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Research Article

Potential of Curcumin Loaded Nanoparticles in Antimicrobial Photodyanamic Therapy

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ABSTRACT
In the past decade, multi-drug resistance of pathogenic bacteria has become a serious problem to public health. Finding novel approaches to combat multi-drug resistant bacteria have therefore become increasingly important. One promising approach is antimicrobial photodynamic therapy (aPDT) which involves the use of photo-sensitizer (nontoxic dyes) that are excited by visible light and produce oxygen free radicals in the presence of oxygen. Many studies report that curcumin inhibits the growth of both gram-positive and gram-negative bacteria. Formulations of curcumin in liposome, nanoparticles, micelles and phospholipids complexes are being prospected to decline its hydrophobicity, increase solubility to amplify blood flow time, and its permeability through membrane barriers. Among these options nano-formulations of curcumin such as nano-crystals, nano-emulsions and polymeric nanoparticle encapsulated curcumin got enormous thrust and advance in the recent years in the category of natural or herbal drugs.There are evidences that support the enhancement of antimicrobial activity and antibiofilm activities of curcumin silica nanoparticles of P.aeruginosa and S.aureus cultures using aPDT. This therapy exhibits significant antimicrobial activity against both bacteria. This review provides an updated information regarding the use of natural products to limit or prevent microbial resistance through use of photosensitizing agents like curcumin.

Keywords: curcumin, photodynamic therapy, nanoparticles, antimicrobial, oxygen-free radicles

INTRODUCTION
Amongst many challenges in the 21st century, antimicrobial resistance is at the top of the chart. It has posed one of the major threats to public health. According to data from the World Health Organization (WHO), infections caused by resistant bacteria affect more than 2 million people and cause more than 20 thousand deaths in the United States and the European Union annually. Infection by resistant strains drastically reduces the probability of an effective treatment and elevates not only the morbidity and mortality of common infections but also increases the associated health costs, which reach billions per year. In the past few years the WHO has been warning that the 'post'-antibiotic" era, where common infections can kill again, is an increasingly real threat(Goel et al., 2008). And, even though the bacterial resistance continues to rise, the rate of new antibiotics development decreased in the past three decades, with no significant therapeutic class discovered since the 1980's(Elfiky, 2020).
The widespread use of conventional antimicrobials (antibiotics and antifungals) has emerged the problem of microbial resistance, which results in persistence of infection, treatment failure, and side-effects of drugs especially when multiple antimicrobials are used(Agel et al., 2019). Due to these shortcomings of the currently available drug treatments, antimicrobial alternatives have been sought[1] widely(Garcez et al., 2007). A promising therapeutic modality for microbial inactivation is antimicrobial Photodynamic Therapy (aPDT), which uses the association of a photosensitizing agent (PS) [e.g., curcumin (CUR)] with light at a suitable wavelength(Trigo Gutierrez et al., 2017). The interaction between PS agent light in the presence of oxygen results in the production of a reactive species, mainly the singlet oxygen and free radicals that promote cell damage and death.(Santos-Parker et al., 2017)
Normally, bacteria persist in structured biofilm ecosystems and rarely in cultures of single species that are traditionally used by microbiologists to study the behaviour of micro- organisms in vitro. In biofilms, microorganisms are remarkably less susceptible towards antimicrobials as compared to their planktonic counterparts(Mirzahosseinipour et

al., 2020). The mechanisms of tolerance and resistance in biofilms include slow penetration of antimicrobials through the biofilm matrix, altered microenvironment within the biofilm, different stress response of bacterial cells, and the formation of a sub-population of so-called persisted cells(Cieplik et al., 2018). Considering that, biofilm infections are caused by a diversity of microbial species, potential resistances within the biofilm and can easily be transferred among different species by horizontal gene transfer(Cas and Ghidoni, 2019). It has been estimated that more than 60% of all microbial infections are caused by biofilms, also with reference to hospital-acquired infections, where sterile conditions are often compromised. Frequent biofilm infections include dental infections (caused by dental plaque), dermal infections, urinary tract infections, middle-ear infections, endocarditis and implant- or catheter-associated infections, whereby at least the latter potentially can lead to serious, i.e. lethal, outcomes for patients(Barros et al., 2020).

Photodynamic therapy has emerged in recent years as a non-invasive therapeutic modality for the treatment of various infections by bacteria, fungi, and viruses. This therapy is defined as an oxygen-dependent photochemical reaction that occurs upon light mediated activation of a photosensitizing compound leading to the generation of cytotoxic reactive oxygen species, predominantly singlet oxygen(Pagonis et al., 2010). It can be applied topically into a periodontal pocket avoiding overdoses and side effects associated with the systemic antimicrobial agent administration(Pal et al., 2020). It also minimizes the occurrence of bacterial resistance. Photodynamic antimicrobial chemotherapy represents an alternate antibacterial, antifungal, and antiviral treatment against drug resistant organism(Howells et al., 2019). Several studies have revealed that curcumin exhibited remarkable antioxidant, anti-inflammatory and anticancer activities(Mbadiko et al., 2020). More recently, researchers have been exploring its activity against several bacterial strains(Zorofchian Moghadamtousi et al., 2014). Numerous nano formulations were prepared to overcome the limitations associated with curcumin such as poor water solubility, instability at physiological pH and low bioavailability. The behaviour and fate of nanoparticles in physiological environments is heavily affected by their physicochemical characteristics(Gupta et al., 2020). Polymeric nanoparticles have exhibited an interesting ability to encapsulate curcumin and enhance its therapeutic effects . Biodegradable polymers like poly lactico glycolic acid (PLGA) have been used to prepare curcumin loaded nanoparticles to be applied in the biopharmaceutical field. Curcumin is one such naturally occurring yellow dye extracted from the rhizomes of turmeric (Curcuma longa), which has been used for more than 4,000 years in traditional Asian and African medicine for the treatment of a variety of ailments(Sun et al., 2017). Here, the authors make an attempt to provide a systemic review analysis concerning the use of aPDT in reduction of microbial resistance with focus on curcumin as the photosensitizing agent.

Antimicrobial Resistance

Antimicrobial resistance (AMR) is a global crisis and potentially a sophisticated threat to public health. It has drawn the attention of fitness experts, health stakeholders, and medical science due to the substantial economic loss that it can cause to individuals and nation as a whole. Various cross-sectional studies and some national surveys in developing countries have shown increase in the burden of antimicrobial resistance. (Acharya and Wilson, 2019) In developing countries antimicrobial resistance is driven by the high incidence of infectious diseases. An appropriate use of antibiotics in treatment, as growth promoters and increased implementation of herbal therapy can be a ray of hope in treating this threat using the natural gold that is turmeric without causing with any unwanted effects to the body. AMR is, nevertheless, a global issue of public health concern. For some 30 years no new antibiotics have been discovered whilst existing ones fail to suppress or kill the target microorganisms. The trend of antibiotic resistance development is illustrated by a recent worldwide analysis. Figure 1 indicates an emerging group of antibiotic resistant bacteria, denominated ESKAPE (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanni, Pseudomonas aeruginosa, and Enterobacter spp.) in human.

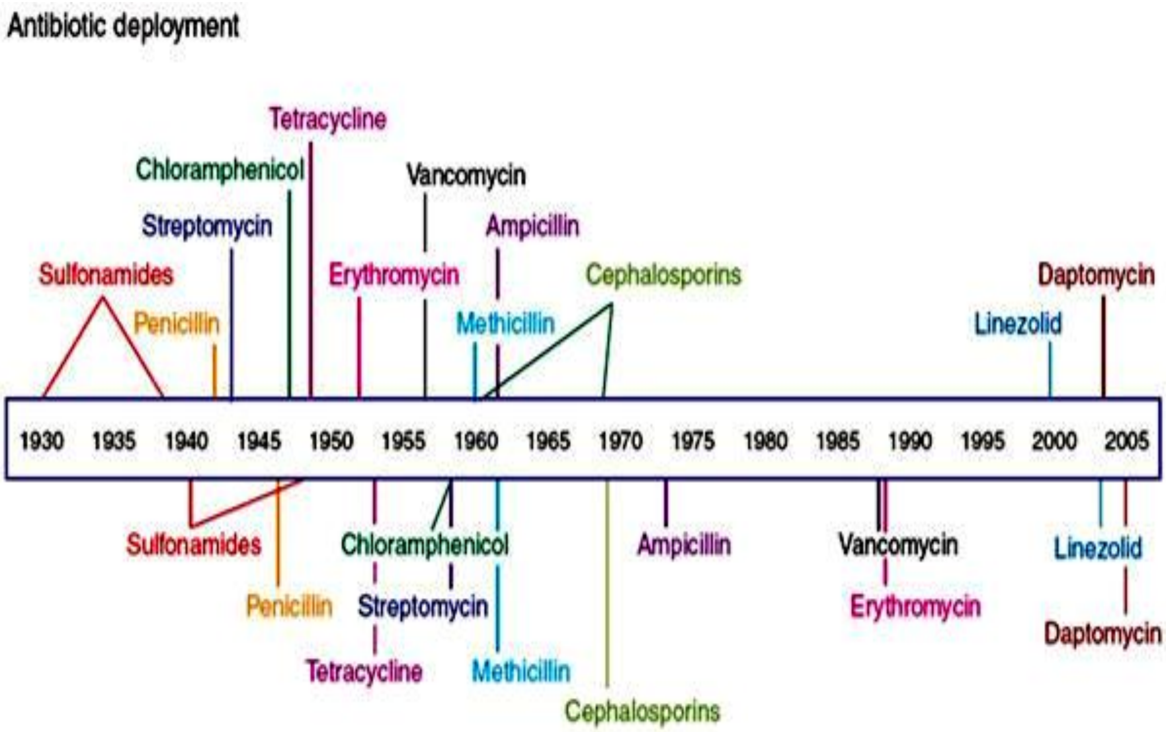

Fig.1: Antibiotic Resistance

As depicted in Figure 2, a designed prisma table is used for the collection of data. As the initiating step, a survey was done via data base searching followed by screening of record. These recorded data is thoroughly analysed before a conclusion is drawn regarding the collection of data.

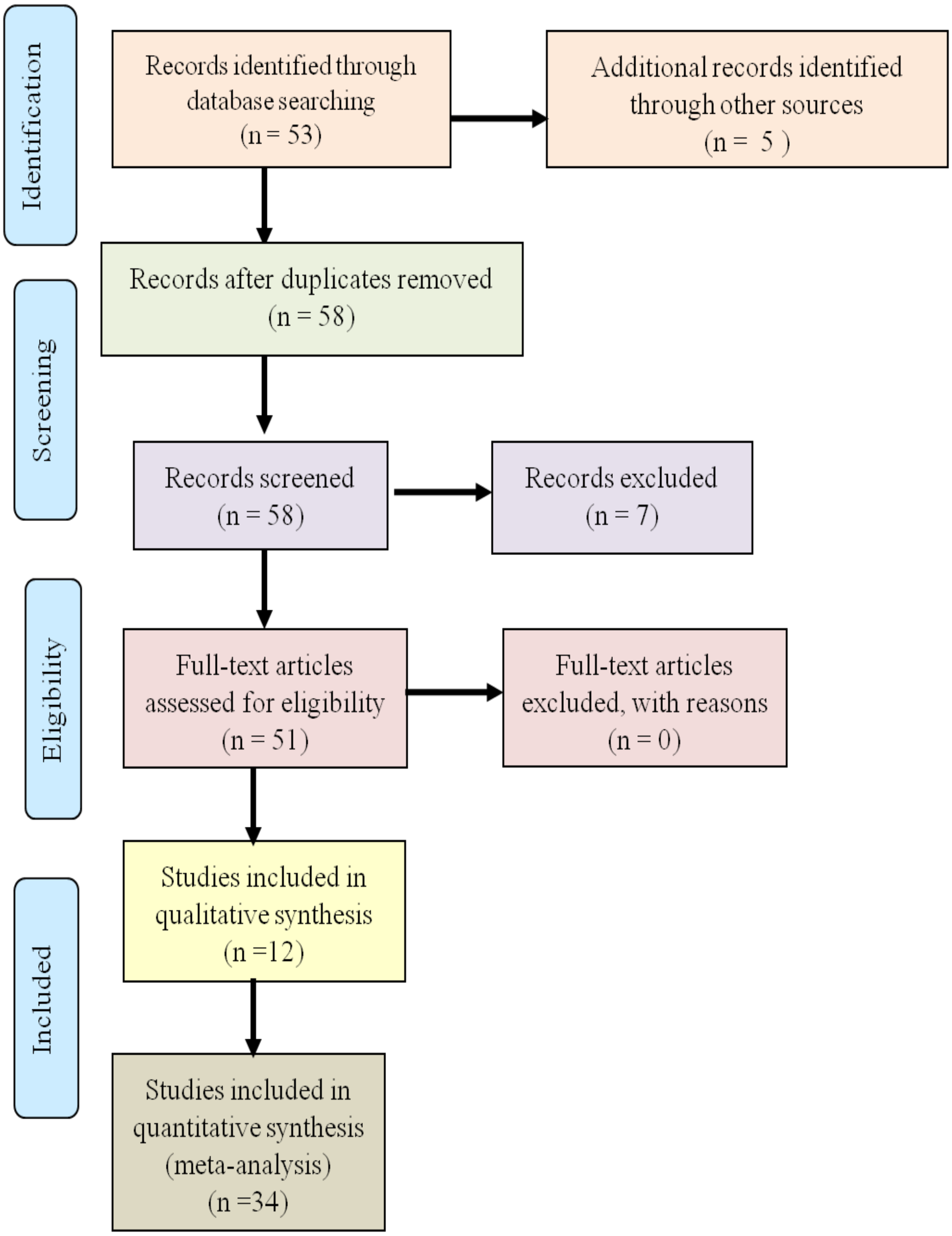

Fig.2: Prisma Table depicting the steps required for collecting data

Development of Antimicrobial Photodynamic Therapy

Antimicrobial Photodynamic therapy (aPDT) had been recently proposed to combat clinically relevant biofilms such as dental biofilms, ventilator associated pneumonia, chronic wound infections, oral candidiasis, and chronic rhinosinusitis. IN this approach, aPDT uses non-toxic dyes called photosensitizers (PS), which can be excited by harmless visible light to produce reactive oxygen species (ROS). It is a multi-stage process including topical photosensitizing agent administration, light irradiation, and interaction of the excited state with ambient oxygen. Yan and his group suggested that in order to control clinically relevant biofilm infections, which prove to be particularly resistance to antibiotic treatment due to embedded microbial cells which firmly attached to microbial biofilms. According to their study, clinically relevant biofilm infections proved to be particularly resistant to antibiotic treatment due to embedded microbial cells which firmly attached to microbial biofilms. This study provide an updated information regarding its applicability in wound and ulcer infections, dental infections, nasal decontamination in addition to Helicobacter pylori infection. (Hu et al., 2018)

To reduce the viability of infected dental caries, curcumin mediated antimicrobial photo-dynamic module was developed using microcosms. After the development of microcosm biofilms on bovine and immersing in McBain medium with 1% sucrose at 370° C for a period of 5 days, the lactic acid concentration was analysed and curcumin condensed the overall effect of the microorganism on biofilm after analysing with blue LED (455 nm). (Cusicanqui Méndez et al., 2018). In a study to decrease multiple resistances of Staphylycoccos bacteria,a novel curcumin loaded PLGA nanoparticles were used to enhance the effectiveness of curcumin, which made it possible to deliver much higher amounts of curcumin than normally possible due to its poor aqueous solubility. The ability to selectively activate curcumin nanoparticles with low-energy LED light to eradicate Staphylococcus saprophyticus subsp. bovis was successfully demonstrated. Furthermore, modifying the surface charge of the nanoparticles using chitosan drastically increased their photo-dynamic penetration ability[4](Agel et al., 2019). After a proposal by the use of aPDT as an alternative for oral candidiasis, improvement of oral candidiasis was targeted using curcumin loaded nanoparticles. The result illustrated that there is a multifoldreduction in the number of the bacteria Candida albican. Encapsulation in NP improved the water solubility of curcumin. Nystatin shows the highest reduction of calcium, followed by aPDT mediated by free CUR, which resulted in immuno-labeling of cytokeratins closer to those observed for healthy animals. Anionic CUR-NP does not show anti-fungal effect, and cationic CUR-NP reduces Ca even in the absence of light as reported by Sakima et al. (Sakima et al., 2018)

CONCLUSION

It could thus be concluded that curcumin mediated antimicrobial photodynamic therapy (aPDT) reduced variability of microorganism as reported by various studies. This provides a substantial improvement in the prevention of anti-microbial resistance. Despite this, as noticed, a trend of dose dependent antimicrobial effect of more is observed in all microorganisms when nano particles are developed. Moreover, designing the dosage form in nano formulation surpassed the water insolubility issue of curcumin thereby enhancing the bioavailability. Nevertheless, more quantitative data needs to be built up for in vivo models to further establish the fact that more and more herbal drugs can be an alternative to antibiotic resistance when antimicrobial photodynamic therapy (aPDT) is a mode to act on the microbes.

Future Perspectives

The research on antimicrobial photodynamic therapy (aPDT) should be conducted extensively on animal models both in vivo and in vitro. Meanwhile, the clinical and pharmacokinetic validation of such formulations will pave the way for inventing novel drugs effective against antibiotic resistance.

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CONFLICT OF INTEREST

The authors do not hold any conflict of interest.

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