

## neurodegeneration disorders need holistic care and treatment – can ayurveda meet the challenge?

With better hygienic conditions and increasing life expectancy, neurodegenerative disorders caused by genetic and/or environmental factors are becoming more prevalent, especially because many of them have a late onset. The changing lifestyle is further aggravating the societal burden of neurological disorders. This has stimulated a great deal of research in recent decades not only to understand the molecular and cellular factors underlying the variety of neurodegenerative disorders but also to find appropriate therapies. The remarkably focused and powerful tools of current biology in conjunction with equally powerful technology are being widely used for these purposes. A variety of experimental models, including yeast, *Caenorhabditis*, *Drosophila*, Zebra fish, mouse, cells in culture etc, have been created to facilitate in-depth understanding of such disorders and to find genetic and environmental factors that suppress or enhance the disorder so that appropriate therapy may be developed. Such multi-pronged approaches have indeed greatly advanced our understanding of these disorders and for several of which drugs with varying degrees of effectiveness have been formulated.

Most of the molecular studies on different neurodegenerative disorders, as also for other diseases/disorders, have been driven by the reductionist approach which identifies one causative factor and seeks to neutralize the pathological effects of the same through a well-defined therapeutic approach. However, with improving information base about the maintenance of homeostasis at cell and at higher levels of body organization, it is becoming clear that even an apparently innocuous malfunction of a small molecule in the cell may have a much wider cascading effect. Although, the so-called “systems biology” is providing increasingly detailed maps of diverse and complicated networks that help maintain homeostasis at cell and organism levels, the network effects are often not taken into serious consideration while searching for remediation. The reductionist approach in biology is analogous to the old fable of several blind people describing an elephant. We need to appreciate that even if a given inherited neurological

disorder, e.g., Huntington’s or the variety of SCAs, can be traced primarily to a defined mutation in a single gene, it is not easy to fathom the depth or extent of consequent pathological outcomes. This is obvious from the fact that a large number of genes affecting very diverse pathways/products have already been identified as suppressors or enhancers of a given neurodegenerative disorder and this list continues to grow. Such interactions, which are indeed real life situations, obviously vitiate the expected therapeutic effects of targeted single molecule specific drug. At the same time, the therapeutic agent itself may have varying degrees of “side-effects” because of direct or indirect interactions with other metabolites. Additional complications originate from expression of the mutant product in non-neural tissues, the consequences of which are often ignored. For example, it is commonly believed that only certain specific neurons suffer from the pathological damage due to expanded polyQ proteins, notwithstanding their wider expression. This is a rather simplistic and poorly substantiated view since the consequences in other tissues have not been examined in depth. Even if no apparent effect is detectable, the subtle effects may actually add to the pathological burden. The point is that any small change in cellular milieu would have transient or longer-lasting wide-ranging consequences for the cellular networks that maintain homeostasis. If these changes go beyond the threshold, condition becomes pathological. Under conditions of disturbed homeostasis, effect of even a mild stress/malfunction can, and often does, get magnified. Unfortunately, most of the drug-discovery programmes fall short of the expected long-term success because of the limited understanding and, more unfortunately, a poor appreciation of the complexly inter-dependent maze of networks that maintains the healthy state of any cell and body.

The neurological/neurodegenerative disorders are obviously much more complex entities because of the so far unfathomable complexities of neural circuits and our very limited understanding of the organization and functioning of the brain and other components of nervous system.

We need a holistic approach to prevent and treat the wide-ranging pathological consequences of neurological/neurodegenerative disorders resulting from genetic and/or environmental factors. Can Ayurveda fulfill this requirement? Several recent studies, including those presented at the recently held XXX Annual meeting of the Indian Academy of Neurosciences, suggest that Ayurveda may indeed provide a good holistic care and treatment provided we understand the rationale behind the different Ayurvedic formulations and their usages.

Ayurveda, the ancient holistic way of maintaining a healthy and happy human life, had a lean phase during the last millennium but in recent decades there has been resurgence in its popularity. Ayurveda has indeed become fashionable as reflected in its commercial exploitation in the form of health tourism and its name being used in a variety of popular consumer products including health foods, tonics and cosmetics. However, in spite of the apparent popularity, it is often also considered to be based more on “faith” than on actual scientific evidence. The absence of modern scientific understanding of Ayurvedic principles, combined with some unhealthy commercial practices have seriously affected its reputation and acceptability.

Practitioners of Ayurveda have, in general, remained blind followers of ancient texts without making serious efforts to understand the bases of classical texts in the light of modern biological, chemical, physical and material sciences. On the other hand, most of the “scientific” studies on Ayurvedic formulations have followed a reductionist approach to identify the “active principle”, ignoring the fact that the holistic philosophy underlying Ayurveda is not in consonance with the search for “active principle”. The general lack of dialogue between the practitioners of Ayurveda and the scientific community continues to be a serious limiting factor in gaining a rational understanding of Ayurvedic principles.

In order to revive the true spirit of Ayurveda and to realize its advantages, there is an urgent need for in depth analysis and understanding of the ancient texts

combined with scientific studies to appreciate the significance and biological bases of the various formulations and practices. These studies not only require a good understanding of Sanskrit, but also of plant sciences, besides human-physiology, molecular biology, chemistry, physics and material sciences. It is obvious that such multi-dimensional approach cannot be handled by individuals. Inter-disciplinary research, involving various disciplines of sciences and experts beyond the mainstream science, is essential. The actual practitioners of Ayurveda also must appreciate the need for application of rigors of modern science, rather than remain confined to what is being passed on as "ancient wisdom".

The bases of various "Dosaprakriti" (Innate disposition) need to be understood in terms of modern physiology, immunology and genomics. Likewise, we need to unequivocally identify the various herbs and their parts used in Ayurvedic formulations and to understand how do the various "Rasayanas" and "Bhasmas" etc work on biological systems. The significance of the elaborate procedures employed in preparations of these formulations need to be understood in chemical and material science perspectives. Understanding of "Pancakarma" requires application of rigorous physiological and immunological approaches.

The biological origins of most Ayurvedic formulations are significant in the context of elaborate complex networks within and between cells of a body that

determine a "healthy" state of body and mind. Unlike the chemically synthesized target-specific drugs, the complex molecular constitution of herbal drugs may be expected to act in a balanced way on the body's systems biology. Many of the orally administered Ayurvedic formulations contain, besides the main drug, one or more vehicle material/s like honey, sugar, jaggery, ghee, milk, warm water, juice of some medicinal herbs etc. as "Anupana", which not only improves acceptability and palatability but also helps in absorption of the main drug; additionally, it may also act as early antidote. The Ayurvedic formulations require very precise and elaborate processing; the importance of seasonal and geographic variations on efficacy of herbal preparations is also described.

The Ayurvedic practices and formulations appear promising for a better health of masses in view of the long history of their usages and the available data from the recent, although limited, controlled experimental studies. In keeping with the common saying "prevention is better than cure", Ayurvedic formulations are believed to be more preventative than curative. The urgent need for detailed in-depth and multi-pronged studies of the ancient texts for understanding them in the context of current scientific language cannot be over-emphasized. At the same time, extensive experimental studies on biological effects of the different formulations in different model systems (normal as well as disease models) are needed. Since the processing and specific multiple

components are stated to be important for the effectiveness of these formulations, attempts to identify the so-called "active principle" would not be appropriate. Instead, studies should be directed to understanding effects of the prescribed processing steps and the seasonal/geographic variations in the source materials on their therapeutic effectiveness. Such studies would obviously require cell biological, biochemical, genomic, RNomic, proteomic and metabolomic approaches. From the point of view of neurosciences, it will be interesting to examine if the prescribed anti-ageing and neuroprotective formulations promote neurogenesis and affect stem-cell maintenance and differentiation. While undertaking such experimental studies, it is of course necessary for the involved investigators not to be carried away and make unsubstantiated claims, which actually have a negative impact. In order to separate myth from facts, we need well designed and objective experimental studies based on appropriate understanding of the mode of preparation and the suggested usages of the traditional formulations. Such approaches would help us understand the science of Ayurveda and then only the Ayurvedic therapy can be applied rationally.

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