Parker-Gentry Award to Uma Ramakrishnan

'*To conquer our niche, we need to understand the consequences of the assets we enjoy*.'

Uma Ramakrishnan, who has made great strides towards understanding the evolutionary significance of tigers, is the first Indian to receive the Parker-Gentry Award. The 2016 award acknowledges her outstanding achievements in conservation ecology.

Uma Ramakrishnan is a molecular ecologist in the National Centre for Biological Sciences. Her research focuses on two aspects: conservation genomics and landscape genetics. She studies the population genetics of tigers using DNA sequences and trends in genetic variation. She is assessing the distribution, abundance and demographic ratios of tigers at the Bandipur National Park, Karnataka, India. She is passionate about the need for tiger conservation in India, as it not only harbours the majority of the tiger population in the world, but it also has maximum genetic variation and, hence, maximum evolutionary potential. In her words, 'tigers are very charismatic, and I think we all agree we cannot afford to let them go extinct'.

According to Ramakrishnan, 'there has been a loss in connectivity between tiger populations in the last 200 years'. She highlighted anthropogenic activities, like urbanization and poaching, as major setbacks for the stabilization of the tiger population. Loss of connectivity and fragmentation of habitats result in resource limitation and unavailability of mates thus compelling inbreeding. This leads to reduced viability. What we need, according to her, is a global integrative approach to confront tiger conservation, instead of local or population level approaches.

Currently, she is developing genomic techniques for testing faecal samples and the opportunity to sequence the whole genomes of extinct species from fossils. Her goals are to develop methods with the ability to generate genomic data from degraded DNA in tiger faeces, and a portable sequencer which could provide genetic data from tiny samples.

The Parker-Gentry Award to Uma Ramakrishnan prompts us to consider amendments to our policies and to provide some room for the conservation of indigenous mammals, which would otherwise be lost forever.

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RESEARCH NEWS

Cool ways to deliver curcumin: practical nutraceutical

Sarah Iqbal

'*The doctor of the future will no longer treat the human frame with drugs, but rather will cure and prevent disease with nutrition*'.

– Thomas Edison

Turmeric roots were originally used as a dye. No one knows what prompted its use in traditional medicine but it has been a vital part of Ayurveda and Chinese medicine since the past 5000 years. Currently turmeric is widely used in Indian cuisine and as a component of cosmetics and food additives[1].

About two centuries ago, Vogel and Pelletier isolated and purified curcumin, the bright yellow pigment isolated from turmeric[2]. A large part of turmeric's healing properties are from curcumin. So scientists have never stopped investigating it since.

In 1949, curcumin was shown to have antibacterial effects[3]. Suddenly, curcumin took the scientific world by storm. By June 2011, there were more than 4000 articles in the National Institutes of Health about this medical wonder. You could throw anything at it: cancer, tuberculosis, injury, burns, etc. and it would be taken care of. In fact, there is not a single cancer cell line that does not succumb to curcumin in a petri dish.

But '*in vivo*', the story was different. Curcumin could not deliver even half of its promise when administered in animals. Most studies never made it past animal trials. As a result, there is not sufficient data to back the gratifying *in vitro* claims of curcumin in humans. Research reveals that though the molecule is active within the body, the problem maybe more fundamental: curcumin is insoluble in water and has a serum half life of 40–45 minutes. So the availability in the system is too little and for too short a time to replicate its touted effects[1,3,4].

Beginning 1960, there have been massive leaps in the field of material science that led to creation of nanomaterials, biocompatible matrices and polymers that can aid drug delivery. Several strategies have emerged: use of drug nanoparticles, conjugation, encapsulation in gels and micelles….[3]

Although several attempts were made to use these strategies, most of them failed[3,4]. Now, three independent groups from India have reported novel strategies for curcumin delivery that can serve to improve its bioavailability[5–8].

Due to its lipophilic nature, curcumin absorbed by the body preferentially interacts with the human serum albumin (HSA) and lipids. So, in theory, conjugation of HSA to curcumin should not alter its biological action. Since HSA is the major transport protein of blood, this could also improve curcumin solubility. Aravind and Krishnan from Thrombosis Research Institute, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, conjugated HSA to curcumin to study its biological action[5]. They tested the conjugate drug in a mice model with Dalton's lymphoma

ascites tumour. And found reduced tumour volume and prolonged survival of tumour-bearing mice with no side effects on either kidney or liver.

Most current therapeutic practices suppress immune cells, subjecting cancer patients to secondary infections. Treatment with curcumin showed an immunomodulatory response exhibiting improved proliferation of lymphocytes. The strategy was found to be effective against both solid tumours and metastasis after surgery, radiation or chemotherapeutic treatment. Since the conjugate used in this case is albumin, it is clinically safe.

Brahmeshwar Mishra, Department of Pharmaceutics, Indian Institute of Technology, Varanasi, used a diametrically opposite approach for increasing the bioavailability of curcumin[6]. One way of improving solubility is reducing size; the other is conjugation with a water soluble compound. Mishra and his team combined both the strategies to create a polymeric curcumin nanoparticle. This they thought would serve two purposes: increased availability of free floating curcumin and improved therapeutic efficiency.

Nanopartcle conjugates were prepared by the emulsification–diffusion–evaporation method with small particle sizes. For conjugation, the research team selected a cationic polymer Eudragit E100 which is known to improve the solubility of many drugs.

When tested on mice with colorectal tumours, the nanoparticle conjugates decreased tumour volume and increased the survival time of tumour-bearing mice as opposed to the elemental form of curcumin. Conjugation with a polymer prevented the rapid degradation of curcumin in the intestinal environment and the reduced size allowed greater penetration into cancer cells, more so in the leaky vasculature of tumours. As the polymer allowed good binding with the gastrointestinal tract, there was higher curcumin activity in colorectal cancers.

Depending on the site of delivery, commercial polymers can also be replaced with natural polymers such as xanthan gum and guar gum. Due to diverse structure and enhanced water retention properties, natural polymers are more suited to grafting – a technique that is used to incorporate desired delivery qualities to polymers. Exploring this idea, Mutalik from Manipal University in collaboration with BLDE College of Pharmacy, Vijayapura and University of Queensland, Australia, synthesized a novel pH sensitive curcumin loaded nanoparticle[7]. The biodegradable particles, devised from agarose-xanthan gum copolymer are unique: they prevent the release of curcumin in an acidic pH (up to a pH of 4.5) and they unload the polyphenol in basic pH (6.8–7.4). This propety become more pronounced when rat coecal contents are added to the basic media. This is presumed to occur due to the action of gut microbes which can digest the polymer and consequently release sufficient quantities of curcumin in the intestine.

The curcumin-copolymer nanoparticles were tested in rats suffering from colitis where they were able to alleviate the symptoms of the disease. Since delivery mechanism ensures that curcumin reaches its target, anti-inflammatory properties of curcumin can be utilized to its full potential. This study provides a proof-of-concept for microflora activated curcumin delivery mechanism for treatment of colitis.

Another team headed by Nirmala Rachel James, Indian Institute of Space Science and Technology, Thiruvananthapuram, succeeded in creating a delivery system that can deliver curcumin specifically to the liver[8]. Previous literature had amply demonstrated the hepatoprotective effect of curcumin. But delivering the molecules to the tumour region in an appropriate concentration proved to be a herculean task.

Nirmala thought of tweaking the specificity of galactose. Liver cells contain asialoglycoprotein receptors that can specifically bind with ligands containing galactose and galactosamine residues. Scientists synthesized this conjugate through a complex multistep procedure: oxidation of alginate, modification of lactobionic acid, grafting of targeting group (modified lactobionic acid) and conjugation of curcumin to galactosylated alginate.

The conjugate self-assembled to form micelles in aqueous environment. When delivery of curcumin was evaluated, scientists found greater internalization of the drug within liver cells on account of cell recognition. Results show enhanced efficacy of the target attached micelles with no associated side effects.

At present, there are two limitations that restrict the use of curcumin in medicine: poor absorption and rapid metabolism. Advances in material science can help overcome these[3,9]. The strategies discussed are a step closer to realizing the full potential of curcumin *in vivo*. Will curcumin serve as the clinical panacea it was thought to be? Only time will tell.

But the strategies that are being adopted now will go a long way in realizing the potential of dietary polyphenols and other classes of chemicals that have potent clinical applications. This may be a paradigm shift in the field of nutraceuticals. In a world where most diseases are caused due to over nutrition, under nutrition or toxic nutrition, it is time to 'let food be thy medicine and medicine be thy food' as the father of medicine, Hippocrates, said.

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