Domestication of Marama Bean in Arid Namibia: Challenges and Opportunities in a Climate Changing Agroecology

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Abstract

*Tylosema esculentum* (Burch.) A. Schreib. (Marama bean), referred to as marama in sections of this article, is an obligate outcrossing native plant with a yield potential of 2 ton/hectare which grows naturally in the deep sandy soils of the Kalahari Desert. It has adapted to the low precipitation levels in that agro-ecosystem. Marama serves as a staple food for the San and Bantus in that area. In Namibia, in the past you could find wild stands of marama in the Khomas region, Omaheke region, and the Otjozondjupa region without much struggle. It is renowned for its brown seeds, which are rich in high-quality oils and proteins. The tuberous root contains a significant amount of starch. The objective of domesticating orphaned marama is to provide farmers in this climate change-prone region with a viable alternative for food and nutrition security. This program, initiated in 2008 with an open-minded mindset, required swift implementation using harsh and occasionally unconventional methods. To introduce indigenous tools for resource-poor farmers, the domestication program prioritized the utilization of farmer-participatory methodologies. It was crucial to integrate old and new approaches to ensure learning from past and present experiences, leading to innovative solutions. There is little research and development of native crops in Africa because most of the currently cultivates crops were brought for use from abroad. Only a few numbers of indigenous African crops can be named. The arid Kalahari region, susceptible to climate change, necessitates the revival of indigenous crops like marama, which are resilient and well-adapted to the region’s conditions and have thrived for centuries. In many discussions regarding the health and nutrition of Africa, the recommendation to consume traditional foods to avoid exposure to modern foods, which may not be genetically compatible, is frequently emphasized. Regardless of their validity, these opinions
must be acknowledged, and steps need to be taken to ensure a positive legacy for future generations. However, this chapter will address the limitations and challenges that exist in this regard. This article will summarize the progress made in the domestication program of the marama bean in Namibia thus far. Furthermore, this article will highlight the challenges that have been faced during the domestication journey for marama bean and other orphaned crops. The domestication program commenced with a broad germplasm collection, characterization, and preselection for breeding. Crop selection in this program was influenced by climate change-related concerns of shorter and uncertain rain seasons, and recurrent droughts. Selection included but was not limited to identifying marama genotypes with superior characteristics, early germination and many seeds per pod were among some of the identified and selected characteristics. The Namibia University of Science and Technology (NUST) has compiled a list of potential marama bean varieties and is currently testing marama seeds in anticipation of their introduction as a new crop alternative with good adaptation to the effects of climate change, since conventional crops like maize underperform due to persistent droughts. Marama bean, if properly developed, holds significant potential to address issues of hunger and malnutrition in arid regions of Southern Africa and other similar territories. The findings presented here are the result of ongoing field research and experiments conducted at multiple sites using superior marama bean varieties.

Keywords

Crop Improvement, Crop Domestication, Drought Tolerance, Food Security, Genetic Improvement, Marama Bean, *Tylosoema esculentum*

1. Introduction

*Tylosoema esculentum* (Burch.) A. Schreib., also known as marama bean or marama, is a perennial legume with valuable crop attributes such as high protein and oil content with protein content ranging between 34.3% and 36.3% and lipids between 32% and 42%. These attributes make it a crucial candidate for domestication as a new crop alternative in arid territories. It naturally grows in the sandy regions of the Kalahari, spanning from Northwestern South Africa to parts of Botswana and the eastern and central regions of Namibia. Indigenous communities in these areas have long relied on it as a staple source of protein throughout recorded history. In agro-research circles, marama bean is considered an orphan crop, which refers to underutilized and under-researched staple food crops in many low-income countries. Orphaned legume crops like marama bean often have limited economic value, resulting in little attention from crop scientists and cultivators (Naylor et al., 2004; Foyer et al., 2016). Other examples of such orphaned legume crops include groundnut (*Arachis hypogaea* L.), grass pea (*Lathyrus sativus* L.), bambara groundnut (*Vigna subterranean* (L.) Verdc.), cowpea (*Vigna unguiculata* (L.) Walp.), and marama bean, which was the most
recently included in the list by the Kirkhouse Trust (https://www.kirkhousetrust.org/stress-tolerant-orphan-legumes-stol), an organization with an interest in legume development in developing countries. Marama bean grows as a perennial creeping vine, producing seeds and tuberous roots that have been traditionally used for food, feed, and pharmaceutical purposes.

Marama bean is often referred to as “green gold” due to the high-value oil and protein content found in its seeds. It is indigenous to Namibia and Botswana, where no other agricultural crops can thrive in the arid zones (Uzabakiriho, 2016). Only a few farmers cultivate small plots of marama bean in Namibia and Botswana, resulting in a total cultivated land area of approximately 50 hectares, with 50% of it dedicated to research by NUST. Countries such as USA and Australia have marama bean under cultivation in some lands. In its natural habitat, the marama bean exhibits remarkable resilience, tolerating summer temperatures as high as 50˚C and freezing winter temperatures. Surface water availability in this region lasts for only about eight weeks annually (Powell, 1987; Bower et al., 1988; Nepolo et al., 2010). Despite these challenging circumstances, marama bean contains a significant amount of protein, estimated to be between 34.3% and 36.3%, surpassing the protein content of soybeans and chickpeas, which is approximately 23%.

Botanically, the genus Tylosema (Schweinf.) [Torre & Hillc] consists of four species: T. esculentum (Burch.) A. Schreib., T. fassoglense (Schweinf.) Torre & Hillc., T. argenteum (Chiov.) Brenan, and T. humifusum (Pic.Serm & Roti Mich.) Brenan. These species are predominantly found in the eastern, central tropical, and southern parts of Africa (Castro et al., 2005). Within the genus, only two stamens are fertile, while the remaining seven or eight stamens are sterile and exhibit a variety of shapes and colors (see Figure 14 and Figure 15). The genus is characterized by a lobed non-spathaceous calyx-limb (Castro et al., 2005).

Tylosema esculentum (Burch.) A. Schreib. is known by various common names in local languages, including gemsbok bean (in English), maramaboontjie, elandsboontjie, and braaiboontjite (in Afrikaans), marama and morama (in Setswana), maramama (in Thonga), Tsi and tsin (in !Kung San), gami (in Khoi), and ozombanui (in OtjiHerero) (Van Wyk & Gericke, 2000). Marama is a perennial species that produces prostrate vines with multiple stems reaching up to three meters in length (see Figure 1, Figure 2, Figure 4, and Figure 5). These vines spread from a large underground woody tuber (Figure 7 and Figure 8) (Powell, 1987). Some scientists refer to the family name Fabaceae to classify this plant family, while others consider it ambiguous. To minimize ambiguity, the vast Fabaceae family, which encompasses 650 genera and over 18,000 species, has been divided into three subfamilies or treated as independent families, as mentioned by Castro et al. (2005).

1) Subfamily Caesalpinioideae or family Caesalpiniaceae (where marama resides)
2) Subfamily Minosoideae or family Mimosaceae
3) Subfamily Faboideae (= Papilionoideae) or family Papilionaceae (= Fabaceae sensu stricto).
Figure 1. Showing Marama seedling (one-month post germination).

Figure 2. Showing vegetative marama patch from Omaheke region, Namibia.

Figure 3. Showing the geographical locations for marama bean cultivation globally (revised from (Omotayo & Aremu, 2020)).
Consequently, the term “Fabaceae” can be utilized in two distinct contexts. In a broad sense (sensu lato), it refers to all three subfamilies of legumes. Alternatively, in a specific sense (sensu stricto), it denotes the Papilionoideae subfamily of the Papilionaceae family, encompassing the genus Faba.

In terms of plant type, the marama bean exhibits a patchy prostrate growth habit, characterized by a creeping phenotype with multiple vines. The leaves are bilobed in shape, displaying a distinctive net venation pattern. The inflorescence is adorned with elaborate and vibrant yellow flowers, while the seeds are spherical.
Figure 6. Dry dark brown marama bean seeds (Average mass 3 g/seed).

Figure 7. Showing a young edible marama root tuber.

Figure 8. A young edible marama root tuber.
and turn dark brown upon reaching maturity. Other taxonomically significant traits include variations in internode length, which can be classified as either short, medium, or large.

Marama bean serves as a significant source of various phytochemicals and nutritional components. Recent literature has extensively documented its chemical composition and made comparisons to other legumes (Holse, Husted, & Hansen, 2010). In terms of proximate composition, marama bean exhibits lower levels of ash and non-structured carbohydrates compared to soybeans and groundnuts. Additionally, it has a higher dry matter content per 100 g, surpassing soybeans and groundnuts (see Table 1). The nutrient content and phytochemicals present in marama bean find applications in the functional food, nutraceutical, and pharmaceutical industries.

Various methods are employed to prepare ripe marama bean seeds, including roasting (Müsel, 2005), frying, or pounding. Additionally, the seeds are utilized for producing cold-pressed oil, butter, and porridge (Müsel, 2005). Thanks to their hard outer shell, the seeds can be stored in pods for extended periods. Furthermore, heated or unheated marama bean seeds can be ground into flours used in diverse food applications. These include the production of Marama milk, a nutritious beverage comparable to soy or cow’s milk, offering alternative refreshment options (Müsel, 2005; Mataranyika et al., 2020). Marama beans are rich in macronutrients essential for human nutrition, such as protein.

Table 1. The table below shows Comparative nutrient composition of marama bean (per 100 g dry matter) with soybean and groundnut.

<table>
<thead>
<tr>
<th>Class</th>
<th>Nutrient</th>
<th>Marama bean</th>
<th>Soybean</th>
<th>Groundnut</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximate</td>
<td>Ash (%)</td>
<td>3.19</td>
<td>4.50</td>
<td>3.80</td>
<td>3.38</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Dry matter (%)</td>
<td>96.22</td>
<td>92</td>
<td>95</td>
<td>94.41</td>
<td>2.17</td>
</tr>
<tr>
<td></td>
<td>Fat (%)</td>
<td>40.06</td>
<td>25</td>
<td>50</td>
<td>38.35</td>
<td>12.59</td>
</tr>
<tr>
<td></td>
<td>Moisture (%)</td>
<td>2.67</td>
<td>7</td>
<td>9</td>
<td>6.22</td>
<td>3.24</td>
</tr>
<tr>
<td></td>
<td>Non-structured carbohydrates (g)</td>
<td>11.85</td>
<td>15</td>
<td>20</td>
<td>15.62</td>
<td>4.11</td>
</tr>
<tr>
<td></td>
<td>Protein (%)</td>
<td>34.71</td>
<td>45</td>
<td>25</td>
<td>34.90</td>
<td>10.00</td>
</tr>
<tr>
<td>Minerals</td>
<td>Calcium (mg)</td>
<td>241</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Chromium (mg)</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Copper (mg)</td>
<td>1.04</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Iodine (mg)</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Iron (mg)</td>
<td>3.95</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Magnesium (mg)</td>
<td>274.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Zinc (mg)</td>
<td>6.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vitamins</td>
<td>Vitamin B12 (mg)</td>
<td>0.043</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Vitamin B6 (mg)</td>
<td>1.56</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

"-" = not done (adopted from (Omotayo & Aremu, 2021)).
fiber, and healthy fats.

Marama bean grows well in soils with small content of organic matter, nitrogen, or phosphorus at temperature range of 28˚C to 37˚C and grows sporadically in the summer. Furthermore, it needs sunshine of light intensity of around 2000 mol·m⁻²·s⁻¹ for three hours on either side of midday (Omotayo & Aremu, 2021). Marama bean requires minimal water content as it can store water in the root, as mentioned by Cullis et al. (2018).

In the wild, the marama seed-to-seed cycle spans between 18 to 24 months. Under favorable conditions with wet soils, germination of the seeds occurs within approximately 8 to 21 days. Following germination, the plant undergoes vegetative growth for 5 to 6 months before experiencing die back. Through marama domestication, one of the objectives is to enhance production capacity and reduce the initial seed-to-seed cycle to 24 months.

During the process of domestication, the interaction between humans, plants, and the environment is carefully planned. Various requirements must be considered for each factor involved. Environmental factors such as water availability and temperature play a crucial role, while human needs include high crop production, palatable flavor, and a deep understanding of plant biology (Kim & Cullis, 2017; Cullis et al., 2018; Cullis & Kunert, 2017; Cullis et al., 2019; Dakora et al., 1999; Chimwamurombe et al., 2016).

While the marama bean is in the vegetative growth stage, a tuberous root develops underground. This root plays a crucial role in the plant’s survival during the winter months when the runners die back. Over the next three to four months, the tuberous root remains dormant until the rainy season arrives. With the onset of rain, new runners emerge from the root, and the marama plant begins to bloom after 1 - 4 months of vegetative growth (refer to Figure 1 and Figure 5). Pollination occurs primarily through the activity of lone bumblebees, resulting in the formation of seed pods. As the perennial cycle continues, the runners experience dieback and regrowth. Eventually, the mature brown pods open, releasing the seeds for dispersion. These pods initially have a purplish color, turn green as the seeds mature, and finally, become brown when the seeds are ready for dissemination (refer to Figure 6). NUST houses a germplasm collection of 521 marama bean accessions, which are considered genetic resources due to their possession of significant traits not found in the species (Chimwamurombe, unpublished data).

Just like in many other plants, marama bean is susceptible to several diseases caused by pathogens such as fungi and bacteria (Chimwamurombe, personal field observations).

2. Methodology

2.1. Collecting Marama Bean Germplasm

Marama bean seeds were collected every 2 km along a line transect from wild stands in most cases except for a few experimental plots where the seeds are col-
lected by picking them in their pods. In the wild stands, there was always evidence of herbivory for wild animals on the pods and on the immature seeds. The best time to collect marama bean is during the period of April to early June. So far 521 accessions were collected and are kept at NUST. These accessions where then use in genetic diversity studies.

2.2. Use of Microsatellites in Diversity Analysis of Marama Bean

Microsatellite markers have successfully facilitated genetic variation analyses in marama bean (Nepolo et al., 2009). Five percent (5%) of the 80 created SSR primers were utilized for evaluating the intra- and inter-specific variability of marama populations, demonstrating the usefulness and informational value of SSRs as markers (Nepolo et al., 2009). This study discovered polymorphic microsatellites that can be employed in marama selection and breeding programs to identify marama phenotypes. Field observations utilized different internode lengths to describe the observed phenotypes (see Figures 9-11). Marama yield features

![Figure 9](image_url). Showing a short internodal length (3 - 4 cm).

![Figure 10](image_url). Showing medium internodal length (5 - 8 cm).
Figure 11. Showing long intermodal length (9 - 15 cm).

Figure 12. Showing marama bean cookies.

Figure 13. Showing marama bean oil and marama bean milk.
show a direct or indirect relationship with germination times and leaf sizes. The analyzed marama bean populations exhibited heterozygosity (H), a marker for genetic variation, with heterozygosity ranging from 0.30 to 0.74 in Namibian germplasm. Genetic diversity, as measured by heterozygosity, is favored by most population geneticists as it quantifies the differences between two randomly chosen alleles from the population (Ayala, 1982; Naomab, 2004; Mason et al., 2005). Some marama populations displayed minimal genetic variety, while others exhibited significant genetic variation. These microsatellite primers can be used as markers in marama bean breeding and genetic diversity conservation efforts. Marama bean DNA markers are valuable for genetic investigations, including gene identification, molecular marker-assisted selection, and genetic mapping, offering hope for further research and advancements (Ayala, 1982; Mason et al., 2005).

3. Results and Discussion

This section summarizes the findings and provides an overview of the current situation on the ground. It also proposes feasible ways forward and outlines the
future perspectives and opportunities.

3.1. Limitation of the Use as Crop Plant and What Is Needed to Promote Cultivation

Marama bean faces certain limitations as a crop plant. One of these limitations is the long seed-to-seed cycle, which prompts farmers to prefer early maturing varieties. Consequently, addressing this issue becomes a crucial breeding objective. Another limitation lies in the low seed yield, which is currently the subject of intensive selection breeding research. Overcoming these limitations would facilitate the promotion of marama bean cultivation as a conventional crop and lobby governments and donor agencies for inclusion in seed production and breeding programs.

3.2. Production Areas—Areas of Major Production and Consumption

The Marama bean growing areas were georeferenced using GPS technology. The waypoints were accurately recorded and converted into a comprehensive database (Nepolo et al., 2009). The collection sites for Marama beans include, but are not limited to, Ozondema, Ombujondjou, Osire, and Otjiwarongo in the Otjozondjupa region, Omitara in the Khomas region, as well as Sandveld, Otjovanjate, Omipanda, Post 3, Harnas, and Okomombonde in the Omaheke region. In the specific study conducted by Nepolo et al. (2009), a total of 391 accessions were obtained from the sampled locations, as indicated in Table 2.

3.3. Production Challenges Regarding Fungal Diseases and Insect Pests

Only a few articles have addressed the fungal population in marama beans (Takundwa et al., 2014). In this analysis, Phoma and A. tenuissima were identified

<table>
<thead>
<tr>
<th>Location</th>
<th>Waypoint</th>
<th>Position</th>
<th>Number of accessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozondema</td>
<td>1</td>
<td>S20 15.921 E18 02.490</td>
<td>25</td>
</tr>
<tr>
<td>Ombujondjou</td>
<td>2</td>
<td>S20 18.600 E17 58.525</td>
<td>26</td>
</tr>
<tr>
<td>Osire</td>
<td>3</td>
<td>S21 02.031 E17 21.244</td>
<td>96</td>
</tr>
<tr>
<td>Otjiwarongo</td>
<td>4</td>
<td>S20 46.092 E16 65.123</td>
<td>50</td>
</tr>
<tr>
<td>Omitara</td>
<td>5</td>
<td>S22 21.596 E18 02.476</td>
<td>19</td>
</tr>
<tr>
<td>Sandveld</td>
<td>6</td>
<td>S22 01.751 E19 08.009</td>
<td>25</td>
</tr>
<tr>
<td>Otjovanjate</td>
<td>7</td>
<td>S20 27.39 31 E16 39.443</td>
<td>20</td>
</tr>
<tr>
<td>Omipanda</td>
<td>8</td>
<td>S21 19.355 E20 04.553</td>
<td>31</td>
</tr>
<tr>
<td>Post 3/Epukiuro</td>
<td>9</td>
<td>S21 39.642 E19 25.092</td>
<td>30</td>
</tr>
<tr>
<td>Harnas</td>
<td>10</td>
<td>S21 47.705 E19 19.921</td>
<td>25</td>
</tr>
</tbody>
</table>
through ITS sequencing. Similar to *A. alternata*, *A. tenuissima* is capable of producing alternariol and tenuazonic acid. Furthermore, in another analysis, *P. brevicompactum, Rhizopus stolonifer, P. olsonii, F. chlamydosporum, F. equiseti*, and once again, *A. solani* were described (Takundwa et al., 2014). However, these species were found in association with leaf lesions of marama bean seedlings (refer to Figure 16), rather than on the beans themselves. The way forward and possible solution to this challenge is to initiate breeding and selection programs for resistance or tolerance to the fungi which are problematic to marama production.

Although potential mycotoxin-producing species were identified in marama beans, the presence of these toxins in the plant remains unknown. Identifying toxigenic species does not necessarily indicate the presence of toxins. The biosynthesis of mycotoxins strongly depends on natural environmental conditions and the growth substrate. For instance, collaborative research with scientists from Benin demonstrated that certain components of cowpeas can inhibit mycotoxin production (Houssou et al., 2009).

Marama beans are known to contain significant amounts of plant secondary metabolites, including polyphenols (Shelembe, 2012). Coumarin derivatives are listed as one example by Shelembe (2012). Recent studies have shown that coumarin derivatives can inhibit the biosynthesis of ochratoxin A by Penicillium and Aspergillus, even at the transcriptional level of the ochratoxin polyketide synthase gene (Mayer et al., 2014). This inhibitory effect is attributed to a feedback mechanism. Shelembe (2012) also mentions vanillic acid and gallic acid as potential secondary metabolites found in marama beans. Recent research has demonstrated that these benzoic acid derivatives possess inhibitory activities against the biosynthesis of aflatoxin by *A. flavus* (Mahoney et al., 2010). Additionally, other polyphenols like chlorogenic acid have been shown to negatively

Figure 16. Showing unidentified caterpillars on green marama bean pods.
influence the manifestation of the alternariol polyketide synthase gene in *A. alternata*, an important contaminant of marama beans, thereby affecting alternariol biosynthesis (Wojciechowska et al., 2014). Collectively, these published results emphasize the significance of the relationship between the host plant and the fungus, highlighting its importance in ensuring product safety.

### 3.4. Current Research Priorities

The current research priorities for marama bean include selecting the best-performing marama bean varieties and determining the phenotypic attributes associated with better performance. Additionally, there have been calls to develop valued food products such as butter and non-animal milk alternatives. *Tylosema esculentum* is still in the transitional phase of domestication and has not yet been fully cultivated to harness its superior nutritional composition. Limited documentation exists regarding the range of available phenotypes or potential agronomic practices for its production. Focused and deliberate research and development efforts are necessary to elevate marama bean from obscurity and sufficiently enhance it to support food security in sub-Saharan Africa and Namibia. The main obstacle to its cultivation is the lack of research funding, which restricts knowledge acquisition. Detailed information on its genetic diversity, adaptability in production, and other agronomic characteristics of productivity is required.

### 4. Conclusion

This article compiled the existing knowledge regarding the marama bean. It also highlights the urgent need to fill existing gaps to advance the development of marama as a cash crop and an alternative protein source in a climate change-prone world. The breeding of superior-performing marama varieties is still a work in progress, requiring financial and technical support for breeding programs. To enhance overall food security, health, and economic viability, developing nations must harness the potential of underutilized native flora. The marama bean, due to its high value in both above and below-ground organs, is often referred to as “green gold” in popular culture. Like many legumes, including peanuts and cowpeas, marama bean seeds are highly nutritious. Furthermore, marama beans are rich in secondary compounds such as phytosterols, phenolic acids, flavonoids, behenic acid, and grifoniilides. Despite its potential, marama beans remain poorly studied in the existing literature, with limited scientific evidence for their food and medicinal uses, as well as their economic advantages. Unfortunately, there is a lack of financial resources and unclear research objectives specifically dedicated to the marama bean. There is a pressing need for research on these native plants, along with the development of effective cultivation protocols (Chirurugwi et al., 2019; Chongtham et al., 2022). Innovative methods, including the use of molecular biology techniques, should be employed to expedite the selection of desirable traits in marama breeding. Fast selection of desirable characte-
characteristics in marama is a recommended approach.

5. Recommendations

The way forward for marama bean lies in intensifying domestication efforts. With the reality of climate change and its adverse effects on many regions, particularly those south of the Sahara, there is a growing need for drought-tolerant legumes like the marama bean to be developed and deployed in drought-prone areas worldwide. Additionally, alongside domestication, it is crucial to enhance the development of value-added marama bean products.

The ecological niche occupied by the marama bean is not conducive to soybeans, as they struggle to thrive in environments characterized by intense drought and heat. This is why the domestication of the marama bean is favoured over other extensively researched crops like soybeans. In this context, the analysis above has revealed several challenges that make domestication difficult but must be overcome to achieve profitable cultivation of marama beans. These factors include the harvesting structure of the marama bean, which requires adaptation to commercial agriculture, as well as the current low yield trait. The use of molecular methods is expected to contribute to a better understanding of the floral biology of the marama bean, enabling artificial controlled crosses.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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