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Anti ageing medicine-unearthing the fountain of youth

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Abstract
Humans have been in search of immortality and eternal youth since ages. Many ancient texts in different cultures have described sages living upto 500-1000 years in the past. Modern man is also trying his best to discover the fountain of youth and unlock the secret to immortal life. With the advancement of science and technology, man has achieved a lot of progress and achieved multiple milestones in this direction. This review will enlist the efforts by human race to discover anti ageing medicine.

Keywords: cord, blood, screening

Introduction
For ages, humans have been on a quest for agelessness or immortality. Agelessness can be defined as one whose physical and mental state appears young for his biological age. Gods and goddesses were considered eternal in many ancient mythologies. In Hindu mythology, Gods or suras became immortal by drinking 'Amrut'. In Greek mythology, immortality was obtained by the gods eating 'ambrosia' and in Chinese mythology, by the gods consuming the 'Peaches of Immortality'. Even ancient Rishis lived for more than 500 years as mentioned in ancient texts by using certain techniques like kriya yoga which are long forgotten.
Humans have always been on a constant search of methods to obtain agelessness or immortality. Many researchers have spent their life searching for answers for the same. This article reviews the demographic plus scientific research conducted till date about man's effort to slow, halt or reverse ageing.

The Blue Zones [1]
In 2004, Dan Beuttner and his team along with National Geographic and National Institute of Ageing determined five geographically distinct areas around the world with statistically significant number of centarians compared to the rest of the world. These five areas dubbed by them as the blue zones are Loma Linda, California, USA; Nicoya, Costa Rica; Sardinia, Italy; Ikaria, Greece and Okinawa, Japan.

Loma Linda, California
The Seventh day Adventist community living here observes Sabbath on every Saturday which is a means to let down or downshift stress. They eat a vegetarian diet mainly consisting of oatmeal, green leafy vegetables, nuts and legumes. Also they lead a very active lifestyle. Average life expectancy is a decade longer than an average American.

Nicoya, Costa Rica
The Nicoyan day starts with a breakfast of Gallo pinto (containing rice and beans) with a basket of homemade corn tortillas and hot coffee. This breakfast is rich in protein, complex carbohydrates and antioxidants. Nicoyans mostly eat fresh fruits and vegetables and eat less of meat. Also water here is rich in calcium and magnesium which helps in preventing heart disease and makes strong bones. Nicoyans believe in "plan de vida" or reason to live which gives them positive attitude.

Sardinia, Italy
Sardinia is home to world's longest living men. The Sardinian diet is mainly plant based consisting of whole-grain bread, beans, garden vegetables and fruits. Meat is mainly consumed on Sundays and on special occasions. Sardinians drink wine moderately especially Cannonau wine which has 2 or 3 times the flavonoids as other wines. This community mainly consists of shepherds who walk miles on mountains daily which gives them the beneficial cardiovascular effects.

Ikaria, Greece
The secret to Ikarian longevity is the Mediterranean diet, with lots of fruits and vegetables, whole grains, beans, potatoes, and olive oil. Ikarians also downshift with a midafternoon break nap. The Ikaria study [2] revealed that modifiable risk factors, such as physical activity, dietary habits, smoking cessation, and midday naps, might depict the secrets of the long livers.

Okinawa, Japan
The home to the world's longest living women, Okinawans follow principles of "Ikigai" or a sense of purpose for one's existence. They form "moai" which is a social support group which is formed in childhood and extends into their 100s. Across Okinawa, these friends meet sometimes daily and sometimes a couple days a week to gossip and to share advice and even financial assistance when required. Okinawans stop eating when 80% full, so they do not overeat and this is called "hara hachi bu" in local language.

Advances in Anti Ageing medicine
Role of Caloric restriction mimetics (CRM)
Calorie restriction is reduction of food intake without causing malnutrition [3] and is known to slow ageing process in many animal studies [4, 5]
Mechanism by which it is achieved is largely unknown but multiple mechanisms have been postulated like insulin/IGF signalling, TOR pathway, sirtuin, etc. As it is very difficult for many to achieve dietary restriction, many drugs have been

developed which mimic the effects of dietary restriction as follows:

Resveratrol

Resveratrol is a polyphenol isolated from red grapes. It activates sirtuin pathway. The ability of resveratrol to mimic the beneficial effects of calorie restriction on the lifespan of *Saccharomyces cerevisiae* was first noted by David Sinclair and co-workers [6]. Resveratrol was subsequently shown to extend longevity in worms, flies, fish, and obese mice [7, 8]. Further studies are required to verify whether resveratrol is a true CRM.

Rapamycin

Rapamycin is an Anti-Biotic, that is proposed as a CRM. It was seen that rapamycin extends the median and maximum lifespan of 20-month-old mice accompanied with a decrease in TOR activity [9]. However, it increases the incidence of diabetes mellitus.

Metformin

Metformin is a biguanide used for treatment of type-2 diabetes mellitus.

Moreover, metformin was shown to have a caloric restriction-related longevity benefit mediated by the activation of AMPK in *C. elegans* [10].

Role of Telomerase

Elizabeth H Blackburn, Carol W Greider and Jack W Szostak were acknowledged with 2009 Nobel Prize in Physiology or Medicine for their discoveries on how chromosomes are protected by telomeres and the enzyme telomerase. Telomeres are repetitive sequences of non-coding DNA located at the end of each chromosome that protect the chromosome from damage and prevent end to end fusion of chromosomes. With each cell division in a somatic cell, telomere attrition occurs till the time of critical attrition wherein telomeres can no longer protect the chromosomes leading to age related problems and cancers. Telomeric DNA with a repetitive G-rich sequence composed of 5′-TTAGGG-3′ can be synthesized de novo by a complex composed of a catalytic subunit known as telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC) that serves as a template [11]. Various studies are trying to insert genes which activate telomerase enzyme *in vivo* so as to slow ageing process.

Role of Gut microbiota

Gut microbiota is a dynamic community of bacteria, fungi, viruses, and microbial eukaryotes [12]. While lifespan refers to the number of years lived, healthspan considers the quality of life and length of life that is disease-free and functional [13]. When the community of various bacteria and other microbes are balanced, coexist peacefully, the microbiome is said to be in a state of eubiosis [14]. Aging is associated with alterations in composition and functional features of intestinal microbiota. They are caused by an age-related decline in immune system functioning (immunosenescence) and a low-grade chronic inflammation (inflammaging), which accompany many aging-associated pathologies [15]. Centenarians and supercentenarians have a higher abundance of microbes in their gut associated with health, including Akkermansia, Christensenellaceae, Bifidobacterium, and Lactobacillus spp., compared to young adults and/or the elderly [16].

Various interventions based on gut microbiota include:

Diet

The Nu-AGE study [17] found that in healthy older adults, plant-based diets are associated with increased alpha-diversity, increased relative abundance of the Bacteroidetes taxa, and increased anti-inflammatory microbials, including Faecalibacterium prausnitzii, Eubacterium rectale, and E. biforme; however, animal-based diets are associated with pro-inflammatory microbes such as Ruminococcus gnavus and Collinsella spp. In most blue zones, the common denominator include plant based diet with lot of dietary fibre. People in Okinawa, Japan, which is one of the blue zone, typically follow the “rainbow diet” i.e. they eat a variety of fruits and vegetables of different colours and spectrum so as to get al l the minerals, fibres and micronutrients in diet.

Probiotics

Probiotics are live microorganisms that in appropriate amounts can benefit host health. Probiotics commonly consist of Lactobacillus spp. or Bifidobacterium spp., which are both correlated strongly with prolonging healthy lifespan [18].

Fecal Microbiota Transplant (FMT)

FMT or stool transplant is the process of transferring fecal microbes from a healthy donor to another person. It is currently tried in Clostridium difficile infections. It is achieved through infusion of stool via colonoscopy, enema, orogastric tube or orally in the form of a capsule containing freeze dried feces from a healthy donor. Transplanting microbiota from long-Living humans into mice results in greater alpha diversity, increased Lactobacillus and Bifidobacterium, increased Roseburia, Faecalibacterium, Ruminococcus, Coprococcus, and decreased lipofuscin and βgalactosidase accumulation in the gut microbiome, all suggesting potential benefits to healthspan [19].

FMT is still in experimental stages and have not obtained approval in humans to prevent ageing due to ethical concerns.

Role of Hormone replacement

Hormone levels progressively diminish with ageing and is associated with decreased bone mineral density (BMD), sarcopenia, reduced sexual desire and reduced immunity. So hormone replacement is widely used as anti ageing medicine [20].

Estrogen and Progestins

Estrogens alone, or together with progesterone, have been used to prevent vertebral and non-vertebral fractures. However, a Women’s Health Initiative (WHI) study reported a higher risk for cardiovascular disease, thromboembolic event, stroke, and breast cancer with a combined treatment of estrogens and progestin [21]. Following the results of the WHI study, new guidelines recommended hormone supplements with lower dose for the shortest amount of time.

Testosterone

Testosterone replacement therapy is useful because it Increases muscle mass, strength, and BMD in elderly men [22]. Adverse effects of testosterone administration include polycythemia and risk of aggravating prostate cancer.

Role of stem cell therapy

As stem cells age, their renewal ability deteriorates, and their ability to differentiate into various cell types is depleted. The development of effective methods to induce and differentiate pluripotent stem cells via cell replacement therapy provides an exciting avenue for the treatment of degenerative age-related diseases [23].

Conclusion

Human quest for an immortal life is unending. With the advancement of technology, humans might be able to achieve this goal in future. However it is more important to remember not to lose our present in search of a better and immortal future. It is important to add life to years rather than to add years to life.

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