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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

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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 poeppigiana (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, gastro-intestinal conditions, gout, epilepsy	Leaves and stems	24	Orhan et al., 2010

Plant/Product	Traditional Use	Part	Compound	Reference
Galium fissurense Ehrend. & Schönb.-Tem. (Rubiaceae)	Diuretic, astringent, gastro-intestinal 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

Plant/Product	Traditional Use	Part	Compound	Reference
Echinosophora koreensis Nakai (Leguminosae)	Microbial infections	Roots	40	Tsuchiya et al., 1996
Echinosophora koreensis Nakai (Leguminosae)	Microbial infections	Roots	41	Tsuchiya et al., 1996
Echinosophora koreensis Nakai (Leguminosae)	Microbial infections	Roots	42	Tsuchiya et al., 1996
Echinosophora koreensis Nakai (Leguminosae)	Microbial infections	Roots	43	Tsuchiya et al., 1996
Sophora leachiana Peck (Leguminosae)	Microbial infections	Roots	44	Tsuchiya et al., 1996

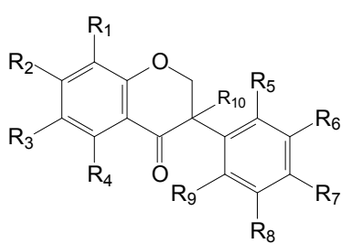
Table 1. Compounds isolated from different parts of plants/products that occur world-wide and their traditional use. Only compounds tested against *Staphylococcus aureus* and *Klebsiella pneumoniae* by means of dilution methods where the MIC-values were up to 50 µg/ml are reported (refer to Tables 2-7 where the classification, chemistry and biological activity of each compound are explained in more detail).

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 R_1 and R_2 (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 R_5, showed that the addition of an extra γ,γ-dimethylallyl group influences activity. Addition at R_3 increases activity and addition at R_1 has an even more pronounced effect in the structural group. Comparison of compounds 30 and 31 (Table 2) showed that substitution at R_5 with a hydroxyl group leads to better activity than substitution with a methoxy group in the specific structural group.



Compound	Structure	Susceptibility (MIC, µg/ml)	
		S. Aureus	*K. Pneumoniae*
1	R_2,R_4,R_6=OH R_3,R_8=γ,γ-dimethylallyl R_7=OCH_3	3.13-6.25*	ND
2	R_2,R_3=2″,2″ dimethylpyran R_4,R_6=OH R_7=OCH_3 R_8=γ,γ-dimethylallyl	12.5- >50*	ND
5	R_2,R_5=OH R_7=OCH_3 (3*S*-enantiomer)	31.2-62.5	ND
8	R_2,R_3=2″,2″ dimethylpyran R_5,R_7=OH (3*R*-enantiomer)	12.5-25*	ND
12	R_1,R_2=2″,2″ dimethylpyran R_3=γ,γ-dimethylallyl R_7,R_9=OH	3.13-12.5*	ND
15	R_1=γ,γ-dimethylallyl R_2,R_3=2″,2″ dimethylpyran R_7,R_9,R_{10}=OH	12.5-25*	ND
21	R_1,R_3=γ,γ-dimethylallyl R_2,R_4,R_6=OH (2*S*-enantiomer)	0.78-1.56*	ND
22	R_2,R_4=OCH_3 R_6=*O*-glc	4	16
23	R_2,R_4=OCH_3 R_6=*O*-[2″-*O*-(5‴-*O*-*trans*-cinnamoyl)-β-*D*-apiofuranosyl]-β-*D*-glucopyranoside	4	16
24	R_2,R_4,R_5=OH R_6=*O*-glc	4	16
25	R_4,R_6=OH R_2=*O*-glc	4	16
28	R_2,R_4,R_6=OH R_3=geranyl (2*S*-enantiomer)	1.23*	ND
29	R_1,R_8=γ,γ-dimethylallyl R_2,R_7,R_9=OH	12.5-25*	ND
30	R_1,R_3=γ,γ-dimethylallyl R_2,R_7=OH R_5=OCH_3 (3*R*-enantiomer)	25- >50	ND
31	R_1,R_3=γ,γ-dimethylallyl R_2,R_5,R_7=OH (3*R*-enantiomer)	3.13-6.25*	ND
32	R_1=γ,γ-dimethylallyl R_2,R_3=2″,2″-dimethylpyran R_5,R_7=OH	6.25-12.5*	ND

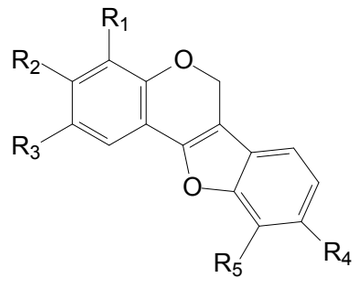
Table 2. Isoflavanones of the following structure isolated from plants and propolis (compound 5) and their activities against *Staphylococcus aureus* (*denotes MRSA strains) and *Klebsiella pneumoniae*. ND, not determined.

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.

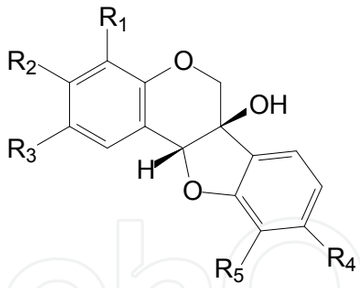
Compared to *S. aureus*, it is noteworthy that significantly fewer compounds have been tested against *K. pneumoniae*. Compounds 22-25 (Table 2) and 20, 26-27 (Table 7) were the only compounds tested using dilution methods. Out of the few compounds tested, compound 20 showed the highest activity and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



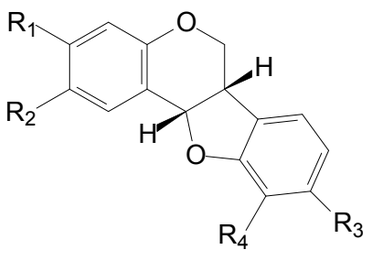
Compound	Structure	Susceptibility (MIC, μg/ml)	
		S. Aureus	*K. Pneumoniae*
3	R_2,R_4=OH R_5=γ,γ-dimethylallyl	12.5*	ND
4	R_2=OH R_4=OCH_3 R_5=γ,γ-dimethylallyl	12.5-25	ND
6	R_2,R_4=OH R_3,R_5=γ,γ-dimethylallyl	3.13-6.25*	ND
9	R_2=OH R_4=OCH_3 R_5=γ,γ-dimethylallyl	12.5-25*	ND
16	R_1,R_5=γ,γ-dimethylallyl R_2,R_4=OH	1.56-3.13*	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.



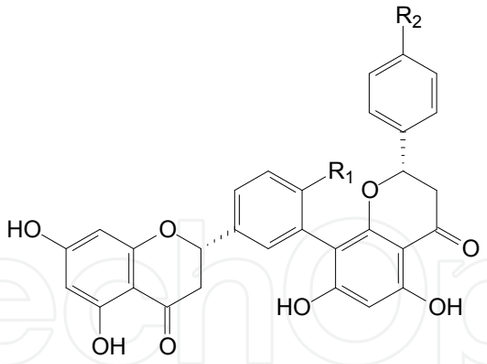
Compound	Structure	Susceptibility (MIC, μg/ml)	
		S. Aureus	*K. Pneumoniae*
7	R_2=OH R_3,R_5=γ,γ-dimethylallyl R_4=OCH_3	12.5-25*	ND
14	R_2,R_4=OH R_3,R_5=γ,γ-dimethylallyl	6.25-12.5*	ND
33	R_1,R_5=γ,γ-dimethylallyl R_2=OH R_4=OCH_3 (6a*S*, 11a*S*-enantiomer)	6.25-25*	ND

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.



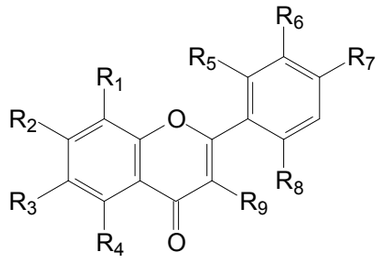
Compound	Structure	Susceptibility (MIC, μg/ml)	
		S. Aureus	*K. Pneumoniae*
10	R_1=OCH_3 R_2=γ,γ-dimethylallyl R_3=OH RR	3.13-6.25*	ND
11	R_1,R_2=2″,2″-dimethylpyran R_3=OH R_4=γ,γ-dimethylallyl	6.25-25*	ND
13	R_1=OH R_3,R_4=2″,2″-dimethylpyran	25*	ND

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.



Compound	Structure	Susceptibility (MIC, µg/ml)	
		S. Aureus	*K. Pneumoniae*
17	R_1,R_2=OCH_3 (2*S*, 2''*S*-enantiomer)	17.5*	ND
18	R_1=OCH_3 R_2=OH (2*S*, 2''*S*-enantiomer)	35.9*	ND
19	R_1,R_2=OH (2*S*-enantiomer)	37*	ND

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*
20	R_5=OH	7.8	7.8
26	R_2,R_4,R_6,R_7=OH R_9=*O*-glc-rha	4	16
27	R_2,R_4,R_7=OH R_9=*O*-glc-rha	4	16
34	R_1=lavandulyl R_2,R_4,R_7,R_8=OH	3.13-6.25*	ND
35	R_1=lavandulyl R_2,R_4,R_5,R_8=OH R_3=prenyl	3.13-6.25*	ND
36	R_7=OCH_3 R_1=prenyl	6.25*	ND

Compound	Structure	Susceptibility (MIC, μg/ml)	
		S. Aureus	*K. Pneumoniae*
37	R_2,R_4,R_5,R_8=OH R_7=OCH_3 R_1=lavandulyl	12.5*	ND
38	R_2,R_4,R_5,R_8=OH R_2,R_4,R_5,R_7,R_8=OH R_3=geranyl	12.5*	ND
39	R_1=geranyl R_2,R_4,R_5,R_7,R_8=OH	>25*	ND
40	R_2,R_4,R_7,R_8= OH R_6=geranyl	3.13-12.5*	ND
41	R_2,R_4,R_5,R_7,R_8=OH R_3=lavandulyl	3.13-12.5*	ND
42	R_1=lavandulyl R_2,R_4,R_5,R_7,R_8=OH	6.25-12.5*	ND
43	R_2,R_4,R_7,R_8=OH R_1=prenyl	6.25-12.5*	ND
44	R_1=lavandulyl R_2,R_4,R_8=OH	12.5*	ND

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.

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.

7. Acknowledgment

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