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Advance and Prospect of Nanoscale Chinese Medicine

Rina Wu

Department of Dermatology, No. 1 Affiliated Hospital of Inner Mongolia Medical College, Inner Mongolia010050, P. R. China

*Corresponding authors. Email: wurinawu506@hotmail.com

Abstract

Over the past few years, nanoscale Chinese medicine has emerged as a new exciting field in which theoretical and experimental studies of structure and function of nanoscale Chinese drugs have become a focus, and the importance of quality standardization of nanoscale medicament of Chinese traditional medicine as specific drugs to the fundamental development in traditional Chinese drugs has begun to be recognized. In particular, Chinese medicine dispersion, surface potentials, envelopment ratio, loading drug amounts, in vivo metabolism dynamics, bio-distribution, drug-releasing in vitro, etc., have become a new interdisciplinary frontier in life science and Chinese traditional medicine. There is an increasing need for a more systematic study of the basic issues involved in traditional Chinese medicine and a more active participation of researchers in the application area of nanoscale traditional Chinese drugs. Some advances have been and are being made in nanoscale Chinese herbs, mineral medicine including mongolia drugs such as cinnabar, with enormous prospect in clinical disease therapy. Here we review some of the main advances in this field over the past few years, explore the application prospects, and discuss the concepts, issues, approaches, and challenges, with the aim of stimulating a broader interest in developing nanoscale Chinese medicine.

Keywords: Chinese medicine; Nanotechnology; Toxicity; Metabolism; Therapy

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1. Introduction

Chinese medicine is the general name of traditional drugs in China, which comes from natural plants, animals and minerals, includes three kinds of formats such as Chinese herbs, drink-slips and nostrum [1]. It is well known that traditional Chinese medicines are composed of complicated compositions, which decides the pharmaceutical complexity of traditional Chinese medicines. How to realize the standardization of traditional Chinese medicine is a great technological challenge. Nanotechnology brings a new chance to solve current problems in development of traditional Chinese medicine [2,3]. The concept of nanoscale Chinese medicine was firstly proposed by prof. Bihui Xu in Huazhong Science and Technology university, and has become a new topic in recent years. Nanoscale traditional Chinese medicine is defined as the effective components with less than 100nm in diameter, effective locations, primary drugs and compound pharmaceutics that are fabricated by nanotechnology. When the traditional Chinese medicine components reach less than 100 nm in diameter, these components are easily separated by using chemical means, qualitatively analyzed by physical tools, and quantitatively analyzed by physical chemical methods, which is helpful to realize the technological standardization of traditional Chinese medicine [4,5].

Absorption, distribution, metabolism and elimination of drugs in life organism is one complicated course, drug effective function is not only dependent on chemical structure components, and also closely associated with drug pharmaceutic types and physical status. To change the physical stages of Chinese medicine pharmaceutics is also an effective pathway to develop new drugs. Nanotechnology can be used to change the physical status of Chinese medicine. When the drug particles reach nanoscale, nanoscale drugs exhibit some novel properties due to quantum effects and surface

effects, which will enhance the drug activity and biological availability as well as targeting, more important, which will be helpful to decrease the toxicity and side-effects of Chinese drugs, and realize the international standardization of Chinese medicine quality evaluation [6,7].

Although many fundamental problems remain unclear, great advances have been made in the development of traditional Chinese medicine with biological and nanoscale character. In the following we review some of the main progresses made over the past decade or so in the preparation of nanoscale Chinese medicine, evaluation of nanoscale Chinese medicine effects, drug delivery systems, explore the application prospects, and discuss the concepts, issues, approaches, and challenges, with the aim of stimulating a broader interest in developing nanoscale traditional Chinese medicine.

2. Advance of nanoscale traditional Chinese medicine

In recent years, nanoscale Chinese medicine has made some progress in these fields such as preparation of nanoscale Chinese medicine, evaluation of nanoscale Chinese medicine effects and drug delivery systems.

2.1 preparation of nanoscale Chinese medicine

Traditional Chinese medicine mainly includes plant drugs such as herbs, and mineral drugs such as cinnabar, etc. Herb drugs are often crushed into nanoscale pieces by ultrasonic devices, and disintegrator under low temperature, and then furtherly were isolated out effective components. Mineral drugs such as cinnabar, etc. often are fabricated into nanoscale drugs by using chaser mill and burst method [1,8]. However, during the period of preparing nanoscale Chinese medicines, how to keep the bioactivity of Chinese drugs is still a great challenge.

2.2 Evaluation of nanoscale Chinese medicine bio-effects

Biological effects of nanoscale Chinese medicine is evaluated from four levels such as molecular level, cell level, animal level and human body level. At first, nanoscale Chinese medicines are analyzed their components and structures. Their bioactive components were isolated and identified. Then, culture different cells and incubate with different dose of nanoscale Chinese medicines, observe a series of cell reactions with the aim of evaluating nanoscale Chinese medicine' cytotoxicity, biological function. Thirdly, establish animal models with different diseases, and feed nanoscale Chinese medicine and observe animal reactions, especially observe the effects of nanoscale Chinese medicine on nerve tissues, important organs such as heart, liver, spleen, lung and kidney, etc. After these evaluations fully show that prepared nanoscale Chinese medicines are no or low toxicity, then those Chinese medicines are used for clinical patients. Clinical patients' therapeutic effects will demonstrate the bioactivity of prepared Chinese medicines. In recent years, some studies fully show that nanoscale Chinese medicine can markedly enhance the bioavailability of Chinese medicine, therapeutic targeting, especially enhance the primary function, simultaneously increase the novel efficacy [9,10]. For example, Mengxiang Li, etc processed traditional Chinese medicine such as asparagus into nanoparticles, and measured the mouse mitochondrial SOD activity, and liver tissue GSH-PX activity, their results showed that nano-scale asparagus exhibits higher antioxidant bioactivity than those prepared by the ultrasonic extraction.

2.3 Pharmaceutical dosage forms of nanoscale Chinese drugs

The nanoscale Chinese medicines are different from traditional primary Chinese medicines, whose bioactivities and bioavailability may be markedly enhanced, therefore, nanoscale Chinese medicine dosages for disease therapy should be lower than that dosage of primary Chinese medicines used. Due to particle size down to nanoscale, vein injection pathway, oral pathway and skin stick pathway should own better efficacy, the concrete pathway should be selected according to patient needs [11,12].

2.4 Nanoscale Chinese medicines delivery system

Nanscale Chinese medicine particles are less than 100 nm in diameter. In recent years, some drug delivery systems are successfully fabricated. For example, solid lipid nanoparticle, liposome, nanostructured lipid carriers, and nanoemulsion, etc. have been successfully prepared, and exploringly used for nanoscale Chinese medicine delivery, and each delivery system has different advantages and shortcomings [13-17]. How to use fully their advantages is also a great challenge.

2.5 Standardization of quality of nanoscale Chinese medicine pharmaceutics

Quality standard of nanoscale Chinese medicines mainly are evaluated from the following nine aspects. No.1 step is morphology observation and particle size distribution. High resolution transmission electron microscopy and scanning electron microscopy are often used to observe the morphological changes of nanoscale Chinese medicines, MALVERN ZETAZIZER 2000 instrument often is used to measure the size distribution of Chinese medicine particles. Particles with more than 5 μm in diameter are often captured by lung capillary vessels, particles with less than 150 nm in diameter target marrow, too small nanoparticles can be swallowed by reticuloendothelial system, particles between 150nm and 200nm in diameter can target body circulation, particles with more than 250 nm in diame-

ter can target spleen, and bigger particles is easier cleaned by kidney. No.2 step is to measure zeta potential of nanoparticles, with the aim to predict the stability of nanoparticle system. No. 3 step is to measure envelopment ratio and the amount of drug loaded. No.4step to measure the in vitro release drug, no.5 step is to measure leakage ratio, No.6 step is to investigate in vivo drug metabolism dynamics, and bio-distribution. No.7 step is to do drug effect test, No.8 step is to measure leftover of organic solvent. No.9 is other specific evaluation for nanoscale Chinese medicine [18-24].

2.6 Advance of mineral Mongolia medicine Cinnabar

As a typical traditional old Chinese medicine, Cinnabar has been widely used in clinical therapy for almost 2000 years in China. Cinnabar can inhibit central neural system excitability and play the role of sedative and hypnotic effect in vivo, while can kill skin bacteria and parasites in vitro. The main composition of cinnabar is HgS, which accounts for almost 96%, the other components include also contain MgS, Bi, Fe, Si, Ba, Ca, Cu, Mn, Sb, As, etc. Due to cinnabar includes mercury element, therefore, cinnabar is considered as the toxic substance, and is suggested to carefully apply for clinical therapy. However, in Chinese Pharmacopoeia of 2000, there are more than 45 kinds of medicines contain cinnabar and take up of 10% in the whole components [1,25,26]. So far, how to remove the toxic compositions or decrease the toxic degree of Cinnabar is still a great challenge. Nanotechnology is used to treat Cinnabar, and bring a potential new chance to develop cinnabar, and it is possible that nanotechnology makes Chinese traditional medicine enter into foreign countries market.

2.6.1 Pharmacological properties of cinnabar

In Chinese Pharmacopoeia, the amount of cinnabar is defined that HgS should be more than 98% in final products. Recent research shows that cinnabar is absolutely toxic in vivo, because under those conditions of anaerobic, pH=7, T=37℃,and free sulfur, HgS can react with methyl materials and generate into methylational HgS, while Human Intestinal tissues has a similar environment, and absorbing cinnabar will increase the risk of poisoning. HgS in blood can conjunction with sulfur-group of hemoglobin by penetrating through the erythrocyte cell membrane, and then distribute into various body organs by mean of blood circulation, for example, kidney has the maximal concentration of Cinnabar, and followed by liver, heart, digestive system, brain and reproductive system. The animal experiments also show that absorption half-life period of cinnabar is 0.2 h, and the peak of HgS in blood is 11h, and half-life period of Hg in vivo is about from 65 to 75 days. Thus, it proves that cinnabar in human body is slow absorption and metabolism, and can accumulate in human body and produce the poisoning. When the amount of Hg in human body reach 100mg, human body will suffer from sensory difficulty, central nerve poisoning and Circulatory failure, and will be dead [27-31].

2.6.2 Toxicity of cinnabar

Regarding the toxicity of cinnabar, some studies show that the toxicity of cinnabar mainly comes from Hg's toxicity. After the patient eats cinnabar for a long time, gathered mercury in human body can cause the dysfunction of Liver and kidney, and finally result in patient's death [31,32].

Some reports show that cinnabar can inhibit central nerve system excitability to some extent. Those mice in the control group is not affected, but the mice in the test group injected with Amphetamine exhibits clear antagonistic function and play significant role in the promotion of hypnotic chloral hydrate and fight against the role of pentylenetetrazol induced convulsions, but do not exhibit the effects on the pentobarbital sleep time and strychnine convulsions. Cinnabar does not exhibit significant acute toxicity to mice. After the rats were feed with cinnabar for three weeks, the liver and kidney exhibit some pathological changes, but these lesions can be restored in two weeks after stopping feeding with cinnabar.

Some other reports show that, no matter where cinnabar is originated from, what kinds of processing methods, cinnabar include still some insoluble and free mercury, which is over 300 times more than the standards of our drinking water. In fact, any Chinese medicine containing cinnabar exist insoluble mercury. After mice were feed with cinnabar for the first day, the amount of mercury in the organs and blood was significantly higher than that in the control group. The cinnabar may decrease fertility of mice, and may affect the offspring through the placenta barrier. Free mercury in cinnabar can accumulate in various organs in vivo. After taking 3 months, mercury in kidney is 644 times higher than that in the control group, and cause kidney pathological changes and abnormal blood biochemical parameters, and also has a similar pharmacological effect in the nervous system [33-35].

2.6.3 Possible mechanism of poisoning of patients treated with cinnabar

Regarding the function mechanism of cinnabar, we consider that the composites of HgS may take main effects in the course of patient therapy. However, for clinical patients, obvious toxic reactions often happen. The possible causes are as follows:

(1) Inappropriate processing methods

Most of the vermilion powders in current clinical application are impure, and even their colors are black,

which may be related to inappropriate processing. Up to date, the methods of processing cinnabar mainly include mechanical method, such as ball mill grinding, which often make free of mercury out of the composites, and produce black cinnabar powder. If patients take this cinnabar, obviously lead to mercury poisoning. Traditional method and the Chinese Pharmacopoeia 2005 version point out that when cinnabar is processed, it was required firstly to draw iron magnet, and then is constantly ground using water flying method, until obtain genuine cinnabar of red powder. Some scholars have analyzed five different kinds of processing methods, such as the water flying method, wet grinding, jet milling, grinding water mill three times and then smashing three second-class floating in boiling water, and results showed that after water flying processing, free mercury and soluble mercury salt has the lowest content. Therefore, the clinical application should choose those with a bright vermilion and better shape and pure particles, and follows the standard of water flying method in Chinese Pharmacopoeia [36-41].

(2) Overdose

Cinnabar can soothe the nerves, thus, can be used to treat epilepsy, spiritual trance, and so on. Clinically, patients with epilepsy and other mental illness, often take high-dose of cinnabar, resulting in frequent cases of poisoning. Hence, it is clear that in the Chinese Pharmacopoeia of 2005 version, cinnabar content should be in the range of 0.1-0.5g in the drug containing cinnabar, and patients generally do not take it at dose over 0.5g/d.

(3) A long-term taking

Patients suffering from intractable insomnia would like take long-term drugs including cinnabar such as Anshen Wan, Tian Wang Bu Xin Dan, Baiziyangxin, which may result in chronic renal failure. Some scholars calculated the amount of human mercury poisoning, no matter what kind of proprietary Chinese medicines containing cinnabar, as long as the continuous take, it is possible to reach toxic levels. As for human body, the residual volume amounted to 100mg of mercury can occur toxic reactions. In accordance with the human body metabolic rate of the mercury, if patient's daily absorption of mercury is 10 mg, residual volume can amount to 100mg in vivo in 10.5 days. Therefore, for general patients, the time of continuous oral cinnabar cannot be more than seven days.

(4) Improper methods of preparation and taking

Decoction of Chinese medicine is used for therapy of insomnia, some coating cinnabar is used to enhance the sedative effect, such as Zhu Fuling, Zhu fushen, zhu Yuan-zhi and so on. The Chinese medicine coated with cinnabar regularly cook with other herbal decoction together, resulting in mercury poisoning. Therefore, the application of cinnabar and medicine coated with cinnabar should be taken together with prepared medical solution or warm water, never cook together with other drugs. Meanwhile, the cinnabar should avoid to be put together with the drugs containing Al element like alum, also can not be placed in aluminum carmine grinding device, or stored in the aluminum containers. Due to chemical reaction with the aluminum, Cinnabar occurs to produce aluminum gray amalgam, leading to poisoning [42-45].

(5) Improper compatibility

Chinese medicines containing cinnabar cannot be used together with iodide and bromide, because in the intestinal tract, those will generate mercury iodide or mercury bromide, and greatly enhance toxicity, and may result in drug-induced enteritis. Most of patients with neurasthenia and insomnia have the opportunity to mix these drugs together. Therefore, patients taking a sedative medicine with cinnabar should not take any western medicine containing bromide mixture.

(6) Physical factors

Children or patients with liver and kidney dysfunction are more vulnerable to mercury poisoning. Therefore, those patients with liver and kidney dysfunction should be forbidden to take drugs with cinnabar. Considering the delicate organs of children, doctors should minimize the dosage and frequency of cinnabar medication for the pediatric patients to prevent damaging organs of children.

2.6.4 Development of nanoscale cinnabar

Some studies showed that cinnabar owns toxicity, its toxicity mainly comes from free mercury, how to get rid of mercy element is also a challengeable problem. However, as nanotechnology develops, HgS drugs can be synthesized by chemical method, and biomoleucles such as BSA, etc. can be used as the assistant reagent to improve the synthesis of different size of HgS composites, those synthesized HgS composites may own better biocompatibility than traditional Chinese medicine cinnabar, their therapeutic effects' studies are underway. In near future, synthesized cinnabar based on the nanotechnology of bottom up is likely to be more suitable for clinical patients.

2.7 Potential application of nanotechnology in development of Chinese medicine

Nanotechnology is a multidisciplinary integrated discipline, meaning not only that micro-nano spatial scale, while, more importantly, a new way of thinking. In recent years, nanotechnology has been applied in the pharmaceutical field, greatly promoted the development of modernization for traditional Chinese medicine [46-52].

Nanotechnology is used in the original drug and its compound preparation of Chinese medicine by manufacturing particle size less than 100nm. Nano-Chinese traditional medicine can not only enhance drug bioavailability, reduce side effects of Chinese medicine to enhance clinical efficacy, but also more convenient and more economical. Chinese medicine cannot easily be absorbed by the human body, after it is treated as nanoscale powder or suspension stage, it can be very easily absorbed by human body, for example, cream composed of nano-medicine can be directly absorbed by the skin, avoid to be injected into human body.

The main advantages of nanotechnology applied in Chinese medicine are as follows: enhanced targeting and improving the medicine's efficacy, as well reducing their toxicity. Nano-medicine may achieve the controlled release effects, also change the route of administration. Through the Nanotechnology, those traditional Chinese medicine is only injected drugs can directly take without changing the preparation of transformation and efficacy of oral administration can greatly simplify the route of administration, making Chinese herbal medicine have more extensive and effective in the clinical application. As reported, with insulin nanocapsules can significantly lower blood sugar levels for 20 days, and in the same experimental conditions, oral administration of free insulin did not affect blood sugar levels.

Nanotechnology can increase the solubility and dissolution rate of Chinese medicine. Drug absorption often dominated by the degree of dissolution in the body. How to improve the solubility and dissolution rate of traditional Chinese medicine for the clinical application of Chinese medicine is extremely important problem. Some are not only insoluble in water, or even insoluble in organic solvents. According to pharmacology, the drug release rate of drug is proportional to the ratio of surface area and inversely proportional to particle size. Therefore, the smaller the particles size of drugs, the more volume the dissolution of drug. Increasing effective components of drug solubility in the gastrointestinal tract can increase significantly the bioavailability of drugs and reduce the action time of drugs, improving finally situation that most insoluble drugs is limited improvement in clinical application in the past.

Nanotechnology can change surface polarity for nano-particle of Chinese medicine. Surface modification of nano-particles can change the hydrophilic or lipophilic phase of Chinese Traditional Medicine, which aims to increase the traditional Chinese medicine's bioavailability and targeting specific treatment by processing different drug particles of different levels solubility and dissolvability.

Nanotechnology can reduce individuals' differences on the drug. The important indicator of nanotechnology applications in drug processing is to reduce individual differences in medicines. Current clinical application of Chinese medicine processing has certain basic individual differences, and almost none of the clinical effectiveness of Chinese medicine is100%. Application of nanotechnology in medicine for forming nano-particles after surface modification or reduce the absorption of individual differences can increase drug effective.

Nanotechnology can promote the standardization and internationality of Chinese traditional medicine. Chinese traditional medicine, because of complex components, complicated process and poor quality control standards, is difficult to enter into international markets. The nanotechnology applications in medicine in preparation for the traditional Chinese medicine can provide new technologies, new processes, which will improve standardization of processing and preparation, and help to meet international standards for traditional Chinese medicine entering into the world pharmaceutical market.

3. Some Major Challenges in nanoscale Chinese medicine

Although traditional Chinese medicine have been used to treat patients for several thousands of years, under current modern medicine, traditional Chinese medicine is facing great novel challenges [51-53].

The first challenge is that, how to quantitatively evaluate the actual therapeutic effects of Chinese medicine. So far the therapeutic effects of Chinese medicine is debated because Chinese medicine's therapeutic effects is identified according to doctor's experience.

The second challenge is that, how to clarify the concrete metabolism course of Chinese medicines in human body? Traditional method is to raise mice with Chinese medicine, and then kill mice, and measure the distribution and concentration in different organs. Because of the complex of Chinese medicine, it is very difficult to obtain the creditable data to demonstrate the concrete metabolism course of Chinese drugs. As the molecular imaging technologies develop fast, in vivo tracking technology become more and more mature, which provides the new chance to track the Chinese drugs in human body. Fully using molecular imaging technology, may solve the metabolism problem of Chinese medicines in human body.

The third challenge is that, how to abolish or reduce the toxicity of Chinese medicine. Up to date, due to technical limitations, it is very difficult to overcome cinnabar poisoning. Nanotechnology brings new chance to solve this problem. Because of nanoscale effects, Chinese medicine such as cinnabar are fabricated into nanoscale, cinnabar's some toxic effects may disappear, or reduce the toxic effects, which is underway of investigation.

The fourth challenge is that, Chinese medicine's structure and function, and their interaction are still not studied well, structural (static and dynamic) analysis

and constitutive modeling of Chinese medicine and the interactions among them is another great challenge.

To date, we still lack good experimental and theoretical methods to investigate, especially quantitatively, many problems in Chinese medicine, including their structural and biological properties. For example, it is still a challenge to fully quantify the dynamic components and changes of Chinese medicine under human physiological condition [53-57].

4. Technological Prospects of nanoscale Chinese medicine

Nowadays, nano-medicine focus on improving the preparation and the traditional dosage forms. As we known, Traditional Chinese medicine formulations have pill, powder, paste, pellet, decoction, and so on, particles large, complex components, unstable, low quantitative criteria, usually not a single active ingredient content, is not conducive to active ingredients absorption. Nanotechnology, especially ultra-fine grinding technology, could increase the dissolution of oral agents in the body's absorption level, and also increase the dispersion of the drug. Obviously, it is a rich technology to improve effectiveness of Chinese medicines. Chinese Herbal Medicine study all focused on its qualitative and quantitative, pharmacodynamics, and targeting problems, but traditional Chinese medicine, especially Chinese medicine compound has its particularity and complexity, to make the reach of patternize and standardization is really difficult. Only with the help of nanotechnology, it will be controlled at 100nm, even 10nm, particles for traditional Chinese medicine, and then separate based on differently properties on temperature, dissolvability, centrifugation, and other physical and chemical means.

The nascent field of nanoscale Chinese medicine presents an exciting vision of the future. The ultimate goal of this field is engineering and construction of functional Chinese medicine at the nanoscale. Exploring nanoscale Chinese medicine may lead to understanding of fundamental laws and principles in biochemistry, biophysics, absorption, distribution, metabolism, biological effects. This new knowledge will enable the design and fabrication of a vast variety of nanoscale Chinese medicine for clinical applications. Top down and Bottom up technologies provide new chance to study and develop Chinese medicine, using nanotechnology to treat Chinese medicine enable enhanced biological availability of Chinese medicine, molecular imprinting, self-assembly, controllable synthesis for fabricating nanoscale Chinese medicine are important techniques and may play critical roles in fabricating functional nanoscale Chinese medicine [58-63].

5. Conclusion remark

Nanotechnology has provided new opportunities for industry, agriculture, national defense development. Many new nanomaterials such as nanotubes, quantum dots, nanowires, nano-devices have been manufactured; their properties and potential applications are already being explored. Once drug processing based on nanoparticle and nano-based medicines technology, there will be different consequences from the traditional methods, for example, toxic substances can disappeared during nano processing, while drugs without toxic have contrary results. Characteristics of nanoparticles cannot be explained by traditional theories [64,65].

Size effect of nanotechnology has proved that when process drugs into nano scale, those will bring a series of features. The use of nanotechnology for traditional Chinese medicine development, take the medicine through the nano-processing, allowing the patient to have a great absorption of drugs, especially for mineral medicine. for instance, Hui-Bi Xu has been studied inorganic arsenic realgar (mainly containing As_2O_3) on the proliferation of the size effect of different particle size such as 100nm, 150nm, 200nm, 500nm, and those nano-particles' effects on human umbilical vein endothelial cell line ECV-304 cell survival and apoptosis. The results show that the relative apoptosis rate was 68.15%, 49.62%, 7.51%, 5.21%, and nanoparticles increased the level of inhibition of mouse sarcoma S180. Besides, abalone is a another kind of mineral medicine, composed of inorganic compounds, observed abalone's different size, including nano, micro, normal, for the effectiveness of serum trace elements, you can see the abalone in the phase of nano a very significant difference . Continuation of traditional Chinese medicine processing methods is thousands of years, through new technologies, and it can be improved to high bioavailability, lower toxicity, significant savings limited resources in traditional Chinese medicine [66]. We believe that nanotechnology will bring traditional Chinese medicine into a novel world, speeding up development of Chinese medicine, and entering into international market.

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