ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Curcumin Nanoparticles: A Therapeutic Review.

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ABSTRACT

Nanotechnology is one of the most interesting areas of research in modern science. In medicine, nanotechnology-based drug delivery system is an advanced method for treating number of dreadful diseases. In the recent years, plant-derived medicines play an important role in health care. The nanoparticles prepared from biological sources do not produce any harmful side effects. Curcumin (1, 7-Bis-(4-hydroxy-3-methoxyphenyl)-hepta-1, 6-diene-3, 5-dione) is a bio-active component isolated from the rhizome of Curcuma longa Linn, which exhibits various pharmacological activities. But the pharmaceutical application of curcumin was limited due to its poor water solubility and bioavailability. However, the clinical studies proved that curcumin nanoparticles exhibit increased solubility and bioavailability. The therapeutic efficacy of curcumin nanoparticles increases by applying the drug in different nanoforms. In this review, the therapeutic applications of curcumin nanoparticles against cancer, microbial infection, acquired immunodeficiency syndrome, malaria, Alzheimer's and inflammatory diseases were discussed.

Keywords: Curcumin nanoparticles, Bioavailability, Drug delivery, Anticancer

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ISSN: 0975-8585

INTRODUCTION

Nanotechnology is a rapidly growing field with its application in science and technology for the purpose of manufacturing novel materials at the nanoscale level [1]. It is a multidisciplinary field which employs techniques from diverse disciplines. Nanoparticles exhibit special features like large surface area, quantum effect and ability to bind and carry compounds like drugs. The physical, chemical, optical and electronic properties of the nanoparticles depend on the size, shape and surface morphology [2, 3]. Nanoparticles synthesis was carried out by two basic methods: bottom up and top down. In the bottom-up method, nanoparticles were formed from molecular components which assemble themselves chemically by recognising similar molecules and in the top-down method, nanoparticles were formed from larger entities [4]. Bottom-up method is frequently used for the chemical and biological syntheses of nanoparticles.

The nanoparticles have been extensively studied and used because of their applications in medicine like drug delivery, probing of DNA structure, detection of protein, tissue engineering, detection of pathogens, destruction of cancer cells and phagokinetic studies [5]. The major application of nanotechnology in medicine was the development of nanoparticles as drug delivery system. The advantages of using nanoparticles are large surface area, controlled particle size, site-specific targetting, bioavailability, stability, biodegradable and controlled release of drug. Metallic nanoparticles like silver, gold, platinum, copper, etc., have been synthesised and used for clinical applications [6, 7]. However, these metallic nanoparticles can be retained and accumulated in the body causing harmful side effects [8]. These limitations can be solved by using biological sources for the synthesis of nanoparticles. The nanobiomaterials do not accumulate in the body and they are proved to be safe.

Natural herbal compounds were used by humans from ancient times for various purposes. Thousands of secondary metabolites were produced by plants as a natural defence mechanism. Most of these metabolites exhibit pharmacological activity which is used for drug design and discovery. Plant-derived drugs play an important role in health care in recent times. Turmeric (*Curcuma longa* Linn), a perennial herb belonging to the Zingiberaceae family, is a traditional medicine in Asia. The typical yellow colour of turmeric is due to the presence of curcuminoids. The curcuminoids are polyphenols which contain three major components: curcumin (77%), demethoxycurcumin (17%) and bisdemethoxycurcumin (3%). Among these, the most bio-active component is curcumin (1, 7-Bis-(4-hydroxy-3-methoxyphenyl)-hepta-1, 6-diene-3, 5-dione). It has been extensively studied because of its various bio-active and pharmacological activities like antioxidant [9], anti-inflammatory [10], antimicrobial [11, 12] and anticancer [13] activities. But the therapeutic use of curcumin was confined due to its poor water solubility, instability and low bioavailability. The main reasons for the low bioavailability of curcumin are poor absorption, high metabolic rate and rapid systemic clearance [14]. To improve its solubility, stability and bioavailability, nanoparticle-based drug delivery system is used. In the last few years, researchers have developed curcumin in different nanoforms like nanosuspension, nanoemulsion, solid-lipid nanoparticles, hydrogel nanoparticles, etc [15]. Several studies proved that curcumin nanoparticles act as a therapeutic agent against a wide spectrum of diseases [16].

CLINICAL IMPORTANCE OF CURCUMIN NANOPARTICLES

Anticancer activity

Cancer is the most common devastating disease diagnosed throughout the world. Conventional treatments like chemotherapy, radiation therapy and surgery cause adverse side effects. Hence, it is essential to develop safer and alternative treatment method to cure this malignant disease. Currently, natural sources like plants are used to discover novel drugs. It is believed that plants contain various life-saving pharmacological compounds which are non-toxic and can be used to treat various types of cancer. Curcumin is a plant product which is used for the treatment of diverse variety of cancer such as pancreatic, oral, breast, prostate, skin, ovary, etc. These effects are mediated by regulating multiple important cellular signalling pathways. Recently, curcumin nanoformulations with enhanced bioavailability, solubility and specific tumour cell targetting were used as novel therapy for cancer.

Breast cancer

Breast cancer is a prevalent disease mainly affecting women worldwide. The *in vitro* studies of curcumin micelles showed increased bioavailability, cytotoxicity and longer half-life in triple negative breast cancer (TNBC) xenografts [17]. TNBC is a highly malignant and aggressive tumour which does not over express oestrogen, progesterone or human epidermal growth factor 2 receptors and they are resistant to chemotherapy [18]. Curcumin-loaded magnetic nanoparticles showed efficient anticancer activity against TNBC cells (MDA-MB-231 cell line) along with imaging and magnetic targetting properties. It stimulated the generation of cellular reactive oxygen species leading to the loss of mitochondrial membrane potential [19]. The combination of curcumin-encapsulated nanoparticles with electroporation technique in MCF-7 human breast cancer cells depicted better anticancer activity [20].

Ovarian cancer

Ovarian cancer comprises different types of cancer depending on the cells from which they form. The major interruption in treating advanced ovarian cancer is chemoradiotherapy resistance. Yallapu et al., formulated monoclonal antibody conjugated with curcumin nanoparticles for enhancing the site specificity and sensitivity of the chemoradiotherapy resistance of ovarian cancer cells. When the cisplatin-resistant A2780CP ovarian cancer cells were treated with the nanoparticle conjugate, it lowered the cell proliferation and promoted apoptosis [21]. Paclitaxel and curcumin-encapsulated nanoemulsion showed anticancer activity against drug resistant SKOV3 and SKOV3 (taxol-resistant) human ovarian adenocarcinoma cells by promoting apoptotic response. Curcumin nanoemulsion suppressed the nuclear factor kappa B (NFκB) activity and down-regulated P-glycoprotein expression [22].

Pancreatic cancer

Bisht et al., synthesised curcumin-loaded polymeric nanoparticles using the co-polymers N-isopropylacrylamide, N-vinyl-2-pyrrolidone and poly (ethylene glycol) monoacrylate. It acts as a potential agent to inhibit the tumour growth in xenograft models of human pancreatic cancer. The combination of nanocurcumin with the drug gemcitabine further arrested the tumour growth with induction of apoptosis, reduction in activation of NFκB and expression of matrix metalloproteinase MMP-9 and cyclin D1. The therapeutic effectiveness of nanocurcumin was confirmed by cell viability and clonogenic assays [23]. Curcumin-loaded magnetic nanoparticles significantly stopped the growth of human pancreatic cancer cells (HPAF-II and Panc-1) in xenograft mouse model. This formulation showed higher stability with increased bioavailability and biodistribution when compared with normal curcumin [24].

Prostate cancer

Prostate cancer is a disease which develops in the prostate gland of the male reproductive system. Gradually, it may spread to other parts of the body like bones and lymph nodes [25]. Curcumin-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles prepared by Yallapu et al., demonstrated the anticancer activity of curcumin nanoparticles against prostate cancer. PLGA-curcumin nanoparticles after incorporation inside the cancer cells, released the bio-active curcumin in the cytosol. It suppressed the nuclear β-catenin and androgen receptor expression, STAT3 and AKT phosphorylation and inhibited the key anti-apoptotic proteins leading to apoptosis [26]. The *in vitro* studies of curcumin-loaded PLGA nanospheres in prostate cancer cell lines showed sustained delivery of curcumin for a prolonged period of time and increased rate of intracellular uptake of nanospheres [27].

Antimicrobial activity

Micro-organisms play a major role in causing numerous infections to humans. Many chemical and natural compounds were used as antimicrobial agents to kill bacteria, fungi, protozoa and virus. Traditionally, turmeric has been used as an antimicrobial agent. Curcumin nanoparticles were used as they are known to possess superior antimicrobial activity than the normal curcumin. Bhawana et al., reported the antibacterial and antifungal activities of nanocurcumin prepared by wet-milling technique. The nanocurcumin was more water dispersible in the absence of any surfactants and highly active against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Penicillium notatum* and *Aspergillus niger*. The nanoparticles penetrated the infected cell by damaging the cell wall and ultimately leading to cell death. The nanocurcumin formulation was more reactive against Gram-positive bacteria than the Gram-negative bacteria [28]. In another study, curcumin-encapsulated nanoparticles inhibited the growth of methicillin-resistant *S. aureus* and *P. aeruginosa* and enhanced the wound-healing activity in an *in vivo* murine wound model [29]. Similarly, the *in vitro* studies of curcumin-loaded chitosan tripolyphosphate nanoparticles on mouse skin suppressed the growth of *S. aureus* and *P. aeruginosa* [30].

Anti-HIV activity

Human immunodeficiency virus (HIV) attacks the immune system by destroying CD^{4+} T cells. The progressive failure of the immunity finally leads to acquired immunodeficiency syndrome (AIDS). The CD^{4+} T cells are a type of white blood cells that protect the body from infections. The antiretroviral drug suppresses the virus, but the complete elimination was not yet achieved. Hence, it is necessary to find an alternative therapy to treat this fatal condition. Gandapu et al., reported that curcumin-loaded apotransferrin nanoparticles prepared by sol-oil technique was very potent to prevent HIV-1 replication by transferrin-mediated endocytosis. Normally, HIV-infected cells express transferrin receptors. Curcumin-loaded apotransferrin nanoparticles bind specifically to the receptor and transport the drug inside the infected cell. Gradually, the drug is released out and the viral cDNA synthesis is blocked leading to the termination of HIV-1 replication [31].

Antimalarial activity

Malaria is caused by parasites and carried by female Anopheles mosquitoes. The *in vivo* studies of curcumin-loaded hydrogel nanoparticles reported by Dandekar et al., showed antimalarial activity. The toxicity studies proved the oral safety and cytotoxic effects of the nanoformulations [32]. Curcumin-loaded chitosan nanoparticles cured the mice infected with *Plasmodium yoelii* by blocking the hemozoin synthesis [33].

Anti-inflammatory activity

In ancient Indian medicine, turmeric has been used as an anti-inflammatory agent. Rocha et al., compared the anti-inflammatory activity of normal curcumin and nanocurcumin in rat. The inhibitory effect shown by nanocurcumin at dose 50 mg/kg was similar to that of normal curcumin at dose 400 mg/kg which proved the improved anti-inflammatory activity of nanocurcumin [34]. Curcumin-encapsulated exosomes were studied for their potency in lipopolysaccharide-induced septic shock mouse model. In that experiment, curcumin delivered by exosome demonstrated more stability, target specificity and they were found in high concentrations in blood [35].

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that occurs all over the world. It is a common type of dementia associated with memory loss and gradual death of brain cells. The neuronal apoptosis occurs due to the accumulation of beta-amyloid plaques and activation of caspase pathway. Cheng et al., explored the activity of nanocurcumin against AD. In their study, the formulated nanocurcumin was orally administered to Tg2576 mice for three months and memory of mice was measured. Nanocurcumin-treated mice showed better cue memory in the contextual fear conditioning test and greater working memory in the radial arm maze test [36]. PLGA-coated curcumin nanoparticles in conjugation with Tet-1 peptide possess anti-amyloid and antioxidant property and it can be used as a potential drug for treating AD [37]. The curcumin-encapsulated PLGA nanoparticles induced neural stem cell proliferation and neurogenesis in the hippocampus and subventricular zone of adult rats by activating the Wnt/β-catenin pathway. Thus, employing nanocurcumin proved to be a better therapeutic approach for the treatment of AD [38].

CONCLUSION

Nanotechnology-based drug delivery system overcomes the limitations of the conventional treatment methods. In this review, the medicinal applications of curcumin nanoparticles were discussed. Curcumin nanoparticles showed higher stability, bioavailability, target specificity, controlled particle size and sustained drug release. Curcumin was used in different nanoforms like nanoemulsion, polymeric nanoparticles, polymeric micelles, etc. These nanoparticles act as a potential agent against various diseases like cancer, microbial infection, AIDS, malaria, AD and inflammatory diseases. To improve the safety and efficacy of the drug, research should be focussed on targetting the infected cells and controlled drug release without toxicity. In the future, more pre-clinical and clinical investigations need to be conducted to determine the hidden potentials of nanocurcumin in the field of pharmaceutical sciences and medicine.

REFERENCES

[1] Albrecht MA, Evans CW, Raston CL. Green Chem 2006; 8: 417-432.
[2] Alivisatos AP. J Phys Chem 1996; 100: 13226-13239.
[3] Murphy CJ. Science 2002; 298: 2139-2141.
[4] Rodgers P. Nat Nanotechnol 2006; 5: 98-119.
[5] Salata O. J Nanobiotechnology 2004; 2(1): 3.
[6] Yamada M, Foote M, Prow TW. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2015; 7(3): 428-445.
[7] Rupareli JP, Chatterjee AK, Duttagupta SP, Mukherji S. Acta Biomater 2008; 4(3): 707-716.
[8] Wang AZ, Langer R, Farokhzad OC. Annu Rev Med 2012; 63: 185-198.
[9] Jayaprakasha GK, Rao LJ, Sakariah KK. Food Chem 2006; 98: 720-724.
[10] Srimal RC, Dhawan BN. J Pharm Pharmacol 1973; 25(6): 447-452.
[11] Tajbakhsh S, Mohammadi K, Deilami I, Zandi K, Fouladvand M, Ramedani E, Asayesh G. Afr J Biotechnol 2008; 7(21): 3832-3835.
[12] Kim MK, Choi GJ, Lee HS. J Agric Food Chem 2003; 51(6): 1578-1581.
[13] Shishodia S, Chaturvedi MM, Aggarwal BB. Curr Probl Cancer 2007; 31(4): 243-305.
[14] Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Mol Pharm 2007; 4(6): 807-818.
[15] Dutta AK, Ikiki E. J Bioequiv Availab 2013; 6: 1-9.
[16] Ghalandarlaki N, Alizadeh AM, Ashkani-Esfahani S. Biomed Res Int 2014; 2014: 1.
[17] Cridge BJ, Larsen L, Rosengren RJ. Oncol Discov 2013; 1: 6.
[18] Carey L, Winer E, Viale G, Cameron D, Gianni L. Nat Rev Clin Oncol 2010; 7(12): 683-692.
[19] Yallapu MM, Othman SF, Curtis ET, Bauer NA, Chauhan N, Kumar D, Jaggi M, Chauhan SC. Int J Nanomedicine 2012; 7: 1761-1779.
[20] Lin W, Cooper C, Camarillo I. The effectiveness of electroporation-based nanocurcumin and curcumin treatments on human breast cancer cells. In: Proceedings of ESA annual meeting on electrostatics; 2014 June 17-19; University of Notre Dame, Notre Dame, Indiana. USA: Electrostatics Society of America; p. 1-7.
[21] Yallapu MM, Maher DM, Sundram V, Bell MC, Jaggi M, Chauhan SC. J Ovarian Res 2010; 3: 11.
[22] Ganta S, Amiji M. Mol Pharm 2009; 6(3): 928-939.
[23] Bisht S, Mizuma M, Feldmann G, Ottenhof N, Hong SM, Pramanik D, Chenna V, Karikari C, Sharma R, Goggins MG, Rudek MA, Ravi R, Maitra A, Maitra A. Mol Cancer Ther 2010; 9(8): 2255-2264.
[24] Yallapu MM, Ebeling MC, Khan S, Sundram V, Chauhan N, Gupta BK, Puumala SE, Jaggi M, Chauhan SC. Mol Cancer Ther 2013; 12(8): 1471-1480.
[25] Ruddon RW. Cancer biology, 4th ed. Oxford University Press, Oxford, 2007, pp. 223.
[26] Yallapu MM, Khan S, Maher DM, Ebeling MC, Sundram V, Chauhan N, Ganju A, Balakrishna S, Gupta BK, Zafar N, Jaggi M, Chauhan SC. Biomaterials 2014; 35(30): 8635-8648.
[27] Mukerjee A, Vishwanatha JK. Anticancer Res 2009; 29(10): 3867-3876.
[28] Bhawana, Basniwal RK, Buttar HS, Jain VK, Jain N. J Agric Food Chem 2011; 59(5): 2056-2061.
[29] Krausz AE, Adler BL, Cabral V, Navati M, Doerner J, Charafeddine RA, Chandra D, Liang H, Gunther L, Clendaniel A, Harper S, Friedman JM, Nosanchuk JD, Friedman AJ. Nanomedicine 2015; 11(1): 195-206.
[30] Mirnejad R, Jahromi MAM, Al-Musawi S, Pirestani M, Ramandi MF, Ahmadi K, Rajayi H, Hassan ZM, Kamali M. Iran J Biotech 2014; 12(3): e1012.
[31] Gandapu U, Chaitanya RK, Kishore G, Reddy RC, Kondapi AK. PLoS One 2011; 6(8): e23388.
[32] Dandekar PP, Jain R, Patil S, Dhumal R, Tiwari D, Sharma S, Vanage G, Patravale V. J Pharm Sci 2010; 99(12): 4992-5010.
[33] Akhtar F, Rizvi MM, Kar SK. Biotechnol Adv 2012; 30(1): 310-320.
[34] Rocha BA, Gonçalves OH, Leimann FV, Rebecca ESW, Silva-Buzanello RA, Filho LC, Araújo PHH, Cuman RKN, Bersani-Amado CA. Adv Med Plant Res 2014; 2(4): 62-73.
[35] Sun D, Zhuang X, Xiang X, Liu Y, Zhang S, Liu C, Barnes S, Grizzle W, Miller D, Zhang HG. Mol Ther 2010; 18(9): 1606-1614.

[36] Cheng KK, Yeung CF, Ho SW, Chow SF, Chow AH, Baum L. AAPS J 2013; 15(2): 324-336.
[37] Mathew A, Fukuda T, Nagaoka Y, Hasumura T, Morimoto H, Yoshida Y, Maekawa T, Venugopal K, Kumar DS. PLoS One 2012; 7(3): e32616.
[38] Tiwari SK, Agarwal S, Seth B, Yadav A, Nair S, Bhatnagar P, Karmakar M, Kumari M, Chauhan LK, Patel DK, Srivastava V, Singh D, Gupta SK, Tripathi A, Chaturvedi RK, Gupta KC. ACS Nano 2014; 8(1): 76-103.