

**Counteracting Resistance with Research on
Natural Antibiotic Sources**

Dahl Clark

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Ever since the development of penicillin as an antibiotic in 1940, scientists have been fighting an ongoing battle against a serious medical problem. Penicillin was the first of many classes of antibiotics, drugs that can specifically kill bacteria (Brown, 1996). Because penicillin and other early antibiotics were able to cure bacterial infections that previously carried a high mortality rate, their use soon became widespread. However, along with increased use of antibiotics came the increased appearance of bacteria resistant to those antibiotics, and this is what constitutes today's problem of antibiotic resistance. One approach that scientists have taken against this problem is to research the discovery of new antibiotics, using data on bacteria and antibiotic mechanisms to determine whether certain compounds found in plant and animal species have any potential as future antibiotics. There has never been a more necessary time for this research than now, since never before has the need for new antibiotics been greater.

Antibiotic resistance is a natural, inevitable byproduct of evolution, a biological process that has largely shaped the development of Earth's life (Campbell, 1999). In recent times, a "huge environmental antibiotic pressure," resulting from the mass production, marketing, and use of antibiotics, has simultaneously contributed to the increase in resistance to these antibiotics through the evolutionary process of natural selection (Baquero, 1997). Since natural selection will always be present whenever the selective pressure of antibiotic use is present, there can be no stop to antibiotic resistance. Therefore, we will constantly need to develop new antibiotics to replace ones that bacteria have grown resistant to.

The need for new antibiotic therapies has never been greater. As described by Seppala (1992), antibiotic resistance has been steadily increasing because of the increased consumption of antibiotics over the last several decades. An example to illuminate this point is the use of erythromycin, a widely-known, widely-used antibiotic. Erythromycin is widely used because it

has been very safe and effective, and because it not only treats *Streptococcus* infections (as in “strep throat”), but also those of the widespread *Mycoplasma pneumonia* and *Chlamydia pneumonia* pathogens, all of which infect the respiratory tract. However, the widespread use of this “safe” drug has not been very effective at keeping erythromycin resistance low.

Seppala points out a troubling correlation between erythromycin resistance and high erythromycin use. Erythromycin use in Finland nearly tripled from 1979 to 1989, and in 1988, an unusually high frequency of resistance to erythromycin in group A streptococci was observed in one geographic region. In late 1990, the frequency of erythromycin resistance increased between 7 and 31 percent in multiple *Streptococcus* tests (Seppala, 1992). We see that in the two years between 1988 and 1990 alone, erythromycin resistance has increased dramatically, reducing the effectiveness of this antibiotic. Antibiotic resistance is not only a problem for erythromycin, but for an entire batch of popular antibiotics such as penicillin, ampicillin, cephalosporin, and vancomycin. For this reason, the discovery of new antibiotics becomes urgently necessary.

Very comforting is the fact that it will not be difficult to discover new antibiotics; such compounds can be readily found in nature. Primarily for defensive protection against bacteria and predators, organisms have evolved a host of antimicrobial compounds, some of which exert their effects only on bacteria. These antimicrobials have the greatest potential to become new antibiotics. After reading multiple articles on this subject, two broad categories were determined from which future antibiotics might be found—animal sources and plant sources. The following sections will deal largely with examples of substances that have shown promise as future antibiotics.

Aceret (1998) gives an example of animal-derived antimicrobials that show promise of being used as antibiotics. The soft coral *Sinularia flexibilis* is rarely overgrown by bacteria or algae, and studies of this curious property have led to the identification of chemical compounds called *diterpenes*. Diterpenes help protect the coral from competitors and predators because of their antimicrobial properties. Two of the five diterpenes tested inhibited the growth of gram-positive bacteria, hinting that this set of compounds may be an important source of new antibiotics. However, of the many diterpenes isolated from *Sinularia*, only one has been studied for antibiotic purposes (Aceret, 1998). Nothing is known yet about whether the other compounds could become future antibiotics, since unfortunately, no research has been done to test those compounds.

While some antimicrobial compounds are made by animals, a much larger warehouse of potential antibiotics is the plant kingdom. This diversity of antimicrobials exists, primarily because of the role these compounds play in the defense of the plant from bacteria and predators (Garcia-Olmedo, 1998). Plants have been shown to contain eight distinct families of antimicrobial peptides, or subunits of proteins, which include the *thionins*, *defensins*, *lipid transfer proteins*, *hevein*- and *knottin*-like peptides, *MBPI*, *IbAMP*, and the recently discovered *snakins* (Garcia-Olmedo, 1998). Some of these compounds may one day find use as antibiotics. Arora and Kaur (1999) describe how spices like garlic and clove have been shown to possess antimicrobial activity; after 2 hours of incubation, a population of *Staphylococcus epidermis* and *Salmonella typhi* were reduced by 93%. Elsom and Hide (1999) point out that the antimicrobial properties of essential plant oils have been recognized for centuries; tea tree oil, obtained from *Melaleuca alternifolia*, is an example of one of these essential oils. Because of their antimicrobial properties, essential oils like the tea tree oil may also find use as antibiotics

someday. These are just a few examples of the many available antimicrobials in the plant kingdom; even more may exist that have yet to be discovered.

There are two main reasons for our timely investigation of potential antibiotic sources. The first reason is that many antimicrobials, such as the ones listed above, have been largely or completely neglected by research (Mahasneh, 1999). Numerous kinds of antimicrobials have been isolated from various plants in the Mediterranean region, but the inhibiting activity of these compounds has been “poorly investigated;” not only this, but no literature at all could be found concerning the antimicrobial activity of some Jordanian folk medicinal plants (Mahasneh, 1999). What we see here is an awareness of the antimicrobial properties of certain plant species, but little or no investigation has occurred to determine the effectiveness of these antimicrobials as antibiotics. The sole result of this neglect is the loss of potential antibiotics; this is why we should investigate these potential sources in a timelier manner.

The second reason why we should not wait to investigate antimicrobial sources proves to be more urgent than the first. With the rapidly increasing loss of biodiversity on the planet, many plant and animal species are permanently becoming lost (Campbell, 1999). Biodiversity loss is important to us because when species become extinct, all of their unique antimicrobial compounds become extinct, and the possibility of discovering any new antibiotics from those species also becomes extinct. It is reasonable to predict that many unknown, but endangered, species of plants might contain useful drugs as well as potential antibiotics, especially since 25% of all prescription drugs in the United States contain substances derived from plants (Campbell, 1999). If we wait to investigate potential sources of antibiotics, many other sources of antibiotics may become permanently lost as we wait. While we cannot hope to discover *all* the

potential antibiotics before species become extinct, we can still try to discover as many as we can.

In ending, the most important point to remember is that we need new antibiotics if we hope to continue our ongoing fight against antibiotic resistance. The resistance problem will not go away by simply studying how resistance increase relates to antibiotic consumption. Only the discovery of new antibiotics can attack the core of the resistance problem by providing an active defense and offense against potentially lethal resistant infections. We can defend ourselves against this threat by developing new antibiotics, and we can launch an offensive against resistance by making the decision to fund more antibiotic research. Our knowledge of antibiotics must continue to evolve with the appearance of resistant bacteria if we hope to maintain our competitive edge as a healthier, happier human species.

References

- Aceret, T. L., Col, J. C., Uchio, Y., and Sammarco, P.W. 1998. Antimicrobial activity of the diterpenes flexibilide and sinulariolide derived from *Sinularia flexibilis*. Quoy and Gaimard 1833 (Coelenterata: Alcyonacea, Octocorallia). *Comparative Biochemistry and Physiology, Part C*. 120:121-126.
- Arora, D. S. and Kaur, J. 1999. Antimicrobial activity of spices. *International Journal of Antimicrobial Agents*. 12:257-262.
- Brown, J. C. March 1996. Jack's "Bugs in the News"— What the Heck is Penicillin? <http://falcon.cc.ukans.edu/~jbrown/penicillin.html>
- Campbell, N. A., Reece, J. B., Mitchell, L. G. 1999. *Biology*, 5th ed. pp.1154-1158. Addison Wesley Longman, New York.
- Elsom, G. K. F. and Hide, D. 1999. Susceptibility of methicillin-resistant *Staphylococcus aureus* to tea tree oil and mupirocin. *Journal of Antimicrobial Chemotherapy*. 43:427-428.
- Garcia-Olmedo, F., Molina, A., Alamillo, J. M., and Rodriguez-Palenzuela, P. 1998. Plant defense peptides. *Biopolymers (Peptide Science)*. 47:479-491.
- Mahasneh, A. M. and El-Oqlah, A. A. 1999. Antimicrobial activity of extracts of herbal plants used in the traditional medicine of Jordan. *Journal of Ethnopharmacology*. 64:271-276.