Nanocurcumin: A Point of Care Formulation to Treat Tuberculosis

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The super drug Curcumin, extracted from dietary spice turmeric, can be converted into nanoparticulate form 'Nanocurcumin' by a simple and facile *in situ* (at the site) approach, a new study has claimed. The innovative *in situ* technology developed by researchers at Institute of Chemical Technology, Mumbai, enables instantaneous generation of Nanocurcuminat point of care. All it requires is a glass of water for dilution. This *in situ* Nanocurcumin has demonstrated improved clearance of tuberculosis infection.

Curcumin manifests widespread applications and has been employed as an anti-inflammatory, anticancer, antioxidant and antibacterial agent. Curcumin is found to be nontoxic in humans at doses up to 8 grams per day, both as a dietary supplement and as a drug. However, the hydrophobic nature of curcumin, resulting into poor water solubility, hinders its effective utilisation as a therapeutic agent. Converting curcumin to its nano form can overcome these obstacles, state the researchers.

Nanoparticles are submicron-sized particles of size ≤1 micron. Nanonisation of particles enable solubility enhancement and can also improve bioavailability (the proportion of drug that enters circulation on administration) of poorly soluble molecules. Furthermore, such nanosystems when confined to 200-600 nm size range can enable targeted delivery to the reticuloendothelial system (defence system of body involved in infections).

The research team has elaborately described the *in situ* methodology employed for preparation of Nanocurcumin in their recent publication in *Bioengineering and Translational* medicine journal.

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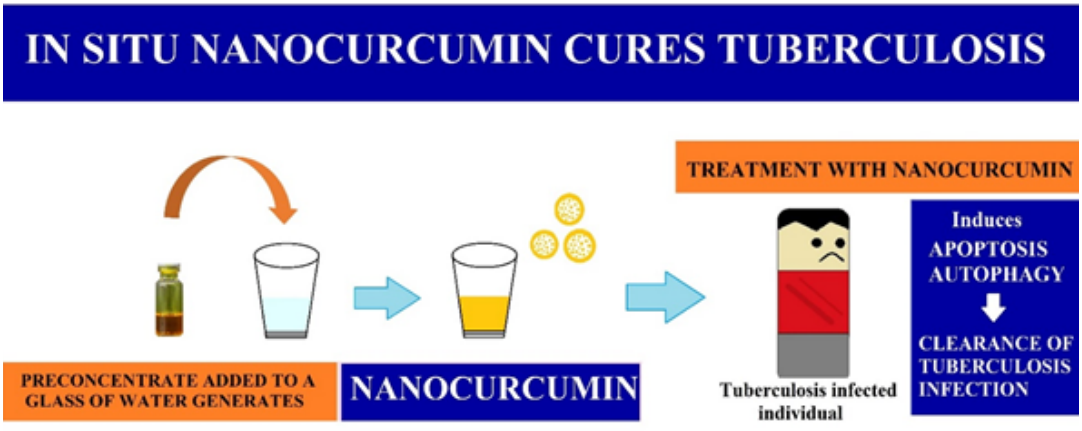

The method simply involves addition of preconcentrate (a premix of curcumin and biodegradable polymer in a pharmaceutically acceptable solvent) to a glass of drinking water on-site. The resultant Nanocurcumin has average particle size of ~200 nanometer and good colloidal stability as indicated by the negative zeta potential.

"*In situ* technology is a radical intensified process that enables rapid formation of nanoparticles at the point of use by simple mixing, overcoming the drawbacks of conventional nanoparticle manufacturing methods", says Prof. Padma Devarajan, the principal investigator of this study. The method is extremely easy to scale up, thus making it cost-effective and advantageous over conventionally used methods.

The team employed Design of Experiment approach (DOE) to arrive at a stable and robust Nanocurcumin formulation. This approach enabled fixing the concentrations of curcumin, polymer, stabiliser and the solvent in which these were dissolved. The software predicted a final stable composition which was utilised for further studies.

Extensive characterisation of Nanocurcumin was carried out using sophisticated techniques. Dynamic light scattering, scanning electron microscopy and transmission electron microscopy were utilised for assessing size and morphology. The amorphous nature of curcumin indicating its conversion to nano form was confirmed by differential scanning calorimetry and X-Ray diffraction techniques. Stability data revealed shelf life of preconcentrate to be >2 years.

The investigators revealed another interesting fact that the *in situ* nanosystem is independent of the volume of water in the glass. They propose that the preconcentrate can be added to any amount of water ranging from 2 teaspoonful (10ml) to half a glassful (100 ml) without any alterations in size and other parameters. "We observed that Nanocurcumin is rugged to dilution. This is highly desirable since the system is meant for dilution at user end", they write.

The research team collaborated with scientists at Radiation Medicine Centre, Bhabha Atomic Research Centre, Mumbai, to evaluate targeting efficiency of Nanocurcumin to the macrophages, the location of intracellular organisms. Macrophages are a type of white blood cells that are

capable of tracking and eating foreign invasions such as microbes, cellular debris and all other particles lacking the typical protein composition. Particles of >200 nanometer size can be readily engulfed by the macrophages. Flow cytometry, high performance liquid chromatography and confocal microscopy techniques confirmed efficient uptake of Nanocurcumin in the macrophages. Additionally, Nanocurcumin revealed negligible cytotoxicity in the macrophages. This indicated suitability of the nanosystem for treatment of intracellular infections.

Tuberculosis is a global health challenge with millions of deaths reported every year. Presently, the only weapon for curing tuberculosis is antibiotics. Side effects of current tuberculosis chemotherapy can be distressing leading to patient non-compliance with long treatment durations. The excellent macrophage targeting ability of Nanocurcumin urged the researchers to study its effect in clearance of tuberculosis infection wherein the causative organism, *Mycobacterium tuberculosis* resides within macrophages. Their findings depicted that the bacterial burden was dramatically reduced following treatment of experimentally infected macrophages with Nanocurcumin.

The investigators went further to understand the mechanism involved in clearance of infection. Interestingly, they observed that Nanocurcumin manipulated body's immune system rather than targeting the bacteria. Western blot and flow cytometry techniques were employed to understand the exact host stimulation mechanism. They observed that Nanocurcumin induced the cellular responses like apoptosis (programmed cell death) and autophagy (orderly degradation and recycling of cellular components). Autophagy induction was evident by conversion of LC3 I to its lipidated LC3 II form and degradation of p62 protein, a prognostic marker for autophagy. Apoptosis was confirmed by evaluating cleaved poly [adenosine di phosphate ribose] (PARP) expression by Western blot and performing propidium iodide staining for flow cytometric analysis.

"Autophagy and apoptosis are inherent responses of the cells to maintain homeostasis. Induction of these responses by Nanocurcumin boosts the immune cells and leads to faster clearance of the bacteria present inside the cells", said Dr Pramod Kumar Gupta, collaborator from Radiation Medicine Centre.

"Being a formulation of natural product, side effects of Nanocurcumin are close to nil. As Nanocurcumin doesn't target the bacteria directly, chances of developing drug resistance are low, thus proving to be a major advantage over existing tuberculosis therapy. Additionally, being a host directed therapy, Nanocurcumin boosts the immunity of the infected individual, indicating less chances of relapse after treatment", he added.

The study provides basic evidence that Nanocurcumin, prepared by simple and innovative *in situ* technology, can improve clearance of *Mycobacterium tuberculosis* from experimentally infected cellular models. The researchers look forward to perform experiments in animal models to provide conclusive evidence. If proven, Nanocurcumin can be used as a curative therapy for treatment of tuberculosis.

The research team from Institute of Chemical Technology comprises of doctoral research fellow Priyanka Jahagirdar and Prof. Padma Devarajan. Dr Pramod Kumar Gupta and Dr Savita Kulkarni are collaborators from Radiation Medicine Centre. The study has been funded by University Grants Commission Basic Scientific Research scheme (UGC BSR).