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Research Article

Application of nano-curcumin as a natural antimicrobial agent against Gram-positive pathogens

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Abstract
Gram-positive bacteria cause various diseases from the superficial skin to deep tissue infections. The capability of causing numerous diseases is due to the production of virulence factors which are tightly regulated by the virulence genes. Various Gram-positive pathogenic bacteria e.g. *Staphylococcus, Mycobacterium,* and *Listeria* are capable of causing lethal infections in humans and animals. Conventional antibiotics, targeted antibiotics, and combinatorial drugs are used as therapeutic agents against Gram-positive pathogens. Due to intricate virulence pathway bacteria readily adopt resistance to available drugs. Therefore, there is need to develop some alternative approaches to combat these infections. Various natural extracts are effective against pathogenic bacteria with or without the available drugs. Curcumin is a natural extract of *Curcuma longas* rhizome, known as turmeric. Curcumin shows various biological activities such as antimicrobial, antioxidant and anti-inflammatory. It also shows strong antibacterial activity against Gram-positive and few Gram-negative bacteria. Besides all these beneficial applications, major drawbacks of curcumin are poor aqueous solubility and less bioavailability. However, drug delivery approaches including nanoformulation are developed to increase its stability *in vitro* and *in vivo* settings. The present review article focused on the translation of potential applications of curcumin in various diseases specifically caused by Gram-positive pathogens. Various methods used for the formulations of curcumin nanoparticles, combinatorial strategies with curcumin nanoparticles and their application in the prevention of infections have been discussed. The present article also discusses the future aspects of curcumin-nanoparticles and its use as an alternative therapeutic approach against pathogens.

Keywords: Alternative therapeutics, Antimicrobial agent, Nanocurcumin, Nanoparticles, Natural antimicrobial agent

INTRODUCTION

The most important Gram-positive human pathogens, such as *Staphylococcus aureus, Streptococcus pneumoniae* and *Enterococci* remain as public health menace (Woodford and Livermore, 2009). The major health -care concern is due to the emergence of resistant strains such as methicillin-resistant *Staphylococcus aureus* (Cornaglia, 2009) and vancomycin-resistant *enterococci* (VRE) strains (Eades *et al.,* 2017). In developing countries, factors such as poor drug quality, improper drug dosage, the high rate of self-medication (Ayukekbong *et al.,*2017), unhygienic conditions, contaminated food, and water supply, poor domestic and animal contact attributed to the development of drug-resistant strains (O'Neill 2015, Grace, 2015). According to a research, four main factors are responsible for microbial resistance such as (i) noncompliance (ii) incor-

rect use of broad-spectrum agents (iii) incorrect dosing and (iv) excess antibiotic usage (Niederman, 2005). The genetic material alteration also leads to the formation of resistant strains by mutation, and it can be an innate, intrinsic, or acquired type (Mihaescu *et al.,* 2007, Decoster *et al.,* 2008). Several Gram-positive pathogens are responsible for various diseases such as skin and soft tissue infections, wound infections, urinary infections, gastrointestinal infections, osteomyelitis, endocarditis, pneumonia, thrombophlebitis, inflammation of breast tissue (mastitis), inflammation of the brain and spinal cord surrounded membrane (meningitis), toxic shock syndrome and septicemia (Nair *et al.,* 2014). An antimicrobial substance that kills or inhibits bacterial growth is called antibiotics (Himaniand Joshi, 2019). Various traditional herbs can inhibit the growth of Gram-positive and Gram-negative bacteria and now these medicinal herbs are used for the treatment of microbial infections (Evans *et al.,* 2002). These herbs include *Azadirachtaindica* (neem), *Curcuma longa* (turmeric)*, Acacia nilotica* L. (Babul), *Withania somnifera* (Ashwagandha) (Dhama*et al.,* 2014). In this review article, we have focused on the therapeutic properties and applications of curcumin, which is an active component of turmeric.

Curcumin is a polyphenolic flavonoid compound obtained by rhizome of turmeric (*Curcuma longa L.*) (Mun *et al.,* 2014). Diferuloylmethane or curcumin is a major phytochemical component of turmeric (Zingiberaceae family), which is responsible for giving the yellow colour to the herb. Curcumin extracted from turmeric by various methods of solvent extraction e.g., Soxhlet, ultrasonic, microwave, and supercritical carbon dioxide, followed by purification via column chromatography (Li *et al.,*2014, Priyadarsini, 2014). For many years, curcumin has been used as a pharmaceutical agent because of its antioxidant, anti-inflammatory, anti-carcinogenic, and antimicrobial properties (Epstein *et al.,* 2010; Naksuriya *et al.,* 2014). It has also wound healing and anti-ageing activities (Akbik *et al.,* 2014; Lima *et al.,* 2011). Curcumin also shows beneficial effects to control blood glucose levels and enhanced mucosal gastric secretion in rabbits (Arun and Nalini, 2002). In 1815, curcumin molecules were isolated the first time and in 1873, Roughley and Whiting had given its chemical structure (Rai *et al.,* 2015), in 1873. In 2014, Priyadarsini reported the chemical formula of curcumin as $C_{21}H_{20}O_6$ with a molecular weight of 368.38 gm/mole. Turmeric contains approximately 77% diferuloylmethane (curcumin I), 17% Demethoxycurcumin (curcumin II), and 6% bisdemethoxycurcumin (curcumin III) components (Fig. 1) (Aggarwal *et al.,* 2007). Curcumin is hydrophobic in nature contains two polyphenolic rings, which consist of o-methoxy phenolic groups, and curcumin shows tautomerization in a pH-dependent condition (Beevers and Huang, 2011).

FUNCTIONAL ASPECTS AND APPLICATIONS OF CURCUMIN

Antimicrobial activity

Naturally occurring substances especially from plants have great potential for controlling food spoilage and infections caused by pathogens. Curcuma is a natural plant product obtained from *Curcuma longa* widely used in medical application (Salehi *et al.,* 2019). *Upendra* and his co-workers found that turmeric at a concentration of 0.8 and 1.0g/L showed significant antifungal activity in plant tissue culture (Upendra *et al.,* 2011). Methanol extracted curcumin obtained by the turmeric used against *Cryptococcus neoformans* and *Candida albicans,* showed antifungal activity with MIC 128µg/mL and 256 µg/mL. Ungphaiboon *et al.,* demonstrated antifungal activity of hexane extracted curcumin against *Rhizobium solani, Erysiphe graminis,* and *Phytophthora infestans* (Ungphaiboon *et al.,* 2005). Curcumin blocks membrane-associated ATPase activity and reduces the secretion of proteinase (Martins *et al.,* 2009). Recently, Hu *et al.,* reported that curcumin act on endoplasmic reticulum and minimize the effect of in *Cryptococcus neoformans* infection (encapsulated yeast) (Hu *et al.,* 2017). Sometime Antiviral therapeutics are still in the nest and there is a lack of effective therapeutic therapies, high cost of antiviral therapies and to overcome the chemical side effects, it compels to investigate the properties of naturally occurring compounds such as a component of green tea (Steinmann *et al.,* 2013), cinnamon (Connell *et al.,* 2016), and various types of herbs against viral infections. Curcumin is a pleiotropic molecule with great potency to show antiviral activity against different kind of viruses e.g., hepatitis viruses, influenza viruses, chikungunya virus (CHIKV) or arboviruses, human immunodeficiency virus (HIV), human papillomavirus (HPV), herpes simplex virus 2 (HSV-2) and also effective against sexually transmitted diseases (Praditya *et al.,* 2019). Gopal and his coworkers compared the bactericidal activity of three types of curcumin particles e.g., macro, micro, and nano against *Escherichia coli*, *Salmonella enteritidis*12021, *Streptococcus mutans*11823, and *Staphylococcus aureus.* The results showed that the bactericidal activity of curcumin nanoparticles was enhanced compared to macro and micro curcumin particles (Gopal *et. al.,* 2016). In a study found that curcumin decorated micelles particles increase the antibacterial activity of miltefosine and alkyl phosphocholines erufosine toward *S. aureus* pathogenic strain (Zaharieva *et al.,* 2019). It has been found that curcumin (MIC 125 to 250 µg/mL) was effective against 10 strains of *S. aureus* (e.g., two ATCC MRSA, and MRSA standard strains, four MRSA from culture collection and four MRSA clinical isolates) (Mun *et al.,* 2013). Curcumin with MIC 256 µg/mL also effective against MSSA (methicillin-susceptible *Staphy-*

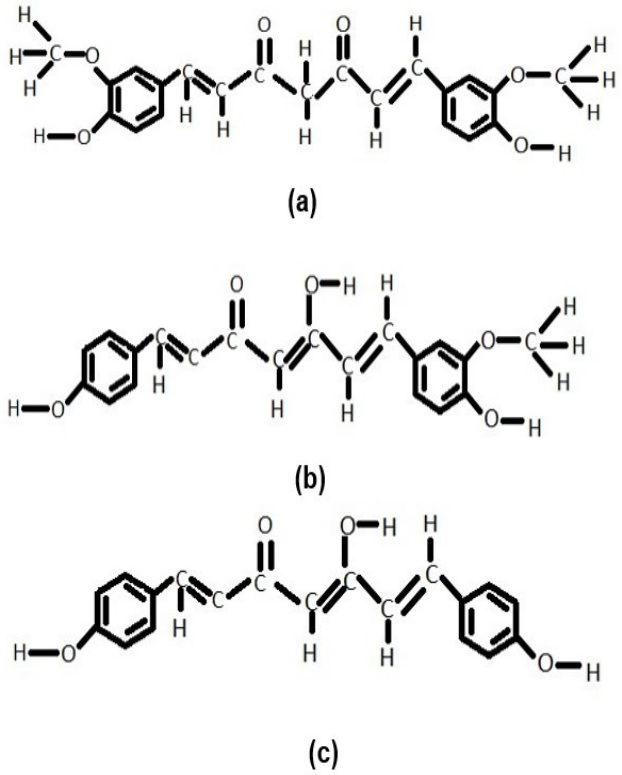

Fig. 1. ***(a)*** *Structure of Diferuloylmethane (Curcumin I)* ***(b)*** *Structure of Demethoxycurcumin (Curcumin II)* ***(c)*** *Structure of Bisdemethoxycurcumin (Curcumin III) (Rai et al., 2015).*

lococcus aureus) (Wang *et al.,* 2016). When curcumin is used in combination with antibiotics such as cefaclor, penicillin, gentamicin, erythromycin, and amikacin, it shows synergistic antibacterial activity (Teow *et al.,* 2016). To understand the curcumin antibacterial activity some researchers demonstrated that curcumin has the potential to interfere with FtsZ (FtsZ homolog in eukaryotes is cytoskeletal tubulin protein) *in vitro* and stops the FtsZ ring (Protofilament) assembly in *Bacillus subtilis*, and observed that curcumin inhibits the bacterial cell proliferation by stopping the assembly of FtsZ mechanism (Rai *et al.,* 2008).Therefore, FtsZ is the novel component of bacteria, which can be a drug target for the development of antimicrobial agents against *S. aureus*atsui *et al.,* 2012; Singh and Panda, 2010). Mun *et al.,*had shown that in the periplasm of Gram-negative and cell surface of Gram-positive bacteria ATP-binding cassette (ABC) transporters are located. ATP-dependent transporting activity of ABC transporters was inhibited by the curcumin in combination with ATPase inhibitors such as N, N-dicyclohexylcarbodiimide (DCCD), NaN_3 by inhibiting the H^+ translocation activity and stops the growth of *S. aureus* MRSA (Mun *et al.,* 2014) and also noted that penicillin-binding protein (PBP) or PBP2 encoded by the *mecAgene* in *S. aureus* MRSA stabilizes the cell wall formation and showed resistant towards β-lactam antibiotics by blocking the interaction between β-lactam and penicillin-binding protein (PBP)(Fig. 2) (Mun *et al.,* 2014). However, a combination of β-lactam antibiotics with curcumin inhibits Mec A gene synthesis in MRSA and enhances the activity of antibiotics (Mun *et al.,* 2014). It is reported that polymeric micelles coated silver particles with curcumin molecules were very effective against *Staphylococcus aureus* and *P. aeruginosa* (Huang *et al.,* 2017). In chicken and mice curcumin was effective in kidney and liver injury caused by aflatoxin induction (Verma *et al.,* 2008; Zhang *et al*., 2016) and minimized the effect of oxidative stress (mediated by aflatoxins) (Wang *et al.,* 2018). Furthermore, the formulation of curcumin loaded PLGA nanoparticles improved the activity of curcumin; PLGA is hydrolyzed into lactic acid and glycolic acid and eliminated outside the cell in the form of H_2O and CO_2 with the help of the Krebs cycle (Lu *et al.,* 2009).

Anti-biofilm activity

Curcumin inhibits the quorum sensing and acts as an inhibitor of biofilm formation (Deryabin *et al.,* 2019). *Pseudomonas aeruginosa* secreted exopolysaccharides polymer substances e.g., imipenem and aminoglycosides, which enhanced biofilm formation. Curcumin's anti-biofilm activity against two *Pseudomonas aeruginosa* strains obtained by cystic fibrosis suffering patients were observed with MIC: 16 µg/m through the crystal violet staining method (Karaman *et al.,* 2013). It is found that curcumin inhibits the expression of biofilm inducing gene (31 quorum sensing (QS) genes) reducing virulence factors such as acyl-homoserine lactone (HSL) secretion, pyrocyanin biosynthesis, and activity of protease (Rudrappa and Bais, 2008). In *S. mutans,* UA159 curcumin could reduce biofilm activity and prevent the maturation of biofilm by exopolysaccharide reduction (Li *et al.,* 2018).

Anti-protozoan activity

Ethanol extraction of turmeric (rhizome) has anti-*Entamoeba histolytica* activity. It also shows anti-Leishmania activity *in vitro* conditions (Koide *et al.,* 2002). Curcumin synthetic derivatives have anti-Leishmania, amazonensis activities (Gomes *et al.,* 2002). Rasmussen *et al.,* reported that curcumin also inhibits the activity of *Plasmodium falciparum* (Rasmussen *et al.,* 2000).

Antioxidant activity

Curcumin has excellent antioxidant activity (Alsamydai and Jaber, 2018). Harmful chemicals, trauma, autoimmune disorders, and infections can be responsible

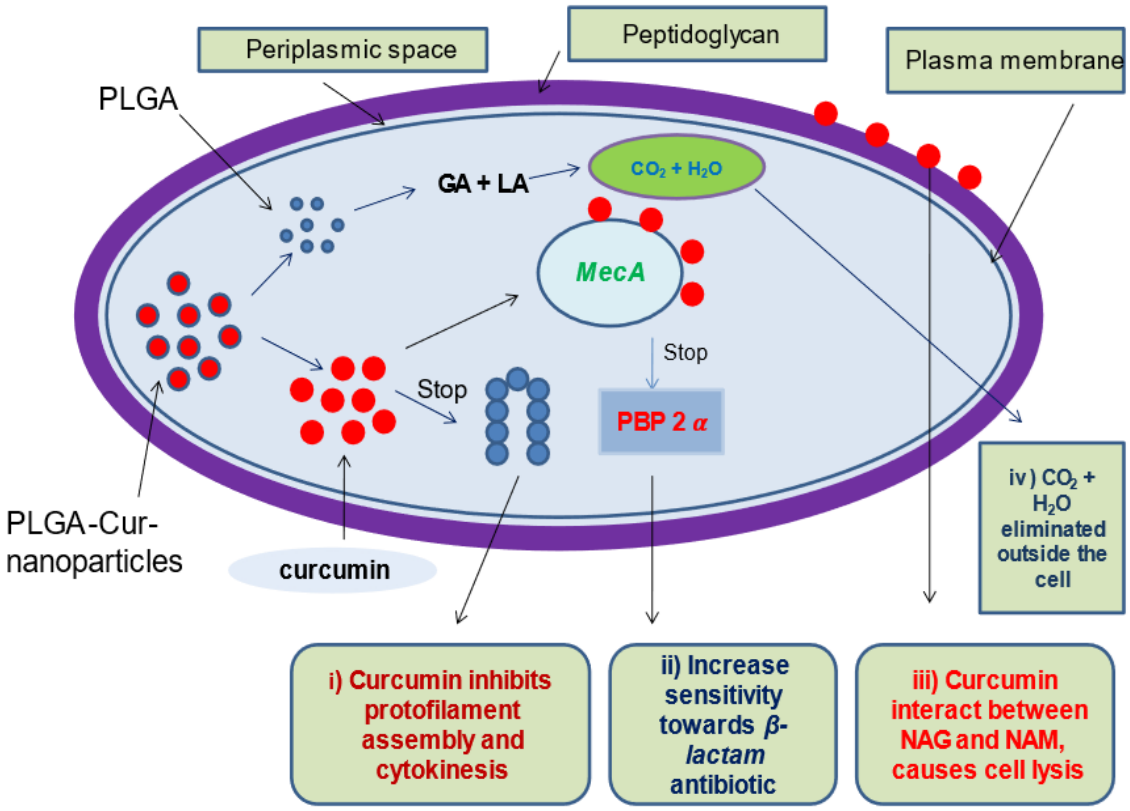

Fig. 2. *Diagrammatic representation of various mode of actions of PLGA curcumin nanoparticles against Gram positive pathogens* ***(a)*** *Curcumin inhibits protofilament assembly and cytokinesis (Rai et al., 2008)* ***(b)*** *Curcumin increase sensitivity towards β-lactam antibiotic (Mun et al., 2014)* ***(c)*** *Curcumin interact between NAG and NAM, causes cell lysis (Mun et al., 2014, Tyagi et al., 2015)* ***(d)*** *Gylcolic acid and Lactic acid eliminate outside the cell in the form of CO_2 + H_2O (Lu et al., 2009).*

for the production of free radicals in the body, curcumin has capacity to protect the cells from free radicals and work as a scavenger for reactive oxygen species (Akram *et al.,* 2010). Curcumin is a bioactive component of turmeric (Kotha and Luthria, 2019), turmeric's water-and-fat-soluble extracts show potent antioxidant activity like vitamin C, vitamin E, and β-carotene (Akram *et al.,* 2010). Curcumin significantly inhibits the peroxidation of lipids in various animal models (Maheshwari *et al.,* 2006). Metabolism of lipoxygenase (LOX), arachidonic acid, and cyclooxygenase (COX) inhibited by the curcumin, which alters the productions of steroidal hormones (Mosovska *et al.,* 2016). Researchers have investigated the antioxidant property of curcumin in animal cells by exposing the oxygen and nitrogen-free radical species and concluded the antioxidant efficacy of curcumin (Rafiee *et al.,* 2019).

Anti-inflammatory activity

A secondary metabolite of curcumin and its volatile oils show great anti-inflammatory activity, 100mg/kg of ethanol extracted turmeric component is significantly administered to male rats in the granuloma pouch model and showed great activity against inflammation. In induced pedal edema doses of 200mg/kg, 400 mg/kg, and 800 mg/kg were active in carrageen. However, turmeric extract showed no activity in the granuloma pouch model when reducing the dose to 50.0 mg/kg (Bhat *et al.,* 2015). Several studies have reported that curcumin inactivates the process of inflammation through various mechanism (Khalil and Mustafa, 2020; Mohammed and Mustafa, 2020). In the case of acute inflammation, oral curcumin was more effective compared to phenylbutazone or cortisone and reduced inflammatory swelling in rats with Freund's adjuvant-induced arthritis. Curcumin is also effective in neutrophil aggregation related to inflammation, in monkeys, at the time of inflammation, it inhibits the biosynthesis of inflammatory prostaglandins and arachidonic acid (Akram *et al.,* 2010). Curcumin Nanomicelle particles had more anti-inflammatory efficacy to inhibit paraquat (PQ) responsible for lung injury (Hosseini *et al.,* 2019).

Anti-carcinogenic activity

Curcumin exhibits anti-carcinogenic properties which act as a panacea for the treatment of various types of cancers in human curcumin inhibits tumor growth and proliferation of cells; it is also capable of suppressing the mutagens and carcinogen's activity in different types of cells (*in vitro* and *in vivo*) (Akram *et al.,* 2010). Curcumin molecule alter the activity of NF-kB factors responsible for the activation of gene related to proliferation, antiapoptotic and invasion (Tan and Norhaizan, 2019). Due to antioxidant and free-radical engulfing properties, curcumin shows anti-carcinogenic activity. It indirectly increases the level of glutathione that helps in liver detoxification from harmful carcinogens and mutagens as well as stops the synthesis of nitrosamine (Akram *et al.,* 2010). Curcumin is a very potent agent for controlling and regulating the metabolic activation and detoxification of harmful mutagens and carcinogens. Curcumin inhibits the action of cytochrome P450 and this enzyme stimulates the action of carcinogens and mutagen (Duvoix *et al.,* 2005). In lung and breast cell lines PLGA curcumin nanoparticles reduced the expression of NF-kB and HIF-1α in the hypoxic tumor microenvironment (Khan *et al.,* 2018). Curcumin enhances metabolizing enzymes and antioxidant activity (Igbal *et al.,* 2003). Curcuminoid exhibits several immunomodulatory effects (Churchill *et al.,* 2000), suppresses the production of superoxide (free radicals) by macrophages and also enhances phagocytic activity of macrophages observed in the curcumin-treated animal model (Lukita-Atmadja *et al.,* 2002).

TARGETED VS. COMBINATIONAL DRUG THERAPY AGAINST GRAM-POSITIVE PATHOGENS

Instead of broad-spectrum antibiotics, narrow-spectrum antibiotics, or targeted antibiotics that are specific for particular pathogenic bacteria either Gram-positive or Gram-negative provides an efficient approach to treat specific resistant pathogens with a less toxic effect on the gut microbiome (Maxson and Mitchell, 2016). Different types of synthetic targeted antibiotic therapies are available against Gram-positive pathogens such as Linezolid, Vancomycin, Teicoplanin, Daptomycin, Tigecycline, and Ceftaroline (Guillamet and Kollef, 2014). Over the targeted antibiotic therapy, combinational drug therapy is an appropriate method for treating multidrug-resistant (MDR) bacteria. Three main mechanisms of antibiotic resistance are described by Walsh in 2000: (i) enzymatic breakdown of *β-lactam* antibiotics with the help of β-lactamases enzymes and phosphorylation or acetylation, adenylation of aminoglycosides (ii) Antibiotic removal from the bacterial cell, through the efflux membrane-bound protein, efflux membrane proteins force out the drug molecules faster than its diffusion hence, decreasing the overall intracellular concentration of antibiotics required to exert the antibiotic effect (iii) Modification of penicillin- binding protein (PBP2a) by the bacteria, PBPs have a lower affinity to β-lactam antibiotics resulted in continuous cell wall synthesis (Worthington and Melander, 2013). In combined drug therapy pairing is done between antibiotic- antibiotic or antibiotic with a non-antibiotic molecule. The combinations of two drugs have a synergistic effect, enhanced killing rate, and increased dosage response in *in vivo* settings (Bhardwaj *et al.,* 2016). Researchers have found that combined drug therapy of curcumin and chemotherapeutics have pharmaceutical activity and also reported their mode of action in vitro and in vivo (Redondo-Blanco *et al.* 2017). The naturally occurring substance used for combination therapy with antibiotics is the most beneficial approach for MDR bacteria. Combinational effect of curcumin with various antibiotics on *S. aureus* by disk diffusion method and found that curcumin increased the antibacterial activities of antibiotics cefotaxime, cefixime, tetracycline, and vancomycin against *S. aureus.* Although cefixime showed the maximum fold increases in the area (52.6% fold increase) against test strain (Worthington and Melander, 2013). In combinational drug therapy, the interaction of two antimicrobial agents is an important factor for the formulation hence, at the time of drug development this factor must be taken into consideration (Moghaddam *et al.,* 2009). Zhang *et al.,* 2020 reported efficacy of chemotherapy medicine and various plant extract such as xanthohumol, curcumin, genistein, proanthocyanidins, mangiferin, luteolin, quercetin, garcinol, and furanodiene against breast cancer and their mechanisms in vivo and in vitro condition. Combinational drug therapy is the most powerful tool for the treatment of various critical diseases like HIV (Richman, 2001), cancer, and antibiotic-resistant infections (Lane 2006, Mitchison and Davies 2012, Fischbach 2011). In a study reported that when paclitaxel combined with curcumin greatly stimulate apoptosis process and antiproliferative in MCF-7 and MDA-MB231 (human breast cell lines) (Calaf *et al*., 2018; Kang *et al.,* 2009; Quispe *et al.,* 2016; Zhan *et al.,* 2014). Combined effect of natural plant products have more potential to fight against breast cancer cells as compare to single plant extract (Kapinova *et al.* 2017; Koh and Pan 2018). Combinational drug therapy is an alternative approach for the treatment of multi and extremely drug-resistant bacterial infections.

THERAPEUTIC APPLICATIONS OF NANOPARTCLES

Nanoparticles are used in different areas successfully due to their high volume-surface ratio and quantum effects; these factors change the nanoparticle proper-

ties such as electrical behavior, reactivity, strength, and *in vivo* nature. Nanoparticles have been used to develop much cheaper, effective, and quicker treatments against pathogens (Duggal, 2011). Previous studies have demonstrated that nanoparticles such as Ag-NPs, TiO2-NPs, and ZnO-NPs (used for sewage treatment) may show the toxic effect on aquatic organisms (Gottschalk *et al.,* 2009), while gold, silver, and copper nanoparticles have the great anticancer potential (Jain *et. al.,* 2012, Jannathul and Lalitha 2015, Sanpui *et. al.,* 2011). Gold nanoparticles showed optical and catalytic properties which makes it unique due to its biocompatible and nontoxic in nature and used in various fields (Nambiar *et al.,* 2018). Anticancer and antidiabetic activities of ZnO-NP have been reported by a group (Umrani and Paknikar 2014, Taccola *et al.,* 2011). CUR -SF (curcumin silk fibroin) nanoparticles are effective and stable drug delivery agent and exhibit anticancer effect against intestinal colon cancer than native curcumin (Xie *et al.,* 2017). The anti-cancer activity may involve in DNA repair, cell proliferation, cell differentiation, angiogenesis, progression and carcinogen metabolism (Rejhova *et al.,* 2018; Singh *et al.,* 2016). Green synthesis of metal nanoparticles has shown beneficial effects due to their less toxicity, cheap and eco-friendly properties compare to other chemical methods (Makarov *et al.,* 2014), synthesis of nanoparticles by the microorganisms have been reported as environmental-friendly alternatives over physical and chemical methods (Makarov *et al.,* 2014). Green synthesis of gold nanoparticles (AuNP's-Cur) observed in HCT-116 and MCF-7 (breast cancer cell lines). Results suggested that AuNP's-Cur effectively reduce apoptotic and proliferation effect in cancer cells compared to curcumin molecule (Elbialy *et al.,* 2019). Similarly, it was suggested that MNP-PEG-Cur nanoparticles (magnetic nanoparticle ornamented with PEGylated curcumin) were good biocompatible drug delivery agent for antitumor drugs (Ayubi *et al.,* 2019). Nambiar *et al.,* 2018 reported that gold nanoparticles formulated together with the plant products had diverse applications in biomedical fields. Polymeric nanoparticles are made up of a long number of repeating units (macromolecules) and arrange in a series showing unique properties and structure, which is useful in biomedical applications (Jain, 2008). Nanoparticles can be successfully used in targeted drug delivery at the site of infection to improve (Duggal, 2011): bioavailability of the drug, successful uptake of less soluble drugs, and targeting of the drug at an appropriate site. Duggal, also reported that nanoparticles possess various kinds of advantages: Enhanced bioavailability potential, reduced toxicity, small amount requirement, and increased surface area of the active agent (Duggal, 2011). Besides metal nanoparticles, polymer-based nanospheres have been made which possess several advantages such as easy to synthesize, cost-effective, biocompatible, biodegradable, nontoxic, soluble in water, non-immunogenic (Bolhassani *et al.,* 2014).

Polymeric nanoparticles that are classified (*in vivo*) as biodegradable are Poly-glycolide (PGA) (Park *et al.,* 2009), Poly (L-lactide) (PLA) (Mainardes *et. al.,* 2010) and non-biodegradable like polyurethane (Fritzen-Garcia *et al.,* 2009). PEG-albumin-curcumin (PAC) nanoparticles exhibits greater anticancer activity against breast cancer cell line due to more bioavailability and long-time stability in blood circulation (Thadakapally *et al.,* 2016). Characteristics of nanoparticles like strength, performance, flexibility, chemical, and physical behaviour advocate their use in pharmaceutical industries and medicine such as: in drug delivery, tumour detection as well as visual monitoring of therapy (Gwinn and Vallyathan, 2006). Different types of nanoparticles and their roles are described in Table 1.

FORMULATION OF CURCUMIN NANOPARTICLES

The studies from the last three decades showed that curcumin exhibits poor absorption, reduced bioavailability, poor metabolism, elimination, and rapid degradation (Krausz *et al.,* 2015). Therefore, to overcome these problems, it is necessary to design an advanced drug delivery system that can enhance the therapeutic translation of curcumin. Chauhan *et al.,* 2014 reported different drug delivery systems like liposome (formulation of curcumin for parenteral administration). Liposome exhibits several properties like high stability, better solubility, high biocompatibility and easy preparation (Moballegh Nasery *et al.,* 2020), nanoparticles (polymeric and solid lipid NPs), and microemulsion (Bansal *et al.,* 2011, Maiti *et al.,* 2007). Polymeric nanoparticles have features like biocompatible, small in size and stay in bloodstream for longer time (Ferrari *et al.,* 2018). Roacho-Perez *et al.,* 2020 reported that magnetic nanoparticles are of low synthesis cost and highly responsive for cancer treatments. Curcumin-nanoparticles are probably the most effective approach for the therapeutic application of curcumin. In this review, we have focused on the formulations of curcumin loaded poly (lactic-co-glycolic) acid (PLGA) nanoparticles and its efficacy against different types of human pathogens. There are several methods for the synthesis of curcumin loaded PLGA nanoparticles (PLGA-cur-NPs). We have discussed all the methods, including the positive and negative aspects of techniques used as below:

Coacervation method

In this method, the polymer is dissolved in ethyl acetate, dichloromethane, or acetonitrile (organic solvent) and curcumin molecules directly suspended within the

Table 1. Various compounds used for the formation of nanoparticles and their diverse role and applications.

Compounds used for Nano-formulation	Applications	Reference
Silver	Antimicrobial, antiviral activity and used in textile industries, water treatment, and sunscreen lotions etc.	Rai, Yadav and Gade, 2009, Sharma, Ria and Lin, 2009
Gold	Used in the identification of protein interactions, detect cancer stem cells, beneficial for cancer diagnosis, and identification of different classes of bacteria.	Baban and Seymour, 1998, Tomar and Garg, 2013
Magnet	Fe_3O_4 (Magnetite) and Fe_2O_3 (maghemite) both are biocompatible NPs, used in manipulation, stem cell sorting, guided drug delivery system, magnetic resonance imaging (MRI), gene therapy, and DNA analysis.	Fan, Chow and Zhang, 2009
Copper	Copper NPs are DNA-cleavage agents, efficient anticancer, and modifiable surface properties by conjugation with various biomolecules including proteins and enzymes.	Fang *et al.,* 2010, Thanh and Green, 2010, Wang et al., 2015, An and Zhang 2017.
Polyethylenimine (PEI)	PEI (cationic polymer) used for nucleic acid delivery, immune dysfunction, cancers and allergy.	Saengkrit *et al.,* 2012, Nguyen and Friedman, 2013
Poly- £- caprolactone (PCL)	PCL is used for the development of contraceptive devices, wound dressings, drug delivery systems as well as fixation devices.	Bilensoy *et al.,* 2009
Polyacrylate	Antibiotic-conjugated Polyacrylate nanoparticles are used as antimicrobial agents.	Turos *et al.,* 2007
A-----lbumin	This is used for the delivery of protein, oligonucleotides, DNA as well as drugs.	Moreno-Vega *et al.,* 2012, Bolhassani *et al.,* 2014
Heparin	Used for the delivery of oligonucleotides, DNA, protein, and drugs.	Moreno-Vega *et al.,* 2012, Bolhassani *et al.,* 2014
Chitosan	Used as a carrier of DNA for gene delivery.	Nguyen *et al.,* 2009
Poly(lactic- co-glycolic acid) (PLGA)	Used as drug release devices, implants to repair fractures, and surgical sutures.	Xiaoling and Haskara 2006, Stevanovic and Skokovic 2009, Stevanovic *et al.,* 2008.

polymeric solution and then leave it to homogenize. High-speed centrifugation is employed for Nanoparticles collection. The disadvantage of this method is that it requires more solvent (Dhivya and Rajalakshmi, 2018).

Single emulsion method

Curcumin NPs are synthesized by dispersing it in a solvent, by ultrasonication or high-speed homogenization to form the emulsion. The solvent evaporated from the emulsion by continuous magnetic stirring under reduced pressure at room temperature. After this, step the emulsion is ultrasonicated then collected, washed (distilled H_2O) to remove additives and allow to lyophilized to create nanoparticles. Curcumin loaded PLGA nanoparticles can also be prepared by the Single emulsion method (Dhivya and Rajalakshmi 2018).

Solvent evaporation method

Two steps involve in the Solvent Evaporation Method (i) Solution of drug-polymer preparation step (ii) dispersing solvent evaporation, and this step helps curcu-

min to dissolve properly. Formation of emulsion that changed into nanoparticle suspension followed by a solvent evaporation process. The advantages and disadvantages of this method are: (i) for evaporation of solvent required low temperature (ii) prevention of thermal deposition can occur. (i) difficulty in the selection of solvent (ii) it is a time-consuming process due to evaporation of the organic solvent (iii) in this method expensive reagents used. PLGA (Poly (lactic acid-co-glycolic acid) curcumin nanoparticles can be formulated by this method (Dhivya and Rajalakshmi 2018).

Solvent displacement method

This method, also called the Nanoprecipitation method, within a suitable solvent a particular polymer is suspended which results in the formation of a polymeric solution. Add natural drug-like curcumin into it. A drug-polymer combination solution is poured into the H_2O by stirring it without interruption after some time gets precipitation. Then left solvent for evaporation by hot airflow. Formation of nano-drugs in the amorphous state by the spray drying method may lead to partial crystallization. In this, polymer and curcumin are dissolved in the same mixture of solvents (Dhivya and Rajalakshmi 2018).

Solvent evaporation method (Solid-in-oil-in-water emulsion; s/o/w)

In this method, PLGA dissolved in chloroform (organic solution) as an oil phase. Free curcumin is added to the PLGA or chloroform solution and after this emulsion is added to a solution of ethanol and PVA (Polyvinyl alcohol) and sonicated. For removing the organic phase (evaporation) of solvent (chloroform) s/o/w emulsion agitated by stirrer. The sample is then centrifuged and washed three times with distilled water. After this, sample is freeze-dried for 24 hrs to obtain nanoparticle dry powder. The nanoparticles are stored at 4 ^{0}C for further use (Mukerjee and Vishwantha 2009, Nair *et al.,* 2012).

Single emulsion-solvent evaporation method

This method is suitable for loading curcumin (a hydrophobic compound) in hydrophilic solvent, PLGA-curcumin nanoparticles can be formed (Cartiera *et al.,* 2010). In the desired amount of ethyl acetate, PLGA polymer dissolved into it after this step drug (curcumin) added to this mixture and for left 30 minutes for complete dissolution (intermittent vortexing). Then Poly (vinyl alcohol) (PVA) is mixed in H_2O that act as a surfactant after this step mixture of curcumin PLGA added into it drop-wise with intermittent vortexing. The mixture is sonicated to create a fine emulsion. Then this emulsion is added to PVA in H_2O and stirred rapidly with a magnetic stirrer for about 3 hours. PVA helps in stabilizing the emulsion and small particles with uniform size are formed. The nanoparticles are collected by centrifugation and washed three times with Milli-Q distilled water. Then at 4 ^{0}C freeze-dried nanoparticles are stored (Mathew *et al.,* 2012).

Double-emulsion or single-emulsion with vitamin e-tpgs

Recently Rebecca *et al.,* used vitamin E-D-β-Tocopherol polyethylene glycol succinate (TPGS) as the emulsifying agent. The major advantage of using TPGS is that it improves emulsification and encapsulation efficiency compared to other emulsifying agents. In a test tube, 100 mg PLGA, and 1 ml of dichloromethane (DCM) or ethyl acetate (EtAc) solvent added in it. Then, 2 ml of 0.3 vitamins E-TPGS is added to the glass test tube. For hydrophobic substances: encapsulant added to the polymer solution directly, then vortex the test tube until encapsulant is homogenously spread over a wide area (dispersed). For hydrophilic substances: the polymer solution with emulsify encapsulant added before starting the addition of drug in buffer or H_2O to the polymeric solution. For emulsification, the polymer and the drug combination ultrasonicated for some time. The polymer solution directly dropped onto the surface of the emulsifier with continuous vortexing. Immediately, the emulsified polymer is ultrasonicated that forms the nanoparticles in the precipitation, and allow the solvent to evaporate (McCall and Sirianni, 2013).

APPLICATION OF PLGA-CURCUMIN NANO PARTICLES

Curcumin is a pleiotropic phytonutrient exhibit number of therapeutic properties, but their optimum potential is hindered by poor solubility, low oral bioavailability, insufficient water solubility leading to low absorption and rapid degradation. To overcome these drawbacks nano vehicles like the drug delivery system were investigated such as curcumin loaded PLGA (polylactide- co-glycolide) nanoparticles for its better activity and bioavailability for cellular absorption (Anand *et al.,* 2010). A study showed that curcumin obtained by the heat extraction method increases the solubility of curcumin 12-fold without any degradation (Kurien *et al.,* 2007). Similarly, nanoformulation enhance the therapeutic and biological applications of curcumin molecules (Karthikeyan *et al.,* 2020). Another study found that curcumin nanoparticles size ranges between 2- 40 nm prepared by the wet-milling technique have a small size, large surface area, and increased bioavailability. These curcumin NPs are more easily dispersed in water as compared to the curcumin without any formulation and show more effective antimicrobial activity against *Escherichia coli, Bacillus subtilis*, *Staphylococ-*

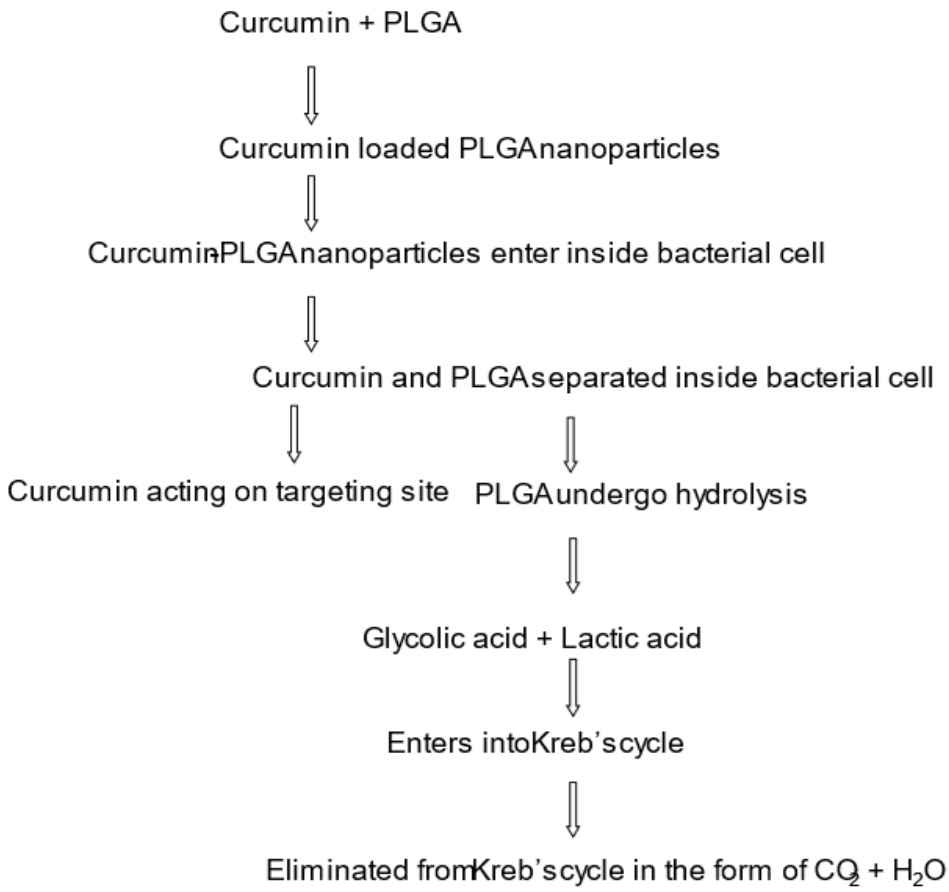

Fig. 3. *Representation of formation of PLGA curcumin nanoparticles and its fate within the living cells (Lu et al., 2009).*

cus aureus, *Pseudomonas aeruginosa,* and two known pathogenic fungi *Penicillium notatum* and *Aspergillus niger* (Bhawana *et al.,* 2011, Shailendiran *et al.,* 2011). Recently, it was reported that PLGA curcumin nanoparticles suppress the NF-kB signaling in mammary glands infected by *Staphylococcus aureus*. Thus, curcumin nanoparticles are also beneficial for murine mastitis (Suresh *et al.,* 2018). Curcumin stability can be enhanced by the micro-encapsulation method which improves the bioavailability and solubility of curcumin and also shows antimicrobial activity against various foodborne pathogens (MIC ranges between 15.7µg/mL to 250µg/mL), e.g. *Escherichia coli, Staphylococcus aureus*, *Bacillus subtilis*, *Yersinia enterocolitica* and *Penicillium notatam*. This suggests that microencapsulated curcumin particles can be used as a food preservative and colourant in food industries (Wang *et al.,* 2009, Wang *et al.,* 2012).

In the present time, one of the most useful applications of curcumin loaded PLGA nanoparticles are in the treatment of different types of human cancer (Mukerjee and Vishwantha, 2009), which is less toxic due to their degradative nature compare to other drugs (Dauda *et al.,* 2017). All these studies suggest that the broad-spectrum activity of this golden spice (turmeric) is successfully enhanced by curcumin loaded PLGA nanoparticles. Curcumin is a hydrophobic molecule that possesses miracle biological activities. Poly (lactic-co-glycolic acid) is one of the most important biodegradable and bioabsorbable polymer which is eliminated by the body itself (Stevanovic*et al.,* 2009). The PLGA polymers are also used as surgical sutures, fracture repair, and medical devices (Xiaoling and Haskara, 2006). PLGA has ester linkages that give hydrolysis reaction in water and forms two monomers glycolic acid and lactic acid which are metabolized and eliminated through the Kreb's cycle as H_2O+ CO_2 (Fig. 3) (Lu *et al.,* 2009).

A variety of antibiotics are used for the treatment as well as prevention of bacterial infections but due to improper use of antibiotics, the emergence of multi-drug resistant strain is a big challenge (Ayukekbong Ntemgwa and Atabe, 2017). Naturally occurring molecules have an excellent opportunity for the development of new therapeutic, which can be effective against various resistant pathogens. Curcumin is a natural compound extracted from turmeric rhizome, it is hydrophobic, and a pleiotropic molecule that gives the yellow color to the turmeric and exhibits different types of therapeutic activities (Allam, 2009, Magalhaes *et al.,* 2009).

Several antimicrobial activities of curcumin have been reported by a group of scientists (Bhawana *et al.,* 2011; Tongnuanchan and Benjakul, 2014) and demonstrated that the turmeric component stopped the activity of *S. aureus* and *E. coli.* The methanolic extract of turmeric exhibited strong antimicrobial activity (Alcaraz *et al.,* 2000, Niamsa and Sittiwet, 2009). Curcumin also shows anti-inflammatory, wound-healing, hypoglycemic, and antioxidant properties as well as induce apoptosis in different types of cells (Aggarwal, Sung 2009, Akram *et al.,* 2010). Moreover, curcumin has several types of therapeutic activities like anticancer and have great potency to reduce the proliferation of cells, metastasis of tumor cells, and transformation(Nakamura *et al.,* 2002, Shishodia *et al.,* 2007). Curcumin also shows the good chemoprotective agent in cancer therapy(Duvoix *et al.,* 2005). Anti-MRSA activity of curcumin sensitizing methicillin-resistant *Stayphylococcus aureus* (MRSA) against various antibiotics (Mun *et al.,* 2014). Instead of this, curcumin has a property to cure different eye-related problems like inflammation of the eye, red eye condition, pain, and loss of vision. Research has shown that curcumin was effective against uveitis disease when 600 mg dose was orally given to the 106 patients twice a day for 12 to 18 months. After a treatment within a few weeks, more than 80% of the patients were relieved from eye abnormalities (Allegri, Mastromarino and Neri, 2010). Turmeric's main component curcumin that is potent antioxidant substances like beta-carotene, vitamins E and C are used for cancer and liver diseases as well as an anti-ageing agent. Besides, curcumin also eases back pain, arthritis, and bursitis by their anti-inflammatory property(Akram*et al.,* 2010). Three different properties of curcumin act together and responsible for the anti-inflammatory action: (i) curcumin reduces the production of inflammatory molecules such as histamine (ii) curcumin enhances the secretion of natural anti-inflammatory hormone (adrenal and cortisol) that increases the blood circulation and eliminate the toxic substance from the body (III) research also confirmed that curcumin also promotes the flow of bile juice by the gall bladder and finally increases the digestion of fat and eliminate toxic/ waste materials outside the body (Akram *et al.,* 2010). Curcumin's antioxidant and anti-inflammatory properties (Surh *et al.,* 2001) minimize the lipid peroxidation and prevents cardiovascular diseases (Smerak *et al.,* 2006).

Curcumin displays broad-spectrum therapeutic activities, but due to its low oral bioavailability, rapid degradation, and poor water solubility, it could not make a clinical impact (Sharma *et al.,* 2007). Curcumin nanoparticles enhance bioavailability (Muqbil *et al.,* 2011). It has been reported that particle size plays an important role in enhancing cellular uptake, absorption, physical stability, and drug release from the nano surface (Feng, 2004). Different types of nanocarriers have been used in drug delivery systems like liposome, solid lipids nanospheres, silicon or carbon as well as dendrimers, etc. (Karuppusamy and Venkatesan, 2017). PLGA is an important biodegradable polymer used in nanomedicine as a drug delivery vehicle, and hydrolysis results in the formation of glycolic acid and lactic acid, metabolized in Kreb's cycle and eliminated as CO_2 and H_2O from the body. PLGA is used as a drug delivery system in humans approved by the European Medicine Agency and US FDA (Mirakabad *et al.,* 2014). Curcumin loaded PLGA nanoparticles exhibited schistosomicidal activity, at the concentration of 50 and 100 µM, 100 % death of parasites caused by these particles at 120 hrs (Luz *et al.,* 2012). Yallapu *et al.,* reported that curcumin loaded nanoparticles effective against ovarian cancer (Yallapu *et al.,* 2010). Curcumin-nanoparticles inhibited first stage metastasis, hence can be used in the cancer treatment (Bisht *et al.,* 2007).

Conclusion

In the present review article, we have explored the characteristics of curcumin, variety of functions, various nano-curcumin formulation methods, their pros and cons, and the importance of PLGA-nano curcumin against pathogenic bacteria. Curcumin is nontoxic and has great therapeutic roles like antimicrobial, antioxidant, anti-inflammatory, anti-cancerous, anti-cholesterol, and antidiabetic as well as shows hepatoprotective, neuronal protective, immune enhancer, cardiovascular and gastrointestinal effects. Curcumin nanoparticles have immense importance in therapeutics and can be used in combinatorial drug therapy such as (I) PLGA-curcumin-nanoparticles combined with first-line antibiotics (amoxicillin, erythromycin, etc) may be effective against multidrug-resistant bacteria. (II) formulation of broad-spectrum antibiotic products that stop the growth of Gram-positive and Gram-negative bacterial infections. (III) formulation of curcumin-based ointment or gel for wound healing and skin infections. Besides this, curcumin may also be effective for crop productivity, and when mixed with soil, it increases the fertility of the soil. Curcumin's antioxidant property is the most important feature, which makes it more powerful as well as increases its therapeutic importance against life-threatening illnesses like AIDS, cancer, tumor, cardiovascular diseases, and lifestyle diseases such as diabetes. Almost all the aspects of curcumin, its role, and applications in therapeutics, emphasizing the antimicrobial properties against Gram-positive pathogens and the use of PLGA-curcumin nanoparticles in combinatorial drug therapy against resistant bacterial

strains which is the prominent necessity of the present time, especially in developing countries have been discussed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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