

efficacy, with potential adverse effects. Many of the substances described so far are synthetic, but there are also natural substances under investigation. Essential oils from thyme and rosemary have been shown to possess sensitizing properties by inhibition of efflux pumps (Fadli et al. 2011).

Efflux pumps are a powerful strategy bacteria use to counter the effects of many different types of antibiotics. Even though research has been ongoing for some time, it has been difficult to find EPIs that either do not have strong adverse effects or inherent cytotoxicity (Mahamoud et al. 2007), and so far no drugs have reached the market (Mahmood et al. 2016; Spengler et al. 2017).

## 17.3 Sensitizing Strategies Circumventing Resistance Mechanisms

Established strategies to make bacteria susceptible to antibiotics often include direct activity against resistance mechanisms, as described above in Section 17.2. However, it is also possible to sensitize bacteria by indirect means by disrupting their basic homeostasis or their resistance growth phenotype. Examples of such strategies will be presented in this section.

### 17.3.1 Manipulating Bacterial Homeostasis

One strategy to accomplish sensitization of antibiotics is to target basic homeostasis of bacteria. Since many species of bacteria share proteins or enzymes that are important for bacterial homeostasis, this strategy has a lot of potential, as successful sensitization of one organism might prove effective against many other organisms. As mentioned under efflux pump inhibitors, one strategy that may have potential is to disrupt the membrane potential and/or proton motive force. This will not only close-circuit the driving force for efflux pumps but will have a general effect on bacterial membrane homeostasis and signaling. Besides the polycation, polymyxin B nonapeptide (PMBN), which was shown to sensitize enteric bacteria to several antibiotics (Vaara and Vaara 1983; Tsubery et al. 2000, 2005), high concentrations of cations have also been shown to be associated with the sensitivity of the fungus *Schizosaccharomyces pombe* to antibiotics (Alao et al. 2015).

Another interesting sensitizing compound is human alpha-lactalbumin made lethal to tumor cells (HAMLET), a protein–lipid complex from human milk, that is acting on the membrane to induce depolarization and specific ion fluxes. Marks et al., showed that this protein–lipid complex can sensitize bacteria to antibiotics (Marks et al. 2012, 2013). Although HAMLET has a direct antibacterial effect against a narrow spectrum of bacterial species, it only has