

Exploration of the role of flavonoids on pest resistance in *Cannabis sativa*

Susannah Huston

College of Agricultural Sciences, Colorado State University

University Honors Program

Dr. Punya Nachappa & Dr. Jacob MacWilliams

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Abstract

Hemp (*Cannabis sativa*) is a growing crop industry in the United States with a wide variety of uses from fiber to CBD extraction; as more is grown there is a higher importance placed on pest management, particularly of the cannabis aphid (*Phorodon cannabis*).

Flavonoids are a category of secondary metabolite found in all plants that show a wide variety of structures and functions, including some levels of negative impacts on insect pests. We explored how varying flavonoid levels in 7 hemp cultivars affect the ability of cannabis aphids to colonize the plant, and focused on the effect of a specific flavonoid, orientin, through artificial feeding assays. Population screening showed a significant difference in aphid populations when comparing varying flavonoid profiles to a cultivar with none. Artificial feeding showed no significance of orientin on cannabis aphids, suggesting potentially a higher concentration is necessary to see negative effects. Knowing that overall flavonoid levels may aid in plant defenses paves the way for future research to focus on specific flavonoids and narrow down which are responsible, and could be potentially targeted for crop improvement and breeding.

Introduction

Hemp (*Cannabis sativa*) is a crop of growing importance across the world, particularly in Colorado it is a growing industry. In 2022 the value of industrial hemp in Colorado was placed at \$238 million, the sixth highest in the United States (USDA, National Hemp Report, 2024). Some varieties are grown for fiber and grain and can be used for both manufacturing and for animal feed (Wortmann 2019). The other side of hemp is growing for extraction of CBD for human health uses (Johnson 2018). Novel applications of this crop continue to develop as more of it is grown in the country, particularly in the area of bioplastics and biofuels (Beluns et al. 2023, Visković et al. 2024).

As with any crop, when growing hemp, pests and weeds must be managed to maintain acceptable yields. Many different insect pests will feed on this plant with varying levels of specialization to this plant alone. Several aphids are reported to feed on hemp, the most significant being the cannabis aphid (*Phorodon Cannabis*) (Cranshaw et al. 2019, Durak et al. 2021). Cannabis aphids feed on plants by piercing and sucking phloem sap, which can directly cause damage to the plant as well as transmit diseases, which have the potential to be far more damaging to the plant (Pitt et al. 2022, McPartland 1996).

Plants have many different mechanisms for defense against herbivory including synthesis of ~200,000 secondary metabolites for protection (Kessler and Kalkse 2018). The role of many secondary metabolites in plant defense against herbivory are still being explored; the large variety of chemicals produced by plants means there are many questions to be asked to get a full understanding of the complex interactions (Divekar et al. 2022). Cannabis plants are known to have high levels of secondary metabolites across many categories including particularly cannabinoids and flavonoids (Bautista et al. 2021, Monyela et al. 2024). Cannabinoids are a

group largely unique to cannabis (Appendino et al. 2022). Previous research has shown that the main cannabinoid found in hemp, cannabidiol (CBD), did not provide defense against cannabis aphids (MacWilliams et al. 2023). This study did not investigate the impacts of other secondary metabolites produced in the plant, instead focusing particularly on flavonoids (Jin et al. 2020). In other plant-insect interaction systems flavonoids have been identified to have negative impacts on the insect including feeding deterrence, digestibility reduction, and acting as toxins (Treutter 2005). There may be a role of flavonoids as a defense mechanism against cannabis aphid herbivory, the primary objective of this study is to determine the impact of overall flavonoid levels within cannabis plants on cannabis aphids.

An additional objective of this study is to assess the role of a specific flavonoid, orientin. Orientin is a water-soluble flavonoid found in multiple plant species, including cannabis (Lam et al. 2015, Jin et al. 2021). Orientin has been shown to have strong antioxidant capabilities, being able to scavenge free radicals more efficiently than similarly structured flavonoids like vitexin (Praveena et al. 2014). The current research for orientin focuses on applications of its antioxidant activity in health, with few studies focusing on insect interactions (Lam et al. 2016). Medical research has shown many different applications such as anti-inflammatory, antimicrobial, and radioprotective uses (Xia et al. 2023, Rashed et al. 2013, Wickramasinghe et al. 2022). Additionally, orientin is being explored for anti-aging and neuroprotective capabilities (An et al. 2012, Qu et al. 2022). The effect of orientin on insect feeding or behavior has not been directly studied, but this compound has been identified in the wings of *Melanargia galathea*, suggesting this insect is able to tolerate its presence in its diet and sequester the compound within the body (Wilson 1984). Flavonoids other than orientin have been shown to have a similar pattern of broad applications. One of these other flavonoids is quercetin, which is known to negatively

impact insect herbivores including *Spodoptera litura* and *Callosobruchus chinensis* (Ramaroson et al. 2022, Riddick 2024). Based on this previous research of flavonoids, it is hypothesized that orientin has similar negative impacts on herbivorous insects.

Materials and Methods

Aphid and Plant Sources

Cannabis aphids were obtained from an indoor hemp facility in Loveland, CO to use in this study. The aphids were reared on Elite (New West Genetics, Fort Collins CO), a fiber and grain hemp cultivar in 45.7 × 45.7 × 76.2 cm cage (BioQuip Products Inc., Rancho Dominguez, CA) under greenhouse conditions (photoperiod of 16:8 (L:D) hours (h) and the day: night temperature was 23:18°C). High- and low-flavonoid cultivars were obtained from the USDA Germplasm Resources Information Network (GRIN) based off their reported flavonoid levels. All plants were grown from seed in Colorado State University’s Plant Growth Facilities and Insectary under the same greenhouse conditions listed above.

Table 1: Flavonoids levels of experimental cultivars (µg/g dried material)

Hemp Cultivar	Cyanidin-3-O-rutinoside	Luteolin-7-O-glucuronide	Orientin
G33369	876	0	7341
G33338	452	6269	2833
G33202	0	4787	0
G33313	0	7283	0
G33203	0	5427	0
G33216	0	7594	0
G33273	0	0	0

Aphid population assays

To determine the impact of flavonoids on aphid performance, three adult aphids were placed on the second-uppermost leaf of 5-week-old plants. The experiment was performed with each genotype caged in its own insect-proof mesh cage (55 cm x 60 cm x 165 cm) to prevent aphid movement between genotypes. Total aphid populations were counted for each plant after 14 and 21 days post-infestation. There were between 6 to 8 replicates per treatment, and analysis for each timepoint was done using a one-way ANOVA followed by Tukey's HSD test point using GraphPad Prism version 10.0.0 for Windows, GraphPad Software, Boston, Massachusetts USA.

Artificial Feeding

To determine the impact of the flavonoid orientin on aphid performance, cannabis aphids were reared on artificial diet supplemented with orientin as previously described in MacWilliams et al. 2023. Artificial feeding chambers were assembled from 55 mm petri dishes covered in two layers of parafilm with the artificial diet designed for *Myzus persicae* (Mittler & Dadd 1962). The volume of diet in each chamber was 250 μ L including the supplemented orientin solution. Ten age synchronized adult aphids were placed onto each chamber and populations were assessed daily for four days.

A stock orientin solution was created by dissolving 25 mg of orientin (Cayman Chemical) into 559 μ L of water to create a 100 mM solution. Experimental concentrations of orientin were 1 mM and 5 mM based on concentrations observed in the cultivars screened. Each treatment had between 2 and 4 replicates, analysis was completed as described above.

Results

To determine the effect flavonoids have on cannabis aphids, aphid populations were monitored for three weeks on high- and low-flavonoid hemp. The aphid population growth

varied between cultivars especially between the high flavonoid cultivars G33202 and G33216 compared to the cultivar with no flavonoids, G33273. There were significantly more aphids on the no flavonoid cultivar compared to G33202 ($F = 3.37, P < 0.01$), G33216 ($F = 3.37, P < 0.01$), G33369 ($F = 3.37, P < 0.05$), G33338 ($F = 3.37, P < 0.05$), and G33203 ($F = 3.37, P < 0.05$) (Figure 1). No significant difference was observed between the cultivars with flavonoids present.

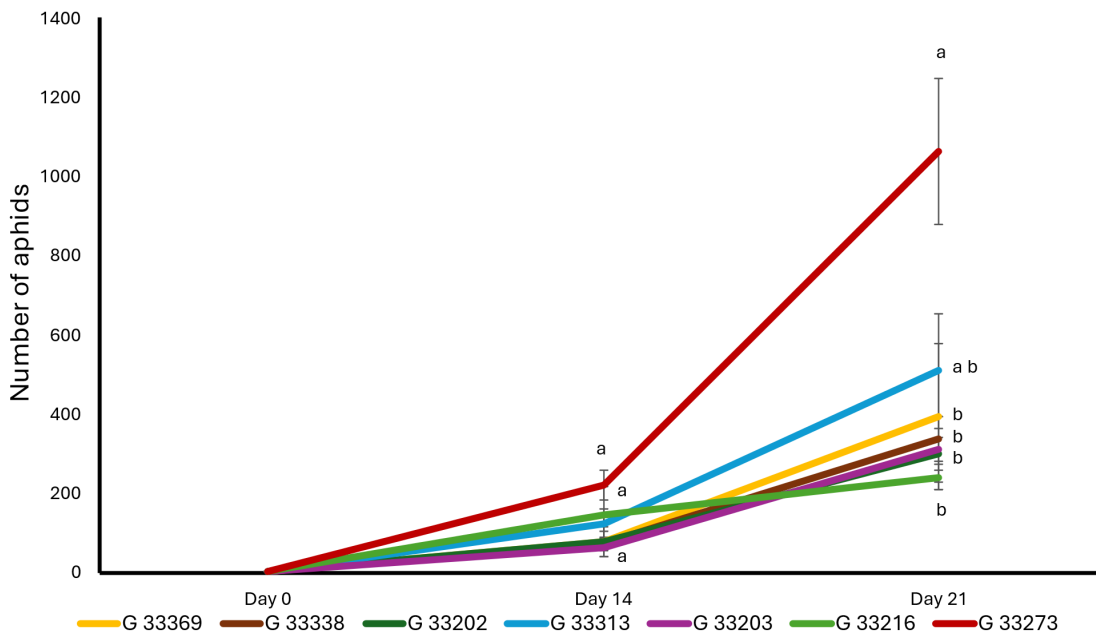


Figure 1: Population of aphids per cultivar across time. At day zero each plant was infested with three adult aphids, followed by population counts at 14 and 21 days post-infestation. Analysis was performed using one way ANOVA with Tukey-HSD for each time point. Different lowercase letters indicate significant differences ($P < 0.05$). Significant differences in populations were observed after day 21 in comparisons between a no flavonoid cultivar (G33273) and the rest of the cultivars with varying levels of flavonoids.

Based on the aphid population data, we further investigated the flavonoid profile of G33369 and G33338. These cultivars were found to have high levels of orientin and cyanidin-3-O-rutinoside (Table 1). These two flavonoids were identified as potential candidates for compounds that may affect aphid feeding and ultimately population as well. Orientin was selected for further analysis due to its solubility in water and ease of obtaining a pure stock for artificial feeding tests. Comparison of diet-only treatments to orientin-containing diets showed no significant differences ($P > 0.05$). The observed trends show a potential negative effect of orientin on fecundity, and no effect on the adult survival.

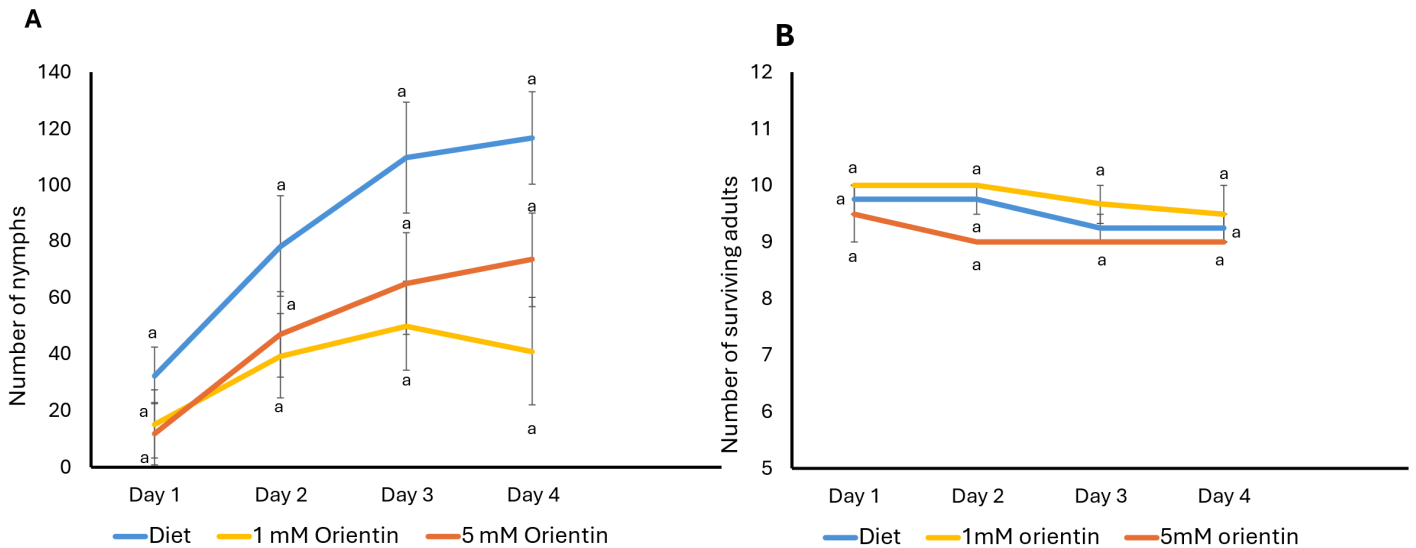


Figure 2: Effects of orientin in artificial feeding on nymphs (A) and adults (B) each day. Ten 7-day old aphids were maintained on artificial diet only or diet supplemented with 1 mM or 5 mM orientin solution in water. Populations were assessed for four days. Different lowercase letters indicate significant differences ($P < 0.05$); no significance was found at this level.

Discussion

Flavonoids are a very chemically diverse group, there could be many potential options for specific compounds that contribute in some way to pest defense (Shen et al. 2022). Cannabis aphid performance was negatively impacted by the presence of flavonoids in the selected cultivars. This is in agreement with reports on other aphid species in response to flavonoids (Riddick 2021). However, the results are not conclusive for which levels of flavonoids contribute the most to reducing aphid performance. Orientin and cyanidin-3-O-rutinoside emerged as the top candidates from the aphid performance on whole plant assays (Figure 1) and the reported flavonoid levels (Table 1). Artificial feeding assays with orientin however showed no difference than the diet control (Figure 2) indicating that at the concentration screened, orientin does not impact aphid feeding. A higher orientin concentration of 15 mM approaches the highest values seen in the cultivars screened (Table 1), and may show a larger effect on aphid feeding than the lower concentrations used in this study. The initial aphids in each feeding chamber generally survived on the orientin-enriched diets; an orientin concentration that begins to show higher rates of mortality among adults and nymphs may aid in the understanding of whether this flavonoid is directly toxic to aphids or simply a feeding deterrent (Sattar et al. 2019). Flavonoids overall seem to be playing a role in defense against cannabis aphids, but it is not clear the level that any single flavonoid is impacting the aphids.

Uncertainty in the role of flavonoids on cannabis resistance to aphids could be attributed to the current lack of understanding of many secondary metabolites found in Cannabis.

Cannabinoids are a major group of secondary metabolites produced that are unique to Cannabis (Andre et al. 2016). Cannabinoids were reported to negatively impact multiple insects including *Manduca sexta* and *Spodoptera frugiperda* (Park et al. 2019, Abendroth et al. 2023). However,

the same cannabinoid screened in cannabis aphids was found to have the opposite effect and increased cannabis aphid fecundity (MacWilliams et al. 2023). This difference shows the same secondary metabolites could have opposite effects depending on the plant–pest interaction. Similar patterns can be seen in the flavonoid quercetin, with insect species including *Calliptamus abbreviatus* showing higher mortality in the presence of quercetin while others such as *Danaus plexippus* see a positive impact in the form of higher oviposition (Huang et al 2024, Haribal & Renwick 1996). Determining a compound to be detrimental to insects can be challenging in the face of these often conflicting observations between species.

Further steps to expand on this research should address both the question of how the aphids directly are affected by specific flavonoids, but also how health of plants is mediated by flavonoid signaling as a result of aphid feeding. Artificial feeding and electrical penetration graph (EPG) techniques can be used to assess the ways in which a flavonoid specifically affects the health and behavior of the aphid, but that does not show how the compounds may be indirectly influencing pests through effects on the plant itself (Stec. et al 2021). Flavonoids could be interacting within the plant to potentially induce other defenses or raise general plant health, and the effect can be generated by insect feeding (Daryanavard et al. 2023, Jing et al. 2024). If the relationship holds true that there is no significant negative effect of orientin on cannabis aphids (Figure 2), it is possible that this compound is acting in this indirect fashion. Orientin levels could be related to generation of a response to feeding stress that in turn increases plant health in some way, rather than directly acting on the insects (Guatam et al. 2023). One potential mechanism of this indirect effect has been seen with other flavonoids in *Arabidopsis* being highly expressed in response to wounding during insect feeding, leading to increased insect resistance (Wang et al. 2021).

To understand more of the relationship with this specific population of hemp cultivars and the flavonoids measured in them, there should be a focus on exploring the role of other relevant flavonoids including an artificial feeding set-up for cyanidin-3-O-rutinoside to be screened similar to orientin. Additionally, more replicates and an additional higher orientin concentration treatment in further artificial feeding may aid in the understanding of this specific compound's effects on aphids. Screening each relevant flavonoid on their own can illuminate direct effects on aphid performance or reveal which may be part of a larger signaling system within the plant as a defense against aphid feeding.

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