Infection and Drug Resistance

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REVIEW

Effects of Glutathione on Antibiotic Susceptibility and Resistance in Bacteria: A Comprehensive Review

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Abstract: Antibiotic resistance has spread globally among bacterial pathogens, becoming a significant challenge to public health. Bacterial cells have an enormous capability to acquire various antibiotic resistance mechanisms. The effectiveness of many antibiotics relies on the intracellular redox balance and the bacteria's ability to mount stress responses. Glutathione (GSH) is an intracellular tripeptide antioxidant that significantly contributes to maintaining optimal redox balance, which may impact bacterial survival during antibiotic treatment. Neutralizing oxidative stress caused by antibiotics can reduce their effectiveness. However, alterations of the redox balance of GSH can impair normal cellular metabolism, making cells vulnerable. Altering the redox balance, either by depleting or increasing levels of GSH, can enhance the effectiveness of antibiotics. The influence of GSH on antibiotics varies depending on the bacterial species and the class of antibiotics used. Due to the vital role of GSH in antibiotic effectiveness, targeting bacterial GSH metabolism can be used as an adjunctive approach to overcome antibiotic resistance. This review summarizes the relationship between GSH and antibiotic susceptibility and resistance in bacteria.

Keywords: glutathione, antibiotic resistance, redox homeostasis, oxidative stress

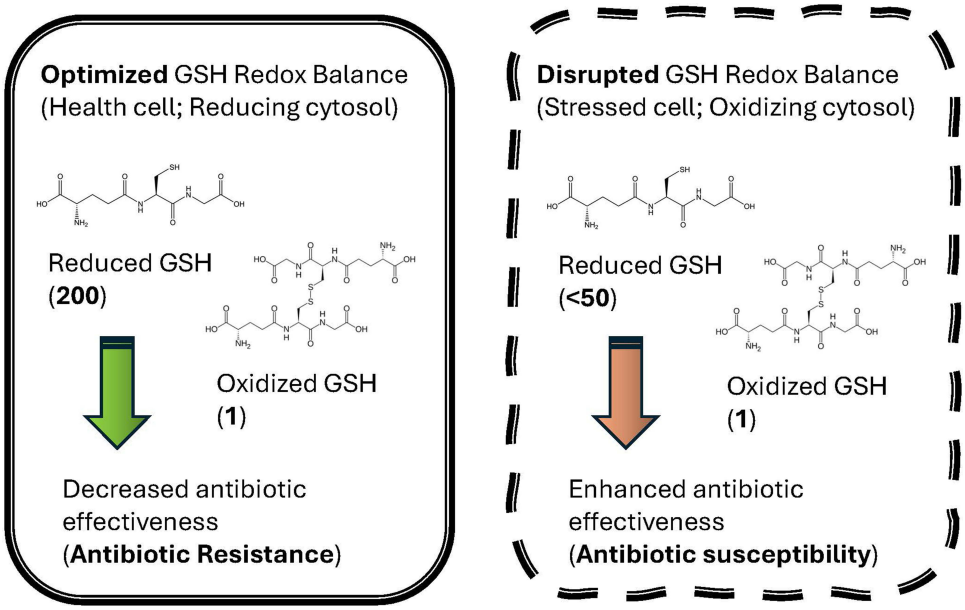
Introduction

Over the past decades, antibiotic resistance of bacterial pathogens has evolved into a major global health concern. The steady rise of resistant bacterial strains can be attributed to this silent pandemic, which undermines the effectiveness of modern medicine. International agencies, including the World Health Organization (WHO), regard antimicrobial resistance as one of the most significant threats to public health worldwide.[1] According to the WHO, in 2019, antibiotic resistance caused an estimated 1.27 million deaths directly and contributed to nearly 5 million deaths worldwide.[2] In the United States alone, an estimated 2.8 million resistant infections and over 35,000 deaths occur each year.[3] Antibiotic resistance also has a significant economic impact, as resistant cases require more costly therapies and more extended hospital stays. The WHO predicts approximately 1 trillion dollars in extra health spending by 2050 due to antibiotic resistance, along with multi-trillion-dollar gross domestic product (GDP) losses.[2] The situation is further aggravated by the fact that no new class of broad-spectrum antibiotics has been marketed since the 1980s.[1] Antibiotic resistance of bacterial pathogens also affects treatment progress, as resistant infections can compromise life-saving procedures such as chemotherapy, surgeries, and organ transplantation.[2] The WHO and other global organizations advocate for a multi-pronged approach to prevent infections, including vaccination, sanitation, antimicrobial stewardship, and the development of new diagnostics and drugs. This comprehensive strategy is crucial for addressing the growing threat of antibiotic resistance and improving global health security.[2,4]

Antibiotic resistance primarily arises when bacteria evolve or acquire genetic mutations that allow them to evade the effects of antibiotic treatment.[5] This allows bacteria to multiply even after exposure to antibiotics. This evolution is driven by selective pressure from antibiotic use, with factors such as decades of overuse, incorrect dosing, and the

https://doi.org/10.2147/IDR.S561116
Received: 16 August 2025
Accepted: 16 December 2025
Published: 9 January 2026

Graphical Abstract



widespread use of antimicrobials in livestock, contributing to the selection of resistant strains.[6] The environment also plays a role in the spread of resistance. Antibiotic residues in soil and water promote the selection of resistant bacteria and support the horizontal transfer of resistance genes between microbes. Over time, these processes have led to the emergence of many "superbugs." For example, surveillance data show that 42% of *Escherichia coli* isolates worldwide are resistant to third-generation cephalosporins and 15% of *Staphylococcus aureus* isolates are methicillin-resistant (MRSA) in elderly individuals.[2,7] Recently, the WHO published a list of drug-resistant pathogens that threaten human health. The list identifies carbapenem-resistant *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacteriaceae*, as well as rifampicin-resistant *Mycobacterium tuberculosis*, as critical threats. High-priority bacteria include fluoroquinolone-resistant *Salmonella Typhi*, vancomycin-resistant *Enterococcus faecium*, and MRSA.[8]

Glutathione (GSH) is a crucial intracellular antioxidant, a tripeptide (γ-glutamyl-cysteinyl-glycine) (Figure 1), and plays a key role in maintaining cellular redox balance. It is present at a diverse range of concentrations (0.1–10 mM) in nearly all Gram-negative bacteria, some Gram-positive bacteria, and all eukaryotic cells.[9,10] GSH primarily protects cells from oxidative stress by neutralizing reactive oxygen and nitrogen species. It also acts as a cofactor for detoxification enzymes, including glutathione peroxidases, thus helping preserve cellular redox homeostasis. Under normal conditions, most cellular GSH exists in its reduced form, with levels typically >100 times higher than those of its oxidized form glutathione disulfide (GSSG).[11,12] Within cells, the GSH structure is relatively resilient because most intracellular

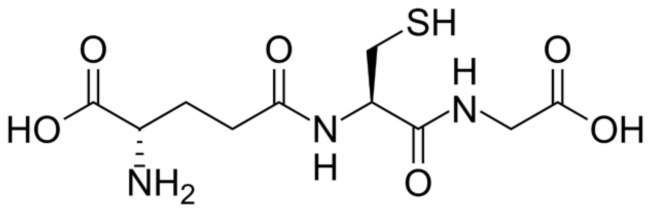


Figure 1 Structure of glutathione. Glutathione is composed of three amino acids (glutamate, cysteine, and glycine). Its distinguished structural feature is the γ-peptide linkage between the carboxyl group of the glutamate side chain and the amino group of cysteine. Cysteine's carboxyl group then forms a standard peptide bond with glycine. The molecular formula is $C_{10}H_{17}N_3O_6S$. Its sequence is γ-L-glutamyl-L-cysteinyl-glycine. A free thiol (-SH) on the cysteine residue is a functional group that is crucial for its antioxidant properties.[12]

proteases target α-linked peptide bonds, while γ-linkages, such as those in this molecule, are generally unaffected.[13] GSH is synthesized via a two-step enzymatic pathway and can be regenerated from GSSG by GSH reductase using NADPH.[14] In bacteria, GSH maintains the redox state of protein thiols and protects cells from acid, oxidative, and osmotic stress. Furthermore, GSH can modulate protein function via S-glutathionylation under oxidative stress.[15] The GSH/GSSG ratio serves as a key indicator of cellular redox status and may influence bacterial tolerance to antibiotics by regulating oxidative stress responses and protein thiol homeostasis. Shifts in this balance can alter the redox environment, potentially affecting bacterial survival under antibiotic pressure.[14]

The intersection of GSH and antibiotic susceptibility or resistance remains relatively underexplored. However, emerging evidence has uncovered several important connections. Many bactericidal antibiotics exert their effects, at least in part, via oxidative damage to cells. Therefore. GSH, as a central redox buffer, could influence antibiotic efficacy. For example, exogenous GSH has been recently shown to synergize with meropenem, significantly enhancing the killing of carbapenem-resistant *Klebsiella pneumoniae*.[16,17] Similarly, supplementation with a GSH precursor (N-acetylcysteine) improved the effectiveness of first-line drugs against *M. tuberculosis*, facilitating enhanced bacterial clearance.[18] In contrast, exogenous GSH decreased the susceptibility to ciprofloxacin and kanamycin in *P. aeruginosa* without significant differences in susceptibility to ampicillin and chloramphenicol.[19] These findings suggest that manipulating the thiol-redox balance could become a novel strategy for combating antibiotic resistance. As new evidence emerges about the role of GSH on antibiotic susceptibility and resistance in bacteria, it is essential to provide a clear overview of this information. This review aims to provide an updated understanding of GSH metabolism, with a focus on how GSH influences antibiotic susceptibility and resistance.

Mechanisms of Antibiotic Resistance: Overview

Bacterial resistance to antibiotics develops by intrinsic traits or by acquiring new genes or mutations. Intrinsic resistance stems from the inherent biological characteristics of a bacterial species and is present before any exposure to drugs. For instance, the outer membrane of Gram-negative bacteria acts as a barrier that prevents many drugs from entering the cell.[20] Similarly, anaerobes, which do not require oxygen for growth, are naturally resistant to aminoglycosides, a class of antibiotics that rely on oxygen for their mechanism.[21] In Gram-negative bacteria, drug entry occurs through porin channels, bilayer diffusion, or passive uptake. Small hydrophilic antibiotics such as β-lactams and fluoroquinolones rely on porins to cross the outer membrane.[22] Reduced porin expression significantly limits their uptake, which leads to resistance against these drugs. In *P. aeruginosa*, low outer membrane permeability is a significant factor contributing to resistance across multiple antibiotic classes.[23] All Gram-positive bacteria are intrinsically resistant to aztreonam, as they do not have penicillin-binding proteins (PBPs) that bind to aztreonam. Similarly, many Gram-positive bacteria chromosomally encode efflux pumps that expel certain antibiotics, such as fluoroquinolones and macrolides.[24]

Acquired resistance arises through genetic mutations or horizontal gene transfer.[25] In practice, pathogens often employ these mechanisms in combination. Bacteria can adopt several biochemical strategies to evade antimicrobial effects. For example, drug inactivation is a strategy that bacteria adopt by producing enzymes that chemically modify or destroy antibiotics.[25] Classic examples are β-lactamases, which hydrolyze the β-lactam ring of penicillins, cephalosporins, monobactams, and even carbapenems.[23] In *Enterobacteriaceae*, a variety of β-lactamases, including extended-spectrum β-lactamases (ESBLs) and carbapenemases (KPC, NDM, VIM, OXA), are present and confer resistance against last-resort antibiotics like carbapenems.[26] Such enzymes render the drug molecules inert before they reach their targets. Another strategy is target-modification. Bacteria alter the binding site of the antibiotic, so the drug no longer fits. For example, MRSA carries the *mecA* gene, which encodes PBP2a, a low-affinity penicillin-binding protein.[23] PBP2a can build a cell wall even in the presence of β-lactams, so MRSA is resistant to all penicillins and cephalosporins. Vancomycin-resistant enterococci (VRE) replace the terminal D-Ala-D-Ala of the peptidoglycan precursor with D-Ala-D-Lac, which vancomycin cannot bind.[27] Point mutations in the DNA gyrase or topoisomerase IV genes confer fluoroquinolone resistance.[28,29] Similarly, methylation or mutation of rRNA can confer resistance to macrolides, lincosamides, or tetracyclines. In each case, a slight change in the drug's target protein prevents binding without abolishing its normal function.[30]

Apart from these, efflux pumps are also a potential mechanism for antibiotic resistance. Many bacteria express membrane transporters that export antibiotics from the cell. These can be specific or broad-spectrum pumps. For example, *P. aeruginosa* possesses Mex pumps,[31] and *E. coli* has the AcrAB-TolC efflux pump, which can pump out β-lactams, fluoroquinolones, tetracyclines, and other antibiotics.[32] Efflux lowers the intracellular drug concentration below inhibitory levels. Overexpression of efflux genes, often on plasmids or via mutations, is common in resistant strains.[33] Another mechanism of bacterial drug resistance is reduced permeability, which prevents the entry of drugs.[25] In Gram-negative bacteria, the loss or mutation of porin proteins restricts the entry of hydrophilic drugs. As a result, carbapenem-resistant *Enterobacteriaceae* often combine the expression of β-lactamases with the loss of porins to evade treatment. Reduced drug uptake serves as a primary line of defense, even before other resistance mechanisms develop.[34]

Biofilm formation is another strategy for antibiotic resistance. Biofilms are structured microbial communities that form when microorganisms adhere to surfaces and secrete a protective extracellular polysaccharide (EPS) matrix. This matrix creates channels that facilitate nutrient flow and waste removal while shielding the bacteria from external threats. Over time, parts of the biofilm can disperse, which allows microbes to colonize new areas.[35,36] Cells in biofilms enter a slow-growing state and are up to 1,000 times more resistant to antibiotics.[37,38] Biofilms both physically prevent drugs from reaching all cells and induce stress responses, such as the production of enzymes that neutralize drugs. Chronic infections by *P. aeruginosa, S. epidermidis*, and other biofilm-forming bacteria often require much higher antibiotic doses.[39] These acquired resistant mechanisms are often employed in conjunction with other mechanisms of antibiotic resistance. For example, a carbapenem-resistant *K. pneumoniae* may carry a plasmid-encoded carbapenemase and have mutated porins.[25] Similarly, *P. aeruginosa* commonly uses low-permeability outer membranes, active efflux, and enzyme production simultaneously to resist multiple drug classes.[40]

GSH in Bacterial Physiology

Biosynthesis, Metabolism, and Distribution

GSH is synthesized through a two-step process involving peptide linkages (Figure 2). First, a gamma-peptide bond is created between the carboxyl group of the glutamate side chain and the amino group of cysteine. This reaction is catalyzed by the enzyme gamma-glutamyl-cysteine synthetase, which is encoded by the gene *gshA*. In the second step, a standard peptide bond is formed between cysteine and glycine, catalyzed by GSH synthetase, which is encoded by the gene *gshB*. Both reactions depend on ATP, and the reaction mechanisms are similar.[12] The *gshA* is controlled by feedback inhibition; specifically, the end-product, GSH, accumulates in the cell and acts as an inhibitor of γ-glutamylcysteine ligase activity, thereby preventing the overproduction of GSH[41] (Figure 2). A sulfhydryl (thiol) from the cysteine is a major functional group for the GSH.[42,43] In *E. coli*, the thiol-reduced form (GSH) is predominant (>99%) and the remaining amount undergoes thiol oxidation to form GSH-disulfide (GSSG) and mixed-disulfides with target compounds. The ratio of GSH/GSSG is 300 to 600, which corresponds to a redox potential (*Eo*') of −240 mV, assuming a total intracellular GSH of 5 mM, pH 7.0, and 25°.[10,44,45] The GSSG is highly toxic since it easily reacts with free sulfhydryl groups from any source. Therefore, maintenance of the ratio (GSH/GSSG) is critical in normal cellular functions.[12]

E. coli has distinct GshA and GshB proteins, while *Listeria monocytogenes* features a single bifunctional enzyme, GshF, which catalyzes both steps within one polypeptide.[47,48] GSH metabolism includes degradation and recycling. Bacteria often express γ-glutamyltranspeptidase (GGT) to cleave GSH into amino acids, and GSH reductase (GR) regenerates reduced GSH from GSSG using NADPH (Figure 2). However, not all bacteria synthesize GSH. Many Gram-negative bacteria, such as *E. coli, Salmonella*, and *P. aeruginosa*, synthesize and utilize GSH in redox and detoxification pathways, whereas many Gram-positive bacteria do not produce GSH, except for those such as *L. monocytogenes* and *Streptococcus agalactiae*.[49] Gram-positive bacteria, such as *S. aureus* and *Bacillus subtilis* produce an alternative low-molecular-weight thiol, bacillithiol, instead of GSH, and *Mycobacteria* use mycothiol.[50,51] Some bacteria cannot synthesize GSH and must import it. *Haemophilus influenzae* and *Lactococcus lactis* cannot make GSH but scavenge it from the environment to boost oxidative defense. In addition, the majority of anaerobic bacteria lack *gshA* and are therefore unable to synthesize GSH.[52] These differences lead to varied antibiotic responses. For instance, in one study, 30 mM GSH strongly inhibited *S. aureus, E. coli*, and *A. baumannii*, but had little effect on *K. pneumoniae* or

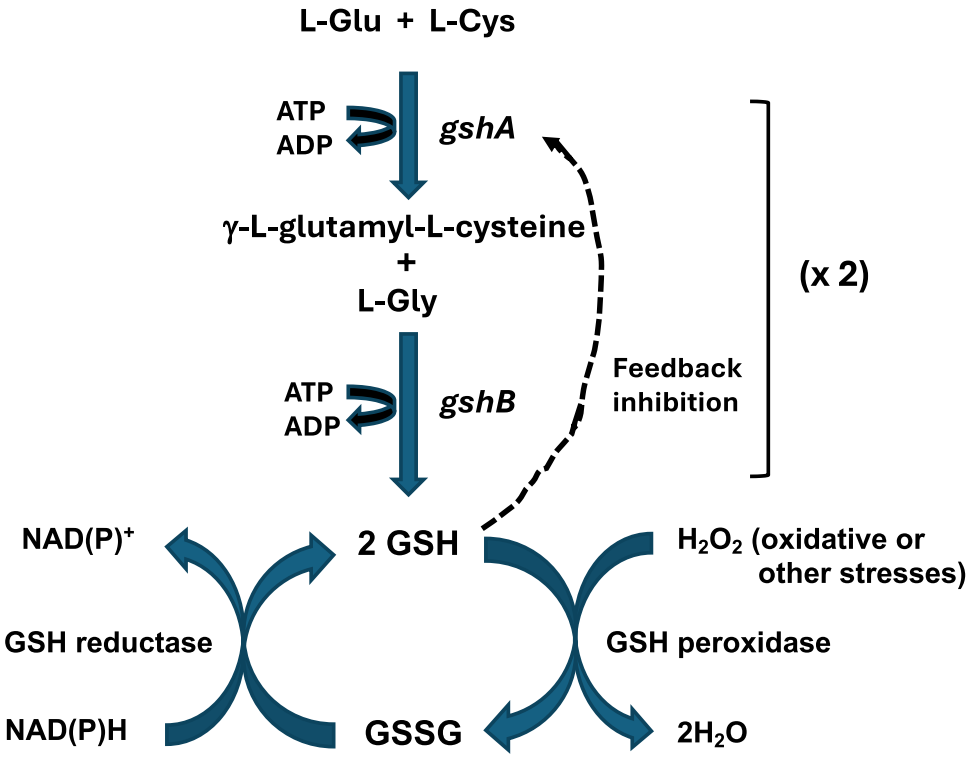


Figure 2 GSH synthesis and redox cycle of GSH. GSH is synthesized by two sequential ATP-dependent reactions catalyzed by γ-glutamyl-cysteine synthetase, encoded by *gshA*, that links the carboxyl group of the glutamate side chain (γ-carboxyl) and the amino group of cysteine, and GSH synthetase encoded by *gshB* that links the carboxyl group of cysteine and the amino group of glycine by a typical peptide bond.[12] Electrons from the functional group (-SH) of two GSH molecules reduce oxidative stress (eg, hydrogen peroxide) to water and oxygen molecules by the GSH peroxidase, and the two GSH molecules are oxidized to form GSH disulfide (GSSG). The GSSG is highly toxic and is reduced to GSH by GSH reductase, using electrons from NADPH.[12,46]

Enterobacter.[53] By contrast, *P. aeruginosa* biofilms were potently disrupted by GSH plus DNase/antibiotic.[54] These species-specific patterns reflect underlying physiological characteristics, including the cell envelope, efflux systems, and thiol metabolism.

Redox Homeostasis and Protection Against Oxidative Stress

GSH is a central redox buffer that preserves intracellular thiol balance by neutralizing reactive oxygen and nitrogen species, thereby maintaining protein cysteines in the reduced state.[55] For example, GSH provides electrons to glutaredoxin enzymes, which reduce oxidized disulfide bonds in proteins and repair oxidative damage.[9] GSH peroxidases and related enzymes use GSH to detoxify peroxides. They reduce hydrogen peroxide and organic hydroperoxides to water or alcohols by oxidizing GSH to GSSG. The oxidized GSSG is then recycled by GSH reductase, sustaining a high intracellular GSH/GSSG ratio. This redox cycle enables bacteria to survive oxidative insults such as H_2O_2, singlet oxygen, as well as acid and osmotic stresses[56,57] (Figure 2). GSH also buffers toxic electrophiles and environmental toxins through conjugation reactions.[14] When GSH is depleted or oxidized, bacteria become hypersensitive to oxidative and nitrosative stress.[58] Beyond its role in redox buffering, GSH has a diverse range of functions. It can serve as a reservoir of reduced sulfur, interfacing with sulfur metabolism and biogenesis of sulfur-containing cofactors.[59] Importantly, GSH mediates regulatory S-glutathionylation of proteins. Under oxidative or nitrosative stress, GSH covalently binds to exposed cysteine thiols on enzymes, protecting them from irreversible oxidation and modulating their activity.[9] This reversible modification acts as a redox-dependent switch in bacterial signaling. GSH also influences metal ion homeostasis. For instance, elevated GSH levels in *L. monocytogenes* increase tolerance to copper and iron stress, suggesting that GSH chelates or buffers excess metal ions to prevent toxicity.[60]

https://doi.org/10.2147/IDR.S561116

The Role of GSH in Antibiotic Resistance Mechanisms

Antioxidant Defense of GSH on Antibiotic Susceptibility

Bactericidal antibiotics typically kill bacteria by generating reactive oxygen species (ROS) within their cells. GSH is a key intracellular thiol that helps neutralize ROS and maintain the balance between protein thiols and disulfides.[61] Bacteria maintain a high ratio of reduced GSH to oxidized glutathione (GSSG) by utilizing GSH reductase, which depends on NADPH. Under antibiotic stress, bacterial metabolism often shifts to regenerate NADPH and recycle GSH.[62] GSH plays a vital antioxidant role by scavenging ROS; it directly reduces H_2O_2 and hydroxyl radicals, effectively neutralizing these harmful oxidants (Figure 2). For example, pretreatment of *E. coli* with GSH significantly reduced the bacterial killing effect of antibiotics such as ampicillin, gentamicin, and norfloxacin, suggesting that GSH neutralizes the antibiotic-induced ROS.[63]

Additionally, ample GSH improves cell viability, whereas its depletion drastically increases susceptibility to ROS-inducing antibiotics.[64] Antibiotic-challenged cells often boost GSH. In *Synechocystis*, exposure to gentamicin stimulated GSH synthesis, whereas a Δ*gshB* mutant was killed by the drug, despite carrying a resistance gene.[65] Similarly, adding GSH to *Pseudomonas* cultures helped restore host-cell GSH recycling and prevented antibiotic-induced oxidative injury.[54] Conversely, the *P. aeruginosa* mutant strain deficient in both *gshA* and *gshB* showed a 4-fold and 8-fold increase in sensitivity to hydrogen peroxide and superoxide, respectively, suggesting antioxidant defense of GSH on antibiotics.[66] These findings demonstrate that GSH buffers antibiotic-generated oxidative stress, whereas a deficiency in GSH or an overload of ROS renders bacteria significantly more vulnerable.

GSH-Mediated Metabolism and Antibiotic Susceptibility

GSH-dependent metabolic pathways also contribute to the detoxification of antibiotics. The primary route is GSH conjugation. Glutathione S-transferases (GSTs) catalyze the attachment of GSH to antibiotics or their reactive byproducts, often leading to inactivation. For instance, in *E. coli*, a plasmid-encoded GST attaches GSH to the epoxide ring of fosfomycin, opening the ring and rendering the drug inactive.[67,68] The GSH-antibiotic conjugate is more water-soluble and can be expelled, reducing the effective drug concentration. In parallel, GSH-linked enzymes detoxify harmful metabolites. For instance, GSH peroxidase and GSH reductase use GSH to eliminate peroxides generated by drug action.[56] Together, these processes function like a bacterial "phase II" detoxification system,[69] diminishing the potency of antibiotics. Consistently, bacterial GSTs have been implicated in antibiotic resistance phenotypes. When GSH conjugation or related pathways are inhibited by gene knockout, bacterial sensitivity to various antibiotics increases.[70]

Bacterial metabolism has a significant impact on the effect of GSH on antibiotic susceptibility. Under antibiotic pressure, bacteria reprogram metabolism to support GSH turnover. For example, antibiotics that induce ROS, like β-lactams or aminoglycosides, often cause bacteria to up-regulate the pentose phosphate pathway for NADPH production, which feeds GSH.[71,72] Carbon flux can also shift. Fluoroquinolone exposure tends to suppress the TCA cycle and activate the glyoxylate shunt, conserving carbon and reducing ROS while channeling electrons into NADPH/GSH synthesis. Aminoglycosides have been reported to promote fermentative metabolism and increase the GSH/NADPH pathway activity.[62] At the same time, amino acid catabolism adapts to support GSH. Enzymes such as glutamate dehydrogenase replenish TCA intermediates and provide glutamate for GSH synthesis. Disrupting these metabolic links sensitizes bacteria to oxidative stress. As one review notes, enzymes in GSH biosynthesis maintain intracellular ROS detoxification, and their inhibition sensitizes cells to oxidative stress.[62]

GSH Depletion and Antibiotic Susceptibility

Intense antibiotic or host-induced stress can deplete bacterial GSH pools, tipping the balance toward cell death. Persistent ROS generation or electrophilic stress can oxidize GSH to GSSG more rapidly than it is reduced, thereby depleting the reduced thiol pool.[73] Some antibiotic treatments can accelerate the depletion of GSH. For example, combinations of redox-active drugs and metal ions, such as copper or silver, can promote thiol oxidation.[74] Experimental evidence highlights the effect. For example, the GSH-deficient (*gshB* knockout) *Synechocystis* strain was far more susceptible to gentamicin, despite carrying a resistance gene.[65] Similarly, a *P. aeruginosa* strain lacking genes for glutathione (*gshA* and

gshB) shows significantly higher susceptibility to carbenicillin, ciprofloxacin, and chloramphenicol.[66] In contrast, preserving GSH by supplementing cysteine or GSH precursors helps bacteria survive oxidative challenge. Thus, depleting GSH, either pharmacologically or by metabolic overload, is a strategy to sensitize bacteria. For instance, inhibitors of GSH synthesis, such as buthionine sulfoximine in laboratory studies, can enhance the killing effect of antibiotics.[75]

Exogenous GSH on Antibiotic Susceptibility

At high concentrations, such as over 10 mM, GSH exhibits antibacterial activity. Concentrations of more than 50 mM GSH, which acidify the medium, inhibited the growth of *S. aureus, E. coli, K. pneumoniae*, and *P. aeruginosa*. Even at neutral pH, exogenous GSH has a concentration-dependent bacteriostatic effect.[76] Additionally, excessive GSH may alter bacterial intracellular redox homeostasis, which paradoxically leads to increased production of ROS and causes oxidative damage.[16] The antibacterial activity of GSH may be specific to bacterial species, requiring levels that exceed their typical physiological amounts. However, at physiological concentration (10 mM), GSH did not affect bacterial growth.[76] Exogenous GSH can markedly alter the efficacy of antibiotics. The effect of GSH on antibiotic susceptibility varies depending on the antibiotics and bacterial species, resulting in synergism, indifference, or antagonism. In carbapenem-resistant *K. pneumoniae*, adding GSH (6 mM) to meropenem resulted in a 2-log greater killing effect and lowered the antibiotic's MIC several-fold.[54] These synergies may arise because GSH disrupts bacterial membranes and metabolism. One study found GSH with meropenem disrupted glycerophospholipid metabolism and increased membrane permeability.[16] Additionally, glutathione increased susceptibility to tetracycline but decreased susceptibility to ciprofloxacin and kanamycin, without a significant difference in susceptibility to ampicillin and chloramphenicol, in *P. aeruginosa*.[19] Similar effects of glutathione were also reported in *A. baumannii, E. coli*, and *S. aureus*.[77–79] Furthermore, a recent report demonstrated that exogenous GSH at physiological concentration (10 mM) enhanced susceptibility to chloramphenicol, novobiocin, and tetracycline, while decreasing susceptibility to ciprofloxacin, erythromycin, and kanamycin in *A. baumannii*.[78] The effect of exogenous GSH on antibiotic susceptibility is summarized in Table 1.

A biofilm in bacteria is a structural community of bacterial cells that are attached to a surface (biotic or abiotic) and embedded in a self-produced matrix of extracellular polymeric substances.[35,36] In *P. aeruginosa* biofilms, combining

Table 1 The Effect of Exogenous Glutathione (GSH; Reduced) on Antibiotic Susceptibility

Bacterial Species	Antibiotics Affected[c]	GSH Levels	Effect Outcome[d]	Ref.
A. baumannii (Carbapenem resistant/MDR)[a]	ATM, CAR, CAZ, MEM, CIP, GEN, TET	11 mM	Synergistic	[80]
A. baumannii (Carbapenem resistant/MDR)	CAM, NOV, TET CIP, KAN, ERY	10 mM	Synergistic /Antagonistic	[78]
A. baumannii (Biofilm)	AMK	30 mM	Synergistic (4–10%)	[53]
E. coli	STR, KAN, GEN, SPE, TET, CAM	10 mM	Antagonistic /Indifference	[77]
E. coli (bla_{KPC-2a} and bla_{KPC-2b})	MEM	10 mM	Synergistic	[17]
E. coli (Biofilm)	CIP	30 mM	Synergistic (1–6%)	[53]
K. pneumoniae (Carbapenem resistant)	MEM	3 to 6 mg/mL	Synergistic	[16]
K. pneumoniae (Carbapenem resistant)	MEM	10 mM	Synergistic	[17]
K. pneumoniae (Biofilm)	CIP	30 mM	Synergistic (0–9%)	[53]
P. aeruginosa	TET, CIP, KAN, CAM, AMP	3 mg/mL	Synergistic /Indifference /Antagonistic	[19]
P. aeruginosa (bla_{KPC-2a} and bla_{KPC-2b})	MEM	10 mM	Synergistic	[17]
P. aeruginosa (Biofilm)	CIP	30 mM	Synergistic (33–54%)	[54]

(*Continued*)

https://doi.org/10.2147/IDR.S561116

Table 1 (Continued).

Bacterial Species	Antibiotics Affected[c]	GSH Levels	Effect Outcome[d]	Ref.
S. aureus	CIP, GEN CAM	10 mM	Synergistic /Indifference	[79]
S. aureus (MRSA/MSSA)[b]	MET, ATM, CAR, CAZ, MEM, CAM, CIP, GEN, TET, VAN	7.5–12 mM	Synergistic	[81]
S. aureus (Biofilm) (MRSA/MSSA)	CIP	30 mM	Synergistic (0–22%)	[53]
Enterobacter sp. (Biofilm)	CIP	30 mM	Synergistic (0–9%)	[53]
Streptococcus pyogenes (Biofilm)	CIP	30 mM	Synergistic (0–12%)	[53]

Notes: [a]MDR, multidrug resistance. [b]MRSA, Methicillin resistant *S. aureus*; MSSA, Methicillin sensitive *S. aureus*. [c]ATM, Aztreonam, [d]Synergistic: Minimum inhibitory concentration (MIC) decreased >4 folds or % decreased for biofilm, Antagonistic: MIC increased >4 folds, Indifference: MIC unchanged or decreased/increased 2 folds. **Abbriviations** CAR, Carbenicillin; CAZ, Ceftazidime; MEM, Meropenem; CIP, Ciprofloxacin; GEN, Gentamicin; TET, Tetracycline; CAM, Chloramphenicol; NOV, Novobiocin; KAN, Kanamycin; ERY, Erythromycin; AMK, Amikacin; MET, Methicillin; VAN, Vancomycin; AMP, Ampicillin; STR, Streptomycin; SPE, Spectinomycin.

10–20 mM GSH with DNase and antibiotics reduced biofilm biomass by 90%.[54] At a concentration of 10 mM, GSH had minimal effects on bacterial growth or biofilm disruption. However, at 30 mM, it reduced growth by over 50% in all tested species, except for *K. pneumoniae* and *Enterobacter* species. Notably, GSH almost completely inhibited *Streptococcus pyogenes*, while *E. coli*, MRSA, and multidrug-resistant *A. baumannii* showed inhibition rates ranging from 52% to 94%. Additionally, biofilm viability decreased by more than 50% across all species. The combination of GSH with amikacin and DNase I resulted in the most substantial reduction in biofilm viability, promoting fibroblast growth while simultaneously reducing bacterial adhesion.[53] The effect of exogenous GSH on biofilm-mediated antibiotic susceptibility is summarized in Table 1.

On the other hand, some GSH precursors and related compounds, including L-cysteine, N-acetyl cysteine (NAC), and GSSG, were also assessed for their impact on antibiotic susceptibility in various bacterial species. L-cysteine is a GSH precursor and impacts thiol homeostasis and antibiotic susceptibility in bacteria. For example, oxidized cysteine (cystine) makes *Salmonella enterica* more sensitive to gentamicin by disrupting the intracellular redox balance, altered the GSH/GSSG ratio, raised ROS, and increased ferrous iron, which potentially fuels the Fenton reaction, all of which contribute to greater bactericidal activity.[70] NAC is a synthetic derivative of L-cysteine, where an acetyl group attached to the nitrogen atom of the amino acid. In bacteria, NAC acts as a cysteine donor for GSH biosynthesis, indirectly influencing the roles of GSH in GSH-producing bacteria.[82] NAC can both enhance and reduce antibiotic efficacy, depending on the bacterial species and antibiotics. In *Edwardsiella tarda*, NAC promotes resistance to several antibiotics (eg, doxycycline) by increasing intracellular GSH, decreasing ROS, increasing efflux pump activity, and lowering membrane permeability.[83] Additionally, NAC showed synergistic bactericidal activity with β-lactams (eg, meropenem) against carbapenem-resistant *K. pneumoniae* and *A. baumannii*.[84] GSSG is an oxidized form of GSH and can alter antibiotic susceptibility in bacteria, but the effects are complex, and depend on the specific antibiotic, the bacterial species, and redox context. A recent study found that exogenous GSSG restores carbapenem susceptibility in *E. coli* carrying metallo-β-lactamase gene ($bla_{\text{NDM-1}}$). Mechanistically, GSSG disrupted the intracellular redox balance and inhibited expression of $bla_{\text{NDM-1}}$ in *E. coli*, thereby potentiating the killing effect of carbapenem.[85]

Interplay Between GSH and Antibiotics

Efflux Pumps

GSH can enhance the bacterial efflux of antibiotics. For example, supplementation with GSH increased active drug efflux in *E. coli*, partly neutralizing ciprofloxacin's action.[86] In *E. coli* exposed to ciprofloxacin, exogenous GSH both quenched ROS and stimulated efflux systems.[87] Notably, GSH protection against antibiotics did not require the AcrAB pump but failed in cells lacking the TolC channel,[88] suggesting that TolC-dependent pumps are involved. Redox-sensitive regulators link GSH to efflux gene expression. In *E. coli*, oxidants promote S-glutathionylation of the MarR repressor (a MarR-family protein), reducing its DNA binding and derepressing the *mar* operon (including *acrAB*).[89] Similarly, in *P. aeruginosa*, the MexR

repressor senses oxidative stress (two Cys residues form disulfides), dissociates from the *mexAB-oprM* promoter, and derepresses efflux under peroxide stress.[90] In short, GSH-rich conditions shift the redox balance of these regulators, promoting pump expression. Efflux regulators also respond to endogenous ligands (eg, AcrR responds to polyamines) to induce *acrAB-tolC*.[91] Thus, GSH can drive efflux-mediated resistance by both enabling antibiotic efflux and modulating the redox state of efflux pump regulators.

Enzymatic Inactivation

GSH participates in antibiotic inactivation via enzymatic conjugation and regulation. The classic example is fosfomycin resistance. Many bacteria carry a plasmid-encoded glutathione S-transferase (FosA) that conjugates GSH to fosfomycin, opening the epoxide ring and inactivating the drug.[92] In this mechanism, bacterial GSH is an essential cofactor, and mutants that are defective in GSH biosynthesis cannot inactivate fosfomycin, even though they possess the resistance gene. GSH also affects β-lactamase activity indirectly. For instance, oxidized glutathione (GSSG) has recently been shown to suppress the expression of the NDM-1 metallo-β-lactamase gene, thereby restoring carbapenem susceptibility in *E. coli*.[85] Thus, an elevated GSH/GSSG ratio may downregulate this antibiotic-degrading enzyme. Although the direct conjugation of β-lactams with GSH is not well-documented, GSH plays a crucial role in maintaining a reducing environment in the cytosol, which is essential for proper enzyme function. Without GSH, oxidative misfolding can lead to the inactivation of certain enzymes.[73] For aminoglycosides, specialized acetyltransferases and nucleotidyltransferases modify the drug. While GSH has no known role in these enzymes, general oxidative stress can impair protein stability. More broadly, bacterial glutathione S-transferases detoxify diverse electrophiles, suggesting that GSH-dependent pathways may stabilize or recycle enzymes that degrade antibiotics. In summary, GSH enables antibiotic inactivation by serving as a substrate for detoxifying enzymes, such as FosA, and by modulating the expression or stability of antibiotic-degrading enzymes, including the downregulation of NDM-1.[73,85]

Target Modification

The influence of GSH on redox homeostasis can impact mutation rates and post-translational modifications of antibiotic targets. By neutralizing ROS, GSH limits DNA damage. Goswami et al found that GSH supplementation counteracts fluoroquinolone-induced oxidative stress and alters expression of DNA repair genes.[87] Thus, high GSH may reduce the mutation rate in genes encoding drug targets such as ribosomal proteins or DNA gyrase. In contrast, GSH deficiency can elevate ROS-driven mutagenesis and promote the development of resistance mutations. Conversely, oxidative stress can trigger S-glutathionylation of protein cysteines. For example, MarR is glutathionylated under oxidative conditions,[89] suggesting that other thiol-containing proteins, potentially including antibiotic targets or regulators, may also be modified in vivo. Such modifications could alter target conformation or activity. In addition, GSH levels play a crucial role in regulating these networks. Transcriptomic analysis has shown that the addition of exogenous GSH can change the expression of stress-response and repair.[87] As a result, GSH-related redox signaling may influence how bacteria react to DNA damage, potentially affecting the development of target mutations or modifications in the presence of antibiotic pressure.

Reduced Permeability

GSH contributes to maintaining membrane integrity and promoting the uptake of antibiotics. It maintains a reducing environment within the envelope. In *E. coli*, the periplasmic GSH is detected by envelope stress regulators. Song et al showed that decreasing periplasmic GSH by deleting the GSH exporter CydD triggers the CpxR/SoxS two-component systems, upregulating the AcrAB-TolC pump and lowering intracellular drug accumulation.[93] In their model, Δ*cydD* mutants had reduced trimethoprim uptake, which was reversed by deleting *acrAB* or by restoring GSH (74). This indicates that low GSH can indirectly reduce permeability via increased efflux. Additionally, GSH prevents membrane oxidative damage. Without sufficient GSH, ROS can peroxidize lipids and form disulfide bonds in periplasmic proteins, potentially stiffening the membrane or altering porin channels.[94] Thus, GSH-deficient conditions may diminish outer-membrane permeability both by oxidative damage and by regulatory downshifts in porins. Overall, GSH helps preserve membrane function; when GSH levels are low, bacterial cells often exhibit decreased antibiotic influx and increased efflux, contributing to antibiotic resistance.

Clinical Relevance and Therapeutic Potential

The interaction between GSH and antibiotics holds significant clinical implications, particularly in the context of rising antimicrobial resistance. GSH influences bacterial physiology and response to antibiotics.[49] Clinically, this interplay can either enhance antibiotic effectiveness or contribute to resistance, depending on the bacterial species and environmental conditions. Evidence shows that elevated intracellular GSH levels in some pathogens, such as *P. aeruginosa* and *S. aureus*, may protect them against oxidative stress induced by antibiotics like aminoglycosides and quinolones.[66] This protection arises because GSH neutralizes ROS, which are essential for the bacterial killing effects of many bactericidal antibiotics. Consequently, bacteria with robust GSH synthesis pathways may display reduced susceptibility to certain drugs. On the other hand, some antibiotics, such as β-lactams, can deplete bacterial GSH, which weakens the defense against oxidative stress and promotes bacterial death.[95] Therapeutically, bacterial GSH levels can be manipulated to overcome antibiotic resistance. Agents that deplete bacterial GSH or inhibit its synthesis could sensitize bacteria to antibiotics, which makes resistant strains more treatable Exogenous GSH administration adds another dimension to therapeutic considerations. The effectiveness of GSH administration may vary depending on the pathogen, type of infection, host condition, and the class of antibiotics used. Therefore, administering GSH alongside antibiotics in the treatment of infectious diseases is a double-edged sword. For example, in tuberculosis, adjunctive GSH therapy enhanced the killing of *M. tuberculosis* by macrophages while reducing inflammatory damage.[96] However, GSH supplementation might protect pathogens by scavenging ROS, reducing drug efficacy in certain contexts.[66] Therefore, the therapeutic use of GSH must be approached cautiously, balancing host protection with potential benefits to bacteria.

Conclusion and Future Perspectives

GSH can significantly shape bacterial response to antibiotics. It acts as a protective antioxidant, such as neutralization of stress responses, modulation of antibiotic targets, and interference with antibiotic activation. The evidence suggests that GSH significantly influences mechanisms of neutralizing ROS, regulating efflux pumps, enzymatic inactivation, and biofilm formation, all of which are pivotal in antibiotic resistance. On the other hand, depletion or elevation of GSH can increase bacterial vulnerability, which can be exploited in antibiotic therapy. This dual nature of GSH makes it an attractive but challenging target for therapeutic applications. Despite these promising insights, several limitations remain in current research. Most existing studies are limited to in vitro or animal models, and data on clinical isolates or patient outcomes are scarce. The concentration and redox state of GSH can vary considerably between bacterial species and environmental conditions, making it difficult to generalize its effects on antibiotic susceptibility. Additionally, the interplay between GSH and other redox systems such as thioredoxin, glutaredoxin, and catalase remains poorly understood. The lack of standardized experimental models and the complexity of bacterial metabolic networks further complicate the interpretation of results. Future research should therefore focus on the specific interactions between bacterial species and antibiotics related to GSH to develop targeted treatment strategies.

Funding

This research received no specific grant from funding agencies in public, commercial, or non-for-profit sectors.

Disclosure

The authors report no conflicts of interest in this work.

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