WisDM Green: Harnessing Artificial Intelligence to Design and Prioritize Compound Combinations in Peat Moss for Sustainable Farming Applications

Peter Wang[1], Kui You[1], Yoon Hun Ong[1], Joe Ning Yeoh[1], Jerica Ong[1], Anh Thanh Lan Truong[1], Agata Blasiak[1], Edward Kai-Hua Chow[1], and Dean Ho[1]

[1]National University of Singapore

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Abstract

The substantial increase in global population and climate change, among other factors have led to global food security and supply chain challenges. The United Nations has laid out an agenda to sustainably achieve zero hunger by 2030 as one of its sustainable development goals. However, sustainably achieving improved food yield has become a challenge as excessive use of fertilizers has also led to adverse environmental impact. To address the aforementioned challenges, WisDM Green, an artificial intelligence (AI)-based platform that aims to pinpoint and prioritize compound (e.g. biostimulants) combinations in peat moss, is harnessed to sustainably improve the yield of Amaranthus cruentus (red spinach). In this proof-of-concept study, from a pool of 8 compounds, WisDM Green-pinpointed combinations (6-Benzylaminopurine/Ethylenediaminetetraacetic Acid Iron (III) and Humic Acid/Seaweed Extract) achieve 26.34±15.80 and 33.59±14.60 increase in %Yield, respectively. The study also indicates that compound combinations may exhibit concentration-dependent synergies and thus, properly adjusting the concentration ratios of combinations may further improve plant yield in the context of sustainable farming.

P. Wang and K. You contributed to this work equally.

Corresponding author(s) Email: agata.blasiak@nus.edu.sg, edwardkchow@nus.edu.sg, biedh@nus.edu.sg

ToC Figure

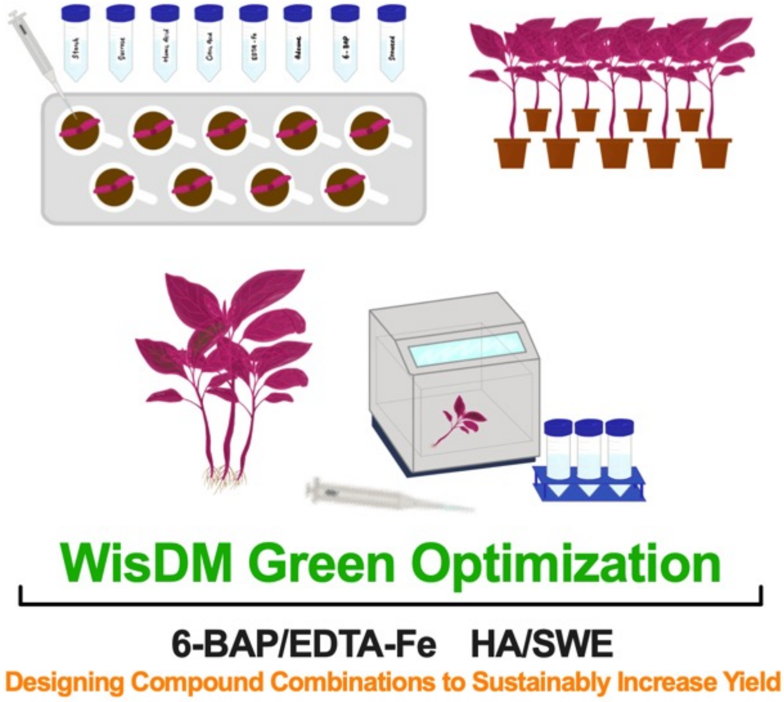


Figure 1: **ToC Figure.** WisDM, an artificial intelligence-based platform, is harnessed to design and prioritize compound combinations to sustainably increase the yield of Amaranthus cruentus (red spinach). This workflow enables the prioritization of WisDM Green-pinpointed combinations, such as humic acid in combination with seaweed extract, and these combinations were able to achieve 15-35% increase in the biological yield of red spinach.

Introduction

Global food security challenges have become apparent due to multiple factors including a substantial increase in the global population, climate change, and water scarcity.[1] By 2050, global food supply chains must ensure sufficient nourishment for an estimated 9 billion people, which is 60% more than the demand at present (Nations; Breene). This rising demand is partly due to shifts to richer diets (e.g. dairy, processed food) in certain parts of the world, which have also included an increase in grain consumption (Breene; Shi et al., 2021). Moreover, substantial climate change and land degradation have further exacerbated food security globally (Fujimori et al., 2019; Hasegawa et al., 2018; Ramankutty et al., 2018; Smith et al., 2020). Specifically, 11.1% of households in the United States were food insecure in 2018 and 12.7% were food insecure in Canada, suggesting that the food security challenge is not specific to underdeveloped regions (Long et al., 2020). This challenge has also been amplified as a result of the COVID-19 pandemic, as availability, access, and stability of the food supply have been compromised (Zurayk, 2020). According to the United Nations, nearly 2.37 billion people did not have access to an adequate food supply in 2020, which accounted for a 15.6% increase from pre-pandemic times (nat). Therefore, continuous efforts to sustain an increasingly stressed food supply chain both during and after the pandemic will be essential.

In the context of agriculture, extensive efforts have been made to increase the production yield of crops. Notably, the overapplication of fertilizers in an effort to enhance yield has been widely employed, resulting in sub-optimal outcomes as well as fertilizer wastage (Good and Beatty, 2011; Yizong Huang, 2000). The excessive use of fertilizers, specifically nitrogen-based formulations, has often resulted in adverse environmental impact, such as soil degradation and harmful effects on aquatic life due to water pollution (Ahmed et al., 2017; Qi et al., 2018; Kopittke et al., 2019; Khan et al., 2018). The emissions of nitrous oxide as a result of microbial conversions have also directly contributed to climate change and global warming (Zhao et al., 2019). Thus, an equilibrium between food security and sustainability must be achieved to meet the demands of population growth while preventing further environmental deterioration.

Recent research strategies have applied advanced technologies including artificial intelligence (AI) and automation towards agriculture, especially crops, in attempt to achieve an equilibrium between sufficient food supply and food production sustainability. For example, controlled-release fertilization strategies have resulted in reductions in greenhouse gas emission and nitrogen leaching without compromising the overall yield (Li et al., 2018; Sikora et al., 2020; Xiao et al., 2019; ul Haq et al., 2020; Wang et al., 2020). Furthermore, multiple studies have harnessed AI to achieve precision agriculture, crop yield prediction, and decision support in agriculture and supply chain management (Zhang et al., 2021; Kouadio et al., 2018; Jung et al., 2021; Basso and Antle, 2020; Kim et al., 2019; Waleed et al., 2020; Geethanjali and Muralidhara, 2020; Ghasemi-Varnamkhasti et al., 2019). These approaches have demonstrated the feasibility and potential benefit from intersecting agriculture and AI and thus, provide a new avenue towards digitized, sustainable farming. Proposing an alternative approach to sustainably achieve improved crop yield, we report the application of an optimization platform, termed WisDM Green, to simultaneously pinpoint suitable compound combinations (e.g. biostimulants) in peat moss and pinpoint their concentration ratios that can mediate positive effects on the yield of *Amaranthus cruentus* (red spinach), which was used for experimental validation in this proof-of-concept study. Red spinach was selected for this study due to its short growing season, manageable growing conditions and importantly, its rising popularity in healthy diets.

This work sought to overcome a pervasive challenge in yield enhancement without reliance on excessive use of fertilizers. While a number of compounds have been proposed as potential mediators of improved crop yield, the importance of pinpointing suitable compound combinations, and the respective concentration of each compound in these combinations is a key barrier towards yield enhancement. For example, the role of compound concentrations in determining which compounds should comprise optimal combinations creates prohibitively large parameter spaces that cannot be resolved through brute force, as the sheer number of experiments required may be insurmountable. To overcome this challenge, WisDM Green interrogated the interaction space from a pool of 8 compounds via an AI-discovered, second-order quadratic series that describes the correlation between compounds and their corresponding biological response (e.g. dry weight). The biomedical implications of this correlation were previously discovered in *in vitro* cellular response to therapeutics using neural networks (Al-Shyoukh et al., 2011). Subsequently, this correlation was validated in multiple *in vitro* and *in vivo* studies for biomedical applications ranging from oncology to COVID-19 (Clemens et al., 2019; Lee et al., 2017; Rashid et al., 2018; Silva et al., 2016; Blasiak et al., 2020, 2021; Abdulla et al., 2020; Ding et al., 2019; Khong et al., 2020). The optimization of treatment outcomes using the second-order quadratic series was further confirmed in prospective human studies (Kee et al., 2019; Pantuck et al., 2018; Zarrinpar et al., 2016; de Mel et al., 2020). Due to the broadly demonstrated effectiveness of this approach towards mediating optimal outcomes in living systems, this study sought to apply this approach for multi-compound prioritization towards positive yield outcomes. It should be noted that previous studies have examined the role of a quadratic model towards optimizing drug combinations to achieve optimal clinical outcomes. However, this current study aimed to bridge the multi-compound design input with plant yield output. In addition, this current study has harnessed WisDM Green and associated drug development-centric approaches to pinpoint unforeseen concentration-dependent compound interactions that may actionably mediate yield improvement with a simultaneous reduction in the concentrations of certain compounds towards sustainable implementation of this approach. Importantly, WisDM Green differs from traditional AI-based approaches as it does not utilize any pre-existing compound information, big data, or *in silico* modeling. Instead, WisDM Green harnesses experimentally obtained data (e.g. biological yield or dry weight) to determine suitable compound combinations and their respective concentration ratios via prospective validation studies. Furthermore, WisDM Green also differs from the response surface methdology (RSM), which has been used to modulate input variables (e.g. magnetic field, minerals) to improve growth and yield in plants (Iqbal et al., 2013; Poothong, 2020). In this study, WisDM Green simultaneously interrogated the interaction space of multiple compounds at various concentration ranges, pinpointing effective combinations based on experimentally-detected compound interactions. However, RSM only assesses 2 input variables at a time to determine the response, or interaction, of the input factors (e.g. magnetic field). Nonetheless, RSM has laid important foundations for paired interactions in farming applications.

In this study, an initial pool of 8 compounds that have previously demonstrated feasibility in enhancing plant yield was finalized using a decision tree. These 8 compounds included Potato Starch (Starch), Sucrose, Humic Acid (HA), Citric Acid (CA), Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), Adenine, 6-Benzylaminopurine (6-BAP), and Seaweed Extract (SWE). Subsequently, WisDM Green assessed their interactions in red spinach that were grown with liquid fertilizers (Starxgrow) to pinpoint unique compound interactions that may lead to improved yield. WisDM Green harnessed prospectively obtained biological yield, or dry weight, data of red spinach grown in a set of compoundcombinations and subsequently, formulated a ranked list of optimal combinations based on percent yield (%Yield), which is the percentage difference in biological yield between treated and control plants. The streamlined workflow to determine compound combinations is outlined in **Figure 2**. Notably, 6-BAP/EDTA-Fe and HA/SWE combinations were able to achieve 26.34±15.80 and 33.59±14.60 increases in %Yield, respectively. Further interaction analysis suggested that compound combinations may have concentration-dependent interactions. Specifically, HA/SWE at concentrations 2 g L^{-1} and 12.5% v/v, respectively, resulted in 33.59±14.60 increase in %Yield; however, adjusting the concentration ratio to 0.25 g L^{-1} and 100% v/v, respectively, HA/SWE resulted in 9.36±14.42 decrease in %Yield. Concentration-dependent synergies observed in this study suggest that WisDM Green-pinpointed combinations containing lower or higher concentrations of specific compounds may potentially improve yield outcomes compared to traditional titration or high concentration approaches. Moreover, the nutrition profiles of red spinach grown with WisDM Green-pinpointed compound combinations had no statistically significant difference when compared to red spinach grown under control conditions, suggesting that improved %Yield may be achieved without compromising nutritional values. In this study, WisDM Green served as a proof-of-concept platform towards sustainable combinatorial design of growth compounds to increase plant yield without fertilizer-driven enhancement. This platform may also be broadly applicable towards other classes of agricultural products. However, further refinement of the platform will need to be considered in order for potential translation into a scalable agricultural workflow.

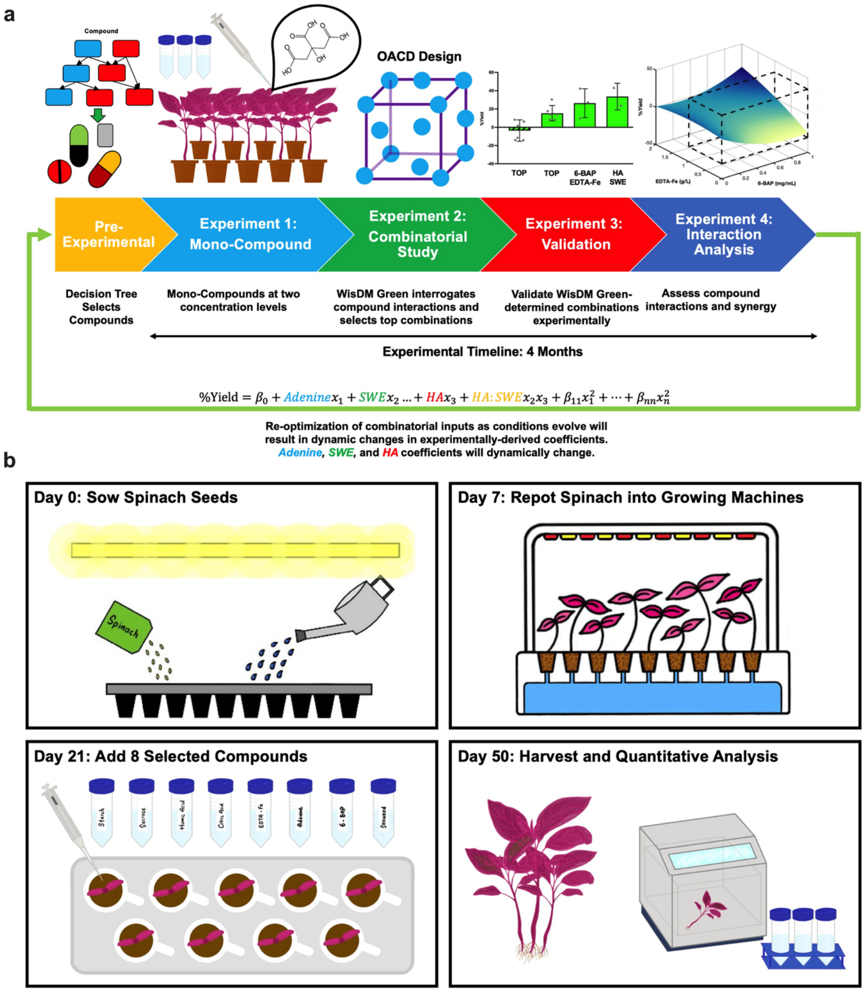


Figure 2: **WisDM Green Workflow and Experimental Timeline. a)** The workflow for WisDM Green to determine effective compound combinations that may increase the %Yield of red spinach. **b)** On day 0, the red spinach seeds were sowed in a cell tray with sufficient water and light. Red spinach were repotted into the gardening machines upon germination on day 7. Compounds individually and in combinations were added to red spinach on day 21. They were harvested on day 50 and quantitatively analyzed.

Experimental Section/Methods

Decision Tree and Compound Preparation

In the pre-experimental stage, the WisDM Green Decision Tree was used to determine appropriate compounds that may enhance agriculture/food production yield. This decision tree integrated several major parameters as outlined in **Figure 3**. A decision whether suitable or not suitable was provided for each compound. In this study, 8 initial compounds were selected for WisDM Green analysis.

Potato Starch (Starch) (Sigma Aldrich, S2004), Sucrose (Sigma Aldrich, S5391), Humic Acid (HA) (Sigma Aldrich, 53680), Citric Acid (CA) (C2404), Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe) (Sigma Aldrich, E6760), Adenine (Sigma Aldrich, A5665), 6-Benzylaminopurine (6-BAP) (Sigma Aldrich, B3274), and Seaweed Extract (SWE) (Horti Flora). All compounds above, except HA and Adenine, were readily soluble and diluted to 2 concentration levels using deionized water (Merck Millipore). Moreover, 6-BAP came as solution (1 mg mL^{-1}), and was diluted to desired concentration levels (mg mL^{-1}). HA and Adenine were dissolved using NaOH (2 M) and HCl (2 M), respectively, and they were subsequently neutralized (pH 7). The unit for the concentration of SWE is expressed in % volume/volume (% v/v).

Red Spinach Growth Protocol

Throughout the WisDM Green workflow, *Amaranthus cruentus* (red spinach) (Everything Green Pte Ltd) seeds were sowed in peat moss (Everything Green Pte Ltd) on day 0 and repotted into gardening machines (9 plants per machine) (Click & Grow LLC) on day 7. The machines provided continuous water supply and 16 h of light per day (**Figure 2b**). On day 21, after reaching seedling stage, Starxgrow Nitrosol Liquid Fertilizer (10.5% N, 2.3% P, 6.8% K, and 1.68% Ca) (Starxgrow) was added to every plant. Mono-compounds and compound combinations were applied to each plant on day 21, except the control red spinach, which contained only the Starxgrow Nitrosol Liquid fertilizer. Water was added to the tank in the machine when level was low. The water in Singapore goes through purification process and may include traces of chlorine (202, a). The parameters of water in Singapore are outlined in **Table 1**. Red spinach were harvested on Day 50. The complete schedule for all 4 experiments is listed in **Table 2**. All plants were randomized across all machines using the example code in the Supporting Information.

Red Spinach Analysis

All red spinach samples were analyzed according to **Table 3**. This series of measurements including biological yield and nutrient content was performed independently by STATS Asia Pacific in Singapore (71 Toh Guan Rd E #02-01/02/06 TCH Techcentre Singapore 608598).

WisDM Green Optimization

In this study, %Yield is defined as the percent change in dry weight, or biological yield, of treated red spinach with respect to the control red spinach that contained only the fertilizer (no additional compounds). The equation to calculate %Yield is outlined in **Equation (1)**:

$$\%Yield = \frac{Dry\ Weight\ of\ Treated\ Red\ Spinach - Dry\ Weight\ of\ Control\ Red\ Spinach}{Dry\ Weight\ of\ Control\ Red\ Spinach} \cdot 100\%$$

Water Parameters	Unit	WHO Guideline	Singapore Average
Microbiological Parameter			
Escherichia coli (***E. coli***)	cfu/100mL	¡1	¡1
Physical Parameters			
Conductivity	µS/cm	-	205
pH Value	Units	-	8.2
Dissolved Solid	mg/L	-	107
Turbidity	NTU	5	0.12
Chemical Parameters			
Acrylamide	µg/L	0.5	¡ 0.1
Antimony	µg/L	20	¡ 1
Arsenic	µg/L	10	¡ 0.5
Aluminum	mg/L	-	0.02
Barium	mg/L	1.3	0.01
Benzene	µg/L	10	¡ 1
Boron	mg/L	2.4	0.3
Cadmium	µg/L	3	¡ 0.2
Calcium	mg/L	-	15
Chloride	mg/L	-	30
Chlorine	mg/L	5	2.38
Chlorite	mg/L	0.7	¡ 0.02
Chloroform	µg/L	300	11
Chromium	mg/L	0.05	¡ 0.01
Copper	mg/L	2	¡ 0.0
Cyanide	mg/L	-	¡ 0.03
DDT and Metabolites	µg/L	1	¡ 0.01
Dioxane, 14	µg/L	50	¡ 1
Edetic Acid	µg/L	600	¡1
Fluoride	mg/L	1.5	0.45
Iron	mg/L	9	0.0
Lead	µg/L	-	¡ 0.5
Mercury	µg/L	6	¡ 0.03
Manganese	mg/L	-	¡ 0.0
Magnesium	mg/L	-	0.28
Nickel	mg/L	0.07	¡ 0.0
Nitrate	mg/L	11	0.07
Nitrite	mg/L	0.9	¡ 0.01
Perchlorate	µg/L	70	¡ 2
Selenium	µg/L	40	¡ 0.5
Sulfate	mg/L	-	7
Silica	mg/L	-	0.83
Sodium	mg/L	-	19
Toulene	µg/L	700	¡ 5
Total Organic Carbon	mg/L	-	0.8
Total Alkalinity (CaCO3)	mg/L	-	40
Total Phosphorous (P)	mg/L	-	0.01
Uranium	µg/L	30	0.01
Vinyl Chloride	µg/L	0.3	¡ 0.1
Xylenes	µg/L	500	¡ 15

Experiment 1/2: Mono-Compound and Combinatorial Study			
Date	Day	Tasks	Water
2021-06-22	0	Sowed Red Spinach Seeds	
2021-06-29	7	Repotted into Machines with Peat Moss	2 L
2021-07-05	13	Added Water	2 L
2021-07-13	21	Added Liquid Fertilizer and Compounds	
2021-07-19	27	Added Water	1 L
2021-07-27	35	Extended the Light Source (25 cm to 40 cm)	1 L
2021-08-11	50	Sent Samples to STATS Asia Pacific	
Experiment 3/4: Validation Study and Interaction Analysis			
Date	Day	Tasks	Water
2021-09-01	0	Sowed Red Spinach Seeds	
2021-09-08	7	Repotted into Machines with Peat Moss	2 L
2021-09-14	13	Added Water	2 L
2021-09-22	21	Added Liquid Fertilizer and Compounds	
2021-09-28	27	Added Water	1 L
2021-10-06	35	Extended the Light Source (25 cm to 40 cm)	1 L
2021-10-21	50	Sent Samples to STATS Asia Pacific	

Table 2: **Experimental Timeline for the WisDM Green Workflow.** The schedules below were strictly complied to ensure consistent conditions across experiments. Dates are in MM/DD/YYYY format.

	Testing Items	Standards & Test Methods
Morphology	Dry Weight	GB/T 8304
	Leaf Size	Australian Journal of Botany, 2003, **51**
	Root Length	
	Water	GB/T 8304
Nutrients	Protein	AOAC 984.13, AOAC 991.2
	Vitamin C	Anal. Chem. Vol. 71, No. 6, 1988
Element Content	P	AOAC 2015.06
	K	
	Ca	
	Mg	
	Fe	
	Mn	
	Zn	

Table 3: **Red Spinach Analyses.** All the performed tests and their respective methods are summarized below.

In **Equation (1)**, control red spinach samples only contained the Starxgrow Nitrosol Liquid Fertilizer with no additional compounds. However, the treated red spinach samples (mono- compounds and combinations) contained both the Starxgrow Nitrosol Liquid Fertilizer and additional compounds. The difference in dry weight between a treated and control spinach divided by the dry weight of control red spinach indicates the percent change in dry weight as a result of the treatment (%Yield).

WisDM Green optimization utilized a set of curated combinations according to a Resolution IV 59-combination OACD, which was generated by combining a 32-combination Resolution IV two-level fractional factorial and a 27-combination three-level orthogonal array (Xu et al., 2013; Lim et al., 2019). The %Yield of all 59 OACD combinations (N = 3) were calculated. WisDM Green correlated all 59 OACD combinations and their respective average experimentally measured %Yield into a second order quadratic series as shown in **Equation (2)**:

$$y = b_0 + b_1x_1 + [?] + b_nx_n + b_12x_1x_2 + b_mnx_mx_n + b_11x_1^2 + [?] + [?] + b_nnx_n^2$$

In **Equation (2)**, y represents the plant's biological response (%Yield) to the addition of compounds, B_0 is the intercept term for the quadratic equation, B_n is the coefficient for the *n*th compound, and B_{mn} is the interaction terms between *m*th and *n*th compound. x_n indicates the concentration levels (0, 1, or 2) of a given compound.

The WisDM Green second order quadratic series was derived from stepwise regression that performed bidirectional elimination of the estimated coefficients using the *P* values from *F*-statistics in MATLAB 2020b (Mathworks, Inc.). This quadratic series was then used to derive the predicted %Yield data for all possible combinations consisting of 8 compounds in three concentration levels ($3^8 = 6{,}561$). Box-Cox transformation was explored to determine appropriate transformations to the %Yield output data. Residual-based outlier analysis was performed based on the residual distribution of the %Yield data.

```
%Load OACD Data and Respective %Yield

data =
[

Starch  Sucrose HA  CA  EDTA-Fe Adenine 6-BAP   SWE %Yield
-1  -1  -1  -1  -1  1   -1  -1  20.5
1   -1  -1  -1  -1  -1  1   1   6.1
-1  1   -1  -1  -1  -1  1   -1  14.6
1   1   -1  -1  -1  1   -1  1   16.5
-1  -1  1   -1  -1  -1  -1  1   43.4
1   -1  1   -1  -1  1   1   -1  -26.6
-1  1   1   -1  -1  1   1   1   3.5
-1  -1  -1  1   -1  -1  -1  -1  -9.3
1   -1  -1  1   -1  1   1   1   -6.8
-1  1   -1  1   -1  1   1   -1  10.5
1   1   -1  1   -1  -1  -1  1   -13.7
-1  -1  1   1   -1  1   -1  1   40.1
```

```
1   -1  1   1   -1  -1  1   -1  32.7
-1  1   1   1   -1  -1  1   1   45.3
1   1   1   1   -1  1   -1  -1  -6.4
-1  -1  -1  -1  1   1   1   1   -5.0
1   -1  -1  -1  1   -1  -1  -1  37.3
-1  1   -1  -1  1   -1  -1  1   17.5
1   1   -1  -1  1   1   1   -1  23.1
...   ...   ...   ...   ...   ...   ...   ...   ...
]

%Define Inputs and Outputs

x = data(: , 1:8);
y = data(: , 9);


%WisDM Green Quadratic Series

result = stepwiselm(x , y, 'quadratic', 'ResponseVar', 'Inhibition', 'PredictorVars', {'Starch', 'Sucros
```

Validation of WisDM Green-determined Combinations

WisDM Green-determined top combinations were subsequently experimentally validated. The workflow to grow red spinach in this experiment followed the aforementioned approach from day 0 to day 50. Aside from the morphological features, validated combinations also had additional nutritional analyses.

Response Surfaces and Bliss Independence Model for Synergy Analysis

Four 2-compound combinations (Adenine/EDTA-Fe, 6-BAP, EDTA-Fe, Adenine/6-BAP, and HA/SWE) were further analyzed via a 4x4 checkerboard design. The design had 16 different combinations with expanded concentrations (0 – 2x Level 2; except 6-BAP) ranging from 0 to 1 g L^{-1} for Adenine, 0 to 2 g L^{-1} for EDTA-Fe, 0 to 1 mg mL^{-1} for 6-BAP, 0 to 2 g L^{-1} for Humic Acid, and 0 to 100% for SWE. Subsequently, the measured %Yield and morphological data for each of the 16 combinations were used to generate a response surface and respective 2-dimenstional heatmap for each 2- compoundcombination in MATLAB 2020b (Mathworks, Inc.). The interaction maps of these 2-compound combinations were generated using GraphPad PRISM 9 (GraphPad Software). The %Yield data were uploaded to SynergyFinder using Bliss Independence Model to quantify synergy in the tested region (Ianevski et al., 2020). The resulting Bliss synergy score data were downloaded and used to generate Bliss Synergy Map using GraphPad PRISM 9 (GraphPad Software).

Financial and Energy Consumption Analysis

Energy consumption was determined based on the number of days (50 days) in which the Click & Grow machines were in use. Since the machines only utilized light for 16 h a day, the total hours in which energy was consumed was 800 h. In accordance to the manufacturer's information on power consumption, each device consumes 6.2 kWh. Furthermore, Singapore's electricity price is currently set at S$0.2255 kW^{-1} h^{-1} (202, b). Calculations for total energy consumption for one machine, one spinach, and total for the experiment were based on the information above. Water consumption was calculated based on the total utilization of water at the time of harvest. A total of 5 L of water was added to each machine for the 50-day growing season. As of 2021, Singapore's National Water Agency charges S$1.52 per m^3 of water. Additionally, the total carbon footprint for red spinach growing cycle was calculated based on Singapore's Operating Margin (OM) GEF, which is 0.4085 kg CO_2 kW^{-1} h^{-1} (tra). The exact pricing of the above-mentioned resources may vary year-to-year and depend on the usage in other jurisdictions. All referenced values are summarized in **Table 4**.

Statistical Analysis

All experiments were performed in at least 3 spinach replicates unless stated otherwise. Standard deviations

<table>
<tr><th colspan="3">Singapore Electricity Standard Price S$0.23/kWh | OM GEF 0.41 kg $\mathbf{CO_2/kWh}$</th></tr>
<tr><td>Energy Consumption/Machine</td><td>10.33 kWh</td><td>S$2.33</td></tr>
<tr><td>Water Consumption/Machine</td><td>5 L</td><td>S$0.01</td></tr>
<tr><td>Total Cost/Machine</td><td>S$2.34</td><td></td></tr>
<tr><td>Total Carbon Footprint/Machine</td><td>4.22 kg CO_2</td><td></td></tr>
<tr><td>Energy Consumption/Spinach</td><td>1.15 kWh</td><td>S$0.26</td></tr>
<tr><td>Water Consumption/Spinach</td><td>0.56 L</td><td>S$ 0.0</td></tr>
<tr><td>Total Cost/Spinach</td><td>S$0.27</td><td></td></tr>
<tr><td>Total Carbon Footprint/Spinach</td><td>0.47 kg CO_2</td><td></td></tr>
</table>

Table 4: **Financial and Energy Consumption Analysis.** The electricity and water usage for the study including carbon footprint are summarized.

(SDs) were determined from the replicates of each sample. The WisDM Green estimated coefficients were analyzed using sum of squares F-test and the significance of P-values served as the removal criterion for each individual coefficient obtained from stepwise regression. Sample distribution was tested with Shapiro-Wilk normality test. The Kruskal-Wallis test was used for multiple comparisons, followed by Dunn's post hoc test for pairwise comparisons. The statistical significance of Bliss synergy scores was determined using one-sample t-test. Student's t-test was performed to determine statistically significant difference of experimental conditions across experiments.

In the WisDM Green optimization step, potential outliers were observed in combinations that had >30 %Yield in standard deviations. To account for biological variation, a strict set of criteria was implemented to remove replicates. Combinations that had >30 %Yield in standard deviations and satisfied at least one of the following exclusion criteria were excluded from WisDM Green analysis. The first factor that was observed to affect red spinach (*Amaranthus cruentus*) growth is spatial bias, and that plants at the corner had less light source. Moreover, the neighboring red plants' height and leaf count also limited the growth and space of some red spinach. In a total of 177 replicates (59 OACD combinations in triplicates), 16 replicates were removed before WisDM Green analysis. Combination 3, 5, 9, 13, 25, 40, 41, and 45 had one replicate that satisfied all three criteria and were subsequently excluded. Combination 17, 24, 27, 49, and 55 had one replicate that satisfied at least two of the three criteria and were removed. One replicate was removed in combination 29 and 59, satisfying one of the three exclusion criteria. Combination 23 had one replicate removed due to experimental error.

Data and Code Availability

All data used in the analysis of this study can be found in this manuscript. Data processing was performed using a custom code written in Python language, and WisDM Green analysis in this study was conducted using a custom code written in MATLAB R2020b (Mathworks, Inc.) with the built-in "stepwiselm" function.

```
from openpyxl import load_workbook
import random
import string

def OACD_read(filename): # put in OACD design and return combination compound and their levels
    fertnames = []
    combinations = dict()
    for i in range(1, 60):
        t = 'Comb_' + str(i) # combination numbering
        combinations[t] = []
```

```
    wb = load_workbook(filename)
    ws = wb['OACD'] # OACD design

    cell_range = ws['A1':'H1']
    cell_range = cell_range[0]
    for cell in cell_range:
        fertnames.append(cell.value)

    for i in range(2,61):
        t = 'Comb_' + str(i-1)
        j = -1
        cell_range = ws['A'+str(i):'H'+str(i)]
        cell_range = cell_range[0]
        for cell in cell_range:
            j += 1
            if cell.value != -1:
                combinations[t].append(fertnames[j] + '_' + str(cell.value))

    wb.close()

    result = [fertnames, combinations]
    return result

def Allocation(filename):
    allocation = dict()  # dictionary store gardening machine pod & combs pairs
    stack_1 = list()  # three lists help randomization
    stack_2 = list()
    temp = list()

    # stack_1 stores the triplicates of 59 combinations
    for i in range(1, 60):
        t = []
        t.append('Comb_' + str(i))
        t *= 3
        stack_1.append(t)

    # stack_1 stores triplicates of controls and traditional fertilizers
    stack_1.append(['Control'] * 3)
    stack_1.append(['Traditional'] * 3)

    wb = load_workbook(filename)  # file for OACD design
    ws = wb['Sheet1']  # sheet containing OACD design

    # stack_1 stores mono compound treatments with triplicates
    cell_range = ws['A1':'H1']
    cell_range = cell_range[0]
    for cell in cell_range:
        t = []
        t.append(cell.value + '_0')
        t *= 3
```

```
    stack_1.append(t)
    t = []
    t.append(cell.value + ’_1’)
    t *= 3
    stack_1.append(t)


random.shuffle(stack_1)  # randomization


# pairing gardening machines with compound treatments
for letter in string.ascii_uppercase:


    car = list()  # temporary list for randomization

    if len(stack_1) < 9:
        pass
        if not stack_2:
            for j in stack_1:
                car.append(j.pop())
            allocation[’Z’] = car

        else:
            for j in stack_1:
                car.append(j.pop())

            random.shuffle(stack_2)
            for j in range(9 - len(stack_1)):
                t = stack_2.pop(0)
                car.append(t.pop())
                if t:
                    temp.append(t)

            stack_1 += stack_2
            random.shuffle(stack_1)
            stack_2 = temp
            temp = []

            allocation[letter] = car

    else:
        pass
        for i in range(9):
            t = stack_1.pop(0)
            car.append(t.pop())
            if t:
                stack_2.append(t)

        allocation[letter] = car
```

```
            pass
            print('machine ' + letter + 'loading combinations completed!!!')
            print(allocation)  # print out results

    wb.close()

    # file store the randomization results
    with open('allocation.txt', 'w', encoding='utf-8') as f:
        for letter in string.ascii_uppercase:
            f.write(letter + ': ' + str(allocation[letter]))
            f.write('\n')

    return allocation


def Application(fertnames, combinations, allocation):

    application = dict()
    for fert in fertnames:
        for i in range(2):
            application[fert + '_' + str(i)] = []
    application['Traditional'] = []

    keys = application.keys()
    comb_names = combinations.keys()

    for letter in string.ascii_uppercase:
        i = 0
        for pod in allocation[letter]:
            i += 1
            if pod in keys:
                application[pod].append(letter + str(i))
            elif pod in comb_names:
                for fert in combinations[pod]:
                    application[fert].append(letter + str(i))

    with open('application.txt', 'w', encoding='utf-8') as f:
        for key in keys:
            f.write(key + ': ' + str(application[key]))
            f.write('\n')

    return application

if __name__ == "__main__":
    [fernames, combinations] = OACD_read('WisDM Green Experiment Design.xlsx')
    allocation = Allocation('WisDM Green Experiment Design.xlsx')
    application = Application(fernames, combinations, allocation)
    print(application)
```

```
from openpyxl import load_workbook
import random

def OACD_read(filename): # return fertilizer name list & combination level dictionary
    fertnames = []
    combinations = dict()
    for i in range(1, 37):
        t = 'Comb_' + str(i) # combination numbering
        combinations[t] = []

    wb = load_workbook(filename)
    ws = wb['Validation Combos']

    cell_range = ws['B1':'F1']
    cell_range = cell_range[0]
    for cell in cell_range:
        fertnames.append(cell.value)

    for i in range(2,38):
        t = 'Comb_' + str(i-1)
        j = -1
        cell_range = ws['B'+str(i):'F'+str(i)]
        cell_range = cell_range[0]
        for cell in cell_range:
            j += 1
            if cell.value != -1:
                combinations[t].append(fertnames[j] + '_' + str(cell.value))

    wb.close()

    result = [fertnames, combinations]
    return result

def Allocation(filename):
    allocation = dict()  # dictionary for pairing gardening machine pods with combinations
    stack_1 = list() # three lists help randomization
    stack_2 = list()
    temp = list()

    # stack_1 stores the triplicates of all combinations
    for i in range(1, 37):
        t = []  # temporary list for randomization
        t.append('Comb_' + str(i))
        t *= 3
        stack_1.append(t)



    # stack_1 stores controls
    stack_1.append(['Control'] * 3)
    stack_1.append(['Control'] * 3)
```

```
    # stack_1 stores mono_treatments of level 1 & 2
    stack_1.append([’Humic Acid_0’] * 3)
    stack_1.append([’Humic Acid_1’] * 3)
    stack_1.append([’Humic Acid_2’] * 3)
    stack_1.append([’EDTA-Fe_0’] * 3)
    stack_1.append([’EDTA-Fe_1’] * 3)
    stack_1.append([’EDTA-Fe_2’] * 3)
    stack_1.append([’Adenine_0’] * 3)
    stack_1.append([’Adenine_1’] * 3)
    stack_1.append([’Adenine_2’] * 3)
    stack_1.append([’6-BAP_0’] * 3)
    stack_1.append([’6-BAP_1’] * 3)
    stack_1.append([’6-BAP_2’] * 3)
    stack_1.append([’Seaweed_0’] * 3)
    stack_1.append([’Seaweed_1’] * 3)
    stack_1.append([’Seaweed_2’] * 3)

random.shuffle(stack_1)  # randomization

    # pair gardening machine pods with combs
    for i in range(ord(’A’), ord(’R’)+1):
        letter = chr(i)

        car = list()  # temporary list for randomization

        if len(stack_1) < 9:
            pass
            if not stack_2:
                for j in stack_1:
                    car.append(j.pop())
                allocation[’R’] = car

            else:
                if stack_1:
                    for j in stack_1:
                        car.append(j.pop())

                random.shuffle(stack_2)
                for j in range(9 - len(stack_1)):
                    if stack_2:
                        t = stack_2.pop(0)
                        car.append(t.pop())
                        if t:
                            temp.append(t)

                stack_1 += stack_2
                random.shuffle(stack_1)
                stack_2 = temp
                temp = []
```

```
                allocation[letter] = car

        else:
            pass
            for i in range(9):
                t = stack_1.pop(0)
                car.append(t.pop())
                if t:
                    stack_2.append(t)

            allocation[letter] = car

        pass
        print(’machine ’ + letter + ’loading completed!!!’)
        print(allocation)  # print out results

    # file stores randomization results
    with open(’allocation validation.txt’, ’w’, encoding=’utf-8’) as f:
        for i in range(ord(’A’), ord(’R’) + 1):
            letter = chr(i)
            # for letter in string.ascii_uppercase:
            f.write(letter + ’: ’ + str(allocation[letter]))
            f.write(’\n’)

    return allocation

def Application(fertnames, combinations, allocation):

    print(fertnames)
    application = dict()
    for fert in fertnames:
        for i in range(3):
            application[fert + ’_’ + str(i)] = []
    application[’Control’] = []

    keys = application.keys()
    comb_names = combinations.keys()

    for i in range(ord(’A’), ord(’R’) + 1):
        letter = chr(i)
        i = 0
        for pod in allocation[letter]:
            i += 1
            if pod in keys:
                application[pod].append(letter + str(i))
            elif pod in comb_names:
                for fert in combinations[pod]:
                    application[fert].append(letter + str(i))

    with open(’application validation.txt’, ’w’, encoding=’utf-8’) as f:
```

```
        for key in keys:
            f.write(key + ’: ’ + str(application[key]))
            f.write(’\n’)

    return application

if __name__ == "__main__":
    [fernames, combinations] = OACD_read(’WisDM Green Experiment Design.xlsx’)
    allocation = Allocation(’WisDM Green Experiment Design.xlsx’)
    application = Application(fernames, combinations, allocation)
    print(application)
```

Results

WisDM Green Decision Tree Selected 8 Compounds

A literature search was conducted to determine an initial pool of compounds (e.g. biostimulants) that may potentially enhance the biological yield (%Yield) of plants. In this study, the biological yield was defined as the total dry weight of the plants including the shoot and root (**Equation 1**). Subsequently, the WisDM Green Decision Tree was utilized to assess the suitability of each compound to the growth of red spinach according to the criteria outlined in **Figure 3**, and a pool of 8 compounds was finalized for WisDM Green combination optimization. These 8 compounds included Potato Starch (Starch), Sucrose, Humic Acid (HA), Citric Acid (CA), Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), Adenine, 6-Benzylaminopurine (6-BAP), and Seaweed Extract (SWE). The WisDM Green workflow was initiated, and plants were grown in accordance with the experimental timeline in **Figure 2 and 4**.

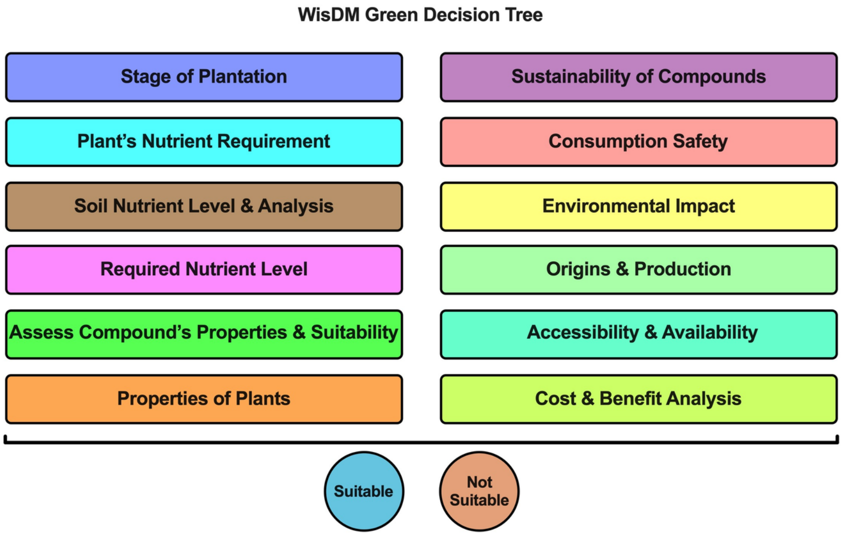


Figure 3: **WisDM Green Decision Tree.** The criteria implemented to select suitable compounds for WisDM Green optimization.

Mono-Compounds were Broadly Ineffective in Increasing %Yield

The WisDM Green optimization process assessed 3 concentration levels (0 indicates absence of a compound, and 1 and 2 represent two concentration levels) for each compound (**Table 5**). Concentrations were referenced

Figure 4: **Growing Red Spinach in the Gardening Machines.** The pictures of red spinach were taken on Day 0, 7, 15, 23, 27, and 31.

to previous studies and were carefully selected in an effort to avoid overrepresenting a single compound. The mono-compound experiment was performed by growing red spinach using level 1 and level 2 concentrations of each compound to assess their individual effect in %Yield (N = 3) (**Equation 1 and Table 5**). All 8 compounds in their level 1 and 2 concentrations had a minimal effect in increasing %Yield, and most compounds resulted in negative %Yield (**Figure 5a and 5b**). Importantly, these 8 compounds demonstrated concentration-dependent correlations between %Yield and their concentrations. Starch, HA, EDTA-Fe, SWE revealed a positive relationship such that the increase in concentrations resulted in improved %Yield. However, the remaining compounds led to a negative relationship between concentrations and %Yield. These correlations suggested that high concentrations of compounds may not always associate with improved %Yield. Though the compounds were broadly ineffective in increasing %Yield, we aimed to test if pairing them correctly may positively impact %Yield.

WisDM Green Compound Combination Optimization

In the WisDM Green design step, a set of 59 compound combinations selected according to a Resolution IV Orthogonal Array Composite Design (OACD) was applied to plants one time only on Day 21 (N = 3) (**Figure 2b and Table 6**). On day 50, the harvested plants were comprehensively quantified. The biological yield of each plant treated with various combinations of compounds were measured, and normalized to the control plants to determine %Yield (**Equation 1 and Figure 5c**). A small number of plant samples (16 out of 177) were excluded due to experimental errors, which are described in detail in Statistical Analysis. This set of experiments was performed along with mono-compounds, and the experimental conditions are illustrated in **Figure 6**.

The WisDM Green analysis correlated the 59 OACD-designed compound combinations and their corre-

Compound	Level 0 Conc.	Level 1 Conc.	Level 2 Conc.
Starch	0	250 mg/L	1 g/L
Sucrose	0	250 mg/L	1 g/L
Humic Acid	0	250 mg/L	1 g/L
Citric Acid	0	250 mg/L	1 g/L
EDTA-Fe	0	250 mg/L	1 g/L
Adenine	0	125 mg/L	500 mg/L
6-BAP	0	0.25 mg/mL	1 mg/mL
Seaweed Extract	0	12.5% (v/v)	50% (v/v)

Table 5: **Concentration Levels for WisDM Green Optimization.** Potato Starch (Starch), Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), and 6-Benzylaminopurine (6-BAP).

sponding %Yield via a second-order quadratic equation, and this correlation can be used to describe the interactions among all 8 compounds (**Equation 2**). Box-Cox transformation suggested a square transformation (%Yield^2) that would improve the fit properties of the %Yield data: residual distributions and the adjusted R^2. No outlier was identified using residual-based outlier analysis (**Figure 7**). The WisDM Green analysis had an adjusted R^2 of 0.732, and the WisDM Green estimated coefficients and statistics for the second order quadratic equation are tabulated in **Table 7**. The analysis provided a ranked list of all possible combinations for 8 compounds at 3 concentration levels (3^8 = 6,561) with their corresponding WisDM Green-predicted %Yield. The top 10 combinations are summarized in **Table 8**, and the top 10 2-compound combinations are tabulated in **Table 9**. 2-compound combinations were further explored to assess their interactions as they may serve as a backbone for the development of sustainable multi-compound combinations. Furthermore, designing effective combinations may be more ecologically sustainable by reducing the practice of fertilizer-driven yield. Subsequently, all of the combinations that were highly ranked for potential yield increase (6-BAP/Adenine/EDTA-Fe, 6-BAP/HA/SWE/Starch, Adenine/EDTA-Fe, 6-BAP/EDTA-Fe, Adenine/6-BAP, and HA/SWE) were selected to experimentally measure their effect on %Yield (**Table 8 and 9**). Notably, HA/SWE, which was pinpointed as one of the top 2-compound combinations, has been identified in multiple studies and determined as a synergistic combination in farming applications (Zhang et al., 2003; F.S. Hameed Al-Marsoumi, 2020; Sandepogu et al., 2019; Prakash et al., 2017). Moreover, in **Table 8**, 6-BAP/Adenine/HA/EDTA-Fe/Sucrose, an ineffective combination (ranked 5,610th out of 6,561), was also included to confirm the dynamic ability of WisDM Green in pointing to combinatorial designs that may have ineffective %Yield. This combination had two identical compounds as the 1st and 2nd ranked combinations, and WisDM Green determined that replacing a few compounds may result in negative %Yield (-37.72).

In addition, WisDM Green interaction analysis further pointed to potential synergistic interactions in the four selected 2-compound combinations in **Table 9**. WisDM Green suggested that Adenine/EDTA-Fe may achieve maximum %Yield at higher concentrations **(Figure 8a)**. The interaction surfaces for 6-BAP/EDTA-Fe and Adenine/6-BAP pointed to potential compound interactions (**Figure 8b and 8c**). In **Figure 8d**, HA/SWE interaction surface suggested a potential synergistic interaction. In terms of sustainability and minimizing environmental impact, these 2-compound combinations were prioritized over other combinations consisting of 3 or more compounds. 2- compound combinations that can achieve similar, or potentially greater, increases in %Yield compared to multi-compound combinations may support the further investigation of sustainable and deployable peat moss formulations guided by AI.

Validation of WisDM Green-pinpointed Combinations

The 1st and 2nd ranked combinations (6-BAP/Adenine/EDTA-Fe and 6-BAP/HA/SWE/Starch) were validated in a subsequent set of experiments (**Table 8**). Additionally, four 2-compound combinations were assessed in expanded concentration ranges (0 – 2x of Level 2; except 6-BAP) to determine their interactions at different concentration ratios (**Table 9**). Importantly, assessing the interactions of Adenine/EDTA-Fe,

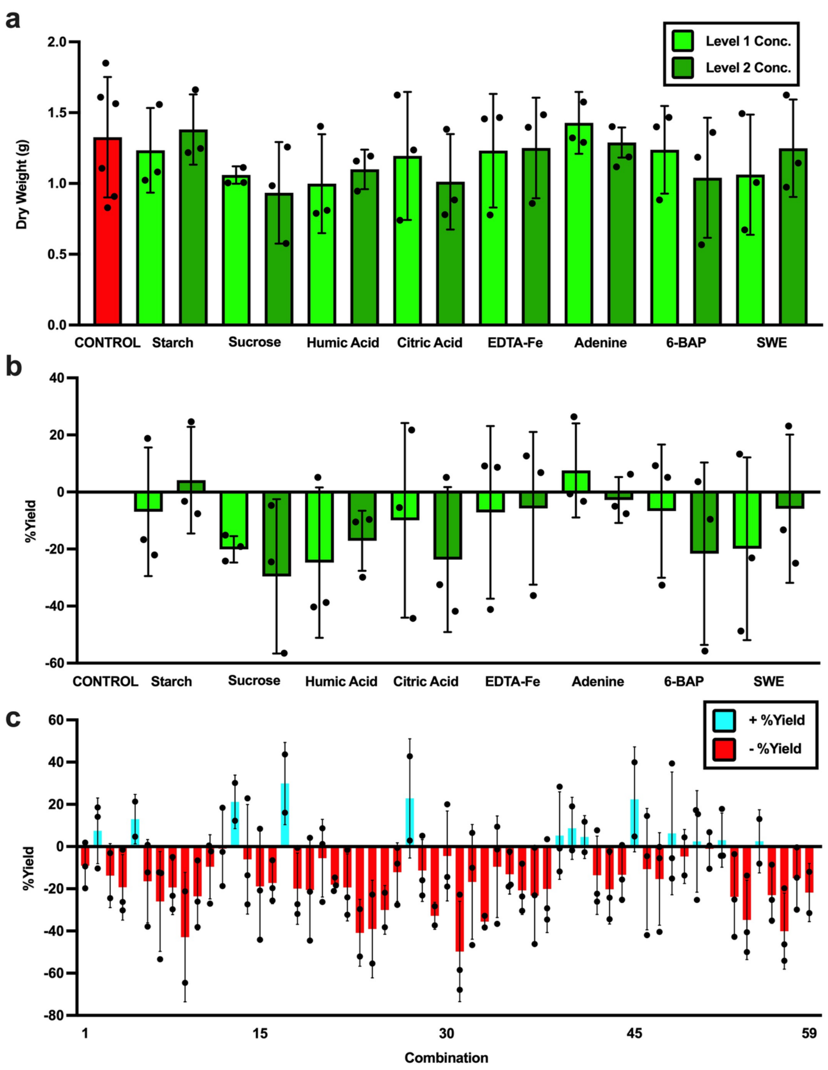


Figure 5: **Dry Weight and %Yield for Mono-Compounds and OACD Combinations.** The effects of each compound in two concentration levels were assessed (N = 3-6). Control red spinach with only liquid fertilizer (red) are compared to the effects of each compound at two concentration levels. The **a)** dry weight (N = 3-6) and **b)** %Yield with respect to control (N = 3-6) are illustrated. **c)** The average %Yield of each OACD combinations are illustrated (N = 3). The combinations are in order from 1 to 59 and positive yield combinations are highlighted in blue and negative yield combinations are highlighted in red. Data points are presented in mean ± SD, and individual replicates are represented in black dots. Kruskal-Wallis test followed by Dunn's post hoc test failed to detect any statistically significant differences in the mono-compound dry weight and %Yield data. Potato Starch (Starch), Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), 6-Benzylaminopurine (6-BAP), and Seaweed Extract (SWE).

6-BAP/EDTA-Fe, and Adenine/6-BAP may provide insight into the interactions of the 1st ranked combination (6-BAP/Adenine/EDTA-Fe), which consisted of all compounds in the aforementioned 2-compound combinations.

In **Figure 9a**, combinations that improved the %Yield of red spinach were highlighted. Notably, the

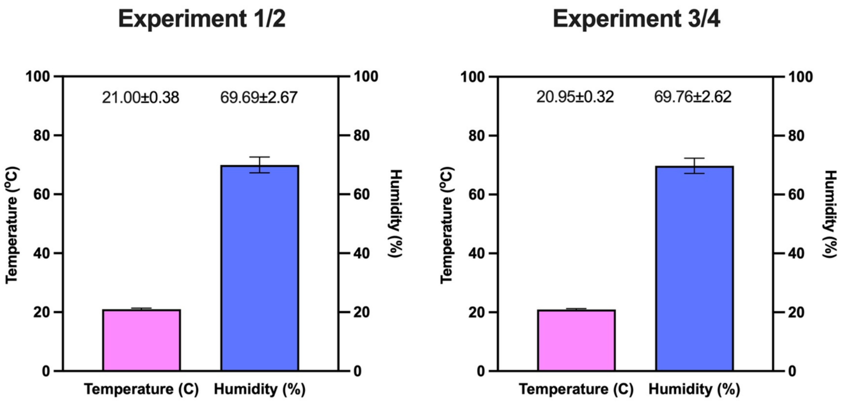


Figure 6: **Experimental Conditions of the Entire Experiment.** The temperatures and humidity measured throughout the experiments were recorded using Qingping Bluetooth Thermometer/Hygrometer Lite (CGDK2). Experiment 1 and 2 (N = 1024) and Experiment 3 and 4 (N = 3638). Data points are presented in mean ± SD. The temperatures recorded for both sets of experiments had no statistically significant difference (Student's t-test; $P > 0.05$). However, statistically significant difference was detected for humidity in both sets of experiments (Student's t-test; $P < 0.001$).

1st ranked combination (6-BAP/Adenine/EDTA-Fe) failed to demonstrate any apparent effect in %Yield (-3.60±11.70) even though it was ranked first among all possible combinations. This can be explained by concentration-dependent interactions observed in **Figure 9b, 9c, and 9d**, which illustrated the response surfaces of all interactions of 6-BAP/Adenine/EDTA-Fe. Though these surfaces may not have strong correlations to explain the relationship between input compounds and the %Yield of plants, they did however provide insight into the response of red spinach growth to the input compounds. Within the dotted black box outlining the WisDM Green-assessed concentrations (0 – Level 2), Adenine/EDTA-Fe and Adenine/6-BAP exhibited slight antagonistic effects and concentration-dependent interactions, which can potentially explain the reason why 6-BAP/Adenine/EDTA-Fe had no effect in %Yield in that range (**Figure 9b and 9d**). The observed concentration-dependent interactions implied that adjusting the concentration ratios of 6-BAP/Adenine/EDTA-Fe may potentially increase the %Yield. Subsequent interrogation of compound interaction demonstrated that adjusting concentration-dependent ratios may markedly enhance %Yield. Of note, the 2nd ranked combination (6-BAP/HA/SWE/Starch) demonstrated an increase in %Yield (15.32±8.42).

When 2-compound combinations were interrogated, the WisDM Green-pinpointed 6-BAP/EDTA-Fe combination, at concentrations 1 mg mL^{-1} and 2 g L^{-1}, respectively, led to 26.34±15.80 increase in %Yield (**Figure 9**). However, 6-BAP/EDTA-Fe at concentrations 0.50 mg mL^{-1} and 1 g L^{-1}, respectively, mediated a negative %Yield (-14.66±15.52). Furthermore, HA/SWE at concentrations 2 g L^{-1} and 12.50% v/v, respectively, resulted in a substantial increase in %Yield (33.59±14.60%). When the concentrations of HA were reduced to 0.25 g L^{-1} and SWE increased to 100% v/v, HA/SWE led to 9.36±14.42 decrease in %Yield. The concentration-dependent interactions of 6-BAP/EDTA-Fe and HA/SWE are illustrated in the response surfaces (**Figure 9c, 9e and 10**). The results suggested certain compounds may require higher concentrations to achieve optimal outcomes, while some may lead to better interactions at lower concentrations when carefully paired in combinations. To demonstrate the fidelity of negative predictivity of WisDM Green, an ineffective combination pinpointed by WisDM Green (6-BAP/Adenine/HA/EDTA-Fe/Sucrose) (**Table 8**) was also validated. This combination had two identical compounds as the top 2 ranked combinations, and WisDM Green determined that replacing some of the compounds may lead to negative %Yield. The experimentally measured %Yield was -6.93±8.27 (**Figure 9a**). The results suggested that properly pairing two compounds in optimal concentration ratios may mediate interactions that facilitate better %Yield enhancement than multi-compound combinations. To reduce the use of fertilizers, which is closely connected to

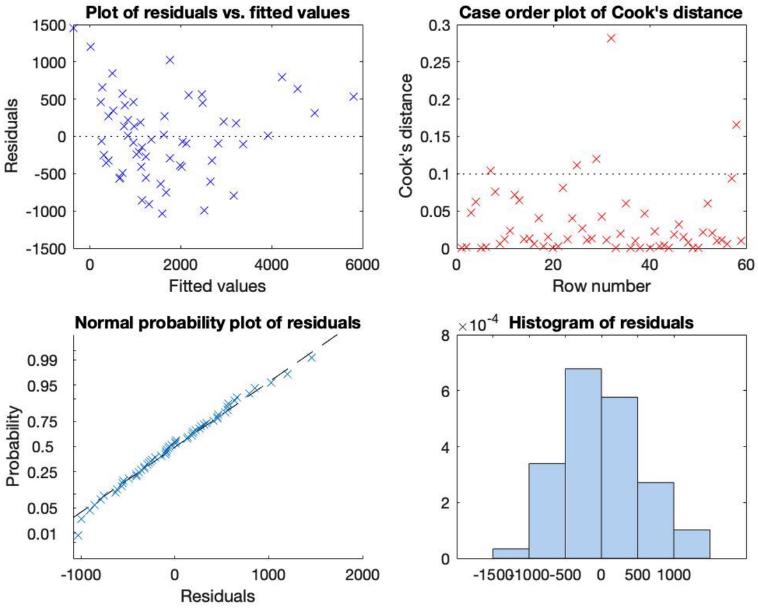


Figure 7: **Outlier Analysis for WisDM Green Analysis on %Yield.** The mean of each individual compound combination (N = 3) was used in the WisDM Green quadratic stepwise regression analysis. Residual-based outlier analysis was performed for each of the OACD-designed combinations. Residual is determined by the difference between the experimentally determined %Yield and the WisDM Green-predicted %Yield. The fit properties of the %Yield data, specifically the distribution of residuals and the WisDM Green model fit, were assessed via the plot of residuals vs. fitted values. In the Cook's distance plot, each row number corresponds to the OACD-designed combinations in **Table 6**. The normal probability plot and the histogram of residuals examined the normality of residual distribution. No outlier was identified in this round of outlier analysis.

environmental impact, appropriately pairing compounds and determining their optimal concentration ratios that can provide yield enhancement may be the most sustainable approach to the future of farming. For example, HA and SWE are both ecologically sustainable, natural compounds, and pairing them in combination and in optimal ratios improved the %Yield. The individual replicates used to plot the response surfaces in **Figure 9** are illustrated in **Figure 11**.The 2-dimensional heatmaps of each response surface are displayed in **Figure 10**.

Assessing Compound Interactions and Synergy Analysis

The experimentally measured %Yield data for the entire concentration ranges in **Figure 9b, 9c, 9d, and 9e** were used to construct the interaction maps shown on the left column in **Figure 12**. The interaction maps provided an assessment on the %Yield of red spinach when grown with these 2-compound combinations at different concentration ratios. Furthermore, the %Yield data at every compound ratio were subsequently analyzed using the Bliss independence model for synergy analysis, which is conventionally used to assess synergy in drug combinations (Liu et al., 2018; Poon et al., 2021). The Bliss independence model assumes that two compounds are mutually nonexclusive and compounds affect %Yield via different pathways, and this approach may provide insight into synergies exhibited by compound combinations. The Bliss synergy maps quantified the synergy exhibited by each concentration ratio using the Bliss synergy score, which quantifies the strength of synergy of a given combination with respect to the mono-compounds. Notably,

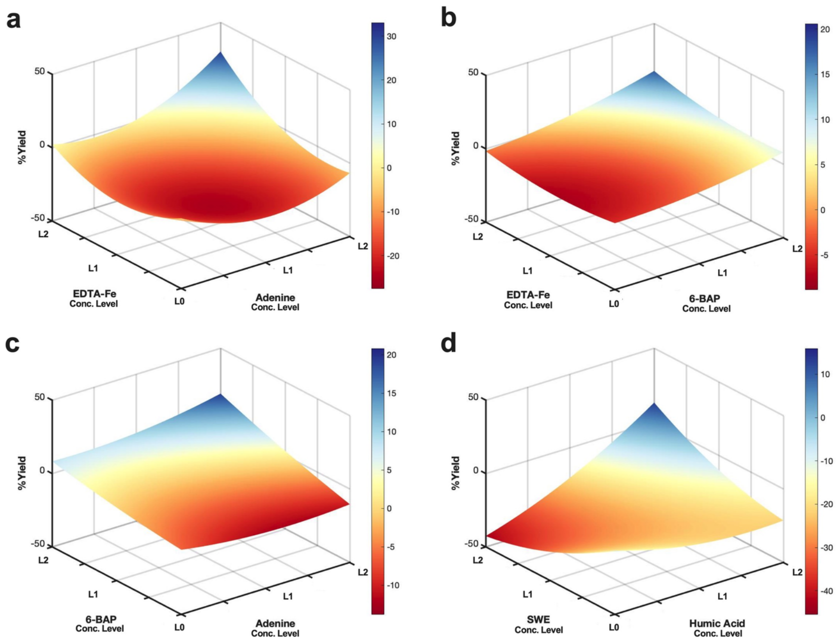
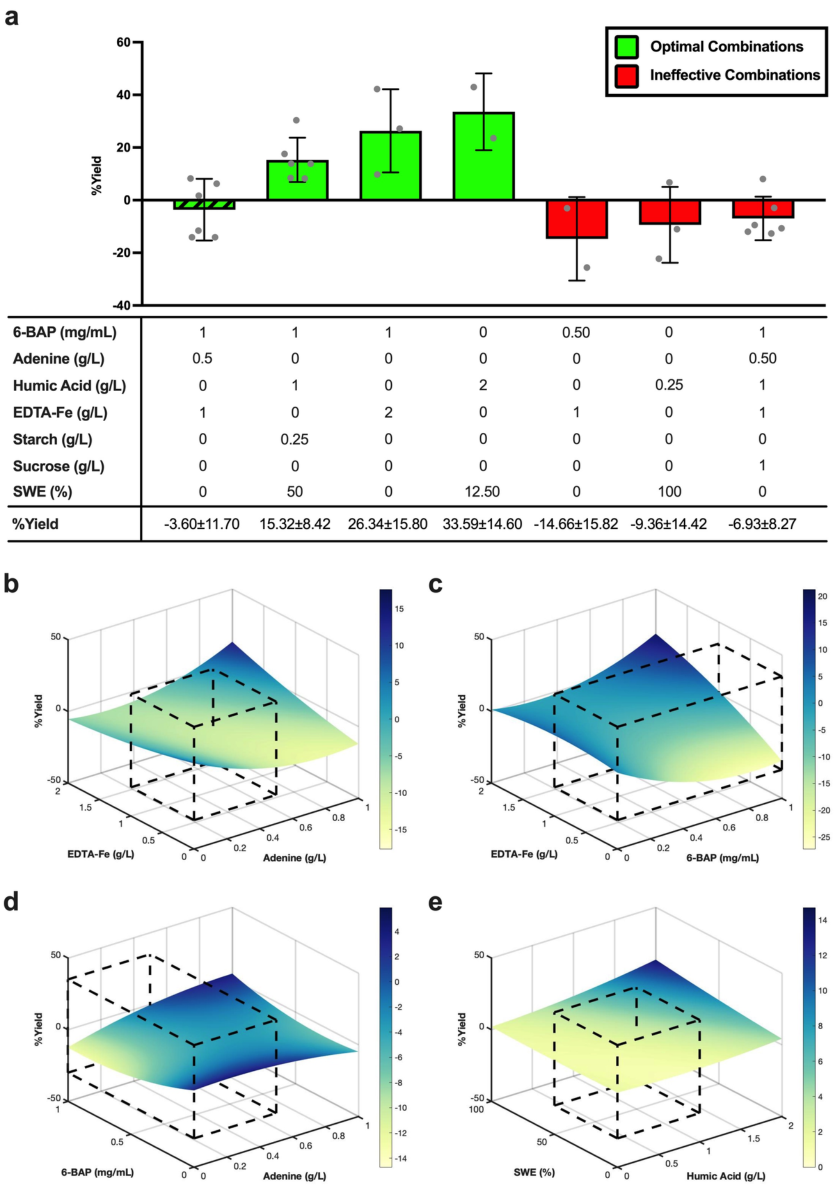


Figure 8: **WisDM Green Interaction analysis.** **a)** WisDM Green analysis suggested that Adenine/EDTA-Fe may have concentration-dependent interactions, and **b)** the surface pointed to a mild interaction between 6-BAP and EDTA-Fe. **c)** The interaction surface indicated that Adenine/6-BAP may have mild concentration-dependent interactions and **d)** HA/SWE may have a strong interaction. Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), 6-Benzylaminopurine (6-BAP), and Seaweed Extract (SWE).

the interaction of 6-BAP/EDTA-Fe at concentrations 1 mg mL^{-1} and 2 g L^{-1}, respectively, highlighted in the response surface analysis (**Figure 9a**), was confirmed to be synergistic via Bliss synergy scores. Similarly, Bliss synergy map also suggested that HA/SWE at concentrations 2 g L^{-1} and 12.5% v/v, respectively, had strong synergy (synergy score of 35.2).

Aside from assessing the %Yield interactions, response surfaces were also constructed to illustrate the potential association between the input compounds and measured morphological features including fresh weight, dry weight, water, shoot length, and leaf count (**Figure 10 and 13**). Though the explanatory power (e.g. R^2) of the input compounds to describe the change in morphological features may not be significant, they however provided insight into the change in morphological features. The response surfaces of Adenine/EDTA-Fe demonstrated concentration-dependent interactions in fresh weight, dry weight, and water, and importantly, they demonstrated a similar concave shape as observed for the %Yield response surface in **Figure 9b**. However, minimal interactions were observed in the surface for shoot length and a mild antagonistic interaction was observed for leaf count. 6-BAP/EDTA-Fe and Adenine/6-BAP demonstrated strong interaction and concentration-dependent interaction, respectively, across all morphological features, and their interactions were similar to that of the %Yield in **Figure 9c and 9d**. The response surfaces of HA/SWE assessing fresh weight, dry weight, and water revealed strong interactions similar to **Figure 9e**. However, concentration-dependent interaction was observed in shoot length and leaf count. Overall, the response surfaces of these morphological features demonstrated similar interactions to the %Yield response surfaces. 6-BAP/EDTA-Fe demonstrated the most uniform interactions across all features. These interactions broadly resulted in improvements across all morphological properties, confirming their highly ranked interactions pinpointed by WisDM Green interaction analysis. The individual replicates used to plot the response surfaces in **Figure 13** are illustrated in **Figure 11**. The 2-dimensional heatmaps and interaction maps of each response surface



6-BAP (mg/mL)	1	1	1	0	0.50	0	1
Adenine (g/L)	0.5	0	0	0	0	0	0.50
Humic Acid (g/L)	0	1	0	2	0	0.25	1
EDTA-Fe (g/L)	1	0	2	0	1	0	1
Starch (g/L)	0	0.25	0	0	0	0	0
Sucrose (g/L)	0	0	0	0	0	0	1
SWE (%)	0	50	0	12.50	0	100	0
%Yield	-3.60±11.70	15.32±8.42	26.34±15.80	33.59±14.60	-14.66±15.82	-9.36±14.42	-6.93±8.27

Figure 9: **Validation of WisDM Green-pinpointed Combinations in Red Spinach and Compound Interaction Analysis. a)**Highlight of WisDM Green-pinpointed optimal and ineffective compound combinations. Data points are presented in mean ± SD. Each replicate is illustrated in gray points (N = 2-6). Kruskal-Wallis test detected statistically significant differences at $P < 0.01$. However, Dunn's post hoc test did not detect pairwise statistical significance. **b-e)** The response surfaces of Adenine/EDTA-Fe, 6-BAP/EDTA-Fe, Adenine/6-BAP, and HA/SWE. The dotted black box represents the original range of concentrations (0 – Level 2) tested. The unit for SWE is % v/v. The heatmaps of each response surface are displayed in Figure 10. Individual replicates used to generate each response surface are illustrated as scatterplots in Figure 11. Statistics and source data of the response surfaces are attached.

are displayed in **Figure 10 and 14**. Experimental conditions across all experiments are defined in **Figure 6**.

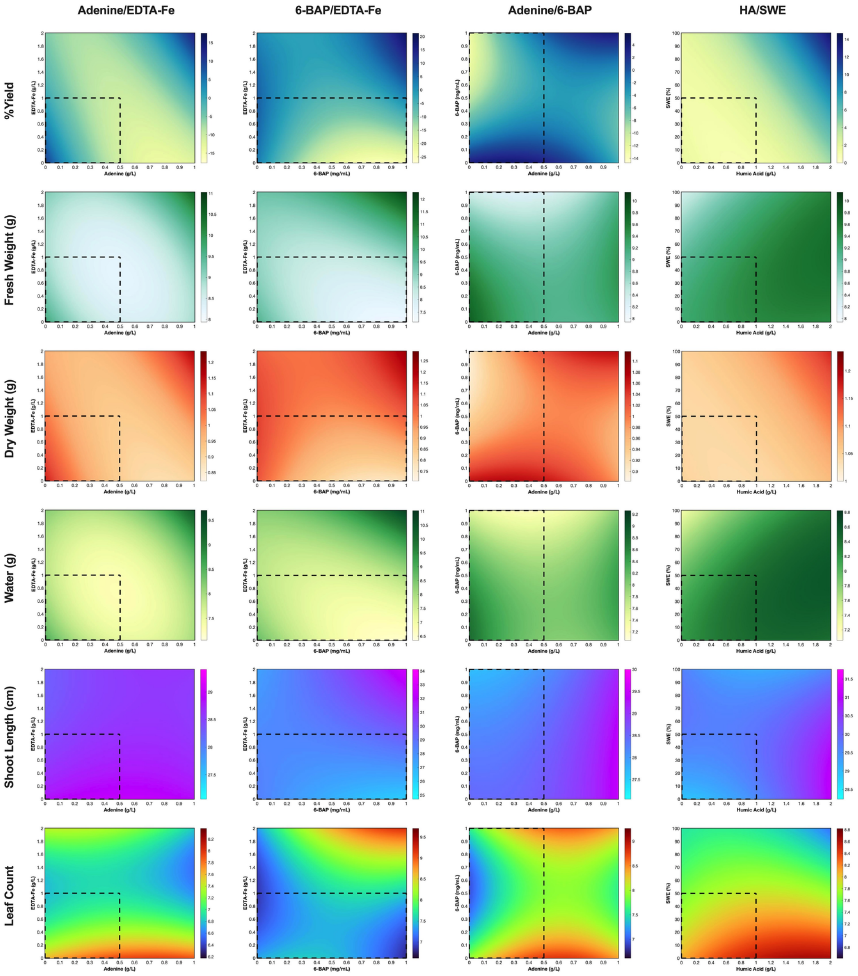


Figure 10: **2-Dimensional Heatmaps of Compound Interaction.** The heatmaps representing the 2-dimensional view of response surfaces for compound interactions in %Yield and morphological features (N = 2-6). The dotted black box represents the original range of concentrations (0 – Level 2) tested. The unit for SWE is % v/v. Statistics and source data are attached. Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), 6-Benzylaminopurine (6-BAP), Humic Acid (HA), and Seaweed Extract (SWE).

Nutritional Analysis

The WisDM Green-designed combinations highlighted in **Figure 9a** mediated an increase in %Yield of red spinach. The nutrients and elements in red spinach grown with these combinations (Level 2 concentrations) were comprehensively assessed and compared to the control red spinach. Three basic morphological features including shoot length, root length, and leaf size were compared to provide an insight into the baseline characteristics of the plants. Total protein, vitamin C, and critical elemental contents were measured. The full comparisons are illustrated **Figure 15**. Notably, the optimal WisDM Green-designed combinations demonstrated a substantial increase in absolute Zn content, which is critical to immune system and metabolism function (Wessels et al., 2021). 6-BAP/HA/SWE/Starch (2^{nd} ranked combination) led to a 15.32±8.42 increase in %Yield, while maintaining an average absolute Vitamin C content at 1.78±0.78 mg, which is 44% higher than the absolute content in control spinach. However, Kruskal-Wallis test followed by Dunn's post

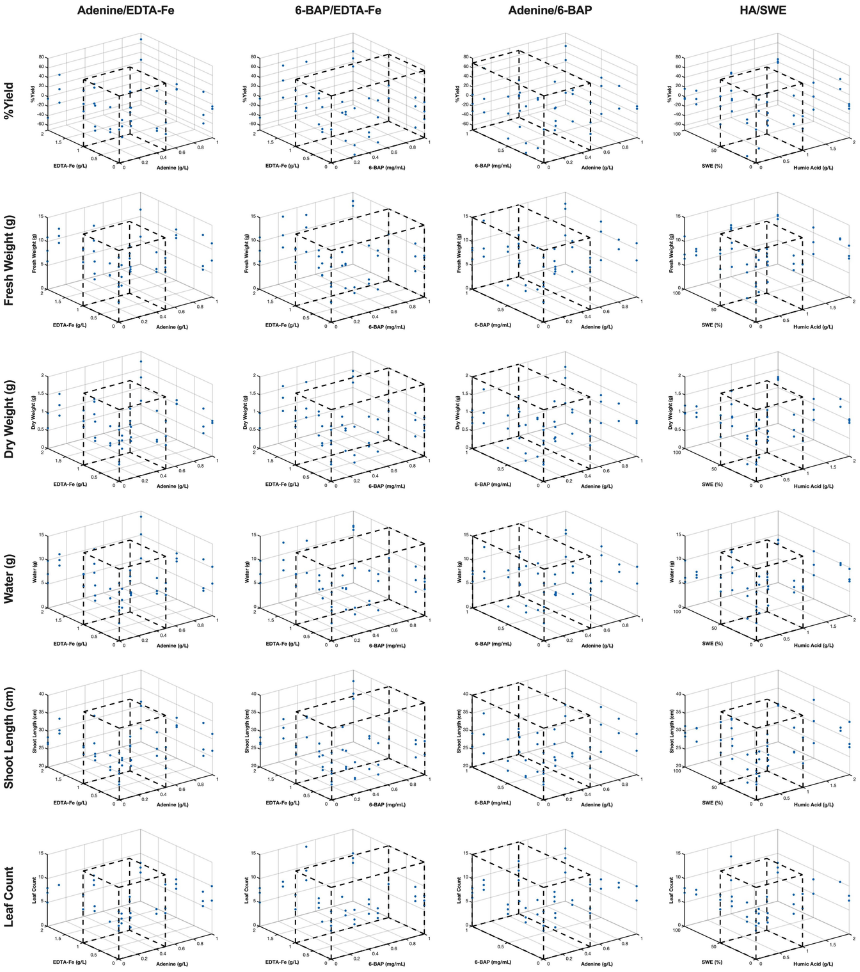


Figure 11: **Scatterplots of Response Surfaces.** Individual replicates used to construct response surfaces for %Yield, fresh weight, dry weight, water, shoot length, and leaf count are presented in scatterplots (N = 2-6). The dotted black box represents the original range of concentrations (0 – Level 2) tested. The unit for SWE is % v/v. Source data are attached. Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), 6-Benzylaminopurine (6-BAP), Humic Acid (HA), and Seaweed Extract (SWE).

hoc test failed to detect any statistically significant difference in morphological features and absolute nutritional contents between control red spinach and those grown with optimal combinations across all assessments. The results suggested that WisDM Green was able to identify compound combinations that substantially increased the %Yield without compromising the absolute nutritional contents of red spinach. It is important to approach these findings as a proof of concept of the platform as conclusions may only be made with additional nutritional analysis.

Financial and Energy Consumption Analysis

The total costs of growing red spinach in this study were comprehensively calculated. All calculations were based on Singapore's electricity standard price of S\$0.2255/kW^{-1} h^{-1} and Singapore's National Water Agency standard price of S\$1.52 per m^3 of water. Growing red spinach requires about 5 L of water per machines (9 plants), which is equivalent to approximately S\$0.01 for one growing cycle. The gardening machines only utilizes light source for 16 h in a day; thus, in one growing cycle, the electricity cost is approximately S\$2.33. Furthermore, to grow one spinach, the water and electricity cost S\$0.001 and S\$0.26, respectively. In sum, the total cost for grow one red spinach using gardening machines is approximately S\$0.27. Additionally, the carbon footprint of growing red spinach is also calculated. The Operating Margin (OM) GEF, which is the average CO_2 emissions emitted per unit net electricity generated in Singapore, is 0.4085 kg CO_2 kW^{-1} h^{-1}. The total carbon footprint per gardening machine and per plant are approximately 4.22 kg CO_2 and 0.47 kg CO_2, respectively. Details of the aforementioned calculations are tabulated in **Table 4**.

Combo	Starch	Sucrose	HA	CA	EDTA	Adenine	6-BAP	SWE	%Yield
1	-1	-1	-1	-1	-1	1	-1	-1	-9.1
2	1	-1	-1	-1	-1	-1	1	1	7.46
3	-1	1	-1	-1	-1	-1	1	-1	-13.79
4	1	1	-1	-1	-1	1	-1	1	-19.32
5	-1	-1	1	-1	-1	-1	-1	1	12.99
6	1	-1	1	-1	-1	1	1	-1	-16.44
7	-1	1	1	-1	-1	1	1	1	-26.03
8	1	1	1	-1	-1	-1	-1	-1	-19.35
9	-1	-1	-1	1	-1	-1	-1	-1	-42.89
10	1	-1	-1	1	-1	1	1	1	-23.59
11	-1	1	-1	1	-1	1	1	-1	-9.59
12	1	1	-1	1	-1	-1	-1	1	-0.94
13	-1	-1	1	1	-1	1	-1	1	21.18
14	1	-1	1	1	-1	-1	1	-1	-6.06
15	-1	1	1	1	-1	-1	1	1	-18.83
16	1	1	1	1	-1	1	-1	-1	-17.26
17	-1	-1	-1	-1	1	1	1	1	29.87
18	1	-1	-1	-1	1	-1	-1	-1	-19.96
19	-1	1	-1	-1	1	-1	-1	1	-20.59
20	1	1	-1	-1	1	1	1	-1	-5.47
21	-1	-1	1	-1	1	-1	1	-1	-18.03
22	1	-1	1	-1	1	1	-1	1	-19.34
23	-1	1	1	-1	1	1	-1	-1	-40.89
24	1	1	1	-1	1	-1	1	1	-39.08
25	-1	-1	-1	1	1	-1	1	1	-30.03
26	1	-1	-1	1	1	1	-1	-1	-12.11
27	-1	1	-1	1	1	1	-1	1	22.82
28	1	1	-1	1	1	-1	1	-1	-11.34
29	-1	-1	1	1	1	1	1	-1	-32.82
30	1	-1	1	1	1	-1	-1	1	-4.46
31	-1	1	1	1	1	-1	-1	-1	-49.71
32	1	1	1	1	1	1	1	1	-16.73
33	-1	-1	-1	-1	-1	-1	-1	-1	-35.58
34	-1	0	0	-1	-1	0	1	1	-9.54
35	-1	1	1	-1	-1	1	0	0	-13.14
36	-1	-1	0	1	0	-1	0	0	-20.75
37	-1	0	1	1	0	0	-1	-1	-23.29
38	-1	1	-1	1	0	1	1	1	-20.1
39	-1	-1	1	0	1	-1	1	1	5.2
40	-1	0	-1	0	1	0	0	0	8.64
41	-1	1	0	0	1	1	-1	-1	4.52
42	0	-1	0	0	-1	0	-1	0	-13.6
43	0	0	1	0	-1	1	1	-1	-20.29
44	0	1	-1	0	-1	-1	0	1	-13.38
45	0	-1	1	-1	0	0	0	1	22.39
46	0	0	-1	-1	0	1	-1	0	-10.67
47	0	1	0	-1	0	-1	1	-1	-15.35
48	0	-1	-1	1	1	0	1	-1	6.24
49	0	0	0	1	1	1	0	1	-4.68
50	0	1	1	1	1	-1	-1	0	2.47
51	1	-1	1	1	-1	1	-1	1	-1.09
52	1	0	-1	1	-1	-1	1	0	3.04
53	1	1	0	1	-1	0	0	-1	-23.81
54	1	-1	-1	0	0	1	0	-1	-34.77
55	1	0	0	0	0	-1	-1	1	2.48
56	1	1	1	0	0	0	1	0	-22.98
57	1	-1	0	-1	1	1	1	0	-40.08
58	1	0	1	-1	1	-1	0	-1	-15.02
59	1	1	-1	-1	1	0	-1	1	-21.76

WisDM Green	Estimate	Significance
Intercept	1496.7	***
Starch	-277.34	*
Sucrose	-319.87	**
HA	-195.08	
CA	-14.62	
EDTA-Fe	-65.67	
Adenine	108.06	
6-BAP	-87.13	
SWE	537.2	***
Starch:Sucrose	524.24	**
Starch:HA	296.38	
Starch:EDTA-Fe	-392.07	*
Starch:Adenine	-658.28	***
Sucrose:CA	400.43	**
Sucrose:6-BAP	-493.52	*
Sucrose:SWE	-389.42	**
HA:EDTA-Fe	-452.78	***
HA:Adenine	-276.61	*
HA:SWE	821.64	***
CA:6-BAP	-436.28	***
EDTA-Fe:Adenine	356.28	**
EDTA-Fe:6-BAP	-361.59	
EDTA-Fe:SWE	-293.39	
6-BAP:SWE	-375.36	**
Starch$^{\mathbf{2}}$	-603.06	*
HA$^{\mathbf{2}}$	780.94	**
Observations	59	
Degrees of Freedom	33	
Correlation Coefficient	0.92	
Adj R$^{\mathbf{2}}$	0.73	
R$^{\mathbf{2}}$	0.85	
F-test	***	

Table 7: **WisDM Green Estimated Coefficients for %Yield Data Analysis and Model Statistics.** Potato Starch (Starch), Humic Acid (HA), Citric Acid (CA), Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), 6-Benzylaminopurine (6-BAP), and Seaweed Extract (SWE). Statistical significance was determined using F-test. *P $<$ 0.05, **P $<$ 0.01 and, ***P $<$ 0.001.

Rank	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5	%Yield
1	6-BAP (2)	Adenine (2)	EDTA-Fe (2)	/	/	33.51
2	6-BAP (2)	SWE (2)	HA (2)	Starch (1)	/	32.33
3	6-BAP (2)	SWE (2)	HA (2)	Starch (2)	/	31.97
4	SWE (2)	HA (2)	Starch (2)	Sucrose (2)	CA (2)	30.76
5	6-BAP (2)	SWE (1)	Adenine (2)	EDTA-Fe (2)	/	30.05
6	6-BAP (2)	SWE (2)	Adenine (1)	HA (2)	Starch (2)	29.06
7	Adenine (2)	EDTA-Fe (2)	Starch (2)	CA (2)	/	28.6
8	6-BAP (2)	Adenine (2)	EDTA-Fe (2)	CA (1)	/	28.22
9	6-BAP (1)	Adenine (2)	EDTA-Fe (2)	/	/	28.19
10	6-BAP (1)	SWE (2)	HA (2)	Starch (1)	/	27.11
5610	6-BAP (2)	Adenine (2)	EDTA-Fe (2)	HA (2)	Sucrose (2)	-37.72

Table 8: **Summary of Top 10 WisDM Green-determined Compound Combinations.** 1st and 2nd ranked combinations were selected to perform subsequent validation study. An ineffective combination (anked 5610) was also included in the subsequent validation study. Concentration levels are included in the parenthesis. Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), 6-Benzylaminopurine (6-BAP), Citric Acid (CA), Humic Acid (HA), and Seaweed Extract (SWE).

Rank	Compound 1	Compound 2	%Yield
67	Adenine (2)	EDTA-Fe (2)	22.48
126	6-BAP (2)	Adenine (2)	19.5
304	6-BAP (2)	EDTA-Fe (2)	14.52
312	6-BAP (2)	Adenine (1)	14.35
387	6-BAP (2)	Starch (1)	13.32
409	Humic Acid (2)	SWE (2)	12.94
477	Adenine (1)	EDTA-Fe (2)	12.04
490	6-BAP (2)	EDTA-Fe (1)	11.7
670	6-BAP (2)	SWE (2)	9.14
685	6-BAP (2)	SWE (1)	8.94

Table 9: **Summary of Top 10 WisDM Green-determined 2-Compound Combinations.** Top 3 combinations and HA/SWE (ranked 409) were selected to perform subsequent validation study. Concentration levels are included in the parenthesis. Potato Starch (Starch), Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), 6-Benzylaminopurine (6-BAP), and Seaweed Extract (SWE).

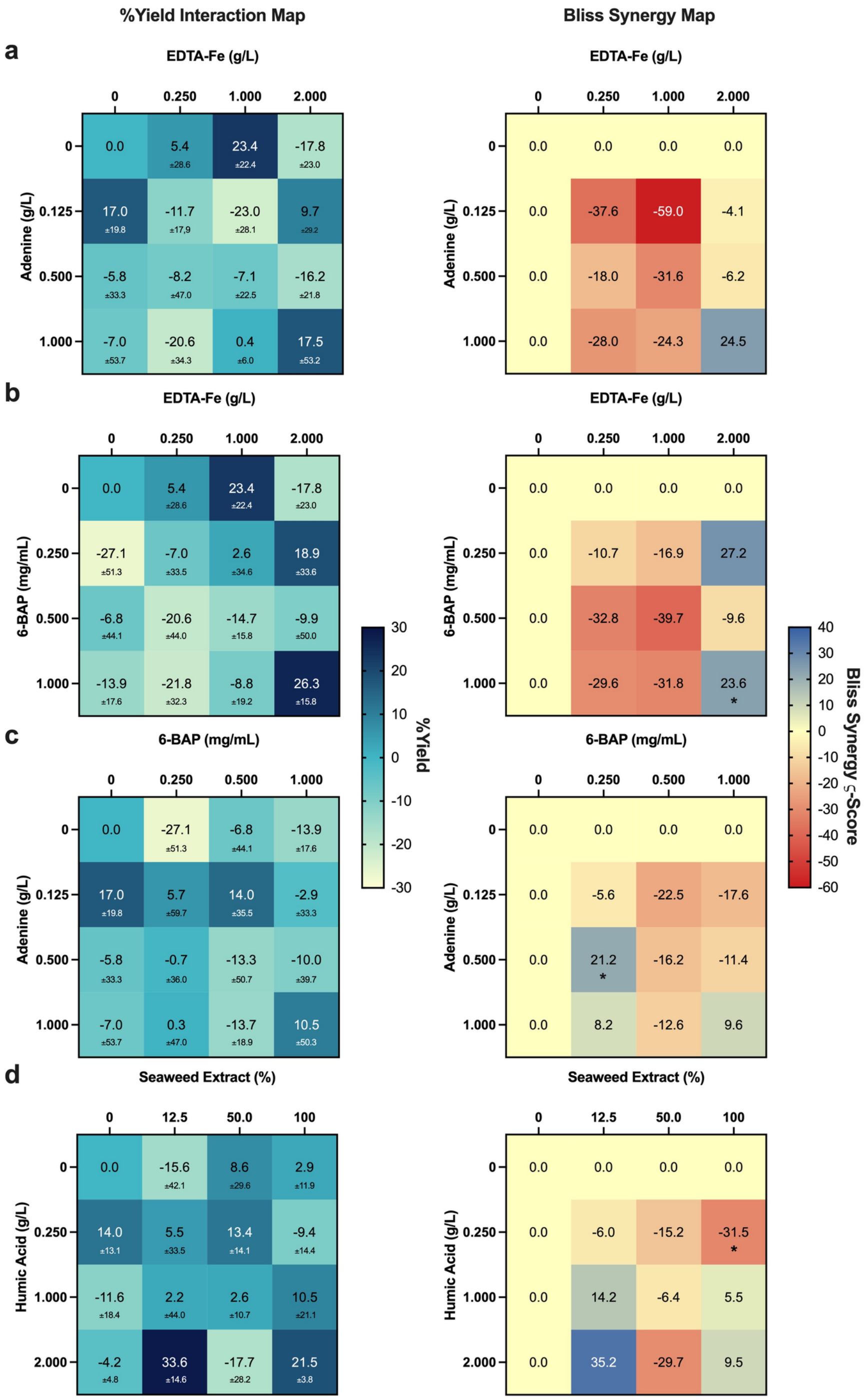


Figure 12: **Interaction Map and Bliss Synergy Map of WisDM Green-pinpointed 2-Compound Combinations. . a-d)** The %Yield of all tested concentration ratios were used to generate an interaction map that illustrates the performance for each combination in different concentration ratios (N = 2-6). %Yield data points are presented in mean ± SD. On the right column of the figure, the Bliss synergy maps indicated the Bliss synergy score for each corresponding combination. Statistical significance of Bliss synergy scores was determined by one-sample t-test ($*P < 0.05$). The unit for SWE is % v/v. Source data are attached.

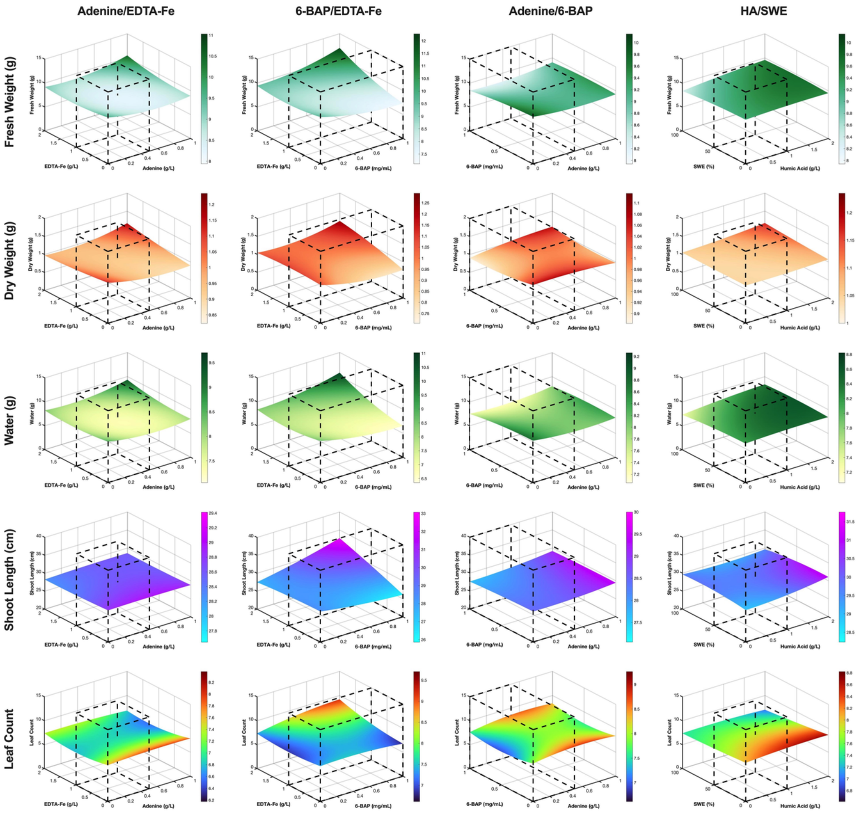


Figure 13: **Interaction Analysis on Red Spinach Morphological Features.** The morphological data for 2-compound combinations were used to generate response surfaces that describe the interactions at different concentration ratios (N = 2-6). The dotted black box represents the original range of concentrations (0 – Level 2) tested. The unit for SWE is % v/v. The heatmaps of each response surface are displayed in Figure 10. Individual replicates and interaction maps for each response surface are illustrated in a scatterplot in Figure 11 and in Figure 14, respectively.

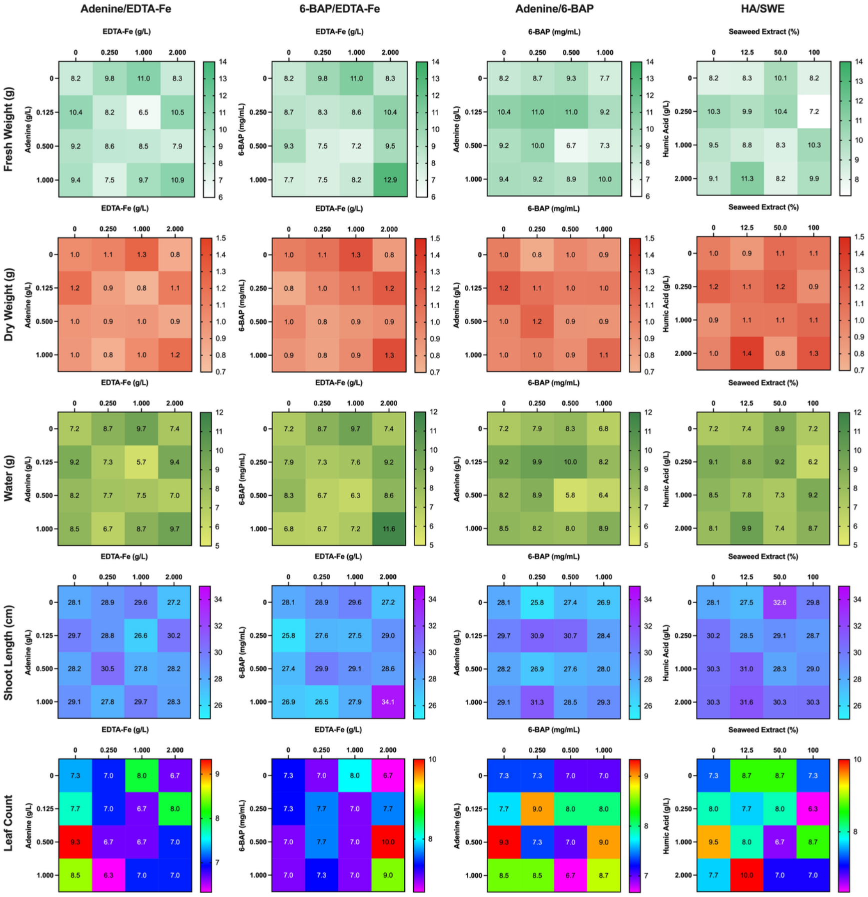


Figure 14: **Interaction Maps on Red Spinach Morphological Features.** The morphological data for 2-compound combinations were used to generate interaction maps that describe the compound interactions at different concentration ratios (N = 2-6). The unit for SWE is % v/v. Ethylenediaminetetraacetic Acid Iron (III) (EDTA-Fe), 6-Benzylaminopurine (6-BAP), Humic Acid (HA), and Seaweed Extract (SWE).

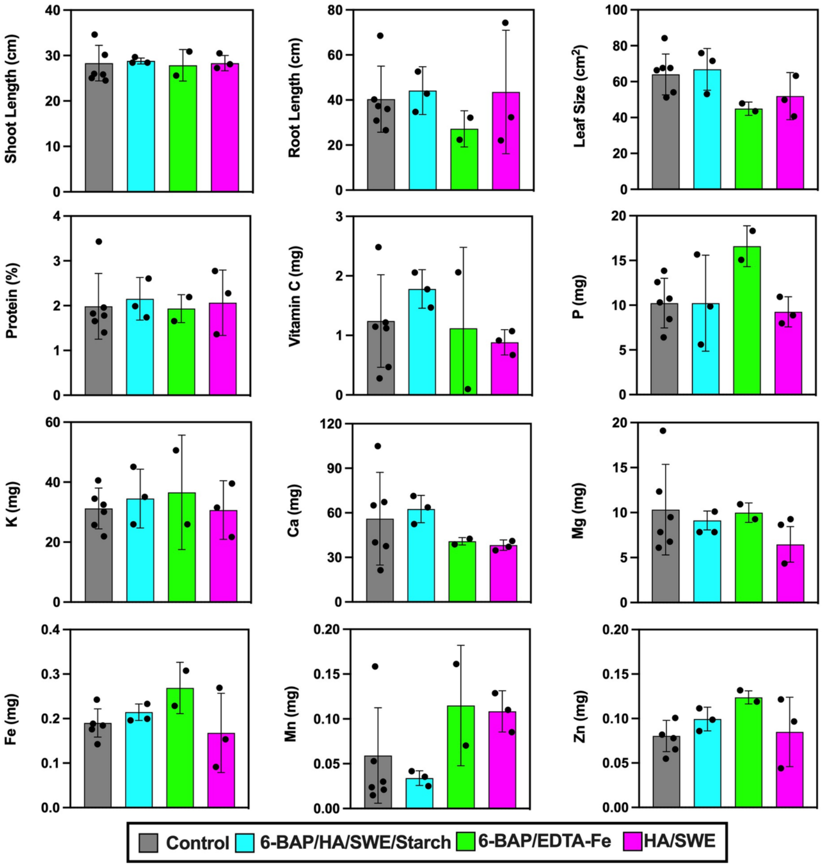


Figure 15: **Nutritional and Morphological Analysis on Validated Combinations.** The nutritional and elemental content of red spinach grown in optimal WisDM Green-designed combinations were assessed and compared to the control red spinach (N = 2-6). Data points are presented in mean ± SD and individual replicate is presented in black dots. Kruskal-Wallis test followed by Dunn's post hoc test failed to detect any statistically significant differences across all comparisons. Source data are attached.

Discussion

Rapid Optimization and Re-Optimization of Compound Combinations

The compound combination optimization only utilized prospectively obtained morphological data of 59 red spinach treated according to the OACD combinations, and did not require any pre-existing datasets for the optimization workflow. With these data, WisDM Green rapidly correlated the relationship between the compound combinations and the %Yield of each treated red spinach via a second order quadratic series to predict the %Yield of all 6,561 possible combinations at three concentration levels. WisDM Green utilized a resolution IV 59-combination OACD, which requires a small but representative sample size, to pinpoint unforeseen compound interactions. Aside from the chosen design, alternative higher resolution OACD's may enhance the predictability of WisDM Green by screening more combinations, which may lead to higher costs. Thus, a balance between the efficient use of resources and predictability must be carefully considered (Lim et al., 2019). Importantly, WisDM Green pinpointed unforeseen compound interactions and concentration ratios that positively impacted %Yield via 2-compound combinations. Therefore, this strategy represents a first step towards improving peat moss formulation by optimizing compound combinations and their concentrations to positively impact %Yield while simultaneously mitigating wastage.

Given the agnostic nature of WisDM Green implementation, it can potentially be expanded to other applications in food production and wider farming communities. These may include cell culture media optimization for cell-based meats, beverage compound selection, viticulture, space farming, and other applications (Massa et al., 2017). WisDM Green is also able to prioritize compound combinations that do or do not contain certain agents. Examples include selecting an optimal combination that does not contain animal products, or perhaps contains only vegan diet-compliant compounds, among other criteria. Moreover, WisDM Green allows multi-parametric optimization to determine the most suitable combinations for a specific desired outcome. For instance, this approach may be used to pinpoint compound combinations that optimize for biological yield without compromising the nutritional content. WisDM Green may also be applicable towards improving the yield of plant-derived compounds for cosmetic or drug synthesis, for example. Furthermore, WisDM Green can be rapidly re-implemented to account for evolving factors such as reagent availability, cost, effectiveness, climate and environmental change, user requirement, and many other parameters (**Figure 2**).

Concentration-dependent Synergy and Sustainable Farming

In this proof-of-concept study, we harnessed a platform technology that we have previously applied in drug combination optimization towards plant biological yield optimization. Similarly, we also explored approaches used in drug development, such as the Bliss independence model, to assess synergies observed in WisDM Green-pinpointed compound combinations (Liu et al., 2018; Poon et al., 2021). In the context of sustainability, rationally optimizing yield enhancement may be closely interconnected with concentration-dependent synergy. Appropriately adjusting concentration ratios to achieve optimal outcomes may substantially reduce the use of compounds, and also further reduce the reliance on fertilizer-driven approach to increase yield. For example, the excessive use of fertilizer has affected aquatic life and increased greenhouse gas emissions (Khan et al., 2018; Bijay-Singh et al., 1995; Qadri and Faiq, 2019; Huang et al., 2017; Malyan et al., 2019; Sedlacek et al., 2020; Ögmundarson et al., 2020). Though efforts have been made to protect the environment via approaches, such as controlled-release fertilizer, properly adjusting the concentration ratios of compounds may result in improved outcomes and reduction in fertilizer usage, which may lead to leaching (Li et al., 2018; Sikora et al., 2020; Xiao et al., 2019; Ögmundarson et al., 2020; Puga et al., 2020).

Foods Show Apparent Decline in Nutrients

Recent studies have pointed to apparent decline in nutrition during the course of food production. Assessing the United States Department of Agriculture (USDA) nutrient content data for 43 garden crops revealed that 6 nutrients (e.g. protein, Ca, P) showed statistically significant nutritional decline between 1950 and

1999 (Davis et al., 2004). The observed declines ranged from 6% to 38%. Furthermore, a systemic review on databases from Australia indicated a 30-50% decline in iron content of vegetables (Eberl et al., 2021). A separate study assessed archived wheat grain samples collected from 1950 to 2016 and discovered an imbalance in carbohydrate/protein content after the 1960's (Mariem et al., 2020). Notably, uptrend increases in CO_2 and temperature were observed in the same time period, suggesting climate change may have impacted both yield and the nutritional content. In 2018, Zhu *et al.* Pointed to altered food nutritional content as a result of rising CO_2 levels (Zhu et al., 2018). Importantly, the health of estimated 138 million to 1.4 billion people may have been impacted by the apparent nutrient declines.

Notably, in this study, the nutritional analysis indicated that WisDM Green-pinpointed combinations were able to achieve improved yield without compromising the nutritional contents. Red spinach grown in 6-BAP/HA/SWE/Starch and 6-BAP/EDTA-Fe demonstrated an increase in iron content when compared to the control plant. In this study, only the %Yield parameter was optimized. Future studies may incorporate multi-parametric optimization to include nutrient content to drive both yield and nutrition to the most desired and balanced levels. Therefore, aside from food security, maintaining nutritious food sources is also a critical challenge that must be addressed.

Food Security in Global and Singapore Contexts

Climate change and socioeconomic considerations have contributed to food security problems globally (Fujimori et al., 2019; Nelson et al., 2018; Cottrell et al., 2019; Meng-Tian HUANG, 2020; Mal et al., 2017; Prosekov and Ivanova, 2018). The outbreak of COVID-19 pandemic has further amplified the issue across the world (O'Hara and Toussaint, 2021). In a global context during this difficult time, 663 million people cannot consume enough food to stay nourished and 1.9 billion people are at least moderately food insecure (Prosekov and Ivanova, 2018; Hazra and Bhukta, 2020; Behnassi et al., 2019). Food security is a complex challenge that requires multiprong approach that includes limiting food waste, increasing food production and adjusting agriculture techniques to achieve high yield in changing climate environment without expanding land dedicated to agriculture. WisDM Green can potentially be deployed to optimize compound combinations regionally and specifically to enhance the production yield of crops in food insecure areas. Singapore also faces food security challenges. Specifically, with limited farming land, Singapore imports 90% of its food products, and 13% of its vegetable supply is locally grown (eat). WisDM Green may serve as a potential strategy to address local, regional, and global challenges in increasing agricultural yield through rational and optimal yield enhancement design. As a highly versatile, dynamic platform, it may optimize combinations based on the availability of compounds regionally and further improve crop yield with optimal combinations in places with limited arable land.

Limitations of WisDM Green

The WisDM Green workflow represented the first step towards designing and optimizing compound combinations to effectively and sustainably enhance the yield of plants. However, to fully resolve the underlying conflicts between fertilizer-driven yield and sustainability, the WisDM workflow must overcome and address several constraints and limitations. This study was conducted under well-controlled, indoor experimental conditions and has yet to explore multi-compound optimization in outdoor settings, which may require re-optimization, specifically of the compounds' concentration ratios. Therefore, WisDM Green implementation in an outdoor setting may reduce its ability to increase %Yield.

This work optimized compound combinations via a second order quadratic series, which was previously applied towards drug combination optimization against a broad spectrum of indications. In drug development, the dose selection is typically limited as toxicity and clinically actionability are critical limiting factors. However, the concentration selection of compounds in this study was not limited by induced toxicity and was mostly referenced to previous studies. The concentration levels were however limited to three per the design of OACD. Therefore, the interrogated compound-concentration parameter space was only limited to the tested concentrations. As such, downstream concentration-escalation studies or OACD designs that incorporate more concentration levels may provide further insight into concentrations that improve plant yield.

This work was based on prospective optimization and validation with the selected 8 compounds. Though the top WisDM Green-pinpointed combinations were able to achieve 15 − 35% increase in %Yield, further studies with an expanded list of compounds may add additional insight into even further improving yield. Importantly, the optimal compound combinations may not have any effect, or sub-optimal outcome, in other species of plants or different experimental conditions. A proof-of-concept study with a single validation model to design compound combinations is unlikely to broadly enhance yield across multiple types of plants. However, subsequent studies to optimize compound combinations in multiple species of plants may enable the discovery of a universal compound combination. Nonetheless, this work provided insight into the role of properly combining compounds at the correctly pinpointed respective concentrations during the process of optimal yield enhancement in agricultural applications.

Furthermore, biological variations were observed across all experiments in this study. All germinated red spinach were obtained from Everything Green Pte Ltd, and they were grown in well-controlled conditions with sufficient lighting and water supply. This study did not pre-select seeds based on germination status. The inherent variability in germination rates across plants contributed to subsequent %Yield data variability, even though all samples were subjected to well-controlled growth conditions in the 9-pod gardening machines. Moreover, the inter-plant variability in morphological features, such as growth rate, may also have resulted in the overall observed variabilities. The red spinach samples randomized across the pods in the gardening machines all had a substantial variation in morphological features (e.g. leaf size, shoot length). For example, we observed that plants provided with compound combinations that resulted in their fast growth tended to limit the space and block light source for a slower growing neighboring plant. The observed trends suggested that a non-randomized design that places plants applied with the same compound in the same proximity may potentially reduce the effects of neighboring samples that exhibit different responses to the compounds. These aforementioned factors may have been the key drivers of the variability observed in %Yield data. As a result, the explanatory power and correlation for the response surfaces were not significant even though they did however provide insight into the changes in morphological features with respect to input compounds (**Figure 9 and 12**).

In this study, compound combinations were manually added to each sample. Experiments relied on the diligence of the study team in terms of ensuring homogeneity of the compound combinations within each sample. The uniform dispersion of the compound combinations applied to each red spinach may be affected by the density of peat moss in each pod. The compaction of peat moss, or soil, may lead to poor root growth, which subsequently affects nutrient uptake. Additionally, due to inter-plant variability in the root system, the uptake of compounds may have contributed to the variability in yield.

Prior to scale-up of the WisDM Green workflow, downstream studies may need to incorporate mixing methodologies or other design considerations that can ensure homogeneity of compound combinations and peat moss in each pod and potentially improve the uniformity of the growth conditions across all samples. Nonetheless, the consistency between predicted and validated outcomes of WisDM Green-pinpointed combinations confirmed the utility of the platform. Further studies may incorporate strategies to address the uniformity of seed selection and spatial layout in order to improve the %Yield data and compound interaction analysis.

Conclusion

In this proof-of-concept study, WisDM Green was experimentally validated towards the prioritization of compound combinations for sustainable farming. Compound combinations pinpointed by WisDM Green demonstrated substantial increase in %Yield, without fertilizer-driven enhancement. Further analysis on compound combinations revealed concentration-dependent interactions, which suggest that properly pairing and designing compound combinations and their respective concentration ratios are critical to achieving improved plant yield. Furthermore, continuous effort to refine and improve WisDM Green is essential before the scale-up and potential integration of the platform for farming applications.

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Conflict of interest

All authors are co-inventors on a provisional patent pertaining to artificial intelligence-enabled platform that optimizes agriculture and food production yield. E.K.-H. Chow and D. Ho are co-founders and shareholders of KYAN Therapeutics, which is commercializing intellectual property pertaining to AI-based personalized medicine.

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