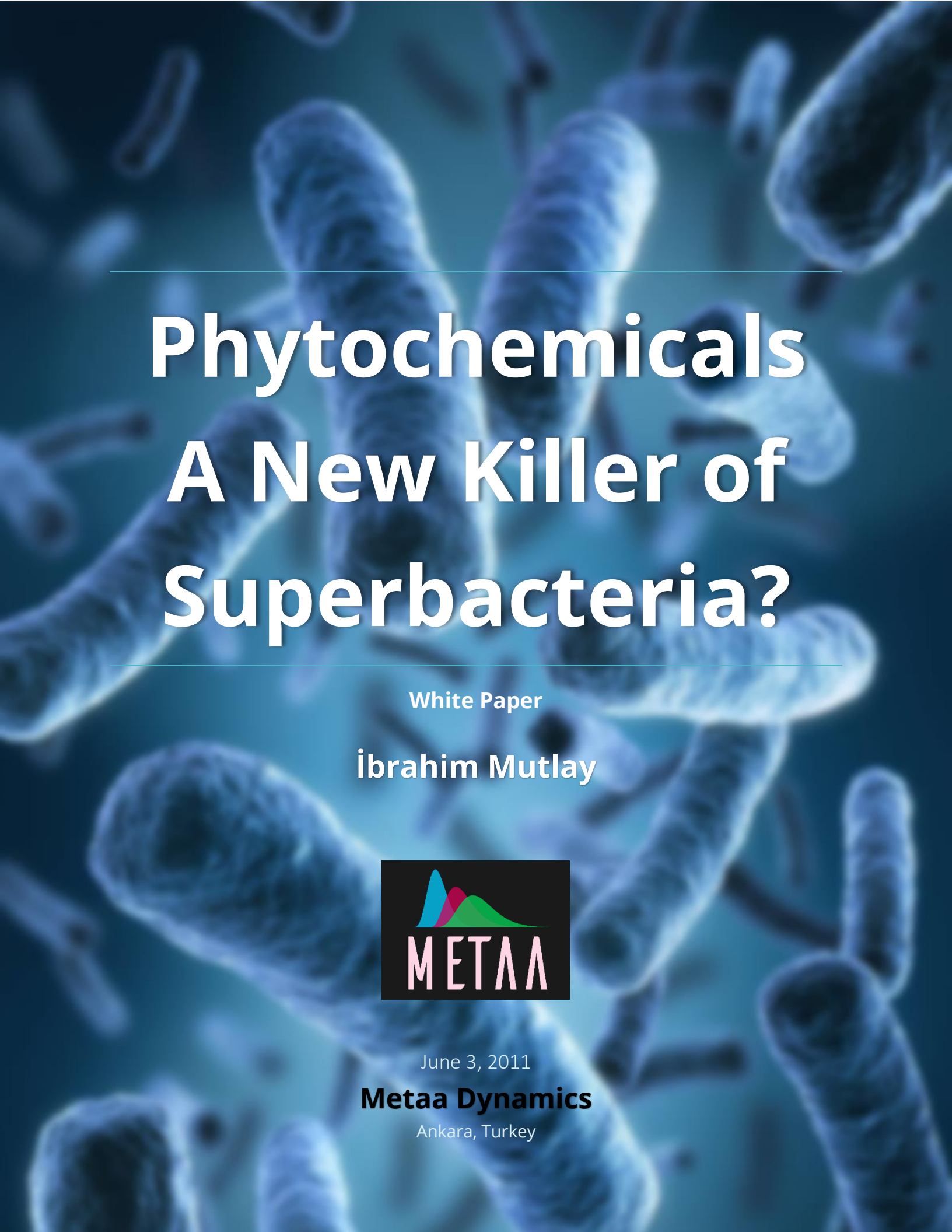

# Phytochemicals A New Killer of Superbacteria?

White Paper

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**Metaa Dynamics**

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# Phytochemicals: A New Killer of Superbacteria?

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Metaa Dynamics

Phytochemicals, biochemical compounds secreted by plants, could be a new weapon-of-choice against the resistant bacteria.



The introduction of antibiotics, beginning with the discovery of penicillin, is one of the most significant developments of the 20th century. Antibiotics had a profound impact on human life expectancy and quality around the world. Saving millions of lives, the worldwide antibiotics market is achieving nearly 40 billion USD [1-3]. But this success is also becoming its own victim. As the usage of antibiotics increases a devastating risk arises: the resistant bacteria. Now plant extracts provide affordable antimicrobials, exciting tools especially for developing countries.

## History

The first general-purpose antibiotic used in modern medicine was prontosil discovered by Gerhard Domagk in 1932, developed by the Bayer Laboratories, and launched in 1935 by the same company. Prontosil is a synthetic diazo dye containing sulfonamide functionality and the first member of a large class of antibacterial agents known as sulfonamides or sulfa drugs. In accordance with the limited use of sulfonamides, there has been only one additional synthetic antibiotic in four decades. This is the oxazolidinone linezolid approved by the US Food and Drug Administration (FDA) in 2000 [1].

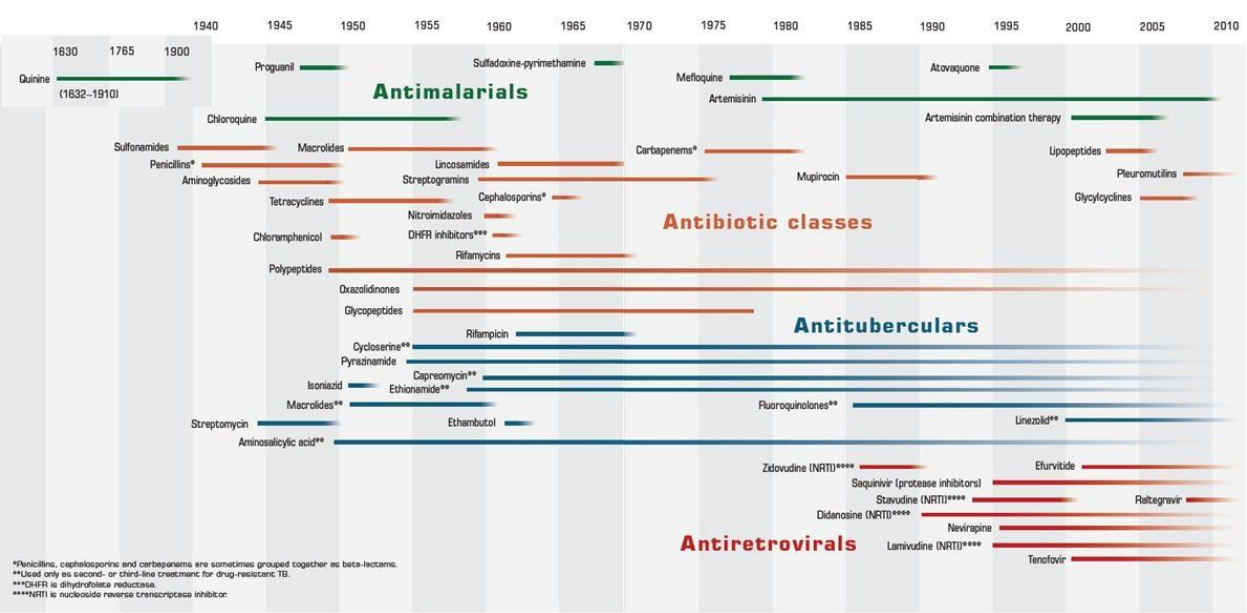


**Figure 1.** History of antibiotics and emergence of the resistance against them [4].

Synthetic antibacterial molecules actually represent only a small fraction of the antibiotics in use today and the most come from natural product-based compounds [1]. The history of naturally occurring antibiotics in modern medicine started in 1928 with the discovery by Alexander Fleming that Penicillium chrysogenum inhibited bacterial growth around it. During the 50s and 60s, several new classes of antibacterial agents were developed from naturally occurring antibiotics and found the clinic use. Among them are the tetracyclines, the phenylpropanoids, the

macrolides, and the glycopeptides [1]. However, after this explosive growth period, the development of new antibacterial agents was rapidly slowed down [1, 2]. Since the early 1960s, only four new classes of antibiotics have been introduced, and none of these has made a major impact yet; antibiotics market is still dominated by antibiotic classes discovered half a century ago. Since then, most new antibiotics have been chemically tailored derivatives of these well-known scaffolds (See Fig. 2) [2]. The approval of the lipopeptide daptomycin in 2003 marked the launch of the first natural product-based antibiotic from a new structure class in 41 years [1].

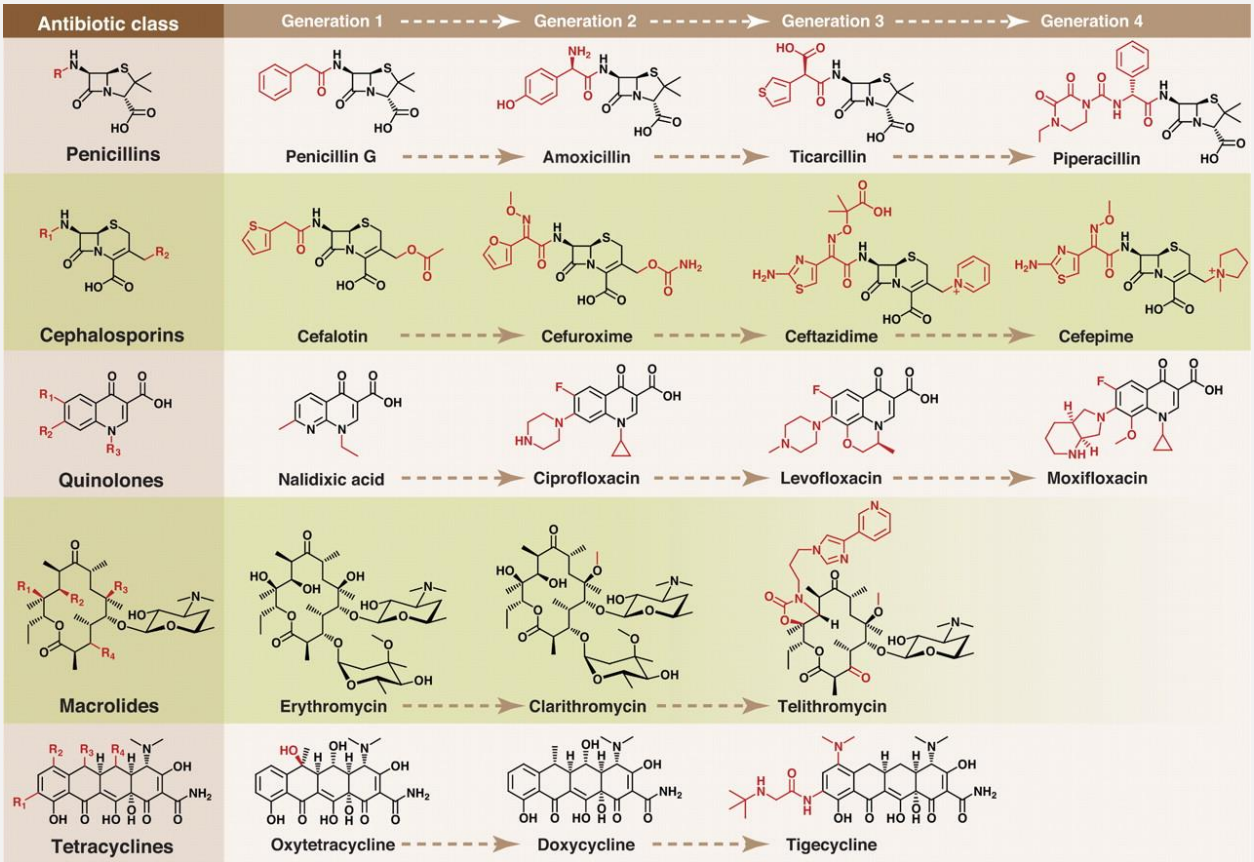


**Figure 2.** The synthetic modification is widely used to create successive generations of antibiotic classes. Scaffolds are colored black; peripheral chemical modifications are colored red. The quinolone scaffold is synthetic, whereas the other scaffolds are natural products [2].

The great deceleration in the introduction of new classes of antibacterial agents nowadays is partly due to a prevailing belief that bacterial infection was a well-understood problem. However, considering the growing problem of antibiotic resistance among clinically relevant pathogens, it soon became clear that this was not the case. Even with the careful use of antibiotics, the inevitable onset of bacterial resistance will demand the continued search for and development of new antibacterial agents. Indeed, resistance to powerful antibiotics such as vancomycin is now a clinically significant problem, and thus the need for new antibiotics is more urgent than ever [1].

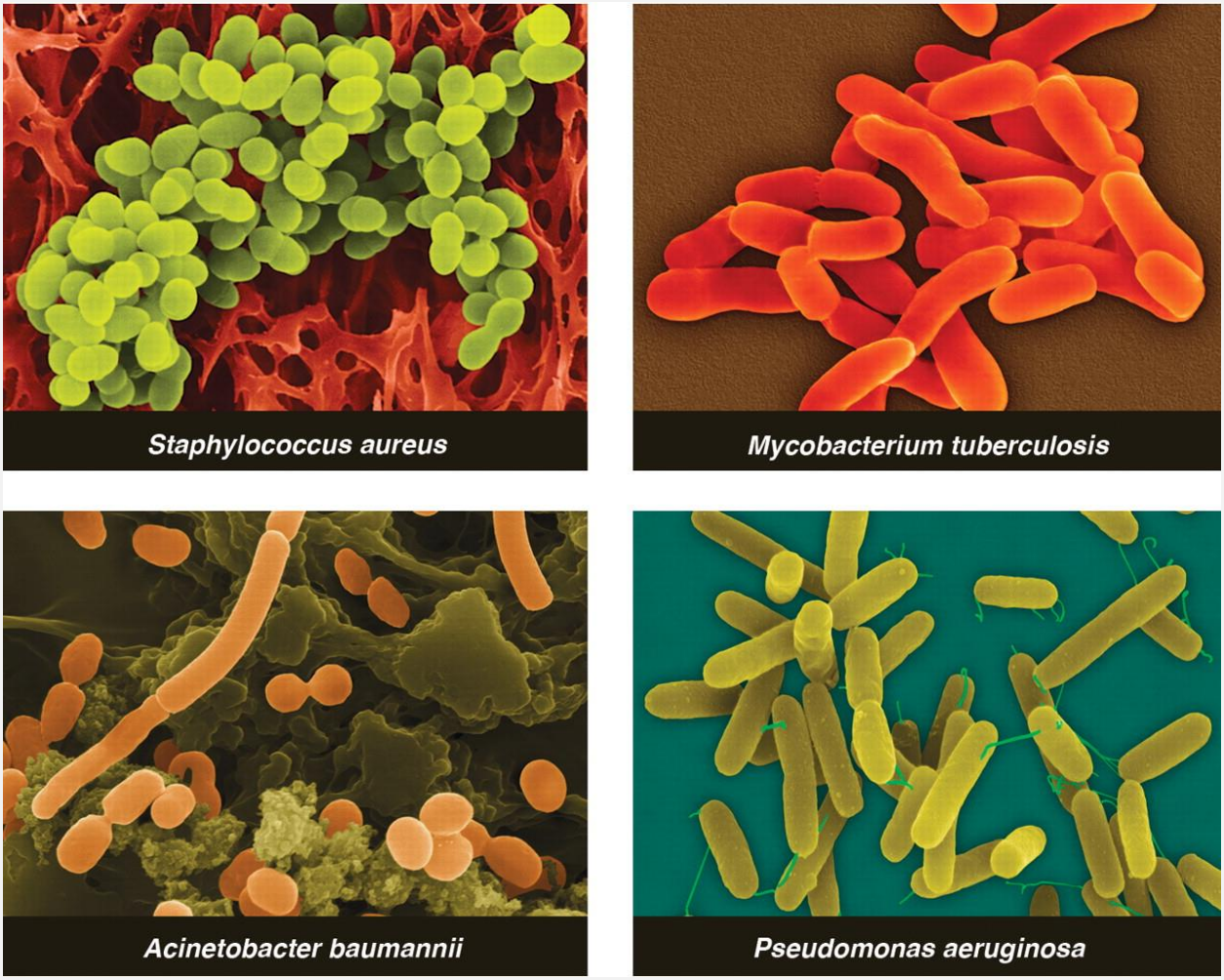


**Figure 3.** These multidrug-resistant strains of bacterial pathogens are a lethal threat to humankind [2].

## The Resistance

Three classes of antibiotic-resistant pathogens are emerging as major threats to public health (See Fig. 3). First, methicillin-resistant Staphylococcus aureus (MRSA) is estimated to cause ~19,000 deaths and 4 billion USD of additional health care costs per year in the USA. Furthermore, the rising prevalence of MRSA increases the likelihood that vancomycin-resistant S. aureus (VRSA) which is just as deadly as MRSA but more challenging to treat will become a new scourge in hospitals [2]. Pathogens from the second class, multidrug-resistant (MDR) and pandrug-resistant (PDR) Gram-negative bacteria, are less prevalent than MRSA, but they pose the serious threat of infections that are truly untreatable. These strains of Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa are resistant to some (MDR) or all (PDR) of the antibiotic classes commonly used to treat Gram-negative bacteria: penicillins, cephalosporins, carbapenems, monobactams, quinolones, aminoglycosides, tetracyclines, and polymyxins. Prospects for finding new antibiotics for Gram-negative pathogens are especially poor: Their outer membrane blocks the entry of some antibiotics, and efflux pumps expel many of the remainder [2]. The third class comprises MDR and extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis (MDR-TB and XDR-TB), which are a rising threat in the developing world. Their treatment requires long time and efforts moreover this may lead to serious side effects and fatal results [2]. All this leaves society vulnerable to highly resistant superbugs and a dangerous outbreak. As only exit strategy to this problem, there is a huge need for new antibiotics: Whereas most drugs will be just as effective in the future as they are today, the inevitable rise of resistance will erode the utility of today's antibiotics.

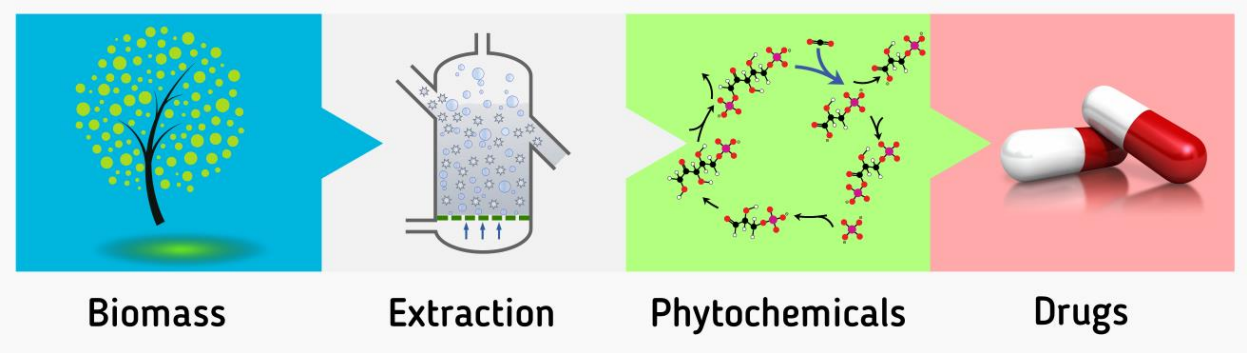


**Figure 4.** Phytochemicals: from source to medicine.

## Phytochemicals

Plant ecology suggests that plants must produce antibacterial metabolites as part of their chemical defense strategy to protect themselves against microbes in their environment including many Gram-positive bacteria. Soil is rich in bacteria, fungi and viruses and it is likely that plants contain latent antimicrobials or synthesize them de novo as part of a phytoalexic response on microbial invasion [5].



Plant extracts, as a “traditional drug”, have not been widely recognized in the mainstream research but a vast number of clinical and in vitro studies have demonstrated the potent bactericidal, antimycotic and antifungal features. These molecules demonstrate efficacy against hospital-acquired isolates and reference strains, even for antibiotic-resistant strains like MRSA and antimycoticresistant Candida species, proved in vitro, representing a cheap and effective antiseptic treatment alternative [6]. Tohidpour et al. compared an essential oil to standard antibiotics tetracycline, ciprofloxacin, gentamicin, trimethoprime-sulfamethoxazol, vancomycine, methicillin and found greater antimicrobial performance against clinical MRSA along with other standard bacterial strains [7].

Chandra et al. reviewed plant-based antimicrobials against the resistant bacteria and listed twenty-eight species with efficient phytochemical compounds [8] (See Table 1). Gibbons points to the distinct molecular structure of phytochemicals which is

different from microbially derived antibiotic natural products such as the tetracyclines and macrolides. It is likely that this chemical uniqueness will give rise to classes of antibacterial which have modes of action which are distinct from existing compounds, e. g., protein synthesis inhibition. It might be that phytochemicals display new mechanisms of action, or activity toward some of the newer targets which are becoming more thoroughly investigated such as type II fatty acid synthase (FAS-II) [5]. This peculiarity makes the phytochemicals one of the best candidates in the war against the superbacteria.

Phytochemicals offer novel opportunities as a powerful, low-cost and readily available antimicrobial. In the days of skyrocketing drug discovery costs, they could revolutionize the research. Particularly the developing countries can manufacture their own pharmaceuticals using the native flora. With their uncharted interaction mechanisms, they could yield efficient but *hard-to-resist* antimicrobials.

| Phytochemicals | Microbes treated |
|---|---|
| Terpenoids, flavanoid, Saponins, Tannins | *S. viridians*, *S. aureus*, *E. coli*, *B. subtilis*, *Shigella sonnei*, *MDR E. coli*, *C. albican*, *K. pneumoniae* |
| Flavanoid, Polyphenol | MDR *Pseudomonas aeruginosa*, *S.* Typhi, *E. coli* |
| Organosulphur compounds (Phenolic compounds), Allicin | *Campylobacter jejuni*, *MDR E. coli*, *C. albican*, *Entamoeba histolytica*, *Giardia lamblia* |
| Coumarins | *S. viridians*, *S. mutans* |
| Glycoprotein | *B. cereus*, *Staphylococcus* spp. |
| Cinnamaldehyde (essential oil) | *Legionella pneumophila*, *MDR E. coli*, *C. albican*, *K. pneumoniae* |
| Flavones | *MDR K. pneumoniae* |
| Curcuminoid (A phenolic compound), turmerone, curlone, Essential oil, curcumins, turmeric oil | *S. typhi*, *E. coli*, *S. aureus*, *B. cereus*, *B. subtilis*, *Ps. aeruginosa*, *B. coagulans*, *A. niger*, *P. digitatum*, Antifungal and antiviral activity |
| Citratus, Essential oil | *C. albicals*, *Aspergillus flavus*, *A. parasiticus* |
| Flavones | *MDR K. pneumoniae* |
| Hypericin (anthraquinone) | Methicillin Resistant *Staphylococcus aureus* and Methicillin sensitive *Staphylococcus* |
| Quinones | *MDR Pseudomonas aeruginosa* |
| Saponins, Canavanine | *Enterococcus faecium*, *S. aureus,* Antifungal |
| Longifoilia, Essential oil | MDR *Staphylococcus aureus* |
| Basilicum, Essential oil | MDR *Staphylococcus aureus*, *S.* Typhi, *Aeromonas hydrophila*, *Pseudomonas* spp. |
| AMPs (antimicrobial peptides) | *E. faecium*, *S. aureus* |
| Vulgare, Essential oil | *B. subtilis*, *B. cereus*, MDR *Staphylococcus aureus* |
| Piperine, Saponin, alkaloid | *MDR B. subtilis*, *Shigella sonnei* |
| RsAFP2 (Antifungal peptide) | *C. albicans* |
| Alkaloids and Non alkaloids | *MDR E. coli*, *K. pneumoniae* (*ESBL*), *E. faecium*(*VRE*) |
| Officinalis, Essential oil | *Streptococcus mutans* |
| Alkaloids, antimicrobial peptides | *Ps. aeruginosa*, *E. coli* |
| Tannins | *S.aureus*, *S. typhimurium*, *A. niger*, *A. flavus*, *S. cerevisae* |
| Alkaloids | *S. aureus*, *S. mutans*, *Microsporum gypseum*, *M. canis* and *Trichophyton rubrum* |
| Essential oil, Eugenol | *Streptococcus mutans*, *Staphylococcus aureus*, *Lactobacillus acidophilus*, *Candida albicans* and *Saccharomyces cerevisiae*, MDR *E. coli*, *K. pneumoniae* |
| Vetivone (vetiver oil) | *Enterobacter* spp. |
| Flavones | *MDR K. pneumoniae* |
| Gingerol | *E. coli*, *Enterobacter* spp., *P. aeruginosa*, *Proteus* spp., *Klebsiella*spp., *S. aureus* and *Bacillus* spp. |

**Table 1.** Efficacy of phytochemicals against bacteria, especially MDR-Multidrug Resistance, ESBL-Extended Spectrum Beta Lactamase, VRE-Vancomycin Resistant Enterococci [8].

## References

[1] K. C. Nicolaou, Jason S. Chen, David J. Edmonds, and Anthony A. Estrada, Recent Advances in the Chemistry and Biology of Naturally Occurring Antibiotics, Angew. Chem. Int. Ed. 2009, 48, 660 – 719

[2] Michael A. Fischbach and Christopher T. Walsh, Antibiotics for Emerging Pathogens, Science 325, 1089 (2009).

[3] http://www.deinove.com/en/profile/strategy-and-markets/antibiotics-market Access Date: 5/5/2018

[4] The Race Against Drug Resistance A Report of the Center for Global Development's Drug Resistance Working Group, Rachel Nugent, Emma Back, Alexandra Beith, 2010 by the Center for Global Development.

[5] Gibbons, Simon. "Phytochemicals for bacterial resistance-strengths, weaknesses and opportunities." Planta medica 74.06 (2008): 594-602.

[6] Patrick H. Warnke, Stephan T. Becker, Rainer Podschun, Sureshan Sivananthan, Ingo N. Springer, Paul A. J. Russo, Joerg Wiltfang, Helmut Fickenscher, Eugene Sherry, The battle against multi-resistant strains: Renaissance of antimicrobial essential oils as a promising force to fight hospital-acquired infections, Journal of Cranio-Maxillofacial Surgery (2009) 37, 392-397.

[7] A.Tohidpour, M.Sattari, R.Omidbaigi, A.Yadegar, J.Nazemi, Antibacterial effect of essential oils from two medicinal plants against Methicillin-resistant Staphylococcus aureus (MRSA), Phytomedicine 17 (2010) 142–145.

[8] Chandra, Harish, et al. "Antimicrobial Resistance and the Alternative Resources with Special Emphasis on Plant-Based Antimicrobials—A Review." Plants 6.2 (2017): 16.