

Could a combination of two simple nutraceuticals slow down ageing disorders?

- Ageing is the accumulation of molecular damage inside the cells of an organism over time.
- Billions of cells die in the body every day and chromosomal particles released by dead cells could potentially be contributing to ageing by damaging the DNA of healthy cells.
- Could neutralising these particles before they reach the healthy cells prevent DNA damage and retard ageing?
- Dr Indraneel Mitra of the Tata Memorial Centre, India, has decided to test this idea by using a combination of the nutraceuticals (foods and food derivatives that act as medicinal alternatives and are consumed for additional health benefits), resveratrol and copper. The results are intriguing.



Ageing is the inevitable process of an organism getting older over time. With the help of the latest medical advancements, people are living longer, which has its obvious advantages. However, it also creates a challenge for societies that will have to inevitably deal with an increase in ageing-related degenerative disorders that severely affect the patients' quality of life.

Keeping this population healthy and active is crucial for both the wider communities and the burdened health systems. This is why researchers around the world have been working on unlocking the molecular mechanisms of ageing and cell death to understand the causes of age-related diseases and improve the quality of life of the elderly. There are many theories that attempt to describe the

biology of ageing; however, none of them can fully explain this multifaceted process.

Dr Indraneel Mitra of the Tata Memorial Centre, Mumbai has recently proposed a new theory of ageing that implicates the particles of chromatin (a complex of DNA and protein) released from the nuclei of dead cells and has conducted an important study to test it.

The biology of ageing

Ageing at a cellular level is a multidimensional process that not only involves changes of the cell's genetic make-up, but also changes in the immune system and metabolism, all crucial elements for chemical reactions in life. The ageing process starts with damage to the DNA,

leading to the formation of faulty proteins that can cause malfunction and even the death of the cell or the organism. Other genetic changes involve the shortening of the telomeres (repeated segments of DNA positioned at the ends of chromosomes), the gradual loss of which determines the life span of the cell, and aneuploidy, which is the presence of an abnormal number of chromosomes in a cell and is strongly associated with ageing and cell death.

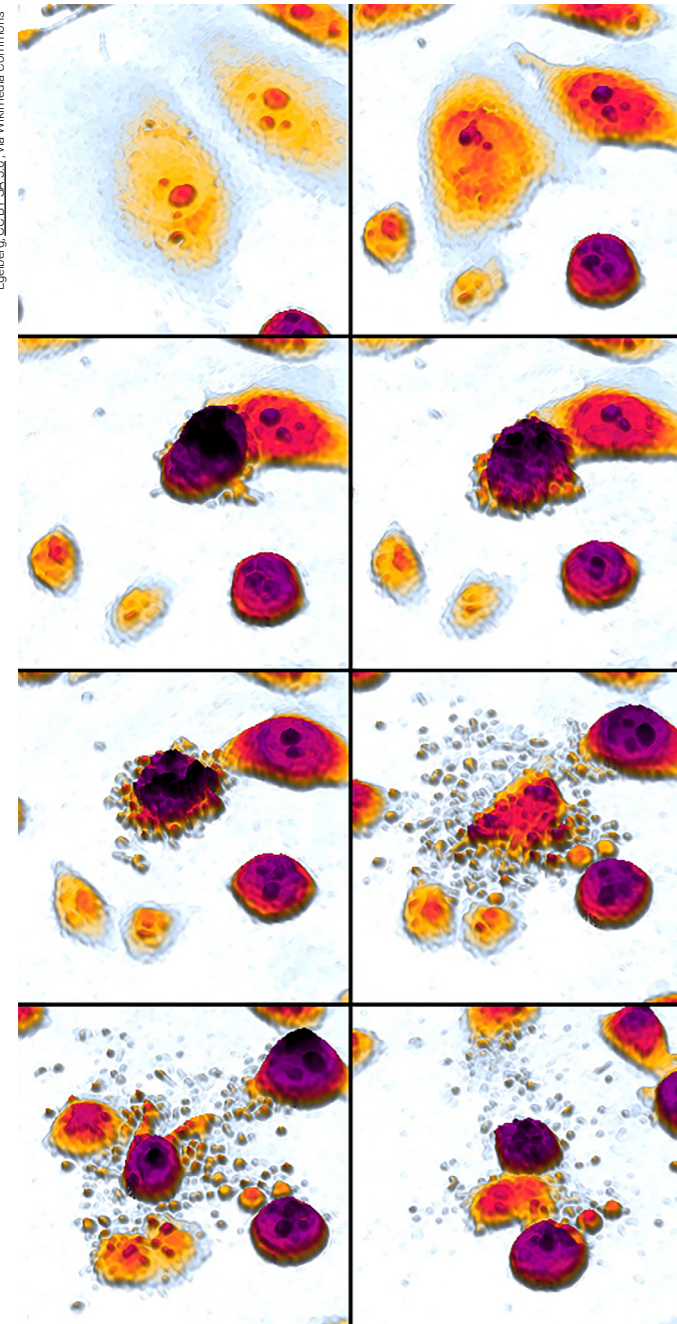
Other signs of ageing include the presence of low-grade, long-standing inflammation of the body tissues, the dysfunction of the metabolic processes, such as the ones taking place in the mitochondria (the energy-producing centres of the cell), and the excessive deposition of a protein called amyloid in brain tissues,

which is associated with the dreaded condition of old age, namely Alzheimer's disease.

What is cell-free chromatin?

Several hundred billion of cells die in the healthy human body every

Cell-free chromatin particles (cfChPs) can enter healthy cells, damage their DNA, and lead to a specific type of cell death, called apoptosis.



Cell-free chromatin particles are responsible for a specific type of programmed cell death, known as apoptosis.

day. The dead cells get broken down and in the process, small shards of genetic material called cell-free chromatin particles (cfChPs) are released in the blood circulation. CfChPs can enter healthy cells, damage their DNA, and lead to a specific type of cell death, called apoptosis, as well as tissue inflammation.

Mittra and his team suspect that the lifelong accumulation of cellular damage inflicted by cfChPs could be the primary cause of ageing,

R-Cu, which can be administered orally, potentially qualifies as a treatment for delaying cell death and ageing.

and that deactivating the circulating cfChPs could retard the changes associated with ageing.

Combining resveratrol and copper

Resveratrol is an antioxidant found in several fruits and plants. Because of its properties against oxidative stress, resveratrol has been studied for its health benefits in humans. Surprisingly, when combined with copper, resveratrol has been shown to act differently – by catalysing the reduction of Cu(II) to Cu(I) with the generation of reactive oxygen species (ROS). More significantly, the combination of resveratrol and copper (R-Cu) can deactivate cfChPs (using ROS as the medium).

ROS are short-lived and highly reactive chemical molecules that can damage life molecules, such as DNA and proteins, when active inside the cells. However, when produced outside the cells, for instance, by oral administration of R-Cu, ROS can have beneficial effects. Leveraging this property, Mittra and his team investigated whether the long-term administration of R-Cu could delay the appearance of the biological signs of ageing by deactivating extracellular cfChPs.

Experimental evidence – a successful combination

For their experiment, the team used 24 mice divided equally into 3 groups: the first group was sacrificed at 3 months (control youth group); the second group was allowed to grow older and at 10 months, was given R-Cu orally for 12 months (treatment group). The third group was also allowed to grow old but was given water instead of the medicine for 12 months (control ageing group).

Blood was collected from all animals at appropriate time points for testing. Animals of the second and third group were sacrificed at 22 months. Finally, tissues of their brains were harvested for examination. The team used a number of laboratory tests on the blood and brain samples. These included measuring the enzyme that neutralises ROS, superoxide dismutase (SOD), in both blood and brain cells and also the levels of cfChPs in the spaces between brain cells (extracellular space). The team also tested for DNA abnormalities, amyloid deposition, and metabolic changes.

The treatment group was found to have significantly higher levels of the enzyme SOD compared to the control ageing group, a finding that indicated SOD protected the DNA of the brain cells from damage by the invading ROS by neutralising them. However, there was a marked reduction in cfChPs present in the extracellular spaces of the brain cells brought about by ROS in the treated mice compared to controlled-ageing mice. The elimination of cfChPs from the extracellular spaces of the brain correlated with a reduction of telomere shortening, amyloid deposition, DNA damage, cell death, inflammation, aneuploidy, and mitochondrial dysfunction. The treated animals also had lower levels of blood sugar, blood cholesterol, and inflammatory markers when compared to the control ageing group.

Is healthy ageing possible?

The long treatment with R-Cu suppressed multiple aspects of cell ageing, and although the mechanism behind this is not entirely clear, the researchers think it is most likely that ROS generated by R-Cu neutralises the cfChPs and prevents cumulative DNA damage of the host cells. Therefore, R-Cu potentially qualifies as a treatment for delaying cell ageing and death. R-Cu is inexpensive, non-toxic, and can be administered orally. Mittra and team hope that this can make R-Cu a strong ally in fighting diseases of old age, such as Alzheimer's disease, eventually making healthy ageing a feasible target.

Mittra and team hope that R-Cu could potentially be a strong ally in fighting diseases of old age, such as Alzheimer's disease.

Personal response

What are your next plans in ageing-related research?

We are planning to study the potential of R-Cu in preventing Alzheimer's disease and other degenerative conditions of old age. We have tied-up with a nutraceutical company, which is going to produce R-Cu in a tablet formulation so that it can be easily administered to humans.

What would be your advice for aspiring researchers looking to follow your career path?

I would advise aspiring researchers to first understand what 'PhD' stands for. It stands for 'Doctor of Philosophy'. In Latin, a doctor means a 'teacher'. In other words, a PhD is supposed to teach philosophy. And what is that philosophy? My understanding of the philosophy of science is that 'no knowledge is permanent' or that 'all knowledge is provisional and potentially fallible'. Therefore, my advice to aspiring scientists would be that they should feel a sense of freedom to challenge anything.

Details



e: Indraneel.mittra@gmail.com

t: +91 9769769720

w: indraneelmittra.agarkarmedia.com

Funding

Department of Atomic Energy, Government of India, through its grant CTCTMC to Tata Memorial Centre awarded to Indraneel Mittra.

Bio

Dr Indraneel Mittra, MBBS, PhD (London), FRCS (England), FASc, FNA, is an Indian cancer surgeon, basic research scientist, and public health researcher. He is the Dr Ernest Borges Chair in Translational Research and Professor Emeritus in the Department of Surgical Oncology at the Tata Memorial Centre (TMC) in Mumbai, India.

Further reading

Raghuram, GV, Tripathy BK, Avadhani, K, et al, (2023) [Cell-free chromatin particles released from dying cells inflict mitochondrial damage and ROS production in living cells](#). *BioRxiv*, [online] 2021.12.30.474529. [Accessed 30/10/2023]

Pal, K, Raghuram, GV, Dsouza, J, et al, (2022) [A pro-oxidant combination of resveratrol and copper down regulates multiple biological hallmarks of ageing and neurodegeneration in mice](#). *Scientific Reports*, [online] 12(1), 17209. [Accessed 24/10/2023]

