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Health Care Innovations
More value, better outcomes, for less

Medical technology has come a long way since the invention of eyeglasses and the stethoscope. The broader availability of mobile internet, the expansion of a more affluent middle class, and an aging global population are all driving change in the healthcare industry, and the associated technology is changing faster than ever before. According to a profile of the healthcare industry by the World Economic Forum, more than a billion people will need re-skilling in medical technology by 2030.

Technology and medicine have gone hand and hand for many years. Consistent advances in pharmaceuticals and the medical field have saved millions of lives and improved many others. As the years pass by and new technology in healthcare continues to improve, there is no telling what medical advances will come next. Also, many of the most interesting new technologies in medicine need to be used together, and integrated attempts to do so already exist. Some tech-inspired institutions, take a concierge-like approach to primary care, putting technology to use in a way that providers get more quality time with their patients. But that is just the beginning.

In 2020 and 2021, the Covid-19 pandemic forced healthcare into the future, and, as a result, several promising medical technologies were tested on a massive scale. In 2022, the question is how those technologies can be used together in a post-pandemic world.

Health Care Innovation is regarded as any combination of activities or technologies that break existing performance tradeoffs in the attainment of an outcome, in a manner that expands the realm of the possible. Defined in health care as providing more for less more value, better outcomes, greater convenience, access and simplicity; all for less cost, complexity, and time required by the patient and the provider, in a way that expands what is currently possible.

Our current health care system s performance can be defined by its rules, policies, regulations, enabling technologies, operating models, customs, and patient and provider preferences; together, these elements comprise the frontier of what is possible. They also serve as the constraints to what can be achieved. For far too long the health care industry s performance, despite attempts to spur progress, has remained at the edge of the frontier. The industry needs to break current constraints and expand the frontier to achieve true breakthrough performance.

Top 10 New Medical Technologies

1. Next Generation of mRNA TECHNOLOGY

   mRNA technology has been put under the spotlight recently as the new vaccines for Covid-19 use this science. With their high effectiveness, capacity for rapid development, and potential for low production costs, mRNA vaccines offer an alternative to the traditional vaccine approach.

   mRNA, or messenger ribonucleic acid, is a single-stranded RNA molecule that carries the genetic information that is derived from DNA. mRNA vaccines work by providing a genetic code to cells to allow them to produce viral proteins, once the proteins have been created the body can then produce an immune response. The success of the Covid-19 mRNA vaccines has given a big boost to efforts to develop other mRNA vaccines for everything, from cancers to ika virus.

   mRNAs potential is thought to extend beyond just vaccines. mRNA can code for just about any protein, so the same basic technology might also allow us to develop all kinds of treatments by getting the body to produce a

drug-like response. Many protein-based drugs such as antibodies made outside the body have proved extremely effective but also extremely expensive. So, by using mRNA technology, development times and costs could be cut by setting the human body to work on manufacturing the proteins instead.

2. VIRTUAL REALITY (VR)

Virtual reality has been around for some time. However, it is now being increasingly used to treat and manage a wide range of psychological illnesses and conditions, from stress and anxiety to dementia and autism. But its capabilities are not just limited to mental health conditions; it is also being used for effective pain management by changing the patients thoughts and perceptions around pain.

VR has also greatly improved the training processes for medical professionals, as it allows you to be transported into the human body. It also helps when doctors are diagnosing, as the patient is able to virtually step into a panoramic view of their body, giving them a better understanding of their disease or condition.

There is still huge, uncovered potential for VR, but its focus areas for medical advancements include preventive healthcare, rehabilitation, assistive living, cancer therapy, and surgery.

3. NEUROTECHNOLOGY

Neurotechnology holds boundless potential to improve many aspects of life. It is already being practically applied in the medical and wellness industries, but also has many future implications for other contexts including education, workplace management, national security, and even sports.

Neurotechnology encompasses all components that are developed to understand the brain, visualise its processes and even control, repair or improve its functions. These components can be computers, electrodes, or any other devices that can be set up to intercept electric pulses that run through the body.

In healthcare, neurotechnology is currently being used in brain imaging, by recording magnetic fields produced by electrical activity within the brain, neurostimulation, stimulating the brain and nervous system to influence brain activity; and in neurodevices, an emerging technology that monitors or regulates brain activity using an implant. Neurodevices are still mostly in the research phase, but it holds major potential for treating brain disorders. An example of this is *Neuralink*. Pioneered by Elon Musk, *Neuralink* is developing a device that would be embedded into the human brain, where it would record brain activity and transmit this data wirelessly to a computer. Researchers would then be able to analyse these findings and use them to electrically stimulate brain activity. If successful, it can possibly be used to cure brain diseases like Alzheimer s and Parkinson s. *Neuralink* has been tested on animals so far, but Elon Musk has said the company hopes to start implanting its chips in humans this year.

Neurotechnology, while therapeutically very exciting, remains very controversial. It raises questions around rights to data and privacy. All-in-all, its future applications are not entirely mapped out but with the continued rise and identification of neurological disorders and conditions, neurotechnology is expected to experience considerable growth in the worldwide healthcare market in the coming years.

4. ARTIFICIAL INTELLIGENCE (AI)

Artificial intelligence (AI) is one of the most exciting technologies changing the healthcare landscape. AI takes on many different forms in healthcare. The primary trend for AI in healthcare will be in utilizing machine learning to evaluate large amounts of patient data and other information. By creating tailored algorithms, programmers can mimic human thought and write programs that can seemingly think, learn, make decisions, and take action.

AI is proving to be very valuable when it comes to detecting diseases early and for confirming an accurate

diagnosis quicker. For example, in breast cancer care, the use of AI is enabling the review of mammograms to be 30 times faster with 99 accuracy, reducing the need for unnecessary biopsies. AI is also being applied to oversee early-stage heart disease, allowing healthcare providers to discover potentially life-threatening problems at earlier and at more treatable stages. In addition, AI is also helping clinicians to create more comprehensive treatment programmes, allowing patients to manage their conditions more effectively.

Drug research and discovery is one of the more recent applications for AI in life sciences. AI is able to streamline the drug discovery processes, by creating more efficient ways to discover and repurpose medicines, significantly cutting down the time it takes to market a new drug and reducing their associated costs.

5. 3D PRINTING

3D printers have quickly become one of the hottest technologies on the market. In healthcare, these game-changing printers can be used to create implants and even joints to be used during surgery. 3D-printed prosthetics are increasingly popular as they are entirely bespoke, with the digital functionalities enabling them to match an individual s measurements down to the millimeter. This allows for unprecedently levels of comfort and mobility.

Using 3D printing for pre-surgical planning is also gaining momentum. Using a realistic replica of an actual patient s anatomy is allowing surgeons to attempt procedures they wouldn t have previously been able to do. The ability to plan a complex surgery and train prior to the procedure itself by using 3D-printed models has the potential to not only increase success rates but also to reduce time in the operating room and recovery time.

The use of printers can create both long-lasting and soluble items. For example, 3D printing can be used to print pills that contain multiple drugs, which will help patients with the organisation, timing, and monitoring of multiple medications. To take 3D printing up another notch, bio-printing is also an emerging medical technology. While it was initially ground-breaking to be able to regenerate skin cells for skin draughts for burn victims, this has slowly given way to even more exciting possibilities. Scientists have been able to create blood vessels, synthetic ovaries and even a pancreas. These artificial organs then grow within the patient s body to replace the original faulty one. The ability to supply artificial organs that are not rejected by the body s immune system could be revolutionary, saving millions of patients that depend on lifesaving transplants every year.

6. PRECISION MEDICINE

As medical technology advances it is becoming more and more personalised to individual patients. Precision Medicine considers the individual variability in genetics, environment, and lifestyle for each patient. For example, when using Precision Medicine to treat a patient with cancer, the medicine can be tailored to them based on their unique genetic make-up. This personalised medicine is far more effective than other types of treatment as it attacks tumors based on the patient s genetics, causing gene mutations and making it more easily destroyed by the cancer medication.

Precision Medicine presents great opportunities in transforming the future of healthcare. While it is currently most advanced in oncology, Precision Medication also has wider, exciting applications, such as in rare and genetic diseases, it also holds some promise in treating infections. However, integrating Precision Medicine into healthcare is set to be a challenging process with issues within infrastructure, inequalities, and knowledge that the industry must overcome before this becomes mainstream.

7. CRISPR

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is the most advanced gene-editing technology yet. It works by harnessing the natural mechanisms of the immune systems of bacterium cells of

invading viruses, which is then able to cut out infected DNA strands. This cutting of DNA is what has the power to potentially transform the way we treat disease. By modifying genes, some of the biggest threats to our health, like cancer and HIV, could potentially be overcome in a matter of years.

CRISPR is also looking promising for treating rare diseases. Cystic Fibrosis (CF) is a genetically inherited rare disorder that affects the functioning of the respiratory and digestive systems. The CF gene causes mutations to alter salt regulation across cell membranes, which results in thickening of mucus that causes problems in lungs, pancreas, and other organs. There are multiple cystic fibrosis-causing mutations, and there are currently several on-going clinical trials to see if CRISPR can be used to correct these mutations. CRISPR is also being seen as a possible way of treating sickle cell disease, which is also caused by a genetic mutation. Until recently, bone marrow transplant was the only real treatment for patients, but CRISPR gene therapy has given patients a new hope.

CRISPR has many potential applications, including correcting genetic defects, treating and preventing the spread of diseases, and improving the growth and resilience of crops. However, despite its promise, the technology also raises ethical concerns, mostly over humanity s right to play God and worries over gene-editing being used to produce designer babies.

8. TELEMEDICINE

Telehealth and telemedicine have become increasingly in demand since the Covid-19 pandemic began in 2020. Telemedicine refers specifically to remote clinical services, while telehealth encompasses remote non-clinical services. With more people adopting a new way of working and living since the pandemic, this is a trend which is likely to continue gaining momentum.

Telemedicine offers a range of benefits for both patients and healthcare providers. It offers great comfort and convenience for patients and can also be cheaper as patients do not need to encounter any secondary costs such as travel expenses or childcare. It can also improve access for other populations, including elderly adults; people who are geographically isolated, and those who are not able to leave their homes. For healthcare providers, telemedicine is also favourable as it reduces overhead expenses, lessens the exposure to illness and infections and allows practitioners to see more people as they can work more flexibly.

The last two years have seen telehealth and telemedicine become more mainstream and hopefully in 2022, technology for virtual-care appointments will continue to advance beyond 1:1 doctor-patient video conferencing. For example, in response to the rising number of patients in need of behavioural therapy for mental health illnesses, we can expect to see technology that will facilitate group sessions, allowing multiple patients to be supported together.

9. HEALTH WEARABLES

The demand for wearable devices has grown since their introduction in the past few years, since the release of Bluetooth in 2000. People today use wearables synced with their phone to track everything from their steps, physical fitness and heartbeat, to their sleeping patterns. With an aging population in much of the developed world, wearables can be effective at prevention of chronic conditions, such as diabetes and cardiovascular disease, by helping patients to monitor and improve their fitness.

Smartwatches remain one of the most popular wearable devices in the healthcare industry, with all the major tech firms such as Apple, Google, and Samsung all taking a share in the market. Depending on the model, they have the capabilities to record sleep patterns, blood pressure, oxygen saturation and electrocardiograms. Manufacturers are currently working on integrating sensors for blood glucose measurement into their smartwatches, which would make it easier for those living with diabetes. As well as smartwatches, smart clothes, smart rings and hearables, are also becoming increasingly popular and are proving to be increasingly

useful in collecting data for clinical research.

Technological advancements don t stop with devices worn on the body, insideables and implantables are also in the process of being developed. So far, these microcomputers, that work from inside the body, have been used to help organs such as the heart and brain function. Insideables, also referred to as smart pills, are considered by many to be the next phase after external wearables. These are swallowed in the form of a hard capsule and send measured values, such as glucose levels, or images from inside the body to aid diagnosis processes. Since implantables and insideables are only just emerging, they are expected to transform healthcare in the years ahead.

10. TECHNOLOGY IN MENTAL HEALTH

It is estimated, that by 2030, depression will be the leading cause of disease burden globally, making the need for new therapies more crucial than ever. Over the last year, many new technologies have emerged that can help address patients ongoing mental health needs.

Increasingly some apps are able to complete patient intakes and provide an initial diagnosis before a patient ever meets with a provider and AI powered tools are transforming the way mental health treatments are delivered. AI chatbots, like *Woebot,* that can help patients practice their cognitive behavioural therapy (CBT) strategies to smartphone apps, and voice recognition software *Ellipsis*, can analyse a patient s voice and speech patterns for warning signs of emotional distress. In addition to this digital symptom tracking is proving crucial for optimising efficient mental health care for the future. Online symptom tracking prompts patients to share data daily. An AI algorithm then analyses that data to identify patterns and alert providers in real time of any warning signs.

Another technology newly being utilized for mental health is the use of video games. Approved in 2020, *EndeavorRx* is the first and only FDA-cleared video game treatment. The game is used to help improve the attention span of children aged 8-12 years old with ADHD and requires a prescription. In clinical studies, 73 of participants reported an increased ability to pay attention. After this success, video games are set to become a more popular, affordable and accessible treatment for a range of health conditions.

Incorporating these top 10 innovations into business models will require changing how health care organizations currently prevent, diagnose, monitor, and treat disease. Leaders should determine which innovations break performance trade-offs, or create more for less, in a way that impacts their core business. They should consider building ecosystems that embrace non-traditional players and sources of knowledge outside their own four walls. They should also consider building pilots before investing in scale, learn to embrace change, and evaluate new revenue sources. And, organizations should strive to be agile in anticipating and adjusting their strategies as innovations continue to evolve.

R. Bangar

(Ravindra Bangar)
Editor

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Original Concept

New Era of Integrated Biomedical Engineering and Medicine: STEM Model of Medicine (STEM^2) Part 2. Gateway to new format of Medical Colleges

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ABSTRACT

We are now in an era of integrated Biomedical Engineering and Medicine. This paper is about the new format of Medical Colleges (or Medical Schools) in which all subjects from anatomy and physiology to medicine and surgery would be structured by STEM. Together, this formatting of subjects can transform medicine into a STEM format of Medicine or STEM^2, which can be incorporated into both education and healthcare delivery.

KEYWORDS: STEM format of Medicine, Anatomical Engineering, Physiological Engineering, Medical Engineering, Surgical Engineering

Section I. New Era of Medicine and Medical Colleges

We are now entering a new era of Medicine and Medical Colleges, as the most significant developments are taking place at the interface of medicine with biomedical engineering, towards the development of life-changing scientific and technological formulation of medical and surgical procedures. So, in this paper we have formatted a novel STEM Model of Medicine, involving biomedical engineering formulations of anatomy and physiology, medicine, and surgery.

In all fields of science and engineering, Colleges offer bachelor s degree as well as higher master s and PhD degrees. In the same way, new era Medial Colleges will offer the basic medical MBBS (or MD degree in US) as well as MD-PhD (Biomedical Engineering) and MD-PhD (Medical & Surgical Engineering) degree programs

For the MD-PhD (Biomedical Engineering) Program, we have outlined computational courses in (i) uantitative Physiology, (ii) Organ Systems Medical Engineering, (iii) Orthopedic and Spinal Surgical Engineering, (iv) Mind-Body Psychosomatic Medicine, (v) Sports Biomechanics and Medicine, (vi) Surgical Engineering, preoperatively designed to be patient-specific.

Next, we have structured a novel MD-PhD (Medical & Surgical Engineering) Program to be offered in the Medical College, involving computational courses in (i) Physiological Engineering, towards quantifying physiological systems and processes, (ii) Medical Engineering, towards precision medicine, and (iii) Surgical Engineering, towards patient-customized surgery for obtaining optimal outcomes. This would be the first such medical program worldwide.

Both these dual degree Programs can educate a new batch of scientific and technological medical doctors, who are learned in biomedical engineering formulations of physiological systems, medical diagnostics, and surgical procedures, and are hence also able to implement them in clinical care.

Section II. Dual Degree MD-PhD Programs

In Section II, we have outlined the steps involved in offering Dual-degree Education Programs.

In (i) MD-PhD (Biomedical Engineering), and in (ii) MD-PhD (Medical & Surgical Engineering). These steps involve completing (i) Master s degree in Biomedical Engineering, and (ii) the basic Medical MBBS degree (or MD degree in US). Then for the Dual degree programs, in the first two years, the students can take the above mentioned advanced prescribed courses. Thereafter, the students can work on their PhD thesis.

Section III. Conclusion

In this way, this paper is setting the stage for a new era of integrated medicine, based on the STEM format of Medicine (or $STEM^2$), resulting in the formulation of new types of computationally based disciplines of Anatomical Engineering, Physiological Engineering, Medical Engineering, and Surgical Engineering. We have elaborately described these disciplines.

While this article is breaking new grounds in terms of new academic programs and disciplines, we have also provided many related References of my journal papers and elaborate book chapters, to substantiate and provide examples of the new academic programs and academic disciplines outlined in this paper. This will enable offering of courses for MD-PhD (Biomedical Engineering) and MD-PhD (Medical & Surgical Engineering) programs.

§New era Medical College: STEM model of Medicine

Now we are entering a new era of Medicine, with the most significant developments taking place at the interface of medicine with biomedical engineering, towards the development of life- changing, technological medical procedures and patient-specific surgical procedures. We have developed the guidelines to develop new era medical college, offering STEM based medical education (MD-PhD) programs, contributing to precision medicine and surgery, and hence to enhanced quality of healthcare delivery. Medicine constitutes the science and engineering of the human body . So, in today s era of advanced science and technology, let us also apply it to our human body, to (i) make precision medical diagnostic systems and appliances, and (ii) design accurate patient-specific surgical procedures and prostheses.

Section I. Background and Raison D'être for a new approach to Medicine, as the most complex of all professional disciplines:

We have been applying advanced Structural Engineering methods to design and construct complex structures that we see around us. Now, Architecture has advanced to architectural design of cities and townships. The Human Body is much more complex than these structures. Besides, it is an active structure that is continually maintained in physiological homeostasis and restructured at the cellular level by molecular biological processes. In fact, the human body is the most complex mini-city architecturally, having the most complicated infrastructure needed to maintain millions of cellular entities living within it.

Hence it is necessary to employ even more advanced methods to (i) analyze and diagnose what is physiologically happening inside the body, (ii) provide preventive care to maintain homeostasis, by mind-body medicine methods, (iii) repair physiological dysfunction, by medications, (iv) repair organ systems dysfunction and failed orthopedic structures, by customized surgery, and (v) build customized prostheses and organ replacements, by 3d printing.

This then calls for a new format of Medical College to educate scientific and technologically competent doctors, to develop and practice precision medicine and surgery. In this modern medical school, we can have new education programs and courses, incorporating STEM formulated biomedical sciences, medicine, and surgery. We are hence proposing to closely involve Biomedical Engineering Departments with Medical Colleges, to (i) make medicine more precise in its diagnostics, (ii) design customized surgical procedures, (iii) improve the patency of implants and prostheses, and (iv) design an efficient health informatics-based healthcare delivery system. We can even have the Biomedical Engineering Departments to be located within the Medical Schools, which would make it more convenient to offer MD-PhD (Biomedical Engineering) Program and MD-PhD (Medical & Surgical Engineering) Program.

I.1STEM Model of Medicine: Biomedical Engineering formulation of Anatomy, Physiology, Medicine, and Surgery:

Through biomedical engineering analysis of anatomical structures, physiological and organ systems, medical tests data, and surgical procedures, we have developed new insights in:

1. **Intrinsic Anatomy,** in how anatomical structures are intrinsically optimally designed for their functional performance, as for example the intrinsic hyperboloid shape of the spinal vertebral body (as a light-weight, high-strength structure), and the ellipsoidal shape of the left ventricle that enables it to contract efficiently.[12-14,27,32,33]
2. **Physiological Engineering,** in quantifying physiological systems and developing indices for their functions and dysfunctions, leading to precision medical diagnostics, such as analyzing how the contraction of the left ventricle (LV) causes its twisting and development of vortices in intra-LV flow, for promoting adequate output into the aorta.[8,17,20,21,27,35,36,45]

3. **Precision Medicine,** by developing biomedical engineering formulation of medical diagnostic and assessment methods and indices, including new concepts of non-dimensional indices in medical assessment, such as cardiac contractility index for risk of heart failure and diabetic index for diabetes diagnosis. [9,10,15,16,17,19,21,24,26,44]
4. **Computational Surgery,** involving customized biomedical engineering analysis of surgical procedures (such as of coronary bypass surgery), and design of prosthetic devices (such as the vertebral body cage for fractured vertebral body, to preserve its intrinsic hyperboloid shape). [22,23,25.28,32,41,42]

Together, they can provide a more rigorous and precision formulation of medicine, which can be incorporated into the courses of the medical curriculum, and then also in clinical care.

I.2. MD-PhD (Biomedical Engineering) Program: involving biomedical engineering formulation of medical and surgical systems

Herein, we are describing Programs in (i) uantitative Physiology, (ii) Organ Systems Medical Engineering, (iii) Orthopedic and Spinal Surgical Engineering, (iv) Sports Biomechanics and Medicine,(v) Mind-Body Psychosomatic Medicine, (vi) Non-dimensional Physiological Indices in Medical Assessment, and (vii) Patient-specific Surgical procedures. These programs can be offered in the MD-PhD (Biomedical Engineering) Program.

1. Quantitative Physiology

Physics formulations of Physiological Systems functions and dysfunctions can enable us to clearly understand the physiological systems functional mechanisms, and then apply them in developing medical diagnostic and monitoring systems. For example, for Cardiovascular Physiology, we can study viscous laminar flow in a tube, and how blood pressure is measured using the sphygmomanometer. The study of Electrical field can enable us to determine the electrical field in a cell membrane and the potential difference across the membrane. Then for Neurophysiology, the physics formulation of the concepts of electrical potential, current, resistance and capacitance can be applied to neurobiology phenomenon of nerve conduction, by enabling us to analyze the resting potential of axon membrane, the action potential from stimulus, and propagation of the action potential in a nerve axon. [43,46-49]

2. Organ Systems Medical Engineering

Cardiovascular Medical Engineering: Left Ventricular Wall Stress and Contractility Index, Vector Cardiogram and ECG Signal Processing; Coronary Blood flow and Myocardial Perfusion, Myocardial Infarct detection and Heart Failure; Intra-Ventricular Blood Flow and Candidacy for bypass surgery; Left Ventricular shape based Contractility index; Pulse wave velocity and Detection of Arteriosclerosis, Aortic Pressure Profile and Aortic stiffness determination; Coronary Bypass Surgery design for maximal patency; Prosthetic Aortic and Mitral Valve designs. [8,25,26,27,29,39-42,44-45]

Respiratory-Pulmonary Medical Engineering: Lung Ventilation modeling for lung disease detection, Lung Ventilatory Index; Lung Gas Transfer performance analysis, Determination of O_2 and CO_2 diffusion coefficients, Non-dimensional Gas-transfer index; Indicators for extubation of Mechanically ventilated COPD patients. [15,30,37,38]

Diabetic Medical Engineering: Glucose-Insulin Regulatory Control systems; Oral Glucose Tolerance Test modeling and model parameters determination; Non-dimensional indices for glucose and insulin responses, Non-dimensional Diabetic Index for Diabetes detection; Automated insulin infusion regulatory system, for lowering blood glucose after a meal. [7,31,35,38]

Renal Medical Engineering: Kidney Functional analysis, Countercurrent mechanisms and modeling of urine concentration, osmolality in the descending and ascending limbs of the Loop of Henle; Compartmental model of renal clearance kinetics; Physiological measurement of the Glomerular Filtration Rate (GFR), relationship between blood creatinine levels and the renal clearance rate, Renal clearance convolution analysis; Renography modeling and determination of normalized urine flow rate index to differentiate between obstructed and normal kidneys. [36]

3. Orthopedic and Spinal Surgical Engineering

Orthopedic Biomechanics and Surgery: Osteoporosis Index for osteoporosis detection; Structural analysis of plate-reinforced fractured bone and Optimal design of fixation plate; Osteosynthesis using hemihelical plates for fixation of oblique bone fractures, Finite Element analysis and design of Bone-Plate assemblies and Helical Fixation plate. [10,11,18,23]

Spinal Biomechanics and Surgery: Biomechanical Simulation of Scoliotic Spinal deformity and Correction, Pre-surgical Finite-element Simulation of Scoliosis Correction, Back Pain biomechanics and treatment; Structural analysis of the Spinal Vertebral body as an intrinsically optimal lightweight and high-strength structure, Fractured Vertebral body fixation techniques (anterior and posterior fixations) and design of a vertebral body cage to preserve the hyperboloid shape of the vertebral body; Structural analysis of Intervertebral Disc as an intrinsically optimal minimally deformed structure under spinal loading, Denucleated Disc model analysis and solution for disc herniation. [1-6,12,13,32,33]

4. Sports Biomechanics and Medicine

This Program involves: Optimal Walking Modality based on

modeling the leg as a Simple-compound pendulum, Optimal Jogging Mode based on Double-compound model of the lower limb; Analysis of Spinning Ball Trajectories of Soccer kicks and Basketball throws, Analysis of high jump and pole vault, Analysis of tennis serves and cricket bowling, Analysis of Ice Hockey Slap shots and Field Hockey Drag flick; Cardiac Fitness Index based on Treadmill test, Evaluation of Hip Joint based on Differential equation model of the Swinging Leg motion, to determine the hip joint damping and stiffness parameters.[34]

5. Mind-Body Psychosomatic Medicine

This Program will involve stimulation of Cakras and Endocrine Glands, causing release of hormones affecting the Organs, resulting in: Mind-body rejuvenation, by boosting cognitive function, increasing gray matter density in the hippocampus, lowering blood pressure and boosting the immune system, reducing depression and easing stress; Triggering of neurohormonal mechanisms that bring about health benefits, as evidenced by increased parasympathetic and reduced sympathetic nerve activity and increased overall HRV, reducing stress and anxiety; Enhanced release of melatonin, which has anti-inflammatory, immune-stimulating, anti-oxidant and regeneration-enhancing properties.

6. Non-dimensional Physiological Indices in Medical Assessment

This is our new Concept of Non-dimensional Physiological Indices (NDPIs) or Physiological Numbers (PHYNs) for analyzing Physiological Systems and Medical Tests Data. We have developed some unique NDPIs, such as: Sports Fitness index, Cardiac contractility index, Lung ventilation Index to detect lung disorders, Diabetes diagnosis index from oral-glucose-tolerance test, Arterial stiffness or arteriosclerosis index, Mitral Valve Elasticity Index from heart sound and echocardiography data, Bone osteoporosis index, Hospital Departments performance-cost indices, and optimizing budget allocation for maximizing patient care with cost-effective hospital operation. [9,21,38]

7. Surgical Engineering, preoperatively designed to be patient-specific

For optimal outcome, surgical procedures can be pre-surgical designed for patients. We have applied this concept to many surgical procedures, ranging from (i) coronary bypass surgery to (ii) fractured vertebral body fixation by means of a fixator designed to simulate the cortical vertebral body s hyperboloid shape. The coronary bypass grafting (CABG) surgical procedure constitutes an effective remedy for high-risk coronary CAD patients. However, its complications and patency are known to be intertwined with the hemodynamics and vascular mechanics of bypass-grafted arterial vessels at the anastomotic sites. In particular, the hemodynamic analysis of CABG blood flow at distal anastomotic sites (which are prone to disturbed flow patterns) is important, to develop anastomoses designs that can enhance the CABG patency. So pre-surgical computational modeling is employed to study how the distal anastomotic geometry can affect the blood flow patterns and the hemodynamic parameters influencing CABG patency. In this way, the optimal anastomotic geometry is designed for a patient.[22,25,42]

I.3 What is needed for Medicine, towards precision (vs. empirical) medicine for the best treatment outcomes:

It is our objective to (i) make medicine more precise in its diagnosis, (ii) improve the outcomes of medical and surgical procedures, and (iii) enhance the patency of medical implants and prostheses.

For this purpose, we need to make Medical Sciences more quantitative, so that they can be translated into more reliable medical and surgical procedures. Now, medical sciences, such as anatomy, physiology, biochemistry, microbiology, molecular biology, pharmacology are undergoing transformation into more scientific and mathematically oriented disciplines. For example, physiology can be taught as physiological physics, anatomy can be taught as anatomical engineering, biology subjects can be taught as systems biology and mathematical biology.

In other words, we need to incorporate the full scope of STEM subjects into Medicine, into both medical sciences and clinical sciences.

Modern Medical Curriculum, to educate scientific and technological doctors to offer the best healthcare to their patients:

Many medical schools in US have started to develop a new medical curriculum, for the next generation of primary care physicians, medical and surgical specialists. This curriculum provides an education that integrates formal classroom-based medical science knowledge with patient-centered and disease-focused medical education. Essentially, the new curriculum features foundational medical sciences courses integrated with early engagement with patients and clinical training, involving teaching medical students about the health care system, and how to integrate use of technology into the practice of medicine. The four inter-woven pillars of this new medical curriculum are Health Systems Sciences, Medical Sciences, Healthcare Informatics, and Clinical Sciences. The shift in this new curriculum is to make students more informed about healthcare delivery system.

However, this modern curriculum does not contribute to precision medicine. In fact, in this modern medical curriculum, there remains the need for (i) engineering-physics-mathematics incorporation into medical sciences, and (ii) biomedical engineering incorporation into clinical sciences, in order to cultivate knowledge for more quantitative medical and

clinical sciences leading to more precise medical and surgical procedures which is where medicine is headed in the 21st century.

For this purpose, we are proposing the following MD-PhD (Medical & Surgical Engineering) Program, to be offered in the Medical College (or Medical School in US and UK), in collaboration with the Biomedical Engineering Department.

I.4.MD-PhD (Medical & Surgical Engineering) Program (to be offered in the Medical College (or Medical School in US and UK) :

With the help of the Biomedical Engineering Department, this novel program will consist of the above-described Courses in:

1. Physiological Engineering (described in Section I.1):

uantifying physiological systems by physics and engineering formatting, and developing indices for their functions and dysfunctions, leading to precision medical diagnostics, such as analyzing how the contraction of the left ventricle (LV) causes its twisting and development of vortices in intra-LV flow, for promoting ejection fraction. [9,17,20,21,27,35,36,38,39,45]

2. Medical Engineering (described in Section I.2):

Cardiovascular Medical Engineering; Renal Medical Engineering; Pulmonary Medical Engineering; Glucose-Insulin Regulatory Diabetic Engineering. [7, 8, 16, 19,20,27,28,29,30,31,36,37]

3. Surgical Engineering (described in Section I.2):

Cardiac Surgical Engineering (in coronary stenting and bypass surgery); Orthopedic and Spinal Surgical Engineering (of bone fracture fixation, joint replacement, and spinal fracture fixation); Computerized surgical simulation to analyze and plan patient-specific surgical procedures for obtaining optimal outcomes. [1-6,10,18,22,23,25,41,42]

This MD-PhD (Medical & Surgical Engineering) would be the first such program worldwide. In fact, both these dual-degree programs would educate a new batch of scientific and technological medical doctors, who are learned in biomedical engineering formulations of medical systems and surgical procedures, and are able to implement them in clinical care.

I.5Textbooks to offer these Courses:

My recent book scan serve as textbooks for many of these courses.

1. Applied Biomedical Engineering (CRC Press, Taylor and Francis, 2009):This book uses a problem-based approach to (i) quantify cardiovascular, respiratory, glucose-insulin regulatory systems, and formulate diagnostic and interventional procedures, (ii) analyze orthopedic and spinal structures and design surgical procedures for fractured structures, and (iii) analyze sports and athletic events, and develop fitness measures.

https://drive.google.com/open?id 0BzOPlHbjWLYta3dje FV0MkRaM c

2. Biomedical Science, Engineering and Technology (InTech Publishers, 2012):

Biomedical Science, Engineering and Technology, by Dhanjoo N. Ghista

Chapter 1: Biomedical Engineering Professional Trail from Anatomy and Physiology to Medicine and Into Hospital Administration: Towards Higher-Order of Translational Medicine and Patient Care.

Chapter 35. Physiological Nondimensional Indices in Medical Assessment: For uantifying Physiological Systems and Analysing Medical Tests Data

3. Cardiology Science and Technology (CRC Press, Taylor and Francis, 2016)

Section 1: Left Ventricular Wall Stress; Left Ventricular Contractility measures; Mechanics of LV Pressure Increase during LV Isovolumic Contraction Phase due to Activation of Myocardial Fibers; Myocardial Infarct induced Left Ventricular Shape Remodeling, and Surgical Ventricular Restoration to restore cardiac contractility, Vector Cardiogram theory and clinical Applications.

Section II: ECG Signal Analysis to detect cardiac arrhythmias, Intra-LV Blood Flow Analysis, and Coronary bypass surgery candidacy; Arterial Pulse wave propagation analysis of pulse wave velocity; Cardiac Perfusion analysis and Computation of Intra-myocardial Blood Flow patterns; Simulation of Blood Flow in Patient-Specific Coronary Arteries: Coronary Bypass surgical graft design for enhancing its patency.

https://drive.google.com/open?id 0BzOPlHbjWLYtR0 i eEF NTNmVGM .

4.Computational and Mathematical Methods in Cardiovascular Physiology (World Scientific, 2018):

This book has transformed Cardiovascular Physiology into a STEM discipline, involving (i) quantitative formulations of heart anatomy and physiology, (ii) technologies for imaging the heart and blood vessels, (iii) fluid mechanics and computational analysis of blood flow in the heart, aorta, and coronary arteries, (iv) design of heart valves, percutaneous valve stents, and ventricular assist devices.

https://www.worldscientific.com/worldscibooks/10.1142/10996

5. Biomedical Engineering Modeling of Pancreatic, Respiratory, and Renal Systems, and Medical Assessments, to be published by Elsevier.

I.5. New Era Colleges of Medicine:

In Section I.2, we have outlined the MD-PhD (Biomedical Engineering) Program, and in Section 1.4, we have described the MD-PhD (Medical & Surgical Engineering) Program. Together these two programs can help to develop a new era Medical Colleges.

Section II. STEM Model of Medicine: Medical College and Biomedical Engineering Department to jointly offer (i) MD-PhD (Biomedical Engineering) Program, and (ii) MD-PhD (Medical & Surgical Engineering) Program

In the Part 1 paper, we have we have outlined the constituents of new era Biomedical Engineering Departments. In this paper Section I, we have described the make-up of a new era Medical College. So now let us bring them together to outline the steps for offering these dual degree MD-PhD (Biomedical Engineering) and MD-PhD (Medical & Surgical Engineering) Programs in a Medical College. For that purpose, ideally new era medical colleges can have biomedical engineering departments within them. In this way, it would make it more convenient for biomedical engineering students to be educated and prepared to enter the medical college to do MD-PhD (Biomedical Engineering) degree or MD-PhD (Medical & Surgical Engineering) degree.

Step 1. Biomedical Engineering Bachelor's Degree

The first two years will comprise of Core Curriculum courses, in Humanities and Social sciences, Chemistry and Biology, Physics and Mathematics, Computer Science and Information Technology.

In year Three, we can offer basic Engineering courses, in Mechanical Engineering (solid and fluid mechanics), Chemical engineering and Transport processes, Electrical Engineering and Electronic Engineering, Computer Engineering and Artificial Intelligence.

In year Four, we can offer fundamental Biomedical Engineering courses, in Biomechanical Engineering, Bioelectrical Engineering, Biochemical Engineering, Signal and Image Processing, Medical Instrumentation.

Step 2:At this stage, we will divide the graduated students into two batches: (i) Admitted to School of Medicine, to do MBBS (or MD in US), followed by MD-PhD (Biomedical Engineering) degree; (ii) Admitted to doing a Master s degree in Biomedical Engineering, followed by PhD in Biomedical Engineering or MD-PhD (Medical & Surgical Engineering),.

Master's Degree in Biomedical Engineering

This will be a 2-year program, during which time the students will take master s degree courses in Physiological Engineering, Organ Systems Engineering, Medical Signal & Image Processing, Medical Instrumentation& Medical Apps, Medical Engineering, as described in Section I.2 or in more detail in Part I.

Then, after passing the PhD qualifying exam, the master s degree graduates can complete the PhD degree in Biomedical Engineering.

Step 3. Complete the 4-year Basic Medical Degree:

For that purpose, Biomedical Engineering bachelor s, master s and doctoral graduates can be admitted to the Medical School, and complete the basic MBBS (or MD) Degree in four years.

Step 4. Do either MD-PhD (Biomedical Engineering) or MD-PhD (Medical & Surgical Engineering):

In years 5 and 6 (after entering the Medical College), the MBBS (or MD) students can take the above-prescribed courses in

(i) Section I.2, for MD-PhD (Biomedical Engineering) degree

(ii) Section I.4, for MD-PhD (Medical and Surgical Engineering) degree.

Thereafter, the students will do PhD Thesis, while also doing internship in the hospital.

Section III. Conclusion

This paper is setting the stage for a new era of medicine, medical education, and medical colleges, based on the coalition of medicine and biomedical engineering, resulting in the engineering of the human body function, and formulation of these new disciplines:

1. Anatomical Engineering: Anatomical structures can be modeled as intrinsically optimally designed for their function, as for example (i) The hyperboloid shaped spinal vertebral body whose generators enable it to efficiently bear compression, bending, and torsional loadings, and (ii) The helically wound fibers of the left ventricle, which can enable it twist and hence contract very efficiently. [12-14,27,32,33]

2. Physiological Engineering: Physiological systems can be engineering model led to illustrate their intricate function, as for example:(i) How the blood flow in the left ventricle (LV) develops vortices in response to the contractile twisting of the ellipsoidal-shaped LV, to enable efficient blood flow out of the LV into the aorta, (ii) How the countercurrent multiplier mechanism in the kidney s loop-of-Henle creates osmotic gradient for active transport of Na from the tubular fluid,

diffusion of H_2O from the tubular lumen into the interstitium, resulting in the production of concentrated urine in the distal tubule and collecting duct. [9,17,19,21,27,35,36,38]

3. Medical Engineering: This can comprise of (i) Cardiovascular Medical Engineering, e.g., Left ventricular normalized wall-stress based contractility index for detecting heart failure;(ii) Pulmonary Medical Engineering, e.g., Non-dimensional Gas-transfer index, involving diffusion coefficients of O_2 and CO_2, to assess the gas-transfer capacity of the lung-capillary system; (iii) Diabetic Medical Engineering, e.g., Oral Glucose Tolerance Test modeling and data simulation to determine the model parameters, for diabetes detection; (iv) Renal Medical Engineering, involving formulation of hemodialysis and peritoneal dialysis for kidney failure. [8,15,16,19,20,21,24,26,27,29,30,31,36,37,45]

4. Surgical Engineering: This can comprise of (i) Biomechanical simulation of Scoliosis Surgical Correction, (ii) Patient-specific Coronary Bypass Surgery, involving pre-surgical analysis of optimal configuration of anastomosis of the graft and occluded coronary artery, to promote long-term patency of the surgical procedure, and (iii) Fractured Vertebral body fixation technique, and design of a vertebral body cage to preserve the intrinsic hyperboloid shape of the fractured vertebral body. [1-6,10,18,22,23,25.41,42]

These new disciplines can now form part of medical education in medical schools, by which we will have an advanced STEM format of Medicine in Medical Colleges, and correspondingly an advanced healthcare delivery system.

CONFLICTS OF INTEREST: None

FINANCIAL SUPPORT: None

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Original Concept

Yogapathy: Meditation Science and Practice, for Psychosomatic Health, Neuroplasticity and Well-being — An Insight

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ABSTRACT

The objective of this paper is to open a new frontier in (i) the science and practice of meditation, (ii) the physiological and spiritual benefits of meditation, and (iii) how meditation enables us to become global citizens and become dedicated to promoting progressive living for all the people in the world. We first present the new science paradigm of Cosmic Consciousness to cosmology, to life origin and evolution. Then, we explain how meditation ideating on Consciousness promotes psychosomatic health and wellbeing. Subsequently, we present the morality foundation of spirituality. Morality comprises Yama (controlling our actions) and Niyama (self-regulation), which are moral guidelines for human development. Morality and spirituality are intertwined. Without morality, we cannot develop spirituality. Meditation strengthens our morality.

We then present how to do meditation, involving three lessons: (i) Ishvara Pranidhana: ideating on the divine entity pervading around us, (ii) Pranayama: breathing pranah — divine vital energy, and (iii) Cakra Shodhana: stimulating and purifying the chakras by which the surrounding endocrine glands release hormones into the organs. We then provide the means to validate the physiological benefit of meditation by presenting our work on electroencephalogram (EEG) response to meditation, showing a shift of the EEG energy state to a lower frequency band, associated with decreased mental tension, increased relaxed state, and tranquility, and then even to intuitional development.

We then describe how meditation affects the brain regions and promotes higher learning capability. We then discuss the benefits of meditation for the spirit, body, and mind. What is important is that meditation involves us with the divine entity, whereby we can lift ourselves above narrow sentimentality in our thinking and actions. This enables us to become global citizens and develop a world without borders. When we recognize how this noble thinking and acting on our part has a big impact on human society, we can become committed to becoming pioneers in developing a new spiritual civilization in this world.

KEYWORDS: Meditation, EEG, Psychosomatic health, Consciousness

ABBREVIATIONS EEG: Electroencephalogram
IP: Intuitional Practice

1. Introduction: Yogapathy connects the mind and chakras, endocrine and neurological systems, thereby influencing mental and physical health, and promoting wellbeing

Meditation involves energizing our mind with ideation on Consciousness, for psychosomatic health, wellbeing, neurological care, and spiritual development. The mind and brain are interrelated. Neurological disorders affect the mind, and psychic disorders affect our thinking and the brain. Yogapathy connects the mind and brain and is associated with mind-brain development and medicine. In this way, Yogapathy opens up a new concept of neurology care, regarding how neurological disorders can be addressed and cured by meditation into higher Consciousness.

The nervous system is linked to the endocrine system. The hypothalamus of the brain connects these two important communication systems, and is responsible for regulating basic needs and stress responses .Linking the mind and the physical body (or the organ systems) are subtle psychic energy centers or chakras, which control our mental propensities and behavioral expressions (as well as the body s organs through the endocrine glands, as indicated later). The chakras are connected by subtle energy channels (*or nadis*), through which the vital (bioplasmic) energy (*or pranah*) is conceived to reach every part of the body. Both mental and physical health and behavioral response of the individual depend on the proper energy balance between the chakras, and thereby the functions of the endocrine and nervous systems. Disease is caused by an imbalance in this energy flow between the chakras, and the dysfunctions of the endocrine and nervous systems. Meditation on the chakras affects the endocrine glands, especially the pineal and pituitary glands, and thereby the brain and the neurological system. How? This article explains this mechanism.

However, this article goes beyond that. **We first present in Section II,** the new science paradigm of the cosmological cycle, involving (i) Cosmic Consciousness devolving into the cosmic mind, expressing the five fundamental factors to form the cosmology (or the universe), (ii) microvita converting matter into the primitive mind and life structures, (iii) the process of organic evolution from primitive life structures to simple plants and animals, and eventually to self-consciousness human beings. This enables us to understand how the physical universe develops from Cosmic Consciousness, how life develops and evolves from the primitive mind into higher mind states, and how human beings can develop higher Consciousness by doing meditation. This sets the stage for presenting Yogapathy. **So, in Section III,** we describe the science of meditation, involving (i) energization of the chakras by which the associated endocrine glands secrete hormones affecting the health state of the organs, and (ii) mentally ideating on Consciousness by which the embedded impressions in the subconscious mind (due to reactions of past actions) get defaced, leading to enlightenment. This explains how meditation involving ideation on Consciousness promotes psychosomatic health and wellbeing and also helps to liberate the mind for progress to enlightenment.

In Section IV, we present the morality foundation of spirituality. Morality comprises Yama (controlling our actions) and *Niyama* (self-regulation), which are moral guidelines for human development. Morality and spirituality are intertwined. Without morality, we cannot develop spirituality. Meditation strengthens our morality, enabling more progressive and harmonious communities and a more evolved society. **Then in Section V,** we present the fundamentals of meditation practice. Therein we describe three Lessons: Lesson 1.*Ishvara Pranidhana,* meaning offering one s mental self to God (or Divine Entity) and making union with God. Lesson 2. *Pranayama,* the science of *Pranah* (vital energy), by which every part of the body becomes filled with the cosmic vital energy, and Lesson 3. *Chakra Shodhana,* literally meaning purification of the chakras, by which the chakras get energized, and the associated endocrine glands release hormones into the organs for their curing. **We then present in Section VI,** the physiological characterization of the meditative state, using EEG to manifest its therapeutic value. When a regular practitioner does meditation, the EEG response to meditation shows a shift of the EEG waves to a lower frequency band, associated with decreased stress, and increased relaxed state and tranquility.

Subsequently, in Section VII, we describe how meditation affects the brain and promotes better learning, by whole brain synchronization, which enhances the learning ability. **Then in Section VIII,** we discuss the meditation s benefits for the spirit, body and mind. **Section IX** takes on a new spiritual paradigm, as to how meditation can promote humanism and global citizenship, by enabling us to rise above the binding dogmatic sentiments of (i) race and religion (which has divided the world), by adopting humanism as the guiding principle, (ii) being capitalists and communists, into being spiritualists, (iii) national superiority (which has caused colonization and empire-building), into being world citizens.

Finally, Section X emphasizes that the evolution of humanity depends on transforming our Consciousness to develop a more heightened civilization conducive for the progressive living of everyone living here.

2. New Science Paradigm: Cosmic Consciousness to Cosmology, to Life origin and Evolution

In the last seventy years, the theory of Relativity has altered our views of space and time, while uantum Physics theory has necessitated a new conception of the nature of matter and energy. Yet, even earlier than that, Max Planck had indicated that he regarded Cosmic Consciousness as fundamental, and matter to be a derivative of Cosmic Consciousness. According to him, we cannot get behind Cosmic Consciousness; everything we talk about, everything we regard as existing, postulates Cosmic Consciousness [1].

In this context, Paul Davies, editor of the book The New Physics[2], has suggested that the role of Cosmic Consciousness in a quantum observation still remains an unresolved issue and that it may be that this frontier-the interface of mind and matter-will turn out to be the most challenging legacy of the New Physics[2]. In a similar vein, Nick Herbert has pondered, in his book review paper *On the End of Physics* in the *New Scientist*[3], that among the successes of modern physics may lurk some tiny murkiness destined to become the seed of the next scientific revolution, just as the quantum behavior of light turned out to be the seed which overthrew classical physics.

There is indeed an increasing concern that the strictly objective, quantitative, and reductionist methodology of the natural sciences is inadequate to investigate the dynamics of mind and Consciousness[4, 5]. By contrast, the science of yoga has evolved as a system to expand the mind and Consciousness, and offers an appropriate methodology to investigate the so-called problem of Consciousness . Clearly, the time for propounding a new paradigm of science, in the form of a Unified Theory of Mind, Matter, and Consciousness, is overdue.

In this New Science paradigm, the first and foremost is the concept of Absolute Consciousness (or Cosmic Consciousness), as the fundamental entity, incorporating the Cognitive and Operative principles. The integration of body and mind in human psychic development (as well as in holistic medicine) is based on this new science paradigm. Starting from here, we will now embark on the trail of the Cosmological cycle (as illustrated in Table 1 and Figure 1), as explained by Prabhat R. Sarkar, in his book Idea and Ideology [6].

Table 1. Cosmological Cycle[7,8]

1.	Cosmic Consciousness
2.	Cosmic Mind
3.	Five Fundamental Factors
4.	Primitive Mind
5.	Mind Development through the unfolding of Consciousness in organisms
6.	Complex organisms, plants, and animals
7.	Human beings (Unit Mind)
8.	Cosmic Consciousness

Stages 1 and 2: As depicted in **Figure 1,** the Cosmic Consciousness first devolves into Cosmic Mind (Consciousness Devolution in Figure 1), and the Cosmic Mind devolves into matter (Devolution into fundamental factors in Figure 1). How? Through the Operative principle, the Cosmic Mind expresses itself into the five fundamental factors (ethereal, aerial, luminous, liquid, and solid), providing the constituents of the physical universe and the basis of cosmology.

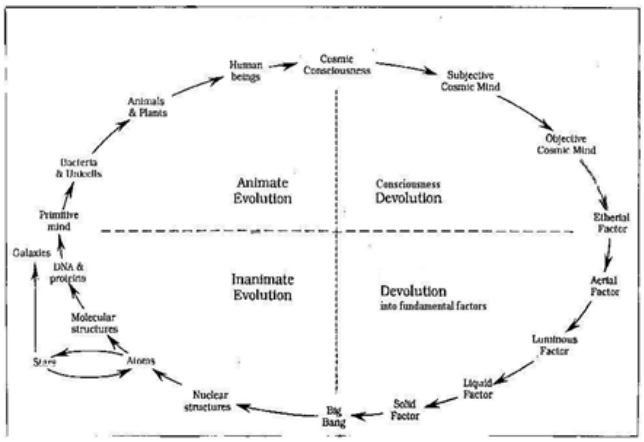

Figure 1: (i) From Cosmic Consciousness to Cosmic Mind, to Big Bang and universe development, (ii) From the development of primitive life, to plants and animals, to human beings[7,8]

Stage 3: The third stage is that of the development of the primitive mind (Inanimate Evolution in Figure 1). In the earlier stage of the Cosmological cycle, the Cosmic mind emanates microvita, which energize matter to form an ectoplasmic mind. Under the influence of microvita, matter evolves into subtler structures through synthetic reactions, thereby providing the templates of primitive life structures, represented by primitive states of mind (and Consciousness), as illustrated in **Figure 2.** The positive feedback keeps the forward reaction going, causing more and more development of ectoplasmic mind material.

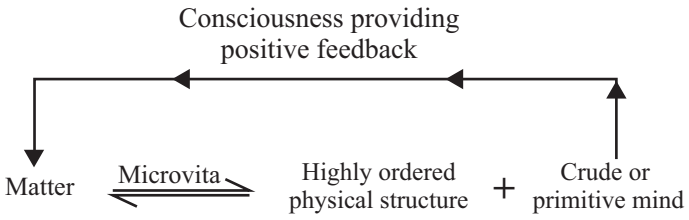

Figure 2: Emergence of a primitive mind and life-structure, through energization of matter by microvita [7,8]

Stage 4: From this point onwards, the process of organic evolution begins and constitutes the fourth stage (Animate Evolution in Figure 1), whereby primitive unicells and bacteria give rise to simple plants and animals, and eventually to self-consciousness human beings. From primitive organisms to complex organisms, there is an unfolding of Consciousness due to the increasing reflection of Consciousness, with a corresponding increase in psychic dilation of the mind and concomitant increase in complexity of the nervous and anatomical structures. Increasing psychic dilation of a living being s unit mind leads to intellectual development, and eventually to parapsychic and intuitional development. The psychic dilation of the mind eventually culminates in its achieving mental liberation, from its psychic propensities embedded in the subconscious mind, based on our interactions and thinking. Eventually, the human mind becomes subtle enough to merge back into Consciousness how, by doing meditation. Simply expressed, the Cosmological cycle is completed when human beings develop cosmic Consciousness [7,8].

3. Meditation: Ideating on Consciousness, promoting Psycho-Somatic Health, and Wellbeing, leading to Enlightenment

3.1. Consciousness pervading all around us, is the focus of meditation

In the previous section, we have explained how Cosmic Consciousness devolves into the Cosmic Mind, which then keeps devolving into the universe (both luminous and physical universes) through the Operative principle. Now we need to recognize that the Cosmic Mind is all-pervading around us here on this Earth, and in the universe surrounding the galaxies. So, for our unit minds to expand and evolve, we need to ideate on the Cosmic Mind. For convenience, let us call the Cosmic Mind as the Divine Entity or Consciousness.

In meditation, we become aware of the presence of the Divine Entity or Consciousness around us, and we address it in the form of a 2-syllabus mantra (to rhyme with our breathing). In this process, we are requesting the Divine Entity to put divine energy (i) into our bodies, by which we get psychosomatic wellness, and (ii) into our minds, by which we can become liberated from our psychic propensities, and become enlightened. So then what is meditation? It is being mindful of the divine presence around us, and our taking time out of our worldly involvements to be with the Divine Entity or Consciousness. So, enlightenment is not an abstract term but is a subjective term by which one feels the divine light within. This can even be validated through auras, using Kirlian Photography [9].

So now we will proceed to describe meditation in terms of (i) energizing the *chakras* by ideating on Consciousness at these *chakras*, to promote psychosomatic health, and (ii) mentally ideating on Consciousness, to obtain liberation from the embedded impressions in the subconscious mind (or *samskaras*).

3.2. Energy Centers (*or Chakras*) and Endocrine Glands, linking the Mind and Body

As indicated earlier, the mind and the physical body are linked by subtle energy centers called the chakras. The chakras are associated with and control specific endocrine glands, as depicted in Figure 3. The chakras regulate organ function through these glands, by stimulating their hormonal secretions; this is how the chakras influence the body. In the human mind, various thoughts are constantly emerging and dissolving. Behind these psychic phenomena are the underlying propensities (formed according to the past-psychic impressions on the mind). The propensities are expressed by the vibrational expression of the chakras, which in turn affect the endocrine glands through their hormonal secretions **(Figure 3).**

Both the expression as well as the control of these propensities is dependent upon the chakras. Emotional stresses (such as anxiety and insecurity) are known to be co-responsible for diseases, such as coronary heart disease and even schizophrenia. When subject to stress, the endocrine glands release hormones into the bloodstream, which affect blood vessel caliber, digestion, metabolism, etc. For instance, when a person becomes extremely afraid, it affects the *Anahata Chakra* (refer to Figure 3), which results in palpitations, inability to act decisively, and even a heart attack.

Both mental and physical health and the behavioral response of the individual depend on the proper energy balance between the chakras and between the endocrine glands to which they are related. Disease is caused by an imbalance in the energy flow to and from one or more chakras.

In meditation, we can energize the chakras by ideating on Consciousness at these chakras, using an appropriate (two-syllable) mantra (which synchronizes with breathing). This in turn energizes the associated endocrine glands (as depicted in Figure 3) to secrete hormones into the organs. In this way, the organ systems get affected and cured of their ailments. For example, energizing the Anahata chakra can help to promote the healthy functioning of the heart.

3.3. Mental Pain and Organ Dysfunction

In this era of increased mental (as opposed to physical) involvements and preoccupation, there is a rise in the prevalence of psychic ailments, neurological diseases, and mental depression. Just as excessive mental interactions and endeavors stress the corresponding physiological system, so also excessive mental interactions and endeavors stress the portions of the mind that perceive and do the work of perception. The ego associated with the "I exist portion " of the mind is what makes the doer portion of the mind perform actions, which can result in outcomes that are either pleasant or painful and subsequently disappointing.

The mind has to always have something to ideate on; it has to have objectivity. In daily life, the objectification of the mind

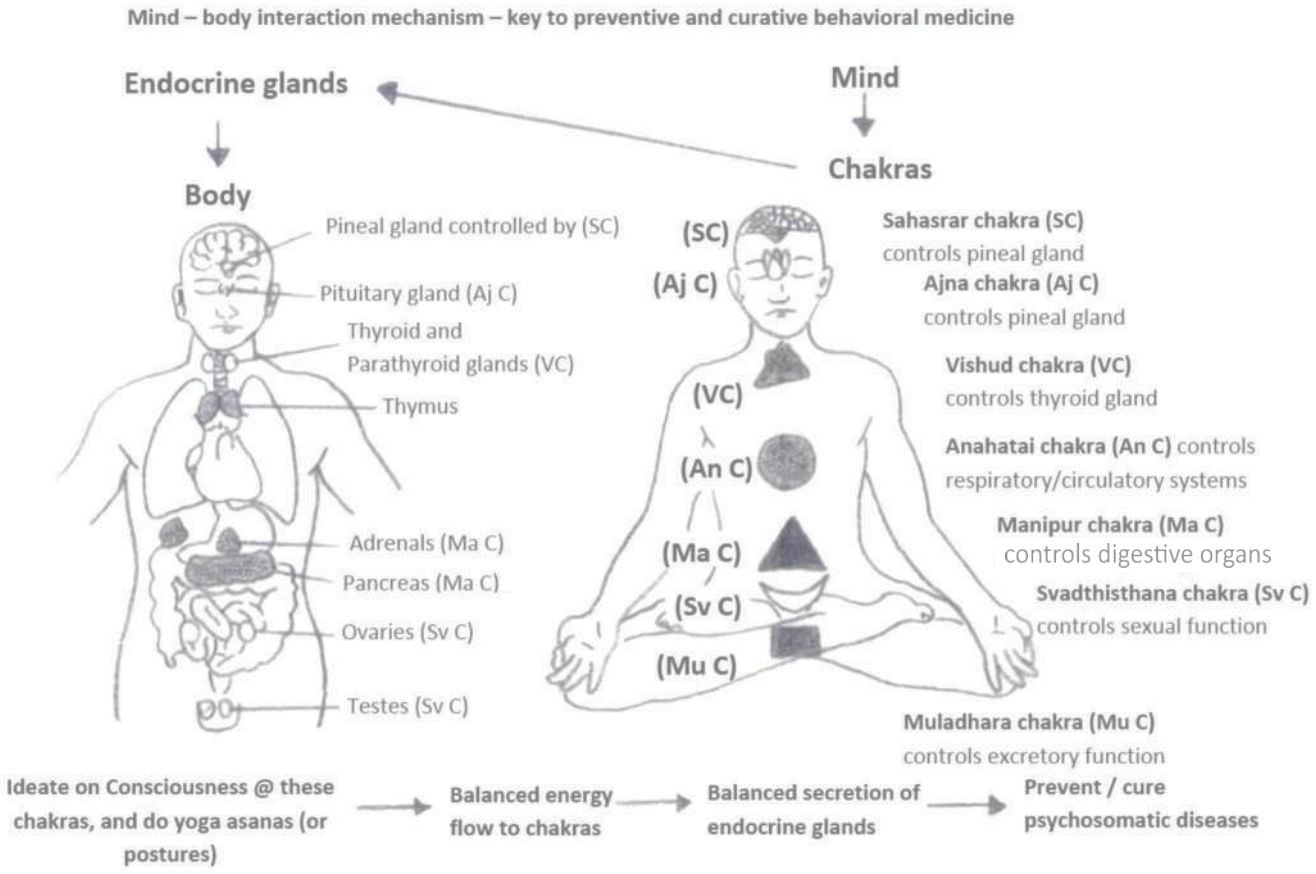

Figure 3: Chakras or Energy Centers and their association with the Endocrine Glands[7,8]

resulting from harsh interactions and painful situations produces deformations of the mind. At times, these situations persist and the resulting feeling of helplessness, at not being able to alleviate or cope with the resulting painful deformations of the mind, produces mental pain and psychic ailments (due to imbalance in energy states of the chakras), also resulting in dysfunction of certain organ systems (due to imbalanced secretions of the endocrine glands).

So then, what is the remedy for the acute and chronic pain states of the mind, and concomitant physiological ailments, resulting from inimical interactions?

3.4. Psychic Forces on the mind

The human mind can be divided into three layers: that which perceives, that which does the work of perception, and that which gives the feeling of existence. The psychic force on the mind, causing deformations of the mind, is thought to result from its interaction with the environment, and also due to the reactive moments of the impressions of the mind caused by one s past interactions and behavior.

These deformations and impressions lend a conditioning property to the mind, which influences the mental/ emotional/ behavioral make-up of a person, and dictates the nature of the response to a certain stimulus from the environment. This response creates additional impressions on the mind, and it creates a centrifugal psychic force (involved with materialistic thinking) on the mind. Such impressions and preoccupations of the mind (such as arrogance of success and disappointment of failure) preclude the mind from being receptive to the attractive centripetal force of Consciousness on the mind (as depicted in **Figure 4**).

3.5. Influence of Consciousness on the mind

By effacing the previously acquired psychic impressions in the subconscious mind and by preventing the formations of new impressions, the mind becomes more amenable to the attractive influence of Consciousness. How? The erasing of past impressions (or samskaras) can be affected by ideating on Consciousness. This elicits positive microvita into the mind, which in turn intensifies the attractive influence of Consciousness on the mind.

How to prevent new psychic impressions? If the perceiving portion of the mind were to ascribe Consciousness to the object of its perception, and if the doer portion of the mind also ascribes the doer activity to Consciousness, then the mind does not acquire new impressions (which are essentially painful because they are only temporarily pleasant).

Thus, by effacing old psychic impressions and preventing new psychic impressions on the mind, the attractive force of Consciousness is felt on the mind, which now starts moving centripetally in the ectoplasmic field of Consciousness, as schematically shown in Figure 4. This provides transcendence to the mind, rejuvenates the mind, and constitutes the basis of psychic expansion (or evolution) of the mind, progressing to enlightenment.

Meditation is termed as *'Dharana'*, meaning the concentration of the mind at a specific point. In the basic lesson of Tantric meditation, the aspirant brings her or his mind to a specific chakra which is her or his spiritual and psychic nucleus. This point (called the *Ista Chakra*) varies from person to person and is indicated by the teacher of meditation at the time of initiation. When the mind is well concentrated on the point, then the process of repeating the mantra begins. If the concentration is lost, the aspirant must again bring his or her mind back to the point of concentration. This practice of bringing one s mind to the point of concentration is a form of *Dharana*

By this process, over time, one s mind gets cleared from its embedded impressions formed by one s actions and interactions. This not only relieves stress but verily brings a peaceful feeling of oneness with divinity, recognized as enlightenment or self-realization (realization of the divinity within oneself).

4. Basic concepts of Morality, as the foundation of Spirituality

The goal of meditation is complete happiness and the method for attaining it lies in the full development of the mind and body. Meditation practice leads to spiritual development. However, Morality is the foundation of spirituality, and they are intertwined. Morality comprises *Yama* and *Niyama*, which are moral guidelines for human development. The idea of morality here is that by controlling our behavior we can achieve a higher state of being and be in perfect equilibrium. In his book, A Guide to Human Conduct, Shrii Shrii Anandamurti has clearly explained the different aspects of *Yama* and *Niyama* [10]. Herein, we will briefly review the five parts of *Yama* and the five parts of *Niyama*, which are part of *Ashtanga Yoga.*

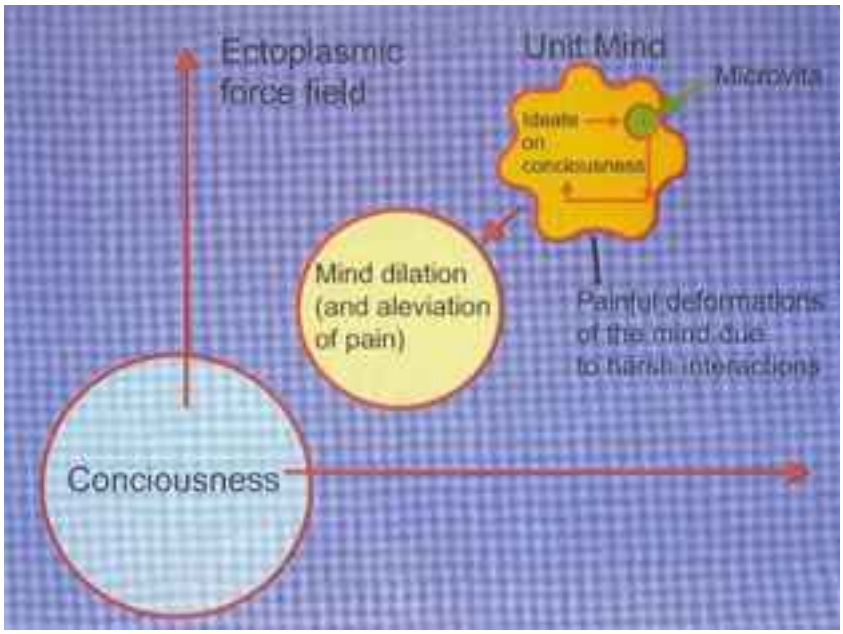

Figure 4: The Consciousness field and the presence or location of mind in it. It is schematized that when a person (or her/his mind) ideates on Consciousness (by meditation), the mind dilates i.e., develops in ectoplasmic density. This, correspondingly, enhances the Consciousness-field force on it and alleviates the mental pain. The mind keeps dilating until it merges into Consciousness, to attain enlightenment leading to salvation or nirvana [7,8]

Yama is the first part of Ashtanga Yoga. It means that which controls , and the practice of *Yama* means to control actions related to the external world.

In *Yama,* the first principle is Ahimsa. Ahimsa means not to harm others in thought, words, and actions. To the best of our capacity, we should never inflict injury on another living being. This principle is sometimes interpreted to mean complete non-violence, but if carried to an extreme it becomes very

impractical. For example, in selecting our diet we should choose the food where Consciousness is less developed before killing highly developed creatures. Another problem is the question of self-defense. Here we can say that to defend oneself against an aggressor or an anti-social person is justifiable.

The second principle of *Yama* is called *Satya*. The definition of *Satya* is action of mind and the use of speech in the spirit of welfare . It means to tell the truth and act in a straightforward and honest way that will promote the welfare of all. In cases where telling the exact truth will harm others, then *Satya* means to say what is best for the welfare of others rather than to tell the exact facts. Adherence to *Satya* brings about tremendous strength of mind and is extremely important for spiritual success.

The third principle is *Asteya*, which means not to take possession of things that belong to others. This means not committing actual theft. Also stealing should not be done mentally. Those who want to steal but who refrain from doing so out of fear of being caught are mentally stealing. *Asteya* means to refrain from both mental and physical stealing.

The fourth principle is *Brahmacarya* and it means to remain attached to Brahma or Divine Entity (the Cosmic Consciousness) by treating all beings and things as an expression of the Cosmic Consciousness. The mind takes the shape of the object of our thought. If we are thinking in a materialistic manner, seeing all things only as material objects, then the mind will gradually become dull. If we can perform all actions remembering that everything in this world is Cosmic Consciousness in a transformed state, then the mind will move towards a state of oneness with Cosmic Consciousness.

The fifth part of *Yama* is *Aparigraha*, and it means not to hoard wealth that is superfluous to our actual needs. It means to live a simple life with only as much physical wealth as is necessary. This amount is variable according to time, place, and person. It is an important principle in both individual and collective life, because if one person or one nation hoards wealth, it may result in starvation and misery for other people. It is an important part of spiritual practice, because if one is always preoccupied with physical objects, then one cannot think about the Divine Entity present all around us.

The second part of *Ashtanga Yoga* is called *Niyama.* *Niyama* means self-regulation. Without self-regulation, it is impossible to attain higher states of Consciousness.

The first principle of *Niyama* is *Shaoca*, which means Purity of mind and body. It includes cleanliness of one s external world such as the body, clothing, and environment, as well as the internal world of the mind. External cleanliness can be achieved by regular cleaning of the body and the environment, while internal purity of mind can be attained by good thoughts. That is, one must substitute a good thought in place of destructive thought. For example, if one feels greedy, one should think about it and then perform a generous action.

The second part of *Niyama* is *Santosa*. It means maintaining a state of mental ease. When the mind hungers for something, it is in a state of uneasiness. Those people who can maintain a state of contentment are following *Santosa*. The achievement of *Santosa* is linked with *Aparighraha* (mentioned previously).

The third principle of *Niyama* is *Tapah*. It means to undergo hardship on the path of personal and collective development. An act that is done in the spirit of service helping others, without expecting anything in return, is *Tapah*. Service should be rendered to people who really need help; let there be no one starving and homeless.

The fourth principle is *Svadhyaya*. It means having a clear understanding of a spiritual subject. One should read and assimilate the meaning of great books and scriptures written by spiritually advanced people. The importance of *Svadhyaya* is that it gives one contact with great personalities, and inspires one to continue on the path of self-realization.

The fifth part of *Niyama* is *Ishvara Pranidhana*. It means to make Cosmic Consciousness the goal of our life. This is done through a process of meditation in which the meditator thinks only of one thought, ideating on the Divine Entity or Cosmic Consciousness. As previously explained, in Tantric meditation the meditator repeats a mantra that reminds her or him of her or his relationship with Cosmic Consciousness. Part of this meditation process also includes steps where the mind is detached from other objects and is focused on the Cosmic Consciousness or God. Here we start our journey into meditation.

We would like to mention here another aspect of *Yoga* which is *Asana*. An *asana* is a posture that is comfortably held. It is the most well-known part of yoga, but it is often misunderstood as well. *Asanas* are not normal exercises such as calisthenics or gymnastics. Asanas are special exercises that have specific effects on the endocrine glands, joints, muscles, ligaments, and nerves.

Thousands of years ago sages used to observe the animals in the forest. They noticed that each animal had certain qualities and that the animals often assumed different poses. By imitating these poses, they began to notice important effects on the human body. For example, the peacock is a bird with a powerful digestive system capable of digesting even a poisonous snake. The ancient sages developed a posture for humans, imitating that of the peacock, which strengthens the human digestive system. Other postures were also developed that exercise other organs and glands.

The most important effect of *asanas* is on the endocrine glands which secrete hormones directly into the bloodstream. The endocrine glands include the pancreas, thymus, thyroid, parathyroid, adrenals, and reproductive glands (testes and ovaries). If the secretion of any gland is too much or too little, then there will be malfunctioning in the body. For example, if the thyroid gland, located in the throat, secretes too much fluid, a person will become thin. If the gland secretes too little fluid, the person will become obese. The reason is that thyroxin, the hormone secreted by this gland, regulates metabolism or the

rate at which the body converts food into energy. *Asanas* can correct the malfunctioning of the thyroid and other glands by putting pressure on the gland, which in effect massages the gland and regulates the amount of blood flowing to that gland.

Asanas also help to keep the spinal cord flexible which is important in retarding the effects of aging on the body. As people grow older the spinal column usually becomes rigid. Proper performance of *asanas* can prevent this process.

Another important effect of *asanas* is that they help various organs of the body to function properly. For example ,several *asanas* massage the stomach and intestines and the organs involved in the digestion of and elimination of wastes. Problems such as indigestion, constipation, gastric ulcer, liver malfunction, etc. can be checked and corrected by performing certain *asanas* in combination with a proper diet.

Let us return to meditation, by *Dharana,* meaning the concentration of the mind at a specific point. In the basic lesson of Tantric meditation, the aspirant brings her or his mind to a specific *chakra* which is her or his spiritual and psychic nucleus. This point (called the *Ishta Chakra*) varies from person to person and is indicated by the teacher of meditation at the time of initiation. When the mind is well concentrated on the point, then the process of repeating the mantra begins. This practice of bringing one s mind to the point of concentration is a form of *Dharana.*

5. Fundamentals of Meditation Practice

5.1. Introduction

Our meditation practice involves the process of ideating on the Divine Entity by recognizing the divine presence around us. This brings in divine energy flowing into one s mind, flooding it with blissful feelings and literally lighting it up. This gives one immense happiness, based on the feeling of being taken care of by the Divine Entity. Through this process, over time one s mind gets cleared from its embedded impressions (or samskaras) formed by one s actions and reactions. This not only relieves stress but verily brings a peaceful feeling of oneness with Divinity , as enlightenment. In simple terms, meditation is taking the time off one s worldly involvements and spending time being with the Divine Entity, who is awaiting this union.

5.2. Goal of Meditation

The goal of meditation is total happiness through union (or *yoga*) with Cosmic Consciousness or God. Meditation is taught in two forms: Group Meditation and Personalized Lessons. Group Meditation involves teaching the process of how to come in contact with and feel one with the Divine Entity or God, and thereby realize the feeling of extreme happiness and peace. Personalized Lessons involve initiation into the process of meditation, with the assignment of personalized *Ishta Chakra* and mantra. A spiritual seeker begins the path of self-realization by receiving initiation into the process of meditation. It is an important event in the life of a *sadhaka* (spiritual practitioner). One learns her or his personal technique of meditation, and thereby the latent spiritual potential within is awakened. It is said that when the disciple is ready, the Guru appears. Meditation used to be taught directly by the Guru, but today for practical reasons it is taught by trained teachers called *acharyas*.

5.3. Our system of Meditation

Herein we will explain three lessons: Lesson 1 called *Ishvara Pranidhana* ,meaning offering one s mental self to God (or Divine Entity) and making union with God. Lesson 2. *Pranayama*, the science of *Pranah*. Lesson 3. *Chakra Shodhana*, literally meaning purification of the chakras[11].

Lesson 1. *Ishvara Pranidhana*

The goal of this lesson is to obtain liberation from *samskaras* or embedded psychic impressions in the subconscious mind. Herein, the aspirant is taught how to ideate on and feel one with God or Divine Entity. This gives one immense happiness, based on the feeling of being taken care of by God. This is done by concentration on one s I feeling or *Ihsta Chakra* (mind center), and the use of a general mantra (or personal or *Ishta mantra* given according to one s individual psychic vibration), to ideate on the Divine Entity. Three steps are required to reach this stage.

Meditation Steps:

Step 1 consists of recognizing and manifesting the presence of the Divine Entity around us in the form of mellow light. In this step, the meditator is only feeling a divine presence and is not aware of surrounding people or structures. This process of mind withdrawal from the surroundings is referred to as ***bhuta suddhi.***

Step 2 involves developing a spirit body, to enable ideation on and union with the Divine Entity. In this step, by a special method, the mind or "I feeling" of the meditator is brought very carefully from its disassociation with the external surroundings, and then from the physical body feeling, to where the "I" sits or the location of one s mind center. At this stage, one is only aware of oneself or one s mind and the Divine Entity (or Cosmic Mind) surrounding it. *This process of mind withdrawal from body feeling is referred to as* ***a'sana suddhi****.*

Step 3 now involves the mind ideating on the Divine Entity using a 2-syllable mantra. The Mantra has a specific meaning and an acoustic sound. The general meaning of all mantras is

You are my Guide, and with your guidance, I can become

divine . This 2-syllable mantra is repeated mentally in consonance with one s in-breath and out-breath. This brings divine energy flowing into one s mind, flooding it with blissful feelings. At in-breath, the Divine Entity is infusing divinity into the mind. Then in response to this, at out-breath, one s mind expands into divine Consciousness and even gets lit up, giving a feeling of being divine.

Through this process over time, one s mind gets cleared from its embedded impressions formed by one s actions and interactions. Clearing the mind from its embedded impressions is referred to as Liberation. During this process of liberation, one s entire mental thinking gets transformed, one s personality and character get elevated, and one s interactions with others enter a new phase. Over time, this brings a peaceful feeling of oneness with divinity known as enlightenment. This is the purport and goal of this meditation lesson.

Lesson 2. *Pranayama*

Concept: The Cosmic vital energy of *Brahma* is around you. You need to take it within you to keep you physically, psychically, and spiritually rejuvenated.

Psycho-philosophy: The cooperative activity of the ten *vayus* (five internal and five external) is known as pranah (vital energy), which functions as the direct cause of life and controls the activities of the physical structure. The collective name of the ten vayus (vital airs or energies) is *pranendriya*. It is a psychic organ , which categorizes and analyzes perceptions received from the sense organs. Its position is in the middle point of *anahata chakra*.

Pranandriya plays the most vital part on the physical and psycho-physical levels. Every activity of *pranendriya* is pulsative, and it is during the state of pause and potentiality that the *citta* (Consciousness) is able to take the form of incoming *tanmatras* (perception). If *pranendriya* is in a state of pause, it creates calmness throughout the psycho-physical structure, to assist the *citta* to perceive the *tanmatras* correctly.

This is the psycho-philosophy behind the practice of *pranayama*, entailing *pranandriya* to remain in a state of equipoise, thereby merging the unit mind into the ocean of Consciousness, to enable the experience of the supramental stratum.

When we concentrate and consciously regulate our breathing, we can store up a great amount of *pranah* in the various nerve centers or *chakras*. Through *pranayama*, every part of the body becomes filled with vital energy, and all diseases can be destroyed from the root.

Performing *Pranayama*: The practitioners are instructed to do *bhuta suddhi* and *a'sana suddhi* withdrawal phases, as explained in the First Lesson. Then, with the first syllable of *Ishta mantra*), one visualizes that the Vital energy (*pranah*) is entering you through the prescribed *chakra*. This Vital energy is being used to replenish oneself physically, psychically, and spiritually. Then, as one exhales (with the second syllable of your *Ishta mantra*), one visualizes that after the Vital energy has been thus utilized, it is now going out through the *chakra*; after this, the *pranah* is replenished again during inhalation.

Proper control of breathing can alleviate many diseases such as heart disease, high blood pressure, asthma, and tuberculosis, among others. Breath control dissolves emotional tensions and relaxes the mind, and increases willpower, concentration, and self-control. Finally, if the Divine Entity s *pranah* is infused, one can get totally sanctified and one s ideas will be divine ideas.

Lesson 3. Chakra Purification (*Chakra Shodhana*)

Background: Chakras are sub-stations of the mind, as illustrated in **Figure 3.** Body and mind depend on the activeness of the chakras. By Chakra Shodhana, the mind and body get purified, and the whole being is elevated.

Concept: The chakras are imbibed with our *vrittis* (embedded sentiments or propensities), which are potential seeds of *samskaras* formation. Hence, we need to purify our defective chakras by stimulating them (at their central point of *ksiti piitha*) with the sacred idea and *bhave* of our *ishta* mantra. Ideas imposed on chakras are propagated through i to the body regions, and the body thereby gets consecrated.

Herein, the practitioners are aware of the chakras and the divine light (of the Divine Entity) around them. Then they primarily concentrate on the controlling point of the *Piitha*. For example, in the case of the *manipur chakra* (triangular in shape and red in color), they can concentrate at its centroid and then stimulate it with the divine light by means of their *Ishtamantra*; this helps the digestive system, and also the pancreatic hormonal secretion gets affected. All chakras are thereby brought into the rhythm of the *ishta mantra*, to create one tune leading to *Paramapurusa*.

Process: The practitioners first place their mind at the central point of *muladhara chakra* and stimulate (or energize) it with their *ishta mantra 2 to 3 times*, with the feeling that in this process the divine light is purifying the *chakra* by wiping off its embedded *vrttis*. Then, they raise their mind to the *svadhisthana chakra* and likewise purify it. They thus keep purifying each *chakra* up to the *sahasrara chakra*. They can now descend, purifying each *chakra* up to the *muladhara chakra.* This constitutes one trip. Like that, they can complete two to three trips.

By ideating at the controlling points of the *chakra* with the *ishta mantra,* the practioners will reach *anandam* and spiritual bliss in the corresponding region. They will reach a stage of divine composure, and when they will reach the *sahasrara chakra*, the

divine nectar secreted from that point will make them realize complete peace pervading their body.

Energizing *chakras* to regulate the organs: The *Chakras* also link the mind and body through their association with the endocrine glands. By this linkage, they also affect the organs and have a physiological curative role. Linking the mind and the physical body (or the organ systems) are these subtle psychic energy centers or *chakras* (depicted in Figure 3), which control our mental propensities and behavioral expressions, as well as the body through the endocrine glands. The *chakras* are connected by subtle energy channels (or *nadis*), through which the vital (bioplasmic) energy (or *pranah*) is conceived to reach each and every part of the body.

The *chakras* are also associated with and control specific endocrine glands, as depicted in Figure 3. The *chakras* regulate organ function through these glands, by stimulating their hormonal secretions; this is how the *chakras* influence the body. So, by spiritually energizing the *chakras* with the *ishta mantra,* the associated endocrine glands can secrete hormones into the organs. In this way, the organ systems get affected and cured of their ailments. For example, energizing the *Anahata chakra* can help to cure hypertension, and energizing the Manipur chakra can help to cure diabetes.

6. Physiological Characterization of the "Meditative State" by EEG, showing its Therapeutic Value

6.1. Association of EEG waves with mental state

States of rest, sleep, and mental activity have been characterized through the frequency analysis of electroencephalographic (EEG) data[12,13]. Electrical activity from the brain is displayed in the form of brainwaves on an EEG waveform. There are four predominant categories of brainwaves based on the level of activity. Beta waves (12 to 38 Hz) are predominant during the normal waking state when one is engaged in cognitive tasks being alert and engaged in problem-solving or decision making. Alpha brainwaves (8 to 12 Hz) are dominant when the mind is quiet, and sometimes during meditation when the mind is in the here and now, i.e. the present moment. Theta brainwaves (3 to 8 Hz) occur mostly in sleep and deep meditation. During this state, the senses are withdrawn from the external world and focused on the internal mind. Delta waves (0.5 to 3 Hz) are present in the deepest state of meditation and during dreamless sleep. It has been noted that a mentally-disturbed person (with a primarily beta EEG pattern) has a lesser proportion of alpha waveforms when compared to one with a calmer mental state.

Characterization of subjective states of feeling indicates that (i) the lack of alpha activity is interpreted as indicating states of alertness, attention, orienting, and anxiety, (ii) the beta state is associated with worry, anger, fear, and frustration, (iii) the alpha state has been noted to be associated with pleasant feeling, wellbeing, tranquility, relaxation, (iv) abundance of alpha-wave activity is considered to represent a state of rest (not sleep), relaxation and relief from concentration, (v) progressive lower frequency states (from beta to alpha and more pronounced increased alpha-activity shift to lower frequency alpha states) are associated with increased relaxation and tranquility, culminating in a deep internalized state (of warmth, love, and contentment) in the theta state, (vi) the theta state is characteristic of the meditative state[14,15].

In the *Ananda Marga* system of meditation or Intuitional Practice (IP), in Lesson 1 (explained above) the practitioner concentrates on a particular *chakra* and mentally incantates a two-syllable mantra (which has the connotation of uniting one s unit mind with Consciousness), synchronous with her/his breathing. Both the *chakra* and mantra are specific to a subject and correspond to her/his intrinsic rhythm and psychic state. In the next section, we now present some physiological characterizations of the meditative state by using EEG.

6.2. EEG Response Characterization of the Meditative State

In our research experiments[16,17], the subjects (four meditators and one non-meditator) sat quietly in an electrically shielded room. An 8-channel Grass EEG, machine was used for recording outputs from the scalp electrodes. The first six channels were used for recording bipolar signals in the order FP_2-C_4, C_4-O_2, T_4-O_2, F_1-C_3, C_3-O_1, and T_3-O_1. The seventh channel was used for recording the ECG, and the eighth for the oculogram.

For each subject, the EEG was recorded for 15 minutes with the subject in a relaxed but mentally active state, with the eyes closed. Then, the meditator was asked to meditate and the non-meditator was asked to concentrate , and their EEG was recorded during this period, which normally lasted for 30 min. A recording of the post-meditative or post-concentration period was also taken for 15 minutes. Frequency spectral analysis of the EEG data was carried out to determine the percentage of waves corresponding to each frequency band, as histograms.

6.3. Results

In all the studied subjects, the EEG pattern showed the absence of sleep spindles that are characteristic of drowsiness. Meaning, the monitored subjects did not sleep, rather they were meditating/concentrating. This was also confirmed by the absence of Rapid Eye Movement (REM) sleep in the oculogram.

Since the occipital leads show the variations in alpha activity prominently, the frequency analysis was carried out for the C_4-O_2 leads only, for this experiment. The EEG analysis of an IP practitioner Subject 1 (a regular practitioner of meditation) is shown in **Figure 5**. The figure shows the percentage of waves corresponding to each frequency band, as histograms. It can be seen that for Subject 1, there is a pronounced shift to a lower frequency spectrum during meditation. **Figure 6** shows the

wave distribution for Subject 2, who is another IP practitioner and instructor. Again, there is an abundance of waves at various frequency bands, but especially there are more waves in the lower theta frequencies. **Figure 7** shows the wave distribution for the non-meditator subject. For this subject, the frequency spectrum in a normal state was in a higher frequency band compared to that of regular meditators. Also, when this subject concentrated there was no shift in the EEG frequency distribution. The distribution is grouped around the intrinsic frequency of 10Hz.

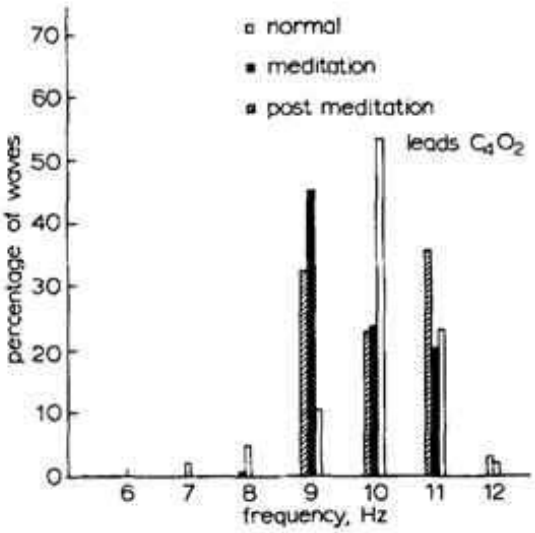

Figure 5: The relative abundance of waves at various frequency bands of Subject 1 who is a regular practitioner of IP, before, during, and after meditation. Adopted from[17].

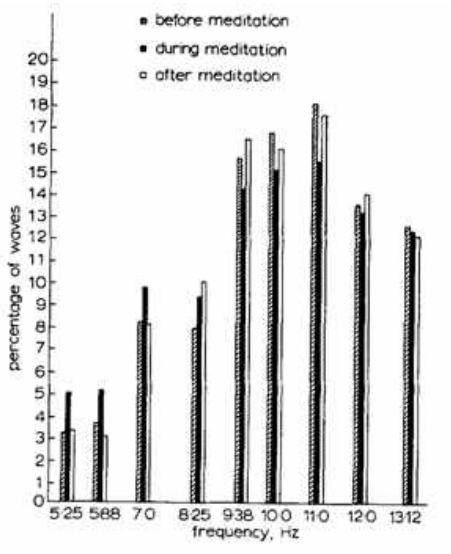

Figure 6: The relative abundance of waves at the various bands for Subject 2 before, during, and after a session of IP. The subject is an adept and an instructor of IP. Adopted from [17]

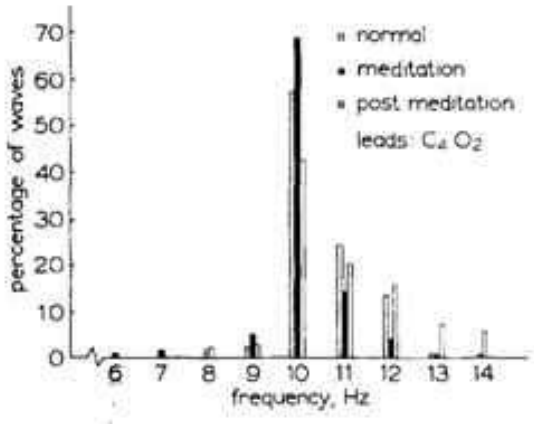

Figure 7: The relative abundance of waves before, during, and after meditation for a non-meditator. Adopted from [17].

For intuitional practice (IP) or practitioners of meditation, we noted that the amplitude/frequency distribution peaked at a lower frequency band during an IP session compared with the distribution before the IP session. Now a shift of the EEG energy state to a lower frequency band is associated with a decreased mental tension and increased relaxed state and tranquility[14,15]. For Subject 1, a 15 ml sample of venous blood was taken before and after meditation to determine the levels of pyruvate, lactate, citrate, and glucose. It was observed that the glucose, lactate, and pyruvate levels reduced by 25 during meditation. A decrease in lactate level indicates a decrease in the metabolic rate. The transformation of the EEG state during meditation, resulting in an energy predominance in the lower frequency band, is an index of the efficacy and therapeutic value of the Intuitional Practice (IP) of meditation.

In other words, the effectiveness of meditation can be characterized in terms of the enhancement of the percentage of (i) EEG alpha waves (8 12 Hz) relative to beta waves (12.5 and 30 Hz), associated with a more relaxed mental state, and (ii) theta waves (4 8 Hz)relative to alpha and beta waves, associated with deeply relaxed mental state and higher consciousness feeling.

7. Effects of meditation on the brain – benefits for students

We will now discuss how meditation influences the brain and the reasons why meditation can help students learning.

1. Meditation puts one in the best brainwave state for "super learning"

Meditation boosts the alpha brainwaves, the predominant state for learning, studying, memorizing, and recollecting large sums of information. You can summon this highly creative and super-enhanced learning state, with meditation.

2. Meditation makes the left and right brain hemispheres work together

It is known that one side of the brain is more mathematical and scientific (left), while the other half is more creative and intuitive (right). Most people use one-half of their brains more than the other, creating an imbalance. Scientists have found that highly successful people use both brain hemispheres in harmony. By meditation, one can achieve whole brain synchronization **(Figure 8)**, and enhance the learning ability.

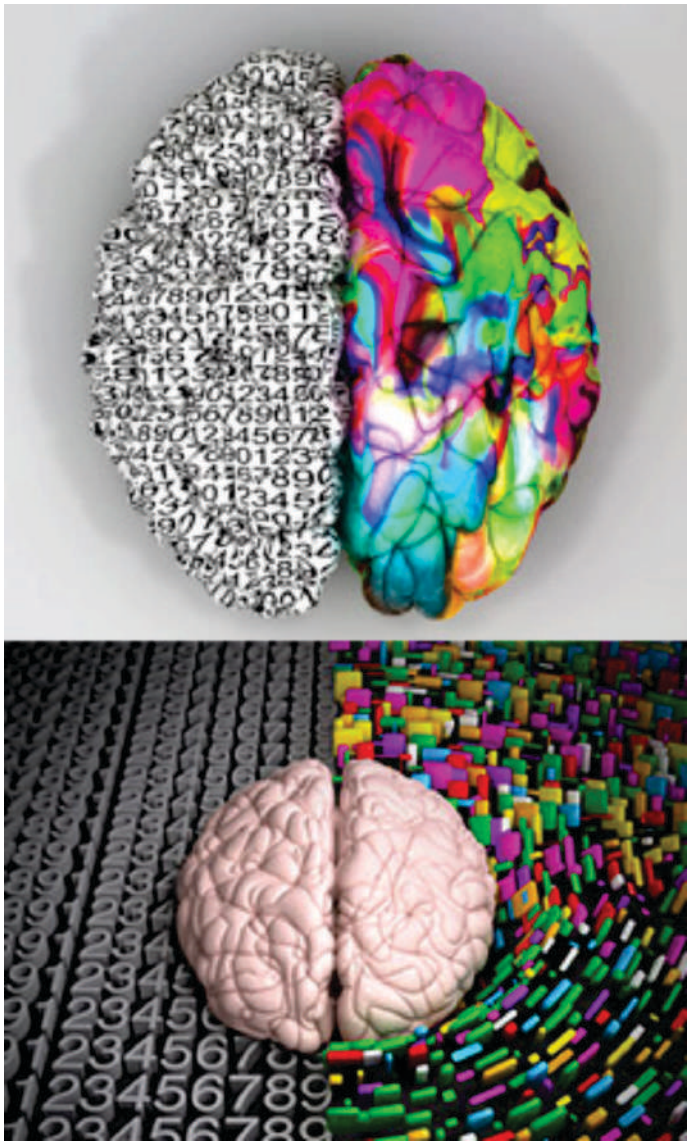

Figure 8: Meditation helps one achieve whole brain synchronization and enhances learning ability.

3 Meditation stimulates learning-associated brain regions

The two parts of the brain that are highly active during memory storage and recall, the Hippocampus and frontal lobe, are particularly stimulated during meditation. By energizing this part of the brain, meditation multiplies the ability to memorize, store, and recollect large sums of information.

8. Meditation Benefits for the Body, Mind, and Spirit

8.1. Body

Reduces Pain. Several studies have identified a connection between meditation and pain. One Journal of Neuroscience study, for instance, showed that after four 20-minute meditation sessions for four days, a group of volunteers rated the same burning pain as 57 percent less unpleasant and 40 percent less intense[18]. Plus, a review of 47 studies published in JAMA Internal Medicine showed that meditation may help ease pain (although it was difficult for the researchers to identify exactly what type of pain) [19].

Boosts immune system. One 2003 study[20] showed a link between an eight-week mindfulness meditation program and better immune function, and another research[21] suggested that meditation could improve the immune system.

Lowers blood pressure. A study co-directed by Dr. Randy usman at Massachusetts General Hospital took patients being treated with typical high blood pressure medication, and taught them a technique called the relaxation response; more than half the patients experienced a drop in blood pressure, sometimes even resulting in reduced medication[22]. Even the Mayo Clinic reports that research suggests that meditation could help manage the symptoms of high blood pressure[23].

Eases inflammation. In 2013, at the University of Wisconsin-Madison and the Center for Investigating Healthy Minds in the Waisman Center, scientists identified a possible link between mindfulness meditation and the relief of inflammatory symptoms among people who suffer from chronic inflammatory conditions[24]. Another small study suggested that mindfulness meditation may reduce loneliness and inflammatory disease risk in older adults[25].

Reduces heart risk. A 2012 study published in the journal Circulation: Cardiovascular uality and Outcomes showed a link between Transcendental Meditation and a reduction in heart attack, stroke, and early death from heart disease in a group of African Americans[26]. After five years of follow-up, the study concluded that meditation reduced the overall risk of heart attack by 48 in the study group. The American Heart Association also states that the stress-busting benefits of different types of meditation can be a boon to heart health [27].

8.2. Mind

Increases brain gray matter. Meditation may just be the right exercise for the brain. A 2009 study showed that MRI scans of

long-time meditators revealed that their certain parts of their brains were larger than those of a control group, particularly in regions known for emotion regulation[28]. Another small study published in 2011 in the journal Psychiatry Research: Neuro-imaging showed that an eight-week mindfulness-based stress reduction program resulted in increases in gray matter in the hippocampus and in the areas of the brain tied to compassion and self-awareness[29].

Cultivates willpower. Stanford health psychologist Kelly Mc Gonigal, Ph.D. told Stanford Medicine s SCOPE blog in 2011 30 that both physical exercise and meditation can help train the brain for willpower: Meditation training improves a wide range of willpower skills, including attention, focus, stress management, impulse control, and self-awareness. It changes both the function and structure of the brain to support self-control. For example, regular meditators have more gray matter in the prefrontal cortex. And it doesn t take a lifetime of practice in fact, brain changes have been observed after even eight weeks of brief daily meditation training.

Builds focus and concentration. A 2010 study published in Psychological Science showed that Buddhist meditation improved focus and attention on a task that was designed to be both boring and demanding[31].

Boosts cognitive function. Another Psychological Science study identified a link between mindfulness training and increased standardized test scores, as well as improvements in working memory[32]. Dr. Sara Lazar, a neuroscientist at Massachusetts General Hospital, who studies mindfulness meditation, told Huff Post that regular meditation may stave off the thinning of the brain s prefrontal cortex, which in turn helps slow down the cognitive function decline that happens later in life [33].

8.3. Spirit

Builds self-knowledge. According to a 2013 article published in Perspectives on Psychological Science, mindfulness (defined as "paying attention to one s current experience in a non-judgmental way") can help people to understand their own personalities[34].

Helps relationship satisfaction. Several studies the practice of mindfulness meditation enables practitioners to have more satisfactory relationships by improving their ability to handle relationship stress and communicate well with their partners [35,36].

Increases compassion. A 2013 study from researchers at Northeastern and Harvard Universities suggested that meditation may be the key to unlocking compassion. The findings, which were published in the journal Psychological Science, showed that volunteers who underwent eight-week training in two types of meditation reacted more compassionately than those who hadn t meditated. Specifically, researchers set up a waiting room where an actor with crutches appeared to be in pain; while other actors ignored her, 15 percent of the non-meditators helped the person in pain, compared with 50 percent of those in the meditating group[37].

Enhances empathy. A small study from Emory University showed that a compassion-based meditation program, called Cognitively-Based Compassion Training (CBCT), might help people to read others facial expressions[38]. It was suggested that CBCT may hold promise for enhancing empathic abilities, by increasing activity in parts of the brain that are of central importance for our ability to recognize the emotional states of others.

9. How meditation can promote Humanism and Global citizenship

In meditation, we are developing and recognizing our involvement with the Divine Entity. This will enable us to rise above the binding dogmatic sentiments of

i. Race and religion (which have divided the world), by adopting humanism as the guiding principle.

ii. Being capitalists and communists, into being spiritualists.

iii. National superiority (which has caused colonization and empire-building), into being Global citizens.

Only then can we become engaged in promoting the UN Sustainable Development Goals[39]:

GOAL 1: No Poverty

GOAL 2: ero Hunger

GOAL 3: Good Health and Well-being

GOAL 4: uality Education

GOAL 5: Gender Equality

GOAL 6: Clean Water and Sanitation

GOAL 7: Affordable and Clean Energy

GOAL 8: Decent Work and Economic Growth

GOAL 9: Industry, Innovation and Infrastructure

GOAL 10: Reduced Inequality

GOAL 11: Sustainable Cities and Communities

GOAL 12: Responsible Consumption and Production

GOAL 13: Climate Action

GOAL 14: Life Below Water

GOAL 15: Life on Land

GOAL 16: Peace and Justice Strong Institutions

GOAL 17:Partnerships to achieve the Goal

10. Spiritual Progress for Everlasting Peace, and our Responsibility to evolve for the Greater Good

Let us imagine for a moment that the fate of the entire human race rested on our shoulders alone - that humanity s evolution depended entirely on our willingness to transform our Consciousness, and become an exemplar of humanity s highest potential for the world.

Imagine that, for us evolving became an evolutionary imperative. Would the quality of awareness and care with which we approached our interactions with others become more profound?

Where the spiritual path really begins to get interesting is when we recognize that transforming ourselves in the deepest possible way is in fact an evolutionary imperative, with profound consequences far beyond ourselves. If we begin to recognize that in everything we do, we are in fact accountable to the Whole, to God the Divine Entity, then something truly miraculous can begin to happen in our dedication to developing a more heightened civilization on our planet Earth, for the progressive living of all the people.

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Original Research Paper

Phenolic Acid Profiling of the Hydro-ethanolic Extract of Momordica charantia L.

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ABSTRACT

Momordica charantia L. (Family- Cucurbitaceae)is the most famous and highly appraised species loaded with a number of beneficial aspects in terms of health and disease, capable of exhibiting several therapeutic activities that have been utilized in the ancient mode of medication for treating health-related problems. Although many active compounds like Charantin derived from spices has been shown to have promising effect on therapeutics in terms of preventing and treating several diseases. The aimof this study is to obtain the most active phenolic acid compound of M. charantia using LC-MS method. To carry out this study 50% ethanolic extract was obtained from 50 g dried powder of M. charantia fruits. The solution was then concentrated, filtered, stored, and used for LC-MS analysis. The extracts were analyzed by the LC-MS method which identified different functional compounds present in the extract whose molecular mass did not match with other compounds when compared with other literature and on Pubchem. Therefore, the newly found structures were considered as novel compounds in M. charantia which can be studied for their structure and anticancer activities.

KEYWORDS: *Momordica charantia,* Medicinal plant, Phenolic acid, LC-MS, Phytochemicals

INTRODUCTION

Phenolic or phenol carboxylic acids are natural versatile compounds present in bound form in different parts of plants. Phenolic acid serves as precursors for many important bioactive molecules that are not only required for therapeutic purpose but also for cosmetic and dietary purpose to make people healthy and active. They are loaded with higher chemo-preventive properties than antioxidant vitamins; hence they are significant to prevent inflammation and cellular damage caused by free radicals in the human body[1,2,3].

Momordica charantia L. (MC) is one of the vegetable plants which is rich in phenolic acids. Though *M. charantia* is commonly consumed as a vegetable, traditionally the whole parts of the plants are used as herbal medicine. Extract obtained from the whole part of the plant is termed as Vegetable insulin which has been proved as hypoglycemic. The fruit of MC is attributed with anti-carcinogenic and hypocholesterolemic effects, while the leaf has been reported as antiviral, antibacterial, and insecticidal, anthelminthic[4,5] and the seed extract has been reported as antileukemic[6]. A part from various pharmacological activities, adverse reactions of *M. charantia* (such as hypoglycemic coma in children and abortion) also have been reported which limits clinical application of *M. charantia*[7,8].

Many studies have been done for analyzing the extracts of *Momordica charantia* by using different methods for solvent extraction such as water extraction studies by LCMS, GC-MS, and Subcritical Water Extraction

(SCWE). In aqueous extracts of *Momordica charantia*, the phenolic compounds are commonly found among them Gallic acid was found to be more active. Studies on the *M. charantia* extract done by using combined solvent as ethanol and water have reported higher cytotoxic activity, whereas extracts obtained from only water shows higher cytotoxic activity than ethanolic extraction. Though bioactivities of *Momordica charantia* extract have been reported, little scientific information is available on the phytochemical components that may relate to its nutraceuticals and pharmaceutical health benefits. The paper seeks for determination of phenolic acid constituents present in the 50 ethanolic extract of *Momordica charantia.* The study is based on a qualitative research design applying instrumental data related to the area of research which can be an invaluable tool to study the Immunomodulatory property of plant products against the number of diseases.

Nature is full of life saving as well as poisonous plants. Variety of plant extracts have been used for thousands of years as folk medicine. They are the fundamental basis of sophisticated traditional medicine systems due to their unrefuted efficacy as a phytomedicine. As per the report released by World Health Organization (WHO)- the consumption of herbal medicine is safe and effective so it has been dramatically increased in developing and industrialized countries for the treatment of several diseases and disorders[9]. Strong religious and mythical beliefs have been also associated with the healing property of many plant products. The immunomodulatory property of plant products is the increasing area of interest for the investigators that could be considered as an invaluable tool for preventing and treating various infectious and non-infectious diseases in the upcoming era. Although many active compounds derived from spices has been shown to have advantageous effect on therapeutics in terms of preventing and treating several diseases, we have proposed to investigate the most active phenolic acid compound of *Momordica charantia* by Liquid chromatography mass spectrometry (LC-MS) method.

Momordica charantia is an herbaceous plant that belongs to Cucurbitaceae family, is more typical of South Asian countries. It is familiar with different local names indifferent languages. The fruit have different varieties, substantially in the shape and bitterness of the fruit. Generally, two varieties of bitter melon are common, namely *karela* (*Momordica charantia* L.var.charantia) and ucche (L. var. muricata (Wild.). The unripen fruit is covered with jagged, triangular teeth and ridges, green to white in colour, bitter in test and is commonly used in traditional dishes. In developing and poor countries the plant has been traditionally used for treatment of diabetes, wounds, gout, leprosy, scabies, constipation as well as a tool for the management of worms and parasites[10, 11]. Medicinal and nutritional application of MC oil also has been reported[12].

Nutrient Profile of *Momordica Charantia*

Momordica charantia plant is composed of bioactive chemicals, vitamins, minerals, and antioxidants. Research has been shown that *Momordica charantia* plant are rich in vitamin A, thiamine, riboflavin, niacin, folate, vitamin B6, vitamin C, vitamin E, minerals (potassium, calcium, zinc, magnesium, phosphorus, and iron), and dietary fiber. The caloric values for leaf, fruit, and seed are reported as 213.26, 241.66 and 176.61 Kcal/100g respectively[13-16].

Phenols, flavonoids, isoflavones, terpenes, anthroquinones, and glucosinolates contents of MC attribute high antioxidant properties to the Mc[17].

Phytochemistry of *Momordica Charantia*

Around 50 cucurbitacins have been isolated from the *Momordica charantia* plant. The cucurbitane type triterpenoids found in plants and which belong to the cucumber family (Cucurbitaceae) are the main chemical constituents of M. charantia. Many cucurbitane-type triterpenoids are isolated from different parts of *M. charantia*[18-22].

Phenolics are chemical components that are synthesized by phenylalanine ammonia-lyase from phenylalanine and cause 91.25 lipid peroxidation inhibition of linoleic acid emulsion[23]. They are applied in the control of human pathogenic infections[24]. Caffeic acid is regarded as the most common of phenolic compounds distributed in the plant flora followed by chlorogenic acid known to cause allergic dermatitis among humans[25]. Phenolics are the host of natural antioxidants that have enormous ability to combat cancer, and are also thought to prevent heart ailments to an appreciable degree and sometimes are anti-inflammatory agents. Till now the cucurbitane type triterpenoids are reported as the key phytochemicals in the *M. charantia*.

MATERIALS AND METHODS

Preparation of Plant Materials

Dried unripe fruits of *M.charantia*, collected from local market were coarsely powdered using regular house hold grinder which was then dissolved in the appropriate solvent for efficient extraction.

Extraction of *Momordica charantia*

Fifty grams of coarsely powdered *M. charantia* fruits were subjected to extraction by the process called maceration (steady-state extraction) using 50 ethanol. A magnetic stirrer was used for the gradient extraction of hydro-ethanol soluble phytoconstituents.

Method

Pastes made from coarsely powdered of *M. charantia* fruits without adding water by using grinder was lyophilized by

freeze-dryer (Alpha 2-4 LD Plus from Christ, GmbH). Fifty grams of the powder were mixed with 350ml of ethanol 350 ml of distil water in a stoppered container to obtain 50 ethanolic extract of *M. charantia* which was then allowed to stand overnight for complete percolation of soluble phytoconstituents. After overnight incubation with 50 ethanol, *M. charantia* was subjected to maceration using a magnetic stirrer. After two hours of magnetic stirring, the solvent mixture was then centrifuged at 5500 RPM for 15 minutes at 25 C. The liquid was strained off and the pellet that remained at the bottom of the centrifuge tube, i.e. marc (the damp solid material) was again collected into another stoppered container and subjected for extraction using a magnetic stirrer. Repeated extraction was done three times with concentration of solvent and after each round; solvent mixture was collected after centrifugation. Finally, the complete solvent mixture was filtered using Whitman s filter paper number-1 and stored at -20 degree celsius.

The Concentration of Plant Extracts

Fifty percent of ethanolic fruit extract was evaporated to remove excess amount of solvent. The obtained solution of ethanolic extract of *Momordica charantia* (EEMC) was concentrated using Rotovapor R-215 (Buchi, Switzerland) which was later filtered and stored in brown bottles at 4 degree celsius. The obtained extract of *M. charantia* was subjected to LC-MS for the analysis. Liquid Chromatography (LC) showed peaks which is followed by Mass Spectrometry (MS). The MS is done to find the mass of the compounds. MS Development was run in Positive Mode.

RESULT AND DISCUSSION

In this study, hydro-ethanolic extracts of *M. charantia* were prepared from its fruits. The extracts were further subjected for LCMS and the data obtained were analyzed. Various methods for solvent extraction of *M. charantia* have been employed in different studies for analyzing the extracts of *M. charantia.* Water extraction of *M. charantia* shows phenolic acid (mostly gallic acid) as well as other compounds such as flavonoids, triterpenoids and fewer amounts of biologically active compounds like momordicoside L, momordicoside1 and momordicoside K[26]. Gallic acid and its derivatives have been shown to have different pharmacological activities (such as antimicrobial, anticancer) in different diseases[27].

Likewise, in methanolic extraction of *M. charantia* done by GC-MS method the compounds mostly seen are alkaloids, steroids, flavonoids, tannins, saponins, cardiac glycoside, phlobatannin, carbohydrate and terpenoids. Studies also indicate the presence of phytochemicals like Vitamin-E, gentisic acid, 1-Pentadecyne, etc in the extracts. Gentisic acid which is present in the extract has shown antioxidant activity[28]. The studies done by others show that ethanolic extraction followed by HPLC analysis shows presence of phenolic compounds, especially gallic acid in *M. charantia*[29].

Since, LC-MS method provides a clear separation of the component therefore, in this study; the extracts were analyzed by LC-MS to determine the peak and molecular weight. The molecular mass obtained is compared with the same molecular mass from the Pubchem structure and from other Literature of *Momordica charantia.*

Based on the data obtained by MS, a total 10 compounds were present in *M. charantia*. Among those, four compounds that differ in molecular weight, were not recognized from the *M. charantia* and literature to date and are predicted to be novel compounds. Further, the extract was subjected to TLC to get the number of peaks and spots and to determine the polar and non-polar compounds. Then, the fractions were introduced to column chromatography in which the compound having high molecular weight appeared first and that with low molecular weight appeared later.

Several functional components of *M. charantia* have been identified. Such types of functional compounds on *Momordica charantia* obtained in the present study are cucurbitane, kuguacin E, Karavilagenin-A, Karavilagenin- D, Karaviloside-IV and Ferulic acid.

Phytochemicals obtained from M. charantia by LC-MS

Cucurbitane:

The cucurbitane-type triterpenoids and their aglycones have been shown to have biological effects beneficial in treating diabetes, obesity, and possess anticancer, anti- HIV, anti-inflammatory and antifeedant properties[30]. Major Cucurbitane compounds obtained from *M.charantia* are Charantin, Kuguacins A-S, Momordicine I, II and III, karavilagenin A, B, C, D and E and karavilosides I, II, III, IV, and V15. Among these, compounds Kuguacin E, Karavilagenin-A, Karavilagenin-D are the cucurbitane-type triterpenoids and Karaviloside-IV is cucurbitane-type triterpenoids glycoside found in presentstudy.

Kuguacin E:

Kuguacin includes Kuguacin A to H type. These are the compounds that belong to cucurbitane type triterpenoids. Among this type of Kuguacin, Kuguacin J type is most studied[31]. The detailed structure of Kuguacin E was established by NMR data as C27H42O4. Its IR spectrum showed absorption at 3536 cm-1, indicating the presence of hydroxyl group. The UV spectrum displayed no conjugated group based on the absence of absorption from 230 nm to 350 nm. The biological activity of the compound Kuguacin E, which is found in this study, has not been shown by any studies in detail to this date.

Karavilagenin-A and Karavilagenin-D are another cucurbitane type triterpenoids obtained in our studies which are studied together with other triterpenoids but haveyet to be studied for their biological activity separately. Likewise, Karaviloside-IV also needs to be studied in detail for biological activities.

Ferulic Acid:

Ferulic acid is an antioxidant and photoprotective agent used in biomedical and cosmetic formulations to prevent skin cancer and senescence. Ferulic acid is a phenolic compound that exhibits anti-inflammatory, antimicrobial, and anticancer properties[32]. As a photo protective agent and antioxidant in biomedical and cosmetic formulations, Ferulic acid also prevents harmful radiation effects both as UV absorber and free radical scavenger[33].

QUALITATIVE ANALYSIS OF THE FRACTION OF *MOMORDICA CHARANTIA* BY LC-MS METHOD

In the figure:1 the main peak shown has molecular weight 437.40 which corresponds to the molecular weight of the compound, kuguacins E (430.61)[34]. Another peak in Figure:1 shows molecular weight 652.50 which corresponds to the molecular weight of Karaviloside-IV (650.88)[34]

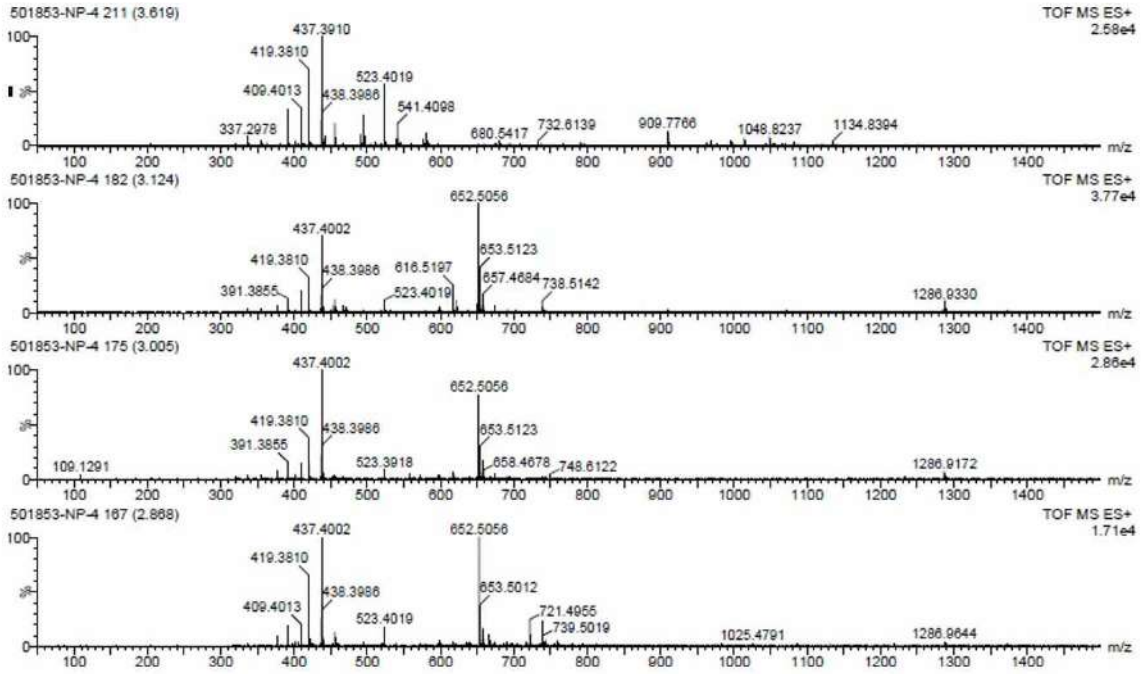

Figure 1: ualitative Analysis of the Fraction of *M. charantia* by LC-MS Method

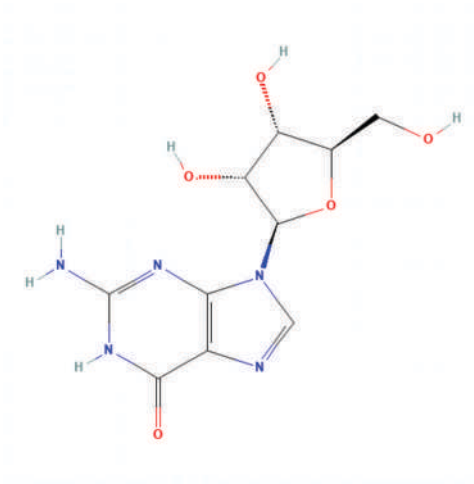

Figure 2(a): Chemical Structure of Kuguacin E (652.50)[34]

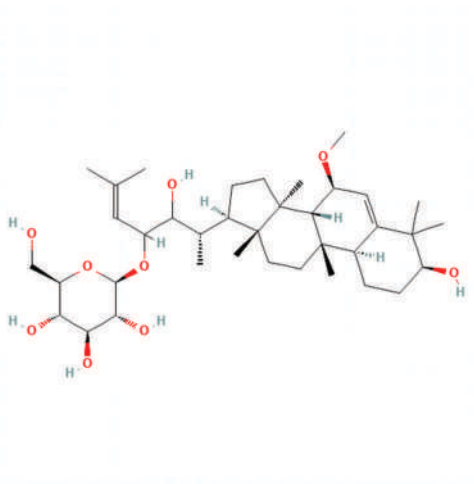

Figure 2(b):): Chemical structure of Karaviloside-IV (437.39)[34]

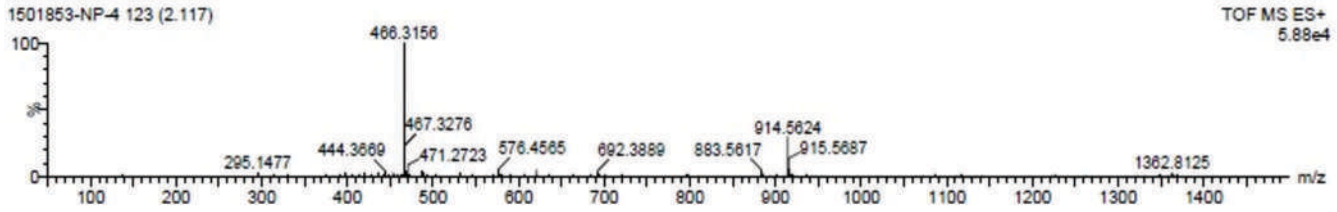

Figure 3: ualitative Analysis of the Fraction of *M. charantiaby* LC-MS Method

The peak shown in the figure 3 shows the molecular weight 466.31 which corresponds to the molecular weight of Karavilagenin-D (470.68)[34]

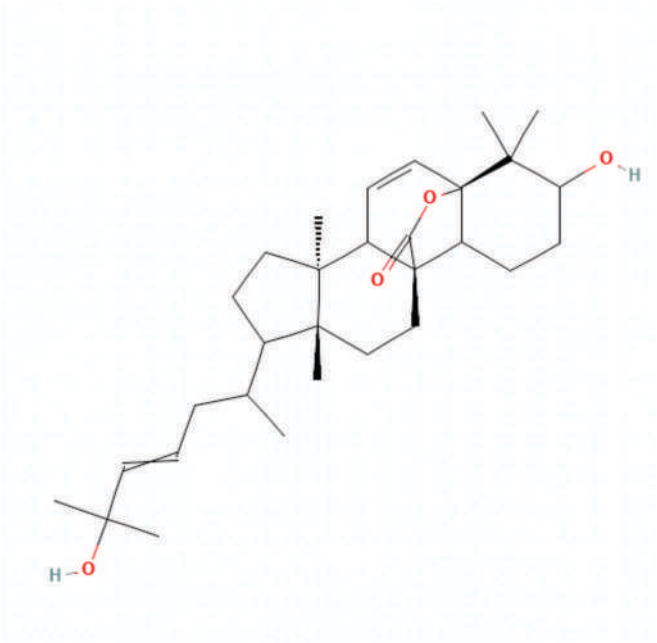

Figure 4: Chemical structure of karavilagenin-D (466.31)[34]

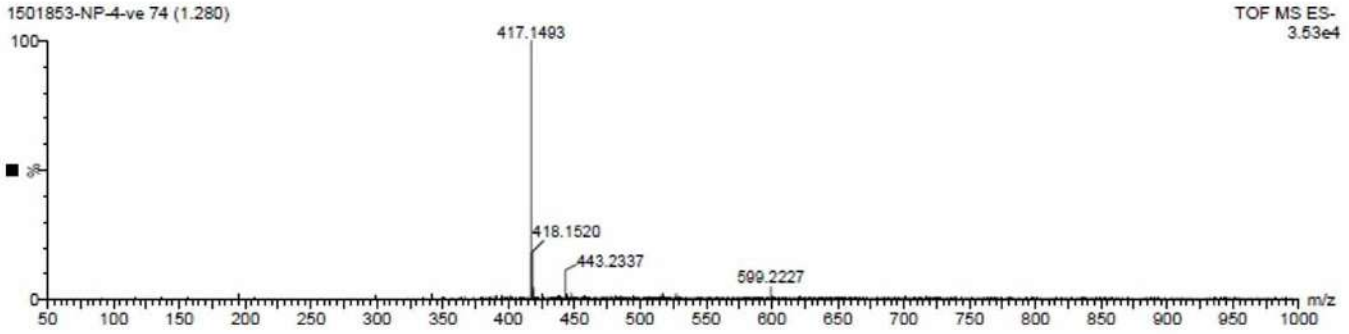

Figure 5: ualitative Analysis of the Fraction of *M. charantia by* LC-MS Method

The peak shown in the figure 5 shows the molecular weight 417.14 which corresponds to the molecular weight of Cucurbitane (414.74)[34]

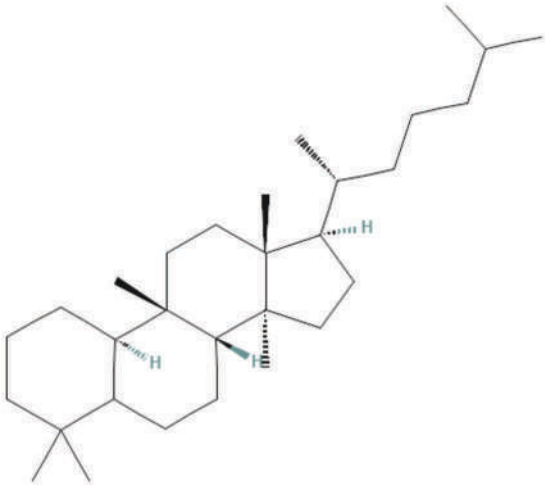

Figure 6: Chemical Structure of Cucurbitane (417.14)[34]

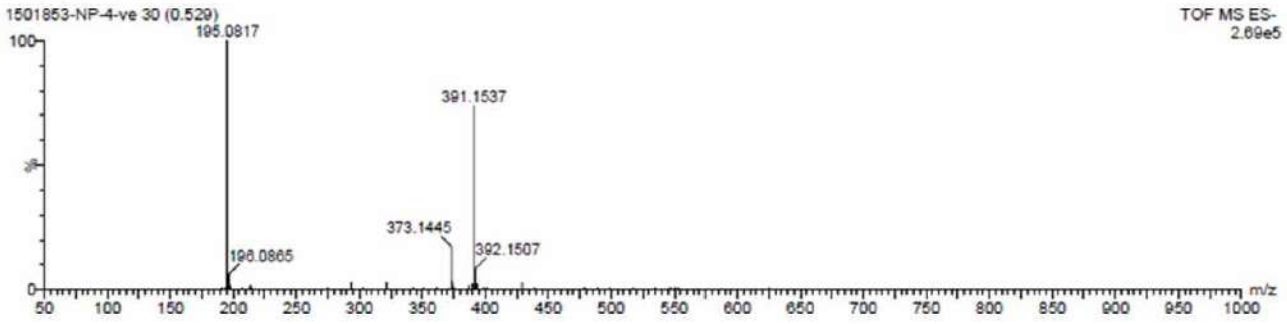

Figure 7: ualitative Analysis of the Fraction of *M. charantiaby* LC-MS Method

The peak shown in Fig: 7.depicts molecular weight 195.08 which corresponds to the molecular weight of Ferulic acid (194.18)[34]

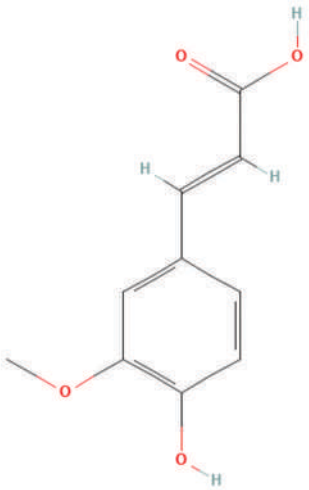

Figure 8: Chemical Structure of Ferulic acid (195.08)[34]

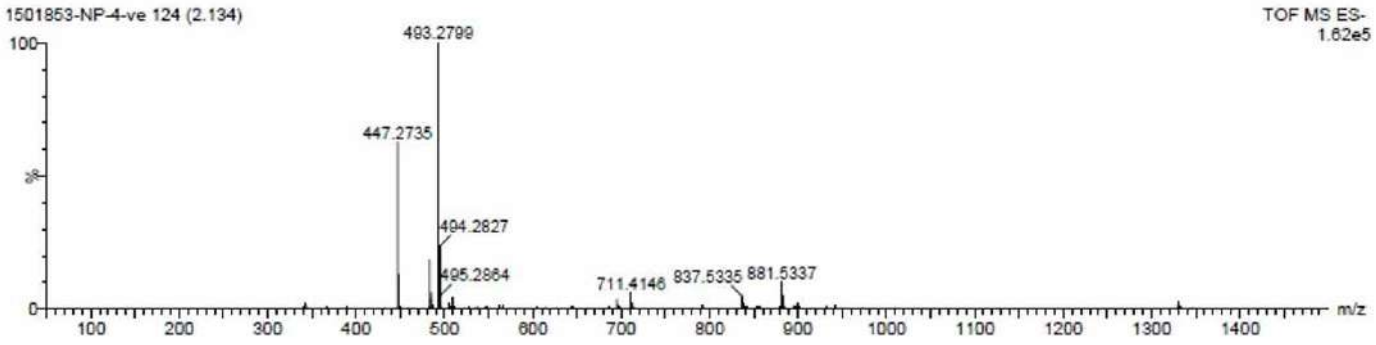

Figure 9: ualitative Analysis of the Fraction of *M. charantia* by LC-MS Method

The peak shown in Figure: 9. shows molecular weight 493.27 which corresponds to the molecular weight of Karavilagenin-A (486.76)[34]

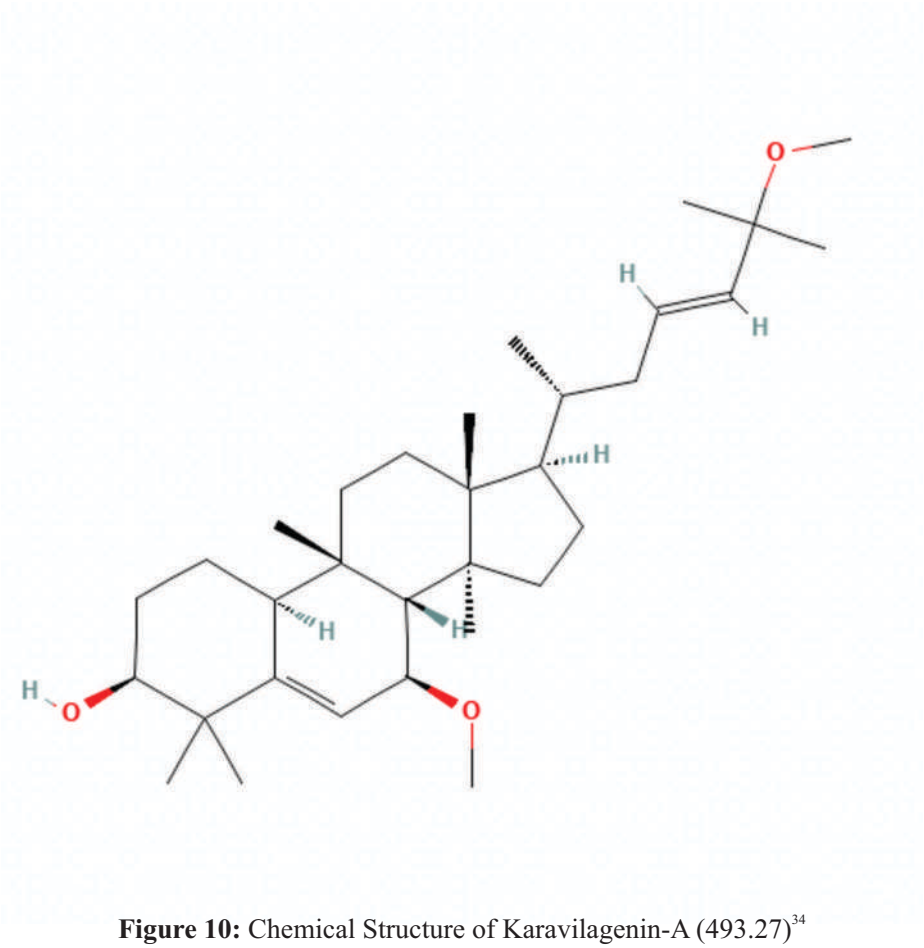

Figure 10: Chemical Structure of Karavilagenin-A (493.27)[34]

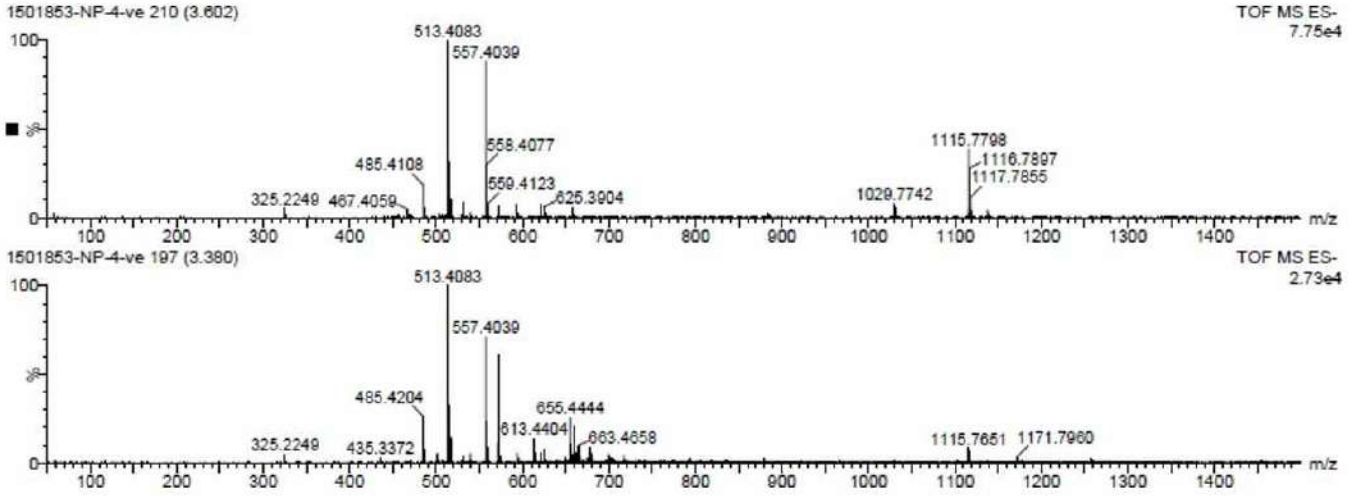

Figure 11: ualitative Analysis of the Fraction of *M. charantia* by LC MS Method

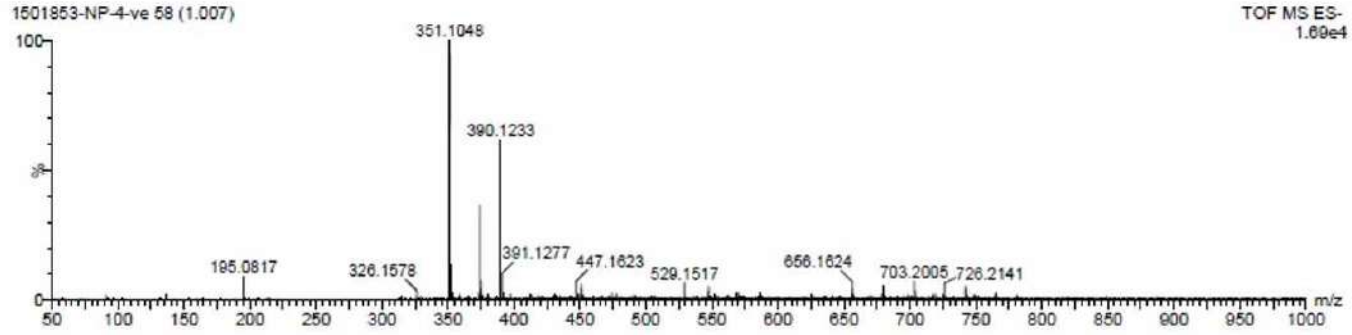

Figure 12: ualitative Analysis of the Fraction of *M. charantia* by LC-MS Method

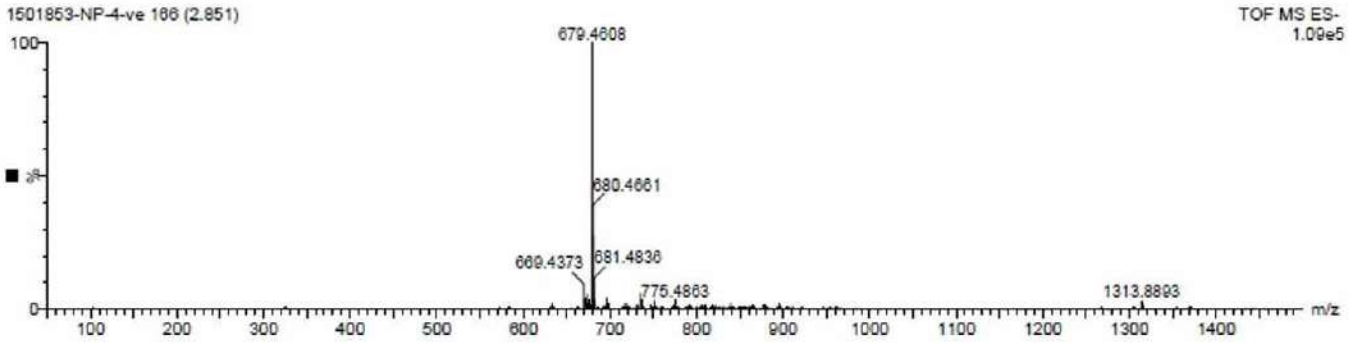

Figure 13: ualitative Analysis of the Fraction of *M. charantia* by LC-MS Method

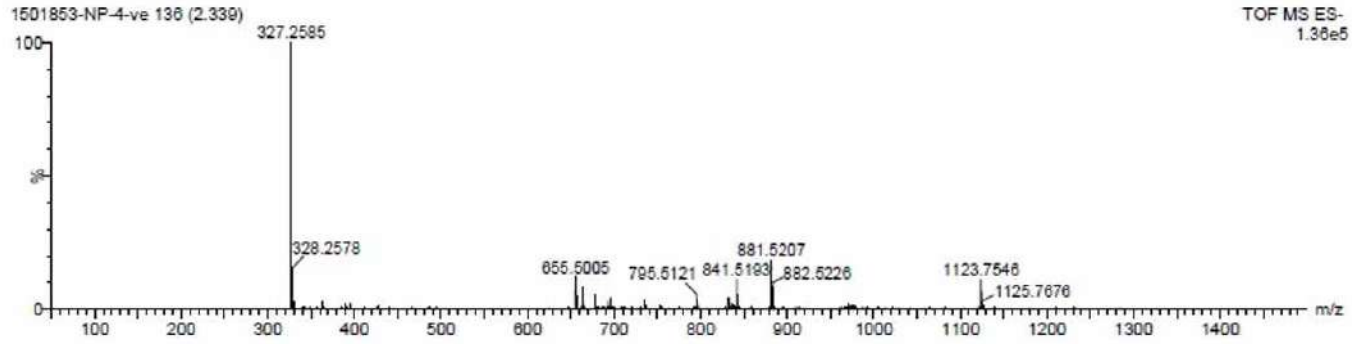

Figure 14: ualitative Analysis of the Fraction of *M. charantia* by LC-MS Method

The peak shown in Figures: 11, 12, 13, and 14 shows molecular weight 513.40, 351.10, 679 and 327.25 respectively which are novel compounds since the compounds of these molecular weight have not been reported from *M. charantia* by any literature till this date. In summary, a total of 10 compounds were found including four novel compounds by using LC-MS method.

CONCLUSION

A simple, effective and suitable method combining LCMS, TLC and Column chromatography was employed to detect the active compounds present in 50 ethanolic extract of *M. charantia* fruit powder. All the studies carried out on the extract of *M. charantia* so far have shown that the extract of *M. charantia* contains different phenolic compounds. In the present study, the LCMS data obtained from 50 ethanolic extracts of *M. charantia* showed ten major compounds out of which four compounds were predicted to be novel compounds. Much more data are available for biological activities of phenolic acids but very less is reported for their metabolites. Among the compounds identified from *M. charantia* the active compound will be further purified and studied for their therapeutical activity and further studies can be carried out to elucidate the structure of these novel compounds as well as can be used in phytosome technology for treatment of cancer and other diseases.

CONFLICTS OF INTEREST: None

FINANCIAL SUPPORT: None

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Case Report

Non-pharmacological Management in Resistant Epilepsy with Intracranial Epidermoid Cyst: Case Report

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ABSTRACT

Epilepsy is known to present with numerous neuro-psychiatric morbidities, one of which is intracranial Epidermoid Cyst. Lack of adequate knowledge about illness and treatment modalities is seen to be a cause of secondary emotional problems and poor medication adherence in the patients, causing further morbidity and poor prognostic outcome. This case reports and discusses the importance of timely detection of underlying organicity and optimal pharmacological management in a case of resistant epilepsy. It also aims to highlight the crucial role of non-pharmacological (psycho-educational) programs in maximising treatment outcome in these patients.

KEYWORDS: Epidermoid cyst, Resistant Epilepsy, Psychoeducation

1. INTRODUCTION

Seizure disorder (epilepsy) frequently presents with other neurological and psychiatric comorbidities, which can cause significant disability to patients and hamper their quality of life[1]. This includes the occurrence of intracranial tumors, of which Epidermoid tumors represent about 0.3 to 1.8 cases. Although epilepsy secondary to Epidermoid Cyst (EC) is relatively rare, it could be assigned to mechanisms of brain tissue infiltration, chemical meningitis or architectural change in epileptogenic areas[2]. EC commonly presents with symptoms of headache, seizures, raised intracranial pressure, cranial nerve deficits, focal cerebral deficits or cerebellar signs[3,4].

However, patients of epilepsy often lack intricate knowledge of their illness and available treatment modalities. As a result, they suffer from emotional distress as well as restriction in daily living and social interaction. Hence, psycho-educational programs curated with intent to improve knowledge and coping with epilepsy, and compliance to medication are being increasingly encouraged[5]. This case is presented to report the radiological evidence of an intracranial EC found while assessing a case of resistant epilepsy, and to highlight the role of psycho-education in long-term management.

2. CASE DETAILS

2.1 History and Examination

A right-handed female aged 13 years and weighing 33 kgs. was brought to Psychiatry OPD by her parents with complaints of episodic loss of consciousness associated with generalized jerky bodily movements lasting for about 30 40 seconds, up-rolling of eyeballs, frothing from mouth and followed by post-episode confusion and

physical weakness lasting about an hour. These episodes started 4 years back and have been more frequent and of longer duration over the years; also present during sleep. On enquiry, she also mentioned feeling fearful when alone, and asking her mother to accompany her during self-care routine. There was history of sleep initiation difficulties and occasional crying spells. The patient is first born of 3 siblings, born of a non-consanguineous marriage. There is no contributory family history.

Developmental history revealed history of delayed cry at birth during normal vaginal delivery at a hospital, with birth weight of 2.5 kgs and a history of 5 days NICU admission on day 3 of birth in view of postnatal jaundice. There was global delay in attaining milestones. She was enrolled in school at the age of 5 years, but had poor understanding of concepts and inability to perform satisfactorily on academic tasks. She dropped out in 2nd standard at the age 9 years after the onset of seizure episodes.

There were no additional behavioral complaints and she gradually learned activities of daily living and self-care with the help of her mother. Menarche was attained 6 months back (age 13 years) and so far, had been irregular. Her parents described her as a child with shy temperament, obedient and cheerful, with occasional irritability and anger spells on provocation.

On general examination she appeared pale, but her vitals were within normal limits. She had kyphoscoliosis of the spinal column with mild atrophy of left side of body, and a limp in gait. No obvious abnormality was noted on facial features to suggest a congenital anomaly or Syndrome, except for short frenum of tongue. An incidental finding of lump in left breast with skin excoriation and retraction of nipple was seen, with no discharge. CNS and other systemic examinations revealed no significant abnormality. On mental status examination, she appeared scared and shy, and was slow to warm up. There were no remarkable findings other than lack of clarity in pronunciations, increased reaction time to verbal responses and anxious affect.

2.2 Investigations

A battery of investigations including complete blood count, ESR, liver, thyroid and renal function tests, blood sugar and lipid profile was conducted and found to be within normal limits. Neuro-imaging (MRI brain) done to screen for underlying organicity revealed gliosis in bilateral parietal lobes, causing ex-vacuo dilatation of left lateral ventricle, like representing post-ischemic sequelae. An extra-axial hypointense (T1) cystic lesion measuring 27 x 13 x 12 mm (hyperintense on T2 and DWI) was seen involving right cerebello-pontine angle and prepontine cistern, causing indentations over right middle cerebellar peduncles, pons and lateral displacement of cisternal segment of right trigeminal nerve. These findings were suggested to be likely representing an Epidermoid Cyst Fig 1-6 . Electro-encephalogram (EEG) showed generalized sharp waves and spikes suggestive of generalized seizure disorder Fig 7 . The patient had earlier been evaluated for Intelligence uotient and had

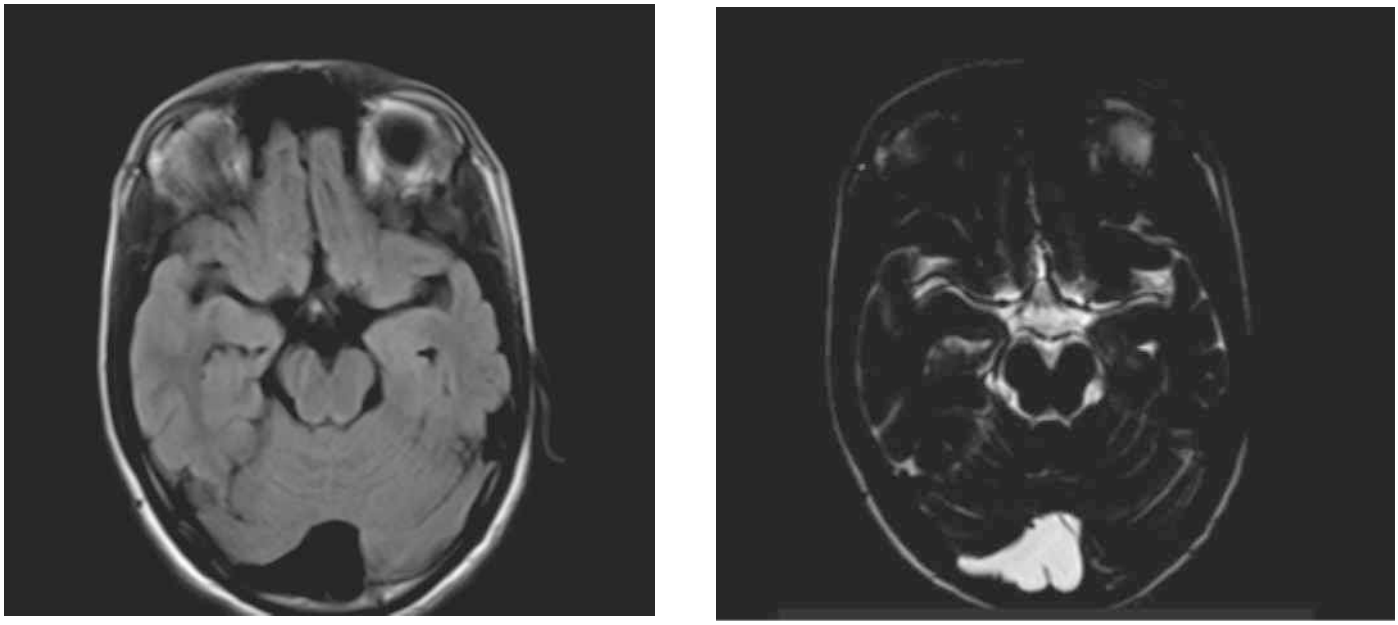


Figure 1,2: Axial section of brain (hyperintense on T2) showing a cystic lesion in posterior end of right hemisphere

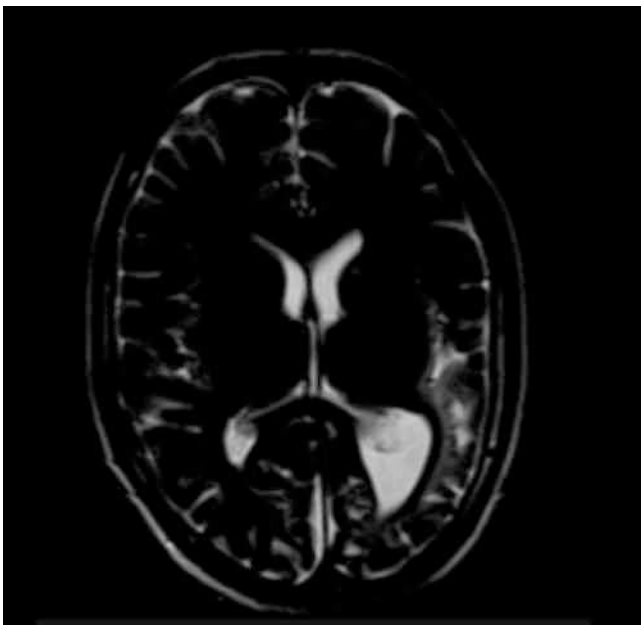


Figure 3: Axial section of brain showing gliosis in bilateral parietal lobes and dilated left lateral ventricle (T2)

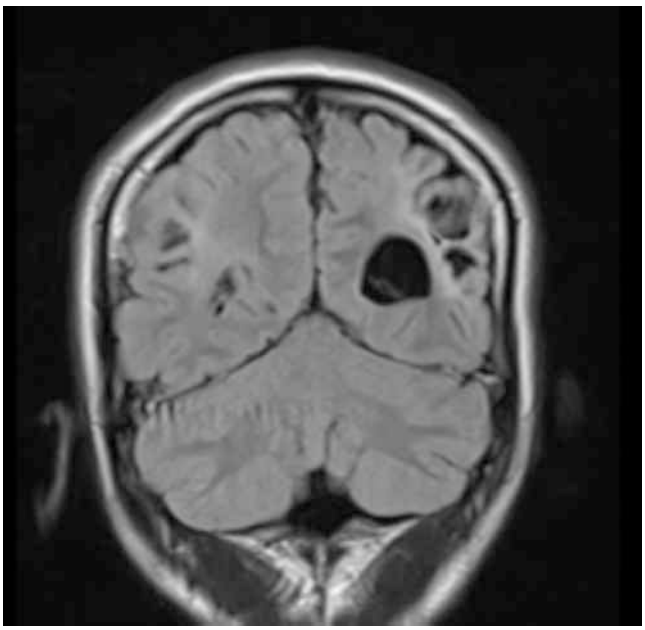
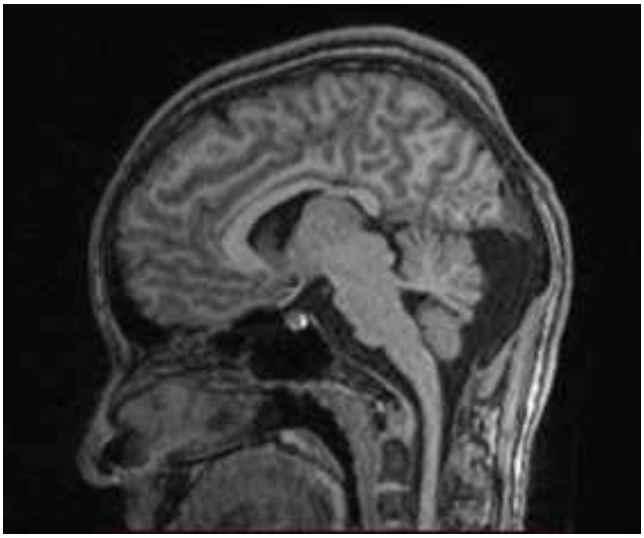


Figure 4: Coronal section of brain showing gliosis of parietal lobes and dilated left lateral ventricle (T1)



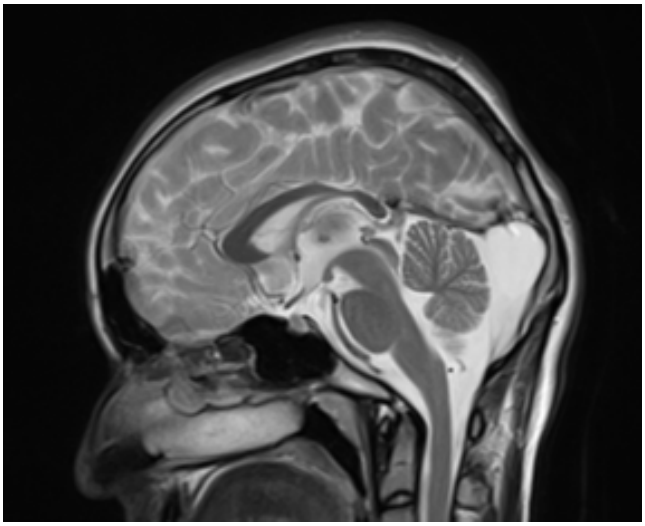


Figure 5,6: Sagittal section of brain showing cystic lesion in cerebello-pontine angle (hyperintense on T2) causing indentation over underlying structures

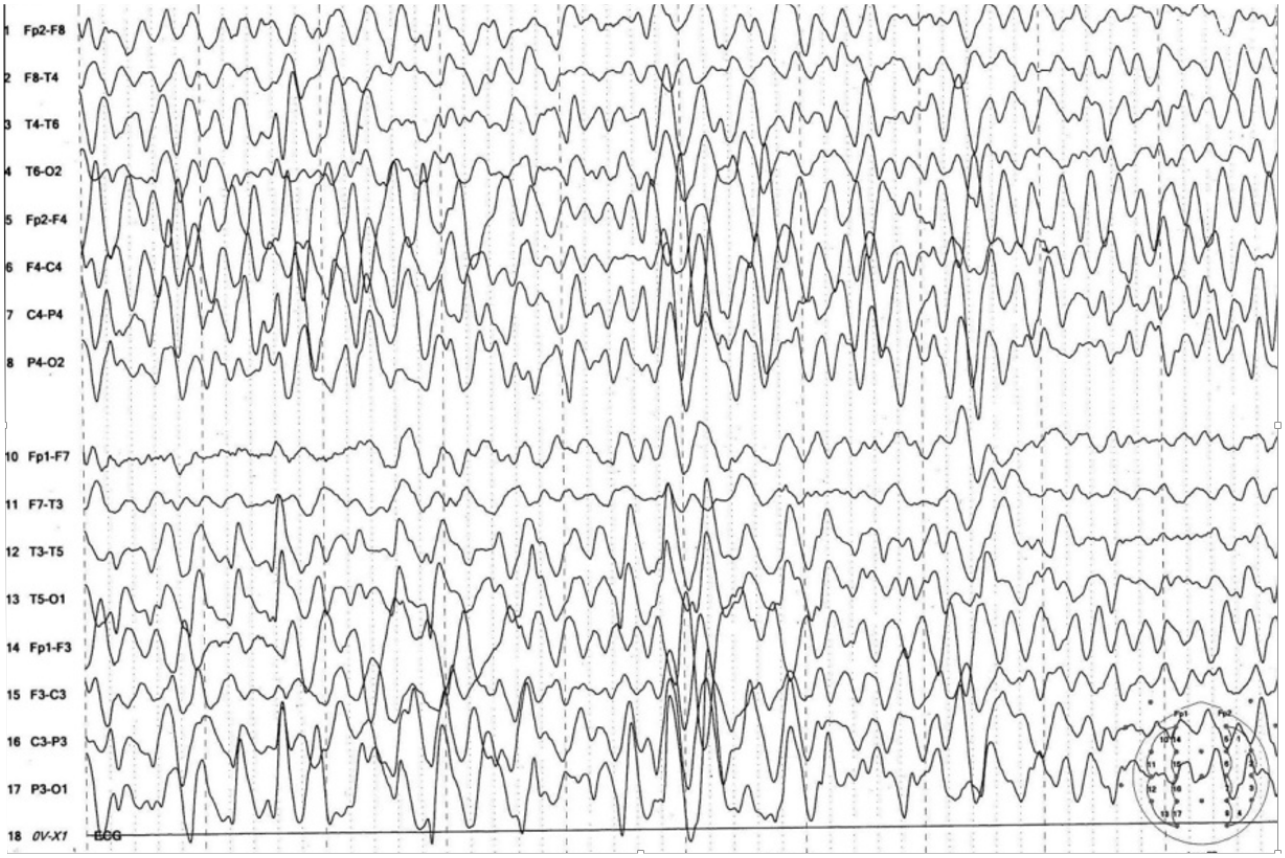


Figure 7: Awake EEG record showing generalized epileptiform activity in the form of spikes, sharp and slow waves

2.3 Management

Based on the clinical history and examination, and as per findings of investigation reports, the patient was diagnosed as Intellectual Disability Disorder with Seizure Disorder, secondary to underlying organicity (intracranial Epidermoid cyst). Her neurotic symptoms were concluded to be reactive to physical illness and its resultant emotional and social repercussions over time. The patient had so far received trials of Levetiracetam (up to 1000 mg/day), and another trial of Phenobarbitone (60 mg/day) in combination with Carbamazepine (up to 600 mg/day) in the past, both of which she had tolerated well, but had shown partial response to.

Considering inadequate response to previous treatment regimen, it was decided to admit the patient for close monitoring and comprehensive management. A trial of Phenytoin (200 mg/day) and Phenobarbitone(120 mg/day) in divided doses was initiated and Carbamazepine was slowly cross-tapered with Valproate (400 mg/day). For one off seizure episode during this cross-over, she was administered Clobazam 10 mg on SOS basis. With gentle rapport-building and after appropriate psycho-education and supportive counselling of both parents, it was observed that her anxiety and withdrawn behavior slowly receded and the patient seemed comfortable during inpatient stay. Over the first week, two episodes of seizures were observed, each lasting less than 3 seconds and with less than 2 minutes of post-ictal confusion. This was a relatively dramatic control over seizure intensity which had not been previously attained.

An opinion from Gynecology team was sought for the lump in breast and treatment initiated in view of an inflammatory lesion. Neurosurgical consultation was done with reference to management strategy for intracranial EC and it was opined that in view of satisfactory improvement in symptoms, surgical resection was not imminent at present. Observation for symptom worsening was suggested and a review was planned over next six months.

On her recent follow up visit no seizure episode has been reported for the past one month. Her mother also reported an improvement in her overall functioning, including emotional responsiveness and cognitive functioning as observed through her active participation in household chores and social interactions.

3. DISCUSSION

The term resistant also known as refractory or intractable epilepsy, appears to be self-explanatory, but its precise definition remains elusive. As per consensus fromThe International League Against Epilepsy (ILAE), drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (as monotherapies or in combination) to achieve sustained freedom from seizure episodes. Although lifelong seizure freedom without adverse effects would be the most clinically relevant outcome of any intervention for epilepsy, some breakthrough seizures could be provoked by sleep deprivation, menstruation, fever or other external factors[6,7]. This case was labelled as resistant epilepsy based on the above criterion.

Psychosocial problems in treating epilepsy are seen to be been a major unmet need. A review article stated that specific interventions for these problems can improve quality of life, social adjustment, and adjustment to seizures in these patients, with outstanding results for refractory cases. Integration of psychosocial management into the mainstream treatment of specialty clinics like Neurology has also been proposed[8]. In line with these recommendations, a study testing efficacy of structured educational programs on drug adherence in epilepsy reported significant improvement in medication adherence (p 0.001), as measured by Morisky Medication Adherence Scale (MMAS)[9].

In another controlled study, researchers conducted analyses with a questionnaire specifically based on epilepsy, and found significant improvement on measures of knowledge (p 0.001), coping and adaptation (p 0.01), illness related anxiety (p 0.05), and seizure management (p 0.05), when implementing the educational program called FAMOSES (modular service package epilepsy for families). It was also found to be helpful in reducing seizure frequency in children (p 0.05)[10]. Advantages of psycho-education in epilepsy are emphasized as lack of perceived stigma in comparison to forceful participation in psychotherapy, and an opportunity for providing basic medical information, triggering mechanisms in epilepsy and various coping skills. Delivery of this information in regional dialects and promoting self-management skills are also highlighted as therapeutic principles[11]. Thus, misconceptions about epilepsy can be reduced by imparting correct information to patients and their families, in turn improving course of illness, optimizing long-term management and preventing complications[5].

Psychosocial outcomes in children and adolescents with epilepsy are particularly compromised due to perceived stigma, behavioural symptoms, academic difficulties and comorbid depression. In such cases, psycho-educational interventions including positive peer support are highly encouraged[12].

This case highlights the much-needed role of relevant, adequate and timely psycho-education of patient and care givers in minimizing emotional health consequences in neuro-psychiatry. Given the adverse long-term implications of such diagnoses on the patient s social and personal life, it is vital to share difficult information sensitively and empathically to the family. Also, effective management of primary presenting problem such as refractory seizures in this case, is crucial for alleviating their immediate stress response.

It is the second case in a series of EC cases being assembled in view of presentation with psychiatric symptoms and psychosocial aspects of management in addition to pharmacotherapy and / or surgical intervention. One such case reported by our team elaborated on psychosis as a manifestation of EC with resistant epilepsy[13].

4. CONCLUSION

Sensitive and appropriate psycho-education is a critical aspect of symptom management in neuropsychiatry. An index of suspicion for underlying organicity is equally important in cases presenting with difficult to treat symptoms like resistant epilepsy.

5. CONFLICTS OF INTEREST: None

6. FINANCIAL SUPPORT: None

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Case Report

Paediatric Traumatic Cataract – A Case Report

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ABSTRACT

Paediatric age group is most prone to the injuries as the child develops skills from daily routine to more complex activities. A large number of injuries, however, heal and some may leave a mark. Traumatic cataract is thus, one of the cause of ocular trauma and a preventable vision loss in children, when presented before a permanent damage and complication. This case reports the management of a case of 12 year old female child belonging to rural area with unilateral poor vision following an ocular trauma which was left untreated for four years.

KEYWORDS: Paediatric traumatic cataract, Ocular trauma

INTRODUCTION

During the growing age, a number of children may experience ocular trauma, resulting from mild-moderate to severe ocular injuries. The prevalence of vision loss is variable and thus not be justified in terms of numbers, but depends upon several factors including the socio-economic status, parenting, infant mortality rates of the country and variable periods of overall development of the child[1]. Ocular injuries are most common cause of unilateral blindness in the children[2]. A worldwide estimate have shown a total of 19 million children with visual impairment and Asia continent with largest number of childhood blindness of around 1 million[3].

Traumatic cataract is defined as an opacification of the lens due to blunt or penetrating trauma to the eye. It can present along with alterations in anterior and posterior segment or as an isolated opacification after a period of time following the injury[4]. Around thirty percent of childhood and adolescent cataracts are traumatic cataracts, being the most common cause of preventable vision loss[5,6].

The exact aetiology and mechanisms of paediatric ocular injuries are uncertain and are in need to evaluate more thoroughly in rural as well as in urban areas. This can help to build sharp strategies and preventive measures to avoid injuries and traumatic vision impairments[7,8]. The Birmingham Eye Trauma Terminology System (BETTS) encompasses the types and effects of mechanical injury, causes of visual impairments, and visual outcomes after the management in a comprehensive manner and made standardization of documentations[9,10]. Thus a medical history including demographic features, site and time of injury, previous ocular condition, and follow up durations are of more importance along with the detailed ocular examination when patient presents to the hospital.

CASE REPORT

A 12 years old female child belonging to rural background was presented to Ophthalmology out-patient department with her father after being referred from tertiary centre. She complained of gradual, progressive diminution of vision in the left eye from last four years when she got hit by a blunt object with a high speed and force while playing. She reported no episode of loss of consciousness, nausea or vomiting. Her past medical history and family history were not significant. Though, she did not have history of any other previous ocular injuries, ocular disease, or prior ocular surgeries. She took conservative treatment from a local practitioner and slowly developed blurred vision which progressed with time.

Examination

Ophthalmic examination revealed decreased visual acuity in the left eye. The uncorrected visual acuity was 6/9 in the right eye and perception of light and rays in the left eye. Standard applanation tonometry revealed pressure of 18 mmHg in the right eye and 20 mmHg in the left eye.

Slit-lamp examination of the right eye did not revealed any significant findings. The left eye examination observed no signs of open globe injury. It observed normal ocular adnexa, clear cornea, and normal anterior chamber depth with no cells or flare in the anterior chamber. The pupil was sluggish reactive with posterior synechiae formation at 12, 2 and 6 o clock. Lens status was rosette shaped dense cataract with dense posterior subcapsular cataract. Gonioscopy observed no angle recession. B-Scan Ultrasonography showed clear vitreous with flat attached retina. On -Ray and Computed tomography, there were no signs of orbit or skull fracture.

Surgical Procedure

The patient and the family members were thoroughly counselled about the patient s condition, proposed surgical procedure, outcome and intraoperative complications. Patient was taken to operative room with informed and written consent from patient and relatives.

The procedure implied the management of synechiae, cataract with posterior continuous curvilinear capsulorhexis, anterior vitectomy and intra-ocular lens implantation under general anaesthesia (Primary posterior capsular opacity was observed during procedure). The post-operative medications were given as Moxifloxacin with Prednisolone tapering over a period of four weeks. Amblyopic treatment was started and patient was discharged with no ocular complaints.

Outcome

On first follow-up after 7 days, the visual acuity of the patient observed significant improvement. The BCVA (Best Corrected Visual Acuity) for the right eye is 6/6 and of the left eye is 6/18 on the Snellen s chart. Intraocular pressure recordings of the right and left eye were 16 and 18 mmHg.

DISCUSSION

Demographic analysis showed more tendency of paediatric traumatic cataract development in boys than in girls (commonly 6 to 10 years of age) because of their activity level and tendencies toward outdoor play[11-14]. The relationship between the age range and final visual acuity is still uncertain[5,14].

Amblyopia and Strabismus are most common complications of paediatric traumatic cataracts, resulting in lifelong poor vision if not treated properly. Several hypothesis attempted to determine the factors that influence final vision; however, some uncertainties still exist[11,15].

CONCLUSION

It has been seen that good visual prognosis of paediatric traumatic cataract has been seen with posterior capsulorhexis, anterior vitrectomy along with intra-ocular lens implantation, followed by effective amblyopia treatment and regular follow-up. However, more comprehensive and prospective studies are needed to confirm this approach.

CONFLICTS OF INTEREST: None

FINANCIAL SUPPORT: None

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Review

Psychological Management of Stroke: A Review

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ABSTRACT

Due to its increasing rate of incidence, stroke is being increasingly recognized as the major cause of death and disability in survivors across the world. Stroke survivors and their caregivers often experience numerous functional daily life activities challenges and limitations after discharging from hospital. Stroke is a family disease and considerable empirical evidence regarding post-stroke management consistently highlights the crucial role of psychosocial interventions in facilitating overall recovery process. Especially, the holistic approach in the post stroke management and rehabilitation of these patients has led to a considerable reduction in the burden of stroke care worldwide. The present review will add the new horizon in existing understanding and guide the future research attempts for the development of new psychosocial paradigms for promoting the optimal rehabilitation of stroke survivors and their carers.

KEYWORDS: Stroke, Psychosocial interventions, Recovery,Rehabilitation

INTRODUCTION

A stroke occurs when a blood clot or a ruptured artery or blood vessel cuts off blood flow to a portion of the brain,[1,2]. It can lead to different problems based on the area of the brain that has been impacted. However, common problems after stroke include impairment in the areas of cognition, speech and language, movement, emotional and behavioural problems among stroke patients[3,4,5,6].

The management of stroke comprises of holistic approach. When working with survivors of stroke, often times, the focus is more on physical symptoms while ignoring other aspects of care including emotional and psychological care. Hence, there needs to be increased recognition of other aspects of care including psychological management. Furthermore, policies and directives from government agencies will also help to bring awareness and target these areas of care. There is also a need to work in a multidisciplinary team, including but not limited to doctors, physiotherapists, speech language pathologists, clinical psychologists, neurologists, social workers, survivors and carers of stroke, to offer the best possible support after a stroke[7,8].

Several studies have highlighted reduced depressive symptoms after psychosocial interventions in stroke survivors and their carers[9,10]. However, there is a little evidence suggesting the role of such interventions in improving OL and coping strategies for stroke survivors and carers. Furthermore, there is a considerable limitation of empirical evidence of such interventions in improving self-efficacy, caregiver strain and overall caregiver satisfaction[9]. In addition, communication skills in stroke caregivers is also found to play a crucial role in decreasing depressive symptoms[11].

After a stroke, many people find it difficult to engage in activities of daily living[12,13]. In addition to slowing their life and increasing dependency, the situation is also known to reduce their self-esteem, feel an intense sense of loss and grief, hopelessness, helplessness, and frustration[14]. Finally, relationship with the caregiver and financial status of the stroke survivor is also known to have an impact on how they feel about the situation.

EMOTIONAL AND BEHAVIOURAL PROBLEMS

Common emotional problems after a stroke includes anger, irritation, frustration, helplessness, catastrophic reaction, loss of motivation, apathy, anxiety and depression[6]. Depression is associated with poor motivation to engage in rehabilitation activities, slower regaining of functioning, longer hospitalizations, etc[15]. Other behavioural and emotional problems such as acting out, shouting, screaming, denial of physical symptoms is also common in survivors of stroke[16].

A longitudinal study revealed encouraging findings indicating that psychological interventions have a longer lasting impact when compared to non-specific support in stroke patients[17]. Furthermore the results suggest that a psychological interventions can help stroke patients to manage effectively the mood related disorders. Similarly another longitudinal study at about 5 years follow ups after a stroke, one-fifth of caregivers experienced symptoms of anxiety and one-quarter had symptoms of depression[18] In addition, stroke survivors cognitive decline was found to be linked to both depressive and anxious symptoms in family caregivers[18].

IDENTIFYING EMOTIONAL ISSUES

Identifying emotional problems following a stroke can be difficult due to overlapping symptoms from the stroke and mental disorders, as well as impairment in cognitive, communication, and physical abilities. There are some evaluation strategies that can be implemented with recognised cut offs for individuals suffering from stroke which may include PH -9, GH - 28, SCID, etc[19]. However, it is important to not rely solely on these but also use our clinical acumen.

Certain risk factors like denial of physical symptoms, prior stressors increase the vulnerability to stress and possibility of psychological distress. Affective symptoms (such as deep sadness, anger, or anxiety), behavioural symptoms (like rapid anger outbursts or crying, rejection of disability, or withdrawal), and cognitive symptoms are the most common (e.g., reduced attention span, impaired memory, or aphasia).

Multiple studies have been done both at 6 month and 12 month time range which highlighted stroke survivors and their family caregivers had better mental health outcomes. In a recent study at 6 months of time range, personalised psychosocial intervention was done which resulted in a significant improvement in caregiver satisfaction[20]. Furthermore, in some studies, a dyadic psycho-educational intervention was found to be efficient in improving stroke survivors functional independence and the burden on family members for a brief period of time while also improving survivors long-term quality of life[21]. However, its effectiveness was found to be uncertain because other psychological and social health consequences for stroke survivors and their family carers have yet to significantly improve following treatment. A study done by Kalra and colleagues which included a randomised, controlled clinical study of 300 stroke primary caregiver in which 3 to 5 inpatient sessions, including one home visit session, were provided as part of the intervention group and included tailored psycho-educational topics as well as skill-building strategies[22]. the study improved a number of survivor and caregiver outcomes. Similarly another study resulted in cost savings in addition to the improved caregiver outcomes[23].

Marginalization and associated social stigma also seem to contribute to social isolation which may result in embarrassment and avoidance across a variety of social situations[24]. Furthermore, some studies have found a link between denial and lessened fear, which has been linked to a delay in seeking medical attention and a poor outcome. As a result, in order to encourage patients to seek help, it is critical to help them overcome their challenges of illness.

One study s results supported the use of an instructional intervention to enhance results such as physical health, cognition, and quality of life in stroke patients, as well as caregiver burden of care. In addition, educational interventions based on ongoing communication with stroke survivors and their families were found to significantly improve depression, whereas educational interventions based on family-mediated exercises were found to significantly improve physical functioning in stroke survivors[25].

The most common challenges and impacts of stroke reported by family members are: Uncertainty about future health status, fear of having another stroke, negative emotions, and role changes after stroke. The qualitative study provides useful information about the difficulties faced by dyads, intervention topics to prioritise, and strategies to maximise feasibility, acceptability, and impact[26].

PSYCHOSOCIAL MANAGEMENT

Depression and Anxiety

Symptoms of anxiety and depression have been shown to respond to pharmacological and non-pharmacological interventions. However, in some studies problem of using medication for depressive symptoms in stroke patients have demonstrated the increased risk of developing negative consequences[27,28,29] indicating that medication should only be given in the case of severe depression. Although the efficacy of CBT in stroke patients has not been extensively studied, there is strong evidence that it is beneficial in the treatment of depressive episodes in the general population as well as in people who suffer from other physical ailments[30].

Depression can be commonly seen in stroke patients[31,32]. The first line of treatment for PSD should be pharmacological therapy with antidepressants and psychotherapy. The SSRI s like escitalopram and paroxetine are the most effective antidepressants, while the most effective psychotherapeutic intervention is cognitive behavioural therapy[33]. Despite the fact that this meta-analysis discovered that CBT has a positive effect on depressive symptoms in Post-Stroke Depression, because of the limitations of the included studies, the indication for CBT remains inconclusive. To validate the benefits of Cognitive Behaviour Therapy in Post-Stroke Depression, future studies of high-quality methodology are warranted[34].

Acupuncture and slow stroke back massage have been shown in some studies to reduce anxiety after a stroke[35]. However, most of psychological interventions still awaits empirical effectiveness in stroke conditions. Cognitive behaviour therapy has been discovered to be highly effective for anxiety disorders in older and working-age people,[34] but it needs to be tested further in stroke survivors. Furthermore, the role of other psychological interventions such as relaxation training, supportive and psychodynamic approaches need to be evaluated further in future researches[36,6,37].

Trauma-focused cognitive therapy is also beneficial in treating post-traumatic traumatic stress in the general public, but its effectiveness in those with post-stroke psychiatric conditions has yet to be determined. As some studies have demonstrated that having stroke itself is considered to be a traumatic event having an adverse downstream effects on physical health in patients and their caregivers[38].

Analyzing the effects of psychosocial interventions by type revealed that social support improved physical function significantly and behavioural therapy significantly reduced depression, but their effect sizes were also small. Recently a study confirmed that psychosocial interventions with stroke patients have a significant effect on physical function and depression, giving the future directions into the implementation of most effective interventions for improving physical function and reducing depression in stroke patients[39].

Functional Limitations

Stroke leads to functional consequences in various areas of a person s life, like social, occupational, personal, and family. Therefore, management efforts must also be focused on addressing these problems. Primary physicians can also aid the coping process by helping stroke survivors understand the illness and its repercussions, and the areas associated that are under their control. This can be achieved using a variety of means such as psycho education; supplying resources that can help them better understand the illness, and the process of rehabilitation, teaching them problem solving skills, etc.

Physicians/ therapists can also help their patients gain a sense of control and see the illness in a more manageable light. Furthermore, helping the patient develop a supportive social support system may also aid in alleviating symptoms of depression and facilitating coping behaviours[40].

Addressing psychological need and having a good support system should be accepted as essentials of the culture of services in stroke[41].

Motivational interviewing and problem solving therapy have a preventive effect. Psychological interventions like distress management, group therapy and music therapy also help, however; the evidence is limited[42]. Providing informational sources to patients and their caregivers, and regular follow ups are also effective ways that help to alleviate patients mood.

Grief counselling can also be used for stroke patients in order to help them deal with the psychological impacts of stroke[43].

Cognitive Rehabilitation

Cognitive rehabilitation has proved to be efficacious in reducing cognitive impairments after stroke and in improving functional outcomes. Based on the area of impairment, detailed profiling can be done and the required rehabilitation training provided[44]. Cognitive rehabilitation requires in depth evaluations of different brain functioning. Cognitive screening measures help to detect post-stroke dementia and also understand the pattern of cognitive impairments following a stroke. Mini Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are widely utilised to screen for areas of cognitive impairment. Middlesex Elderly Assessment of Mental State MEAMS is also shown to be sensitive to detect cognitive impairment after stroke.

Cognitive rehabilitation is an important step in the stroke rehabilitation process that employs fundamentals of restorative neurology and neuropsychology. The cognitive rehabilitation process includes assessing cognitive functions, identifying specific areas of impairment, and providing treatment, goal settings on the basis of which appropriate rehabilitation strategies are planned .At present, there is numerous sources of evidence to support the efficacy of cognitive rehabilitation for stroke neglect and aphasia . Specific intervention may also help

with apraxia, inattention, and executive dysfunction. Reparative strategies are the first treatment option for patients who have memory problems. Aside from specific cognitive deficits, emotional and physical disturbances, as well as social support, all have an impact on functional recovery. Comprehensive and integrated cognitive rehabilitation programmes are required to improve stroke patients day-to-day functioning[45].

According to the research, adding a strengths-based psycho education programme to the current rehabilitation protocol for stroke survivors may help survivors families manage a smooth transition to care[46]. Another study found that: (1) CRT reduced cognitive impairment as measured by MOCA and MMSE scores; (2) CRT lessened anxiety as measured by HADS anxiety and SAS scores; and (3) CRT had a role in remission of depression as measured by HADS depression and SDS scores in patients after stroke. Results: Comprehensive rehabilitation training (CRT) helped stroke patients recover from cognitive impairment and reduce the incidence of post stroke anxiety, depression, and dementia. It significantly prevented the impairment of cognitive function, anxiety, and improved activities of daily living in stroke patients[47,46].

Self Management

Patients self-management of stroke and other chronic conditions can be viewed as an iterative procedure encompassing multidimensional strategies for meeting self-identified needs in order to deal with problems in their daily activities. Self-management does not have a universal definition, however it is generally identified as a person s capacity to deal with the symptoms, therapeutic interventions, physical and mental effects, and lifestyle changes that are associated with living with a chronic disease. Rather than an end point or result in and of itself, self-management is chiefly a multi - dimensional process that affects and leads to outcomes. Systematic reviews of studies on the effects of self-management interventions found that self-management intervention strategies may enhance life quality and thus self-efficacy in post-stroke patients[48,49]. Self-management interventions may improve self-management, self-efficacy, life quality everyday routines, and other psychological functions in stroke patients over the age of 65 [50]. Although psychological support and emotional support appear to be more effective, self-management techniques may enhance the efficiency and emotional well-being of nurse-led stroke aftercare[51].

In self-management strategies, exercises have also been recommended by the American Stroke Association guidelines as a part of optimal stroke rehabilitation[52]. Furthermore, it encourages stroke survivors to actively reflect on followed by taking initiative and responsibility for their daily activities[53]. This method can be supported by incorporating social networks and social contexts. Another comprehensive study recommends a comparable strategy in a qualitative meta-synthesis which appears to be worthwhile to investigate the psychosocial self-management support which is found to be especially beneficial for elderly people suffering from stroke[54].

Peer support is important self-management interventions which may help stroke survivors improve their physical and psychological outcomes[55,56]. The evidence regarding the effects of peer support on community engagement and life quality is mixed, emphasising the need for additional high-quality research to back up these findings[57].

Considerable literature identifies numerous mechanisms of action through which peers can help with stroke management. First, in a study examining the standards of a group self-management treatment, stroke survivors revealed that they believed peers could assist problem solving and experience sharing because they had experienced the same stroke. Second, peers can provide emotional support by validating thoughts that two-tenths of stroke survivors currently believe are insufficient. Finally, qualitative results from the Chronic Illness Self-Management Programme indicate that peers provide a social comparison platform[58,59].

CONCLUSION

Psychosocial interventions have shown effectiveness in improving overall health related outcomes and promoting positive sense of well being. The current review has attempted to examine the utility of these interventions. Existing evidence suggest the role of self management and adaptation to new learning approaches in improving health related outcomes and self-efficacy. In addition, neuropsychological interventions, adapting to new coping strategies and activities of daily living are being given the utmost importance in the emerging researches. However, despite having considerable empirical support and utility of various psychosocial interventions in post stroke management, several shortcomings have been identified in our present review. Firstly with respect to emotional disturbances, there has still been limited evidence regarding the efficacies of various interventions in ameliorating depressive and anxiety symptoms. Secondly, lack of empirical support has also been noticed in improving life quality, self-efficacy& adaptable coping strategies for stroke survivors and their caregivers. Thirdly, due to the increasing incidence or number of stroke patients there is a strong need for trained and skilled specialists which is still lacking. Lastly, empirical support on the effects of psychosocial methods is also found to be limited. Hence, more researches on various psychosocial interventions are strongly warranted to further examine the format and optimal number of sessions.

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Review

Phosphodiesterase Inhibitors: A Review

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ABSTRACT

Phosphodiesterase Inhibitors are class of drugs, actively inhibiting the specific target Phosphodiesterase Enzymes (PDE).FDA approved to be used in myriad of disorders such as Chronic Obstructive Pulmonary Disease (COPD), Erectile Dysfunction (ED), Benign Prostatic Hyperplasia (BPH), Pulmonary Artery Hypertension (PAH), Bronchial Asthma (BA) etc. The primary mechanism of PDE Inhibitors is smooth muscle relaxation and bronchodilation by inhibiting Cyclic Guanosine Monophosphate (cGMP) and Cyclic Adenosine Monophosphate (cAMP) degradation by acting on Nitric Oxide (NO) led pathway. This role of PDE Inhibitors is beneficial in so many conditions, as cGMP and cAMP pathways are present in numerous areas. We present a review on current state uses of PDE Inhibitors and their potential future therapy of experimental uses having off label effects utilising the Nitric Oxide led pathways as the core basis.

KEYWORDS: Phosphodiesterase Enzyme (PDE), cAMP, cGMP, Nitric Oxide, Platelet aggregation, Sildenafil, Tadalafil.

INTRODUCTION

Henry Hyde Salter was a British physician who is considered to be the first to document Phosphodiesterase (PDE) inhibitor. In his book on asthma, he advised having a strong cup of coffee empty stomach in the morning to control asthmatic attack, which actually denoted the weak PDE inhibitory effect of caffeine[1].

It is understood that PDE Inhibitors are the drugs which acts by blocking the PDE Enzyme and its five subtypes. This in turn ceases the inactivation of the Cyclic Adenosine Monophosphate (cAMP) and Cyclic Guanosine Monophosphate (cGMP) which are the secondary messengers in the intracellular compartment.

HISTORY

The first documentation for the isolation of these enzymes are found in the year of 1970, which was done from rat brains[2]. Weiss and Hait first identified the pharmacological and therapeutic properties of PDE in 1977[3].

Beavo identified and classified the multiple subtypes of PDE and placed them under the PDE Super family umbrella. (Table □ 1)[4]

Given the widespread tissue expression of PDE, a wide range of drugs are available targeting various conditions.

Table 1: Phosphodiesterase Inhibitors and Drug Examples

Group	Expressive Tissue	Inhibiting Drugs
PDE-1	Smooth muscles, lung, brain, heart	KS-505a, Vinpocetine
PDE-2	Platelets, Liver, Lung, Adrenal Gland	EHNA
PDE-3	Adipose tissue, Inflammatory precursors, Cardiac Cells	Milrinone, Cilostazol, Anagrelide
PDE-4	Sertoli cells, renal cells, nervous cells	Roflumilast, Cilomilast
PDE-5	Smooth muscle cells, vascular cells, platelets	Sildenafil, aprinast
PDE-6	Photoreceptor cells	Dipyridamole
PDE-7	Skeletal tissue, cardiac cells, pancreatic cells, T Immune cells (Lymphocytes)	IC242
PDE-8	Testicular cells, hepatic cells, ovarian cells	aprinast
PDE-9	Renal, hepatic, nervous, lung	BAY-73-6691
PDE-10	Testicular cells	-
PDE-11	Salivary glands, pituitary cells	-

INDIVIDUAL SUBTYPES AND MECHANISMS

The primary mechanism of the PDE is to isolate the phosphate molecule from the target ell and reduce the amount of cAMP / cGMP. Now when this enzyme is inhibited through selective blockade it stops from cAMP and cGMP to degrade further and in turn preserving their primary effect such as bronchodilation, vasodilation, smooth muscle relaxation etc.

PDE-3

PDE-3 inhibitors specifically target the cardiac cells, they increase the cAMP volume in the peripheral vasculature as well as myocardial cells and platelets, resulting in peripheral vasodilation, increased ionized calcium in myocardial cells and preventing platelet aggregation. These properties are effective in treatment of Peripheral Vascular Disease (Arterial) and heart failure. Milrinone, Cilastazole, Anagrelide are commonly employed[5].

PDE-4

PDE-4 has a degradative impact on the cAMP substrate. They are the most abundant of all the PDE subtypes. There are around 20 subtypes of PDE-4 Inhibitors. PDE-4 target hydrolyzation of cAMP in both nervous and immune cells[6]. PDE-4 inhibitors have multiple uses. Their cognition benefits are well known to improve long term memory[7] along with numerous other cognition benefits such as alertness[8]. They also prevent excitotoxic damage to neuronal cells[9]

There are distinct subvariants of PDE-4 inhibitors, differentiated on the basis of target action and mechanism.The

Table 2: Sub Variants of PDE 4

Sub Variants	Expression, Action
PDE4A, PDE4D	Antidepressant
PDE4-B	Antipsychotic
PDE4-C	Expressed in peripheral circulation (Anti-Inflammatory), alcohol de-addiction
PDE4-D	Area postrema Potent emetic

prototype examples of PDE -4 Inhibitors:

- Cilomilast
- Crisaborole
- Ibudilast
- Roflumilast
- Rolipram

Apart from constitutional adverse effects such as vomiting, nausea, Roflumilast is notorious to cause urinary tract and upper respiratory tract disorders[10].

PDE-5

The fifth subtype of PDE Inhibitors, PDE-5 is a cGMP related variant. It was first isolated from platelets in rat blood in the year of 1978, termed as cGMP-PDE[11]. The first PDE-5 Inhibitor to be given in humans was aprinast. It was given in patients suffering from exercise induced asthma, it was given for its bronchodilator effect[12]. PDE-5 Inhibitors were also considered as a promising agent in cardiovascular medicine due to their effects on vaso-relaxation and smooth muscle relaxation[13]. After being studied its effect in rat blood, in 1992 Rajfer et al[14]. studied that similarly as in rat blood, the Nitric Oxide (NO) formation was stimulated by Electrical Field Stimulation (EFS) in human corpus cavernosum also, which in turn bringing relaxation. This effect was particularly diminished, or if not then its reduced in impotent males. He further studied aprinast and demonstrated that it further stimulates the relaxation of corpus cavernosum induced by Nitric Oxide, giving us the most widely employed use of PDE-5 Impotency[14].

PDE-5 Inhibitor agents such as Sildenafil Tadalafil and Vardenafil are used in the treatment of erectile dysfunction[15]. Due to their affinity for cGMP and effect on Nitric Oxide reducing pathway, PDE-5 inhibitors are also used in treating some variants of pulmonary hypertension and benign prostatic hyperplasia. In patients suffering from PAH, PDE-5 inhibitors have significant effect on mortality and also on substantial improvement in quality of life, more so in patients suffering from PAH due to right heart failure[16].

PDE-5 was initially discovered by a British physician named Henry Salter, who discovered the bronchodilator effects of caffeine when a bronchial asthma patient got relief from his symptoms after having a strong cup of coffee[17]. And for the beneficial effects of Angina, initial pre-clinical work was started by Pfizer. Current available marketable agents are Sildenafil, Tadalafil, aprinast, Vardenafil, Icaria etc[18].

PDE- 7, 9, 10

uinazoline a type of PDE-7 inhibitor has been used for its neuroprotective and anti-inflammatory effects[19].

The primary metabolite of caffeine Paraxanthine, inhibits the PDE-9 receptor whose primary affinity is with cGMP. It is almost similar to PDE-5 in expression, especially in corpus cavernosum[20].

A common opioid alkaloid derivative Papaverine is proven to inhibit the PDE-10 receptor. The PDE-10 is seen exclusively in the striatum, and they increase cAMP and cGMP following

inhibition by agents such as Papaverine. It was documented that PDE10-A inhibition increases the cAMP level, this effect correlates to the hypoactivity in brain. The determinant of this action is mainly related to the elevation in cAMP levels by the inhibitors and its capacity to do so[21].

improve attention, cognition, memory registration, inhibition, and processing information. The Long Term Potentiation (LTP) is a favourable property of these PDE Inhibitors. Hope lies on a potential isotope of PDE Inhibitor that helps in aged brain such as in Alzheimer which has acceptable rate of side effects[24].

Table 2: Summary of various PDE - Inhibitors

PDE Group	Disease Target
PDE 2	Acute Respiratory Distress Syndrome, Sepsis[22]
PDE 3	PVD, Heart failure etc.
PDE 4	Depression, Alzheimer's disease, Memory Loss etc.
PDE 5	Erectile Dysfunction, Pulmonary Hypertension, Premature Ejaculation, Renal Failure
PDE 7	Anti Inflammatory
PDE 9	Psychostimulant
PDE 10	Antipsychotic

NOVEL POTENTIAL USE

Neuroprotective Role

Numerous disquiets related to the central nervous system over the period of time end up tarnishing the structural format of the architecture. This leads to dysfunctional CNS and also a dysregulated and curtailed repair. To counteract the damage by nervous system disorders and trauma, the intracellular signals comprising mainly of cGMP and cAMP which regulates the inflammation, cell death (neuronal), immune response, neuroplasticity has to be altered. As we discussed earlier, PDEs have an inhibitory effect on these regulators.

In an event of neurotrauma or pathology, PDEs hydrolyse the cGMP and cAMP to 5□GMP and 5□AMP. This inhibits the ongoing process and promotes inflammation and destruction. Inhibiting this PDEs effect has a potential role in neuroprotective and repair process[23].

Out of the entire family, PDEs 2,4,5,9,10 has been proven to

Pleiotropism and Cardiovascular Medicine

The PDE-5 inhibitor Tadalafil, Sildenafil has been also proven to improve the left ventricular function when given with Doxorubicin (Anthracycline derivative □ chemotherapeutic agent) and it also has an inhibitory effect in LV dysfunction and apoptosis caused by Doxorubicin. Inhibition has been led by the same cGMP and cAMP upregulation along with the reactive oxygen species (ROS) superoxide dismutase (SOD). This effect does not hamper the chemotherapeutic effect of the agent[25,26,27].

The ROS (Mitochondrial) has been reported to improve killing of neoplastic cells. Doxorubicin acts by increased production of ROS in cancer cells[26]. When combined with sildenafil, this production is further increased exponentially. This killings are independent of p53[28].

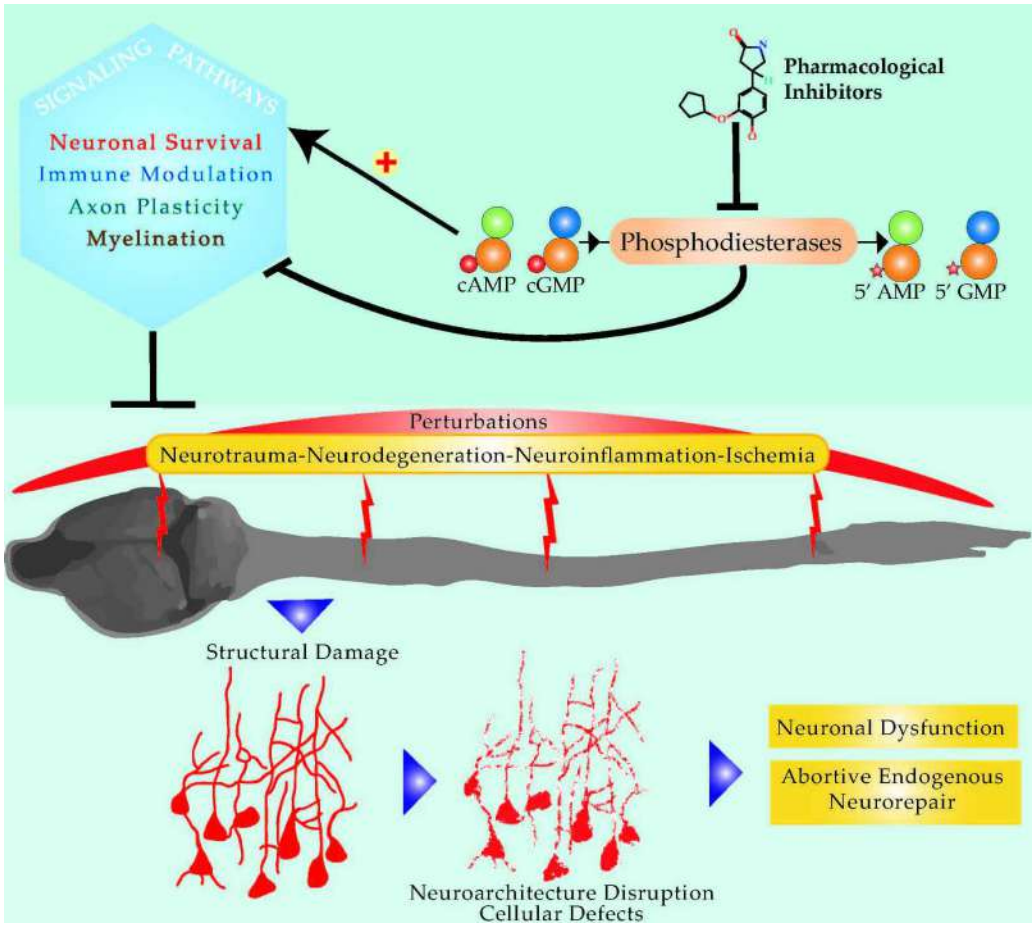

Figure 1: Role of PDEs in Neurodegeneration and therapeutic role of PDE Inhibitors[23]
(Image re-used under creative commons licence)

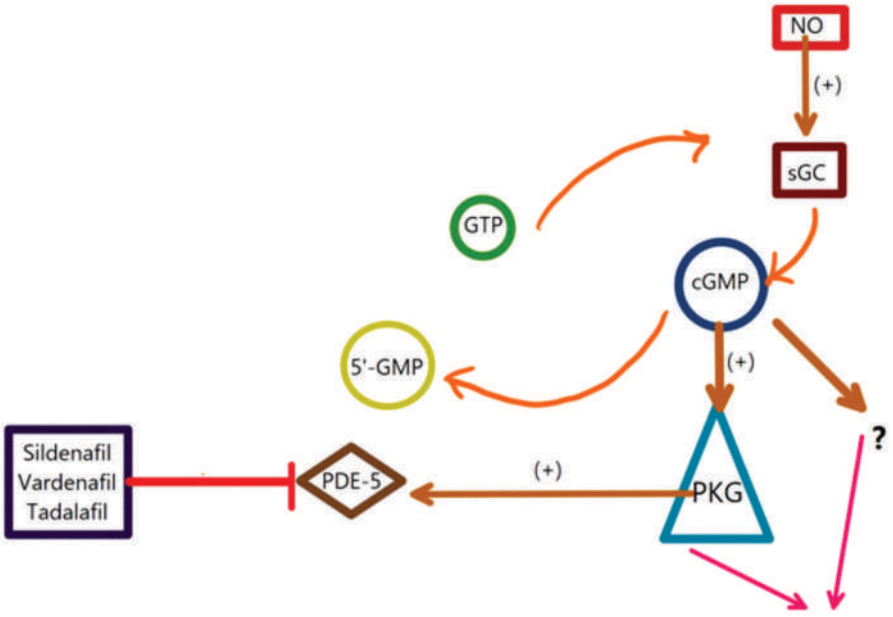

Figure 2: cGMP PDE 5 Site of action Pathway
(Image redrawn from Gross G[29].)

The increase in cAMP could potentially affect cardiac function, vascularity of heart and the tonicity. They have been proven useful also in stroke (cerebral and cardiac), peripheral vascular disorders and severe heart failure[30]. Pentoxifylline was the first PDE inhibitor to be approved in treatment of limb claudication. However, studies were inconclusive for the same[31,32] The most recent addition in the similar use-case is Cilastazole. The therapeutic benefits are much better compared to Pentoxifylline[33]. It is reported that Cilastazole reduces plasma triglyceride (TGL) levels, and upsurges High Density Lipoproteins (HDL)[34]. Cilastazole has also been shown to reduce the occurrence of coronary restenosis post Percutaneous Transluminal Coronary Angioplasty (PTCA)[35]. Current state of PDE Inhibitors in cardiovascular disease is limited to two approved agents. Pentoxifylline and Cilastazole for intermittent claudication in oral form and Milrinone for acute congestive heart failure intravenously[36].

shown to reduce the serum Lactate Dehydrogenase (LDH) levels with substantial increase lymphocyte count[39]. Milrinone has also shown to improve cardiac function and beneficial in immune dysregulation in septic conditions when given with Esmolol[40]. Reduction in pulmonary arterial pressure and mean arterial pressure is seen in early stages of ARDS induced by severe COVID-19 with Sildenafil[41].

The world entered in a stage of Pandemic because of the havoc created by the deadly SARS CoV -2. The viral pneumonia caused by SARS CoV -2 virus led to severe immune response and dysregulated cytokine recruitment leading to severe ARDS and residual deadly fibrosis. The effect on NO led cGMP cAMP axis of PDE-5 is being studied as a phase three trial given the fact that PDE5 primarily has pulmonary expression. They reduce the cytokine recruitment and alveolar necrosis[42].

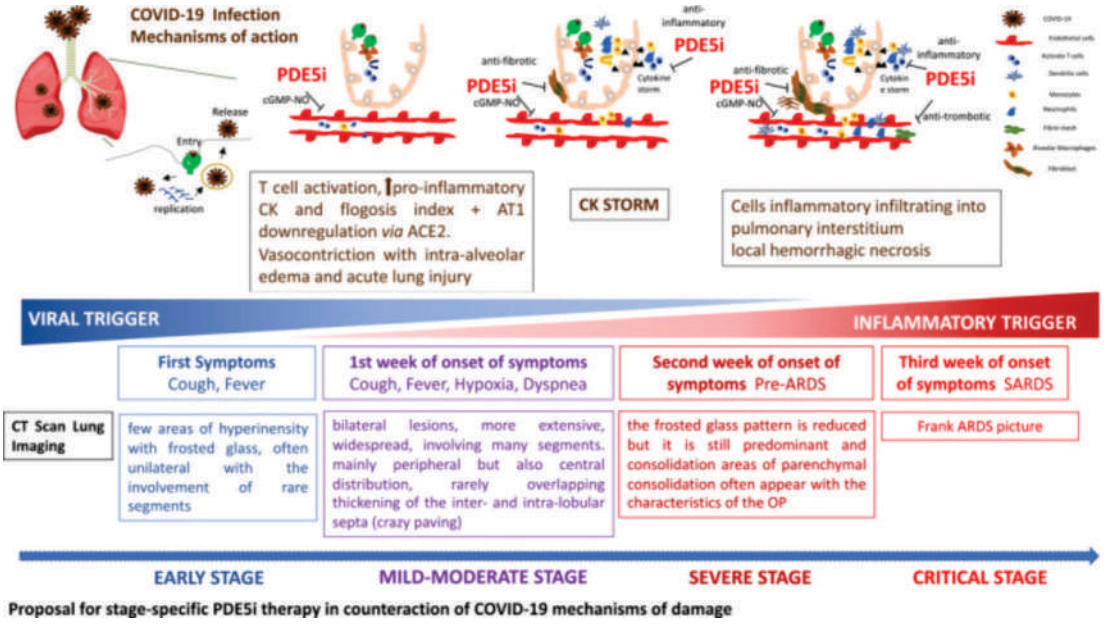

Figure 3: A proposal for PDE Inhibitor in COVID -19

(Image re-used under public health emergency permission. Image by Isadora AM et al[42].)

Acute Lung Injury and COVID -19

The story of PDE Inhibitor started with beneficial effect of caffeine in bronchial asthma patients due to its bronchodilator properties[1]. But in Acute Lung Injury especially such as ARDS, pneumonia or acute exacerbations of COPD, the pathology is mainly due to dysregulated immune response and cytokine recruitment. In a study done by Salari et al. it was reported that Aminophylline significantly reduced Epidermal Growth Factor Levels (EGF) when introduced in mechanically ventilated patients with PEEP. Both in conjunction reduced the overall Acute Physiology and Chronic Health Evaluation (APACHE) Pi score[37]. Experimental evidence shows that Pentoxifylline improves the oxygen transport and hemodynamic stability in critically ill patients suffering from septic shock[38]. Pentoxifylline was also

Anti-Platelet Therapy

Platelet aggregation is a vital step in the coagulation cascade. The pivotal messengers cAMP and cGMP do exert a robust inhibition on the essential platelet function. The basic principle behind the potential role of PDE Inhibitors in platelet aggregation inhibition is increasing the platelet activating nucleotide which in turn interferes with the cytoskeletal fibrinogen activation, recruitment of pro-inflammatory mediators and degranulation. This affect can be achieved by activating the quintessential cAMP and cGMP pathways[47].

Caffeine was administered as a 250mg oral dose thrice a day for a week in healthy volunteers, they all showed reduced platelet aggregation, upregulation of platelet adenosine receptors and increased cAMP[48]. This characteristic of caffeine as a platelet

inhibitor was first seen in 1967[49]. Only PDE2, PDE3 and PDE5 have been seen being secreted from platelets[50].

- **PDE-2**

PDE-2 acts by hindering the thrombin led platelet aggregation due to nitroprusside[51].

Currently numerous thienylacyl hydrazone derivatives are studied as a PDE-2 representative for their platelet aggregating characteristic[52].

- **PDE-3**

PDE3A is the primary subtype of PDE3 exerted by platelets.[53] Anagrelidehas been found to be causing thrombocytopaenia in humans[54] even though it is a platelet aggregator inhibitor[55]. Another agent Cilastazole also hinders platelet aggregation. It more commonly acts on platelet aggregation led by ADP, collagen fibres and arachidonic acid[56,57]. An enhanced antiplatelet effect was seen when Cilastazole was given in combination with aspirin plusclopidogrelin primary PTCA patients of Myocardial Infarction[58,59]. Along with this Cilostazol has been used in preventing stent restenosis also[60].

Cilastazole has been widely lauded as an excellent agent to prevent stroke and myocardial infarction. Numerous studies including Cilastazole Stroke Prevention Study (CSPS 1&2) shows that Cilastazole reduces the stroke risk significantly along with that it is proven better than Aspirin prophylaxis alone[61,62].

After being discovered to inhibit platelet aggregation in rabbits,[63] all eyes turned to Dipyridamole as another potential antithrombotic element of PDE3 □ PDE5 inhibitor especially in stent restenosis[64]. Dipyridamole enhances the Nitric Oxide inhibition on rabbit as well as human platelets[65]. However, there is scarce clinical literature to support the evidence that Dipyridamole can be used as a singular anti platelet agent. But combination use has been promising. The two large scale ESPS2 & ESRIT trial concluded that when used with low-dose of aspirin in cerebrovascular stroke patients, the outcome is more favourable than aspirin alone[66,67]. The American College of Chest Physicians (ACCP) took charge over these studied and in 2008 started recommending dual Anti-platelet therapy with Dipyridamole in stroke or ischaemic event patients[68]. Not just with aspirin, dipyridamole has been proven to be more efficacious in thrombus prevention in patients with artificial heart valves with warfarin prophylaxis[69].

- **PDE -5**

A very potent PDE-5 inhibitor Sildenafil is widely used in treatment of Erectile Dysfunction. But along with this, there is promising role of Sildenafil as anti platelet agent. Very few clinical studies have been employed for the use-case. In a clinical study of healthy volunteers, sildenafil hindered the collagen led platelet aggregation (in doses of 100mg), with enhanced effect if given in conjunction with nitrates[70].

In a study of 30 healthy male volunteers Sildenafil was administered in doses of 50 and 100mg in two randomised groups to see platelet aggregation. It was seen that Sildenafil did in fact improve platelet aggregation ex-vivo, more so on 100mg dose. However ADP led platelet aggregation remained unaffected[71].

This led to research gap in PDE-5 Inhibitor□s effect on ADP Induced platelet aggregation. Following up on that, In another study done on 30 male healthy individuals, different PDE-5 agent Tadalafil was administered in a single dose of 10/20 mg to observe its effect on platelet aggregation. The study observed that Tadalafil is actually an effective platelet aggregation inhibitor when induced by ADP and Collagen. The 20mg dose proved to be more effective.

CONCLUSION

PDE Inhibitors are diverse class of drugs having significant therapeutic benefit in numerous diseases. Because of its affect on cAMP and cGMP pathways, they do have a promising role in so many new areas, which are still yet unknown. Be it from using it in ED, Acute Lung Injury or Platelet aggregation, the future looks promising for PDE Inhibitors and appropriate clinical backing is required to prove the theoretical claims.

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Commentary

Help Seeking Behavior: A Crucial Life Skill

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In simple words, seeking help is a basic ability to ask for assistance from others when one is in need. Humans are by definition social beings and we need each other not only to connect meaningfully but also to depend during the times of need. It s safe to say that the need for help is universal for humans.

One of the most common words and concepts learnt very early on in life are help and helping but interestingly the idea of seeking help still makes many people uncomfortable. It can be said that helping comes easy because it is associated with a power position of giving, virtue of compassion, kindness and a consequent feeling of satisfaction.

Asking for help on the contrary seems to be mistakenly associated with being weak or inadequate. There are fears of being judged, rejected or having to hear a no with asking for help. It also involves the feeling of giving another a superior place in one s life, becoming obligated and feeling pressured. These beliefs and assumptions surrounding help seeking behaviors discourage people from reaching out for assistance and they continue to feel emotional overwhelm, which affects their physical, emotional, social, occupational as well spiritual wellbeing.

It is commonly observed that there are significant gender differences in help seeking behaviors. Females and males tend to differ in their help seeking behaviors. Additionally it has been observed that seeking help in some areas of life comes easy compared to others.

Help seeking behavior has immense importance for one s well being. Thus, it is crucial to become open to seeking help. Following are some of the ways that can assist in help seeking.

Identifying one s irrational beliefs about help seeking: it is crucial to identify one s irrational and limiting beliefs about help seeking. Socio-culturally popular stereotypes, notions and beliefs can impact one s attitude towards help seeking. It is frequently seen that people are less open to seeking help in a culture that looks down upon seeking help. Thus it is important to identify the irrational cultural beliefs that discourage help seeking.

Logical understanding of help seeking: after identifying the irrational beliefs that stop one from seeking help.

Normalizing asking for help: It is very important to normalize the need to ask for help. Recognizing oneself as human, and accepting that one cannot do it all or be it all, all the time is key, needing help is human, and asking for it is intelligent as it helps in efficient resolution of issues.

Helping others respectfully: One of the most beautiful gestures is to help others, it brings joy and also makes one feel that it is okay to be in the place of a receiver. As helper and helpee both are humans and both are equally respectable. Helping respectfully shifts the negative perspective around seeking help.

Counting the benefits of help seeking behavior: It is important to count the benefits of help seeking behavior.

Keeping a diary and recording how a problem got solved easily, on time and did not exhaust one with help seeking behavior helps in the maintenance of help seeking behavior.

CONCLUSION

Help seeking behaviors needs to be encouraged as an essential life skill in all the areas of life for all. Interdependence needs to be understood as a basic human need and schools need to teach the importance of timely help seeking behaviors to young children. This shall normalize the idea of seeking help in people and minimize the hesitation and stigma.

If only individuals could identify the need for help, had access to adequate help and reach out for timely intervention, most problems could be nipped in the bud.

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Announcement

Pacific Group Plans Longitudinal Studies and an International Conference on Food, Genetics and Pathogenesis of Diseases

(Presumptive Note)

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Food and nutrients either directly or indirectly through genetic variation in the humans can lead to pathogenesis of a variety of diseases, including cardio-metabolic, psychosomatic, somato-psychic and even malignant aliments. Though, nutrients and foods usually interact with genes in a benign manner, but sometimes, this interaction can have fatal outcomes"[1]. Therefore, diet, genetics and disease studies are gaining significance world over with the coming up of ever newer evidences that "nutrition can contribute to disease pathogenesis directly as well as indirectly genetic variation[2]. Increasing number of cardio-metabolic deaths are largely linked to eating habits of people. Nutrigenomic and nutrigenetic studies have been exploring interaction between nutrients and genes.

In view of this, the **Pacific Group of Universities proposes to study food borne, dietary, nutritional, nutrigenomic and nutrigenetic etiology of aliments and diseases along with an international conference.**

DIETARY CHANGES AND INCREASING PREVALENCE OF CHRONIC DISEASES

Drastic changes are taking place in the human diet from traditional and ethnic foods to a wide range of pre -cooked and packaged foods. It is associated with an unparalleled increase in the prevalence of chronic diseases. Kitchen inventories have also been undergoing changes very fast. For instance, with respect to cooking inventories, till 1990s the cooking oils being used were mostly the mustard, groundnut, sesame, coconut etc. Today, the share of these conventional oils has come down to one fourth, as 50 of these conventional oils have been replaced by palmolein and 25 by the soybean oil. **Soyabean oil has recently been linked to genetic degeneration in the brain, leading to retardation of as many as 100 genes[3]. Likewise, palm oil is also being linked to atherosclerosis as well as certain aliments of heart, liver and kidneys, including cancer after culinary use [4].**

Food Nutrients and Health Studies are Vital: The nutrients in food enable the cells in our bodies to perform their necessary functions. These nutrients are nourishing substances in food that are essential for the growth, development and maintenance of body functions. Nutrients give our bodies instructions about how to function. In the sense, food can be seen as a source of information for the body[5]. Thus, nutrition goes beyond calories or grams, and good foods or bad foods.

Nutritional Genomics is Vital for Future Generations' Health Profile: Nutritional Genomics has gained much significance because, food induced genomic changes, including gene expressions(s) and gene variations not only affect the health and eruption of diseases of the person eating those foods, but his or her off-springs and later generations might also suffer from a host of health related problems. Nutritional genomics comprises nutrigenomics and nutrigenetics - these would be explained little later in this article.

Palm oil and Disease Pathogenesis: Palm oil contains 52 percent saturated fatty acids and is therefore considered hazardous to cardiovascular health. Oxidized palm oil

presents even greater health risks. **The oxidization in palm oil occurs during processing for culinary use, generating toxins that adversely affect the heart, liver, kidneys and lungs[6]. Though, raw or unprocessed palm oil isn't associated with these effects when fresh; however, studies link a boost in atherosclerosis development in as little as six months when reheating of palm oil occurs to cook foods. Palm oil can reduce the effectiveness of medicines designed to reduce blood clotting, such as warfarin, enoxaparin and dalteparin[7].**

Moreover, carcinogenesis from palmolein is also emerging as major health concern[8]. Processing and heating of palm oil causes glycidyl fatty acid esters (GEs) to form. When digested, these GEs break down and release glycerol, known for its carcinogenic effects in animals. The same may be suspected in humans.

Soybean Oil and Genetic Degeneration in Brain: In a recent study at the University of California (UC) at Riverside, researchers reported a link between soybean oil and genetic changes in the brains of mice. Researchers in 2015 examined the potential contribution of soyabean to cause obesity and diabetes and reconfirmed it. Soybean oil has shown impact on the brain, especially changes in the hypothalamus, a brain region associated with a number of functions like body weight, metabolism, body temperature, reproduction and stress response. **The researchers also concluded that certain genes in the mice that were given soybean oil weren't operating properly. Identifying about 100 of them, they noticed one particular gene that produces oxytocin, also known as the love hormone and essential for parent-child bonding seemed to be impaired in mice that ate soybean oil. Among those mice, oxytocin levels were lower than normal, when the researchers tested coconut oil on the mice. They found, it didn't produce as many gene changes in the hypothalamus as the soybean oil did[9,10].**

FOOD, GENE EXPRESSION AND GENETIC VARIATION

The interaction between nutrition, metabolism, and gene expression is mandatory for maintenance of body homeostasis. Nutrition related or dependent disorders have been reported to be the result of a combination of nutrients with multiple genes not with single gene[11,12]. Genetic variation is the major basis for person-to-person divergence in response to diet. Understanding how genetic variation influences gene expression and recognizing genetic variants as risk factors for human nutrition dependent or related disorders is the focus of nutrigenetics[13].

NUTRITIONAL GENOMICS

Nutrition is found to define and mark the gene expression and metabolic responses with marked effect on the individual s health condition and susceptibility to disease[14]. Nutrients also regulate the transcription factors that modify the gene expression, up or down, consequently, adjust the metabolic responses at the molecular level. Nutritional Genomics comprises Nutrigenomics as well as Nutrigenitics.

Nutrigenetics explains mechanism by which genetic variations define the risk of individual to diseases, nutrient daily requirements, cellular metabolic response and behavior towards the bioactive dietary components or nutritional therapy. The main target of that is to clarify the impact of the gene variability on the interaction between nutrients and diseases. Nutrigenomics explains the genome-broad impact of nutrition, especially the functional effect of various food components on the (- omes) branch of science including genome, transcriptome, proteome, and metabolome[14].

DIET AND CARDIO-METABOLIC DISEASE RELATIONSHIPS

It is well established that excess sugar, salt, or fat in diet raise the risk for certain diseases. Healthy eating lowers risk for heart disease, stroke, diabetes, and other health conditions. A healthy eating for humans indeed comprises vegetables, fruits, whole grains, and fat-free or low fat dairy products; includes beans, eggs, and nuts; with less saturated and trans fats, sodium, and added sugars[15]. The major cardio-metabolic diseases, stroke and type 2 diabetes are largely related to food and anxiety, etc.

In U.S., the highest percentage of cardio-metabolic disease-related death (9.5) was related to excess consumption of sodium. Not eating enough nuts and seeds (8.5), seafood omega-3 fats (7.8), vegetables (7.6), fruits (7.5), whole grains (5.9), or polyunsaturated fats (2.3) also increased risk of death compared with people who had an optimal intake of these foods/nutrients. Eating too much processed meat (8.2), sugar sweetened beverages (7.4) and unprocessed red meat (0.4) also raised the risk of heart disease, stroke and type 2 diabetes related deaths[16].

NUTRIENTS, GENES AND DISEASE PATHOGENESIS

Nutrigenomics and nutrigenetics explore the interaction between nutrients and genes. This may reveal the genome wide effects of nutrients on transcriptome, proteome, and metabolome in cells, tissues, or organisms. It may also be useful in understanding how nutrients can affect the metabolic pathways and how these regulations can be inhibited in the early phase of diet related and diet dependent diseases[17]. Major Findings of nutritional genomics reveal that how diet ingredients change the gene structure and or gene expression, and consequently the human genome. Besides the genes dependent on dietary factors in its regulation may have a role in the commencement, extent, advancement, and progression of chronic diseases[18].

APPENDIX: SOME EXAMPLES OF NUTRITIONAL GENOMICS

Examples of Nutrigenomics: Dietary cholesterol performs an inhibitory effect on the transcription - hydroxy-methylglutary-CoA reductase gene. Dietary polyunsaturated fatty acids repress mRNA production of fatty acid synthase in hepatocytes through decreasing mRNA for lipogenic enzymes. This process depends on the degree of instauration of fatty acids[19].

Phenylketonuria is an example of single gene mutation. And such patients should avoid phenylalanine-rich food. Many Asian populations have the problem of deficiency of the aldehyde dehydrogenase enzyme, which is responsible for metabolism of ethanol. This leads to an annoying manifestation in affected individuals after ingestion of alcohol[20].

Examples of Nutrigenetics: The methyletetetrahydrofolate reductase gene (MTHFR) is a well-defined example of a gene-nutrient interaction. MTHFR is involved in the metabolism of folic acid and maintenance of the normal blood level of homocysteine. A particular MTHFR gene SNP is associated with elevated homocysteine levels in the blood of carriers, especially if there is a dietary deficiency of folic acid[21].

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New Drug Approvals

- **Quviviq (daridorexant) Tablets**

  Date of Approval: January 7, 2022
  Company: Idorsia Ltd.
  Treatment for: Insomnia

  uviviq (daridorexant) is a dual orexin receptor antagonist (DORA) for the treatment of insomnia.

  FDA Approves uviviq (daridorexant) for the Treatment of Adults with Insomnia.

- **Cibinqo (abrocitinib) Tablets**

  Date of Approval: January 14, 2022
  Company: Pfizer Inc.
  Treatment for: Atopic Dermatitis

  Cibinqo (abrocitinib) is a Janus kinase (JAK) 1 inhibitor for the treatment of adults with refractory, moderate-to-severe atopic dermatitis (AD).

  FDA Approves Cibinqo (abrocitinib) for Adults with Moderate-to-Severe Atopic Dermatitis.

- **Ryaltris (mometasone furoate and olopatadine hydrochloride) Nasal Spray**

  Date of Approval: January 13, 2022
  Company: Glenmark Pharmaceuticals, Inc.
  Treatment for: Allergic Rhinitis

  Ryaltris (mometasone and olopatadine) nasal spray is a corticosteroid and antihistamine combination for the treatment of seasonal allergic rhinitis (SAR) in patients 12 years of age and older.

  FDA Approves Ryaltris (mometasone and olopatadine) Nasal Spray for Seasonal Allergic Rhinitis.

- **Kimmtrak (tebentafusp-tebn) Injection**

  Date of Approval: January 25, 2022
  Company: Immunocore
  Treatment for: Uveal Melanoma

  Kimmtrak (tebentafusp-tebn) is a bispecific gp100 peptide-HLA-directed CD3 T cell engager indicated for the treatment of HLA-A 02:01-positive adult patients with unresectable or metastatic uveal melanoma.

  FDA Approves Kimmtrak (tebentafusp-tebn) for the Treatment of Unresectable or Metastatic Uveal Melanoma.

- **Vabysmo (faricimab-svoa) Intravitreal Injection**

  Date of Approval: January 28, 2022
  Company: Genentech
  Treatment for: Macular Degeneration, Diabetic Macular Edema

  Vabysmo (faricimab-svoa) is a bispecific antibody targeting the vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) pathways for the treatment of neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema (DME).

  FDA Approves Vabysmo (faricimab-svoa) for the Treatment of Neovascular (Wet) Age-Related Macular Degeneration and Diabetic Macular Edema.

- **Spikevax (Moderna COVID-19 Vaccine) (COVID-19 Vaccine, mRNA) Injection - formerly mRNA-1273**

  Date of Approval: January 31, 2022
  Company: Moderna, Inc.
  Treatment for: Prevention of COVID-19

  Spikevax (COVID-19 Vaccine, mRNA) is an mRNA vaccine that can be used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

  Moderna Receives Full U.S. FDA Approval for COVID-19 Vaccine Spikevax.

- **Enjaymo (sutimlimab-jome) Injection**

  Date of Approval: February 4, 2022
  Company: Sanofi
  Treatment for: Cold Agglutinin Disease

  Enjaymo (sutimlimab-jome) is a classical complement inhibitor indicated to decrease the need for red blood cell (RBC) transfusion due to hemolysis in adults with cold agglutinin disease (CAD).

  FDA Approves Enjaymo (sutimlimab-jome) for Use in Patients with Cold Agglutinin Disease.

- **Fleqsuvy (baclofen) Oral Suspension**

  Date of Approval: February 4, 2022
  Company: Azurity Pharmaceuticals, Inc.
  Treatment for: Spasticity

  Fleqsuvy (baclofen) is an oral suspension formulation of baclofen for the treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.

  FDA Approves Fleqsuvy (baclofen oral suspension) for the Treatment of Spasticity.

- **Pyrukynd (mitapivat) Tablets**

  Date of Approval: February 17, 2022
  Company: Agios Pharmaceuticals, Inc.
  Treatment for: Pyruvate Kinase Deficiency

  Pyrukynd (mitapivat) is a pyruvate kinase activator indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.

  FDA Approves Pyrukynd (mitapivat) as First Disease-Modifying Therapy for Hemolytic Anemia in Adults with Pyruvate Kinase Deficiency.

- **Nephro Scan (technetium Tc 99m succimer) Injection Kit**

  Date of Approval: February 22, 2022
  Treatment for: Diagnosis and Investigation

  Nephro Scan (kit for the preparation of technetium Tc 99m succimer injection) is a radioactive diagnostic agent indicated for use as an aid in the scintigraphic evaluation of renal parenchymal disorders.

  FDA Approves Nephro Scan (Kit for the Preparation of Technetium Tc 99m Succimer Injection) for Radiodiagnostic Imaging.

- **Carvykti (ciltacabtagene autoleucel) Suspension for Intravenous Infusion**

  Date of Approval: February 28, 2022
  Company: Janssen Pharmaceutical Companies
  Treatment for: Multiple Myeloma

  Carvykti (ciltacabtagene autoleucel) is a BCMA-directed CAR-T immunotherapy for the treatment of patients with relapsed or refractory multiple myeloma.

  FDA Approves Carvykti (ciltacabtagene autoleucel) BCMA-Directed CAR-T Immunotherapy for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma.

- **Norliqva (amlodipine besylate) Oral Solution**

  Date of Approval: February 24, 2022
  Company: CMP Pharma, Inc.
  Treatment for: High Blood Pressure, Coronary Artery Disease, Angina

  Norliqva (amlodipine besylate) is an oral solution formulation of the approved calcium channel blocker amlodipine for the treatment of hypertension and angina in patients with coronary artery disease.

  FDA Approves Norliqva (amlodipine) Oral Solution for Hypertension and Coronary Artery Disease.

- **Vonjo (pacritinib) Capsules**

  Date of Approval: February 28, 2022
  Company: CTI BioPharma Corp.
  Treatment for: Myelofibrosis

  Vonjo (pacritinib) is a JAK2/FLT3 multikinase inhibitor for the treatment of myelofibrosis patients with severe thrombocytopenia.

  FDA Approves Vonjo (pacritinib) for the Treatment of Adult Patients with Myelofibrosis and Thrombocytopenia.

- **Releuko (filgrastim-ayow) Injection**

  Date of Approval: February 25, 2022
  Company: Kashiv BioSciences, LLC
  Treatment for: Neutropenia Associated with Chemotherapy, Neutropenia

  Releuko (filgrastim-ayow) is a recombinant human granulocyte colony-stimulating factor biosimilar to Neupogen indicated for the treatment of neutropenia associated with chemotherapy and related conditions.

  FDA Approves Releuko (filgrastim-ayow), a Biosimilar to Neupogen.

- **Adlarity (donepezil) Transdermal System**

  Date of Approval: March 11, 2022
  Company: Corium, Inc.
  Treatment for: Alzheimer s Disease

  Adlarity (donepezil transdermal system) is a once-weekly transdermal formulation of the approved acetylcholinesterase inhibitor donepezil indicated for the treatment of Alzheimer s type dementia.

  FDA Approves Adlarity (donepezil transdermal system) for Treatment of Patients with Alzheimers Disease.

- **Nasonex 24HR Allergy (mometasone furoate monohydrate) Nasal Spray**

  Date of Approval: March 17, 2022
  Company: Perrigo Company plc
  Treatment for: Allergic Rhinitis

  Nasonex 24HR Allergy (mometasone furoate monohydrate) is a corticosteroid nasal spray available over-the-counter for the temporary relief of the symptoms of hayfever or other upper respiratory allergies.

  FDA Approves Nasonex 24HR Allergy (mometasone furoate) Nasal Spray for OTC Use.

- **Ztalmy (ganaxolone) Oral Suspension**

  Date of Approval: March 18, 2022
  Company: Marinus Pharmaceuticals, Inc.
  Treatment for: CDKL5 Deficiency Disorder

  talmy (ganaxolone) is neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD).

  FDA Approves talmy (ganaxolone) for Seizures Associated with CDKL5 Deficiency Disorder.

- **Opdualag (nivolumab and relatlimab-rmbw) Injection**

  Date of Approval: March 18, 2022
  Company: Bristol Myers Squibb
  Treatment for: Melanoma

  Opdualag (nivolumab and relatlimab-rmbw) is programmed death receptor-1 (PD-1) blocking antibody and lymphocyte activation gene-3 (LAG-3) blocking antibody combination indicated for the treatment of unresectable or metastatic melanoma.

  FDA Approves Opdualag (nivolumab and relatlimab-rmbw) for the Treatment of Patients with Unresectable or Metastatic Melanoma.

- **Xelstrym (dextroamphetamine) Transdermal System**

  Date of Approval: March 22, 2022
  Company: Noven Pharmaceuticals, Inc.
  Treatment for: ADHD

  elstrym (dextroamphetamine) transdermal system is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults and children 6 years and older.

  FDA Approves elstrym (dextroamphetamine) Transdermal System for the Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

- **Hyftor (sirolimus) Topical Gel**

  Date of Approval: March 22, 2022
  Company: Nobelpharma America, LLC
  Treatment for: Facial Angiofibroma Associated with Tuberous Sclerosis

  Hyftor (sirolimus topical gel) is an mTOR inhibitor immunosuppressant indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older.

  FDA Approves Hyftor (sirolimus topical gel) for Facial Angiofibroma Associated with Tuberous Sclerosis.

- **Locametz (gallium Ga 68 gozetotide) Injection**

  Date of Approval: March 23, 2022
  Company: Novartis Pharmaceuticals Corporation
  Treatment for: Positron Emission Tomography Imaging

  Locametz (kit for the preparation of gallium Ga 68 gozetotide injection) after radiolabeling with gallium-68, is a radioactive diagnostic agent used for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer.

  FDA Approves Locametz (kit for the preparation of gallium Ga 68 gozetotide injection) for PSMA PET Imaging in Patients with Prostate Cancer.

- **Pluvicto (lutetium lu 177 vipivotide tetraxetan) Injection**

  Date of Approval: March 23, 2022
  Company: Novartis
  Treatment for: Prostate Cancer

  Pluvicto (lutetium lu 177 vipivotide tetraxetan) is a radioligand therapeutic agent indicated for the treatment of prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC).

  FDA Approves Pluvicto (lutetium Lu 177 vipivotide tetraxetan) Targeted Radioligand Therapy for Treatment of Progressive, PSMA-Positive Metastatic Castration-Resistant Prostate Cancer.

- **Tlando (testosterone) Capsules**

  Date of Approval: March 28, 2022
  Company: Antares Pharma, Inc.
  Treatment for: Hypogonadism, Male

  Tlando (testosterone) is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

  FDA Approves Tlando (testosterone undecanoate) for Male Hypogonadism.

(Ravindra Bangar)
Editor

Call for Papers

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Number references consecutively in the order in which they are first mentioned. Identify references in text, tables, and captions by Arabic numerals superscripted above the line.

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These should be marked with and proprietary drug names should be capitalised e.g. Cifran.

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- Acorn AD, Management of rheumatoid arthritis. In: Brwon CC, Davies GH. (eds) Inflammatory diseases. 3rd edn. London: Apple, 1992;203-30
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Reviewers' Guidelines

ETHICS AND RESPONSIBILITY

We are committed to upholding the integrity of the work we publish. Pacific Journal of Medical and Health Sciences takes issues of copyright infringement, plagiarism or other breaches of best practice in publication very seriously. We seek to protect the rights of our authors and we always investigate claims of plagiarism or misuse of published articles. Equally, we seek to protect the reputation of our journal against malpractice. Submitted articles may be checked with duplication-checking software. Where an article is found to have plagiarized other work or included third-party copyright material without permission or with insufficient acknowledgement, or where the authorship of the article is contested, we reserve the right to take action including, but not limited to: publishing an erratum or corrigendum (correction); retracting the article (removing it from the journal); taking up the matter with the Head of Department or Dean of the author's institution and/or relevant academic bodies or societies; banning the author from publication in the journal in question or appropriate legal action.

We recommend that if reviewers suspect any of the following problems with any article that they are reviewing that they contact the journal editor to discuss the situation without delay. Reviewers should keep all information about such matters confidential and not discuss them with colleagues other than the journal editor.

1. If you suspect that the paper has been either published or submitted to another journal.
2. If you suspect that the paper is duplicating the work of others.
3. If you suspect that there might be problems with the ethics of the research conducted.
4. If you suspect that there might be an undeclared conflict of interest attached to the paper (Editors might have more information about this than you do so it is best to check).

We recommend that reviewers should think carefully about their own potential conflicts of interest relating to the paper before undertaking the review. They should also notify the editor if they become aware of the identity of the author during blind peer review. Additionally, reviewers should be careful not to make judgments about the paper based on personal, financial, intellectual biases or any other considerations than the quality of the research and written presentation of the paper.

PURPOSE OF PEER REVIEW

It is widely accepted that Peer Review is the most valid form of research evaluation and it is a cornerstone in the process of bringing academic research to publication in the following ways:

Evaluation - Peer review is an effective form of research evaluation to help select the highest quality articles for publication.

Integrity - Peer review ensures the integrity of the publishing process and the scholarly record. Reviewers are independent of journal publications and the research being conducted.

Quality - The filtering process and revision advice improve the quality of the final research article as well as offering the author new insights into their research methods and the results that they have compiled. Peer review gives authors access to the opinions of experts in the field who can provide support and insight.

TYPE OF PEER REVIEW OF JOURNAL

Double blind peer review - names are hidden from both reviewers and the authors.

HOW TO REVIEW ARTICLES

Referees are sent invitations to review papers by journal editors. These requests are made via email. If you are asked to provide a review, in order to avoid delays, we would be grateful if you could let us know as soon as possible if you are unable to complete it at the time or if a problem arises after the invitation has been accepted. Suggestions for alternative reviewers are always gratefully received!

Below we present some advice and guidance about how to conduct a review and put together a reviewer report that will be effective and beneficial to authors:

ETIQUETTE

Timeliness - We understand that our reviewers are busy so it won't always be possible for invitations to be accepted. Please let us know as soon as possible if they need to refuse a review or if a problem arises after the invitation has been accepted. Most journal editors are grateful to receive suggestions about someone else that might be suitable to do the review if you have to decline the invitation.

Conflict of Interest - it is important to highlight to the journal editor any conflict of interest that you feel might occur if you review the paper. Please do so as discretely and as quickly as possible.

Discussion -- it is important to discuss with the journal editor any concerns that you have about the paper or their specific requirements for review if you are being invited to review for the first time. Editors are usually open to discussing their expectations and journal requirements with reviewers.

Ethics -Refer ethics and responsibility related to peer review.

INDIVIDUAL JOURNAL REVIEWER GUIDELINES

These guidelines include a list of questions and will usually offer the reviewer the chance to make general comments

- Read the paper very carefully.
- Relevance to the publication (most editors will reject at submission those articles that do not match the aims and scope of the journal, but it is worth considering this as you read the paper).
- Significance of the research within the field.
- Originality of the work conducted. It is also important to consider whether the author has ever published a substantially similar paper elsewhere (if you suspect the work may not be original, please view our ethics page for information about how to deal with a variety of situations).
- The methodology employed during the research.
- Technical accuracy.

STRUCTURE AND COMMUNICATION

- Accuracy of references
- Overall Structure of the paper, communication of main points and flow of argument
- uality of written language and structure of the article
- Effectiveness of the article abstract and introduction (some journals will request
- Whether the argument is clear and logical and the conclusions presented are supported by the results or evidence presented
- Whether the title of the article is suitable or effective
- Whether the abstract is a good summary of the article
- Whether the work meets with the article types accepted by the journal

The accessibility of the paper to a broad readership

Whether the paper is internally consistent

FEEDBACK IN YOUR REVIEWER REPORT - GIVING ADVICE TO AUTHORS AND SUGGESTING REVISIONS

Be as objective as possible in your comments and criticisms and avoid making negative comments about work referenced in the article

Be specific and as constructive as possible in your criticism. Be clear about what needs to be added or revised.

If relevant, make suggestions about additional literature that the author might read to enrich or improve their arguments

You should ensure that you are clear which of your comments you are happy for the author to see and which are meant specifically for the journal editor in order to avoid confusion or bad feeling

While peer reviewers should feel free to make general comments on written quality and make suggestions about how articles might be improved by broadening reading of other literature, it is not the job of the peer reviewer to rewrite articles or suggest detailed changes to wording

MAKING A DECISION

Recommend whether a paper should be accepted, rejected or revised (major or minor revisions)

Most importantly, keep all activity, content and comments relating to the paper confidential

Most important - keep all activity, content and comments relating to the paper confidential.

Publication Ethics and Publication Malpractice Statement

Our publication ethics and publication malpractice statement is mainly based on the Code of Conduct and Best-Practice Guidelines for Journal Editors (Committee on Publication Ethics, 2011).

EDITORS' RESPONSIBILITIES

Publication Decisions

The editor is responsible for deciding which of the papers submitted to the journal will be published. The editor will evaluate manuscripts without regard to the authors race, gender, sexual orientation, religious belief, ethnic origin, citizenship, or political philosophy. The decision will be based on the paper s importance, originality and clarity, and the study s validity and its relevance to the journal s scope. Current legal requirements regarding libel, copyright infringement, and plagiarism should also beconsidered.

Confidentiality

The editor and any editorial staff must not disclose any information about a submitted manuscript to anyone other than the corresponding author, reviewers, potential reviewers, other editorial advisers, and the publisher, as appropriate.

Disclosure and Conflicts of Interest

Unpublished materials disclosed in a submitted paper will not be used by the editor or the members of the editorial board for their own research purposes without the author s explicit written consent.

REVIEWERS' RESPONSIBILITIES

Contribution to Editorial Decisions

The peer-reviewing process assists the editor and the editorial board in making editorial decisions and may also serve the author in improving the paper.

Promptness

Any selected referee who feels unqualified to review the research reported in manuscript or knows that its prompt review will be impossible should notify the editor and withdraw from the review process.

Confidentiality

Any manuscripts received for review must be treated as confidential documents. They must not be disclosed to or discussed with others except as authorized by the editor.

Standards of Objectivity

Reviews should be conducted objectively. Personal criticism of the author is inappropriate. Referees should express their views clearly with supporting arguments.

Disclosure and Conflict of Interest

Privileged information or ideas obtained through peer review must be kept confidential and not used for personal advantage. Reviewers should not consider manuscripts in which they have conflicts of interest resulting from competitive, collaborative, or other relationships or connections with any of the authors, companies, or institutions associated with the papers.

AUTHORS' DUTIES

Reporting Standards

Authors of original research reports should present an accurate account of the work performed as well as an objective discussion of its significance. Underlying data should be represented accurately in the paper. A paper should contain sufficient detail and references to permit others to replicate the work. Fraudulent or knowingly inaccurate statements constitute unethical behavior and are unacceptable.

Originality, Plagiarism and Acknowledgement of Sources

Authors will submit only entirely original works, and will appropriately cite or quote the work and/or words of others. Publications that have been influential in determining the nature of the reported work should also be cited.

Multiple, Redundant or Concurrent Publication

In general, papers describing essentially the same research should not be published in more than one journal. Submitting the same paper to more than one journal constitutes unethical publishing behavior and is unacceptable. Manuscripts which have been published as copyrighted material elsewhere cannot be submitted. In addition, manuscripts under review by the journal should not be resubmitted to copyrighted publications. However, by submitting a manuscript, the author(s) retain the rights to the published material.

Authorship of the Paper

Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study. All those who have made significant contributions should be listed as co-authors. The corresponding author ensures that all contributing co-authors and no uninvolved persons are included in the author list. The corresponding author will also verify that all co-authors have approved the final version of the paper and have agreed to its submission for publication. Disclosure and conflicts of interest

All authors should include a statement disclosing any financial or other substantive conflicts of interest that may be construed to influence the results or interpretation of their manuscript. All sources of financial support for the project should be disclosed.

Fundamental errors in published works

When an author discovers a significant error or inaccuracy in his/her own published work, it is the author s obligation to promptly notify the journal editor or publisher and to cooperate with the editor to retract or correct the paper in form of an erratum.

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PMCH
HEALTH ADVISORS

DEPARTMENT OF ONCOLOGY

SCALP COOLING MACHINE

Rajasthan's First Scalp Cooling Machine has been established in Pacific Medical College and Hospital, Udaipur for providing US FDA Approved Scalp Cooling Therapy to Cancer Patients to prevent hair-loss due to Chemotherapy.

PACIFIC IVF CENTER

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