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The Susceptibility of *Staphylococcus aureus* and *Klebsiella pneumoniae* to Naturally Derived Selected Classes of Flavonoids

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1. Introduction

The emergence of multi-drug resistant organisms has increasingly become a global public health issue. Rational and appropriate uses of antibiotics as well as strict infection control measurements are recommended in order to reduce the emergence of antibiotic resistant bacteria (Tseng et al., 2011). The complexity in treating multi-drug resistant infections has led to an increase in the search for novel and effective antibiotics, especially structures originating from natural products. Promising molecules could serve as lead compounds to be developed and researched further.

This chapter aims to review the susceptibility of two of the most common micro-organisms that are often implicated in antibiotic resistant infections, namely the Gram-positive *Staphylococcus aureus* and Gram-negative *Klebsiella pneumoniae* against natural products, specifically plants. Numerous researchers have investigated the susceptibility of these bacteria to plant extracts as well as to the individual components thereof. Flavonoids as a group of compounds originating from natural products have been investigated against these bacteria.

Flavonoids are diverse polyphenolic compounds which are widely distributed in the plant kingdom. They are abundantly found in natural sources like fruits, vegetables, seeds, nuts, flowers, tea, wine honey and propolis and therefore form part of the normal diet of humans (Cook & Samman, 1996). Many reports claim the usefulness of flavonoids in medical conditions, including anti-inflammatory, oestrogenic, antimicrobial, antioxidant and chelating, vascular and antitumour activities (Cook & Samman, 1996; Cushnie & Lamb, 2005). Flavonoids consist of a C15 skeleton composed of two phenolic rings, namely the A and B rings linked through a heterocyclic ring, C. They are classified according to their biosynthetic origin into major classes including flavones, flavonols, flavanones, chalcones, flavanols, anthocyanidins, isoflavones and dihydroflavonols. Substitution patterns vary and some flavonoids occur as glycosides which are hydrolysed in the human gut to the aglycones. Flavonoids also occur as monomers, dimers or oligomers (Cook & Samman, 1996; Cushnie & Lamb, 2005).

Many reports exist on the antimicrobial activity of flavonoids (Basile et al., 2010; Du Toit et al., 2009; Tanaka et al., 2011). Extracts as well as isolated compounds were tested against a...
comprehensive panel of micro-organisms. Methods of assessing the activity include different diffusion and dilution methods. However, many flavonoids are insoluble in water and will thus have a low rate of diffusion in an aqueous medium such as agar, leading to inaccurate results. Therefore, only results based on dilution methods will be considered and discussed.

Extracts are complex mixtures of many chemical compounds in different ratios and the results of such studies are not contributing to the understanding of the activity of specific flavonoids. Studies that investigated the antibacterial activity of individual flavonoids isolated from natural products will be reviewed instead.

Various parameters have been used to express the antimicrobial activity of flavonoids. The minimum inhibitory concentration (MIC) will be considered and values up to 50 μg/ml will be reported. It must be appreciated that varying laboratory conditions and technical skills will have an influence on published results generated by different research groups and used in this review. The question also arises whether flavonoids exhibit bactericidal or bacteriostatic activity. Although some studies suggest that flavonoids are capable of bactericidal activity, the interpretation of the results remains inconclusive and it has been suggested that bacterial aggregates may be formed, thereby reducing the number of colony forming units in viable counts (Cushnie & Lamb, 2005).

2. Staphylococcus aureus

Staphylococcus aureus has long been recognised as an important pathogen in many diseases, for example the toxic shock syndrome, vasculitis and glomerulonephritis. The bacterium is commonly found in the nose and upper respiratory tract, locations that play an important role in the epidemiology and pathogenesis of infection. Therapy of infection has become problematic due to an increasing number of methicillin-resistant strains (MRSA). The difference between MRSA and methicillin-susceptible strains is that MRSA is resistant to β-lactamase stable β-lactam antibiotics. Often this is also associated with resistance to many other antibiotics, which limits the therapeutic options. The prevalence of MRSA has also increased world-wide and new therapeutic agents, optimisation of infection control measures and introduction of new medical devices with a reduced risk of infection are being investigated (Kluytmans et al., 1997).

3. Klebsiella pneumoniae

Klebsiella pneumoniae is being considered the most common causative pathogen for infections caused by antibiotic-resistant bacteria. The rate of resistance to carbapenems has increased to more than 25% in the European Union in 2009 (Tseng et al., 2011). The nasopharynx and gastrointestinal tract are commonly colonised by the bacterium and it is well known to cause community-acquired bacterial pneumonia, occurring particularly in chronic alcoholics and showing characteristic radiographic abnormalities due to severe pyogenic infection which has a high fatality rate if untreated. It is an opportunistic pathogen that would most likely attack immunocompromised patients who are hospitalised and suffer from severe underlying diseases such as diabetes mellitus and chronic pulmonary obstructive diseases. The three most common conditions caused by Klebsiella spp. are urinary tract infections, septicaemia and wound infections. Septicaemia is particularly problematic in premature infants and patients in intensive care units (Podschun & Ullmann, 1998).
4. Occurrence of flavonoids in plant sources

Several studies have identified flavonoids in natural products. Many flavonoid-containing plants are used therapeutically for the treatment of a variety of non-microbial illnesses as well as microbial infections. Flavonoids were derived from different parts of the plant and tested against S. aureus and K. pneumoniae. The vast number of identified compounds in studies were limited to cases where antibacterial activity was measured by means of dilution methods and where susceptibility was up to 50 μg/ml, providing a workable approach. At least 44 different compounds were identified according to the criteria, listed in Table 1 and their properties reviewed (Tables 2-7).

| Plant/Product          | Traditional Use                    | Part        | Compound | Reference               |
|------------------------|------------------------------------|-------------|----------|-------------------------|
| Erythrina costaricensis Micheli (Leguminosae) | Microbial infections | Stems | 1 | Tanaka et al., 2009 |
| Erythrina costaricensis Micheli (Leguminosae) | Microbial infections | Stems | 2 | Tanaka et al., 2009 |
| Erythrina poeppigiana (Leguminosae) | Microbial infections | Roots | 3 | Tanaka et al., 2004 |
| Erythrina variegata (Leguminosae) | Microbial infections | Roots | 4 | Tanaka et al., 2004 |
| Brazilian red propolis | Inflammation, heart disease, diabetes, cancer | | 5 | Oldoni et al., 2011 |
| Erythrina variegata (Leguminosae) | Microbial infections, inflammation | Roots | 6 | Tanaka et al., 2002 |
| Erythrina variegata (Leguminosae) | Microbial infections, inflammation | Roots | 7 | Tanaka et al., 2002 |
| Erythrina variegata (Leguminosae) | Microbial infections, inflammation | Roots | 8 | Tanaka et al., 2002 |
| Erythrina variegata (Leguminosae) | Microbial infections, inflammation | Roots | 9 | Tanaka et al., 2002 |
| Erythrina variegata (Leguminosae) | Microbial infections, inflammation | Roots | 10 | Tanaka et al., 2002 |
| Erythrina variegata (Leguminosae) | Microbial infections, inflammation | Roots | 11 | Tanaka et al., 2002 |
| Erythrina variegata (Leguminosae) | Microbial infections, inflammation | Roots | 12 | Tanaka et al., 2002 |
| Erythrina variegata (Leguminosae) | Microbial infections, inflammation | Roots | 13 | Tanaka et al., 2002 |
| Plant/Product | Traditional Use | Part | Compound | Reference |
|---------------|-----------------|------|----------|-----------|
| Erythrina variegata (Leguminosae) | Microbial infections, inflammation | Roots | 14 | Tanaka et al., 2002 |
| Erythrina variegata (Leguminosae) | Microbial infections | Roots | 15 | Tanaka et al., 2011 |
| Erythrina variegata (Leguminosae) | Microbial infections | Roots | 16 | Tanaka et al., 2011 |
| Cycas circinalis (Cycadaceae) | Purgative | Leaflets | 17 | Moawad et al., 2010 |
| Cycas circinalis (Cycadaceae) | Purgative | Leaflets | 18 | Moawad et al., 2010 |
| Cycas revoluta Thumb (Cycadaceae) | Rheumatic fever, expectorant, astringent, flatulence, vomiting, oestrogen-dependent cancer | Leaflets | 19 | Moawad et al., 2010 |
| Feijoa sellowiana Berg (Myrtaceae) | Perfume, microbial infections, inflammation, cancer | Fruits | 20 | Basile et al., 2010 |
| Lonchocarpus minimiflorus (Noctuidae) | Microbial infections | Bark | 21 | Salvatore et al., 1998 |
| Viscum album ssp. album (Loranthaceae) | Hypertension, epilepsy, exhaustion, anxiety, arthritis, vertigo, degenerative inflammation of the joints, cancer | Leaves and stems | 22 | Orhan et al., 2010 |
| Viscum album ssp. album (Loranthaceae) | Hypertension, epilepsy, exhaustion, anxiety, arthritis, vertigo, degenerative inflammation of the joints, cancer | Leaves and stems | 23 | Orhan et al., 2010 |
| Galium fissurense Ehrend. & Schönb.-Tem. (Rubiaceae) | Diuretic, astringent, gastrointestinal conditions, gout, epilepsy | Leaves and stems | 24 | Orhan et al., 2010 |
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| Plant/Product | Traditional Use | Part            | Compound | Reference               |
|---------------|-----------------|-----------------|----------|-------------------------|
| *Galium fissurese* Ehrend. & Schönb.-Tem. (Rubiaceae) | Diuretic, astringent, gastrointestinal conditions, gout, epilepsy | Leaves and stems | 25 | Orhan et al., 2010       |
| *Cirsium hypoleucum* DC. (Asteraceae) | Haemorrhoids, peptic ulcers, cough, bronchitis | Aerial parts | 26 | Orhan et al., 2010       |
| *Cirsium hypoleucum* DC. (Asteraceae) | Haemorrhoids, peptic ulcers, cough, bronchitis | Aerial parts | 27 | Orhan et al., 2010       |
| *Artocarpus sepicanus* (Moraceae) | Microbial infections, asthma, tuberculosis, rheumatic fever | Leaves | 28 | Radwan et al., 2009      |
| *Erythrina zeyheri* (Leguminosae) | Microbial infections, asthma, tuberculosis, rheumatic fever | Roots | 29 | Tanaka et al., 2003      |
| *Erythrina zeyheri* (Leguminosae) | Microbial infections, asthma, tuberculosis, rheumatic fever | Roots | 30 | Tanaka et al., 2003      |
| *Erythrina zeyheri* (Leguminosae) | Microbial infections, asthma, tuberculosis, rheumatic fever | Roots | 31 | Tanaka et al., 2003      |
| *Erythrina zeyheri* (Leguminosae) | Microbial infections, asthma, tuberculosis, rheumatic fever | Roots | 32 | Tanaka et al., 2003      |
| *Erythrina zeyheri* (Leguminosae) | Microbial infections, asthma, tuberculosis, rheumatic fever | Roots | 33 | Tanaka et al., 2003      |
| *Sophora exigua* Criab (Leguminosae) | Microbial infections | Roots | 34 | Tsuchiya et al., 1996    |
| *Sophora exigua* Criab (Leguminosae) | Microbial infections | Roots | 35 | Tsuchiya et al., 1996    |
| *Sophora exigua* Criab (Leguminosae) | Microbial infections | Roots | 36 | Tsuchiya et al., 1996    |
| *Sophora exigua* Criab (Leguminosae) | Microbial infections | Roots | 37 | Tsuchiya et al., 1996    |
| *Sophora exigua* Criab (Leguminosae) | Microbial infections | Roots | 38 | Tsuchiya et al., 1996    |
| *Sophora exigua* Criab (Leguminosae) | Microbial infections | Roots | 39 | Tsuchiya et al., 1996    |
5. Flavonoids and bacterial susceptibility

The flavonoids identified in different plants/products which were investigated for their antibacterial activity using dilution methods, were divided into 6 structural types and the susceptibility of *S. aureus* and *K. pneumoniae* reviewed. Some of the strains of *S. aureus* were MSRA.

Structural types were used in order to compare similar structures and to determine the influence of substituents on these structures. Susceptibility was also compared where the methods were similar to reduce the presence of too many variables.

Compounds 17-19 (Table 6), which are biflavonoids, exhibited the weakest activity against *S. aureus* in comparison with all the other structures. This may be attributed to the size and stereochemistry of the molecules. The compounds exhibiting the highest activity were compounds 16 (Table 3) and 21 (Table 2), which interestingly share the same substitution pattern at R₁ and R₂ (which were substituted with a γ,γ-dimethylallyl and hydroxyl group respectively). Comparison of compounds 3, 6 and 16 (Table 3), which were all substituted with a γ,γ-dimethylallyl group at R₅, showed that the addition of an extra γ,γ-dimethylallyl group influences activity. Addition at R₃ increases activity and addition at R₁ has an even more pronounced effect in the structural group. Comparison of compounds 30 and 31 (Table 2) showed that substitution at R₅ with a hydroxyl group leads to better activity than substitution with a methoxy group in the specific structural group.

![Chemical structure of flavonoids](image-url)
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| Compound | Structure | Susceptibility (MIC, μg/ml) |
|----------|-----------|-----------------------------|
|          |           |                            |
| 1        | R₂R₄R₅=OH |                            |
|          | R₃R₆=γ,γ'-dimethylallyl | 3.13-6.25* ND |
|          | R₇=OCH₃  |                            |
|          | R₂R₃=2",2" dimethylpyran | 12.5- >50* ND |
|          | R₄R₆=OH  |                            |
|          | R₇=OCH₃  |                            |
| 2        | R₈=γ,γ'-dimethylallyl | 3.13-12.5* ND |
|          | R₂R₅=OH  |                            |
| 5        | R₂=OCH₃ (35-enantiomer) | 31.2-62.5 ND |
| 8        | R₂R₃=2",2" dimethylpyran | 12.5-25* ND |
|          | R₅R₇=OH  |                            |
| 12       | R₃=γ,γ'-dimethylallyl | 0.78-1.56* ND |
|          | R₆=O-glcy |                            |
| 22       | R₈=O-glcy |                            |
| 23       | R₈=O-[2"-O-(5"-trans-cinnamoyl)-β-D-apiofuranosyl]-β-D-glucopyranoside | 4 16 |
| 24       | R₆=O-glcy |                            |
| 25       | R₆=O-glcy |                            |
| 28       | R₃=geranyl (2S-enantiomer) | 1.23* ND |
| 29       | R₄R₅=OH  |                            |
| 30       | R₃=γ,γ'-dimethylallyl | 12.5-25* ND |
|          | R₂R₇=OH  |                            |
| 31       | R₈=O-glcy (3R-enantiomer) | 3.13-6.25* ND |
| 32       | R₈=O-glcy |                            |

Table 2. Isoflavanones of the following structure isolated from plants and propolis (compound 5) and their activities against Staphylococcus aureus (*denotes MRSA strains) and Klebsiella pneumoniae. ND, not determined.

A study by Du Toit and co-workers reported little activity of the flavonoids luteolin, eriodictyol and quercetin against S. aureus and MIC-values could not be determined. These
flavonoids are commonly found in propolis (Du Toit et al., 2009). Combinations of flavonoids at different concentrations as well as other components present in the propolis could account for its antimicrobial activity.

Compared to *S. aureus*, it is noteworthy that significantly fewer compounds have been tested against *K. pneumoniae*. Compounds 22-25 (Table 2) and 20, 26-27 (Table 7) were the only compounds tested using dilution methods. Out of the few compounds tested, compound 20 showed the highest activity and it also has the least number of substituents. Future research should investigate the activity of more compounds against *K. pneumoniae*.

New drug targets in the bacterial structure are important. Drugs will be less susceptible to resistance if it has several modes of action. Pharmacokinetic parameters such as bioavailability and plasma protein binding are also important, since successful traditional use indicates that the drug has successfully reached a specific target.

![Chemical structure](image)

| Compound | Structure | Susceptibility (MIC, μg/ml) |
|----------|-----------|----------------------------|
| 3        | R₂,R₁=OH  | S. Aureus: 12.5*            |
|          | R₃=γ,γ-dimethylallyl | K. Pneumoniae: ND |
| 4        | R₄=OCH₃   | S. Aureus: 12.5-25           |
|          | R₅=γ,γ-dimethylallyl | K. Pneumoniae: ND |
| 6        | R₂,R₄=OH  | S. Aureus: 3.13-6.25*        |
|          | R₃,R₅=γ,γ-dimethylallyl | K. Pneumoniae: ND |
| 9        | R₄=OCH₃   | S. Aureus: 12.5-25*          |
|          | R₅=γ,γ-dimethylallyl | K. Pneumoniae: ND |
| 16       | R₁,R₅=γ,γ-dimethylallyl | S. Aureus: 1.56-3.13* |
|          | R₂,R₄=OH  | K. Pneumoniae: ND |

Table 3. Isoflavonoids of the following structure isolated from plants and their activities against *Staphylococcus aureus* (*denotes MRSA strains) and *Klebsiella pneumoniae*. ND, not determined.
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![Flavonoid Structure](image)

| Compound | Structure | Susceptibility (MIC, μg/ml) |
|----------|-----------|-----------------------------|
|          |           | **S. Aureus** | **K. Pneumoniae** |
| 7        | R₂=OH, R₃=R₄=γ,γ-dimethylallyl, R₅=OCH₃ | 12.5-25* | ND |
| 14       | R₂=R₃=R₄=OH, R₅=γ,γ-dimethylallyl | 6.25-12.5* | ND |
| 33       | R₂=OH, R₃=R₄=γ,γ-dimethylallyl, R₅=OCH₃ (6aS, 11aS-enantiomer) | 6.25-25* | ND |

Table 4. Isoflavonoids of the following structure isolated from plants and their activities against *Staphylococcus aureus* (*denotes MRSA strains) and *Klebsiella pneumoniae*. ND, not determined.

![Flavonoid Structure](image)

| Compound | Structure | Susceptibility (MIC, μg/ml) |
|----------|-----------|-----------------------------|
|          |           | **S. Aureus** | **K. Pneumoniae** |
| 10       | R₁=OCH₃, R₂=R₃=γ,γ-dimethylallyl, R₄=OH RR, R₅=2″,2″-dimethylpyran | 3.13-6.25* | ND |
| 11       | R₂=R₃=OH, R₄=γ,γ-dimethylallyl | 6.25-25* | ND |
| 13       | R₃,R₄=2″,2″-dimethylpyran | 25* | ND |

Table 5. Isoflavonoids of the following structure isolated from plants and their activities against *Staphylococcus aureus* (*denotes MRSA strains) and *Klebsiella pneumoniae*. ND, not determined.
Table 6. Biflavonoids of the following structure isolated from plants and their activities against *Staphylococcus aureus* (*denotes MRSA strains*) and *Klebsiella pneumoniae*. ND, not determined.

| Compound | Structure | Susceptibility (MIC, μg/ml) |
|----------|-----------|-----------------------------|
|          |           | *S. Aureus* | *K. Pneumoniae* |
| 17       | R₁,R₂=OCH₃ (2S, 2"S-enantiomer) | 17.5* | ND |
| 18       | R₁=OCH₃ | 35.9* | ND |
| 19       | R₁,R₂=OH (2S, 2"S-enantiomer) | 37* | ND |

| Compound | Structure | Susceptibility (MIC, μg/ml) |
|----------|-----------|-----------------------------|
|          |           | *S. Aureus* | *K. Pneumoniae* |
| 20       | R₃=OH | 7.8 | 7.8 |
| 26       | R₂,R₄,R₆,R₇=OH | 4 | 16 |
| 27       | R₉=O-glcp-rha | 4 | 16 |
| 34       | R₁=lavandulyl | 3.13-6.25* | ND |
| 35       | R₁=lavandulyl, R₂,R₄,R₇,R₈=OH | 3.13-6.25* | ND |
| 36       | R₁=prenyl | 6.25* | ND |
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### Table 7. Flavones of the following structure isolated from plants and their activities against *Staphylococcus aureus* (*denotes MRSA strains*) and *Klebsiella pneumoniae*. ND, not determined.

| Compound | Structure | Susceptibility (MIC, μg/ml) |
|----------|-----------|-----------------------------|
|          |           | *S. Aureus* | *K. Pneumoniae* |
| 37       | R₂,R₄,R₅,R₈=OH R₁=lavandulyl R₇=OCH₃ | 12.5* | ND |
| 38       | R₂,R₄,R₅,R₈=OH R₃=geranyl | 12.5* | ND |
| 39       | R₂,R₄,R₅,R₇,R₈=OH R₁=geranyl | >25* | ND |
| 40       | R₂,R₄,R₇,R₈=OH R₆=geranyl | 3.13-12.5* | ND |
| 41       | R₂,R₄,R₅,R₇,R₈=OH R₃=lavandulyl | 3.13-12.5* | ND |
| 42       | R₂,R₄,R₅,R₇,R₈=OH R₁=lavandulyl | 6.25-12.5* | ND |
| 43       | R₂,R₄,R₅,R₇,R₈=OH R₁=prenyl | 6.25-12.5* | ND |
| 44       | R₂,R₄,R₈=OH R₁=lavandulyl | 12.5* | ND |

### 6. Conclusion

The traditional use of medicinal plants is useful as a guideline in the quest for new drugs. Furthermore plants are a source of novel lead compounds which would generally not have been synthesised. Extraction of these biologically active lead compounds may be expensive and slow and the activity of lead compounds may also not be sufficient to encourage commercialisation. These compounds may also have undesirable side effects, it is therefore important to periodically review the results of research conducted, ruling out unnecessary variation of parameters, to determine the most promising structures. The process of drug design and development could then be accelerated.

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