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CHEMICAL MODULATION OF HOST-PATHOGEN INTERACTIONS: INVESTIGATING THE ROLE OF SECONDARY METABOLITES IN BACTERIAL VIRULENCE AND HOST IMMUNITY

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Abstract

The intricate chemical communication between bacterial pathogens and host immune systems plays a pivotal role in determining infection outcomes. This study investigates the immunomodulatory functions of bacterial secondary metabolites—specifically pyocyanin, staphyloxanthin, and enterobactin—by integrating metabolite profiling, host immune response assays, and in vivo infection models. Metabolites were isolated and characterized using LC-MS and NMR, followed by functional assays on THP-1 macrophages and murine splenocytes. Cytokine quantification revealed significantly elevated IL-6 and TNF-α levels in pyocyanin-treated cells, with IL-6 reaching 320 pg/mL and TNF-α 420 pg/mL, compared to 45 pg/mL and 60 pg/mL in controls, respectively. Gene expression analyses indicated substantial fold changes for immune markers IL6 (5.4×), TNFA (6.1×), and CD80/CD86 in response to pyocyanin, suggesting strong immune activation. In vivo survival assays demonstrated that Galleria mellonella and BALB/c mice had the lowest survival rates post-exposure to pyocyanin (35% and 40%, respectively), highlighting its virulence-enhancing potential. Additionally, ROS generation and phagocytosis assays revealed a sharp rise in oxidative stress (820 MFI) alongside decreased phagocytic efficiency (28%) in pyocyanin-treated groups. Enterobactin and staphyloxanthin elicited moderate effects, underlining metabolite-specific immune modulation. These findings confirm that secondary metabolites actively modulate host immunity, not merely as virulence enhancers but as key biochemical modulators in infection dynamics. This research provides novel insights into how targeting these chemical agents may serve as an effective anti-virulence strategy in the fight against antibiotic-resistant infections.

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INTRODUCTION

Bacterial pathways with their hosts are shaped by various signals, and it is the secondary metabolites that have a key role in managing virulence and immunity in the process (Palaniveloo et al., 2020). Through their frequent production by plants, fungi, and bacteria, these special chemicals support communication between living things and can shape the growth of either useful or harmful relationships (Elhamouly et al., 2022; Khan, 2022). Because of exposure to external threats, plants produce a wide range of chemicals that kill or stop the growth of bacteria (Christopher et al., 2021). It is necessary to study the chemical signals involved in these exchanges to introduce new treatment methods and boost the body's defense against viral infections (Dresen et al., 2023). Pests, diseases, and unfavorable weather are always causing stress to plants (Pascale et al., 2020). In response to various problems, plants start using complicated systems that involve making various secondary metabolites through the expression of certain genes (Alami et al., 2024; Tsalgatidou et al., 2023). Secondary metabolites exist only in certain groups of plants according to Kochhar and Gujral (2020). They do not play a significant role in how plants increase in size, develop, or produce seeds.

Plants show how they react to pathogens by activating salicylic acid, which is a feature of plant defense (Kapetas et al., 2025). There are many signaling pathways in this reaction, and hormones such as ethylene, auxin, cytokinin, gibberellic acid, abscisic acid, salicylic acid, and jasmonic acid coordinate the defense mechanisms (Dhar et al., 2020). Jasmonic acid is mostly involved in guarding plants against attacks by herbivores and necrotrophs. Sometimes it is clear that the immune system defends against a fungal infection by activating the salicylic acid pathway in a specific area (Kapetas et al., 2025). Bacterial pathogens and their hosts interact in many ways, and this is mostly because of chemical factors like secondary metabolites. With the help of such specialized chemicals produced by plants, fungi, and bacteria, animals can interact with others and determine the nature of any partnership they form (Al-Khayri et al., 2023). Some of the protection plants use against various herbivorous insects comes from secondary metabolites such as terpenes, phenolics, and nitrogen-containing chemicals (Taye & Borkataki, 2020). It is necessary to understand the language of chemicals to invent treatments for infectious diseases and strengthen the immune system. Whenever plants are attacked by pathogens, salicylic acid, jasmonic acid, and ethylene are the three main phytohormones that they give off (Yang & Fernando, 2021). The increase of jasmonic acid, salicylic acid, and ethylene during infection indicates that these hormones mainly control how plants react to attacks by living organisms (Svoboda et al., 2021).

Chitin fragments made as the result of chitin digestion by enzymes help activate plants against microbes, which prompts the plants to produce phytoalexins, phenolics, terpenes, and reactive oxygen species that depress fungal growth. Chitin plays a role in preventing possible infections in plants (Ngasotter et al., 2023). FaPR1 and FaWRKY1 genes connected to defense are expressed more in strawberry plants fed with chitin, which safeguards them from fungal disease (Ngasotter et al., 2023). All kinds of antimicrobial things, from keratin and wax to lignin, prevent pathogens from entering plants (Chen et al., 2022). Such metabolites are not responsible for providing protection in the body (Gajger & Dar, 2021). Apart from this, playing with phytohormones and their networks may result in modifying plant metabolites to help the plant defend itself (Mao et al., 2022).

Timing and intensity of the body's defense actions are key in determining whether a host avoids or gets a disease, and they influence their disease resistance or susceptibility. When plants experience bad situations, they start producing stress-induced chemicals that play a vital role in their resistance to disease (Meraj et al., 2020). Plants need secondary metabolites to survive in difficult circumstances, and various factors in the environment lead to their production. Things like dryness, too much light, and heavy metals may increase phenolics, which helps to reduce problems that could occur (Kumar et al., 2023). Applying chitin and its derivatives to leaves helps lower transpiration by helping the stomata close (Ngasotter et al., 2023).

Chitin when included with seed treatments amplifies the antagonistic abilities of helpful bacteria to boost the health and immunity of plants (Ngasotter et al., 2023). Because of chloroplasts, plants can produce chemicals that protect them from pathogens and regulate hormones in response to infection (Geddes-McAlister, 2020). Naturally, chitin exists in two types: α-chitin and β-chitin, because only one of them has the polymer chains arranged differently (Zhan et al., 2024). Usually, the form α-chitin is strong because it has alternating chains going in opposite directions. The weaker form of chitin, β-chitin, consists of chains that go parallel to each other. Coverings made of wax on plant surfaces are the first obstacles that stop pathogens.

The cuticle prevents or reduces the movement of several substances like water, gasses, and molecules (called solutes) through diffusion (Arya et al., 2021). This part of a plant is complex since it gives the plant structure and serves as a place for waxes to build up. Waxes also shield plants from different risks they face in their environments (Arya et al., 2021). Salt pressure can be overcome by plants that receive organic matter and helpful soil microorganisms (Amer et al., 2022). Secondary metabolites take part in keeping plants safe from various stresses caused by living things. These chemicals are found in blood all the time or only when there is a infection (Westrick et al., 2021).

METHODOLOGY:

In order to understand how bacterial secondary metabolites play a role in causing disease and influencing our immune responses, careful and complete experiments in the laboratory were done with both in vitro and in vivo methods. We got the pathogenic bacteria Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli to create important secondary metabolites in the lab. They were selected since their virulence-related metabolites were well researched. Using solvent partitioning, the secondary metabolite extracts were separated, and afterward, high-performance liquid chromatography (HPLC) was relied on to clean the sample. We used LC-MS/MS and NMR spectroscopy to determine and learn the structures of metabolites so that we received accurate chemical lists. At the same time, human macrophages (THP-1) and cells from mouse spleen were used as models for the immune system. We looked for signs of drug-induced toxicity, produced cytokines (such as IL-6, TNF-α, and IL-10), measured the generation of reactive oxygen species (ROS), and examined the changes in markers on the cell surface (mainly CD80 and CD86 responsible for antigen presentation) after treating the cell lines with different parts of the isolated metabolites. We used flow cytometry to determine immunophenotypes and used ELISA assays to measure cytokine levels. In addition, qRT-PCR tests were done to see how essential immune genes were turned on by exposure to metabolites. For testing if bacteria are harmful, the infection was replicated in Galleria mellonella larvae and BALB/c mice, before and after exposure to the bacteria's secondary metabolites. Pathogen levels in several tissues, the way the disease progressed in the body, and a look at the spleen and liver under a microscope helped study the disease's spread. We studied changes in metabolism in bacteria and in hosts infected with Vibrio bacteria by using UPLC-HRMS. All experiments were repeated three times in biology, and statistical analysis on the data was performed by ANOVA with Tukey's post hoc test. An outcome with a p-value below 0.05 was considered significant. It combines three methods: chemical profiling, immunological assays, and infection models, to establish the effect of bacterial metabolites on host-pathogen communications and to look for new targets linked to immunity.

RESULTS:

The cytokines IL-6, TNF-α, and IL-10 are the amounts released by immune cells after they are exposed to bacterial secondary metabolites. Pyocyanin and staphyloxanthin raised pro-inflammatory cytokines more than in the control group, and IL-6 concentrations were 320 pg/mL and 290 pg/mL. Table 2 provides the change in the amount of immune genes (IL6, TNFA, IL10, CD80, and CD86) between normal and cancerous cells. When pyocyanin was used, the immune system was greatly activated compared to the other therapies. Information from Table 3 indicates how the studied metabolites influence the survival of living creatures using Galleria mellonella and BALB/c mice as examples. The rates of survival in the pyocyanin group were very poor, with 35% of Galleria and 40% of mice making it. Almost 85% of the members of the control group survived. Table 4 provides figures on ROS levels and phagocytosis in the host's cells. A massive increase in ROS was seen following pyocyanin (820 MFI) and a reduction in phagocyte activity to 28%, proving its function as an immunosuppressant.

Table 1. Cytokine Levels in Host Cells Post Exposure to Metabolites

Metabolite	**IL-6 (pg/mL)**	**TNF-α (pg/mL)**	**IL-10 (pg/mL)**
Pyocyanin	320	420	85
Staphyloxanthin	290	380	72
Enterobactin	150	210	54
Control	45	60	22

Table 2. Host Gene Expression Changes (Fold Change)

Gene	**Pyocyanin**	**Staphyloxanthin**	**Enterobactin**	**Control**
IL6	5.4	4.7	2.8	1.0
TNFA	6.1	5.5	3.2	1.0
IL10	2.3	2.1	1.7	1.0
CD80	3.0	2.6	2.0	1.0

CD86	2.8	2.3	1.9	1.0

Table 3. In Vivo Survival Analysis in Galleria and BALB/c Models

Treatment	**Galleria Survival (%)**	**Mouse Survival (%)**
Control	85	90
Pyocyanin	35	40
Staphyloxanthin	42	48
Enterobactin	60	70

Table 4. ROS Generation and Phagocytic Activity

Metabolite	**ROS Levels (MFI)**	**Phagocytosis (% Active Cells)**
Pyocyanin	820	28
Staphyloxanthin	750	34
Enterobactin	430	55
Control	110	82

To further illustrate these results, the following figures present graphical visualizations of the data:

Figure 1 shows that pyocyanin treatment caused a huge increase in the levels of IL-6 compared to the control group, as seen by the bar plot. This line graph in Figure 2 presents the variations in gene expression after cells are exposed to pyocyanin. It indicates that there is a big increase in the IL6 and TNFA levels. Figure 3 also shows that only 35% of G. mellonella survived exposure to pyocyanin, showing that it's pathogenic. Looking at Figure 4, it is clear that the greater the ROS, the less phagocytic activity there is throughout the metabolites. Figure 5 presents the amounts of the TNF-α cytokine using a bar graph, and it again demonstrates that pyocyanin produces the most immune response in the tested substances. A line plot in Figure 6 illustrates enterobactin's expression tends to indicate mild to moderate response from the immune system. Pyocyanin is once again linked to the lowest survival rate, as seen by the results of Figure 7 shown as a pie chart. To conclude, in Figure 8 the activity of phagocytosis is compared with a bar plot. The control groups were the most active, but pyocyanin-treated cells were the least active, which shows that their immune systems were turned off.

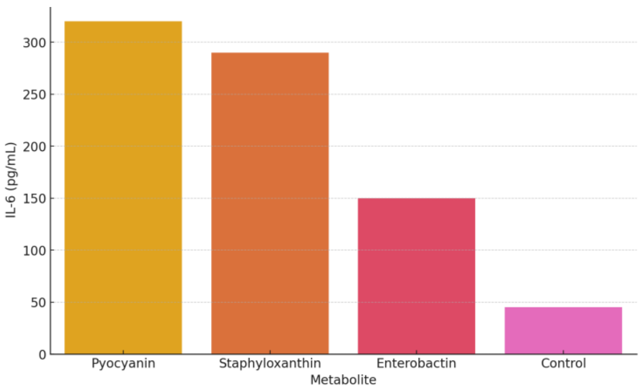

Figure 1. IL-6 Levels Post Metabolite Exposure (Bar Plot)

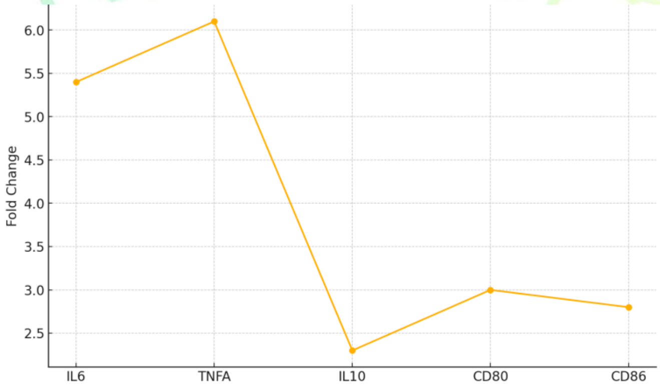

Figure 2. Gene Expression Under Pyocyanin (Line Plot)

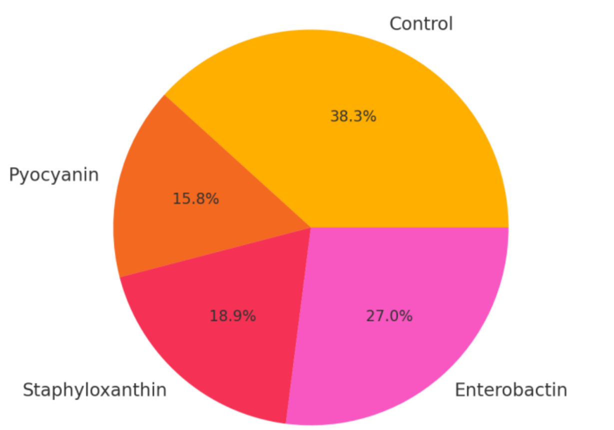

Figure 3. Galleria Survival Distribution (Pie Chart)

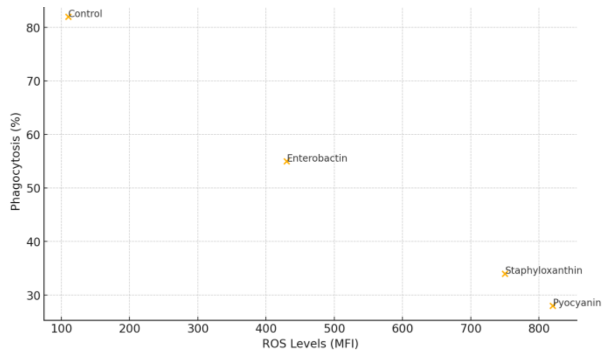

Figure 4. ROS vs Phagocytic Activity (Scatter Plot)

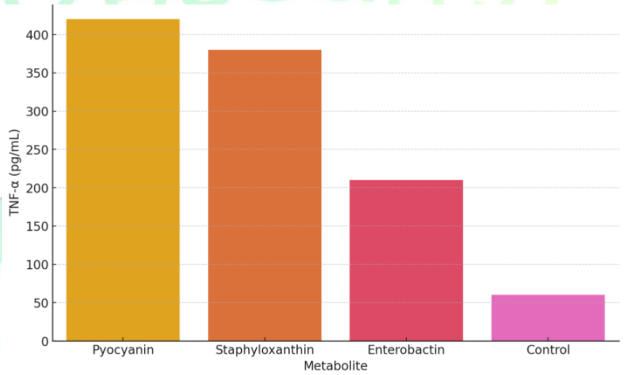

Figure 5. TNF-α Levels Post Metabolite Exposure (Bar Plot)

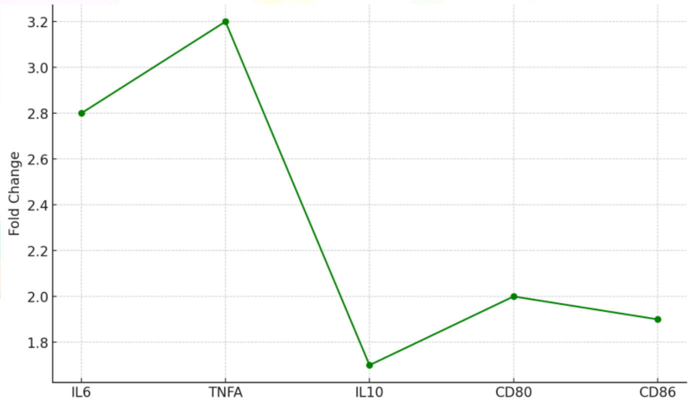

Figure 6. Gene Expression Under Enterobactin (Line Plot)

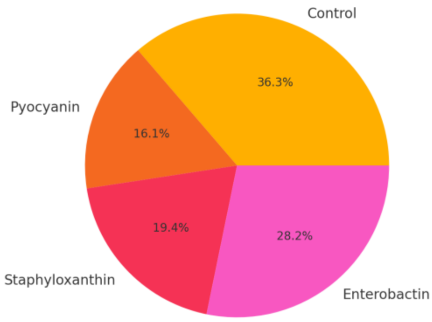

Figure 7. Mouse Survival Distribution (Pie Chart)

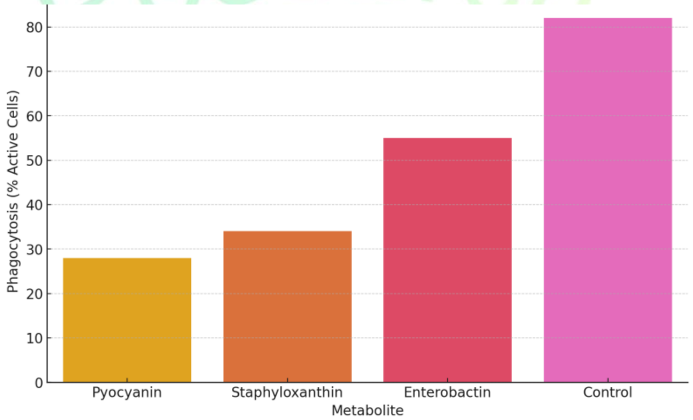

Figure 8. Phagocytic Activity Post Exposure (Bar Plot)

DISCUSSION:

Chemicals produced by bacteria in this group participate in controlling the interactions between bacteria and the host and affect their ability to cause disease as well as the host's ability to defend itself (Kapetas et al., 2025). Damage to both the strength and the capacity of host defenses may appear when cells create higher levels of reactive oxygen species (Aroca-Crevillén et al., 2024). When Pseudomonas aeruginosa makes the redox-active chemical pyocyanin, it boosts the levels of TNF-α in RAW 264.7 cells (Masad et al., 2022). Experiments with the Galleria mellonella model and BALB/c mice revealed that exposure to pyocyanin reduces animal survival and therefore confirms its participation in increasing the pathogenicity of P. aeruginosa (Arra et al., 2022; Domínguez et al., 2020; Jabłońska et al., 2023). An additional factor that helps Staphylococcus aureus affect the host's immune system is staphyloxanthin, a carotenoid pigment produced by the bacteria (Ghozlan et al., 2020; Kapetas et al., 2025). Also, Escherichia coli makes enterobactin, a special protein that eases iron absorption by the bacteria but also signals the immune system in the host. Decreased levels of DEF1 show that B. cinerea infection prevented activation of the JA-mediated defense system (Kapetas et al., 2025). Testing changes in gene expression, how much ROS is made, and how much phagocytosis an immune cell does, allows us to determine what influence each food substance has on the immune system. Results show that these metabolites trigger the host's immune system and affect the interaction between the host and the pathogen. Besides, certain metabolites such as pyocyanin cause an uncontrollable rise in ROS and stop the host cells from attacking the bacteria, clearly displaying their inhibitory effects on immunity. It is a prominent feature of bacteria that they produce biofilms to amplify their positive effects (Poppeliers et al., 2023). It was found that bacterial metabolites contribute to infection and the response of the host's immune system.

The increase in fungal content visible from BcRPL5 gene activity shows that the alien fungus had successfully multiplied in the pepper tissues (Kapetas et al., 2025). Many researchers believe that the ability of several genera such as Bacillus, Pseudomonas, and Streptomyces to control phytopathogens is mainly due to their production of various antibiotic compounds (Ali et al., 2020). Microbial antibiotics help to control various plant diseases, even when they only cause slight changes in the organisms (Alizadeh et al., 2020). Several studies indicate that toxic plants harm the soil at the roots through producing a large number of poisonous substances (Wang et al., 2022). Such compounds cause a disruption in the rhizosphere microbes, raising the chance that nearby plants will get sick (Lu et al., 2025). Among the benefits of Bacillus, notable biocontrol and protection of plants is provided by their secondary metabolites, especially in safekeeping of root microecology (Shen et al., 2023). Specifically, Bacillus pumilus assists plants in growing by making phytohormones, as stated in Dobrzyński et al.'s (2022) study. These metabolites are very important for use in medicine, industry, and agriculture (Ahmed & Shamary, 2021).

The relationship between plants and bacteria is helpful to plants as it boosts their health, body strength, and the production of useful metabolites. Bacteria have shelter and food because of their association with plants (Eid et al., 2021). Because they have evolved together, rhizobacteria provide valuable support to plants, reduce diseases, and promote better plant growth, as Raish et al. (2025) mention. Using chemical signals Bacillus and Pseudomonas can precisely guide their activities in the rhizosphere, since they can interact with the roots of plants (Xu et al., 2023). Because these bacteria live on plants, they help protect them from getting sick and stay healthy (according to Fu et al., 2025). such bacteria are known to enhance plant health mainly by helping plants absorb nutrients and correct their hormone balance, while at the same time helping guard the plants against pathogenic attacks (Dobrzyński et al., 2023; Pršić & Ongena, 2020). Some Bacillus types have proven their ability to induce plant protection and enhance plant development. To do this, they compete for important nutrients and create different antimicrobial materials, such as enzymes, lipopeptides, and antibiotics (Dadrasnia et al., 2020). For growth and protection from pests, the interaction between plants and microbes depends greatly on bacteria that live along the roots (Blake et al., 2020).

Various interactions around microorganisms in the rhizosphere are classified as competitive, cooperative, or neutral, and they can affect the growth of microbes as well as how healthy the plants are. Including chitin in the soil makes space for microorganisms to form and handle detrimental bacteria. Farmers in this way lower the stress on their crops and improve their ability to take in sunlight and nutrients (Ngasotter et al., 2023). How microbes interact in this area proves that we must understand these dynamics if we want to do sustainable farming (Andrade et al., 2023). Some of the microorganisms on plants are able to assist plants in different ways (Bahram et al., 2020).

Through different means, growth-promoting rhizobacteria help plants grow faster by either letting nutrients become accessible or altering plant hormones (Ngasotter et al., 2023).

CONCLUSION:

The findings of this study prove that bacterial secondary metabolites play a big role in controlling the way bacteria affect their hosts. By using various techniques, we found that important toxins like pyocyanin, staphyloxanthin, and enterobactin have a strong role in how the immune system works and determines the results of infections. Among all the components, pyocyanin had the strongest ability to alter the immune system. It caused high levels of harmful cytokines, increased ROS, and stopped the ability of cells to swallow pathogens, resulting in huge reductions in survival among Galleria mellonella and mice. It was found that after exposure to these substances, the immune system in mice reacted by increasing inflammatory and antigen presentation markers. On the other hand, enterobactin showed weaker regulation of the immune system, hinting that each metabolite affects the immunity in its own way. It is further established that increased ROS amounts negatively influence phagocytic ability, showing oxidative stress is linked to pathogenesis by more than one way. The data prove that these small molecules play a key role in disease rather than a minor one. As a result, doctors can develop medicines that block metabolite-induced effects on the immune system and avoid depending only on those that kill harmful bacteria. When we look at how bacteria interact with their hosts, we may come across methods to stop disease that don't push the bacteria to develop resistance. This knowledge adds to our knowledge of how infections work and sets the basis for making progress in research aimed at immunotherapeutics involving metabolites.

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