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Opportunities for plant natural products in infection control

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The continued spread of antimicrobial resistance represents one of the most serious infectious disease threats to global health. There is consensus that a key component of addressing this threat is to replenish the waning pipeline of antimicrobials, with attention being paid to novel mechanisms of action. This includes the development of new classes of classic bacteriostatic and bactericidal antibiotics as well as antivirulence drugs, and it is especially in these areas where plant natural products demonstrate great potential. To this end, we discuss the unique characteristics of plant natural products, the advantages of plants as a resource for anti-infective drug discovery, and recent technologies that have further enabled this path of inquiry. As a result of emerging realization of their advantages, plant natural products have recently enjoyed increased scrutiny in antimicrobial lead discovery, and they will continue to serve as a source of leads. We conclude that plant natural products represent a promising and largely untapped source of new chemical entities from which novel anti-infectives can be discovered.

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Introduction

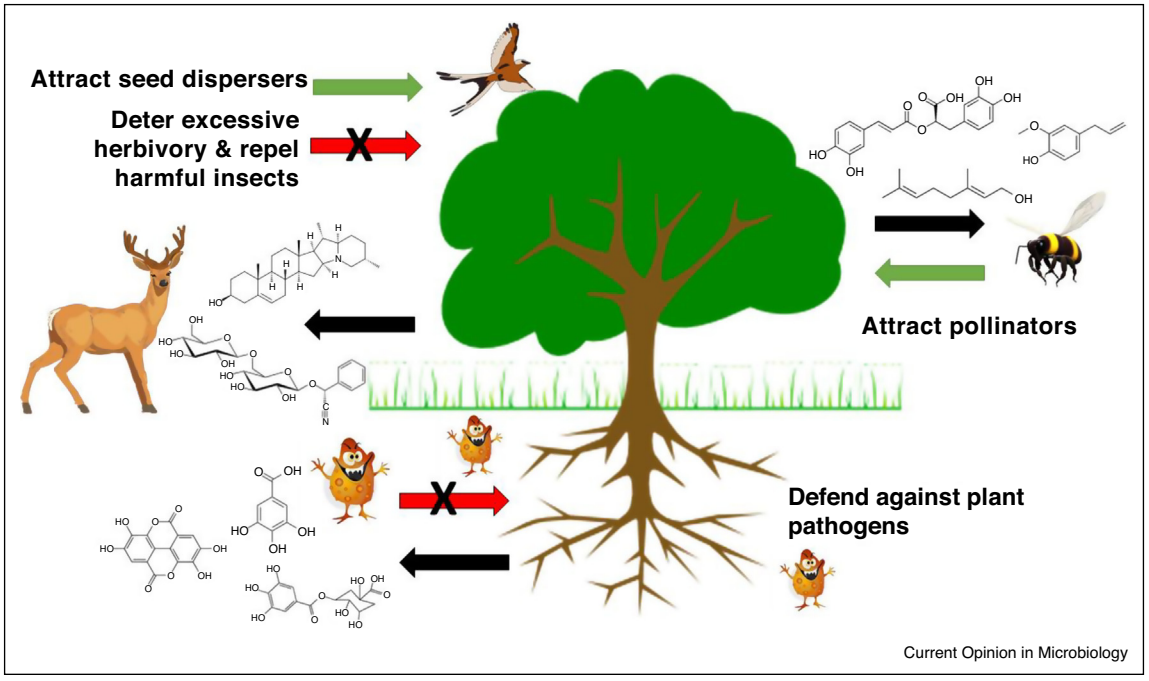
As antimicrobial resistant infections become more and more common, the need for new drugs that circumvent resistance arises as one of the main challenges in combatting this global health phenomenon [1]. Indeed, numerous voices in the literature have cited innovation in anti-infective drug discovery as one of the most important aspects of infection control moving forward [2,3]. This innovation includes the development of drugs that inhibit microbial growth through novel mechanisms of action as well as drugs that work otherwise to attenuate pathogenicity, such as by inhibiting virulence factor production. The latter category of drugs is largely projected to serve as a source of adjuvants to antibiotics that may enhance potency and delay the onset of antimicrobial resistance [4,5•]. This projection has received much attention in the literature, with much *in vivo* evidence supporting the effectiveness of adjuvants in infection treatment [6,7]. Herein we elaborate as to how natural products are especially well-positioned to help fill this gap in the anti-infective pipeline.

Plant secondary metabolites

Most plants produce hundreds if not thousands of unique compounds as an adaptation to their environment for the purpose of self-defense and interaction with other organisms in the environment; these are collectively referred to as plant secondary metabolites, or natural products (Figure 1). The set of total compounds contained in any plant tissue in fact represents a chemical library from which bioactive compounds may be mined [8]. Such libraries possess many characteristics highly favorable for drug discovery. Chief among these is their chemical and structural diversity, which stands in excess of many synthetic small molecule libraries [9]. With this diversity, plant natural products largely belong to the biologically relevant chemical space, which represents the subset of all chemicals that possess bioactivity (Figure 2); they are also largely metabolite-like, thus largely allowing for recognition by transport systems for entry into tissue [2,10–12]. Lead discovery efforts over the last two decades have shifted toward the screening of less structurally complex synthetic compounds, and while there have been many success stories from these campaigns, infectious diseases remain one of the areas that often require chemically and structurally complex molecules [13].

Of the plant natural products explored to date, those tested for microbial growth inhibiton have tended to exhibit weaker potency and selectivity than microbial natural products [14], with some exceptions. Acylphloroglucinols from S. Johns Wort species (*Hypericum* spp.) have demonstrated MICs in the range 0.5–1 μg/mL in methicillin resistant *Staphylococcus aureus* (MRSA) isolates [15••]. At the same time, plant natural products are very clearly rich in anti-virulence properties, with numerous

Figure 1



Plants are sessile and individuals cannot physically move toward resources or away from threats in the environment. Instead, plants produce secondary metabolites — also known as natural products — as chemical communication tools in response to environmental cues. These metabolites are differentiated from the ubiquitous primary metabolites — which include carbohydrates, lipids, proteins, and nucleic acids — and are used for the basic processes involved in maintaining plant life. Secondary metabolites also come at an additional energy cost to the plant, and thus are not produced without reason. Some of the purposes that these compounds serve are in defense against predation and herbivory, attraction of pollinators and seed dispersers, and competition with other organisms in the environment. Secondary metabolites are responsible for the colors, flavors and odors of plant species.

single compounds currently in development to this end [14,16,17]. Epigallocatechin gallate, a major component of green tea catechins, was identified as a promising non-bactericidal antivirulence agent against *Streptococcus pneumoniae* [18•]. Hamamelitannin, a tannin found in the bark and leaves of American witch hazel (*Hamamelis virginiana*), and derivatives thereof are being actively studied for the potentiation of vancomycin in biofilm-associated MRSA infections [19,20••]. INP1855 is a derivative of 8-hydroxyquinoline, synthesized in roots of the diffuse knapweed (*Centaurea diffusa*) and was identified in a screen of a synthetic small molecule library [21,22]. It was confirmed to inhibit the injectisome and flagellar type III secretion systems in *Pseudomonas aeruginosa*, thereby impairing virulence [23••]. There are also examples of synthetic small molecule antivirulence compounds that resemble plant natural product pharmacophores. One example is Compound 22, an isoquinolone mannoside that targets the type 1 pilus adhesin FimH in *Escherichia coli* [24]. Another example is virstatin, an isoquinoline that targets pili biogenesis in *Acinetobacter baumannii* [25,26].

Ethnobotany as a drug discovery tool

In addition to the diversity and drug-like chemical character of plant natural products, the ability to explore this chemical space in a targeted fashion using the lens of ethnobotany — the study of how people use plants — represents a major advantage. This is made possible by the centuries-old practices of traditional medicine in societies across the world, which have identified indications for countless different plant preparations. A recent report on the State of the World's Plants noted that there are at least 28 187 species that have been documented as being used in traditional medicine [27]. While there is no accurate report of how many of these have been investigated to date for their pharmacologic potential, it could be estimated that only a few hundred have been subjected to in depth pharmacologic analysis for bioactivity and chemical composition.

An example of where ethnobotany has guided the discovery of antimicrobial compounds is the immensely successful antimalarial, artemisinin. Malaria is a mosquito-borne infectious disease caused by parasitic protozoans belonging to the *Plasmodium* genus. In 1967, a plant screening research program under the name *Project 523* was set up by the Chinese government with the goal of discovering novel antimalarial chemicals [28]. Tu Youyou was part of a group working on the isolation of antimalarial candidates from plants used in traditional Chinese