

Drug Design by Ayurveda Sages

Modern Discoveries Rationalize Ancient Intuitions

Life is constant struggle for survival. And as Charles Darwin stated in his book, 'The Origin of Species', the plants and animals (including human beings) have adapted and evolved through centuries of struggle. Human being is an assembly of highly evolved organ systems. Each system has a basic structural and functional unit- a gene. The genes control the existence of cells in a cycle of birth-growth-transformation-reproduction-deterioration and death. Thus the genome as a whole orchestrates the symphony of biological activity called life.

One such key gene in human body is 'p53', a protein which is very crucial in multicellular organisms where it regulates the cell cycle and functions as a tumor suppressant. p53 has been described as 'The Guardian of Genome' because of its role in conserving life stability by preventing genome mutation. The name is due to its molecular mass which is 53 kilodalton fractions of cell proteins.

In 1979, when I was a second year undergraduate student of Ayurveda, p53 was first identified by scientists like Arnold Levine, David Lane and William Old in UK. It had been hypothesized to exist before as the target of the SV40 virus, a strain that induced development of tumors. Although it was initially presumed to be an oncogene, its character as a tumor suppressor gene was revealed in 1989. At this year, I was in second year of my post-graduation. The journey of p53 is as evolving and fascinating as 35 years of my career in healthcare.

The Ayurveda sages with their intuitive knowledge and keen observations of nature designed several herbal combinations to restore health and treat many lifestyle disorders. Till recently, the rationale for these combinations were poorly understood or could possibly explain only through Ayurvedic principles. However, the recent discoveries amazingly elicit the rationale of choosing particular herbs for specific disorders. This possibly reveals the missing link of mechanism of action of herbs as deep as at genomic level. There is immense research available

on medicinal plants which have their beneficial effects on 'p53'. Many herbs in Ayurveda which are traditionally used to treat cancers and autoimmune disorders are surprisingly 'p53' activators.

In normal cells, the p53 protein level is low. DNA damage and other stress signals may trigger the increase of p53 proteins, which have three major functions: growth arrest, DNA repair and apoptosis (cell death). The growth arrest stops the progression of cell cycle, preventing replication of damaged DNA. During the growth arrest, p53 may activate the transcription of proteins involved in DNA repair. Apoptosis (programmed cell death) is the "last resort" to avoid proliferation of cells containing abnormal DNA.

Defective p53 could allow abnormal cells to proliferate, resulting in cancer. Around 50% of all human tumors contain p53 mutants. Loss of p53 activity also results in various autoimmune disorders such as systemic lupus erythematosus (SLE), psoriasis, rheumatoid arthritis and many others.

There is a vast amount of information available in the published scientific literature about the defective changes in p53. In sync, there are also several studies which confirm that exercise and caloric restriction activate the anti-cancer protein p53. Caloric restriction is also linked to the novel, lifespan regulating function of p53 which may be evolutionarily. Ayurveda describes caloric restriction (Mitahar) and exercise (Prishram) as Ashwinikumars (the twin deities who are Gods' physician and surgeon).

A study published in Journal of Investigative Dermatology (1998) reveals that Curcumin (active ingredient of Curcuma long- haldi) induces a p53-dependent apoptosis in human basal cell carcinoma cells. In another study on human breast cancer cells, curcumin induced apoptosis through p53.

A recent study has observed that, terpenoids from Ginger (Zingiber officinale) induce apoptosis by activating p53 and therefore acts a potent anti-cancer agent, especially in endometrial cancer. Another commonly available herb piper longum through its active chemical constituent piperlongumin inhibits cell proliferation through p53 pathway. Psoralen (chemical ingredient of

seeds of *Psoralea corylifolia*, widely known as Bakuchi) and ultraviolet-A (UVA) radiation is established treatment of psoriasis and other skin diseases. PUVA is highly effective in eliminating hyperproliferative cells in the epidermis, but its mechanism of action has not been fully elucidated. In a recent study by AB Santamaria, DW Davis, it was concluded that PUVA induces apoptosis through p53. A number of studies show that resveratrol (an important plant chemical in Draksha- *Vitis vinifera*) induces cell death in different types of cancers, both in humans and animal models. Dr Jerson L. Silva at the Universidade Federal do Rio de Janeiro, Brazil, tested the effects of resveratrol in a human non-small lung carcinoma cell line carrying only a partial fragment of the p53 gene and found that resveratrol treatment restores the defects in p53 to continue its normal functioning of tumour suppression. Draksha- *Vitis vinifera* is one of the important ingredients of Charak Pharma's antioxidant formulation 'Richelth'.