Potential Natural Antibacterial Agent for *P. gingivalis* Periodontitis Infection: A Comprehensive Review of Source, Structure and Mechanism actions

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ABSTRACT

Background: *the pathogenic bacteria P. gingivalis grows in the oral cavity. This bacterium could attack immune system which lead to inflammation of most tissues. P. gingivalis can cause a variety of serious and dangerous condition such as periodontitis, Alzheimer, rheumatoid arthritis, diabetes, and pneumonia. Antibiotics have been used for years as a treatment against this bacterium, like metronidazole, amoxicillin, and clindamycin.*
Method: *P. gingivalis is reported to be resistant to these antibiotics, thus exploration to discover alternatives has been demanded.*
Result: *natural product compounds are known to have antibacterial activity and cause fewer side effects. Turmeric, eucalyptus, and several other plants have been reported to have antibacterial activity against P. gingivalis with a MIC of 1g/mL from an ethyl acetate leaf extract of eucalyptus.*
Conclusion: *Decent antibacterial activity could be used as a reference to discover new drugs as alternatives against P. gingivalis.*

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INTRODUCTION

Dental disease can become a chronic disease if not treated properly. Chronic diseases of the teeth and dentition are associated with gingivitis or periodontitis which can cause inflammation and damage the bone supporting the teeth. The inflammation can lead to complications and form periodontal pockets between the gums and teeth.[1] Periodontal disease is also linked to other diseases such as cardiovascular disease and diabetes.[2] This dental infection is caused by various types of bacteria such as *Porphyromonas Gingivalis, Aggregatibacter actinomycetecomitans*, and *Fusobacterium nucleatum*.[3] However, *P. gingivalis* is a known as pathogenic bacteria that plays a major role in periodontal disease.[4, 5] *P. gingivalis* infects teeth through the action of the cycstein proteases lysin and arginine-gingipain during the initiation and progression of inflammation.[6] Studies on the effect of *P. gingivalis* on periodontal disease have been conducted on mice as test animals that showed gingival inflammation and alveolar bone loss.[7]

P. gingivalis is a Gram-negative bacterium which incorporated with “red complex”. This group of bacteria consist of *P. gingivalis, Treponema denticola*, and *Tannerella forsythia.*[8, 9] *P. gingivalis* has been reported as the cause of periodontitis or tooth loss disease.[10, 11] In 2020 Mei et al and Olsen et al reported that *P. gingivalis* has a role in several dangerous diseases such as Alzheimer’s, rheumatoid arthritis, diabetes, and pneumonia.[12, 13] The high complexity of the diseases caused by *P. gingivalis* showed the urgency of discovering alternative treatments.

P. gingivalis has shown significant resistance against commercial antibiotics such as 21.56% against metronidazole, 25.49% against amoxicillin, and 23.52% against clindamycin.[14] Thus, antibacterial exploration has become important. Curcumin, a phenolic compound found in turmeric, has been shown to exhibit antibacterial activity against *P. gingivalis,* which causes periodontitis inflammation.[15] Aside from curcumin, phloroglucinol-sesquiterpene-coupled, which is isolated from eucalyptus, showed antibacterial activity to inhibit the growth of *P. gingivalis*.[16] The emphasis of this review is on natural compounds having antibacterial activity against *P. gingivalis*. In this review, we also discuss the isolation technique and bioassay of natural compounds against *P. gingivalis.* Furthermore, we also discussed the treatment mechanism produced by *P. gingivalis*.

P. gingivalis BACTERIA

P. gingivalis is an anaerobe Gram-negative bacterium which is attached to liposaccharide-lipid A at its membrane. This lipid formed a thin layer which stimulated the inflammation on the cell.[17] Lipopolysaccharide in *P. gingivalis* is hard to dissociate, so that causes drug resistance.[18] The growth of this bacteria in the cell is supported by arginine amino acid and lysgingipains produced by its reproduction protein. Proliferation will be prolonged if Arg and Lys gingipains are inhibited. When *P. gingivalis* attacks human albumin serum, it becomes *P. gingivalis* proliferate media. As a result, *P. gingivalis* caused a disease complications since albumin is producing blood plasma protein.[19] *P. gingivalis* will inflame every area of the human body since it is transmitted by the blood. *P. gingivalis* has been linked to some diseases such as pneumonia, pancreatic cancer, gastrointestinal, periodontitis or tooth loss.

TREATMENT MECHANISM OF DISEASE CAUSED BY *P. gingivalis*

2.1 Periodontitis

Periodontitis, or tooth loss, is mostly caused by the bacterium *P. gingivalis.* This bacterial growth inside the oral cavity uses albumin in human blood as a media.[12, 19] More than 200 million adults all around the world have been attacked by these bacteria and have suffered great inflammation, which leads to periodontitis.[20] Periodontitis mechanisms start with *P. gingivalis,* which has been growing on the oral cavity surface exploiting complement growth media (red and white molecules). The rapid growth rate caused other oral bacteria to change their composition and quantity so that brown shafts appeared. Significant composition changes cause inflammation periodontitis, which is characterized by an exfoliated oral cavity. Chronic periodontitis will cause tooth loss.[9] Periodontitis which caused by *P. gingivalis* is called a virulence factor. Virulence factor is a damaged host which is caused by molecules or organism (bacteria, fungi, virus, and protozoa).[21] Antibiotics that have been used as a treatment for periodontitis are amoxicillin, metronidazole, azithromycin, and moxifloxacin. However, these antibiotics are reported to be resistant against *P. gingivalis.*[22] Therapeutic method has also been developed like Cortexyme Inc® corporation does as a periodontitis preventive measure.[23]

2.2 Alzheimer

Alzheimer's disease is a neurodegenerative disease that causes memory and thinking ability loss. One of the causes of this disease is the expression of a toxic active proteolytic protease protein named gingipains from *P. gingivalis.* Gingipains caused amyloid-protein (APP) precursor or amyloid shriveled and neurofibrillary cleavage, resulting in normal nerve system degeneration.[24, 25] Nerve cell death which caused by gingipains could be induced by a small molecule such as COR286 and COR271. Commercial antibiotics such as moxifloxacin and doxycycline have been tested *in vitro*, yet they are still not effective enough to protect nerve cells from gingipains.[26]

2.3 Rheumatoid Arthritis

Rheumatoid arthritis (RA), or joint inflammation, is an inflammation chronic disease. The late treatment could lead to paralysis. This disease is carried by the presence of autoimmune induced bacteria *P. gingivalis.*[27] RA mechanism starts with the peptidyl arginine deiminase (PAD) enzyme produced by *P. gingivalis.* The PAD enzyme is an enzyme that produces citrullinated protein, which is known to be the cause of RA. Thus, this mechanism determines the role of *P. gingivalis* in inducing RA through PAD production.[28, 29]

Chronic RA treatments have been developed to lessen paralysis and disability. DMARD (Disease Modifying Antirheumatic Drug) therapeutic already known as an effective initial treatment for RA. The combination of DMARD with conventional drugs such as methotrexate, glucocorticoids is reported to be more effective than DMARD alone. However, commercial drugs could provoke another disease. Exploration of natural compounds is necessary to increase the effectiveness treatment of RA along with DMARD.[30, 31]

2.4 Diabetes

Diabetes has been a familiar deathly disease to us. Aside from genetic, the disease could be caused by bad dietary. High sugar blood level is a potential environment for bacteria to growth such as *P. gingivalis.*[32] *In vivo* study on rat male adult reported that adding *P. gingivalis* could rise the sugar blood level.[33] The main mechanism of how *P. gingivalis* could rise the sugar blood level still remain unknown. Deteriorate of periodontitis and diabetes due to *P. gingivalis* requires treatment to each disease since we cannot treat them at once before knowing the mechanism.[34]

2.5 Pneumonia

Pneumonia is a deathly inflammation disease. The inflammation of this disease is due to induction of anaerobe bacteria such as *P. gingivalis. P. gingivalis* has the ability to manipulate the immune system of host through gingipains.[10] Although anaerobe bacteria cannot survive in warm temperature such as the lungs, gingipains still able to induce interleukin (IL)-8 and IL-6. IL-6 and IL-8 are cytokine secretion of inflamed the lungs. By the induction of gingipains on IL-6 and IL-8, *P. gingivalis* takes on the role of pneumonia cause.[35]

The treatment can be achieved through preodontal therapy. The oral cavity, being the initial site for the growth of *P. gingivalis* is treated to suppress its proliferation. This therapy could reduce the number of *P. gingivalis* thus suppress the effect on pneumonia.[36]

NATURAL PRODUCTS AS ANTIBACTERIAL AGENT OF *P. gingivalis*

3.1 Phenolic

Phenolic compounds are generally known to have many hydroxyl groups. In the mechanism of inhibiting pathogenic bacteria, hydroxyl groups play an important role in damaging the bacterial cell membrane. Especially Gram-negative bacteria have structures that are coated with an outer membrane and cover the cell wall externally. The outer membrane can block antibiotics from entering the cell because it is composed of lipopolysaccharides. Hydroxyl groups on phenolic compounds can affect the integrity of the cell membrane by releasing protons.[37] In addition, there are porin channels in the bacterial cell membrane that can facilitate hydrophilic antibacterials to diffuse into the cell.[38] Phenolic compounds can also inhibit bacterial cells through this system.[39] The activity of phenolic compounds against *P. gingivalis* are described in Table 1. The structure of these compounds is shown in Figure 1.

Table 1. Activity of phenolic compounds from plant materials against *P. gingivalis*

Plants	Extract	MIC (µg/mL)	Reference
Turmeric (*Curcuma longa*)	Curcumin (**1**)	62.5	40
		12.5	41, 42
		125	39
		20 (suppress percentage 40%)	43, 44
Cinnamomum zeylanicum essential oil	Cinnamaldehyde (**2**)	2 µM	45
Monechma ciliatum seed	Coumarin (**3**)	50	46
Zingiber officinale Roscoe	10-gingerol (**4**)	6	47
	12-gingerol (**5**)	15	47
Amphipterygium adstringens bark	6-(16′*Z*-nonadecenyl)-salicylic acid (**6**)	12	48
	6-(8′*Z*-pentadecenyl) salicylic acid (**7**)	18	
	6-nonadecenyl salicylic acid (**8**)	70	
	6-pentadecyl salicylic acid (**9**)	126	
Olea europaea	Oleuropein (**10**)	625 µM/mL	49, 50
	Hydroxytyrosol (**11**)	156 µM/mL	
	Oleocanthal (**12**)	156 µM/mL	
	Oleacin (**13**)	312 µM/mL	
Citrus limon peel	8-geranyloxypsolaren (**14**)	0.3 µM	47
	5-geranyloxypsolaren (**15**)	0.15 µM	
	5-geranyloxy-7-methoxycoumarin (**16**)	0.45 µM	
Magnolia officinalis	Honokiol (**17**)	25 µM/mL	51
	Magnolol (**18**)	25 µM/mL	
Grapes skin	Resveratrol (**19**)	78.12-156.25 µM/mL	52
Acronychia baueri Schott	3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans*-propenoic acid (**20**)	31.3 as antibiofilm	53
M. paniculate	Murrangatin (**21**)	100	54
	Murrangatin acetate (**22**)	100	
	Micropubescin (**23**)	100	
Licorice root	Licochalcone A (**24**)	10	55

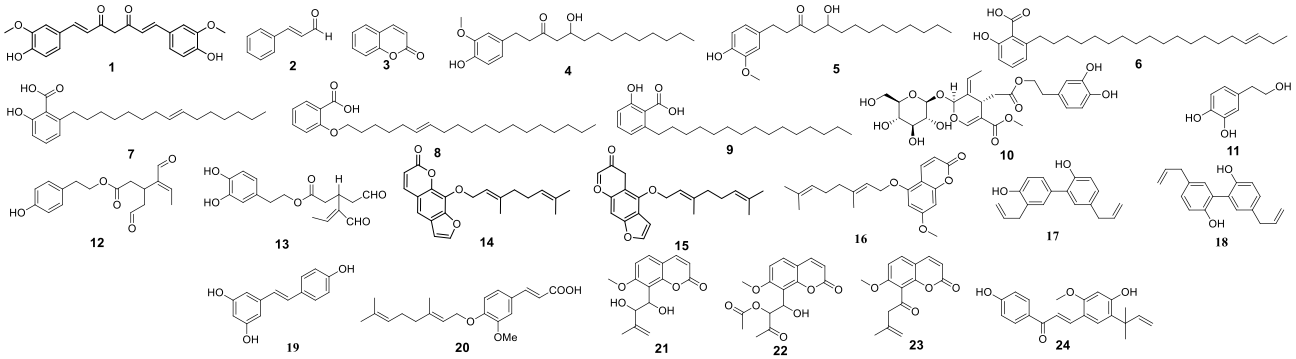

Figure 1. Phenolic Structure of curcumin (**1**), Cinnamaldehyde (**2**), Coumarin (**3**), 10-gingerol (**4**), 12-gingerol (**5**), 6-(16¢Z-nonadecenyl)-salicylic acid (**6**), 6-(8¢Z-pentadecenyl) salicylic acid (**7**), 6-nonadecenyl salicylic acid (**8**), 6-pentadecyl salicylic acid (**9**), oleuropein (**10**), hydroxytyrosol (**11**), oleocanthal (**12**), oleacin (**13**), 8-geranyloxypsolaren (**14**), 5-geranyloxypsolaren (**15**), 5-geranyloxy-7-methoxycoumarin (**16**), Honokiol (**17**), magnolol (**18**), resveratrol (**19**), 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans*-propenoic acid (**20)**, Murrangatin (**21**), murrangatin acetate (**22**), micropubescin (**23**), licochalcone A (**24**)

3.2 Terpenoid

In terpenoid compounds, the mechanisms studied for bacterial inhibition can be through two processes:,oxygen uptake and oxidative phosphorylation. In aerobic microbes, growth is affected by the concentration of available oxygen. As fo bacterial cell respiration in the cytoplasmic membrane, a biochemical process called oxidative phosphorylation occurs.[56] The presence of terpenoid compounds can have chemical interactions on the cytoplasmic membrane that cause the release of oxidative phosphorylation thus changing the cellular respiration of bacteria.[57] In another study it was reported that terpenoids can provide bacteriostatic effects through carbonylation, but cannot provide bactericidal effects. In addition, lipophilicity, water solubility, and the presence of hydroxyl groups in the terpenoid structure also affect the antibacterial action so that terpenoids have potential as antiseptics.[58] Some mechanisms proposed for diterpenes like hardwickiic was the compound may block cell membranes due to their lipophilicity structure. The lipophilicity aids insertion into the cell membrane, and the presence of a hydrophilic group that interacts with a phosphorylated group on the membrane may increase bacterial lysis.[59] The activity of terpenoid compounds against *P. gingivalis* are described in Table 2. The structure of these compounds is shown in Figure 2.

Table 2. Activity of terpenoid compounds from plant materials against *P. gingivalis*

Plants	Extract	MIC (µg/mL)	Ref.
Eucalyptus globulus	Macrocarpal A (**25**)	0.39	60
	Macrocarpal B (**26**)	0.78	
	Macrocarpal C (**27**)	0.2	
	Macrocarpal D (**28**)	0.39	
	Macrocarpal H (**29**)	0.78	
	Macrocarpal I (**30**)	6.25	
	Macrocarpal J (**31**)	6.25	
	Eucalyptone (**32**)	1.56	
Illicium lanceolatum	α-santal-1en-10-one (**33**)	5-20	61
P. linteus fruit	*trans*-γ-monocyclofarnesol (**34**)	5.9	62
	γ-ionylideneacetic acid (**35**)	34.1	
Copaifera spp	Polyalthic acid (**36**)	3.12-12.5	63
	Hardwickiic acid (**37**)	6.25	
	Kaurenoic acid (**38**)	1.59-12.5	
	ent-hardwickiic acid (**39**)	>10	
	13*E*-*ent*-labda-7,13-dien-15-oic-acid (**40**)	>10	

Mikania glomerata	Kaurenoic acid (**38**)	6.25-12.5	64
Vitis vinifera	Maslinic acid (**41**)	4.9	65
	24*Z*-isomasticadienolic acid (**42**)	2.4	
	Oleanolic acid (**43**)	9.9	
	Oleanonic aldehyde (**44**)	625	
Copaifera langsdorfii	Copalic acid (**45**)	3.1	66
Ceanothus americanus	Ceanothic acid (**46**)	62	67
	27-hydroxyceanothetric acid (**47**)	1250	
Myrmecodia pendans	Phloroglucinol-sesquiterpene (**48**)	11.5 mm (inhibition zone)	68
P. tobira	R1-barrigenol (**49**)	100 (MBC)	69
Iostephane heterophylla	Xanthorrhizol (**50**)	6.8	70
Viguiera arenaria	*ent*-pimara-8(14),15-dien-19-oic acid (**51**)	1.25	71
	ent-8(14),15-pimaradien-3β-ol (**52**)	10	
	Sodium salt of compound **51** (**53**)	1	
Laurus nobilis L	Deacetyl laurenobiolide (**54**)	500	72
	Laurenobiolide (**55**)	250	
Melia toosendan	12-ethoxynimbolinins C (**56**)	15.6	73
	1-cinnamoyltrichilinin (**57**)	31.3	

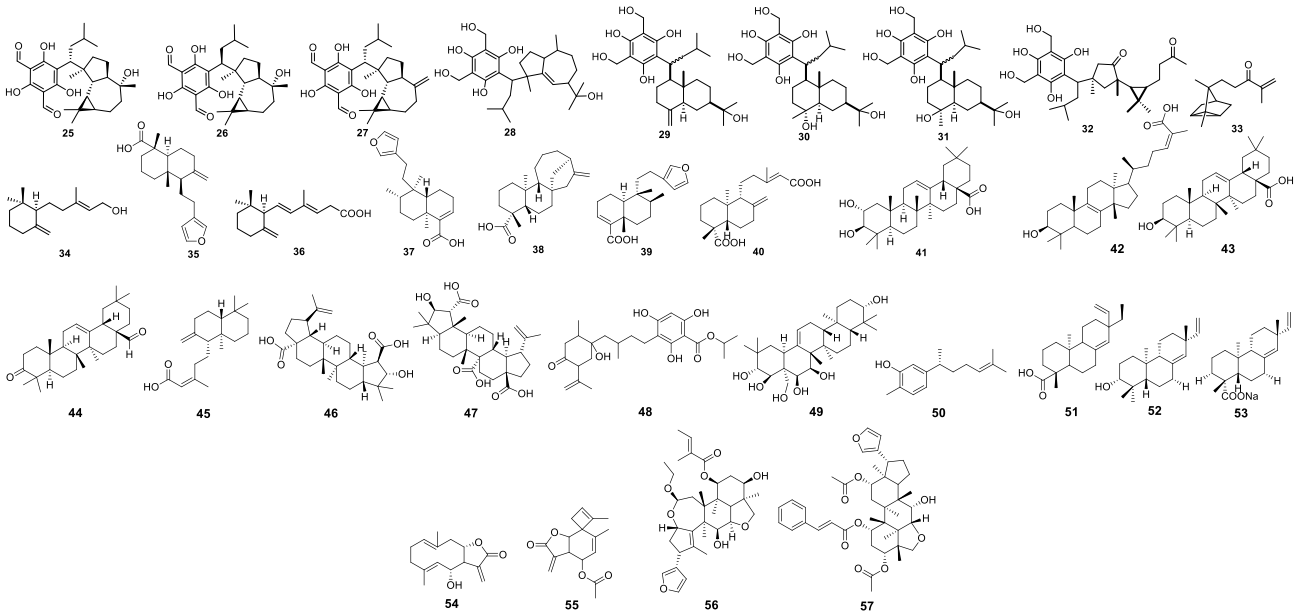

Figure 2. Terpenoid Structure of macrocarpals A (**25**)**,** macrocarpals B (**26**), macrocarpals C (**27**), macrocarpals D (**28**), macrocarpals H (**29**), macrocarpals I (**30**), macrocarpals J (**31**), eucalyptone (**32**), α-santal-1en-10-one (**33**), *trans*-γ-monocyclofarnesol (**34**), γ-ionylideneacetic acid (**35**), Polyalthic acid (**36**), hardwickiic acid (**37**), kaurenoic acid (**38**), *ent*-hardwickiic acid (**39**), 13*E*-*ent*-labda-7,13-dien-15-oic-acid (**40**), Maslinic acid (**41**), 24*Z*-isomasticadienolic acid (**42**), oleanolic acid (**43**), oleanonic aldehyde (**44**), copalic acid (**45**), ceanothic acid (**46**), ceanothetric acid (**47**), phloroglucinol-sesquiterpene (**48**), R1-barrigenol (**49**), Xanthorrhizol (**50**), *ent*-pimara-8(14),15-dien-19-oic acid (**51)**, *ent*-8(14),15-pimaradien-3β-ol (**52**), sodium salt of 54 (**53**), deacetyl laurenobiolide (**54**), laurenobiolide (**55**), 12-ethoxynimbolinins C (**56**), 1-cinnamoyltrichilinin (**57**).

3.3 Fatty Acid

Fatty acids can damage bacterial cells through several mechanisms: detergent activity that causes membrane disruption, plasma membrane interaction with fatty acids, transport of fatty acids into the cytosol through the cell membrane, and chemical interaction of proteins in the cell membrane with fatty acids. These mechanisms can cause cell lysis, formation of pores in cells, disruption of protein binding, and changes in cell membranes.[74, 75] The activity of fatty acids against *P. gingivalis* are described in Table 3. The structure of these compounds is shown in Figure 3.

Table 3. Activity of fatty acids from plant materials against *P. gingivalis*

Plants	Extract	MIC (µg/mL)	Ref.
Roccella fuciformis	(+)-roccellic acid (**58**)	46.9	76
Monechma ciliatum seeds	Oleic acid (**59**)	≤15	46
	1,2-dioleoylglycerol (**60**)	≤100	
	1,3-dioleoylglycerol (**61**)	100	
Foeniculum vulgare	Petroselinic acid (**62**)	5	77
P. linteus	Phellidene fatty acid E (**63**)	155	62
Enteromorpha linza	Stearidonic acid (**64**)	9.76	78
	ɣ-linolenic acid (**65**)	9.76	

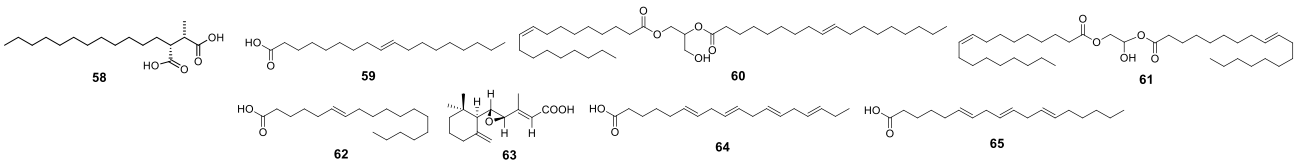

Figure 2. Fatty Acid roccellic acid (**58**), oleic acid (**59**), 1,2-dioleoylglycerol (**60**), 1,3-dioleoylglycerol (**61**), petroselinic acid (**62**), phellidene fatty acid E (**63**), stearidonic acid (**64**), ɣ-linolenic acid (**65**)

3.4 Flavonoid

Flavonoids contain prenyl groups, alkyl chains, alkylamino, and heterocyclic groups that affect different antibacterial mechanisms depending on each group in the structure. The main mechanism as an antibacterial is through interaction with the cell membrane. The lipophilicity or hydrophilicity of the flavonoid structure determines the interaction that occurs on the outside or inside of the cell bilayer.[79] The more polar flavonoid compounds will penetrate the bacterial cell wall, then break down cell proteins and damage the cytoplasmic membrane, it leads the bacterial cell death.[80] The activity of flavonoid compounds against *P. gingivalis* are described in Table 4. The structure of these compounds is shown in Figure 4.

Table 4. Activity of flavonoids from plant materials against *P. gingivalis*

Plants	Extract	MIC (µg/mL)	Ref.
Rhubarb root	Rhein (**66**)	2500	81
Grean tea	Epigallocatechin (**67**)	125-500	82
Pelargonium sidoides	Proanthocyanidins (**68**)	90%	83
Kaempferia pandurate root	Panduratin A (**69**)	4	84
Glycyrrhiza uralensis	Licorisoflavan A (**70**)	1.56	85
	Licorisoflavan C (**71**)	6.25	
	Licorisoflavan D (**72**)	6.25	
	Licorisoflavan E (**73**)	12.5	
	Licoricidin (**74**)	3.125	
Syzygium aromaticum	Biflorin (**75**)	625	86
	Kaempferol (**76**)	20	
	Rhamnocitrin (**77**)	625	
	Myricetin (**78**)	20	
Polygonum tinctorium	Kaempferol (**74**)	25-100	87
Vaccinium vitis-idaea L.	epicatechin-(4β→8)-epicatechin-(4β→8,2β→O→7)-catechin (**79**)	100	88
Perilla seed	Luteolin (**80**)	12.5-50	89
M. flabellifolia	3′,4′,5′,7-tetramethoxyflavone (**81**)	100	90
	Flavan-3-ol (**82**)	100	
Lonicera caerulea	Cyanidin-3-O-glukosida (**83**)	36.3% for biofilms	91

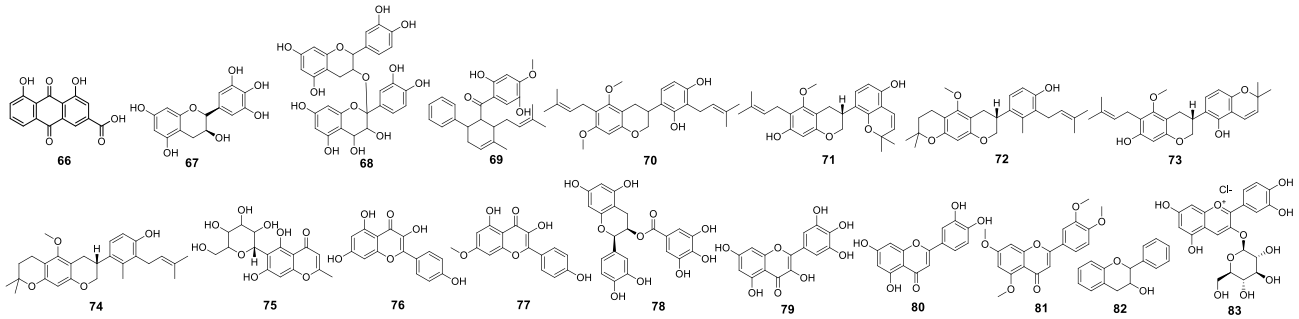

Figure 4. Flavonoid structure of rhein (**66**), epigallocatechin (**67**), Proanthocyanidins (**68**), panduratin A (**69**), licorisoflavan A (**70**), licorisoflavan C (**71**), licorisoflavan D (**72**), licorisoflavan E (**73**) and licoricidin (**74**), Biflorin (**75**), kaempferol (**76**), rhamnocitrin (**77**) and myricetin (**78**), epicatechin-(4β→8)-epicatechin-(4β→8,2β→O→7)-catechin (**79**), Luteolin (**80**), 3′,4′,5′,7-tetramethoxyflavone (**81**), flavan-3-ol (**82**), cyanidin-3-O-glukosida (**83**).

3.5 Other Compounds

In general, there are many other secondary metabolite compounds in plants. One of them is alkaloid compounds which also have potential as antibacterials. In bacterial cell walls, alkaloids can prevent the formation of cell layers, so that they do not form completely and cause death.[80] In addition, based on the biosynthetic pathway, alkaloids are formed from amino acids, so they can form chemical interactions with DNA in bacteria that cause cell division disorders. This can also lead to bacterial cell death.[92] The activity of alkaloids and the other compouds against *P. gingivalis* are described in Table 5. The structure of these compounds is shown in Figure 5.

Table 5. Activity of other compounds from plant materials against *P. gingivalis*

Plants	Extract	MIC (µg/mL)	Ref.
Var. druidarum	Hypoprotocetraric acid (**84**)	250	76
I. tinctoria	Tryptanthrin (**85**)	6.25-12.5	93
Vitis vinifera	5-hydroxymethyl-2-furfural (**86**)	16	65
Solenostemma argel leave	Argeloside I (**87**)	60	94
Garcinia kola seed	8*E*-4-geranyl-3,5-dihydroxybenzophenone (**88**)	62.5	95
	δ-garcinoic acid (**89**)	31.3	
M. toosendan	Trichilinin B (**90**)	31.5	73
Piper cubeba	(-)-Cubebin (**91**)	400	96
	(-)-O-methylcubebin (**92**)	200	
	(-)-O-benzylcubebin (**93**)	300	
	(-)-O-acetylcubebin (**94**)	>400	
M. toosendan fruit	1α-trigloyloxy-3α-acetoxyl-7α-hydroxyl-12β-ethoxynimbolinin (**95**)	31.25	97

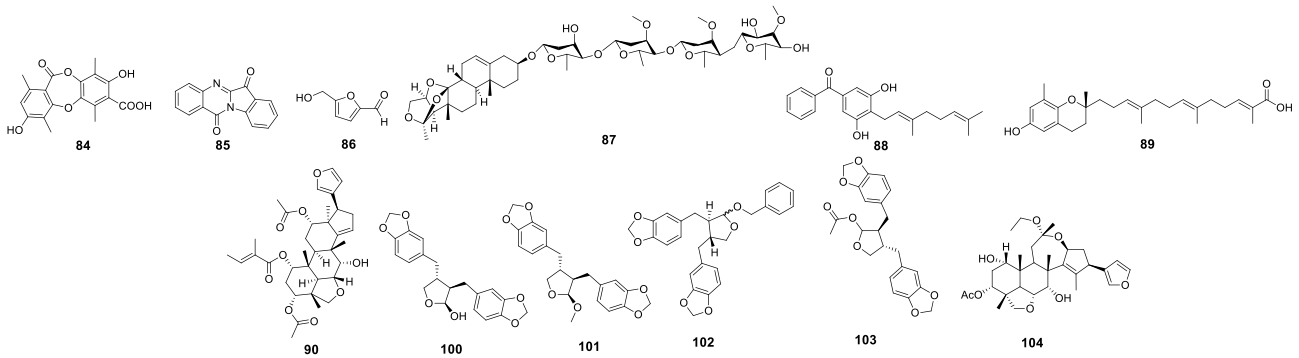

Figure 9. Other Compounds Structure hypoprotocetraric acid (**84**), Tryptanthrin (**85**), 5-hydroxymethyl-2-furfural (**86**), argeloside I (**87**), 8*E*-4-geranyl-3,5-dihydroxybenzophenone **(88**), δ-garcinoic acid (**89**), Trichilinin B (**90**), (-)-Cubebin (**100**),

(-)-O-methylcubebin (**101**), (-)-O-benzylcubebin (**102**) and (-)-O-acetylcubebin (**103**), 1α-trigloyloxy-3α-acetoxyl-7α-hydroxyl-12β-ethoxynimbolinin (**104**)

CONCLUSION

P. gingivalis is one of the pathogenic bacteria found in many dental diseases. It causes other diseases such as alzheimer's, rheumatoid arthritis, diabetes, and pneumonia. The use of natural materials is one of the efforts to find natural antibacterial agents for the treatment of *P. gingivalis* infection. Several groups of compounds such as phenolics, flavonoids, terpenoids, fatty acids, and other compounds have been reported to provide specific antibacterial mechanisms against *P. gingivalis*. Several compounds from different plants have also been reported to provide excellent activity to inhibit *P. gingivalis*.

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