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SHORT COMMUNICATION

Pharmacovigilance on sexual enhancing herbal supplements

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Abstract The use of herbal medicines continues to expand rapidly across world and many people show positive interest to use herbal products for their health. The safety of herbal supplements has become a globally major concern in national and international health authorities due to increasing adverse events and adulterations.

It is difficult to analyze herbal products that cause adverse events due to lack of sufficient information and expertise. Inadequate regulatory measures, weak quality control system and uncontrolled distribution channels are some of reasons that enhance the informal pharmaceutical market. In recent years, the unfulfilled desire for sex has been a subject that has aroused increasing public interest with respect to improve sexual functions. The use of herbal medicines substantially increased due to escalated prevalence and impact of sexual problems worldwide and estimates predicting the incidence to raise over 320 million by year 2025. The various reasons to use herbal supplements in men may be due to experiencing changes in erectile dysfunction (ED) due to certain medical conditions such as diabetes and hypertension and bodily changes as a normal part of life and aging.

There is a lack of adequate evidence, no impetus to evaluate and absence of any regulatory obligations to undertake rigorous testing for safety and efficacy of herbal supplements before they sold over-the-counter (OTC). Pharmacovigilance on herbal supplements is still not well established. Sexual enhancing herbals are on demand in men health but informal adulteration is growing issue of concern. Recently, increase in use of herbal supplements for erectile dysfunction has laid a path for many illegal compositions. This paper explores facts and evidences that were observed in

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different countries attempting to demonstrate the importance of strengthening regulatory system to strengthen the application of pharmacovigilance principles on sexual enhancing supplements. We hereby explore the problem of sexual herbal supplements from pharmacovigilance perspectives.

We provide insights into the various concerns and call for collaboration to resolve the problem. We highly recommend to include herbal medicines in national pharmacovigilance systems and to establish comprehensive national pharmacovigilance program to raise the awareness about herbal medicines particularly those used in enhancing sexual desire.

1. Rapid communication

1.1. Background

Pharmacovigilance is defined as the study of the safety of marketed drugs under the practical conditions of clinical usage in large communities (Mann and Andrews, 2002). The use of herbal medicines continues to expand rapidly across the world and many people show positive interest to use herbal products for their health. The safety of herbal supplements has become a globally major concern in the national and international health authorities due to increasing adverse events and adulterations (World Health Organisation, 2004). It is difficult to analyse the herbal products that cause adverse events due to lack of sufficient information and expertise. Inadequate regulatory measures, weak quality control system and uncontrolled distribution channels are some of the reasons that enhance the market of herbal supplements (Shaw et al., 2012) (see Table 1).

1.2. The problem

In recent years, the unfulfilled desire for sex has been a subject that has aroused increased public interest with respect to improved sexual functions. The use of herbal medicines substantially increased due to escalated prevalence and impact of sexual problems worldwide and estimates predicting the incidence to raise over 320 million by the year 2025 (Aytac et al., 1999).

1.3. Insights of reasons and causes

The various reasons to use herbal supplements in men may be due to experiencing changes in erectile dysfunction (ED) due to certain medical conditions such as diabetes and hypertension and bodily changes as a normal part of life and aging (Potts et al., 2006). The other reasons may be attributed to unwilling to discuss such issues with doctors and disliking drug-mediated erections (Choi et al., 2012). Many herbal supplements are claimed to benefit men seeking to enhance erectile function and performance. These remedies often claim to be safe and effective yet often adulterated with some of the pharmaceutical ingredients and their analogues (e.g., sildenafil-Viagra®).

1.4. Implications of herbal sex remedies on consumers

This practice is illegal and places consumers at risk for potentially serious side effects from these drugs such as abnormal vision, headaches, myalgia, dizziness, flushing and dyspepsia (Clewell et al., 2010), and may lead to death. People using Phosphodiesterase type 5 (PDE-5) inhibitors mainly suffer from erectile dysfunction (ED).

The use of such remedies is associated with side effects and drug–drug interactions as these persons may have co-morbid conditions as diabetes and cardiovascular diseases and taking numerous medications and denoted by poly-pharmacy.

In order to avoid these adverse consequences some patients turn to natural products such as herbal supplements. (United States Food and Drug Administration, 2006a). The United States-US Food and Drug Administration (FDA) reports suggest that more than one-third of herbal dietary supplements marketed for sexual enhancement purchased on the internet and store shelves are affected (United States Food and Drug Administration, 2008). Many consumers perceive these products as completely safe because they often sold with labelling, suggesting that they are natural ingredients that have been approved by FDA for treating ED (Shamloul, 2010; Shah et al., 2012). Lack of adequate evidence, no evaluation, and absence of any regulatory obligations undertake rigorous testing for safety and efficacy of herbal supplements before they sold over-the-counter (OTC). There are also risks attendant upon self-medications and unmonitored use of these herbal products. Due to consumer huge demand and lack of strong pharmacovigilance these adulterated herbal products are widely marketed in the world.

A recent report from the Internet and Health Fraud Team survey claims one-third of the purchased "dietary supplements" asserts spur sexual enhancement containing sildenafil or vardenafil as active ingredient (Food and Drug Administration, 2012). Other example, Rock Hard for Men (with unknown manufacturer) marketed as natural supplement in Australia contains two potent PDE-5 inhibitors and a sulfonylurea, glyburide (Australian Government, 2012). One study in Singapore found that 77% of "natural" sex supplements collection from informal markets containing undeclared pharmaceuticals and more than half of them contains greater than therapeutic dosages of pharmaceutical adulterants (Low et al., 2009). This study also highlighted that 18% of sexual enhancement supplements adulterated with lidocaine, naproxen and chloramphenicol. Alarmingly, in a Netherlands study nearly 75% of sexual enhancing supplements contain experimental drugs (Venhuis and de Kaste, 2012).

Studies on some of the natural supplements such as Yohimbine, Ginseng and Maca to regain the sexual vigour are burdened with serious adverse effects. (American Urological Association, 2014; Shin et al., 2010; Jang et al., 2008). A systematic review by *Ernst and associates* on yohimbine recorded serious adverse effects but the incidence was low, similarly with red Ginseng (Ernst et al., 2006). Therefore, it is questionable whether the benefits of these herbal supplements outweigh its

Table 1 Causality categories: *The causality categories described by the Uppsala Monitoring Centre*.

1	*Certain*	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drugs (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary
2	*Probably/likely*	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition
3	*Possible*	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
4	*Unlikely*	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provides plausible explanations
5	*Conditional/unclassified*	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment, or the additional data are under examination
6	*Unassessable/unclassifiable*	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified
As a step towards harmonization in drug regulation in the countries of the European Union (EU), three causality categories were proposed by the EU pharmacovigilance working parties		
Category A		''Reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable''
Category B		''Reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain and may be even doubtful, e.g. because of missing data, insufficient evidence or the possibility of another explanation''
Category C		''Reports where causality is, for one or another reason, not assessable, e.g. because of missing or conflicting data''

risk. In particular, all these studies were supported by manufacturers and are vulnerable to a degree of possible bias. This may be one concern; therefore, the conclusions generated by them may be false-positive.

1.5. The pharmacovigilance program on herbal remedies

The current laws regulating sexual enhancing supplements assume that all supplements are safe until the dozens of deaths are reported due to adverse events. The identification of the new ingredients in these supplements is a complex and time consuming task, and regulatory authorities act only after the prolonged exposure of consumers to these tainted supplements. *Cohen and co-workers* described that clinicians should advise patients that there are only two types of products available: (1) those that might be safe but do not work and (2) those that might work but are not safe (Cohen and Venhuis, 2013). Therefore, patients should be counselled by their pharmacists to avoid these unsafe remedies before selling them. Global regulatory authorities should collaborate to create a global database of identified adulterated products with their analytical techniques to permit swift identification of illegal products. It should be kept in mind that a number of men are at risk of yielding to the temptation of using these supplements for improving their sexual functions.

Furthermore, regulatory authorities should apply a strong pharmacovigilance program to monitor herbal products. The campaign may take the form of advertising in media and implementation of standard operation procedures (SOPs). To assess an extensive array of toxicological evidence of herbal supplements pharmacovigilance safety programs should be adopted. Identifying the causes behind the public use of herbal medicines in enhancing sexual desire, may underline the strategies needed to implement global pharmacovigilance system.

2. Conclusions

There is a high concern about the use of sexual herbal remedies. The problem is of complex origin with safety and health impact on public. Pharmacovigilance regulation of the trading of sex herbal remedies is of paramount importance. The pharmacological bases of such remedies to boost libido need to be explored. The concerns are not about whether it works but to delve deeper how it works.

The safety profile of such remedies is of major concern. Studies and multifaceted research are needed and scientific evidence-based herbal remedies to support their utility are deemed to support the legal authorities establishing a pharmacovigilance surveillance programs to govern the marketing of sexual herbal remedies.

3. Recommendations

We highly recommend to include herbal medicines in active national pharmacovigilance systems surveillance programs and to establish comprehensive national pharmacovigilance program to raise the awareness about herbal medicines particularly those used in enhancing sexual desire.

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