The Integration of Nanomedicine with Traditional Chinese Medicine: Drug Delivery of Natural Products and Other Opportunities

Journal:	*Molecular Pharmaceutics*
Manuscript ID	mp-2022-00882x.R2
Manuscript Type:	Review
Date Submitted by the Author:	n/a
Complete List of Authors:	Zeng, Muling; Wuyi University Guo, Dongdong; Wuyi University, School of Biotechnology and Health Sciences Fernández-Varo, Guillermo ; Hospital Clinic de Barcelona, Service of Biochemistry and Molecular Genetics; CIBEREHD Zhang, Xu; Wuyi University, School of Biotechnology and Health Sciences Fu, Siqi; Second Xiangya Hospital Department of Dermatology Ju, Shijie; Wuyi University, School of Biotechnology and Health Sciences Yang, Huiling; Wuyi University, School of Biotechnology and Health Sciences Liu, Xingfei; Wuyi University, School of Biotechnology and Health Sciences Wang, Yachao; Shenzhen University First Affiliated Hospital, Neurology Zeng, Yu; Xiangya Hospital Central South University, Department of Neurosurgery; Changsha Medical University, First Clinical Department Casals, Gregori; Hospital Clinic de Barcelona, Biochemistry and Molecular Genetics Casals, Eudald; Wuyi University, School of Biotechnology and Health Sciences

The Integration of Nanomedicine with Traditional Chinese Medicine: Drug Delivery of Natural Products and Other Opportunities

Muling Zeng[1], Dongdong Guo[1], Guillermo Fernández-Varo[2,3], Xu Zhang[1], Siqi Fu[4]， Shijie Ju[1], Huiling Yang[1], Xingfei Liu[1], Ya-Chao Wang[5], Yu Zeng[6,7,], Gregori Casals[2,*] and Eudald Casals[1,*]*

[1] School of Biotechnology and Health Sciences, Wuyi University, Jiangmen, 529020, China

[2] Service of Biochemistry and Molecular Genetics, Hospital Clinic Universitari, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Carrer de Villarroel, 170, 08036 Barcelona, Spain

[3] Departament of Biomedicine, University of Barcelona, Barcelona, Spain

[4] Department of Dermatology, Second Xiangya Hospital Central South University, Changsha, 410011, China

[5] The Institute of Translational Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen 518035, China

[6] Department of Neurosurgery, Xiangya Hospital Central South University, Changsha, 410008, China

[7] First Clinical Department of Changsha Medical University, Changsha, 410219, China

***Corresponding authors e-mail:**

Yu Zeng: zengyu@csu.edu.cn

Gregori Casals: casals@clinic.cat

Eudald Casals: eudaldcm@gmail.com

KEYWORDS: Traditional Chinese Medicine; Nanomedicine; Natural Products; Combination Therapy; Regulation; Safety; Drug Delivery.

ABSTRACT

The integration of progressive technologies such as nanomedicine with the use of natural products from Traditional Medicine (TM) provides a unique opportunity for the longed-for harmonization between traditional and modern medicine. Although several actions have been initiated decades ago, a disparity of reasons including some misunderstandings between each other are limiting the possibilities of a truly complementation. Herein, we analyze some common challenges between nanomedicine and Traditional Chinese Medicine (TCM). These challenges, if solved in a consensual way, can give a boost to such harmonization. Nanomedicine is a recently born technology while TCM is serving Chinese people since thousands of years ago. However, for these disciplines, the regulation and standardization of many of the protocols, especially related to the toxicity and safety, regulatory aspects, and manufacturing procedures are under discussion. Besides, both TCM and nanomedicine still need to achieve a wider social acceptance. Herein, we first briefly discuss the strengths and weaknesses of TCM. This analysis serves to focus afterward on the aspects where TCM and nanomedicine can mutually help to bridge the existing gaps between TCM and western modern medicine. As discussed, many of these challenges can be applied to TM in general. Finally, recent successful cases in the scientific literature that merge TCM and nanomedicine are reviewed as examples of the benefits of this harmonization.

1. INTRODUCTION

Traditional Medicine (TM) is an ancient knowledge that may contribute to solve many of the health problems that medicine is facing today.[1] Most of these problems are derived from the blossom of industrial and technological developments that have emerged as a result of the industrial revolution initiated three centuries ago. Despite the great benefits these developments have brought, in most cases they have progressively distanced us from nature. As a consequence, Earth is experiencing increasing levels of water, soil, and air pollution. In addition, humankind is being confronted with a climate emergency that may adversely affect health in known and unknown ways.[2-4] Besides, owing to those developments, human lifespan is increasing to the highest levels ever seen; however, this comes with an increase of chronic and degenerative diseases such as Parkinson's, Alzheimer and other types of degeneration, among others.[5] The economic and social development, which sometimes seems to neglect the laws of nature, also entails other detrimental health-related consequences such as the increase of the rates of cancer and the subsequent onset of resistance to cancer treatments,[6-9] the resistance to antibiotics,[10-12] and the appearance of new pandemics, e.g. Ebola, SARS, MERS, H1N1, and COVID19, which during the last twenty years have demonstrated how fast infections can spread across the planet.[13,14] All in all, sustainable medical approaches are increasingly needed to redress those excesses of the past, along with promoting a harmonious way of living more congenial with the pace of nature.

In this respect, TM describe human beings as a microcosm within the entire universe, which is interconnected with the nature and subjected to its principles. Based on this, TM brings nature and its elements to the forefront and aims to take advantage of the possibilities of natural products to become remedies for diseases. TM refers to the sum of health practices, approaches, knowledge, skills, and beliefs indigenous to different cultures -and that may incorporate plant,

animal, and mineral-based medicines- used to treat, diagnose, and prevent physical and mental illness and to maintain well-being. The different TMs include traditional European medicine, traditional Chinese medicine (TCM), traditional Korean medicine, traditional African medicine, Ayurveda, Siddha medicine, Unani, ancient Iranian medicine, traditional Iranian medicine, medieval Islamic medicine, Muti, and Ifá. In some countries TM has been integrated into national health systems. However, other countries where TM has not been incorporated into the national health care system. In such cases, it is often referred as "complementary" or "alternative" medicine.[15]

TCM is one of the most known and practiced TM. Briefly, it is based on the understanding of the *qi*, a circulating life force that exists everywhere with unlimited potential. In medicine, the *qi* can be understood as the vital fluid and energy that flow along the *jingluo* (meridians, i.e. a sort of channels) throughout our bodies. A healthy body keeps a balanced *qi* by maintaining the balance of the *yin* and *yang*, the opposite qualities or manifestations of the *qi*. This recalls, for instance, how modern medicine is pointing out that the immune system (present throughout the body) works by maintaining a dynamic balance of pro-inflammatory and anti-inflammatory signals and cells, i.e., between oxidant and antioxidant systems and between M1 and M2 macrophage polarization.[16-18] Similarly, more than 2000 years ago TCM already deduced the intimate connection between the lungs and the guts, described in the Yellow Emperor’s Classic of Medicine treatise. Recently, modern medical knowledge is beginning to point the key role of the gut microbiota in whole-body health,[19] which can even affect the activity of distant organs, such as the brain's physiological, behavioral, and cognitive functions through alterations in the immune system.[20-21]

Nowadays, most of the modern healthcare systems in the world rely on western medicine. This is evidence based and can be understood as the system in which medical professionals, such as doctors, nurses, pharmacists, and therapists, treat diseases using medical treatments, such as drugs, radiation, and/or surgery. Furthermore, in the past century, the growth of the largest pharmaceutical companies has focused primarily on western medicine, which rely on the search for a specific cause to explain a disease state to search for a drug -the "magic bullet"- that target specifically such cause of the disease. Randomized and controlled clinical trials are then conducted to provide the evidence that the drug is effective, and eventually, the drug is released to the market. However, nowadays it is being clearer that the understanding of human physiology cannot be reduced to a single -often too simplistic- explanation. Hence, both western and pharmaceutical industries are realizing the potential of high throughput analyses of whole-body functions and turning their interests towards combinatorial therapies with different active ingredients and their combination with natural products to address multiple-cause diseases.[22-23] In this scenario, the holistic approach of TCM, and TM in general, to health and disease, with thousands of years of empirical observation and practices, has much to offer for today's health emergencies. This, and many other examples, evidence the need and the benefits of the convergence between traditional and modern medical systems.

In fact, many voices are arising towards a harmonization and complementation of TM and western medicine to reinforce the best potentialities of each one and compensate for their weaknesses.[24] As an example, in 2014-2015, the Science journal commissioned, edited, and published three issues devoted to TM, "The Art and Science of Traditional Medicine", being the first issue specifically focused on TCM.[25-27] In parallel, after the efforts started at the turn of the millennium,[28-30] the World Health Organization (WHO) launched in 2014 the WHO Traditional Medicine Strategy (2014-2023)[31] to disseminate the general situation of the global

use of TM. In 2018 the WHO included it for the first time in its influential global medical compendium, the International Statistical Classification of Diseases and Related Health Problems (ICD11), where 3,106 terms from traditional medicines and their English translations were adopted.[32]

Despite these efforts of convergence, there are still several aspects that need to be addressed to achieve this harmonization. For instance, key challenges identified for TCM modernization typically include safety issues, standardization and regulatory aspects. Besides, social perception is another drawback. For instance, a recent News Feature published in Nature suggested that many western-trained physicians and biomedical scientists perceive the practices of TCM as unscientific, unsupported by clinical trials, and sometimes dangerous.[33,34] In addition, potential adverse effects have been also described.[35,36] It is worth noting that introducing different practices and technologies in other cultures is the result of a combination of technical and social forces. Thus, if those practices and technologies are not accepted by society, no matter how good they are, they will not be implemented.

Herein, the aim of this work is to analyze and discuss how the convergence between TCM -and the use of natural products in TCM- and nanomedicine, a recently developed technology compared with the millennia of different TCM experience, can contribute towards the harmonization between western and eastern approaches to health and disease. Other reviews and articles are mostly focused on the development of nanocarriers that can deliver natural products to targeted organs and tissues, and in the modernization of TCM preparation technologies with nanoengineering.[37-43] However, it is also worth focusing on other common challenges between nanomedicine and TCM. For instance, nanomedicine is a new medical technology that is trying to find its way into international pharmaceutical and medical markets. To this, a wide body of knowledge of novel nanosafety and nano-regulatory principles has been

developed[44-46] which may be applied to the products of TCM that enter into clinical trials (of course, taking into account the specificities of those natural compounds). Furthermore, nanomedicine also had to address since its beginning the concerns of the society.[47-51] The core of this work is devoted to the analysis of these and other aspects. To this, the strengths and weaknesses of TCM are first discussed, to later explore the mutual benefits of the complementation between TCM and nanomedicine **(Figure 1)**. Finally, as representative cases of the good marriage between nanomedicine and TCM, the last section offers a review of selected recent high impact studies that merge these disciplines in different medical areas such as therapeutic developments, cancer treatment, biosensing, acupuncture and development of new materials.

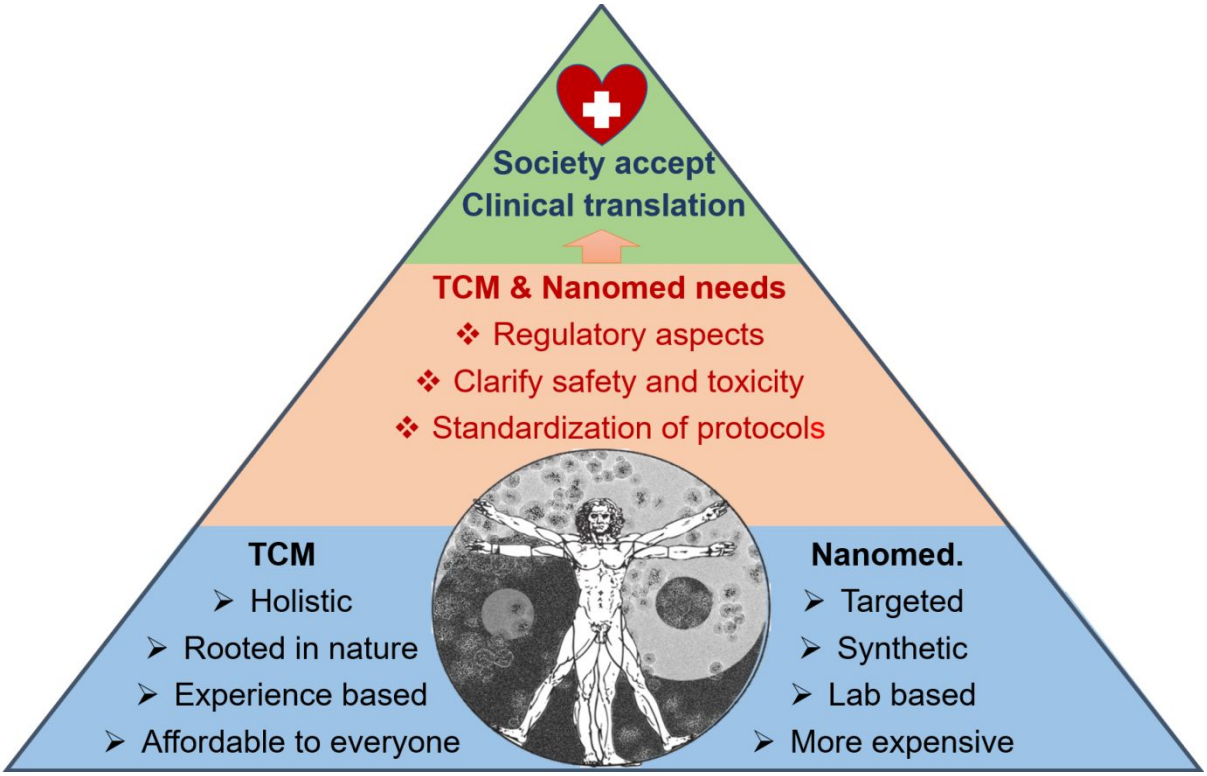


Figure 1. The diverse strengths of TCM and nanomedicine and the joint efforts to overcome their respective challenges will allow both disciplines to accelerate the path towards clinical translation of promising therapies for the benefit of the patients. This may also show possibilities of complementation between western medicine and TM.

2. STRENGTHS OF TCM

TCM has numerous strengths that make it an ideal knowledge to contribute to fighting global health problems. However, the process of its internationalization from their distinctive origins is facing a series of setbacks due to both external reasons and some inherent characteristics that can be applied to all TMs. Next, by looking at the different internal and external factors that can affect TCM internationalization, its strengths and weaknesses are briefly summarized. This analysis may serve to identify where current modern medical approaches can benefit from the introduction of TM and the opportunities arisen from the complementation between modern technologies such as nanomedicine and TM.

2.1. All-encompassing and integral perspective

TCM can be considered as an integral system of knowledge and practices that address all types of illnesses with special focus on their prevention. TCM looks for the balance of all the body functions and to enhance the own body's capacities. Contrary to western medicine, which has been traditionally more focused on specific molecular targets, the holistic approach of TCM offers more opportunities for the treatment of metabolic, chronic and other to-date incurable diseases. The case of cancer treatment is a good example. Most common approaches are focused on treating the tumor leaving other healthy organs exposed to side effects. TCM, by addressing the overall health of the individual, aims to offer treatments that are not detrimental to the rest of the organs and tissues.[52-55] This is considered a topic of special interest worldwide in cancer research.

2.2. Ancient and rooted in nature

Another advantage is the experience of thousands of years of TCM in discovering and employing bioactive natural products or their combinations. This is important since, nowadays,

the process of synthetic drug discovery is expensive and time-consuming. On average, a new compound takes at least ten years to complete the journey from discovery to market. And only the big pharmaceutical companies can afford to invest the estimated 1 billion USD it costs.[56,57] In addition, synthetic drugs are often associated with more undesired side effects compared with the natural products used in TCM. As a consequence, the development of new synthetic compounds for medicine remains at an unsatisfying state. Hence, taking advantage of the already known effects of the compounds of TMs is undoubtedly a great benefit. The most world-renowned case of a product that emerged from TCM is artemisinin. It was first isolated by Tu Youyou group in 1971 at the Institute of Chinese Materia Medica from the plant *Artemisia annua*. The beneficial effects of Artemisia annua against fever of different origin were already described by Ge Hong around 1700 years ago. Tested against malaria,[58] it became a powerful treatment for this deadly disease and become renowned worldwide. Artemisinin has since then saved millions of lives and Tu won the Nobel Prize in Physiology and Medicine in 2015.[59,60] Nowadays, to meet the rising demand of artemisinin due to the high number of malaria cases in many countries, alternative sources of artemisin production are being sought. For instance, back in 2004 the Bill & Melinda Gates Foundation funded a project to develop a genetically engineered yeast to obtain artemisinic acid, which Sanofi is commercializing. In addition, other approaches to increase artemisin production are being under research, including transgenic and non-transgenic systems. Apart from this, nowadays several others products of TCM are already serving the global community.

2.3. Sustainable and affordable to everyone

Traditional treatments are in many cases less expensive than current pharmaceutical developments, which are often dependent on large investments. Thus, adapting and combining the products and remedies of TCM with western medicine solutions can contribute not only to

improved therapies with synergistic effects but also to a considerable cost reduction. Another advantage is the reduction of the impact of synthetic chemicals released into nature, since the occurrence of chemical drugs in the environment is an important source of environmental pollution and a global concern. Wastewater treatment plants are often unable to filter out chemical compounds of synthetic drugs and other pharmaceutical and cosmetic products. These chemicals may end up in freshwater systems and into the oceans with a negative impact on the quality of drinking water and marine ecosystems (see e.g., the cases of the presence of considerable amounts of diclofenac, ibuprofen and methylparaben among others, in wastewaters).[61] All in all, treatments that incorporate TCM, and TM in general, products and practices can be more environmentally sustainable and more accessible to all, especially in developing countries that cannot afford expensive treatments. In this way, TM can play a major role in the improvement of the health of every single woman and man on Earth.

2.4. Personalized and experience-based

Another advantage is that TCM can work as a personalized medicine based on the dynamic observation of the patient carried out by the practitioner. This is important as many factors that determine an individual's health status are specific to that individual and the data and conclusions drawn from the study of large groups, which is common in western medicine, may not apply to some individuals. Currently, western medicine is also aware that the development of patient-precise treatments must be based on the knowledge of individual genetics, the monitoring of the progress of the disease, and the pharmacokinetic and metabolic response of the patient to available drugs. As a consequence, a new area of research on personalized medicine is booming worldwide,[62-64] where TCM can offer its ancient knowledge on personalized treatments.

3. WEAKNESSES OF TCM

As in everything, knowing the weaknesses is as important as knowing the strengths. It can provide a clearer understanding of the factors that are constraining future developments. In the case of TCM, modernization of the technologies, standardization, and regulatory and safety aspects have been identified as key challenges that TCM needs to develop and build.[1,65,66] Among technical shortcomings, it has been recognized that efforts in the knowledge of the natural products employed by TCM have been directed towards their *chemistry*, i.e., identification, separation and purification of active principles. Fewer efforts have been addressed towards *biology* in terms of functional and mechanistic studies. Hence, key insights into the biochemistry and mechanisms of action are still lacking. For instance, the molecular targets of most products and compounds of TCM remain unclear. This is now being addressed with the current progress of the life sciences and the modernization of biotechnology techniques, such as advances in systems biology, DNA sequencing, high throughput screening, bioinformatics, etc. But still, there are some areas that can benefit from modern technologies.

3.1. In preparation technologies

The preparation technologies to obtain compounds of TCM are still not up-to-date. For instance, for hard mineral medicines, traditional processing methods of calcining and quenching are still used. For herb medicines, which are richer in fibers and thus more difficult to crush, the preferred method is extracting techniques with aqueous solutions.[67] Here, the modernization of these preparation technologies would allow keep up with the competitive advantages of modern chemical drugs in terms of purity, dosage and production capacity. Remarkably, improved preparation technologies can also enhance the physicochemical properties. This can be translated to address another pitfall of many products from TCM which

is their low bioavailability. Additionally, this will improve the biological activity of those products.

3.2. In the social perception

It is a key aspect for the full deployment and acceptance of the potentialities of TM around the globe. A paradigmatic case was the controversy raised when the Food and Drug Administration approved kanglaite for a phase II trial in treating non-small-cell lung cancer in 2003. Kanglaite, extracted from the seeds of the herb *Coix lacryma-jobi* (Job's tears) was at that time the first drug derived from TCM to go into clinical trials in the United States. A News Focus titled "The New Face of Traditional Chinese Medicine"[68] was published in the Science journal claiming that TCM texts were based on unreliable, fanciful and irrelevant empirical observations. Other Letters to the Editor were also published alleging that there were several unfounded postulates in that New Focus.[69] This situation has not significantly changed. Nowadays, many of the components and practices of TCM are still perceived in western countries as unsafe and not scientifically based (see e.g., the News Feature article published in Nature in 2017 and 2018).[33,34] Here, the mutual understanding between different cultures is imperative. Indeed, different cultures have evolved with different philosophical and language systems, lifestyles, and have developed different medical theoretical systems, each one with its own perspective to approach human health and disease. For instance, Eastern or some African medicine theories have many ancient terms difficult to adapt to Western science and medicine. This leads to a lack of understanding of the theories of TCM in countries where it is not widely used, thus hindering its acceptance by the international community when judging only using the standards of modern western medicine.[70,71]

3.3. In quality indicators, standardization and regulation

In general terms, TCM is more complex and comprehensive than western medicine. From their holistic perspective of human health and disease, multi-target and multi-functional methodologies are adopted to achieve the overall restoring of body health. To this, the products from TCM usually consists of many active principles, and these ingredients may play a synergistic activity. Therefore, their composition and activity are more difficult to accurately describe compared with single synthetic drugs. In addition, there is a great variability in the materials taken directly from nature (a higher batch-to-batch variability), compared with controlled manufactured products. Furthermore, TCM products often consist of a complex mixture of compounds. All this compromises the scientific quality of control indicators, the harmonization of the different safety studies and the effectiveness of inter-assay conclusions for those products. This has important consequences for the standardization and regulation of TCM and makes it difficult for their products to enter clinical trials.[34,72-74] Current drug and pharmaceutical regulation follow mostly methodologies and procedures established from the western approach. In addition, the implementation required in some countries may be different than those international standards for pharmacology and toxicology. All this increases the doubts amongst western medicine in the perception of TCM.[34]

4. MUTUAL BENEFITS AND CURRENT LIMITATIONS OF THE INTEGRATION OF TCM AND NANOMEDICINE

The fast development of nanomedicine in the last 20 years makes it a major player in the technological revolutions of this 21st century in new materials, green energies, electronics and medicine among others. New nanomaterials and new technologies enabled by the miniaturization of devices have become incredibly important for the industry. This is owing to the possibilities of integrating novel and multiple functions thanks to the nanoscale dimensions. Particularly in medicine, the development of new nanostructures to improve current treatments or address unmet clinical needs leads to the burgeoning field of nanomedicine, where the efforts materials science, biochemistry, medicine and physiology converge. Nanomedicine is usually defined as the application of the knowledge and tools of nanotechnology for medical purposes, including the use of nanomaterials for monitoring health status and the diagnosis, control, prevention, and treatment of diseases. One differential aspect of nanomedicine respect other types of medicine is that it develops and apply materials and technologies with nanometer length scales.[75] Although it is difficult to establish strict size limits, typically they are defined as between 1-100 nm. A second differential aspect of nanomedicine is that those materials display novel properties respect the same materials of larger sizes that can be used for diagnosis, prevention and treatment of diseases. A wide variety of nanomaterials are used in nanomedicine including, but not limited to, polymeric nanoparticles, liposomes, organic and inorganic nanoparticles, solid-lipid nanoparticles and nanoemulsions.

Nanomedicine can benefit the clinical practices in many ways. Especially important is the possibility to unify in a single multimodal/multifunctional nanosized particle diagnosis[76-78] and different therapy modalities (chemo-, thermo-, radio-, immune-, etc), which is garnering vast interest from researchers and pharmaceutical companies.[6,79-83] This type of nanostructures,

known as theranostic nanomaterials, are perfectly suited for matching the requirements of personalized medicine, which is pushing a shift in the R&D approaches for new drug developments.[63,64, 75, 84, 85] Importantly, this shift is more aligned with the holistic perspective adopted by TM. Furthermore, with the engineering of the materials at the nanoscale, new nanoparticles can be designed to package and transport drugs directly to the site of action inside the body, which allow to decrease the dose of the drug and minimize side effects. However, there are still some drawbacks for the full implementation of nanomedicine, such as the potential toxicity of some nanomaterials, their pharmacokinetic profile, how the modifications they can undergo inside the body may affect the reactivity, and the burst release of loaded drugs in vivo that decrease the amount reaching the target site. From these differential characteristics of nanomedicine, the combination of the advances of nanomedicine with the knowledge of TCM can leverage the strengths of TCM and nanomedicine and improve their respective weaknesses **(Table 1)**, and contribute to driving TCM towards their modernization and to an unprecedented application around the globe. Indeed, not all the branches of TCM would be benefited at the same extent. For instance, drug delivery of natural compounds extracted from TCM receives a lot of attention from researchers worldwide and many successful cases have been reported (see sections 4.1 and 5). However, loading of mixtures containing large macromolecules is still challenging. In addition, acupuncture (section 5.4) and cupping (section 5.5) can benefit from the miniaturization of devices and electronic components, while moxibustion, massage and *qigong* (movement and concentration exercises) are less prone to be benefited from the advances of nanotechnology. Next, we summarize and described the proposed other areas where nanomedicine and TCM can help each other, including the modernization of preparation technologies to extract and purify TCM products (section 4.2), the regulatory aspects (section 4.3), and the social acceptance (section 4.4).

Table 1. *Summary of the key points described in our analysis of the strengths and weaknesses of TM, highlighting the aspects where TM may contribute to the improvement of nanomedicine and the aspects where nanomedicine may contribute to the improvement of TCM.*

Strengths of TCM	TCM contribution to Nanomedicine
Personalized and experience based. It's a personalized medicine based on the dynamic observation of the patient carried out by the practitioner.	Knowledge for the development of the new area of personalized medicine.
Ancient and rooted in nature. Experience of thousands of years of TCM in discovering and employing bioactive natural products or their combinations.	A source of bioactive natural products for the development of new drugs and treatments.
Sustainable and less expensive. Traditional treatments are usually less costly and more accessible to some countries and represent a tool to help achieve universal health coverage.	Reduction of the costs for drug development, since the process of synthetic drug discovery is expensive and time-consuming. Reduction of the occurrence of chemical drugs in the environment (an important source of environmental pollution and a global concern)
All-encompassing and integral perspective. Extensive empirical observations and experience based on holistic philosophy. ***Multi-target and multi-functional methodologies*** are adopted to achieve the overall restoring of body health.	Western medicine, and nanomedicine in particular, has started to turn its attention to high throughput analyses of whole-body functions to understand the mechanisms of health and disease, and to use combinatorial therapies to increase efficiency and reduce side-effects.
Weaknesses of TCM	**Nanomedicine may contribute to TCM**
Low bioavailability. Many natural products have been found to be bioactive and with low toxicity. However, most of them cannot be applied as first-in-line drugs for therapies owing to their limited bioavailability.	Nanocarriers may provide enhanced bioavailability and stability, site-targeting delivery, sustained release and dosing efficiency.

In preparation technologies. Traditional processing (e.g. calcination, quenching, crushing) are still widely used.	Modernization of preparation procedures to keep up with the competitive advantages of modern chemical drugs in terms of purity, dosage and production capacity.
In the social perception. Texts and practices of TCM are often perceived as unreliable, fanciful, and from irrelevant empirical observations.	Research in nanomedicine is being developed in public and private laboratories worldwide. The integration of TCM can pave the way for their worldwide acceptance. Nano-TCM products are excellent candidates to be applied successfully in combinatorial therapies for to-date incurable diseases, which may help both nanomedicines and TCM to be broadly accepted
In quality indicators, standardization and regulation. Products from TCM usually consists of many active principles with synergistic effects which compromises the scientific quality control indicators and the effectiveness of different safety studies and inter-assay conclusions. This makes it difficult for those products to enter into clinical trials	Experience in interdisciplinary activities and strong intersectoral links between academia, industry, and regulatory agencies, that have been formed in an effort to standardize nanomaterials and their procedures of preparation.

4.1. Drug delivery improves pharmacokinetics, safety and bioavailability of natural products

The first fruits of the efforts of the combination of nanomedicine and TCM can be seen in the great success in the transport and delivery of natural bioactive compounds of therapeutic interest using a wide range of newly developed nanocarriers, including liposomes, niosomes, dendrimers, polymers, inorganic and organic nanoparticles and metal-organic frameworks (see e.g. Liu *et al*.[40], or more recently in Pelaz *et al*.[75] and Zheng *et al*.)[86] Thus, the many benefits derived from the use of nanocarriers may be applied to the products from TCM. First, nanocarriers enhance the stability and bioavailability of natural substances that are poorly soluble in water, thus improving the dosing efficiency. Second, the pharmacokinetics of the natural substances can be modified through the surface functionalization of the nanocarriers with targeting moieties such peptides and antibodies to achieve a controlled site-targeting delivery, thus minimizing potential side effects. Third, nanocarriers can be designed with different functional agents at their surface that act as a gate that protects the active compounds until an external stimulus is applied, thus achieving a sustained and controlled release. Finally, recent breakthroughs in nanotechnology are yielding nanoplatforms with the ability to cross the Blood-Brain Barrier, so far non-permeable for most of the drugs.[87] Hence, the application of nanotechnology to TM can contribute to expanding the use of a wide range of natural medicinal compounds.

It is worth noting the important role of nanotechnology in bringing inorganic materials to medicine in a safe way. This is a field where the merging of both inorganic and natural substances can be highly beneficial. Briefly, inorganic nanoparticles are nowadays developed to load, protect and carry natural substances and, at the same time, they can be used as antennas that can be excited in biologically transparent environments (e.g., nanoparticles used for

thermotherapy,[88,89] phototherapy,[90,91] and sonotherapy,[92,93] among others. In addition, many inorganic nanoparticles have shown therapeutic action by themselves,[94] e.g. iron oxide nanoparticles, which were first approved by the US Food and Drug Administration for MRI imaging (Resovist®)[95] and afterward for providing iron ions in chronic kidney patients with anaemia (Feromuxytol®)[96] and for magnetic hyperthermia neuroblastoma ablation (Nanotherm®).[97] Furthermore, different nanomaterials are being explored and used as nanocatalysts (e.g. CeO_2, Fe_3O_4, MnO_2) for their antioxidant and anti-inflammatory activities.[98-103] In addition, they have physical and chemical signatures that differ from those of biological tissues, therefore facilitating the tracking and monitoring by many biomedical imaging techniques[104] which enable simultaneous imaging and therapeutic intervention. Thus, it is possible to unify the pharmacokinetic profile of the nanomaterials and products from TM in a single nanoconstruct which may have synergic effects.

For all this, pharmaceutical industries are gearing their interest towards the combination of therapies with natural products and the targeting capabilities of nanomaterials. Nowadays, pharmaceutical giants are already establishing such libraries of natural products. And it is here where TMs can provide their long experience in developing natural product libraries. For instance, in the case of TCM, over 11 000 herb plants are registered in different TCM-related pharmacopeia. Currently, several TCM-related databases, have been developed such as TCM-ID,[105] TCMGeneDIT,[106] HIT,[107] TCMID,[108,109] TCMSP,[110] TCMMESH,[111] which include information on herbs and their components, and the ETCM, an Encyclopedia of Traditional Chinese Medicine, which includes multiple aspects of clinical and functional essential information on more than 400 TCM herb species, 4000 TCM formulas, 7000 herbal ingredients, 2200 validated or predicted drug targets, as well as 3000 related diseases.[112,113] This and many other libraries and repositories, may provide useful data and tools for new opportunities of TCM and nanomedicine joint research and drug discovery.

4.2. Modernization of preparation technologies: towards standardization

Another aspect where TCM can benefit from the recent advances of nanomedicine is in modernization of preparation technologies. It has been previously mentioned that one of the shortcomings that TCM is addressing is the modernization of the methods for the obtention and preparation of the compounds prescribed in TCM. These methods still rely on traditional technologies that yield preparations with low bioavailability, low solubility, and poor control of the characteristics of the different batches and the final dosage. Here, nanomedicine can offer different technologies that have been developed to prepare nanomaterials employing top-down approaches, such as ultra-fine pulverization, mechanical comminution, nanocrystallization, laser ablation, high-pressure nanofluidization, etc.[114] Substances from TCM prepared in such nanoscale form will greatly increase their surface area which, in turn, generates a higher number of active sites (see examples in next section). This will provide the final preparation with improved physicochemical characteristics that will enable to shorten the time of decoction and improve the solubility, bioavailability and dissolution rate of the substances. Furthermore, the rational design of the processing routes, the modernization of production equipment and the applications of quality control methods will facilitate the normalization and standardization of TCM.

4.3. Regulation and Safety

Regulatory issues and the overall social perception are two other aspects that are still not completely solved for both TCM and nanomedicine. In the case of nanomaterials, despite their tremendous potential in medicine and the promising preclinical results obtained by researchers[98,102,105] only a few of them have reached the bedside.[116,117] The first efforts were done after the discovery of liposomes by British haematologist Alec D. Bangham in the 1960's,[118] at the Babraham Institute, in Cambridge. The medical use of liposomes was

primarily directed at targeted drug delivery, especially for the delivery of insoluble drugs. Twenty years later, a liposomal formulation with the chemotherapeutic drug doxorubicin encapsulated was developed.[119] The use in the clinic was approved in 1995, which, under the trade name of Doxil®, is considered the first FDA-approved nano-drug. After this, few others (less than a hundred liposomal formulations, organic and polymer particles of nanometric size have been approved[116,117,118] and fewer in the case of inorganic nanocrystals, e.g. the mentioned case of iron oxide nanoparticles. Notably, some of the approved COVID-19 vaccines are based on mRNA encapsulated lipid nanoparticles.[121,122]

Recently we have reviewed the causes that delay the effective implementation of nanomaterials in clinical applications[98,115,123] and some similarities with TCM can be drawn. For instance, the accurate description of the substances employed. In the cases of nanomaterials, under the same label, e.g. "iron oxide nanoparticles" a wide variety of different iron oxide particles in terms of size, surfaces state, concentration, crystalline phase, colloidal stability, etc., have been used in a multiplicity of works, which generates confusion when results are discrepant. The variability of the nanomaterials used and their sometimes poorly described characterization recalls the case of the great variability of characteristics of a natural compounds extracted from nature. Indeed, it is very difficult to compare data from different laboratories when neither materials nor methods are fully standardized and documented. Even more, at the earlier efforts of nanomedicine, nanomaterials were poorly characterized and the measurements were done by different techniques depending on the availability of the different research groups. As a consequence, there were discrepant reports of either medical benefits or toxicity for the same nanomaterial.[124] For instance, the mentioned case of "iron oxide nanoparticles", which in the same year it was reported as neurotoxic[125] and promising for nerve cell regeneration,[126] or the case of cerium oxide nanoparticles, which in the same year appear different reviews pointing out beneficial[101] and adverse[127] medical effects. In addition, most

early studies on the safety of nanomaterials were based on traditional toxicological approaches, treating nanomaterials like any other molecules and neglecting the unique characteristics that provide them with a different reactivity compared with their atomic and bulk counterparts.[128] Therefore, after twenty years of nanosafety research, still contradictory results and the lack of reproducibility of many studies generated uncertainties among the consumers and the regulatory agencies, which depend on scientifically based advice for their decisions.[44]

This situation started to change recently owing to plenty of interdisciplinary activities and strong intersectoral links between academia, industry, and regulatory agencies, that have been formed in an effort to standardize materials and procedures. A massive amount of data on the toxicity and the absorption, distribution, metabolism, and excretion (ADME) profiles of nanomaterials has been generated.[45] However, plenty of data available is not the same as full understanding. Thus, standardization efforts have been promoted for the large databases of nanosafety studies based on published literature which cover a wide range of nanomaterials, including inorganic nanoparticles, graphene, carbon dots, carbon nanotubes, etc. are also available.[45] For instance, several European Commission-funded projects established the Nanosafety Cluster, a platform that coordinates the nanosafety research and provides strategic direction for the European Union and its member states. Similarly, the European Chemicals Agency (ECHA) established the European Observatory for Nanomaterials in an effort to unify the dispersed efforts of researchers and provide transparency and information on nanomaterials to the general public. In the U.S., the FDA has recently released a guidance for industry on drug products, including biological products, that contain nanomaterials,[129] to accelerate their approval.

Similar strategies are being applied in the case of TCM and TMs. For instance, recently, it has been established the African Medicines Agency, a harmonization effort to facilitate regional collaborations and with the aim of coordinate national and sub-regional medicines regulatory systems and conduct regulatory oversight of selected medical products including TMs.[130] Similarly, in 2019, National Medical Products Administration in China launched the Action Plan of Regulatory Science, an official initiative to advance the regulatory capacity of TCM with the adoption of regulatory science.[131] Regulatory Science is nowadays being adopted by different drug regulatory authorities which also include the FDA, the European Medicines Agency (EMA) and the Japanese Pharmaceutical and Medical Devices Agency. It aims to provide improved scientific support to regulatory decisions based on the best available scientific basis.[132] Thus, sharing these efforts of regulation and the strategies for standardization may speed up the approval of both nanomedicines and traditional medicines. Another recent example is the creation of The Committee on Herbal Medicinal Products by the EMA, which issues scientific opinions on herbal substances and preparations, including traditional herbal medicinal products and with the aim of achieve a harmonized legislation for these products.[133] This involves big data and should be an integral part of the future work in TCM where specialists in nanomedicine and TCM including chemists, material scientists, molecular biologists, and medical doctors may work together to make even greater medical achievements.

4.4. Social acceptance

As mentioned above, no matter how good a technology is, if society doesn't embrace it, that technology will not make its way into society to benefit people. In this case, research in nanomedicine, and nanotechnology in general, is being developed in thousands of public and private laboratories from western and eastern. The integration of traditional medicines in this

research is taking place, paving the way for worldwide acceptance. However, some difficulties of acceptance for both nanomedicine and TCM can be observed. First, although nanomedicine has broad support from the scientific community, it is experiencing a negative perception by some sectors of the public. Behind these reluctances it could be that nanomedicine is still at its infancy and that part of the population is poorly informed of the latest advances in research.[134-136] In addition, the safety of new nanomaterials is another aspect that is under debate amongst the scientific community, which generates doubts and uncertainties among the population and even the experts.[44]

In the case of TCM, reluctances for its acceptance, even inside scientific communities, are often due to cross-communication difficulties. As mentioned before TCM and modern western medicine have evolved within different language systems and cultural backgrounds. In addition, while in many countries medical doctors are usually trained in both TCM and western medicine, in western countries the core of medicine and related disciplines is almost exclusively the western approach, being only optional the study of TCM. The lack of knowledge and understanding of the theories of TCM and the difficulties in translating those in a community accustomed exclusively to modern science and medicine could explain that some scientists and physicians regard TCM as unscientific. Therefore, there is still work to be done before TCM and nanomedicine are broadly accepted into society. Importantly, the aspects that need to be taken into account for this acceptance are different for TCM and nanomedicine. Thus, a good collaboration between these disciplines could help each other to reach the acceptance by the different segments of the population that are reluctant to each one of them. For instance, nowadays, western modern medicine has started to turn its attention to high throughput analyses of whole-body functions to understand the mechanisms of health and disease. Here, TCM may greatly contribute with their extensive empirical observations and experience based on holistic philosophy. Considering the improvement of the knowledge of

TCM in western medicine studies, and by the refinement of TCM observations with modern technologies, TCM can overcome the above-mentioned reluctances. In addition, especially since the advent of nanotechnology and the use nanocarriers, combinatorial therapies are in the focus of current pharmaceutical developments to address to-date incurable diseases. Nano-TCM products are excellent candidates to be used successfully in such combinatorial therapies, which may help both nanomedicines and TCM to be broadly accepted.

5. SUCCESSFUL CASES OF BLENDING TCM AND ACTIVE INGREDIENTS FROM TCM WITH NANOMEDICINE.

An exhaustive review of all articles and works that merge nanotechnologies and TCM is a daunting task out of the scope of this review. Currently, thanks to advances in biochemistry and in the isolation, purification and characterization of active principles, plenty of TCM compounds known to have pharmacological properties have been studied and their mechanisms of action have been revealed. Plenty of examples can be found in many other reviews, especially in the protection, transport and delivery of such compounds using nanocarriers and also in the improvement of the preparation technologies (see e.g. recent ones in references).[38,41,42,86,137,138] Herein, apart from drug delivery, several other studies appeared in established journals that cover different areas of biomedicine and material science, such as combinatorial therapies, biosensing, acupuncture, manufacturing of TCM products and development of new nanomaterials, have been selected. Indeed, this selection is not detrimental to other exceptional works published in many other journals. We hope the multiplicity of successful cases presented here in different areas of biomedicine may encourage young scholars and researchers to drive their efforts in this promising area of research and development.

5.1. Cancer treatment.

As said, plenty of TM compounds have antitumoral properties; see e.g., the list of TCM-derived products used for cancer chemotherapy in Western medicine in Efferth *et al*.[139] and most recently in Xiang *et al*.[137] including camptothecin (traditionally extracted from *Camptotheca acuminata*), cantharidin (from *Mylabris phalerata*), and vinblastine and vincristine (from *Catharanthus roseus*) among others. However, the traditional administration and dosage forms hinder an effective application, and the pharmaceutical industry is seeking new ways of implementation of these treatments to reduce side effects and improve efficiency in the target site. Nanostructured materials have been widely investigated during the last two decades as drug carriers to the site of disease with the advantage of reducing the doses required -and hence the side effects-, and enabling sustained release, thus improving bioactivity. Indeed, this technology has been also applied for an efficient delivery of active ingredients and compounds of TM.

For instance, it was already shown in the study of Lam *et al*. how antitumoral drugs applied in a multi-drug combination strategy with natural products can achieve synergistic antitumor outcomes with fewer side effects.[140] More recently, Liu *et al*. showed how arsenical drugs (in the form of pegylated arsene nanodots) achieved considerable higher therapeutic efficacy in different solid tumors when combined with β-elemene.[141] This may further expand the clinical applications of β-elemene, one of the isomers of elemene, a lipid-soluble sesquiterpene isolated from the herbal medicine *Curcuma zedoaria*, a rhizome used to treat several types of cancer.[142-144] β-elemene exert its mechanism of action by regulating the expression of molecules involved in tumor angiogenesis and metastasis including matrix metalloproteinases and the vascular endothelial growth factor. Also, β-elemene has been shown to have regulatory effects on the immune response and may sensitize cancer cells to other

chemotherapeutic agents, which may explain these findings. Another example is the work of Xu *et al*. showing a nanostructure comprising doxorubicin and BML (1-butyl-3-methylimidazolium-l-lactate), a microwave radiation sensitizer, into fucoidan conjugated liposomal nanoparticles.[145] Fucoidan, obtained from brown algae, has been used as raw material for treating kidney disease for 2000 years ago. It has been shown that fucoidan prevent the binding of the VEGF to its cell membrane receptor, thus impeding the formation of new vessels by which tumor cells receive oxygen and nutrients.[146] The nanoconstruct developed by Xu *et al.*[145] displayed enhanced therapeutic efficacy of thermal-chemotherapy for the treatment of advanced stages of hepatocellular carcinoma.

In addition, the mere combination of different natural products in a single nanodevice may achieve those synergistic antitumoral effects. Zhang *et al*. designed a nanodelivery system consisting of a combination of quercetin and alantolactone and showed that this nanodrug induced synergistic immunogenic cell death and significantly inhibited tumor growth in a murine model of orthotopic microsatellite-stable colorectal cancer, which is resistant to immunotherapy **(Figure 2)**.[147] Quercetin is an antioxidant compound widely present in different TMs. For instance, in TCM it is the main component of the Yang-Yin-Qing-Fei-Tang formula used in the treatment of chronic obstructive pulmonary emphysema, bronchitis, and different types of pneumonia, among others, and consists of an herbal mixture that comprises 13 medicinal plants,[148] and it is also part of the Zi Shen Huo Luo Formula with proved cardioprotective effects.[149] On the other hand, alantoalactone is present in the extracts of *Inula helenium L.* and *Inula racemos* herbs and in other plants of the family Asteraceae. Apart from antitumoral effects, it has traditionally shown anti-inflammatory, antimicrobial and neuroprotective activities.[150]

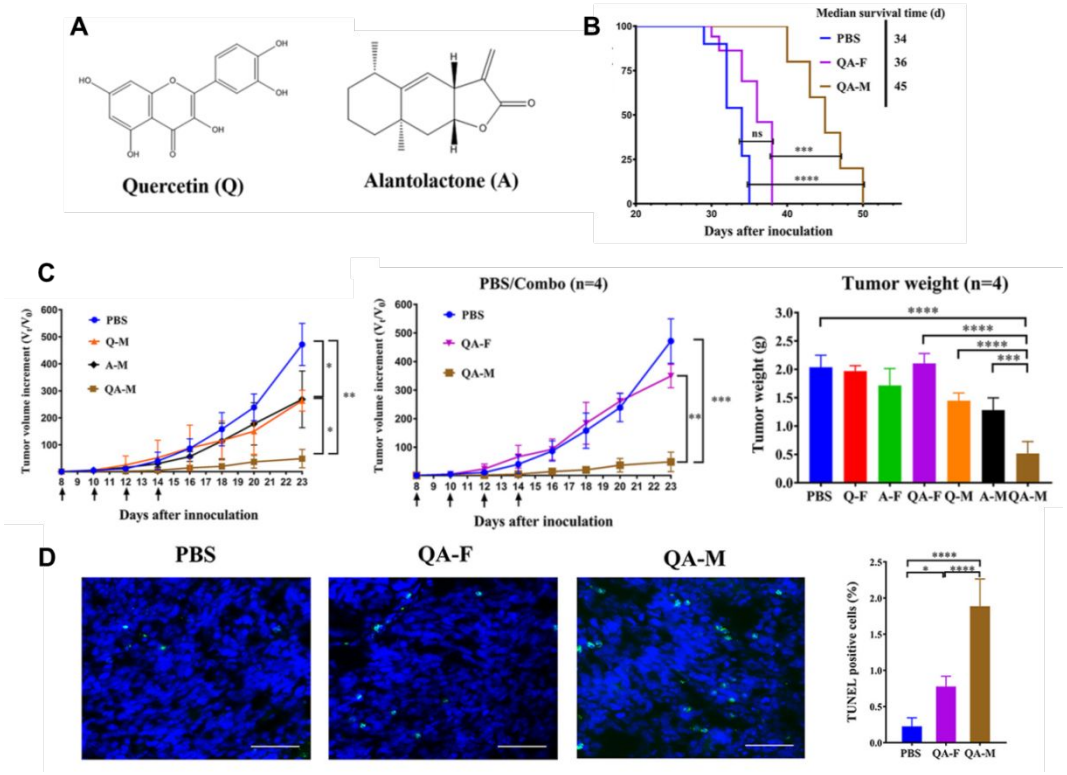


Figure 2. Delivery of natural products in cancer therapies. It is the most common field of combination of TM and nanomedicine. For instance, the work of Zhang et al. showed the synergistic effects in a murine model of orthotopic microsatellite-stable colorectal cancer of the co-de-livery of quercetin (Q) and alantolactone loaded inside nanometric micelles of 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy-poly(ethylene glycol 2000) (DSPEPEG2000) and D-α-tocopherol polyethylene glycol succinate (TPGS). **A.** Chemical structure of Q and A. **B.** Survival with the administration of PBS, Q and A not loaded inside the micelles (free, QA-F) and loaded inside the micelles (QA-M). **C.** Inhibition of tumour growth comparing the administration of micelles with only quercetin (Q-F) or alantolactone (A-F), QA-F and QA-M with Q at 3 mg/kg and A at 9 mg/kg. **D.** TUNEL-positive cells (%) in tumours of each group. Adapted with permission from Zhang et al. ACS Nano, 2019, 13(11), 12511-12524. Copyright © 2019, American Chemical Society.[147]

5.2. Other therapeutical purposes.

Indeed, beyond cancer therapies, the integration of TM and nanomedicine may improve many other areas of medicine. In cardiology, the work of Liu *et al*. showed that a natural herb-crosslinked hydrogel carrying rat bone marrow mesenchymal stem cells (rBMSCs) facilitated the efficient restoration of cardiac function when injected into the infarct region of rats.[151]

Specifically, the authors used a tyramine-modified hyaluronic acid (HA-Tyr) and puerarin (an isoflavonoid from the root of *Radix puerariae*). Puerarin possesses a wide range of pharmacological properties including antioxidant activity and the modulation of the expression of inflammatory cytokines.[152] Authors formed an injectable HA-Tyr-Puerarin hydrogel encapsulating the rBMSCs, which exerted the cardioprotective action through the modulation of the microenvironment by scavenging active oxygen and releasing oxygen. The same year, Aliakbari *et al*. showed the multiple protective roles of baicalein (5,6,7-trihydroxy-2-phenyl-4H-1-benzopyran-4-one), a major flavonoid from *Scutellaria baicalensis*, against the alpha-synuclein aggregates associated with the onset and development of Parkinson's disease.[153] To this, the authors encapsulated baicalein, which inhibits fibrillation, and detoxifies aggregates of α-synuclein, into zwitterionic nanoliposomes to increase its solubility, stability, and availability.

Another interesting example is the restoration of a large segmental nerve defect (c.a. 10 mm) using polyurethane nanofibers loaded with gastrodin,[154] a bioactive component of the herb *Gastrodia elata*. Gastrodin is known to display neuroprotective and anti-inflammatory effects owing to its antioxidant activity. In this study, Yang *et al*. achieved the recovery of sciatic nerve function by creating an appropriate microenvironment for nerve regeneration, mainly by down-regulating iNOS and TNF-α expression owing to gastrodin activity.[154] Thus, it decreased the inflammatory response that implanted fibers for nerve guidance inevitably trigger, which hinders the regeneration process of nerve damage. Altogether, it facilitated the optimization of Schwann cells function and induced nerve fibers formation along with angiogenesis.

TCM is also a broad source of antimicrobial agents to develop multidimensional strategies to fight against the increasing antimicrobial resistance due to the abuse and misuse of traditional antibiotic molecules developed during the second half of last century. For

instance, Li *et al*. developed different natural self-assembling modes between berberine and two flavonoid glycosides in aqueous solution forming nanoparticles or nanofibers (depending on preparation conditions).[155] The flavonoids used were baicalin and wogonoside, the main active components in *Scutellariae radix*, while berberine, traditionally used for the treatment of diabetes and infections, is widespread in many natural plants from the *Berberis* genus. These two nanostructures exhibited different and enhanced antibacterial properties compared with berberine and offer a novel supramolecular self-assembly strategy that may be applied to construct similar nanoscale antibacterial drugs comprising other natural compounds **(Figure 3)**. In addition, berberine-loaded chitosan/heparin nanoparticles were previously found to be effective against *Helicobacter pylori* eradication in vitro and in vivo.[156]

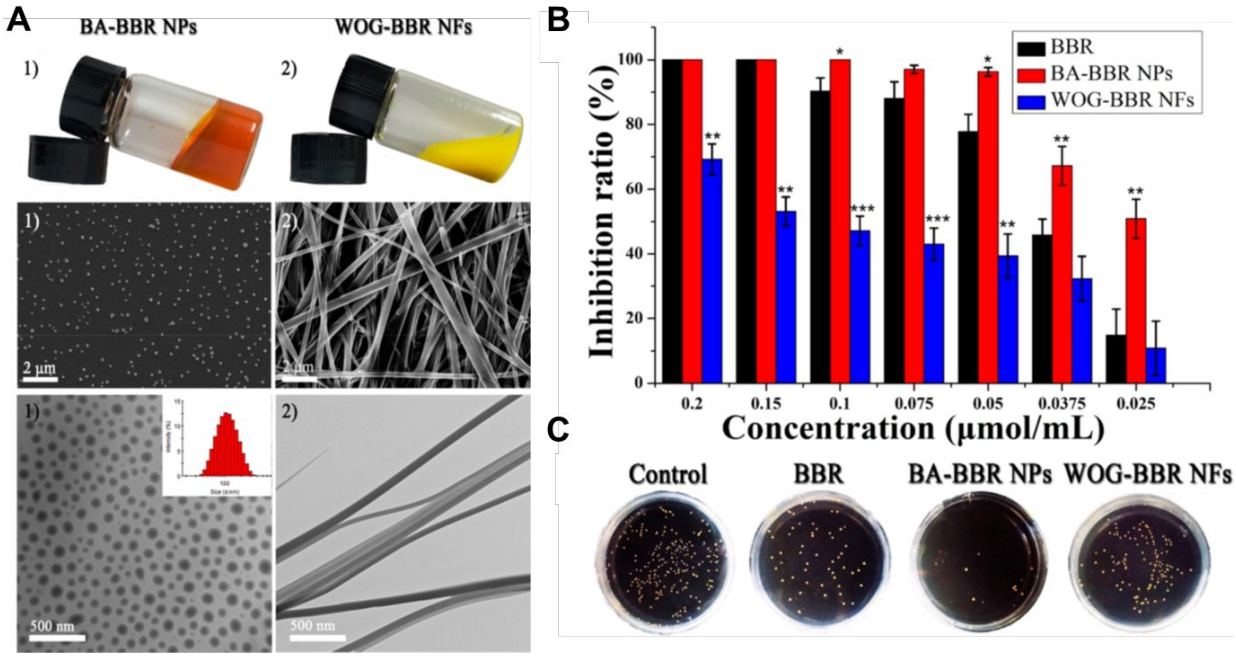


Figure 3. Integration of TM and nanomedicine in nanobiotics. For instance, Li et al. discovered natural self-assembly modes of berberine (BBR) with baicalin (BA) and wogonoside (WOG), forming nanoparticles and nanofibers, which showed significant improvement of their antibacterial and biofilm removal ability. **A.** Characterization of the natural self-assemblies of nanoparticles of BA-BBR and nanofibers of WOG-BBR. **B.** Inhibition ratio of free BBR, and the self-assemblies of nanoparticles of BA-BBR and nanofibers of WOG-BBR on Staphylococcus aureus measured by a plate counting method. C. Staphylococcus aureus treated with culture medium (control), and with 0.05 μmol/mL of BBR, BA-BBR nanoparticles and WOG-BBR nanofibers; *,$P < 0.05$; **, $P <$

0.01; ***, P < 0.001, vs BBR. Reprinted (adapted) with permission from Li et al. ACS Nano 2019, 13(6), 6770–6781. Copyright © 2019, American Chemical Society.[155]

5.3. Research on the development of TCM products at the nanoscale.

Beyond direct therapeutic effects, it is also worth mentioning that the development of nanotechnologies enables the isolation, manipulation and even the fabrication of many of traditionally used natural products at the nanoscale level. This implies a modification of their physical and chemical properties which consistently shows enhanced therapeutic effects. For instance, Deng *et al*.[157] found that natural nanoparticles extracted and purified from cuttlefish ink (CINPs) can efficiently reprogram tumor-associated macrophages from immune-suppressive M2-like phenotype to antitumor M1-like phenotype through the activation of mitogen-activated protein kinase. In addition, CINPs exhibited in this study a high photothermal effect and tumor cell killing ability when irradiated with near-infrared light. Cuttlefish is the original source of an astringent formula traditionally used to hold in and stop bleeding, and to control stomach acidity and alleviates pain. Now, this study shows that its nano-formulation could inhibit tumor growth by synergizing immunotherapy and photothermal therapy **(Figure 4)**.

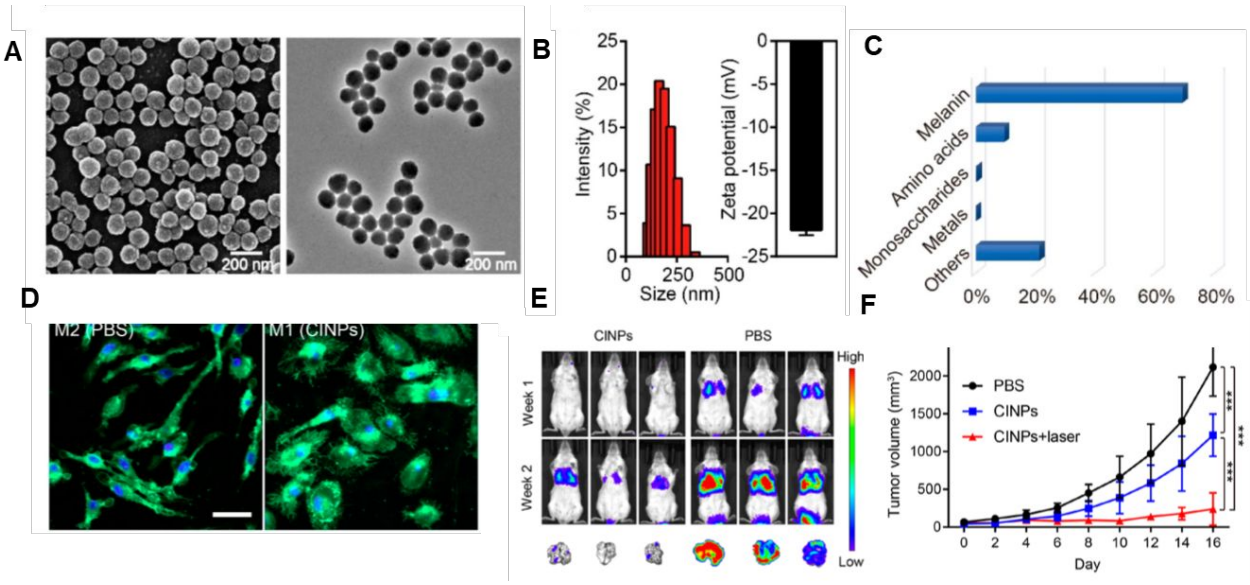


Figure 4. Fabrication at the nanoscale level of TM products. The work of Deng et al. is based on the extraction and purification of natural nanoparticles (CINPs) extracted from cuttlefish. These nanoparticles repolarize macrophages from immune-suppressive M2 to antitumor M1 phenotype and exhibit a high antitumoral effect in a tumor model of lung metastases in female BALB/c mice under near-infrared irradiation. **A.** SEM and TEM images of the purified CINPs. **B.** Hydrodynamic size distribution and ζ-potential of CINPs. **C.** Chemical composition of CINPs. **D.** Representative confocal images of the modification of the cell shape from M2 bone marrow-derived cells to CINPs treated M1 bone marrow-derived cells. Scale bar, 30 μm. E. In vivo antitumor study tracking the spreading and growth of intravenously injected luciferase-CT26 cells after PBS or CINPs treatment. F. Tumor growth curves after treatment with PBS, CINPs (immunotherapy) and CINPs irradiated (multimodal immune and phototherapy). This last one almost completely inhibits tumor growth accompanied by more active immune responses. Reprinted (adapted) with permission from Deng et al. ACS Nano 2019, 13(8), 8618–8629. Copyright © 2019, American Chemical Society.[157]

5.4. Acupuncture.

Acupuncture is an age-old healing practice in TCM. Briefly, it involves inserting thin, solid, metallic needles into targeted areas of the body, which become activated by specific and gentle movements of the hands of the practitioner or, more recently, also with electrical stimulation. Despite acupuncture being often regarded as a form of complementary or alternative medicine, especially in western medicine, different studies have shown that it can be effective for a variety of conditions, and to alleviate pain and restore well-being.

Nanotechnology can improve traditional acupuncture in different ways. For instance, the recent efforts in materials science and technology are enabling the development of bionanosensors with unprecedented levels of physical, chemical and biological sensing. These new devices can largely increase the specificity and sensitivity of the detection of the analytes, also in real-time. This provides excellent tools for studying their biological functions.[158] For this purpose, different acupuncture needles with the tip covered with nanomaterials for biosensing are being developed. For instance, the work of Zhou *et al*. presented a molybdenum disulfide (MoS2) and platinum nanoparticles (PtNPs) layer-modified microneedle sensor coating a conventional stainless steel acupuncture needle.[159] This construct served as the electrode substrate for a real-time monitoring of hydrogen peroxide (H_2O_2) release from living cells. More recently, Jia *et al*. designed a Ni6MnO8 nanoflake construct coating steel acupuncture needle as an electrode substrate which, in addition, showed outstanding efficiency towards the amperometric detection of ascorbic acid.[160]

Remarkably, owing to the development of omics sciences, it will be possible in the near future to integrate this dynamic and highly sensitive detection with temporal and spatial (including different tissues and body areas) data to reveal signaling pathways of the disease and injury sites. This will enable a deeper insight into the mechanisms of acupuncture treatment. And this is on the basis of the i-Needle proposed in a Science article in the special issue devoted to TM.[161] Different studies are undergoing in this direction. For instance, in an article published in Nature this year Liu *et al*.[162] showed the neuroanatomical basis of how electroacupuncture can drive the vagal–adrenal axis to activate neurons to switch off inflammation.

5.5. Theranostics.

Another example of how TCM products can merge with nanocarriers to improve theranostics is provided in the study of Wei *et al*.[163] These authors found that evodiamine can act as a chemotherapeutic agent and also as a contrast agent for positron emission tomography/computed tomography (PET/CT) imaging owing to its ability of 68Ga-chelation **(Figure 5)**. Evodiamine is an alkaloid extracted from the fruit of *Evodia rutaecarpa* and it has been an active component traditionally used to treat several chronic diseases such as abdominal pain, vomiting, headaches and colds, among others. In this study, the properties of evodiamine were applied for the first time for antitongue cancer. Through the loading of evodiamine and the photosensitizer indocyanine green inside a liposomal nanoplatform nanoplatform, this study shows to development of a noninvasive diagnostic imaging and combinatorial therapy against oral squamous cell carcinoma, the most common malignant epithelial neoplasm affecting (and disfiguring) the oral cavity. Specifically, this TCM-nanoplatform shows dual imaging (fluorescence and PET/CT) and tri-modal (chemo/chemodynamic/photodynamic) therapy properties, with superior stability, and significant anticancer activity in vitro, and that can deeply penetrate the tumor with a significant power for inhibiting cancer cell proliferation and finally induce cancer cell apoptosis both in vitro and in vivo.

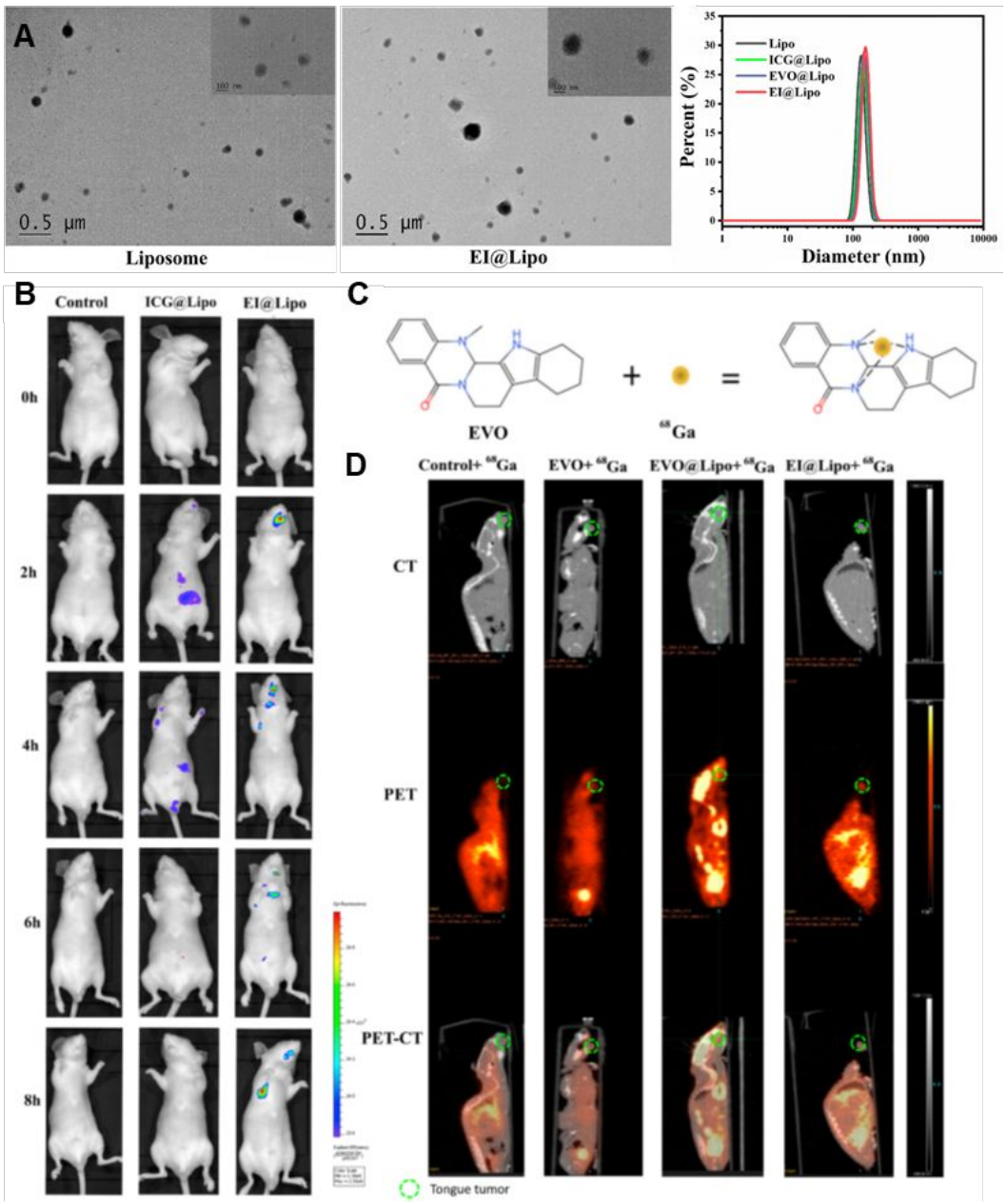


Figure 5. Nano-TCM products with improved theranostic properties. A. Characterization of the nanoliposome system encapsulating evodiamine and indocyanine (EI@Lipo). Left, non-loaded nanoliposomes. Center, loaded nanoliposomes. Right, size distribution by Dynamic Light Scattering of the various nanoliposomes ranged from 110 nm to 120 nm. **B.** 808 nm excitation fluorescence images of control, indocyanine, and EI@Lipo 2 h after the tail injection. **C.** The reaction between EVO and ^{68}Ga. **D.** The PET-CT images of control+^{68}Ga, EVO+^{68}Ga, EVO@Lipo+^{68}Ga, and EI@Lipo+$_{68}$Ga after 0.5 h of tail injection. The tongue tumour is signalled in a green circle. **B and D** show the bimodal live imaging of EI@Lipo on the tumour-bearing murine model of tongue cancer in situ. Reproduced from Wei et al, Bioact. Mater., 2021, 6(7), 2144-2157, © 2021, the Authors. Reproduced under Under a Creative Commons license.[163]

5.6. Others applications

The insight in TCM knowledge also influence technological developments in other fields of medicine. For instance, Shang *et al*. presented the design of ionohydrogel to be used as a printable bioelectronic device inspired in cupping therapies.[164] In this type of therapy, the practitioner place special cups on the patient skin for a few minutes to create suction to reduce pain, inflammation, restore blood flow, and overall relaxation and well-being. The device developed by Shang *et al*. incorporates microneedle patches that generate a pathway through the skin in such a way that skin interstitial fluid can be readily harvested by vacuum and glucose is monitored in real-time. In another work, Chu *et al*. developed a wearable piezoelectric sensing system that imitates and record the 3-finger pulse palpation signals that TCM practitioners use.[165] The authors show how this system allows the medical assessment of common heart problems (such as arrhythmia) and the possibility to measure and read blood pressure **(Figure 6)**.

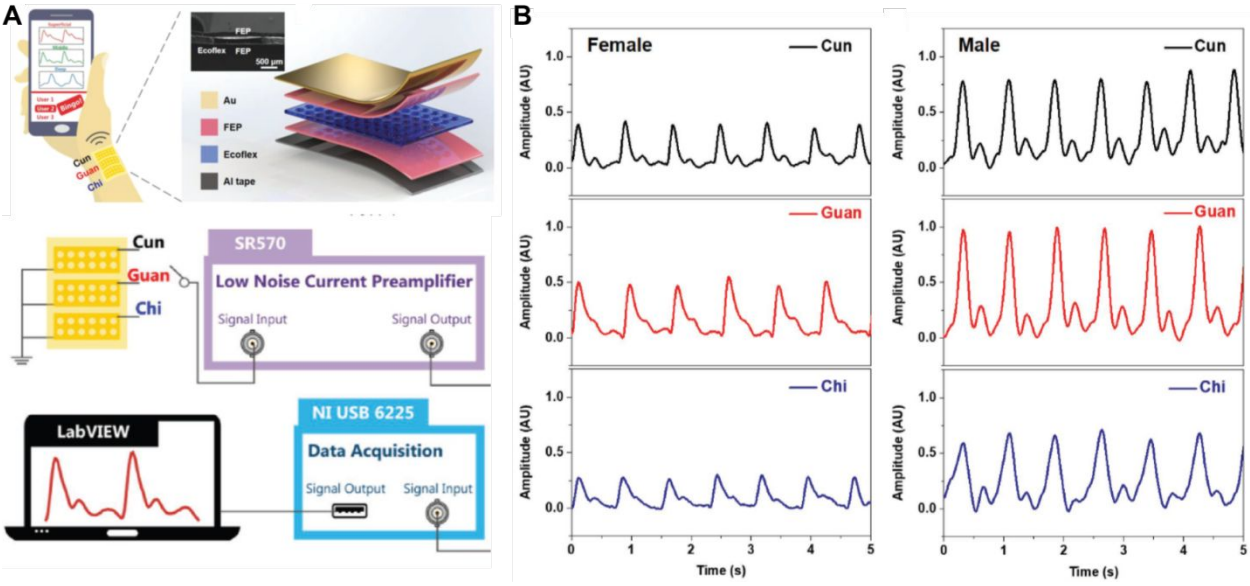


Figure 6. A Wearable piezoelectric sensing system inspired by the 3-finger pulse palpation signals commonly used by doctors practicing in TCM. In Chu et al., an active and flexible pulse wave sensing system based on fluorinated ethylene propylene (FEP)/Ecoflex/FEP and a 50 nm thin layer of gold. A. The three pulse sensors illustrated at the Cun, Guan, and Chi pulse locations for

the applications in medical assessments. The signals can be transmitted wirelessly to a mobile device such as a cell phone, computer or the cloud for data analyses. B. Examples of recording of a 26-year-old female volunteer and a 28-year-old male volunteer. Reprinted (adapted) with permission from Chu et al. Adv. Funct. Mater., 2018, 1803413, Copyright © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[165]

Interestingly, TCM has also served as inspiration for the development of new nanomaterials. Although this is somehow out of the scope of this review it is worth mentioning the work of Zhang *et al*. on the synthesis of a new large pore zeolite, which the authors named SYSU-3 (Sun Yat-sen University no. 3).[166] Large pore zeolites have important applications for processing larger molecules but also as structural components in regenerative medicine and bone tissue engineering. For this achievement, the authors used a novel sophoridine derivative as an organic structure-directing agent. Previously utilized OSDAs for such type of synthesis are extremely expensive, and no large pore zeolites (pore opening larger than 14-ring) were obtained. The sophora alkaloids used in this work were extracted from sophora herbs and seeds. Importantly this kind of new structure-directing agents can be easily modified to fabricate other novel and specific extra-large pore zeolite structures.

6. CONCLUSIONS

In this work, we have presented the key aspects where nanomedicine and TCM may complement each other to take a step forward towards the common objective of fighting global health challenges of the 21st century. Nowadays, humankind is facing the consequences derived from the blossom of industrial and technological developments that started during the industrial revolution initiated three centuries ago, which have progressively distanced us from nature, in terms of high rates of cancer, antibiotic resistance, epidemics, etc. To redress this, on the one hand, we can take a look at TCM, which is serving Chinese population since thousands of years ago, and its persistence and maintenance through the times deserves special attention. On the other hand, nanomedicine is emerging as a disruptive and promising technology, but its therapeutics and diagnostics breakthroughs are not yet settled in the clinical practice, and the translation of promising nanomedicines is being delayed. In this work we have first reviewed the strengths and weaknesses of TCM, one of the most widespread and used TM. This analysis allows identifying the opportunities to develop improved medical benefits derived from the introduction of TM in progressive technologies such as nanomedicine. In addition, it also allows identifying aspects where nanomedicine may provide an opportunity towards TM modernization, standardization, and wide social acceptance.

Certainly, some branches of TCM can be benefited at a higher extent from the introduction of nanotechnology advances, such as the use of nanocarriers for the protection, transport and delivery of herbal remedies or the miniaturization of devices and electronic components in acupuncture and cupping therapy. Other branches hardly can find a direct benefit. Remarkably, we have observed similar technical, regulatory and social challenges that both nanomedicine and TCM are facing for clinical translation and worldwide acceptance of their respective medical solutions. This includes the harmonization of preparation and

characterization protocols, the safety and regulatory aspects, and the social perception. We envision here a window of opportunity where mutual help between TCM and nanomedicine will contribute to bridge the existing gaps between TCM and modern western medicine, and hence, to contribute to address global health challenges.

7. FUTURE DIRECTIONS

Future directions to drive this integration could be summarized as follows:

- **To continue integrating the benefits derived from the use of natural compounds with progressive technologies.** This is a field of high success in current research in terms of the development of improved targeted therapies and synergic biological effects. This may satisfy the demands of sustainability and robust scientific basis of modern treatments;

- **To harmonize standards in safety and regulation.** This should not only take place in response to a specific safety concern. It must be part of the daily scientific work, including the issuing of recommendations for policy regulations. In addition, this should be done with the aim to pave the way for the approval of both new nano-TCM products and new treatments that take advantage of the best knowledge of TCM and modern western medicine;

- **Cross-communication.** The knowledge of theories and practices of both TCM and nanomedicine by is key for TCM modernization and the harmonization of both disciplines. The use of different concepts and terminologies has to be known by both parties. Here, there is a substantial difference between TCM and western medical doctors. Usually, TCM doctors have been cross-trained in both TCM and western medicine, while this is still not common in western countries. Many cases where TCM has been regarded as unscientific could be attributed to a

lack of understanding by non-trained scientists and doctors. Thus, a significant proportion of TCM training could be also part of the core medical education in order to diminish cultural and language gaps. And, in turn, TCM can gradually introduce modern language terminology to describe the scientific basis and analysis of its knowledge. Nowadays, the rapid development of communications facilitates cultural exchanges, which should be done with a truly aim to understand each other;

- **Clinical translation of nano-TCM products.** The challenges for the clinical translation of medicine that incorporate nanomaterials and products from TCM are not different from those faced by nanomedicines and TCM separately. As reviewed recently for the case of nanomedicines and herbal medicines,[84,95] the critical determinants that need to be carefully addressed to translate the nano-TCM products to the clinical practice are related to their toxicity, safety and fate in the long-term, as well as their pharmacokinetics, i.e. the development of ADME models to the understand their precise biodistribution and evolution inside the human body. In addition, nano-TCM products will need to be produced under Good Manufacturing Practice (GMP) conditions. This is challenging owing to the fact that the procurement of GMP reagents for the preparation of nanomaterials are not on the drug discovery pipeline of pharmaceutical companies and chemical producers and due to the high variability of the proposed TCM products. Thus, the development of pharmacological products will require the strict definition of the nano-TCM product characteristics. This refers to the dosage amount of the active principle, the size of the nano-TCM product, purity, colloidal stability, and the presence of excipients and potential by-products;

- **Engage young researchers.** Finally, but not less important, the merging of both technologies, one ancient -not out of date but full of wisdom and more congenial with the pace of nature- and the other recently born, may engage the new generation of students and

researchers to gear their interest and efforts towards the study of the myriad of benefits of integrating TCM with new technological developments. Similar to the previous point, innovative educational approaches should be implemented with a common lexicon to foster improved collaborations in the future. All this will be part of future breakthroughs and improved treatments for the health of the entire world population.

AUTHOR INFORMATION

Corresponding authors

Yu Zeng: zengyu@csu.edu.cn

Gregori Casals: casals@clinic.cat

Eudald Casals: eudaldcm@gmail.com

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conceptualization, M.Z., G.C., and E.C.; Original draft preparation, M.Z., D.G., X.Z., S.J., H.Y., X.Y.; Review and editing, G.F-V., S.F., Y.W., Y.Z., G.C. and E.C.; Supervision, G.C., and E.C.; Project administration, M.Z. and E.C.

Funding Sources

This research was funded by by the National Natural Science Foundation of China (22005221 to M.Z.), the Wuyi University (2018TP010 to E.C., 2018TP011 and 2020FKZX05 to M.Z.), the Jiangmen City (2020JC01007 to M.Z.), the Ministerio de Economía y Competitividad of Spain (PI19/00774 to G.F-V and G.C.).

ABBREVIATIONS

BA: Baicalin; BBR: Berberine; CINPs: Cuttlefish ink nanoparticles; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; ICD: International Statistical Classification of Diseases and Related Health Problems; NMPA: National Medical Products Administration of China; PET/CT: Positron emission tomography-computed tomography scan;

rBMSCs: Rat bone marrow mesenchymal stem cells; TM: Traditional Medicine; TCM: Traditional Chinese Medicine; VEGF: Vascular endothelial growth factor; WOG: Wogonoside WHO: World Health Organization.

REFERENCES

1. Qiu, J. When the East meets the West: the future of traditional Chinese medicine in the 21st century. *Natl. Sci.* **2015**, *2*, 377-380, doi:10.1093/nsr/nwv049.

2. Air quality guidelines—global update 2021 (WHO): https://apps.who.int/iris/handle/10665/345329. Accessed on 2022, July 22nd.

3. Cohen, A.J.; Brauer, M.; Burnett, R.; Anderson, H.R.; Frostad, J.; Estep, K.; Balakrishnan, K.; Brunekreef, B.; Dandona, L.; Dandona, R.; et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* **2017**, *389*, 1907-1918, doi:10.1016/S0140-6736(17)30505-6.

4. Collaborators, G.B.D.R.F. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **2016**, *388*, 1659-1724, doi:10.1016/S0140-6736(16)31679-8.

5. Abbott, A. Dementia: A problem for our age. *Nature* **2011**, *475*, S2-S4, doi:10.1038/475S2a.

6. Casals, E.; Gusta, M.F.; Cobaleda-Siles, M.; Garcia-Sanz, A.; Puntes, V.F. Cancer resistance to treatment and antiresistance tools offered by multimodal multifunctional nanoparticles. *Cancer Nanotechnol.* **2017**, *8*, 7-7, doi:10.1186/s12645-017-0030-4.

7. Doyle, L.A.; Yang, W.; Abruzzo, L.V.; Krogmann, T.; Gao, Y.; Rishi, A.K.; Ross, D.D. A multidrug resistance transporter from human MCF-7 breast cancer cells. *Proc. Natl. Acad. Sci.* **1998**, *95*, 15665-15670, doi:10.1073/pnas.95.26.15665.

8. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: the next generation. *Cell* **2011**, *144*, 646-674, doi:10.1016/j.cell.2011.02.013.

9. Holohan, C.; Van Schaeybroeck, S.; Longley, D.B.; Johnston, P.G. Cancer drug resistance: an evolving paradigm. *Nat. Rev. Cancer* **2013**, *13*, 714-726, doi:10.1038/nrc3599.

10. Alekshun, M.N.; Levy, S.B. Molecular mechanisms of antibacterial multidrug resistance. *Cell* **2007**, *128*, 1037-1050, doi:10.1016/j.cell.2007.03.004.

11. Leeb, M. A shot in the arm. *Nature* **2004**, *431*, 892-893, doi:10.1038/431892a.

12. MacLean, R.C.; San Millan, A. The evolution of antibiotic resistance. *Science* **2019**, *365*, 1082-1083, doi:10.1126/science.aax3879.

13. Hu, H.-y.; Yan, F.; Zhu, J.-m.; Karuno, A.P.; Zhou, W.-w. Intercontinental transmission and local demographic expansion of SARS-CoV-2. *Epidemiol. Infect.* **2021**, *149*, e94, doi:10.1017/S0950268821000777.

14. Qiu, J. One world, one health: combating infectious diseases in the age of globalization. *Natl. Sci.* **2017**, *4*, 493-499, doi:10.1093/nsr/nwx047.

15. Alves, R.R.N.; Rosa, I.M.L. Biodiversity, traditional medicine and public health: where do they meet? *J. Ethnobiol. Ethnomed* **2007**, *3*, 14, doi:10.1186/1746-4269-3-14.

16. Cicchese, J.M.; Evans, S.; Hult, C.; Joslyn, L.R.; Wessler, T.; Millar, J.A.; Marino, S.; Cilfone, N.A.; Mattila, J.T.; Linderman, J.J.; et al. Dynamic balance of pro- and anti-inflammatory signals controls disease and limits pathology. *Immunol. Rev.* **2018**, *285*, 147-167, doi:10.1111/imr.12671.

17. Mills, C.D.; Kincaid, K.; Alt, J.M.; Heilman, M.J.; Hill, A.M. M-1/M-2 Macrophages and the Th1/Th2 Paradigm. *J. Immunol.* **2000**, *164*, 6166-6173, doi:10.4049/jimmunol.164.12.6166.

18. Wynn, T.A.; Chawla, A.; Pollard, J.W. Macrophage biology in development, homeostasis and disease. *Nature* **2013**, *496*, 445-455, doi:10.1038/nature12034.

19. Almeida, A.; Mitchell, A.L.; Boland, M.; Forster, S.C.; Gloor, G.B.; Tarkowska, A.; Lawley, T.D.; Finn, R.D. A new genomic blueprint of the human gut microbiota. *Nature* **2019**, *568*, 499-504, doi:10.1038/s41586-019-0965-1.

20. Mayer, E.A.; Knight, R.; Mazmanian, S.K.; Cryan, J.F.; Tillisch, K. Gut microbes and the brain: paradigm shift in neuroscience. *J. Neurosci.* **2014**, *34*, 15490-15496, doi:10.1523/JNEUROSCI.3299-14.2014.

21. Wang, Y.; Kasper, L.H. The role of microbiome in central nervous system disorders. *Brain. Behav. Immun.* **2014**, *38*, 1-12, doi:10.1016/j.bbi.2013.12.015.

22. https://www.pharmaceutical-technology.com/comment/pfizer-novartis-nash-partnership/. Accessed on 2022, July 22nd.

23. https://web.archive.org/web/20171004085534/https://www.pharma.us.novartis.com/news/media-releases/novartis-receives-fda-approval-first-its-kind-kisqalir-femarar-co-pack-initial. Accessed on 2022, July 22nd.

24. World Health, O. *WHO global report on traditional and complementary medicine 2019*; World Health Organization: Geneva, 2019.

25. The art and science of traditional medicine Part 1: TCM today - A case for integration. *Science* **2014**, *346*.

26. The Art and Science of Traditional Medicine Part 2: Multidisciplinary Approaches for Studying Traditional Medicine. *Science* **2015**, *347*, 337-337, doi:10.1126/science.347.6219.337-c.

27. The art and science of traditional medicine Part 3: The global impact of traditional medicine. *Science* **2015**, *350*.

28. World Health Organization. Programme on Traditional, M. WHO traditional medicine strategy 2002-2005. **2002**.

29. World Health Organization. Regional Office for the Western, P. *Traditional and Modern Medicine : Harmonizing the Two Approaches : a Report of the Consultation Meeting*

on Traditional and Modern Medicine : Harmonizing the Two Approaches, 22-26 November 1999, Beijing, China; Manila : WHO Regional Office for the Western Pacific: 1999 1999.

30. World Health Organization. Regional Office for the Western, P. *Second Consultation Meeting on Traditional Medicine : Harmonizing the Two Approaches, Gyeongju, Republic of Korea, 17-20 September 2003 : report*; Manila : WHO Regional Office for the Western Pacific: 2003 2003.

31. Organization, W.H. *WHO traditional medicine strategy: 2014-2023*; World Health Organization: Geneva, 2013.

32. Organization, W.H. *International classification of diseases for mortality and morbidity statistics (11th Revision) (Retrieved from https://www.who.int/classifications/icd/en/, accessed on 2022, July 22nd.*

33. Cyranoski, D. Why Chinese medicine is heading for clinics around the world. *Nature* **2018**, *561*, 448-450, doi:10.1038/d41586-018-06782-7.

34. Traditional Chinese medicine needs proper scrutiny. *Nature* **2017**, *551*, 541, doi:10.1038/d41586-017-07650-6.

35. Okaiyeto, K.; Oguntibeju, O.O. African Herbal Medicines: Adverse Effects and Cytotoxic Potentials with Different Therapeutic Applications. *Int. J. Environ. Res. Public Health* **2021**, *18*, doi:10.3390/ijerph18115988.

36. Yuan, H.; Ma, Q.; Ye, L.; Piao, G. The Traditional Medicine and Modern Medicine from Natural Products. *Molecules* **2016**, *21*, 559.

37. Bonifácio, B.V.; Silva, P.B.d.; Ramos, M.A.D.S.; Negri, K.M.S.; Bauab, T.M.; Chorilli, M. Nanotechnology-based drug delivery systems and herbal medicines: a review. *Int. J. Nanomedicine* **2014**, *9*, 1-15, doi:10.2147/IJN.S52634.

38. Chen, M.; Zhou, X.; Chen, R.; Wang, J.; Ye, R.D.; Wang, Y.; Wu, C.; Mahato, R.I. Nano-carriers for delivery and targeting of active ingredients of Chinese medicine for hepatocellular carcinoma therapy. *Mater. Today* **2019**, *25*, 66-87, doi:https://doi.org/10.1016/j.mattod.2018.10.040.

39. Enrico, C. Chapter 3 - Nanotechnology-Based Drug Delivery of Natural Compounds and Phytochemicals for the Treatment of Cancer and Other Diseases. In *Studies in Natural Products Chemistry*, Atta ur, R., Ed.; Elsevier: 2019; Volume 62, pp. 91-123.

40. Liu, Y.; Feng, N. Nanocarriers for the delivery of active ingredients and fractions extracted from natural products used in traditional Chinese medicine (TCM). *Adv. Colloid Interface Sci.* **2015**, *221*, 60-76, doi:10.1016/j.cis.2015.04.006.

41. Ma, Z.; Fan, Y.; Wu, Y.; Kebebe, D.; Zhang, B.; Lu, P.; Pi, J.; Liu, Z. Traditional Chinese medicine-combination therapies utilizing nanotechnology-based targeted delivery systems: a new strategy for antitumor treatment. . *Int. J. Nanomedicine.* **2019**, *14*, 2029-2053, doi:https://doi.org/10.2147/IJN.S197889.

42. Qiao, L.; Han, M.; Gao, S.; Shao, X.; Wang, X.; Sun, L.; Fu, X.; Wei, Q. Research progress on nanotechnology for delivery of active ingredients from traditional Chinese medicines. *J. Mater. Chem. B* **2020**, *8*, 6333-6351, doi:10.1039/D0TB01260B.

43. Zheng, Y.; Wang, Y.; Xia, M.; Gao, Y.; Zhang, L.; Song, Y.; Zhang, C. The combination of nanotechnology and traditional Chinese medicine (TCM) inspires the modernization of TCM: review on nanotechnology in TCM-based drug delivery systems. *Drug Deliv. Transl. Res.* **2021**, *12*, 1306-1325, doi:10.1007/s13346-021-01029-x.

44. Shatkin, J.A. The Future in Nanosafety. *Nano Lett.* **2020**, *20*, 1479-1480, doi:10.1021/acs.nanolett.0c00432.

45. Yan, L.; Zhao, F.; Wang, J.; Zu, Y.; Gu, Z.; Zhao, Y. A Safe-by-Design Strategy towards Safer Nanomaterials in Nanomedicines. *Adv. Mater.* **2019**, *31*, 1805391, doi:https://doi.org/10.1002/adma.201805391.

46. Chen, X.; Zhang, Y.S.; Zhang, X.; Liu, C. Organ-on-a-chip platforms for accelerating the evaluation of nanomedicine. *Bioact. Mater.* **2021**, *6*, 1012-1027, doi:https://doi.org/10.1016/j.bioactmat.2020.09.022.

47. Maynard, A.D. Nanotechnology: assessing the risks. *Nano Today* **2006**, *1*, 22-33, doi:https://doi.org/10.1016/S1748-0132(06)70045-7.

48. Satterfield, T.; Kandlikar, M.; Beaudrie, C.E.H.; Conti, J.; Herr Harthorn, B. Anticipating the perceived risk of nanotechnologies. *Nat. Nanotechnol.* **2009**, *4*, 762-758, doi:10.1038/nnano.2009.265.

49. Schütz, H.; Wiedemann, P.M. Framing effects on risk perception of nanotechnology. *Public Underst. Sci.* **2008**, *17*, 369-379, doi:10.1177/0963662506071282.

50. Service, R.F. Is Nanotechnology Dangerous? *Science* **2000**, *290*, 1526-1527, doi:10.1126/science.290.5496.1526.

51. Siegrist, M.; Wiek, A.; Helland, A.; Kastenholz, H. Risks and nanotechnology: the public is more concerned than experts and industry. *Nat. Nanotechnol.* **2007**, *2*, 67-67, doi:10.1038/nnano.2007.10.

52. Gao, L.; Wu, X. Comparison of traditional Chinese medicine with Western medicine cancer therapy. *Chin. J. Clin. Oncol.* **2008**, *5*, 231-234, doi:10.1007/s11805-008-0231-z.

53. Lu, S.-Y.; Chen, J.-J.; Pan, J.-I.; Fu, Z.-X.; Wu, J.-L.; Hsieh, T.-C. The Association Between Different Patterns of Traditional Chinese Medicine Treatment and All-Cause Mortality Among Cancer Patients. *Integr. Cancer. Ther.* **2019**, *18*, 1534735418823273, doi:10.1177/1534735418823273.

54. Tao, W.; Luo, X.; Cui, B.; Liang, D.; Wang, C.; Duan, Y.; Li, X.; Zhou, S.; Zhao, M.; Li, Y.; et al. Practice of traditional Chinese medicine for psycho-behavioral intervention improves quality of life in cancer patients: A systematic review and meta-analysis. *Oncotarget* **2015**, *6*, 39725-39739, doi:10.18632/oncotarget.5388.

55. Zhang, L.; Wu, C.; Zhang, Y.; Liu, F.; Zhao, M.; Bouvet, M.; Hoffman, R.M. Efficacy comparison of traditional Chinese medicine LQ versus gemcitabine in a mouse model of pancreatic cancer. *J. Cell. Biochem.* **2013**, *114*, 2131-2137, doi:10.1002/jcb.24561.

56. Tobinick, E.L. The value of drug repositioning in the current pharmaceutical market. *Drug News Perspect.* **2009**, *22*, 119-125, doi:10.1358/dnp.2009.22.2.1303818.

57. Wouters, O.J.; McKee, M.; Luyten, J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA* **2020**, *323*, 844-853, doi:10.1001/jama.2020.1166.

58. Klayman, D.L. Qinghaosu (artemisinin): an antimalarial drug from China. *Science* **1985**, *228*, 1049-1055, doi:10.1126/science.3887571.

59. Su, X.-Z.; Miller, L.H. The discovery of artemisinin and the Nobel Prize in Physiology or Medicine. *Sci. China Life Sci.* **2015**, *58*, 1175-1179, doi:10.1007/s11427-015-4948-7.

60. Tu, Y. Artemisinin-A Gift from Traditional Chinese Medicine to the World (Nobel Lecture). *Angew. Chem., Int. Ed. Engl.* **2016**, *55*, 10210-10226, doi:10.1002/anie.201601967.

61. Petrie, B.; Barden, R.; Kasprzyk-Hordern, B. A review on emerging contaminants in wastewaters and the environment: Current knowledge, understudied areas and recommendations for future monitoring. *Water Res.* **2015**, *72*, 3-27, doi:https://doi.org/10.1016/j.watres.2014.08.053.

62. Allison, M. Is personalized medicine finally arriving? *Nat. Biotechnol.* **2008**, *26*, 509-517, doi:10.1038/nbt0508-509.

63. Herrmann, I.K.; Rösslein, M. Personalized medicine: the enabling role of nanotechnology. *Nanomedicine* **2016**, *11*, 1-3, doi:10.2217/nnm.15.152.

64. Hodson, R. Precision medicine. *Nature* **2016**, *537*, S49-S49, doi:10.1038/537S49a.

65. Chan, K.; Hu, X.-Y.; Razmovski-Naumovski, V.; Robinson, N. Challenges and opportunities of integrating traditional Chinese medicine into mainstream medicine: A review of the current situation. *Eur. J. Integr. Med.* **2015**, *7*, 67-75, doi: 10.1016/j.eujim.2014.12.006.

66. Wang, X.; Zhang, A.; Sun, H.; Yan, G.; Wang, P.; Han, Y. Chapter 1 - Traditional Chinese Medicine: Current State, Challenges, and Applications. In *Serum Pharmacochemistry of Traditional Chinese Medicine*, Wang, X., Ed.; Academic Press: 2017; pp. 1-6.

67. Yan, G.; Wang, Y.; Han, X.; Zhang, Q.; Xie, H.; Chen, J.; Ji, D.; Mao, C.; Lu, T. A Modern Technology Applied in Traditional Chinese Medicine: Progress and Future of the Nanotechnology in TCM. *Dose-Response* **2019**, *17*, 1559325819872854, doi:10.1177/1559325819872854.

68. Normile, D. The New Face of Traditional Chinese Medicine. *Science* **2003**, *299*, 188-190, doi:doi:10.1126/science.299.5604.188.

69. Xue, T.; Roy, R. Studying Traditional Chinese Medicine. *Science* **2003**, *300*, 740-741, doi:10.1126/science.300.5620.740.

70. Huang, C.-D.; Liao, K.-C.; Chung, F.-T.; Tseng, H.-M.; Fang, J.-T.; Lii, S.-C.; Kuo, H.-P.; Yeh, S.-J.; Lee, S.-T. Different perceptions of narrative medicine between Western and Chinese medicine students. *BMC Med. Educ.* **2017**, *17*, 85-85, doi:10.1186/s12909-017-0925-0.

71. Tseui, J.J. Eastern and western approaches to medicine. *West. J. Med.* **1978**, *128*, 551-557.

72. Ekor, M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front. Pharmacol.* **2014**, *4*, doi:10.3389/fphar.2013.00177.

73. Li, F.-S.; Weng, J.-K. Demystifying traditional herbal medicine with modern approach. *Nature Plants* **2017**, *3*, 17109, doi:10.1038/nplants.2017.109.

74. Raynor, D.K.; Dickinson, R.; Knapp, P.; Long, A.F.; Nicolson, D.J. Buyer beware? Does the information provided with herbal products available over the counter enable safe use? *BMC Medicine* **2011**, *9*, 94, doi:10.1186/1741-7015-9-94.

75. Pelaz, B.; Alexiou, C.; Alvarez-Puebla, R.A.; Alves, F.; Andrews, A.M.; Ashraf, S.; Balogh, L.P.; Ballerini, L.; Bestetti, A.; Brendel, C.; et al. Diverse Applications of Nanomedicine. *ACS Nano* **2017**, *11*, 2313-2381, doi:10.1021/acsnano.6b06040.

76. Parolo, C.; Sena-Torralba, A.; Bergua, J.F.; Calucho, E.; Fuentes-Chust, C.; Hu, L.; Rivas, L.; Álvarez-Diduk, R.; Nguyen, E.P.; Cinti, S.; et al. Tutorial: design and fabrication of nanoparticle-based lateral-flow immunoassays. *Nat. Protoc.* **2020**, *15*, 3788-3816, doi:10.1038/s41596-020-0357-x.

77. Ates, H.C.; Brunauer, A.; von Stetten, F.; Urban, G.A.; Güder, F.; Merkoçi, A.; Früh, S.M.; Dincer, C. Integrated Devices for Non-Invasive Diagnostics. *Adv. Funct. Mater.* **2021**, *31*, 2010388, doi:10.1002/adfm.202010388.

78. Howes, P.D.; Chandrawati, R.; Stevens, M.M. Colloidal nanoparticles as advanced biological sensors. *Science* **2014**, *346*, 1247390, doi:10.1126/science.1247390.

79. Chen, H.; Zhang, W.; Zhu, G.; Xie, J.; Chen, X. Rethinking cancer nanotheranostics. *Nat. Rev. Mater.* **2017**, *2*, 17024, doi:10.1038/natrevmats.2017.24.

80. Ju, Y.; Dong, B.; Yu, J.; Hou, Y. Inherent multifunctional inorganic nanomaterials for imaging-guided cancer therapy. *Nano Today* **2019**, *26*, 108-122, doi:https://doi.org/10.1016/j.nantod.2019.03.006.

81. Lin, L.S.; Yang, X.; Zhou, Z.; Yang, Z.; Jacobson, O.; Liu, Y.; Yang, A.; Niu, G.; Song, J.; Yang, H.H.; et al. Yolk-Shell Nanostructure: An Ideal Architecture to Achieve Harmonious Integration of Magnetic-Plasmonic Hybrid Theranostic Platform. *Adv. Mater.* **2017**, *29*, doi:10.1002/adma.201606681.

82. Xie, J.; Lee, S.; Chen, X. Nanoparticle-based theranostic agents. *Adv. Drug Deliv. Rev.* **2010**, *62*, 1064-1079, doi:10.1016/j.addr.2010.07.009.

83. Alagarsamy, K.N.; Mathan, S.; Yan, W.; Rafieerad, A.; Sekaran, S.; Manego, H.; Dhingra, S. Carbon nanomaterials for cardiovascular theranostics: Promises and challenges. *Bioact. Mater.* **2021**, *6*, 2261-2280, doi:https://doi.org/10.1016/j.bioactmat.2020.12.030.

84. Liu, W.-b.; Dong, S.-h.; Hu, W.-h.; Gao, M.; Li, T.; Ji, Q.-b.; Yang, X.-q.; Qi, D.-b.; Zhang, Z.; Song, Z.-L.; et al. A simple, universal and multifunctional template agent for personalized treatment of bone tumors. *Bioact. Mater.* **2021**, doi:https://doi.org/10.1016/j.bioactmat.2021.10.027.

85. Fröhlich, H.; Balling, R.; Beerenwinkel, N.; Kohlbacher, O.; Kumar, S.; Lengauer, T.; Maathuis, M.H.; Moreau, Y.; Murphy, S.A.; Przytycka, T.M.; et al. From hype to reality: data science enabling personalized medicine. *BMC Medicine* **2018**, *16*, 150, doi:10.1186/s12916-018-1122-7.

86. Zheng, Y.; Wang, Y.; Xia, M.; Gao, Y.; Zhang, L.; Song, Y.; Zhang, C. The combination of nanotechnology and traditional Chinese medicine (TCM) inspires the modernization of TCM: review on nanotechnology in TCM-based drug delivery systems. *Drug Deliv. Transl. Res.* **2021**, doi:10.1007/s13346-021-01029-x.

87. Tang, W.; Fan, W.; Lau, J.; Deng, L.; Shen, Z.; Chen, X. Emerging blood–brain-barrier-crossing nanotechnology for brain cancer theranostics. *Chem. Soc. Rev.* **2019**, *48*, 2967-3014, doi:10.1039/C8CS00805A.

88. Cherukula, K.; Manickavasagam Lekshmi, K.; Uthaman, S.; Cho, K.; Cho, C.-S.; Park, I.-K. Multifunctional Inorganic Nanoparticles: Recent Progress in Thermal Therapy and Imaging. *Nanomaterials* **2016**, *6*, 76, doi:10.3390/nano6040076.

89. Zhang, L.; Su, H.; Cai, J.; Cheng, D.; Ma, Y.; Zhang, J.; Zhou, C.; Liu, S.; Shi, H.; Zhang, Y.; et al. A Multifunctional Platform for Tumor Angiogenesis-Targeted Chemo-Thermal Therapy Using Polydopamine-Coated Gold Nanorods. *ACS Nano* **2016**, *10*, 10404-10417, doi:10.1021/acsnano.6b06267.

90. Cui, X.; Zhang, J.; Wan, Y.; Fang, F.; Chen, R.; Shen, D.; Huang, Z.; Tian, S.; Xiao, Y.; Li, X.; et al. Dual Fenton Catalytic Nanoreactor for Integrative Type-I and Type-II Photodynamic Therapy Against Hypoxic Cancer Cells. *ACS Appl. Bio Mater.* **2019**, *2*, 3854-3860, doi:10.1021/acsabm.9b00456.

91. Rozhkova, E.A.; Ulasov, I.; Lai, B.; Dimitrijevic, N.M.; Lesniak, M.S.; Rajh, T. A High-Performance Nanobio Photocatalyst for Targeted Brain Cancer Therapy. *Nano Lett.* **2009**, *9*, 3337-3342, doi:10.1021/nl901610f.

92. Canavese, G.; Ancona, A.; Racca, L.; Canta, M.; Dumontel, B.; Barbaresco, F.; Limongi, T.; Cauda, V. Nanoparticle-assisted ultrasound: A special focus on sonodynamic therapy against cancer. *Chem. Eng. J.* **2018**, *340*, 155-172, doi:10.1016/j.cej.2018.01.060.

93. Qian, X.; Zheng, Y.; Chen, Y. Micro/Nanoparticle-Augmented Sonodynamic Therapy (SDT): Breaking the Depth Shallow of Photoactivation. *Adv. Mater.* **2016**, *28*, 8097-8129, doi:10.1002/adma.201602012.

94. Arvizo, R.R.; Bhattacharyya, S.; Kudgus, R.A.; Giri, K.; Bhattacharya, R.; Mukherjee, P. Intrinsic therapeutic applications of noble metal nanoparticles: past, present and future. *Chem. Soc. Rev.* **2012**, *41*, 2943-2970, doi:10.1039/C2CS15355F.

95. Reimer, P.; Balzer, T. Ferucarbotran (Resovist): a new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: properties, clinical development, and applications. *Eur. Radiol.* **2003**, *13*, 1266-1276, doi:10.1007/s00330-002-1721-7.

96. Schwenk, M.H. Ferumoxytol: a new intravenous iron preparation for the treatment of iron deficiency anemia in patients with chronic kidney disease. *Pharmacotherapy* **2010**, *30*, 70-79, doi:10.1592/phco.30.1.70.

97. Maier-Hauff, K.; Ulrich, F.; Nestler, D.; Niehoff, H.; Wust, P.; Thiesen, B.; Orawa, H.; Budach, V.; Jordan, A. Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme. *J. Neurooncol.* **2011**, *103*, 317-324, doi:10.1007/s11060-010-0389-0.

98. Casals, E.; Zeng, M.; Parra-Robert, M.; Fernández-Varo, G.; Morales-Ruiz, M.; Jiménez, W.; Puntes, V.; Casals, G. Cerium Oxide Nanoparticles: Advances in Biodistribution, Toxicity, and Preclinical Exploration. *Small* **2020**, *n/a*, 1907322, doi:10.1002/smll.201907322.

99. Hirst, S.M.; Karakoti, A.S.; Tyler, R.D.; Sriranganathan, N.; Seal, S.; Reilly, C.M. Anti-inflammatory properties of cerium oxide nanoparticles. *Small* **2009**, *5*, 2848-2856, doi:10.1002/smll.200901048.

100. Wang, H.; Wan, K.; Shi, X. Recent Advances in Nanozyme Research. *Adv. Mater.* **2019**, *31*, 1805368, doi:https://doi.org/10.1002/adma.201805368.

101. Xu, C.; Qu, X. Cerium oxide nanoparticle: a remarkably versatile rare earth nanomaterial for biological applications. *NPG Asia Mater.* **2014**, *6*, e90-e90, doi:10.1038/am.2013.88.

102. Yang, B.; Chen, Y.; Shi, J. Nanocatalytic Medicine. *Adv. Mater.* **2019**, *31*, 1901778, doi:https://doi.org/10.1002/adma.201901778.

103. Zhao, T.; Wu, W.; Sui, L.; Huang, Q.; Nan, Y.; Liu, J.; Ai, K. Reactive oxygen species-based nanomaterials for the treatment of myocardial ischemia reperfusion injuries. *Bioact. Mater.* **2022**, *7*, 47-72, doi:https://doi.org/10.1016/j.bioactmat.2021.06.006.

104. Modena, M.M.; Rühle, B.; Burg, T.P.; Wuttke, S. Nanoparticle Characterization: What to Measure? *Adv. Mater.* **2019**, *31*, 1901556, doi:10.1002/adma.201901556.

105. Chen, X.; Zhou, H.; Liu, Y.B.; Wang, J.F.; Li, H.; Ung, C.Y.; Han, L.Y.; Cao, Z.W.; Chen, Y.Z. Database of traditional Chinese medicine and its application to studies of mechanism and to prescription validation. *Br. J. Pharmacol.* **2006**, *149*, 1092-1103, doi:10.1038/sj.bjp.0706945.

106. Fang, Y.C.; Huang, H.C.; Chen, H.H.; Juan, H.F. TCMGeneDIT: a database for associated traditional Chinese medicine, gene and disease information using text mining. *BMC Complement. Altern. Med.* **2008**, *8*, 58, doi:10.1186/1472-6882-8-58.

107. Ye, H.; Ye, L.; Kang, H.; Zhang, D.; Tao, L.; Tang, K.; Liu, X.; Zhu, R.; Liu, Q.; Chen, Y.Z.; et al. HIT: linking herbal active ingredients to targets. *Nucleic Acids Res.* **2011**, *39*, D1055-1059, doi:10.1093/nar/gkq1165.

108. Huang, L.; Xie, D.; Yu, Y.; Liu, H.; Shi, Y.; Shi, T.; Wen, C. TCMID 2.0: a comprehensive resource for TCM. *Nucleic Acids Res.* **2018**, *46*, D1117-d1120, doi:10.1093/nar/gkx1028.

109. Xue, R.; Fang, Z.; Zhang, M.; Yi, Z.; Wen, C.; Shi, T. TCMID: Traditional Chinese Medicine integrative database for herb molecular mechanism analysis. *Nucleic acids research* **2013**, *41*, D1089-1095, doi:10.1093/nar/gks1100.

110. Ru, J.; Li, P.; Wang, J.; Zhou, W.; Li, B.; Huang, C.; Li, P.; Guo, Z.; Tao, W.; Yang, Y.; et al. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. *J. Cheminformatics* **2014**, *6*, 13, doi:10.1186/1758-2946-6-13.

111. Zhang, R.-z.; Yu, S.-j.; Bai, H.; Ning, K. TCM-Mesh: The database and analytical system for network pharmacology analysis for TCM preparations. *Sci. Rep.* **2017**, *7*, 2821, doi:10.1038/s41598-017-03039-7.

112. The Encyclopedia of Traditional Chinese Medicine, http://www.tcmip.cn/ETCM. Accessed on 2022, July 22nd.

113. Xu, H.Y.; Zhang, Y.Q.; Liu, Z.M.; Chen, T.; Lv, C.Y.; Tang, S.H.; Zhang, X.B.; Zhang, W.; Li, Z.Y.; Zhou, R.R.; et al. ETCM: an encyclopaedia of traditional Chinese medicine. *Nucleic Acids Res.* **2019**, *47*, D976-d982, doi:10.1093/nar/gky987.

114. Aryal, S.; Park, H.; Leary, J.F.; Key, J. Top-down fabrication-based nano/microparticles for molecular imaging and drug delivery. *Int. J. Nanomedicine* **2019**, *14*, 6631-6644, doi:10.2147/IJN.S212037.

115. Ghorbani, M.; Izadi, Z.; Jafari, S.; Casals, E.; Rezaei, F.; Aliabadi, A.; Moore, A.; Ansari, A.; Puntes, V.; Jaymand, M.; et al. Preclinical studies conducted on nanozyme antioxidants: shortcomings and challenges based on US FDA regulations. *Nanomedicine* **2021**, *16*, 1133-1151, doi:10.2217/nnm-2021-0030.

116. Bobo, D.; Robinson, K.J.; Islam, J.; Thurecht, K.J.; Corrie, S.R. Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date. *Pharm. Res.* **2016**, *33*, 2373-2387, doi:10.1007/s11095-016-1958-5.

117. Ventola, C.L. Progress in Nanomedicine: Approved and Investigational Nanodrugs. *P T* **2017**, *42*, 742-755.

118. Bangham, A.D.; Horne, R.W. Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. *J. Molec. Biol.* **1964**, *8*, 660-IN610, doi:https://doi.org/10.1016/S0022-2836(64)80115-7.

119. Gabizon, A.; Goren, D.; Fuks, Z.; Barenholz, Y.; Dagan, A.; Meshorer, A. Enhancement of adriamycin delivery to liver metastatic cells with increased tumoricidal effect using liposomes as drug carriers. *Cancer Res.* **1983**, *43*, 4730-4735.

120. Jones, A.A.D., III; Mi, G.; Webster, T.J. A Status Report on FDA Approval of Medical Devices Containing Nanostructured Materials. *Trends Biotechnol.* **2019**, *37*, 117-120, doi:10.1016/j.tibtech.2018.06.003.

121. Khurana, A.; Allawadhi, P.; Khurana, I.; Allwadhi, S.; Weiskirchen, R.; Banothu, A.K.; Chhabra, D.; Joshi, K.; Bharani, K.K. Role of nanotechnology behind the success of mRNA vaccines for COVID-19. *Nano Today* **2021**, *38*, 101142, doi:https://doi.org/10.1016/j.nantod.2021.101142.

122. Lim, S.A.; Cox, A.; Tung, M.; Chung, E.J. Clinical progress of nanomedicine-based RNA therapies. *Bioact. Mater.* **2021**, *12*, 203-213, doi: 10.1016/j.bioactmat.2021.10.018.

123. Casals, E.; Gusta, M.F.; Piella, J.; Casals, G.; Jimenez, W.; Puntes, V. Intrinsic and Extrinsic Properties Affecting Innate Immune Responses to Nanoparticles: The Case of Cerium Oxide. *Front. Immunol.* **2017**, *8*, 970, doi:10.3389/fimmu.2017.00970.

124. Krug, H.F. Nanosafety Research—Are We on the Right Track? *Angew. Chem. Int. Ed.* **2014**, *53*, 12304-12319, doi:10.1002/anie.201403367.

125. Pisanic, T.R.; Blackwell, J.D.; Shubayev, V.I.; Fiñones, R.R.; Jin, S. Nanotoxicity of iron oxide nanoparticle internalization in growing neurons. *Biomaterials* **2007**, *28*, 2572-2581, doi:https://doi.org/10.1016/j.biomaterials.2007.01.043.

126. Elsevier Health Sciences. "Nanomedicine Opens The Way For Nerve Cell Regeneration." ScienceDaily. www.sciencedaily.com/releases/2007/05/070520091842.htm. Accessed on 2022, July 22nd.

127. Yokel, R.A.; Hussain, S.; Garantziotis, S.; Demokritou, P.; Castranova, V.; Cassee, F.R. The yin: an adverse health perspective of nanoceria: uptake, distribution, accumulation, and mechanisms of its toxicity. *Environ. Sci. Nano* **2014**, *1*, 406-428, doi:10.1039/C4EN00039K.

128. Casals, E.; Gonzalez, E.; Puntes, V.F. Reactivity of inorganic nanoparticles in biological environments: insights into nanotoxicity mechanisms. *J. Phys. D: Appl. Phys.* **2012**, *45*, 443001, doi:10.1088/0022-3727/45/44/443001.

129. https://www.fda.gov/media/109910/download. Accessed on 2022, July 22nd

130. Ncube, B.M.; Dube, A.; Ward, K. Establishment of the African Medicines Agency: progress, challenges and regulatory readiness. *J. Pharm. Policy Pract.* **2021**, *14*, 29, doi:10.1186/s40545-020-00281-9.

131. The Center People's Government of the PRC. NMPA has initiated the "Action Plan on Regulatory Science in China. http://www.gov.cn/xinwen/2019-05/02/content_5388253.htm. Accessed on 2022, July 22nd.

132. Gispen-de Wied, C.C.; Leufkens, H.G.M. From molecule to market access: Drug regulatory science as an upcoming discipline. *Eur. J. Pharmacol.* **2013**, *719*, 9-15, doi:https://doi.org/10.1016/j.ejphar.2013.07.021.

133. Knoess, W.; Wiesner, J. The Globalization of Traditional Medicines: Perspectives Related to the European Union Regulatory Environment. *Engineering* **2019**, *5*, 22-31, doi:https://doi.org/10.1016/j.eng.2018.11.012.

134. Feindt, P.H.; Poortvliet, P.M. Consumer reactions to unfamiliar technologies: mental and social formation of perceptions and attitudes toward nano and GM products. *J. Risk Res.* **2020**, *23*, 475-489, doi:10.1080/13669877.2019.1591487.

135. Capon, A.; Gillespie, J.; Rolfe, M.; Smith, W. Perceptions of risk from nanotechnologies and trust in stakeholders: a cross sectional study of public, academic, government and business attitudes. *BMC Public Health* **2015**, *15*, 424, doi:10.1186/s12889-015-1795-1.

136. Joubert, I.A.; Geppert, M.; Ess, S.; Nestelbacher, R.; Gadermaier, G.; Duschl, A.; Bathke, A.C.; Himly, M. Public perception and knowledge on nanotechnology: A study based on a citizen science approach. *NanoImpact* **2020**, *17*, 100201, doi:https://doi.org/10.1016/j.impact.2019.100201.

137. Xiang, Y.; Guo, Z.; Zhu, P.; Chen, J.; Huang, Y. Traditional Chinese medicine as a cancer treatment: Modern perspectives of ancient but advanced science. *Cancer. Med.* **2019**, *8*, 1958-1975, doi:10.1002/cam4.2108.

138. Zhang, J.; Hu, K.; Di, L.; Wang, P.; Liu, Z.; Zhang, J.; Yue, P.; Song, W.; Zhang, J.; Chen, T.; et al. Traditional herbal medicine and nanomedicine: Converging disciplines to improve therapeutic efficacy and human health. *Adv. Drug Deliv. Rev.* **2021**, *178*, 113964, doi: 10.1016/j.addr.2021.113964.

139. Efferth, T.; Li, P.C.; Konkimalla, V.S.; Kaina, B. From traditional Chinese medicine to rational cancer therapy. *Trends Mol. Med.* **2007**, *13*, 353-361, doi:10.1016/j.molmed.2007.07.001.

140. Lam, W.; Bussom, S.; Guan, F.; Jiang, Z.; Zhang, W.; Gullen, E.A.; Liu, S.H.; Cheng, Y.C. The four-herb Chinese medicine PHY906 reduces chemotherapy-induced gastrointestinal toxicity. *Sci. Transl. Med.* **2010**, *2*, 45ra59, doi:10.1126/scitranslmed.3001270.

141. Liu, C.; Sun, S.; Feng, Q.; Wu, G.; Wu, Y.; Kong, N.; Yu, Z.; Yao, J.; Zhang, X.; Chen, W.; et al. Arsenene Nanodots with Selective Killing Effects and their Low-Dose Combination with ß-Elemene for Cancer Therapy. *Adv. Mater.* **2021**, *33*, 2102054, doi:10.1002/adma.202102054.

142. Buhrmann, C.; Popper, B.; Kunnumakkara, A.B.; Aggarwal, B.B.; Shakibaei, M. Evidence That Calebin A, a Component of Curcuma Longa Suppresses NF-κB Mediated Proliferation, Invasion and Metastasis of Human Colorectal Cancer Induced by TNF-β (Lymphotoxin). *Nutrients* **2019**, *11*, 2904.

143. Toden, S.; Okugawa, Y.; Jascur, T.; Wodarz, D.; Komarova, N.L.; Buhrmann, C.; Shakibaei, M.; Boland, C.R.; Goel, A. Curcumin mediates chemosensitization to 5-fluorouracil through miRNA-induced suppression of epithelial-to-mesenchymal transition in chemoresistant colorectal cancer. *Carcinogenesis* **2015**, *36*, 355-367, doi:10.1093/carcin/bgv006.

144. Weng, W.; Goel, A. Curcumin and colorectal cancer: An update and current perspective on this natural medicine. *Sem. Cancer Biol.* **2022**, *80*, 73-86, doi:10.1016/j.semcancer.2020.02.011.

145. Xu, J.; Cheng, X.; Tan, L.; Fu, C.; Ahmed, M.; Tian, J.; Dou, J.; Zhou, Q.; Ren, X.; Wu, Q.; et al. Microwave Responsive Nanoplatform via P-Selectin Mediated Drug Delivery for Treatment of Hepatocellular Carcinoma with Distant Metastasis. *Nano Letters* **2019**, *19*, 2914-2927, doi:10.1021/acs.nanolett.8b05202.

146. Koyanagi, S.; Tanigawa, N.; Nakagawa, H.; Soeda, S.; Shimeno, H., Oversulfation of fucoidan enhances its anti-angiogenic and antitumor activities. *Biochem. Pharmacol.* **2003**, *65*, 173-9, doi: 10.1016/s0006-2952(02)01478-8.

147. Zhang, J.; Shen, L.; Li, X.; Song, W.; Liu, Y.; Huang, L. Nanoformulated Codelivery of Quercetin and Alantolactone Promotes an Antitumor Response through Synergistic Immunogenic Cell Death for Microsatellite-Stable Colorectal Cancer. *ACS Nano* **2019**, *13*, 12511-12524, doi:10.1021/acsnano.9b02875.

148. Li, H.; Tan, L.; Zhang, J.W.; Chen, H.; Liang, B.; Qiu, T.; Li, Q.S.; Cai, M.; Zhang, Q.H. Quercetin is the Active Component of Yang-Yin-Qing-Fei-Tang to Induce Apoptosis in Non-Small Cell Lung Cancer. *Am. J. Chinese Med.* **2019**, *47*, 879-893, doi:10.1142/s0192415x19500460.

149. Song, X.; Zhao, Y.; Wang, S.; Wang, Y.; Chen, Q.; Zhao, H.; Wang, H.; Tian, S.; Yu, H.; Wu, Z. Zi Shen Huo Luo Formula Enhances the Therapeutic Effects of Angiotensin-Converting Enzyme Inhibitors on Hypertensive Left Ventricular Hypertrophy by Interfering With Aldosterone Breakthrough and Affecting Caveolin-1/Mineralocorticoid Receptor Colocalization and Downstream Extracellular Signal-Regulated Kinase Signaling. *Front. Pharmacol.* **2020**, *11*, 383, doi:10.3389/fphar.2020.00383.

150. Liu, X.; Bian, L.; Duan, X.; Zhuang, X.; Sui, Y.; Yang, L. Alantolactone: A sesquiterpene lactone with diverse pharmacological effects. *Chem. Biol. Drug Des.* **2021**, *98*, 1131-1145, doi:10.1111/cbdd.13972.

151. Liu, Y.; Zhang, X.; Wu, T.; Liu, B.; Yang, J.; Liu, W., Chinese herb-crosslinked hydrogel bearing rBMSCs-laden polyzwitterion microgels: Self-adaptive manipulation of micromilieu and stemness maintenance for restoring infarcted myocardium. *Nano Today* **2021**, *41*, 101306, doi:10.1016/j.nantod.2021.101306

152. Zhang, L., Pharmacokinetics and drug delivery systems for puerarin, a bioactive flavone from traditional Chinese medicine. *Drug. Deliv.* **2019**, *26*, 860-869, doi:10.1080/10717544.2019.1660732.

153. Aliakbari, F.; Mohammad-Beigi, H.; Abbasi, S.; Rezaei-Ghaleh, N.; Lermyte, F.; Parsafar, S.; Becker, S.; Tafreshi, A.P.; O'Connor, P.B.; Collingwood, J.F.; et al. Multiple Protective Roles of Nanoliposome-Incorporated Baicalein against Alpha-Synuclein Aggregates. *Adv. Funct. Mater.* **2021**, *31*, 2007765, doi: 10.1002/adfm.202007765.154.

Yang, H.; Li, Q.; Li, L.; Chen, S.; Zhao, Y.; Hu, Y.; wang, L.; Lan, X.; Zhong, L.; Lu,

D. Gastrodin modified polyurethane conduit promotes nerve repair via optimizing Schwann cells function. *Bioact. Mater.* **2022**, *8*, 355-367, doi:10.1016/j.bioactmat.2021.06.020.

155. Li, T.; Wang, P.; Guo, W.; Huang, X.; Tian, X.; Wu, G.; Xu, B.; Li, F.; Yan, C.; Liang, X.J.; et al. Natural Berberine-Based Chinese Herb Medicine Assembled Nanostructures with Modified Antibacterial Application. *ACS Nano* **2019**, *13*, 6770-6781, doi:10.1021/acsnano.9b01346.

156. Lin, Y.H.; Lin, J.H.; Chou, S.C.; Chang, S.J.; Chung, C.C.; Chen, Y.S.; Chang, C.H. Berberine-loaded targeted nanoparticles as specific Helicobacter pylori eradication therapy: in vitro and in vivo study. *Nanomedicine* **2015**, *10*, 57-71, doi:10.2217/nnm.14.76.

157. Deng, R.-H.; Zou, M.-Z.; Zheng, D.; Peng, S.-Y.; Liu, W.; Bai, X.-F.; Chen, H.-S.; Sun, Y.; Zhou, P.-H.; Zhang, X.-Z. Nanoparticles from Cuttlefish Ink Inhibit Tumor Growth by Synergizing Immunotherapy and Photothermal Therapy. *ACS Nano* **2019**, *13*, 8618-8629, doi:10.1021/acsnano.9b02993.

158. Zhang, H.; Han, G.; Litscher, G. Traditional Acupuncture Meets Modern Nanotechnology: Opportunities and Perspectives. *Evid.-based Complement. Altern. Med.* **2019**, *2019*, 2146167, doi:10.1155/2019/2146167.

159. Zhou, J.-X.; Tang, L.-N.; Yang, F.; Liang, F.-X.; Wang, H.; Li, Y.-T.; Zhang, G.-J. MoS2/Pt nanocomposite-functionalized microneedle for real-time monitoring of hydrogen peroxide release from living cells. *Analyst* **2017**, *142*, 4322-4329, doi:10.1039/C7AN01446E.

160. Jia, H.; Zhao, J.; Qin, L.; Zhao, M.; Liu, G. The fabrication of an Ni6MnO8 nanoflake-modified acupuncture needle electrode for highly sensitive ascorbic acid detection. *RSC Adv.* **2019**, *9*, 26843-26849, doi:10.1039/C9RA03850G.

161. Nardini, C.; Carrara, S.; Liu, Y.; Devescovi, V.; Lu, Y.; Zhou, X. i-Needle: Detecting the biological mechanisms of acupuncture. *Science* **2014**, *346*, S21.

162. Liu, S.; Wang, Z.; Su, Y.; Qi, L.; Yang, W.; Fu, M.; Jing, X.; Wang, Y.; Ma, Q. A neuroanatomical basis for electroacupuncture to drive the vagal–adrenal axis. *Nature* **2021**, *598*, 641-645, doi:10.1038/s41586-021-04001-4.

163. Wei, Z.; Zou, H.; Liu, G.; Song, C.; Tang, C.; Chen, S.; Zhang, G.; Ran, J.; Wang, Y.; Yin, X.; et al. Peroxidase-mimicking evodiamine/indocyanine green nanoliposomes for multimodal imaging-guided theranostics for oral squamous cell carcinoma. *Bioact. Mater.* **2021**, *6*, 2144-2157, doi:10.1016/j.bioactmat.2020.12.016.

164. Shang, Y.; Wu, C.; Hang, C.; Lu, H.; Wang, Q. Hofmeister-Effect-Guided Ionohydrogel Design as Printable Bioelectronic Devices. *Adv. Mater.* **2020**, *32*, 2000189, doi:10.1002/adma.202000189.

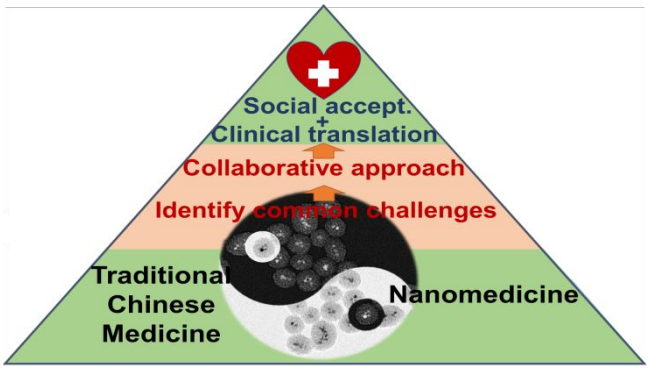
165. Chu, Y.; Zhong, J.; Liu, H.; Ma, Y.; Liu, N.; Song, Y.; Liang, J.; Shao, Z.; Sun, Y.; Dong, Y.; et al. Human Pulse Diagnosis for Medical Assessments Using a Wearable Piezoelectret Sensing System. *Adv. Funct. Mater.* **2018**, *28*, 1803413, doi:10.1002/adfm.201803413.

166. Zhang, C.; Kapaca, E.; Li, J.; Liu, Y.; Yi, X.; Zheng, A.; Zou, X.; Jiang, J.; Yu, J. An Extra-Large-Pore Zeolite with 24×8×8-Ring Channels Using a Structure-Directing Agent Derived from Traditional Chinese Medicine. *Angew. Chem., Int. Ed. Engl.* **2018**, *57*, 6486-6490, doi:10.1002/anie.201801386.

For Table of Contents Use Only

The Integration of Nanomedicine with Traditional Chinese Medicine: Drug Delivery of Natural Products and Other Opportunities

Muling Zeng[1], Dongdong Guo[1], Guillermo Fernández-Varo[2,3], Xu Zhang[1], Siqi Fu[4]， Shijie Ju[1], Huiling Yang[1], Xingfei Liu[1], Ya-Chao Wang[5], Yu Zeng[6,], Gregori Casals[2,*] and Eudald Casals[1,*]*



This review analyses how the combination of the advances of nanomedicine with the ancient knowledge of TCM can leverage the strengths of TCM and nanomedicine and improve their respective weaknesses.