

Role of secondary metabolites in plants as growth promoter and inducing resistance against pathogenicity and parasitism

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Abstract - The plants produce secondary metabolites (SMs) as defence compounds against both abiotic and biotic stresses. These stresses instigate the secretion and release of SMs by up or down-regulating the concerned genes involved in their synthesis. The secretion of SMs varies with the plant's genetic constitution and accordingly they are susceptible or resistant. These metabolites mostly act as deterrents or antifeedants, allelochemicals, toxins or precursors of other metabolites that defend plants from stresses. However, some pathogens use these metabolites as a signal for host recognition or nutrition rather than using them as toxins or deterrents. The SMs activate different signalling pathways e.g. terpenoids modulate the calcineurin pathway, sesquiterpenoids modulate the jasmonic acid and salicylic acid pathway, polyphenols activate the jasmonic acid and phenylpropanoid pathway, and alkaloids activate the salicylic acid pathway to protect against pathogens and herbivores. Polyphenolic compounds provide resistance to different microbes by expressing different pathogenesis-proteins and hypersensitive reaction-mediated cell death and eliminate pathogens by altering the membrane permeability (inhibiting efflux pump), cell wall integrity, suppressing enzyme activity, free radicals' generation, inhibiting protein biosynthesis, damaging DNA and reducing the expression of virulent genes. Flavonoids help plants sustain pathogen stresses through the changes in the auxin transport process. The pathogen exposure upregulate genes of alkaloid synthesis pathways such as tyrosine decarboxylase (TyDC), S-norcochlorine synthase (NCS), codeinone reductase 2-like (COR-2), and StWRKY8 transcription factors which in turn accumulate alkaloids in large amounts. Plant exposure to pathogens leads to hypersensitivity reactions and phytoalexin accumulation. The plant's treatment of salicylic acid and jasmonic acid upregulated downstream transcription factors, increased the expression of defence proteins, triggered the synthesis of SMs, and provided resistance against multiple pathogens. Pathogens and herbivores have also coevolved to cope with defence metabolites by detoxifying the toxic metabolites, converting toxins into useful products, evolving their food choice, fast digestive system, expulsion of toxins, and down-regulation of the gene-producing secondary metabolites. This review article gives a molecular insight into the genes and regulatory proteins controlling the synthesis of SMs, which may help decipher the role of the biosynthetic pathway intermediates and thereby scoring genes providing resistance to various stresses. The article comprehensively describes the roles of different SMs in plant defence and their molecular mechanisms of action.

Keywords - Secondary metabolites, Plant defence mechanisms, Abiotic and biotic stress, Plant-pathogen interactions, Signal transduction pathways.

I. INTRODUCTION

Secondary metabolites, also called specialised metabolites, secondary products, or natural products, are organic compounds produced by any lifeform, e.g. bacteria, archaea, fungi, animals, or plants, which are not directly involved in the normal

growth, development, or reproduction of the organism. Instead, they generally mediate ecological interactions, which may produce a selective advantage for the organism by increasing its survivability or fecundity. (Croteau, R., Kutchan, T. M., & Lewis, N. G. 2000). Specific secondary metabolites are often restricted to a narrow set of species within a phylogenetic group. Secondary metabolites often play an important role in plant defense against

herbivory and other interspecies defenses. Humans use secondary metabolites as medicines, flavourings, pigments, and recreational drugs.

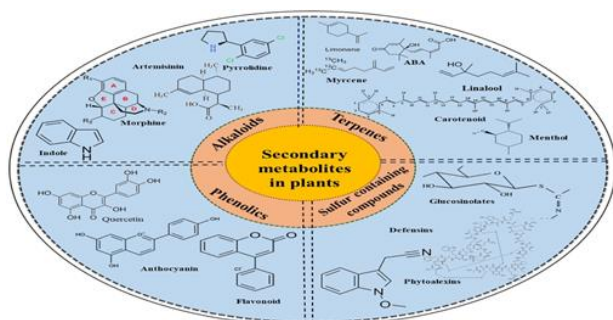


Fig. Secondary metabolites

Plants are capable of producing and synthesizing diverse groups of organic compounds and are divided into two major groups: primary and secondary metabolites. Secondary metabolites are metabolic intermediates or products which are not essential to growth and life of the producing plants but rather required for interaction of plants with their environment and produced in response to stress. Their antibiotic, antifungal and antiviral properties protect the plant from pathogens. Some secondary metabolites such as phenylpropanoids protect plants from UV damage. The biological effects of plant secondary metabolites on humans have been known since ancient times. The herb *Artemisia annua* which contains Artemisinin, has been widely used in Chinese traditional medicine more than two thousand years ago. Plant secondary metabolites are classified by their chemical structure.

Plants, as sessile organisms, face an array of challenges in their environments, including attacks from herbivores, pathogens, and abiotic stressors like drought, salinity, and extreme temperatures. Unlike animals, plants cannot escape these threats, so they have evolved intricate and multifaceted defense systems to ensure their survival and reproduction. (Bennett, R. N., & Wallsgrove, 1994). These defense mechanisms are broadly categorized into physical, chemical, and biological strategies, each uniquely tailored to deter adversaries or mitigate environmental stress. From structural barriers like thickened cell walls and trichomes to biochemical responses involving the synthesis of

secondary metabolites, plant defenses operate at multiple levels and are often highly specific. A key component of plant defense is the production of secondary metabolites, which are not directly involved in growth or reproduction but serve critical roles in protection. These compounds act as toxins, repellents, or signaling molecules, helping plants combat herbivores and pathogens, attract beneficial organisms, and adapt to changing environments. Moreover, plants rely on complex signaling pathways to detect threats and mobilize appropriate defense responses, often balancing the trade-off between growth and defense. Understanding plant defense systems is not only crucial for comprehending plant biology but also holds significant implications for agriculture and medicine. Enhanced knowledge of these systems can inform strategies to develop pest-resistant crops, reduce reliance on chemical pesticides, and discover novel pharmaceuticals derived from plant secondary metabolites. The study of plant defense systems, therefore, bridges ecological, agricultural, and biotechnological domains, showcasing the resilience and ingenuity of plant life in the face of adversity.

Role of Secondary Metabolites in Plant Defense Systems

Secondary metabolites play an indispensable role in plant defense systems, contributing significantly to their ability to survive in challenging environments. (Verma, N., & Shukla, S., 2015). These compounds, which are not directly involved in primary metabolic processes such as growth and reproduction, serve as chemical and structural barriers against a wide range of biotic and abiotic stressors. (Wink, M., 1988). Their diverse chemical structures and functions highlight the evolutionary ingenuity of plants in developing sophisticated defense strategies. Plants face numerous threats in their environments, ranging from herbivorous insects and pathogenic microbes to harsh abiotic conditions such as UV radiation, extreme temperatures, and drought. Unlike animals, plants lack a mobile immune system and must rely on static or localized responses to counteract these threats. Secondary metabolites form a core component of these responses, operating as defensive chemicals or signal molecules that can deter attackers, attract beneficial organisms, or

initiate protective responses. These metabolites are typically grouped into three major classes: alkaloids, phenolics, and terpenoids. Each group exhibits distinct defensive properties that can target specific threats or offer broad-spectrum protection.

Pathogenic microbes, including bacteria, fungi, and viruses, also exert selective pressure on plants to develop robust defense mechanisms. Secondary metabolites are vital in providing resistance against these pathogens. Phytoalexins, for example, are a class of secondary metabolites synthesized by plants in response to pathogen attack. These compounds exhibit antimicrobial properties, inhibiting the growth of pathogens or neutralizing their virulence factors. Resveratrol, a stilbene phytoalexin produced by grapevines, demonstrates antifungal activity against *Botrytis cinerea*, the causal agent of gray mold. Similarly, saponins disrupt fungal cell membranes by binding to sterols, leading to cell lysis. These pathogen-specific responses highlight the precision with which plants deploy secondary metabolites to protect themselves. Secondary metabolites also serve as mediators of indirect defense mechanisms, where plants recruit other organisms to assist in their protection. For instance, volatile organic compounds (VOCs) released by plants under herbivore attack can attract predatory or parasitic insects that prey on herbivores. Terpenoids, such as limonene and myrcene, are commonly involved in this process. Maize plants infested with caterpillars release a blend of terpenoid VOCs that attract parasitic wasps, which lay their eggs in the caterpillars, ultimately reducing herbivore pressure on the plants. This intricate ecological interplay underscores the multifunctionality of secondary metabolites in plant defense.

Plant secondary metabolites in medicine

Many drugs used in modern medicine are derived from plant secondary metabolites.



Extraction of taxol from barks of Pacific Yew.

The two most commonly known terpenoids are artemisinin and paclitaxel. Artemisinin was widely used in Traditional Chinese medicine and later rediscovered as a powerful antimalarial by a Chinese scientist Tu Youyou. She was later awarded the Nobel Prize for the discovery in 2015. Currently, the malaria parasite, *Plasmodium falciparum*, has become resistant to artemisinin (Feng, Xet al.,2020)alone and the World Health Organization recommends its use with other antimalarial drugs for a successful therapy. Paclitaxel the active compound found in Taxol is a chemotherapy drug used to treat many forms of cancers including ovarian cancer, breast cancer, lung cancer, Kaposi sarcoma, cervical cancer, and pancreatic cancer. Taxol was first isolated in 1973 from barks of a coniferous tree, the Pacific Yew. (Verpoorte, R. 1998).

Morphine and codeine both belong to the class of alkaloids and are derived from opium poppies. Morphine was discovered in 1804 by a German pharmacist Friedrich Sertürner. It was the first active alkaloid extracted from the opium poppy. It is mostly known for its strong analgesic effects, however, morphine is also used to treat shortness of breath and treatment of addiction to stronger opiates such as heroin. Despite its positive effects on humans, morphine has very strong adverse effects, such as addiction, hormone imbalance or constipation. Due to its highly addictive nature morphine is a strictly controlled substance around the world, used only in very severe cases with some countries underusing it compared to the global average due to the social stigma around it.



Opium field in Afghanistan, the largest grower of opium.

Codeine, also an alkaloid derived from the opium poppy, is considered the most widely used drug in the world according to World Health Organization. It was first isolated in 1832 by a French chemist Pierre Jean Robiquet, also known for the discovery of caffeine and a widely used red dye alizarin. Primarily codeine is used to treat mild pain and relief coughing although in some cases it is used to treat diarrhea and some forms of irritable bowel syndrome. Codeine has the strength of 0.1-0.15 compared to morphine ingested orally, hence it is much safer to use. Although codeine can be extracted from the opium poppy, the process is not feasible economically due to the low abundance of pure codeine in the plant. A chemical process of methylation of the much more abundant morphine is the main method of production.

Atropine is an alkaloid first found in *Atropa belladonna*, a member of the nightshade family. While atropine was first isolated in the 19th century, its medical use dates back to at least the fourth century B.C. where it was used for wounds, gout, and sleeplessness. Currently atropine is administered intravenously to treat bradycardia and as an antidote to organophosphate poisoning. Overdosing of atropine may lead to atropine poisoning which results in side effects such as blurred vision, nausea, lack of sweating, dry mouth and tachycardia.

Resveratrol is a phenolic compound of the flavonoid class. It is highly abundant in grapes, blueberries, raspberries and peanuts. It is commonly taken as a dietary supplement for extending life and reducing the risk of cancer and heart disease, however there is no strong evidence supporting its efficacy. Nevertheless, flavonoids are in general thought to have beneficial effects for humans. Certain studies shown that flavonoids have direct antibiotic activity. A number of in vitro and limited in vivo studies shown that flavonoids such as quercetin have

synergistic activity with antibiotics and are able to suppress bacterial loads.

Digoxin is a cardiac glycoside first derived by William Withering in 1785 from the foxglove (*Digitalis*) plant. It is typically used to treat heart conditions such as atrial fibrillation, atrial flutter or heart failure. Digoxin can, however, have side effects such as nausea, bradycardia, diarrhea or even life-threatening arrhythmia.

Abiotic stressors, such as UV radiation, drought, and temperature extremes, also challenge plant survival. Secondary metabolites play a critical role in mitigating the damage caused by these stressors. Flavonoids, a subgroup of phenolic compounds, are particularly effective in protecting plants from UV radiation. They absorb harmful UV-B rays, preventing DNA damage and oxidative stress. Additionally, flavonoids act as antioxidants, scavenging reactive oxygen species (ROS) generated under stressful conditions. In droughtstressed plants, the accumulation of phenolic compounds such as lignin reinforces cell walls, reducing water loss and providing structural integrity.

Another essential function of secondary metabolites lies in their role as signaling molecules in plant defense. These compounds can trigger systemic acquired resistance (SAR) or localized defense responses. Salicylic acid, derived from phenolic metabolism, is a crucial signal molecule in SAR, mediating the activation of defense genes throughout the plant. Similarly, jasmonic acid and its derivatives, which belong to the oxylipin pathway, regulate responses to wounding and herbivory. These signaling molecules coordinate the production of secondary metabolites and other defense-related proteins, ensuring an integrated response to threats. The production and allocation of secondary metabolites are tightly regulated processes, as their biosynthesis can be metabolically expensive. Plants must balance the trade-off between growth and defense to optimize their survival and reproductive success. Environmental cues and the type of stress encountered often determine the allocation of resources to secondary metabolism. Secondary metabolites, including terpenes, phenolics and nitrogen (N) and sulphur (S)

containing compounds, defend plants against a variety of herbivores and pathogenic microorganisms as well as various kinds of abiotic stresses.(M mazid et al.,2011). More than about 20 000 secondary metabolites have now been identified and their isolation and characterization continues at an undiminishing rate (PG Waterman.,2007).

Plants have evolved complex defense system to overcome the biotic and abiotic stresses as natural systems poses plenty of opposing forces on plants.(Aguirre-Becerra et al., 2020).

Variety of stress forces together affects the plants so, any change in metabolic physiology of plant cannot be referred to be associated with a specific particular stress factor. In context of specific stress, several response pathways are invoked, and in signaling response pathways for pathogens and herbivorous insects, several inter-connections exists. Some of these response pathways are induced by infection and some are performed regardless of antimicrobial nature. Formation of pathogen's cell wall degrading enzymes and synthesis of polymeric barriers to hinder pathogen entrance are some of the other means of plant defense . Additionally plants have specific recognition and signaling systems that enables plant to detect pathogen entrance rapidly and initiate an effective defense response. Plants have also evolved to respond subsequent microbes attack in case if they get infected.The role of secondary metabolites extends beyond direct defense to include allelopathy and ecological competition. Allelopathic compounds, such as phenolics and terpenoids, are released into the soil to suppress the germination and growth of neighboring plants, thereby reducing competition for resources. Juglone, a naphthoquinone produced by black walnut trees, inhibits the growth of nearby plants by disrupting their cellular respiration. This competitive strategy exemplifies how secondary metabolites can influence plant-plant interactions and shape community dynamics. In addition to their defensive roles, secondary metabolites contribute to the mutualistic relationships plants form with other organisms. For example, flavonoids and terpenoids are involved in attracting pollinators and seed dispersers, ensuring reproductive success.

Anthocyanins, a type of flavonoid, provide the vibrant colors of many fruits and flowers, serving as visual cues for pollinators. Similarly, nectar contains secondary metabolites that attract and reward pollinators, while also deterring nectar robbers through the inclusion of toxic or bitter compounds. Human agriculture and medicine have also benefited from the defensive properties of secondary metabolites. Many plant secondary metabolites have been harnessed as pesticides, pharmaceuticals, and nutraceuticals. Pyrethrins, derived from chrysanthemum flowers, are natural insecticides widely used in pest control.

Alkaloids such as quinine and artemisinin have revolutionized the treatment of malaria. Furthermore, phenolic compounds, including flavonoids and lignans, are recognized for their antioxidant and antiinflammatory properties, contributing to human health. Despite their extensive roles in plant defense, secondary metabolites are not without limitations. Their production can be influenced by environmental factors, genetic variability, and the co-evolutionary arms race between plants and their attackers. For instance, herbivores and pathogens often evolve mechanisms to detoxify or bypass plant secondary metabolites. Monarch butterfly larvae, which feed on milkweed, have adapted to tolerate cardenolides, a group of toxic secondary metabolites, allowing them to exploit this food source without competition. Research into secondary metabolites continues to uncover new insights into their functions and applications. Advances in genomics, metabolomics, and synthetic biology are enabling scientists to understand and manipulate the biosynthetic pathways of secondary metabolites (Harborne, J. B.,2007) These approaches hold promise for enhancing crop resistance to pests and diseases, reducing the reliance on chemical pesticides, and developing new pharmaceuticals.

Involvement in Plant Immunity and Pathogen Recognition

Secondary metabolites are intimately linked to the immune system of plants. (Dixon, R. A.,2001). The complex molecular signaling pathways that underlie plant immune responses often rely on the

production of secondary metabolites. One of the central concepts in plant immunity is the ability to recognize pathogen-associated molecular patterns (PAMPs) and trigger defense responses. Secondary metabolites, such as phenolic acids, play a crucial role in this process by acting as signal molecules that activate defense mechanisms. Upon pathogen invasion, plants trigger two main types of immune responses: PAMP-triggered immunity (PTI) and effector-triggered immunity (ETI).

Secondary metabolites are involved in both these pathways. For example, phenolic compounds such as flavonoids and lignans are involved in the PTI response by promoting the formation of defense-related molecules like reactive oxygen species (ROS), which can inhibit pathogen growth and help repair damaged tissue. Additionally, during ETI, which occurs when a plant recognizes a specific pathogen effector molecule, the production of secondary metabolites such as phytoalexins is rapidly induced. These compounds exhibit direct antimicrobial activity and help limit the spread of the infection.

Plant secondary metabolites play a fundamental role in structuring interactions between plants and herbivores, with consequences for population dynamics, community structure and trait evolution (Bocso, N. S., & Butnariu, M., 2022)..

There is growing recognition that these compounds can mediate tritrophic interactions among plants, herbivores, and their natural enemies (War A. R. et al., 2012) For example, although secondary metabolites can reduce survivorship and reproduction, their consumption can also benefit herbivores by reducing parasitism or predation. Similarly, plant secondary metabolite consumption slows the growth of some protozoan gut parasites of insects, including the causal agents of human diseases such as Chagas and leishmaniasis.

Plant secondary metabolites are not only found in leaves but are also common in floral rewards such as nectar. For example, a broad survey revealed that virtually all plant species' floral nectar contained non-protein amino acids, 36% contained phenolics and 8% contained alkaloids. Although bees are generally pollinating mutualists of plants, bees can

also broadly be considered herbivores that consume nectar and pollen. As such, they are exposed to an extensive array of secondary metabolites as both larvae and adults. Like other herbivores, bees are integrated in trophic systems that include both host plants and natural enemies. Parasites are strongly implicated in the decline of both managed and wild bees, but impacts of dietary secondary metabolites on bee-disease dynamics remains a largely unexplored frontier.

II. CONCLUSION

As autotrophs, plants are key components of terrestrial ecosystems, and plant secondary metabolite chemistry plays a significant role in mediating interactions with herbivores. Here we demonstrate that some compounds with well-described anti-herbivore effects can reduce parasite loads within pollinators. We found little evidence for direct negative effects of secondary metabolites on the consumers themselves, and for anabasine, bees were stimulated to consume rather than avoid the compound in nectar. Future work should examine how secondary metabolites such as anabasine can function as deterrents to insect herbivores in leaves while also increasing consumption by pollinating mutualists. Fox, E. M., & Howlett, B. J. (2008). One possibility suggested by our results is that bees could self-medicate by consuming plant secondary metabolites when they are infected with parasites.

Plants have evolved to synthesize a huge variety of secondary metabolites to cope with herbivores. The use of plants rich in active antimicrobial substances has been the foundation for traditional medicine systems and this has been extensively documented. Additionally, plants have been used in plant protection for thousands of years.

The use of the multidisciplinary nanobiotechnology approach could facilitate the incorporation of plant secondary metabolites in different sustainable agricultural systems by providing suitable delivery formulations. Secondary metabolites play a major role in the adaptation of plants to the changing involved in the protective role. (Edreva, A et al., 2008) More efforts should be put into the creation of novel,

stable formulations of plant secondary metabolites with proven pesticidal activity. The loosened legislation and registration processes for plant-based pesticides could also prompt progress in the integration of botanical pesticides in sustainable plant protection.

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