

Retraction

Retracted: Anti-Quorum Sensing in Pathogenic Microbes Using Plant-Based Bioactive Phytochemicals

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This article has been retracted by Hindawi, as publisher, following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of systematic manipulation of the publication and peer-review process. We cannot, therefore, vouch for the reliability or integrity of this article.

Please note that this notice is intended solely to alert readers that the peer-review process of this article has been compromised.

Wiley and Hindawi regret that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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- [1] K. Subramanian, H. Selvaraj, B. K. P. Sampath Renuga, V. S. and W. Aruni, "Anti-Quorum Sensing in Pathogenic Microbes Using Plant-Based Bioactive Phytochemicals," *Advances in Materials Science and Engineering*, vol. 2022, Article ID 7532086, 7 pages, 2022.

Review Article

Anti-Quorum Sensing in Pathogenic Microbes Using Plant-Based Bioactive Phytochemicals

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Infectious disease-causing pathogenic microorganisms grow rapidly within quorum sensing mediated biofilms. Attempts are made to restrict quorum sensing in pathogens, and the formation of biofilms has paved the way for the identification of bioactive phytochemicals. Anti-QS compounds have been proven to reduce bacterial pathogenicity in the past. Medicinal plants provide an enticing repertoire of phytochemicals with distinct microbial disease-controlling potential due to the vast spectrum of secondary metabolites included in extracts such as phenolics, quinones, flavonoids, alkaloids, terpenoids, and polyacetylenes. This review makes a specialty of the bioactive molecules produced using vegetation which have a target closer to quorum sensing accompanied via biofilm formation in pathogenic microbes.

1. Introduction

The communication between cells allows the pathogenic microorganisms to exchange information about cell density and adjust gene expression is termed quorum sensing. This enables the bacterial pathogens to create an impact on the environment or the host [1]. The microorganisms attach on a surface and proliferate which also produces extracellular polymers that consolidate the attachment and form a matrix of biofilm which leads to a change in phenotype. The formation of biofilm also involves the attachment to a substrate, microcolonies formation, and also the complex channels that form new planktonic cells are formed. The methods which consist of biofilm formation, virulence issue expression, production of secondary

metabolites, strain adaption mechanisms are regulated with the aid of quorum sensing. It is far a key regulator of the virulence factors and biofilm formation in pathogens especially in gram-negative microorganism. The study is carried out to test the bacterial culture extract of a particular strain for its inhibitory effects on virulence factors and biofilm formation of the bacterial culture are regulated by quorum sensing, both in vitro and in vivo [2]. Often, quorum sensing is loosely correlated with the number of cells. The aggregation of a compound called an autoinducer requires the induction of a quorum-sensing gene. The more the cells in a given room, the faster the autoinducer builds up and more likely it can reenter the cells after a cell produces an autoinducer, and the molecule easily diffuses out of the cell.

Quorum sensing has been involved within the developmental tolerance to and the law of many antimicrobial remedies in the immune device. Blocking quorum sensing by a drug increases the liability of the organism that infects the host acquires a defense mechanism. Much bacterial pathogenicity is regulated by quorum sensing, regulation of this kind of mechanism may suppress the virulence [3]. Quorum sensing inhibitors are useful in attenuating the pathogenicity of bacteria regarding the boom of multi antibiotic-resistant bacteria. The intervention of quorum sensing had been an innovative approach to control infections in bacteria, as it manages the spanned words as you want, the pathogens depend on quorum sensing [4]. The arena health employer (WHO) record states that 80% of the arena's population is the usage of herbal medication for healthcare.

Many other studies that are focused on phytochemicals play an important role in the prevention, treatment, and management of various illnesses as it has reduced side effects, for their efficacy and affordability [5]. Phytochemicals that acquire medicinal values are used as a novel drug by increasing the potential of a plant by ayurveda to improve human health with its medicinal properties.

Quorum sensing plays a crucial role in the improvement of novel anti-infectives. Pathogenic for virulence, microbes depend on the quorum sensing mechanism to regulate the expression of the gene. The molecules that are responsible for quorum sensing inhibition that tends to suppress biofilm formation and virulence factors are said to be quorum sensing inhibitors (QSIs). It engaged furanones and some of the glycosylated flavonoids, bismuth porphyrin, structural analogs, complexes, glycolmonoterpenols, and other nanomaterials. Quorum sensing inhibitory activity is carried out due to the similarity in the structure of furanones with AHL some other studies said that furanones may function by the degradation of LuxR type of protein or reducing the DNA binding activity of LuxR which is a transcriptional regulatory protein. The formation of biofilm and virulence factors so as to be managed by quorum sensing was reduced by sulphoraphane erucin [6].

2. Quorum Sensing in Gram-Negative and Gram-Positive Bacteria

Autoinducers that belong to the first class are used by Gram-negative bacteria, the second class is used for Gram-positive bacteria and the third class of biomolecules is used for both Gram-negative and Gram-positive bacteria. Quorum sensing is used by both Gram-positive and Gram-negative bacteria. Secreted oligopeptides and two-component systems, which comprise membrane-bound sensor kinase receptors and cytoplasmic transcription factors that direct gene expression changes are commonly used in gram-positive systems.

Gram-negative bacteria produce acylated homoserine lactone (AHL) as its autoinducers, that are synthesized by LuxI type of enzyme which is a signal synthase encoded by the first gene of Lux operon [1] (Figure 1)

2.1. Gram Negative Bacterial Quorum Sensing Arrangement. The complex LuxR-AHL binds to DNA promoting and activation of genes manipulates through the quorum sensing. The LuxR/3-oxo-C6-HSL complex turns on the transcription by the promotor lux operon promotor, which suggested the rise to different genes by the side of Lux AB genes that encode luciferase and Lux CDE, encoding the enzymes producing the substrate for luciferase observed via bioluminescence. The molecules diffuse passively through the bacterial membrane and get gathered each intracellular and extracellularly with respect to the cell density. Quorum sensing circuits are observed in above 25 species of Gram-negative bacteria.

The LasR-autoinducer complex activates the expression of every other *P. aeruginosa* quorum-sensing machine by triggering unique target genes of 2d magnificence that encode the sigma factor rhamnosyl transferase stationary portion, which involves the synthesis of biosurfactant/hemolysin rhamnolipid and also the genes that include pyocyanin antibiotic and pyocyanin synthesis. A Gram-negative microbe that can be contained in water and soil, like *Chromobacterium violaceum*, a number of things that include antibiotics, cyanide hydrogen, proteases, chitinase, and especially violacein, a purple pigment that is water-insoluble with a purple pigment involvement of phenotypic response to AHLs [7].

2.2. Quorum Sensing System in Gram Positive Bacteria. Numerous techniques that respond to the increase in mobile density are controlled by Gram-positive microorganisms, but in contradiction to Gram-negative microorganisms using HSL autoinducers. These high-quality gram-bacteria use peptides that are processed from precursors that can be used for quorum sensing as autoinducers. Indicators are actively transported outside the cell, where they interact with external domains of membrane-bound sensor proteins. The transduction of the sign that could be created by phosphorylation cascade ends the activation of DNA binding protein by affecting the transcription of precise genes so that each sensor protein is selective to its peptide signal. In the case of Gram-positive bacteria, the peptide signal precursor locus is being translated to precursor protein which is cleaved to form a processed peptide autoinducer signal.

Further, many different Gram-positive bacteria show off oligopeptides signaling systems alongside AI-2. Developing and responding to the mixture of these signals permit bacteria to note their own populace nitrogen tiers and also the density of population of others in its locality. A properly-defined response to indicators or response that is based on the combinatorial sampling of various kinds of signals may want to permit microorganisms to constantly regulate the behavior depending on the institution of species [1].

3. Phytochemicals against Quorum Sensing

The possible inhibitors of quorum sensing are phytochemicals present in plant extracts that include quercetin, myricetin, kaempferol, baicalin, eugenol, and 6-gingerol.

QUORUM SENSING

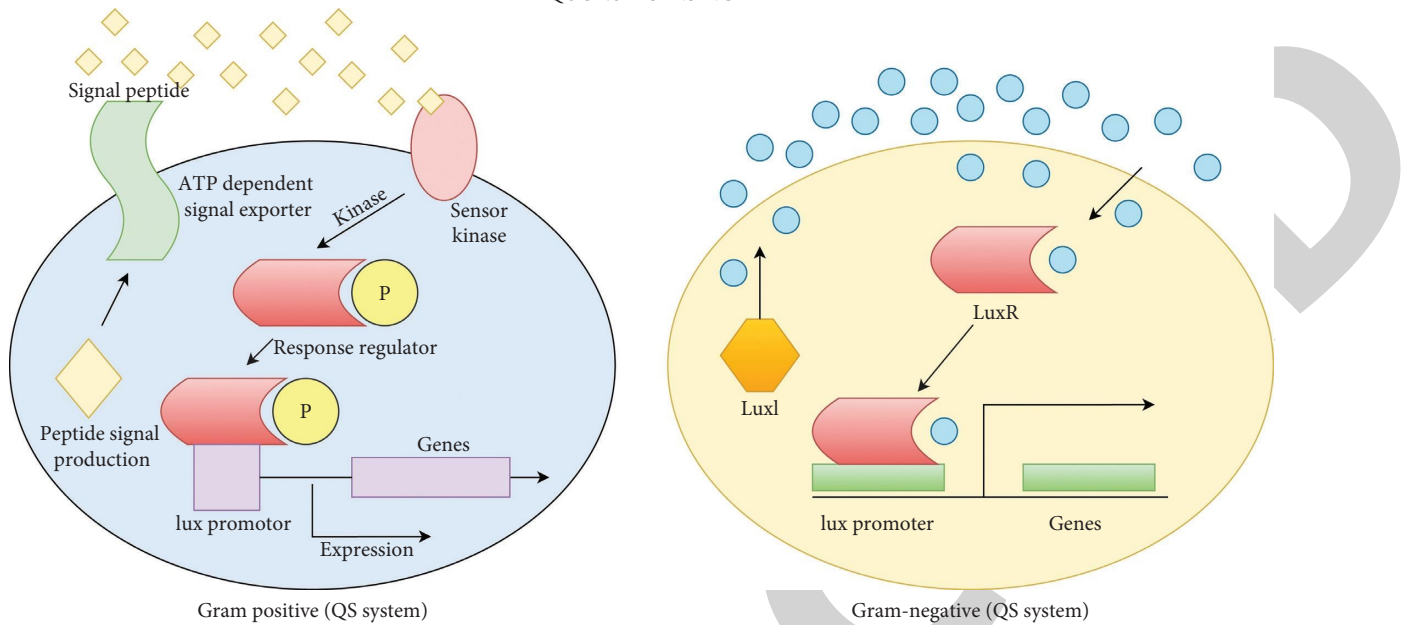


FIGURE 1: Quorum sensing arrangement in gram-positive and gram-negative bacteria.

Notable substitutes for synthetic antibacterial drugs are bioactive compounds from plant extracts with anti-quorum sensing activities, especially among multidrug resistant (MDR) pathogens, flavanones such as naringenin, eriodictyol, and taxifolin [8, 9], flavonoids such as quercetin, myricetin, kaempferol [10], eugenol [11], are some of the big quorum sensing inhibitors [12], and baicalin [13].

Most of the flavonoids exhibit inhibitory interest with quorum sensing. Coumarin, is a phenolic compound observed by using cinnamon, includes numerous naturally acquired compounds [14, 15]. *Dalbergia trichocarpa* bark [16], 6-gingerol, a stinky oil received from fresh ginger and rosmarinic acid, includes a new bioactive compound, oleonic aldehyde coumarate (OLAC), an effective quorum sensing inhibitor [17, 18].

The administration of flavonoids to the pathogen suppresses the production of virulence elements. A note on structure-interest courting is essential to inhibit LasR/RhlR and hydroxyl moieties present in flavone-a ring spine [19]. A few extracts exhibit fine end result quorum sensor inhibitor screening which includes extracts of cauliflower, celery salt, lawn cress, chervil, lemongrass, radish, thyme, and water-cress. The aqueous extract of *Conocarpus erectus*, *Callistemon viminalis*, *Bucida buceras* inhibit the mortality of *C. elegans*. A few different essential oils together with cinnamon, lavender, and peppermint showed anti-quorum sensing hobby [20].

Studies show that some natural products' phytochemical extracts interfered with AHL pastime. Better inhibitory activity against the development of violacein mediated by AHL was expressed in raspberry, blueberry, and grape extracts. A number of herbs and spices expressed an effective reaction in reducing the inhibition of production of violacein mediated by the AHL concern. Basil, thyme, and brassica oleracea had the strongest pastime and decreased

formation of pigments, followed by rosemary, ginger, and turmeric with a decreased formation of violacein. Figure 2 shows numerous virulence factors in bacteria that include motility swarming for its quorum sensing gene expression, which is regulated. The extracts were also investigated for the inhibitory activity on quorum sensing [21].

Recent studies are carried out for the investigation of the aspect of food ecology quorum sensing. Signaling compounds are including autoinducers 1 and 2 existing in foods especially in milk, meat, and vegetables. Food matrices are of solid environment except liquid food. The food matrices are mostly of the solid environment with the exception of liquid foods that give rise to pathogens that get trapped and localized at high densities where there is increased growth rates and biofilm formation. The pathogenic activity and formation of biofilm are affected by the presence or growth of microbial species as well as the cell-cell interactions that occur in the solid food matrix, by determining the capability of a pathogen to produce quorum sensing. Various reports had suggested that the target to quorum sensing would be a novel strategy for the inhibition of biofilm infections [22]. On this controversy, researchers are increasingly investigating the herbal products for the novel therapeutic and antimicrobial agents that act as nontoxic inhibitors of quorum sensing by controlling infectious microbes that appear to resist the bacterial strains. In recent times it is assessed that 10% of terrestrial flowering plants of various communities are being used as therapeutic agents but only 1% have been recognized and validated [1].

3.1. Anti-Quorum Sensing. Thereby, phytochemicals are the richest reservoir that is available for therapeutics. The antimicrobial activity of some phytochemicals is not well known for its exact mechanism of antimicrobial functions.

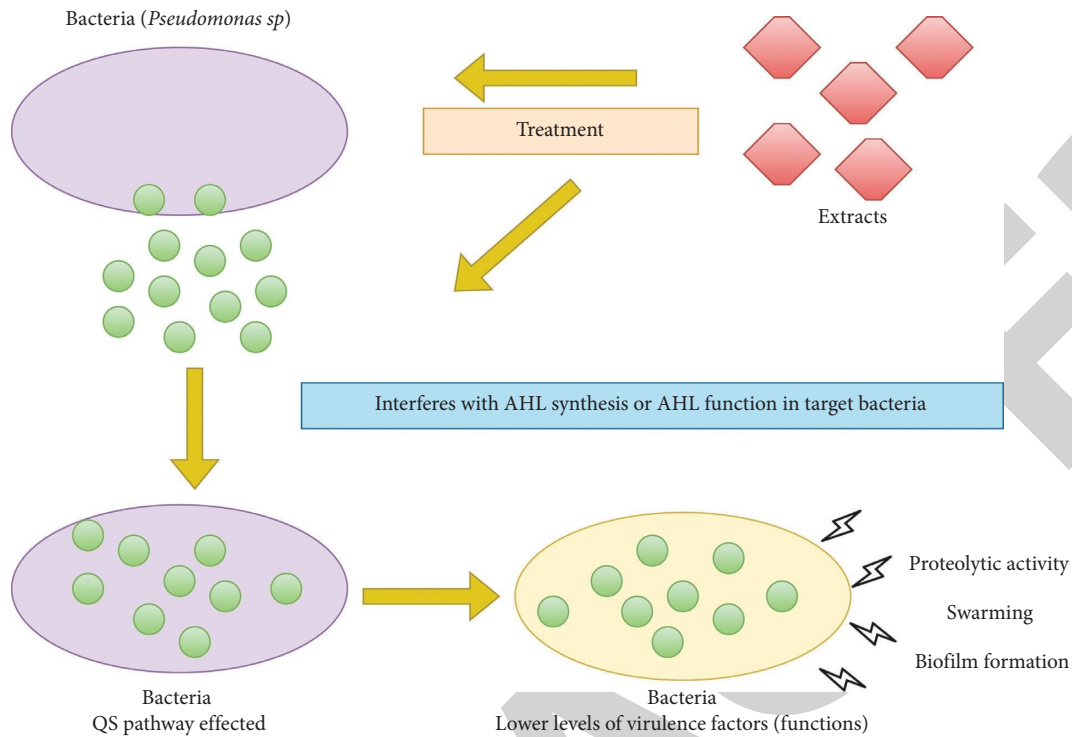


FIGURE 2: Representation of quorum sensing, modulates the pathogenic virulence on phytochemicals.

Various types of phytochemicals that inhibit quorum sensing such as polyphenols have the ability to affect the formation of biofilm in some pathogens [23].

Selectivity, virulence decrease, and lack of resistance to quorum sensing are all advantages of anti-quorum sensing drugs. The anti-quorum sensing activity of phytochemicals is not well defined and is found to contain antimicrobial efficacy that is mediated by quorum sensing inhibition. Most of the flora contribute to being the source for medicines and the development of pharmaceutical products. Quorum quenching molecules are also identified in plants are also being reported. Many plants have been established which are constricted symbiotic or syntrophic associations with pathogens. The phytochemical molecules or the extracts of various fruits, herbs, and spices are noted for their ability against quorum sensing. One of the best examples includes a eukaryotic organism such as Australian red alga *Delisea pulchra* [1], which produces metabolites interfering with bacterial communication known as halogenated furanones. These compounds show various biological activities such as the display of antifouling and antimicrobial properties. Some furanones particularly hinder the process of N-acylated l-homoserine lactone (AHL) regulation by the acceleration of degrading AHL receptor protein. The detection of phytochemicals against pathogens inhibits the regulation of quorum sensing of bacterial colonization and virulence factors provide an alternative for anti-infective agents [24].

The extracts of plants acted as quorum sensing inhibitors when there is a similarity in the chemical structure of AHL or quorum sensing signals or the capability of degradation of signal receptors (LuxR/LasR) [21]. Some plants produce GABA (γ -aminobutyric acid), which acts as the promotor

for which the N-acylated l-homoserine lactone (AHL) signal is degraded by lactonase in *A. tumefaciens*, thereby limiting the process of quorum sensing-infection. The extracts of *Curcuma longa* produce curcumin and act as the inhibitor for genes expressing virulence factors in *P. aeruginosa* PA01. Various diversities of apples and their derivative extracts like cider exhibit quorum sensing inhibiting activity which is probably it is due to the polyphenol present in hydroxycinnamic acids, rutin, and epicatechin that behave as anti-quorum sensing agents against *C. violaceum* in a synergistic manner [25, 26]. Anti-quorum sensing activities are reported for *L. nobilis*, *S. oleraceus*, *R. officinalis*, *T. capensis*, *J. sambac*, *P. alba*, and *P. nigra* extracts, which have the ability to decrease the production of violacein. Cinnamaldehyde and its derivatives contain an extensive quorum sensing regulation which includes the formation of biofilm and quorum sensing mediated by AI-2 in various other pathogens such as *P. aeruginosa* and *Vibrio* sp. Furocoumarins that are present in grapefruit inhibit those activities of autoinducers 1 and 2 in *V. harveyi* and also the formation of biofilm in some pathogenic organisms. Isolimonic acid and deacetyl nomilinic acid 17 β -D-glucopyranoside which are the limonoids, that are present in orange seeds may cause more than 90% inhibition of autoinducer 2 in *V. harveyi* at 100 $\mu\text{g/ml}$ concentration shows AI mediated bioluminescence [7].

The production of naringenin which is driven by the LasI and RhlI genes reduces the production of acyl homoserine lactones N-(3-oxododecanoyl)-l-homoserine lactone (3-oxo-C12-HSL) and N-butanoyl-l-homoserine lactone (C4-HSL). Flavan-3-ol catechin reduces the quorum sensing production that mediates virulence factors that include

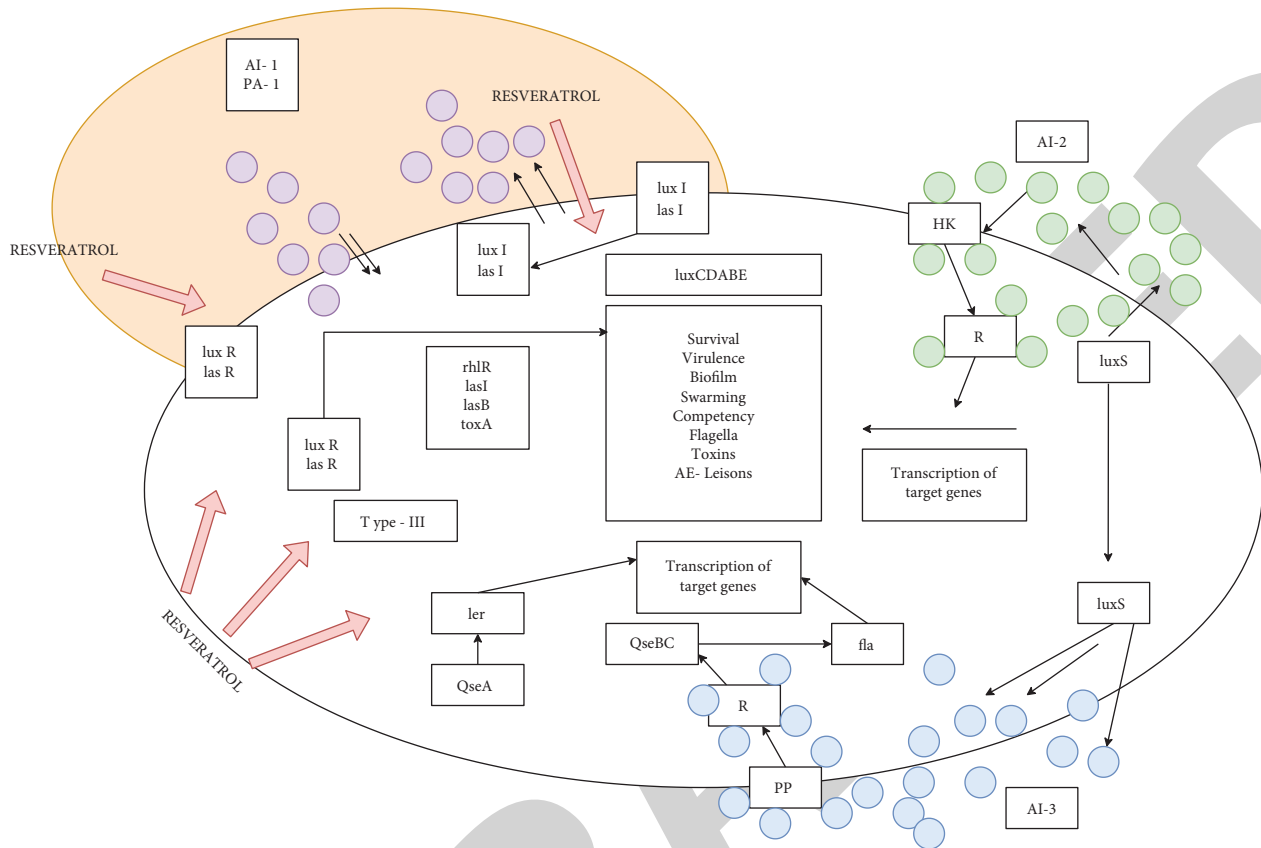


FIGURE 3: Representation of phytochemicals that inhibit quorum sensing.

pyocyanin, elastase, and also the formation of biofilm in *P. aeruginosa* PAO1 [27]. Varieties of legumes that include clover, peas, and yam beans are reported to have the ability of AHL degradation [28]. The roots of *Ocimum basilicum* commonly known as sweet basil which produce rosmarinic acid have the ability to disrupt the biofilm formed by *E. coli* [21]. AHL-lactonase enzyme expression is stimulated by salicylic acid which is a phenolic plant secondary metabolite. Ursolic acid at $10 \mu\text{g/ml}$ has the capability to reduce the formation of biofilm by 79% formed by *E. coli* and 57–95% in *V. harveyi* and *P. aeruginosa* PAO1. Quorum sensing associated gene expressions can be inhibited by the extracts of broccoli and its constituents which then downregulates the virulence attributes of *E. coli* O157 : H7 both in-vitro and in-vivo, vegetal like Brassicaceae possess the potential to get developed as an anti-infective agent. Some other extracts such as ethanol and ethyl acetate from *Hypericum conatum*, express quorum sensing inhibition activity on *C. violaceum* which limits the violacein production [29].

Polyphenol compounds that contain the moiety present in gallic acid which includes ellagic acid and tannic acid that are induced by several plant species acquiring the capability of specifically interfering AHL mediated signaling which in turn by blocking the communication of pathogens [23]. For example, ellagitannins which include punicalagin and ellagic acid which are abundant in pomegranates and berries exhibit in concentration that is higher than $300 \text{ mg}/100 \text{ g}$. The gut microbiota hydrolyses ellagitannins to ellagic acid which

are eventually metabolized to create urolithin-A and B, by which these metabolites are accumulated in the gut where predominant activities are performed. For example, Urolithin-A has the capability of regulating the bacterial growth in the intestines of rats before and after the induction of inflammation chemically. Both urolithin-A and urolithin-B also have the ability to inhibit the quorum sensing associated processes up to 40% and there could be a decrease in the levels of AHL that is initiated by Enteropathogen *Y. enterocolitica* up to 45%. Some examples include chestnut honey with high inhibitory activity on the other hand orange and rosemary honey was inefficient [1]. Truchado et al. hypothesized that one of the main factors that affect inhibition is that floral origin irrespective of its geographic location.

Many phytochemical extracts inhibit the quorum sensing activity by hindering the AHL activity by the competence with them for their structural similarity and also by the acceleration to degrade LuxR/LasR receptors of AHL inhibitors. It was experimentally reported that fruits, herbs, and spice extracts had a better quorum sensing inhibitory activity at sublethal concentrations. Although there are various inhibition processes carried out it was also observed that two different mechanisms in combination have the capability of phytochemicals to restrict the AHL activity and by regulating the synthesis of AHL by the pathogens [30]. The natural phytochemical extracts have the ability to regulate quorum sensing by the inhibition of signal

molecules that had never been indicated. Various extracts that act as quorum sensing inhibitors decreased the accumulation of two pathogenic bacteria PAO1 and *E. coli*. The results were reported on the ability of phytochemicals to regulate quorum sensing at multiple levels as shown in Figure 3 [21]. Many plant extracts have been described as effective alternatives to conventional pesticides, and their ingredients have been employed in food preservation due to their promising anti-QS action against a number of food pathogenic bacteria.

Also, it was found that phytochemical extract from *Camellia sinensis* significantly declined and the conjugative R plasmid in *E. coli* is transferred which is related to quorum sensing [31]. Therefore, phytochemicals have the ability to inhibit quorum sensing followed by its virulence factors and formation of biofilm in the pathogenic microorganisms revealed the strategy of antimicrobial chemotherapy. This method may lead to the novel identification of safe anti-pathogenic drug from the phytochemicals which has no risk of antibiotic resistance and contains low toxic levels.

Potential anti-quorum sensing properties are proved to be present in traditional medicinal plants against pathogens. Different phytochemical extracts, extracted from plants include flavonoids which are more potent in decreasing the effect of quorum sensing in various pathogens. Some extracts of plants that exhibit potential quorum sensing include *Cassia alata*, *Camellia nitidissima*, *Parkia javanica*, *Nepenthes alata*, *Brassica oleracea*, *Terminalia bellirica*, *Pistacia atlantica*, and *Laserpitium ochridanum*. The upcoming medicines prefer plant as its genesis, in which the phytochemical extracts are being explored further to flourish as an effective substitute to reduce the misconsumption and excessive use of antibiotics on the health of humans. Some phytochemicals such as essential oils obtained from cinnamon, norfloxacin, chrysin, and curcumin revealed the least MIC value [7].

4. Conclusion

The use of extracts from vegetative sources or pure compounds of plants for biocontrol approaches when in contrast with other conventional treatments express some advantages in particular comparatively. Certainly, such foods that are conventionally treated are regarded to be green and natural. Even though, there is no biocontrol approach that has the perspective of the issue entirely, such kinds of approaches altogether initiate a tool to act in a combined and compatible way through various implementations either applied individually or in combination. A better understanding of the phytochemical for the potential diffidence of quorum sensing is of eminent significance to research which aimed for the discovery and progression of new anti-quorum sensing phytochemicals that have the ability to prevent infectious human pathogens. Such antipathogenic compounds in contradiction to antibacterial compounds may not kill the bacteria or inhibit the entire growth and would likely prevent the resistant strain development. Eventually, in recent years, plant bioengineering, in particular, may influence the bacterial association; for example, quorum

sensing strategies suppress the influence of pathogenic microorganisms. Phytochemistry, with the use of inhibitors for various targets or quorum sensing activities, could be a major benefit in the confront against multiantibiotic bacterial diseases.

Data Availability

The data used to support the findings of this study are included in the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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