SYNERGISTIC COMBINATION OF ANCIENT INDIAN HERBAL FORMULATIONS WITH MODERN ALLOPATHIC PRESCRIPTIONS IS NEED OF THE HOUR

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Ancient Indian Ayurvedic system of medicine is believed to be one of the oldest systems of medication in the world. Use of medicinal plants and their products has been the central theme of the Ayurvedic medicaments that involved age old practices through trial and error experiments in designing potent herbal formulations of high therapeutic significance. Approximately, 25 per cent of all prescription drugs currently being utilised the world over are originally derived from plants. Herbal medicines are believed to be safe with less side-effects, cost effective and easily accessible. However, the lack of evidence-based data on therapeutic efficacy, clinical and scientific standardisation of phytochemicals of medicinal plants are some hindrances in the path of Ayurvedic herbal medicines to be globally accepted as credible mainstream medications. Though allopathic is the most preferred system of medication in the world today, the genesis of iatrogenic disorders through side effects remains to be the biggest challenge. Synthetic and semi-synthetic drugs pose greater burden to the hepatic and renal systems of the body, and in many cases even thier failure. Synergistic combination of Ayurvedic herbal formulations with allopathic drugs is an innovative practice quite capable of addressing the challenge of side effects. The review deals with the science of synergy, herb-drug interactions and their clinical validation as thrust areas of research and development in phytomedicines. Nonetheless, an urgent need causing standardisation of phytochemicals of herbal medicines in the line of allopathic drugs has been emphasised in order to suit the mindset of people, medical practitioners, and doctors of the present digital era. Hopefully, the present exposition would educate the readers to appreciate and embrace ancient Indian traditional medicine as a global credible scientific system of medications. Furthermore, predicting nanotechnologised Ayurvedic herbals as integrative medicaments of the future generation of the genomic era is not seer's fictional exaggeration.

Keywords: Ayurveda, Allopathic, Synergy, Phytomedicine, Iatrogenic, Isobole, Side-effects

Introduction

The history of medications is as old as human beings themselves. Various kinds of medicinal and healthcare systems based on plants, natural products, synthetic therapeutics and other life processes have been developed and got differentiated in different parts of the world so as to ensure human survival and well being. At present, very recently developed Allopathic system of medicine and health care in the early 19th Century in Europe and North America is the most widely followed system of medications world over because of its diagnostic accuracy, and technological advancement in designing drugs and treatment methodologies. However, some of the ancient traditional systems such as Indian, Chinese, Japanese, Tibetan, Arabic, Greek and Romans are still in practice at the place of their origin, whilst very few of them are globally being followed as Complementary or Alternative medicines. Indian systems of medicines include six traditions, viz., Ayurveda, Siddha, Unani, Homeopathy,

Sowa-Rigpa, and folklore, of which Ayurveda is the oldest in not only Indian medicine systems but also in the entire world's traditional systems of medicines, which is thought to be 5000 years old, and can be remotely linked to the Indus Valley Civilisation (Rivera *et al*., 2013). Ayurveda literally means science of longevity; it was not only to cure illness and afflictions but also to preserve health and ensure a long happy personal and social life. The origin of Ayurveda is attributed to *Atharvaveda*, which describes several human diseases with their treatments. Later on, the Ayurvedic science became more systematic and organised during 6th Century BC to 7th Century AD, which is known as *Samhita* period, characterised by classical works such as *Charaka samhita* and *Sushruta samhita* dealing with evolution of a complete health care system with physicians and surgeons at the helm (Narayanswami, 1981). The philosophy of Ayurveda believes in universal inter-connectedness among mind, body and spirit of the people with the universe, where body is regarded as *prakriti*, and life forces as *doshas* existing in three forms: *Kapha*, *Pitta*, and *Vata* comparable to Yin-Yang and biologic humors of Chinese and ancient Greek systems of medicines, respectively. Any imbalance caused to these forms results in diseases. Ayurvedic practitioners prescribe individualised treatments to balance the *doshas* in order to treat a disease that include herbs or proprietary ingredients, diet, yoga and life style recommendations. In India, about 85 per cent of the population use some form of Ayurvedic therapy as primary health care (Kamboj, 2000). In the USA and European countries, Ayurveda is considered a complementary healthcare option, with many people employing Ayurvedic elements such as massage, medication or cleansing therapies. Nowhere in the world except in the Indian subcontinent, Ayurveda has been able to keep its identity as a mainstream medical system due to lack of standardisation of the active phytochemicals of herbal medicines for counter-indications, side effects and toxicities in the line of allopathic medicines. There have been several reviews on various aspects of Indian traditional medicine available in literature till date however, very little focus on pros and cons of innovative practices in amalgamating traditional herbal medicines with conventionally used allopathic prescriptions which can do miracles through synergistic action. Through this review, the author wishes to highlight the great potential of such innovations in bringing traditional ancient Indian herbal medicine to the global mainstream of medications. Hopefully, the present exposition would educate the readers to appreciate and embrace ancient Indian traditional herbal medicine as a global credible scientific system of medications.

Allopathy as the most Preferred System of Medications in the World

Allopathic medicine is the most preferred choice of medication in the world today, since it is basically a drug-oriented methodology that relies on three things, hypothesis, experimentation and results. Growing popularity and preference of the allopathic medicine and health care system can be attributed to intrinsic and extrinsic factors.

Intrinsic factors include *inter alia*, effectiveness of drugs and surgical procedures during emergency, use of advanced technologies with efficient and accurate diagnostic techniques, understanding of molecular mechanism of pathogenesis and appropriate therapeutics with targeted action, and identification of correct pathogenic microorganisms and quick targeted action thereupon. Some of the extrinsic factors include availability of infrastructure and human resources, socioeconomic conditions, treatment costs, morbidity pattern and political economy of health care services. According to Rudra (*et al*. 2019) allopathic system utilisation in India accounts for over 90 per cent without any significant difference across rural and urban areas, and about 6.9 per cent of people prefer AYUSH services (3.5 per cent ISM, and 3.0 per cent homeopathy) across rural and urban. However, the modern allopath is not free from problems. There are several disadvantages of the system that include *inter alia,* side effects of therapeutics; genesis of iatrogenic disorders, inadequacy in treating chronic diseases such as arthritis, hyperacidity, and allergies; time consuming and very costly process of discovery of a new drug; lack of remedies in case microorganisms become resistant to drugs. In addition, the allopathic system pays no heed to the vital elements such as spiritualism, divinity and social health as practised in ancient traditional medicines such as Ayurveda.

Indian traditional medicinal herbal system as progenitor of modern allopathic drugs

Traditional herbal medicines imply plant preparations brought to therapies with the desired results through many years of trial and error experimentations. According to the World Health Organisation (WHO) estimate, the worldwide use of herbal medicines exceeds two to three times that of conventional allopathic drugs.

Though, allopathy being the most preferred system of medications the world over today, it still utilises several potent drugs, which are derived from Indian traditional medicinal herbs, some well known examples include Ephedrine (*Ephedra gerardiana*), Digoxin (*Digitalis purpurea*), Reserpine (*Rauwolfia serpentine*), Ajmalcine, Vincristine, and Vinblastine (*Catharanthus reseus*), Atropine (*Atropa belladonna*), Asprin and Salicin (*Salix alba*), Berberine (*Berberis vulgaris*), Codeine and Morphine (*Papaver somniferum*), and Colchicine (*Colchicum autumanale*). Currently, plant derived medicines are being widely utilised as antibiotics, antifungal, antitumour, anticancer, antidiabetic, anticholesterol, analgesic, anti-inflammatory, anti-depressants, antimalarial as well as cardiac stimulant, central nervous system stimulants, and psychoactive drugs with scientific credibility. Approximately, 75 per cent of new anticancer drugs marketed between 1981 and 2006 were derived directly from plants or plant compounds. In reality, approximately, 25 per cent of all prescription drugs currently being utilised world over are originally derived from plants. Furthermore, traditional herb based Ayurvedic system, according to its philosophy, seek to diagnose imbalance in *doshas* before the occurrence of disease, hence the disease could be effectively prevented well in advance. It is able to cure chronic diseases effectively and safely. Moreover, the Ayurvedic treatment is safe with less side-effects, easily accessible and cost effective. However, there are several disadvantages of the

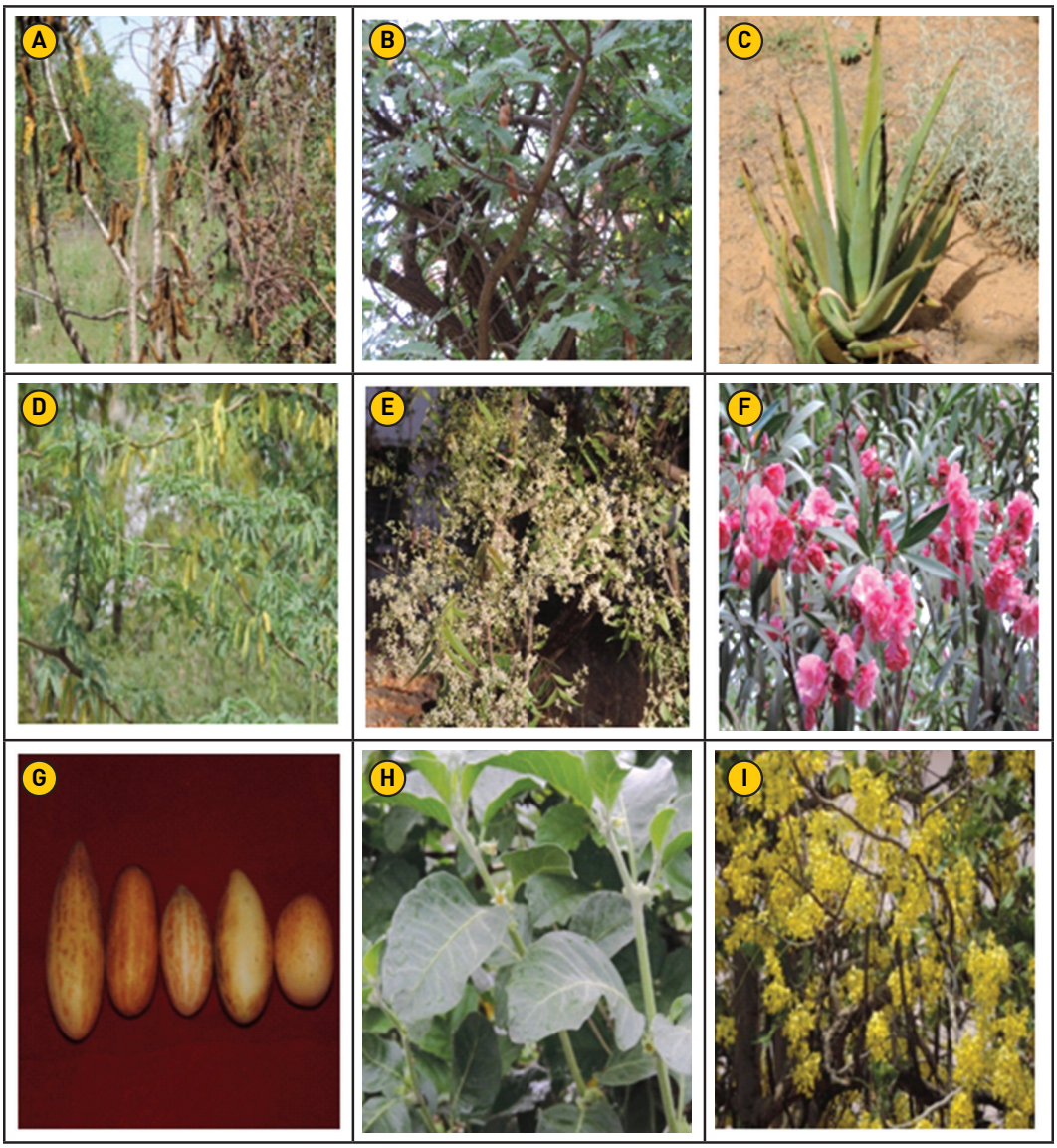

Fig. 1. Plant sources of scientifically/clinically validated phytomedicines used in combination with allopathic drugs or other plant extracts to elicit additive, synergistic, or antagonistic effects; A. *Mucuna pruriens* B. *Tamarindus indica* C. *Aloe vera* D. *Acacia Senegal* E. *Azadirichta indica* F. *Nerium oleander* G. *Cucumis melo var. agrestis* H. *Withania somnifera* I. *Cassia fistula*

system that include, delayed mode of action, inadequacies in case of emergency conditions and lack of evidence based data on efficacy of therapeutics in disease management, are some hindrances in the path of its global acceptance as medications of the mainstream.

Science of Aynergism and Herb-drug or Drug-drug Interactions in Amalgamation of Indian Traditional Herbal Therapeutics with Allopathic Medicines

Synergy research in phytomedicine is the outcome of the quest for the development of evidence based clinical research database for the standardisation of traditional herbal formulations used to exhibit desired results in healing. It is a recent development and is currently being viewed as key research area of the future. It holds the great potential of revolutionising the present mainstream systems of medications the world over that would pave the way for the beginning of new generation of highly effective medicaments, the integrative medicine. With the development of new tools and techniques in molecular biology and analytical chemistry, an unexpected change of paradigm in chemotherapy has taken place, involving gradual transition from mono-substance therapy to a multi-drug therapy. An understanding of reactions between herbal ingredients and other drugs that could either be herbal medicines and/or allopathic medicines is of particular importance when serious and/or life threatening diseases are being treated such as rheumatic diseases, geriatric diseases, hypertension, cancers and AIDS that essentially require multi-drug therapies. This is not a new paradigm for the Ayurvedic or Chinese systems since the multi-target therapy has been in practice in these systems through ages that involved preparation of herbal extracts containing varieties of bioactive compound, which could have exhibited synergistic effects in curing the disease. Though we know several examples of synergistic effects of Ayurvedic medicines, the exact mechanism of such effects is still unknown. Knowing the exact mechanism of the synergistic effects in phytotherapy is more difficult, because the herbal extracts consist of mixtures of major compounds, minor concomitant agents, and fibres, which can all be involved in synergy effects. Whereas, the demonstration of improved effectiveness of allopathic drug combinations is relatively simple since they use mixtures of single pure substances, whose pharmacology in most instances is known.

Co-administration of Herbal Extract and Allopathic Drugs, and Mechanism of Herb-drug Interactions

When herbal extract and allopathic drugs are co-administered in a patient, they exhibit chemical or pharmacological interactions, which may alter the effect of either agent, leading to decreased or increased effectiveness or severity of adverse effects. Two general modes of actions have been ascribed to herb-drug interactions, pharmacokinetic and pharmacodynamic

interactions. Pharmacokinetic interaction between herb and drug brings about quantitative alteration with respect to drug absorption, drug distribution, drug metabolism and bioavailability; and drug elimination through hepatic and renal clearance. For example, cytochrome P450 isoenzyme family is the common pathway for metabolism of drug molecules in the liver. Many allopathic anti-diabetic drugs such as pioglitazone, repaglinide, rosiglitazone, glibenclamide, glimepiride serve as substrates for the cyt-isoenzyme system, while many herbal constituents have been identified as the inhibitors of some iso-enzymes of the cyt-isoenzyme system such as Ginkgo and St John's Wort, thereby affecting metabolism (elimination or bioavailability) of the allopathic drugs in the body of patients. Whilst, pharmacodynamic interaction can modify the herb-drug actions in a qualitative manner through effects on various organs, receptor sites or enzymes, such interactions can result in additive, antagonistic or synergistic effects.

Mathematical modelling of the mechanism of herb-drug or drug-drug interactions in eliciting additive, antagonistic and synergistic effects.

Though many authors have made attempts to demonstrate the mechanism of synergy effects of phytomedicines, they remain somehow unrealistic in their interpretations since they followed theoretical path and were unable to provide experimental model for it. However, Berenbaums approach to experimental demonstration of synergistic effects of phytomedicines using animal model or *in vitro* assay seem practically plausible. His mathematical modeling of synergy effects with the help of isobole curves [Fig.2] and equations could interpret the mechanism of this highly complex phenomenon in a seemingly realistic way. The following three equations explain the mechanism of drug-drug interaction in different ways, where **E** = observable effect, $\mathbf{d_a}$ and $\mathbf{d_b}$ are two doses of components a and b of the mixture of phytomedicines.

Equation 1. $E(d_a \text{ and } d_b) = E(d_a) + (d_b)$

Eq. 1. denotes zero (0) or additive interaction, in other words, the effect of two components, viz., a and b of the mixture of phytomedicine would be their summation, i.e., **a+b**. Summation effect of **a** and **b** has been shown as a diagonal line in the isobole (Fig. 3).

Example: All heart glycosides target (inhibition) Na^+ and K^+ dependent ATP-ase even though their concentrations differ. Interaction between the most clinical used cardiac glycoside, digoxin and endogenously present cardiac glycosides, ouabain, marinobufagin and telocinobufagin and their inhibitory effect on Na^+, K^+ ATP-ase of human kidney was studied. It was observed that all glycosides function in additive manner.

Equation 2. $E(d_a \text{ and } d_b) \leftarrow E(d_a) + (d_b)$

Eq. 2. denotes the overall effect with antagonistic interaction, which is less than expected from the summation of the individual effects of **a** and **b** in the mixture of phytomedicine. A convex curve would be obtained in the isobole as shown in Fig. 2.

Example: Herbal extract of *Hypericum perforatum* (HP) (St John's Wort) with anti-HIV retro viral drugs, such as indinavir, lamivudine and amprenavir, show

antagonistic effect, thereby decreasing the effectiveness of anti-HIV drugs. HP induces the production of cytochrome 3A4, which is involved in the break-down of anti-HIV drugs in liver for their excretion from the body. Therefore, anti-HIV drugs do not kill viruses or reduce viral density in blood. So, the patient would not lose his/her potency to infect healthy persons Durr *et al.*, 2000.

Equation 3. $E(d_a \text{ and } d_b) \rightarrow E(d_a) + E(d_b)$

Eq. 3. denotes the synergistic interaction with potentiated or over-additive effect, the overall effect of the two components, **a** and **b** when applied together as a mixture would show greater effect than expected by the summation of their individual effects. It has been shown as a concave curve in the isobole.

Example: *Cannabis sativus* contains several phytochemicals of which Tetrahydrocannabinol (THC) and Cannabidiol are shown here in therapy. *Cannabis* and THC possess anti-spastic effects in addition to their hallucinogenic, antiemetic, anxiolytic appetite stimulating, anti-inflammatory and analgesic effects. In clinical experiments, cannabis extract has been shown to exhibit greater muscle anti-spastic effect as compared to pure THC. The cannabis extract with equimolar THC content was more effective anti-spastically than THC alone. Since THC free extract was not so effective in showing anti-spastic effect, concomitant constituents of the cannabis extract probably cannabidol may be responsible for the synergistic effect. Cannabidol promotes an increase in the transport of anandamide through the brain membrane, which is not done by THC.

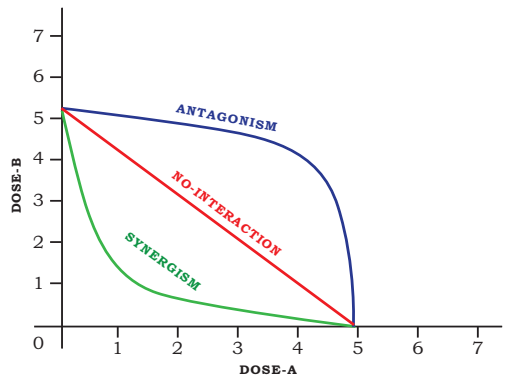

Fig. 2. Isoboles showing effect of drug-drug interaction: zero interaction, synergism and antagonism (after Berenbaum, 1989)

Scientifically/clinically validated Ayurvedic herb-Allopathic drug interactions showing additive, synergistic or antagonistic effects in curing diseases

*Momordica charantia (*Bitter gourd) extract when clinically co-administered with 50 per cent of the full clinical doses of allopathic or conventional drugs, metformin and glibenclamide, greater hypoglycemic (decreased serum glucose) effect was observed in patients as compared to full clinical doses of metformin or glibenclamide alone, thereby exhibiting additive and synergy effects.

Allium sativum (garlic) tablets when clinically co-administered with metformin, greater hypoglycemic effect (decreased blood glucose level) was observed in patients as compared to those patients who received only metformin treatment. Garlic synergistically enhances the effect of metformin if taken in combination (Ashraf *et. al.* 2011). In addition, rat experimental models showed reduced tubular toxicity induced by gentamicin in combination with garlic.

Aloe vera, and *Aloe barbadensis*, their major bioactive compounds include carbohydrates (mannan, galactose rich polysaccharides), and galacturonic acid. *Aloe vera* has been reported to possess anti hyperglycemic activities (decreased blood glucose level). Conventional anti-diabetic allopathic medicine glibenclamide inhibits ATP sensitive K+-channels of pancreatic β-cell membranes, thereby resulting in depolarisation of cell membrane and subsequent release of insulin. Hence, *Aloe vera* in combination with glibenclamide or other anti-diabetic drugs, has an additive effect. In other words, co-administration of *Aloe vera* with other antidiabetic drugs has been shown to have greater anti hyperglycemic effect, when compared to the sole therapy with glibenclamide, pioglitazone or repaglinide.

Cassia fistula (polyphenols and antioxidants), and *C. occidentalis* (flavonoids) have anti hyperglycemic properties. *C. fistula* has been shown to possess comparable anti-hyperglycemic activities as glibenclamide in rats. Allopathic antidiabetic medicines such as glibenclamide, glimepiride, glipizide, nateglinide, and rosiglitazone serve as substrates for hepatic enzyme CYP2C9, whilst *Cassia* is inhibitor of that enzyme thereby a combination of herb and drug may cause additive effect in anti-diabetic medications.

Piper betle (*Paan*) if taken with antipsychotic allopathic drugs such as flupentixol and fluphenazine; bradykinesia, tremour, rigidity and stiffness of body parts may occur. Procyclide is used to treat Parkinson's if consumed with *Piper betle*, bradykinesia and rigidity of body may be caused. Whilst *P. betle* and asthma drugs (prednisolone and salbutamol) if consumed together, there would be loss of control of asthma. *P. betle* along with beta blockers, calcium channel blockers (digixin) may slow down heart beats (bradycardia).

Piper nigrum (black pepper) prolongs the presence of the drugs such as phenytoin, propranol, rifampicin and theophylline by inhibiting their cytochrome isoenzymes of liver for which they serve as substrates. Therefore, effectiveness of mentioned drugs would be enhanced.

Coffee arabica and *Camelia sinensis* contain caffeine, if consumed with drugs such as clozapine and lithium, used to treat mental disorders, the level of drugs in blood is elevated. Through this action, caffeine enhances the effectiveness of the drugs. Moreover, caffeine also enhances theophylline level in blood, which is used to treat asthma, thereby enhancing its effectiveness.

Capsicum sp., if consumed with theophylline drug, absorption and bioavailability of drug in the body is increased. It also causes enhancement in toxicity of drug.

Cucurbita sp., if consumed along with anticoagulant warfarin, effectiveness of the drug is enhanced.

Acacia senegal (gum arabic), *Commiphora mukul* (guggal), and *Cyamopsis tetragonolobus* (guar gum), any of these if consumed with any of these allopathic drugs such as metformin, amoxicillin, digoxin, and propranolol, reduced absorption of drugs occur. Therefore, effects of the drug are also decreased.

Allium sativum (garlic) and *Zingiber officinale* (ginger) have been shown to prolong the time for clot formation during bleeding, if consumed with anti-coagulant drug warfarin.

Cyamopsis sp. (guar gum), if consumed along with allopathic drugs such as digoxin, metformin, bumetanide, pencillin and glibenclamide, the absorption rates of these drugs are decreased; therefore, reduced levels of drugs in blood would result in low effectiveness.

Cassia fistula fruit pulp exhibits similar activities with many drugs. *Plantago ovata* (isubgol), being a laxative, may decrease absorption of many drugs, thereby lowering the levels of drugs in blood. Such conditions render medicines ineffective in curing diseases.

Azadirachta indica has been shown to exhibit additive effects with anti-diabetic drugs such as glimepiride, glucotrol, micronase and orinase; therefore such combinations may cause hypoglycemia.

Nerium oleander, along with digoxin, exhibits additive effect and an increased risk of cardiac toxicity.

Tamarindus indica, along with asprin, increases the bioavailability of the medicine in the body, therefore, adverse effects may be increased.

Synergistic amalgamation of herbal extracts to enhance the efficacy of herbal formulations in disease control

Amalgamation of various plant extracts has been routinely followed in the preparation of efficacious herbal medicines since vedic periods in India; however, many of them have not been accepted globally due to lack of clinical validation and scientific standardisation. Following examples include research and development in clinical validation of some synergistic Ayurvedic herbal formulations. Mucuna pruriens and *Withania somnifera* are traditional herbal medicines known to have neuroprotective effects due to the L-DOPA, a precursor of dopamine in Mucuna seed powder. Root extract of Withania, withanoloides when co-administered with Mucuna seed powder in paraquat induced Parkinson's mice, a significant decrease in elevated nitrite levels, and lipid peroxidation found in Parkinson's mice. The effect was observed to be synergistic.

Cinchona officinalis bark yields alkaloids called quinine, it is used to cure malaria. Pharmacodynamic synergy has been demonstrated between pure doses of quinine and plant extracts of traditional herbs. Pharmacokinetic interactions occur, for example, between constituents of *Artemisia annua* tea so that its artemisinin is more rapidly absorbed than the pure drug. A herbal combination of *Artemisia annua* leaves, *Curcuma longa* rhizome and *Piper nigrum* seeds has been shown to possess potent antimalarial properties; however, it has not been clinically validated (Rasoanaivo *et. al.* 2011).

Ancient Indian herbalist's forward pharmacology vs. Present generation Indian's onus of reverse pharmacology

We, the Indians, proudly admire our ancestors who immensely contributed to the ancient scientific discoveries, and remember their names with great pride as naturalists and sages such as Charaka, Sushurta and Patanjali who tirelessly worked to acquire knowledge of botanicals with healing capabilities, which are today known as Ayurvedic herbal medicines. In course of time, the knowlege of traditional Ayurvedic medicines became the centre of attractions

for the world community because of their perceived notions of life-threatening side effects of many allopathic drugs. It is quite scientific and natural to believe that humans and plants have passed through similar kinds of co-evolutionary processes; hence, phytochemicals are undoubtedly more compatible to human physiological systems as compared to the synthetic drugs in healing. Literature survey on clinical validation and scientific standardisation of phytochemicals of therapeutic values, clearly indicate that non-Indians are increasingly more engaged in such studies and researches since they believed our ancestral herbalists but want to clear their doubts over safety issues of Ayurvedic herbs. In reality, the responsibilities of addressing global safety concerns of Ayurvedic herbal formulations should have been onus of the present generation Indians for hassle free global acceptance of Ayurvedic medicines. It would have been a great tribute and honour paid to our ancient herbalists in a real sense. Moreover, active involvement of present generation Indians in research and development of medicinal plants, particularly focusing on synergistic interactions and toxicities, have a great potential of generating huge revenues for the country. For example, there are some diseases whose effective treatments are still unknown; however, billions of US dollars are spent annually on their treatments. World wide annual spending on Alzheimer's disease is about 15 billion dollars, whose effective treatments are not in place. If clinically validated Ayurvedic formulations are made available to the world community even for prevention of the disease, 15 billion US dollar world market would be available to India.

Conclusion

Although, the allopathic medicare is the youngest of all systems of medications, it remains to be the most preferred choice of the world today because of its credible, evidence based scientific system of health care. With unprecedented growth and development in science and technology during last few decades, electronics and digital technologies have revolutionised the diagnostic techniques and drug designing methodologies of the present day medical sciences. However, the growing adherence of the people to the allopathic system, which is basically a drug oriented treatment has resulted in the creation of many iatrogenic disorders. The iatrogenic disorders are different kinds of health problems, which arise due to the side effects of doctor`s prescriptions. The main constraint of the modern allopathic system is that many of its drugs have side effects that could be life threatening, particularly in case of complex diseases such as cancers, AIDS, geriatric and cardio vascular diseases where prolonged multi-drug therapies are required. Synthetic or semi-synthetic drugs pose greater burden to the hepatic and renal systems of the body, and in many cases rendering them to fail. The solution to current problems lies in innovations, that is, exploration of traditional systems of medicines, which could serve as complementary or alternative to the allopathic. The ancient Indian Ayurvedic system of medicaments holds great potential in this regard and attempts have been made to use Ayurvreda as complementary to the western system of medicine. Quite recently, synergistic combination of herbal

formulations with allopathic drugs has been identified as a key area of future research. Several medicinal herbal formulations have been clinically validated for counter-indications, side effects, and toxicities in the l ine of allopathic medicines. The ayurvedic system of herbal formulations deserves to be the most efficacious of all traditional systems of medications for synergistic amalgamation with allopathic drugs in the amelioration of side effects of the latter. Hopefully, the standardised Ayurvedic herbal formulations would soon acquire the status of mainstream medication of the world. Furthermore, predicting nanotechnologised ayurvedic herbals as integrative medicaments of the future generation of the genomic era is not a fictional exaggeration.

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