

Herbal Fixed Dose Combinations in Nepal: Growing Concerns in a Developing Country

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ABSTRACT

Herbal medicines are mostly prepared as a combination therapy that has been used since therapeutic was first practiced. Combination products, also known as Fixed Dose Combinations (FDCs) of herbal remedies are in widespread use in Nepal. Herbal FDCs are in common practice because it is believed to have better adherence, less side effects and easy accessibility. Nevertheless, combination products possess greater risk of adverse effects, increases costs associated with treatments and leads to an ineffective dosages. Herbal FDCs are used extensively in Nepal although the rationality beyond the use of these combinations is still unidentified and at times are questionable. Legislations governing the use of herbal medicines is lacking in Nepal. Many herbal FDCs are not supported by any scientific data and test for the presence of ingredients mentioned in the package insert/container label is always difficult. A FDC of herbal products must be based on clear criteria that guarantee consumer safety and appropriate indications. These criteria helps to protect the consumers or patients from the misleading claims and risk associated with the use of unjustifiable combination of herbal substances. Strict monitoring from the regulatory body and the public awareness on the cost as well as advantages and disadvantages of herbal FDCs is urgently required.

Keywords: Combination therapy, Herbal medicines, Irrational drug use

INTRODUCTION

Beginning from the earliest day of mankind, herbal medicines that formed the basis of healthcare, is still widely used all over the world [1]. Medical systems is broadly classified into *biologically based* (modern medicines or pharmaceuticals that are based on physiology and evidence base) and *non-biological based* (herbal, ayurveda, unani, homeopathy, that are based on cultural interpretation and influence of events). The pragmatic use of herbal medicines as non-biological medicine is often observatory, trial and error for a prolonged period of time [2]. Medicinal herbs are a major component in traditional Chinese medicine, accounting for approximately one-fifth of the entire Chinese pharmaceutical market. More than 600 different herbs have been used in China to treat medical ailments [3]. In the ninth century herbs from Japan were documented in the first pharmacopeia of Japanese traditional medicine [4]. In India, ayurveda is practiced as a herbal medical system that included diet and herbal remedies in disease prevention and treatment [5].

Herbal medicines are mostly prepared as a combination therapy that has been used since therapeutic was first practiced [1]. Combination therapy is common worldwide due to several reasons but the rationale behind this combination is questionable [6]. Combination products, also known as Fixed Dose Combinations (FDCs), are combinations of two or more active drugs in a single dosage form [7]. In spite of the questionable benefit, the practice of herbal FDCs has continued to be a primary source of healthcare especially in developing countries which has stimulated considerable public health concerns relating to their uncertain safety and efficacy issues when used concomitantly with regular standard medications [8].

Nepal, a developing country landlocked between India and China shares an open border with India. This allows an easy penetration of Indian pharmaceutical market in Nepal. The scenario of FDCs use in Nepal and India is alarming [6,9-12]. A recent study in India reported that large number of government unapproved FDCs (internationally restricted and banned drugs) were available in market and the sales volume of these FDCs were high [10]. In Nepal, despite the existence of regulatory guidelines and formularies, FDCs such as cough and cold preparations, nutritional supplements, dermatological and several herbal combinations are in widespread use [13]. There has

been a tendency to manufacture several irrational combinations of various therapeutic categories like of analgesics, antibacterial, anti-diarrheals, etc. which was reported in a market survey conducted in six major cities of Nepal [14]. Plant based treatment are considered to be one of the most popular complementary treatments in Nepal, although there has been absence of any specific legislation to regulate the safety, efficacy, quality, sale-distribution, promotion and utilisation of herbal medicines [15].

Herbal FDCs are in common practice because of its improved adherence, reduced cost, less medication errors, easy accessibility etc. Reasons for choosing herbal preparations over pharmaceuticals include perceived 'naturalness' and belief of lower severity of side effects [16,17]. There have been a greater interest in herbal medicines due to multiple factors such as, the belief that pharmaceutical medication are expensive, over prescribed and often unsafe because of multiple adverse effects. Although herbal combinations are perceived as safe, all the biologically active substances have a potential to induce harm as well as therapeutic benefit. The incidence of adverse outcomes is increased when two or more substances are administered concurrently. Often herbal remedies are used in combination usually FDCs. However, the scientific literature supporting the efficacy of herbal therapies is incomplete [17]. The justification of the potency and therapeutic value of the herbal FDC are very few [6,17-20]. Although the literature that addresses the topic of investigation is sparse, in this paper we include a snapshot of key herbal FDCs that are commonly used in Nepal.

Identification and Categorization of FDCs

In this study, we undertook secondary analyses of medications that were collected in study originally designed to investigate perception of community pharmacist in patient counselling and continued pharmacy education in Nepal [21]. A prospective study was conducted between January and March 2008 in six major cities of Nepal (Biratnagar, Birgunj, Kathmandu, Bhairahawa, Pokhara and Nepalgunj) that represented four out of five development regions in Nepal. Ten randomly selected community pharmacies from each city were included in the study. In addition, information from the drug regulatory authority (www.dda.gov.np) and pharmaceutical manufacturers were also collected. Some of the commonly used

Name	Formulation	Composition	Indication	Manufacturer
Adliv	Syrup	Bhringraj 250 mg + Bhumiya malaki 250 mg + Kalmegh 100 mg + 3 other combinations.	Hepatitis, anorexia	Albert David Ltd.
Adliv forte	Capsule	Bhringraj 250 mg + Bhumiya malaki 250 mg + 2 other combinations.	Cholelitholytics and hepatic protectors	Albert David Ltd.
Amlycure D.S.	Syrup	Bhringraj 750 mg + Bhuiamla 750 mg + Kasni 600 mg + 28 other combinations	Hyperbilirubinemi, viral hepatitis, appetite enhancer	Aimil Pharmaceuticals Ltd.
Amycordial	Tablet	Ashok Ghan 50 mg + Lodhra Ghan 50 mg + Vanshlochan 30 mg + Sudh Laksha 30 mg + Rasaunt 20 mg + Praval Pishti (AFI)1 20 mg + Mukta Shukti + Bhasam (AFI)2 20 mg + Mandoor Bhasam (AFI)3 20 mg + Phitkari Sudh 10 mg + Bansa Patr Ghan 10 mg + Chikni Supari 50 mg + Shatavar 50 mg + Ashwagandha 45 mg + Manjith 30 mg + Jeevanti 30 mg + Nagkesar 30 mg + Draksh Kali 20 mg + Rakt Chandan 20 mg + Kutaj 20 mg + Santra Chilka 20 mg + Mochras 20 mg + Chaulai Mool 20 mg + Gainda Patr 20 mg + Amla 20 mg + Sunthi 15 mg + Phool Priyangu 10 mg + Excipients (A) Q.S	Menorrhagia, unexplained infertility, pre-menstrual syndrome, leucorrhoea & vaginitis	Aimil Pharmaceuticals Ltd.
Cystone	Tablet	Shilapushpa 130mg + Pasanabheda 98mg + Manjishtha 32mg + Nagaramusta 32mg + Apamarga 32mg + Gojha 32mg + Sahadevi 32mg + Shilajeet 26mg + Hajrul yahood bhasma 32mg	Prevention and treatment of urolithiasis, crystalluria, prevention of post lithotripsy, as an adjuvant in chronic UTI, nonspecific urethritis	Himalaya Herbal Healthcare
Cystone	Syrup	Gokshura 91mg + Punarnava 67mg + Manjishtha 32mg + Pasanabheda 53 mg + Mustaka 42 mg + Kulattha 21 mg + Shatavari Trikatu 20 mg + Ushira 21 mg + Karchura 14 mg + Saindhava 50 mg + Suvarchika 42.5 mg + Yavakshara 5mg + Narasara 2.5mg		
Dabur Honitus	Syrup	Tulsi 50 mg + Mulethi 50 mg + Banapsha 50 mg + 9 other combinations	Relief from cough, sore throat	Dabur India Ltd.
Gasex	Tablet	Prativisha 65 mg + cowrie bhasma 32 mg + Shankh bhasma 32 mg + 6 other combinations	Dyspepsia, indigestion, flatulence, abdominal distension and belching	Himalaya Drug Company
Honitus	Syrup	Banphasa 50 mg + Basaku 25 mg + Kantakari 50 mg + 9 other combinations.	Relief from cough, sore throat	Dabur India Ltd.
Liv 52	Tablet	Himsra 65 mg + Kasani 65 mg + Mandura bhasma 33 mg + Kakamachi 32 mg + Arjuna 32 mg + Kasamarda 16 mg + Biranjasipha 16 mg + Jhavuka 16 mg	Viral hepatitis, alcoholic liver disease, pre-cirrhotic conditions and early cirrhosis, anorexia, fatty liver, jaundice	Himalaya Herbal Healthcare
Liv 52	Syrup	Himsra 34 mg + Kasani 34 mg + Mandura bhasma 16 mg + Kakamachi 16 mg + Arjuna 16 mg + Kasamarda 8 mg + Biranjasipha 8 mg + Jhavuka 8 mg		
Neeri	Syrup	Sudh Shilajeet 200 mg + Shwet Parpati 150 mg + Sheetal chini 100 mg + 17 other combinations	Urinary calculi, urinary tract infections, cystitis, burning micturition	Aimil Pharmaceuticals Ltd.
Rumalaya Forte	Tablet	Shallaki 240 mg + Guggulu Suddha 200 mg + 70 mg + Yashti-madhu 70 mg + Gokshura 60 mg + Guduchi 60 mg	Rheumatoid arthritis, osteoarthritis, arthralgia, gout	Himalaya Herbal Healthcare
Siotone	Capsule	Ashwagandha 550 mg + Kapikachu 100 mg + Purified Silajit 250 mg + 2 other combinations	Loss of appetite, anorexia	Albert David Ltd.

[Table /Fig-1]: Some of the registered herbal fixed dose combinations in Nepal and their compositions.

herbal FDCs registered in Nepal and their compositions are shown in [Table/Fig-1].

Advantages and Disadvantages of Fixed Dose Combinations

Many of these preparations contain their drugs in fixed combinations and therefore presumed to have some advantages and a few disadvantages. Some of the presumed advantages and disadvantages of FDCs are shown in [Table/Fig-2,3] respectively [6,7,22,23].

Sl. No.	Advantages of FDCs
1	Dosage schedules are made simpler so that it may improve compliance and improve treatment outcomes.
2	Reduces unintentional medication errors.
3	Favors synergistic combinations (for e.g. trimethoprim/sulfamethoxazole combination allows each drug to selectively interfere with successive steps in bacterial folate metabolisms).
4	Supports easy medication management, handling and procurement.
5	Reduced cost on manufacturing, packing and shipping.

[Table/Fig-2]: Some of the presumed advantages of fixed dose combinations.

Is FDC of herbal drugs justifiable?

The World Health Organization (WHO) has defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today [24]. In phytotherapy fixed combination of herbal

medicinal products are in widespread use. A FDC of herbal products must be based on clear criteria that guarantee consumer safety and appropriate indications. These criteria help to protect the consumers or patients from the misleading claims and risk associated with the use of unjustifiable combination of herbal substances [25]. Several studies suggest that the many ayurvedic preparations have no any proven efficacy and their combination cannot be justifiable [6].

Sl. No.	Disadvantages of FDCs
1	Many times FDCs are more expensive than separate tablets.
2	Requires a serious bioavailability testing such as in the case of rifampicin used as FDC for tuberculosis.
3	If an individual observes any side effects or allergic reactions to at least one component on FDCs, the combination must be discontinued and replaced by separate tablets. This issue is however, also observed with single dose formulations.
4	Inflexible dosing regimen makes it difficult to cater individual patient's needs.
5	Because of different elimination half-life of individual components, pharmacokinetic property of FDCs cannot be adjusted easily.

[Table/Fig-3]: Some of the presumed disadvantages of fixed dose combinations.

Herbal Fixed Dose Combinations Registered in Nepal

In recent time, the use of herbal medicinal product and supplements has increased tremendously in Nepalese market. It is been noticed more than 50 new herbal pharmaceutical manufacturer and more than 500 herbal combinations product are been registered at Department of Drug Administration in past one decade [26]. Some of the registered herbal FDCs in Nepal and their compositions are listed in [Table/Fig-1].

Monitoring of Herbal Fixed Dose Combinations

In context of Nepal, monitoring of herbal medicines is yet to be initiated [27]. Safety evaluation criteria that regulate the use of herbal ingredients to be used in medical preparations are missing. Immense attention is needed since several herbal FDCs contain compounds such as arsenic, lead and mercury in an amount liable to cause harm [28]. In global context, the Uppsala monitoring centre in collaboration with WHO started a project that aims to attain global standardization for herbal medicines which helps to standardize information about herbal medicines along with their scientific names and therapeutic implications, which can vary widely between countries [29].

The use of steroids in the herbal FDCs is next issue which has to be addressed. All the concerned regulatory authorities should govern the practice of including potent pharmacologically active compounds such as steroids into herbal preparations [17]. A special licencing system is warranted in countries where strict control mechanism for registering and controlling herbal FDCs are not in place. This enables all concerned health authorities to screen the constituents present in herbal FDCs so that the safe and correct use is ensured [30]. The national health authorities should focus more on consumer education and qualified practice in the provision of herbal medicines [31].

Safety Profile of Herbal Fixed Dose Combinations

While the use of herbal medicines is increasingly rapidly worldwide, their safety is a common global concern. Although the concerned regulatory authorities are trying to safeguard the rational use of herbal combinations, it has become a very complicated issue because of different regulatory requirements, safety monitoring, absence of qualified practitioners and consumer education [32]. Many herbal and ayurvedic preparations do not have any proven efficacy. The proposed dosage of fixed combination and the contribution of each active substance must be justified in herbal combinations [25].

CONCLUSION

Herbal FDCs are used extensively in Nepal although the rationality beyond the use is still unidentified. A similar scenario may be seen even in other developing countries. The herbal FDC products do not have any proven efficacy and there are very few justifications on the potency and the therapeutic value of these combinations. Strict monitoring from the regulatory body and the public awareness on the cost as well as advantages and disadvantages of herbal FDCs is urgently required. There is also immense need for development of regulations to monitor herbal FDCs for their safety, efficacy and utilization pattern.

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