Chapter

Evaluation of Trans-Resveratrol as a Treatment for Periodontitis

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Abstract

Periodontitis is a globally prevalent inflammation-mediated disease that can result in varying degrees of destruction to the tissues supporting the teeth. The microbial pathogenic dysbiosis, oxidative stress, and deregulated inflammation, found in patients with periodontitis, make it a multifaceted condition that is difficult to fully resolve. Further to this, periodontitis has been associated with other systemic inflammatory conditions. Trans-resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a plant-derived molecule present in many foods, which have been shown to exhibit antimicrobial, antioxidant, anti-inflammatory, and regenerative properties. However, trans-resveratrol has been reported to have physicochemical shortcomings, which make its clinical translation a challenge. This review outlines a critical analysis of identified samples from the scientific literature that was conducted to assess the potential of RES as a viable therapeutic for periodontitis. The potential for the improvement of the limiting pharmacological profile of trans-resveratrol via nanoformulation is also explored.

Keywords: periodontitis, trans-resveratrol, nanotechnology, pharmacognosy, pharmacology

1. Introduction

Periodontal disease (PD) is a chronic condition accompanied by a progressive pathogenic biofilm that continuously triggers inflammation, potentially resulting in the loss of both soft and bony periodontal tissues. Ultimately, in severe cases, edentulism may result (**Figure 1**) [1].

Although aspects such as age, genetics, or sex can affect the chance of developing PD, there are also modifiable risk factors that have been identified. That is, smoking, nutrition (e.g., low vitamin D and calcium), and poorly managed diseases (e.g., diabetes, rheumatoid arthritis, and obesity) as well as stress, have also been found to play a significant role in susceptibility [2–4].

According to several epidemiological reports, the prevalence of PD is increasing over time. In fact, current publications indicate that approximately 10% of the global population presents with severe periodontitis, while almost half of the remaining 90% of all adults present with a less severe form of the disease. By and large, the most conservative estimate places the prevalence of PD at approximately 50% of the adult population worldwide [1, 5–7].

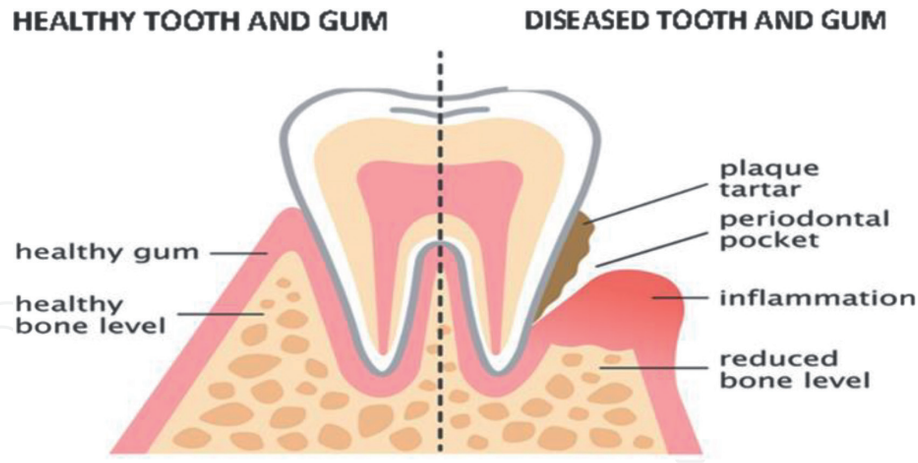

Figure 1.
An illustration of a healthy tooth and periodontal tissue (left side) compared to periodontal disease (right side).

Since people suffering from PD may experience chronic pain and tissue destruction, which can lead to anxiety and depression, the overall loss of quality of life has become an additional area of epidemiological observation. In fact, the deleterious impact of PD on wellness has recently been quantified using the index for Oral Health-Related Quality of Life (OHRQoL) and it was reported that the quality of life significantly decreases proportionally to the severity of PD [8, 9].

Additionally, PD has been found to have a widespread detrimental economic impact. For example, a recent study using accumulated data from the USA and 32 European countries, reported the approximate expenditure due to PD to be $154.06B in the USA, and 158.64B Euros in Europe [10].

Overall, a body of epidemiological evidence has emerged, reporting the increasing prevalence, economic burden, and diminished quality-of-life for a large enough portion of the global population, that PD has gained attention as growing concern of global proportion.

Although compiled review reports pertaining to the epidemiology of PD have been used as a benchmark, the distinction between gingivitis, mild to moderate PD, and more severe disease forms, has been inconsistent, creating a lack of comparability between and within the various epidemiological demographics [11].

Despite these steps towards unified categorisation, the ability to compare studies may still be diminished by the variation in classification of PD between clinicians and investigators [11–13].

2. Other inflammation-mediated conditions associated with PD

The conflicting reports, regarding the extent and severity of PD in the epidemiological literature, do not change the legitimate growing concern around the prevalence of the disease, especially when one considers the many inflammation-mediated systemic diseases with which it has been associated. For example, several reports indicate that PD can potentially increase the chance of developing heart disease [14–20], neurodegenerative disease [21–23], and autoimmune disease [24, 25] (**Figure 2**).

Further to this, chronic PD has been linked to a range of malignancies [26–30] and respiratory diseases [31–34] (**Figure 2**). Accordingly, the necessity for more ways to effectively prevent, manage, and treat PD, remains paramount.

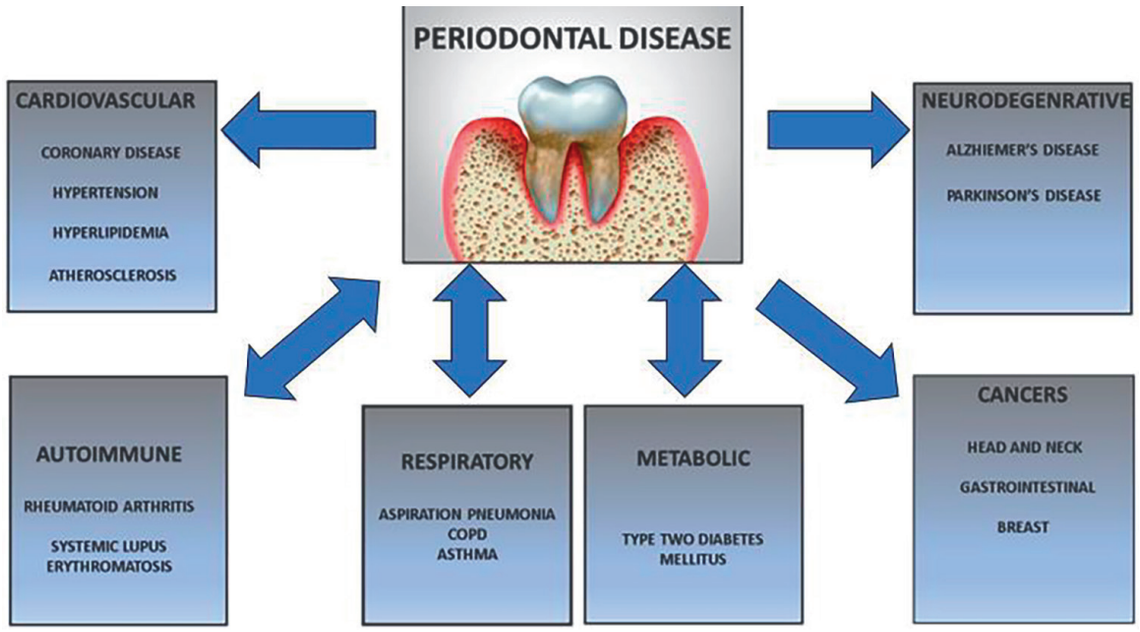

Figure 2.
An overview of some of the diseases that have been associated with PD.

3. Healthy periodontium and the pathogenesis of periodontitis

The periodontium consists of the tooth's surrounding anatomical structures, which include, from superficial to deep, the gingiva, gingival ligament, root cementum, and alveolar bone (**Figure 3**).

In a healthy periodontium, the supportive anatomical structures adhere to the tooth by way of connective and epithelial tissue types [35]. The epithelia exist as different subtypes around the erupted tooth and have been described as the first line of defence, protecting the underlying tissues of the periodontium from microbial infiltration from the oral cavity (**Figure 4**) [35]. The pathogenesis of PD first involves

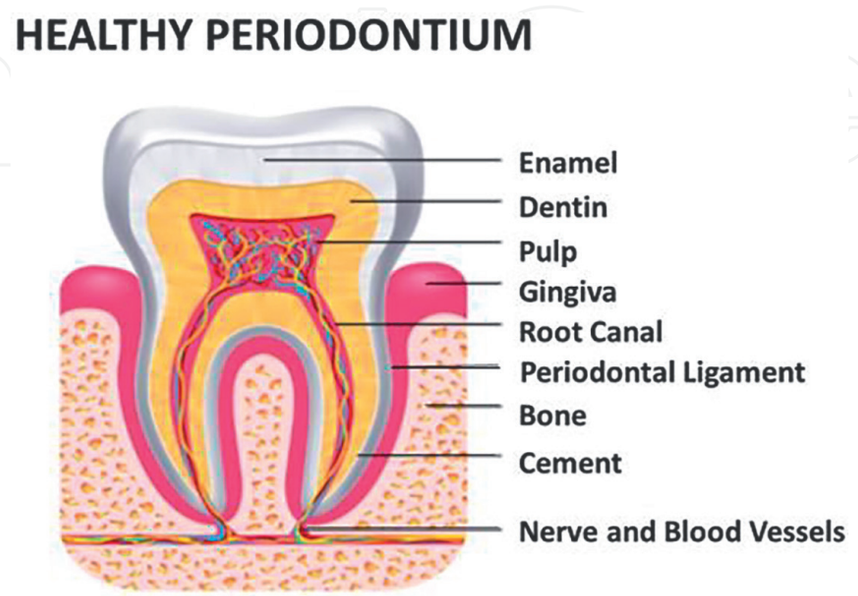

Figure 3.
An illustration of a healthy tooth and its surrounding structures (i.e., periodontium).

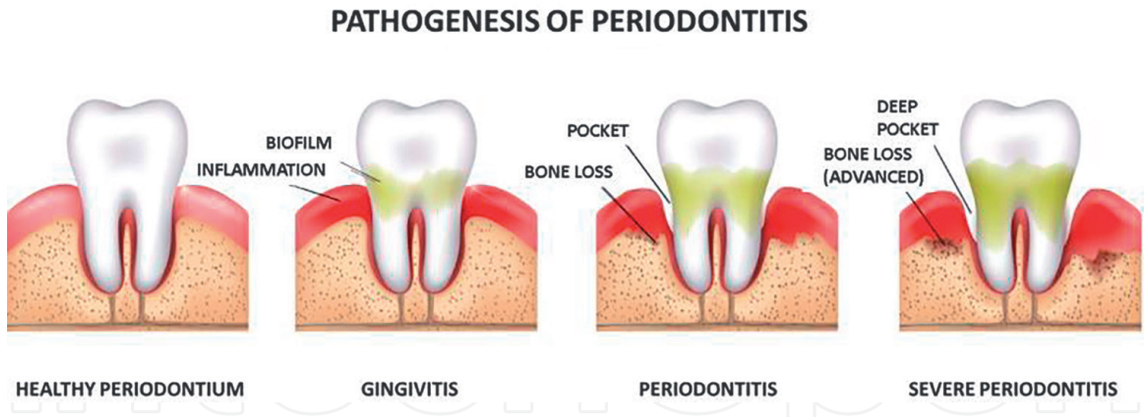

Figure 4.
An overview of the pathogenesis of PD starting with gingivitis progressing to severe PD.

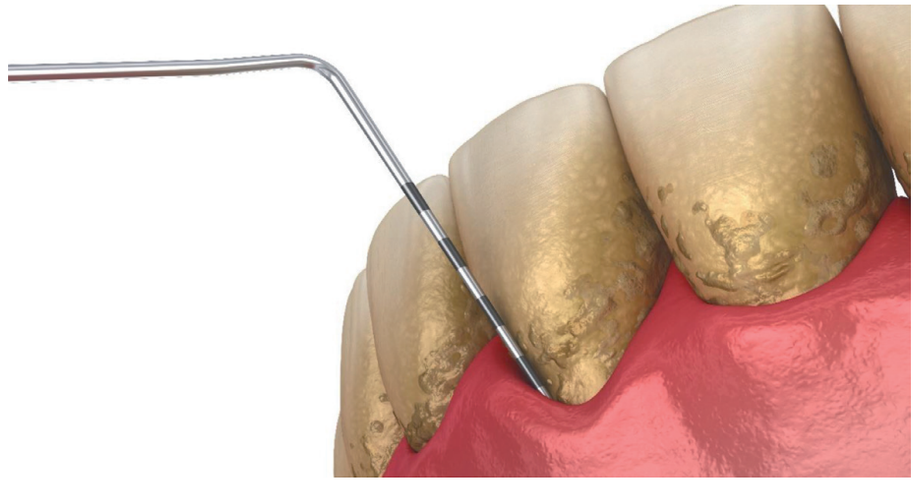

Figure 5.
Measuring of the depth of periodontal pockets with a probe is part of the diagnostic criteria predicting the severity of periodontal disease.

a shift in the oral milieu which optimizes the formation of a dysbiotic microbial biofilm, resulting gingival inflammation, which then progresses to the subgingival region (**Figure 4**) [36].

Clinically, people suffering from PD present with bleeding gingiva upon probing and varying degrees of detachment (i.e., clinical attachment loss [CAL]) of the gingiva from the tooth as measured with a periodontal probe (ada.org) (**Figure 5**).

4. Porphyromonas gingivalis and its central role in the pathogenesis of PD

Understanding further details of the disease process of PD from the perspective of the oral microbiome can assist in the creation of novel preventative and treatment applications.

Overall, bacteria, fungi, viruses, and protozoa are among the estimated 1000 microbial species that make up the oral microbiome. However, more than 700 microbes are bacterial, giving investigators a rationale for focusing on the bacterial taxa of the oral cavity, when examining health status [36–38].

Keystone pathogen, *P. gingivalis* (*Pg*), is a Gram-negative, anaerobic, non-motile, a-saccharolytic bacteria, which is a part of the normal flora of the subgingival region of the oral cavity, becomes an opportunistic pathogen when the microenvironmental factors permit it to thrive [39].

Also of note, is lipopolysaccharide (LPS), a feature found in the cell walls of Gram-negative bacteria, which triggers an inflammatory response as a pathogen-associated molecular pattern (PAMP). inflammation [40].

Detection by the host complement system is avoided due to the capsule, which is seen in most strains of *Pg* [41]. Also, the bacterial virulence factors, FimA and Mfa, which are proteins that make up the bacterial appendages, fimbriae, and pili, allow *Pg* to adhere to the periodontal cells whilst encouraging agglutination between bacteria, thus promoting the formation of a pathogenic biofilm [39, 42–44] (**Figure 6**).

Following adherence to the gingival epithelia, *Pg* can enter into its host cell with ease, due to the secretion of the serine phosphatase, SerB, which enters the host cell and triggers the de-polymerisation of cytoskeletal actin microfilaments [45] (**Figure 6**).

For increased success in gaining an intracellular foothold, *Pg* also employs a sophisticated secretory system (e.g., Type IX Secretory System [T9SS]), which spans the periplasmic space and allows for the passage of its secretory products from the cytoplasm into the extracellular environment [46, 47].

Further to this, gingipains are involved in the manipulation of the host immune system, making them key players in tissue destruction through chronic inflammation. For example, gingipains have been found to degrade many cytokines as well as the CD4 and CD8 integral membrane proteins of T lymphocytes, creating interference within the host's adaptive immune system [46, 48–50].

Moreover, an autoimmune attack on host tissue is assisted by the effector protein, peptidylarginine deaminase (PAD), which post-translationally modifies host proteins through citrullination, setting them up as immune targets [46, 51, 52] (**Figure 6**).

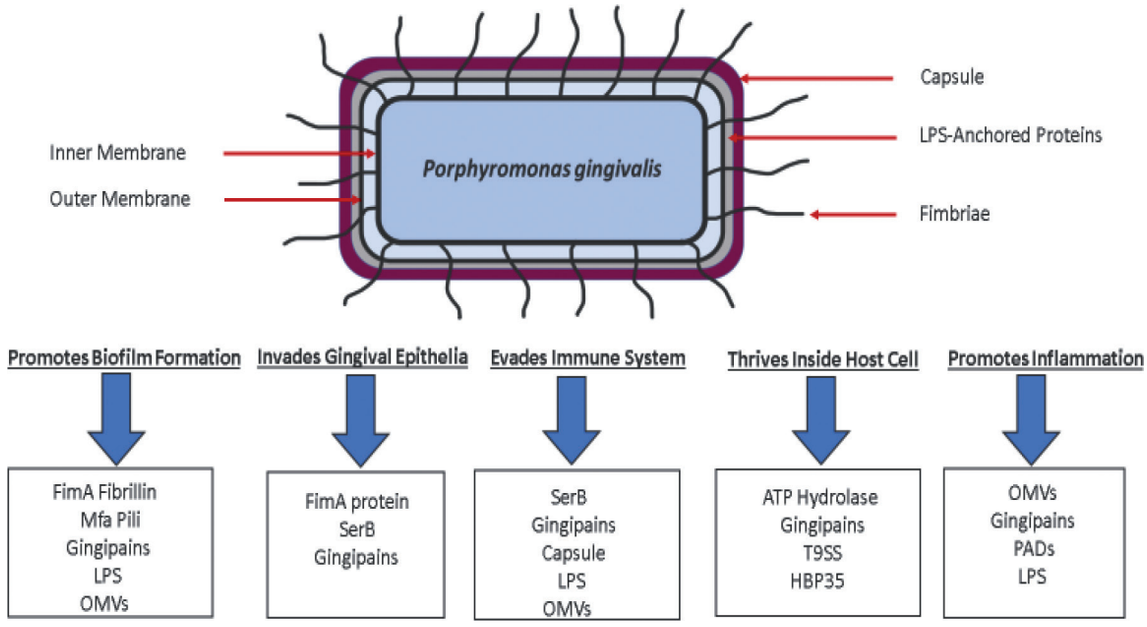

Figure 6.
A schematic of the major virulence factors of Porphyromonas gingivalis and a general overview of their involvement in pathogenicity.

Other significant virulence factors of *Pg* include outer membrane vesicles (OMVs), which are released from most Gram-negative bacteria and can infiltrate places that the bacteria cannot. However, those derived from *Pg*, are armed with an outer membrane layer, consisting of a capsule, LPS, and gingipains, enclosing an internal compartment loaded with effector proteins and other macromolecules such as nucleic acids. Indeed, OMVs are pro-inflammatory agents of cytotoxic destruction aiding in biofilm formation, as well as the manipulation and evasion of the host immune response [46, 53] (**Figure 6**).

5. *Pg* links to PD-related diseases

Common and frequent activities like mastication and oral care, have been found to release oral pathogens and their components into the lymphatic and cardiovascular systems of PD patients. Therefore, periodontal *Pg* infections likely act as pathogenic reservoirs, possibly promoting certain systemic diseases [52, 54].

5.1 Neurodegenerative disease

A 2021 study by Franciotii et al. hypothesised that there is a "bidirectional oral-brain" highway through which neurodegenerative processes are stimulated by pro-inflammatory oral processes and *vice versa* [55].

Most importantly, initiatives towards the innovation of preventative measures for PD have been recommended, especially since the global population is ageing [55].

5.2 Head and neck cancer

The reports regarding *Pg* infection as a risk factor for oral squamous cell and oesophageal carcinoma, align with the emerging perspective in the clinical arena linking chronic systemic inflammation to serious disease states [23, 56–59].

5.3 Cardiovascular disease

Regarding PD as it relates to cardiovascular disease, decades of literature reflect a close association [15, 19, 60]. DNA (i.e., 16S rDNA) from *Pg* has been identified in atheroma isolated from patients with coronary heart disease through PCR analysis [61]. Interestingly, *Pg* may also encourage atherosclerosis by switching HDL properties from antiatherogenic to proatherogenic via the manipulation of monocytes [62].

Further to this, *Pg* has been shown to invade and multiply within coronary endothelia *in vitro*, whilst damaging the smooth muscle cells and possibly distorting the vasodilatory mechanism of the central arterial system [63, 64].

Overall, the literature encourages appreciation of the clinical significance of the assault on the coronary endothelia demonstrated by *Pg*, especially since the vasculature acts as a vital line of defence for the cardiovascular system [63, 65].

5.4 Respiratory disease

Mortality risks from aspiration pneumonia are high in geriatric populations [66]. Of note, *in vitro* studies have identified *Pg* as a potent pro-inflammatory agent in

isolated respiratory epithelia cells [67]. Additional *in vitro* studies identified *Pg*-derived OMVs as significant bacterial virulence factors which connect PD to respiratory disease [68].

5.5 Liver disease

It is worth noting that a significant correlation ($P < 0.05$) between non-alcoholic steatohepatitis (NASH) and oral *Pg*, has been reported. Furthermore, following treatment for PD, an improvement of liver function, displayed by the normalisation of AST and ALT, has been demonstrated [54, 69].

5.6 Diabetes mellitus

The relationship between PD and diabetes mellitus (DM) has also been studied with respect to *Pg.* For example, gingipains carried by OMVs derived from oral *Pg*, decreased the insulin sensitivity of hepatocytes whilst hepatocytes invaded by *Pg* were also found to display a decrease in glycogen synthesis *in vitro* (human) and *in vivo* (mouse model) [70].

5.7 Rheumatoid arthritis

DNA sequences from *Pg* have been isolated from the synovial fluid and bloodstream of patients with rheumatoid arthritis (RA). Further to this, the consistently reported relationship between an oral *Pg* infection and RA has encouraged medical clinicians to place more emphasis on the oral health of their patients [71].

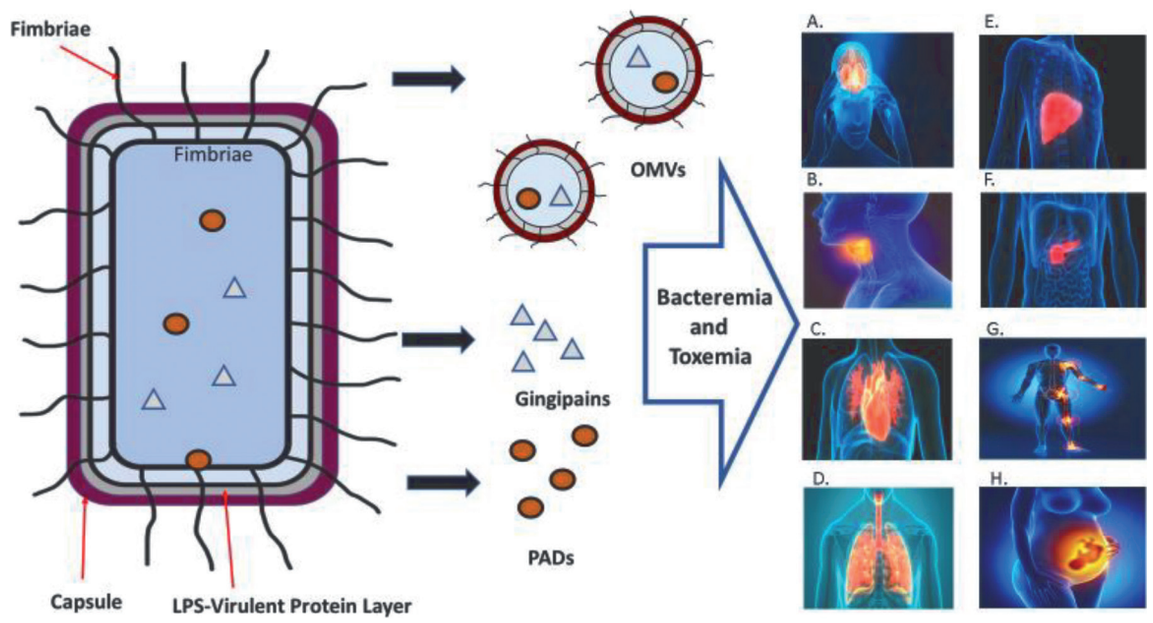

Figure 7.
The virulence factors of Pg and the systemic illnesses with which they have been associated. (A) Alzheimer's disease, Parkinson's disease, depression, (B) head and neck cancers, (C) atherosclerosis, myocardial infarction, aortic aneurism (D) aspiration pneumonia, (E) non-alcoholic fatty liver disease (NASH) (F) diabetes mellitus (G) rheumatoid arthritis (H) adverse pregnancy outcomes.

5.8 Adverse pregnancy outcomes

Pg DNA has also been detected in the amniotic fluid, umbilical cord, and placenta of women who encountered pregnancy complications such as preeclampsia and preterm birth [72]. Additionally, results from animal studies suggest that the mechanism involves the direct invasion and damage of the uterine and placental tissue [65].

The adage that correlation does not mean causation, should be considered, and although *Pg* cannot be the sole etiological agent of all the systemic diseases with which it is associated, there is accumulating evidence demonstrating its value as a modifiable risk factor for the prevention, management, and treatment of PD and other systemic diseases (**Figure 7**) [65].

6. Treatment of PD

Typically, treatment for periodontitis includes physical removal of the biofilm and calculus from under the gingiva by way of scaling and root planning (SRP) followed by comprehensive care (CC) (www.NHS.uk; www.ADA.org) (**Figure 8**). Whereas, in cases where more severe destruction has occurred, flap surgery is performed, which is often accompanied by expensive reconstructive treatments and/or procedures. In all cases of PD, patients are advised to adhere to lifelong CC to mitigate any further destruction [73–76].

Adjunct therapies are often combined to optimise results following SRP [76]. For example, one type of host modulation therapy (HMT) consisting of a sub-antimicrobial dose of doxycycline (SDD), is an internationally approved adjunct treatment for PD. SDD acts through the inhibition of the pathogenic collagenase activity in the host, thus decreasing inflammation and tissue destruction [77].

Interestingly, some naturally occurring phytonutrients also may work through the management of the host inflammatory response. For example, chemically modified curcumin has been shown to be safe and effective for the treatment of PD and other inflammation-mediated diseases in animal models [77–79]. Another bioactive phytonutrient of interest is trans-resveratrol, which in combination with curcumin, has been gaining attention as a supplement for the prevention and treatment of PD and other inflammation-mediated conditions [80].

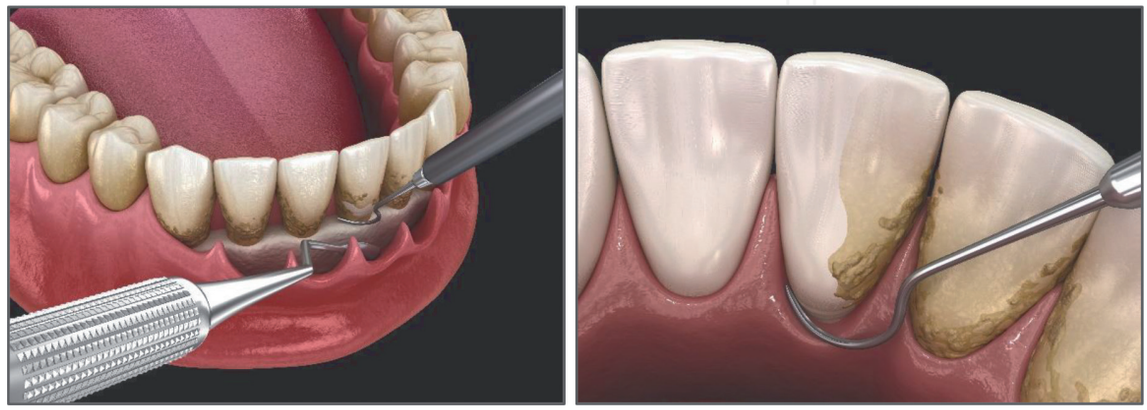

Figure 8.
Scaling and root planning with an open (left) and closed (right) curettage for the treatment of periodontitis.

7. Resveratrol: a bioactive polyphenol with attractive medicinal properties

Trans-resveratrol (trans-3,5,4′-trihydroxystilbene) (RES) is a polyphenol that can be sourced from various edible plants, which has demonstrated antioxidant, anti-inflammatory, antimicrobial, anticancer, and restorative properties [81–84]. Therefore, RES is positioned in alignment with the treatment principles for PD and the diseases with which it has been associated (**Figure 9**).

Even though RES is found in a breadth of plant-based foods (e.g., red wine, berries, peanuts, and dark chocolate), the naturally occurring concentrations of RES are not substantial enough (e.g., 0.1–0.7 mg/L in red wine) to reasonably attain the therapeutic values reported in the scientific literature (e.g., an oral dose of approximately 10 mg/kg body) [86–88].

Consequently, the purified and optimised extracts of RES are often used in research and some products have been made commercially available as wellness supplements (https://megaresveratrol.net; https://biotivia.com/pages/transmax-tr-1).

However, RES is a hydrophobic molecule and therefore, like other promising phytotherapeutics such as curcumin, has poor water solubility (<0.05 mg/mL). RES has also been found to rapidly metabolise *in vivo* and revert to its less stable isomer when exposed to light, demonstrating its instability and photosensitivity, respectively [85].

Additionally, the low oral bioavailability of RES has been considered a significant obstacle to its clinical translation, resulting in the development of drug carrier models. In fact, there is ample evidence indicating that nano-formulation may be a successful strategy to improve the pharmacological indices of RES under physiological conditions [89–91].

Interestingly, the design of functional foods also includes the application of nanotechnology, via the incorporation of liposomal nanocarriers or other nano-encapsulated systems. In this way, the therapeutic potential of customised, effective, and stable fortified foods with specific pharmacokinetic parameters, such as steady time-release, can be investigated [92].

Indeed, both oral and buccal delivery systems, such as those possible via functional food design, have plausible applications regarding PD therapeutics, especially since the primary target area for treatment is in the oral cavity. In fact, many nano-formulations also aim to enhance the delivery and efficacy of targeted therapeutics by engineering combinations of selected bioactive molecules that offer specific properties that promise to optimise the probability of the desired treatment outcome [93].

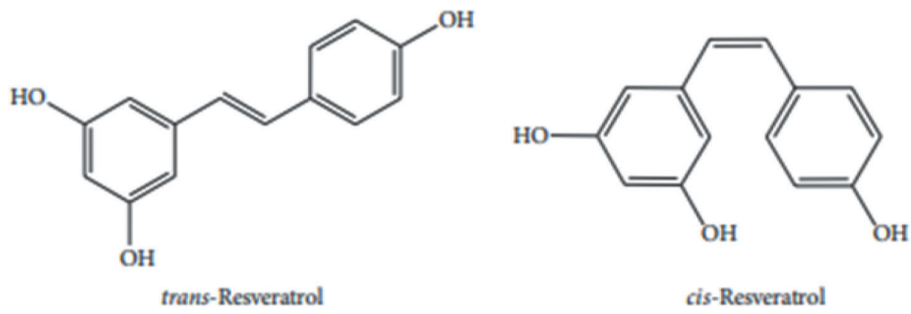

Figure 9.
The molecular structures of trans-resveratrol (trans-3,5,4′-trihydroxystilbene) (RES) (see left), which is the more stable, and therefore bioactive form compared to its isomer, cis-resveratrol (see right) (Gambini et al. [85]).

8. The attenuation of inflammatory processes by RES *in vitro*

The modulation of deregulated inflammation, which has been consistently reported for RES in the *in vitro* reports within the literature, is a central treatment principle for a viable therapeutic for PD. Additionally, *in vitro* studies allow for a breadth of experiment parameter manipulation not afforded by *in vivo* studies. So, although such studies cannot probe disease development and treatment, they can support the elucidation of mechanisms of action, thus identifying potential molecular targets for therapeutic applications.

For example, studies that used LPS-stimulated human gingival fibroblasts (HGFs), found through ELISA, and MTT assays, that RES significantly decreased IL-6 and IL-8, but did not increase cell viability. Interestingly, once RES was combined with the polyphenol silymarin (SIL), the viability increased in combination with the decrease in IL-6, IL-8 as well as TNF-α, suggesting that RES- ± SIL have a more widespread modulatory effect on LPS-induced inflammation [94, 95].

Additionally, in 2014, Fordham et al. examined the effect of RES (plus antioxidants, phloretin, silymarin, hesperetin) on LPS-stimulated peripheral blood mononuclear cells (PBMCs) obtained from healthy human donors. ELISA showed that RES decreased the secretion of IL-1β, IL-6, and IFN-ɣ in the LPS-induced PBMCs. Further to this, TNF-α was attenuated at the level of mRNA, as determined by RT-PCR. The researchers concluded that hesperetin and RES significantly inhibited ($p < 0.05$) the inflammatory response in LPS-stimulated PBMCs [96].

9. The influence of RES on regenerative processes in periodontal cells

RES has also shown promise regarding the restoration of periodontal tissue, which is a crucial part of the complete treatment of PD. For example, in a complex human *in vitro* and *in situ* study, Wang and colleagues reported that RES preserved cell aggregation and osteo-differentiation of normal human periodontal ligamental stem cells (HPLSCs) treated with TNF-α. In this study, histological analysis confirmed that RES treatment (even pre-implantation) improved regeneration in tissue originating from both healthy and pro-inflammatory microenvironments [97].

In accordance, Yuan and colleagues also found through histochemical analysis, RT-PCR, Western blot, and ELISA, that RES attenuated TNF-α – induced osteogenic suppression in HPLSCs *in vitro* [98].

10. RES as an attenuator of risk factors and conditions associated with PD

It has been well-established that PD is associated, to varying degrees, with a collection of modifiable risk factors as well as a myriad of systemic inflammation-mediated diseases [24, 99]. Hence, studies examining the effect of RES on PD in combination with purported comorbidity, and/or risk factor, could contribute to the argument regarding the breadth of its benefits.

Studies employing the integration of RA, DM, cigarette smoking, or osteoporosis (OP) into the induced-PD model have demonstrated that RES may assist in the mitigation of the periodontal damage contributed by associated risk factors and concomitant conditions. For example, with cigarette smoking added to the animal

model, it was found that RES decreased both alveolar bone loss and oxidative stress [100, 101]. Additionally, using a ligature-induced PD model, RES was found to reduce alveolar bone loss and attenuate hyperglycemia in diabetic mice [102, 103].

Another study, which employed an induced-PD and RA animal model, determined immunoenzymatically, that both Ibuprofen and RES reduced the tissue levels of anti-cyclic citrullinated peptide antibody (ACCPA) by 99 and 72%, respectively ($p < 0.05$), and RES alone, was reported to reduce serum rheumatoid factor (RF) ($p < 0.05$) [101].

Interestingly, the results of a study that used an induced-PD model which concurrently induced osteoporosis (OP) by ovariectomising the rats, suggested that RES may reduce alveolar bone loss in oestrogen-deficient rats via the attenuation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, making NADPH oxidase a potential drug target for RES [104].

Also of note, an extensive *in vitro* study showed the potential for RES to address *Pg*-related disease, with a particular focus on the prevention of Alzheimer's disease. Using a human *in vitro* model for neuroinflammation, Bahar and Singarao demonstrated that RES successfully modulated the ROS and deregulated inflammation. A total of 96 genes were analysed in *Pg* LPS-induced human neuroblastoma cells via qPCR followed by pathway analysis. In this way, RES was found to diminish NF-κB, neuroinflammatory acute phase pathways [105].

11. Animal studies: the amelioration of ligature-induced PD by RES

Although microbial dysbiosis is a necessary early occurrence in the pathogenesis of PD, the resulting chronic inflammation is the causal factor regarding its progression and continuous tissue destruction [106, 107]. Therefore, an effective therapeutic approach for the mitigation of PD would be to address the pathogenetically deregulated inflammatory pathways, mediators, and markers, encouraging the system to return to balance without deleterious side effects.

In a commonly used animal model, PD is induced by fitting a ligature around the neck of pre-selected molar teeth. Typically, PD that is induced in this way predictably presents with significant alveolar bone loss, accompanied by the increased expression of pro-inflammatory genes such as those for IL-1β, IL-6, and TNF-α. Notably, increased mRNA expression of genes coding for osteoclastogenic proteins and receptor activator of nuclear factor-k B ligand (RANKL) has also been reported when applying this model [108].

Morphometric analysis [27, 100, 101, 103, 109–111] and/or Micro-CT [104, 112–114] has been employed to demonstrate that RES reduced the alveolar bone loss from experimentally induced PD. The micro-CT analyses also reported improved bone density, suggesting that at the very least, RES has therapeutic potential as an adjunct to traditional SRP. This of course is caveated by emphasising the dependence of this data on the relevance of the PD animal model, and the need for validation with human studies.

12. Low bioavailability and stability: an obstacle to the clinical translation of RES

The poor water solubility of RES is well established. However, RES is highly stable in aqueous solutions of acidic pH. Moreover, researchers must consider that RES

degrades rapidly in buffers of 7.4 pH or higher [115]. For example, RES incorporated into buffered cell medium was found to degrade to 50% of its original concentration within 24 h of incubation at 37°C [115]. Hence, many of the *in vitro* studies, which assume that the pre-determined RES concentration is consistent for the study duration, are likely to produce misleading results regarding therapeutic dose.

Research has emerged employing novel RES formulations to overcome the pharmacological limitations and optimise therapeutic potential, ultimately improving its clinical translation [116–119].

13. Overcoming therapeutic limitations of RES by the application of nanotechnology

RES has been reported as having notably poor water solubility as well as high sensitivity to heat and pH [115]. Also, since RES is unstable under physiological pH and temperature, *in vivo* assays are challenging to design and *in vitro* assays are likely to have low translatability [92, 120, 121].

Additionally, oral administration of RES has demonstrated unfavourable pharmacokinetics due to its extensive first pass, resulting in the accumulation of potentially recycled conjugates, RES-glucuronides, and RES-sulphates; although these metabolites have also been found to possess biological activity, it may not match that of the parental compound [85].

Previous reports highlighting the physicochemical limitations of RES indicate that meticulous consideration of aqueous solubility, pH, temperature, and light, during the experimental design phase is crucial for the optimisation of clinical translation [122].

Consequently, the search for effective strategies for the improvement of the limited oral bioavailability and stability, is a complex, yet necessary, undertaking for the successful development of RES as a therapeutic.

Regarding RES, improvement of one or more physicochemical and/or pharmacological parameters has been reported when in a nano form, indicating the potential of nanotechnological formulation as a viable strategy for improving its physicochemical stability and pharmacological profile.

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are commonly employed to improve the therapeutic potential of hydrophobic drugs such as RES. Furthermore, findings that assessed the pharmacological potential of RES-loaded SLNs and NLCs, indicated their higher stability and sustained release compared to RES in its bulk form [123–128].

Further to this, studies seeking out to fortify and/or functionalise foods with RES, reported that nanoencapsulation substantially increased thermostability and photostability whilst retaining or optimising the desired biological activity. For example, an *in vitro* investigation examining the nano-encapsulation of RES in starch, conducted at pH 7.4 at 37° C, was reported to demonstrate an almost ten-fold increase in drug retention following a food extrusion process, as well as higher anti-diabetic, anti-obesity, and antioxidant effects, compared to bulk RES [129].

Similarly, the sustained release of RES from ZEIN-encapsulated nanoparticles (NPs) under physiological conditions (pH 7.4, 37°C) was reported [130] and casein-encapsulated RES NPs, designed by Penlava et al., were found to be stable through a continuous pH range mimicking those of the gastrointestinal compartments (i.e., pH 1.2 for 2 h and pH 6.8 for 2–24 h). Interestingly, the latter study

also demonstrated *in vivo* (using rats), a ten-fold increase in oral availability of casein-nano-encapsulated RES compared to the bulk form as determined by blood plasma assays over a 24 h period following a single oral dose of 15 mg/kg of RES (in ddH_2O and PEG) or casein-encapsulated RES NPs [131].

These studies and others bring to light the prospect of the customisation of functional foods, to serve as both local and systemic delivery system for the effective prevention, management, and treatment of PD.

14. Restoration of tissue damage from PD: potential of current Nano RES formulations

Nano-RES formulations intended specifically for the treatment of PD, are only beginning to emerge. For example, Berta et al., reported a nano-formulated RES-cyclodextrin mouthwash that was found to reduce plaque and bleeding gums in children [132]. Nonetheless, there are several nano RES formulations, intended to treat other conditions, which could, in theory, be studied as potential formulations for PD, with little divergence from the original formula.

For example, in a 2021 study, Li and colleagues produced nano-hydroxyapatite-RES-chitosan (CS) microspheres for bone generation, which could potentially be used to restore bone loss due to PD [133].

Also, electrospun 3-D nano-scaffolds loaded with RES, consisting of a biodegradable polymer (PLA)-biopolymer-gelatin (GEL) nano-scaffold was found to repair cartilage defects in the rat model [134].

Notably, monodispersed, spherical chitosan-zinc oxide-RES (CS-ZnO-RES) nanoparticles (NP) (38 nm) engineered by Du et al., were reported to attenuate gestational DM (GDM) [135].

Moreover, the successful application of nano-RES as a potential treatment for AD has been reported by Sun et al., who designed a RES-loaded mesoporous selenium-Fc-β-cyclodextrin-Borneol nanoparticle that crossed a blood-brain barrier model [136].

15. RES has evolved to be a viable agent for the treatment of PD

RES has been shown to execute biological action that alleviates deregulated inflammation, and restores both soft and bony tissues, *in vitro*, and *in vivo*, via modulation on the genetic, protein, and cellular level, thus strengthening the case for RES as a therapeutic for PD. Further to this, improvement of the pharmacokinetic and physicochemical limitations of RES has been demonstrated via nanoformulation. There is now much work to be done in identifying and optimising the ideal nanoformulation and administration route to achieve optimal benefit from the activities RES has demonstrated.

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