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Review

Recent Progresses on Inhibition of Bacterial Biofilms by Resveratrol: A Systematic Review Covering a Ten-Year Period

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Abstract: The trans-isomer of resveratrol is a naturally occurring bioactive compound, and it is important because of its biological properties, which are beneficial to health. In recent years, interest in the antimicrobial activity of this molecule has grown; little is known, however, about its antibiofilm activity. This systematic review focused on the advances in research on the topic, in the decade up to 2021. With most studies coming from Asia, research on trans-resveratrol, alone or associated, has shown potential for exploration by the food industry. Low concentrations of the compound exhibit activity against biofilm formation by pathogenic bacteria whose inhibition mechanisms are multifactorial and involve quorum sensing. Few bacterial species, however, have been investigated up to now.

***Keywords*:** quorum-quenching, naturally occurring polyphenols, trans-resveratrol

1. Introduction

Resveratrol is a naturally occurring polyphenol found in numerous botanical sources, especially *Vitis vinifera* [1]. The highest amounts of trans-resveratrol are found in seeds [2], berry skin [3], and leaves [4], while in by-products from grapes, the highest concentrations are in juice rather than wine [5].

There are two isomeric forms of resveratrol but only the trans-isomer (3,4,5'-trihydroxy-trans-stilbene) is biologically active [6]. Chemically, the molecule is formed by two phenyl groups linked together by a styrene bond [7]. Trans-resveratrol has polar and non-polar regions, which contribute to the pharmacological properties, such as anti-inflammatory activity [8], and antioxidant [9], antitumor [10], cardioprotective [11], hypolipidemic [12], antidiabetic [13], and neuroprotective [14] activities.

In addition, trans-resveratrol exhibits activity against a wide spectrum of pathogenic microorganisms found in humans [15], which include viruses [16], protozoa [17], yeasts [18], and bacteria [19]. Additionally, trans-resveratrol-derived forms efficiently disrupt planktonic cell attachment and colonization by causing damage to the bacterial membrane [20-21]. On the other hand, the effect of trans-resveratrol on biofilm formation and on the activity of preformed biofilms also involves interference with the expression of biofilm-related genes [22]. Thus, the inhibition of virulence factors such as biofilm formation in important pathogens will increase the success of treatments, as well as the prevention of antibiotic resistance [23].

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In recent years, the formation of biofilms has been closely related to multidrug resistance [24]. In the hospital environment, biofilm colonization is present on different surfaces, including devices used with patients and inside the water distribution system [25]. The World Health Organization lists 12 bacteria as global priority pathogens in terms of multidrug resistance to antibiotics. These are divided into three levels. Critical level: *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacteriaceae (including *Escherichia coli* and seven genera); High level: *Enterococcus faecium*, *Staphylococcus aureus*, *Helicobacter pylori*, *Salmonella* spp. and *Neisseria gonorrhoeae*; and Medium level: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Shigella* spp. [26]. It is noteworthy that all these microbes can form biofilms as a means to escape the biocidal action of many antibiotics, representing a serious threat to healthcare [27-28].

The innovative use of bioactive natural products as a means to eradicate biofilms through unique growth-independent mechanisms has become a matter of interest in recent years [29]. Reducing these pathogens may reduce the risk of spreading infections in the hospital environment [30]. Not reducing pathogens can result in an increase in mortality and morbidity from infection, as well as longer hospital stays and higher health system costs [31].

Although much is known about trans-resveratrol [32], there is little understanding of how the antibiofilm activity of the molecule occurs via the inhibition of quorum sensing (QS), a mechanism that regulates gene expression in response to fluctuations in cell-population density that is an emerging topic in terms of new antimicrobials. In recent years, interest in the anti-QS activity of trans-resveratrol has increased [33]. Thus, this present systematic review aimed to carry out a compilation of what has been described on the subject throughout the past decade.

2. Material and methods

In the first week of April 2021, four databases were consulted, as follows: MEDLINE, PubMed, Science Direct and Periódicos CAPES. These were selected following the guidelines of the Ministry of Health of Brazil [34]. The search included only original open access articles published in English between April 1, 2011 and April 1, 2021. The keywords "resveratrol", "biofilm" and "quorum sensing" were searched in any part of the text. As a second filter, the words "quorum quenching" and "antibiofilm" were then used. Duplicate articles in the consulted platforms were excluded, as well as review articles, technical notes, book chapters, letters, thesis, articles in the press and original articles with access only to the abstract. The selected documents were analyzed and compiled in a table containing the objectives and results.

3. Results

Five documents were identified from a total of 13 publications analyzed (Figure 1). The Pubmed platform was the database with the highest number of articles. The articles were published between 2013 and 2021 with 80% of them in the last five years (Table 1). A limited number of bacterial species were investigated: *Escherichia coli* [35], *Listeria monocytogenes* [36-37], *Listeria innocua* [37], *Chromobacterium violaceum* [38], *Pseudomonas aeruginosa* [38] and *Salmonella* Typhimurium [39].

Asia was the region of the globe with the major interest in the topic, accounting for 80% of the articles, followed by Europe. India was the country with the most publications (40%). No publications were identified from the Americas, Africa and Oceania. The areas of research were Food Science, Engineering, Biochemistry and Biomedicine.

Trans-resveratrol has been evaluated as a pure substance [36-37], plant extract [35] or commercial formulation [38-39]. Concentrations between 10 and 400 µg/mL of trans-resveratrol exhibited an inhibitory action on cell growth, as well as on the stability of biofilms (reductions between 32 and greater than 90%). Furthermore, the compound was shown to reduce the motility of planktonic cells, as well as increase the susceptibility of the biofilm to the action of antibiotics. However, the antibiofilm effect was not associated with a reduction of planktonic cell growth. The reason was that trans-resveratrol appears to disturb distinct cellular behaviors, such as biofilm formation, motility, and the QS system independently, without exhibiting bactericidal activity [35-36].

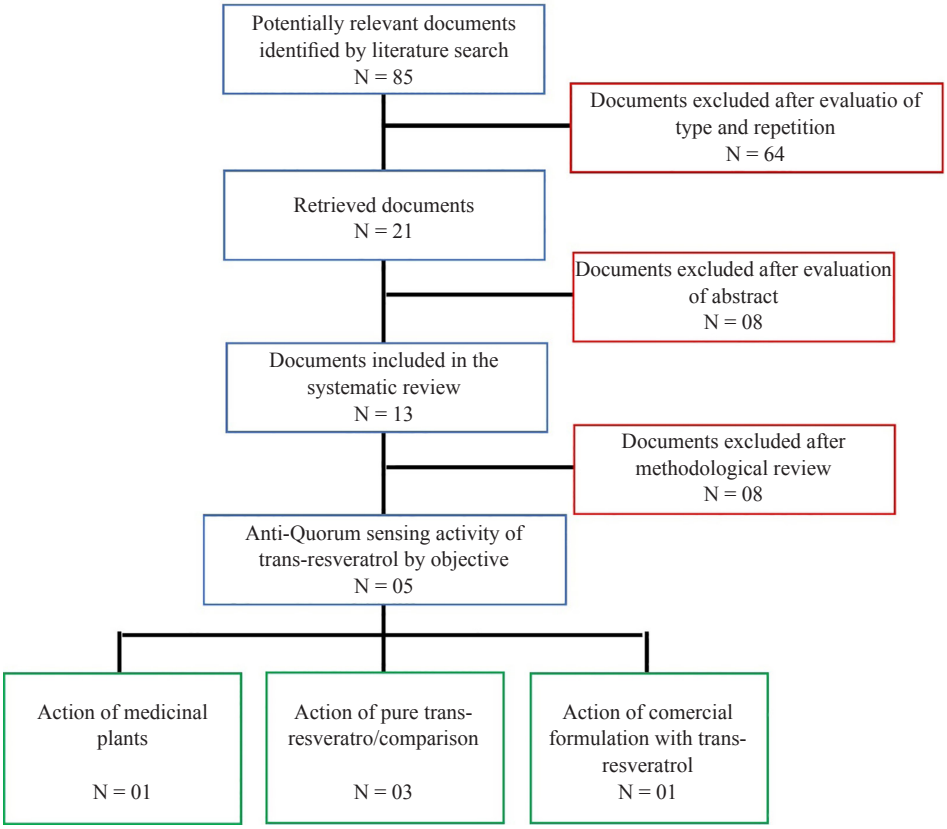

Figure 1. The evaluation process of included documents

Table 1. Studies applying trans-resveratrol as an anti-QS agent and its effects on biofilm disturbance and/or motility reduction (2013-2021)

Reference	Aims	**Results**
[35]	To test 498 Chinese medicinal plant extracts against 9 strains of *E. coli*: 5 enterohemorrhagic (EHEC) and 4 commensals.	10 µg/mL of trans-resveratrol presented in *Carex dimorpholepis* extract reduced motility and biofilm formation of EHEC *E. coli* strains, without affecting viability. Commensal strains were not inhibited.
[37]	To study the antibiofilm activity on *L. monocytogenes* and *L. innocua*.	200 µg/mL of trans-resveratrol caused bactericidal action and inhibited biofilm formation in both species. The activity on the biofilm was also verified at subinhibitory concentrations (100 and 50 µg/mL).
[38]	To investigate the anti-QS activity of a formulation containing (in %): trans-resveratrol (50), sunflower lecithin (1) and grape seed oil (1), against *C. violaceum* 12472, and *P. aeruginosa* PAO1.	QS systems inhibition was concentration-dependent (200-25 µg/mL). This resulted in reduced pigment expression (violacein and pyocyanin), motility, and biofilm formation. *P. aeruginosa* PAO1 also had an increased susceptibility of the biofilm to antibiotics.
[39]	To compare the anti-QS effect of trans-resveratrol with coumarin and verify the antibiofilm action of the combination of both substances against *S.* Typhimurium.	The MIC of isolated trans-resveratrol was > 400 µg/ml. Inhibition of biofilm formation was concentration-dependent, and had no effect at 200 µg/mL. When trans-resveratrol 10 µg/ml was associated with coumarin 12.5 µM, *S.* Typhimurium biofilm growth was inhibited by about 32%. This percentage enhanced with the increase of trans-resveratrol concentration, made the combination more effective than with the individual compounds.
[36]	To evaluate the MIC and sub-MIC of trans-resveratrol and three other natural active compounds in the control of the biofilm formation of *L. monocytogenes* CMCC54004. Concentrations ranged between 12.5 and 400 µg/mL.	Reduced trans-resveratrol cell viability as well as biofilm formation were concentration dependent. Furthermore, the compound was the most effective other substances tested. Subinhibitory concentrations at 50 and 100 µg/mL of trans-resveratrol negatively regulated some genes related to biofilm formation: *agr*A, *agr*C, *agr*D (anti-QS), instead of genes involved in motility and associated with flagella (*deg*U, *mot*B and (*fla*A). In addition, trans-resveratrol was the only molecule that did not down-regulate the expression of the *sig*B gene, responsible for stress responses.

MIC-Minimum Inhibitory Concentration
E. coli-Escherichia coli; L. monocytogenes-Listeria monocytogenes; L. innocua-Listeria innocua; C. violaceum-Chromobacterium violaceum; P. aeruginosa-Pseudomonas aeruginosa; S. Typhimurium-*Salmonella* Typhimurium

Additionally, the highest activity of trans-resveratrol was seen to be concentration-dependent, but the compound remained active in subinhibitory concentrations. At 10 µg/mL, trans-resveratrol exhibited antimicrobial activity, although concentrations around 100-200 µg/mL were more commonly used for tests due to guarantee greater reliability regarding the expected antimicrobial effect. All bacteria evaluated were sensitive, but *Chromobacterium violaceum* and *Pseudomonas aeruginosa* exhibited the most significant results in terms of disturbance of the biofilm stability associated with anti-QS mechanisms [38].

4. Discussion

Trans-resveratrol was first characterized by Dr. M. Takaoka in 1939, from the root extract of white hellebore (*Veratrum grandiflorum*) [40]. It was only in the 1990s that the first studies were carried out on the biologically active properties of the compound, including the inhibition of the growth of Gram-positive and Gram-negative bacteria in concentrations less than 100 µg/mL [41].

With the evolution of research, a higher complexity in the mechanism of inhibition of trans-resveratrol has been identified, involving down-regulation of genes required in the process of cell division in prokaryotes [42], as well as a unique growth-independent mechanism in *S. aureus* [43] and *E. coli* [44].

The analysis of publications on the activity of trans-resveratrol involving these mechanisms indicated an evolution of knowledge about the properties and mechanisms of action of the compound. Information, however, is still scarce and the universe of bacterial pathogens evaluated is still very limited [45], but first studies indicated a tendency to meet the demands of the food industry [39] (Figure 2).

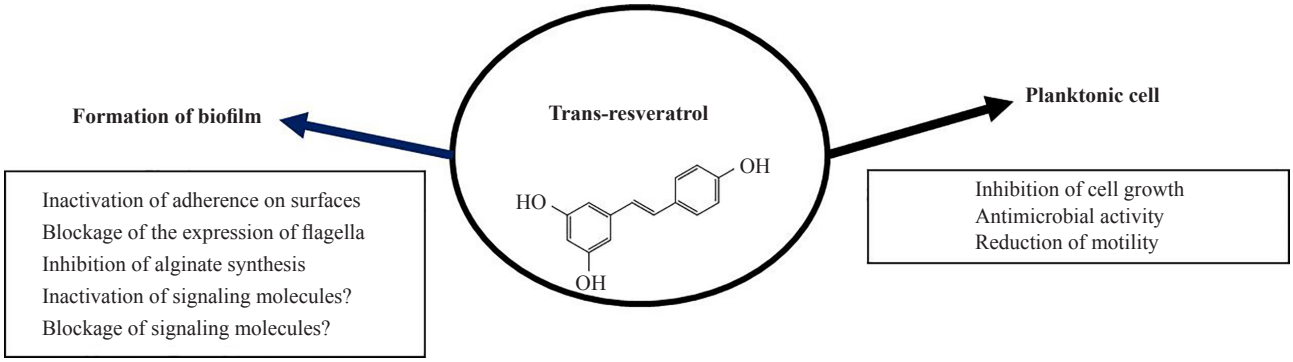

Figure 2. The action of trans-resveratrol on food bacteria. The anti-QS activity modulates gene inactivation through unknown mechanisms and disturbs cell adhesion and motility (blue arrow). Planktonic cells are inhibited by mechanisms different than anti-QS.

The main target of studies with trans-resveratrol has gone beyond the classic assays of the molecule's anti-inflammatory or antioxidant activity, with a new focus on the molecule's antimicrobial activity, which includes disturbing the stability of planktonic and sessile cells. Two documents expressly see themselves as the first to report this: the first document reported the fact that their research generated a robust list of traditional Chinese medicinal plants with motility inhibitory properties for *E. coli*, with emphasis on *Carex dimorpholepis*, the plant with the highest trans-resveratrol content [35]. The second document also stated that their study was the first report of the antibiofilm activity of trans-resveratrol against *Listeria* spp. in food [37].

Biofilms protect microorganisms from various environmental stresses, ensuring the development and persistence of populations resistant to different compounds, including antibiotics [46]. Thus, the search for substances with antibiofilm properties is legitimate, in terms of combating important pathogens [47].

The development of biofilm depends on various phenotypic and genotypic characteristics of pioneer cells, involving motility and QS systems [48]. It is known that flagellar motility regulates initial colonization, as well as acts in the development of biofilm architecture [49]. The suppression of genes associated with motility contributes to

preventing biofilm formation, however many mechanisms are known to regulate motility. These mechanisms seem to vary among bacteria and which only future investigations can clarify [39]. This opens a new frontier of research involving other bacterial species.

A second important mechanism for the establishment of a biofilm is more complex and depends on cell density and expression of intercellular signaling. Interference of naturally occurring active molecules in bacterial QS mechanisms offers an attractive strategy for combating infections and multi-resistant antibiotic pathogens [38]. This perspective has become the trend in more recent studies with trans-resveratrol [36, 39].

The assessment of inhibition of biofilm formation by trans-resveratrol has also been investigated in terms of the viability of planktonic cells [37]. The compound involved has already been tested alone [36], associated with another naturally occurring compound [39] or as a content of a commercial formulation [38]. Inhibition, in all cases, was also shown to be dependent on the concentration of trans-resveratrol. In addition, the association of the compound with coumarin was beneficial because trans-resveratrol potentiated the antibiofilm effect [39]. It is also important to emphasize that the antibiofilm activity neither was a consequence of a previous bactericidal action, nor interfered with the motility of the planktonic cells [35]. Based on these findings trans-resveratrol is suggested as one of the botanical polyphenols with a key-role in maintaining the structure of a microbial community in the relationships between plants and bacteria [50].

Many naturally-occurring molecules demonstrate their activity in very low concentrations; trans-resveratrol is one example of this [36]. Even at subinhibitory concentrations, the compound can down-regulate genes of QS systems and intercellular signaling mechanisms [36, 38-39]. This action is of interest because the genes of QS systems are also implicated in the expression of many bacterial virulence factors, such as biofilm formation [51] and pigment synthesis [52].

In addition, from the results obtained with bacterial species exposed to trans-resveratrol, studies have noted that the inhibition of different genes associated with QS systems is poorly understood [39]. This suggests that there may be several and still unknown pathways that control the formation and stability of biofilms in other bacterial species not studied so far. The potential of these pathways being able to interact with QS systems and genes related to the adhesion and expression of flagella is promising for the food and medical sciences.

5. Conclusion

Trans-resveratrol, alone or associated with other compounds, is an antibiofilm active molecule with great potential for exploitation by the food industry. Its mechanism of action seems to relate to the type of cell more than to the rate of growth of a certain bacterial population. Additionally, it has been shown that trans-resveratrol negatively regulates different genes in the same microorganism and this mechanism is perhaps common to prokaryotes. Additionally, even though interest in the topic has increased in recent years, a limited number of bacterial species have been evaluated up to the time of this writing. Future investigations will increase the spectrum of these microorganisms, revealing, consequently, the complexity of anti-QS and antibiofilm mechanisms of trans-resveratrol in various pathogens.

Conflict of interest

The authors declare that there are no conflicts of interest.

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