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Miracle Remedy: Inhibition of Bacterial Efflux Pumps by Natural Products

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Abstract

The emergence of multidrug resistance among bacteria is a burning issue nowadays, and demanded for the discovery of the potential chemicals to deal with that resistance problem. Among several mechanisms of acquiring resistance, the over-expression of efflux pumps is very important. Efflux pumps can efflux out a large number of structurally unrelated drugs making them ineffective, which illustrates the importance of efflux pump inhibitors. Here we review the literature on efflux pump inhibitors (EPIs) from the plant sources, which will help to regain the activity of the existing antibiotics. The discovery of the new classes of natural EPIs demands further studies to explore their potential to work in synergy with existing antibiotics.

Keywords: *Salmonella typhi*; Efflux pump; EPIs; Multidrug resistance

Introduction

On the global scale, infections that are caused by *Salmonella* are gaining importance due to their significant socio-economic impact. It has been reported that each year 3 billion human infections are caused by *Salmonella* worldwide. *Salmonella Typhi* and *Paratyphi*, are causative agents of enteric fever [1]. According to the survey of World Health Organization (WHO), 21.7 million illnesses are due to typhoid fever annually and it is the fourth largest cause of deaths in Pakistan [2]. *Salmonella Typhi* and *Paratyphi* are transmitted by fecal-oral route in humans and do not have any environmental or animal adaptation [3].

We have been fortunate enough to be living through "The Golden Age of Antibiotics" from the mid 1940's until relatively recently. During this period, we were capable of controlling the causative agents of major infections, a period which revolutionized the history of medicine and saved countless lives. But due to the emergence of antibiotic resistance, now there is an end of this golden age [4]. Antibiotic resistance emerged soon after the introduction of first antibiotic by Sir Alexander Fleming in 1945 [5]. The first antibiotic resistant strain of *Salmonella Typhi* was emerged in 1950's while multidrug resistance isolates were emerged in the 1980's which were resistant to all first line antibiotics [6,7].

There are several means by which bacteria become resistance to antibiotics. They can take foreign genes for resistance by conjugation, transformation or transduction (Figure 1). They can also become resistant by induced or spontaneous genetic mutations. Many resistant genes are present on the plasmids so they can easily transfer between and across the species. When organisms are exposed to antibiotics, the resistant ones are naturally selected, so in this way resistant spread readily through a bacterial ecosystem [8].

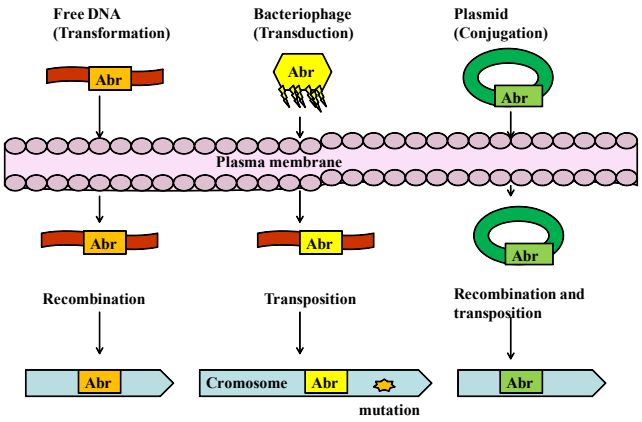


Figure 1: Mechanisms of acquiring resistance, Modified from [9].

Antibiotic resistant bacteria are becoming problematic as they are more fatal than wild type and have less prognostic and predictive value. Use of antibiotics for a prolonged time also kill the normal microflora of the body due to which severity of infection is enhanced [10].

Microorganisms resist to microorganisms by various ways which include: 1- Modification or inactivation of drugs, 2- alteration of drug target site, 3- alteration of metabolic path and efflux of antibiotic from the bacterial cells (Figure 2) [11].

With the advent of unique resistant patterns, drug resistant bacteria continue to worsen globally and existing antibiotics are now not so effective and we are moving towards the "pre-antibiotic era". To cope with the current situation of antimicrobials resistance, new and novel approaches and strategies need to be worked out.

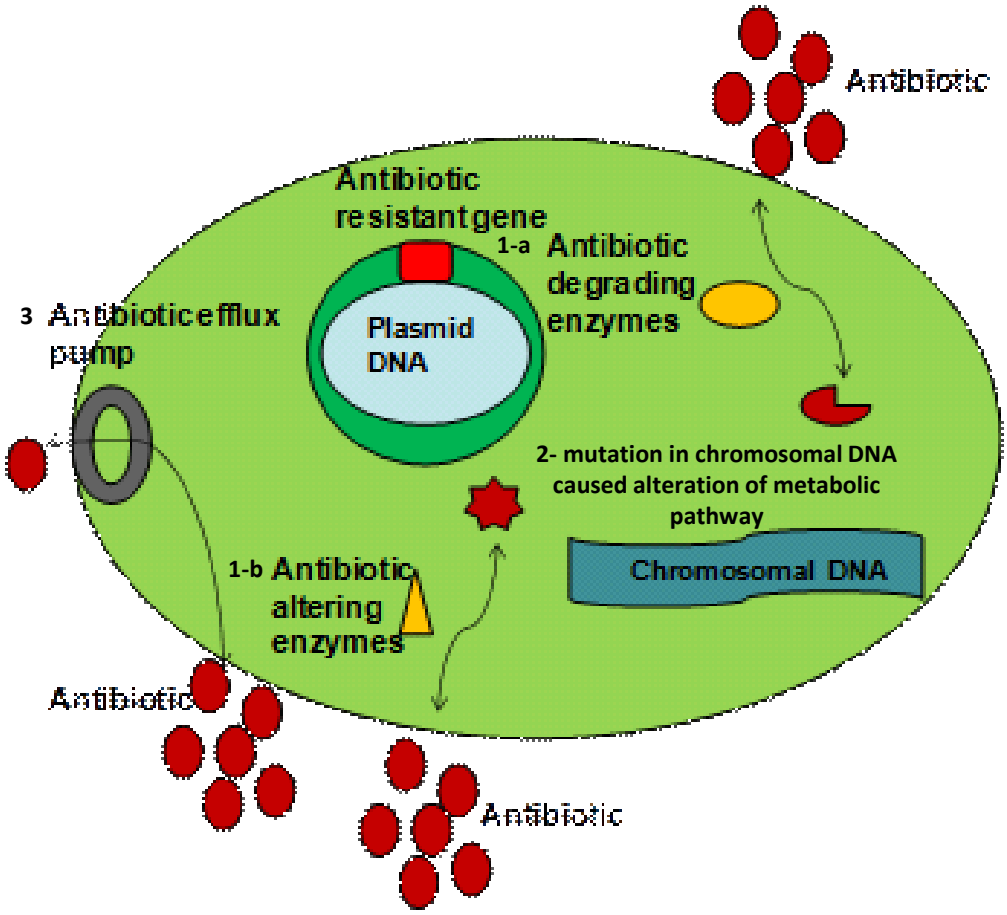


Figure 2: Different types of antibiotics resistance, Modified from [11].

Antibiotic efflux in bacteria was reported first time in the late 1970's. There are approximately 350 transporter proteins that are identified in *Salmonella* [12]. Efflux pumps consist of proteins that acquire different conformations in order to expel foreign killers from the cells. These pumps located in the cytoplasm and span from outer cell membrane to the cytoplasm in Gram-positive bacteria while in Gram-negative bacteria they have to pass an additional layer of periplasm [13].

Drug efflux pumps of bacteria have been characterized into five classes as: resistance nodulation division superfamily (RND) [14], ATP binding cassette superfamily (ABC) [15], major facilitator superfamily (MFS) [16], Multidrug and toxic extrusion family (MATE) [17] and Small multidrug resistance family (SMR) [18].

Existing literature suggest that efflux pumps have significant role in development of antimicrobials resistance in bacteria, so there is a need to understand their physiology to reveal the interesting perspectives for the development of their inhibitors that can be used in combination therapy along with existing antibiotics.

Herbal medicines continue to play a key role to solve health problems worldwide, especially in the developing countries where medicinal plants have long and unceasing history of use [19]. The use of medicinal plants for health care management is very attractive because they are cheap, locally available and effective. The bacteria required at least a decade to acquire resistance against them [20].

A wide variety of secondary metabolites of therapeutic value have been produced by plants. In the world, only 5-10% of all known plants species have been investigated chemically. By adequately exploring this vastly untapped resource, the probability of novel chemotherapeutic compounds could be increased [21].

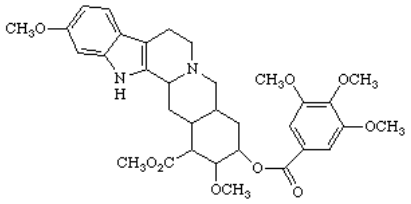
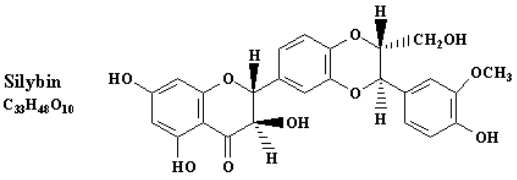
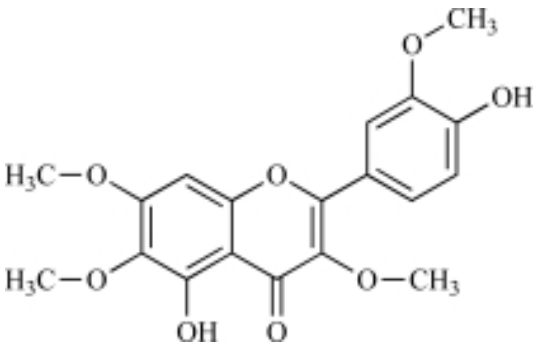
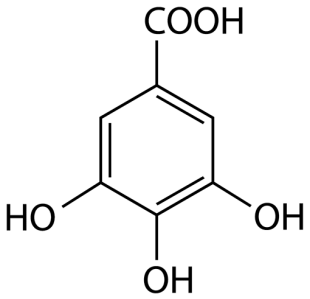
While the plant extracts are routinely used as direct antibacterial compounds, using these compounds in synergy with existing antibiotics is more promising as it recycles old and cheaper antibiotics that are not in use due to resistance [22]. These compounds play with the mechanisms of resistance rendering these strategies of bacteria ineffective.

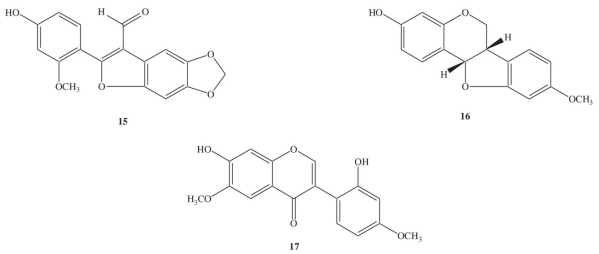
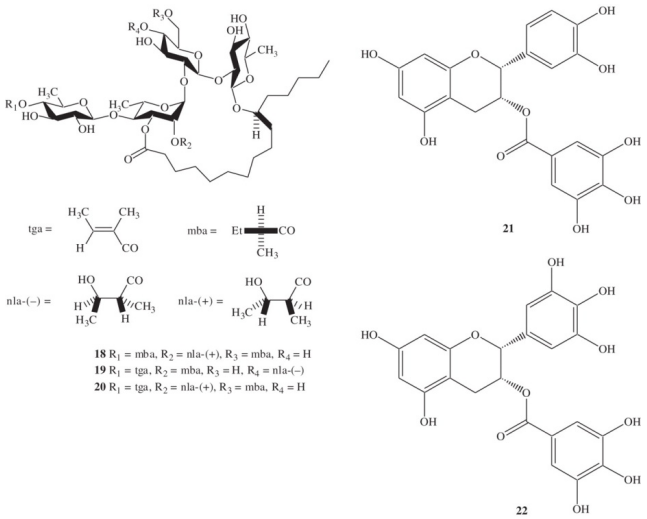
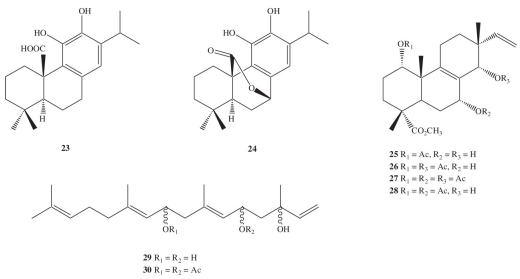
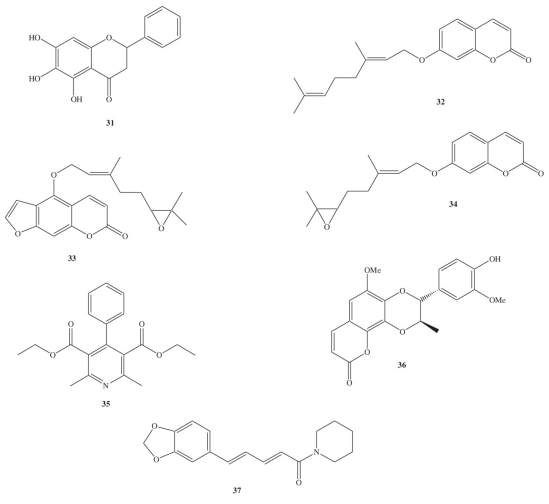
One approach to deal with resistance is to block the efflux pumps by efflux pump inhibitors (EPIs) derived from plant source. The EPI strategy is aimed to block the efflux pumps so that concentration of antibiotics increased in the bacterial cells and they can easily access to their target site [23]. This approach increases the therapeutic effect of conventional drugs even at low concentration. As the EPIs exert no pressure directly on the bacterial cells, this could reduce the emergence and spread of resistance [24].

A number of researchers have found that indeed plant metabolites can enhance the activity of antibiotics (Table 1) [25-27]. The compounds that have activity against resistant bacteria are variably been termed as modulating, resistance modifying or reversal agents.

To enhance the activity of antibiotics, different medicinal plants have been used in synergy with antibiotics. For example when fluoroquinolones are administered in combination with oregano essential oil, the activity of drugs against extended-spectrum beta-lactamase producing *E. coli* is enhanced [37]. Similarly, synergistic action of terpenoids derived from plants and antibiotics have been reported [38,39]. In another combinational strategy, flavonoids derived from plants and antibiotics were applied against multidrug resistant isolates of *Klebsiella pneumonia* [40]. Moreover, it has been found that action of cefotaxime can be enhanced by the aqueous extract of Terminalia chebula [41] and gallotannin extracted from Terminalia chebula has potential to inhibit efflux pumps of multidrug resistance Escherichia coli [42].

Such studies are very important to combat the problem of multidrug resistance developed by infectious pathogens, and for the re-introduction of existing antibiotics into clinical utility. There are only a limited number of research groups working on identifying inhibitors of efflux pumps from natural sources. Time and cost for identifying EPI is another issue, however, chemical diversity of plants have make them attractive option as a source of efflux pump inhibitors.

Efflux pump inhibitor	Plant name	Structure	Reference
Reserpine	*Rauwolfia vomitoria*	 Reserpine	[28]
Silybin	*Silybum marianum*	 Silybin $C_{33}H_{48}O_{10}$	[29]
Chrysoplenetin	*Artemisia annua*		[30]
Gallic acid	*Punica granatum*		[31]

Spinosan A	*Dalea spinosa*		[32]
Orizabin XIX	*Ipomoea tricolor*		[33]
Carnosic acid	*Rosmarinus officinalis*		[25]
Baicalein	*Thymus vulgaris*		[34]

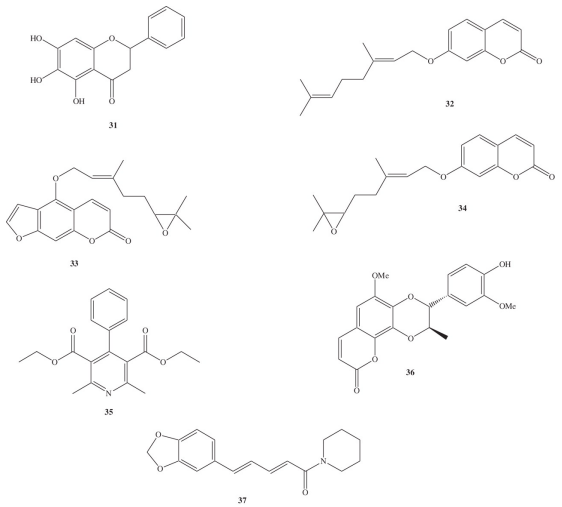
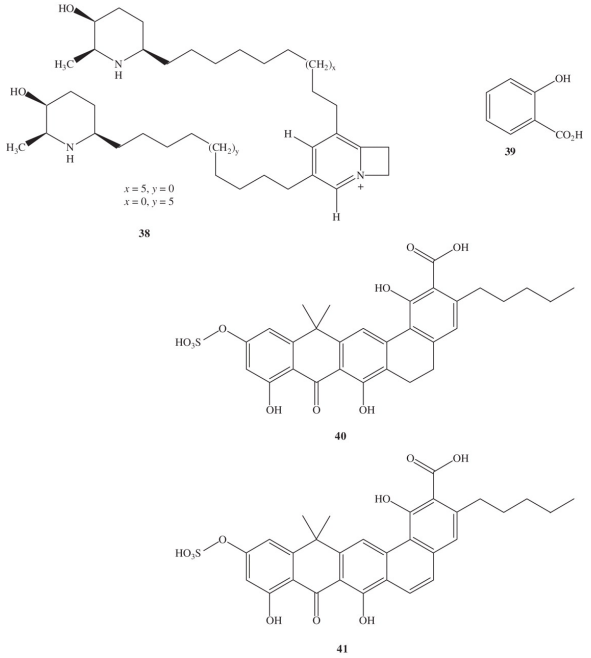
Piperine	*Piper nigrum*		[35]
Juliflorine	*Prosopis juliflora*		[36]

Table 1: List of efflux pump inhibitors from plant sources

Conclusion

Multidrug resistance due to the over-expression of efflux pumps is an upcoming clinical issue, rendering many of the existing antibiotics ineffective. To combat this MDR problem there is an urgent need for new antibiotics with novel modes of action. One promising approach is to explore phytochemicals that can interfere with the bacterial efflux pumps. Currently, no EPI from natural sources is in the clinical utility that can act effectively in synergy with antibiotics; however, extensive research is on-going to identify these useful chemicals.

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