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- Review -

Interaction with Polyphenols and Antibiotics

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Polyphenols are secondary metabolites produced by higher plants and have been used as antiallergic, anticancer, antihypertensive, antiinflammatory, antimicrobial and antioxidant agents. They are generally divided into flavonoids and non-flavonoids. The antimicrobial activity of flavonoids are stronger than that of non-flavonoids. The skeleton structures of flavonoids possessing antimicrobial activity are chalcone, flavan-3-ol (catechin), flavanone, flavone, flavonol and proanthocyanidin. The flavonols are shown antibacterial activity against several gram-positive bacteria (*Actinomyces naeslundii, Lactobacillus acidophilus* and *Staphylococcus aureus*) and gram-negative bacteria (*Fusobacterium nucleatum, Porphyromonas gingivalis*, *Prevotella melaninogenica* and *Prevotella oralis*). Among of non-flavonoids, caffeic acids, ferulic acids and gallic acids showed antimicrobial activity against gram-positive (*Listeria monocytogenes* and *S. aureus*) and gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). These are found to be more efficient against the *E. coli, L. monocytogenes, P. aeruginosa* and *S. aureus* than antibiotics such as gentamicin and streptomycin. The kaempferol and quercetin showed synergistic effect with ciprofloxacin and rifampicin against *S. aureus* and methicillin resistant *S. aureus* (MRSA). Epigallocatechin gallate (EGCG) acts synergistically with various β-lactam antibiotics against MRSA. In particular, the epicatechin, epigallocatechin (EGC), EGCG and gallocatechin gallate from Korean green tea has antibacterial activity against MRSA clinical isolates and the combination of tea polyphenols and oxacillin was synergistic for all the clinical MRSA isolates.

Key words : Antibacterial activity, kaempferol, polyphenols, quercetin, synergistic effect

Introduction

Since the discovery of penicillin by Fleming in the 1928, antibiotics are clinically important medicines, but the emergence of antibiotic resistant strains has become an issue. Infections caused by antibiotic resistant strains are increasing worldwide in both outpatients as well as hospitalized patients. Despite the development of new antibiotics, the abuse and misuse of antibiotics are constantly causing antibiotic resistance. Antibiotic resistance can be induced in all available classes of antibiotics [7]. Antibiotic resistance has become a clinically serious problem as the antibiotic resistant strains has increased and multidrug resistant strains have emerged in many strains that cause disease in human. The most serious problem is that there is no available therapy for infection by antibiotic resistant strains and there is a steady increase in resistance to commonly used antibiotics. The most of multidrug resistant strains are becoming common cause of infections during the acute and long term treatment in the hospital. Therefore, various therapy to reduce the problem of antibiotic resistance have been proposed.

The interest in natural products with antimicrobial activity has increased as a new therapeutic agent for infectious diseases that can replace conventional antibiotics [7, 8, 13]. As the emergence of antibiotic resistance increase in both hospitals and community acquired infections, the antibacterial activity of plant-derived compounds is attracting attention [13, 15]. Among plant-derived compounds, antimicrobial activity of polyphenols has been extensively investigated in vegetables and medicinal plants against a wide range of pathogenic microorganism. Polyphenols are secondary metabolites produced by higher plants and have been used as antiallergic, anticancer, antihypertensive, antiinflammatory, antimicrobial and antioxidant agents. They are generally divided into flavonoids and non-flavonoids. Flavonoids are subdivided into anthocyanidins, flavanols, flavanones, flavones, flavonols and isoflavones. In particular, flavan-3-ols, flavonols and tannins showed the

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wide spectrum and higher antimicrobial activity compared to other polyphenols. The most of them are able to suppress a number of microbial virulence factors (such as inhibition of biofilm formation, reduction of host ligands adhesion and neutralization of bacterial toxins) and show synergistic effect with antibiotics [38]. Several studies on the antibacterial activity of flavonoid-rich products was reported that new compounds of flavonoid with bactericidal rather than bacteriostatic effect was increasing the activity of antibiotics through synergistic interactions [5, 16, 21]. *Staphylococcus aureus* and methicillin resistant *S. aureus* (MRSA) are among the most significant gram-positive pathogens. As several MRSA strains have become multidrug resistant endemic pathogens, new therapies are needed to treat these widespread infections [37]. Therefore, the use of natural antimicrobials could play a positive role in reducing the rates of infection.

Polyphenols in nature

Polyphenols are secondary metabolites ubiquitously distributed in all higher plants, which have important roles as defense against plant pathogens and animal herbivore aggression and as response to various abiotic stress such as rainfall and ultraviolet radiation. They are present in plant tissues mainly as glycosides and generally divided into flavonoids and non-flavonoids [8, 13, 25].

Flavonoids are widely distributed in flowers, fruits, nuts, seeds, stems and vegetables of plants kingdom as secondary metabolites [25]. The general structure of flavonoids is the 15-carbon skeleton (C6-C3-C6), which consists of two benzene rings (A and B) linked through a heterocyclic pyrene ring (C) (Fig. 1) [8, 13]. Flavonoids are classified on the basis of the chemical nature and positon of substitutes

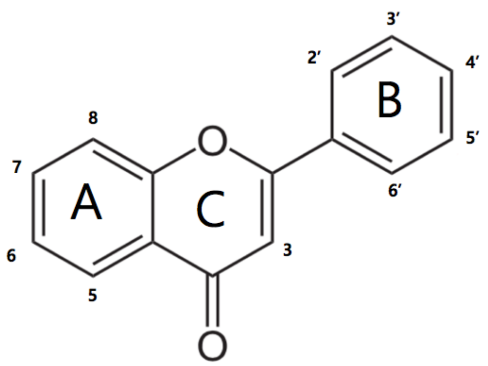


Fig. 1. The general structure of the flavones (a class of flavonoids), with rings named and positions numbered [13].

on the A, B and C rings. The flavonoids are the most important plant pigments for flower coloration producing yellow, red and blue pigmentation in flowers [13, 24]. The flavonoids are promoted physiological survival of plant, protecting it from fungal pathogens and UV-B radiation in leaves [13, 24]. Flavonoids are involved in photosensitization, energy transfer, the actions of plant growth hormones and growth regulators, control of respiration and photosynthesis, morphogenesis and sex determination [13]. Several flavonoids are formed as antimicrobial barriers in plants response to microbial infection.

The main groups of non-flavonoids are phenolic acids, stilbenes and lignans are found primarily in the flesh of the grape berry.

Medicinal effects of polyphenols

The polyphenols have been reported to possess many useful properties, including antiinflammatory activity [32], antimicrobial activity, enzyme inhibition, oestrogenic activity [9, 13, 23, 25], antiallegic activity, antioxidant activity [13], cytotoxic antitumour activity and vascular activity [24, 34]. Havsteen was reported on the biochemistry and medical significance of the flavonoids [25, 26].

Antibacterial activity of flavonoids

Several flavonoids are formed as antimicrobial barriers in plants response to microbial infection. The number of studies on flavonoids as potential antimicrobial agents have been reported. The skeleton structures of flavonoids possessing antibacterial activity are chalcone, flavan-3-ol (catechin), flavanone, flavone, flavonol and proanthocyanidin (Fig. 2).

The flavan-3-ols (catechins) are mainly found in green and oolong tea (*Camellia sinensis*), so they are called tea catechins. The tea catechins such as (-)-gallocatechin-3-gallate, (-)-epiga llocatechin-3-gallate, (-)-catechin-3-gallate and (-)-epicatechin -3-gallate inhibited the growth of the *Bacillus cereus, Campylo bacter jejuni, Clostridium perfringes*, *Escherichia coli, Streptococcu s mutans* and *Vibrio cholerae* [1, 7, 18, 28, 33]. Among tea catec hins, many studies on the antibacterial, antifungal and antivi ral activities of the epigallocatechin gallate (EGCG) has been reported. EGCG was inhibited the growth of 56 clinical isolat es of *Helicobacter pylori*, a urease producing gastric pathogen including 19 isolates highly resistant to metronidazole and clarithromycin at concentration of 100 mg/ml, *in vitro*. Those clinical isolates with antibiotic resistance also showed a similar

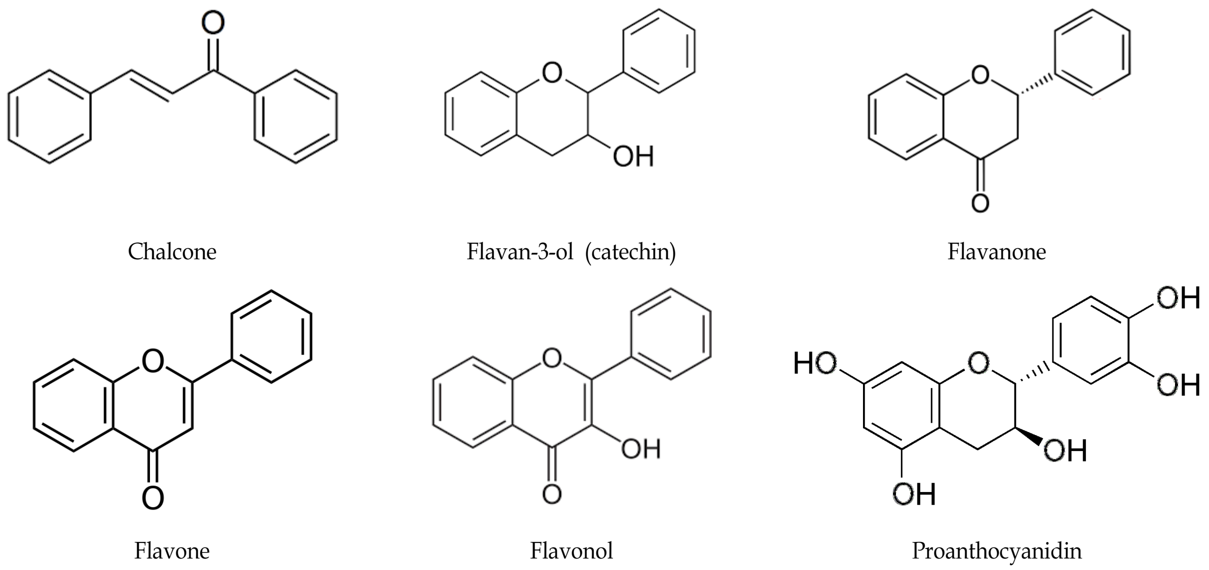


Fig. 2. Structures of flavonoid classes possessing antibacterial activity: chalcone, flavan-3-ol (catechin), flavanone, flavone, flavonol and proanthocyanidin [13].

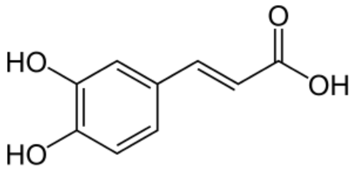
EGCG sensitivity [39]. EGCG did not affect growth of *E. coli* O157:H7 at concentration of 25 mg/ml, but showed significant antipathogenic effect because it decreased some virulence factors such as biofilm formation and bacterial swarm motility [29].

Tannins are subclassified into ellagitannins (hydrolyzable tannins), gallotannins and proanthocyanidins (condensed tannins). The proanthocyanidins are present in bark, fruits, leaves and seeds of many plants. The proanthocyanidins from berries was inhibited the growth of uropathogenic *E. coli*, cariogenic *S. mutans* and oxacillin resistant *S. aureus* [10, 17, 19]. Ellagitannins are hydrolysable tannins and main phenolic compounds of cloudberry, raspberry and strawberry. They inhibited to different extents the growth of intestinal bacteria such as *Bacillus* sp., *Campylobacter* sp., *Clostridium* sp., *E. coli, Helicobacter* sp., *Salmonella* sp. and *Staphylococcus* sp. [27]. The gallotannins such as a penta-O-galloylglucose, hexa-O-galloylglucose, hepta-O-galloylglucose, octa-O-galloylglucose, nona-O-galloylglucose and deca-O-galloylglucose from mango kernels showed antibacterial activity against food borne bacteria. Gram-positive bacteria were generally more susceptible than gram-negative bacteria. The minimal inhibitory concentration (MIC) against *B. cereus, Bacillus subtilis, Clostridium botulinum, C. jejuni, L. monocytogenes* and *S. aureus* at concentration of 0.2 mg/ml or less. The enterotoxigenic *E. coli* and *Salmonella enterica* were inhibited at concentration of 0.5-1 mg/ml. But, lactic acid bacteria exhibited strong resistance. The antibacterial activity of gallotannins is due to their strong affinity for iron and it is also related to the inactivation of membrane binding proteins [20].

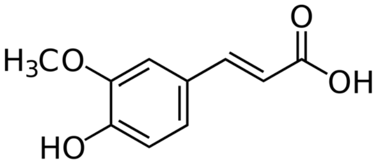
The flavonols are shown antibacterial activity against several gram-positive bacteria (*Actinomyces naeslundii*, *Lactobacillus acidophilus* and *S. aureus*) and gram-negative bacteria (*Fusobacterium nucleatum, Porphyromonas gingivalis, Prevotella melaninogenica* and *Prevotella oralis*). The antimicrobial activity of flavonoids is caused by various mechanisms of action, and the most convincingly mechanism is the aggregation effect on the bacterial cells [4, 14, 31]. Alvesalo *et al.* reported that the morin, myricetin, rhamnetin and quercetin was decreased the infectivity of *C. pneumoniae* in human cultured cell line (HL cells) by 50% compared to the untreated controls at concentration of 0.5 to 50 mM [3]. The rhamnetin was more effective than morin and quercetin, because it has a methoxy group on the A ring, which is an electron donating group. The flavonols are capable of penetrating cell phospholipid membranes, therefore able to exert their antibacterial activity also inside the cell [3].

Antibacterial activity of non-flavonoids

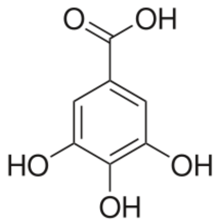
The antibacterial activity of non-flavonoids is weaker than that of flavonoids. Among of non-flavonoids, caffeic acids, ferulic acids and gallic acids (Fig. 3) showed antibacterial activity against gram-positive bacteria (*L. monocytogenes* and *S. aureus*) and gram-negative bacteria (*E. coli* and *P. aeruginosa*). They have been found to be more efficient



Caffeic acid



Ferulic acid



Gallic acid

Fig. 3. Structures of non-flavonoid classes possessing antibacterial activity: caffeic acid, ferulic acid and gallic acid.

against the *E. coli*, *L. monocytogenes*, *P. aeruginosa* and *S. aureus* than antibiotics such as gentamicin and streptomycin. But, chlorogenic acid showed no activity against gram-positive bacteria [13, 15].

Combination with polyphenols and antibiotics

The misuse and overuse of antibiotics has raised the problem of antibiotic resistant that have acquired the ability to survive existing drugs at clinically relevant concentrations in very serious diseases, such as AIDS, chronic infections caused by bacterial biofilms, diarrhea, gonorrhea, influenza, malaria, pneumonia and tuberculosis. Therapeutic options of infection by these antibiotic resistant pathogens such as penicillin resistant, methicillin resistant and vancomycin resistant *S. aureus* or multidrug resistant *V. cholerae* are extremely limited and is a challenge for the development of next generation of antibiotics.

Recently, several researches have proposed that polyphenols could be used in combination with antibiotics in order to their potential efficacy, to lower antibiotic dose, and therefore to reduce antibiotic adverse reactions [2, 11, 12, 21, 22].

The synergistic effect of combination with two flavonols (kaempferol and quercetin) and rifampicin against clinical rifampicin resistant and methicillin resistant *S. aureus* (MRSA) isolates *in vitro* was reported [6, 30, 37]. When kaempferol and quercetin were used alone they showed slight β-lactamase inhibition, but exhibited excellent β-lactamase inhibitory effect when combined with rifampicin (57.8 and 75.8%, respectively). The antibacterial activity of ciprofloxacin, a fluoroquinolones derivative, was greatly enhanced by addition of the kaempferol and quercetin. The antibacterial mechanism of quinolones is the bond with topoisomerase IV of *S. aureus*, which causes cell death, mainly thanks to DNA synthesis inhibition, cessation of growth, and numerous double stranded DNA breaks in the bacterial chromosome. Since kaempferol and quercetin inhibit the catalytic activity of different bacterial topoisomerases and this may indicate the synergistic activities between ciprofloxacin and kaempferol/quercetin [40].

Many studies was reported that EGCG acts synergistically with various β-lactam antibiotics against MRSA [36]. The polyphenol extract containing epicatechin gallate (ECG), EGC, EGCG, epicatechin and gallocatechin gallate from Korean green tea has antibacterial activity against 13 strains of MRSA clinical isolates and 17 strains of methicillin susceptible *S. aureus* (MSSA). The MICs of oxacillin for each of the 13 MRSA strains were decreased between 8-fold and 128-fold when these strains were treated with tea polyphenols, demonstrating that the combination of tea polyphenols and oxacillin was synergistic for all the clinical MRSA isolates [35].

Conclusion

Although antibiotics are needed for the therapy of infectious diseases caused by microorganisms, abuse and misuse of antibiotics have caused problems of antibiotic resistance. Infectious diseases caused by antibiotic resistant pathogens have a limited therapeutic option because they have no definite therapy, and can become serious diseases to humans. To develop of new antibiotics with antimicrobial activity against antibiotic resistant pathogens, it is necessary to study the development of antibiotics with new mechanism of action and antibiotics derived from natural products. Polyphenol, a secondary metabolite secreted by plants to protect themselves from plant pathogens and insects, is a natural products with potential for development as an new antibiotic because of its excellent antimicrobial activity against gram-positive and gram-negative human pathogens and its synergistic effect of combination with antibiotics.

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초록 : 폴리페놀 화합물과 항생제의 상호작용

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항산화, 항알러지, 항염증, 항암, 항고혈압, 항균 활성을 나타내는 폴리페놀 화합물은 고등식물에 의해 생산되는 2차 대사산물이다. 일반적으로 폴리페놀 화합물은 플라보노이드와 비 플라보노이드 화합물로 나뉘며 병원균에 대한 항균활성은 비 플라보노이드 화합물에 비해 플라보노이드 화합물이 우수하다. 항균활성을 나타내는 플라보노이드 화합물은 칼콘, 플라반-3-올(카테킨), 플라바논, 플라본, 플라보놀, 프로안토시아니딘 등이며 플라보놀 화합물은 그람 음성 세균(*Fusobacterium nucleatum, Porphyromonas gingivalis*, *Prevotella melaninogenica, Prevotella oralis*)과 그람 양성 세균(*Actinomyces naeslundii, Lactobacillus acidophilus*, *Staphylococcus aureus*)에 대해 항균활성을 나타낸다. 비 플라보노이드 화합물 중에서 항균활성을 나타내는 화합물은 커피산, 갈릭산, 페룰산 등이며 그람 양성 세균(*Listeria monocytogenes, S. aureus*)과 그람 음성 세균(*Escherichia coli*, *Pseudomonas aeruginosa*)에 대해 젠타마이신, 스트렙토마이신보다 우수한 항균활성을 나타낸다. 플라본 화합물인 캠퍼롤과 퀘세틴은 단독 사용보다는 리팜피신, 시플록사신과 병용하였을 때 *S. aureus*와 메티실린 내성 *S. aureus* (MRSA)에 대해 시너지 효과를 나타내었고, 에피갈로카테킨 갈레이트(EGCG)는 베타락탐계 항생제와 병용했을 때 MRSA 에 대한 대해 시너지 효과를 나타내었다. 특히 한국 녹차에서 분리된 에피카테킨, 에피갈로카테킨, 에피갈로카테킨 갈레이트, 갈로카테킨 갈레이트 등의 차 폴리페놀류는 임상에서 분리한 MRSA에 대해 항균활성을 나타내었고 옥사실린과 병용했을 때 시너지 효과를 나타내었다.