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REVIEW: ANTIBACTERIAL ACTIVITY OF *POLYSCIAS FRUTICOSA* AND MOLECULAR MECHANISM OF ACTIVE COMPOUNDS

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ABSTRACT

Bacterial resistance continues to develop, research on natural medicine is needed for development of compounds that might be used as an effective alternative treatment for pathogenic bacteria with minimal toxic effects. Natural medicine has an important role in the discovery of new drugs. Search for active compounds from plants has been done, especially *Polyscias fruticosa* plant or known as *kedondong laut* which potentially to be developed as a drug. *P. fruticosa* has anti-inflammatory, antibacterial, and gastrointestinal treatment activities. Purpose of this study was to determine compounds in *P. fruticosa* that has antibacterial activity, and to determine mechanism of action of antibacterial compounds.

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This research was done using SLR (Systematic literature review) method. Data sources used scientific databases to obtain relevant sources related to the compounds and antibacterial activity of *P. fruticosa*, as well as the molecular mechanism of the active compounds.

Results of literature review of *P. fruticosa* plant (leaves, roots, stems) contain active compounds such as bisdesmosidic saponins, $_{22}$-dihydro-$_{24}$isopropylcholesterol and triterpenoid oleanolic acid, gallic acid, quercetin, polyscioside J, polyscioside K, ladyginoside, chikusetsusaponin Iva, heptadeca 1,8(E) diene 4,6 diyne 3,10-diol and falcarinol and. *P. fruticosa* plant has antibacterial activity and also has various mechanisms of action on bacterial cells, such as inhibiting cell wall synthesis, increasing membrane permeability, inhibiting ATP synthesis, inhibiting fatty acid synthesis, inhibiting biofilm formation, inhibiting amino acid (protein) synthesis, and working on cytoplasmic membranes.

1. INTRODUCTION

Infectious diseases in developed and developing countries are a problem of morbidity and mortality for many years. This disease is transmitted from human to human or from animal to human caused by microbes such as bacteria, viruses, parasites, and fungi. Antimicrobials used for infection therapy include antibacterial/antibiotic, antiviral, antiprotozoal, and antifungal. In general, antibiotics are widely used and has potential to cause resistance. Bacterial resistance against antibiotics is a primary problem in medication in this century. The increasing usage of antibiotics in animals and humans and the lack of research related to new antibiotics are contributing factors in bacterial resistance [1].

General mechanism of bacterial resistance is that the antibiotic does not reach the target (formation of an efflux pump), the antibiotic is inactivated by bacterial enzymes, and changes in molecular structure of target antibiotic (mutation) Bacterial resistance to

antibiotics continues to increase every year. Therefore, it requires attention of researcher related to research on natural ingredients or development of active compounds from natural ingredients that may be used as an effective alternative treatment for bacteria that cause infection with minimal toxic effects [2,3].

Natural ingredients, especially plants, are basic traditional medication and has on important role in discovery and development of new drugs, this is very relatable to bioactive compounds contained in it. Medicines from nature has been classified as genuine natural products, semi-synthetic products, and synthetic products [4].

Polyscias fruticosa is a family of Araliaceae which has potential to be developed as medicine. *P. fruticosa* has anti-inflammatory, antibacterial properties, and also can be used for gastrointestinal treatment. Previous research had proven that this plant extract has antioxidant, anticancer, antihistamine, antiasthmatic, and antidiabetic activities. *P. fruticosa* contain chemical compounds such as alkaloid, glucosamine, saponin, flavonoid, tannin. Pharmacological activity of this plant is made possibly by presence of saponin, phenolic and flavonoid compounds [5,6,7,8,9].

In this literature review will be discussed related to phytochemical content of *P. fruticosa* plant, antibacterial activity of *P. fruticosa* plant against pathogenic bacteria, and molecular mechanism of the active compound.

2. METHOD

This research used Systematic Literature Review (SLR) method. Data sources used scientific databases such as Science Direct, PubMed and Google Scholar to obtain relevant sources about specific problems related to phytochemical of *P. fruticosa* plant, antibacterial activity and molecular mechanism of antibacterial compounds.

3. RESULT AND DISCUSSION

3.1 Phytochemical Of *Polyscias fruticosa* Plant

Results of literature search related to *P. fruticosa* plant, these plant contain various phytochemical contents which can be seen in **Table 1** below.

Table 1. Literature review of phytochemical content of *P. fruticosa* plant

No.	Research Title	Research Subject	Method	Result
1	*α*lpha-Amylase and *α*lpha-Glucosidase Inhibitory Saponins from *P. fruticosa* Leaf [8]	Saponin compounds on *Polyscias fruticosa* leaves	Maceration using methanol solvent. Isolation using chromatography	Saponin compounds, bisdesmosidic. *3-O*-[*β*-D-glucopyranosyl(1→4)-*β*-D-glucuronopyranosyl] oleanolic acid 28-O-*β*-D-glucopyranosyl ester; polyscioside D; and 3-O-{*β*-D-glucopyranosyl-(1→2)-[*β*-D-glucopyranosyl(1→4)]-*β*-D-glucuronopyranosyl} oleanolic acid 28-*O*-*β*-D-glucopyranosyl(1→2)-*β*-D-galactopyranosyl ester
2	Onè unusuàl sterol from *P. fruticosa* [11]	Sterol compounds	Extraction, diethyl eter solvent. Isolation using chromatography	22-dihydro-24-isopropylcholesterol and oleanolic acid triterpenoid compounds
3	Impact of Roasting to Total Phenolic, Flavonoid and Antioxidant Activity in Root, Bark and Leaf of *P. fruticosa* [12]	Phenolic and flavonoid compounds in *Polyscias fruticosa* roots, barks, and leaves	Phenolic test: Folin-Ciocalteu method. Flavonoid test: aluminum calorimetric	Phenolic and flavonoid compounds in root, bark and leaves.
4	The èffects of different	Gallic acid and	Extraction. EtOH, MeOH,	Gallic acid and quercetin compounds.

	extràction conditions on the polyphenol, flavonoids components and antioxidant activity of *P. fruticosa* root [13]	quercetin compounds in *Polyscias fruticosa* roots	and aceton solvents. asam galat dan kuersetin: Metode spektrofotometry UV-Vis	
5	Polysciosides J, K two new oleanane-type triterpenoid saponins from the leaf of *P. fruticosa* [5]	oleanan type-triterpenoid saponin compounds in *Polyscias fruticosa* leaves	Extract was purified using chromatography. Structure elucidation using UV-Vis, IR, MS, NMR 2D and 1D.	Polyscioside J, polyscioside K, ladyginoside and chikusetsusaponin Iva compounds

P. fruticosa contain bioactive compounds such as alkaloids, saponins, flavonoids [10]. Phytochemical screening of *P. fruticosa* plant was dominated by compounds belonging to saponin, triterpenoid. Extract of *P. fruticosa* leaves was isolated and resulted bisdesmosidic saponin compounds (**Table 1**) (**Figure 1)** [8]. Sterol compounds, namely dihydro-24-isopropylcholesterol and triterpenoid oleanolic acid (**Figure 2**) has been isolated from *P. fruticosa* plant extract which was extracted using petroleum ether-diethyl ether solvent in a ratio of 1:1 at room temperature [11].

Another study also reported that active compounds contained in *P. fruticosa* plant are phenolic, flavonoid, saponin and triterpenoid compounds [12]. Extraction using a solvent of 50% methanol 70% and acetone 90%, obtained *P. fruticosa* root extract containing gallic acid and quercetin compounds (**Figure 3**), concentration of compounds obtained was 96.09 g gallic acid and 58.30 g quercetin [13]. *P. fruticosa* leaves contain a lot of active compounds such as quercitrin, polyscioside, glycosides, flavonoid glycosides and oleanolic acid glycosides [14,15]. Oleanic aglycone type of o in leanolic acid compound

saponin group isolated from *P. fruticosa* plant has been previously reported [16].

Compounds of saponin group isolated from bark of *P. fruticosa* roots has been reported. The compound is 3-*O*-ß-*D*-glucopyranosyl, 3-*O*-ß-*D*-ramnopyranosyl (1-2) ß-D-ramnopyranosyl (1-3) D-glucopyranosyl, 3-*O*-ß-*D*-glucopyranosyl (1-2) D-glucopyranosyl, and [17]. Another study isolated compounds of *P. fruticosa* leaves, and found that it contained two new oleanic-type triterpenoid saponins along with two known saponins (**Table 1**, **Figure 4**) [18]. Active compounds derived from polyacetylene such as falkarinol and heptadeca 1,8 (*E*) diène-4,6-dïene-3,10 diol (**Figure 5**) has been isolated from *P. fruticosa* plant [19].

P. fruticosa plant contain active compounds. *P. fruticosa* leaves contain saponins, triterpenoids, flavonoids, phenolic compounds and oleanan-type triterpene saponins. *P. fruticosa* roots contain phenolic and flavonoid compounds. *P. fruticosa* barks also contains phenolic and flavonoid compounds with different concentrations. It is necessary to pay attention to method of extracting and isolating compounds from *P. fruticosa* plant, whether it is the equipment used, the choice of solvents, temperature, which will greatly affect compounds contained in *P. fruticosa* plant.

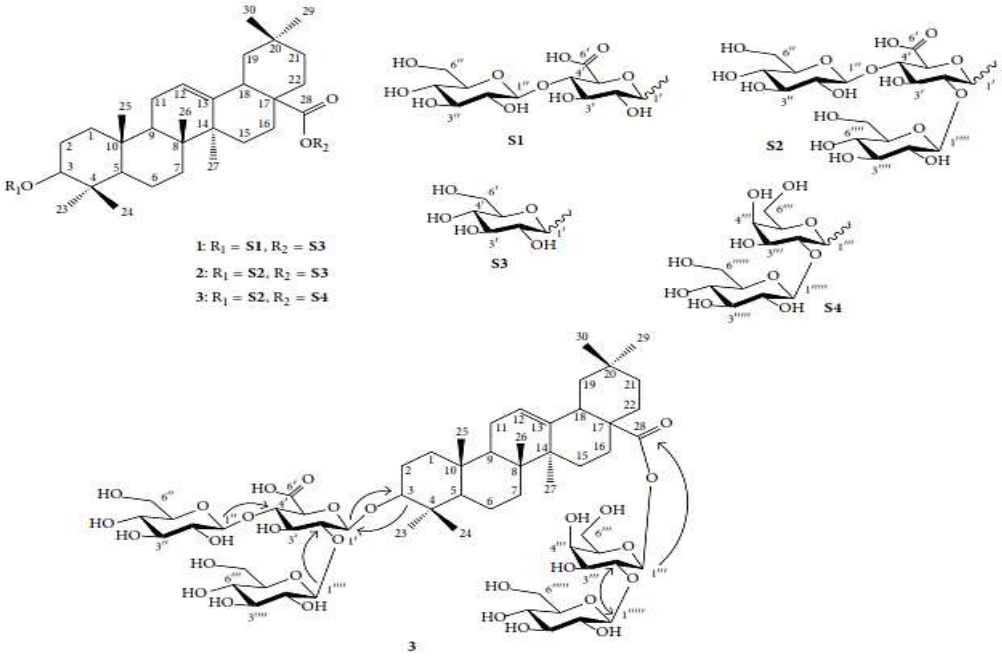

Figure 1. Structure of Bidesmodic Type-Saponin [8]

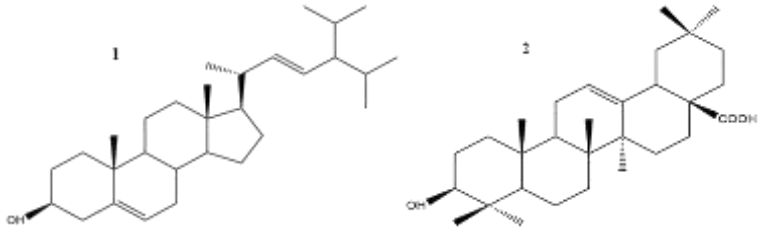

Figure 2. Structure of dihydro-24-isopropylcholesterol (1) and oleanolic acid triterpenoid (2) compounds [11]

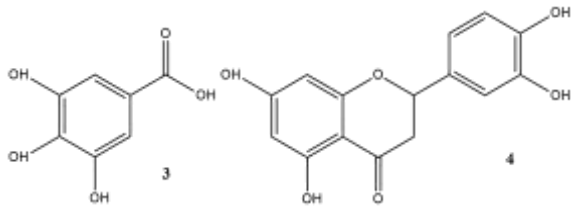

Figure 1. Structure of gallic acid (3) and quercetin (4)

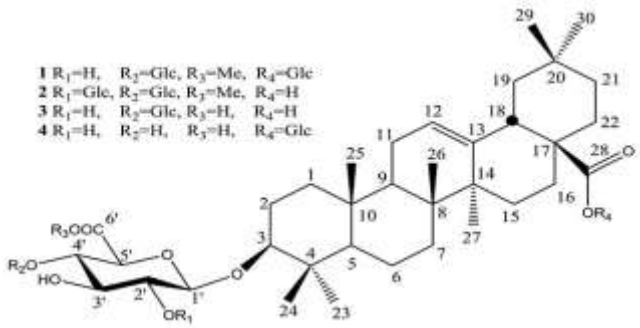

Figure 2. Structure of oleanan 1-4 type-saponin triterpene group [5]

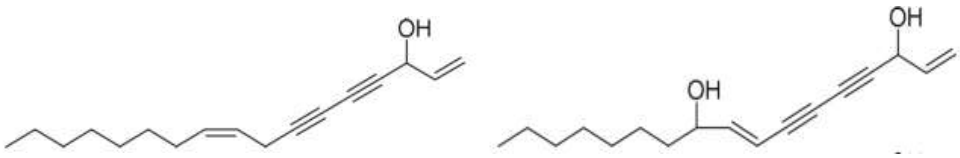

Figure 3. Structure of falkarinol [5] and heptadèca 1,8 (*E*)-diene-4,6-diène-3,10-diol [6]

3.2 Antibacterial Activity Of *Polyscias Fruticosa* Plant

Results of literature search related to antibacterial activity of *P. fruticosa* plant can be seen in **Table 2** below.

Table 2. Literature review of antibacterial activity of *P. fruticosa* plant and active compounds

No	Research Title	Research Subject	Antibacterial Test Method	MIC-MBC Activity
1	Antibacterial activity of *P. fruticosa* leaves extract against MRSA growth [6]	96% ethanol extract of *P. fruticosa* leaves	Agar diffusion. Determination of inhibitory zone	Extract of 25% against MRSA= 12,50 mm Extract of 50% against MRSA= 15,33 mm Ekstrak 75% pada MRSA= 15,83 mm Ekstrak 100% pada MRSA 16,50 mm

2	Antibacterial and Antibiofilm Activity of Flavonoids and Saponins Derivate from *A. tatarica* against *P. aeruginosa* [20]	saponin flavonoid derivative	Liquid dilution	All compounds has range of values of MIC 295.5-1988.1 μM and MBC 472.8-2485.1 μM against positive Gram and negative Gram
3	Antibacterial Activities and Mode of Action of Ferulic and Gallic Acids Against Pathogen Bacterià [21]	Phenolic derivative	Liquid dilution	MIC of gallic acid against *S. aureus* (1750 μg/mL), *and Listeria monocytogenes* (2000 μg/mL), *E. coli* (1500 μg/mL), *P. aeruginosa* (500 μg/mL)
4	Flavonoids Analyses and Antimicrobial Activity of Various Parts of *P. macrocarpa* Fruit [22]	Flavonoid derivative (rutin, quercetin, Apigenin, naringin, kaempferol, luteolin, Myricetin)	Agar difusion. Determination of inhibitory zone	Conc. of 0,3 mg/*disc*. Was active against *Enterobacter aerogenes, E. coli, Klebsiella pneumoniae, P. aeruginosa, Bacillus cereus, B. subtilis, M. luteus, S. aureus*
5	Inhibitor Effect of Quercetin on Periodontàl Pathogens *In Vitro* [23]	Quercetin compound	DLiquid dilution, MIC determination	MIC of quercetin was 0,0125 μg/mL against *Porphyromonas gingivalis and* 0,1 μg/mL against *Actinobacillus*.
6	Antibacterial and antibiofilm activity of quercetin against clinical isolates of *S. aureus* and *S. saprophyticus* with resistance profile [24]	Quercetin compound	Liquid dilution MIC and Antibiofilm determination	Has activity against MSSA, MRSA, VISA dan VRSA

7	The synergy and mode of action of quercetin + amoxicillin against amoxicillin-resistant *Staphylococcus epidermidis* [25]	Amoxicilin+ quercetin compound	MIC determination, enzyme test, permeabilitas membran and TEM method	MIC of amoxicilin was 16 μg/mL, quercetin was 256-384 μg/mL. concentration of amoxicillin + quercetin inhibitory fraction was 0,5. Quercetin has inhibition of β-lactamase.
8	Evàluating the Antibactèrial Properties of Polyacetylene and Glucosinolate Compounds with Further Identification of Their Presence within Various Carrot and Broccoli [29]	Polyacetylene derivative	Liquid dilution	MIC was 12,5-37,6 μg/mL against *B. cereus, S. aurèus,* MRSA

P. fruticosa leaves extract has antibacterial activity on positive Gram-Cocci, namely *S. aureus* bacteria that resistant to methicillin- or MRSA- by in vitro. Average diameter of inhibitory zone of the extracts with concentrations of 25, 50, 75, and 100% were 12.50, 15.33, 15.83, and 16.50 mm, respectively [6]. Research of *P. fruticosa* plant has also been done by a group of researchers from Laboratory of Organic Chemistry, Brawijaya University, Malang, that *P. fruticosa* is one of medicinal plant that has antibacterial properties. Root bark of *P. fruticosa* contain saponin-derived compound, namely -D-glucopyranosil [17] which has antibàcterial activity against negative Gram (*E. coli*, *P. aeruginosa*) and positive Gram (*Listeria monocytogenes*) bacteria, each with MIC value were 994, 0; 497.0; 1988.1 μM, and MBC were 1192.8; 596.4; 2485.1 μM [20].

P. fruticosa roots contains gallic acid and quercetin compounds [13]. Gallic acid is a phenolic substance that has antibacterial activity against *E. coli*, *P. aeruginosa*, *S. aureus*, *L. monocytogenes* with MIC values were 2000, 1750, 500, 1500 μg/mL, respectively [21]. Based on research, quercetin compound (concentration of 0.3 mg/disc) a flavonoid derivative has antibacterial activity against *S. aureus*, *E. aerogenes*, *E. coli*, *K. pneumonia*, *P. aeruginosa*, *B. cereus*, *B. subtilis*, *M. luteus* with an inhibitory zone of 9.3-23.3 mm [22]. In vitro study also showed that quercetin was active against negative Gram *bacillus P. gingivalis* with a minimum inhibitory value (MIC) were 0.0125 μg/mL and 0.1 μg/mL against *Actinobacillus* [23]. Quercetin compound is active against methicillin-resistant *S. aureus* (MRSA) with MIC value 500 μg/mL, vancomycin intermediate *S. aureus* (VISA) value MIC 125 and 150 μg/mL, methicillin-susceptible *S. aureus* (MSSA) bacteria with MIC value 250 μg/mL, *Staphylococcus saprophyticus* resistant-oxacillin with MIC value 62.5-125 μg/mL, vancomycin-resistant bacteria *S. aureus* (VRSA) and *S. saprophyticus* resistant oxacillin-vancomycin with MIC value 500-1000 μg/mL [24].

Another study showed that quercetin can fight amoxicillin-resistant *S. epidermidi*s. The results of observation also showed synergistic activity of quercetin + amoxicillin against *S. epidermidis* bacteria with concentration of inhibitory fraction of 0.5 [25]. If concentration of the inhibitory fraction is equal or less than 0.5 then combination of the two compounds can be said to be synergistic. On the other hand, if it is greater than 0.5, the combination compound will show antagonism [26]. Leaf and roots of *P. fruticosa* has antibacterial activities against *S. aureus* (highest concentration 50 mg/mL=9.8 mm),

B. subtilis (highest concentration 50 mg/mL=11.0 mm) and *E. coli* (highest concentration). 50 mg/mL=13.0 mm) [27]. *P. fruticosa* plant is known to has strong antibacterial activity against positive Gram-Cocci but inactive against negative Gram-Bacillus, and the compound that responsible for this activity is polyacetylene group from leaves, including hèptadeca 1,8 (*E*) diene 4-6-diene-3 10-diol and falcarinol [19]. Another study reported that falkarinol compounds has antibacterial activity on positive Gram (*B. subtilis* and MRSA) and negative Gram (*E. coli* and *P. aeruginosà*) with minimum inhibitory concèntration (MIC) was 3.1-50 μg/mL [28].

Other studies also reported that falkarinol compounds has antibacteriàl activity against positive Gram bacteria such as MRSA, *S. aureus*, and *B. cereus* with MIC value were 18.8; 37.6;, 12.5 μg/mL, respectively [29].

Research has shown that *P. fruticosa* plant has oleanolic acid compounds [11], and this compound has antibacterial activity against *S. aureus*, MRSA, *Enterococcus faecalis* and *M. tuberculosis* strain H37Rv [30]. Previous research reported by Liang et al., (2016) that oleanolic acid compounds has activity against negative Gram bacteria such as *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and positive Gram *B. subtilis* [31].

Based on the description, *P. fruticosa* plant has antibacterial activity. This is very relatable to compounds contained in the plant. Compounds that act as antibacterial are influenced by physical and chemical properties. As explained above, the concentration of extract or compound were different, and this affects its antibacterial effect. An extract or compound has a good bacterial inhibitory effect (>20 mm)

if the concentration is getting smaller.

3.3. Mechanism of Molecular Action of Antibacterial Compounds

Results of a literature search related to mechanism of action of antibacterial compounds can be seen in **Table 3** below.

Table 3. Literature review of antibacterial mechanism of bioactive compounds

No	Research Title	Compounds	Activity	Target
1	Antibiotic additive and synergistic action of rutin, morin and quercetin against MRSA [45]	Quercetin	Active against MRSA	Cytoplasmic membrane
2	Bacteriostatic Effect of Quercetin as àn Antibiotic Alternative *In Vivo* and Its Antibactèrial Mechanism *In Vitro* [46]	Quercetin	Acitive against. *aureus* dan *E. coli*	Cell walls, membrane, ATP, protein
3	Antibacterial properties of compounds isolated from *Carpobrotus edulis* [30]	Oleanolic acid	Active against *Listeria monocytogenes*	Cell walls
4	Oleanolic acid and ursolic acid inhibitors peptidoglycan biosynthesis	Oleanolic acid	Active against *S. mutans*	Cell walls

	In *Streptococcus mutans* UA159 [38]			
5	Antimicrobial Mechanism of action oleanolic and ursolic Acids On *Streptococcus mutans* Ua159 [39]	Oleanolic acid	Active against *Streptococcus mutans*	Peptidoglycan, amino acid, fatty acid, ATP
6	Antibacterial Activities and Mode of Action of Ferulic and Gallic Acids Against Pathogen Bacterial [21]	Gallic acid	Active against , *S. aureus, L. monocytogenes, E. coli*, and *P. aeruginosa.*	Cytoplasmic membrane
7	Suppression of bacterial cell signalling, biofilm formation and type III secretion system by citrus flavonoid [47]	Quercetin	Active against *E. coli*, *Vibrio cholerae*, *S. typhi*	*Quorum sensing* (biofilm)
8	Flavonoid inhibitor as novel antimycobacterial agents targeting RV0636, a putative dehydratase enzyme involved in *M. tuberculosis* fatty acid synthase [48]	Quercetin	Active against *Mycobacterium*	ß-ketoacyl-ACP reductase, FAS-II, enoyl-ACPreductase, and ß-hydroxy acyl-ACP dehydratasè

9	Characterization of quercetin binding site on DNA gyràsè [49]	Quercetin	Active against *E. coli*	DNA gyrase

3.3.1 Oleanolic Acid Compounds

Oleanolic acid compounds belong to triterpenoid saponin group. Saponin has detergent-like properties that can increase and/or interfere permeability of cell membrane of bacteria that caused damage to bacterial cells. Saponin can interact with cholesterol and/or lipid (**Figure 6**) in eukaryotic cell membranes and with lipid A in prokaryotic cells (bacteria), which is part of lipopolysaccharide (LPS, **Figure 7**) in negative-Gram bacteria. These interaction increase permeability of bacterial cell walls and membrane which results in cell leakage. The activity of saponin related to membrane permeability is associated with amphipathic which is influenced by fungtional group aglycone, long chain of saccharides, and sugars in glycosidic chain [32,33].

Saponin compounds has antibacterial activity by lowering surface tension of bacterial cell walls because saponin has an active component, namely aglycones which are membranolytic. This results interaction of saponins on the surface of bacterial cell walls and the formation of a single ion channel. The existence of this single ion channel causes cell membrane instability thereby inhibiting activity of enzymes, especially those that play role in ion transport for bacterial survival [34]. Several other actions of saponin has been previously reported including for bacteriophage therapy, inhibition of bacterial adhesion [35,36,37].

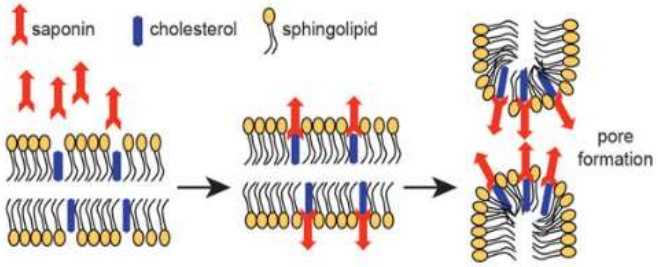

Figure 4. Saponin-lipid/kolesterol interaction [33]

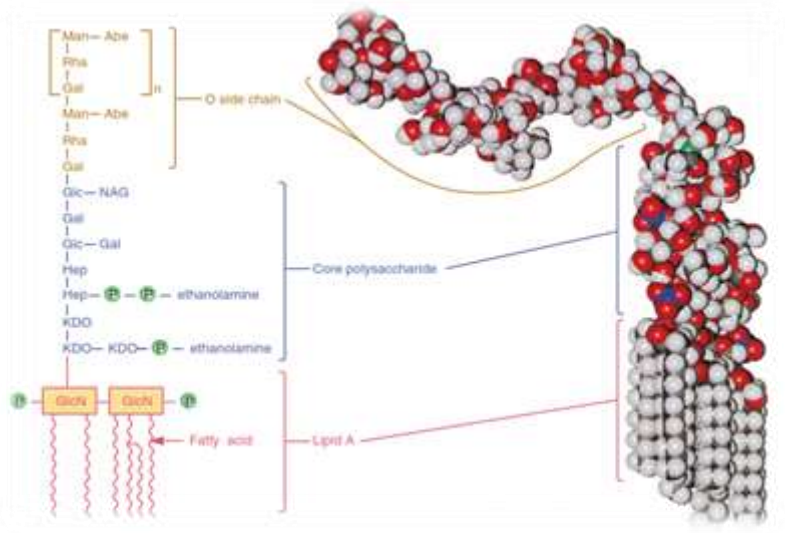

Figure 5. Structure of lipopolysaccharide (LPS)

Oleanolic acid compound (**Figure 2**) has an antibacterial mechanism on cell walls of positive Gram bacteria (*L. monocytogenes)* by influencing peptidoglycan metabolism. This compound also inhibit the energy required for efflux pump in bacterial cells, resulting accumulation of intracellular compounds [30]. Oleanolic acid acts on cell walls of *Streptococcus mutans* bacteria by inhibiting translocation of MurNAc-pentapeptide which functions in peptidoglycan biosynthesis [38]. Other studies has also proven that oleanolic acid is active against *S. mutans* by inhibiting peptidoglycan biosynthetic pathway, fatty acid synthesis, amino acid synthesis, andATP synthesis [39].

3.3.2 Quercetin

Quercetin is a flavonoid compound. Flavonoids act on cytoplasmic membranes (probably producing hydrogen peroxide), the compounds are flavonols (**Figure 8**), flavan-3-ol (**Figure 9**), and flavanols (**Figure 10**). These three compounds also decrease energy metabolism of bacteria. Flavan-3-ol and isoflavone compounds (**Figure 11**) inhibition of dihydrofolate reductase enzyme and topoisomerase II or DNA gyrase [40,41,42]. There are two types of topoisomerase that are important in synthesis of nucleic acids (DNA) in bacteria, namely topoisomerase II (DNA gyrase) and IV. Topoisomerase enzyme is an enzyme that changes configuration or topology of DNA by cutting one of DNA strands in DNA double helix and reconnecting it (resealing) so that it can make positive DNA strands or negative DNA strands in bacterial cells. Bacterial dihydrofolate reductase enzyme function is to convert dihydrofolic acid to tetrahydrofolic acid (**Figure 12**). Tetrahydrofolic acid plays an important role in synthesis of purines (adenine, guanine) and several amino acids such as methionine and glycine [2].

Suppression of bacterial cell walls synthesis by flavonoid compounds with the mechanism of inhibiting enzyme *D*-ala *D*-ala ligase. This enzyme is very important to catalyze *D*-ala *D*-ala ligation in the process of preparing peptidoglycan precursor and has been considered as a target for antibacterial drugs in recent years [43]. Flavonoid compounds are known to has a quorum-sensing inhibitory mechanism (communication system between bacterial cells in the formation of biofilms) which is facilitated by TraR and RhIR receptor signals [44].

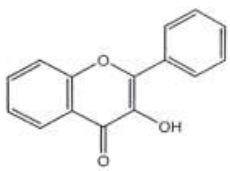

Figure 6. Flavonol

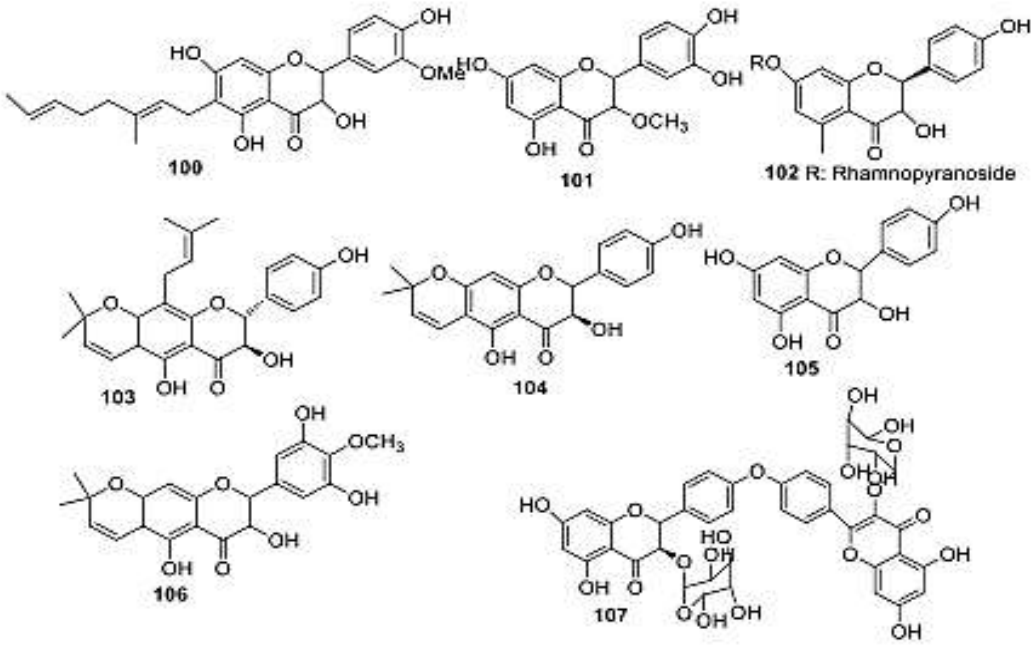

Figure 7. Flavan-3-ol derivatives

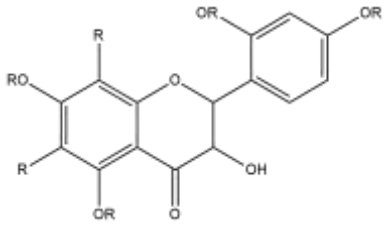

Figure 8. Flavanol

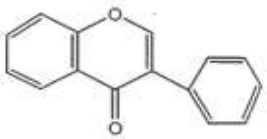

Figure 9. Isoflavon

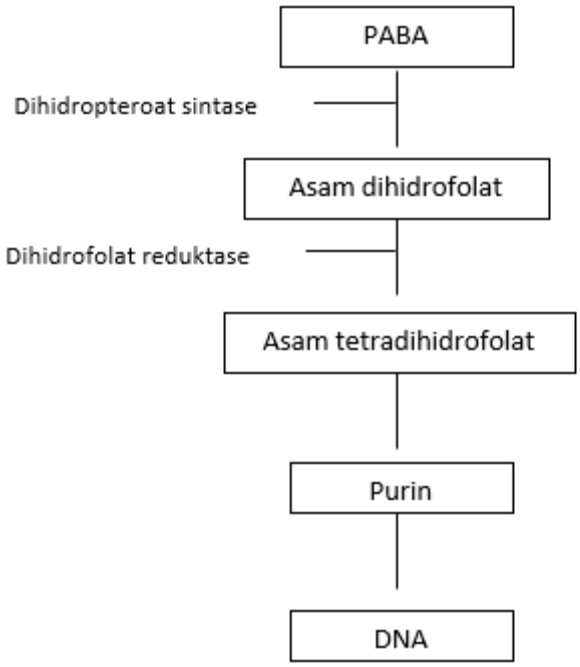

Figure 12. Purine synthesis in bacteria

Previous studies has shown that quercetin combined with rutin (**Figure 13**) and morin (**Figure 14**) has a mechanism of action on cytoplasmic membranes of MRSA bacteria which is characterized by release and high concentration of extracellular potassium [45]. Another study reported that quercetin has an antibacterial action mechanism by binding to the cell membranes and cell walls of bacteria and resulting increased permeability. This causes the cell contents escape outside the cell and also affects activity of ATP [46]. Quercetin also inhibits protein synthesis, affects gene expression in cells, and ultimately causing bacterial cell lysis or death. Other studies has shown that quercetin inhibits quorum sensing which is an intercellular signaling molecule that is important in formation of biofilms of *E. coli*, *Vibrio cholerae*, and *S. typhi* bacteria [47]. Quercetin has mechanism by inhibition on hydroxy acyl ACP dehydratases, ketoacyl-ACP reductase, fatty acid synthase/FAS-II enzyme, enoyl ACP reductase in *Mycobacterium* sp. [48].

Quercetin can also inhibit bacterial DNA replication by binding to enzyme DNA gyrase [49].

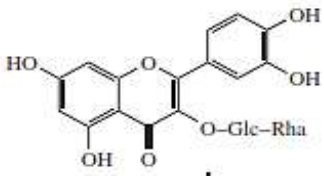

Figure 10. Structure of rutin

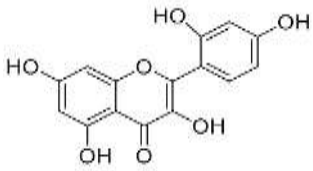

Figure 11. Structure of morin

3.3.3 Gallic Acid

Gallic acid is a phenolic derivative compound. Phenol compounds are bioactive molecules, and play an important role in increase antibacterial activity against resistant pathogen through various mechanism of action. Gallic acid is a phenolic compound that reacts on the surface of cell membranes of positive Gram (*S. aureus, L. monocytogenes*) and negative Gram (*E. coli, P. aeruginosa*) bacteria which causes damage to cytoplasmic membrane, release important intracellular component, which ultimately results in death bacterial cells [21].

Chebulinic acid, anthraquinone are phenolic compounds that show inhibition of DNA gyrase enzyme. Research of chebulinic acid was done by molecular docking, it was found that this compound inhibits DNA gyrase enzyme of quinolone-resistant *M. tuberculosis*. Anthraquinone derivatives (haloemodin) inhibitor DNA gyrase in *Enterococcus faecium* and MRSA (Patel *et al*., 2015; Duan et al., 2014). P-coumaric, caffeic acid, and ferulic acid (Hydroxycinamic acids), has mechanism of action by disrupting integrity of bacterial cell membranes.

P-coumaric is most effective because it contains a highly lipophilic group [50].

P. fruticosa plant has bioactive compounds with various mechanisms of antibacterial action. Triterpenoid saponin compounds such as oleanolic acid has mechanism in cell walls by influencing biosynthesis of peptidoglycan, inhibiting energy needed by efflux pump, inhibiting ATP and amino acid synthesis. Quercetin has mechanism on bacterial walls and membranes, inhibiting protein synthesis, inhibiting bacterial biofilm formation, inhibiting fatty acid synthesis (FAS enzyme), DNA replication (DNA gyrase). Gallic acid is a phenolic that acts on bacterial membranes. Mechanism of antibacterial action of *P. fruticosa* plant described above is summarized in following figure.

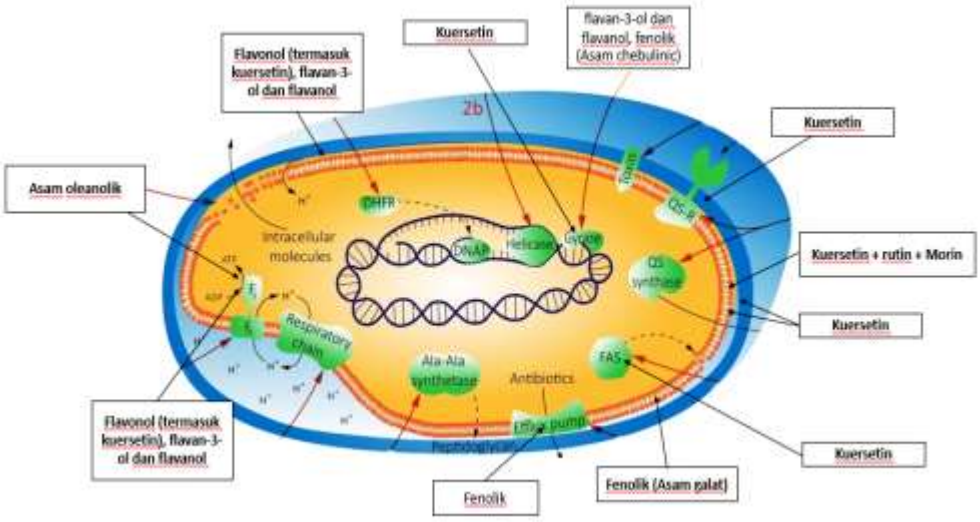

Figure 12. Mechanisms of Antibacterial Compounds

4. CONCLUSION

P. fruticosa plant contain bisdesmosidic saponins, 22-dihydro-24-isopropylcholesterol and oleanolic triterpenoid compounds, gallic acid, quercetin, polyscioside J, polyscioside K compounds, ladyginoside and chikusetsusaponin Iva, heptadeca 1,8 (E) diene-4,6-diyne-3, 10-diol and falcarinol.

Oleanolic acid, gallic acid, quercetin compounds has good antibacterial activity. Molecular mechanism of oleanolic acid compounds as inhibitors of cell wall synthesis, increasing membrane permeability, inhibiting ATP, inhibiting fatty acid synthesis, and inhibiting formation of amino acids. Quercetin compounds has mechanism of inhibiting cell wall synthesis, increasing membrane permeability, inhibiting protein synthesis, inhibiting biofilm formation, and ATP formation, and gallic acid compounds having a mechanism by acts on cytoplasmic membranes causing cell leakage.

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6. REFFERENCES

[1]. PERMENKES Tentang pedoman umum penggunaan antibiotik. 2011.

[2]. Radji M. *Mekanisme Aksi Molekuler Antibiotik dan Kemoterapi*. 2014. Jakarta. Penerbit Buku Kedokteran EGC

[3]. Liu Q, *et al*. 2017. Antibacterial and Antifungal Activity of Spices, *IJM Science*. 2017. 18:1-62

[4]. Newman. DJ and Cragg GM. Natural product as sources of new drug's from 1981 to 2014. *JNP*. 2016. p629-661

[5]. Do V.M, Tran C.L, Nguyen T.P. Polysciosides J and K, two new oleanane-type triterpenoid saponins from the leaves of *Polyscias fruticosa* (L.) harms. Cultivating in an Giang Province, Vietnam. *Natural Product Research*. 2018. 1-6

[6]. Sari Z.W.P, Ismail A, Dhanardhono T. Aktivitas Antibakteri Ekstrak Daun Kedondong Laut Terhadap Pertumbuhan *S. aureus* Resisten Metisilin. *JKD*. 2019. 8:580-587

[7]. Koffuor G.A *et al*. Anti-inflammatory and safety assessment of *Polyscias fruticosa* leaf extract in ovalbumin-induced asthma. *BJMMR*. 2014. 3:337-342

[8]. Hanh T.T.H, Dang N.H, Dat NT. 2016. α-amylase and α-glucosidase inhibit saponins from *Polyscias fruticosa* leaves. *J Chem*. 2016.

[9]. Vo.V.C. *Dictionary of Vietnamese medicine plants*. Hanoi. 2012. Publisher of Medicine

[10]. Do.T.L. *Nhung cay thuoc va vị thuốc Viet Nam*. 8th ed. 2004. Vietnam.

[11]. Tram N.T.T, Tuyet H.D, Minh. One unusual sterol from *Polyscias fruticosa*. *Can Tho U J Sci*. 2017. 7:33–36

[12]. Nguyen MP. Impact of Roasting to Total Phenolc, Flavonoids and Antioxidant Activity in Root, Bark and Leaves of *Polyscias fruticosa*. *JPRIl.* 2020. 13-17

[13]. Nguyen NQ, Nguyen MT, Nguyen VT, Trieu L, Le T, Khang T, Giang, Thach NQ, Hung TT. The effects of different extraction conditions on the polyphenol, flavonoids components and antioxidant activities of *Polyscias fruticosa* roots. *IOP*. 2020. [736] 022067. p1-8

[14]. Huan V.D, Yamamura, Ohtani K, Kasai, Yamasaki K, Nguyen T.N, Hoang M.C. Oleanane saponins from *Polyscias fruticosa*. 1998. 451–457

[15]. Luyen, N *et al*., Flavonoid glycoside as inhibit of α-amylase isolated from the leaves of *Polycias fruticosa*. *JMM*. 2012. 17 '(6) 348–351.

[16]. Proliac J, Chaboud A, Rougny A, Gopalsamy N, Raynaud J, Cabalion P. A oleanolic saponin from *Polyscias fruticosa* harms var. Yellow leaves. 1996. 51, 611–612

[17]. Masruri, Elvina D.I, Kristianingsih, Edi P, Rahman MF, Rurini R. Identification of Triterpenoide Compound from

Polyscias fruticosa Root Bark. 2007. 45-47

[18]. Do V.M, Tran C.L, Nguyen T.P. Polysciosides J and K, two new oleanane type triterpenoid saponins from the leaves of *Polyscias fruticosa*. Vietnam. *Natural Product Research*. 2018. 1-6

[19]. Lutomski J *et al*., Polyacetylene in the *Araliaceae* family. *Herba Polonica*. 1992. 38'3:137-140

[20]. Stankovic J *et al*., Antibacterial and Antibiofilm Activity of Flavonoid and Saponin Derivate from *Atriplex tatarica* against *Pseudomonas aeruginosa*. *JNP*. 2019. 82, 1487-1495

[21]. Borges A *et al*., Antibacterial Activity and Mode of Action of Ferulic and Gallic Acids Against Pathogenic Bacteria. *MDR*. 2013. 1-10

[22]. Hendra R, Ahmad S, Sukari A, Ahukor M.Y, Oskoueian . Flavonoid analysis and antimicrobial activity of various parts of *Phaleria macrocarpa* boerl fruit. *IJMS*. 2011. 3422-3431

[23]. Geoghegan, F., Wong, R., and Rabie, A. Inhibitory effect of quercetin on periodontal pathogens *in vitro*. *PR.* 2010. 24(6), 817–820

[24]. Junior S.D *et al*., Antibacterial and antibiofilm activity of quercetin against clinic isolates of *Staphyloccocus aureus* and *Staphylococcus saprophyticus* with resistance profile. *IJEAB.* 2018. 3. 1948-1958

[25]. Siriwong S, Teethaisong Y, Thumanu K, Dunkhunthod B, Eumkeb G. The synergy and mode of action of quercetin plus amoxicillin against amoxicillin-resistant *S epidermidis.* BMC *Pharmacology and Toxicology*. 2016. 17(1), 39

[26]. Odds F.C. Synergy, antagonism, and what the chequerboard puts between them. *JAC*. 2003. 52:1

[27]. Bensita M.B, Nilani P, Sandhya SM. Studies on the adaptogenic and antibacterial properties of *Polyscias fructicosa*. *ASL*. 1999. 18, 231–246

[28]. Kobaisy M, Abramowski Z, Lermer L, Saxena G, Hancock RE, Towers GH, Doxsee D, Stokes RW. Antimycobacterial polynes of Devil's Club (*Oplopanaxhorridus*), a North American native medicinal plant. *JNP*. 1997. 60, 12101213

[29]. Hinds L *et al*. Evaluating the Antibacterial Properties of Polyacetylene and Glucosinolate Compounds with Further Identification of Their Presence within Various Carrot (*Daucus carota*) and Broccoli (*Brassica oleracea*) Cultivars Using High-Performance Liquid Chromatography with a Diode Array Detector and Ultra Performance Liquid Chromatography-Tandem Mass Spectrometry Analyses. *JAFC.* 2017.

[30]. Martins A, Vasas A, Viveiros M, Molnár J, Hohmann J, Amaral L. Antibacterial properties of compounds

isolated from *Carpobrotus edulis*. International Journal of Antimicrobial Agents. 2011. 37, 438-444

[31]. Liang Z, Wang X, Huang L, Li Q, Guan T, Luo H, Yang XS, Hao XJ. 1α,2α-Epoxy-3β-hydroxy oleanolic acid derivatives regulation of the metabolism, haemolysis and β-lactamase gene expression in vitro and their structure–microbicidal activity relationship. *Bioorganic & Medicinal Chemistry Letters*. 2016. 3870–3875

[32]. Arabski M *et al*. Effects of saponins against clinical *E. coli* strains and eukaryotic cell line. *Journal of Biomedicine and Biotechnology*. 2011. 1-6

[33]. Moses T, Kalliope K. Papadopoulou, Anne O. *Review article*: Metabolic and functional diversity of saponins, biosynthetic intermediates and semi-synthetic derivatives. *Crit Rev Biochem Mol Biol*. 2014. 1–24

[34]. Hoffmann and David. Medical Herbalism: The Science and Pratice of Herbal Medicine. 2003. Inner Traditions/Bear.

[35]. O'Flaherty S, Ross RP, and Coffey A. Bacteriophage and their lysins for elimination of infectious bacteria: Review article. *FEMS Microbiology Reviews*. 2009. vol. 33, no. 4, pp. 801–819

[36]. Montdargent B and Letourneur D. Toward new biomaterials. *Infection Control and Hospital Epidemiology*. 2000. vol. 21, no. 6, p. 404–410

[37]. Mamelli L, Petit S, Chevalier J. New antibiotic molecules: bypassing the membrane barrier of *Gram negative* bacteria increases the activity of peptide deformylase inhibitors. *PLoS ONE*. 20009. 4:7. 6443

[38]. Park S.N *et al*. Oleanolic acid and ursolic acid inhibitor peptidoglycan biosynthesis in *Streptococcus mutans* UA159. *BJM*. 2015. 46:2. 613-617

[39]. Park S.N, Lim Y.K, Choi M.H, Cho E, Bang I.S, Kim J.M, Ahn S, Kook J. Antimicrobial Mechanism of Oleanolic and Ursolic Acids on *Streptococcus mutans* UA159. *CM*. 2017.

[40]. Chinnam N *et al*. Dietary bioflavonoids inhibit Escherichia coli ATP synthase in a differential manner. *IJBM*. 2010. 46(5), 478–486

[41]. Gradisar H, Pristovsek P, Plaper A, Jerala R. Green tea catechins inhibit bacterial DNA gyrase by interaction with its ATP binding site. *JMChemistry*. 2007. 50(2), 264–271

[42]. Wang Q, Wang H, Xie M. Antibacterial mechanism of soybean isoflavone on *Staphylococcus aureus*. *AM*. 2010. 192(11), 893–898.

[43]. Wu D, Kong Y, Han C, Chen J, Hu L, Jiang H, Shen X. D-Alanine: D-alanine ligase as a new target for the flavonoids quercetin and apigenin. *IJAA*. 2008. 32(5), 421–426.

[44]. Zeng Z, Qian L, Cao L, Tan H, Huang Y, Xue X, Zhou S. Virtual screening for novel quorum sensing inhibitors to eradicate biofilm formation of *Pseudomonas aeruginosa*. *Applied Microbiology and Biotechnology*. 2008. 79(1), 119

[45]. Amin MU, Khurram M, Khattak B, Khan J. Antibiotic additive and synergistic action of rutin, morin and quercetin against *methicillin resistant Staphylococcus aureus*. BMC *Complementary and Alternative Medicine*. 2015. 15(1), 59.

[46]. Wang S, Yao J, Zhou B, Yang J, Chaudry MT, Wang M, Xiao F, Li Y, Wenzhe Y. Bacteriostatic Effect of Quercetin as an Antibiotic Alternative In Vivo and Its Antibacterial Mechanism In Vitro. *Journal of Food Protection*. 2018. 81 (1). p 68–78

[47]. Vikram A, Jayaprakasha GK, Jesudhasan PR, Pillai SD, Patil BS. Suppression of bacterial cell-cell signalling, biofilm formation and type III secretion system by citrus flavonoids. *J. Appl. Microbiol*. 2010

[48]. Brown AK *et al*. Flavonoid inhibit as novel antimycobacterial agents targeting Rv0636, a putative dehydratase enzyme involved in *Mycobacterium tuberculosis* fatty acid synthase II. *Microbiology*. 2007. 153, 3314–3322

[49]. Plaper A *et al*. Characterization of quercetin binding site on DNA gyrase. *Biochem. Biophy. Res. Comm*. 2003. 306. p530–536.

[50]. Campos FM *et al*. Cell membrane damage induced by phenolic acids on wine lactic acid bacteria. *Int J Food Microbiol.* 2009. 135(2):144–51.

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