The New Antibacterial Properties of the Plants: Quo vadis Studies of Anti-virulence Phytochemicals?

José Luis Díaz-Nuñez¹, Rodolfo García-Contreras² and Israel Castillo-Juárez*¹

¹ Laboratorio de Fitoquímica, Posgrado de Botánica, Colegio de Postgraduados, Texcoco, Mexico, ² Departamento de Microbiología y Parasitología, Facultad de Medicina, Universidad Nacional Autónoma de México, Ciudad de México, Mexico

The recent increase in bacterial resistance to antibiotics has motivated the resurgence of the study of natural antimicrobial products. For centuries, plants have been recognized for their bactericidal properties. However, in the last two decades, it has been reported that several plant derived metabolites at growth subinhibitory concentrations also tend to have anti-virulence properties, since they reduce the expression of factors that cause damage and the establishment of pathogenic bacteria. In this area of study, plants have been positioned as one of the main natural sources of anti-virulence molecules, but only a small portion of the plant species that exist have been investigated. Also, anti-virulence studies have been primarily focused on analyzing the ability of extracts and compounds to inhibit quorum sensing and biofilms formation in vitro. This mini-review discusses the current panorama, the trends in the study of anti-virulence phytochemicals, as well as their potential for the development of antibacterial therapies.

Keywords: antimicrobial phytochemicals, anti-virulence, quorum sensing, virulence factors, adjuvants

INTRODUCTION

Bacteria are social cells that use quorum sensing (QS) to communicate with organisms of the same species, between species, as well as with other domains of life (Banerji et al., 2020). QS systems (QSS) involve the release of chemical signals called autoinducers, to perceive the presence and concentration of other cells (Castillo-Juárez et al., 2017). This allows them to exhibit multicellular behaviors and regulate the gene expression of various phenotypes at the population level, as among them, production of metabolites (pigments, antibiotics) and virulence factors, including the formation of biofilms (Castillo-Juárez et al., 2015). It is estimated that 80% of chronic bacterial infections form biofilms that promote adherence to host cells and allow them to withstand massive doses of antibiotics and evade the immune response (Townsley and Shank, 2017).

Anti-virulence activity (anti-pathogenic or anti-infectious) is a broad concept that refers to the ability to prevent production of the factors responsible for establishment, damage and spread, but without affecting bacterial viability (LaSarre and Federle, 2013; Totsika, 2016). It has been proposed that development of anti-virulence therapies is a viable strategy for control of bacterial infections, with the possibility of avoiding or reducing the appearance of resistance (Defoirdt, 2018; Scoffone et al., 2019). In the last two decades, many plant species and phytochemicals have been identified as having anti-QS and anti-biofilm properties.
In this mini-review, the current situation of anti-virulence phytochemicals, the evidence, and the challenges faced by this field of research were analyzed.

**ANTI-VIRULENCE PROPERTIES OF BACTERICIDAL PHYTOCHEMICALS**

Natural products of microbial origin are the main source of bactericidal compounds, which had a “golden age” in the middle of the last century and prompted the development of commercial antibiotics (Brown and Wright, 2016). However, despite being one of humanity’s greatest scientific discoveries, the alarming increase in bacterial resistance has put their efficacy and future use at risk (López-Jácome et al., 2019). Nevertheless, it should be noted that only a small proportion of the total bioactive molecules in nature have been explored, so new antibiotics continue to be sought (Li et al., 2019; Stokes et al., 2020). Different strategies are being used to avoid the “nightfall” of this class of molecules and favor the emergence of a second “golden age” (Figure 1).

Although the trend in development of antimicrobials has focused on their growth inhibitory properties, it has also been reported that antibiotics at sub-inhibitory concentrations can modulate QSS, virulence (Davies et al., 2006; Khan et al., 2020b), and biofilm formation (Khan et al., 2020a). For example, linezolid has been reported to reduce production of virulence factors from *Staphylococcus aureus* (Bernardo et al., 2004). Also, azithromycin interferes with QS, reduce gene expression and the production of autoinducers in *Pseudomonas aeruginosa*, while streptomycin does so in *Acinetobacter baumannii* (Nalca et al., 2006; Saroj and Rather, 2013). Interestingly, this phenomenon has also been identified in drugs of mass consumption such as aspirin (El-Mowafy et al., 2014) and ibuprofen (Dai et al., 2019), in fermented products, and in various bactericidal phytochemicals (Muñoz-Cazares et al., 2017). Thus, the effect of metabolites at low concentrations on microbial social networks and virulence regulation is a frontier issue that increases the number of molecules to be explored at sub-inhibitory concentrations (Figure 1).

**CHALLENGES AND TRENDS IN THE STUDY OF ANTI-VIRULENCE PHYTOCHEMICALS**

In recent decades, it has been reported that many natural products, especially phytochemicals, exhibit anti-virulence properties when evaluated at subinhibitory concentrations (Brown and Wright, 2016; Silva et al., 2016; Muñoz-Cazares et al., 2017; Mulat et al., 2019). Within natural products, plants are an important source of anti-virulence molecules, but most have been evaluated only in vitro. They are not new chemical structures, and many have been reported as bactericidal (Muñoz-Cazares et al., 2017).

The trend in studies related to identification of the anti-virulence mechanism of phytochemicals has focused on showing that they interrupt some element of the QSS. The in silico approach has been widely used through computational methods, such as molecular docking, to suggest the interaction of phytochemicals with LuxR-type receptor proteins and/or LuxI-type synthases (Deryabin et al., 2019). Multi-omics analysis (proteomic, transcriptomic, and metabolomic) has shown that some phytochemicals interfere with the expression of various QS genes, but also with other non-QS genes. Such is the case of coumarin, which reduces the expression of genes involved in QS, type 3 secretion system (T3SS), and metabolism of cyclic diguanylate in *P. aeruginosa* (Zhang et al., 2018). In the same way, ajoene reduces the expression of virulence factors in *P. aeruginosa* and *S. aureus* by inhibiting small regulatory RNAs (Jakobsen et al., 2017; Table 1). However, some reports identify natural products that can inhibit other anti-virulence targets such as other secretion systems, adhesion molecules, toxins, two-component systems, key enzymes, curli, flagellum as well as metabolic processes involved in the formation and maturation of biofilms (Muñoz-Cazares et al., 2018).

Several anti-virulence phytochemicals have been shown to reduce establishment and damage caused by bacteria in vivo, mainly in the nematode *Caenorhabditis elegans* in murine models (Castillo-Juárez et al., 2015) and animals of importance in aquaculture (Zhao et al., 2015). Also, they have preventive effects on phytopathogenic bacterial infections in some models with *Arabidopsis thaliana*, *Brassica oleracea* and *Solanum tuberosum*, among others (Jhosi et al., 2015; Sivaranjani et al., 2016). Although there is evidence that disruption of virulence by phytochemicals is a potential strategy to prevent disease, there are emerging issues and challenges that have been little studied and are detailed below (Mulat et al., 2019).

**Anti-virulence Phytochemicals and Their Role in the Daily Diet**

One of the trends is related to the role of anti-virulence phytochemicals present in edible plant species and their ability to prevent infectious processes (Givskov, 2012; McCarthy and O’Gara, 2015). Although it is thought that plants are unlikely to contain concentrations of phytochemicals high enough to counteract established bacterial infections, it has been proposed that their continuous consumption may prevent development of chronic infections (Givskov, 2012). This is still difficult to conclude, but, QS inhibitors have been identified in some edible species such as garlic (Bjarnsholt et al., 2005), oilseeds (Pérez-López et al., 2018), and hibiscus acid isolated from *Hibiscus sabdariffa* (Cortes-López et al., 2021), which have been shown to have anti-virulence properties and reduce bacterial pathogenicity in mice (Table 1).

**Phytochemicals as Inducers de QS**

Bactericidal molecules commonly have a dose-response effect, but at subinhibitory concentrations, they can exhibit multiple effects on bacterial cells (Davies et al., 2006; Figure 1). Hormesis is a phenomenon that commonly occurs at low concentrations and is characterized by antagonistic activities (stimulate/inhibit) exhibited by the same molecule, depending on the concentration...
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**FIGURE 1** Schematic representation of the current status of antimicrobial strategies: “The world of the inhibitory”. The tip of the iceberg represents the bactericidal compounds that have been discovered, while the light of the beacon searches for current strategies to prevent the “dusk” of this class of molecules. The resurgence of research in natural products, repurposing drugs for use as antibiotics, nanoparticles, chemical synthesis of new bactericides, as well as advances in computer science, omics, artificial intelligence, and synthetic biology are playing a relevant role in the development of new bactericides (Zakeri and Lu, 2013; Pushpakom et al., 2018; Li et al., 2019; Stokes et al., 2020). However, in this analogy the strategy of “shooting to kill,” allows some pathogenic microorganisms to live and generate resistance; in addition, in the “crossfire” beneficial microorganisms are eliminated. In the “world of the sub-inhibitory,” the number of bioactive molecules to be explored is greater, and the strategy is based on “disarming without killing,” in theory, will not induce resistance. At values below the minimum inhibitory concentration (MIC), the compounds exhibit different effects, among which are anti-virulence, and signal molecule activity, and they have hormetic and adjuvant effects (Cox et al., 2017). The term “anti-virulence agent” also includes peptides, enzymes, and antibodies. QS, quorum sensing; TS33, type 3 secretion system and TCS, two-component systems.

(Mattson, 2008; Martel et al., 2019; Figure 1). Although the hormetic effect of phytochemicals has been reported in other biological activities (Martel et al., 2019), their clinical use could be complicated by a change in concentration that can stimulate virulence. It has been reported that furanone and other inhibitors can inhibit or activate QS depending on the concentration (Martinelli et al., 2004; Welsh et al., 2015; Yao et al., 2019). Similarly, some natural products with no bactericidal activity can stimulate the formation of biofilms (Ranieri et al., 2018). In the case of phytochemicals, the hormetic effects have been little studied, but linalool and eugenol have been reported to have this type of effect on biofilm formation and the rhamnolipids production of *P. aeruginosa* PAO1 (Kim Y. G. et al., 2015). Also, coumarin was reported to affect swarming of *Ralstonia solanacearum* (Chen et al., 2016) and capsaicin to affect biofilm formation in *P. aeruginosa* PAO1 and *Serratia marcescens* (Rivera et al., 2019).

**Effects of Anti-virulence Phytochemicals on the Microbiome**

So far, inhibition of virulence regulation systems appears to be advantageous in combating pathogenic bacteria. However, there are still few studies on its effect on the QS systems of beneficial bacteria, the microbiome in general, or on the host (McCarthy and O’Gara, 2015; Lakes et al., 2020). Unlike in vitro monoculture trials, pathogenic bacteria develop in polymicrobial communities where they interact with environmental factors and different specific signaling molecules (many of them still unknown) that can determine the virulence of the pathogen (Banerji et al., 2020). We now know that the intestinal microbiome participates in many aspects of health; microbiota-host interactions influence obesity, inflammatory and digestive processes, and certain psychiatric conditions, among others (Burdet et al., 2019). In this context, it has been seen that alteration of the microbiome by exposure to penicillin at sublethal doses in the early stages of development induces metabolic alterations and affects expression of genes involved in host immunity, favoring obesity induced by a high-fat diet (Cox et al., 2014). Similarly, some phytochemicals commonly ingested in the diet (phenolic compounds, terpenes, and alkaloids) affect intestinal bacterial groups and it is suggested that they may affect host microbial ecology and physiology when administered at bactericidal concentrations (Lakes et al., 2020). Moreover, recent studies suggest that in complex microbial communities, interference with QS severely affects microbiome composition. However, up to the moment of this review, we did not find reports related to the effect of anti-virulence phytochemicals on the microbiome at sub-inhibitory concentrations (Nguyen et al., 2019; Waheed et al., 2020).

**Development of Combination Anti-virulence Therapies**

Some of the strategies to potentiate the efficacy of anti-virulence molecules are the development of combination therapies of inhibitors with different targets (Fong et al., 2018; Ranieri et al., 2018). However, although the mechanism of action of most...
| Phytochemical | Plant species | Effect | Anti-virulence activity/target | Preclinical trials | References |
|---------------|---------------|--------|--------------------------------|--------------------|------------|
| Ajoene        | *Allium sativum* | Quorum quenching, anti-biofilm | Reduces biofilm formation and production of QS-regulated virulence factors/ Inhibits small regulatory RNAs, such as RsmY and RsmZ in *P. aeruginosa* and RNAIII in *S. aureus*. | Reduced the bacterial load of *P. aeruginosa* in a mouse model of lung infection. | Jakobsen et al., 2012, 2017 |
| Baicalin      | *Scutellaria baicalensis* | Anti-biofilm, quorum quenching, and adjuvant | Reduces biofilm formation and production of QS-regulated virulence factors in *P. aeruginosa*. Improves the bactericidal effects of some conventional antibiotics. | Reduced the number of bacteria in a mouse peritoneal implant infection model. | Luo et al., 2017 |
| Berberine     | *Coptis japonica var. major Satake, Phellodendron chinense Schne der* | Adjuvant | Inhibitor of the MexXY dependent aminoglycoside efflux | NA | Morita et al., 2016 |
| Curcumin      | *Curcuma longa L.* | Quorum quenching, anti-biofilm | In the form of ZnO/curcumin nanocomposites, reduces expression and production of QS-regulated virulence factors in *P. aeruginosa*/CI-QS | Increased survival of specific pathogen-free albino mice injected with *P. aeruginosa*. | Prateeksha et al., 2019 |
| b-sitosterol  | Various plant species | Anti-toxin | Prevents cell lysis caused by pneumolysin and other cholesterol-dependent toxins/ It interferes with binding sites of the toxin (Thr459 and Leu460) with cholesterol | Reduced bacterial load in lungs and mortality of mice intranasally infected with *Streptococcus pneumoniae* | Li et al., 2015 |
| Cinnamaldehyde | Commercially obtained | Adjuvant | NA | Increased bactericidal activity of tobramycin and baicalin hydrate, favoring elimination of *B. cenocepacia* in lungs of mice | Brackman et al., 2011 |

(Continued)
### TABLE 1 | Continued

| Phytochemical               | Plant species                        | Effect                                      | Anti-virulence activity/target                                                                 | Preclinical trials                                                                 | References                       |
|------------------------------|--------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------------------------|
| 6-gingerol                   | Zingiber officinale                  | Anti-biofilm and quorum quenching           | In *P. aeruginosa*, reduces biofilm formation, swarming, rhamnolipid production, pyocyanin, and exoprotease activity/CI-QS | Increased survival of specific pathogen-free mice injected with *P. aeruginosa*       | Kim H. S. et al., 2015           |
| Glycyrrhizin                 | Glycyrrhiza uralensis                | Anti-toxin                                  | Inhibits the interaction of the heat-labile enterotoxin of enterotoxigenic *E. coli* with *G* of intestinal epithelial cells | Prevented enterotoxin-induced fluid accumulation (antidiarrheal effect) in the patented mouse gut assay | Chen et al., 2009                |
| Hibiscus acid                | Hibiscus sabdariffa L.               | Anti-biofilm and quorum quenching           | In *P. aeruginosa*, reduces biofilm formation, swarming, alkaline protease, and elastase activity/ CI-QS | In a mouse model of dermonecrosis, it reduced establishment, damage, and systemic spread | Cortes-López et al., 2021        |
| (-)-hopeaphenol (resveratrol tetramer) | Anisoptera thurifera and *A. polyandra* | T3SS inhibitor                            | Block expression and secretion of the effector proteins ExoS from *P. aeruginosa* and Yop in *Yersinia pseudotuberculosis* | NA                                                                               | Zetterström et al., 2013         |
| Saturated fatty acids        | *Helianthus annuus* L., *Salvia hispanica* L. and *Amaranthus hypochondriacus* L. | Quorum quenching                           | Reduce violacein production and the activity of alkaline exoprotease/CI-QS                      | Increased survival of mice infected with *Chromobacterium violaceum*                 | Pérez-López et al., 2018         |
| Tirucallane-type triterpenoids | *Schinus terebinthifolia* Raddi       | Quorum quenching                           | *S. aureus*: accessory gene regulator (agr) (leuococcin A (lukA), glycerol ester hydrolase or lipase (gehB), nuclease (nuc)) and d-toxin production | Reduce dermonecrosis in a murine model caused by *S. aureus*                         | Tang et al., 2020                |
| Vitexin                      |                                      | Anti-biofilm, quorum quenching, and adjuvant | The combination azithromycin and gentamicin increase antibiofilm activity and reduces the production of QS-regulated virulence factors in *P. aeruginosa*/ CI-QS | Reduced the number of bacteria in a mouse peritoneal implant infection model           | Das et al., 2016                 |

T3SS, type 3 secretion system; NA, not available; CI-QS, possible competitive inhibition with QS receptor proteins.
Induction of Resistance

The premise of the anti-virulence strategy is based on removing the pathogenicity of microorganisms without directly affecting their viability, so that, arguably, strong selection pressures are not generated to induce resistance (McCarthy and O’Gara, 2015). However, some reports indicate that furanone C-30 at subinhibitory concentrations generates resistance by a mechanism that involves the expression of expulsion pumps for this compound (Maeda et al., 2012; García-Contreras et al., 2016). Also, it is suggested that the presence of “cheaters” (bacteria that do not participate in collective communication but do benefit from the products that are produced) in populations may favor resistance because they would be naturally resistant to QS inhibitors (Kalia et al., 2014). Moreover, a recent finding in Escherichia coli suggest that QS inhibition may promote conjugation of plasmids and increase the mutation rate, hence favoring the generation of resistance (Li et al., 2021). This is one of the most debated issues in this area; however, to date no reports have shown that anti-virulence phytochemicals induce resistance.

Patents, Preclinical, and Clinical Studies

Although several patents for anti-virulence agents have been published, most focus on their ability to block QS or prevent biofilm formation, and there are few studies that corroborate the effect at the preclinical (Table 1) or clinical level (Kalia et al., 2019). In the specific case of phytochemicals, studies on their ability to act on biofilms abound, but clinical trials remain scarce (Reuter et al., 2016). In this regard, the study of garlic as an anti-QS agent in the treatment of cystic fibrosis stands out; the study reports a reduction in symptoms and an improvement in lung function (Smyth et al., 2010). Another is the anti-biofilm formulation based on Hymus vulgaris, Eugenia caryophyllus, and lactobacilli for the treatment of bacterial vaginosis, in which administration by slow-release capsules was able to reduce signs and symptoms in 80% of patients (Murina et al., 2018).

CONCLUSION AND PERSPECTIVES

Among natural products, plants have played a discrete role in the discovery of bactericidal compounds, but they have thus far been positioned themselves as the main source of anti-virulence molecules. However, studies of anti-virulence phytochemicals have focused mainly on analyzing their quorum quenching and antibiofilm properties in vitro. The few preclinical trials conducted have identified only preventive effects and they have not yet been shown to counteract established infections. In this regard, it is suggested that the anti-virulence activity registered in bacterial monocultures and ideal growth conditions (rich media) cannot always be extrapolated to the complex conditions that occur in the host (Davies et al., 2006; Turovskiy et al., 2007; Juárez-Rodriguez et al., 2021). Reports exist that indicate that host environmental factors and the presence of other microbial species may interfere with virulence expression (Sabag-Daigle et al., 2012; Ismail et al., 2016). Recently, it was reported that myristic acid, which reduces virulence in vitro, behaves as a signal molecule stimulating the pathogenicity of P. aeruginosa in a dermonecrotic mouse model (Juárez-Rodriguez et al., 2021). Furthermore, it has been discovered that in some murine models the T3SS are the main virulence determinants, while the QS seems to have a more discrete role (Miki et al., 2010; Soto-Aceves et al., 2019; Juárez-Rodriguez et al., 2021). Thus, deciphering the ecological context in which virulence is regulated in vivo will be decisive for the development of effective therapies.

On the other hand, some required characteristics of an ideal anti-virulence molecule have been proposed. Most of them are the same as those expected for other bioactive compounds: high specificity, stability and absence of side effects (Kalia et al., 2019). However, other desirable properties such as not generating resistance or not negatively altering the host microbiome, have been little studied. Another important characteristic is that they should have no bactericidal activity against the pathogen or the microbiome (Davies et al., 2006). Also, hormetic effects that can stimulate virulence should be absent, and they should have the ability to inhibit several anti-virulence targets simultaneously. The latter can help reduce possible side effects derived from the administration of multi-drug therapies and decrease resistance selection.

Furthermore, it is important to expand research into other anti-virulence targets on which the phytochemicals may be acting. One of them is the T3SS, which even though various synthetic molecules have been described that inhibit it, the number of phytochemicals reported with this activity is scarce. In this regard, the preclinical results obtained with (-)-hopeaphenol are very important (Zetterström et al., 2013; Table 1). Also, anti-toxin properties are important, as in the case of β-sitosterol and glycyrrhizin, which protect from damage caused by bacterial toxins (Chen et al., 2009; Li et al., 2015; Table 1). Finally, the use of nanoparticles to potentiate the effect of phytochemicals is a strategy with which good results have been obtained at the preclinical level, as has been demonstrated with curcumin (Prateeksha et al., 2019; Table 1). All these trends contribute to the resurgence of the study of natural antibacterial products, with great potential to help solve the current crisis of antibiotics.
AUTHOR CONTRIBUTIONS
All the authors have contributed equally to the proposal, writing, and editing of the manuscript and also read and approved the final version of the manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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