



Review

Polymyxins–Curcumin Combination Antimicrobial Therapy: Safety Implications and Efficacy for Infection Treatment

Chongshan Dai ^{1,*}, Yang Wang ¹, Gaurav Sharma ², Jianzhong Shen ¹, Tony Velkov ³ and Xilong Xiao ^{1,*}

¹ Department of Veterinary Pharmacology and Toxicology, College of Veterinary Medicine, China Agricultural University, No.2 Yuanmingyuan West Road, Beijing 100193, China; wangyang@cau.edu.cn (Y.W.); sjz@cau.edu.cn (J.S.)

² Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA; Gaurav.Sharma@utsouthwestern.edu

³ Department of Pharmacology & Therapeutics, Faculty of Medicine, School of Biomedical Sciences, Dentistry and Health Sciences, the University of Melbourne, Parkville 3052, Australia; Tony.Velkov@unimelb.edu.au

* Correspondence: daichongshan@cau.edu.cn (C.D.); xiaoxl@cau.edu.cn (X.X.); Tel.: +86-156-5282-6026 (C.D.); +86-010-6273-3377 (X.X.)

Received: 5 April 2020; Accepted: 3 June 2020; Published: 9 June 2020



Abstract: The emergence of antimicrobial resistance in Gram-negative bacteria poses a huge health challenge. The therapeutic use of polymyxins (i.e., colistin and polymyxin B) is commonplace due to high efficacy and limiting treatment options for multidrug-resistant Gram-negative bacterial infections. Nephrotoxicity and neurotoxicity are the major dose-limiting factors that limit the therapeutic window of polymyxins; nephrotoxicity is a complication in up to ~60% of patients. The emergence of polymyxin-resistant strains or polymyxin heteroresistance is also a limiting factor. These caveats have catalyzed the search for polymyxin combinations that synergistically kill polymyxin-susceptible and resistant organisms and/or minimize the unwanted side effects. Curcumin—an FDA-approved natural product—exerts many pharmacological activities. Recent studies showed that polymyxins–curcumin combinations showed a synergistically inhibitory effect on the growth of bacteria (e.g., Gram-positive and Gram-negative bacteria) *in vitro*. Moreover, curcumin co-administration ameliorated colistin-induced nephrotoxicity and neurotoxicity by inhibiting oxidative stress, mitochondrial dysfunction, inflammation and apoptosis. In this review, we summarize the current knowledge-base of polymyxins–curcumin combination therapy and discuss the underlying mechanisms. For the clinical translation of this combination to become a reality, further research is required to develop novel polymyxins–curcumin formulations with optimized pharmacokinetics and dosage regimens.

Keywords: polymyxin B; colistin; curcumin; oxidative stress; mitochondrial dysfunction

1. Introduction

The World Health Organization [1] has highlighted antimicrobial resistance as a major global health concern [1]. As no new classes of antibiotics will be available for Gram-negative ‘superbugs’ in the near future, we have to develop novel polymyxin combination therapies [2]. Polymyxins were firstly discovered in 1947 from different species of *Bacillus polymyxa* [3]. There are five members in the polymyxins family, i.e., polymyxin A, B, C, D and E (also named colistin). Out of these, only polymyxins B and colistin are used in clinical practice, as agents against multi-drug resistant (MDR) Gram-negative

pathogens, in particular *Pseudomonas aeruginosa* (*P. aeruginosa*) *Acinetobacter baumannii* (*A. baumannii*) and *Klebsiella pneumoniae* (*K. pneumoniae*). They differ by only one amino acid (Figure 1a) [4–11].

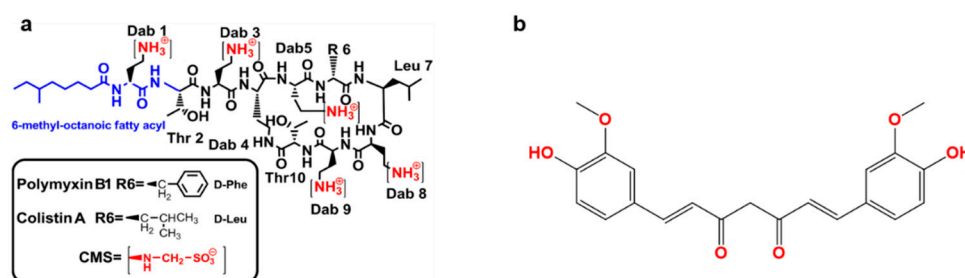


Figure 1. The structure of polymyxin B and colistin (a) and curcumin (b). CMS—colistin methanesulfonate; Thr—threonine; Leu—leucine; Phe—phenylalanine; Dab— α,γ - diaminobutyric acid.

Unlike polymyxin B, which is available in the clinic as the sulfate salt, colistin is used in the clinic as an inactive pro-drug, colistin methanesulfonate (CMS) (Figure 1a) [12,13]. Polymyxin B is available for intravenous, oral and topical use and CMS for parenteral use; both can be delivered by inhalation [14]. Plasmid carried mobilized colistin resistance (*mcr*) gene-mediated polymyxin resistance has been increasingly reported in MDR Gram-negatives worldwide. Polymyxin resistance implies a total lack of antibiotics against Gram-negative ‘superbugs’, without the availability of novel antibiotics in the near future, the development of superior polymyxin combinations to combat a ‘post-antibiotic era’ is paramount [15,16]. This has brought the effectiveness of polymyxin monotherapy into question. Unfortunately, only increasing the dose of polymyxins to overcome resistance is not an option due to toxic side effects (i.e., nephrotoxicity and neurotoxicity) [17]. Previous clinical observations showed that the rates of nephrotoxicity occurred in approximately 60% after patients received colistin or polymyxin B therapy [18]. Based on the narrow therapeutic indices of polymyxins, a key strategy for overcoming resistance and concomitantly ablating unwanted side effects is combining polymyxins with other agents. Although polymyxin-antibiotic combinations exhibit well-confirmed synergistic effects against bacterial growth in vitro [19,20]. The clinical findings from randomized, controlled prospective trials have shown that these combinations have no increased benefits compared to their respective monotherapies [19,20]. Moreover, some polymyxin-antibiotic combinations may increase the risk of renal failure (e.g., colistin–vancomycin combination) [20].

Secondary metabolite natural products have been at the forefront of drug candidates for the treatment of cancer, infection and neurodegenerative diseases for decades [21]. Natural products have been the source of most of our antibacterial armamentarium and efforts over the last 30 years [22]. Recent studies have shown that combining polymyxins with curcumin has many pharmacological and toxicological benefits over monotherapy with each compound per se including: (1), the in vitro synergy against various strains of MDR bacteria [23], including polymyxin resistant isolates [24]; (2), protection against polymyxin-induced nephron- and neuro-toxicity [25–27]; (3), curcumin supplementation improves recovery from the bacterial infection or LPS—induced inflammatory response or sepsis [28–33]. Importantly, human clinical trials indicated that curcumin displays good safety and tolerability [34–36]; oral administration of curcumin at eight grams per day over three months or a single oral dose of 12 grams has no marked adverse effect [37,38].

In combination with curcumin, polymyxins hold great promise as combination therapy for infections caused by MDR Gram-negative pathogens. In this review, we summarize the current understanding of the underlying molecular mechanisms on nephro- and neuroprotection and synergistic effects on bacterial growth of this novel combination.

2. Curcumin

Curcumin, also known as diferuloylmethane, E100 or natural yellow 3 (International Union of Pure and Applied Chemistry (IUPAC) name is (1E, 6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, Figure 1b), is a natural polyphenol extracted from the rhizome of *Curcuma longa* [39]. Curcumin displays many beneficial pharmacological activities, such as anti-inflammatory, anti-oxidant, antitumor and notably, antimicrobial activities [24,40–43]. The direct antibacterial activities of curcumin have been widely studied [44,45]. It is purported that the anti-inflammation and antioxidant abilities may contribute to the indirect antibacterial activities of curcumin by modulating the interaction of host cells with bacteria or via increasing the potential loading dose of a combination antibiotic drug by inhibiting the unwanted adverse effects.

2.1. Antibacterial Activity of Curcumin

Curcumin exhibits antibacterial activities against both Gram-negative and Gram-positive bacteria, including MDR and polymyxin-resistant isolates [44,45]. Curcumin has been shown to disrupt filamenting temperature-sensitive mutant Z (FtsZ) protofilament activity that orchestrates bacterial cell division [46]. In contrast to its action on mammalian cells, in bacteria, curcumin induces the production of reduced reactive oxygen species (ROS), including superoxide anions ($O_2^{\bullet-}$), hydroxyl radicals ($\bullet OH$) and hydrogen peroxide (H_2O_2), which kills bacteria by damaging proteins, lipids and DNA [47–49]. ROS-mediated phototoxicity also contributes to the antibacterial activities of curcumin [50]. Curcumin inhibits the expression of biofilm initiation genes and quorum sensing (QS) genes, and downregulates the virulence factors including the production of acyl-homoserine lactone (HSL), pyocyanin biosynthesis and elastase/protease activity [51,52]. A study from Mun et al., showed that the minimum inhibitory concentration (MIC) values of curcumin against 10 strains of *Staphylococcus aureus* (*S. aureus*) ranged from 125 to 250 $\mu g/mL$ [53]. Moreover, curcumin displays significant antibacterial activity against the stomach ulcer-causing pathogen *Helicobacter pylori* (*H. pylori*) with MIC values ranging from 5 to 50 $\mu g/mL$ against 65 clinical isolates [54]. Another study with a crude aqueous rhizome extract of *Curcuma longa* showed MIC value of 4 to 16 $\mu g/mL$ against strains of *S. epidermis* ATCC 12228, *S. aureus* ATCC 25923, *K. pneumonia* ATCC 10031 and *E. coli* ATCC 25922 [55]. The rhizome extract of *Curcuma longa* includes primarily curcumin and other derivative compounds such as curdione, isocurcumenol, curcumenol, curzerene, β -elemene, germacrone and curcumol [56]. Notwithstanding its direct antibacterial activities, curcumin displays potent synergistic effects when combined with antibiotics (e.g., oxacillin, ampicillin, polymyxin B and norfloxacin) [23,53].

The therapeutic potential of curcumin is limited owing to its poor oral bioavailability and insufficient solubility in aqueous solvents. Therefore, oral curcumin often present poor absorption, fast metabolism and quick systemic elimination in animal experiment and human clinical trial [44,45,52]. Researchers have attempted to solve these problems by developing new drug delivery methods such as liposomes, solid dispersion, microemulsion, micelles, nanogels and dendrimers [52]. For example, the poly (lactic-co-glycolic acid) (PLGA) polymeric nanocapsules for the delivery of curcumin can enhance its solubility (increase by ~1500-fold, compared to free curcumin) and antibacterial activity (MIC values decrease by ~2-fold, compared to free curcumin) [57]. In another example, curcumin- β -cyclodextrin nanoparticle complex formation exhibited a potent bactericidal activity by increasing the production of ROS and inhibiting electron transport; polyelectrolyte-coated monolithic nanoparticle formation exhibited a potent bacteriostatic effect by increasing membrane depolarization and reducing ATP concentrations [58].

2.2. Effect of Curcumin on Bacteria or Its Toxin-Induced Inflammatory Response

The curcumin structure has functional groups that contribute to its ability to scavenge ROS including phenyl rings, carbon-carbon double bonds and β -diketone structures [59]. Curcumin also directly targets a plethora of pathways that play important roles in the inflammatory response,

oxidative stress and cell death, including cyclooxygenase 2 (COX-2), lipoxygenase, protein kinase B (PKB, also named Akt), toll-like receptor (TLR)-4, nuclear factor erythroid 2-related factor 2 (Nrf2), glycogen synthase kinase (GSK)-3 β , phosphorylase-3 kinase, focal adhesion kinase, glutathione, xanthine oxidase, pp60 src tyrosine kinase and ubiquitin isopeptidase [60–63]. These signals and/or pathways also play critical roles in response to bacterial infection or its pathogenic factors (e.g., α -hemolysin and lipopolysaccharide [LPS])-mediated pathology [29,64–66]. For example, curcumin has an inhibitory effect on NF- κ B activation, the release of interleukin (IL)-8 and matrix metalloproteinase-3 and metalloproteinase-9 activity induced by *H. pylori* infection in the stomach of mice or cell culture with a dose-dependent manner [67,68]. Curcumin can also inhibit LPS-induced activation of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome and the secretion of IL-1 β and high mobility group box 1 (HMGB1) [69–71].

3. Synergistic Antibacterial Effects of the Polymyxin in Combination with Curcumin

The putative primary mechanism of action of polymyxins is the disruption of the Gram-negative outer membrane through an initial electrostatic interaction that results in cation displacement (Ca²⁺ and Mg²⁺) and subsequent binding to the lipid A component of LPS, leading to leakage of the cytoplasmic content and ultimately causing cell death [72]. As a secondary killing effect, polymyxins induce ROS [73]. The inhibition of bacterial respiration has also been associated with the bacterial killing action of polymyxins [74].

Polymyxin resistance is conferred by mcr-mediated structural modifications of LPS that act to reduce the negative charge of the outer membrane, which in turn repels the polymyxin molecule [75]. The two main LPS modifications conferring polymyxin resistance are the addition of phosphoethanolamine (PetN) and 4-amino-4-deoxy-L-arabinose (AraN) to the lipid A [76]. Recently, plasmid-mediated colistin resistance was reported in *Enterobacteriaceae* due to the PetN transferase mcr-1 [15].

In vitro time-kill curves for polymyxin B in combination with curcumin showed a marked synergistic effect against antibiotic-susceptible and—resistant Gram-positive (*Enterococci*, *S. aureus* and streptococci) and Gram-negative (*A. baumannii*, *E. coli*, *P. aeruginosa* and *S. maltophilia*) bacterial isolates associated isolated from traumatic wound infections [23]. The synergistic effect may result from the ability of polymyxin to permeabilize the outer membrane which facilitates the access of greater concentrations of curcumin to its intracellular targets (Figure 2) [24]. Curcumin may also overcome the polymyxin-resistance by inhibiting the activities of efflux pumps where located in outer membrane (OM) or inner membranes (IM) [24].

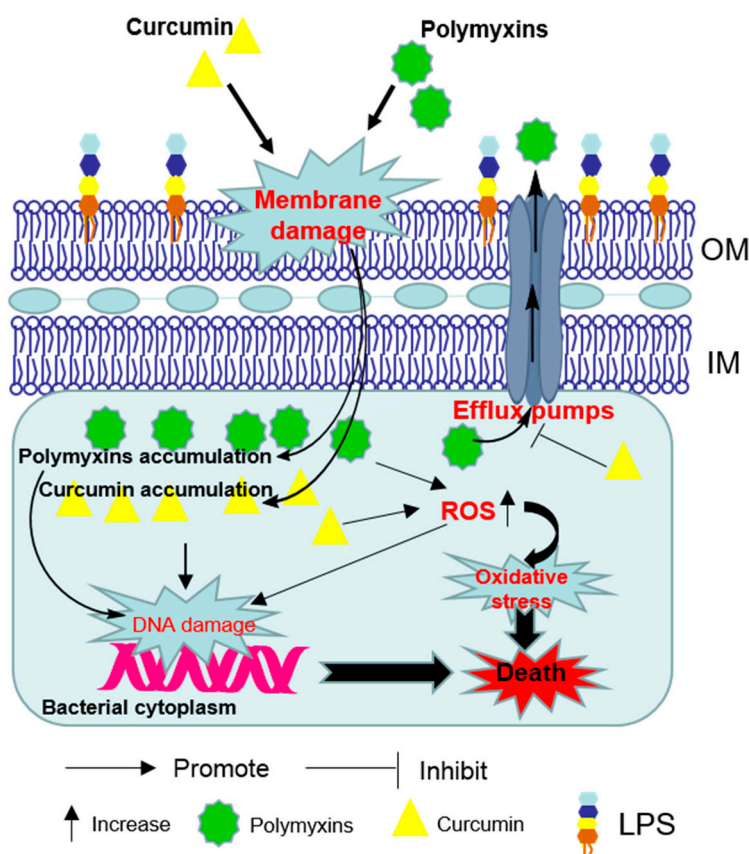


Figure 2. Schematic diagram depicting the synergistic bacterial killing mechanism of the polymyxins–curcumin combination. Polymyxins permeabilize the Gram-negative outer membrane and thereby promote curcumin enter the bacterial cell. Bacterial cell death finally ensues via reactive oxygen species (ROS) production, oxidative stress and DNA damage. Curcumin may also overcome the polymyxin-resistance by disturbing the activities of efflux pumps. OM—outer membrane; IM—inner membranes; LPS—lipopolysaccharide.

4. Polymyxin-Induced Nephrotoxicity and Protective Effect of Curcumin

Nephrotoxicity is the major dose-limiting factor of polymyxins in clinical practice and it occurs in up to 60% of patients after intravenous administration [18]. Clinical manifestations include a decrease in creatinine (CRE) clearance, as well as proteinuria, oliguria (low output of urine) and cylindruria (presence of casts in the urine) [18,77,78]. Pathologic characteristics of colistin or polymyxin B-induced nephrotoxicity were included tubular dilation and tubular epithelial cell vacuolation and necrosis, tubular casts and inflammatory cell infiltration [79–81]. In clinical practice, serum CRE and blood urea nitrogen (BUN) are usually employed as the biomarkers of renal function. However, their use as the biomarkers has some limitations in polymyxin therapy, such as dependence on nutrition, age, sex and body mass and is likely to reflect already advanced damage. Studies in animal models showed that kidney injury molecule 1 (KIM-1), Cystatin C and α -glutathione S-transferase may be more reliable markers than CRE or BUN to monitor renal function during polymyxin therapy [82,83].

Our understanding of the molecular mechanisms underlying polymyxin-induced nephrotoxicity have significantly advanced in the past 15 years owing to the pioneering work of the Li group from Monash University, Australia [84–96]. Their recent studies have revealed significant renal accumulation of polymyxins using immunostaining, fluorescence microscopy, mass spectrometry imaging and X-ray fluorescence microscopy (XFM) [84–87]. Predominant accumulation of polymyxin B was distinct in the renal cortex, in particular the renal proximal tubular cells, but much less in the distal tubular cells [84,85]. Moreover, polymyxins substantially accumulate in proximal tubular cells via

(MDA), nitrate stress-related nitric oxide (NO) and inducible nitric oxide synthase activities and inflammation response were significantly increased in the kidney tissues from colistin-treated mice [80,104]. Additionally, the activation of transforming growth factor (TGF)- β /nicotinamide adenine dinucleotide 3-phosphate oxidase-4 (NOX-4) pathway contributes to the production of ROS in kidneys of mice; inhibition of TGF- β expression markedly attenuated colistin-induced renal damage in mice, indicating that TGF- β /NOX-4 pathway may play a critical role in colistin-induced nephrotoxicity [105].

Curcumin has been shown to protect against colistin-induced nephrotoxicity via inhibition of oxidative stress, inflammation and apoptosis. A previous study reported that curcumin supplementation (e.g., at 200 mg/kg/day for 3 days) markedly protects against glycerol-induced acute kidney injury by inhibiting oxidative damage and activating Nrf2 pathway in rats [106]. A similar molecular mechanism has also been detected in the protection of curcumin against gentamicin-induced nephrotoxicity in rats [107]. Consistent with these findings, curcumin supplementation (e.g., at 200 mg/kg/day for 6 days) can also markedly improve colistin-induced nephrotoxicity via the inhibition of oxidative stress, apoptosis, NO signaling and inflammatory response (i.e., decreases the tumor necrosis factor- α [TNF- α], interleukin-6 [IL-6] in the kidney tissue) in a rat model [27]. Our recent data reveal that curcumin after oral administration at 50 and 200 mg/kg/day for 7 days can be detected and accumulated in multiple organs of mice, including kidney tissues [25]. It was shown that curcumin can promote Nrf2 translocation into nuclei through modification of cysteine sulfhydryl groups in Kelch-like ECH-associated protein 1 (Keap1), a principal negative regulator of Nrf2 in the cytoplasm. The binding of Nrf2 and antioxidant responsive element (ARE) in nuclei activated the transcription activity of ARE that mediates the expression of antioxidant gene such as heme oxygenase-1 (HO-1), CAT and SOD [108]. Indeed, curcumin can directly activate Nrf2/ARE pathway and protects against oxidative stress-mediated apoptotic cell death [109]. Therefore, the activation of Nrf2/HO-1 may contribute to the protective effect of curcumin against colistin-oxidative damage in the kidney tissues. Besides, it has been reported that curcumin supplementation can protect some drugs (e.g., cisplatin, glycerol and doxorubicin) or toxins (e.g., potassium dichromate, maleate and arsenic)-induced nephrotoxicity by inhibiting oxidative stress, ER stress, inflammatory response, NO pathway, ferroptosis, p53 pathway, MAPK, AMP-activated protein kinase (AMPK) pathways, Akt pathway or activation of autophagy [106,110–116]. The previous study showed that the antioxidant ascorbic acid can protect against colistin-induced nephrotoxicity and cellular apoptosis. Meanwhile, ascorbic acid altered the pharmacokinetics of colistin in a rat model, the total body clearance of colistin decreased from 3.78 ± 0.36 mL/min/kg (colistin alone group) to 2.46 ± 0.57 mL/min/kg (ascorbic acid + colistin co-treatment group), and the half-life of plasma colistin concentration increased from 1.20 ± 0.23 (colistin alone group) h to 3.91 ± 0.42 h (ascorbic acid + colistin co-treatment group) [94].

5. Colistin-Induced Neurotoxicity and Protective Effects of Curcumin

Neurotoxicity caused by colistin has been observed in a dose-dependent manner that may be associated with colistin accumulation in the nerve tissues [25]. In contrast to nephrotoxicity, the incidence of neurotoxicity associated with the use of polymyxins is less commonly reported in the literature, despite being a significant clinical complication [117]. Patients who received intravenous polymyxins have been reported to present with potential neurological symptoms including dizziness, vertigo, visual disturbances, hallucinations, confusion, seizures, ataxia, facial and peripheral paresthesias [117–119]. Mild neurotoxicity symptoms (e.g., paresthesias) is more frequent than others, especially in elderly patients, but are often ignored due to the lack of effective assessment protocols [117–120]. An early study reported that paresthesias and ataxia as the major neurotoxicity symptoms occur about in the 29% of patients that received intravenous administration of CMS at the dose of over 5 mg/kg/day (range from 5.7 to 8.0 mg/kg/day) [121]. A recent study indicated that intravenous administration of high doses of polymyxin B (range from 3 to 6 mg/kg/day) may increase the clinical outcome, but the neurotoxicity events also increased in patients [122].

Investigation of polymyxin uptake into the central nervous system (CNS) and neuronal cells is a critical aspect of understanding the neurotoxicity. The blood–brain barrier (BBB) is the “first barrier” that mediates the uptake of the drug into neuronal cells in the brain tissues, and it only allows small molecules that both have the low molecular mass (<450 Da) and high lipid solubility to pass [123]. The tight junctions of the interendothelial domains limit the passage of large hydrophilic molecules cross the BBB and this is considered as the main reason underlying the low BBB penetration of polymyxins (molecular mass of colistin and polymyxin B are ~1155 Da and ~1,203, respectively) [124]. This may also explain the higher incidence in peripheral nervous system (PNS)- than CNS- mediated polymyxin neurotoxicity in clinic [117,119,125]. It is negligible in the brain uptake of colistin when healthy mice were received a single intravenous dose (5 mg/kg) or subcutaneous dose (40 mg/kg) [124,126–128]. However, Wang et al., showed that the continuous administration of intravenous colistin sulfate at 15 mg/kg/day for 7 days to mice significantly increased the colistin concentration in brain tissues without BBB damage [129]. Consistently, our group showed that colistin could be accumulated in nerve tissues including the brain, cerebellum and sciatic nerve with the abnormal neurobehavioral and electrophysiology changes when mice were intraperitoneally injected with colistin sulfate at 18 mg/kg/day for 7 days [25,120,130–132]. It has also been demonstrated that the intravenous administration of LPS can increase the BBB transport of colistin in mice, indicating that systemic inflammation (e.g., CNS infections and sepsis) may increase the colistin concentrations in the brain tissues [124,126–128]. Our *in vitro* studies have shown that the absorption of colistin into mouse primary cortical neuronal cells is in a concentration-dependent manner [133]. As above mentioned, megalin, PEPT2, and OCTN2 can mediate the uptake of colistin into kidney cells [91,97,99,134]. Notably, the expressions of megalin, PEPT2, and OCTN2 are also detected in neuronal cells [135–137], and as such may mediate polymyxin uptake into neurons.

Due to its high oxygen use and high content of polyunsaturated fatty acids, the CNS was well known to be particularly vulnerable to oxidative damage [138]. Mitochondria play a critical role in maintaining basic cellular functions, including cellular energy metabolism, ATP production and triggering cellular apoptosis and autophagy [138]. We have shown that mitochondria in the cerebrum and sciatic nerve tissues showed abnormal ultrastructure (e.g., disruption of cristae and swelling) and functions when mice were intravenously injected with colistin at 15 mg/kg/day for 7 days [131,139]. Mitochondrial dysfunction was also detected in primary chick neuronal cells when they were treated with colistin at 4.15 and 8.3 µg/mL for 24 h [140]. Excessive ROS from mitochondria can lead to lipids, proteins and DNA damage and ultimately results in cell death [141]. Our recent study showed that colistin treatment (200 µM for 24 h) significantly induced the increase in the levels of intracellular ROS with a decrease in the levels of glutathione (GSH) levels and the activity of the antioxidant enzymes SOD and CAT in the N2a neuronal cells [142]. These data lend substantial evidence that oxidative stress and mitochondria dysfunction play critical roles in colistin-induced neurotoxicity. Moreover, Nrf2 is suggested as the “housekeeping” gene in response to oxidative stress. Nrf2 activation can transcriptionally activate the expression of several phase II enzymes, including HO-1, SOD and CAT [92]. Not surprisingly, the upregulation of Nrf2/HO-1 pathway in N2a cells and the cerebral cortices of mice treated with colistin were detected [131–133,142]. These evidences suggested that the activation of Nrf2/HO-1 plays a protective role in polymyxins-induced neurotoxicity.

It has been reported that the main pathways of colistin-induced apoptosis in neuronal cells involve the intrinsic mitochondrial and extrinsic death receptor pathways [142–145]. Colistin treatment can cause an increase in the Bax/Bcl-2 ratio and cytochrome C (CytC) release, in cascade to triggering the activations of caspases-3 and -9 and inducing apoptotic death in N2a and PC12 neuronal cells [142–144]. Similar in kidney cells, colistin treatment of PC12 cells also exhibited the increased expression of Fas and Fas-L, followed to activate caspase-8 through the FADD [145]. Notably, the pan-caspase inhibitor Z-VAD-FMK can partially block colistin-induced apoptotic death in N2a neuronal cells, highlighting the role of caspases activation in intrinsic and extrinsic apoptotic pathways [142]. In a mouse model, the marked increase of GRP78, an ER stress marker, was detected in the cerebral cortical

tissues, indicated the ER stress may also contribute to colistin-induced neurotoxicity [132]. Our recent studies showed that colistin treatment (200 μ M) of N2a neuronal cells downregulated the expression of mammalian target of rapamycin (mTOR) and phospho (p)-p70S6 kinase (p70s6k) and upregulates unc-51 like autophagy activating kinase 1 (ULK1) expression, suggesting that mTOR inhibition-mediated autophagy is triggered in the process of colistin-induced apoptosis in neuronal cells [128]. In addition, colistin-induced neuronal cell death also involves p53, MAPK and PI3 K/Akt/c-AMP response element-binding (CREB) pathways, and their roles are shown in Figure 4 [26,27,78,81,132,142,146–150].

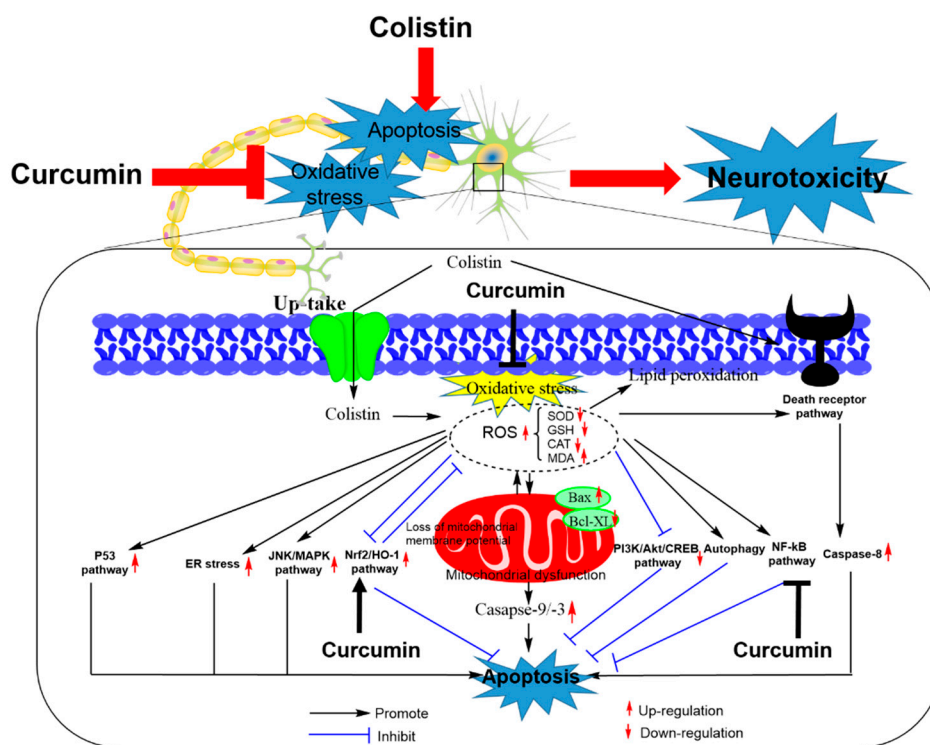


Figure 4. Schematic diagram depicting the major apoptosis pathways involved in colistin-induced neurotoxicity and the potential targets of curcumin. Colistin-induced apoptosis involves oxidative stress, the activation of death receptor and mitochondrial pathways by upregulating the Bax/Bcl2 ratio, inducing the loss of membrane potential and production of reactive oxygen species [ROS] and activating caspases-3, -8 and -9. Colistin-induced apoptosis also involved the activation of p53, nuclear factor kappa B (NF- κ B), ER stress, c-Jun *N*-terminal kinases (JNKs)/MAPK pathways and the inhibition of the PI3 K/Akt/CREB pathway. The activation of autophagy and Nrf2/HO-1 pathways inhibits colistin-induced apoptosis. Curcumin ameliorates colistin-induced apoptosis and neurotoxicity by targeting the Nrf2/HO-1, NF- κ B and oxidative stress pathways.

Curcumin supplementation effectively protects against colistin treatment-induced neurotoxicity *in vitro* (e.g., mouse primary and N2a neuronal cells) and animal models (e.g., mice and rats) (Figure 4) [25–27]. Curcumin indicated the potential application as a neuroprotective agent with an ability to cross the BBB [40,151,152]. Our *in vitro* data showed that curcumin could effectively improve colistin-induced oxidative stress and apoptotic cell death in N2a neuronal cells by up-regulating the activities of the intracellular SOD, CAT and GSH levels, and promoting the activation of Nrf2/HO-1 pathway [26]. Curcumin treatment also downregulated the expression of NF- κ B and NF- κ B-regulated genes that are involved in the process of inflammatory response and apoptotic death in N2a cells [26]. In a rat model, oral administration of curcumin at the dose of 200 mg/kg/day for 6 days significantly improved colistin-induced inflammatory response, oxidative stress damage and apoptosis in the brain tissues (e.g., cerebral cortex and cerebellar cortex tissues) [27]. Our study revealed that oral administration of curcumin at the dose of 200 mg/kg/day for 7 days significantly ameliorated

colistin-induced sciatic nerve damage by inhibiting oxidative stress, apoptosis and upregulating the nerve growth factor (NGF)/Akt and Nrf2/HO-1 pathways (Figure 5) [25]. Mechanically, NGF treatment promotes cell survival of nerve cells via the activation of Akt pathway [25]. The activation of Akt caused by NGF stimulation significantly attenuated colistin-induced apoptotic death and the inhibition of axon growth in N2a and PC12 neuronal cells, which involved the activation of Nrf2/ARE pathway [132,150,153]. Nerve growth factor plays a decisive role in promoting the growth and survival of peripheral sensory and sympathetic nerve cells [150]. Our recent study demonstrated that NGF administration could significantly inhibit colistin-induced peripheral neurotoxicity in mice [154]. Consistently, NGF treatment per se can inhibit colistin-induced oxidative stress and apoptosis in PC12 cells [150]. Thus, the protective effect of curcumin on colistin-induced peripheral neurotoxicity is partly attributed to the activation of NGF/Akt pathway.

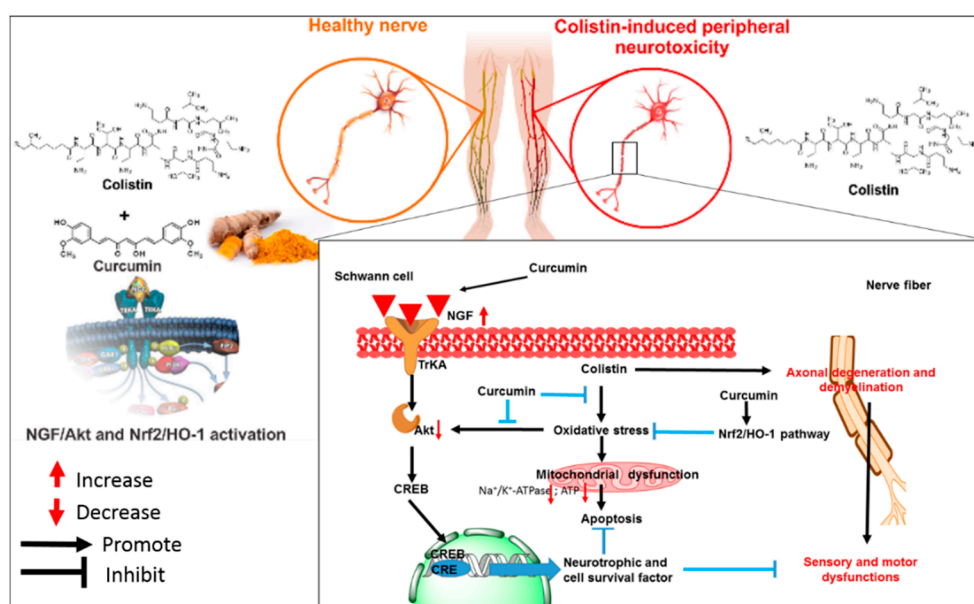


Figure 5. Schematic diagram depicting the putative action of curcumin against colistin-induced peripheral neurotoxicity. Oral administration of curcumin improves colistin-induced dysfunctional motor and sensory symptoms by inhibition of oxidative stress and activation of the NGF/Akt and Nrf2/HO-1 pathways in the sciatic nerve tissues of mice. The figure is a revision from Dai, et al., [26] and [154].

6. Conclusions

During the past two decades, parenteral polymyxin B and colistin have been increasingly used for the treatment of problematic Gram-negative pathogens. Notwithstanding, neurotoxicity and nephrotoxicity remain the major dose-limiting factors hampering the clinical utility of these essential last-line antibiotics. Increasing reports of polymyxin resistance in the nosocomial setting and widespread environmental polymyxin resistance due to the plasmid *mcr-1* has rattled the cage for the long-term therapeutic utility of polymyxins. Polymyxin combination treatments with FDA approved drugs and natural products is an emerging strategy for overcoming the aforementioned unwanted side-effects and bacterial resistance. Combining polymyxins with the existing drugs is prudent, in the view that FDA approved drugs have known pharmacokinetic and safety profiles; therefore, combination therapies could be fast-tracked into clinical practice. Curcumin is an FDA- approved natural product exhibiting many pharmacological antioxidant and healing activities. An increasing body of literature suggests that polymyxins–curcumin combination therapy has a synergistic inhibitory effect on the bacterial growth and lowers polymyxin-induced nephrotoxicity and neurotoxicity via inhibition of oxidative stress, mitochondrial dysfunction, inflammation and apoptosis. Future clinical trials of

polymyxins–curcumin combination therapy are certainly warranted, albeit there is currently a dearth of data on optimal dosage regimens and pharmacokinetics for the combination, both of which require further studies.

Author Contributions: Writing—original draft preparation, C.D.; writing—review and editing, C.D., T.V., X.X., Y.W., J.S., G.S. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the Key Projects in the Chinese National Science and Technology Pillar Program during the 12th Five-year Plan Period (2015BAD11B03). T.V. was supported by the Australian National Health and Medical Research Council (NHMRC).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. The World Health Organization. *Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics*; WHO: Geneva, Switzerland, 2017.
2. Tyers, M.; Wright, G.D. Drug combinations: A strategy to extend the life of antibiotics in the 21st century. *Nat. Rev. Microbiol.* **2019**, *17*, 141–155. [\[CrossRef\]](#)
3. Koyama, Y.; Kurosasa, A.; Tsuchiya, A.; Takakuta, K. A new antibiotic “colistin” produced by spore-forming soil bacteria. *J. Antibiot.* **1950**, *3*, 457–458.
4. Braine, T. Race against time to develop new antibiotics. *Bull. World Health Organ.* **2011**, *89*, 88–89.
5. Zowawi, H.M.; Harris, P.N.; Roberts, M.J.; Tambyah, P.A.; Schembri, M.A.; Pezzani, M.D.; Williamson, D.A.; Paterson, D.L. The emerging threat of multidrug-resistant gram-negative bacteria in urology. *Nat. Rev. Urol.* **2015**, *12*, 570–584. [\[CrossRef\]](#)
6. Demiraslan, H.; Cevahir, F.; Berk, E.; Metan, G.; Cetin, M.; Alp, E. Is surveillance for colonization of carbapenem-resistant gram-negative bacteria important in adult bone marrow transplantation units? *Am. J. Infect. Control* **2017**, *45*, 735–739. [\[CrossRef\]](#)
7. Karlowsky, J.A.; Lob, S.H.; Kazmierczak, K.M.; Hawser, S.P.; Magnet, S.; Young, K.; Motyl, M.R.; Sahm, D.F. In vitro activity of imipenem/relebactam against gram-negative escape pathogens isolated in 17 European countries: 2015 smart surveillance programme. *J. Antimicrob. Chemother.* **2018**, *73*, 1872–1879. [\[CrossRef\]](#)
8. Adams-Sapper, S.; Gayoso, A.; Riley, L.W. Stress-adaptive responses associated with high-level carbapenem resistance in kpc-producing klebsiella pneumoniae. *J. Pathog.* **2018**, *2018*, 11. [\[CrossRef\]](#)
9. Exner, M.; Bhattacharya, S.; Christiansen, B.; Gebel, J.; Goroncy-Bermes, P.; Hartemann, P.; Heeg, P.; Ilschner, C.; Kramer, A.; Larson, E.; et al. Antibiotic resistance: What is so special about multidrug-resistant gram-negative bacteria? *GMS Hyg. Infect. Control* **2017**, *12*, Doc05.
10. Oliveira, V.D.; Rubio, F.G.; Almeida, M.T.; Nogueira, M.C.; Pignatari, A.C. Trends of 9416 multidrug-resistant gram-negative bacteria. *Rev. Assoc. Med. Bras.* **2015**, *61*, 244–249. [\[CrossRef\]](#)
11. Perez, F.; Adachi, J.; Bonomo, R.A. Antibiotic-resistant gram-negative bacterial infections in patients with cancer. *Clin. Infect. Dis.* **2014**, *59*, S335–S339. [\[CrossRef\]](#)
12. Nation, R.L.; Velkov, T.; Li, J. Colistin and polymyxin b: Peas in a pod, or chalk and cheese? *Clin. Infect. Dis.* **2014**, *59*, 88–94. [\[CrossRef\]](#)
13. Nation, R.L.; Garonzik, S.M.; Thamlikitkul, V.; Giamarellos-Bourboulis, E.J.; Forrest, A.; Paterson, D.L.; Li, J.; Silveira, F.P. Dosing guidance for intravenous colistin in critically-ill patients. *Clin. Infect. Dis.* **2017**, *64*, 565–571. [\[CrossRef\]](#)
14. Li, J.; Nation, R.L.; Turnidge, J.D.; Milne, R.W.; Coulthard, K.; Rayner, C.R.; Paterson, D.L. Colistin: The re-emerging antibiotic for multidrug-resistant gram-negative bacterial infections. *Lancet Infect. Dis.* **2006**, *6*, 589–601. [\[CrossRef\]](#)
15. Liu, Y.Y.; Wang, Y.; Walsh, T.R.; Yi, L.X.; Zhang, R.; Spencer, J.; Doi, Y.; Tian, G.; Dong, B.; Huang, X.; et al. Emergence of plasmid-mediated colistin resistance mechanism mcr-1 in animals and human beings in china: A microbiological and molecular biological study. *Lancet Infect. Dis.* **2016**, *16*, 161–168. [\[CrossRef\]](#)
16. Napier, B.A.; Band, V.; Burd, E.M.; Weiss, D.S. Colistin heteroresistance in enterobacter cloacae is associated with cross-resistance to the host antimicrobial lysozyme. *Antimicrob. Agents Chemother.* **2014**, *58*, 5594–5597. [\[CrossRef\]](#)

17. Garonzik, S.M.; Li, J.; Thamlikitkul, V.; Paterson, D.L.; Shoham, S.; Jacob, J.; Silveira, F.P.; Forrest, A.; Nation, R.L. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob. Agents Chemother.* **2011**, *55*, 3284–3294. [[CrossRef](#)]
18. Hartzell, J.D.; Neff, R.; Ake, J.; Howard, R.; Olson, S.; Paolino, K.; Vishnepolsky, M.; Weintrob, A.; Wortmann, G. Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. *Clin. Infect. Dis.* **2009**, *48*, 1724–1728. [[CrossRef](#)]
19. Ni, W.T.; Shao, X.D.; Di, X.Z.; Cui, J.C.; Wang, R.; Liu, Y.N. In vitro synergy of polymyxins with other antibiotics for acinetobacter *Baumannii*: A systematic review and meta-analysis. *Int. J. Antimicrob. Agents* **2015**, *45*, 8–18. [[CrossRef](#)]
20. O'Hara, J.A.; Ambe, L.A.; Casella, L.G.; Townsend, B.M.; Pelletier, M.R.; Ernst, R.K.; Shanks, R.M.Q.; Doi, Y. Activities of vancomycin-containing regimens against colistin-resistant acinetobacter *Baumannii* clinical strains. *Antimicrob. Agents Chemother.* **2013**, *57*, 2103–2108. [[CrossRef](#)]
21. Salam, A.M.; Quave, C.L. Opportunities for plant natural products in infection control. *Curr. Opin. Microbiol.* **2018**, *45*, 189–194. [[CrossRef](#)]
22. Silver, L.L. Natural products as a source of drug leads to overcome drug resistance. *Future Microbiol.* **2015**, *10*, 1711–1718. [[CrossRef](#)] [[PubMed](#)]
23. Betts, J.W.; Sharili, A.S.; La Ragione, R.M.; Wareham, D.W. In vitro antibacterial activity of curcumin-polymyxin b combinations against multidrug-resistant bacteria associated with traumatic wound infections. *J. Nat. Prod.* **2016**, *79*, 1702–1706. [[CrossRef](#)]
24. Kaur, A.; Sharma, P.; Capalash, N. Curcumin alleviates persistence of acinetobacter *Baumannii* against colistin. *Sci. Rep.* **2018**, *8*, 11029. [[CrossRef](#)]
25. Dai, C.; Xiao, X.; Zhang, Y.; Xiang, B.; Hoyer, D.; Shen, J.; Velkov, T.; Tang, S. Curcumin attenuates colistin-induced peripheral neurotoxicity in mice. *ACS Infect. Dis.* **2020**, *6*, 715–724. [[CrossRef](#)]
26. Dai, C.; Ciccotosto, G.D.; Cappai, R.; Tang, S.; Li, D.; Xie, S.; Xiao, X.; Velkov, T. Curcumin attenuates colistin-induced neurotoxicity in n2a cells via anti-inflammatory activity, suppression of oxidative stress, and apoptosis. *Mol. Neurobiol.* **2018**, *55*, 421–434. [[CrossRef](#)]
27. Edrees, N.E.; Galal, A.A.A.; Monaem, A.R.A.; Beheiry, R.R.; Metwally, M.M.M. Curcumin alleviates colistin-induced nephrotoxicity and neurotoxicity in rats via attenuation of oxidative stress, inflammation and apoptosis. *Chem. Biol. Interact.* **2018**, *294*, 56–64. [[CrossRef](#)]
28. Lin, X.P.; Xue, C.; Zhang, J.M.; Wu, W.J.; Chen, X.Y.; Zeng, Y.M. Curcumin inhibits lipopolysaccharide-induced mucin 5ac hypersecretion and airway inflammation via nuclear factor erythroid 2-related factor 2. *Chin. Med. J.* **2018**, *131*, 1686–1693. [[CrossRef](#)]
29. Lobo de Sa, F.D.; Butkevych, E.; Nattramilarasu, P.K.; Fromm, A.; Mousavi, S.; Moos, V.; Golz, J.C.; Stingl, K.; Kittler, S.; Seinige, D.; et al. Curcumin mitigates immune-induced epithelial barrier dysfunction by campylobacter *Jejuni*. *Int. J. Mol. Sci.* **2019**, *20*, 4830. [[CrossRef](#)]
30. Santos, A.M.; Lopes, T.; Oleastro, M.; Gato, I.V.; Floch, P.; Benejat, L.; Chaves, P.; Pereira, T.; Seixas, E.; Machado, J.; et al. Curcumin inhibits gastric inflammation induced by helicobacter pylori infection in a mouse model. *Nutrients* **2015**, *7*, 306–320. [[CrossRef](#)]
31. Schaeffers, M.M.; Breshears, L.M.; Anderson, M.J.; Lin, Y.C.; Grill, A.E.; Panyam, J.; Southern, P.J.; Schlievert, P.M.; Peterson, M.L. Epithelial proinflammatory response and curcumin-mediated protection from *Staphylococcal* toxic shock syndrome toxin-1. *PLoS ONE* **2012**, *7*, e32813. [[CrossRef](#)]
32. Zhou, J.; Miao, H.; Li, X.; Hu, Y.; Sun, H.; Hou, Y. Curcumin inhibits placental inflammation to ameliorate lps-induced adverse pregnancy outcomes in mice via upregulation of phosphorylated akt. *Inflamm. Res.* **2017**, *66*, 177–185. [[CrossRef](#)]
33. Kumari, A.; Dash, D.; Singh, R. Curcumin inhibits *Lipopolysaccharide* (lps)-induced endotoxemia and airway inflammation through modulation of sequential release of inflammatory mediators (tnf-alpha and tgf-beta1) in murine model. *Inflammopharmacology* **2017**, *25*, 329–341. [[CrossRef](#)]
34. Sharma, R.A.; McLelland, H.R.; Hill, K.A.; Ireson, C.R.; Euden, S.A.; Manson, M.M.; Pirmohamed, M.; Marnett, L.J.; Gescher, A.J.; Steward, W.P. Pharmacodynamic and pharmacokinetic study of oral curcuma extract in patients with colorectal cancer. *Clin. Cancer Res.* **2001**, *7*, 1894–1900.
35. Anand, P.; Kunnumakkara, A.B.; Newman, R.A.; Aggarwal, B.B. Bioavailability of curcumin: Problems and promises. *Mol. Pharm.* **2007**, *4*, 807–818. [[CrossRef](#)]

36. Gupta, S.C.; Patchva, S.; Aggarwal, B.B. Therapeutic roles of curcumin: Lessons learned from clinical trials. *AAPS J.* **2013**, *15*, 195–218. [[CrossRef](#)]
37. Cheng, A.L.; Hsu, C.H.; Lin, J.K.; Hsu, M.M.; Ho, Y.F.; Shen, T.S.; Ko, J.Y.; Lin, J.T.; Lin, B.R.; Ming-Shiang, W.; et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res.* **2001**, *21*, 2895–2900.
38. Lao, C.D.; Ruffin, M.T.T.; Normolle, D.; Heath, D.D.; Murray, S.I.; Bailey, J.M.; Boggs, M.E.; Crowell, J.; Rock, C.L.; Brenner, D.E. Dose escalation of a curcuminoid formulation. *BMC Complement. Altern. Med.* **2006**, *6*, 10. [[CrossRef](#)]
39. Lopez-Malo, D.; Villaron-Casares, C.A.; Alarcon-Jimenez, J.; Miranda, M.; Diaz-Llopis, M.; Romero, F.J.; Villar, V.M. Curcumin as a therapeutic option in retinal diseases. *Antioxidants* **2020**, *9*, 48. [[CrossRef](#)]
40. Ghosh, S.; Banerjee, S.; Sil, P.C. The beneficial role of curcumin on inflammation; diabetes and neurodegenerative disease: A recent update. *Food Chem. Toxicol.* **2015**, *83*, 111–124. [[CrossRef](#)]
41. Aggarwal, B.B.; Surh, Y.-J.; Shishodia, S. *The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease*; Springer: New York, NY, USA, 2007; Volume 595.
42. He, Y.; Yue, Y.; Zheng, X.; Zhang, K.; Chen, S.H.; Du, Z.Y. Curcumin, inflammation, and chronic diseases: How are they linked? *Molecules* **2015**, *20*, 9183–9213. [[CrossRef](#)]
43. Gunes, H.; Gulen, D.; Mutlu, R.; Gumus, A.; Tas, T.; Topkaya, A.E. Antibacterial effects of curcumin: An in vitro minimum inhibitory concentration study. *Toxicol. Ind. Health* **2016**, *32*, 246–250. [[CrossRef](#)]
44. Poonam, T.; Madhuri, S.; Himani, K.; Anita, K.; Kasturi, M.; One, Z.D.J.P. Bactericidal activity of curcumin I is associated with damaging of bacterial membrane. *PLoS ONE* **2015**, *10*, e0121313.
45. Praditya, D.; Kirchhoff, L.; Bruning, J.; Rachmawati, H.; Steinmann, J.; Steinmann, E. Anti-infective properties of the golden spice curcumin. *Front. Microbiol.* **2019**, *10*, 912. [[CrossRef](#)]
46. Rai, D.; Singh, J.K.; Roy, N.; Panda, D. Curcumin inhibits ftsz assembly: An attractive mechanism for its antibacterial activity. *Biochem. J.* **2008**, *410*, 147–155. [[CrossRef](#)]
47. Ezraty, B.; Gennaris, A.; Barras, F.; Collet, J.F. Oxidative stress, protein damage and repair in bacteria. *Nat. Rev. Microbiol.* **2017**, *15*, 385–396. [[CrossRef](#)]
48. Van Acker, H.; Coenye, T. The role of reactive oxygen species in antibiotic-mediated killing of bacteria. *Trends Microbiol.* **2017**, *25*, 456–466. [[CrossRef](#)]
49. Gao, Y.; Wu, J.; Li, Z.; Zhang, X.; Lu, N.; Xue, C.; Leung, A.W.; Xu, C.; Tang, Q. Curcumin-mediated photodynamic inactivation (pdi) against dh5alpha contaminated in oysters and cellular toxicological evaluation of pdi-treated oysters. *Photodiagn. Photodyn.* **2019**, *26*, 244–251. [[CrossRef](#)]
50. Freitas, M.A.; Pereira, A.H.; Pinto, J.G.; Casas, A.; Ferreira-Strixino, J. Bacterial viability after antimicrobial photodynamic therapy with curcumin on multiresistant staphylococcus aureus. *Future Microbiol.* **2019**, *14*, 739–748. [[CrossRef](#)]
51. Rudrappa, T.; Bais, H.P. Curcumin, a known phenolic from curcuma longa, attenuates the virulence of pseudomonas aeruginosa pao1 in whole plant and animal pathogenicity models. *J. Agric. Food Chem.* **2008**, *56*, 1955–1962. [[CrossRef](#)]
52. Moghadamtousi, S.Z.; Kadir, H.A.; Hassandarvish, P.; Tajik, H.; Abubakar, S.; Zandi, K. A review on antibacterial, antiviral, and antifungal activity of curcumin. *Biomed. Res. Int.* **2014**, *2014*, 186864.
53. Mun, S.H.; Joung, D.K.; Kim, Y.S.; Kang, O.H.; Kim, S.B.; Seo, Y.S.; Kim, Y.C.; Lee, D.S.; Shin, D.W.; Kweon, K.T.; et al. Synergistic antibacterial effect of curcumin against methicillin-resistant *Staphylococcus aureus*. *Phytomedicine* **2013**, *20*, 714–718. [[CrossRef](#)] [[PubMed](#)]
54. De, R.; Kundu, P.; Swarnakar, S.; Ramamurthy, T.; Chowdhury, A.; Nair, G.B.; Mukhopadhyay, A.K. Antimicrobial activity of curcumin against helicobacter pylori isolates from India and during infections in mice. *Antimicrob. Agents Chemother.* **2009**, *53*, 1592–1597. [[CrossRef](#)] [[PubMed](#)]
55. Niamsa, N.; Sittiwet, C. Antimicrobial activity of curcuma longa aqueous extract. *J. Pharmacol. Toxicol.* **2009**, *4*, 174–177.
56. Chen, C.; Long, L.; Zhang, F.; Chen, Q.; Chen, C.; Yu, X.; Liu, Q.; Bao, J.; Long, Z. Antifungal activity, main active components and mechanism of curcuma longa extract against *Fusarium graminearum*. *PLoS ONE* **2018**, *13*, e0194284. [[CrossRef](#)]
57. Wu, W.F.; Wang, J.N.; Li, Z.; Wei, B.; Jin, J.; Gao, L.; Li, H.D.; Li, J.; Chen, H.Y.; Meng, X.M. 7-hydroxycoumarin protects against cisplatin-induced acute kidney injury by inhibiting necroptosis and promoting sox9-mediated tubular epithelial cell proliferation. *Phytomedicine* **2020**, *69*, 153202. [[CrossRef](#)]

58. Shlar, I.; Droby, S.; Rodov, V. Modes of antibacterial action of curcumin under dark and light conditions: A toxicoproteomics approach. *J. Proteom.* **2017**, *160*, 8–20. [[CrossRef](#)]
59. Tan, B.L.; Norhaizan, M.E. Curcumin combination chemotherapy: The implication and efficacy in cancer. *Molecules* **2019**, *24*, 2527. [[CrossRef](#)]
60. Aggarwal, B.B.; Harikumar, K.B. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int. J. Biochem. Cell Biol.* **2009**, *41*, 40–59. [[CrossRef](#)]
61. Sharma, R.A.; Gescher, A.J.; Steward, W.P. Curcumin: The story so far. *Eur. J. Cancer* **2005**, *41*, 1955–1968. [[CrossRef](#)]
62. Aggarwal, B.B.; Kumar, A.; Bharti, A.C. Anticancer potential of curcumin: Preclinical and clinical studies. *Anticancer Res.* **2003**, *23*, 363–398.
63. Zhou, H.; Beevers, C.S.; Huang, S. The targets of curcumin. *Curr. Drug Targets* **2011**, *12*, 332–347. [[CrossRef](#)] [[PubMed](#)]
64. Xu, F.; Diao, R.; Liu, J.; Kang, Y.; Wang, X.; Shi, L. Curcumin attenuates *Staphylococcus aureus*-induced acute lung injury. *Clin. Respir. J.* **2015**, *9*, 87–97. [[CrossRef](#)] [[PubMed](#)]
65. Zhang, J.; Zheng, Y.; Luo, Y.; Du, Y.; Zhang, X.; Fu, J. Curcumin inhibits lps-induced neuroinflammation by promoting microglial m2 polarization via trem2/ tlr4/ nf-kappab pathways in bv2 cells. *Mol. Immunol.* **2019**, *116*, 29–37. [[CrossRef](#)]
66. Bai, X.; Oberley-Deegan, R.E.; Bai, A.; Ovrutsky, A.R.; Kinney, W.H.; Weaver, M.; Zhang, G.; Honda, J.R.; Chan, E.D. Curcumin enhances human macrophage control of mycobacterium tuberculosis infection. *Respirology* **2016**, *21*, 951–957. [[CrossRef](#)] [[PubMed](#)]
67. Foryst-Ludwig, A.; Neumann, M.; Schneider-Brachert, W.; Naumann, M. Curcumin blocks nf-kappab and the motogenic response in helicobacter pylori-infected epithelial cells. *Biochem. Biophys. Res. Commun.* **2004**, *316*, 1065–1072. [[CrossRef](#)] [[PubMed](#)]
68. Kundu, P.; De, R.; Pal, I.; Mukhopadhyay, A.K.; Saha, D.R.; Swarnakar, S. Curcumin alleviates matrix metalloproteinase-3 and -9 activities during eradication of *Helicobacter pylori* infection in cultured cells and mice. *PLoS ONE* **2011**, *6*, e16306. [[CrossRef](#)] [[PubMed](#)]
69. Yin, H.P.; Guo, Q.; Li, X.; Tang, T.T.; Li, C.L.; Wang, H.X.; Sun, Y.X.; Feng, Q.; Ma, C.H.; Gao, C.J.; et al. Curcumin suppresses il-1 beta secretion and prevents inflammation through inhibition of the nlrp3 inflammasome. *J. Immunol.* **2018**, *200*, 2835–2846. [[CrossRef](#)]
70. Kim, D.C.; Lee, W.; Bae, J.S. Vascular anti-inflammatory effects of curcumin on hmgb1-mediated responses in vitro. *Inflamm. Res.* **2011**, *60*, 1161–1168. [[CrossRef](#)]
71. Karlstetter, M.; Lippe, E.; Walczak, Y.; Moehle, C.; Aslanidis, A.; Mirza, M.; Langmann, T. Curcumin is a potent modulator of microglial gene expression and migration. *J. Neuroinflamm.* **2011**, *8*, 125. [[CrossRef](#)]
72. Poirel, L.; Jayol, A.; Nordmann, P. Polymyxins: Antibacterial activity, susceptibility testing, and resistance mechanisms encoded by plasmids or chromosomes. *Clin. Microbiol. Rev.* **2017**, *30*, 557–596. [[CrossRef](#)]
73. Sampson, T.R.; Liu, X.; Schroeder, M.R.; Kraft, C.S.; Burd, E.M.; Weiss, D.S. Rapid killing of acinetobacter *Baumannii* by polymyxins is mediated by a hydroxyl radical death pathway. *Antimicrob. Agents Chemother.* **2012**, *56*, 5642–5649. [[CrossRef](#)] [[PubMed](#)]
74. Yu, Z.; Qin, W.; Lin, J.; Fang, S.; Qiu, J. Antibacterial mechanisms of polymyxin and bacterial resistance. *Biomed. Res. Int.* **2015**, *2015*, 679109. [[CrossRef](#)] [[PubMed](#)]
75. Needham, B.D.; Trent, M.S. Fortifying the barrier: The impact of lipid a remodelling on bacterial pathogenesis. *Nat. Rev. Microbiol.* **2013**, *11*, 467–481. [[CrossRef](#)] [[PubMed](#)]
76. Olaitan, A.O.; Morand, S.; Rolain, J.M. Mechanisms of polymyxin resistance: Acquired and intrinsic resistance in bacteria. *Front. Microbiol.* **2014**, *5*, 643. [[CrossRef](#)] [[PubMed](#)]
77. Kofteridis, D.P.; Alexopoulou, C.; Valachis, A.; Maraki, S.; Dimopoulou, D.; Georgopoulos, D.; Samonis, G. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: A matched case-control study. *Clin. Infect. Dis.* **2010**, *51*, 1238–1244. [[CrossRef](#)] [[PubMed](#)]
78. Gai, Z.B.; Samodelov, S.L.; Kullak-Ublick, G.A.; Visentin, M. Molecular mechanisms of colistin-induced nephrotoxicity. *Molecules* **2019**, *24*, 653. [[CrossRef](#)]
79. Dezoti-Fonseca, C.; Watanabe, M.; Vattimo-Mde, F. Role of heme oxygenase-1 in polymyxin b-induced nephrotoxicity in rats. *Antimicrob. Agents Chemother.* **2012**, *56*, 5082–5087. [[CrossRef](#)]

80. Dai, C.; Tang, S.; Wang, Y.; Velkov, T.; Xiao, X. Baicalein acts as a nephroprotectant that ameliorates colistin-induced nephrotoxicity by activating the antioxidant defence mechanism of the kidneys and down-regulating the inflammatory response. *J. Antimicrob. Chemother.* **2017**, *72*, 2562–2569. [[CrossRef](#)]
81. Wallace, S.J.; Li, J.; Nation, R.L.; Rayner, C.R.; Taylor, D.; Middleton, D.; Milne, R.W.; Coulthard, K.; Turnidge, J.D. Subacute toxicity of colistin methanesulfonate in rats: Comparison of various intravenous dosage regimens. *Antimicrob. Agents Chemother.* **2008**, *52*, 1159–1161. [[CrossRef](#)]
82. Ghilissi, Z.; Hakim, A.; Mnif, H.; Ayadi, F.M.; Zeghal, K.; Rebai, T.; Sahnoun, Z. Evaluation of colistin nephrotoxicity administered at different doses in the rat model. *Ren. Fail.* **2013**, *35*, 1130–1135. [[CrossRef](#)]
83. Keirstead, N.D.; Wagoner, M.P.; Bentley, P.; Blais, M.; Brown, C.; Cheatham, L.; Ciaccio, P.; Dragan, Y.; Ferguson, D.; Fikes, J.; et al. Early prediction of polymyxin-induced nephrotoxicity with next-generation urinary kidney injury biomarkers. *Toxicol. Sci.* **2014**, *137*, 278–291. [[CrossRef](#)] [[PubMed](#)]
84. Azad, M.A.K.; Roberts, K.D.; Yu, H.D.H.; Liu, B.Y.; Schofield, A.V.; James, S.A.; Howard, D.L.; Nation, R.L.; Rogers, K.; de Jonge, M.D.; et al. Significant accumulation of polymyxin in single renal tubular cells: A medicinal chemistry and triple correlative microscopy approach. *Anal. Chem.* **2015**, *87*, 1590–1595. [[CrossRef](#)] [[PubMed](#)]
85. Yun, B.; Azad, M.A.K.; Wang, J.; Nation, R.L.; Thompson, P.E.; Roberts, K.D.; Velkov, T.; Li, J. Imaging the distribution of polymyxins in the kidney. *J. Antimicrob. Chemother.* **2015**, *70*, 827–829. [[CrossRef](#)] [[PubMed](#)]
86. Velkov, T.; Yun, B.; Schneider, E.K.; Azad, M.A.; Dolezal, O.; Morris, F.C.; Nation, R.L.; Wang, J.; Chen, K.; Yu, H.H.; et al. A novel chemical biology approach for mapping of polymyxin lipopeptide antibody binding epitopes. *ACS Infect. Dis.* **2016**, *13*, 41–51. [[CrossRef](#)] [[PubMed](#)]
87. Manchandani, P.; Zhou, J.; Ledesma, K.R.; Truong, L.D.; Chow, D.S.; Eriksen, J.L.; Tam, V.H. Characterization of polymyxin b biodistribution and disposition in an animal model. *Antimicrob. Agents Chemother.* **2016**, *60*, 1029–1034. [[CrossRef](#)]
88. Sivanesan, S.S.; Azad, M.A.K.; Schneider, E.K.; Ahmed, M.U.; Huang, J.; Wang, J.; Li, J.; Nation, R.L.; Velkov, T. Gelofusine ameliorates colistin-induced nephrotoxicity. *Antimicrob. Agents Chemother.* **2017**, *61*, e00985-17. [[CrossRef](#)]
89. Azad, M.A.K.; Sivanesan, S.; Wang, J.; Chen, K.; Nation, R.L.; Thompson, P.E.; Roberts, K.D.; Velkov, T.; Li, J. Methionine ameliorates polymyxin-induced nephrotoxicity by attenuating cellular oxidative stress. *Antimicrob. Agents Chemother.* **2017**, *62*, e01254-17. [[CrossRef](#)] [[PubMed](#)]
90. Roberts, K.D.; Azad, M.A.; Wang, J.; Horne, A.S.; Thompson, P.E.; Nation, R.L.; Velkov, T.; Li, J. Antimicrobial activity and toxicity of the major lipopeptide components of polymyxin b and colistin: Last-line antibiotics against multidrug-resistant gram-negative bacteria. *ACS Infect. Dis.* **2015**, *1*, 568–575. [[CrossRef](#)]
91. Lu, X.; Chan, T.; Xu, C.; Zhu, L.; Zhou, Q.T.; Roberts, K.D.; Chan, H.K.; Li, J.; Zhou, F. Human oligopeptide transporter 2 (pept2) mediates cellular uptake of polymyxins. *J. Antimicrob. Chemother.* **2016**, *71*, 403–412. [[CrossRef](#)]
92. Dai, C.; Tang, S.; Deng, S.; Zhang, S.; Zhou, Y.; Velkov, T.; Li, J.; Xiao, X. Lycopene attenuates colistin-induced nephrotoxicity in mice via activation of the nrf2/ho-1 pathway. *Antimicrob. Agents Chemother.* **2015**, *59*, 579–585. [[CrossRef](#)]
93. Dai, C.; Li, J.; Tang, S.; Li, J.; Xiao, X. Colistin-induced nephrotoxicity in mice involves the mitochondrial, death receptor, and endoplasmic reticulum pathways. *Antimicrob. Agents Chemother.* **2014**, *58*, 4075–4085. [[CrossRef](#)] [[PubMed](#)]
94. Yousef, J.M.; Chen, G.; Hill, P.A.; Nation, R.L.; Li, J. Ascorbic acid protects against the nephrotoxicity and apoptosis caused by colistin and affects its pharmacokinetics. *J. Antimicrob. Chemother.* **2012**, *67*, 452–459. [[CrossRef](#)]
95. Yousef, J.M.; Chen, G.; Hill, P.A.; Nation, R.L.; Li, J. Melatonin attenuates colistin-induced nephrotoxicity in rats. *Antimicrob. Agents Chemother.* **2011**, *55*, 4044–4049. [[CrossRef](#)] [[PubMed](#)]
96. Ma, Z.; Wang, J.; Nation, R.L.; Li, J.; Turnidge, J.D.; Coulthard, K.; Milne, R.W. Renal disposition of colistin in the isolated perfused rat kidney. *Antimicrob. Agents Chemother.* **2009**, *53*, 2857–2864. [[CrossRef](#)] [[PubMed](#)]
97. Suzuki, T.; Yamaguchi, H.; Ogura, J.; Kobayashi, M.; Yamada, T.; Iseki, K. Megalin contributes to kidney accumulation and nephrotoxicity of colistin. *Antimicrob. Agents Chemother.* **2013**, *57*, 6319–6324. [[CrossRef](#)]
98. Hori, Y.; Aoki, N.; Kuwahara, S.; Hosojima, M.; Kaseda, R.; Goto, S.; Iida, T.; De, S.; Kabasawa, H.; Kaneko, R.; et al. Megalin blockade with cilastatin suppresses drug-induced nephrotoxicity. *JASN* **2017**, *28*, 1783–1791. [[CrossRef](#)]

99. Visentin, M.; Gai, Z.; Torozi, A.; Hiller, C.; Kullak-Ublick, G.A. Colistin is substrate of the carnitine/organic cation transporter 2 (octn2, slc22a5). *Drug Metab. Dispos.* **2017**, *45*, 1240–1244. [[CrossRef](#)]
100. Li, Z.D.; Luo, J.; Jia, L.H.; Wang, X.Y.; Xun, Z.K.; Liu, M. Cytochrome c suppresses renal accumulation and nephrotoxicity of polymyxin b. *Hum. Exp. Toxicol.* **2019**, *38*, 193–200. [[CrossRef](#)]
101. Azad, M.A.K.; Akter, J.; Rogers, K.L.; Nation, R.L.; Velkov, T.; Li, J. Major pathways of polymyxin-induced apoptosis in rat kidney proximal tubular cells. *Antimicrob. Agents Chemother.* **2015**, *59*, 2136–2143. [[CrossRef](#)]
102. Eadon, M.T.; Hack, B.K.; Alexander, J.J.; Xu, C.; Dolan, M.E.; Cunningham, P.N. Cell cycle arrest in a model of colistin nephrotoxicity. *Physiol. Genom.* **2013**, *45*, 877–888. [[CrossRef](#)]
103. Yun, B.; Zhang, T.; Azad, M.A.K.; Wang, J.; Nowell, C.J.; Kalitsis, P.; Velkov, T.; Hudson, D.F.; Li, J. Polymyxin b causes DNA damage in hk-2 cells and mice. *Arch. Toxicol.* **2018**, *92*, 2259–2271. [[CrossRef](#)] [[PubMed](#)]
104. Lee, T.W.; Bae, E.; Kim, J.H.; Jang, H.N.; Cho, H.S.; Chang, S.H.; Park, D.J. The aqueous extract of aged black garlic ameliorates colistin-induced acute kidney injury in rats. *Ren. Fail.* **2019**, *41*, 24–33. [[CrossRef](#)] [[PubMed](#)]
105. Jeong, B.Y.; Park, S.R.; Cho, S.; Yu, S.L.; Lee, H.Y.; Park, C.G.; Kang, J.; Jung, D.Y.; Park, M.H.; Hwang, W.M.; et al. Tgf-beta-mediated nadph oxidase 4-dependent oxidative stress promotes colistin-induced acute kidney injury. *J. Antimicrob. Chemother.* **2018**, *73*, 962–972. [[CrossRef](#)] [[PubMed](#)]
106. Wu, J.; Pan, X.; Fu, H.; Zheng, Y.; Dai, Y.; Yin, Y.; Chen, Q.; Hao, Q.; Bao, D.; Hou, D. Effect of curcumin on glycerol-induced acute kidney injury in rats. *Sci. Rep.* **2017**, *7*, 10114. [[CrossRef](#)] [[PubMed](#)]
107. He, L.; Peng, X.; Zhu, J.; Liu, G.; Chen, X.; Tang, C.; Liu, H.; Liu, F.; Peng, Y. Protective effects of curcumin on acute gentamicin-induced nephrotoxicity in rats. *Can. J. Physiol. Pharm.* **2015**, *93*, 275–282. [[CrossRef](#)]
108. Deck, L.M.; Hunsaker, L.A.; Vander Jagt, T.A.; Whalen, L.J.; Royer, R.E.; Vander Jagt, D.L. Activation of antioxidant nrf2 signaling by enone analogues of curcumin. *Eur. J. Med. Chem.* **2018**, *143*, 854–865. [[CrossRef](#)]
109. Dai, C.; Li, B.; Zhou, Y.; Li, D.; Zhang, S.; Li, H.; Xiao, X.; Tang, S. Curcumin attenuates quinocetone induced apoptosis and inflammation via the opposite modulation of nrf2/ho-1 and nf-kb pathway in human hepatocyte l02 cells. *Food Chem. Toxicol.* **2016**, *95*, 52–63. [[CrossRef](#)] [[PubMed](#)]
110. Klionsky, D.J.; Abdelmohsen, K.; Abe, A.; Abedin, M.J.; Abeliovich, H.; Acevedo Arozena, A.; Adachi, H.; Adams, C.M.; Adams, P.D.; Adeli, K.; et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy* **2016**, *12*, 1–222. [[CrossRef](#)] [[PubMed](#)]
111. Ortega-Dominguez, B.; Aparicio-Trejo, O.E.; Garcia-Arroyo, F.E.; Leon-Contreras, J.C.; Tapia, E.; Molina-Jijon, E.; Hernandez-Pando, R.; Sanchez-Lozada, L.G.; Barrera-Oviedo, D.; Pedraza-Chaverri, J. Curcumin prevents cisplatin-induced renal alterations in mitochondrial bioenergetics and dynamic. *Food Chem. Toxicol.* **2017**, *107*, 373–385. [[CrossRef](#)] [[PubMed](#)]
112. Avila-Rojas, S.H.; Tapia, E.; Briones-Herrera, A.; Aparicio-Trejo, O.E.; Leon-Contreras, J.C.; Hernandez-Pando, R.; Pedraza-Chaverri, J. Curcumin prevents potassium dichromate (k2cr2o7)-induced renal hypoxia. *Food Chem. Toxicol.* **2018**, *121*, 472–482. [[CrossRef](#)]
113. Guerrero-Hue, M.; Garcia-Caballero, C.; Palomino-Antolin, A.; Rubio-Navarro, A.; Vazquez-Carballo, C.; Herencia, C.; Martin-Sanchez, D.; Farre-Alins, V.; Egea, J.; Cannata, P.; et al. Curcumin reduces renal damage associated with rhabdomyolysis by decreasing ferroptosis-mediated cell death. *FASEB J.* **2019**, *33*, 8961–8975. [[CrossRef](#)]
114. Molina-Jijon, E.; Aparicio-Trejo, O.E.; Rodriguez-Munoz, R.; Leon-Contreras, J.C.; Del Carmen Cardenas-Aguayo, M.; Medina-Campos, O.N.; Tapia, E.; Sanchez-Lozada, L.G.; Hernandez-Pando, R.; Reyes, J.L.; et al. The nephroprotection exerted by curcumin in maleate-induced renal damage is associated with decreased mitochondrial fission and autophagy. *Biofactors* **2016**, *42*, 686–702. [[CrossRef](#)]
115. Sankar, P.; Telang, A.G.; Kalaivanan, R.; Karunakaran, V.; Suresh, S.; Kesavan, M. Oral nanoparticulate curcumin combating arsenic-induced oxidative damage in kidney and brain of rats. *Toxicol. Ind. Health* **2016**, *32*, 410–421. [[CrossRef](#)]
116. Benzer, F.; Kandemir, F.M.; Kucukler, S.; Comakli, S.; Caglayan, C. Chemoprotective effects of curcumin on doxorubicin-induced nephrotoxicity in wistar rats: By modulating inflammatory cytokines, apoptosis, oxidative stress and oxidative DNA damage. *Arch. Physiol. Biochem.* **2018**, *124*, 448–457. [[CrossRef](#)]
117. Falagas, M.E.; Kasiakou, S.K. Toxicity of polymyxins: A systematic review of the evidence from old and recent studies. *Crit. Care* **2006**, *10*, R27. [[CrossRef](#)]
118. Weinstein, L.; Doan, T.L.; Smith, M.A. Neurotoxicity in patients treated with intravenous polymyxin b: Two case reports. *Am. J. Health Syst. Pharm.* **2009**, *66*, 345–347. [[CrossRef](#)]

119. Wahby, K.; Chopra, T.; Chandrasekar, P. Intravenous and inhalational colistin-induced respiratory failure. *Clin. Infect. Dis.* **2010**, *50*, e38–e40. [[CrossRef](#)]
120. Dai, C.; Tang, S.; Li, J.; Wang, J.; Xiao, X. Effects of colistin on the sensory nerve conduction velocity and f-wave in mice. *Basic Clin. Pharmacol. Toxicol.* **2014**, *115*, 577–580. [[CrossRef](#)]
121. Bosso, J.A.; Liptak, C.A.; Seilheimer, D.K.; Harrison, G.M. Toxicity of colistin in cystic fibrosis patients. *DICP* **1991**, *25*, 1168–1170. [[CrossRef](#)]
122. John, J.F.; Falci, D.R.; Rigatto, M.H.; Oliveira, R.D.; Kremer, T.G.; Zavascki, A.P. Severe infusion-related adverse events and renal failure in patients receiving high-dose intravenous polymyxin b. *Antimicrob. Agents Chemother.* **2018**, *62*, e01617-17. [[CrossRef](#)]
123. Hitchcock, S.A. Blood-brain barrier permeability considerations for cns-targeted compound library design. *Curr. Opin. Chem. Biol.* **2008**, *12*, 318–323. [[CrossRef](#)]
124. Jin, L.; Nation, R.L.; Li, J.; Nicolazzo, J.A. Species-dependent blood-brain barrier disruption of lipopolysaccharide: Amelioration by colistin in vitro and in vivo. *Antimicrob. Agents Chemother.* **2013**, *57*, 4336–4342. [[CrossRef](#)]
125. Loho, T.; Dharmayanti, A. Colistin: An antibiotic and its role in multiresistant gram-negative infections. *Acta Med. Indones.* **2015**, *47*, 157–168.
126. Jin, L.; Li, J.; Nation, R.L.; Nicolazzo, J.A. Effect of systemic infection induced by pseudomonas aeruginosa on the brain uptake of colistin in mice. *Antimicrob. Agents Chemother.* **2012**, *56*, 5240–5246. [[CrossRef](#)]
127. Jin, L.; Li, J.; Nation, R.L.; Nicolazzo, J.A. Impact of p-glycoprotein inhibition and lipopolysaccharide administration on blood-brain barrier transport of colistin in mice. *Antimicrob. Agents Chemother.* **2011**, *55*, 502–507. [[CrossRef](#)]
128. Jin, L.; Li, J.; Nation, R.L.; Nicolazzo, J.A. Brain penetration of colistin in mice assessed by a novel high-performance liquid chromatographic technique. *Antimicrob. Agents Chemother.* **2009**, *53*, 4247–4251. [[CrossRef](#)]
129. Wang, J.; Yi, M.; Chen, X.; Muhammad, I.; Liu, F.; Li, R.; Li, J.; Li, J. Effects of colistin on amino acid neurotransmitters and blood-brain barrier in the mouse brain. *Neurotoxicol. Teratol.* **2016**, *55*, 32–37. [[CrossRef](#)]
130. Dai, C.; Li, J.; Lin, W.; Li, G.; Sun, M.; Wang, F.; Li, J. Electrophysiology and ultrastructural changes in mouse sciatic nerve associated with colistin sulfate exposure. *Toxicol. Mech. Methods* **2012**, *22*, 592–596. [[CrossRef](#)]
131. Dai, C.; Li, J.; Li, J. New insight in colistin induced neurotoxicity with the mitochondrial dysfunction in mice central nervous tissues. *Exp. Toxicol. Pathol.* **2013**, *65*, 941–948. [[CrossRef](#)] [[PubMed](#)]
132. Dai, C.; Ciccotosto, G.D.; Cappai, R.; Wang, Y.; Tang, S.; Hoyer, D.; Schneider, E.K.; Velkov, T.; Xiao, X. Rapamycin confers neuroprotection against colistin-induced oxidative stress, mitochondria dysfunction, and apoptosis through the activation of autophagy and mtor/akt/creb signaling pathways. *ACS Chem. Neurosci.* **2018**, *9*, 824–837. [[CrossRef](#)]
133. Dai, C.; Ciccotosto, G.D.; Cappai, R.; Wang, Y.; Tang, S.; Xiao, X.; Velkov, T. Minocycline attenuates colistin-induced neurotoxicity via suppression of apoptosis, mitochondrial dysfunction and oxidative stress. *J. Antimicrob. Chemother.* **2017**, *72*, 1635–1645. [[CrossRef](#)]
134. Lee, S.H.; Kim, J.S.; Ravichandran, K.; Gil, H.W.; Song, H.Y.; Hong, S.Y. P-glycoprotein induction ameliorates colistin induced nephrotoxicity in cultured human proximal tubular cells. *PLoS ONE* **2015**, *10*, e0136075. [[CrossRef](#)]
135. Daniel, H.; Kottra, G. The proton oligopeptide cotransporter family slc15 in physiology and pharmacology. *Pflug. Arch.* **2004**, *447*, 610–618.
136. Spuch, C.; Ortolano, S.; Navarro, C. Lrp-1 and lrp-2 receptors function in the membrane neuron. Trafficking mechanisms and proteolytic processing in Alzheimer's disease. *Front. Physiol.* **2012**, *3*, 269. [[CrossRef](#)]
137. Courousse, T.; Bacq, A.; Belzung, C.; Guiard, B.; Balasse, L.; Louis, F.; Le Guisquet, A.M.; Gardier, A.M.; Schinkel, A.H.; Giros, B.; et al. Brain organic cation transporter 2 controls response and vulnerability to stress and gsk3beta signaling. *Mol. Psychiatry* **2015**, *20*, 889–900. [[CrossRef](#)]
138. Ikonomidou, C.; Kaindl, A.M. Neuronal death and oxidative stress in the developing brain. *Antioxid. Redox Signal.* **2011**, *14*, 1535–1550. [[CrossRef](#)] [[PubMed](#)]
139. Dai, C.; Tang, S.; Biao, X.; Xiao, X.; Chen, C.; Li, J. Colistin induced peripheral neurotoxicity involves mitochondrial dysfunction and oxidative stress in mice. *Mol. Biol. Rep.* **2019**, *46*, 1963–1972. [[CrossRef](#)]

140. Dai, C.; Zhang, D.; Li, J.; Li, J. Effect of colistin exposure on calcium homeostasis and mitochondria functions in chick cortex neurons. *Toxicol. Mech. Methods* **2013**, *23*, 281–288. [[CrossRef](#)]
141. Stowe, D.F.; Camara, A.K. Mitochondrial reactive oxygen species production in excitable cells: Modulators of Mitochondrial and cell function. *Antioxid. Redox Signal.* **2009**, *11*, 1373–1414. [[CrossRef](#)]
142. Dai, C.; Tang, S.; Velkov, T.; Xiao, X. Colistin-induced apoptosis of neuroblastoma-2a cells involves the generation of reactive oxygen species, mitochondrial dysfunction, and autophagy. *Mol. Neurobiol.* **2016**, *53*, 4685–4700. [[CrossRef](#)] [[PubMed](#)]
143. Lu, Z.; Chen, C.; Wu, Z.; Miao, Y.; Muhammad, I.; Ding, L.; Tian, E.; Hu, W.; Ni, H.; Li, R.; et al. A dual role of p53 in regulating colistin-induced autophagy in pc-12 cells. *Front. Pharm.* **2017**, *8*, 768. [[CrossRef](#)] [[PubMed](#)]
144. Ahmed, M.U.; Velkov, T.; Lin, Y.W.; Yun, B.; Nowell, C.J.; Zhou, F.; Zhou, Q.T.; Chan, K.; Azad, M.A.K.; Li, J. Potential toxicity of polymyxins in human lung epithelial cells. *Antimicrob. Agents Chemother.* **2017**, *61*, e02690-16. [[CrossRef](#)] [[PubMed](#)]
145. Jiang, H.; Li, J.; Zhou, T.; Wang, C.; Zhang, H.; Wang, H. Colistin-induced apoptosis in pc12 cells: Involvement of the mitochondrial apoptotic and death receptor pathways. *Int. J. Mol. Med.* **2014**, *33*, 1298–1304. [[CrossRef](#)]
146. Dai, C.; Xiao, X.; Li, J.; Ciccotosto, G.D.; Cappai, R.; Tang, S.; Schneider-Futschik, E.K.; Hoyer, D.; Velkov, T.; Shen, J. Molecular mechanisms of neurotoxicity induced by polymyxins and chemoprevention. *ACS Chem. Neurosci.* **2019**, *10*, 120–131. [[CrossRef](#)] [[PubMed](#)]
147. Zhang, L.; Zhao, Y.; Ding, W.; Jiang, G.; Lu, Z.; Li, L.; Wang, J.; Li, J.; Li, J. Autophagy regulates colistin-induced apoptosis in pc-12 cells. *Antimicrob. Agents Chemother.* **2015**, *59*, 2189–2197. [[CrossRef](#)] [[PubMed](#)]
148. Zhao, W.; Pan, X.; Li, T.; Zhang, C.; Shi, N. *Lycium barbarum* polysaccharides protect against trimethyltin chloride-induced apoptosis via sonic hedgehog and pi3k/akt signaling pathways in mouse neuro-2a cells. *Oxid. Med. Cell. Longev.* **2016**, *2016*, 9826726. [[CrossRef](#)]
149. Lu, Z.; Miao, Y.; Muhammad, I.; Tian, E.; Hu, W.; Wang, J.; Wang, B.; Li, R.; Li, J. Colistin-induced autophagy and apoptosis involves the jnk-bcl2-bax signaling pathway and jnk-p53-ros positive feedback loop in pc-12 cells. *Chem. Biol. Interact.* **2017**, *277*, 62–73. [[CrossRef](#)]
150. Tian, E.; Hu, W.; Miao, Y.; Muhammad, I.; Zhang, L.; Xia, C.; Ding, L.; Zhang, Q.; Li, R.; Chen, C.; et al. Preventive effects of nerve growth factor against colistin-induced autophagy and apoptosis in pc12 cells. *Toxicol. Mech. Methods* **2018**, *29*, 177–186. [[CrossRef](#)]
151. Barta, A.; Janega, P.; Babal, P.; Murar, E.; Cebova, M.; Pechanova, O. The effect of curcumin on liver fibrosis in the rat model of microsurgical cholestasis. *Food Funct.* **2015**, *6*, 2187–2193. [[CrossRef](#)]
152. Garcia-Nino, W.R.; Pedraza-Chaverri, J. Protective effect of curcumin against heavy metals-induced liver damage. *Food Chem. Toxicol.* **2014**, *69*, 182–201. [[CrossRef](#)]
153. Lu, Z.; Jiang, G.; Chen, Y.; Wang, J.; Muhammad, I.; Zhang, L.; Wang, R.; Liu, F.; Li, R.; Qian, F.; et al. Salidroside attenuates colistin-induced neurotoxicity in rsc96 schwann cells through pi3k/akt pathway. *Chem. Biol. Interact.* **2017**, *271*, 67–78. [[CrossRef](#)] [[PubMed](#)]
154. Dai, C.; Xiong, J.; Wang, Y.; Shen, J.; Velkov, T.; Xiao, X. Nerve growth factor confers neuroprotection against colistin-induced peripheral neurotoxicity. *ACS Infect. Dis.* **2020**. [[CrossRef](#)] [[PubMed](#)]

