Review Articles

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The "Top 50 High Impact Researches of Traditional Medicine" published in 2021

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Abstract

In recent years, significant progress has been achieved in both basic and clinical research within the field of traditional medicine, garnering increasing attention worldwide. To further promote a high-quality and international development of traditional medicine, the editorial board of *Acupuncture and Herbal Medicine* provided a collection of the "Top 50 High-impact Researches of Traditional Medicine" published in 2021 through objective indicators and a strict selection process. The findings of the selected articles have a significant academic influence and possess considerable academic value both nationally and internationally. The selected articles cover a wide range of topics, including clinical research, acupuncture, pharmacology, chemistry, biosynthesis, medicinal plant resources, and new formulation and drug delivery system research on traditional medicine. Therefore, this article outlines the selection process of the top 50 high-impact research articles, analyzes their research characteristics, and provides a brief summary of their new findings and perspectives in the field of traditional medicine.

Keywords: Academic influence,Ethnopharmacology, High-impact research, Traditional medicine

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Introduction

In the past decades, vast progress has been achieved in both basic and clinical research on acupuncture and herbal medicine, attracting an increasing attention worldwide. To facilitate the academic exchanges and exhibit the translation of research achievements during the modernization of traditional medicine, the editorial board of *Acupuncture and Herbal Medicine (AHM)* organized the selection of high-impact articles in the field of traditional Chinese medicine (TCM), ethnopharmacology, and acupuncture. Following a rigorous evaluation process, the "Top 50 High-impact Researches of Traditional Medicine" published in 2021 were selected and subsequently announced at the opening ceremony of the New Era Summit Forum on High Quality Development of the Association of Traditional Chinese Medicine on April 11, 2023.

The aim of the present article is to describe the selection procedure of those selected articles and briefly summarize their contents as well as the perspectives in the field of traditional medicine.

Selection of the "Top 50 High-impact Researches of Traditional Medicine" published in 2021

The selection process comprised four steps including nomination, evaluation, expert review, and announcement. This selection activity was organized by the journal *AHM* with the support of the Association of Traditional Chinese Medicine. The selection was conducted from five dimensions: journal, article, author, public, and academic influences. These research studies were selected by indexing in databases, expert recommendations, and self-recommendations. The final selection process included multiple stages, such as online public voting, peer expert voting, and expert consensus. Based on a comprehensive evaluation, a total of 50 research articles were ultimately selected (Table 1).

These 50 high-impact research articles covered several areas: clinical, acupuncture, phytochemical, biosynthetic, herbal medicine resource research, new formulations and drug delivery system (DDS), and pharmacological research. Of the total selected articles, 32 reported researches from the institutes in China, nine reported joint researches between China and other countries, whereas nine reported researches from institutes in the

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Table 1

Summary of the top 50 high-impact research articles on traditional medicine in 2021

No.	Research area	Title	Journal	Author
1	Clinical research	Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial	*Phytomedicine*	Hu et al. [1]
2	Clinical Research	Detection of an anti-angina therapeutic module in the effective population treated by a multi-target drug Danhong injection: a randomized trial	*Signal Transduction and Targeted Therapy*	Liu et al.[2]
3	Clinical research	Efficacy and safety of mulberry twig alkaloids tablet for the treatment of type 2 diabetes: a multicenter, randomized, double-blind, double-dummy, and parallel controlled clinical trial	*Diabetes Care*	Qu et al.[3]
4	Clinical research	Effects of Tai Chi or conventional exercise on central obesity in middle-aged and older adults: a three-group randomized controlled trial	*Annals of Internal Medicine*	Siu et al.[4]
5	Acupuncture research	Effectiveness of electroacupuncture or auricular acupuncture vs usual care for chronic musculoskeletal pain among cancer survivors: the PEACE randomized clinical trial	*JAMA Oncology*	Mao[5]
6	Acupuncture research	Efficacy of intensive acupuncture versus sham acupuncture in knee osteoarthritis: a randomized controlled trial	*Arthritis & Rheumatology*	Tu et al.[6]
7	Acupuncture research	Efficacy of acupuncture for chronic prostatitis/chronic pelvic pain syndrome: a randomized trial	*Annals of Internal Medicine*	Sun et al.[7]
8	Acupuncture research	Greater somatosensory afference with acupuncture increases primary somatosensory connectivity and alleviates fibromyalgia pain *via* insular aminobutyric acid: a randomized neuroimaging trial	*Arthritis & Rheumatology*	Mawla et al.[8]
9	Acupuncture research	Integrative effects and vagal mechanisms of transcutaneous electrical acustimulation on gastroesophageal motility in patients with gastroesophageal reflux disease	*American Journal of Gastroenterology*	Zhang et al.[9]
10	Acupuncture research	A neuroanatomical basis for electroacupuncture to drive the vagal-adrenal axis	*Nature*	Liu et al.[10]
11	Acupuncture research	Electroacupuncture ameliorates beta-amyloid pathology and cognitive impairment in Alzheimer disease *via* a novel mechanism involving activation of TFEB (transcription factor EB)	*Autophagy*	Zheng et al.[11]
12	Phytochemical research	Antioxidant and enzyme-inhibitory activity of peppermint extracts and essential oils obtained by conventional and emerging extraction techniques	*Food Chemistry*	Pavlić et al.[12]
13	Phytochemical research	Solubilization and extraction of curcumin from *Curcuma longa* using green, sustainable, and food-approved surfactant-free microemulsions	*Food Chemistry*	Degot et al.[13]
14	Biosynthetic research	Expansion within the CYP71D subfamily drives the heterocyclization of tanshinones synthesis in *Salvia miltiorrhiza*	*Nature Communications*	Ma et al.[14]
15	Biosynthetic Research	Chromosome-level genome assembly of *Ophiorrhiza pumila* reveals the evolution of camptothecin biosynthesis	*Nature Communications*	Rai et al.[15]
16	Biosynthetic research	Complete biosynthesis of the potential medicine icaritin by engineered *Saccharomyces cerevisiae* and *Escherichia coli*	*Science Bulletin*	Wang et al.[16]
17	Biosynthetic research	Structure-based engineering of substrate specificity for pinoresinol-lariciresinol reductases	*Nature Communications*	Xiao et al.[17]
18	Resource research	The chromosome-level reference genome assembly for *Dendrobium officinale* and its utility of functional genomics research and molecular breeding study	*Acta Pharmaceutica Sinica B*	Niu et al.[18]
19	Resource research	The nearly complete genome of *Ginkgo biloba* illuminates gymnosperm evolution	*Nature Plants*	Liu et al.[19]
20	Resource research	Analysis of the *Coptis chinensis* genome reveals the diversification of protoberberine-type alkaloids	*Nature Communications*	Liu et al.[20]
21	Resource research	Genome sequences reveal global dispersal routes and suggest convergent genetic adaptations in seahorse evolution	*Nature Communications*	Li et al.[21]
22	Resource research	Incipient diploidization of the medicinal plant *Perilla* within 10,000 years	*Nature Communications*	Zhang et al.[22]
23	Resource research	The chromosome-scale reference genome of safflower (*Carthamus tinctorius*) provides insights into linoleic acid and flavonoid biosynthesis	*Plant Biotechnology Journal*	Wu et al.[23]
24	Pharmacological research	Artemisia annua L. extracts inhibit the *in vitro* replication of SARS-CoV-2 and two of its variants	*Journal of Ethnopharmacology*	Nair et al.[24]
25	Pharmacological research	Multimodal identification by transcriptomics and multiscale bioassays of active components in Xuanfeibaidu formula to suppress macrophage-mediated immune response	*Engineering*	Zhao et al.[25]
26	Pharmacological research	Systems pharmacological study illustrates the immune regulation, anti-infection, anti-inflammation, and multi-organ protection mechanism of Qing-Fei-Pai-Du decoction in the treatment of COVID-19	*Phytomedicine*	Zhao et al.[26]

(Continued)

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No.	Research area	Title	Journal	Author
27	Pharmacological research	Desulfovibrio vulgaris, a potent acetic acid-producing bacterium, attenuates nonalcoholic fatty liver disease in mice.	*Gut Microbes*	Hong et al.[27]
28	Pharmacological research	Elucidation of the anti-inflammatory mechanism of Er Miao San by integrative approach of network pharmacology and experimental verification	*Pharmacological Research*	Guo et al.[28]
29	Pharmacological research	Multi-level fingerprinting and cardiomyocyte protection evaluation for comparing polysaccharides from six Panax herbal medicines	*Carbohydrate Polymers*	Liu et al.[29]
30	Pharmacological research	Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota	*Signal Transduction and Targeted Therapy*	Wang et al.[30]
31	Pharmacological research	*Rhus coriaria* L. (Sumac) demonstrates oncostatic activity in the therapeutic and preventive model of breast carcinoma	*International Journal of Molecular Sciences*	Kubatka, et al.[31]
32	Pharmacological research	A SIRT1 activator, ginsenoside Rc, promotes energy metabolism in cardiomyocytes and neurons	*Journal of the American Chemical Society*	Huang et al.[32]
33	Pharmacological research	Activated PKB/GSK-3 β synergizes with PKC- δ signaling in attenuating myocardial ischemia/reperfusion injury *via* potentiation of NRF2 activity: Therapeutic efficacy of dihydrotanshinone-I	*Acta Pharmaceutica Sinica B*	Zeng et al.[33]
34	Pharmacological research	Berberine is an insulin secretagogue targeting the KCNH6 potassium channel	*Nature Communications*	Zhao et al.[34]
35	Pharmacological research	Cordycepin ameliorates nonalcoholic steatohepatitis by activation of the AMP-activated protein kinase signaling pathway	*Hepatology*	Lan et al.[35]
36	Pharmacological research	Integrative lipidomic and transcriptomic study unravels the therapeutic effects of saikosaponins A and D on non-alcoholic fatty liver disease	*Acta Pharmaceutica Sinica B*	Li et al.[36]
37	Pharmacological Research	Cryptotanshinone specifically suppresses NLRP3 inflammasome activation and protects against inflammasome-mediated diseases	*Pharmacological Research*	Liu et al.[37]
38	Pharmacological research	Discovery of herbacetin as a novel SGK1 inhibitor to alleviate myocardial hypertrophy	*Advanced Science*	Zhang et al.[38]
39	Pharmacological research	Scutellarin inhibits caspase-11 activation and pyroptosis in macrophages *via* regulating PKA signaling	*Acta Pharmaceutica Sinica B*	Ye et al.[39]
40	Pharmacological research	Sinomenine ester derivative inhibits glioblastoma by inducing mitochondria-dependent apoptosis and autophagy by PI3K/AKT/mTOR and AMPK/mTOR pathway	*Acta Pharmaceutica Sinica B*	Zheng et al.[40]
41	Pharmacological research	Tanshinone I, a new EZH2 inhibitor restricts normal and malignant hematopoiesis through upregulation of MMP9 and ABCG2	*Theranostics*	Huang, et al.[41]
42	Pharmacological research	Triptonide is a reversible non-hormonal male contraceptive agent in mice and non-human primates	*Nature Communications*	Chang et al.[42]
43	Pharmacological research	Facile and label-free fluorescence strategy for evaluating the influence of bioactive ingredients on FMO3 activity *via* supramolecular host-guest reporter pair	*Biosensors & Bioelectronics*	Yu et al.[43]
44	Pharmacological research	HERB: a high-throughput experiment- and reference-guided database of traditional Chinese medicine.	*Nucleic Acids Research*	Fang et al.[44]
45	New formulations and drug delivery system	Tumor-specific carrier-free nanodrugs with GSH depletion and enhanced ROS generation for endogenous synergistic anti-tumor by a chemotherapy-photodynamic therapy	*Chemical Engineering Journal*	Lan et al.[45]
46	New formulations and drug delivery system	Green synthesis of silver nanoparticles using *Annona muricata* extract as an inducer of apoptosis in cancer cells and inhibitor for NLRP3 inflammasome *via* enhanced autophagy	*Nanomaterials (Basel)*	Jabir et al.[46]
47	New formulations and drug delivery system	Synergetic delivery of triptolide and Ce6 with light-activatable liposomes for efficient hepatocellular carcinoma therapy	*Acta Pharmaceutica Sinica B*	Yu et al.[47]
48	New formulations and drug delivery system	Chinese herb microneedle patch for wound healing	*Bioactive Material*	Chi et al.[48]
49	New formulations and drug delivery system	More natural more better: triple natural anti-oxidant puerarin/ferulic acid/polydopamine incorporated hydrogel for wound healing	*Journal of Nanobiotechnology*	Ou et al.[49]
50	New formulations and drug delivery system	A biodegradable antibacterial alginate/carboxymethyl chitosan/ Kangfuxin sponges for promoting blood coagulation and full-thickness wound healing	*International Journal of Biological Macromolecules*	He et al.[50]

ABCG2: ATP binding cassette subfamily G member 2; AKT: protein kinase B; AMPK: AMP-activated protein kinase; EZH2: enhancer of zeste homolog 2; MMP9: matrix metalloproteinase-9; mTOR: mammalian target of rapamycin; NLRP3: NOD-like receptor thermal protein domain associated protein 3; PI3K: phosphoinositide 3-kinase; PKA: protein kinase A system; SGK1: serum-and glucocorticoid-inducible kinase 1.

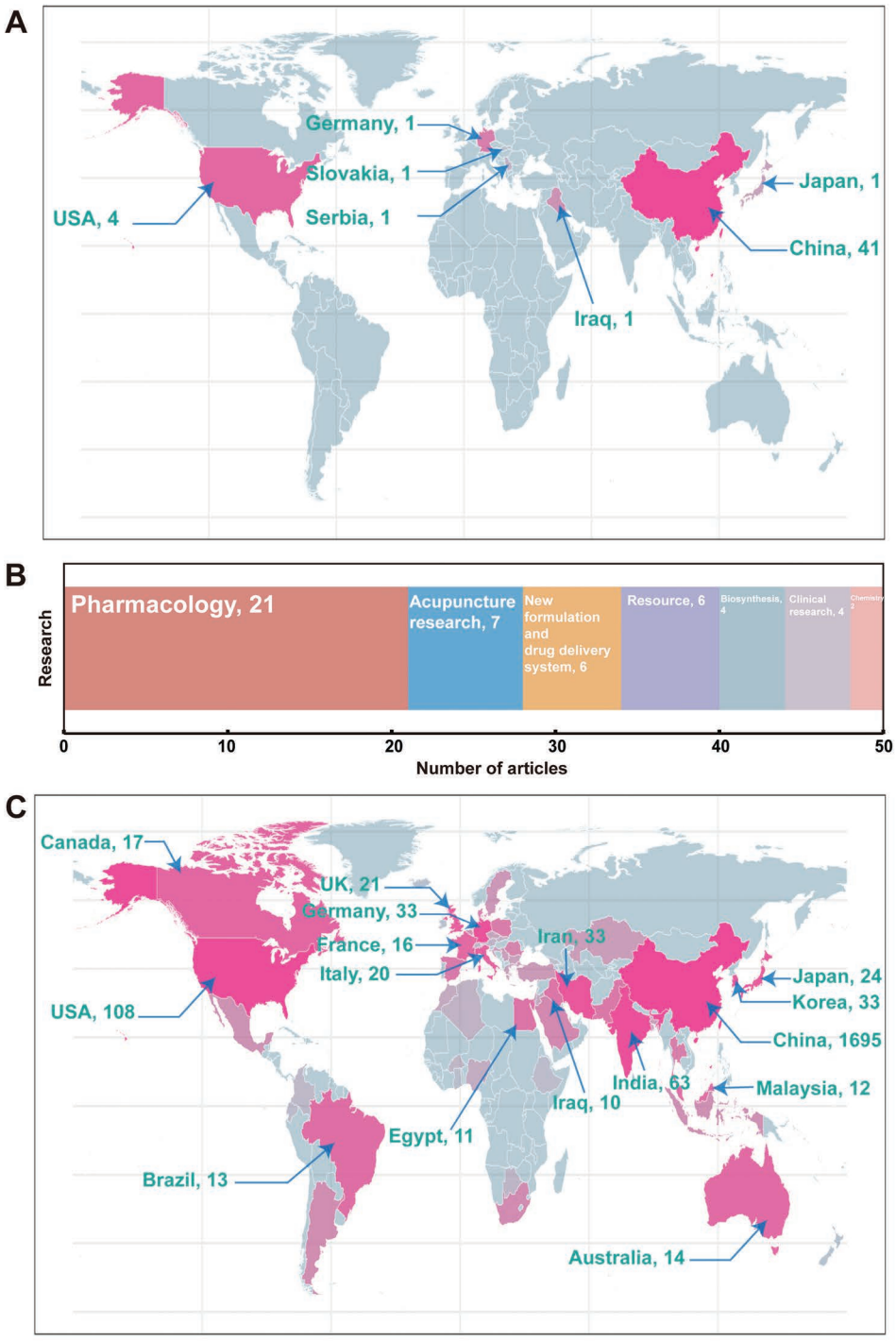

Figure 1. Summary of the characteristics of the top 50 high-impact research articles on traditional medicine in 2021. (A) Distribution of the countries which conducted the research reported by the top 50 high-impact research articles; (B) Statistics on the research fields of the top 50 high-impact research articles; (C) Maps of the countries citing the top 50 high-impact research articles (citations > 10 until August 24, 2023).

United States, Germany, Japan, and six other countries (Figure 1). Additionally, 11 articles involved research accomplished through international cooperation involving 15 institutes from 10 different countries. All publications were published across 32 journals, with the most impactful journal boasting an impact factor of 69.5 and an average impact factor of 17.77 across all journals. Renowned journals, such as *Nature*, *Annals of Internal Medicine*, *Signal Transduction and Targeted Therapy*, *Nature Communications*, *Acta Pharmaceutica Sinica B*, and *Pharmacological Research*, were included among them. Among these journals, *Nature Communications* had the highest number of publications among the selected articles, with a total of eight articles. Moreover, among the 50 high-impact research articles, the study that garnered the most citations obtained a total of 259 citations. The average number of citations for the selected articles was 45.72 (until August 24, 2023). Figure 2 shows the high-frequency keywords among the selected articles.

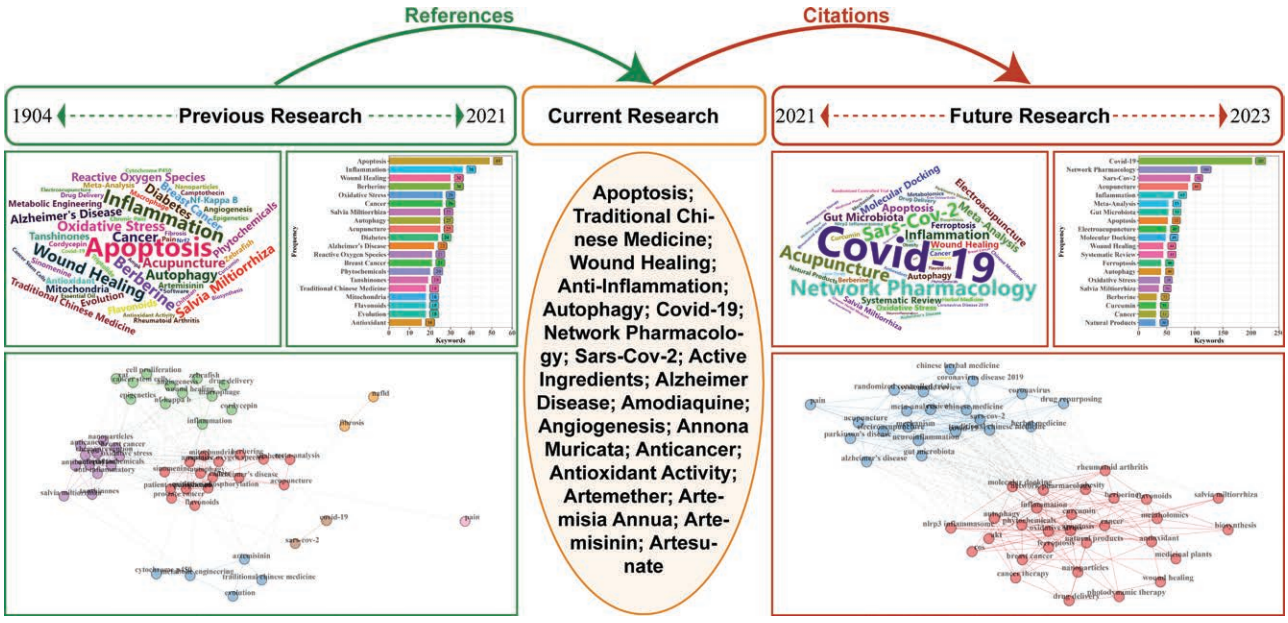

Figure 2. Visualization map generated using high-frequency keywords from the references and citations of the top 50 high-impact research articles on traditional medicine in 2021.

Research progress of the top 50 high-impact research articles on traditional medicine

Clinical and acupuncture research

The acquisition of high-quality clinical evidence is imperative for attaining worldwide recognition and facilitating the extensive utilization of traditional medicine. Among the top 50 high-impact research articles, a total of 9 clinical studies provided high-quality evidence for the efficacy and safety of TCM therapies, including components, formulae, and Chinese patent medicine, as well as non-pharmacological approaches, such as acupuncture and Tai Chi[1–9]. These high-impact studies had randomized, controlled, parallel designs, with a maximum of 920 participants from 31 institutions across China. Furthermore, two fundamental studies on acupuncture have showcased substantial progress, indicating a significant landmark in the realm of basic research on acupuncture[10–11].

Clinical evidence on the use of Chinese herbal medicine

With regard to Chinese herbal medicine, the combination of conventional treatment with Lianhuaqingwen capsules demonstrated efficacy in improving the recovery rate and alleviating symptoms, such as fever, cough, fatigue, and chest discomfort, in patients with coronavirus disease (COVID-19)[1]. Another clinical trial conducted by Liu et al., encompassing a pre-selected study of 62 cases utilizing RNA sequencing, confirmed the efficacy, safety, and effective treatment module of Danhong injection, a polycomponent drug, in patients with chronic stable angina. This study presented an innovative approach to identifying the therapeutic module of multi-target drugs by leveraging modular flexibility in populations exhibiting differential responses[2]. A study demonstrated that Sangzhi alkaloids (SZ-A), an active component of alkaloids isolated from the Chinese medicinal herb "mulberry twig," exhibit hypoglycemic effects equivalent to acarbose in patients with type 2 diabetes (T2D)[3]. This phase IIa clinical trial, conducted by Siu et al., encompassing 23 clinical institutions and 600 patients with T2D, represents the largest randomized controlled trial (RCT) on plant natural products for the treatment of T2D that has been conducted worldwide. In addition, the trial provided medical evidence for the clinical application of SZ-A. As a traditional Chinese physical practice and therapy, Tai Chi was shown to be effective in reducing waist circumference in adults with central obesity in comparison with conventional exercise[4].

Achievements in clinical and basic research in acupuncture

Significant advancements in clinical and basic research led to a notable progress in the field of acupuncture in 2021, resulting in substantial recognition from the global academic community. The dissemination of these meticulously conducted studies substantiates the efficacy of acupuncture in both the prevention and treatment of significant chronic ailments, thereby furnishing crucial empirical evidence for the evolution of acupuncture from an empirical practice to a medicine grounded in scientific evidence. The clinical benefits of acupuncture for chronic non-malignant pain have been established; however, their effectiveness in cancer survivors remain uncertain. We were delighted to note multicenter RCT conducted in the United States determining the effectiveness of electroacupuncture or auricular acupuncture for chronic musculoskeletal pain in cancer survivors. The research findings provide evidence that electroacupuncture and auricular acupuncture can achieve greater pain reduction compared with conventional treatments. Consequently, these non-pharmacological interventions present a promising alternative for alleviating pain among cancer patients[5]. Another RCT conducted in China, assessed the efficacy of intensive acupuncture (thrice weekly for 8 weeks) versus sham acupuncture for the treatment of knee

osteoarthritis (OA). That study concluded that intensive electroacupuncture resulted in reduced pain and improved function at week 8, compared with the effects of sham acupuncture. These effects also persisted though week 26. This clinical trial provided high-quality evidence of the clinical efficacy of electroacupuncture in the treatment of OA[6]. Acupuncture has promising effects on chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS); however, high-quality evidence is scarce. An RCT conducted by Sun et al. involving 440 participants found that compared with sham therapy, 20 sessions of acupuncture treatment conducted over 8 weeks resulted in a significant improvement in symptoms of moderate to severe CP/CPPS. These beneficial effects were sustained even 24 weeks after the treatment[7].

Acupuncture has shown promising results in the treatment of fibromyalgia. The study undertaken by Mawla et al.[8] indicated that the somatosensory component of acupuncture modulates the primary somatosensory functional connectivity associated with insular neurochemistry to reduce pain severity in fibromyalgia. Gastroesophageal reflux disease (GERD) is defined as a condition that appears when the reflux of stomach contents results in troublesome symptoms. The collaborative research conducted by Zhang et al. has provided evidence that transcutaneous electrical acustimulation (TEA) has the potential to improve the reflux-related symptoms in patients with GERD. Additionally, TEA has been found to increase the distal contractile integral, reduce the incidence of ineffective esophageal contractions during wet swallows, and improve the gastric accommodation and slow waves. The improvement in GERD symptoms might be attributed to the integrative effects of TEA on these gastroesophageal functions mediated *via* the vagal mechanism[9].

In the field of basic acupuncture research, Liu et al. collaborated on a study that aimed to elucidate the mechanisms underlying the efficacy of electroacupuncture. This seminal investigation, which was published in the journal *Nature*, represented a noteworthy achievement and a significant advancement in the field of basic acupuncture research. They found that electroacupuncture drove vagal-adrenal network to suppress the inflammation *via* Prokr2-expressing neurons at the ST36 acupoints, all of which were reversed by selectively destroying Prokr2$^+$ neurons. This study provided a neuroanatomical basis for the selection and specificity of acupoints in driving specific autonomic pathways which would have substantial clinical advantages[10]. Alzheimer disease (AD) is the most prevalent neurodegenerative disorder leading to dementia in older adults. Zheng et al. provided evidence supporting the potential efficacy of "Three-needle Electroacupuncture for Intelligence" (TNEA) as a promising treatment or adjunctive therapy for AD. In that study, acupuncture reduced the amyloid beta (A4) precursor protein (APP), C-terminal fragments of APP, and β-amyloid (Aβ) load, and inhibited glial cell activation in the prefrontal cortex and hippocampus of 5xFAD (an animal model of AD with Aβ pathology). The TNEA activated transcription factor EB by inhibiting the AKT-MAPK1-MTORC1 pathway, thus promoting the autophagy-lysosomal pathway in the brain[11].

Chemistry, biosynthesis, and resource research on herbal medicine

With the aid of modern analytical approaches, such as liquid chromatography/mass spectrometry analysis and genome sequencing, researchers are able to rapidly identify the bioactive constituents of medicinal plants and elucidate the biosynthetic mechanisms of secondary plant metabolites. Among the 50 selected articles, 12 studies were selected for reporting novel techniques for isolating and detecting bioactive components, biosynthetic pathways of plant natural products, as well as the genomes and evolution of important medicinal plants.

Applying novel extraction methods to obtain the active compounds from herbal medicine

Traditional processes for extracting active components from herbs involve the extensive use of harmful organic solvents and energy, with low target selectivity and extraction yields. Several advanced extraction techniques, such as supercritical fluid extraction (SFE), and ultrasound-assisted, microwave-assisted, enzyme-assisted, and surfactant-free microemulsion (SFME) extractions, have been developed in recent years, which are more environment-friendly and efficient. Two articles published in 2021 that utilized novel extraction methods for plant extracts were selected. Pavlić et al.[12] demonstrated that microwave-assisted hydrodistillation and SFE are efficient in recovering essential oils and other lipophilic components from peppermint extracts, respectively. Degot et al.[13] developed an SFME system with water/ethanol/triglyceride triacetin as solvents to realize the green and sustainable extraction of curcuminoids. A comparison of the extraction ability showed that the optimized SFME method extracted > 50% curcuminoids compared with the ordinary ethanol/water mixture.

Biosynthesis of active compounds in medicinal plants

The furan D-ring in tanshinones differentiates them from other abietane-type diterpenoids produced by many plants of the Lamiaceae family; however, the biogenesis of the D-ring has remained elusive for over a decade. Ma et al.[14] sequenced the genome of an almost homozygous line (bh2-7) of *Saccharomyces miltiorrhiza*. They revealed that CYP71D375 and CYP71D373 are responsible for the hydroxylation of C16 in miltirone and they followed heterocyclization to afford the furan D-ring in tanshinones. Rai et al.[15] adopted an ordered multi-scaffolding and experimental validation approach to generate a near-complete genome assembly of *Ophiorrhiza pumila*, a producer of camptothecin. The comparative multi-omics analysis revealed that the emergence of strictosidine synthase was a key event for monoterpene indole alkaloids biosynthesis in plants. Wang et al.[16] identified a prenyltransferase and a methyltransferase from *Epimedium sagittatum* that participate in icaritin biosynthesis. Based on this finding, the authors reconstituted the icaritin biosynthetic pathway in microbial hosts and achieved the *de novo* biosynthesis of this potential anticancer drug. Xiao et al.[17] determined the crystal structures of *Ii*PLR1, a pinoresinol-lariciresinol

reductase from *Isatis indigotica*, and two pinoresinol reductases (AtPrR1 and AtPrR2) from *Arabidopsis thaliana*. The structures enabled the elucidation of the molecular mechanism behind the substrate specificity of these enzymes.

Genomic studies on the medicinal plant species

Genome sequences provide the foundation for understanding the genome biology and evolution of plant species used in TCM, as well as the biogenesis of secondary metabolites from these resources. Six articles on the genomes of six widely used plant species in TCM were selected. Niu et al.[18] obtained the first chromosome-level reference genome of *Dendrobium officinale* and assembled them into 19 pseudochromosomes. Based on the comparative genomic analysis and transcriptional analysis of *D. officinale*, the biosynthesis of polysaccharides, alkaloids, and flavonoids was proposed. The high-quality genome of *D. officinale* is expected to facilitate further functional genomics research and its molecular breeding. Liu et al.[19] reported a high-quality genome of *Ginkgo biloba*, with a size of 9.87 Gb. From this genome assembly, they proposed that the genome of *G. biloba* had undergone seed plant whole-genome duplication (WGD) but lacked the lineage-specific WGD events. The rhizomes of *Coptis chinensis* ("Huanglian" in Chinese) is used in many classic TCM formulae. The main active ingredients of *Coptis* rhizomes include berberine, coptisine, jatrorrhizine, palmatine, columbamine, epiberberine, and magnoflorine. Liu et al.[20] obtained a chromosome-scale genome assembly of *C. chinensis* and found the occurrence of a single round of ancient WGD in this plant. The functionally characterized genes involved in berberine biosynthesis were mapped to the chromosomes of the *C. chinensis* genome. Moreover, Cch00017825, a member of the CYP719A1 subfamily, was characterized as a dual-functional enzyme with the (*S*)-canadine synthase and stylopine synthase activities.

Li et al.[21] performed a *de novo* assembly of the genome (420.66 Mb with 22 super-scaffolds) of male seahorse (*Hippocampus erectus*). Subsequently, they re-sequenced the genomes of 358 seahorse specimens from 21 species. The genome analyses revealed that seahorses dispersed over long distances and their diversification was aided by changing ocean currents and tectonic events. *Perilla* is widely used in East Asia as a medicinal and oil plant. Zhang et al.[22] presented the high-quality, chromosome-scale genomes of *Perilla frutescens* (tetraploid) and *Perilla citriodora* (diploid). Comparative analyses of the *Perilla* genomes suggested the occurrence of post-neolithic allotetraploidization within 10,000 years. Safflower (*Carthamus tinctorius* L.) is a member of the Asteraceae family, which has high linoleic acid (LA) and flavonoid contents. Wu et al.[23] reported a high-quality genome assembly of safflower by the combination of PacBio single-molecule real-time sequencing, Hi-C sequencing, and a genetic linkage map. Comparative genomic analyses showed that genes encoding proteins of the fatty acid desaturase 2 and chalcone synthase families, which are responsible for the biosynthesis of LA and flavonoids, respectively, were expanded *via* tandem duplications in safflower. The genome sequence of safflower provides the foundation for elucidating the molecular mechanism behind the accumulation of unsaturated fatty acids in the seeds and of flavonoids in the flowers.

Pharmacological research and applications of new technologies and methods

The rapid developments of modern biological techniques, such as omics, high-throughput screening, and genome-editing, provide opportunities to reveal the pharmacological effects of herbal medicines and the mechanism of action on *in vitro*, *ex vivo*, and *in vivo* models. The active components and substances of herbal medicines were identified and used in multiple novel tools and models. The largest proportion of selected articles (21/50) can be classified into this category, indicating the increasing research interest in this area. Among the top 50 high-impact research articles, eight have conducted basic research on the pharmacological effects or pharmacodynamic material basis of herbal medicines or TCM formulae. Additionally, 11 studies carried out in-depth research on the mechanisms and targets of the active ingredients found in herbal medicines. Furthermore, two studies successfully established a high-throughput experimental database of TCM and a supramolecular sensing strategy. These breakthroughs have introduced new technologies and methods for discovering the active ingredients from herbal medicines.

Dissecting the pharmacological effects of TCM formulae/herbs and the discovery of active compounds from herbal medicine

TCM played an important role in fighting the COVID-19 pandemic. Among the top 50 high-impact research articles on traditional medicine published in 2021, three pharmacological studies elucidated the mechanisms and active compounds of TCM in the prevention and treatment of various pathological stages of COVID-19. Nair et al. reported the *in vitro* antiviral activity of *Artemisia annua* L. extracts against the SARS-CoV-2 and its two latest variants, B1.1.7 and B1.351. They also confirmed that these effects can be achieved at concentrations attainable through an oral administration of the plant substance in humans[24]. Xuanfei Baidu formula (XFBD) is a first-class TCM formula used for COVID-19 patients with symptoms of "Shi Du Yu Fei." Zhao et al.[25] conducted a comprehensive investigation into the pharmacological mechanisms and active components of XFBD in modulating inflammation using multimodal approaches of MS-based network pharmacology, transcriptome analysis, and multiscale biological assays. Their findings offered biological insights into the clinical effectiveness of XFBD and shed light on its therapeutic potential in the treatment of COVID-19. Qingfei Paidu (QFPD) decoction, a multi-component herbal formula, is also widely in China used to treat COVID-19. Zhao et al.[26] employed systematic pharmacological methods to investigate the mechanism of action of QFPD in treating COVID-19. The research findings unveiled significant targets and pathways regulated by QFPD, elucidating its immunomodulatory, anti-infective, anti-inflammatory, and multi-organ protective effects. Furthermore, crucial

targets and functions were validated through a series of *in vitro* experiments, offering valuable insights for the systematic analysis of TCM prescriptions.

In addition, a series of high-quality studies on the pharmacological and effective substance basis of TCM formulae/herbs have been selected. Hong et al.[27] conducted a comprehensive investigation utilizing a multi-omics approach to explore the specific gut bacteria and associated metabolites that are regulated by *Astragalus* polysaccharide. They elucidated the role and mechanism of *Desulfovibrio vulgaris*, a potent acetic acid-producing bacterium, in the improvement of non-alcoholic fatty liver disease (NAFLD) in high-fat diet-induced mice by *Astragalus* polysaccharide. These findings provided novel evidence to explain the mechanism of action through which *Astragalus* polysaccharide ameliorates NAFLD. Guo et al.[28] employed a comprehensive approach of network pharmacology and experimental validation to investigate the potential key compounds, targets, and pathways involved in the therapeutic mechanism of Er Miao San (EMS), a TCM formula, for treating inflammatory diseases. Additionally, they successfully demonstrated that EMS exhibits significant anti-inflammatory properties in patients with arthritis by effectively inhibiting the inflammatory cytokines.

The study conducted by Liu et al.[29] included a focused investigation on the composition and activity differences of polysaccharides in *Panax* species. This study systematically characterized the multidimensional chemical fingerprint spectra of polysaccharides obtained from six different *Panax* herbal medicines, and also evaluated their potential cardiomyocyte protective effects, providing an important basis for the development and utilization of these polysaccharides. The study by Wang et al.[30] provided novel evidence that the oral administration of berberine can augment the biosynthesis of tetrahydrobiopterin in intestinal flora through vitamin-like mechanisms, as demonstrated by spatial metabolomics and modern mass spectrometry analysis techniques. This process subsequently enhances the production of L-dopa by tyrosine hydroxylase, thereby enhancing brain function. This offers theoretical substantiation for the utilization of berberine in the management of Parkinson disease. The study by Kubatka et al.[31] demonstrated that the extract of *Rhus coriaria* L. (Sumac) exhibited significant anti-tumor effects in syngeneic 4T1 mice and chemically-induced rat mammary carcinoma models, as well as anticancer activity against a variety of cancer cell lines.

Elucidation of the potential targets and mechanisms of action of the monomer compositions

The investigation of the targets and mechanisms of action of the medicinal substances from TCM is vital for understanding the biological basis of TCM theory and unraveling its modern scientific implications. Huang et al.[32] demonstrated that ginsenoside Rc functions as a Sirtuin 1 (SIRT1) agonist, thereby enhancing energy metabolism in cardiomyocytes and neurons. Furthermore, they validated that the interaction between ginsenoside Rc and the SIRT1 residue site augments its activity. These findings offer novel perspectives on the molecular mechanism underlying the protective properties of ginsenoside Rc. Zeng et al. conducted a comprehensive investigation on dihydrotanshinone-I (DT), a bioactive compound found in *Salvia miltiorrhiza*. Their study revealed that DT has the ability to activate the PKC-δ-regulated NRF2 nuclear import signaling, while simultaneously inhibiting the nuclear export through the PKB/GSK-3β/Fyn cascades. This dual mechanism enhances the accumulation and activation of NRF2 signaling within the nucleus, leading to the amelioration of myocardial ischemia/reperfusion injury[33]. The study conducted by Zhao et al.[34] provided a comprehensive analysis of the novel target of berberine's hypoglycemic effects, highlighting its distinct mechanism in contrast to the traditional insulin secretagogues. The findings elucidated that berberine effectively enhances the channel closure through a direct interaction with KCNH6 potassium channels, thereby impeding KCNH6 currents and prolonging high glucose-dependent cell membrane depolarization, and consequently augmenting insulin secretion. Furthermore, clinical trials have corroborated the therapeutic efficacy of berberine in alleviating diabetes without inducing hypoglycemia.

In the study conducted by Lan et al.[35], cordycepin, the active component of *Cordyceps militaris*, exhibited potential as an inhibitor of AMP-activated protein kinase (AMPK)α. This inhibition of AMPKα leads to the suppression of non-alcoholic steatohepatitis through the activation of the AMPK pathway, thereby reducing hepatic steatosis, inflammation, and fibrosis. Li et al.[36] employed a multi-omics approach combined with bioinformatics and elucidated the therapeutic effects of saikosaponin A and saikosaponin D, the active constituents of *Radix bupleuri*. Their findings demonstrated that these compounds effectively ameliorate hepatic steatosis and impede the advancement of NAFLD through the inhibition of fatty acid biosynthesis. The study conducted by Liu et al.[37] demonstrated that cryptotanshinone (CTS), a major component extracted from the traditional herb *S. miltiorrhiza* Bunge, effectively inhibits the activation of the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome in macrophages by blocking the Ca^{2+} signaling and inducing the mitochondrial reactive oxygen species (ROS). This study confirmed the specific inhibitory properties of CTS on the NLRP3 inflammasome. Zhang et al. provided a comprehensive analysis of the identification of herbacetin, a compound derived from *Rhodiola rosea*, a traditional Chinese medicinal herb, as a novel inhibitor of serum-and glucocorticoid-inducible kinase 1 (SGK1). This finding holds true in effectively alleviating myocardial hypertrophy, thereby offering potential therapeutic benefits for patients afflicted with heart failure. Moreover, this study provides a new research strategy for efficient discovery of potent compounds from herbal medicines[38].

The study conducted by Ye et al.[39] elucidated that scutellarin, a natural flavonoid, exhibits inhibitory effects on caspase-11 activation in macrophages. This inhibition is achieved through the modulation of protein kinase A system (PKA) signaling, consequently suppressing the activation of atypical NLRP3 inflammasome. These findings highlight scutellarin as a promising drug candidate for further investigation and development of therapeutic

interventions targeting bacterial sepsis-related conditions. Sinomenine is a type of biologically active compound extracted from the medicinal herb *Sinomenium acutum*. Zheng et al.[40] conducted a structural modification and optimization on sinomenine and carried out a series of studies on the screened sinomenine derivative sino-wcj-33, which exhibited potent anti-glioblastoma activity by inducing autophagy *via* phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and AMPK/mTOR signaling pathways. Xu et al. conducted a study revealing the direct interaction between Tanshinone and histone H3K27 methyltransferase enhancer of zeste homolog 2 (EZH2). This interaction has been found to inhibit the activity of the polycomb repressive complex 2 (PRC2) enzyme and subsequently upregulate matrix metalloproteinase-9 (MMP9) and ATP binding cassette subfamily G member 2 (ABCG2), thereby regulating both normal and malignant hematopoietic functions. These findings provide confirmation that Tanshinone serves as a novel inhibitor of EZH2[41]. Chang et al. reported that triptonide, a natural compound extracted from the Chinese medicinal herb *Tripterygium wilfordii* Hook F, exhibits reversible male contraceptive effects in both mice and monkeys. Additionally, they confirmed that triptonide specifically targets SPEM1, thereby disrupting its interactions with junction plakoglobin during spermiogenesis[42].

Emerging technologies and methods for the screening and identification of active compounds from herbal medicines

Under the guidance of the original theory of TCM, the integration of innovative multidisciplinary technologies and methodologies has the potential to improve the analysis of TCM's mode of action and enable new breakthroughs in the fields of herbal medicines. Yu et al.[43] developed a simple and label-free fluorescence indicator displacement analysis method using a supramolecular sensing strategy. This technique enables the identification of trimethylamine within the FMO_3 enzymatic system, employing a "switch-on" mode. The investigation was centered on the traditional formula, Xuefu Zhuyu Decoction (XFZYD), to explore the regulatory impacts of 10 compounds exhibiting favorable pharmacokinetic behavior in XFZYD on FMO_3 activity. This research offers novel concepts and technical approaches for the screening of active ingredients in herbal medicines.

To enhance the facilitation of modernization of TCM and provide guidance for contemporary drug discovery endeavors through data, the research team led by Fang et al. successfully developed the HERB database. HERB, a specialized high-throughput experimental and reference database for TCM, effectively amalgamates various databases pertaining to TCM. This comprehensive repository encompasses an extensive compilation of Chinese medicines and their constituents, thereby furnishing substantial data support for pharmacological research in the context of modern drug discovery within the realm of TCM[44].

New formulations and DDS of TCM

The research and development of new formulations and DDS facilitate the medicinal and biomedical application of TCM. The treatments for cancer and wound healing in TCM were included in the top 50 high-quality research, involving nano-DDS (NDDS)[45–46], liposomes[47], microneedle patch[48], hydrogel[49], and sponges[50]. These high-impact studies are an accumulation of studies on TCM-based formulations and DDS.

TCM-based formulations and DDS for cancer treatment

Cancer remains one of the most significant global health challenges, requiring continuous research to develop innovative and effective therapeutic strategies. TCM-based formulations and DDS present potential therapy for the treatment of cancer. Jabir et al. reported that *Annona muricata* peel extract can be used as a reducing agent for the preparation of silver nano-particles, which show potential therapeutic effects for treating cancer and inflammation[46]. Meanwhile, the poor clinical application of TCM is also improved by DDS. Yu et al.[47] showed that synergetic delivery of triptolide and Ce6 by liposomes can prevent the severe systemic toxicity of triptolide, increase the low solubility, and reduce the rapid elimination. In addition, the TCM compound is not only used as a therapeutic drug but also used to respond to the microenvironment. Lan et al. prepared a gambogic acid (GA)-based NDDS for anti-tumor effects[45]. The results showed that GA-based NDDS induces efficient apoptosis of MCF-7 cells and provides a significant anti-tumor effect by GSH depletion and increased ROS levels. Overall, the TCM compound helps in the design of formulations and DDS, to avoid adverse effects during clinical application.

TCM-based formulations and DDS for wound healing

Wound healing is related to ROS levels. TCM has been demonstrated to significantly promote wound healing against oxidative damage due to its excellent anti-oxidant and anti-inflammatory activities. The combination of multiple anti-oxidant TCM compounds provides a novel approach to wound healing and skin regeneration. For example, the codelivery of integrated puerarin, ferulic acid, and polydopamine into a hydrogel accelerates wound healing by relieving oxidative damage[49]. Meanwhile, some new preparations are also used in TCM to promote wound healing, which include composite sponges and microneedle patches[48,50]. This new form enhances the value of TCM therapy and expands its application for disease therapy.

Implications and perspectives

The selection of the top 50 high-impact research in traditional medicine is based on a comprehensive evaluation of practical clinical requirements, global applications, and the international suitability of research methodologies and technical resources. Collectively, these rationales for incorporation ensure the clinical significance, international impact, and employment of dependable and commensurable research methodologies in the selected studies. The publication of the above-mentioned findings represents the state-of-art progress in the field of traditional medicine in recent years. As traditional medicine

is increasingly being recognized, not only researchers in China but also international scholars participated in the scientific investigation of traditional medicine using modern technologies as well as the innovation of novel methodology and tools. In this context, the globalization of traditional medicine will be greatly promoted by fostering increased recognition and the acceptance of its principles and therapeutic approaches among diverse nations and regions.

The compilation of the top 50 high-impact research in traditional medicine collectively reflects the trends in traditional medicine research in recent years. Specifically, this signifies an improvement in the quality of evidence regarding the clinical effectiveness of traditional medicine, further investigation into the underlying mechanisms of traditional medicines, introduction and utilization of multidisciplinary technological tools, and strengthening of international collaboration. As TCM formulae/herbs and commonly have multiple constituents, the primary goal of research was a clear description of the scientific principle of TCM underlying its clinical efficacy. In the majority of the 50 selected papers, a multi-discipline technology was employed to reveal the mechanism of action of TCM formulae/herbs through identifying specific targets and signaling pathways of active substances. Phenotypic screening and bioactivity-guided screening were feasible methods used to discover those active substances. The pharmacological effects of TCM formulae/herbs were vastly investigated in conventional biochemical and cellular assays, as well as co-culture models, three-dimensional cultured organoids, organ-on-a-chip, and transgenic animals. The design of the novel formulations of TCM for treating diseases were also achieved by nanotechnology.

An increased amount of high-quality clinical evidence has been obtained to prove the benefits of traditional medicine; however, the current studies have some limitations. First, the comprehensive clinical trials to validate the efficacy of TCM in chronic diseases, including cancer and cardiovascular diseases, are still rare, which may hinder its wide acceptance and recognition by the international community. Additionally, there is an insufficient provision of scientific explanations regarding the mechanism of action of TCM formulae/herbs related to concepts of multi-components, multi-targets, and multi-pathways. The present studies predominantly focused on isolated components or a limited number of substances within the TCM formulae, which may lead to neglecting the synergistic effects of TCM.

In summary, researchers in the field of traditional medicine have made a great progress through inter-disciplinary research and will also benefit from the application of emerging tools, such as single-cell sequencing, multi-omics, high-content analysis, and artificial intelligence.

Conclusion

In recent years, the global recognition and impact of TCM have witnessed a steady expansion, with its widespread use across more than 190 countries and regions globally. Especially during the COVID-19 pandemic, the effectiveness of TCM in prevention, rehabilitation, and long-term symptomatic relief has gained international attention and recognition. Furthermore, the incorporation of evidence-based medicine in traditional medicine has contributed to the evolution of traditional medicine from relying solely on "experience" to being supported by "evidence." This transformation has not only improved the quality of research in the field but has also played a vital role in fostering the global acceptance of traditional medicine[51].

To further promote a high-quality and international development of traditional medicine, it is essential to communicate the "scientific story of traditional medicine." The selection of high-impact academic achievements in traditional medicine is one of the important measures to enhance the influence of TCM and ethnopharmacology within the international scientific community. In this way, the latest and most valuable scientific findings in the field of traditional medicine can not only be comprehensively presented but can also contribute to increasing public awareness and trust. Furthermore, the communication and collaboration between the field of traditional medicine and other disciplines have been strengthened, thereby promoting the inter-disciplinary integration of traditional medicine.

It is for the first time that the editorial board of *AHM* has selected the "Top 50 High Impact Researches of Traditional Medicine" published in 2021 through objective indicators and a strict selection process. The chosen research findings exhibit a significant academic influence and possess considerable academic value both nationally and internationally, representing the pinnacle of academic achievements in the field of traditional medicine. With the concept of exhibiting the "scientific story of traditional medicine" to the research community, *AHM* will regularly summarize research findings on traditional medicine and annually organize this event as a long-term project. The purpose of this initiative was to dynamically present the annual high-impact academic research and innovative achievements in traditional medicine, while fully utilizing the role of academic leadership. We hope more researchers and experts join us and dedicate to the modernization of traditional medicine through the successive publication of high-impact academic achievements.

Conflicts of interest statement

Junhua Zhang and Yuanlu Cui are editorial board members of this journal. None of the other authors declare any conflicts of interest.

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Author contributions

Xiao Li, Dong Xu, Jianfeng Tu, Bo Pang, Xiaohui Yan, Yuanlu Cui, and Yuefei Wang are the main drafters of the manuscript. Junhua Zhang, Yi Wang, and Cunzhi Liu conceived the manuscript idea, and revised and provided critical version of the manuscript. All authors contributed

to the revision of the manuscript and approved the final manuscript.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

All data generated or analyzed during this study are included in this published article.

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