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Revisiting an 'old' antibiotic class polymyxins by drug combination therapy targeting Gram-negative superbugs: *Toyyiban* perspective

Mohd Hafidz Mahamad Maifiah[1]*, Muhammad Shirwan Abdullah Sani[1] and Nusaibah Abd Rahim[2]

[1]International Institute for Halal Research and Training (INHART), Level 3, KICT building, International Islamic University Malaysia (IIUM), Selangor Darul Ehsan

[2]School of Pharmacy, Faculty of Health and Medical Science, Taylor's University, 47500 Subang Jaya, Selangor

Abstract: The Islamic concept of *halalan- halalan-toyyiban* encompasses medicines and pharmaceuticals. Halal pharmaceuticals mean the products are free from any unlawful (haram) constituents while in another aspect, toyyib pharmaceuticals particularly concern on the products' wholesomeness, quality and safety. Polymyxins, an 'old' class antibiotic have been employed as the last-line defence for infections caused by multidrug-resistant (MDR) Gram-negative pathogens. Nevertheless, the exceptional clinical applications of polymyxins are restrained due to their dose-limiting nephrotoxicity and neurotoxicity. In addition, pharmacokinetic/pharmacodynamic (PK/PD) studies indicate that polymyxin monotherapy often fails to achieve an effective *in vivo* plasma exposure concentration, potentially lead to the emergence of bacterial heteroresistance. To optimise the significant potential of polymyxins, therefore, polymyxin combination therapy has been recommended. The strategy provides some advantages as it significantly confers safer clinical dosage of polymyxins administration thus likely to reduce its toxicity effects. Looking from the *halalan-toyyiban* perspective, this review discusses on the synergistic killing of polymyxin combination for the treatment of MDR Gram-negative infection to reduce its potential toxicity and emergence of resistance.

Keywords: Halalan- *halalan-toyyiban*; Halal pharmaceutical; Polymyxins; Polymyxin combination therapy

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*Correspondence:
Mohd Hafidz Mahamad Maifiah, International Institute for Halal Research and Training (INHART), Level 3, KICT building, International Islamic University Malaysia (IIUM), Selangor Darul Ehsan; mhafidzmaifiah@iium.edu.my

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Introduction

The concept of halal (lawful or permissible) and haram (forbidden) constitutes a principle of Islamic law (Shariah) (Al-Qaradawi, 2000). The concept has always and commonly been associated with food and services (e.g. Islamic finance). In spite of that, unlimited to the aforementioned scope, the principle is significantly applied in justifying the consumption of particular products to be taken including medicines and pharmaceuticals. The word toyyib is the Arabic term which is always paired with the word halal refers to a product or something that is clean, pure, and wholesome in term of quality and safety. Halal and toyyib pharmaceuticals (generally refers to halal pharmaceuticals) refers to any medicinal product for example drug, as according to the Islamic law it is free of any haram element or forbidden source produced with a very high quality and void of toxicity (Norazmi & Lim, 2015). The escalating awareness and knowledge about the concepts and wide exposure on issues pertaining to halal has recently developed great interests among the Muslims and unsurprisingly to also non-Muslims looking from both Shariah and economic perspectives.

Among the greatest challenges in the modern world today to human health is the global dissemination of multidrug-resistant (MDR) pathogens, in particular Gram-negative bacteria. The paradoxical trends of the constant declining of novel antibiotic discovery and development as well as the rapid emergence of life-threatening infections of 'superbugs' (Jones *et al.*, 2008) necessitate a resurgence of the available antibiotic polymyxins as the last-line arsenal (Arnold *et al.,* 2007). Nevertheless, studies indicate that polymyxins induce notable nephrotoxicity following administration of higher daily dosage (Abdelraouf *et al.,* 2012). In addition, the finite *in vivo* pharmacokinetic/pharmacodynamic (PK/PD) profiles of polymyxins showed that polymyxin monotherapy generates sub-optimal plasma concentrations (Bergen *et al.,* 2010). As a result, this has led to the emergence of polymyxin resistance and significantly compromised their clinical benefits (Bergen *et al.,* 2010). In order to address this crucial problem, polymyxin combination therapy has been suggested as a viable alternative resolution to polymyxin monotherapy (Bergen *et al.,* 2015). In this review, the discussion is focusing on the application of polymyxin-combination therapy as a method to increase its efficacy while at the same time minimise its toxicity effects.

Halal pharmaceuticals: A *halalan-toyyiban* aspect to promise safety

Recently, the Islamic concepts of halal, haram and toyyib have been adopted and extended in the field of medicines and pharmaceuticals. A major concern from consumers particularly among the Muslims is about the use of haram (forbidden) materials

in many medicinal products (Halim et al., 2014). In turn, toyyib is a term that always been referred to goods and products of high quality standard which contain wholesome elements comprised of — cleanliness, pureness, and harmless produced based on standard process and procedures (Sarriff & Abdul Razzaq, 2013). A number of studies have been reported pertaining to issues on halal and toyyib as discussed from different viewpoints. Studies have been conducted for example on the measurement of level of halal awareness, current practice of healthcare providers on halal or haram medications and searching for halal alternative in the formulation of medicinal products (Zarif et al., 2013; Sadeeqa et al., 2015). Importantly, the concepts should be understood in the atmosphere of modern and contemporary world as the dynamic understanding of each term are accordingly evolved. To cater the various and complex issues in the medicine and pharmaceutical areas therefore this requires the contribution and integration of knowledge of different viewpoints from the religious scholars, legal authorities and Muslims medical practitioners and experts.

Realising the importance to comply for the halal certification, the Department of Standard Malaysia has published a national standard on halal pharmaceutical, MS 2424:2012. The guideline provides a clear definition on halal pharmaceuticals — comprising both the halal and toyyib elements. Drugs and antibiotics are commonly derived of microorganisms (including bacteria, viruses, fungi and protozoa) and natural chemicals. According to the Islamic principle, all microorganisms and chemicals are halal except those prohibited by the competent authority due to its harm and toxicity effects when consumed (Malaysian Standard, 2012). Apart from the issue of forbidden use of any non-halal material, the one that always being a major concern to both Muslims and non-Muslims consumers is on the safety aspect of the products.

An important scope of the halal pharmaceuticals is to ensure that the medicines must be safe for human consumption as it should be non-poisonous, non-intoxicating or non-hazardous to health according to prescribed dosage (Malaysian Standard, 2012; Peng & Abdul Karim, 2013). Drugs and antibiotics are always being associated with side and toxicity effects which limited its applications in clinical practices. Ideally, good and effective drugs should only produce a very minimal toxicity and side effects. Therefore, drugs must be constituted of materials that not only permissible according to the shariah law but also must be safe for consumption. In this review, a type of 'old' drug polymyxins is discussed to enhance its efficacy and reduce its toxicity by adopting antibiotic combination therapy.

Polymyxins: The last-line arsenal for 'superbugs'

Polymyxins are an 'old' class of cationic polypeptide antibiotic (~1200 Da in mass) derived from the spore-forming Gram-positive soil bacterium, Paenibacillus polymyxa (Arnold et al., 2007). Polymyxins were used clinically since the late 1950s but was abandoned in the 1970s due to cases of nephrotoxicity and neurotoxicity (Falagas & Kasiakou, 2006). Due to the limited development and discovery of new and effective drugs, polymyxins have been revisited as the last-line and effective treatment for MDR Gram-negative bacterial infections since the 1990s. As an ancient antibiotic, polymyxins have never been subjected to any proper or standardise drug development procedure and just recently a greater focused have been given to optimise its clinical potentials (Poirel et al., 2017).

Polymyxins are structurally made up of a cyclic heptapeptide ring between the amino group of the side chain of the diaminobutyric acid (Dab) residue at position 4 and the carboxyl group of the C-terminal threonine residue at position 10 (Figure 1) (Velkov et al., 2013). The five non-proteogenic Dab residues render their polycationic activity at pH 7.4 with hydrophobic residues at positions 6 and 7 and an N-terminal fatty acyl group. The bactericidal killing of polymyxins is conferred by its amphipathic property of both lipophilic and hydrophilic groups in its structure (Velkov et al., 2013). Polymyxin B and colistin (also known as polymyxin E) are the two classes being used in clinic. Both polymyxin B and colistin are made up of L-configuration amino acid residues but only differ at their hydrophobic region at position 6 with the presence of D-phenylalanine in polymyxin B while D-leucine in colistin.

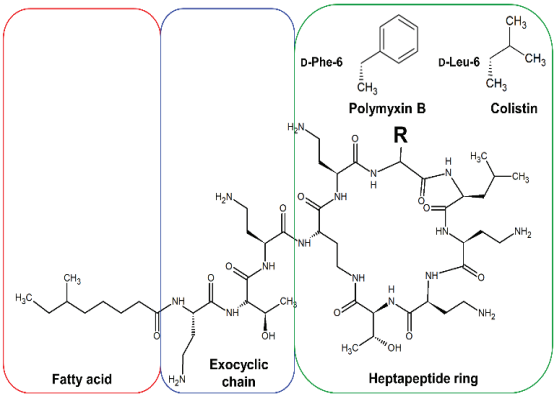

Figure 1. Chemical structures of polymyxin B and colistin

Mode of actions of polymyxins

Polymyxins (both polymyxin B and colistin) generally display bactericidal action with narrow spectra activity against Gram-negative bacteria (Yahav et al., 2012). A number of mechanisms have been elucidated on the mode of action of polymyxins (Deris et al., 2014; Trimble et al., 2016; Velkov et al., 2013; Yu, et al., 2015). Nevertheless, the detailed mechanism of polymyxin-induced bactericidal killing still remains indefinite. The most established polymyxins killing mechanism is via the 'self-promoted uptake' pathway (Yahav et al., 2012). The model proposed that polymyxins predominantly initiate its binding to and disorganise the outer membrane structure of Gram-negative bacteria to eventually cause membrane disruption, osmotic imbalanced and finally cell death.

The first is binding of polymyxins with the lipid A structure of the bacterial outer membrane (OM); the electrostatic interaction is exerted as a result of the protonation of free amines present on the positively charged Dab residues of polymyxins with the negatively charged phosphate groups of the lipid A domain (Figure 2) (Velkov et al., 2013). The destabilisation of the lipopolysaccharide (LPS) leaflet of the bacterial OM is predominantly due to the displacement of divalent cations (Mg2+ and Ca2+) which are essential for bridging the adjacent LPS molecules. This eventually let the insertion of the hydrophobic regions (i.e. N-terminal fatty acyl tails and amino acid residues at position 6 and 7 of polymyxins) into the outer leaflet of OM. Polymyxins may enter the periplasmic space and interact with the phospholipids embedded in the inner leaflet of OM and inner membrane to disrupt bacterial phospholipid membrane structure. The changes cause significant expansion of the outer membrane then lead to a local membrane disturbance and osmotic imbalance. Later, this will increase the permeability

of bacterial membrane structure to finally induce cell death (Zavascki et al., 2007).

Though the general mechanism of antibiotic killing associated with oxidative stress is somehow disputable (Dong et al., 2015; Dwyer et al., 2009; Iris Keren et al, 2013; Kindrachuk et al., 2011), several studies have indicated that the mechanism of bacterial killing of polymyxin induce the generation of reactive oxygen species (ROS) (Belenky et al., 2015; Cabiscol et al., 2000; Dong et al., 2015; Dwyer et al., 2009; Dwyer et al., 2007; Sampson et al., 2012). In addition, polymyxins can potentially inhibit the respiratory chain enzymes for example NADH-quinone oxidoreductase, NADH cytochrome c and NADH dehydrogenase (Deris et al., 2014; Mogi et al., 2009; Sampson et al., 2012).

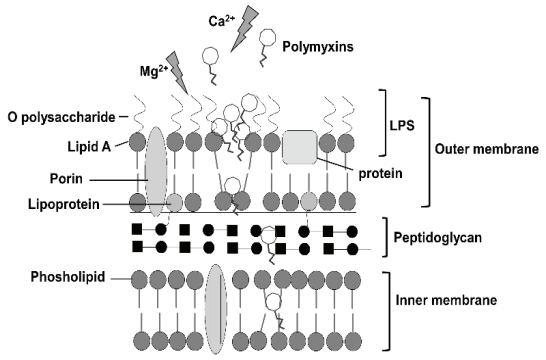

Figure 2. Mode of action of polymyxin via the 'self-promoted uptake' pathway. The electrostatic interaction is between the Dab residues on polymyxin and the lipid A phosphoresters of LPS. The insertion of hydrophobic regions of the *N*-terminal fatty acyl tail and amino acid residues at position 6 and 7 of polymyxins induces significant imbalanced of cations (Mg^{2+} and Ca^{2+}) which finally induce cell death.

Polymyxin-induced nephrotoxicity

The clinical use of intravenous polymyxins has been reported to cause notable nephrotoxicity in up to 60% of patients (Falagas & Kasiakou, 2006). The toxicity were attributed majorly to the intramuscular colistimethate sodium administration, an inactive prodrug form of colistin (also known as colistin methanesulphonate [CMS], described below) (Bergen et al., 2006). The administration of CMS was markedly associated with the higher daily dosage (above 2.5 to 3 μg/mL) compared to the current dose recommendation (Falagas & Kasiakou, 2006, Poirel et al., 2017).

Nevertheless, recent data revealed that the incidence of polymyxin-induced nephrotoxicity was lower compared to the old reported cases. In a comparative study of patients with ventilator-associated pneumonia caused by an Acinetobacter baumannii infection, the results demonstrated that the incidence of CMS-induced nephrotoxicity (24%) was much lower than the effect of intravenous imipenem/cilastatin administration (42%) (Garnacho-Montero et al., 2003). In addition, Hartzell et al. (2009) reported that the administration of CMS caused only mild renal dysfunction, without the occurrence of renal replacement therapy and permanent kidney damage. Polymyxin-induced nephrotoxicity is known to be dose-dependent effect potentially due to the disruption of cellular membrane integrity, which allows the influx of ions and water to finally cause cell lysis (Berg et al., 1996, 1998). In contrast, neurotoxicity occurs less often than nephrotoxicity.

Pharmacokinetics and pharmacodynamics: Dose-limiting toxicity

A number of extensive pharmacokinetics/pharmacodynamics (PK/PD) studies have been conducted to further comprehend and optimise the clinical benefits of polymyxins. Both polymyxin B and colistin indistinguishably display in vitro bactericidal effect against MDR Gram-negative bacteria with the same mode of action (Bergen et al., 2012). Nevertheless, the drugs show remarkable differences in term of their in vivo PK profiles which significantly affecting their clinical outcomes in patients (Nation et al., 2015).

Colistin is administered as an inactive prodrug of the sodium salt of colistin methanesulphonate (CMS), also known as colistimethate, whereas the administration of polymyxin B is as its active form (sulphate salt) (Nation et al., 2015). In contrast to the polymyxin B, the complex structure of CMS confers it becomes less potent in bactericidal killing and induce more toxic effects (Cheah et al., 2015). After parenteral administration, CMS is converted to colistin with a slow increase in plasma concentration. The route of clearance of CMS is predominantly via the kidneys whereas colistin mainly via other routes as it is extensively reabsorbed in the renal tubules (Li et al., 2003, 2006).

It has been shown that intravenous administration of 3 million units (240 mg) of CMS for every 8 hr takes about 36 hr to achieve colistin steady-state plasma concentration of 2 mg/L in patients with no renal impairment indicating the low plasma exposure to colistin (Plachouras et al., 2009). Garonzik et al. (2011) reported a largest population PK model (n=105) investigated the disposition of colistin following intravenous CMS administration in critically ill patients. In this study, the average steady-state plasma colistin concentration was highly variable between the patients (0.48–9.38 mg/L) given that the plasma concentration of formed colistin is highly influenced by renal function (Garonzik et al., 2011). In turn, as polymyxin B is administered as active drug, therefore its disposition is relatively simple and rapidly to reach steady-state concentrations (Sandri et al., 2013).

Generally based on the PK/PD data analysis, there are two major concerns in the polymyxins monotherapy. First, the unlikely of polymyxins to achieve the effective or optimal plasma concentration and second is the rapid emergence of polymyxin resistance. Clinical studies demonstrated that CMS monotherapy with the currently recommended dosage regimens were unlikely to produce an optimal in vivo plasma exposure particularly in patients with moderate-to-good renal function and/or for causative pathogens with MICs of > 1.0 mg/L (Karvanen et al., 2013; Markou et al., 2012). Approximately 47% to 67% mortality rates have been recorded in patients subjected to polymyxin monotherapy (Elias et al., 2010; Kvitko et al., 2011; Rigatto et al., 2015; Tuon et al., 2014). It is important to note that, both colistin and polymyxin B exhibit rapid concentration-dependent killing against Gram-negative bacteria but it is often following with the rapid re-growth (heteroresistance subpopulation) (Poudyal et al., 2008).

Polymyxin combination therapy: A strategy to enhance antibiotic killing and reduce toxicity

The crucial problem of MDR bacterial infections can be managed by implying antibiotic combination therapy as it has been successfully demonstrated in several in vitro and clinical

studies (Tamma et al., 2012). At least, antibiotic combination therapy is rationally performed to achieve three objectives (i) to increase the empiric spectrum coverage provided by different antibiotics (or potentially more) of distinct mechanisms of actions, (ii) to enhance clinical efficacy and induce synergy between antibiotics due to the limited PK/PD profile of single drug treatment and, (iii) to limit the emergence of heteroresistant subpopulation (Lehar et al., 2009).

Combination therapy is often administered in a case that requires empirical coverage of acute infection before the microorganisms have been identified or where pathogens are not easily identified that commonly involve a multi ranging bacterial infection (Rybak & McGrath, 1996). The synergy between two agents is defined as a greater-than-log2 increase in in vitro bacterial killing relative to the killing effect of each agent alone (Figure 3) (Tamma et al., 2012). Generally, two conditions that are recommended for the application of synergistic combination, first is for infection with the development of resistance and second when there is a prevalent failure of antibiotic single treatment (Rybak & McGrath, 1996).

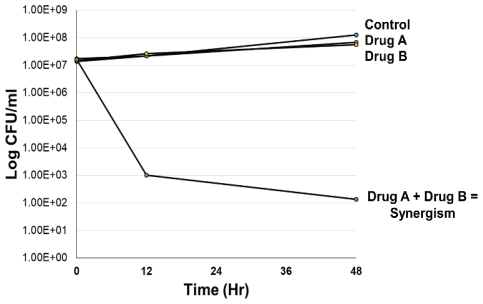

Figure 3. Model of time-kill kinetics of drug combination therapy. The effect of drug A and drug B combination therapy produces synergistic killing against bacteria significantly minimise the emergence of heteroresistance subpopulation.

An observational study recorded that approximately 25–50% of patients with bacteraemia, surgical site infections, pneumonia and septic shock in ICUs have been treated with drug combination therapy (Tamma et al., 2012). A comparative meta-analysis study of carbapenemase-producing Enterobacteriaceae infections showed that the mortality rates in combination therapy was 27%, whereas in monotherapy was 38%, suggesting the survival advantage of the antibiotic combination treatment (Tzouvelekis et al., 2014). Nevertheless, clinical evidence showing the efficacy of antibiotic combination therapy is considerably insufficient as more data are largely required to support for the antibiotic combination strategy.

Polymyxin combination therapy has become an alternative solution to the polymyxin monotherapy and the approach has been increasingly applied in hospital setting (Bergen et al., 2015). The great advantage of polymyxin combination therapy with other antibiotics allows the use of lower concentrations of each antibiotic, thus reducing their adverse toxic effects (Rigatto & Falci, 2016). Several in vitro and clinical studies on polymyxin combination treatment have shown synergy against MDR Gram-negative pathogens, including A. baumannii, Pseudomonas aeruginosa and Klebsiella pneumoniae (Rigatto & Falci, 2016; Zavascki et al., 2007). A number of in vitro studies of colistin and carbapenem combination, in particular doripenem synergistically killed MDR P. aeruginosa, K. pneumoniae and A. baumannii (Abdul Rahim et al., 2015; Deris et al., 2012; Oleksiuk et al., 2014; Principe et al., 2013). In addition, the combination of colistin and tigecycline or meropenem have been shown to significantly increase the survival rates of patients (Qureshi et al., 2012; Tumbarello et al., 2012). It has also been demonstrated that the colistin-carbapenem combination significantly limit the emergence of colistin resistance (Abdul Rahim et al., 2015; Shields et al., 2012; Zusman et al., 2013). Furthermore, evidence from several in vitro and clinical studies showed that the combination of polymyxin and rifampicin synergistically kill MDR Gram-negative pathogens (Lee et al., 2013; Parchem et al., 2016; Tascini et al., 2013).

Conclusion

In conclusion, every consumer is responsible to ensure all products that they want to consume including medicines and pharmaceuticals are toyyib which are clean, with high quality, efficacy and safe of any toxicity. The concept — *halalan- halalan-toyyiban* therefore is crucially important to comply for the halal certification in halal pharmaceuticals. The limitation of polymyxin monotherapy due to its dose-limiting toxicity effect and potential emergence of resistance has importantly becoming a driving factor to the employment of polymyxin combination therapy.

Conflict of Interest

The authors declare that there is no conflict of interest in this work.

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