1. Introduction

This article aims to report (1) the scientific aspects of system biology that governs the mechanism of xenobiotics-host interaction; (2) the beauty and the odds of xenobiotics in the biological system; (3) integrative risk-benefit assessment on using xenobiotics for medication purpose; (4) global trend of conceptual change in risk management from product-oriented pharmacovigilance to proactive pharmacovigilance planning for risk minimization; (5) summary of public information regarding to potential risk underlying co-medication of licensed drugs with complementary/alternative medicine (CAM), traditional Chinese medicine (TCM) and nutraceuticals; (6) epidemiological aspects in co-medication of licensed drugs with herbal medicine; and (7) opinion on system building for safe medication in societies where irrational medication and co-medication is prevalent.

2. System biology

2.1 The biological system

The biological system is full of mechanisms in manipulating the action and the destination of xenobiotics, i.e. drugs and food, in the body. Mechanisms governing the xenobiotic-host interaction include absorption, distribution, metabolism and excretion (ADME, Fig. 1). Typical examples associated with xenobiotic-host interaction are the change of drug efficacy due to the competition of drugs and food in intestinal absorption, the interference of drugs or food in the rate and the profile of metabolism, modification of drug distribution by food or other drugs, the change of renal clearance due to the competition of food and drugs for excretion transporters in the kidney, and the occurrence of drug resistance due to the modification of ADME process (Wishart, 2007).

2.2 Evidence-based medicine

The biological activity, i.e. the pharmacodynamic outcome, is used to be the major concern in conventional drug research and development. Pharmacokinetic (PK) evaluation, the descriptor of drug-host interaction, is usually conducted at the later stage of drug development. However, the disposition of the biological active substances in the body system determines the success of these substances to become therapeutic agents. As a consequence, the successful rate of bringing chemical entities from preclinical to clinical stage was rather low, estimated to be 1/2000 (Nassar-1, Nassar-2, 2004). The failure in most cases is due to the unsatisfactory PK after the chemical entities enter the biological system (Fig. 2) (Grossman, 2009).
Fig. 1. ADME determines the destination of xenobiotics in biological system.

Fig. 2. Integrative pharmacodynamic and pharmacokinetic outcome determines the therapeutic efficacy of drugs.

3. The beauty and odds of xenobiotics in the biological system

Biological processing of xenobiotics via ADME determines the feasibility of medicinal substances to become effective therapeutic agents (Eddershaw et al., 2000; Ekins et al., 2010; Lombardo & Waters, 2011; Ruiz-Garcia et al., 2008). Factors affecting the fate of xenobiotics may exist anywhere along the ADME process and may lead to a change of well designed and documented pharmacokinetic profiles of registered pharmaceuticals (Harris et al., 2003; Yang C. Y. et al., 2006). Risk and benefit assessment is thus not only on the medicinal substances per se, but also on factors affecting the biological processing of these substances.
3.1 The sites and the mechanisms of xenobiotic–host Interaction

Scientific evidences regarding to the sites and mechanisms of xenobiotic–host interaction are emerging. It is well documented that transporters in the intestine, liver, kidney and brain are involved in the uptake and the efflux of chemical substances like food and drugs (Brandsch et al., 2008; Oostendorp et al., 2009; Rubio-Aliaga & Daniel, 2008; Yang et al., 2006; Zhou, 2008). The pharmacological effect and the disposition of drugs are thus highly influenced by the function of transporters located in specific tissues (Ayrton & Morgan, 2008; Calcagno et al., 2007; Türk & Szakács, 2009; Yuan et al., 2008). Evidence also supported the consequence of the involvement of transport proteins in the pharmacokinetic variability and the safety of drugs in human use (Tsuji, 2006).

3.2 Drug-drug and drug-food interaction along biological processing of xenobiotics

Reports demonstrated that transporters in the intestine for absorption and in the kidney for excretion showed characteristics of broad substrate specificity, indicating the possibility of drug-drug and drug-food interactions. The pitfalls of transporter-mediated drug-drug, drug-food or drug-herbal interaction is thus an important issue to be elaborated for drug safety concern (Huang & Lesko, 2004; Pal & Mitra, 2006; Ward, 2008). Kidney, for example, is one of the important sites of drug-drug and drug-food interaction. The competition of renal transporter between drugs and food may change the bioavailability of drugs due to the change of renal clearance rate (Bachmakov et al, 2009; Kindla et al., 2009; Li et al., 2006; Tsuda et al., 2009; Wojcikowski, 2004). Thus a predictable ADME-toxicity modulation is important in the process along drug development (Szakács et al., 2008).

The metabolic system processing the biotransformation of xenobiotics provides another pitfalls for drug-drug and drug-food interaction (Tirona & Bailey, 2006). Reports indicated that hepatotoxicity (Brazier & Levine, 2003; Furbee et al., 2006; Holt & Ju, 2006; Schiano, 2003; Tang, 2007; Wang et al., 2006) and renal toxicity (Wojcikowski et al., 2004) of xenobiotics are associated with the formation of reactive metabolites no matter they are from synthetic or herbal resources (Venkatakrishnan & Obach, 2007; Zhou et al., 2007).

3.3 Risk-benefit assessment of pharmaceutical products

As potential risks in relation to the administration of xenobiotics are frequently reported, the biological activity is not the only criteria for the justification of medicinal substances for therapeutic use. The integrative judgment of medicinal substance-host interaction based on the quality, safety and efficacy is essential for risk-benefit assessment in drug approval. In order to increase the successful rate, strategy in new drug development is thus evolved from the conventional sequential involvement of chemistry, pharmacodynamics (PD), toxicity (tox) and pharmacokinetics (ADME/PK) (Fig. 3a) to parallel PD/PK assessment (Fig. 3b) for optimizing drug efficacy. Novel approaches are using biological ADME mechanism for new drug design at early stage of drug discovery (Fig. 3c) (Dingemanse & Appel-Dingemanse, 2007). Evidence-based justification of drug-drug and drug-food interaction also becomes a standard procedure for safety evaluation of new drug application by pharmaceutical regulatory bodies (Hartford et al., 2006; Zhang et al., 2008).

3.4 Pharmacovigilance

Genetic and culture differences such as food and nutritional intake are among the factors that influence the therapeutic outcome of drugs. Therefore, safety evaluation of marketed...
Fig. 3. The evolution of strategies in drug development from (a) sequential involvement of PD, ADME/PK to (b) PD and ADME/PK abreast and to (c) ADME for new drug design.

drugs should be based on good quality of evidence of the growing population that take the drug after a reasonably long period of time (Laupacis et al, 2002). In order to overcome the fragmentation of information, pharmacovigilance requires comprehensive risk-benefit assessment based on the accumulated data of the population using the individual pharmaceutical product (McFarlance, 2002).

4. Potential risk from co-medication

4.1 Polypharmacy
Polypharmacy is widespread in the general population, especially in the elderly. Besides registered medicine, the population of CAM users is growing, especially in the aged and in patients with chronic disease (Chung et al., 2009; Desai & Grossberg, 2003; Kennedy, 2005; McKenna & Killoury, 2010; Miller et al., 2008; Nowack et al., 2009; Ohama et al., 2006; Ramage-Morin, 2009). The most prevalent use of CAM are for treating cardiovascular disease, pain healing, cancer adjuvant therapy and obesity (Izzo, 2005). According to a questionnaire-based survey research on CAM use, 55% of the 356 patients registered in hospital emergency department have tried at least one CAM therapy within the past 12 months, 17% have tried CAM for their presenting medical problem (Li et al., 2004). A considerable large portion of patients take CAM with registered medicines without notification to professionals. Therefore, standard tools for regular monitoring of pharmacovigilance have its limitation. Safety threat as a result of drug-CAM interaction emerges from various scientific and pharmacoepidemiological reports (Anastasi et al., 2011; Balbino & Dias, 2010; Chiang et al., 2005; Cockayne et al., 2005; Sim & Levine, 2010; Smith et al., 2011; Tarrirai et al., 2010). As it is not evidence-based, risk from polypharmacy especially from co-medication of prescribed drugs with CAM is inevitable. A UK perspective report raised an increasing awareness of herbal use and the need to develop pharmacovigilance practice (Barnes, 2003).

4.2 Social aspects in relation to the risk of medication and polypharmacy
Polypharmacy implies a potential risk of pharmacovigilance in societies where co-medication is prevalent. Taiwan for example is known for its outstanding national health
insurance program which benefits 99% of the population. The welfare-like program rendered Taiwanese a potential overuse of the healthcare system, as indicated by the high physician’s visit per person and the large number of drug items per prescription (Table 1) (Department of Health, 2008; Gau, 2007; Huang, & Lai, 2006; Hsu et al., 2004). Moreover, most of the prescriptions are massively dispensed in hospitals, with a released rate of 0.41% (year 2008) to community pharmacies on refills for patients with chronic disease (Bureau of National Health Insurance, Department of Health, 2011). The imbalanced distribution of pharmacy service between hospitals, clinics and community pharmacies further reflects the lack of mechanism for risk prevention on medication (Table 2).

| Physician’s visits (no. of visits/person/year) | Taiwan | OECD countries |
|---------------------------------------------|--------|----------------|
| Drug items per prescription                | 4.2    | 1.9            |
| Drug expenditure to total national health insurance cost | 25% | ~15%           |

Table 1. Statistics of medication profile in Taiwan. Data of year 2008 are from National Health Insurance Database.

|                          | Number of prescriptions | Number of pharmacists | Prescriptions dispensed /pharmacist/day |
|--------------------------|-------------------------|-----------------------|----------------------------------------|
| Medical Center           | 31,172,000              | 725                   | 154                                    |
| Regional Hospital        | 34,368,000              | 880                   | 139                                    |
| Local hospital           | 35,137,000              | 770                   | 160                                    |
| Clinics                  | 217,052,000             | 8,404                 | 91                                     |
| Community Pharmacy       | 31,290,000              | 3,348                 | 33                                     |

Table 2. Distribution of prescriptions to pharmacy for dispensing in Taiwan. Data of year 2008 are from National Health Insurance Database.

4.3 Regulatory aspects in relation to the risk of polypharmacy
CAM are marketed without license in most of the developed countries. Claims for therapeutic efficacy of CAM are thus prohibited or limited to authorized indications (World Health Organization, 2001 & 2004; Ziker, 2005). However, traditional Chinese medicine (TCM) are classified as licensed drugs in oriental societies. For example, TCM are separately registered from conventional pharmaceutical products via bilateral regulatory systems in Taiwan. Drug adverse events are managed via bilateral reporting systems as well. With the requirement of good manufacturing practice (GMP), the number of license issued to conventional medicine decreased drastically. The number of TCM license, on the other hand, increased with a significantly high growth rate (Table 3). The separation of regulatory and administrative management on conventional medicine and TCM leads to the fragmentation of information regarding to polypharmacy. Patients and consumers are thus facing an unknown risk from irrational co-medication.
Table 3. Licenses issued for conventional pharmaceutical products and TCM in Taiwan.

| Year | Conventional pharmaceutical products | TCM products |
|------|---------------------------------------|--------------|
|      | Prescription | Over-the-counter | Prescription | Over-the-counter |
| 1995 | 14718        | 7152          | 2394        | 4663          |
| Total in 1995 | 21,870 | 7,075          |
| 2006 | 4235        | 1385          | 4663        | 6444          |
| Total in 2006 | 5,620 | 11,107        |

4.4 Pharmaco-epidemiological aspects in relation to the risk of polypharmacy

Herbal medicine includes TCM, CAM and nutraceuticals. With the prevalence of CAM use, inappropriate commercial advertisements in the media are also prevalent. According to a report of survey study in Taiwan, the identified illegal advertisement of products with therapeutic claims on cable TV counts for 12% of total healthcare related advertisements (183 out of 1591 cases), of which 41% goes to food and nutraceuticals and 15% goes to TCM (Fig. 4a). The illegal advertisement rate is even higher on radio, with TCM ranked the top (53%) followed by nutraceuticals (31%) (Fig. 4b). Most of the advertisements are claims for weight reduction and for the treatment of erectile dysfunction while are lack of evidence.

Fig. 4. Identified illegal advertisement of medicinal products in year 2004 on cable TV (a) and (b) radio in Taiwan (data are from Taiwan Drug Relief Foundation).

The incidence rate of end-stage renal disease (ESRD) of Taiwan ranked the top among the world (Fig. 5) (United States Renal Data System, 2006). The prevalence rate of ESRD in Taiwan raised from 1 per 2999 population in year 1991 to 1 per 498 population in 2006 (Fig. 6) (National Kidney Foundation, 2006). Reports indicated that herbal therapy was positively associated with chronic kidney disease (Bagnis et al., 2004; Chang et al., 2001; Chang et al., 2007; Guh et al., 2007; Nowack, 2008; Zhou et al., 2007). Safety issue in relation to polypharmacy becomes a challenge to the authority and the medical society.
5. Risk management of medication

5.1 Global trend on risk management of pharmaceutical products

Two conceptual aspects regarding to risk management on medication were introduced by International Conference on Harmonization (ICH) (Bahri & Tsintis, 2005; Moseley, 2004; Tsintis & La Mache, 2004). Pharmacovigilance Specification (PV) addressed the evidence-based justification of drug safety throughout the life cycle of individual pharmaceutical
product from preclinical development to post-market use. Pharmacovigilance Planning (PVP) emphasizes risk prevention and minimization of medication use (Callreus, T. 2006; Cappe et al., 2006).

5.2 From pharmacovigilance to pharmacovigilance planning
Following the conceptual initiation of PVP, the Council for International Organizations of Medical Sciences (CIOMS) and ICH developed and published Topic ICH E2E Guidance in 2005 as an action to implement PVP (International Conference on Harmonization, 2005). The guidance addresses the identification of all possible signals of risk regarding to drug use. Evidence-based approaches to risk assessment, such as genetic/racial and cultural factors (food and nutrition), are included. Pharmaco-epidemiological study becomes important for risk analysis (Fig. 7).

Fig. 7. The evolution of risk management of medication from product-oriented pharmacovigilance to risk management in pharmacovigilance planning.

5.3 System building for safe medication
The change from PV to PVP indicated the evolution from product-oriented risk management on individual medicine to a proactive risk prevention and minimization of medication. However, the risk management for pharmacovigilance initiated by ICH is essentially based on the refinement of safety-signal identification of registered pharmaceutical products. What is less addressed is the medicinal-type products without drug license. Risk prevention and minimization is thus difficult to be implemented in societies where patients tend to take conventional medicine and CAM without evidence-based justification in mind.

There is urgent need to call for public attention for the system building of safe medication. Risk and benefit assessment should be conducted on subjects who take all kinds of medicinal products via an un-biased integrative justification process. Humanity-based medication thus should be justified by the quality, safety and efficacy of medicines, no matter they are from synthetic, biological, biotechnological or herbal resources.
5.4 GDDP is essential for implementing pharmacovigilance planning
Following the guideline of Good Dispensing Practice (GDP), safe medication is fundamentally guaranteed for patients taking licensed pharmaceutical products. However, besides professional pharmacists, stakeholders involved in product and information delivery, namely product providers, medical professionals, the third party drug payers, media, patients and consumers, and policy makers in charge of food and drug administration, should also be responsible for the system building of safe medication. The concept of Good Dispensing and Delivery Practice (GDDP) is thus proposed. In this aspect, good practice in the delivery of medicinal products as well as medication information is equally important to good dispensing practice (Fig. 8). This is especially important in societies where the due process of safe medication is not properly implemented by the authority. For example, due to the lack of a due process in the separation of prescription from dispensing in Taiwan, irrational co-medication is common. A study on risk factor analysis of co-medication of cisapride and erythromycin identified that the major risk came from the mal-prescription of medical professionals (Gau et al., 2007).

Fig. 8. Good Dispensing and Delivery Practice is essential for the system building of safe medication.

6. Conclusion
Risk of medication not only comes from registered drugs but also from irrational use and co-use of all types of products claiming therapeutic effect. Evidence-based medication is thus important for the system building of safe medication. The use of medicinal products needs to be evolved from pharmacovigilance of individual products to humanity-based integrative risk-benefit assessment for risk minimization. Although challenging the culture in societies prevalent of irrational medication and co-medication is most likely unwelcome, mechanism for consumer protection on system building for risk minimization need to be continuously addressed, proactively designed and pragmatically implemented.

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