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Flavonoids: A safe alternative to antibiotics for livestock

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Abstract
Antimicrobial resistance (AMR) has been a growing threat to the effective treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. Extended spectrum cephalosporins (third generation cephalosporins such as ceftriaxone and cefotaxime) gained widespread clinical use in the early 1980s and were developed due to the increasing prevalence of ampicillin-hydrolysing β-lactamases (TEM-1, TEM-2 and SHV-1) in Enterobacteriaceae, non-glucose fermenting Gram negative bacilli. Among 109 new antibacterial drugs, permitted with in the year 1981–2006, 69% originated from natural products, and 21% of antifungal drugs were natural derivatives or compounds mimicking natural products. Biological activity of flavonoids was first reported in citrus peel and were found to be effective in preventing the capillary bleeding and fragility associated with scurvy. The flavonoids hydroxylating the prenyl groups of stipulin, the compounds obtained, angusticornin B and bartericin A, had a superior antimicrobial activity. Because of the low-toxic nature of flavonoids, the combination of antibiotics and flavonoids is a potential new strategy for developing therapies for infections caused by ESBL-producing bacteria in the future.

Keywords: Flavonoids, alternative, antibiotics, livestock

Introduction
Antimicrobial resistance (AMR) has been a growing threat to the effective treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. Major crises responsible are; increasing frequency of AMR phenotypes among microbes an evolutionary response to the widespread use of antimicrobials; The large and globally connected human/ animal population allows pathogens in any environment access to all of humanity; The extensive and often unnecessary use of antimicrobials by humanity provides the strong selective pressure that is driving the evolutionary response in the microbial world. Non-therapeutic antimicrobial uses are also associated to the promulgation of multidrug resistance (MDR), including resistance against drugs that were in no way used on the farm (Marshall and Levy, 2011) [11].

Extended spectrum cephalosporins (third generation cephalosporins such as ceftriaxone and cefotaxime) gained widespread clinical use in the early 1980s and were developed due to the increasing prevalence of ampicillin-hydrolysing β-lactamases (TEM-1, TEM-2 and SHV-1) in Enterobacteriaceae, non-glucose fermenting Gram negative bacilli, and some respiratory pathogens such as *Haemophilus influenzae* and *Moraxella catarrhalis*. In 1983, a β-lactamase capable of hydrolysing extended-spectrum cephalosporins was acknowledged, on the basis of genetic and functional characteristics in strains of *Klebsiella pneumoniae* from Germany (Arlet and Philippon. 1991) [2]. Because of their spectrum of activity against oxyimino cephalosporins, these enzymes became known as extended spectrum β-lactamases (ESBLs). ESBLs, which have been isolated from a wide variety of Enterobacteriaceae, as well as *Pseudomonas aeruginosa* and Capnocytophaga ochracea, (Barroso *et al*., 2000) [3] strictly defined as β-lactamases capable of hydrolysing penicillins, broad- and extended-spectrum cephalosporins, and monobactams, and are inhibited by clavulanic acid (functional group as given by Bush-Jacoby-Medeiros (1995) [5].

The global problem of striking development of bacterial resistance to synthetic antibiotics has led researchers to believe the use of other natural products with antibiotic actions e.g. medicinal plants. It could be effectual alternative basis for much therapeutics, particularly after the recent dramatic failures of antibiotics against multi-drug resistant microorganisms. In some Asian and African countries, 80% of the population depends on conventional medicine for primary healthcare and more than 100 countries have policy for herbal medicines

(Giday *et al*., 2009) [9].
Among 109 new antibacterial drugs, permitted with in the year 1981–2006, 69% originated from natural products, and 21% of antifungal drugs were natural derivatives or compounds mimicking natural products (Yusuf *et al*., 2001) [21]. Even following the antibiotic era and until currently, many effective drugs listed globally were from plant origin like Atropine, Ephedrine, Digoxin, Morphine, Quinine, Reserpine and Tubocurarine (Gilani and Rahman, 2005) [10]. The phytochemicals with antimicrobial properties have a wide activity range, according to the species, the topography and climate of the country of origin, with different active principles (Ruddock 2000; Byarugaba, 2004) [15, 6]. Variations in the chemical composition modify their antimicrobial activity. Plants contain several secondary metabolites such as tannins, terpenoids, alkaloids, and flavonoids, which have been found *in vitro* with antimicrobial properties.
Biological activity of flavonoids was first recommended by Szent-Gÿorgyi (1938), who reported that citrus peel flavonoids were effective in preventing the capillary bleeding and fragility associated with scurvy. The broad spectrum of biological activity within the group and the multiplicity of actions displayed by a certain individual members make the flavonoids one of the most promising classes of biologically active compounds (Tereschuk *et al*., 2004) [19].

Occurrence
Flavonoids in the past known as bioflavonoids/Flavonols (quercetin, myricetin, and kaempferol) and flavones (apigenin and luteolin) included in aromatic compounds, are phenolic structures ubiquitous in photosynthesizing cells and are commonly found in fruit, vegetables, nuts, seeds, stems, flowers, tea, wine, propolis and honey. Quercetin is also a predominant component of onions, apples, and berries. Such flavanones as naringin are typically present in citrus fruit, and flavanols, particularly catechin, are present as catechin gallate in such beverages as green or black tea and wine. The activity of quercetin has been at least partially attributed to the inhibition of DNA gyrase, whereas sophoraflavone G and (-)-epigallocatechin gallate inhibit cytoplasmic membrane function, and licochalcones A and C inhibit energy metabolism (Tegegn *et al*., 2019) [18].

Structure and Properties
The fundamental structural attribute of flavonoid compounds is the 2-phenylbenzopyrane or flavane nucleus, consisting of two benzene rings associated all the way through a heterocyclic pyrane ring. In total, there are 14 classes of flavonoids, differentiated on the basis of the chemical nature and position of substituents on the different rings. The antibacterial properties of flavonoids are thought to come from the capability to form complexes with both extracellular and soluble proteins, as well as with bacterial membranes (Barton 2000; Andersson 2005) [4, 1]. The flavonoids hydroxylating the prenyl groups of stipulin, the compounds obtained, angusticornin B and bartericin A, had a superior antimicrobial activity (Ndhlala *et al*., 2009) [13].
Recently two flavonoids (6-hydroxy-7-methoxyluteolin and the xanthone 8-carboxymethyl-1, 5, 6-trihydroxy 3-methoxyxanthone) extracted from the leaves of Leiothrix spiralis, a South American plant belonging to the Eriocaulaceae family, showed a promising activity on Escherichia coli and Pseudomonas aeruginosa. Some flavonoids also revealed activity against M. tuberculosis (Marjorie, 1999) [12].

Antimicrobial effect
The *in vitro* activities of 18 antibiotics and 12 flavonoids against 20 ESBL-producing *K. pneumoniae* isolates were evaluated. All of these isolates were susceptible to imipenem and cefmetazole, but were resistant to ampicillin, ampicillin/sulbactam, aztreonam, cefazolin, cefoperazone, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, piperacillin and ticarcillin. Susceptibilities to amikacin, amoxicillin/clavulanate, cefoxitin, ciprofloxacin and gentamicin were variable (Carolyn *et al*., 2014) Myricetin, a flavonol, inhibited ESBL-producing *K. pneumoniae* isolates at a high minimum inhibitory concentration (MIC) (MIC (90) value 256 mg/mL), but exhibited significant synergic activity against ESBL-producing *K. pneumoniae* in separate combination with amoxicillin/clavulanate, ampicillin/sulbactam and cefoxitin. Because of the low-toxic nature of flavonoids, the combination of antibiotics and flavonoids is a potential new strategy for developing therapies for infections caused by ESBL-producing bacteria in the future. (Rong-Dih *et al*., 2005) [14].
In a study the potent *in vitro* antibacterial activity of ClCl-flav—a novel synthetic tricyclic flavonoid were tested using the minimum inhibitory concentration (MIC), time kill and biofilm formation assays, fluorescence microscopy and scanning electron microscopy to study the mechanism of action. The compound showed significantly enhanced antibacterial activities, 32 to 72-fold more active than other synthetic flavonoids. At twice the MIC, all Escherichia coli and *Klebsiella pneumoniae* cells were killed within 1 h. Also ClCl-flav presented good anti-biofilm activity. The mechanism of action is related to the impairment of the cell membrane integrity. No or very low cytotoxicity was evidenced at effective concentrations against Vero cells. Based on the strong antibacterial activity and cytotoxicity assessment, ClCl-flav has a good potential for the design of new antimicrobial agents. (Cornelia *et al*., 2018) [8].
The crude extracts (dichloromethanic and ethanolic) and some compounds (8 flavonoids and 5 steroids) isolated from Chromolaena squalida (leaves and stems) and Chromolaena hirsuta (leaves and flowers) have been evaluated against 22 strains of microorganisms including bacteria (Gram-positive and Gram-negative) and yeasts. All crude extracts, flavonoids and steroids evaluated showed actives, mainly against Gram-positive bacteria (Silvia *et al*., 2003) [17].

Mechanism of action
The activity of quercetin, has been at least partially attributed to inhibition of DNA gyrase. It has also been proposed that sophoraflavone G and (-)-epigallocatechin gallate inhibit cytoplasmic membrane function, and that licochalcones A and C inhibit energy metabolism. Other flavonoids whose mechanisms of action have been investigated include robinetin, myricetin, apigenin, rutin, galangin, 2,4,2'-trihydroxy-5'-methylchalcone and lonchocarpol A. These compounds represent novel leads, and future studies may allow the development of a pharmacologically acceptable antimicrobial agent or class of agents. Enzymatic digestion and high-resolution MS analysis of differentially expressed proteins from *S. aureus* with and without exposure to antibiotic flavonoids allowed for the characterization of global protein alterations induced by metabolite treatment. A total of 56, 92, and 110 proteins were differentially expressed

with bacterial exposure to 1, 2, or 3, respectively. The connectivity of the identified proteins was characterized using a search tool for the retrieval of interacting genes/proteins (STRING) with multitargeted S. aureus inhibition of energy metabolism and biosynthesis by the assayed flavonoids. (Wael *et al*., 2017) [20].

Conclusion

The battle against these microorganisms is never ending, but we can beat them by changing our strategy and returning back to nature, using phytocheminals that survived against microbes since millions of years. Plants remain a inimitable and less exploited source of bioactive compounds, and ethno botanical research tools can be used to guide future research pains and slim down the search to the most likely source candidates. In addition to tests for classic bacteriostatic and bactericidal activity, it is also essential to examine complex plant extracts and individual compounds for activity against alternative bacterial targets, such as virulence and pathogenesis, as well as host-directed targets. Future optimization of these compounds through structural modification may consent to the expansion of a pharmacologically adequate antimicrobial agent or group of agents.

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