in stark contrast to the major classes of antibiotics (e.g., penicillins, quinolones), each of which has experienced the development of resistant strains as a result of widespread clinical application. Given the low level of antibiotic resistance that has developed since its original commercial introduction, it might seem logical to apply this medication to other types of bacterial infections, but this is not possible. Nitrofurantoin is uniquely capable of treating urinary tract infection, but other bacterial infections are not effectively treated with this drug.

In order to understand how this drug has retained its position in the medicine cabinet, one must examine both its mechanism of action and its pharmacokinetic properties. In the case of nitrofurantoin, there are multiple mechanisms of action that kill invading bacteria. Studies have shown that this drug kills bacteria via DNA damage, RNA damage, protein damage, and inhibition of the citric acid cycle.[25] The fact that it acts through multiple mechanisms explains the lack of resistance development. Resistance develops as a result of natural selection and mutation. In order for bacteria to develop resistance to penicillin, only one mechanism of action must be overcome. In the case of nitrofurantoin, however, mutations that confer resistance to at least the four mechanisms listed must all occur in a single organism. The odds of this occurring are so small that it almost never occurs.

Interestingly, the antibacterial activities of nitrofurantoin are driven by a structural feature that would be avoided in modern drug discovery programs, an aryl nitro group. This particular functionality is avoided in most modern drug discovery programs as it is a known risk factor for carcinogenicity, mutagenicity, and teratogenicity. In both humans and bacteria, aryl nitro groups are activated by the enzyme nitroreductase, which converts the nitro group to a nitroso group, a reactive functionality that damages DNA, RNA, and proteins via nucleophilic reactions and redox chemistry.[26] When these events occur in a bacteria, the organism dies and the patient is happy (Figure 13.12(a)), but if these events occur in cells of the patient, the results can be catastrophic (e.g., cancer, toxicity, Figure 13.12(b)). How is it

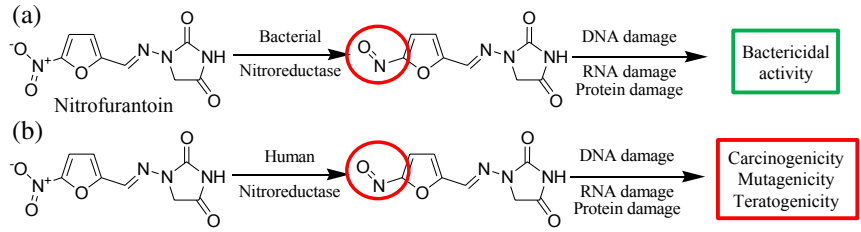

FIGURE 13.12 (a) Bacterial Nitroreductase converts nitrofurantoin to the corresponding nitroso compound (red) which kills bacteria via DNA damage, RNA damage, and proteins damage. (b) Human Nitroreductase also converts nitrofurantoin to the corresponding nitroso compound (red) which is a potential carcinogen, mutagen, and teratogen.