ACCORDING to the Alzheimer’s Disease International, a new case is registered every 3.2 seconds. Accordingly, 9.9 million people add to the global list of people with Alzheimer’s Disease (AD) every year.

The statistics also indicate that the actual numbers may be much higher, as the studies show that, the number of cases is higher in the developing nations where there are economic challenges and lack of awareness, as compared to the developed nations. More than 58% of the registered cases now live in low- and middle-income countries, and by 2050 this is expected to rise to 68%. One report estimates that 90% of the cases go undiagnosed in India. The mortality rate of AD is increasing alarmingly and is now the second leading cause of death in the world.

With the availability of improved health care, life expectancy has increased and so has the risk of AD, which afflicts the geriatric population. Presently, there are more than 50 million people with AD; the figures are expected to double every 20 years. The fastest growth in the elderly population is in China, India and other south Asian countries.

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What is Alzheimer’s Disease?
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As the cells die, the functions that come under the working of the region begin to deteriorate. This gradual loss of cognitive ability leads to memory loss; inability to recognise faces or recall names; slurred speech, mobility and vision; behaviours of acute apprehension, aggression and agitation are marked symptoms of the progression of the disease.

There is impairment of executive functions such as rationality, organising, planning and sequencing tasks. In the later stages, patients may lose the ability to walk, perform simple tasks and exhibit incontinence, forcing many to be bedridden and depend heavily on caregivers. Studies also indicate that women are more prone to this condition than men.

Brain Basics
The average human brain is a complex cluster of nearly 100 billion neurons. These cells branch out to form an intricate network. Our memories and thoughts transfer through the neurons in the form of tiny electrical pulses. Since the nerve cells are not physically interconnected with each other, they form non-contact junctions called synapses.
Our brain is equipped with a trillion such synapses. At these synapses, information is transferred from one cell to the other by way of chemicals called neurotransmitters. At the junctions, a burst of neurotransmitters diffuses into the receptor neurons to pass on the message. It is in this manner that several neural patterns are formed in our brain, which define our thoughts, memories, actions, and habits.

Neurotransmitters are made up of amino acids — the building blocks of proteins. Amyloid is a general term used for common protein fragments that are produced during nerve functioning. Beta-amyloid is a protein snippet that breaks away from the Amyloid Precursor Protein.

In a healthy brain, these fragments are broken down by enzymes and get flushed out of the body by the Blood-Brain Barrier (BBB) — a protection shield for the brain which filters out toxins and pathogens. The BBB is a tight packing of endothelial tissues that act as a doorway to allow only those molecules that are needed by the surrounding brain tissue, such as fats, proteins or glucose.

### Plaques and Tangles

The hallmark of AD is the formation of Amyloid Plaques. Beta-amyloid fragments are sticky in nature and tend to clump together to form plaques. Such plaques do not get flushed out effectively, seriously interfering with synaptic transmissions.

Another form of a neural protein called Tau resides inside the nerve cells which forms fibres called Neurofibrillary tangles that construct microtubules to transfer nutrients within the cells. In AD, an anomaly of the protein Tau fails to build the necessary microtubule structure, hampering the health of the neuron. The tangles harden within a neuron disrupting the normal function of the cell.

As plaques and tangles begin to accumulate, it leads to pathological conditions like oxidative stress and neuroinflammation which leads to the death of the brain cells. The AD brain starts to degrade gradually. As the cells die, the corresponding functions wither away. There is a marked shrinking of the brain.

Few medications such as donepezil, rivastigmine, galantamine and memantine that are available provide temporary relief from the associated symptoms and are not capable of arresting the progression. Moreover, they come with substantial side effects. The condition of AD can currently be only managed.

### Risk Factors

- **Age:** Once we hit 65 years of age, the risk of developing AD doubles every five years.
- **Genetics:** Research indicates that genes can play a role in getting AD. A first-degree relative diagnosed with AD increases the chance of the other members getting affected. Science is yet to understand why AD runs in families, but genes, lifestyle and environmental factors are found to play a role. The risk gene is identified as APOE-e4.
- **Cardiovascular diseases:** Studies indicate that with a history of cardiovascular disease, one is more susceptible to develop AD. The primary reason being, the heart is responsible for pumping the much-needed oxygen and nutrients to the brain. Any anomaly related to the heart puts the brain in jeopardy as well.
- **Traumatic brain injury:** Research indicates that a blow on the head or a brain injury involving loss of consciousness for more than 30 minutes increases the development of AD manifold.
- **Formal education and AD:** Studies have linked fewer years of formal education as a risk factor to develop AD. Although not very clear, some scientists believe that fewer years of learning relates to a lesser number of neural routes and in turn lesser use of the brain, making certain areas inactive. The inactivity leads to an impairment of alternative paths to develop for neuron-to-neuron communication.

## Now There is Hope!

Pathbreaking research by Indian scientists has now opened new vistas to offer remedial measures for AD. Indian scientists at the Indian Institute of Integrative Medicine, IIIM, Srinagar — a CSIR undertaking — have discovered a therapeutic remedy to combat AD.

“Five years ago, we started an initiative at IIIM to tap into the vast knowledgebase and resources of Indian medicinal herbs to tackle the growing concern of AD and dementia,” said Dr. Ram Vishwakarma, Director of IIIM. “Relentless research by our team zeroed-in on saffron — which is cultivated abundantly in the valley of Kashmir — as a potent candidate for improving and protecting cognitive health,” he explained.

Yazan S. Batarseh and Amal Kaddoumi, University of Louisiana, Munroe and the Indian team comprising Drs Sonali S. Bharate, Vikas Kumar, Ajay Kumar, Ram Vishwakarma and Sandip B. Bharate from IIIM, Jammu, collaborated to investigate the methods by which *Crocus sativus* (saffron) worked against AD. Saffron was found to be highly effective in arresting AD, and clinical tests showed that it worked as a therapeutic remedy for Alzheimer’s. Their research was published in the journal *ACS Chemical Neuroscience, 2017.*
Further, the scientists conducted the preclinical development of the saffron extract — IIIM 141 — to integrate it into modern medicine in the form of a slow releasing nutraceutical formula. The team tested the product on various cellular and animal models before confirming the action of the compounds. A patent is pending for their product, while the study is published in the journal *ACS Omega, 2018*.

“Saffron has unique compounds which act as inhibitors on beta-amyloid plaques,” explained Dr. Sandip Bharate, Senior Scientist, Integrative Medicine, IIIM. “The compound labelled IIIM-141 is extracted from the stigma of saffron flowers; after systematic study, we found the compound had a protective and therapeutic effect on AD,” he elaborates.

**The Saviour Duo**

The research established that two compounds ‘crocin’ and ‘crocetin’ play key roles as inhibitors of beta-amyloid plaques. Crocin is a hydrophilic carotenoid glycoside, a compound which is a bioactive metabolite. Metabolites are natural reaction intermediaries and products of physiological metabolism which trigger essential activities in the human body such as signalling, stimulation and inhibitory functions.

When crocin is hydrolysed in the stomach, it transforms to an aglycone, Crocetin, a fat-soluble compound. Aglycone is the compound remaining after the glycosyl group on a glycoside is replaced by a hydrogen atom — Crocetin.

Dr. Bharate gives an insight into the way the pair of chemicals acts on the plaques: “Upon oral administration, crocin the major constituent of Saffron extract gets slowly released from the capsules over a long period. Crocin hydrolyses inside the gastrointestinal tract to its lipophilic aglycone crocetin. This lipophilic crocetin gets easily permeated across the cell membrane and reaches the blood circulation. The controlled release of crocin from the formulation creates a favourable scenario for its bioactivation to its metabolite crocetin, and thus it produces a higher ratio of crocetin/crocin in the blood circulation. Because of its lipophilic nature, crocetin rapidly crosses the blood-brain barrier (BBB) and reaches the brain to exert its biological effect on it. The aglycone, crocetin, is the bioactive metabolite responsible for all therapeutic benefits of saffron.”

The team developed an extract containing IIIM-141 and formulated it into a slow-releasing capsule which is easily ingested. The product and the formulation technology has been licensed to M/s Pharmanza Herbals Pvt Ltd, Gujarat, which will market it as a dietary supplement initially, in the US and Indian markets, once the necessary approvals come from the FSSAI and USFDA.

This formula is beneficial to the high-risk and early onset groups. The suggested dosage will act both as a preventive and curative remedy. “We are also taking the work forward and working with the medical fraternity to develop a new therapeutic drug based on the saffron extract,” concludes Dr. Vishwakarma.

**Young Onset AD**

- Although AD is commonly associated with the elderly, it can affect younger people too.
- About 5% develop the symptoms before the age of 65; those affected by AD who belong to the age group of 45-65 are said to have Young-onset dementia or Work-age dementia.
- The causes that affect the elderly are all seen in the young-onset too.
- The symptoms include withdrawal from work and social activities, problems in keeping schedules, finishing tasks at home or work, severe memory lapses and excessive anxiety.

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