demonstrated that the natural spice compound cumin effectively inhibited drug transport activity from LmrS (Kakarla et al. 2017a). Because these MFS drug efflux mechanisms share homologous sequences and structures, it is predicted that they share similar mechanisms of transport across the membrane. Thus, transporters in this large superfamily will become important as investigators seek to elucidate these mechanistic commonalities for modulation of clinical drug and multidrug resistances.

8.1.2.2 Bacterial RND Multidrug Efflux Pumps

The RND antimicrobial efflux pump systems represent another large superfamily of transporters (Nikaido 2018). Many of these RND efflux pumps are driven by a proton motive force as their prime source of energy (Nikaido and Takatsuka 2009). Several key RND transporters assemble into a tripartite complex, consisting of an integral cytoplasmic membrane component, a periplasm-associated fusion protein, and an outer membrane channel protein (Misra and Bavro 2009).

Two of the most extensively studied RND drug efflux pumps are the AcrB multidrug efflux pump from *E. coli* (Nikaido and Zgurskaya 2001; Pos 2009) and the MexB multidrug efflux pump from *Pseudomonas aeruginosa* (Poole 2001; Blair and Piddock 2009). Both of these RND drug transporters have been structurally crystallized to high resolutions and extensively studied at the mechanistic level (Murakami et al. 2002; Sennhauser et al. 2009). The AcrB pump is part of an overall multimeric complex, AcrAB-TolC, which is composed also of the periplasmic fusion protein, AcrA, and the outer membrane associated channel, called TolC, all residing within the Gram-negative cell wall of the *E. coli* bacterium (Blair and Piddock 2009). Likewise, the MexAB-OprM efflux system is structurally organized in a similar fashion (Poole 2001; Puzari and Chetia 2017). Together, these two RND antimicrobial transporter systems constitute suitable targets for efflux inhibition in bacteria (Wang et al. 2016). Other RND efflux pumps include the MtrCDE system from *Neisseria gonorrhoeae* specific for structurally distinctive hydrophobic chemicals (Rouquette et al. 1999; Johnson and Shafer 2015) and the CusCBA system from *E. coli* conferring heavy metal resistance (Long et al. 2012). The crystal structures of both MtrD and CusA have been determined at about 3.5 Å resolution (Long et al. 2010; Bolla et al. 2014). A related RND zinc-specific pump called ZneA from *Cupriavidus metallidurans* has been crystallized, and its structure was revealed to 3 Å resolution (Pak et al. 2013). Since the RND transporters are found in both prokaryotic and all eukaryotic organisms, it will be interesting to gain a finer understanding of the tripartite assemblages in organisms without Gram-negative walls.

8.1.2.3 Bacterial MATE Drug Pumps

The transporters belonging to the MATE superfamily in bacteria provide multidrug resistance functions (Kuroda and Tsuchiya 2009). The members within the MATE superfamily have been subcategorized into three smaller