Growth and Yield of *Peperomia pellucida* on Watering Frequency and Different Types of Planting Media as an Eco-friendly Domestication Effort

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Abstract. *Peperomia pellucida* L., known as Chinese betel, is a tropical herb rich in vitamin C and has potential as an alternative food source. However, research on its optimal cultivation techniques remains limited. This study aimed to analyze the effect of watering frequency and planting medium on the growth and yield of *P. pellucida* as part of an eco-friendly domestication effort. The method used is experimental research with a completely randomized design with two factors. Factor 1 is watering frequency, with three levels; factor 2 is the planting medium, with three different types, and there are three replicates for each treatment combination. Based on the results of analysis of variance (ANOVA) followed by Duncan's test. Results showed that watering once a day combined with compost medium produced the highest growth and yield, indicating its suitability for sustainable cultivation. The highest vitamin C content was found in P1M3 (watered every two days and using chopped fern media) at 78.86%. Other parameters such as water, carbohydrate, and antioxidant content did not show significant differences. This research is expected to provide important information for the efficient and sustainable optimization of *P. pellucida* to enhance its nutritional and economic potential.

1 Introduction

Chinese betel is a wild-growing tropical plant with great potential for domestication as a horticultural crop. The public considers the chinese betel as a useless wild weed. In fact, Chinese betel have many health benefits. Chinese betel contains secondary metabolite compounds that are beneficial for health. The chinese betel plant *(Peperomia pellucida)*

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contains several active compounds, including alkaloids, terpenoids, tannins, saponins, flavonoids and phenols, which have antibacterial activity [1]. These secondary metabolites play a crucial role in the fundamental metabolism of plants [2]. In the midst of the food security crisis and the threat of environmental degradation, the development of local plants, such as chinese betel, is highly relevant to supporting the concept of sustainable and eco-friendly agriculture. However, despite its potential, scientific information on cultivation factors that affect the growth, yield, primary metabolite content, vitamin C, and antioxidant content of chinese betel is still limited.

This study was conducted to evaluate the effect of watering frequency and variation in planting media on the growth, yield, primary metabolite content, vitamin C content, and antioxidant activity of *P. pellucida* in a screenhouse environment. The two main factors studied, water and growing media, are fundamental aspects in agronomy that determine the success of cultivation. The selection of the right watering frequency aims to balance plant water requirements with resource efficiency, while the variation of growing media provides insight into how soil texture and water retention capacity affect plant physiology. Therefore, it is necessary to cultivate Chinese betel with the correct watering frequency so that it remains available throughout the season and can be utilized for health benefits [3]. This study is important for developing domestication techniques that are not only environmentally friendly but also applicable on a small to medium-scale agribusiness.

In the context of agribusiness, the results of this study provide an initial basis for developing alternative commodities that are economically valuable and easy to cultivate on a large scale. In addition, the domestication approach, which involves manipulating the growing environment is a form of application of plant breeding science, particularly in the selection stage of environmental adaptation. This research also reinforces the position of *P. pellucida* grown without synthetic fertilisers, providing a competitive advantage in the local food crop that promotes sustainable agriculture.

2 Research method

This research has several stages. The first Chinese betel cultivation was carried out in the Screenhouse, Faculty of Agriculture, Universitas Sebelas Maret Surakarta, at an elevation of 95 meters above sea level (masl) and with coordinates of Latitude 070 56' 110"‘S and Longitude 1100 85’ 201" E. The second stage, analysis of the proximate content, vitamin C, and antioxidants in Chinese betel leaves from the samples, was conducted at the Biochemistry Laboratory, Faculty of Agriculture, Universitas Sebelas Maret.

2.1 Cultivation process

This cultivation research employed a completely randomized design (CRD) with two factorials. Factor number one was watering frequency with three levels (P1: watering once a day, P2: watering once every two days, P3: watering every three days). Factor number two was the planting medium (M1: compost medium-brand’s Bokashi, M2: broken bricks, M3: chopped fern – brand’s Andam Pakis). There were nine treatment combinations, each with three replications. Thus, there were 27 experimental units. The variables observed in this study included plant height, number of leaves, fresh weight, root-shoot ratio, and plant proximate content. The data obtained were analyzed using analysis of variance (ANOVA) at 5% error level. If a significant difference is found, further tests are conducted using Duncan's Multiple Range Test (DMRT) at a 5% significance level. Sample code for treatment: Treatment *P1M1* consists of watering once a day using compost media, while *P1M2* involves watering once a day using brick media. Treatment *P1M3* applies watering once a day with

chopped fern media. For treatments with watering once every two days, *P2M1* uses compost media, *P2M2* uses brick media, and *P2M3* uses chopped fern media. Meanwhile, for watering once every three days, *P3M1* applies compost media, *P3M2* uses brick media, and *P3M3* uses chopped fern media.

2.2 Proximate, vitamin C and antioxidant test

At this testing stage, it is carried out immediately after the plants are harvested. The proximate test is only used to determine the moisture content, and carbohydrate content. Moisture content was analyzed by thermogravimetry using a Moisture Analyzer (Ohaus MB45, USA; accuracy ±0.01 g; temperature up to 200 °C). Carbohydrates were calculated by a different method.

Vitamin C and antioxidant activity were determined spectrophotometrically using a UV-Vis Spectrophotometer (Shimadzu UV-1800, Japan; wavelength range: 190–1100 nm, accuracy ±0.3 nm). Vitamin C was measured at 265 nm and antioxidant activity was evaluated using the DPPH method at 517 nm.

3 Results and discussion

3.1 Growth results of Chinese betel cultivation

Plant growth is influenced by various factors that can be classified into two, namely internal factors (plant genetics) and external factors (growing environment). Several environmental factors, including temperature, climate, elevation, water availability, and type of planting medium, influence the growth and yield of chinese betel plants. Chinese betel plants cultivated in suitable conditions will thrive and yield well. The choice of cultivation location is crucial to ensure the success of betel cultivation efforts.

The highest temperature recorded at the research location was 27^0C, and the lowest temperature was 24^0C; therefore, the average temperature at the research location was 25.8^0C. The average temperature at the research location was slightly less than ideal for the growth of Chinese betel plants. The optimal temperature for betel plants to grow is 15-25^0C [4]. Temperature is a significant abiotic factor that can significantly impact plant growth and yield. The highest relative humidity at the research location is 89% and while the lowest is 65%, resulting in an average relative humidity of 80.6%. Indicates that the relative humidity at the research location is the optimal level for the cultivating of chinese betel plants. The optimal level of relative humidity required by betel plants is around 80-90%. Humidity levels of 80% are ideal for betel growth, while the optimal average temperature for forest betel growth is around 26.65°C [5].

3.1.1 Plant height

Table 1 shows that the treatment of watering frequency and the use of planting media types have a significant effect on the growth of chinese betel plant height. Chinese betel plants achieve the best results when treated with daily watering and the use of compost as planting media, resulting in an average plant height of 13.83 cm. The frequency of watering had a significant effect on the growth rate (all parameters), which was reduced over time as the watering regime was extended from 3 days to 7 days[6]. An insufficient water supply may slow down photosynthesis, which in turn limits plant growth in height.

Table 1. Results of Duncan's further test on the effect of watering frequency and use of planting media on the height of Chinese betel plants.

Treatment	Plant Height (cm)	Duncan Test
P1M1	13.83	a
P2M1	10.61	ab
P3M1	12.21	ab
P1M2	5.06	cd
P2M2	3.97	d
P3M2	5.46	cd
P1M3	8.41	bc
P2M3	11.85	ab
P3M3	8.84	bc

Note: The same letters in the Duncan Test column indicate no significant difference in the Duncan test (DMRT) at the 5% level.

P1M1 group is significant to P1M2, P2M2, P3M2, P1M3 and P3M3, P2M1 group is significant to P1M2, P2M2 and P3M2, P3M1 group is significant to P1M2, P2M2 and P3M2, P1M2 group is significant to P2M3 group, and P2M2 group is significant to P1M3, P2M3 and P3M3 groups. The P1M1 treatment produces the highest plant height compared to the other treatments because the availability of plant nutrients is sufficient. Plant height growth has a close relationship with the need for nitrogen elements that can stimulate relatively rapid vegetative growth. Physiologically, N plays a role in the synthesis of proteins, chlorophyll, and nucleic acids. Nitrogen also regulates the transition from vegetative to generative stages, affecting the structure of the crown and plant height [7].

Based on the analysis of variance for the treatment of watering frequency and the use of different planting medium types, a p-value of <0.005 was obtained. Because the p-value <0.05, it can be concluded that the treatment of watering frequency and the use of planting medium types showed a significant difference in plant height, so further Duncan tests are needed.

The success of plant growth can be seen from various aspects, one of which is plant height. Chinese betel plants that yield the highest results in terms of plant height are those treated with daily watering and the use of compost soil media. Regular watering will maintain water conditions in the media, allowing plants to absorb water effectively and resulting in increased height and leaf number [8].

3.1.2 Number of leaves

Table 2 shows that the treatment of watering frequency and type of planting media has a significant influence on the number of chinese betel leaves produced. Chinese betel plants achieve the best results when treated with daily watering and the use of compost as planting media, yielding a variable number of leaves with an average value of 59 leaves per plant. Compost triggers an improvement in soil structure, allowing for maximum vegetative growth, which in turn affects plant height and increases the number of leaves significantly [9].

According to Duncan's further test results, it was found that the P1M1 group differed significantly from the P2M1, P3M1, P1M2, P2M2, P3M2, P1M3, P2M3, and P3M3 groups. The P2M1 group is significant to the P1M1 group. The P3M1 group is significant to the P1M1, P1M2, P2M2, and P3M2 groups. The P1M2 group is significant to the P1M1, P3M1, and P2M3 groups. The P2M2 group is significant to the P1M1, P3M1, and P2M3 groups. Water availability is a key factor in determining the number of leaves a plant develops. If the plant does not receive sufficient water before it flowers, it will have fewer leaves and reduced photosynthetic activity.

Table 2. Results of Duncan's follow-up test on the effect of watering frequency and use of planting media on the number of Chinese betel leaves

Treatment	Number Of Leaves	Duncan Test
P1M1	59.83	a
P2M1	17.07	bcd
P3M1	27.13	b
P1M2	5.80	d
P2M2	4.73	d
P3M2	8.93	cd
P1M3	15.70	bcd
P2M3	21.93	bc
P3M3	13.80	bcd

Note: Identical letters in the Duncan Test column indicate no significant difference in the Duncan test (DMRT) at the 5% level.

Leaf growth in plants is an indicator of plant growth; the more leaves that grow, the greater the opportunity for plants to carry out photosynthesis. As the principal sites of photosynthesis, leaves determine the plant's potential for energy conversion. A higher leaf count corresponds to a larger surface area for the interception of CO2 and light. Plants with the highest number of leaves are found in treatments with daily watering frequency and the use of compost as planting media. Planting media mixed with compost can provide nutrients for plants to form leaves. With the increase in the number of leaves, the plant produces more carbohydrates, which are produced by generated through the photosynthesis process, thereby accelerating plant growth and development [10].

3.1.3 Fresh weight of plants

Based on Table 3, it can be seen that the highest fresh weight of chinese betel is achieved in the treatment where watering is done once a day and compost is used as planting media, which amounts to 14.49g. Chinese betel plants that are watered once a day have the highest weight compared to other watering frequencies in all types of plant media. The fresh weight of the plant is directly proportional to its water content; therefore, the higher the water content in the plant, the higher its fresh weight. Media with 100% compost produced greater fresh weight in lettuce shoots, indicating optimal availability of nutrients and moisture [11].

Table 3. Results of Duncan's follow-up test on the effect of watering frequency and planting media on the fresh weight of Chinese betel

Treatment	Fresh weight of plants	Duncan Test
P1M1	14.49	a
P2M1	13.58	a
P3M1	4.82	b
P1M2	1.06	b
P2M2	0.39	b
P3M2	0.51	b
P1M3	5.95	b
P2M3	3.40	b
P3M3	2.72	b

Note: Identical letters in the Duncan Test column indicate no significant difference in the Duncan test (DMRT) at the 5% level.

Fresh weight is a combination of the development and growth of plant tissues, including plant height, leaf number, and root weight. The water content and nutrient content influence the fresh weight of plants in the plant tissue cells. Plants subjected to shorter irrigation

intervals (5 days) consistently demonstrated significantly higher average fresh and dry weights compared to those maintained under prolonged watering schedules. Besides being used as a growth parameter, the fresh weight variable also plays a role in determining the quality of plant yield.

According to the results in Table 3, it was found that group P1M1 was significantly different from groups P3M1, P1M2, P2M2, P3M2, P1M3, P2M3 and P3M3. Additionally, group P2M1 was significantly different from groups P1M2, P2M2, P3M2, P1M3, P2M3, and P3M3. Shorter watering intervals increased plant height and leaf number, and biomass weight in many crops [12].

3.1.4 Crown root ratio

The crown root ratio is the ratio of the dry weight of the roots to the dry weight of the crown plant. Plant root development correlates with crown development under water stress conditions, which causes changes in the crown root ratio. The crown root ratio is used to determine the ability of Chinese betel plants to maintain functional balance in stressful environment. The crown root ratio is plastic, which is also influenced by the availability of water, nitrogen, oxygen, and low temperatures.

Table 4. Results of Duncan's follow-up test on the effect of watering frequency and use of planting media on the crown root ratio of Chinese betel

Treatment	Crown Root Ratio (gram)	Duncan Test
P1M1	0.11	a
P2M1	0.03	b
P3M1	0.03	b
P1M2	0.02	b
P2M2	0.01	b
P3M2	0.01	b
P1M3	0.03	b
P2M3	0.02	b
P3M3	0.02	b

Note: Identical letters in the Duncan Test column indicate no significant difference in the Duncan Test (DMRT) at the 5% level.

Based on Table 4, there is an interaction between the frequency of watering and the planting media on the crown root ratio. The highest ratio of root crown weight was found in the treatment of watering once a day and using compost planting media, namely 0.11 g. The P1M1 group is significant to the P1M1 group. P1M1 group was significant to P2M1, P3M1, P1M2, P2M2, P3M2, P1M3, P2M3 and P3M3 groups. A negative correlation was observed between nitrogen (N) supply and the root-to-shoot ratio, with the ratio incrementally increasing as N availability declined. Plant roots play a crucial role in resource acquisition and plant performance when soil nutrient availability is limited. The availability of nutrients for plants will affect the root-to-crown ratio mechanism [13].

3.2 Plant proximate, vitamin C and antioxidant test

Proximate test is a test of a product that is carried out with the aim of knowing the various kinds of nutritional content in the product. The proximate test is carried out after the plants are harvested in a fresh state.

Table 5. Proximate test on Chinese betel plant with frequency of watering and the use of growing media

Treatment	Water (% wb)	Carbohidrat (% wb)	Vit.C (mg/100g)	Antioxidant (% inhibisi)
P1MI	95.20 a	2.78 ab	45.57c	0.33 b
P1M2	95.13 a	2.79ab	49.15c	0.35 b
P1M3	95.78 a	1.43c	78.86a	0.46 a
P2M1	95.08 a	2.84ab	69.44b	0.40 ab
P2M2	94.46 a	3.60a	49.63c	0.25 b
P2M3	95.36 a	2.22b	75.14a	0.48 a
P3M1	94.75 a	2.95ab	66.01b	0.50 a
P3M2	95.08 a	2.66ab	62.04b	0.50 a
P3M3	94.70 a	3.40a	62.56b	0.48 a

Note: Numbers followed by the same letter in the same column indicate no significant difference in Duncan's test (DMRT) at the 5% level.

In Table 5, it is noted that chinese betel plants have a very high-water content, reaching 95%. The results of the DMRT analysis on the water content of chinese betel are followed by the same letter which means that there is no real difference. The highest water content was found in the treatment using chopped fern (P1M3) planting media. Because the fern planting media has a high-water binding capacity. Fern planting media has the advantages of a high water-binding capacity, good aeration and drainage and is not easily weathered [14].

Table 5 shows that the Chinese betel plant also contains carbohydrates. Further DMRT analysis results showed that the carbohydrate levels in each treatment were significantly different. The carbohydrate content results for sample P1M3 are followed by different letters, indicating a significant difference in results. This sample (P1M3) showed the lowest carbohydrate content (1.43%) when treated with a once-daily watering frequency and using chopped fern media. The highest carbohydrate content in chinese betel is usually achieved under optimal watering conditions (neither too little nor too much), as this allows the stomata to open fully to absorb CO_2 and keep the photosynthesis process running at its highest rate. Photosynthesis increases the accumulation of carbohydrates, including sucrose, starch, and soluble sugars.

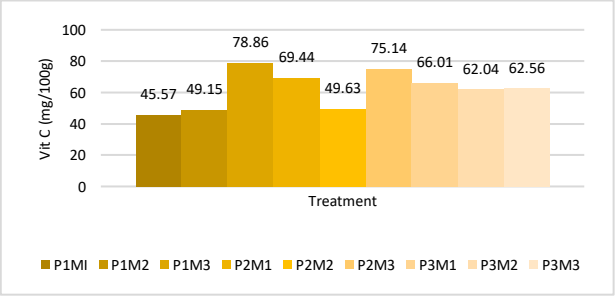

Fig. 1. Diagram of vit c content of Chinese beteL

Proximate tests on the Chinese betel plant revealed a relatively high vitamin C content. Fig. 1 Research has shown that 100g of fresh Chinese betel contains 45-78% vitamin C. Vitamin C levels exhibited significant differences between treatments. The highest levels in this study were observed in the treatment with daily watering frequency and chopped fern growing media, reaching levels of 78.86%. The process of vitamin C formation is strongly influenced by photosynthesis and the biosynthetic reactions that occur. Therefore, several nutrients such as N, P, and K are crucial because they are related to photosynthesis, enzyme reactions, and energy transfer, which in turn influence vitamin C formation. Ascorbic acid

(Vitamin C) is indispensable for maintaining the operational integrity of photosynthesis, fulfilling a variety of critical functions within the chloroplasts.

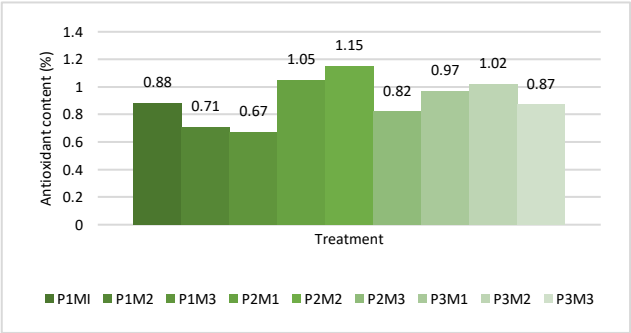

Fig. 2. Diagram of Chinese betel antioxidant content

The data showed that Chinese betel also contains antioxidants in the range of 0.67- 1.15%. Fig. 2, shows that the difference in antioxidant levels was not significant among the treatments. There is no definite benchmark regarding "how much difference" in antioxidant results is considered not significantly different. In this research case the difference is determined to be greater than 1, which suggests that the results above do not exhibit a significant difference, which can be confirmed by calculating the difference in the results of each sample, as the results are less than the specified difference value. The highest antioxidant levels in this study were observed in the treatment with watering every other day and a planting medium of broken bricks, which yielded a value of 1.15%. Watering the broken brick media every two days can increase antioxidant levels because partial drought conditions trigger plants to produce antioxidants as a defense mechanism against stress, while the broken bricks as an inorganic medium provide good aeration and drainage, preventing problems such as root rot that can inhibit the production of antioxidants and rients, and support the formation of healthy roots for optimal rient absorption [15].

4 Conclusion and recommendation

Based on the study's results, there is an interaction between watering frequency and the use of different planting media types on the growth and yield of Chinese betel. The combination of watering once a day and using compost as the growing medium (P1M1) resulted in the highest growth and yield of Chinese betel in terms of plant height (26.4 cm), number of leaves (57 leaves), fresh weight of cuttings (14.49 g), and root-to-shoot ratio (0.11 g).

The results of the Chinese betel showed the presence of water, carbohydrates, vitamin C, and antioxidants. The content of water, carbohydrates, and antioxidants showed no significant difference among the treatments. Meanwhile, the vitamin C content showed significant differences among the various treatments. The highest vitamin C content was in the P1M3 treatment (78.86 mg/100g).

Therefore, if the objective is to achieve high plant growth or as part of an environmentally friendly domestication effort, the selection of media and watering frequency is very influential, and it is recommended to use the P1M1 treatment. Meanwhile, for the content results (water, carbohydrates, and antioxidants), neither the plant media nor the watering frequency shows a significant effect.

References

1. S. Kosasih, N. Ginting, L. Chiuman, I. Nyoman, E. Lister, The Effectiveness of Peperomia Pellucida Extract Against Acne Bacteria, Technol. Sci. Am. Sci. Res. J. Eng. **59**, 149 (2019).
2. H. Ningsih, H.M. Puspitasari, Z. Arifin, A. Via, P. Mars, Analysis of Primary Metabolite Content in Shallot Bulbs from Bantul and Sragen Basic Steps for Plant Breeding, **8**, 199 (2025).
3. C.O. Matondang, Nurhayati, Pengaruh Cekaman Air Terhadap Pertumbuhan Dan Produksi Tanaman Kopi, BEST J. (Biology Educ. Sains Technol. **5**, 249 (2022).
4. V. Hiremata, M. Narayanaswamy, R.M. Shet, Assessment of Growth and Yield Parameters in Arecanut (Areca Catechu L.) through Correlation and Path Analysis under Hilly Zone of Karnataka, J. Hortic. Sci. **17**, 333 (2022) https://doi.org/10.24154/jhs.v17i2.992.
5. A. Hamid, E. Wahyuningsih, N. Chaerani, J. Kehutanan, F. Pertanian, U. mataram, J. Majapahit No, Karakteristik Habitat Sirih Hutan (Aristolochia Tagala) Sebagai Pakan Larva Troides Helena Di Kawasan Taman Nasional Gunung Rinjani Kabupaten Lombok Timur (Habitat Characteristics of Forest Betel (Aristolochia Tagala) as Food for Troides Helena Larvae In , J. Biol. Dan Pendidik. Biol. **2**, 26 (2025) https://doi.org/10.71024/bioindikator.2025.v2i1.296.
6. F. Soboyejo, O.E. Ade-Ademilua, Growth and Antidiabetic Activities of Peperomia Pellucida L. Plants Grown under Different Watering Regimes, Unilag J. Med. Sci. Technol. **5**, 1 (2017).
7. M.A. Husna, N. Agriculture, T. Academy, M. Maliha, R. Islam, Growth and Flowering of Lisianthus with Different Nitrogen Doses, (2023) https://doi.org/10.18801/jbar.300223.308.
8. J. Jamaludin, M.G. Ranchiano, Pertumbuhan Tanaman Vanili (Vanilla Planifolia) Dalam Polybag Pada Beberapa Kombinasi Media Tanam Dan Frekuensi Penyiraman Menggunakan Teknologi Irigasi Tetes, J. Agro Ind. Perkeb. **9**, 65 (2021) https://doi.org/10.25181/jaip.v9i2.1867.
9. S. Suvendran, M.F. Acevedo, B. Smithers, S.J. Walker, P. Xu, Soil Fertility and Plant Growth Enhancement Through Compost Treatments Under Varied Irrigation Conditions, Agric. **15**, 1 (2025) https://doi.org/10.3390/agriculture15070734.
10. N. Augustien, K. Dan, H. Suhardjono, Peranan Berbagai Komposisi Media Tanam Organik Terhadap Tanaman Sawi (*Brassica Juncea* L.) Di Polybag [Role Of Various Media Composition Of Organic Plant Planting Mustard (*Brassica Juncea* L.) In Polybag], Agritop J. Ilmu-Ilmu Pertan. **1**, 54 (2023).
11. M. Marutani, S. Clemente, Compost-Based Growing Media Improved Yield of Leafy Lettuce in Pot Culture, Agronomy **11**, 1 (2021) https://doi.org/10.3390/agronomy11091762.
12. S. Naz, M.A. Anjum, B. Siddique, S.A.H. Naqvi, S. Ali, H. Sardar, S.T.A. Haider, M.A. Zulfiqar, H. Azeem, S. Ullah, S. Pasand, Z. Khan, Effect of Sewage Water Irrigation Frequency on Growth, Yield and Heavy Metals Accumulation of Tomato and Okra, Pakistan J. Agric. Res. **33**, 798 (2020) https://doi.org/10.17582/journal.pjar/2020/33.4.798.809.
13. H. Bacher, Y. Sharaby, H. Walia, Z. Peleg, Modifying Root-to-Shoot Ratio Improves Root Water Influxes in Wheat under Drought Stress, J. Exp. Bot. **73**, 1643 (2022) https://doi.org/10.1093/jxb/erab500.

14. T. Sudartini, D. Zumani, D. Diantini, Pengaruh Sungkup Dan Jenis Media Tanam Terhadap Pertumbuhan Bibit Anggrek Dendrobium Saat Aklimatisasi, Media Pertan. **5**, 31 (2020) https://doi.org/10.37058/mp.v5i1.2136.
15. A.M. Pisoschi, A. Pop, F. Iordache, L. Stanca, G. Predoi, A.I. Serban, Oxidative Stress Mitigation by Antioxidants - An Overview on Their Chemistry and Influences on Health Status, Elsevier Masson SAS, Eur. J. Med. Chem. **209**, 112891 (2021) https://doi.org/10.1016/j.ejmech.2020.112891.