DETERMINATION OF THE SHELF LIFE AND EXPIRY DATE OF HERBAL COMPOUND DRUGS: A REVIEW

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Abstract : Herbal medicines are being used by nearly about 80% of the world's population. With the advancements in herbal drug treatments, it has now been observed that many of the constituents present in the drug may react with each other, raising concerns about the stability of such formulations. A detailed literature review of Unani classics and modern resources was made to find out what methods of shelf-life determination may be suitable for Unani drugs; especially compound drugs, in the present era. Three methods, viz., activity-based standardization, determination of biologically active compound and standardization of herbal drugs on various physical, chemical and other parameters were found to be suitable and practically applicable. These methods may be reproduced at various intervals to determine the time when the drug loses its characteristic properties, i.e., its shelf-life.

KEYWORDS: Shelf-life, standardization, activity determination, herbal drugs.

The plant kingdom represents an almost inexhaustible source of biologically active compounds. Some of the most useful drugs have been derived from plants; in addition, many of their active constituents have been used as models for the synthesis of many therapeutically important medicines. The Unani system of medicine employs a large number of drugs which are of herbal origin. This system of medicine has been given due recognition by the World Health Organization besides many other health agencies. Due to the increasing demand of Unani drugs and consideration of the commercial angle, the quality control of the herbal drugs has become essential[(1)].

Variety of reasons has been cited for the need for scientific evaluation and standardization of herbal drugs. Most of the traditional knowledge about medicinal plants was in the form of oral knowledge that had been eroded/corroded or distorted due to a variety of reasons. Lack of proper documentation, more particularly the practical aspects, details of sourcing of medicinal plants and their post harvest handling etc. was one of such reasons. Also there was no uniform or standard procedure for maintaining the inventory and the practical knowledge on the collection of medicinal plants were never properly documented. There is a prevalence of using plants and plant

based products in various contemporary and traditional systems of medicine, without any written documentation or regulation. Therefore, it is essential that such uses of natural products be documented and studied in systematic manner and develop standard protocols for collection, processing, packaging and storing, etc. Phytochemical investigations along with biological screening to understand the therapeutic dynamics of medicinal plants etc. will help in developing quality parameters and help in the standardization and shelf-life determination of these drugs.

ANCIENT UNANI SCHOLARS'CONCEPT OF SHELF LIFE OF DRUGS

The promotive, preventive, corrective and curative approach in health care and the medicinal plants processing such properties are indeed the strength of the Unani System of Medicine. The ancient scholars of Tibb-e-Unani organized, codified and synthesized the medicinal wisdom with sophisticated theoretical foundation and philosophical explanations. Determination of the shelf-life of drugs was an important area of concern for the ancient Unani scholars. Most of the eminent scholars have provided useful information in this context. However, most of the literature contains a detailed description related to storage and preservation of single drugs, and their shelf-life on storage; while the same information regarding compound drugs is relatively rare.

Rabban Tabri (770-850 AD) was perhaps the first physician to put a spotlight on this important issue. In his famous book *Firdous al-Hikmah*, he stated that *Tiryāq Akbar* remains effective for atleast 30 years after preparation and sometimes even more[(2)]. Ibn Sina (980-1035 AD) mentioned in *Al-Qanūn fil-Tib* that gums and resins remain effective for about three years after procurement; in general, they should be considered ineffective if they solidify[(3)]. These may be considered as the early hypotheses which paved the way for future research on storage and life of herbal drugs.

Ali Ibn Abbas Majusi (930-994 AD) pioneered the research in developing methods for the determination of shelf life of single as well as compound drugs. The estimation of lives of drugs as mentioned by him is based on visual and other physical examination of the drugs under question. For example, he states that oils should be considered effective till they retain their original odour. In addition to this, a very interesting research in his treatise *Kāmil-us-Sanā'h* is the concept of human and animal trials for determination of efficacy of drugs which is practically a modern concept. He introduced the concept of determining the potency of *tiryāq* (antidotes) by testing them on diseased persons. Or the drug may be tested on animals like hen, this method helps in determining whether the *tiryāq* is effective at a certain period of time[(4)]. Needless to say, this method may be used for the activity-determination and standardization of other drugs also.

Ibn Sina (980-1035 AD) mentioned in his famous treatise *Al-Qānūn fil-Tib* that the shelf life of a drug depends on the collection and storage; the drugs which are fresh when procured have a better life[(3)]. In the same vein, the renowned scholar Md. Abdul Hakeem mentioned that the shelf life depends on three factors: type of the drug, its constituents and their structural organization.

Depending on the above factors, the drugs lose their efficacy over a certain period of time. For instance, gold and silver remain potent for many years, while other metals like iron and copper lose their medicinal value after comparatively lesser period of time. The drugs of plant origin have an even lesser shelf life. Leaves remain effective for one to two years, while gums like scammony remains effective for twenty years and opium remains effective for about fifty years. The shelf life of vegetable oils depends on their temperament. The oils which are cold and moist in temperament become ineffective within two to three weeks only. However, it has been mentioned about *Roghan Balsān* that its efficacy increases with time. The drugs of animal origin remain effective depending on the type of tissue. Soft tissues like blood etc remain effective for one year, while the harder tissues like horns may be used for many years[(5)].

DIFFERENT APPROACHES FOR DETERMINATION OF SHELF LIFE OF HERBAL DRUGS

Many different methods have been proposed for standardization of herbal drugs which may be used as a parameter for determining the shelf-life of a given drug. Based on an extensive literature review, the most feasible methods are discussed here.

Ideally, the method for measuring the biological potency of a herbal drug should correlate the pharmacological activity of the drug with specific chemical markers. However, such correlative studies are difficult, as the specific compounds may not be identified. Activity-based standardization is a simple approach. It is based on the inhibition of activity of a particular enzyme related to the disease. Enzyme assays have distinct advantages: Spectrophotometric or fluorimetric enzyme assays have high sensitivity and specificity; and allow accurate measurement of changes in enzyme activity. The concentration of the herbal drug required to inhibit 50% of a fixed amount of enzyme activity is termed the IC50 value for enzyme inhibition. Thus, under defined conditions, a herbal drug should give a fixed IC50 value for enzyme inhibition. If the IC50 values are reproducible, the assay can be reliably used in the activity-based standardization of the said herbal drug. The same method can be used to determine the time when the potency of the drug decreases, i.e., the shelf-life or expiry date of the drug.

Candidate enzymes selected for activity-based standardization of herbals should satisfy three main criteria. First and foremost, the enzyme must show significant activation during the progression of the disease for which the herbal drug is prescribed. Secondly, the enzyme assay must be sensitive, specific and reproducible. Thirdly, a detailed chemo-profile of the herbal drug should be available. The results of a study suggested that aging Triphala powder loses potency with respect to its ability to inhibit hyaluronidase and collagenase enzyme activities. This approach can be extended to other herbal drugs which inhibit other disease-related enzymes or activate protective enzymes[(6)].

There are certain unique advantages in using enzyme assays for activity-based standardization of herbal drugs. The correlative data between IC50 value of enzyme inhibition and a particular chemical marker provides a simple and definitive

method for standardizing the potency of the herbal drug. This is because the enzyme chosen is strongly involved in the progression of the disease for which the herbal drug is prescribed.

Another useful method is the determination of the biologically active compound which is valuable because it may serve as a marker to confirm the bioactivity of the drug, without any human or animal trial. In indigenous/traditional systems of medicine, the drugs are primarily dispensed in raw form as decoctions, tablets, *ma'jūn* (electuary) etc. Drug extract are a rarity rather than a rule. Thus medicinal plant parts should be authentic and free from harmful materials like pesticides, heavy metals, microbial or radioactive contamination, etc. In addition, the bioactive extract may be standardized on the basis of active principle or major compound(s) along with fingerprints[(7)].

The bio-activity and the concentration of the active compound in the drug may be assessed at various intervals of time to determine the shelf-life and expiry date of the drug. However, this method may be applicable in case of single drugs only. It is recommended that in case of a herbal medicinal product containing a natural product or a herbal drug preparation with constituents of known therapeutic activity, the variation in component during the proposed shelf-life should not exceed ± 5% of the initial assay value, unless justified[(8)].

WHO has set certain standards for herbal drugs. These parameters may be assessed at different intervals of time and the changes noted, so as to determine the time when the drug loses its characteristic properties. This may be helpful in determining the shelf life of herbal drugs. The method may be applied to compound drugs also.

It includes the following parameters[(9)]:

S. NO.	PARAMETER	DETAILS
1.	Botanical parameters	Sensory evaluation: Visual macroscopy, touch, odour, taste.
		Foreign matter: Plants, animals, minerals etc.
		Microscopy: Histological observation and measurements.
2.	Physico-chemical properties	TLC/HPTLC fingerprint
		Ash value: Total ash, acid-insoluble ash, water-soluble ash and sulphated ash.
		Extractive values: In hot water, cold water and ethanol.
		Moisture content and volatile matter: Loss on drying, azeotropic distillation etc.
		Volatile oils: By steam distillation.
3.	Pharmacological parameters	Bitterness value: Unit equivalent bitterness of standard solution of quinine hydrochloride.
		Haemolytic property: On ox blood by comparison with standard reference solution of saponin.
		Astringent property: Tannins that bind to standard Frieberg Heid powder.
		Swelling index: In water.
		Foaming index: Foam height produced by 1 gm of substance under specified conditions.
4.	Toxicological parameters	Arsenic: Stain produced on $HgBr_2$ paper in comparison to standard stain.
		Pesticide residues: Includes total organic chloride and total organic phosphorous.

		Heavy metals: like cadmium and lead.
		Microbial contamination: Total viable aerobic count of pathogens.
		Aflatoxins: By TLC using standard aflatoxins: (B_1, B_2, G_1 and G_2)
		Radioactive contamination.

CONCLUSION

Herbal medicines are being used by nearly about 80% of the world's population. Presently, India contributes less than 1% to the global herbal market. With the advancements in herbal drug treatments, it has now been observed that many of the constituents present in the drug may react with each other, raising concerns about the stability of such formulations. Natural products are often prone to deterioration, leading to possible loss of active component or production of inactive metabolites or toxic substances on storage. This area needs to be addressed in order to determine the efficacy of the formulation[(1)].

The challenge in the present century is to discover methods of shelf-life determination which do not interfere with the drug form of compound herbal preparation, along with being effective and acceptable by the modern standards. It is well known that the activity of any herbal preparation is not the result of a single compound, but the synergistic effect of the large number of compounds present in the herbal drug. Therefore, making extracts of herbal drugs and standardizing them does not provide the answer.

Based on the above literature review, activity-based standardization appears to be the most suitable method for shelf-life determination of herbal compound drugs. The primary reason being that it does not interfere with the drug form; therefore, it is equally suitable to be applied in case of both single and compound drugs. Therefore, it measures the synergistic activity of the drug as a whole, and not its extracts or components. Secondly-the data generated by such studies will be largely reproducible as it will be based on enzyme activity, which will facilitate the development of an evidence-based medicine; and third-once the data and studies for all drugs are established, it is likely to prove to be a very simple and cost-effective method for shelf-life determination. Also, since the activity-based determination of shelf life measures the inhibition of activity of a particular enzyme related to the disease, it is an additional gain for medical science. In addition, the drug may be standardized on botanical and other parameters discussed above to facilitate homogenization of knowledge.

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