky, 2020). The second is *Chloridea subflexa*, a species of straw moth that damages *Physalis* fruit, and has been found throughout the USA, Central America, and parts of South America (Campos de Melo et al., 2017; Sell et al., 2021).

Larval infestation by *C. subflexa* of *Physalis* fruit results in reduced fruit quality and, therefore, yield loss (Campos de Melo et al., 2017; González-Pérez & Guerrero-Beltrán, 2021; Oppenheim et al., 2018). *C. subflexa* is a narrow specialist on *Physalis* species. Though *P. angulata* is its preferred host, the moth lays its eggs on several *Physalis* species (Oppenheim et al., 2018). The eggs hatch, and the young larvae chew through the inflated calyx and into the fruit, making it unfit for sale.

In addition to direct damage to the fruit, defoliation, or loss of leaf tissue, results in an overall decrease of plant growth, which can lead to reduced fruit yields (Weber et al., 2021). *L. daturaphila*, the three-lined potato beetle, is a pest insect that causes defoliation on *P. peruviana*. *P. peruviana*, known as goldenberry, is agronomically valuable in South America as an export crop, and has been predicted to increase in demand in the USA (Durinck, 2020a, 2020b; Goldenberry: discover the nutritional benefits of this exotic Colombian fruit, 2024; Goldenberry (Physalis peruviana) Production Systems For CSA Farms, 2020). Both the adult three-lined potato beetles and the larvae feed on the leaves of *P. peruviana* plants, and can cause complete defoliation (Volesky, 2020). The high potential of damage by *L. daturaphila* reduces the likelihood that growers would be willing to adopt *P. peruviana* for cultivation. During the *Physalis* Improvement Project, participants observed that *L. daturaphila* caused more damage to *P. peruviana* when compared with *P. grisea* (Van Eck, 2022). This difference in insect activity may be due to variation in specialized metabolite profiles between the two species (Van Eck, 2022).

Because *P. grisea* experiences less damage from *L. daturaphila* than *P. peruviana*, it can be used as a model to investigate the insect resistance mechanisms responsible for the observed differences in herbivory. In turn, knowledge gained from work with *P. grisea* has the potential to be extrapolated for imparting resistance to *L. daturaphila* in *P. peruviana*, if the resistance observed in *P. grisea* is indeed caused by natural variation of specific metabolites. Ongoing research is being conducted to determine the nature of resistance to *L. daturaphila* in *P. grisea* with a current focus on a particular class of specialized metabolites, known as withanolides.

While metabolite conferred insect resistance can involve multiple players or even synergistic interactions, withanolides are a primary interest at this time because their negative effects on multiple insect species have been reported, including a beetle in the family Chrysomelidae, which *L. daturaphila* is also a member of (Ascher et al., 1981; Bado et al., 2004; Cir et al., 2008). Withanolides are prevalent across the genus *Physalis*, with 351 different compounds being reported. Withanolides also exhibit a wide range of biological properties beyond insect antifeedant effects, including anti-inflammatory activity and chemotherapeutic properties (Ascher et al., 1981; Huang et al., 2020; Shenstone et al., 2020; Wu et al., 2022). All of these attributes make withanolides a potential dual purpose breeding target in terms of versatility because they have applications in human nutrition and medicine, as well as insect resistance. However, before becoming breeding targets for insect resistance, it is important to know the specific compounds and mechanisms through which they confer resistance in *P. grisea*, and whether they can be elevated to increase resistance in *P. peruviana*.

Analysis of *P. grisea* and *P. peruviana* withanolide profiles has illuminated significant differences in types and quantities between the two species (*unpublished data*). Similar to the work described here regarding fruit abscission traits, the effect withanolide composition on insect interactions in each of these species can be empirically investigated through application of CRISPR/Cas9-generated mutant lines that would have different profiles. For example, if *P. grisea* mutant lines have the same withanolide content as *P. peruviana*, and withanolides are indeed the underlying mechanism of insect resistance, then the *P. grisea* mutants should experience the same level of insect damage as the wild-type *P. peruviana*. This reverse genetic approach to study withanolides and their potential role in insect interactions demonstrates the utility of *P. grisea* as a model species to understand biological mechanisms in plant–insect interactions, which can be applied to related species such as *P. peruviana*.

The *Physalis* programs described here clearly illustrate the value of integrating community participant-driven science with research to readily identify and address undesirable characteristics. Through targeted efforts to address problematic agronomic traits such as sprawling growth habit, fruit size and retention, and insect susceptibility, researchers are employing cutting-edge gene editing technologies to

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accelerate the domestication process of underutilized species. Looking forward, utilization of enhanced germplasm generated by gene editing, combined with traditional plant breeding, has the potential to integrate all traits of interest more rapidly into elite lines that better match the ideotypes most desirable for large-scale farming.

5 | FUNDAMENTAL RESEARCH STUDIES

In addition to research aimed at improvement of *P. grisea* agronomic traits, this species can serve as a model to understand the fundamental biology underlying traits such as inflated calyx syndrome and paralog evolution. Findings from this fundamental research will help broaden the understanding of development and genetic architecture across the plant kingdom.

5.1 | Genetic basis of inflated calyx syndrome

Inflated calyx syndrome (ICS) is a condition in which the individual sepals of the calyx develop around the fruit and coalesce to form a fully closed, inflated calyx (Hu & Saedler, 2007). This syndrome has been described in the literature, yet little is known about the underlying genetic mechanisms that control it. In a study published by He et al. (2023), *P. grisea* was used as a model to identify genes involved in the development of the inflated calyx. In a reverse-genetic approach, CRISPR/Cas9 was leveraged to target MADS-box transcription factors predicted to influence calyx development. Notably, of the 11 targeted candidate genes, only a single nucleotide variation in an *APETALA (AP2)*-like transcription factor resulted in the absence of the inflated calyx (He et al., 2023).

By understanding the regulatory networks governing calyx development, researchers could develop strategies to manipulate it in crops for agronomic benefit. For example, manipulation of the calyx in *P. grisea* and its relatives could result in a new market class of these fruit in which there was no need to remove the calyx prior to packaging, shipping, and sale. Currently, in supermarket sales of *P. peruviana*, the calyx is removed from the fruit to allow consumers to assess its quality (Van Eck, 2022). However, removal or even breakage of the calyx is suspected to create microtears in the fruit epidermis, potentially leading to reduced shelf life (*unpublished data*). Therefore, if formation of the calyx can be genetically manipulated or bred to reduce coverage of the fruit, this would reduce processing time for sale, increase consumers' ability to assess fruit quality, and potentially increase shelf-life.

5.2 | Paralog compensation and evolutionary biology

P. grisea has also been used to study how paralog compensation is affected by time and increased sequence divergence (Kwon et al., 2022). Compensation is an interaction between paralogs resulting from gene duplication and the subsequent subfunctionalization, neofunctionalization, and pseudogenization of the duplicated gene (Albalat & Cañestro, 2016; Conrad & Antonarakis, 2007; Kuzmin et al., 2022; Kwon et al., 2022; Panchy et al., 2016). Compensation is evolutionarily important for plants as a backup to ensure biological function even in the absence of the primary gene that encodes the function (Kwon et al., 2022). One can think of this mechanism as similar to a backup generator. *P. grisea* proved to be an excellent model species, alongside tobacco (*Nicotiana tabacum*) and petunia (*Petunia hybrida*), for studying compensation of a gene that contributes to plant organ (i.e., flowers) number and size.

CRISPR/Cas9-mediated editing that led to disruption of expression in the *P. grisea* gene *CLAVATA3* (*PgCLV3*) resulted in meristem enlargement and organ overproliferation (Kwon et al., 2022). In *P. grisea* it has been shown that a paralog of this gene, *CLAVATA3/ESR-RELATED 9* (*PgCLE9*), can compensate for *PgCLV3* when disrupted, and thereby prevent a mutant phenotype. This is in contrast with other solanaceous species, such as tobacco, where the paralog is not present and therefore disruption of the primary gene *CLV3* does result in the mutant phenotype (Kwon et al., 2022). The absence of a mutant phenotype that occurs in *P. grisea* when only either *PgCLV3* or *PgCLE9* are disrupted can be attributed to one of the genes remaining active (Kwon et al., 2022). Additionally, mutation in the *P. grisea* paralog *PgCLE9* alone does not produce a strong mutant phenotype, but when both the primary gene and the paralog are disrupted, there is a strong mutant phenotype because there is no longer any compensation from one of the genes for the other.

In this gene compensation case study, *P. grisea* was a useful model for understanding both floral and fruit phenotypes, as well as evolutionary biology and paralog interaction phenotypes. Gene compensation is important to understand in the context of phenotype manipulation or crop improvement. For example, if a phenotype of interest is controlled by a set of gene paralogs, editing a single paralog may not have the desired phenotypic effect due to compensation between the paralogs. The presence of compensation, therefore, must be understood for precise phenotype modification.

5.3 | Gene conservation

Lastly, *P. grisea* served as a model to study conservation of gene function (Hendelman et al., 2021). CRISPR/Cas9-mediated mutagenesis of a *P. grisea* gene, *PgWOX9*, resulted in embryo lethality. However, targeted mutagenesis of the cis-regulatory regions of *PgWOX9* resulted in plants with shoot apical meristem termination, additional branching, flowers with more petals, and fused flowers (Hendelman et al., 2021). Other solanaceous species with various mutations in these same cis-regulatory regions have similar phenotypes. These results suggest that pleiotropic activity of the *WOX9* gene is conserved across species and is regulated by the same cis-regulatory elements (Hendelman et al., 2021). This highlights the significance of *P. grisea* as a versatile tool for investigating a range of fundamental research topics, from plant development to the evolution of gene function.

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6 | CONCLUSION

In summary, *P. grisea* holds significant promise both as a model species for scientific research and as a fruit crop within the Solanaceae family. Despite its long history of cultivation and its importance in local food systems, the domestication status of *P. grisea* remains unclear due to a lack of comprehensive studies on its genetic architecture and phenotypic variation. Historically, there have not been any crop improvement efforts through breeding; therefore, *P. grisea* still retains many unimproved traits that inhibit its widespread adoption and cultivation. However, ongoing efforts to understand the biology behind undesirable agronomic characteristics and to improve these traits are shedding light on its potential as a future fully domesticated crop. The *Physalis* Improvement Project exemplifies the potential of utilizing available genetic resources for quickly improving agronomically important traits.

Through targeted approaches using CRISPR/Cas9 gene editing, researchers aim to understand, and potentially improve, desirable traits such as fruit size and retention, and to understand insect resistance mechanisms for application in related species such as *P. peruviana*. These efforts hold promise for improving *P. grisea* as a crop and also contribute to our broader understanding of plant biology and evolution. Moreover, *P. grisea* serves as a valuable model for studying fundamental biological processes such as the inflated calyx syndrome and gene paralog compensation. The ongoing research on *P. grisea* underscores its significance as both a model organism for understanding fundamental biology in related species and for demonstrating how the untapped potential of an underutilized crop can be realized for agronomic production to contribute towards food security.

AUTHOR CONTRIBUTIONS

S.M.D., E.M.T., and J.V.E. conceived and organized the manuscript. S.M.D. and E.M.T. wrote and edited the manuscript. J.V.E. and Z.L. read and provided feedback towards the manuscript. S.M.D., E.M.T., J.V.E., and Z.L. approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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