A Recent Update on Undeclared Chemicals in Herbal Formulations

Department of Pharmaceutical Sciences, Maharshi Dayanand University
Rohtak, 124001, India.

Abstract:
Adulteration of herbal supplements with undeclared synthetic drugs or by mixing the analogues of prescription can cause a significant risk to public health. Consumers of such adulterated products are at risk of developing serious adverse reactions, potentially leading to pulmonary hypertension, moderate aortic regurgitation, a prominent right heart failure, hypokalemia and even death. These analogues are not declared on the labeling and often created by replacing or adding functional groups to the original chemical. Thus, herbal manufacturers have made it more difficult for the analysts to detect these undeclared pharmaceutical analogues into their products. Although DSHEA has given responsibility to the FDA to enforce guidelines for safety and claims, but as per the regulations, FDA can investigate a supplement only after a safety problem has been reported in a particular formulation thus giving the herbal manufacturers enough courage to launch their unscrupulous products into the market. Therefore, a current need arises to check these practices for the proper quality control of these herbal formulations. In this regard, the enforcement of strict manufacturing guidelines, approval process and quality control conditions may well be a step forward towards the safer use of industrially produced herbal products. Moreover, quality and efficacy of medicinal products should be assessed by randomised clinical trials (RCT) before licenses can be issued.

Key words: Herbal formulations, quality control of herbals, synthetic adulterants in herbals.

Introduction:
Safety issues related to herbal medicine are complex, and comprise possible toxicity of natural herbal constituents, presence of contaminants or adulterants, and potential interactions between herbs and prescription drugs[1]. Many patent medicines manufactured in Asian countries contain toxic ingredients, such as heavy metals, as well as prescription drugs or unapproved ingredients that may or may not be identified on the label[2]. Some products claim to be natural or to contain only herbal ingredients, but actually contain potentially harmful ingredients not listed on the product labels or in promotional advertisements. The unlabeled ingredients are surreptitiously mixed into the products, some calling themselves dietary supplements and the products are sold on the Web or in some retail stores[3]. These products have not been approved by the Food and Drug Administration (FDA), are illegal, and may be potentially harmful to unsuspecting consumers[4].

There is an emerging trend where over-the-counter products, frequently represented as dietary supplements, promoted mainly for bodybuilding, weight loss, sexual enhancement, pain and diabetes contain hidden active ingredients that could be very harmful. These deceptive products poses a threat to consumer who may unknowingly take products laced with varying quantities of approved prescription drug ingredients, controlled substances, and untested and unstudied pharmaceutically active ingredients[5]. It is believed that these analogues made the products tough to regulate, developed to evade detection by the FDA, and to reduce the risk of patent-infringement lawsuits[6].

Till date, several scientific studies have been reported regarding the adulteration of herbal formulations with synthetic compounds yet a little is known about regulatory aspects, recent market trends and their health hazards. Present paper intends to present the recent status of these aspects along with possible measures to be undertaken to overcome this serious problem.

Health Hazards
People consuming these type of formulations are unaware of the undeclared analogues and thus at a risk of serious adverse effects[7]. There are several examples of undeclared chemicals admixed with herbal formulation to enhance their activity but pose a serious threat to the human health for example: Sibutramine, an appetite suppressant prescribed for weight reduction, raises blood pressure and heart rate and may interact with other medications to cause serotonin syndrome and may present a significant risk for patients with a history of coronary artery disease, congestive heart failure, arrhythmias or stroke: Rimonabant, an investigational agent hung up in the FDA approval process, has been associated with increased risk of depression and suicidal
thoughts: Cetilistat, an experimental drug for treating obesity is not approved for sale in the US and phenolphthalein, a suspected carcinogen is now being removed from the market has been used for over a century as a laxative[4,8,9,10].

The inclusion of furosemide and other diuretics like bumetanide (available only via prescription) in some of these supplements may result in dehydration and hypokalemia; other contaminants, such as benzodiazepines and antidepressants, mask the side effects of stimulants while conferring an increased risk of dependence[6,6]. Fenfluramine, a banned appetite suppressant linked to valvular heart disease and pulmonary hypertension where an analogue of fenfluramine, N-nitrosofenfluramine was used in slimming products and associated with more than 800 cases of liver toxicity in Japan[11,12]. Ephedrine, a stimulant drug that is legally marketed over-the-counter for temporary relief of asthma but can pose a risk to people with certain cardiovascular conditions[13]. However, ephedra’s risks are potentially much more serious for competitive athletes than for the general population since it acts like an adrenaline boost, stressing the heart, raising blood pressure, and increasing metabolism. Although FDA is reviewing ephedrine alkaloids under the Dietary Supplement Health and Education Act (DSHEA) to assess about their safety use by persons engaged in strenuous exercise. Moreover, the stimulating effects of ephedra may mask the signs of fatigue, causing even the most well conditioned athletes to push beyond their physical limits[14]. The use of thyroid hormones as slimming aids carries a risk of hyperthyroidism and related cardiovascular complications since thyroid function tests showed a suppressed thyroid-stimulating hormone (TSH) level and an elevated free thyroxine (FT4) level[11,15]. Propranolol, a prescription beta blocker drug has no place in the treatment of obesity that can pose a risk to people with bronchial asthma and could cause postural hypotension[9]. Even more dangerous is the detection of oral synthetic antidiabetic drugs in herbal capsules or tablets, used to cure diabetes[1].

Market Trends of Herbal Adulteration With Undeclared Chemicals

There is a tendency of herbal manufacturers to adulterate the formulations which are very popular for general body strength, memory enhancers, increase in sexual potency, weight loss, diabetes etc., with a very high sales output. There is a wide variety of herbal products available in the market which contains steroidal precursors. Consumers believe these products boost testosterone levels and speed muscle growth and thus, targeted to athletes and body builders as performance enhancers and marketed as anti-aging products or dietary supplements. For example, tetrahydrogestrinone, or THG, a purely synthetic, non-naturally occurring, highly potent anabolic steroid, derived directly by simple chemical modification from gestrinone, a synthetic product, approved in Europe for the treatment of endometriosis, a painful condition of pre-menopausal women but is explicitly banned by the U.S. anti-doping agency as an anabolic drug. Furthermore, THG is structurally related to a controlled substance trenbolone, a strong veterinary anabolic steroid approved in the U.S. to increase rate of weight gain and/or improved feed efficiency in beef cattle[13].

Adulteration is concealing addition of undeclared drugs, or other substances with therapeutic effects, to a health product. In 2008, Poon et al[14] analysed “Chang Qing Chun” capsules which literally meant “young forever” was an herbal supplement available over the counter for weight reduction, and thereby identified undeclared caffeine, antheraquiones, riboflavin, nicotinamide, pyridoxine, N-nitrosofenfluramine, fenfluramine, sibutramine, phenolphthalein and propranolol present in significant quantities whereas another herbal formulation, “Qing Zhi Mei,” also found to contain caffeine, antheraquiones, ephedrine, fenfluramine, propranolol, and phenolphthalein as well as animal thyroid tissue.

Most of herbal remedies used, e.g. to lose weight may contain anorectics, laxatives, or diuretics, whereas drugs recommended to treat rheumatic disease may contain various analgesics or steroids, have only vague description or claim “good for nerves”, “slimming herbal capsules”, “good for bones and joints”, or “for male strength”[1]. A drug named Qnexa that promises to help lose weight, also lowers blood pressure, blood sugar and cholesterol, has been banned by an FDA panel for associated dangerous side-effects[16].

A herbal supplement used by a Dutch cyclist who tested positive for ephedrine contained Ephedra as a stated ingredient but also contained significant amounts of another alkaloid stimulant that was not declared as an ingredient[17].

A recent analysis concluded that analogues of phosphodiesterase type 5 inhibitors had been detected in more than half of 26 supplements marketed for the enhancement of sexual function. The FDA is advising consumers not to purchase marketed nationally as dietary supplements, because these products contain undeclared ingredients such as adulterations of erectile dysfunction products (Blue Steel Hero, Zencore), sibutramine in Confidence apple cider vinegar capsules, body-building supplements with hepatotoxic steroids (various Xtreme products), and eyelash-lengthening cosmeceuticals[18].

Over-the-counter androstenedione is contaminated with 19-norandrostenedione, which produces a positive urine test for Nandrolone; furthermore, some brands of androstenedione are grossly mislabeled[19].

In 1997, US market withdrawn after studies the weight loss supplement sold under the name Que She and marketed as "an all-natural blend of Chinese herbs" contains not only fenfluramine, a stimulant which cause serious heart valve damage, but also three other potentially harmful drugs beta-blocker propranolol, which can harm people with asthma and certain heart conditions; prescription weight loss drug sibutramine, which has been linked with increased risk of heart attack and stroke in patients with a history of heart disease; and the stimulant ephedrine[12,20]. Huang et al[20] in 1997 found that around 24% out of 2609 samples of traditional Chinese medicines analyzed in
Taiwan were adulterated with synthetic drugs of various pharmacological activities. Koh et al. [23] reported similar adulteration profile in Chinese herbal remedies analyzed in Singapore in 2000. Ernst [22] published a systematic review of 22 studies done on adulteration of Chinese herbal remedies with synthetic drugs in the period of 1990-2000.

In April 2006, French health authorities reported an incident causing one death and several hospital admissions after taking a “slimming aid” made of powdered thyroid extract [14]. A synthetic analogue of vardenafil, in which the N-ethylpiperazine ring and the sulphonyl group had been removed was identified in a new herbal product for male erectile dysfunction & was confirmed to be a hydrolysis product of vardenafil by HPLC-DAD, LC-MS-MS and 1HNMR [23].

A thione derivative of sidenafil also called thiomethisosildenafil, has been reported recently as an adulterant in a herbal supplement [24].

Compounds with chemical structures similar to that of sildenafil were isolated and purified during the analysis of some herbal products marketed for treatment of erectile dysfunction [25].

**Regulatory aspects:**

All forms of food and non-food supplements fall under the jurisdiction of the FDA. In 1991, WHO prepared draft guidelines providing valuable assistance to national regulatory authorities, scientific organizations, and manufacturers to undertake assessment of documentation of submissions for assessment of herbal medicines, which were adopted by the 6th International Conference on Drug Regulatory Authorities (ICDRA) [26].

DSHEA passed in 1994, reduced the regulation of dietary supplements and broadened the category to include new ingredients, such as herbal and botanical products. Requirements for good manufacturing practice and accurate labelling are also included therein. Quality control of supplement manufacturing is trusted to supplement companies. This control includes precision with ingredient levels and labelling and avoidance of undeclared ingredients or contaminants [27].

The Food, Drug, and Cosmetic Act (FDCA) prohibit introducing adulterated products into interstate commerce. Manufacturers are subject to fines and/or imprisonment [17,28]. "The FDA is committed to protecting public health and stopping the illegal marketing of unapproved drugs,” said Kim Hartman [29], in Washington. The European Union legislation requires herbal products to be authorized for marketing if they are industrially produced and if their presentation or their function, or both, bring them inside its definition of a medicinal product where, The German Federal Health Agency Commission E formed in 1978 has produced standard monographs which contain pharmacological, toxicological, and clinical documentation for controlling herbal medicines to evaluate the safety and efficacy of 380 herbal medicines [25,30,31].

In India, regulatory affairs of herbal drugs are mainly controlled by Indian Drugs and Cosmetic Act 1940 which there under made provisions for labelling, manufacturing etc. and different sections for each category of drugs such as section 33E include misbranded drugs. Likewise, section 33 EE for adulterated drugs and section 33EEE for spurious drugs. Labelling provisions of herbal drugs under rule 161 must include the name of the formulation, true list of the ingredients used in the formulation together with the quantity of each ingredient and if the list is long, a separate list should be enclosed with the packing and reference be made on the label. Violation of the act by the manufacturer shall be liable to penalty under section 33J [32].

**Recommendations:**

Although, regulatory agencies throughout the world are well aware of the importance of the huge herbal market as well as malpractices prevailed into the market for earning fast bucks by the manufacturer. Several amendments have also been made to check these practices but it is observed that these regulations are not enough to control and therefore it is needed that these regulations should be made more stringent and comprehensive. A few recommendations are suggested which can be helpful.

- Special licensing should be required for the safer use of industrially produced herbal products since it offers opportunities before marketing to screen the declared constituents, demand proof of product quality, restrict the level of potentially hazardous constituents, and enforce warnings about correct and safe use.
- Data analysis using modern analytical methodologies should be strengthened to assess contaminants and to provide a range limit accepted generally according to guidelines for food substances.
- The label of a dietary supplement must include a statement of identity (product name) that identifies the product as a dietary supplement, nutrition information, a list of any ingredients not listed in the Supplement Facts panel, the name and address of the manufacturer, packer, or distributor, the net quantity of contents.
- Quality of herbal medicinal products assured the efficacy, should be assessed by randomised clinical trials (RCT) before licenses can be issued. Enforcement of appropriate regulations and rigorous practices imposing higher standards on dietary supplements may help to sort out problems on the control issues.
- Manufacturers must qualify their suppliers before receiving goods, incoming ingredients must be quarantined until their identity is confirmed using scientifically valid methods of analysis, and all components of dietary supplements must meet specifications established by the manufacturer regardless of where the ingredient was sourced.
- The state authorities should provide infrastructural facilities for establishing new units or expanding the existing ones alongwith technical support to improve the prospects in the domestic market as well as on the exports front.
- Awareness programmes or workshops on GMP or on QC or exhibitions should be organised at regular intervals by the government for the quality control and ayurvedic production techniques.
• The Government agencies should procure and standardize medicinal herbs and distribute them to the industrial units and more sample testing laboratories should be set up. Additionally, Government should insist the dealers of raw materials to sell only the certified and standardized herbs.

Conclusion:
Herbal preparations, often promoted as pure natural remedies as a viable alternative to pharmaceutical drugs, and equated with harmless is misleading[33]. Thus the public's belief that herbal and natural products are safer than synthetic medicines should only be ascertained by imposing strict regulatory standards on these products. Also, modern analytical techniques such as HPLC, GC-MS[24], LC-MS, LC-MS-MS should be widely employed and developed further to detect intentional adulterants in herbal remedies

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Corresponding Author: Monika Hooda,
M.Pharm(pharmacognosy), Dept of Pharmaceutical Sciences,
M.D.University, Rohtak, Haryana, India.

Contact no: +91-9467525527.

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