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SCOPE OF TRANSLATIONAL RESEARCHES IN AYURVEDIC SYSTEM OF MEDICINE: AN OVERVIEW

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Abstract: *The science of Ayurveda is based on logical amalgamation of sound principles of its philosophy and science, not on mysticism, magic and anecdotes. Ayurveda is based on its unique principles of health and disease. The theories of Ayurveda) were established by many ancient sages after rigorous testing in several ways and proving the same with reasoning. The promotion of Ayurveda as the most important alternative to existing systems of medicine and their medical practices with Ayurvedic principles, requires the pathway analysis of crude and active components and its practice for health benefits, disease prevention, therapeutics and ultimately ageing. The linkage between "the past" and "the future" of medicine is much more important and can give us new insights for better understanding health, disease and possible solutions. This review is basically focused on Ayurvedic system of medicine and the role of translational researches in this potential system of medicine.*

Keywords: *Ayurveda, Health, Life Style, Translational Medicine.*

Introduction: Ayurveda literally means "the knowledge of life". In Sanskrit, the word Ayurveda consists of the words Ayu, meaning "life" and veda, meaning "knowledge" or "science". The growth of science depends upon research and there is no denying the fact that the understanding of the health care personnel, scientists and researchers today, in any given stream of science is because of research. The fundamental purpose of research is to know the truth and to benefit the society. In terms of medical research, it aims at knowing or re establishing the new molecules / drugs which are effective for different diseases. Scientific journals spread the new knowledge, push forward the frontiers of current knowledge in every aspect, allow publication of creative ideas and form the basis of ongoing innovations. Reasons that drive research include-the desire to know the truth, and the quest for knowledge, the desire of recognition amongst peers and to enhance one's image and prestige. Over a period we have moved from expert based medical practice to evidence based medical practice.

People have been using Ayurvedic medicines for thousands of decades. Currently, the conventional modern medicine predominated over Ayurveda even after a number of side effects. The human body is naturally dependent upon herbs which constitute the ocean of molecules for treatment of not only known but also for many unknown diseases. Thus, we hypothesize that out of all the available systems of medicine, Ayurvedic medicine has greater potential in the future. The systemic review of existing scientific literature and the evidences based on emerging technologies clearly illustrate the future of human health and diseases will be highly dependent on Ayurvedic medical sciences.

Systems Biology & Bio-informatics: In the post-genomic era, genome-wide functional screenings for targets of diseases are the most recent and practical approach. Recent developments in computational biology and bioinformatics have provided biologists with some systematic methods to analyze these molecular networks in a cellular context. Collectively predicated as systems biology, it aims to analyze relationships among elements (nodes) in a given system or the emergent properties of the system. Cellular networks that

model the cellular response to a given perturbation would include protein-protein interaction networks (PPI: encode the information of proteins and their physical interactions); signal transduction and gene regulatory networks (STN and GRN: show regulatory relationships between transcription factors and/or regulatory RNAs, as well as the signalling pathways that confer these responses); and the metabolic networks [1].

The major contribution from the bio-informatics resources in the development and enrichment of traditional herbal medicine could be perspective captures the uniqueness and complexity of drug action in a cell. Such holistic perspective also avoids the pitfall of being too reductionist and in effect, mollifies some criticisms from traditional ethnopharmacologic researchers [2]. Interest in the use of herbal products has grown dramatically in the western world. Recent estimates suggest an overall prevalence for herbal preparation use of 13% to 63% among cancer patients. With the narrow therapeutic range associated with most anticancer drugs, there is an increasing need for understanding possible adverse drug interactions in medical oncology [3].

Ayurvedic system has described a large number of such medicines based on plants or plant product and the determination of their pharmacological, pharmacognostical characters can provide a better understanding of their active principles and mode of action. As they are able to grow and produce valuable products under dessert conditions they have great potential for covering the global desert areas into green belts leading to environmental improvement on one hand and providing valuable Ayurvedic crude drugs in addition to supplementing the bio-energy resources as renewable fuels.

Totalistic Approach of Ayurvedic System & Changing Worldview: The basic principle in Ayurveda is to provide greater priority to total wellness and health rather than to make selective treatment. It has become very popular as it uses reagents and remedies essentially drawn from nature and is both eco- and bio-friendly. Ayurvedic medical system practices the use of dry powder or crude extract, and assignment of bioactivities to a particular compound is not preferred. Interestingly, the mainstream pharmaceutical research is also on its way towards veering from mono-molecular or single target approach to combinations and multiple target strategies. Perhaps, multi-site mechanisms of action of herbal preparations from the crude extracts may offer greater chances for success where conventional single-site agents have been disappointing. Auspiciously, many of these traditional herbal medicines are now increasingly being appreciated with Western models of integrative health sciences and evidence-based approach both in research and practice.

Despite the recent revolutions in biotechnology and genome research, an estimated 80% of the world population still has no access to modern medicine and obtain benefits from the time-tested alternative systems of medicine. As more genomes have been sequenced and gene functions elucidated, time has come to bring the valuable ancient medicinal knowledge to the rapidly expanding genomic landscapes. It is envisioned that systematic identification and characterization of gene targets could lead to deeper appreciation of the chemo-diversity in an herbalist's "brown bag". It is, however, feared that by reducing traditional medicine to their mere molecular effectors the investigators could "lose sight of the forest for the trees" and as such, inspired by the holistic character of traditional medicinal systems to study functions of drug-responsive genes, Deocaris and others have entertained the idea of applying a systems biology perspective in comparing gene regulatory circuits in an herbal preparation vis-à-vis some of its bioactive components.

Strength of Ayurvedic System: Ancient medical sciences of Ayurveda divided into eight branches: Shalya (surgery); Shalakya (diseases above the neck); Kayachikitsa (medicine proper); Bhutavidya (mental diseases); Kaumarabhritya (care of infancy); Agada (toxicology); Rasayana (Rejuvenation & longevity); Vajikarana (Aphrodisiacs). Ayurveda stands to contribute to areas of preventive and promotive health care, disease risk management, early-stage management and prevention of complications of chronic diseases, along with disease-modifying treatments. We expect that future practitioners require to be so trained to enhance health care through integrative Ayurveda equipped with these strengths, with dignity and a high level of self-esteem. Ayurveda centered holistic psychopharmacological strategy evolving from our efforts to identify plants potentially useful for preventing and combating illnesses and diseases could be a more rapid, rational, economically feasible, and realistic one for resolving such discrepancies and paradoxes [4].

Psychosomatic Diseases& Rasayana Therapy: Rasayana is can be advised to both diseased and healthy individual in order to strengthen one's body as well as mind. Aachaar Rasayana is one among Nitya Rasayana (for using on daily basis) which is nothing but the codes and conduct advocated by Acharya Charaka in Rasayana chapter of Charaka Samhita. It is the summarized form of Swasthavritta. In present day medical practice it is observed that major proportion of the population is suffering from the diseases of psychosomatic origin. In present scenario the management of psychosomatic disorders includes the use of psychotropic drugs, psychotherapy, behavior therapy, biofeedback etc. along with concurrent undertaking of the treatment for organic dysfunction [5]. In this regard, ancient Ayurveda Acharyas have given equal consideration to physical, psychological, food nutritional and behavioral patterns of an individual. When the ancient and modern concepts are reviewed, the biological, psychological and social factors seem to be influential on the state of health and illness of an individual. Aachara Rasayana makes an individual strong (immune) physically, mentally, spiritually, socially (personality wise) and morally by means of codes and conducts and use of some Nitya Rasayana Dravyas.

Biotechnology and Ayurveda: Biotechnology with its specializations like genomics, proteomics, genetic engineering etc. has made immense advances in deciphering disease conditions, disease progression, and prognosis and even up-to certain level cure for particular conditions. Genomics can play important role both in prevention and treatment of many diseases. The advanced technologies used in genomics and related sciences can help in understanding role of genes in diseases and health. The use of these technologies and concepts for generating scientific evidence behind concepts of Ayurveda can open up many interesting avenues [6].

Structural and functional genetic differences in humans can take the form of single nucleotide polymorphisms (SNP), copy number variations (CNVs), and epigenetic or gene expression modifications. As per current research, in human 99.5 % genetic similarity is found and almost all physiological or anatomical variations amongst person to person are due to 0.5% diversity in single nucleotide polymorphism (SNP) and other variations in nucleotides [7]. These inherited inter-individual variations in DNA sequence contribute to phenotypic variation, influencing an individual's anthropometric characteristics, risk of diseases and response to the environment. Characterizing genetic variation may bring improved understanding of differential susceptibility to disease, differential drug response, and the complex interaction of genetic and environmental factors, which go on to produce each phenotype. Ayurveda, the traditional system of Indian medicine has well-defined system of constitutional types used in prescribing medication bearing distinct similarities to contemporary pharmacogenomics. The pharmacogenomics can become useful for understanding genetic basis of concept of constitutional type “Prakriti”. In the Ayurveda system of medicine, predisposition to a disease as well as selection of a preventive and curative regime is primarily based on phenotypic assessment of a person which includes one’s body constitution termed “Prakriti” [8].

Cancer and Ayurveda: There exist plethora of evidence for scientific basis of Ayurveda and one need to adopt an unbiased neutral opinion to see the promising way forward for drug discovery with support of Ayurveda. Because ancient sciences are not limited to one religion or geographical area, they should be used for benefit of health care system in totality. A recent, exciting discovery relates to the concept of “shared pathology” between cancer and metabolic syndrome [9]. One major pathway common to cancer and metabolic syndrome is chronic inflammation, which is a major driving force in carcinogenesis. Indeed, chronic inflammation precedes most cancers and is considered as a “hallmark” of the neoplastic process. Modern science is yet to discover effective remedies for deadly diseases such as cancer, AIDS, or other hematological and auto-immune disorders. These diseases are very complicated in nature with complexity at every level—anatomy, physiology, biochemistry, molecular biology and gene expression. So treating such diseases is a big challenge. The word ‘cancer’ may be new to the 5,000 year old Indian system of medicine, Ayurveda, which relies on natural substances for healing. But ancient Ayurvedic classics are aware of the clinical features, resembling cancer, with the names such as *Apachi*, *Gulma*, *Granthi*, and *Arbuda*. Following are names of some of the conditions mentioned in Ayurvedic classics that

have relevance to cancer manifestations in modern medicine

Cardiovascular Diseases and Ayurveda: The deterioration of vessel walls structure could be grouped in three pathologies-(1) Clogging of vessels with cholesterol and plaque, (2) Damaged areas due to increased pressure and free radical activity (3) Loss of vessel wall thickness. The good news is that cardiovascular disease is mainly a result of unhealthy lifestyle decisions and is therefore preventable, and often reversible, by natural means. Basically, degenerative conditions occur mainly due to the imbalance of the three humors, which maintains the equilibrium of the body, mainly the vata controls the whole sensory and motor activities of the body. Brain is the center of all these activities, due to ageing process the neurons get degenerated or its efficiency get decreased which is maintained by the phlegm. Thus a disturbance in the normalcy is the root cause of further complications. Along with vata and kapha, the pitta provides the fire, the energy for individual cells to digest and absorb its active elements and to maintain its functions, this get decreased with age. This needs to be treated.

Emerging New Diseases and Ayurveda: Food is the major source for serving the nutritional needs, but with growing modernization some traditional ways are being given up. Affluence of working population with changing lifestyles and reducing affordability of sick care, in terms of time and money involved, are some of the forces that are presently driving people towards thinking about their wellness. There has been increased global interest in traditional medicine. Efforts to monitor and regulate traditional herbal medicine are underway. Ayurveda, the traditional Indian medicine, remains the most ancient yet living traditions. Although India has been successful in promoting its therapies with more research and science-based approach, it still needs more extensive research and evidence base. Increased side effects, lack of curative treatment for several chronic diseases, high cost of new drugs, microbial resistance and emerging, diseases are some reasons for renewed public interest in complementary and alternative medicines. Numerous nutraceuticals combinations have entered the international market through exploration of ethnopharmacological claims made by different Ayurvedic therapeutic practices [10].

Ayurveda and Modern Medicine: Currently western medicine has assumed the central position in mainstream global healthcare. However, these developments do not seem to address all the problems facing global health care caused by overemphasis on pharmaco-therapeutic drug developments. On the other hand, Ayurveda which is founded on genuine fundamentals, has the longest uninterrupted tradition of healthcare practice, and its holistic approach to healthcare management emphasizes disease prevention and health promotion; if it opens up to incorporate emerging new knowledge into mainstream, it will certainly provide a broad-based opportunity to address the majority of the problems that have emerged from global healthcare requirements. To bring these solutions to bear, however, it will be necessary to progress from the present "utilitarian ethos" to a "unifying ethos" for realization of medical integration [11].

Immune Disorders and Ayurveda: Ayurveda contains extensive knowledge of various diseases and their therapeutic approaches. It essentially relied on nature and the immune system of an individual, and therapeutic interventions were introduced only to augment the immune system. Ayurveda had eight specialties, including psycho-neuroscience (a combination of psychology, clinical psychology and psychiatry) and a unique promotive therapy encompassing nutrition, rejuvenation and geriatrics. The symptoms of various brain disorders, including memory disorder, were well defined. The goal of Ayurveda was to help an individual to achieve his cherished goal of leading a healthy life of 100 years. To achieve this, great emphasis was laid on nutrition, diet and a good conduct by the two great exponents of Ayurveda viz. Charak and Suśruta. By following these regimens, an individual could lead a less stressful life free from emotional disturbances. Both Charak and Suśruta had believed that these in combination with rasayana (rejuvenating) plants could enable an individual to lead a healthy life of 100 years [12].

The conceptual frameworks of health in *Ayurveda* are essentially based upon the doctrine operating through the principle of samanya and visesa, i.e., Heterology *versus* Homology. This was further extrapolated by Acharya Charak as loka-purusa samya (equilibrium between an individual-microcosm and cosmos-macrocosm) by establishing the continuum between the ecological triangles of soma-surya-anila (moon-sun-air) with the tridisika (three-dimensional) bio-triangle of kapha-pitta-vata. Here it would be

pertinent to emphasize that kapha, pitta and vata cannot be translated into one word, as many western scholars and educated Indians tend to do and translate kapha as phlegm, pitta as bile and vata as wind, thereby giving a most erroneous interpretation. Kapha can be appropriately translated as one of the body humors, which forms the solid substratum of the body, including immune strength; pitta is another bio-humor, which is responsible for the entire digestive and metabolic functions; and vata is the bio-humor responsible for energetic and neural activities [13].

As an ecological balance between soma-surya-anila (moon-sun-air) sustains the entire universe, the physiological homeostasis (constancy of milieu interior) of the human body is sustained by a harmonious balance between principal bio-humors sustaining the immunity, metabolic, energetic and neural activities. The individual living being is considered a miniature replica of the universe and comparatively similar activities are taking place inside the microcosm of the human body as are occurring universally in the macrocosm.

In Ayurveda, Rasayana (or science of rejuvenation) is a unique concept and is one of the eight specialized branches of Astang-Ayurveda. The main object of rasayana therapy is the management of age-related disorders. The principal physiological effect of *rasayana* is to improve and revitalize the physiological and endocrine functions of the body, to decelerate the aging process and to make an individual more responsive and resistant to disease, *i.e.*, to improve body function by strengthening the immune system. The rasayanas are postulated to act through a psycho-endocrinological immune axis [14]. Various compounds of plant origin have been widely investigated since ancient times for their possible immunomodulatory properties as well as for the treatment of a wide range of diseases [15]. The potential of Ayurvedic philosophy and medicines needs to be recognized and converted into real life treatment paradigm.For instance, various controlled drug trials carried out to validate standardized Ayurvedic drugs using modern medicine protocol to treat Rheumatoid Arthritis and Osteoarthritis (OA) knees. Several of the latter are published. The trials consistently demonstrate excellent safety of Ayurvedic medicines but often fail to unequivocally show superior efficacy. Some key findings of a recently unpublished trial in OA knees are also presented to show equivalence between Ayurvedic medicine and celecoxib and glucosamine, and thus, it was speculated that equivalence trials may be a way forward. The data from the trials also supports the Ayurvedic 'Rasayana' concept of immune-modulation and healing.

We need to interpret logic of Ayurveda when, adopting modern science tools in drug development and validation and much research is required. Validation of Ayurvedic medicines using the latter approach may lead to evidence based Ayurveda-Modern Medicine interface. Also, in pursuit of finding better treatment solutions, we ought to step beyond the realm of only drugs and attempt validation of comprehensive specific treatment package as per classical Ayurveda. Finally, validation of a combined (Ayurveda and modern medicine) therapeutic approach with superior efficacy and safety is likely to be a major leap in overcoming some of the current frustrations to treat difficult disorders like arthritis using only modern medicines [16].

Rheumatological Disorders & Ayurveda: Undoubtedly, precise translation of Ayurvedic nomenclature into modern medical terminology is difficult. However, distinctions are made between different articular disorders, descriptions of which bear resemblance to Rheumatoid Arthritis (RA) and Osteoarthritis (OA). In many Indian languages, Vata, distinct from vata dosha, is a common colloquial term used to denote rheumatism. When primarily affecting joints, it is often called "*Sandhivata" (*sandhi = joint). Many forms of arthritis were described along with the nervous system disorders in the classic texts [16, 17]. The condition of Amavata, Srikanta has been described a dreadful, painful, swollen polyarticular affection similar to RA. *Vata dosha* plays a major role in the causation of arthritis. Joints and soft tissues are affected by "*ama*", produced in the gut due to "weakened" agni, food indiscretions, or disturbed *dosha* equilibrium, resulting in inflammatory and obstructive processes. In Ayurveda, arthritis is linked to the GIT. Ayurvedic formulations invariably target joints, gut, *and* immune systems. How intriguing, even surprising, that thousands of years later, modern medicine should find such an essential immune-mediated link between certain gut disorders and inflammatory arthritis.

Application of Rasayana Remedies: Several publications support purported anti-inflammatory and biologic effects of some popular anti-arthritic Ayurveda medicinal plants [18, 19, 20, 21, 22,

[23], demonstrating immunomodulation. Such an immunologic basis is conceptually captured by the "*Rasayana*" (means "strengthening and rejuvenating") branch of Ayurvedic science [24, 25, 26]. Ayurvedic pharmacopeias [27] contain lucid descriptions of *Rasayana* properties of medicinal herbs and minerals, several of which are used to treat arthritis.

Rasayana aims to increase the body's resistance to disease (*vyadhi-kshamatva*), delay aging, and promote body strength and intellect. *Rasayana* practices in daily life are rejuvenating and in disease promote healthy recovery. The prime example of a *Rasayana* plant is *Withania somnifera (Aswagandha)*, [28, 29, 30, 31] extensively used in Ayurvedic medicine, and often compared to Ginseng; its immunomodulatory, anti-inflammatory, and hence anti-arthritic, and other biologic effects have been extensively documented. *Ricinus communis (Erand*/castor oil) and *Guggul* extracts (*Commiphora mukul, Boswellia serrata*) are prime examples of potent anti-arthritic medicinal plants named in Charaka Samhita (CS). Numerous other *Rasayana* plants, especially *Withania somnifera*, are common components of anti-rheumatic medications. Other well-standardized formulations manufactured on a large scale by the Ayurvedic pharmaceutical industry are *Dashamool, Mahayograj Guggul, Vatavidhwansa, Suvarna Bhasma, Guggul, Yograj Guggul,* and *Triphala Churana*. Several of these have potent laxative action. *Guggul* preparations often contain ash (*Bhasma*) of minerals such as gold (*Suvarna Bhasma*), silver, copper, iron, mica, mercury, sulfur, zinc, lead. It is fascinating that "gold" in its Ayurvedic ash form has been used to treat arthritis since ancient times, while modern medicine inadvertently discovered its use as disease-modifying anti-rheumatic drug (DMARD) in the last century. CS describes complex poultice preparations made by mixing herbs, minerals, and animal meat. Certain medicated massage oils like Bala taila, [32] also used in the treatment of arthritis, may contain more than 50 ingredients.

Treatment of arthritis usually begins with two basic processes: *snehana* (oleation) and *swedana* (sweating, heating). While diaphoretic, steam bath, may be used to carry out the latter, oily preparations are administered orally, through medicated enemas (Basti), or massage for oleation. These aim to cleanse and purify the body to restore *tridosha* equilibrium. Such drugs are administered to patients through multiple routes concurrently or sequentially. *Panchakarma (Five Processes)* comprises treatments curative to dosha imbalance, including emetics (*Vamana*), purgatives (*Virechana*), medicated oily enema (*Anuvasana Basti*), medicated decoction/dry enema (*Asthapana Basti/Niruhana*), and oleation/nasal purgation (*Shirovirechana/Nasya*). Guided by therapeutic response, *Panchakarma* procedures are indicated for specific stage of disease. They are widely used to treat many forms of arthritic conditions, including RA

Potential Lead for Cancer Therapy: Withaferin A (WA), a bioactive constituent of Ayurvedic medicinal plant Withania somnifera, is a potent apoptosis inducer in cancer cells but the mechanism of cell death induction is not fully characterized. A study was undertaken to determine the role of mitogen-activated protein kinases (MAPK), including c-jun NH_2 -terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 MAPK, and anti-apoptotic protein myeloid cell leukemia-1 (Mcl-1) in regulation of WA-induced apoptosis using human breast cancer cells [33]. Efficacy of withaferin A (WA), an Ayurvedic medicine constituent for prevention of mammary cancer and its associated mechanisms were investigated using mouse mammary tumor virus-neu (MMTV-neu) transgenic model [34]. Withanolides such as withaferin A (WA) and withanolide A (WLD) are its bioactive constituents reported as promising drug candidates in cancer and neurological disorders respectively [35].

Despite significant advances toward targeted therapy and screening techniques, breast cancer continues to be the leading cause of cancer-related deaths and the most frequently diagnosed cancer among women in the USA and worldwide [36]. The clinical utility of ER antagonists is often limited by side effects [36]. Thus, the identification of novel agents that can suppress growth of both ER-positive and ER-negative human breast cancers and are still relatively safe is highly desirable.

Gugulipid (GL, guggul, guggal, or gugul lipid) is the ethyl acetate extract of the gum guggul resin (raw material) is a highly valued botanical medicine that has been safely used for thousands of years in the Indian Ayurvedic medicine for the treatment of different ailments, including lipid disorders, rheumatoid arthritis, ulcers, osteoarthritis, bone fractures, epilepsy and obesity [37, 38, 39, 40, 41, 42, 43, 44, 45]. In 1986, GL was granted approval in India for marketing as a lipid-lowering drug (Indian Pharmacopeia 2007:

pgs. 2038–2040). Several products of standardized formulations of *Commiphora mukul* are already in human use as cholesterol-lowering agents [40, 41, 42, 43]. The z- and E-forms of guggulsterone (Gug, 4,17) [46]. Pregnadie-3, 16-dione have been identified as major active components of GL [37, 38, 39, 40, 41, 42, 43, 44, 45]. Numerous studies suggest that many edible phytochemicals have cancer chemopreventive and chemotherapeutic potential [47]. The evidences of the anti-cancer activity of Gugs were provided by several laboratories [46, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58]. Inhibitory effect of Gug on the growth of the human prostate cancer cells were investigated previously [48, 49, 50, 51]. Their results have shown that z-Gug significantly inhibits the proliferation of PC-3, LNCaP and DU145 human prostate cancer cells, but not that of the normal human prostate epithelial cell line PrEC [49, 50, 51]. Based on these data, it was hypothesized that GL might be more effective in the growth inhibition of prostate cancer cells because it contains a number of steroids, including the two isomers z- and E-Gugs. Therefore, anti-cancer potential of GL in human prostate cancer cells were investigated by Xiao *et al.*, 2011. Their data were the first to show that GL has a stronger anti-cancer potential in human prostate cancer cells than z-Gug, one of its active constituents, as evidenced by greater inhibition of cell growth. It is reported that treatment with GL (3 μmol standardized to z-Gug, daily for 3 weeks) resulted in the enhancement of cetuximab activity in the xenograft model of head and neck cancer [55]. Gugs-mediated suppression of cancer cell proliferation has also been reported in head and neck cancer cells [55], leukemia cells [46, 57], lung cancer cells [57], human breast cancer cells [54], skin cancer cells [56], and colon cancer cells [58]. Gug treatment inhibited angiogenesis *in vitro* and *in vivo* to block prostate and colon cancer growth [49, 58]. They were the first to report the anti-cancer effect and mechanism of GL on human breast cancer cells.

Centratherum anthelminticum (L.) Kuntze (scientific synonyms: Vernonia anthelmintica; black cumin) is one of the ingredients of an Ayurvedic preparation, called "Kayakalp", commonly applied to treat skin disorders in India and Southeast Asia. Despite its well known anti-inflammatory property on skin diseases, the anti-cancer effect of C. anthelminticum seeds on skin cancer is less documented. Later on investigate the anti-cancer effect of Centratherum anthelminticum (L.) seeds chloroform fraction (CACF) on human melanoma cells and to elucidate the molecular mechanism involved [59].

Pharmacological Researches on Some Potential Ayurvedic Herbal Drugs: Datura stramonium L., a wild-growing plant of the Solanaceae family, is widely distributed and easily accessible. It contains a variety of toxic tropane alkaloids such as atropine, hyoscamine, and scopolamine. In Eastern medicine, especially in Ayurvedic medicine, D. stramonium has been used for curing various human ailments, including ulcers, wounds, inflammation, rheumatism and gout, sciatica, bruises and swellings, fever, asthma and bronchitis, and toothache. A few previous studies have reported on the pharmacological effects of D. stramonium; however, complete information regarding the pharmacology, toxicity, ethnobotany and phytochemistry remains unclear. Ethnomedicinally, the frequent recreational abuse of D. stramonium has resulted in toxic syndromes. D. stramonium, in the form of paste or solution to relieve the local pain, may not have a deleterious effect; however, oral and systemic administration may lead to severe anticholinergic symptoms. For this reason, it is very important for individuals, mainly young people, to be aware of the toxic nature and potential risks associated with the use of this plant. This comprehensive review of D. stramonium includes information on botany, phytochemistry, pharmacology, toxicology and ethnomedicinal uses [60].

The genus “Datura” (Solanaceae) comprises all the nightshades and agricultural plants, including potato, tomato, coffee and pepper. Classification of different species within Datura genus relies heavily on genetic markers, which suggests that this genus has huge variation due to mutation [61, 62]. D. stramonium, the most common species within this family, is native to Asia, but is also found in the United States, Canada, and the West Indies. It is widespread with higher abundance in temperate, tropical and subtropical regions [63]. Traditionally, D. stramonium has been used for mystic and religious purposes [64], and as an herbal medicine with narcotic effects or to treat asthma [65]. The seed of D. stramonium is smoked to al achieve hallucinogenic experiences as well [66]. D. stramonium is toxic when consumed improperly. Accidental poisoning of humans and animals, which consumed food sources contaminated with D. stramonium has been reported [67]. In areas

where millet, wheat, rye, corn, and bean seeds are used for human consumption, and where D. stramonium is a common weed, the grain sometimes has been contaminated with Datura seeds [68].

In Ayurvedic medicine, D. stramonium is described as a useful remedy for various human ailments including ulcers, wounds, inflammation, rheumatism and gout, sciatica, bruises and swellings, fever, asthma and bronchitis, toothache, etc [69]. Many folk medicine remedies use D. stramonium therapeutically. In the Hindu religion, the seed of D. stramonium is believed to be associated with the God Shiva, which can promote misuse of the plant on religious occasions, such as Shivaratri and Swasthani Puja [70]. In modern medicine, the therapeutic uses of D. stramonium are overshadowed by its toxic effects. The administration of large amounts of D. stramonium affects the central nervous system with symptoms such as confusion, bizarre behavior, hallucinations and subsequent amnesia. Though death by D. stramonium poisoning is rare, recovery may take several days [68]. Therefore, a thorough understanding of the possible pharmacological and toxicological effects of D. stramonium is needed.

Phytochemical studies of D. stramonium have been conducted since the early 1930s. The major phytochemicals isolated from D. stramonium are tropane alkaloids, atropine and scopolamine [71]. It is reported that the whole plant contains 0.26% alkaloids. Seeds of Datura contain the alkaloid daturine, first isolated, purified and crystallized by Geiger and Hesse, in 1833. Von Planta (1850) pronounced daturine to be identical with atropine, the principal belladonna alkaloid; later, Ladenburg differentiated daturine into atropine and hyoscyamine, the latter alkaloid predominating. Schmidt, however, contended that atropine predominates. The seeds contain fatty oil (25%), from which a new fatty acid, daturic acid (C17H34O2), was isolated. Dohme concluded that the stems contain more alkaloids (0.3% to 0.4%, volumetrically) than even the seeds (0.25% to 0.29%), and the seeds contain more alkaloid than the leaves (0.21% to 0.23%, and 0.27% for green leaves) [72]. Suggest hyoscyamine as the main alkaloid in both diploid and tetraploid hairy root cultures of D. stramonium [73]. Report the percentage of atropine and scopolamine in different developmental stages and the parts of the Datura [74]. Their study suggested that the root contained lower levels of scopolamine than that of atropine and the same goes for the stem. In stems, atropine was almost three times higher than scopolamine. However, leaves and seeds contained higher level of scopolamine than that of atropine. Recently, reported the different alkaloids from D. stramonium seeds such as N-trans-feruloyl tryptamine, hyoscyamilactol, scopoletin, umckalin, daturaolone, daturadiol, N-trans-ferulicacyl- tyramine, cleomiscosin A, fraxetin, 1-acetyl-7-hydrox-beta-carboline, and 7-hydroxy-beta-carboline-propionic acid [75].

In Ayurveda, different parts of D. stramonium are used for various human ailments when applied both locally and through oral administration, but classic Ayurveda lacks specific knowledge on the toxicity of D. stramonium. The pharmacological effect of D. stramonium described above can be applied through modern or alternative herbal medicine approaches. D. stramonium should only be used therapeutically while under the care of knowledgeable health care professionals. The adverse effects of D. stramonium can be extremely severe and detrimental. Therefore, even in light of its many beneficial effects, the risk-benefit ratio should be always taken into consideration before using D. stramonium.

In the recent years, the interest and research in medicinal plants have increased in a great deal. Ayurvedic medicines and formulations developed from ancient Indian herbal systems are renowned for their various important applications. *Berberis aristata* - an Indian medicinal plant, which belongs to the family Berberidaceae is an ayurvedic herb used since ancient times. It is also known as Indian berberi, Daruharidra, Daruhaldi, Darvi and Chitra. The plant is useful as anti-pyretic, anti-bacterial, anti-microbial, anti-hepatotoxic, anti-hyperglycaemic, anti-cancer, anti-oxidant and anti-lipidemic agent. B. aristata extracts and its formulations are also useful in the treatment of diarrhoea, haemorrhoids, gynaecological disorders, HIV-AIDS, osteoporosis, diabetes, eye and ear infections, wound healing, jaundice, skin diseases and malarial fever. The ethnobotany, pharmacognosy and pharmacological uses of B. aristata which will give insights in developing potentially new bio-actives from the plant scaffolds. This also highlights the patenting trends, the new compositions developed using the actives from B. aristata and the different assignees [76].

Plants of ethnomedicinal importance have contributed for the development of many new pharmacologically effective molecules/chemical entities to modern medicine. India, the country having one of the richest biodiversity of its flora in its forest, with numerous tribal inhabitants, is able to contribute a lot from ethnomedicine to the ailing humanity. *Cordia macleodii Hook* (Boraginaceae), an ethnomedicinal plant has been highlighted for its wound healing, aphrodisiac and hepatoprotective activities. It is a medium-sized tree, known as Panki/Shikari by the tribals, rarely found in the forests of Orissa, Chhattisgarh and Madhya Pradesh. So far, the plant has been studied neither for its pharmacognostical characters nor for its pharmacological actions except its hepatoprotective activity [77].

Ixora coccinea Linn., (Rubiaceae) commonly known as jungle of geranium and red ixora, is an evergreen shrub found throughout India. Depending on the medical condition, the flowers, leaves, roots, and the stem are used to treat various ailments in the Indian traditional system of medicine, the Ayurveda, and also in various folk medicines. The fruits, when fully ripe, are used as a dietary source. Phytochemical studies indicate that the plant contains important phytochemicals such as lupeol, ursolic acid, oleanolic acid, sitosterol, rutin, lecocyanadin, anthocyanins, proanthocyanidins, glycosides of kaempferol and quercetin. Pharmacological studies suggest that the plant possesses antioxidative, antibacterial, gastroprotective, hepatoprotective, antidiarrhoeal, antinociceptive, antimutagenic, antineoplastic and chemopreventive effects, thus lending scientific support to the plant's ethnomedicinal uses [78].

Genetics and Ayurveda: Collaborative research involving Ayurveda and the current sciences is undoubtedly an imperative and is emerging as an exciting horizon, particularly in basic sciences. Some work in this direction is already going on and outcomes are awaited with bated breath. For instance the 'ASIIA (A Science Initiative in Ayurveda)' projects of Dept of Science and Technology, Govt of India, which include studies such as Ayurvedic Prakriti and Genetics. Further intense and sustained collaborative research needs to overcome a subtle and fundamental challenge-the ontologic divide between Ayurveda and all the current sciences. Ontology, fundamentally, means existence; elaborated, ontology is a particular perspective of an object of existence and the vocabulary developed to share that perspective [79].

Potential of Ayurvedic Herbs in DM : Type-2 diabetes mellitus is a persistent health problem that requires innovative strategies to improve health and needs a multifactorial approach for the treatment. Saptarangyadi Ghanavati, a new formulated Ayurvedic compound consists of herbs with anti-diabetic potential, in addition to folklore herb Saptarangi (Salacia chinensis) has been evaluated [80].

Cognitive Dysfunction, Neuro-degeneration & Ayurveda: Cognitive dysfunction is a major health problem in the 21st Century, and many neuropsychiatric disorders and neurodegenerative disorders, such as schizophrenia, depression, Alzheimer's disease dementia, cerebrovascular impairment, seizure disorders, head injury and Parkinsonism, can be severely functionally debilitating in nature. In course of time, a number of neurotransmitters and signaling molecules have been identified which have been considered as therapeutic targets. Conventional as well newer molecules have been tried against these targets. Phytochemicals from medicinal plants play a vital role in maintaining the brain's chemical balance by influencing the function of receptors for the major inhibitory neurotransmitters. In traditional practice of medicine, several plants have been reported to treat cognitive disorders. Ayurveda describes some medicinal herbs focusing on their neuroprotective active phytochemical substances like fatty acids, phenols, alkaloids, flavonoids, saponins, terpenes etc. The evidence for resistance of neurons to various stressors by activating specific signal transduction pathways and transcription factors have also been obtained . It was observed that a number of herbal medicines used in Ayurvedic medicine contain multiple compounds and phytochemicals that may have a neuroprotective effect which may prove beneficial in different neuropsychiatric and neurodegenerative disorders. Though the presence of receptors or transporters for polyphenols or other phytochemicals of the herbal preparations, in brain tissues remains to be ascertained, compounds with multiple targets appear as a potential and promising class of therapeutics for the treatment of diseases with a multifactorial etiology [81].

Neurodegeneration is a process involved in both neuropathological conditions and brain ageing. It is known that brain pathology in the

form of cerebrovascular and neurodegenerative disease is a leading cause of death all over the world, with an incidence of about 2/1000 and an 8% total death rate [82]. Cognitive dysfunction is a major health problem in the 21st century, and many neuropsychiatric disorders and neurodegenerative disorders, such as schizophrenia, depression, Alzheimer's Disease (AD) dementia, cerebrovascular impairment, seizure disorders, head injury, Parkinsonism etc can be severely functionally debilitating in nature [83]. Neuroprotection refers to the strategies and relative mechanisms which are able to defend the central nervous system (CNS) against neuronal injury due to both acute (e.g. stroke or trauma) and chronic neurodegenerative disorders (e.g. Alzheimer's disease and Parkinson's disease) [84]. Moreover, stroke and dementia are a source of high individual and family suffering mainly because of the lack of efficient therapeutic alternatives. The latter motivates research efforts to identify the mechanisms of neuronal death and to discover new compounds to control them.

The past decade has also witnessed an intense interest in herbal medicines in which phytochemical constituents can have long-term health promoting or medicinal qualities. In contrast, many medicinal plants exert specific medicinal actions without serving a nutritional role in the human diet and may be used in response to specific health problems over short- or long-term intervals. Phytochemicals present in vegetables and fruits are believed to reduce the risk of several major diseases including cardiovascular diseases, cancers as well as neurodegenerative disorders. Therefore people who consume higher vegetables and fruits may be at reduced risk for some of diseases caused by neuronal dysfunction [85, 86].

Herbal medicine has long been used to treat neural symptoms. Although the precise mechanisms of action of herbal drugs have yet to be determined, some of them have been shown to exert anti-inflammatory and/or antioxidant effects in a variety of peripheral systems. Now, as increasing evidence indicates that neuroglia-derived chronic inflammatory responses play a pathological role in the central nervous system, anti-inflammatory herbal medicine and its constituents are being proved to be a potent neuroprotector against various brain pathologies. Structural diversity of medicinal herbs makes them a valuable source of novel lead compounds against therapeutic targets that are newly discovered by genomics, proteomics, and high-throughput screening. Previously, in a review the importance of phytochemicals on neuroprotective function and other related disorders, in particular their mechanism of action and therapeutic potential were described [87].

The brain has a large potential oxidative capacity but a limited ability to counteract oxidative stress [88]. Oxidative stress has been implicated in mechanisms leading to neuronal cell injury in various pathological states of the brain, including neurodegenerative disorders. Although the brain accounts for less than 2% of the body weight, it consumes about 20% of the oxygen available through respiration. Therefore, because of its high oxygen demand, the brain is the most susceptible organ to oxidative damage [88]. Phytopharmaceuticals are gaining importance in modern medicine as well as in traditional system of medicine owing to their therapeutic potential. Novel antioxidants may offer an effective and safe means of bolstering body's defense against free radicals. Central nervous system cells are able to combat oxidative stress using some limited resources like, vitamins, bioactive molecules, lipoic acid, antioxidant enzymes and redox sensitive protein transcriptional factors. However, this defense system can be activated/ modulated by nutritional antioxidants such as polyphenols, flavonids, terpenoids, fatty acids etc. Plant derived alternative antioxidants (AOX) are regarded as effective in controlling the effects of oxidative damage, and hence have had influence in what people eat and drink [89, 90].There is ample scientific and empirical evidence supporting the use of antioxidants for the control of neurodegenerative disorders. As the focus of medicine shifts from treatment of manifest disease to prevention, herbal medicine (with its four pillars of phytochemistry, phytopharmacy, phytopharmacology and phytotherapy) is coming into consideration, being a renaissance of age-old human tradition.

Phytochemical based antioxidants may have neuroprotective (preventing apoptosis) and neuroregenerative roles [91], by reducing or reversing cellular damage and by slowing progression of neuronal cell loss. In nature, AOX are grouped as endogenous or exogenous. The endogenous group includes enzymes (and trace elements part-of) like superoxidase dismutase (zinc, manganese, and copper), glutathione peroxide (selenium) and catalase, and proteins like albumin, transferrin, ceruloplasmin, metallothionein and haptoglobin. The most

important exogenous AOX are dietary phytochemicals (such as polyphenols, quinones, flavonoids, catechins, coumarins, terpenoids) and the smaller molecules like ascorbic acid (Vitamin C), alpha-tocopherol (Vitamin E), beta-carotene vitamin-E, and supplements [92, 93]. Though their mode of action is not yet completely elucidated and clinical trials involving them are still relatively scarce, AOX offer a promising approach in the control or slowing down progression of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, ischaemic and haemorrhagic stroke [93, 94].

Cardiac Diseases and Ayurveda: Despite clinical efficacy, lack of scientific validation has limited the effective use of Ayurvedic drugs. Cardoguard is an Ayurvedic antihypertensive drug formulated by Nagarjuna Herbal Concentrates Ltd., Kerala, India. Left ventricular hypertrophy (LVH) is a modifiable risk factor, and regression of LVH reduces the propensity for adverse cardiovascular events. This study was taken up with the objective of evaluating the efficacy of Cardoguard in the prevention of cardiac remodeling. The results suggested that prevention of LVH by Cardoguard is possibly mediated through inhibition of extracellular signal-regulated kinases and protein kinase C-ε signaling pathways. Reduced expression of 3-nitrotyrosine in response to the treatment suggests that prevention of cardiac remodeling by Cardoguard is mediated by reduction of oxidative stress [95].

Conclusion: Science evolves through a rigorous and continuous research, Ayurveda, the ancient Indian system of health care and longevity needs to be validated on modern scientific research methodology taking care not to compromise with its basic tenets and philosophy. A full system validation would be the right approach in this direction. Scientific studies cannot make progress without the publication of research findings, which must welcome and withstand the scrutiny of peers.

Integrative medicine has the potential to improve rates of screening and uptake of preventive services through an emphasis on a strong therapeutic alliance, prevention, teaching, and holistic care. It culminated in the evolution of the concept of a golden triangle partnership consisting of modern medicine, traditional medicine, and life sciences. As multi-level efforts are being made to translate the concept into research and later into clinical practice, several new challenges are also emerging. We need to understand medicines or systems which existed in use before emergence of current "synthetic era" and visualize the future of medicine and health care in the "technology era". The linkage between "the past" and "the future" of medicine is much more important and can give us "new directions" for better understanding health, disease and possible solutions. By using these in combination with comprehensive lifestyle changes, mind-body medicine interventions, and recommendations with a strong therapeutic alliance, the promotion and protection of health at the community level will be achieved. Development of Nation without adequate consideration for health safeguards can prevent the improvement of living conditions for the very people whom the development efforts were intended to benefit.

References

1. Surgucheva, I., Gunewardena, S., Rao, H.S., Surguchov, A. (2013). Cell-Specific Post-Transcriptional Regulation of γ-Synuclein Gene by Micro-RNAs. *PLoS One.* 2013 Sep 11;8(9):e73786. doi: 10.1371/journal.pone.0073786
2. Deocaris, C.C., Widodo, N., Wadhwa, R., Kaul, S.C. (2008). Merger of ayurveda and tissue culture-based functional genomics: inspirations from systems biology. *J Transl Med.* 18;6:14.
3. Hadjibabaie, M., Badri, S., Ataei, S., Moslehi, A.H., Karimzadeh, I., Ghavamzadeh, A. (2013). Potential drug-drug interactions at a referral hematology-oncology ward in Iran: a cross-sectional study. *Cancer Chemother Pharmacol.* 71(6):1619-27.
4. Kalantar-Zadeh, K., Kopple, J.D. (2006). Obesity paradox in patients on maintenance dialysis. *Contrib Nephrol.* 151:57-69.
5. Eckhardt-Henn, A. (2013). Psychosomatic vertigo disorders. *HNO*. 61(9):777-80
6. Kang, L., Cui, X., Zhang, Y., Yang, C., Jiang, Y. (2013). Identification of miRNAs associated with sexual maturity in chicken ovary by Illumina small RNA deep sequencing. *BMC Genomics.* 14:352.
7. Levy, M.A., Garg, A., Tam, A., Garten, Y., Rubin, D.L. (2007). Lesion Viewer: a tool for tracking cancer lesions over time. *AMIA Annu Symp Proc.* 11:443-7.
8. Prasher, B., Negi, S., Aggarwal, S., Mandal, A.K., Sethi, T.P., Deshmukh, S.R., Purohit, S.G., Sengupta, S., Khanna, S., Mohammad, F., Garg, G., Brahmachari, S.K. Indian Genome Variation Consortium, Mukerji, M. (2008). Whole genome expression and biochemical correlates of extreme

constitutional types defined in Ayurveda. *J Transl Med.* 9;6:48.
9. Rao, R.K., Reddy, K.R.C., Nathani, N. (2013). Integrative Approach to Metabolic Disorders. Published by Mahima Research Foundation and Social Welfare, Varanasi pp. 1-157.
10. Pandey, M.M., Rastogi, S., Rawat, A.K. (2013). Indian traditional ayurvedic system of medicine and nutritional supplementation. *Evid Based Complement Alternat Med.* 376327. doi: 10.1155/2013/376327. Epub 2013 Jun 23.
11. Raut, AA. (2011). Integrative endeavor for renaissance in Ayurveda. *J Ayurveda Integr Med.* 2(1):5-8.
12. Singh, H.K. (2013). Brain enhancing ingredients from Āyurvedic medicine: quintessential example of Bacopa monniera, a narrative review. *Nutrients*. 6;5(2):478-97.
13. Singh, R.H. (2010). Banaras Hindu University, Varanasi, India. Personal communication.
14. Singh, L. (1977). *Studies on the anti-anxiety effect of the medya-rasayana drug, Brāhmi (Bacopa monniera)*. M.D. Thesis, Faculty of Medical Sciences, Banaras Hindu University, Varanasi, India.
15. Tilwari, A., Shukla, N.P., Pathirissery, U.D. (2011). Immunomodulatory activity of the aqueous extract of seeds of Abrus precatorius Linn (Jequirity) in mice. *Iran J Immunol.* 8(2):96-103.
16. Chopra, A., Saluja, M., Tillu, G. (2010). Ayurveda-modern medicine interface: A critical appraisal of studies of Ayurvedic medicines to treat osteoarthritis and rheumatoid arthritis. *J Ayurveda Integr Med*. 1(3):190-8.
17. Srikanta, Murthy, K.R. (1993). Delhi, India: Chaukhambia Orientalia; Madhava Nidanam (roga viniscaya) of Madhavakara (English translation), Chapter 22.
18. Thatte, U., Chhabria, S., Karandikar, S.M., Dahanukar, S. (1987). Immuno-therapeutic modifications by Indian medicinal plants. *Indian Drugs.* 1987;25:85–7.
19. Thatte, U.M., Dahanukar, S.A. (1989). Immunotherapeutic modification of diverse infectious states by Indian medicinal plants. *Phytother Res.* 1989;3:43–8.
20. Patwardhan, B., Kalbag, D., Patki, P.S., Nagsampagi, B.A. (1991). Search of immunomodulatory agents: A review. *Indian Drugs*. 1991;28:249–54.
21. Upadhyay, S.N. (1997). *Therapeutic potential of immunomodulatory agents from plant products*. In: Upadhyay SN, editor. New Delhi: Narosa Publishing House; 1997. pp. 149–54.
22. Katiyar, C.K., Brindavanam, Tiwari, P., Narayana, D.B. (1997). *Immunomodular products from Ayurveda: current status and future perspectives.* In: Upadhyay SN, editor. Immunomodulation. New Delhi: Narosa Publishing House. pp. 163–87.
23. Rege, N.N., Thatte, U.M., Dahanukar, S.A. (1999). Adaptogenic properties of six *Rasayana* herbs used in Ayurvedic medicine. *Phytother Res.* 13:275–91.
24. Mishra, B. (1999). In: 9th ed. Bhavmishra, *Bhavprakasha Nighantu.*, editors. Vol. 1. Nighantu, Varanasi: Chaukhambha Sanskrit Sansthan; p. 11.
25. Frawley, D., Lad, V. (1994). *The Yoga of Herbs*. Delhi, India: Motilal Banarsidass Publishers Pvt Ltd; 1994.
26. Chopra, A. (2000). Ayurvedic medicine and arthritis. *Rheum Dis Clin North Am.* 2000;26:133–44.
27. Srikanta, Murthy, KR. (1993). Delhi, India: Chaukhambia Orientalia; Madhava Nidanam (roga viniscaya) of Madhavakara (English translation), Chapter 28.
28. Budhiraja, R.D., Sudhir, S. (1987). Review of biological activity of withanolides. J *Sci Ind Res.* 46:400–8.
29. Begum, V.H., Sadique, J. (1988). Long term effect of herbal drug Withania Somnifera on adjuvant induced arthritis in rats. *Indian J Exp Biol.* 26:877–82.
30. Ghosal, S., Lal, J., Shrivastava, R., Bhattacharya, S.K., Upadhyay, S.N., Jaiswal, A.K., et al. (1989). Immunomodulatory and CNS effects of sitoinosides IX and X, two new glycowithanolides from W somnifera. *Phytother Res.* 3:201.
31. Ziauddin, M., Phansalkar, N., Patki, P., Diwanay, S., Patwardhan, B. (1996). Studies on the immunomodulatory effects of Ashwagandha. *J Ethnopharmacol.* 50:69–76.
32. Sharma, P.V. (1994). *Chikitsa Sthana*, Chapter 28. Delhi, India: Chaukhambia Orientalia; Charaka Samhita (English translation) pp. 142–56.
33. Hahm, E.R., Lee, J., Singh, S.V**.** (2013). Role of mitogen-activated protein kinases and Mcl-1 in apoptosis induction by withaferin A in human breast cancer cells. *Mol Carcinog.* doi: 10.1002/mc.22050.
34. Hahm, E.R., Lee, J., Kim, S.H., Sehrawat, A., Arlotti, J.A., Shiva, S.S., Bhargava, R., Singh, S.V. (2013). Metabolic alterations in mammary cancer prevention by withaferin a in a clinically relevant mouse model. *J Natl Cancer Inst.* 105(15):1111-22.
35. Patil, D., Gautam, M., Mishra, S., Karupothula, S., Gairola, S., Jadhav, S., Pawar, S., Patwardhan, B. (2013). Determination of withaferin A and withanolide A in mice plasma using high-performance liquid chromatography-tandem mass spectrometry: application to pharmacokinetics after oral administration of Withania somnifera

aqueous extract. *J Pharm Biomed Anal.* 2013 Jun;80:203-12

36. Siegel, R., DeSantis, G., Virgo, K., Stein, K., Mariotto, A., Smith, T., Cooper, D., Gansler, T., Lerro, C., Fedewa, S., Lin, C., Leach, C., Cannady, R.S., Cho, H., Scoppa, S., Hachey, M., Kirch, R., Jemal, A., Ward, E. (2012). Cancer treatment and survivorship statistics. *CA Cancer J Clin.* 13:220–241.
37. Badmaev, V., Majeed, M., Pacchetti, B., Prakash, L. (2003). Standardiation of Commiphora Mukul extract in dislipidemia and cardiovascular disease. *NUTRA Foods*. 13:45–51.
38. Shishodia, S., Harikumar, K.B., Dass, S., Ramawat, K.G., Aggarwal, B.B. (2006). The guggul for chronic disease: ancient medicine, modern targets. *Anticancer Res.* 13:3647–3664.
39. Sinal, C.J., Gonzalez, F.J. (2002). Guggulsterone: an old approach to a new problem. *Trends Endocrinol Metab*. 13:275–276.
40. Urizar, N.L., Liverman, A.B., Dodds, D.T., Silv, F.V., Ordentlich, P., Yan, Y., Gonzaleg, F.J., Heyman, R.A., Mangelsdorf, D.J., Moore, D.D. (2002). A natural product that lowers cholesterol as an antagonist ligand for FXR. *Science.* 2002;13:1703–1706.
41. Urizar, N.L., Moore, D.D. (2003). GUGULIPID: a natural cholesterol-lowering agent. *Annu Rev Nutr*. 13:303–313.
42. Szapary, P.O., Wolfe, M.L., Bloedon, L.T., Cucchiara, A.J., DerMarderosian, A.H., Cirigliano, M.D., Rader, D.J. (2003). Guggulipid for the treatment of hypercholesterolemia: a randomized controlled trial. *JAMA.* 13:765–772.
43. Zhu, N., Rafi, M.M., DiPaola, R.S., Xin, J., Chin, C.K., Badmaev, V., Ghai, G., Rosen, R.T., Ho, C.T. (2001). Bioactive constituents from gum guggul (Commiphora wightii) *Phytochemistry*. 13:723–727.
44. Gujral, M.L., Sareen, K., Tangri, K.K., Amma, M.K., Roy, A.K. (1960). Antiarthritic and anti-inflammatory activity of gum guggul (Balsamodendron mukul Hook) *Ind J Physiol Pharmacol.* 13:267–273.
45. Xiao, M., Xiao, D. (2012). Gugulipid, an Extract of *Ayurveda* Medicine Plant *Commiphora Mukul* as a potent agent for cancer chemoprevention and cancer chemotherapy. *Med Chem.* 13(6):1000e105.
46. Samudio, I., Konopleva, M., Safe, S., McQueen, T., Andreeff, M. (2005). Guggulsterone induce apoptosis and differentiation in acute myeloid leukemia: identification of isomer-specific antileukemic activities of the pregnadienedione structure. *Mol Cancer Ther*. 2005;13:1982–1992.
47. Surh, Y.J. (2003). Cancer chemoprevention with dietary phytochemicals. *Nat Rev Cancer*. 2003;13:768–780.
48. Xiao, D., Zeng, Y., Prakash, L., Badmaev, V., Majeed, M., Singh, S.V. (2011). Reactive oxygen species-dependent apoptosis by Gugulipid extract of *Ayurveda* Medicine Plant *Commiphora Mukul* in human prostate cancer cells is regulated by c-Jun N-Terminal kinase. *Mol Pharmacol*. 13:499–507.
49. Xiao, D., Singh, S.V. (2008). Guggulsterone, a constituent of Indian Ayurvedic medicinal plant *Commiphora mukul*, inhibits angiogenesis *in vitro* and *in vivo*. *Mol. Cancer Ther.* 13:171–180.
50. Singh, S.V., Choi, S., Zeng, Y., Hahm, E.R., Xiao, D. (2007). Guggulsterone-induced apoptosis in human prostate cancer cells is caused by reactive oxygen intermediate-dependent activation of c-Jun NH_2-terminal kinase. *Cancer Res.* 13:7439–7449.
51. Singh, S.V., Zeng, Y., Xiao, D., Vogel, V.G., Nelson, J.B., Dhir, R., Tripathi, Y.B. (2005). Caspase-dependent apoptosis induction by guggulsterone, a constituent of Ayurvedic medicinal plant *Commiphora mukul*, in PC-3 human prostate cancer cells is mediated by Bax and Bak. *Mol Cancer Ther.* 2005;13:1747–1754.
52. Cheon, J.H., Kim, J.S., Kim, J.M., Kim, N., Jung, H.C., Song, I.S. (2006). Plant sterol guggulsterone inhibits nuclear factor-κB signaling in intestinal epithelial cells by blocking IκB kinase and ameliorates acute murine colitis. *Inflamm Bowel Dis.* 13:1152–1161.
53. Cui, J., Huang, L., Zhao, A., Lew, J.L., Yu, J., Sahoo, S., Meinke, P.T., Royo, I., Pelaez, F., Wright, S.D. (2003). Guggulsterone is a farnesoid X receptor antagonist in coactivator association assays but acts to enhance transcription of bile salt export pump. *J Biol Chem.* 13:10214–10220.
54. Ichikawa, H., Aggarwal, B. (2006). Guggulsterone inhibits osteoclastogenesis induced by receptor activator of nuclear factor-κB ligand and by tumor cells by suppressing nuclear factor-κB activation. *Clin Cancer Res.* 13:662–668.
55. Leeman-Neill, R.J., Wheeler, S.E., Singh, S.V., Thomas, S.M., Seethala, R.R., Neill, D.B., Panahanden, M.C., Hahm, E.R., Joyce, S.C., Sen, M., Cai, Q., Freilino, M.L., Li, C., Johnson, D.E., Grandis, J.R. (2009). Guggulsterone enhances head and neck cancer therapies viainhibition of signal transducer and activator of transcription-3. *Carcinegesis*. 13:1848–1856.
56. Sarfaraz, S., Siddiqui, I.A., Syed, D.N., Afaq, F., Mukhtar, H. (2008). Guggulsterone modulates MAPK and NF-κB pathways and inhibits skin tumorigenesis in SENCAR mice. *Carcinogenesis.* 13:2011–2018.
57. Shishodia, S., Aggarwal, B.B. (2004). Guggulsterone inhibits NF-kappaB and IkappaBalpha kinase activation, suppresses expression of anti-apoptotic gene products, and enhances apoptosis. *J Biol Chem*. 13:47148–47158.

58. Kim, E.S., Hong, S.Y., Lee, H.K., Kim, S.W., An, M.J., Kim, T.I., Lee, K.R., Kim, W.H., Cheon, J.H. (2008). Guggulsterone inhibits angiogenesis by blocking STAT3 and VEGF expression in colon cancer cells. *Oncol Rep.* 13:1321–1327.
59. Looi, C.Y., Moharram, B., Paydar, M., Wong, Y.L., Leong, K.H., Mohamad, K., Arya, A., Wong, W.F., Mustafa, M.R. (2013). Induction of apoptosis in melanoma A375 cells by a chloroform fraction of Centratherum anthelminticum (L.) seeds involves NF-kappaB, p53 and Bcl-2-controlled mitochondrial signaling pathways. *BMC Complement Altern Med.* 10;13:166.
60. Bhakta Prasad Gaire, Lalita Subedi. (2013). A review on the pharmacological and toxicological aspects of Datura stramonium L. *Journal of Chinese Integrative Medicine*. 11 : 2.
61. Fornoni, J., Núnez-Farfán, J. (2000). Evolutionary ecology of Datura stramonium: genetic variation and costs for tolerance to defoliation. *Evolution*. 54(3) : 789-797.
62. Luna-Cavazos, M., Bye, R. (2011). Phytogeographic analysis of the genus Datura (Solanaceae) in continental Mexico. *Rev Mex Biodivers.* 82: 977-988.
63. Berkov, S., Zayed, R., Doncheva, T. (2006). Alkaloid patterns in some varieties of Datura stramonium. *Fitoterapia*. 77(3) : 179-182.
64. Ajungla, L., Patil, P.P., Barmukh, R.B., Nikam, T.D. (2009). Influence of biotic and abiotic elicitors on accumulation of hyoscyamine and scopolamine in root cultures of Datura metel L. *Indian J Biotechnol.* 8(3) : 317-322.
65. Dessanges, J.F. (2001). A history of nebulization. *J Aerosol Med.* 14(1) : 65-71.
66. Diker, D., Markovitz, D., Rothman, M., Sendovski, U. (2007). Coma as a presenting sign of Datura stramonium seed tea poisoning. *Eur J Intern Med.* 18(4) : 336-338.
67. Naudé, T.W., Gerber, R., Smith, R.J., Botha, C.J. (2005). Datura contamination of hay as the suspected cause of an extensive outbreak of impaction colic in horses. *J S Afr Vet Assoc*. 76(2) : 107-112.
68. Norton, S. (2008).*Toxic effects of plants*. In: Klaassen CD. Caserett and Doull's toxicology, the basic science of poisons. 7th ed. New York: McGraw Hill, 1110.
69. Kirtikar, K.R., Basu, B.D. (1999). *Indian medicinal plants.* 2nd ed. Volume III. Dehradun: International Book Distributors, 1999. 1783-1787.
70. Gaire, B.P. (2008). *Monograph on Datura stramonium*. Kaski, Nepal: Pokhara University Press, 1-114.
71. Jakabová, S., Vincze, L., Farkas, A., Kilár, F., Boros, B., Felinger, A. (2012). Determination of tropane alkaloids atropine and scopolamine by liquid chromatography-mass spectrometry in plant organs of Datura species. *J Chromatogr A.* 1232: 295-301.
72. Khare, C.P. (2007). *Indian medicinal plants*. Delhi: Rajkamal Electric Press, 203.
73. Berkov, S., Pavlov, A., Kovatcheva, P., Stanimirova, P., Philipov, S. (2003). Alkaloid spectrum in diploid and tetraploid hairy root cultures of Datura stramonium. *Z Naturforsch C.* 58(1-2) : 42-46.
74. Iranbakhsh, A., Oshaghi, M.A., Majd, A. (2006). Distribution of atropine and scopolamine in different organs and stages of development in Datura stramonium L. (Solanaceae). Structure and ultrastructure of biosynthesizing cells. *Acta Biol Crac Ser Bot.* 48(1) : 13-18.
75. Li, J., Lin, B., Wang, G., Gao, H., Qin, M. (2012). Chemical constituents of Datura stramonium seeds. *Zhongguo Zhong Yao Za Zhi.* 37(3) : 319-322.
76. Potdar, D., Hirwani, R.R., Dhulap, S. (2012). Phyto-chemical and pharmacological applications of Berberis aristata. *Fitoterapia*. 83(5):817-30.
77. Bhide, B., Pillai, A.P., Shukla, V.J., Acharya, R.N. (2011). Pharmacognostic evaluation of leaf of Cordia macleodii Hook., An ethnomedicinally important plant. *Ayu.* 32(2):254-7.
78. Baliga, M.S., Kurian, P.J. (2012). Ixora coccinea Linn.: traditional uses, phytochemistry and pharmacology. *Chin J Integr Med.* 18(1):72-9.
79. Nayak, J. (2012). Ayurveda research: Ontological challenges. *J Ayurveda Integr Med.* 3(1):17-20.
80. Singh, K.S., Chandola, H., Kaur, M., Ravishankar, B. (2012). Evaluation of Saptarangyadi Ghanavati in the management of Apathyanimittaja Prameha w.s.r. to type-2 diabetes mellitus. *Ayu.* 33(3):368-73.
81. Kumar, G.P., Khanum, F. (2012). Neuroprotective potential of phytochemicals. *Pharmacogn Rev.* 6(12):81-90.
82. Kolominsky, Rabas. P.L., Sarti, C., Heuschmann, P.U., Graf, C., Siemonsen S., Neundoerfer, B., et al. (1998) A prospective communitybased study of stroke in Germany. The Erlangen Stroke Project (ESPro): Incidence and case fatality at 1, 3, and 12 months. *Stroke.* 29:2501–6.
83. Commenges, D., Scotet, V., Renaud, S., Jacqmin-Gadda, H., Barberger, Gateau, P., Dartigues, J.F. (2000). Intake of flavonoids and risk of dementia. *Eur J Epidemiol.* 6:357–63.
84. Kumar, V. (2006). Potential medicinal plants for CNS disorders: An overview. *Phytother Res.* 20:1023–35.
85. Selvam, A.B. (2008). Inventory of Vegetable Crude Drug samples housed in Botanical Survey of India, Howrah. *Pharmacognosy Rev.* 2:61–94.
86. Lobo, V., Patil, A., Phatak, A., Chandra, N. (2010). Free radicals, antioxidants and functional foods: Impact on human health. *Pharmacogn Rev.* 4:118–26.

87. Pueyo, I.U., Calvo, M.I. (2009). Phytochemical Study and Evaluation of Antioxidant, Neuroprotective and Acetylcholinesterase Inhibitor Activities of Galeopsis ladanum L. extracts. *Pharmacognosy Mag.* 5:287–90.
88. Weiss, R.F., Fintelmann, V. (2000). Herbal Medicine. Stuttgart: Thieme; pp. 3–20.
89. Viana, M., Barbas, C., Banet, B., Bonet, M.V., Castro, M., Fraile, M.U., et al. (1996). *In vitro* effect of a flavonoid-rich extract on LDL oxidation. Atherosclerosis. 123:83–91.
90. Pinder, R.M., Sandler, M. (2004). Alcohol, wine and mental health: Focus on dementia and stroke. *J Psychopharm*. 18:449–56.
91. Moosmann, B., Behl, C. (2002). Antioxidants as treatment for neurodegenerative disorders. *Expert Opin Investig Drugs.* 11:1407–35.
92. Larson, R.A. (1988). The antioxidants of higher plants. *Phytochemistry*. 27:969–78.
93. Berger, M.M. (2005). Can oxidative damage be treated nutritionally? *Clin Nutr*. 24:172–83.
94. Floyd, R.A. (1999). Antioxidants, oxidative stress and degenerative neurological disorders. *Proc Soc Exp Biol Med*. 222:236–45.
95. Sankar, V., Nair, R.R., Harikrishnan, V.S., Fernandez, A.C., Kumar, C.S., Madhavachandran, V. (2012). Cardoguard, an Ayurvedic antihypertensive formulation, prevents cardiac remodeling in spontaneously hypertensive rats by inhibition of ERK and PKCε signaling pathways. *Can J Physiol Pharmacol.* 90(5):627-35.