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Review

Antibacterial and antifungal properties of resveratrol

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ABSTRACT

Resveratrol is a naturally occurring polyphenolic antioxidant that has received massive attention for its potential health benefits, including anticarcinogenesis, anti-aging and antimicrobial properties. The compound is well tolerated by humans and in recent years has been widely used as a nutraceutical. Its common use makes it interesting to investigate with respect to antimicrobial properties both as a single agent and in combination with conventional antibiotics. Resveratrol displays antimicrobial activity against a surprisingly wide range of bacterial, viral and fungal species. At subinhibitory concentrations, resveratrol can alter bacterial expression of virulence traits leading to reduced toxin production, inhibition of biofilm formation, reduced motility and interference with quorum sensing. In combination with conventional antibiotics, resveratrol enhances the activity of aminoglycosides against *Staphylococcus aureus*, whereas it antagonises the lethal activity of fluoroquinolones against *S. aureus* and *Escherichia coli*. Whilst the antimicrobial properties of the compound have been extensively studied in vitro, little is known about its efficacy in vivo. Nonetheless, following topical application resveratrol has alleviated acne lesions caused by the bacterium *Propionibacterium acnes*. There are currently no in vivo studies addressing its effect in combination with antibiotics, but recent research suggests that there may be a potential for enhancing the antimicrobial efficacy of certain existing antibiotic classes in combination with resveratrol. Given the difficulties associated with introducing new antimicrobial agents to the market, nutraceuticals such as resveratrol may prove to be interesting candidates when searching for solutions for the growing problem of antimicrobial resistance.

1. Introduction: beneficial health effects of resveratrol

In recent years, resveratrol has attracted immense attention due to its potential health benefits [1]. One example is known as the 'French paradox', where consumption of red wine, having a high content of resveratrol, has been linked to low mortality caused by cardiovascular diseases in the French population despite their high intake of saturated fat [2,3].

Since then, resveratrol has been extensively studied for a variety of different health-beneficial effects, including, but not limited to, anti-inflammation, anti-carcinogenesis, anti-obesity, anti-diabetes type 2, anti-aging, cardiovascular protection and neuroprotection, which is reviewed elsewhere and therefore is not the focus of this review [4–7]. In addition to the extensive investigations on a multitude of diseases, resveratrol has also been examined for its antimicrobial properties against bacteria, fungi and viruses. This review concerns the antimicrobial properties of resveratrol, with special emphasis on its antibacterial properties.

2. Natural occurrence and structure of resveratrol

Resveratrol (3,5,4'-trihydroxystilbene) is a naturally occurring polyphenolic antioxidant belonging to the stilbene family. The stilbene family consists of a C6–C2–C6 carbon skeleton (1,2-diphenylethylene), where resveratrol is a hydroxylated derivative (Fig. 1) [8]. Resveratrol is present in numerous plants such as peanuts (*Arachis hypogea*), blueberries and cranberries (*Vaccinium* spp.), Japanese knotweed (*Polygonum cuspidatum*) a traditional Asian herbal medicine, and most importantly as a natural source for human consumption in grapevines (*Vitis vinifera*) [9]. Being a natural phytoalexin, resveratrol is synthesised de novo by plants in response to damage by fungal attack [10–12] and ultraviolet (UV) irradiation [10]. In a bunch of grapes, resveratrol synthesis is most predominant in the non-infected grapes that surround grapes infected with a fungus to limit the spread of the fungus to healthy grapes, as demonstrated with the fungus *Botrytis cinerea*, the causal

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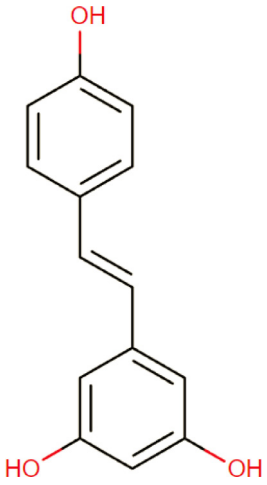

Fig. 1. Structure of resveratrol.

organism of grey mould [13]. Resveratrol exists both in a *cis* and *trans* isomer [4], with the *trans* isomer being the most abundant form in red wine [14] and the most studied due to its greater availability and higher stability [15]. Red wine generally has a greater concentration of resveratrol than white wine [16]. The average red wine contains 1.9 mg/L *trans*-resveratrol but it may reach concentrations up to 14.3 mg/L [14].

3. Antibacterial targets for resveratrol

Resveratrol is a promiscuous molecule that interacts with more than 20 proteins in eukaryotic organisms [17]. As an example, crystallisation complexes have determined a binding site for resveratrol to bovine ATP synthase in the F_1-domain in a pocket between a β-subunit and the γ-subunit [18]. Conservation of the ATP synthase residues suggests a similar binding pocket for resveratrol in *Escherichia coli* [19]. Resveratrol binds reversibly to ATP synthase, partially inhibiting both ATP hydrolysis and ATP synthesis functions of the ATP synthase in the facultative aerobe *E. coli* [19]. ATP hydrolysis is also inhibited in *Mycobacterium smegmatis* [20], and the metabolic activity of *Arcobacter* spp. is reduced by resveratrol [21]. Supplementation of resveratrol to *E. coli* cells prevents growth on the non-fermentable carbon source succinate and limits growth on fermentable glucose, suggesting that resveratrol inhibits oxidative phosphorylation [19]. As *E. coli* mutants lacking ATP synthase are able to grow in the presence of fermentable carbon sources such as glucose, pyruvate or lactate, ATP synthase cannot be the only target leading to growth inhibition in *E. coli* [22]. Second, resveratrol induces DNA fragmentation and concomitant upregulation of the SOS stress-response regulon in *E. coli*, however inhibition of growth is not directly related to DNA fragmentation and SOS stress-response upregulation [23]. Resveratrol-treated *E. coli* cells are elongated, hence the cell division apparatus is also affected by resveratrol and this occurs via suppression of *ftsZ* expression [23]. FtsZ is a key protein in septum formation during cell division and thus resveratrol is suggested to inhibit FtsZ-mediated septum formation and cell division [23]. Finally, resveratrol treatment has been correlated with membrane damage of cells owing to increased potassium leakage and increased propidium iodide uptake [24]. In contrast, resveratrol-induced membrane damage is not detected for *Staphylococcus aureus* [25].

The pleiotropic effects of resveratrol suggest that multiple targets may exist in bacterial species, however the mechanism for bacterial growth inhibition remains incompletely understood.

4. Antifungal and antibacterial activities of resveratrol

Resveratrol has been extensively studied for its ability to inhibit the growth of bacteria, fungi and viruses. Antiviral activities are reviewed elsewhere and have therefore been omitted from this review [26,27].

4.1. Antifungal activity

Generally, resveratrol displays better antifungal than antibacterial activity, as demonstrated by the minimum inhibitory concentrations (MICs) highlighted in Table 1. For the fungal dermatophytes *Trichophyton mentagrophytes, Trichophyton tonsurans, Trichophyton rubrum, Epidermophyton floccosum* and *Microsporum gypseum*, the inhibitory activity of resveratrol is approximately 25–50 μg/mL [28]. For the fungal species *Candida albicans, Saccharomyces cerevisiae* and *Trichosporon beigelii*, the inhibitory activity is 10–20 μg/mL [29], however other studies have not detected antifungal activity against *C. albicans* [30–32]. Resveratrol displays inhibitory activity against the plant pathogen *B. cinerea*, the causal organism of grey mould, where reduced germination of *B. cinerea* conidia and mycelial growth is observed at concentrations of 60–140 μg/mL [11].

4.2. Antibacterial activity

For a limited number of bacterial species, resveratrol inhibits growth at concentrations <100 μg/mL, including *Bacillus cereus* (MIC = 50 μg/mL) [33], *M. smegmatis* (MIC = 64 μg/mL) [34], *Helicobacter pylori* (MIC = 25–50 μg/mL) [35–37], *Vibrio cholerae* (MIC = 60 μg/mL) [38], *Neisseria gonorrhoeae* (MIC = 75 μg/mL) [30], *Campylobacter coli* (MIC = 50 μg/mL) [39] and *Arcobacter cryaerophilus* (MIC = 50 μg/mL) [21]. The inhibitory activity of resveratrol against *Mycobacterium tuberculosis* is 100 μg/mL [40].

For many bacterial species, resveratrol only displays growth inhibitory activity at concentrations >100 μg/mL. Notable Gram-positive pathogens with MICs of approximately 100–200 μg/mL include *S. aureus* [28,30,33,41], *Enterococcus faecalis* [28,33] and *Streptococcus pyogenes* [30]. Several studies have reported lower susceptibilities for several Gram-negative pathogens (MIC > 200 μg/mL) compared with Gram-positive pathogens, including *E. coli* [33,41], *Klebsiella pneumoniae* [33], *Salmonella enterica* serovar Typhimurium [33,41] and *Pseudomonas aeruginosa* [28,33,41]. This observation may result from poor penetration of resveratrol across the outer membrane of some Gram-negative bacteria or be the result of active extrusion of resveratrol by efflux pump systems.

Since resveratrol inhibits the ATP synthase in different bacterial species, it remains to be explored whether different requirements for bacterial energy generation partially account for alternating levels of susceptibility to resveratrol.

Some remarkable discrepancies exist between reported MICs, e.g. for *S. aureus* ATCC 25923 the MIC has been reported as 100 μg/mL in one study [33] but as >1000 μg/mL in another study [42]. One explanation for such variation may be differences in growth medium (Mueller–Hinton and Luria–Bertani, respectively), however in general conflicting results on resveratrol susceptibility between studies warrant additional investigation.

4.3. Inactivation of efflux pump systems can increase resveratrol susceptibility

One mechanism that decreases susceptibility to resveratrol is the presence of functional efflux pump systems. In several Gram-negative bacteria the efflux pump AcrAB–TolC actively extrudes numerous antimicrobials [43]. In *E. coli*, a *tolC* mutant displayed four-fold greater susceptibility to resveratrol compared with the

Table 1
Antimicrobial activity of resveratrol against bacteria and fungi.

Organism	Identifier	MIC (μg/mL)[a]	Reference
Gram-positive bacteria			
Bacillus cereus	ATCC 11778	50	[33]
	NCTR-466	1000	[42]
Bacillus megaterium	11561	250	[41]
Staphylococcus aureus	ATCC 25923	100	[33]
	3 clinical isolates	100–200	[33]
	ATCC 29213	171	[28]
	N315	>100	[40]
	8325-4	125	[41]
	RN450	150	[66]
	Clinical isolate	>200	[30]
	Clinical isolate	350	[55]
	ATCC 25923	>1000	[42]
	JE2	256	[25]
	Newman	512	[25]
	COL	128	[25]
Enterococcus faecalis	ATCC 29212	100	[33]
	ATCC 29212	342	[28]
	ATCC 29212	100	[40]
	ATCC 19433	1000	[42]
	ATCC 27274	1000	[42]
	ATCC 29212	128–256	[25]
Enterococcus faecium	D344R	128	[25]
Mycobacterium tuberculosis	H37Rv	100	[40]
Mycobacterium smegmatis	ATCC 700084 ($mc^2$155)	64	[34]
Streptococcus pneumoniae	HM145	100	[40]
Streptococcus pyogenes	Clinical isolate	>200	[30]
Propionibacterium acnes	ATCC 25746	180	[45]
	ATCC 29399	186	[45]
	ATCC 33179	196	[45]
	ATCC 6919	>1000	[42]
Listeria monocytogenes	LMG16779	200	[44]
	LMG16780	200	[44]
	LMG13305	200	[44]
	NCTC7973	128	[25]
Gram-negative bacteria			
Escherichia coli	ATCC 25922	>400	[33]
	Clinical isolate	>400	[33]
	K-12	500	[41]
	BW25113	400	[66]
	Clinical isolate	>200	[30]
	AG100	>1000	[42]
	ATCC 47004	250	[42]
	ATCC 35695	>512	[25]
Klebsiella pneumoniae	ATCC 13883	>400	[33]
	Clinical isolate	>400	[33]
	ATCC 13883	250	[42]
	ATCC 700721	>512	[25]
Salmonella enterica serovar Typhimurium	ATCC 13311	>400	[33]
	ST329	500	[41]
	ATCC 14028	>1000	[42]
Pseudomonas aeruginosa	ATCC 27853	>400	[33]
	Clinical isolate	>400	[33]
	ATCC 27853	342	[28]
	PAO1	1000	[41]
	Clinical isolate	>200	[30]
	PAO1	>1000	[42]
	PAO1	>1000	[71]
	PAO1	>512	[25]
Helicobacter pylori	ATCC 43504	25	[35]
	ATCC 700392	50	[36]
	ATCC 700824	50	[36]
	15 clinical isolates	25–100	[36]
	26 clinical isolates	37–1280 (MBC)	[37]
Arcobacter butzleri	LMG 10828	100	[21]
	AB36/11	100	[39]
	INSA776	100	[39]
Arcobacter cryaerophilus	LMG 10829	50	[21]
Haemophilus ducreyi	9 isolates	250–500 (MCC)	[46]
Neisseria gonorrhoeae	Clinical isolate	75	[30]
Neisseria meningitidis	ATCC 13090	125	[30]
Vibrio cholerae	MCVO9	60	[38]
Fusobacterium nucleatum	ATCC 10953	100	[52]
Campylobacter jejuni	225421	100	[39]
Campylobacter coli	873	50	[39]

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Table 1 (*continued*)

Organism	Identifier	MIC (μg/mL)[a]	Reference
Fungi			
Trichophyton mentagrophytes	ATCC 18748	25–50	[28]
Trichophyton tonsurans	ATCC 28942	25–50	[28]
Trichophyton rubrum	ATCC 18762	25–50	[28]
Epidermophyton floccosum	ATCC 52066	25–50	[28]
Microsporum gypseum	ATCC 14683	25–50	[28]
Candida albicans	TIMM 1768	20	[29]
	Clinical isolate	>200	[30]
	ATCC 90028	>128	[31]
	ATCC 76615	>128	[31]
	SC5314	>300	[32]
Saccharomyces cerevisiae	KCTC 7296	10–20	[29]
Botrytis cinerea	SP1	60–140	[11]
Trichosporon beigelii	KCTC 7077	10	[29]

MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration; MCC, minimum cidal concentration.
[a] Data are the MIC unless otherwise stated.

wild-type [41], whilst an *acrB* mutant was eight-fold more susceptible to resveratrol [42]. Similarly, a *P. aeruginosa* mutant deficient in the MexAB–OprM efflux pump displayed two-fold greater susceptibility relative to the wild-type [41]. Use of the efflux pump inhibitor phenylalanine-arginine β-naphthylamide (PAβN) reduces the resveratrol MIC in *Arcobacter butzleri* and *A. cryaerophilus* by 16- and 4-fold, respectively [21]. Increased efficacy of resveratrol in the presence of PAβN has also been observed for *E. coli* and *Proteus mirabilis* [42].

The observation that inactivation of efflux pump function increases the inhibitory activity of resveratrol suggests that the antibacterial efficacy of resveratrol is partially attributed to interaction with cytoplasmic or periplasmic targets in Gram-negative bacteria.

4.4. Bacteriostatic or bactericidal effect of resveratrol

Time–kill curves have been used to determine whether the effect of resveratrol is bactericidal or bacteriostatic against several bacterial species. At 2–3 × MIC, resveratrol is bacteriostatic against *Bacillus subtilis* [33], *S. aureus* [25,33], *E. faecalis* [33] and *Listeria monocytogenes* [44]. In contrast, resveratrol displays bactericidal activity against *Propionibacterium acnes* [45], *Haemophilus ducreyi* [46], *Campylobacter* spp. [39] and *Arcobacter* spp. [21,39]. Furthermore, resveratrol displays fungicidal activity against *C. albicans* [29].

5. Antivirulence properties

Virulence is the ability of a pathogen to cause disease in a host, and virulence factors are the mechanisms by which the pathogen causes damage to the host (e.g. by excretion of toxins) as well as mechanisms to establish an infection (e.g. factors for adhesion, invasion, colonisation and biofilm production) [47]. Expression of virulence genes is often tightly regulated for timely and co-ordinated adaptation to the environment, e.g. by quorum sensing (QS) or two-component systems (TCSs) [47]. The therapeutic applicability of antivirulence molecules concerns the rationale for disarming the pathogen of abilities to cause harm to the host and relying on the host immune system to eradicate the bacteria [48]. The antivirulence properties of resveratrol are highlighted in Table 2 and are outlined below.

5.1. Antibiofilm properties

Bacteria can live as planktonic cells or in aggregates attached to surfaces, referred to as biofilms. In biofilms, bacteria produce an extracellular material in which the cells are embedded [49]. The advantage of biofilm formation by bacteria is the establishment of a more stable environment in order to provide protection against environmental challenges, including phagocytosis and antimicrobial agents [50]. Biofilm formation is a clinically important issue as it is associated with chronic and recurrent infections [51].

Resveratrol has been studied on various bacterial pathogens for its ability to reduce biofilm formation. For the Gram-negative anaerobic bacterium *Fusobacterium nucleatum*, which is implicated in dental plaque, resveratrol inhibits biofilm formation at concentrations (4–64-fold below the MIC) that do not affect the growth of planktonic cells [52]. Furthermore, resveratrol displays antibiofilm properties against the Gram-negative pathogens *V. cholerae* at concentrations 2–6-fold below the MIC [38] and *E. coli* [53] as well as against the Gram-positive bacterium *P. acnes* [54]. In *E. coli*, the effect is mediated by reduced expression of genes (*csgA* and *csgB*) encoding for curli production, which are important for biofilm formation [53]. For the Gram-positive pathogen *S. aureus*, resveratrol inhibits biofilm formation at a concentration 3–4-fold below the MIC, and in combination with vancomycin resveratrol displays a strong effect in eradicating established biofilms [55]. In contrast, in two other studies resveratrol did not reduce biofilm formation in *S. aureus* [56,57], indicating that testing conditions and strain variation may influence the impact.

5.2. Antimotility properties

For several bacterial species, motility is important in the colonisation stage [58]. Motility can occur, for example, via swimming and swarming, which require production of functional flagella and twitching that require type IV pili [59].

At subinhibitory concentrations of resveratrol, *P. mirabilis* displays reduced swarming ability in a dose-dependent manner [60]. Suppression of swarming in the presence of resveratrol is dependent on the TCS protein RsbA, which is a negative regulator of swarming [60]. Resveratrol reduces swimming and swarming in *E. coli* through downregulation of several motility and flagella genes [53]. Reduced swarming ability has also been reported for *Vibrio vulnificus* [61].

5.3. Toxin interference

Bacterial pathogens secrete a multitude of structurally and functionally different toxins and they are often highly important in the development of disease [47]. Interestingly, a few reports

Table 2
Antivirulence properties of resveratrol.

Virulence factor	Effect and organism	Concentration (μg/mL)	Reference
Biofilm	Reduction in biofilm production by *Fusobacterium nucleatum*	1.5625–25	[52]
	Reduction in biofilm production by *Escherichia coli*	50–100	[53]
	Reduction in biofilm production by *Propionibacterium acnes*		[54]
	Reduction in biofilm production by *Vibrio cholerae*	10–30	[38]
	Reduction in biofilm production by *Staphylococcus aureus*	100–150	[55]
	No reduction in biofilm formation by *S. aureus*	20–100	[57]
	No reduction in biofilm formation by *S. aureus*	100	[56]
	Reduction in biofilm production by *Burkholderia* spp.	25 μM	[65]
	Reduction in biofilm production by *Arcobacter butzleri* and *Campylobacter* spp.	12.5–50	[39]
	Reduction in biofilm production by *Listeria monocytogenes*	50–100	[44]
Motility	Reduction in swarming by *E. coli*	20	[53]
	Reduction in swarming by *Proteus mirabilis*	15–60	[60]
	Reduction in swarming by *Vibrio vulnificus*	30 μM	[61]
Quorum sensing (QS)	Reduction in QS by *Yersinia enterocolitica*	10–20	[64]
	Reduction in QS by *Burkholderia* spp.	25 μM	[65]
Toxins	Reduced haemolysis by *P. mirabilis*	30–60	[60]
	Reduced haemolysis by *S. aureus*	20	[57]
	Reduced haemolysis by *S. aureus*	10–100	[56]
	Reduced toxin expression by *V. vulnificus*	10–30 μM	[61]
	Suppressed toxin activity by *V. cholerae*	300–400 μM	[62]
Adhesion	Reduced adhesion to host cells by *V. vulnificus*	10–30 μM	[61]
Colonisation	Decreased urease activity by *Helicobacter pylori*	6.25–400	[36]

indicate that resveratrol in some cases interferes with toxin expression. In *V. vulnificus*, RtxA1 is a multifunctional cytotoxic toxin important for lethality in mice, and resveratrol treatment reduces *rtxA1* expression [61]. In *V. cholerae*, resveratrol inhibits cholera toxin (CT) endocytosis into host cells and directly binds CT and hence may potentially inhibit CT-induced diarrhoea [62]. Resveratrol also greatly inhibits haemolysis of human blood cells by *S. aureus*, but the mechanism of inhibition remains unknown [56,57].

5.4. Interference with quorum sensing (QS)

QS systems enable bacteria to respond to cell density and, through cell–cell communication, to regulate gene expression. In bacterial pathogens, QS often controls virulence gene expression allowing a co-ordinated attack that may overwhelm host defences [63]. QS involves the production and release of signal molecules, called autoinducers, that increase as a function of cell density. A threshold limit of the autoinducer is detected by the bacteria, leading to alterations in gene expression [63]. In *Yersinia enterocolitica* and *Erwinia carotovora*, resveratrol inhibits synthesis of the autoinducers *N*-acyl-homoserine lactones at a concentration that does not affect growth parameters [64]. Resveratrol also interferes with QS systems in *E. coli* and *Chromobacterium violaceum* through an uncharacterised mechanism [65].

Taken together, resveratrol affects multiple virulence traits at concentrations up to 64-fold below growth-inhibitory concentrations. Whether resveratrol may have any applications as an antivirulence compound needs to be assessed in suitable animal models.

6. Resveratrol in combination with conventional antimicrobials

In addition to working as an antimicrobial compound by itself, resveratrol has also been investigated for potential effects in combination with conventional antibiotics. In *E. coli*, resveratrol (at 0.5 × MIC) antagonises the bactericidal activity of ciprofloxacin, kanamycin, oxolinic acid and moxifloxacin, whereas oxacillin lethality is unaffected [66]. For *S. aureus*, resveratrol antagonises the lethal activity of daptomycin, moxifloxacin and oxacillin [66] and levofloxacin [67]. The mechanism of antagonism is suggested to involve a reduction in reactive oxygen species (ROS) by resveratrol [66], which has antioxidant properties and thus protects macromolecules against damage by ROS [68]. Generation of ROS has been implicated as contributing to the lethality of bactericidal antibiotics [69] and, by scavenging ROS, resveratrol may suppress the bacterial killing with the mentioned antibiotics [66].

In contrast, resveratrol (at 0.5 × MIC) potentiates the efficacy of aminoglycosides approximately 16-fold against *S. aureus* and to a lesser extent against other Gram-positive pathogens such as *Staphylococcus epidermidis, Enterococcus faecium* and *E. faecalis* [25]. The mechanism of potentiation has been hypothesised to occur via inhibition of ATP synthase [25], as inactivation of genes encoding ATP synthase in *S. aureus* also sensitises this pathogen to aminoglycosides [70]. Furthermore, resveratrol enhances aminoglycoside activity against biofilms produced by *P. aeruginosa*, however the combinations of resveratrol and four different aminoglycosides did not display synergy on planktonic cells [71].

Taken together, resveratrol interferes with the inhibitory activity of different classes of antibiotics. Whether these effects are also evident in animal models remain to be explored.

7. In vivo antimicrobial activity of resveratrol

Several studies in humans have demonstrated that resveratrol displays high absorption yet low bioavailability of unchanged resveratrol following oral administration [72,73]. Resveratrol is readily metabolised following oral administration, with sulfate– and glucuronide–resveratrol conjugates reaching 3–8-fold higher plasma concentrations than free resveratrol [73]. Following oral administration of 5 g of *trans*-resveratrol as a single dose, the peak plasma level of resveratrol was 539 ng/mL at 1.5 h after administration and the mean plasma concentration was approximately 52 ng/mL at 24 h after administration [73]. Similarly, oral administration of 1 g of resveratrol resulted in an average 73 ng/mL of resveratrol in plasma after 1 h [74]. The low bioavailability of orally administered resveratrol limits this route of administration for potential systemic use of resveratrol for the treatment of bacterial infections, considering the inhibitory concentrations needed. Given that there is rapid turnover of resveratrol in humans and that higher plasma concentrations of resveratrol conjugates are observed compared with the non-modified compound, it could be interesting

to investigate the antimicrobial properties of such conjugates. Intravenous (i.v.) administration of resveratrol has also been investigated in humans, however the administered dose was low (0.2 mg) and resveratrol was still quickly metabolised [72], indicating that i.v. administration of resveratrol may also have limited, if any, antimicrobial applications for systemic infections. Finally, topical administration of resveratrol may still potentially enable the use of concentrations with a beneficial effect against different infectious diseases.

A few studies have investigated the therapeutic application of resveratrol against infectious diseases in animal models or human trials. The bacterium *P. acnes* is a contributing factor in the pathogenesis of acne vulgaris, one of the most common skin diseases [75]. In a human study, acne vulgaris patients treated with resveratrol (at a concentration of 1 mg/g of final preparation) experienced a significant reduction in facial acne lesions compared with treatment with the vehicle alone. Whether the therapeutic effect of resveratrol on acne vulgaris is a result of antimicrobial or anti-inflammatory properties was not elucidated in the study [76]. In contrast, in a study of experimental periodontitis in rats, continuous use of resveratrol did not promote any beneficial effect in reducing important oral periodontopathic bacteria [77]. Furthermore, topical application of resveratrol reduces lesion formation on the skin of mice by herpes simplex virus [78] and reduces replication of herpes simplex virus in the vagina of mice [79].

More studies are required to elucidate the potential of topical administration of resveratrol for the control of bacterial and fungal skin diseases, potentially in combination with conventional antimicrobials.

8. Conclusion

Resveratrol has gained significant scientific and public interest owing to acclaimed health-beneficial effects [1]. Substantial work conducted in vitro and in various animal models has documented potential benefits to human health following administration of resveratrol, however such benefits still remain to be documented in human clinical phase 3 trials [80]. Although clinical evidence for the acclaimed health benefits is largely lacking [1,80], resveratrol has still gained significant market traction as a dietary supplement [81]. In a recent survey, 18% of respondents in the USA had used resveratrol supplements, whereas only 3% had used them in Denmark [81].

In addition to the potential effects of resveratrol on various diseases, e.g. cancer, the compound also displays antimicrobial properties against bacterial, fungal and viral pathogens. As detailed in this review, resveratrol can inhibit bacterial and fungal growth, alter the expression of virulence factors, reduce biofilm formation, reduce motility and affect the susceptibility of bacteria to various classes of conventional antibiotics (Tables 1 and 2). However, the antimicrobial properties of resveratrol displayed in vitro are all at higher concentrations than have currently been achieved in human plasma following oral administration [72]. The low bioavailability of orally administered resveratrol limits this route of administration for systemic use of resveratrol for the treatment of bacterial and fungal infections [73]. However, it is currently not known whether metabolised resveratrol conjugates retain antimicrobial activity. If resveratrol conjugates retain antimicrobial activity, the plasma concentrations of effective resveratrol and derivatives may potentially be higher than currently expected.

An avenue for exploration of resveratrol as an antimicrobial agent is via topical administration, where higher concentrations of resveratrol are achievable. One human study demonstrated a positive effect on lesion reduction in acne vulgaris, however it is not known whether this effect is due to antibacterial properties against *P. acnes* [76]. The field of in vivo antimicrobial efficacy of resveratrol remains largely unexplored, and future studies are warranted to elucidate antimicrobial efficacy following topical administration to treat various skin infections. Furthermore, resveratrol interacts with the efficacy of certain classes of conventional antibiotics and this may be needed to be taken into consideration during antibiotic regimen design [25,66]. Resveratrol potentiates the efficacy of aminoglycosides against several Gram-positive pathogens, and combinations should be tested in *vivo* for enhanced treatment efficacy [25]. Therefore, it will be interesting to investigate in animal models whether resveratrol can have any applicability as a potentiator for aminoglycosides. In contrast, the implication of resveratrol consumption as a dietary supplement could also potentially reduce the efficacy of certain antibiotic classes such as fluoroquinolones [66,67], which requires further investigations in animal models. As with so many other antimicrobial compounds, problems with resistance may arise and, as an example, enzymatic inactivation of resveratrol has been demonstrated [82]. Investigations in suitable animal models are greatly needed to assess the clinical potential of resveratrol as monotherapy or in combination with conventional antibiotics.

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Not required.

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