Original Article

An Updated Review on Herb-Herb Combination (Polyherbal Therapy) and Their Evaluation for Therapeutic Enhancement and Advancement

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I. INTRODUCTION

Ayurveda is one of the traditional systems of medicines with an established history from many centuries. This ancient Vedic knowledge, also called Ayurveda medicine, is considered one of the oldest healing sciences and has been preserved to this day. Indigenous in India, Ayurveda is known as the **"Mother of All Remedies"** thousand of years ago. Etymologically, it is the combination of two Sanskrit words ayur (life) and veda (science or knowledge), meaning "the science of life," and focuses on harmony and balance in all aspects of life, including the mind, body and life spirit. [1]
In Ayurveda, the Panchamahabhutas or the five elements i.e. Vayu (air), Teja (fire), Aap (water), Prithvi (earth) and Akasha (aether) are believed to build the living microcosm (human beings) and the macrocosm (external universe). When combined in pairs, the Panchamahabhutas form the Tridosha or the three humors namely **Vata** (responsible for body movement), **Pitta** (responsible for bodily chemical reactions such as metabolism and temperature) and **Kapha** (responsible for movement of body, growth, protection, lubrication and feeding). [2] All this constitutes the constitution or Prakriti of an individual, which determines both the physical and mental qualities of man. The concept is that health is achieved when there is a balance between these three basic doshas, while an imbalance causes illness. Based on these Panchamahabhutas and Tridosha, an individual's Prakriti is determined and a distinctive treatment plan can be prescribed based on their unique constitution. [3]

The basic philosophy behind Ayurveda is to avoid preventing unnecessary suffering and live a long and healthy life. Unlike allopathic medicines which primarily use synthetic chemicals designed for specific target receptors and primarily provide symptomatic relief. Ayurveda involves the use of natural agents such as diet, exercise, meditation, yoga, mental hygiene, herbs, spices, minerals, sounds, smells and mechano-procedures to eliminate the root cause of the disease by restoring balance while creating a healthy life-style to prevent the imbalance from reoccurring. [4] Ayurveda is considered holistic as it aims to integrate and balance the body, mind and spirit to prevent disease and promote well-being, longevity, happiness and vitality. [2,3,4]

In terms of literature, the fourth Veda written during the Indian Civilization, Atharva-veda is the first authentic text dealing with the nature of existence, pathogenesis and principles of treatment, health and disease. Here in the Atharva-veda, the healing verses of Ayurveda can be predominantly found, in which more than a hundred hymns are mentioned as cures for diseases, including fever, leprosy, consumption, heart diseases, injury, headaches, parasites, disease related to eye and ear, poisoning, epilepsy and rheumatism. [5] The uniqueness of this ancient medical system lies behind the wide variety of healing method used: Charms, animal and plant juices, natural sources (sun and water) as well as human inventions. The eight treatment branches of Ashtanga have also been mentioned here as: Kaya Chikitsa (Internal medicine), Shalya Tantra (Surgery), Shalakya Tantra (diseases of ear, nose, throat and eye), BhutaVidya (Psychiatry), Kaumarbhritya (Pediatrics), Agada Tantra (Toxicology), Rasayana (Rejuvenation therapy) and Vajeekarana (Aphrodisiac therapy). Early Ayurveda texts like Chakara Samhita and Sushruta Samhita developed from the knowledge of Atharva-veda. While the former focuses on the causes of disease and a person's constitution, the latter emphasizes on Ayurvedic surgery and its techniques in detail. [3,4,5]

The history of Ayurveda dates back to pre-Vedic periods (4000 B. C.-1500 B. C.). According **to Ayurvedavatarana** (the lineage of Ayurveda), Lord Brahma, the Hindu God of Creation, imparted his **"knowledge of life"** to Daksha Prajapati and Ashwins, later to Indra. Then this knowledge is transferred to different rishis (paths), in which these Ayurvedic students wrote various treatises based on their interpretations. Here **Bhardwaj** and **Dhanvantari** received knowledge from Indra. They then developed the medicine school and surgery school respectively. [5] In Chakara Samhita, Indra is said to have transmitted Ayurvedic teachings to Bhardwaj, who in turn taught these teachings to **Atreya.** The followers of Atreya wrote their own samhitas, the **Agnivesha Samhita** being the accepted one. It is then revised, edited and completed by Chakara about 800 years later. On the other hand, **Sushruta Samhita** mentioned

transfer of knowledge from Indra to Dhanvantari, with Bhardwaj. The followers in this school like Sushruta wrote Sushrutasamhita and collected Dhanvantri's teachings and additional insights. [4,5,6,7,8]

HERBAL AND SYNTHETIC DRUGS

With about 45,000 plant species, the Indian subcontinent is one of the mega biodiversity centers. This wealth of flora has contributed to its status as a reservoir of herbals throughout human history. Some 15,000 medicinal plants have been registered in India, where communities use 7,000-7,500 plants to cure various diseases. *Ayurveda* has approximately 700 type of herbs listed in its medicinal systems. The use of these herbs is mentioned in ancient *Ayurvedic* literature such as *Sushruta Samhita and Chakara Samhita*. [7]

The discovery of herbs is complemented by knowledge of the method of isolation, purification and characterization of the active ingredients and the way of preparation. The term "herbal medicinal product" refers to the part/parts of a plant (roots, barks, leaves, flowers, seeds, stems etc.) used in the manufacture of medicinal products. Each part of the herbs is fully utilized for the various pharmacological effects they can produce and processed into a variety of herbal preparations including **Hima** (Cold infusion), Kwatha (Decoction), ***Phanta*** (Hot infusion), **Arka (**Liquid Extract), **Churna** (Powders), ***Taila*** (Medicinal oil), ***Guggul*** (Resins and balsams) etc. [4,8]

Due to the handiness of chemical analysis methods in early 19th century, scientists began extracting and modifying the active ingredients of herbs, leading to a shift from crude herbs to synthetic pharmaceuticals. At this point, the use of medicinal herbs began to decline. However, synthetic drugs are relatively more expensive and despite their powerful pharmacological activity, they have many undesirable side effects. Today, people are again turning to herbal medicines that come from nature and claim to be safer. [9]

Table: 1 Synthetic Drugs used derived from Plants [10]

Synthetic Drugs (trade / other Name)	Functions	Plant Derivatives
Asculetin (Esculetin)	Anti-dysentry	*Fraxinus rhynchophylla* (Oleaceae)
Ajmalicine (Yohimibine, Raubasine)	Circulatory disorder (in treatment of high blood pressure)	*Rauwolfia serpentina* (Apocynaceae)
Digitalis (Foxgloves)	Cardiac Glycosides	*Digitalis purpurea* (Plantaginaceae)
Ephedrine (Corphedra, Emerphed, Akovaz)	Sympathomimetics (CNS stimulant	*Ephedra sinica* (Ephedraceae)
Morphine (Statex, Ms Contin, Sevredol)	Analgesic	*Papver somniferum* (Papaveraceae)
Noscapine (Narcotine Tusscapine, terbenol)	Antitussive	*Papver somniferum* (Papaveraceae)
Picrotoxin (cocculin)	Analeptic	*Anamrita cocculus* (Menispermiaceae)
Reserpine (serpasil)	Anti-Hypertensive	*Rauwolfia serpentine* (Rauvolfioideae)
Quinine (Qualaquin)	Anti-malarial	*Cinchona ledgeriana* (Rubiaceae)
Salicylic acid (Precursor of asprin)	NSAIDS	*Filipendula ulmaria* (Rosaceae)
Sennosides (Sennaglycoside)	Laxative	*Cassia angustifolia* (Fabaceae)
Vincristine (leurocristine)	Anticancer	*Catharanthus rosues*(periwinkle)
Xanthotoxin (methoxsalen, oxsoralen)	Leukoderma; Vitiligo	*Ammimajus* (Apiaceae)

History of Herbal drugs

Since prehistoric times, medicinal plants have travelled the world with a long a long recorded history. They were used in ancient Egyptian, Chinese, Greek and Indian medicine for various therapeutic purposes; while Native Americans and Africans use herbs in their healing rituals as part of their heritage. The system of Indian Ayurveda has incorporated herbs as one of its most powerful healing ingredients, recorded in literature as **Samhitas** and **Vedas.**[9]

Ayurvedic Herbals

Based on the source material of origin, *Ayurvedic* medicines are divided into three groups namely **mineral, herbal and animal**. Among them, herbal formulation has recently gained great importance and growing global attention. This scenario is evident because in recent years, a large increase in the use of herbal formulations has been observed in developed countries where market expansion has taken place in European countries and the United States. [10] The World Health Organization (WHO) evaluates that 80% of the world's population still depend primarily on traditional medicines for their health care. [9,10]

Due to current scientific advancement, more and more pharmacologically active ingredients of *Ayurvedic* medicines and their use in pharmacotherapy have been identified. Basically, it is the phytochemicals of herbs that lead to the desired healing effect, such as alkenyl phenols, saponins, flavonoids, tannins, alkaloids, phorbol esters, terpenoids and sesquiterpenes lactones. [9] An isolated herb may even restrain more than one of the aforementioned phytochemical constituents, which acts synergistically to produce a pharmacological action. [10]

In *Ayurveda*, herbs are known to control various bodily functions along with cleanse and nourish human body. Each herb has five groups known as *rasa*, *veerya*, *vipaka*, *prabhava* and *karma*.

- ***Rasa*** (taste that tongue experiences upon coming in contact with herbs): In *Rasa* there are six tastes (*Madhura* meaning Sweet, *Amla* meaning Sour, *Lavana* meaning Salty, *Katu* meaning Pungent, *Tikta* meaning Bitter, *Kashaya* meaning Astringent) and each taste is made of two out of the five elements. Also, each taste has an effect on *dosha*.
- ***Veerya*** (energy which an herb delivers when consumed): Veerya can be *sheeta* meaning cooling or *ushna* meaning heating. Also, the former is said to be found in sweet, astringent and bitter herbs, which cools the body, reducing irritation and inflammation. The latter is derived from acidic, salty and spicy herbs that improve blood circulation, aid digestion and promote sweating.
- ***Vipaka*****:** *Vipaka* is Post-digestive effect. There are basically three types of *Vipaka i.e. Amla meaning sour, Madhura meaning sweet* and *Katu* meaning pungent, each shows different effects on the *dosha*.
- ***Prabhava:*** *Prabhava is*special and unique power of an herb which has variable action. However, these herbs do not fit in the category of other herbs that possess the same *rasa*, *veerya* or *vipaka*.
- ***Karma*** relates to therapeutic action: These are classified as Deepana meaning stimulant, Pachana meaning digestive, *Shodhana* meaning purification, *Anuloman* meaning Carminative and *Virechana* meaning purgative. Apart from this, the doses, time of intake and *Anupana* are also point up in the study of herbals under *Ayurveda. [4]*

There are generally two types of Ayurvedic herbal formulas: Kasthoushadhies i.e. pure herbal preparations and Rasaushadhiesie. herbo-bio-mineral metallic preparation, the latter containing additional minerals for its therapeutic effects. [2,4,12]

Single Versus Polyherbal versus Allopolyherbal Formulation

The drug formulation in Ayurveda is mainly based on two concepts: the use of **individual drug**/herbs, and the use of combination of several drugs/herbs, called PHF (Polyherbal formulations). This traditional approach to herbal therapy helps to combine various herbal medicinal plants to create additional therapeutic potency, commonly known as **polyherbalism** or **polypharmacy**. [11] The "Sarangdhar Samhita", Ayurvedic literature has emphasized the concept of polyherbsin this system of traditional medicines. In traditional Indian systematic medicine, herbal plant products with combined herbal are more than just considered. It is also known that Ayurvedic herbal dosage forms are also available in market, most of which contain polyherb formulations (PHF). [12] Although the active phytocomponents of individual plants have been well- identified, they are generally present in small amounts, insufficient to produce the desired therapeutic effect in curing disease. [13]

To solve this problem, scientific studies have shown that the combination of these plants with different potenciescan have a positive effect compared to the use of the plant alone. This positive theory of herb-herb interaction is called **Synergism. [14]** Examples of Ayurvedic herbal combinations: Ginger in combination with black pepper and long pepper potentiate their warming and expectorating effects; the combination of Liquorica and Asafoetida reduces blood sugar levels, obesity and dyslipidemia; black pepper and cumin are traditionally used together to reduce gas and bloating caused by poor digestion. [9]
Due to the synergistic effect, polyherbalism provides certain benefits that are not available in the individual herbal formulation.

ADVANTAGES OF POLYHERBAL FORMULATION AND ITS SYNERGISTIC EFFECT

- Polyherbal formulations have herbal pharmacological agents capable of exerting synergistic, antagonistic, potentiating and agonistic effects on their own due to their various associated active ingredients. These pharmacological principles dynamically work together to achieve maximum therapeutic efficacy with minimal side effects [14].
- Depending on the nature of the interaction, there are two synergistic mechanisms of actions (i.e., pharmacokinetic and pharmacodynamic).
- In reference of pharmacokinetic synergism, the herb's ability to facilitate the absorption, distribution, metabolism and excretion of other herbs is sought. On the other hand, Pharmacodynamics synergism studies the synergistic effect when active ingredients with similar therapeutic activity target a similar receptor or physiological system.
- Apart from that, the multitude is believed that multiplicity of factors and complications are believed to cause diseases that in most cases result in both visible and invisible symptoms. Here, the combination of herbs can work on multiple targets at once for complete relief [14].
- Due to synergism, polyherbalism offer that a single herbal formulation lacks. It is obvious that a better therapeutic effect can be achieved with a single multi-component formulation. This would require a lower dose of the herbal preparation to achieve the desired pharmacological effect, reducing the risk of harmful side-effects. In addition, PHFs offer greater patient convenience by eliminating the need to take more than one herbal formulation at a time, indirectly leading to better compliance and therapeutic effects. All of these benefits have resulted in PHF becoming more popular over the unique herbal formulation in the market. [15] The Polyherbal formulation also contains multiple types of molecules against disease complications, so different molecules cure disease through different mechanisms, thus providing comprehensive therapy against disease [16].

An important hypothesized advantage of herbal medicines over traditional single-component medicines is the presence of multiple active compounds that together can produce a potentiating effect that may not be achieved with a single compound. Polyherbal formulations shows herbal pharmacological agents that can exert synergistic, potentiatiating,

agonistic and antagonistic effects on their own due to the different active ingredients involved. These pharmacological principles dynamically work together to achieve maximum therapeutic efficacy with minimal side effects. [15]
It is evident that **better therapeutic activity** can be achieved with a multi-active phytoingredient formulation. Therefore, a **lower effective dose** of the herbal formulation would be required to achieve the desired therapeutic effect, reducing the risk of unwanted bad side-effects. PHFs also eliminate the need to take more than a single different formulation, which is beneficial to the individual and indirectly leads to improved therapeutic effects. Many of the PHFs have been shown to have desirable pharmacological and clinically therapeutic effects. All of these satisfying benefits of PHFs have increased their spread in the market compared to purely herbal supplements.

Table 2: List of Marketed polyherbal formulation, source and its Pharmacological action [13]

Name of Polyherbal Formulation (Manufacturer)	Ingredients Used (Name of herbal Plants)	Pharmacological Activity and Pharmacological Uses
Dihar (Rajsha Pharmaceuticals, Ahmadabad, lndia)	Syzygium cumini	**Anti-hyperglycemic, Anti-hyperlipidemic, Antioxidant**
	Momordica charantia	
	Embelica officinalis	
	Gymnema sylvestre	
	Enicostemma littorale	
	Azadirachta indica	
	Tinospora cordifolia	
	Curcuma longa	
Diabet (Herbal Galenicals, lndia)	Curcuma longa	**Antidiabetic**
	Cosciniurn fenestratum	
	Strychnos potatorum	
	Tamarindus indica	
	Tribulus terrestris	
	Phyllanthus reticulates	
Arthosansar (Pradhan Herbal Company, B a n g a l o r e , lndia)	Comiphora wightii	**Anti Arthritic Anti-inflammatory and Analgesic**
	Boswellia serrata	
	Pluchea lanceolata	
	Ricinus communis	
	Zingiber officinale	
	Withani somnifera	
Kutajarista (Laboratory preparation)	Madhuca longifolia	**Used in Diarrhoea, Used in Irritable Bowel Syndrome, Anti Secretory, immunomodulatory and ant motility and in the treatment of sprue,**
	Holarrhena antidysenterica	
	Gmelina arborea	
	Woodfordia fruticosa	
	Vitis vinifera	
	Honey	
	Jaggery	
Vidakana Choornam (Kerala India)	Embelia ribes	**used in jaundice and steaosis (Fatty Liver), and for liver problems**
	Morigna oleifera	
	Piper longum	
Triglize (tablets) (Apex Laboratories Ltd., Chennai lndia)	Terminalia arjuna	**Antioxidant Activity, Antidiuretic Used for the treatment of obesity, hypertension, ischemic heart diseases and peripheral vascular diseases**
	Cissus quadrangularis	
	Boerhaavia diffusa	
	Commiphora mukul	
	Phyllanthus embilica	
	Terminalia bellirica	
	Terminalia chebula	
	Tribulus terrestris	
	Alliurn sativurn	
	Trigonella foenumgraecum	
Bharangyadi (Panchamrit Herbals, India)	Clerodendrurn serratum	**Antiasthmatic**
	Hedychium spicatum	
	Lnula racemosa	

DIADVANTAGES:

PHF is not always curable, it is also sometimes considered antagonistic and therefore certain products should not be taken together. Such incompatibility may be due to quantitative incompatibility, quantitative, energetic or functional. [15]
For example: **Ghee** should be avoided in equal proportions with honey due to unfavourable taste and temperature; laxatives with astringents taken at the same time show an antagonistic effect, in which they terminate each other. Therefore, well-designed clinical trials of these preparations are nedded before they are commercially available to ensure compatibility of multiple herbs in PHF formulation. [10]

Homeopaths often use Allopathic medicine to treat or suppress symptoms or pathophysiological processes of diseases or conditions. Allopathic medicine consists primarily of the science of anatomy, physiology and the structure-function relationship between cells and the biochemistry of tissues and organs. It emphasizes on the diagnosis, treatment and cure of disease through drugs, surgery, radiation therapy and other treatment methods. Allopathy is based on three major steps: Hypothesis, experimentation, observation and finally theory or conclusion. Combining allopathic drugs with polyherbal has proven to be more effective than using them separately. [17]

ADVANTAGES OF ALLOPOLYHERBAL FORMULATION

There are a number of advantages associated with the use allopolyherbal medications compared to pharmaceuticals. Examples are the following:

1. Reduces the risk of unwanted side effects: Natural herbal drug and extracts from vegetables, fruits, spices, etc., which helps to cure various incurable diseases without side effects, which is sometime not possible with allopathy therapy. Whereas most of the allopathic medicines are manufactured synthetically and thus have one side effect or the other. Therefore, the combination of polyherbal with allopathic medicine reduces or overcomes the side effect of allopathic dug which has a large number of side effects.
2. Effective for chronic conditions: allopolyherbal formulations tend to be more beneficial or effective for long-standing health conditions.
3. They are effective even at low dose and safe at high doses.
4. Helps in the treatment of most chronic diseases that cannot be completely cured with allopathic medicines.

All the above reasons: safety, Effectiveness, cost-effectiveness and better acceptance have made PHF a treatment of choice, ensuring high acceptance by patients and an excellent therapeutic effect [15].

Table 3: Allopolyherbal medicine available[16, 17]

PolyherbalDrugs	Allopathicdrugs
Trigonella foenum graceum	Glipizide
Momordica charantia	
Aegle maremelos	
Wheat germ oil	Glibenclamide
Fresh juice of coriander sativum	
Aloe vera	
Camellia sinensis	Glibenclamide
Foeniculum vulgare	
Punica granatum	
Trigonella foenum-graceum	

Challenges in Herbal Formulation [18]

a. A major challenge is to objectively assess conflicting epidemiological, toxicological and other data and to verify the plant materials used.
b. Management within risk areas
c. Communicating uncertainty
d. Pharmacological, clinical documentation and toxicological
e. Pharmacovigilance
f. Understand why adding harmful additives works evaluating “drug” interactions
g. Limitations on clinical trials and people available
h. Standardization
i. Safety and efficacy assessment

Factors Affecting Safety and Quality

a. Quality of raw materials
b. Complexity of herbal ingredients
c. Chemical contamination due to heavy metals
d. Selection of chemical markers
e. Deterioration with synthetic chemical drugs
f. Drug counterfeiting
g. Improper collection
h. Imperfect preparation
i. Bad storage
j. Coarse substitution with plant material
k. Replacing with exhausted drugs

Restrictions of Herbal Formulation [18,19]

a. Unsystematic harvesting and poor post-harvest handling practices.

b. Lack of research on developing of high- yielding strains, domestication etc.
c. Improper cultivation and propagation methods.
d. Inefficient processing techniques resulting in low yields and poor quality products.
e. Poor quality control procedures.
f. Lack of current good manufacturing practices.
g. Lack of R & D in product and process development.
h. Marketing difficulties.
i. Lack of qualified staff and equipment.
j. Lack of on-site equipment manufacturing facilities.
k. Lack of access to the latest technologies and market information.

EVALUATION OF HERBAL DRUG

Herbal drug evaluation is an important tool in the formulation of high-quality herbal products. The adulteration and substitution of herbal drugs is the hot issue of the herbal medicine industry. Adulteration is a practice whereby the original crude drug is partially or totally replaced by other substances lacking or inferior to therapeutic and chemical properties, or by the addition of inferior or contaminated drugs, or a completely different medicine than the original. [20]

Adulteration may take place by two ways:

1. Direct or intentional adulteration
2. Indirect or unintentional adulteration

1. **Direct or intentional adulteration:** Direct or intentional adulteration is intentional, which generally includes practices in which an herbal drug is partially or totally substituted for other inferior products. Due to the morphological resemblance to real herb, many inferior commercial varieties are used as adulterants. These may or may not have chemical or therapeutic potential.

2. **Indirect or accidental adulteration:** Unintentional or undeliberately adulteration, sometimes without the bad faith of the manufacturer or supplier. They get mixed in with the original drug because they weren't properly harvesting or trimming. [21]

WHO Guidelines for Quality Standardized Herbal Drug: On the basis of active principles or major compounds, the bioactive extract should be standardized along with the chromatographic fingerprints (HPLC, TLC, HPTLC and GC). [22]

The Standardization Of Crude Drug Materials Includes The Following Steps [20,21,22]:

1. Authentication (Collection stage, collected plant parts, regional status, botanical identity such as phytomorphology, microscopic and histological analysis, taxonomic identity etc.)
2. Foreign matters (harvested herbs must be free from soil, insect parts, animal droppings etc.)
3. Organoleptic evaluation (sensory properties like taste, appearance, odor, feel of the drug etc.)
4. Diagnostically relevant tissue present in the drug powder (Macroscopic evaluation,).
5. Ash values and extractive values (Chemical Evaluation).
6. Volatile matter
7. Determination of moisture content
8. Determination of heavy metals like cadmium, lead, arsenic.
9. Pesticide residue - WHO and FAO (Food and Agriculture Organization) set limit values for pesticides commonly found in herbs. These pesticides are mixed with the herbs during the growing season. Pesticides such as DDT, BHC cause serious side effects in human, especially when raw drugs are mixed with these active ingredients.
10. Microbial contamination, usually from medicinal plants containing bacteria and mold, comes from the soil and atmosphere. Analysis of E. coli and mold provides insight into harvesting and production practices. [20,21,22]

Organoleptic or Macroscopic Evaluation: Organic evaluation of drugs by sensory organs (skin, eye, tongue, nose and ear) or microscopic evaluation, which includes the evaluation of drugs by colour, smell, taste, size, shape, and special characteristics, such as touch, texture, etc. is the qualitative evaluation technique based on the study of the morphological and sensory profile of whole drugs. Cinchona fractured surfaces are prominent characteristics.
The aromatic smell of umbelliferous fruits (Coriander, Ajwain, Fennel) and the sweet taste of liquorice are the examples of this type of evaluation where the smell of drugs depends on the type and quality of odorants (volatile oils) present. [23]

Microscopic Evaluation: This involves a detailed examination of the drug and can be used to identify drugs by their known histological characters. It is mainly used for qualitative evaluation of raw drugs organized in whole and powder form using microscope. Using a microscope that detects various trichomes, cell tissues, starch granules, stomata, calcium oxalate crystals and aleurone grains are some of the important parameters that play an important role in identifying certain crude drug. The raw drug can also be identified microscopically by cutting the thin TS (transverse

section), LS (Longitudinal section) especially in the case of wood and staining them with the proper staining reagents e.g. starch and hemicelluloses can be recognized by the blue colour with iodine solution. [22,23]

Chemical Evaluation: Most drugs have defined chemical components to which their biological or pharmacological activity is attributed. Qualitative chemical tests are used to identify certain drugs or to test their purity. The Isolation, purification and identification of the active ingredients is based on chemical evaluation methods. [24]

Resin evaluation test: acid value, sulphated ash

Balsam test evaluation: acid value, saponification value, best values.

Volatile oils evaluation test: acetyl and ester values.
Qualitative chemical tests are useful for identifying chemical constituents and detecting adulterants. [20]

Physical Evaluation: Physical constants are sometimes taken into account to evaluate certain drugs. These include moisture content, melting point, viscosity and solubility in various solvents, optical rotation, specific gravity, refraction. All of these physical properties are useful in identifying and detecting compounds present in plants. [24]

Biological Evaluation: There are some drugs which possess specific biological and pharmacological activity which is used for their evaluation. In fact, this activity is due to a specific type of components present in the plant extract. With the help of bioassays, the potency of the drug in its preparation can be assessed.

Stability testing of herbal products
Herbal drugs consist of different type of ingredients. The finished phytotherapy products usually have a low concentration of active ingredients. The purpose of a stability test is to test how the quality of herbal products changes over time under the influence of environmental factors such as temperature, light, oxygen, humidity, other ingredient or excipients in dosage form, drug particle size, microbial contamination, contamination of trace metals, leaching of containers and establishing a recommended storage condition and shelf life.[26] Depending on the weather conditions, only storage conditions can be determined. Stability studies should be carried out on at least three production batches of herbal products for the proposed shelf life usually referred to as long-term stability, conducted under natural atmospheric conditions. With the help of modern analytical techniques such as spectrophotometry, HPLC, HPTLC and the use of appropriate guidelines, it is possible to generate robust stability data on herbal products and predict their shelf life. [26,27]

Analytical methods for Herbal products
Analysis of herbal preparations is most often done by high-performance liquid chromatography (HPLC) or gas chromatography (GC) and thin layer chromatography (TLC) methods, quantitative determinations by UV visible spectroscopy or combinations of the same. HPLC and GC methods can be used for identification and purity tests, as well as for the detection of individual compounds to be determined during analysis. [29]

Shelf-life
Shelf life determination for herbal medicines is the same as for chemically defined APIs. It is recommended that in the case of a herbal medicinal product containing a natural product or a preparation of a herbal medicinal product with components of known therapeutic activity, the variation of the component during the course of the proposed conservation does not exceed the ± 5% of the value of the initial value of the test, unless there is a justification to extend the range to ±10% or even more, relative changes from baseline (95- 105% or 90-110% of baseline) are shown. [24,29]

Importance of Stability testing: It helps in evaluation of the effectiveness of a drug. Stability studies are used to develop appropriate packaging information for product quality, strength, purity & integrity throughout its shelf life. It is used to determine the shelf life. The mechanisms that intervene in the change of the product or make the stability of the product unstable affect several factors such as the loss of integrity of the packaging, loss of content uniformity change in concentration of active component, alteration in bioavaibility, formation of toxic degradation product. The following foreseeable changes may occur in the herbal medicine during storage and when determining shelf life: Hydrolysis (reaction with water leads to product degradation), Oxidation, Racemization, Geometric isomerization, Temperature, Moisture and Light. [27]

Oxidation: oxidation is the loss of electrons while reduction is the gain of electrons and redox reaction (combination of oxidation and reduction) is the transfer of electrons between chemical species and plant products.

Racemization: Racemization is a conversion of an optically active compound by heat or chemical reaction into an optically inactive form in which half of the optically active substance becomes its mirror image [29]

Geometric isomerization: The products can be in trans or cis form. One form may be more therapeutically active.

Polymerization: There is a combination of two or more identical molecules to form a much larger & more complex molecule.

Temperature: The rate of most chemicals increases with increasing temperature. Most of the drug degrades at high temperature.

Moisture: Moisture absorbed on the surface of a solid drug often increases the rate of decomposition, if it is susceptible to hydrolysis.

Light: Many types of chemical reactions induced by exposure to high energy light. Autoxidation of the volatile oil / fixed oil takes place and substance is coloured. [24,26,27]

THE EFFICACY-DRIVEN APPROACH FOR EVALUATION OF HERBAL MEDICINE

Botanicals are complex and diverse mixtures. The extraction and identification of putative active components in the whole herb or herbal formulation requires innovative approaches as well as significant laboratory investments. Evidence of clinical efficacy is required and the total investment is very expensive, although success is not guaranteed. A more cost-effective approach is needed to find bioactive components in herbs. So that a statement for the development and the evaluation of plant based drugs will be further accepted, to consider various aspects of a plant based drug, including the safety, effectiveness, quality and consistency of the composition, and the mode of action. [28]

- A particular need for research in this area is to understand the quality of herbs, which can vary greatly. Also, herbs can be misidentified and contamination or adulteration is common. Herbs must be fully authenticated.
- A basic chemical quality control dataset can be generated through chromatographic studies, and details of species related to the origin of production are generated through DNA fingerprinting. Quality is also important in terms of the absence of pesticides, heavy metals, fungi, and microbes. Each batch of herb must undergo evaluation and verification against standard extract records provided by the relevant academic institution in China. [28]
- However, the existing standards for labelling herbal samples are far from satisfactory. New technologies can create chemometric profiles of a known herb to assess quality, as well as help identify and quantify biologically active chemical components.
- This practice brings the quality control of herbal medicine to a more effective level and will support its use in modern medicines. Ensuring the quality and consistency of herbal medicines is very important, but issues of potency and mode of action must also be addressed.
- An assay approach that combines biochemical, biological and chemometric tests in a “layered” system provides a useful platform for the overall evaluation of herbal medicines. Parallel tests of traits or biological effects with chemometric selection are performed on crude plant extracts before parallel tests of other fractions and their combinations, as shown in Fig.1. [28]
- The purpose of chemometric analysis is to identify the biologically active chemical groups, not the compound, and to provide a chemical fingerprinting technique that leads to the identification of multiple target compounds with known and partially known chemical properties. The chemometric fingerprint analysis technique allows to compare the chemical compositions of different samples using all the detected through their total chromatograms obtained from gas chromatography, liquid chromatography, LLC mass spectrometry (MS) and others.
- In summary, the development and evaluation of herbal medicines requires a comprehensive research approach that includes chemometric testing of herbs for quality, consistency and identification of bioactive components as well as experimental procedures and clinical studies to confirm efficacy and mode of action. [28]

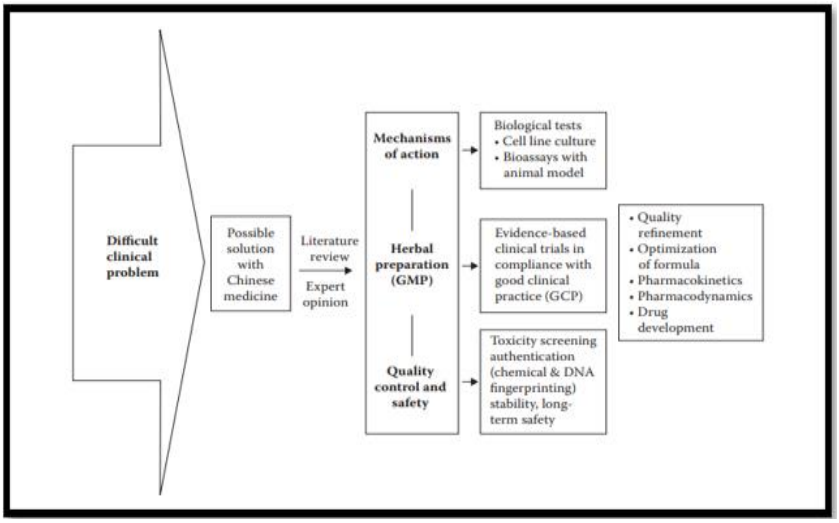

Fig 1: The efficacy-driven approach to evaluate herbal medicine

Herbal medicines: Challenges and Regulations

Regulatory criteria for introducing herbal medicines, traditionally used as part of approved health therapies, face several difficulties. In a survey of 129 countries, WHO reported the following problems with herbal medicines: lack of research data, proper mechanisms to control herbal medicines, education and training, experience within national health authorities and control bodies, information sharing, safety monitoring, and methods for evaluating their safety and effectiveness.[30] The support required by different countries includes exchange of information on regulatory issues, workshops on safety monitoring of herbal medicines, general guidelines on research and evaluation of herbal medicines, provision of databases, workshops on herbal medicines regulation and international meetings.[30,31]

National guidelines are the basis for defining the role of traditional medicines in national health programs to ensure that the necessary regulatory and legal mechanisms are put in place to promote and uphold best practice to ensure the authenticity, safety, and efficacy of traditional medicines and therapies, ensure and provide equitable access to health resources and their resource information [22] Another basic requirement is the harmonization of the market for herbal medicines for industry, health professionals and consumers [30,31]. Herbal medicines are generally sold as dietary supplements, but there is no common legal framework across countries. Therefore, information on the clinical indications for their use, efficacy, and safety are influenced by the traditional experience available at each site.

Reason for the Need of Polyherbal Formulation [60,61]

As mentioned before, the herbal formulation has recently started gaining popularity all over the world, due to the fact that the polyherbal formulation acquires certain benefits that are not present in allopathic drugs. Polyherbal formulations show great efficacy in various diseases due to the presence of active phytochemicals and these therapeutic effects are further enhanced when compatible herbs are formulated together in polyherbal formulations.[32,33] Although modern allopathy comes with undesirable side effects, including vomiting, seizures, fatigue, diarrhoea, hair loss, insomnia, confusion, dry mouth, impotency, organ toxicity and even death. Example: Patients prescribed NSAIDs for the treatment of rheumatoid arthritis (RA) may also experience renal and gastrointestinal side effects, including gastric ulcers, dyspepsia, salinity and fluid retention with hypertension. To do this, they can opt for Ayurvedic therapies in which these side effects are absent or negligible. [34,35,36]

Quality, Safety, and Scientific Evidence

Herbal medicine has been widely used over the years to treat and prevent disease, promote health and improve the length and quality of life. However, a systematic approach to evaluate their safety and effectiveness is lacking. The holistic approach to health care makes herbal medicine very appealing to many people, but also makes scientific evaluation very difficult as many factors need to be taken into account. Herbal medicines are widely available and although many assume that herbal medicines are safe, they are often used in combination and extracted from plant sources with their own variability in species, growing conditions, and biologically active constituents. Herbal extracts can be contaminated, adulterated and contain toxic compounds. Quality control of herbal medicines directly affects their safety and effectiveness. However, data on the composition and quality of most herbal medicines is scarce, not only due to the lack of adequate guidelines or government requirements, but also due to the lack of adequate research methodologies or recognized for evaluating traditional medicines [37]. Additionally, there is very little research on whole-plant blends because the drug approval process does not allow for undifferentiated blends of natural chemicals. Isolating every active ingredient in every herb would be time time-consuming and expensive, making it unprofitable for manufacturers [38].

Another problem is that despite the popularity of herbal and dietary supplements, some herbal products in the market are likely to be of poor quality and questionable effectiveness, even though there effectiveness has been proven. The herb has been shown to work in controlled studies of high-quality product. There is a belief that herbs, being natural products, are inherently safe with no side effects and that efficacy can be achieved over a wide range of dosages. Although herbs can have undesirable side effects, there are no fixed “doses,” and herb–herb interactions are possible. [39]

An important hypothetical advantage of herbal medicines over traditional single-component drugs is the presence of several active compounds, which together can produce a stimulating effect that cannot be achieved with a single compound. [40] This advantage poses a unique challenge for the identification and separation of active components. Compounds identified by activity-guided fractionation should be tested in appropriate animal models to assure in vivo activity. Ideally, the composition of the whole botanical extract should be standardized and free from potential hazards, and the plants specifically intended for the production of botanical extracts should be grown under controlled conditions and come from a characterized genetic source consistent with a taxonomic coverage of species, genus and cultivar or other additional identifiers. Records should be kept on the origin of seeds, growing locations and conditions, and exposure to any chemical treatments such as pesticides [40]. Since the environment can significantly affect the phytochemical profiles and potency of the final botanical product, botanical extracts can vary from year to year and be significantly affected by temperature, drought as well as by geographic location. Therefore, biochemical profiles should be used to ensure that a consistent material is used to produce a plant extract. The concentration step can also be difficult, and the process of concentrating active compounds to a sufficient level can negatively affect their solubility and bioavailability. Therefore, increasing potency by increasing concentration can be counterproductive, and the use of solubilizers and bioenhancers should be considered same as for drugs [41]. Although in theory herbal medicines should

be well characterized and herbal dietary supplements should be manufactured to the same quality standards as drugs, the real world practice is very different from pure drug. Herbs contain various compounds, many of which cannot be identified and often there is no identifying component, and chemical fingerprinting is still in its infancy and absent from virtually all herbs [42]. This complicates the standardization of herbs, although some can be made to contain a standardized amount of a key component or class of components, like ginsenosides for ginseng products. However, even where these key compounds have been identified and a standard content agreed or proposed, there is no assurance that individual commercial products will carry this.

Another interesting aspect is that herbal materials for commercial products are obtained from cultivated medicinal plants and wild plant populations. The expansion of the market for plant-based products could lead to overexploitation of plants and threaten biodiversity. Poorly managed harvesting and cultivation practices could lead to the extinction of endangered plant species and the destruction of natural resources. It is believed that 15,000 of the 50,000–70,000 species of medicinal plants are threatened with extinction. [43]The efforts of Botanic Gardens Conservation International are essential to the conservation of plant populations and the knowledge of how to prepare and use herbs for medicinal purposes.

RESEARCH NEEDS

The need for research in the area of herbal medicines is huge, but it is outweighed by the potential health benefits and the sheer size of the market. Research into the safety, quality, molecular effects, and clinical effectiveness of the many commonly used herbs is needed. Emerging scientific techniques and approaches provide the required testing platform for this. Genomic testing and chemical fingerprinting techniques using dashboard testing platforms are now available for ultimate authentication and quality control of herbal products. Their use should be regulated to protect consumers, but questions of efficacy remain pending and until sufficient amount of scientific evidence accumulate from experimental and controlled studies in humans [44,45,46]. Authentication for the potential protective effect of selected herbs is usually based on experiments demonstrating biological activity in a relevant in vitro bioassay or on experiments using animal models. In certain cases, this is supported by both epidemiological studies and a limited number of human intervention experiments. [47] In general, international research on traditional herbal medicines should be subject to the same ethical requirements as any research involving humans, with information shared between different countries. This should include collaborative partnership, scientific validity, social value, fair subject selection, favourable risk-benefit ratio, informed consent, independent review, and respect for the subjects [44]. However, the time, logistics, and expense of conducting large, controlled human trials of an herb's clinical efficacy are prohibitive, especially when the focus is on health promotion. Therefore, there is an urgent requirement to develop new biomarkers that are more clearly linked to health (and disease) outcomes. Predictive biomarkers and subtle but detectable signs of early cellular changes that can be attributed to the onset of certain diseases are needed.

Research is also needed to address the challenges of identifying active compounds in plants, and there should be research-based verification on whether whole herbs or extracted compounds are superior. The issue of herb–herb interaction is also important and requires further awareness and investigation as polypharmacy and polyherbacy are widespread [48,49,50,51]. The use of new technologies such as nanotechnology and new emulsification methods in the formulation of herbal products is likely to affect the bioavailability and potency of herbal ingredients and this should also be investigated. Smart detection methods and metabolic engineering offer exciting technologies for the discovery of new active ingredients based on natural substances. Advances in rapid genetic sequencing coupled with the manipulation of biosynthetic pathways may provide a great resource for future drug discovery [52]. This may result in some agents that failed in previous studies being re-examined and redesigned using new technologies to see if they can be altered for better efficacy and fewer side effects. [60,61]

For example, maytansine, isolated from the Ethiopian plant Maytenusserrata in the early 1970s, showed promising results in preclinical testing, but was abandoned after further study in the early 1980s when it proved ineffective in clinical trials; later, scientists isolated related compounds, ansamitocins, from a microbial source. A derivative of maytansine, DM1, has been conjugated to a monoclonal antibody and is currently being tested for prostate cancer.

LIMITATIONS OF POLYHERBAL FORMULATION

When herbal combinations with active constituents are made together, they may show better activity to the single extract. But, presence of many constituents can lead to chemical instability. While India produces and exports the majority of Ayurvedic Polyherbal preparation is somewhat less stringent, despite the introduction of Drugs and Cosmetic Act to control manufacturing and quality control. [54,55] According to good clinical practice, toxicity studies and clinical trials of herbal formulations are not required for patent application and granting of manufacturing licenses to the manufacturer of Ayurvedic herbal formulation. Examples of ayurvedic herbs in polyherbal formulation with their possible drug-herb interaction are given below [56,57,58]

Table: 4 Ayurvedic herbs in poly herbal formulation with their possible drug-herb interaction

Ayurvedic Herbal Plants in Polyherbal Formulations	Possible drug-herb interaction
Garlic (*Allium sativum*),Ginger (*Zinger officinale*),Ginkgo (*Gingko biloba*)	Interfere with NSAIDs (Non steroidal anti-inflammatory Drugs) and warfarin by enhancing the risk of bleeding, mainly due to inhibition of platelet aggregation, limited production of coagulation mediators
Meadowsweet(*Filipendula ulmaria*) foranti-inflammatory action and heartburn, Stomach ulcer, Arthritis ,Gout	Displacement of highly protein bound drugs. (e.g., Warfarin and Carbamazepine, thus increasing adverse effects of these drugs)
St. John's wort (*Hypericum perforatum*) for depression treatment and in treatment of wounds	Induce hepatic microsomal enzyme cytochromeP-450, thus increases the metabolism of certain drugs such as digoxin and theophylline, rendering them less effective.

CONCLUSION:

Herbs, plants, and ethno botanicals have been used since the earliest days of mankind and are still used around the world to promote health and treat disease. Plants and natural sources form the basis of modern medicine today and contribute significantly to the commercial drug preparations that were manufactured today. About 25% of prescription drugs worldwide are derived from plants. Nevertheless, herbs are often used rather than drugs in health care. For some, herbal medicine is preferred method of treatment, for others, herbs are used as a complimentary therapy to traditional pharmaceuticals. However, in many developing countries, traditional medicine, of which phytotherapy is a fundamental component, is the only health system available or affordable. Whatever is the reason, those who use herbal medicines need to be sure that the products they buy are safe and contain what they are supposed to contain, whether it is a specific herb or an amount specific to a specific plant ingredient. Consumers should also obtain scientific information on dosage, contraindications, and effectiveness. Achieving this requires global harmonization of legislation to guide the responsible production and marketing of herbal medicines. If sufficient scientific evidence of an herb's benefit is available, such legislation should permit its appropriate use to encourage the use of that herb so that those benefits can be realized for the promotion of public health and the disease treatment.

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