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POLYHERBAL FORMULATION: AN EMERGING TREND IN HERBAL DRUG FORMULATION

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ABSTRACT
Drug formulation in Ayurveda is based on two principles; use of a single drug or use of more than one drug. The latter is known as **polyherbal formulation**. The concept of polyherbalisim is peculiar to Ayurveda although it is difficult to explain in terms of modern parameters. Historically the Ayurvedic literature "Sarandhar Samhita'' highlights the concept of synergism behind polyherbal formulations. Traditional herbal medicine and their preparations have been widely used for the thousands of years in developing and developed countries owing to its natural origin and lesser side effects or dissatisfaction with the results of synthetic drugs.It involves the use of natural elements to eliminate the root cause of the disease by restoring balance, at the same time create a healthy life-style to prevent the recurrence of imbalance.The present review deals with need of the various polyherbal formulations. Information on traditional herbal formulations was documented in the form of research and review articles in various journals. The aim of this review is to summarize the different types of herbs used for the preparation of polyherbal formulations, their therapeutic potentials including clinical and preclinical results along with their safety and efficacy. This review will also throw light on the standardization and evaluation aspects of herbal drugs which enable the young researchers to get a clear picture of the current trend in the herbal research work.

KEY WORDS: Ayurveda, Standardization, Synthetic Drug.

INTRODUCTON
Herbal medicines have been using by the people of all over the world. They were widely used in ancient Chinese, Greek, Egyptian and Indian medicine for various therapies purposes. The subcontinent of India is well-known to the world as one of the major biodiversity centers with about 45,000 plant species. In India, about 15,000 medicinal plants have been recorded, in which the communities used 7,000-7,500 plants for curing different diseases.Ayurveda is one of the traditional medicinal systems with an established history of many centuries. Furthermore known as Ayurvedic Medicine, this ancient Vedic knowledge is considered to be one of the oldest healing sciences and has survived until the present generation over many centuries of tradition. Originated in India thousands of years ago, Ayurveda is known as the "Mother of All Healing".[1] Etymologically speaking, it is the combination of the Sanskrit words ayur (life) and veda (science or knowledge), which means "the science of life," focusing on bringing harmony and balance in all areas of life including mind, body and spirit.[2]

Drug formulation in *Ayurveda* is based on two principles: Use as a single drug and use of more than one drugs, in which the latter is known as **polyherbal formulation** (PHF). This key traditional therapeutic herbal strategy exploits the combining of several medicinal herbs to achieve extra therapeutic effectiveness, usually known as poly pharmacy or poly herbalism. In the traditional system of Indian medicine, plant formulations and combined extracts of plants are chosen rather than individual ones. It is known that *Ayurvedic* herbals are prepared in a number of dosage forms, in which mostly all of them are polyherbal formulations.(PHF).[3]

Advantages
As mentioned before, PHF starts to gain its popularity recently worldwide, owing to the fact that PHF possesses some advantages which is not available in allopathic drugs.

1. Firstly, PHFs are known to express high effectiveness in a vast number of diseases. As it is established that the therapeutic effects of herbal medicines are exerted due to the presence of different phyto-constituents and the

effects are further potentiated when compatible herbals are formulated together in PHFs.[4]

2. PHFs are usually found to have wide therapeutic range. Most of them are effective even at a low dose and safe at high dose, thus they have superior risk to benefit ratio.[5]

3. PHFs (confined to those appropriately manufactured and used) result in fewer side effects as compared to synthetic drugs. Although modern allopathic drugs are designed for efficacious therapeutic results, administration of most of them come with unwanted side-effects, such as insomnia, vomiting, fatigue, dry mouth, diarrhoea, seizures, impotency, confusion, hair loss, organ toxicities and even death! Patients prescribed with non-steroidal anti-inflammatory drugs for rheumatoid arthritis (RA) treatment may experience mainly gastrointestinal and renal side effects, including dyspepsia, gastric ulceration, salt and fluid retention, as well as hypertension.[6,7]

4. Since PHFs are a product of the nature, they are relatively cheaper, eco-friendly and readily available than allopathic drugs. Their demand is increasing globally due to better affordability and easy accessibility.

5. All the above reasons: Effectiveness, safety, cheap, ubiquity and better acceptance, made PHF an ideal treatment of choice, hence higher compliance by the patients and excellent therapeutic effect is ensured.

Disadvanatages

Though polyherbal formulations are beneficial to mankind in many aspects, they are still affected by some pitfall which affects the treatments.

1. Sources and manufacturing processes of PHF are directly or indirectly associated with the efficacy of the product. Patients, Ayurvedic practitioners, as well as the law and regulations governing the production of herbal products are also sometimes responsible for poor efficacy.

2. The concurrent use of allopathic drugs with PHFs sometimes leads to dangerous drug-herb interaction which in turn affect their pharmacological action and prone to show some adverse effects and the disease condition is further deteriorated. Many Ayurvedic herbs commonly used in formulation of PHFs are reported to contribute to drug-herb interactions.[8]

3. The clinical reproducibility of Ayurvedic Poly Herbal Formulations is difficult to achieve. Ayurvedic Pharmacopoeia of India, also known as "Ayurvedic formulary of India," provides monographs on thepreparation of Ayurvedic PHF, thus showed a way to standardizing the preparation of PHFs. Still, this is not sufficient enough to ensure reproducibility of every batch of PHFs.[9]

4. Charaka samhitahas stressed on the factors to be considered while selecting the starting material of the PHFs, including habitat, season in which it grows, harvesting conditions, method of storage andpharmaceutical processing.[10] However, the constituents of crude raw herb materials may vary as an effect of different geographical locations, climatic conditions, environmentalhazards, harvesting methods, collection protocols and etc., thus it is not easy to standardize the end product for a reproducible quality.[11] This batch to batch variation would directlyaffect the effectiveness and safety of the PHFs. The need to alter the dosage regimen to obtain required therapeutic effect also seems to be tedious.

The toxicity cases of Ayurvedic herbal formulations is prevailing but remained unsolved. It is well known that presence of heavy metals in pharmaceuticals is not accepted, even in trace amount,to avoid toxicity. In contra, the concept of Rasa shastra is being practiced in a huge number of Ayurvedic PHFs, in which metals are added for their therapeutic applications, forming Rasausadhies.(herbo-bio-mineral metallic preparations) They claimed to have innate qualities such as quick action, lesser dose, tastelessness, prolonged shelf life and better palatability.[12] Drug experts have estimated that approximately 6000 medicines in the "Ayurvedic Formulary" which deliberately contain at least one metal, most widely used are mercury and lead. These toxic elements are known to be possess nephrotoxic, hepatotoxic, neurotoxic and hematotoxic effects.[13] Fortunately, this problem is not found in Kasthoushadhies, which are pure herbal preparations devoid of metals.

Although these toxicity cases are now in alarming level, proper attention is not being paid to combat this problem. Globally, the number of adverse reactions reported or recorded through pharmacovigilance programs is still negligible, mainly due to the false belief that Ayurvedic PHFs are always safe.

Table. 1: Global scenario of polyherbal product.

Commercial Name	Formulation with scientific names	Country	Pharmacological Activity	Scientific evaluation	Reference
Diabrid	*Gymnema sylvestre,Momordica charantia,Eugenia Jambolana,Trigonella graeceium*	India	Anti-diabetic	Clinical trial phase 1	[14]
Hepax-A	*Plumbago zeylanica, Picrorrhiza kurroa, Piper nigrum, Zingiber officinale, Sodii carbonas impura, Phyllanthus emblica, Terminalia chebula, Calcii oxidum Potassii carbonas impura.*	India	Hepatoprotective	In-vivo	[15]
Majoon Suranjan	*Lawsonia inermis, Foeniculum vulgare, Capparis spinosa, Terminalia chebula, Ipomoea turpethum, Apium graveolens, Zingiber officinalis, Convulvulus scammony, Colchicum luteum, Cassia angustifolia, Piper nigrum, Coriandrum sativum, Rosa damascus, Origanum vulgare,Pyrethrum indicum, Plumbago zelanicum,Verbascum thapus, Ricinus communis oil*	India/ Pakistan	Antiarthriticactivity	In-vivo	[16]
Praneem	*Azadirachta indica (Neem) along with purified Saponins from Sapindus mukerosi and Mentha citrata oil*	India	Vaginal microbocides	In-vivo	[17]
Zyflamend	*Ocimum sanctum, Curcuma longa, Zingiber officinale, Camellia sinensis, Rosmarinus officinalis,Polygonum cuspidatum,Berberis vulgaris, Origanum vulgar, Scutellaria baicalensis and Coptis chinensis*	USA	Prostate cancer	In-vitro	[18]
Bharunadi ghritha	*Crataeva religiosa, Strobilanthes ciliatus, Asparagus racemosus, Plumbago zeylanica, Chenomorpha fragrans, Aegle marmelos, Aristolochia bracteolate, Solanum melongena, Aerua lanata, Pongamia glabra, Holoptelia integrifolia, Premna corymbosa, Terminalia chebula, Moringa olifera, Desmostachya bipinnata, Semicarpus anacardium*	India	Head and Neck cancer	Clinical trial Phase 1	[19]
Ovoutoline	*Glycyrrhiza glabra, Saraca indica, Symplocos racemosa, Tinospora cordifolia, Asparagus racemosus, Valeriana walchii and Holarrhena antidysenterica*	India	Post menopausal symptoms	In-vitro	[20]
Daouri	*Khaya senegalensis , Odina acida ,Lophira lanceolata, Paullinia pinnata L. and Pteleopsis suberosa*	Togo/Ghana	Anti-diarrhoal, anti-malarial	In-vivo	[21]
KOB03	*Atractylodis RhizomaAlba, Astragali Radix, Saposhnikoviae Radix, Osterici Radix, Scutellariae Radix*	South Korea	Anti-allergic	In-vivo	[22]
Okudiabet	*Stachytarpheta angustifolia, Alstonia congensis bark and Xylopia aethiopica fruits extract*	Nigeria	Anti-diabetic	In-vivo	[23]
Joshanda	*Zizyphus jujuba , Onosma bracteatum and Glycyrrhiza glabra*	Pakistan	Antibacterial, commom cold	In-vitro	[24]
Wu-Zi-Yan-Zong	*Cuscuta chinensis Lam. Lycium barbarum L. Rubus chingii Hu. Schizandra chinensis (Turcz.) Baill. Plantago asiatica L. Epimedium brevicornu Maxim*	China	Neuro-inflammatory disease	In-vivo	[25]
AVS022	*H. perforate, C. micracantha, C. indicum, F. racemosa,and T. triandra*	Thailand	Anti-oxidant	In-vitro	[26]
Tongat Ali	*Eurycoma longifolia Jack.,*	Malaysia	Increase sexual	In-vivo	[27]

	Cistanche deserticola Y.C.Ma.		stamina		
EMSA eritin	*Glycine max, Cocos nucifera and Red rice.*	Indonesia	Stimulation of erythropoiesis	In-vivo	[28]
Nefang	*Mangifera indica, Psidium guajava, Carica papaya L, Cymbopogon citratus, Citrus sinensis, Ocimum gratissimum*	Cameroon	Anti-malarial	In-vivo	[29]
Prasarani sandhan	*Paederia foetida L., Piper longum L., Piper chaba Hunter., Plumbago zeylanica L., Zingiber officinale Roscoe., Allium sativum*	Bangladesh	Immunomodulatory	In-vivo	[30]

Who Guidelines for Quality Standardized Herbal Formulations

1) Quality control of crude drugs material, plant preparations and finished products.
2) Stability assessment and shelf life.
3) Safety assessment; documentation of safety based on experience or toxicological studies.
4) Assessment of efficacy by ethno medical information and biological activity evaluation

Comparision of Polyherbal Formulation with Alopathy

The herbal products are now becoming more popular than the synthetic allopathic drugs due to their low toxicity and long standing experience of use in the traditional literatures like the Ayurvedic. Due to side effects of synthetic steroidal contraceptives, interest has been focused on the indigenous plants for possible contraceptive effect. Although the contraceptives containing estrogen and progesterone are effective and popular, owing to the risk associated with these drugs have increased the need for suitable product from indigenous medicinal plants that can be used as alternative of pills. One of the greatest arguments against traditional medicine is the lack of scientific proof of its effectiveness. There is insufficient scientific investigation on most of the claims made by the traditional medicine practitioners.[31] There is another problem of safety where people think that traditional herbs are safe and harmless since they are natural and are not invented in the laboratory. But use of these herbs may possibly expose the patient to unknown complications.[32] For instance aristolochic acid and other components present in some herbs can cause adverse renal effects and renal toxicity.[33] Some herbal formulations used to treat liver disease may be hepatotoxic themselves.[34] There is also possible serious reaction between herbal therapy and biomedical medications. A survey says that most patients do not inform their physician that they are taking herbal treatment. This may result in serious and deadly reaction. The most common published and worst herb drug reaction is of St John's wort (Hypericum perforatum) and drugs that are metabolized by cytochrome P450, CYP 3A4 isoenzymes used without informing their physicians patients use St John's wort to treat depression. This may have various adverse effects. The woman taking oral contraceptives with St John's wort may cause breakthrough menstrual bleeding, unexpected pregnancy. Other problems with traditional medicine are the lack of hygiene and precise dosage.[35]

Challenges In Herbal Medicines[36]

A key challenge is to objectively assess conflicting toxicological,epidemiological, and other data and the verification of herbalmaterials used. The following key issues remain.

1. Management within ranges of risk
2. Communication of uncertainty
3. Pharmacological, toxicological, and clinical Documentation
4. Pharmacovigilance
5. Understanding why addition of harmful additives works
6. Evaluating "drug" interactions
7. Constraints with clinical trials and people available
8. Standardization
9. Safety, and efficacy assessment.

Factors Affecting Quality and Purity of Herbal Medicines[37]

1. Drug adulteration

Adulteration may be defined as mixing or substituting the original drug material with other spurious, inferior, defective, spoiled, useless other parts of same or different plant or harmful substances or drug which do not confirm with the official standards.
Adulteration may takes place by two ways:
- Direct or intentional adulteration
- Indirect or unintentional adulteration.

Examples for Adulteration,
A. With artificially manufactured materials, e.g. nutmeg is adulterated with basswood prepared to the required shape and size, the colored paraffin wax is used in place of beeswax.

B. With inferior quality materials, e.g. *Belladonna* leaves are substituted with *Ailanthus* leaves, *papaya* seeds to adulterate *Piper nigrum.*

C. With harmful / fictitious substances drugs, e.g. Pieces of amber colored glass in colophony, limestone in asafetida, lead shot in opium, white oil in coconut oil, cocoa butter with stearin or paraffin.

D. Adulteration of powders, e.g. powder liquorice or gentian admixed with powder olive stones, under the name of cinchona. Etc.

2. Faulty collection

3. Imperfect preparation

Non removal of associated structures e.g. stems are collected withleaves, flowers, fruits. Non-removal of undesirable parts orstructures e.g. cork should be removed from ginger rhizome.Proper drying conditions should be adhered. Improper drying maylead to unintentional adulteration e.g. if digitalis leaves are dried above 65 °C decomposition of glycosides by enzymatichydrolysis.

4. Incorrect storage

Deterioration happens especially during storage, leading to theloss of the active ingredients, production of metabolites with noactivity and, in extreme cases, the production of toxic metabolites.Physical factors such as air (oxygen), humidity, light, andtemperature can bring about deterioration directly or indirectly.

5. Gross substitution with plant material.

6. Substitution with exhausted drugs.

DISCUSSION

Currently scientist are trying to explore development of new Polyherbal therapy or using old traditional polyherbal formulation that have been used for many decades such as Ayurveda, whose history goes back to 5000 BC., is one of the ancient health care systems,[38] Korean traditional medicine such as Mahwangyounpae-tang (MT), consisting of 22 types of herbal extracts in treatment of respiratory disorder,[39] African Herbal Formula (AHF) consists of a combination of plant materials originally developed by a family in southern part of Nigeria and passed on to generations. Over the years, AHF has been applied by members of the family and close-associates for all kinds of health problems and it is very popular among the low socio-economic class,[40] Haya people of Kagera region in north western Tanzania are endowed with a culture rich in traditional Medicine practice owed to an extensive intercultural exchange among the diverse ethnic tribes of the Lake Victoria Basin[41] and Traditional Unani medicine in Pakistan and India where it is popularly practiced among the large segment of its population. It originated in Greece, founded by old ancient Greek philosophers, and was documented by Muslims during the glorious period of Islamic civilization. It was brought to the Indo-Pak subcontinent by Muslim scholars and practiced here for centuries.[42]

CONCLUSION

Although polyherbal formulation is commonly used in many parts of the world, but the scientific evidence is still lacking. Many herbal therapies are still under in-vivo evaluation and have not been evaluated by clinical trials. Moreover, safety evaluations such as toxicological studies have not performed. There is need of time to evaluate polyherbal formulation using scientific methods such as clinical trial, possible bioactive compounds and mechanism of action for the future world.

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