

General Overview of Phenolics from Plant to Laboratory, Good Antibacterials or Not

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ABSTRACT

The emergence and rapid development of seriously drug-resistant pathogens have created the greatest danger to public health and made the treatment of infectious diseases ineffective; to control the antibiotic-resistant microbes, the discovery of new effective antibacterials with new mechanisms of action against bacteria remains an urgent task to control the bacterial resistance. The paucity of infections in wild plants supports the role of innate defense system of plants. Many researchers nominate the natural extracts to act against bacterial resistance mechanisms, and the majority of them have now been focused on the combination of plant extracts and antibiotics to define the availability of resistance modification agents. Only very few numbers of natural products are successful to reach experiments circle beyond the *in vitro* assays. Phenols and phenolic acids could serve as good candidates to the natural antibacterial arsenal. The pyrogallol-based compounds are more potent than others such as catechol or resorcinol, gallic acid, and the hydroxycinnamic acid (ferulic acid) are destructing the bacterial cell wall of *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, leading to leakage of cellular contents. These compounds have stronger activity against Gram-positive microorganisms, and some of them showed good synergism with antibiotics, for example, pentagalloylglucopyranose, is shown a synergism with penicillin G against methicillin-resistant *S. aureus*, another example is the interesting synergism between epicatechin gallate and oxacillin where the minimal inhibitory concentrations of oxacillin reduced around 500 times by the addition of epicatechin gallate to the antibiotic.

Key words: Antibacterial, *Escherichia coli*, gallic acid, *Staphylococcus aureus*

INTRODUCTION

The discovery of penicillin was the start of antibiotics era which had a big victory to defeat pathogens for over 70 years; however, the emergence and rapid development of seriously drug-resistant pathogens have created the greatest danger to public health and made the treatment of infectious diseases ineffective.^[1]

Bacteria can resist antibiotic/s by several means: (1) the modification of protein targets to antibiotics; (2) the production of enzymes which can degrade or modify the antibiotic structure rendering it unsuccessful in infections treatment; (3) the changes of cell wall permeability due to mutations; (4) the use of the pumping system to expel the antibiotics molecules.^[2,3] Based on the various mechanisms of bacterial resistance listed above, resistance-modification agents (RMAs) which may address the resistance problem have been explored to modify the antibacterial resistances. The details of resistance modification mechanisms and RMAs were reviewed in detail by Abreu *et al.*^[3] In this review, we tried to present the bacterial resistance problem in simple tailoring where the story has begun by presenting the resistance problem, mechanisms of resistance, and one of the solutions which is the possibility of using the

phytomedicines in treatment protocols, specifically the *in vitro* assay of some phenols and phenolic acids, which are widely distributed in the plant kingdom. Searching for the credible information was accomplished using EBSCO as a searching engine to search for the most important *in vitro* experiments on phenols and phenolic acids during the last 20 years.

ANTIBACTERIAL RESISTANCE

The emergence of resistant strains to antibacterials was determined by the level of exposure of the pathogen to antibacterials, biochemical, and physiological effects of drugs on the microorganisms (pharmacodynamics) and the pharmacokinetic properties of the antibiotics.^[4] The using of the antibacterials in a wrong dose and the general abuse of the antibacterials were the contributing factors of the emergence and dissemination of resistance.^[5] The resistant microbes do not respond to the antibacterials due to either expression of resistance phenotype or inherent resistant genes.^[6]

The multidrug resistance is more serious than the resistance to a single antibiotic. Examples are the methicillin-resistant *Staphylococcus aureus* (MRSA) and the toughest type of *S. aureus* which also resists vancomycin.^[3] These kinds of bacteria cause around 25,000 dead cases and cost the European economy more than 1 billion euros.^[2]

To control the antibiotic-resistant microbes, the discovery of new effective antibacterials with new mechanisms of action against bacteria remains an urgent task to control the bacterial resistance.^[7] The WHO adopted

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several strategies to address the resistance problems such as using the antibiotics in the right dose and duration of treatment, enhancing healthy environment to control transmission of resistant strains, and supporting the research for finding new antibiotics.^[8] The use of synergism between antibiotics is also an important strategy to control drug resistance by targeting more than one site of action and increases the bioavailability or the modification of resistance mechanisms.^[9]

PLANTS AS SOURCES OF ANTIBACTERIALS

Plant extracts have been utilized from ancient times to treat various ailments, particularly in Asia. A major proportion of the world's population depends on traditional medicine for a healthy life.^[10] In modern drug discovery and development processes, phytochemicals play a key role at the early stage of "lead" discovery, i.e. discovery of the bioactive (determined by various bioassays) natural molecule, which could be an ideal drug candidate itself or as a lead compound to develop for its structural analogs.^[11,12]

Some of the phytochemicals are utilized by the plants themselves as a cover against many invaders, therefore playing a distinctive role as antibacterials.^[13] The paucity of infections in wild plants supports the role of innate defense system of plants.^[14] Many researchers nominate the natural extracts to act against bacterial resistance mechanisms, and the majority of them have now been focused on the combination of plant extracts and antibiotics to determine the existence and abundance of RMAs.^[15,16]

Giant companies in pharmaceutical sector have invested a huge amount of money to synthesize chemical compounds without biological activities due to lack of special stereochemistry which natural products can offer; therefore, an increase in drug discovery from nature in the future will be expected.^[17] Another important motive to discover natural products and produce alternatives to the limited or failed therapeutic protocols is the unlimited diversity of natural leads which are biologically active or ready for development and structure optimization strategies. In addition to that, the toxicity and low margin of safety of some antibacterials have promoted the interest in search for novel antibacterial products from other sources, particularly plant secondary metabolites (phytochemicals).^[17]

There are different phytochemical approaches to follow for searching of natural antibacterials. The plant species are selected randomly and then their phytochemicals are categorized to different chemical groups. The second approach is the random selection of plant species followed by antibacterial assays; the third approach is to follow previous reports of researchers.

The most important approach is the follow-up of ethnomedical or traditional uses of plants against microbial infections.^[18] Traditional medicines such as Ayurveda and Chinese medicine provide information about the medicinal use of plants. Information acquired from books, herbals, review articles, notes placed on voucher herbarium specimens, field work, and computer databases, such as NAPRALERT.^[19]

The best way to find new antibacterial molecules with new mode of action is the following of an organized-bioguided extraction method. The starting of the bioguided extraction studies faced many challenges; one of those challenges is the authentication of the plant materials.^[20] The authentication step is crucial for the following steps because inaccurate identification of the plant specimen leads definitely to false results. Another important challenge is the limited quantities of some active metabolites in the plant species, in addition to limitation of the collected plant quantity due to protection rights of some plants.^[21]

The problem of shortage in medicinal plants is serious and must be put in the circle of care; therefore, the European Medicines Agency launched the controlled agricultural and collection code of practice to ensure a

sustainable plants collection.^[20] In addition to the previously mentioned challenges, only very few numbers of natural products are successful to reach experiments circle beyond the *in vitro* assays.

Drug discovery of compounds from natural sources is hindered by the complexity of the chemical structures of natural molecules which have complex stereochemistry and functional groups; sometimes, this makes their synthesis in laboratories, a tedious task compared to pharmaceutical compounds produced by medicinal chemistry;^[22] however, the complex stereochemistry of natural compounds could be advantageous from another side of view.

Extraction of antibacterial natural products

To extract the phytochemicals, researchers can use open extraction system or closed (continuous) system like refluxing with Soxhlet or Clevenger apparatus. Extraction of phytochemicals is carried out using water or alcohol or other organic solvents such as hexane, methanol, or ethyl acetate under heat or at room temperature. Most of the antibacterials are extracted by an aqueous alcoholic solution which is later dried by rotary evaporator under vacuum.^[23]

Antibacterial assay methods

The assays of antibacterials from plants are conducted with crude plant extract^[24] and/or pure compounds.^[25,26] Disk or agar well diffusion assay and broth micro- or macro-dilution assay are the most important assays used to evaluate the antibacterial activities.^[27,28] The bioautographic method^[29] is another way for the determination of antibacterial effects.

To detect the antibacterial action, the researchers can use the disk diffusion method, in which a paper disk contained the natural extract or pure compound is laid on top of an inoculated agar plate. The volume or quantity of the natural material deposited on the paper disks, the thickness of the agar layer, and whether a solvent is used can affect the results considerably between studies. In the agar well test, when many extracts are placed for assay or plenty of bacteria need to be tested, the material assayed for antibacterial activity is introduced into wells cut of agar plate.^[30,31]

In broth dilution method, the antibacterial activity parameter such as the minimal inhibitory concentration (MIC) is quantified by detecting the optical density (OD) using an automated spectrophotometer or by counting the viable colonies left after incubating the inoculum in the existence of the antibacterial materials for a defined period of time. Although this method is accurate, it is a tedious process and requires a longer period of time than OD measurement. Resazurin (Alamar blue) can be used in microplate assay method as a highly sensitive indicator, accurately reflect the activity of the bacterial cells.^[32] The Alamar blue assay method is sensitive enough to be compared with OD measurement and viable colonies counting, and it is more sensitive than the agar dilution method.^[33]

The time-kill assay is used to define the time required to reach a bactericidal or bacteriostatic level. The time-kill kinetic graph is presented by plotting the number of viable cells remaining in the broth after addition of the natural extract versus time. The destruction of the bacterial cell by antibacterial agent and loss of cellular contents can be studied by scanning electron microscopy.^[34,35]

IN VITRO ANTIBACTERIAL ACTIVITIES OF SOME PHENOLS AND PHENOLIC ACIDS

Phenols such as catechol and pyrogallol showed activity against some microorganisms. For example, pyrogallol showed MIC 2.4–2500 µg/ml and pyrocatechol MIC range: 4.9–312.5 µg/ml against several microorganisms causing periodontitis.^[36] Taguri *et al.*

recorded the antibacterial activities of 22 polyphenolic structures against several Gram-positive and Gram-negative bacteria; the results revealed that the pyrogallol-based compounds were more potent than others such as catechol or resorcinol.^[37] There was evidence that increased hydroxylation of those phenols results in increased toxicity or antibacterial activities.^[38] The mechanisms of action of simple phenols are probably proceed through interaction with sulfhydryl groups in microbial enzymes, leading to inhibition of those enzymes or due to nonspecific proteins interactions.^[39] The structures of some phenols and phenolic acids are shown in Figure 1.

Some phenolic acids such as caffeic acid have antibacterial activities. Caffeic acid showed MIC equal to 1600 µg/ml against *S. aureus* and *Escherichia coli* compared to ampicillin which showed MIC 0.1 and 3.2 µg/ml, respectively.^[40] Gallic acid is a phenolic acid showing an effect against *Enterococcus faecalis*.^[41] It also showed the greatest effect, among several phenolic compounds, against a group of bacterial strains including *Pseudomonas aeruginosa*, *S. aureus*, *Moraxella catarrhalis*, *E. faecalis*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae*.^[42] Gallic acid showed good activity against *Campylobacter* and produced bactericidal activity against two *Campylobacter coli* strains with MIC equal to 61.5–125 µg/ml.^[43]

In another study, the antibacterial activities of gallic acid and ferulic acid were detected against several bacterial isolates. Gallic acid showed MIC equal to 500 µg/ml against *P. aeruginosa*, 1500 µg/ml against *E. coli*, 1750 µg/ml against *S. aureus*, and 2000 µg/ml against *Listeria monocytogenes*; MIC of ferulic acid was 100 µg/ml against *E. coli* and *P. aeruginosa* and 1100 µg/ml and 1250 µg/ml against *S. aureus* and *L. monocytogenes*, respectively. Minimal bactericidal concentrations for both compounds against all microorganisms were 2500–5500 µg/ml.^[44]

Gallic acid and ferulic acid affect the bacterial cell wall of *S. aureus*,

E. coli, and *P. aeruginosa*, producing local damage and leakage of cellular materials.^[44]

Wild polish mushrooms, which contain protocatechuic acid, 4-hydroxybenzoic acid, vanillic acid, syringic acid, caffeic acids, and p-coumaric and ferulic acids, showed intermediate antibacterial activities with MIC ranging from 156 to 5000 µg/ml, against a range of Gram-positive and Gram-negative bacteria with a stronger activity against Gram-positive microorganisms.^[45]

Methyl gallate, a major metabolite from *Galla rhois*, an Asian plant collected in Korea, showed anti-*Salmonella* behavior against several *Salmonella* strains with MIC ranging from 3.9 to 125 µg/ml.^[46] The *in vivo* therapeutic activity of methyl gallate was well proved by the absence of lethargy and liver problems, the two common consequences of *Salmonella* in treated mice.^[46] Methyl gallate demonstrated good antibacterial effect against *E. coli* and *Shigella flexneri* with MIC of 30 µg/ml.^[47]

Three *Potentilla* species were found to be rich in hyperoside, (+)-catechin, caffeic acid, ferulic acid, rutin, and ellagic acid, which were tested for their antibacterial activities. *P. fruticosa* had the highest effect against Gram-positive bacteria, Gram-negative bacterium (*P. aeruginosa*), and a fungus *Candida albicans* with MIC values of 0.78–6.25 mg/ml.^[48]

Plant polyphenols interact with each other to improve the antibacterial actions.^[49] Polyphenolic compounds present in a *Cistus salvifolius* extract showed synergism. Flavonoids in combination with ellagitannins in certain percentage showed inhibition against the growth of *S. aureus*.^[49]

The combination of isoquercitrin (10 µg/ml) with gallic acid (10 µg/ml) was successful in inhibition the growth of *S. aureus*, while their MIC separately was 10 times more.^[50] The ethyl acetate fraction from the ethanol extract of *Searsia chirindensis* was the most active antibacterial fraction, which contained methyl gallate, myricetin-3-O-arabinopyranoside, myricetin-3-O-rhamnoside, kaempferol-3-O-rhamnoside, and

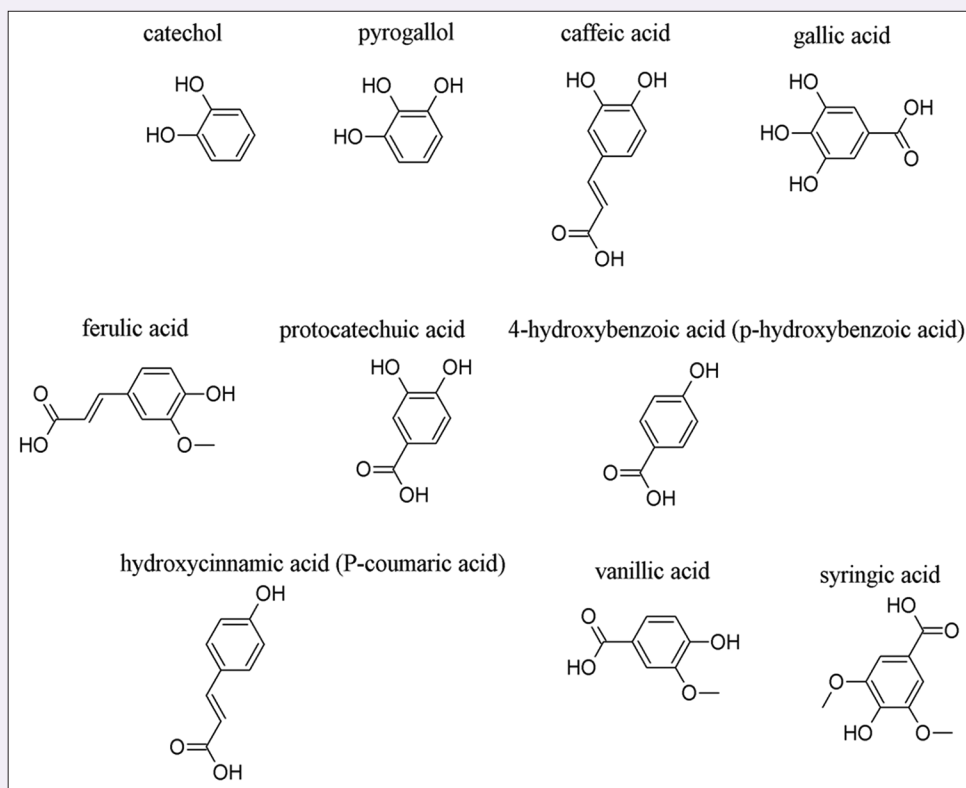


Figure 1: Structures of some phenols and phenolic acids

quercetin-3-O-arabinofuranoside. The MICs of these compounds ranged from 30 to 250 µg/ml against *Campylobacter jejuni*, *E. coli*, *S. flexneri*, and *S. aureus*.^[47]

The seed kernels of *Mangifera indica* L. consisted of the following phenolic acids: gallic acid, methyl gallate, and pentagalloylglucopyranose. The extract inhibited the growth of MRSA, due to the major phenolic principle, pentagalloylglucopyranose, which showed a synergism with penicillin G against MRSA.^[51]

Some phenolic compounds such as hydroquinone, thymol, carvacrol, butylated hydroxyanisole, and octyl gallate were assayed against *S. aureus*. As a result, octyl gallate had MIC equal to 21 µg/ml; hydroquinone had MIC 103 µg/ml, and carvacrol and thymol showed MICs of 413 µg/ml.^[52]

Panduratin A, a natural chalcone compound extracted from *Kaempferia pandurata* Roxb, had potent activity against *S. aureus* with MIC equal to 0.06–2 µg/ml. An interesting study of synergism between phenolic materials and penicillins demonstrated the lowering MIC of oxacillin around 500 times by epicatechin gallate.^[53,54]

Acylphloroglucinols (Olympicins A–E) isolated from the aerial parts of the plant *Hypericum olympicum* L. cf. *uniflorum* were evaluated as antibacterial agents against MRSA and multidrug-resistant *S. aureus*. Olympicin A had MIC of 0.5–1 µg/ml; others had MIC between 84 and 128 µg/ml against several *S. aureus* isolates.^[55] Arzanol, a very strong anti-staphylococcal drug from *Helichrysum italicum* ssp. *Microphyllum*, had MIC equal to 1–4 µg/ml against different *S. aureus* strains.^[56] Potent fraction isolated from *Hypericum beanie* contained two acylphloroglucinols, 1,5-dihydroxy-2-(2'-methylpropionyl)-3-methoxy-6-methylbenzene, and 1,5-dihydroxy-2-(2'-methylbutanoyl)-3-methoxy-6-methylbenzene. This mixture showed MIC equal to 16–32 µg/ml against multidrug-resistant *S. aureus*.^[57]

Catechin gallate, epicatechin gallate, and epigallocatechin gallate showed β-lactamase and penicillin-binding protein 2a (PBP2a) inhibition to potentiate the antibiotic activity against *S. aureus* and MRSA.^[58-60] Using epigallocatechin gallate (25 µg/ml) can restore MIC of imipenem to <4 µg/ml against around 18 MRSA isolates out of 24 isolates.^[59] Epigallocatechin gallate (50 µg/ml) inhibited Tet (K) pump and increased intracellular concentration of tetracycline and ultimately its activity.^[60] Epicatechin gallate decreased the MIC of norfloxacin 4 times against *S. aureus* with NorA.^[61]

Ethyl gallate and other alky gallate caused cell wall disruption of the methicillin-sensitive *S. aureus* and MRSA and potentiated the antibacterial activities of β-lactam antibiotics, probably by inhibition of PBP2a.^[62] Gallic acid showed synergism with sulfamethoxazole or tetracycline against several *P. aeruginosa* isolates^[63] and with streptomycin against the same Gram-negative isolate^[64] by disruptions of cell wall integrity.

CONCLUSION

Phenols and phenolic acids could play a positive role in the treatment of infections caused by resistant bacteria since they have the abilities to link with and disable some bacterial enzymes essential for bacterial cell wall synthesis in a way, which may modify the course of resistance of certain kinds of bacteria such as *S. aureus*. The combination of those phenolics with certain antibiotics is indeed better than claiming the use of those weak to moderate active antibacterial agents as a sole therapy; however, we must not forget that some local communities still use plant extracts containing phenols and phenolic acids for the treatment of some ailments such as bacterial infections, and the *in vitro* results of the antibacterial activities support those ethnomedical use.

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Conflicts of interest

There are no conflicts of interest.

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