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Abstract

Background: *You Gu Wu Yun* (有故无殒), a Chinese ancient medicine application principle, has played an important role in Traditional Chinese Medicine (TCM) clinical practice so far.

Materials and Methods: It emphasized that disease, medicine and treatment method were interconnecting and the relationship among these three aspects should be handled reasonably. The major factors (including organism status, medicine source, medicine processing, compatibility of medicines, dose and course, dosage form) under the three aspects which have a more important and direct influence on the medicine clinical effect should be considered seriously in the TCM application.

Results: However, it was analyzed that most of side effects of TCM may be due to the incorrect application, which violated this principle to a certain degree. In order to help people to understand the safety and toxicity of TCM objectively and provide a rational guidance for the safe and effective application of TCM, we will introduce the concept of *You Gu Wu Yun* and discuss these factors having influence on medicine in this review. An example will be shown in order to clarify how these factors work in medicine.

Conclusions: As a unique medical system, TCM has its own theoretical basis and treatment principle. It stresses syndrome differentiation, namely personalized medicine. Therefore, it is critical to handle the relationship among disease, medicine and treatment for safe and effective medicine application.

Key words: *You Gu Wu Yun*; TCM application; Safety; Efficacy; Factors

Introduction

As an important part of Chinese medical system, Traditional Chinese Medicine (TCM) has been used for over 4000 years in China and is applied widely around the world as a kind of alternative/complementary medicine at present. In 2007, the U.S. Food and Medicine Administration (FDA) acknowledged TCM as belonging to the whole medical system, and it showed that TCM was accepted to a certain degree by FDA (Cong et al., 2007). Meanwhile, the increasing expenditure in TCM indicates the market of TCM is substantial (Nahin, 2010; China, 2013). Moreover, the rich resource makes TCM to be a promising reservoir for novel medicines development in the aspects like anti-cancer, anti-virus, anti-rheumatism and so on. However, the reports about the side effects of TCM make people doubt about its safety, which has impeded its application. But, after analysis, the factors affecting the safety of TCM may be due to the intrinsic toxicity, inappropriate utilization, substitution, incorrect preparations, overdose and so on (Koh et al., 2000).

Therefore, is it possible that the undesirable effects of TCM can be avoided as far as possible? What factors should be considered in the TCM application? Maybe we can find the answer in the past clinical practice of Chinese ancient TCM practitioners when utilizing medicines. As a result, we found that medicines shall be used to treat diseases under the thought of syndrome differentiation, a character of TCM theory. And

as a kind of specific application of syndrome differentiation, *You Gu Wu Yun*, documented in *The Yellow Emperor's Classic of Internal Medicine*, has been a medicine application principle for thousands of years. It stressed that the three aspects (disease, medicine, treatment method) had great influence on the clinical effects of TCM, and only by keeping the balance between the three aspects can medicine reveal its curative effects. Otherwise, it would cause deleterious effects. At present, Chinese TCM practitioners and researchers have reached a common view that factors that can affect TCM clinical effect include organism status, species, producing area, harvesting, storage, processing, compatibility of medicines, dose and course, dosage form, cooking and taking methods and so on. And the six factors as organism status, medicine source (containing species, producing area, harvesting, storage), processing, compatibility of medicines, dose and course, dosage form under the three aspects above have a more important and direct influence on the safety and efficacy of TCM.

In order to help people to comprehend the safety and toxicity of TCM more objectively and dialectically, and also provide reference for TCM safe and appropriate using in clinic. In this review, we will discuss the concept of *You Gu Wu Yun* and the six main factors which can impact on the safety and efficacy of TCM application under these three aspects: disease or the organism status, medicine (medicine source, medicine processing), treatment method (compatibility of medicines, dose and course, dosage form). Finally, an example will be shown so as to clarify how these factors work on the medicine.

Materials and Methods

The Concept of the *You Gu Wu Yun*

You Gu Wu Yun is an ancient medicine application principle recorded in *Su Wen* (part of *The Yellow Emperor's Classic of Internal Medicine*). In the original text, the issue that whether the poisonous medicine can be used to treat the pregnant was discussed and it concluded that this sort of medicines could be used to treat pregnancy diseases, but doctor must stop using medicine when the symptom started to remit to avoid patients suffering the medicine's side effect. Thus, the medicine would not be harmful to the pregnant women and the fetus would keep healthy. Generally, *You Gu Wu Yun* was proposed just as pregnancy medicine utilization principle at first, but its application scope was enlarged to all kinds of diseases treatment with the development of TCM. Nowadays, this principle could be understood as following: disease, medicine and treatment method are interconnecting and interactional, and every link can be closely related to the clinical effects of medicine (Fig. 1).

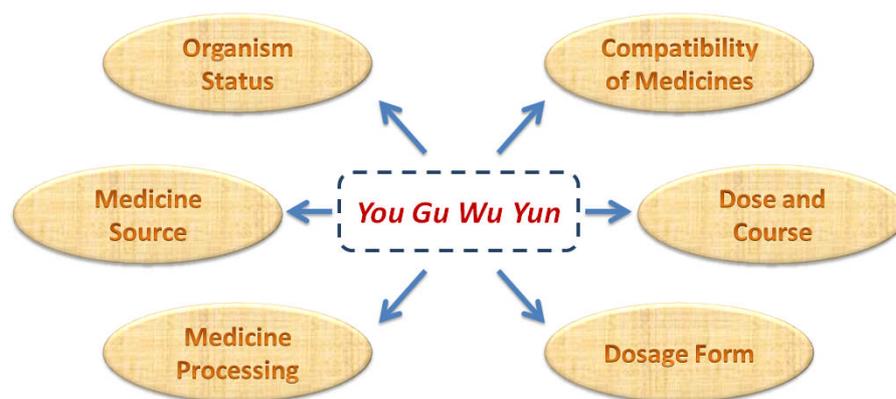


Figure 1: Factors that could have impact on the effect of medicine under *You Gu Wu Yun*

Firstly, disease or the organism status determines the effect of medicine. For example, *Aconiti Lateralis Radix Praeparata* (Fuzi), its cardiotoxicity has been identified, but it also could be used to treat cardiovascular diseases (Lin et al., 2007; Zhang et al., 2012). Secondly, the quality of medicine will directly influence its safety and efficacy, which requires that we should control the medicine source strictly and choose the medicine processed products reasonably. Thirdly, to achieve the goal of safe and effective remedy, the treatment methods (including compatibility of medicines, dose and course, dosage form) should be determined by the property of medicine and the clinical needs. Therefore, neglecting any point of these aspects would decrease the curative effects of medicine or even produce the side effects.

Discussion

The Considered Factors of TCM Application under *You Gu Wu Yun*

Organism Status

Organism is the receptor of the medicine pharmacological activity and the same medicine used in different status may reveal different effects, even the contrary effects. As a proof, the total extract of *Rhei radix et rhizoma* (Dahuang) showed hepatotoxicity and hepatoprotection respectively in normal rats and CCl₄-treated rats at different dose levels (Wang et al., 2011). Researchers studied the effect of *Curculiginis rhizome* (Xianmao) and the results suggested that Xianmao could activate PXR and induce CYP3A activity of L02 cells in deficiency-cold state, but with no effect in normal state (Xue et al., 2013). In the past, Chinese ancient TCM practitioners had realized the relationship between organism status and medicine effects, so some toxic medicines as *Pinelliae Rhizoma* (Banxia), *Rhei radix et rhizoma* (Dahuang), *Aconiti Lateralis Radix Praeparta* (Fuzi) had been used to treat corresponding diseases and reacted good curative effects (Table 1). These examples have proved the viewpoint from cell level, tissue level and clinical practice that the effects of medicine are related to the organism status.

You Gu Wu Yun reflects the thought of syndrome differentiation that the medicine application must be associated with the correct indications, which is the same as the Western medical idea personalized medicine that believes the best medical intervention can improve health to the right patient (Katsios et al., 2010). Hence, seizing organism status correctly is the first step for medicine reasonable utilization.

Medicine Source

TCM has rich resources which can be prepared from plants, animals and minerals; almost 12870 kinds of TCM resources were prescribed. Therefore, many medicines got from different sources may be used as the same one in the clinic, but the contents of the chemical compounds of medicines may change significantly with plant species (Ye et al., 2002). For instance, many species in *Salvia* genus were used as *Salviae miltiorrhizae radix et rhizoma* (Danshen) in different districts of China, but the content of tanshinones varied by different species and the content of tanshinones in *Salvia miltiorrhiza* Bge. was the highest (Li et al., 2008). Moreover, medicine derived from different sources could impact on TCM product. Zhi-Zhu-Wan (ZZW), a famous Chinese medical preparation used to treat functional dyspepsia, contains *Aurantii fructus immaturus* (Zhishi) which can be originated from *Citrus sinensis* Osbeck. Or *Citrus aurantium* L. The results of pharmacokinetics showed that hesperetin and naringenin were both detected in plasma in the case of ZZW containing *Citrus aurantium* L., while only hesperetin was found in plasma in the case of ZZW containing *Citrus sinensis* Osbeck, and the pharmacokinetic properties of hesperetin were different between the two cases of ZZW (Cao et al., 2010). Besides, medicine from different sources may show different effects. In the past, *Stephania tetrandra radix* (Fenfangji) and *Aristolochia fangchi radix* (Guangfangji) were both used as Fangji to dispell wind, relieve pain, clear damp. However, the report about the outbreak of terminal renal failure in Belgium caused people's attention to TCM toxicity, and the investigation result found that it was because of the Guangfangji from Aristolochiaceae which contains aristolochic acid replacing the Fenfangji from Menispermaceae in the weight-loss regimen (Vanherweghem, 1998).

Therefore, to further control the crude medicines quality, Good Agricultural Practice (GAP) has been established and extended gradually since 1998 in China. Medicines planted in GAP bases showed superiority compared with ordinary medicines in effective compound content, heavy metal content and pesticide residue.

Medicine Processing

Medicine processing is a unique character of TCM, and many medicines are used in clinic practice after being processed by appropriate methods (including dry stir-frying, stir-frying in liquid, soaking, steaming and so on) based on the TCM theories, medicine property and clinical requirement. The purposes of processing is enhancing curative effect, decreasing toxicity and enlarging application range. For instance, after steamed with wine, the oleanolic acid content in processed *Ligustri lucidi fructus* (Nvzhenzi) was higher than that in the crude medicine, and the hepatoprotection of processed product was stronger (Yusheng et al., 1993). *Genkwa flos* (Yuanhua) is a poisonous medicine which can cause

Table 1: Examples of preparations containing toxic medicines in pregnancy treatment

Prescription	Prescription source	Medicines and original plants	Preparation	Clinical application
Dachengqi Tang	Shang Han Lun (about AD 200, Monograph of Zhang Zhong Jing)	Dahuang (<i>Rhei radix et rhizoma</i>) from <i>Rheum palmatum</i> L., <i>Rheum tanguticum</i> Maxim. ex Balf. or <i>Rheum officinale</i> Baill. Houpu (<i>Magnoliae officinalis cortex</i>) from <i>Mabnolia officinalis</i> Rehd. et Wils. or <i>Magnolia officinalis</i> Rehd. et Wils. var. <i>biloba</i> Rehd. et Wils. Zhishi (<i>Aurantii fructus immaturus</i>) from <i>Citrus aurantium</i> L. or <i>Citrus sinensis</i> Osbeck. Mangxiao (<i>Natrii Sulfas</i>)	Decoction	Pregnancy constipation
Ganjiang Renshen Banxia Wan	Jin Gui Yao Lue (about AD 200, Monograph of Zhang Zhong Jing)	Ganjiang (<i>Zingiberis Rhizoma</i>) from <i>Zingiber officinale</i> Rosc. Renshen (<i>Ginseng radix et rhizoma</i>) from <i>Panax ginseng</i> C. A. Mey. Banxia (<i>Pinelliae Rhizoma</i>) from <i>Pinellia ternate</i> (Thunb.) Breit.	Pills	Pregnancy vomiting
Fuzi Tang	Jin Gui Yao Lue (about AD 200, Monograph of Zhang Zhong Jing)	Fuzi (<i>Aconiti Lateralis Radix Praeparata</i>) from <i>Aconitum carmichaelii</i> Debx. Fuling (<i>Poria</i>) from <i>Poria cocos</i> (Schw.) Wolf Renshen (<i>Ginseng radix et rhizoma</i>) from <i>Panax ginseng</i> C. A. Mey. Baizhu (<i>Atractylodis macrocephalae rhizoma</i>) from <i>Atractylodes macrocephala</i> Koidz. Baishao (<i>Paeoniae radix alba</i>) from <i>Paeonia lactiflora</i> Pall.	Decoction	Pregnancy yang deficiency

metabolic disturbances and hepatotoxicity (Geng et al., 2013) and yuanhuafine may be associated with its toxicity (Chen et al., 2013). Studies found that after processed with vinegar, the genkwanin content and toxicity of Yunahua both decreased, while its pharmacological action increased (Yuan et al., 1996; Zhao et al., 1998). Moreover, medicine will have a broader application area in clinic after processing by changing the property of medicine. For example, the nature of *Rehmanniae radix* (Dihuang) turned to be warm from cool after processed, then it could be used for nourishing yin and tonifying blood (Commission, 2010). The change of the variation of efficacy probably relates to the catalpol/iridoid glycosides de-compounding and glucose increase (Wang et al., 2009). Therefore, in order to ensure the quality of medicine processed products, State Food and Medicine Administration (SFDA) has launched the Good Manufacturing Practice (GMP) certification for Chinese medicine processed products enterprises since 2003 and the companies that do not have GMP from SFDA cannot manufacture the Chinese medicine processed products since the end of 2007.

Compatibility of Medicines

The curative effect of a single medicine may not be strong because of the complex pathogenesis and progression of diseases, and various side effects of a single medicine may also block its application (Keith et al., 2005). Therefore, in order to get better curative effects and fewer side effects, medicines often were utilized as multi-medicines prescription, and the compatibility meant the combination of two or more medicines according to the TCM theories, the properties of medicines and clinical needs. In consequence, over 100,000 prescriptions were used in the TCM history (Qiu, 2007).

On the one hand, one of the purposes of compatibility of medicines is enhancing the curative effect. For example, *Corydalis rhizome* (Yanhusuo) and *Angelicae dahuricae radix* (Baizhi) have been used together for promoting blood circulation, alleviating gastralgia, hypochondriac pain, headache and dysmenorrheal (Zhang et al., 2011). After combined with Baizhi, the content of dl-tetrahy-dropalmatine, the active ingredient of Yanhusuo corydalis alkaloids, which has significant analgesic effect (Yuan et al., 1995), in rats' plasma was higher when corydalis alkaloids of Yanhusuo was administrated with total coumarins and/or volatile oil of Baizhi (Liao et al., 2010). On the other hand, another purpose of compatibility of medicines is decreasing the medicine toxicity. For instance, *Tripterygium wilfordii* Hook F. (Leigongteng) is often used with *Glycyrrhizae radix et rhizoma* (Gancao) to avert its side effects and the mechanism of the decreasing toxicity effect of Gancao may relate to the immune modulation, anti-inflammatory and antidotal effects of glycyrrhizin (Zhang et al., 2007; Li et al., 2008).

Dose and Course

In the original text, *You Gu Wu Yun* had discussed the importance of dose and course, and pointed out that medicine may be harmful to the pregnant woman and fetus when dosage exceeded the rational range, which reflected the understanding of Chinese ancient TCM practitioners to the relationship between dosage and medicine safety.

On the one hand, dose is a critical factor to control medicine safety and efficacy, and the risk of side effect will be greatly decreased as long as one stays in the reasonable dose range. For instance, *Bufois venenum* (Chansu), used for heartfailure, pain and cancers treatment, was found to lead to breathlessness, cardiac arrhythmia, coma and seizure at high dose levels (Dasgupta et al., 2000). Based on clinical experience and its toxicity, the Pharmacopoeia of the People's Republic of China suggested that the safe dose range of Chansu is 0.015-0.03g (Commission, 2010). *Strychni semen* (Maqianzi) can be used for rheumatism, musculoskeletal injuries and limb paralysis remedy in clinic, but overdose could lead to strychnine poisoning as muscle spasms or convulsions (Chan, 2002). Hence, its suggested dose range in the Pharmacopoeia of the People's Republic of China is 0.3-0.6g (Commission, 2010). However, it does not mean that just these well known toxic medicines need be noticed. For example, *Ginseng radix et rhizome* (Renshen), a common tonic medicine used widely in the globe, could cause undesirable effects such as gastrointestinal upset, insomnia, vomit, diarrhea, anxiety, headache, hypertension, after abuse (Thompson et al., 2002; Seely et al., 2008). Therefore, we should be careful even while using some medicines which are generally considered as nontoxic. On the other hand, course is also the significant factor in clinical practice, and it was recorded in *The Yellow Emperor's Classic of Internal Medicine* that when using high toxic medicine, stop using them when the disease was 60% cured; when using toxic medicine, stop using them when the disease was 70% cured;

when using slight toxic medicine, stop using them when the disease was 80% cured; when using nontoxic medicine, stop using them when the disease was 90% cured.

Dosage Form

As the final clinical application modality, the form of preparation is of importance. In the past, medicines were made into many forms (including decoction, powder, pill, sublimed preparation, etc.) by Chinese TCM practitioners according to the treatment requirement and medicine property. For example, Chinese ancient doctors thought that Chinese traditional pills could be used for chronic disease because of their prolonged effects, and nowadays people took Liu-Wei-Di-Huang-Wan to treat kidney deficiency (Zhang, 2007). Moreover, because an inappropriate dosage form may result in a high probability of ineffective therapy (Seager, 1998), dosage form selection should be considered physically and chemically stable, manufacturable, and bioavailable (Singhal et al., 2004). For instance, berberine is a natural isoquinoline alkaloid derived from herbal medicine such as *Coptidis rhizome* (Huanglian), and it has been mainly used to treat diarrhea and gastroenteritis. But, the poor intestinal absorption is a barrier for the wide application of berberine. After designed with chitosan, the absorption of berberine was improved and the reason may be due to the ability of chitosan to enhance the berberine paracellular pathway in the intestinal tract (Chen et al., 2012). Furthermore, the development of novel medicine delivery system also provides a wider platform for TCM safe and effective application. The novel medicine delivery system such as liposome, nanoparticles, phytosome, emulsions, microspheres have showed great ability in improving bioavailability, prolonging medicine release and decreasing toxicity, etc.

An Application Example, Fuzi

Fuzi, a poisonous medicine came from the lateral roots of *Aconitum carmichaelii* Debx., was used for relieving pains, relieving cough and asthma, chronic stomatitis and pharyngitis in clinic (Wang, 1999). Furthermore, the curative effects in cardiovascular system, rheumatoid arthritis, hypercholesterolemia, portal hypertension (Lin et al., 2007; Huang et al., 2010; Zhao et al., 2012; Tong et al., 2013) have made Fuzi be concerned by researchers. However, the toxicity of Fuzi induced by aconitine alkaloids have been a serious problem for its application, and patients present predominantly with neurological, cardiovascular, gastrointestinal features (Chan, 2009). Nevertheless, in order to avoid its side effect, the rational application of Fuzi shall consider factors mentioned before based on *You Gu Wu Yun*.

Commonly, because of hot nature, Fuzi was suggested to treat cold syndrome but not hot syndrome. However, in clinical practice, there was a report about using Fuzi to treat hot syndrome and getting good efficacy (Xie, 1992). Meanwhile, Fuzi was regarded as a taboo medicine in pregnancy remedy because of its toxicity. However, Zhang Zhong Jing (a famous Chinese ancient doctor, AD 150-215) recorded using Fuzi Decoction to treat a pregnant woman with yang deficiency syndrome in his monograph *Jin Gui Yao Lue* (Zhang, 2005), which indicated that Fuzi utilization should be associated with organism status.

The source of Fuzi is also an important factor influencing its safety because of the alkaloids amount and type varying with the place of harvest and species (Chan et al., 1994). It was reported that in some districts of China, Fuzi which originated from Sichuan Province, was replaced by another which originated from Yunnan Province having greater toxicity, which caused Fuzi poisoning.

Fuzi was used combined with other medicines to decrease its toxicity usually. Studies found that after combined with Gancao, the content of aconite alkaloids decreased (Pei et al., 2009), and the mean residence time of three diester diterpenoid alkaloids of Fuzi (aconitine, mesaconitine, hypaconitine) in vivo were extended and their absorption doses were added (Zhang et al., 2013). In order to strengthen the hot nature of Fuzi, it often combined with *Zingiberis rhizome* (Ganjiang) and the effect in improving energy metabolism may be the molecular mechanism of dispelling cold and warming yang (Yu et al., 2012). Therefore, to take advantage of Fuzi better, these compatibilities of medicines have been applied in the pharmaceutical production and could be found in the TCM products (Table 2).

In practical application, Fuzi was required to be processed to decrease its toxicity and the processed products included Yanfuzi, Heishunpian, Baifupian (Commission, 2010). After been processed, aconitine and the total alkaloids contents can decrease to 90% and 65% respectively because of the hydrolysis of aconite alkaloids to less toxic aconine derivatives and benzyaconine (Sun, 1984). Researchers found

Table 2: The compatibility of Fuzi with other medicine in the Pharmacopoeia of the People's Republic of China

Prescription	Medicines and original plants (medicine 1 and medicine 2)	Proportion (medicine 1 and medicine 2)	Preparation	Clinical application	Quality control standards
Sini Tang	Fuzi (<i>Aconiti Lateralis Radix Praeparta</i>) from <i>Aconitum carmichaelii</i> Debx. Gancao (<i>Glycyrrhizae radix et rhizoma</i>) from <i>Glycyrrhiza uralensis</i> Fisch., <i>Glycyrrhiza inflata</i> Bat. or <i>Glycyrrhiza glabra</i> L.	1 : 1	Oral solution	Warming yang and expelling cold, etc.	Glycyrrhizic Acid \geq 0.5mg/ml
Fuzi Lizhong Wan	Fuzi (<i>Aconiti Lateralis Radix Praeparta</i>) from <i>Aconitum carmichaelii</i> Debx. Ganjiang (<i>Zingiberis Rhizoma</i>) from <i>Zingiber officinale</i> Rosc.	1 : 1	Pills	Abdominal pain, vomiting, diarrhea, hands and feet cold caused by yang deficiency, etc.	Liquiritin \geq 0.6mg/g in water-honeyed pills Liquiritin \geq 3mg/pill in big-honey pills
Zaizao Wan	Fuzi (<i>Aconiti Lateralis Radix Praeparta</i>) from <i>Aconitum carmichaelii</i> Debx. Dahuang (<i>Rhei radix et rhizoma</i>) from <i>Rheum palmatum</i> L., <i>Rheum tanguticum</i> Maxim. ex Balf. or <i>Rheum officinale</i> Baill.	1 : 2	Pills	Stroke, hemiplegia, limbs numb, pain, spasm, etc.	Aconitine limited

that crude Fuzi and its processed products have bioactivity difference with the toxicity varying. In the study of effect on splenic lymphocytes growth, crude Fuzi showed stronger inhibitory effect than Yanfuzi, while Baifupian showed stronger promotion effect than Danfupian (Liu et al., 2013). These results indicated that Fuzi processed products had lower toxicity than crude Fuzi, which explained the rationality of utilizing processed products in clinic.

Because of the narrow therapeutic index of aconite alkaloids (Tai et al., 1992), the dose of Fuzi should be controlled strictly. In a clinical research, 4 (24%) of 17 patients got ventricular tachycardia, the main death reason of aconitine poisoning, under a large dose (Lin et al., 2004). Due to the repeated reports of toxicity, the recommended dose range of Fuzi is 3-15g in the Pharmacopoeia of the People's Republic of China.

In addition, tincture preparations (a preparation of medicinal wine) could cause aconitine poisoning because of toxic alkaloids dissolving in alcohol efficiently, so patients should be discouraged from using this dosage form of Fuzi.

Conclusions

The safety issue is always the focus point of TCM application, and we should recognize that the effects of medicine in clinic will be influenced by many factors (organism status, medicine source, medicine processing, compatibility of medicines, dose and course, dosage form) and the curative effect and toxicity also should be understood correctly. As a unique medical system, TCM has its own theoretical basis and treatment principle. It stresses syndrome differentiation, namely personalized medicine. Therefore, it is critical to handle the relationship among disease, medicine and treatment for safe and effective medicine application. Firstly, grasping the essence of disease accurately based on the correct differentiation syndrome is the basis for rational medicine application. Secondly, overall understanding for medicine source, property and effect, and controlling the quality of medicine are the guarantee of the use of symptom-relatively and reliable medicine in clinic. Thirdly, selecting reasonable treatment method according to the property of medicine and clinical needs could make full use of medicine and avoid undesirable effect. For example, when using strong-effect medicine, the dosage should grow from small to big, and we should notice the development of disease during the period and adjust the therapeutic schedule appropriately. Only by doing what we have mentioned above can we achieve the delicate balance between the disease, medicine and treatment method.

At present, with the advanced development of technology, more and more new methods are introduced into the TCM research. The successful application of Genomics, proteomics, metabolomics provided more platforms for the TCM studies. Furthermore, some scholars proposed establishing bioactivity database, integrative database, pharmacovigilance to develop TCM mechanism research and evaluate the safety of TCM and its preparations (Wang et al., 2009; Cheng et al., 2010; Xue et al., 2013). However, there still are some issues that deserve our attention. Firstly, the lack of high-level Traditional and Complementary Medicine education may influence the safe and qualified practice of TCM. Therefore, to get a safe and effective remedy, doctors who use TCM should learn about relative knowledge and theory of TCM. Secondly, the shortage of research data was the most difficult thing faced by 105 member states of World Health Organization (WHO) in the regulatory issues, which means that we need more research data to evaluate the safety of TCM (Organization, 2013). Thirdly, under the TCM theories, the effect of medicine should be associated with corresponding syndrome, but the current efficacy evaluation of TCM mostly based on common animal models which may not be the one with corresponding syndrome. Thus, the results got from these studies whether it can illustrate the effect of medicine roundly deserved our thinking.

Furthermore, *You Gu Wu Yun* also has a significant meaning to toxicity and safety evaluation of TCM. As we know, the effects of medicine on different organism status may be different. Medicine may show remedial effect under the pathological state while it may show toxic effect under the normal state. For instance, we have discussed the hepatotoxicity and hepatoprotection of *Rhei radix et rhizoma* (Dahuang) before. But current toxicity and safety assessment of TCM mostly based on normal animal models but not ill ones. So we should carry on the comparison researches of TCM toxicity on different organism status to evaluate TCM more scientifically. Even so, as a promising medical resource, it is necessary to pay close attention to TCM research, though it may be a difficult work.

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