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•Review•

Progress in approved drugs from natural product resources

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[ABSTRACT] Natural products (NPs) have consistently played a pivotal role in pharmaceutical research, exerting profound impacts on the treatment of human diseases. A significant proportion of approved molecular entity drugs are either directly derived from NPs or indirectly through modifications of NPs. This review presents an overview of NP drugs recently approved in China, the United States, and other countries, spanning various disease categories, including cancers, cardiovascular and cerebrovascular diseases, central nervous system disorders, and infectious diseases. The article provides a succinct introduction to the origin, activity, development process, approval details, and mechanism of action of these NP drugs.

[KEY WORDS] New drugs; Natural products; Structural modification
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Introduction

Natural products (NPs) are secondary metabolites with specific activities that are extracted and isolated from plants, animals, microorganisms, and marine organisms. These compounds are produced by organisms to fulfill signaling or defense functions. For millennia, researchers have sought medicinal remedies derived from NPs for the treatment of diseases. Historical records such as the ancient Egyptian Ebers Pharmacopoeia documented the use of willow bark infusion to alleviate rheumatic pain, while modern advancements led to the development of aspirin as an antipyretic and analgesic drug. Similarly, GE Hong's *The Handbook of Prescriptions for Emergencies* (East Jin Dynasty) recorded *Artemisia annua* as a treatment for malaria before artemisinin was discovered by TU Youyou's team [1]. With advancements in analytical techniques and identification methods, approximately 150 000−300 000 NPs with well-defined structures have been identified thus far. The open-access COCONUT database lists 407 270 naturally occurring compounds, with around 65% derived from plants and a mere 0.5% from animals or marine organisms [2].

The 2020 review by Newman and Cragg provides a comprehensive summary of therapeutic drugs approved globally from 1981 to 2019 [3]. It highlights that over 400 novel molecular entities, either directly derived from NPs and plants or modified from NPs, have received approval for drug therapy. Their analysis reveals a gradual decrease in the proportion of NP-derived drugs among all approved pharmaceuticals, a trend that has stabilized over the last 15 years (Fig. 1A) [3]. Over the past five years, the U.S. FDA's approval rate of NP-derived drugs has hovered between 20% and 40% (Fig. 1B) [4]. Although significant advancements in synthetic pharmaceutical chemistry and high-throughput virtual screening have resulted in a decrease in the proportion of new drugs developed from NPs over recent decades, the search for novel therapeutics from natural sources continues to be a critical avenue in drug discovery.

According to the clinical treatment requirement for various diseases, this review introduces 65 representative drugs that are either directly derived from NPs or their derivatives [5, 6]. These drugs have been approved by regulatory authorities, such as the National Medical Products Administration (NMDA), the United States Food and Drug Administration (FDA), the European Medicines Agency, and the Japan Pharmaceuticals and Medical Devices Agency. Among these drugs, 29 were developed in China, while the remaining 36 received approval internationally. The drugs span several therapeutic categories: 22 anticancer drugs, 11 cardiovascular and cerebrovascular disease drugs, 17 anti-infective drugs, 4 central nervous system disease drugs, 6 digestive system disease drugs, 3 immunomodulatory drugs, and 2 metabolic drugs (Fig. 1C). We categorized the drugs based on their origin country—China, the United States, and other countries.

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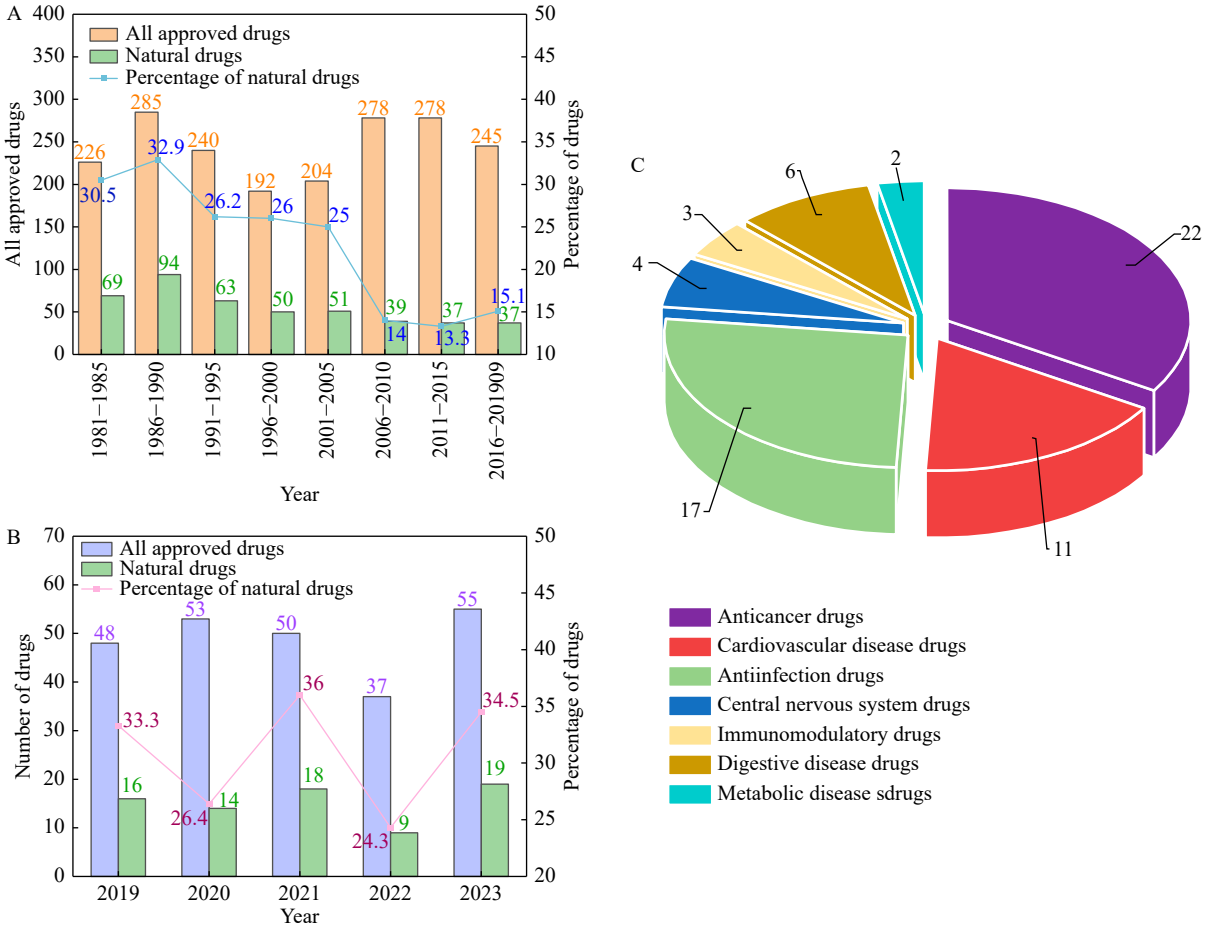

Fig. 1 Statistics of approved natural drugs and the classification of drugs in this review. (A) The percentage of natural drugs in all approved drugs between 1981 to 201909. (B) The percentage of NPs in all approved drugs in FDA from 2019 to 2023. (C) Classification of 65 natural products by disease.

Some NPs and their derivatives have undergone extensive research, leading to approval in multiple countries. To illustrate the drug development process effectively, we classified NPs according to the earliest research approval country and the timeline of the earliest research approval for each product. For example, 10-hydroxycamptothecin, initially approved in China for cancer treatment, is discussed in the context of China, even as its derivatives, such as irinotecan and topotecan, have been approved in Japan, the United States, and elsewhere, showcasing the global impact and collaborative nature of NP-derived drug development.

Natural Drugs Approved in China

Anticancer drugs

Indirubin and meisoindigo

The bisindole alkaloid compound, indirubin (**1**, Fig. 2), derived from the traditional Chinese medicine Indigo Naturalis, is the primary bioactive component in the Chinese medicinal formula "Danggui Longhui Wan". It demonstrates a wide spectrum of pharmacological effects, including anticancer, anti-inflammatory, neuroprotective, and antiviral activities. In the 1970s, the Institute of Hematology of the Chinese Academy of Medical Sciences identified indirubin as an effective component in leukemia treatment, with clinical data showing a therapeutic efficacy of 84%, leading to its approval for medical use in China [7]. Due to indirubin's gastrointestinal irritation, researchers pursued a structural modification to decrease its toxicity while enhancing its therapeutic impact. This led to the development of meisoindigo (**2**), which showed a higher tumor inhibition rate and fewer side effects compared to indirubin. As a result, a tablet formulation of meisoindigo was approved for the treatment of chronic myelogenous leukemia in China in 1992. Further experimental research on cells and animals demonstrated that both indirubin and meisoindigo act as inhibitors of cyclin-dependent kinases, playing a crucial role in regulating the Janus kinase-signal transducer and activator of transcription 3 (JAK/STST3) signaling pathway. This mechanism is pertinent in treating various cancers, including breast, lung, liver, ovarian cancer, neuroblastoma, and leukemia. Additionally, they have been shown to inhibit glycogen synthase kinase-3β, dual-specificity tyrosine-phosphorylation-regulated kinase 1A, among other kinases, while also offering neuroprotective effects and reducing inflammation [8].

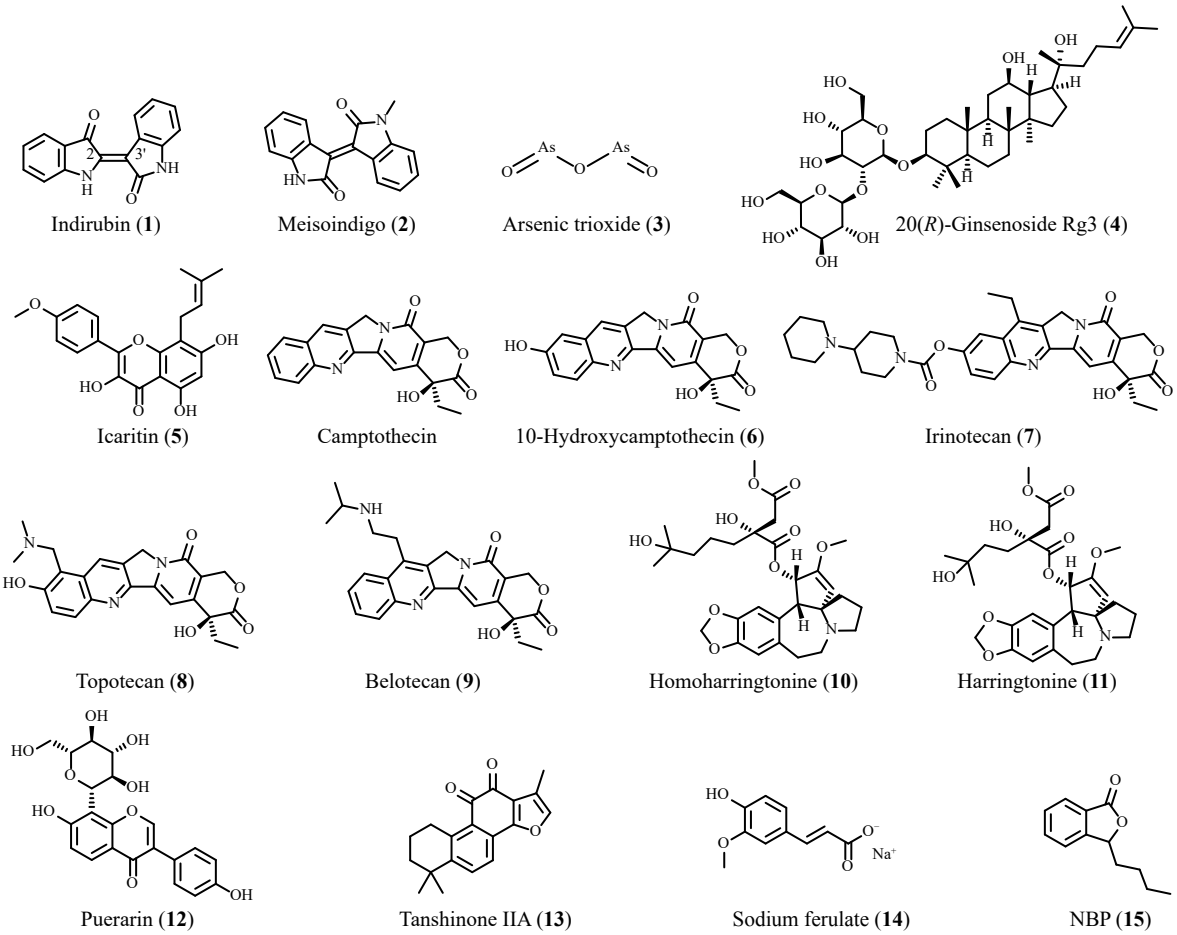

Fig. 2 Anticancer and cardiovascular and cerebrovascular diseases drugs approved in China.

Arsenic trioxide

Arsenic trioxide (**3**), known traditionally as "Pi Shuang", is an acidic amphoteric oxy-arsenide with a longstanding use in traditional Chinese medicine for treating malaria and skin diseases [9]. It is also one of the oldest known poisons. In the late 1980s, a significant breakthrough was achieved by Chinese scientists, led by ZHANG Tingdong, who utilized arsenic trioxide injections to treat acute promyelocytic leukemia (APL) patients. This innovation resulted in an exceptional clinical cure rate of 91%, quickly drawing global attention to the therapeutic potential of arsenic trioxide. Around the same time, all-*trans* retinoic acid potassium was identified for its remarkable efficacy in APL treatment, albeit with a notable drawback of high relapse rates post-chemotherapy. A pivotal advancement was made by CHEN Zhu and colleagues, who significantly enhanced APL treatment outcomes by combining arsenic trioxide with all-trans retinoic acid, establishing it as a standard treatment option for APL [10]. Arsenic trioxide was officially approved for APL treatment in China in 1999. Its mechanism of action involves targeting the promyelocytic leukemia-retinoic acid receptor alpha fusion proteins, disrupting tumor cell differentiation, and inducing apoptosis to achieve its therapeutic effects [10]. Further research has expanded the application of arsenic trioxide beyond leukemia, demonstrating its efficacy in treating pancreatic cancer, hepatocellular carcinoma, lung cancer, colorectal cancer, and other tumor types. Several preparations are currently undergoing clinical trials, underscoring the broad potential of arsenic trioxide in oncology [11]. Additionally, the observed synergistic effects of arsenic trioxide, when combined with other therapeutic agents, offer promising avenues for future cancer treatments.

20(R)-Ginsenoside Rg3

20(*R*)-Ginsenoside Rg3 (Rg3, **4**), a dammarane-type ginsenoside extracted from *Panax ginseng*, is known for its pharmacological benefits, including anticancer properties, anti-inflammatory effects, and immune system modulation [12]. Despite its potent therapeutic potential, the natural occurrence of Rg3 in ginseng is extremely low, at merely 0.000 003%, which significantly hinders its application and development. Fuli and colleagues overcame this challenge by achieving an impressive 95% purity of Rg3 through the hydrolysis of total ginsenosides. Leveraging this advancement, Atelier Pharma introduced the "Senyi Capsule" with Rg3 as its primary active ingredient. This capsule specifically targets the vascular endothelial growth factor, inhibiting tumor neoangiogenesis and metastasis. Consequently, the formulation was approved in China in 2003 for the treatment of non-small-cell lung cancer (NSCLC), gastric cancer, colon cancer, and hepatocellular carcinoma [13]. In a continued effort to explore the thera-

peutic scope of ginsenosides, Yijinsheng Capsules, based on 20(*S*)-protopanaxadiol—a final metabolite of ginseng saponin—are currently undergoing phase III clinical trials as a postoperative adjuvant treatment for lung cancer [12].

Icaritin

Icaritin (**5**), an 8-isopentenylflavonoid derived from the *Epimedium* genus, displays a broad spectrum of pharmacological activities, including bone repair promotion, anti-inflammatory effects, and anticancer properties. *In vitro* studies have revealed icaritin's capability to regulate the interleukin-6 (IL-6)/JAK/STST3 signaling pathway and influence various immune cell populations, such as $CD8^+$ T cells and $CD4^+$ Th1/Th2 cells. This regulatory effect enhances icaritin's therapeutic potential in treating liver cancer [14]. A recent clinical trial highlighted icaritin's significant impact on reducing mortality risk and improving survival outcomes for patients with advanced hepatocellular carcinoma. Consequently, in 2022, an icaritin softgel capsule was authorized for treating advanced hepatocellular carcinoma in China [15]. Building on icaritin's success, a novel anti-tumor drug, SNG1153, is currently in Phase I clinical trials in both China and the United States. This drug introduces a novel modification by replacing the methoxy group at C4 on the benzene ring with a trifluoromethyl group, potentially offering a new therapeutic mechanism and enhanced efficacy against tumors [16].

Camptothecin and its derivatives

Camptothecin, an alkaloid with a pentacyclopyrroquinoline core, was isolated in the 1960s by Wall and colleagues from *Camptotheca acuminata* (Nyssaceae), a plant native to China. Its potent anticancer activity against various cancers, such as gastric, rectal, and leukemia, has been well-documented. Nonetheless, camptothecin's clinical application has been limited by its side effects and poor water solubility. Early efforts to enhance its solubility through the development of a water-soluble sodium salt led to a reduction in anticancer efficacy and an increase in toxicity due to the ring-opened form of the compound [17]. 10-Hydroxycamptothecin (**6**), the first commercially available drug derived from camptothecin, was developed by Chinese scientists. Approved in China in 1986, it has shown considerable therapeutic success against digestive tract tumors, lung cancer, and leukemia [18]. The mechanism underlying its efficacy involves the inhibition of topoisomerase I, crucial for DNA transcription and translation, leading to cell death. This discovery paved the way for the development of several camptothecin derivatives, including irinotecan (**7**), approved in Japan in 1994 for advanced colon cancer and other solid tumors; topotecan (**8**), approved in the United States in 1996 for small-cell lung cancer; and belotecan (**9**), approved in Korea in 2005 for small-cell lung and ovarian cancers [19]. Beyond these marketed drugs, a range of novel camptothecin derivatives such as 9-amino camptothecin, silatecan, DX-8951f, and GG211 have entered clinical studies. Additionally, camptothecin-based antibody-drug conjugates like IMMU-132 and DS-8201a have shown promising anticancer effects in clinical trials and are currently in Phase III, anticipating future market introduction [20]. These developments underscore the continuing innovation and therapeutic potential of camptothecin derivatives in cancer treatment.

Homoharringtonine and harringtonine

Homoharringtonine (HTT, **10**) and harringtonine (**11**) are alkaloids primarily sourced from the *Cephalotaxus* genus, distinguished by the addition of a methylene group in HHT's side chain. Both compounds have been recognized for their broad-spectrum anticancer activities. In the 1970s, Chinese researchers embarked on clinical trials using HHT and harringtonine to treat acute myeloid leukemia (AML) and chronic granulocytic leukemia (CML), achieving notable therapeutic success with clinical cure rates ranging from 45% to 88% [21, 22]. Following these promising results, both homoharringtonine and harringtonine injections received approval in China in 1987 [23]. The journey of HHT in the United States further underscored its therapeutic potential, particularly in clinical trials for chronic myeloid leukemia (CML), highlighting its remarkable efficacy. It was not until 2012 that the FDA granted approval for HHT as a treatment option for CML cases resistant to tyrosine kinase inhibitors [24]. The mechanism by which HHT and harringtonine achieve their anticancer effects involves binding to the A-site of the ribosomal peptidyl transferase, inhibiting protein synthesis and translation, which in turn impedes tumor cell growth and induces apoptosis [25]. Despite their efficacy, the clinical use of HHT is associated with significant adverse effects, including myelosuppression and cardiotoxicity. This highlights the ongoing need for the development of derivative drugs that maintain the therapeutic benefits of HHT while minimizing toxicity and improving bioavailability, ensuring safer and more effective treatment options for patients.

Cardiovascular and cerebrovascular disease drugs

Puerarin

Puerarin (**12**), an isoflavone extracted from *Pueraria lobata*, is recognized for its wide-ranging pharmacological benefits, including vasodilation, cardioprotection, antidiabetic, antipyretic, and anti-infective effects [26]. Research has shown that puerarin promotes vasodilation by activating large conductance voltage and calcium-activated potassium channels. Additionally, it offers cardiac protection by stimulating calcium-activated potassium channels and reduces the size of cerebral infarctions by enhancing the expression of critical proteins such as hypoxia-inducible factor-1, inducible nitric oxide synthase, and tumor necrosis factor-α [27]. Clinical trials have validated puerarin's effectiveness in alleviating angina pectoris symptoms, decreasing von Willebrand factor and endothelin-1 levels in the blood, and elevating postoperative nitric oxide levels [28]. Currently, puerarin is employed in the clinical management of various cardiovascular conditions, including coronary artery disease, heart failure, and angina pectoris. Its injectable formulation was authorized for medical use by regulatory bodies in China in 1993, underscoring its therapeutic value in cardiovascular and cerebr-

ovascular disease treatment.

Tanshinone IIA

Salviae Miltiorrhizae Radix et Rhizoma, a cornerstone of traditional Chinese medicine, significantly contributes to cardiovascular disease management. Tanshinone IIA (**13**), the primary lipophilic component extracted from *Salvia miltiorrhiza*, is a diterpenoid known for its cardioprotective, anti-atherosclerotic, anti-inflammatory, anticancer, and antioxidant activities [29]. However, the clinical application of tanshinone IIA has been limited by its poor water solubility and low intestinal absorption rates. To overcome these limitations, tanshinone IIA was chemically modified into sodium tanshinone IIA sulfonate, which exhibits improved metabolic stability. Shanghai Pharmaceutical Company pioneered the development of tanshinone IIA sodium sulfonate injection, which was approved for medical use in China in 1995. This formulation has proven effective in treating angina pectoris, coronary artery disease, and myocardial infarction, among other conditions, by influencing nitric oxide synthase and cationic amino acid transporter proteins, among other pathways [30]. In addition to tanshinone ⅡA, other water-soluble constituents of *Salvia miltiorrhiza*, such as salvianolic acid A, salvianolic acid B, and danshensu, share similar pharmacological properties. As a result, various formulations, including salvianolic acid for injection, salvianolic acid drop pills, granules, and tablets, have been developed to offer therapeutic alternatives for cardiovascular and cerebrovascular diseases. These preparations are favored for their rapid onset of action and high bioavailability [31], underscoring the ongoing innovation in deriving effective treatments from traditional herbal medicines.

Sodium ferulate

Ferulic acid, a phenolic acid compound present in numerous plants, is a key ingredient in traditional Chinese medicines such as Angelicae Sinensis Radix and Chuanxiong Rhizoma, offering a broad spectrum of pharmacological effects. These include inhibition of platelet aggregation and antithrombotic, anti-inflammatory, antioxidant, and immunomodulatory activities [32]. Despite its diverse benefits, ferulic acid's clinical utility is limited by its poor water solubility. Sodium ferulate (**14**), the sodium salt form of ferulic acid, enhances aqueous solubility and structural stability, making it more conducive for clinical applications. Research has shown that sodium ferulate provides significant protection against myocardial cell hypoxia and ischemia-reperfusion injury. It also demonstrates remarkable effectiveness in treating atherosclerosis, thrombosis, migraine headaches, and vascular headaches, among other conditions [33]. Clinical studies have validated sodium ferulate's capacity to reduce whole blood viscosity in elderly patients with coronary artery disease, inhibit platelet aggregation, and prevent erythrocyte accumulation. These actions contribute to preventing or ameliorating the progression of coronary artery disease [34]. Approved in China in 1990 for injection, sodium ferulate is utilized in treating cardiovascular and cerebrovascular diseases, including atherosclerosis, coronary artery disease, and cerebrovascular disease. Furthermore, sodium ferulate aids in regulating vascular endothelial diastolic function through the enhancement of nitric oxide release and the suppression of endothelin levels. It also exhibits antithrombotic properties by inhibiting the expression of platelet agonists and the activation of *p*-selectin [35], highlighting its multifaceted role in cardiovascular health management.

N-butylphthalide

Apigenin, also known as *N*-butylphthalide (NBP, **15**) and derived from *Apium Graveolens*, is recognized for its wide range of pharmacological properties, including anti-thrombotic, anti-convulsant, antioxidant, and anti-inflammatory effects [36]. Chinese researchers, led by FENG Yipu, have highlighted NBP's effectiveness in mitigating ischemic brain injury. They demonstrated its ability to reduce the area of cerebral infarction by enhancing blood flow within the brain and promoting angiogenesis, thereby offering protection against ischemic damage. Clinical trials have further substantiated NBP's beneficial effects in patients with acute ischemic stroke, showing significant therapeutic outcomes and a lower rate of adverse effects compared to placebo treatments [37]. Following these findings, NBP soft capsules received approval in China in 2002 for the treatment of mild to moderate acute ischemic stroke cases, marking a significant advancement in the management of this condition.

Central nervous system drugs

Huperzine A

Huperzine A (**16**, Fig. 3), an alkaloid extracted from the *Huperzia* and *Phlegmariurus* genera, features a unique structure that ensures high lipid solubility and effective permeability across the blood-brain barrier. It has been extensively studied for its role in inhibiting acetylcholinesterase, which leads to an increase in acetylcholine levels, positioning it as a promising candidate for the prevention and treatment of dementia. Moreover, huperzine A shows the potential in slowing down or even reversing early-stage dementia pathology, thanks to its antagonistic effects on the *N*-methyl-D-aspartate (NMDA) receptor [38]. Clinical trials in China have validated huperzine A's efficacy and safety for Alzheimer's disease (AD) patients, revealing significant enhancements in memory and cognitive functions without the occurrence of severe side effects [39]. These positive outcomes led to the official approval of huperzine A in China in 1994 for both the prevention and treatment of Alzheimer's disease, highlighting its therapeutic value in neurodegenerative disease management.

Gastrodin

Gastrodin (**17**), identified as 4-hydroxybenzyl alcohol-4-*O*-*β*-D-glucoside and derived from *Gastrodia elata*, is the primary bioactive component known for its wide-ranging pharmacological effects, including neuroprotective, cardioprotective, antioxidant, anti-inflammatory, and anticancer properties [40]. Studies have underscored gastrodin's neuro-

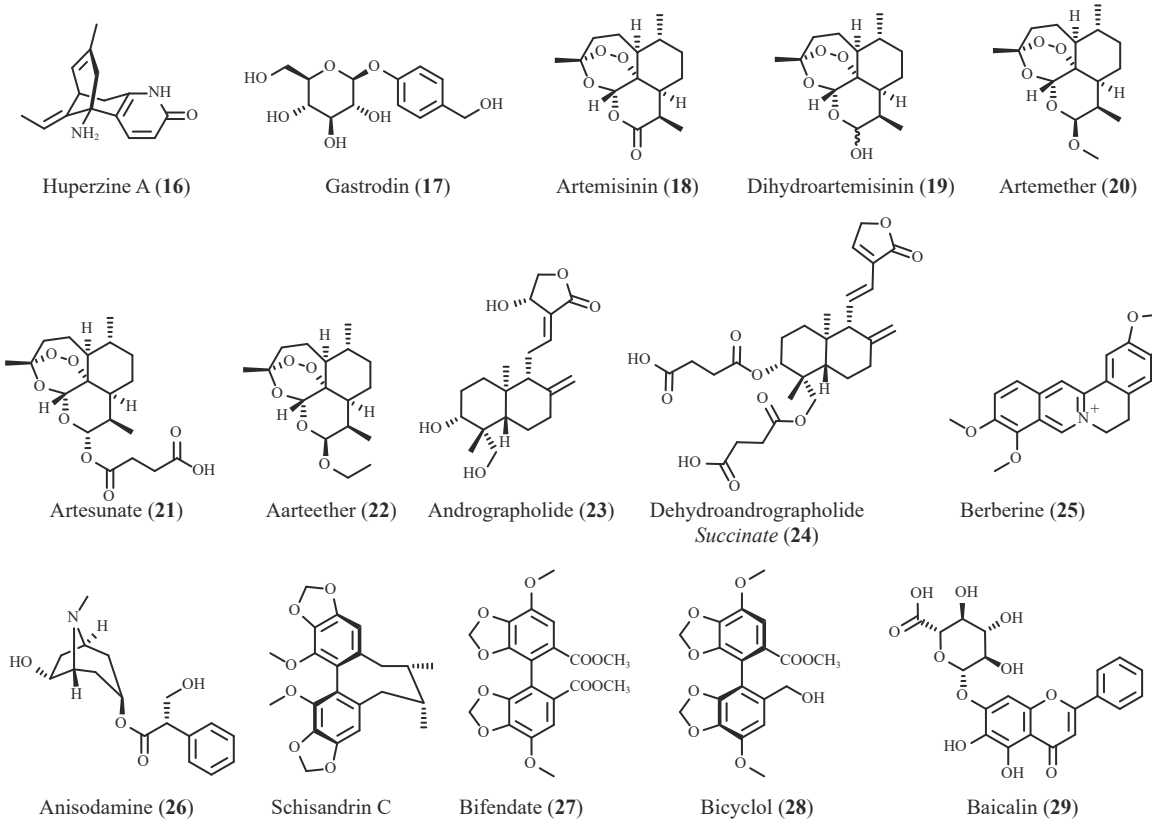

Fig. 3 Central nervous system, anti-infection, and digestive disease drugs approved in China.

protective actions, which include inhibiting abnormal neuronal conduction, reducing *β*-amyloid accumulation, and enhancing the production of neurotrophic factors. Additionally, gastrodin offers protection against oxidative stress-induced brain damage by regulating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, thereby boosting the expression of antioxidant proteins and preventing mitochondrial apoptosis. Given the strong link between neurological disorders and inflammation, gastrodin also plays a crucial role in modulating the nuclear factor-kappa B (NF-*κ*B) and mitogen-activated protein kinase (MAPK) signaling pathways. This modulation helps in suppressing the release of pro-inflammatory cytokines, effectively reducing neurological inflammation [41]. Gastrodin tablets were approved in China in 1984 for the treatment of traumatic brain injury, neurasthenia, and headaches, reflecting its therapeutic versatility and importance in managing a variety of neurological conditions.

Anti-infection drugs

Artemisinin and its derivatives

Artemisinin (**18**), a sesquiterpene lactone extracted from *Artemisia annua*, features a unique peroxide bridge that contributes to its broad pharmacological profile, including antiplasmodial, antiarrhythmic, anti-inflammatory, anticancer, and anti-lupus erythematosus activities [42]. In the 1970s, TU Youyou's team made a groundbreaking discovery that ether extracts of *A. annua* offered significant therapeutic benefits in treating clinical malaria. This led to the isolation and identification of artemisinin as the key active ingredient. Artemisinin was approved as a first-line anti-malarial drug in China in 1986, marking a major advancement in malaria treatment. The research team further modified artemisinin by converting the carbonyl group at the C10 position into a hydroxyl group, producing dihydroartemisinin **(19)**, a hemiacetal compound with superior clinical efficacy. Dihydroartemisinin received a new drug certificate from the Chinese Ministry of Health in 1992 [43]. Building on dihydroartemisinin, several novel artemisinin-based pharmaceuticals have been developed, including artemether (**20**), artesunate (**21**), and arteether (**22**). Artemether, with improved lipid solubility due to the addition of a methyl group, was formulated as an oil injection and approved in China in 1987. Artesunate, a succinic acid monoester derivative of dihydroartemisinin, notable for its enhanced water solubility and bioavailability, was also approved for injection in China in 1987. However, both artemether and artesunate exhibit short *in vivo* half-lives. To extend the antimalarial effect, a fixed-dose combination of artemether and lumefantrine, known as compound artemether tablets, was developed and received FDA approval in 2009. Similarly, a combination of artesunate and amodiaquine, termed artesunate-amodiaquine tablets, was introduced in China in 2007. The injectable hemp oil formulation of arteether, developed in the Netherlands in 2000, offered another innovative approach to malaria treatment [44, 45]. Artemisinin acts by inhibiting the Plasmodium falciparum

calcium ATPase protein 6, leading to an increase in cytosolic calcium ion concentration in the parasite and ultimately its eradication [46]. This mechanism underscores the effectiveness of artemisinin and its derivatives in treating malaria, earning them recognition as the cornerstone of malaria therapy by the World Health Organization (WHO). These developments have not only had a profound impact on malaria treatment in China but have also been instrumental in global efforts to combat this disease.

Andrographolide and its derivatives

Andrographolide (**23**), a diterpene lactone derived from *Andrographis paniculata*, is recognized for its antibacterial, anti-inflammatory, and antiviral properties [47]. Its mechanism for antiviral action is particularly notable, as it involves preventing vesicular acidification, which interferes with the cytoplasmic transport of viruses, thereby inhibiting viral replication and protein synthesis. This mode of action renders andrographolide a promising candidate for the treatment of respiratory tract infections. However, the compound's clinical application is limited by its poor solubility and low bioavailability, necessitating chemical modification for enhanced therapeutic use [48]. Potassium Sodium Dehydroandrographolide Succinate (**24**) is a water-soluble, injectable form of andrographolide produced through esterification with succinic anhydride, followed by re-salting. This modified version demonstrates a broad-spectrum antiviral effect and received approval in China in the 1970s for treating viral pneumonia and upper respiratory tract infections [49]. Kalii Dehydrographolidi Succinas, another injectable formulation of andrographolide succinate, is indicated for medical conditions similar to influnin. As research into andrographolide-related drugs continues to expand, the importance of assessing the potential for adverse effects remains critical. The development and approval of these formulations highlight the ongoing efforts to harness andrographolide's therapeutic potential while addressing its pharmacokinetic limitations.

Berberine

Berberine (**25**), an isoquinoline alkaloid derived from various plants such as *Hydrastis canadensis*, *Coptis chinensis*, *Berberis vulgaris*, *Berberis aristata*, and *Tinospora cordifolia*, showcases a wide array of pharmacological effects, including antibacterial, anticancer, hypoglycemic, antiulcer, and neuroprotective properties [50]. Berberine hydrochloride preparations have proven to be highly effective against a broad spectrum of bacteria, including *Dysentery bacilli*, *Escherichia coli*, and *Diplococcus pneumoniae*, with notable efficacy in treating infections caused by *D. bacilli* [51]. Berberine hydrochloride tablets, developed for clinical use, are extensively used in treating intestinal infections such as bacterial gastroenteritis and dysentery, receiving approval in China in 1981 for this purpose. Research indicates that berberine's mechanism of action includes disrupting bacterial cell membranes and inhibiting DNA and protein synthesis, which effectively hampers bacterial replication and contributes to its strong antibacterial activity [52].

Digestive disease drugs

Anisodamine

Anisodamine (**26**), an alkaloid found in the Solanaceae family, including *Atropa belladonna*, *Duboisia hybrid*, and *Scopolia tangutica*, is naturally occurring in the dextrorotatory form. In clinical settings, it is utilized as a chemically synthesized racemic drug [53]. Like atropine and scopolamine, anisodamine acts as an antagonist of M-cholinergic receptors. Its molecular structure, featuring a β-OH group at the C6 position, limits scopolamine's ability to cross the blood-brain barrier and produce central effects. Nonetheless, anisodamine shares peripheral anticholinergic effects with atropine, proving effective in smooth muscle relaxation, reducing vasospasm, and enhancing microcirculation, among other therapeutic benefits [54]. Clinical studies have shown that administering anisodamine hydrobromide to patients undergoing cardiopulmonary resuscitation for cardiac arrest significantly improves microcirculation, coronary endothelial function, blood gas indices, and cognitive function [55]. Pharmacological research indicates that anisodamine's effectiveness in treating septic shock involves activating α7 nicotinic acetylcholine receptors, inhibiting thromboxane synthesis, and reducing granulocyte and platelet aggregation [56, 57]. Moreover, it mitigates smooth muscle spasms through antagonism of muscarinic acetylcholine receptors and addresses organophosphorus poisoning, highlighting its broad therapeutic applications [58].

Bifendate

Schisandra chinensis, a plant widely used in traditional Chinese medicine, gained attention in the 1970s when Chinese researchers discovered its hepatoprotective properties through Schisandrae Chinensis Fructus preparations, notably reducing serum glutamic-pyruvic transaminase levels in patients with viral hepatitis. Schisandrin C, a biphenyl-containing lignan isolated from this plant, has shown hepatoprotective effects in pharmacological studies by lowering serum glutamic pyruvic transaminase levels in liver-injured mice and maintaining liver tissue integrity. It has also shown efficacy against hepatic lipid peroxidation induced by 50% ethanol in mice [59]. Due to schisandrin C's limited natural availability, Chinese scientists have synthetically modified it to create bifendate (**27**), which offers improved oral bioavailability. Following successful clinical trials that confirmed bifendate's hepatoprotective effectiveness, it was approved in China in 1983 as an oral solution [60]. Further modification of schisandrin C led to the development of bicyclol (**28**), achieved by reducing a carboxymethyl ester to a hydroxymethyl in the biphenyl bis ester structure. Bicyclol has demonstrated significant anti-hepatitis viral activity, including the reduction of serum alanine aminotransferase and aspartate aminotransferase levels and the inhibition of hepatitis B virus replication in patients. It received approval in China in 2001 for treating chronic viral hepatitis, non-alcoholic fatty liver disease, and drug-induced liver injury, marking significant advancements

in hepatoprotective drug development [61].

Baicalin

The medicinal plant *Scutellaria baicalensis* is extensively used in clinical practice for its efficacy in managing liver, gallbladder, and pancreatic disorders, alongside its anti-allergic, anti-infective, and anti-rheumatic properties. Baicalin (**29**) is identified as the primary bioactive component of *S. baicalensis*. This traditional Chinese medicinal herb is applied in treating acute and chronic hepatitis by inhibiting the Lysine-specific histone demethylase 1A receptor [62]. Following a clinical trial conducted in 1982, baicalin was approved in China, demonstrating its safety and tolerability in healthy subjects, as indicated by the lack of significant liver or organ toxicity after a single oral administration ranging from 100−2800 mg [63]. It is important to highlight that baicalein is a hydrolyzed derivative of baicalin, which is converted into baicalein through hydrolysis by *β*-glucuronidase in the intestine upon oral ingestion. Furthermore, baicalein undergoes metabolic processing by uridine diphosphate-glucuronosyltransferase during systemic circulation, converting it back to baicalin [64]. This conversion process illustrates the complex pharmacokinetic profile of baicalin and baicalein *in vivo*. Thus, when using baicalin or baicalein, either alone or in combination with other medications, it is crucial to consider the potential for pharmacokinetic interactions in clinical settings, ensuring the safe and effective application of these compounds.

Natural Drugs Approved in the United States and Other Countries

Anticancer drugs

Vinca alkaloids

Vinblastine (**30**, Fig. 4), classified among the monoterpene indole alkaloids and originally derived from the plant *Catharanthus roseus*, is widely used in the treatment of various cancers, including lymphoma, ovarian cancer, breast cancer, and lung cancer. As a microtubule-targeting agent, vinblastine impedes cell proliferation by binding to *α*/*β*-tubulin heterodimers, leading to G_2-M phase cell cycle arrest. It was approved for use as a sulfate injection in the United States in 1961 [65]. Following this, vincristine (**31**), another alkaloid with a mechanism of action similar to that of vinblastine but distinguished by the replacement of the *N*-methyl group on the indole ring with an *N*-formyl group, was identified. Vincristine is notably more effective against hematological cancers compared to vinblastine. Its sulfate injection form was approved in the United States in 1963 for the treatment of acute lymphoblastic leukemia, lymphoma, and multiple myeloma [66]. The clinical use of both drugs is somewhat limited by their neurotoxicity. However, advances in chemical synthesis have led to the development of derivatives with reduced neurotoxic effects. For example, vindesine (**32**) was granted approval in the United Kingdom in 1979 for treating acute lymphoblastic leukemia and lymphoma; vinorelbine (**33**) received approval in France in 1989 for managing advanced NSCLC, metastatic breast cancer, and ovarian cancer; while vinflunine (**34**) obtained French approval in 2009 for addressing metastatic bladder cancer [67]. The development of vinblastine analogs showcases significant progress in cancer therapy, underscoring the importance of continuous innovation in drug formulation to enhance clinical efficacy while minimizing adverse effects, particularly neurotoxicity and myelosuppression. These developments highlight the ongoing effort to optimize cancer treatment regimens, balancing therapeutic benefits against potential risks.

Taxanes

Paclitaxel (**35**), a diterpenoid alkaloid originally isolated from the bark of *Taxus brevifolia*, stands out as a potent anticancer agent. As discovered by Horwitz *et al*., paclitaxel functions as a microtubule protein inhibitor, blocking the depolymerization of microtubules and thereby halting the DNA replication process within cancer cells [68]. One of the primary challenges with paclitaxel is its limited aqueous solubility. To address this, Bristol-Myers Squibb developed a polyoxyethylene castor oil-based formulation for injection, significantly improving its delivery and effectiveness against recurrent ovarian and breast cancers, leading to FDA approval in 1992. Further advancements have led to the development of novel formulations, including paclitaxel liposomes, albumin-conjugated paclitaxel, and paclitaxel polymeric micelles. These formulations aim to reduce the side effects associated with paclitaxel co-solvents, enhance its solubility, and improve its targeting capabilities for treating a variety of cancers, such as ovarian, breast, NSCLC, and pancreatic cancers [69]. The scarcity of paclitaxel in *T. brevifolia* has prompted the development of semi-synthetic analogs like docetaxel (**36**) by Sanofi, which not only addresses the yield issue but also increases the drug's anticancer efficacy and water solubility. Docetaxel was approved in the United States in 1996 for treating advanced breast cancer and NSCLC [70]. Cabazitaxel (**37**), another paclitaxel derivative, received FDA approval in 2010 for metastatic castration-resistant prostate cancer treatment [71]. Research into paclitaxel combinations is ongoing, with a phase III clinical trial showing that the Carboplatin-Paclitaxel/Nab-Paclitaxel chemotherapy regimen combined with Pembrolizumab significantly improves health-related quality of life for patients with metastatic squamous NSCLC. This supports the potential use of Pembrolizumab in combination with chemotherapy as a first-line treatment for this condition. Additionally, combining paclitaxel with the apoptosis inhibitor LCL161 has shown promise in treating triple-negative breast cancer, further broadening the therapeutic applications of paclitaxel formulations and illustrating the continuous innovation in cancer therapy [72].

Podophyllotoxin and its derivatives

Podophyllotoxin (**38**), an aryl tetrahydronaphthalene-type lignan sourced from the *Podophyllum* genus of the Berberidaceae family and other species like *Dysosma versipellis*, *Diphylleia sinensis*, and *Sinopodophyllum hexandrum*, showcases a wide array of pharmacological properties, including

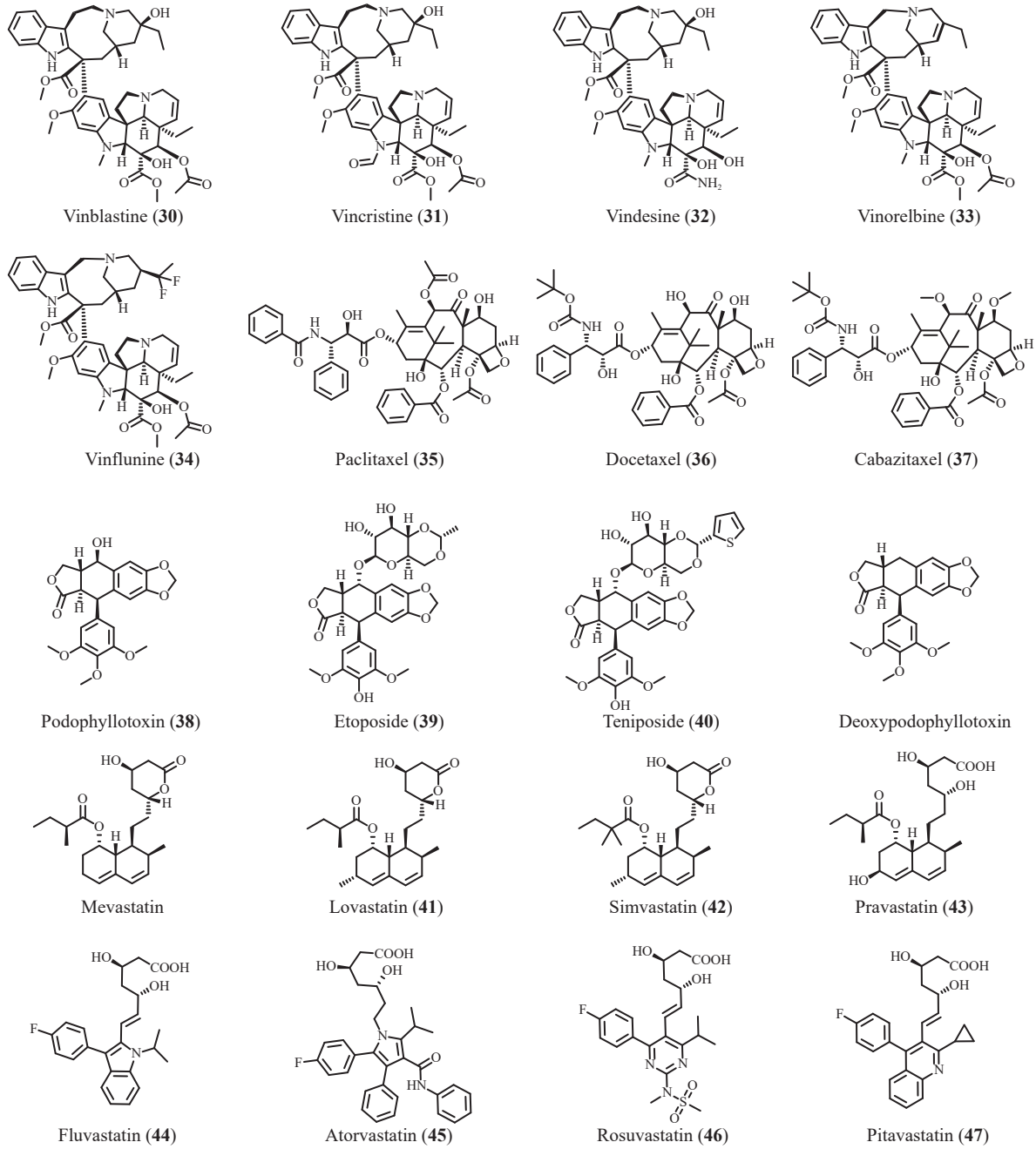

Fig. 4 Anticancer and cardiovascular disease drugs approved in the United States and other countries.

anticancer, anti-inflammatory, antibacterial, and antiviral activities [73]. In the United States, a concentrated 0.5% cream or aqueous solution of podophyllotoxin has been approved since 1990 for treating human tumor viruses, such as condyloma acuminatum and genital warts, and is also recommended by the World Health Organization as a first-line therapy for condyloma acuminatum. Podophyllotoxin's potent microtubule inhibitory toxicity has been recognized for its excellent anticancer capabilities, inhibiting cell division and serving as a potential therapeutic agent for various malignancies, including NSCLC, breast cancer, acute myeloid leukemia, lymphoma, among others [74]. Due to podophyllotoxin's inherent cytotoxicity, chemical modifications have led to the development of etoposide (**39**) and teniposide (**40**). These derivatives work by inducing DNA damage and triggering apoptosis through the inhibition of topoisomerase II, disrupting the stability of enzyme-DNA complexes. Etoposide has found clinical use in treating a range of cancers, such as NSCLC, ovarian cancer, and testicular cancer, while teniposide is primarily used in the therapy of acute lymphoblastic leukemia [75]. The FDA approved etoposide and teniposide in 1981 and 1992, respectively. Furthermore, deoxypodophyllotoxin, a podophyllotoxin derivative, exhibits strong inhibition against microtubule proteins but suffers from poor water

solubility. ZHU Xiong and colleagues have utilized hydroxypropyl-*β*-cyclodextrin to prepare a water-soluble deoxypodophyllotoxin injection, demonstrating significant inhibitory activity against a broad spectrum of tumor cells. This formulation is currently undergoing phase I clinical trials in China for the treatment of solid tumors, highlighting the ongoing efforts to harness podophyllotoxin and its derivatives for cancer therapy while managing their cytotoxic profiles [76].

Cardiovascular disease drugs

Statins

The journey of statins, pivotal in cholesterol management, began with the work of Japanese researcher Akira Endo, who discovered mevastatin from *Penicillium nitatum*. Mevastatin, a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA), showed promise in preclinical experiments for its cholesterol-lowering capability. However, its development was paused after carcinogenic effects were observed in animal studies [77]. Subsequently, lovastatin (**41**), another HMG-CoA reductase inhibitor derived from *Aspergillus terreus*, was isolated by Merck in the United States. Distinguished by an additional methyl group on the naphthalene ring compared to mevastatin, lovastatin successfully demonstrated its effectiveness in reducing low-density lipoprotein cholesterol and plasma triglycerides during Phase II clinical trials, with fewer adverse effects. This breakthrough led to its FDA approval in 1987, marking it as a significant advancement in cholesterol-lowering medications [78]. Simvastatin (**42**), developed by Merck Sharp & Dohme, further improved upon lovastatin's structure by incorporating a methyl group into its side chain, enhancing its inhibitory activity against HMG-CoA reductase and its safety profile. Launched in the United States and Europe in 1989 [79], simvastatin, like lovastatin, is a prodrug that is activated *in vivo*. Pravastatin (**43**), another milestone in statin development, differs from its predecessors by undergoing lactone ring-opening to form dihydroxyvaleric acid, which does not rely on cytochrome P450 for metabolism, thus offering a better therapeutic safety profile. It was approved in Japan in 1989 [80]. The statin family expanded with the synthesis of fluvastatin (**44**), atorvastatin (**45**), rosuvastatin (**46**), and pitavastatin (**47**), each establishing its place as essential medications with wide-reaching clinical use. These drugs work by inhibiting HMG-CoA reductase, thus reducing mevalonate production, a precursor in the sterol synthesis pathway, effectively lowering cholesterol levels [81]. Recognized for their contribution to cardiovascular health, these statins are listed as essential medicines by the World Health Organization, underscoring their critical role in modern medicine.

Immunomodulatory drugs

Cyclosporin A

Cyclosporin A (**48**, Fig. 5), a lipophilic cyclic undecapeptide, is sourced from several fungi, including *Tolypocladium inflatum*, *Fusarium solani*, *Neocosmospora varinfecta*, and *Aspergillus terreus*. It is distinguished by its potent immunosuppressive capabilities, which crucially reduce the risk of infection induction or exacerbation, making it invaluable in the clinical setting for organ transplantation [82]. The mechanism of action of cyclosporin A involves its inhibition of calmodulin phosphatase. It achieves this by binding to cyclophilin A, subsequently forming a complex that curtails the production of inflammatory factors, thereby facilitating immunosuppression [83]. This action is pivotal in preventing the rejection of transplanted organs. Recognizing its significant clinical utility, the United States FDA approved injections and soft gels of Cyclosporin A in 1983 for use in preventing organ rejection during transplantation procedures. This approval marked a significant advancement in the field of transplant medicine, offering a new level of support for patients undergoing these life-saving procedures.

Tacrolimus

Tacrolimus (**49**), a novel macrolide immunosuppressant isolated from *Streptomyces tsukubaensis*, operates similarly to cyclosporin A as both are calcineurin inhibitors. However, tacrolimus and cyclosporin A differentiate in their molecular interactions; tacrolimus binds to the FK-506 binding protein, whereas cyclosporin A forms a complex with cyclophilin A [84]. This distinction contributes to tacrolimus's enhanced immunosuppressive efficacy compared to cyclosporin A.Clinical evaluations in the United States, particularly focusing on liver and kidney transplants, have demonstrated tacrolimus's superiority in patient survival rates and its significant reduction in the occurrence of transplant rejection. These findings have established tacrolimus as a first-line immunosuppressive treatment, leading to its FDA approval in 1993 for liver and kidney transplantations. This approval has significantly impacted the management of transplant patients, offering them a more effective option for preventing organ rejection and improving transplant outcomes [85].

Rapamycin

Rapamycin (**50**), a triene macrolide, is sourced from various actinomycetes including *Streptomyces hygroscopicus*, *Streptomyces iranensis*, and *Actinoplanes* sp.. Initially identified for its antifungal properties against pathogens like *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*, rapamycin's spectrum of efficacy does not extend to Gram-negative bacteria. Its clinical significance emerged from studies demonstrating its capacity, both as a standalone treatment and in conjunction with cyclosporine, to prevent kidney transplant rejection, leading to its FDA approval in 1999 as an oral immunosuppressant for organ transplantation [86]. As the pioneering inhibitor of the mammalian target of rapamycin (mTOR), rapamycin inhibits key antigens and cytokines, including interleukin-2, interleukin-4, and interleukin-15, which are crucial for the activation and proliferation of T-lymphocytes. Moreover, it forms a potent immunosuppressive complex with FK560-binding proteins, effectively inhibiting the activation of mTOR proteins [87]. This mechanism of action places rapamycin as a cornerstone in the management of transplant rejection, showcasing its unique role in the arsenal of immunosuppressive therapies.

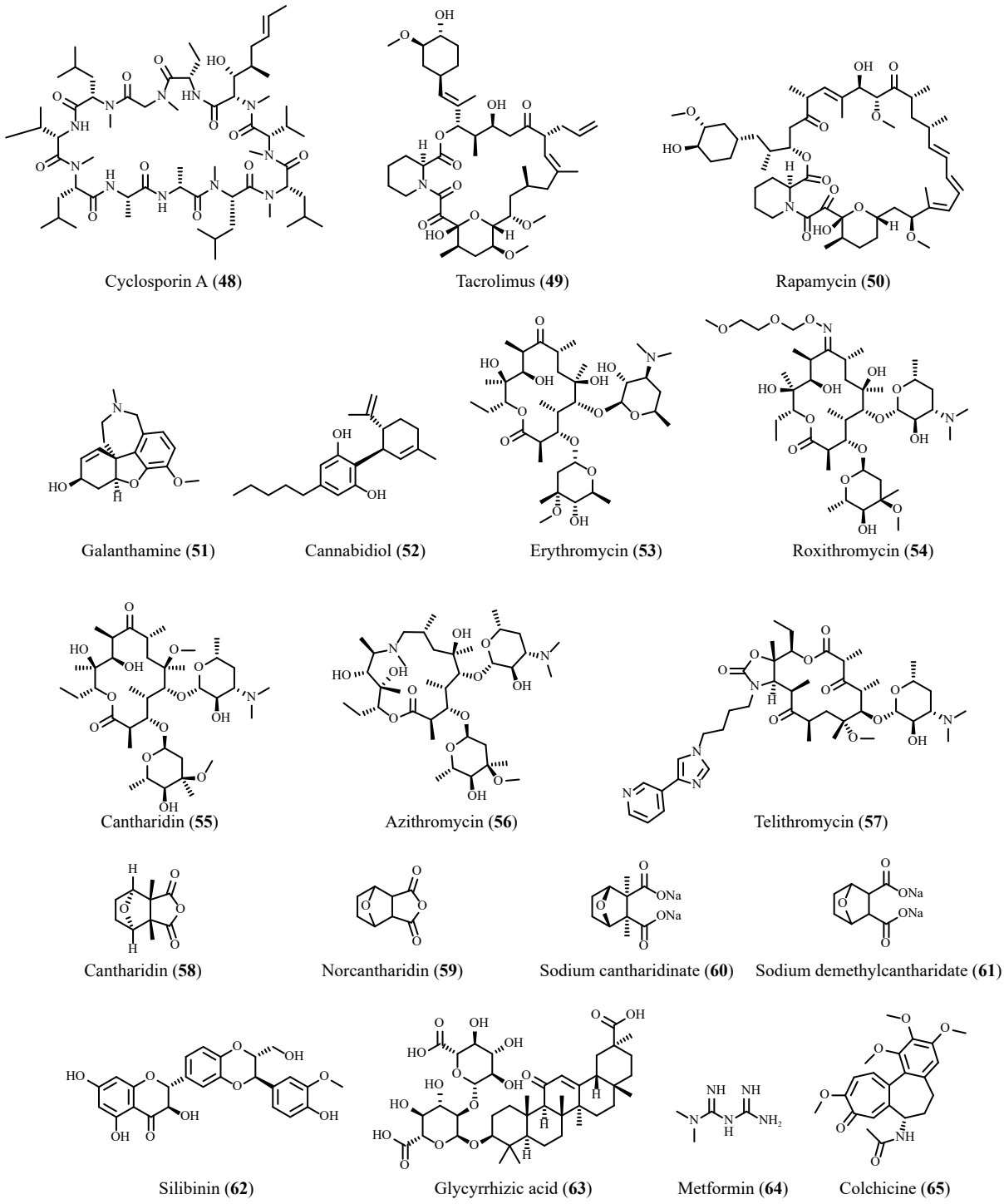

Fig. 5 Immunomodulatory, central nervous system, antibiotic, digestive, and metabolic disease drugs approved in the United States and other countries.

Central nervous system drugs

Galanthamine

Galanthamine (**51**), an alkaloid from the Amaryllidaceae family, serves as a reversible competitive inhibitor of acetylcholinesterase (AChE) and modulates nicotinic acetylcholine receptor variants. In the early 1950s, Mashkovskii made a significant discovery that galantamine exhibited antagonistic effects on non-depolarizing neuromuscular blocking agents and enhanced acetylcholine's action on muscle through the inhibition of AChE [88]. This foundational work paved the way for its exploration as a therapeutic agent for Alzheimer's disease (AD), given its ability to cross the blood-brain barrier. Galantamine's therapeutic action in AD stems from its dual mechanism: modulating the activity of nicotinic

acetylcholine receptors to boost neurotransmitter release, including acetylcholine and glutamate, and inhibiting AChE to increase inter-synaptic acetylcholine levels. This results in cognitive and functional benefits for patients with AD [89]. A pivotal US-based clinical trial involving 636 patients with mild to moderate AD demonstrated that treatment with galantamine, either alone or in combination with other medications, significantly improved cognitive functions and overall patient well-being over six months, supported by a favorable safety profile [90]. Approved in the United States in 2001 for the treatment of mild to moderate AD, galantamine hydrobromide tablets have contributed significantly to the management of this condition, offering symptomatic relief and enhancing the quality of life for many patients.

Cannabidiol

Cannabidiol (CBD) (**52**), a monoterpene phenolic compound extracted from *Cannabis sativa*, showcases a wide spectrum of pharmacological effects, including analgesic, anticonvulsant, anxiolytic, neuroprotective, and anti-inflammatory properties. Initially isolated in the 1940s by Adams and colleagues, CBD has been extensively studied for its capacity to cross the blood-brain barrier, offering therapeutic benefits for epilepsy and other neurological conditions while maintaining a favorable safety profile. Its significant impact on neurological disorders led to the FDA's approval in 2018 for the treatment of Dravet and Lennox-Gastaut syndromes, rare forms of epilepsy. This approval marked a milestone in the recognition of CBD's medical utility, further expanded in 2020 to include treatment for seizures associated with tuberous sclerosis complex [91]. CBD's mechanism of action is distinct from that of traditional cannabinoids, as it does not exhibit high affinity for cannabinoid receptors such as cannabinoid receptor 1 (CB1) [92]. Instead, it acts as a negative modulator of these receptors, influencing central and peripheral neurotransmission without eliciting the psychoactive effects typically associated with THC, the primary psychoactive component of cannabis. This unique pharmacological profile of CBD underscores its potential as a therapeutic agent for a broad range of conditions beyond epilepsy, including anxiety disorders and inflammatory diseases, highlighting its importance in contemporary medical practice.

Antibiotic drugs

Erythromycin and its derivatives

Erythromycin (**53**), a macrolide antibiotic derived from *Streptomyces erythraeus* or *Arthrobacter* sp., features a 14-membered lactone ring with two sugar moieties. It exerts a potent inhibitory effect against a broad spectrum of bacteria, including gram-positive bacteria, certain gram-negative bacteria, and chlamydia, making it a valuable treatment for respiratory tract infections and skin infections [93]. Due to its structural instability and susceptibility to inactivation by acid-catalyzed spiroketal formation, modifications such as conversion into salts or esters have been employed to enhance erythromycin's stability. This has led to the development of derivatives like erythromycin ethylsuccinate, erythromycin stearate, erythromycin etoposide, and erythromycin ethyl carbonate [94]. Roxithromycin (**54**), an oxime derivative of erythromycin with a 9-alkoxy substitution, maintains comparable bacteriostatic activity to erythromycin but boasts greater acid stability and higher oral bioavailability. It was approved for use in France in 1986 [95]. Clarithromycin (**55**), a 6-*O*-methyl derivative of erythromycin developed by Taisho Pharmaceutical in Japan, offers improved pharmacokinetic properties and a reduced incidence of adverse reactions. It was successfully introduced to the market in 1986 [96]. Azithromycin (**56**), characterized by the substitution of a methyl group at the C9 position of the lactone ring, broadens the antimicrobial spectrum, enhances oral absorption, and minimizes gastrointestinal irritation. Approved in the United States in 1986 [97], azithromycin represents a significant advancement in macrolide antibiotics. Telithromycin (**57**), derived from clarithromycin and featuring a ketolactone structure, shows markedly increased antibacterial activity against both sensitive and resistant bacterial strains. With a short half-life, rapid action, and 57% oral bioavailability, it was approved in Germany in 2001 [98] for respiratory tract infections after a successful phase III clinical trial by Sanofi-Aventis in France. Macrolides exert their bacteriostatic effect by binding to the 50S subunit of the bacterial ribosome, inhibiting translocation processes during protein synthesis [99]. Despite their therapeutic value, the emergence of bacterial resistance highlights the ongoing need for novel macrolide development to maintain efficacy in bacterial infection management.

Cantharidin and its derivatives

Cantharidin (**58**), a monoterpenoid derived from beetles in the Coleoptera and Meloidae family, has been traditionally used to treat molluscum contagiosum. Research has shown that cantharidin effectively inhibits serine/threonine protein phosphatases 1 and 2A, displaying potent antitumor properties against a range of cancers, including breast cancer, bladder cancer, hepatocellular carcinoma, leukemia, and multiple myeloma, by inducing cell cycle arrest and apoptosis [100]. However, its clinical use has been limited due to significant irritant effects on the urinary and digestive systems. In the United States, cantharidin, formulated in a collodion vehicle, has been applied since the 1950s for molluscum contagiosum treatment, though FDA approval for its marketing was withdrawn due to a lack of sufficient clinical evidence [101]. Conversely, China approved cantharidin in 2015 for condyloma acuminatum and infectious molluscum contagiosum treatment. In a significant development, VP-102 (cantharidin, 0.7% *W*/*V*, topical solution) by Verrica Pharmaceuticals was approved by the FDA in 2023 for treating infectious molluscum contagiosum in the United States, marking a notable advancement in therapeutic options for this condition. To address cantharidin's toxicity, researchers have developed derivatives like norcantharidin (**59**), sodium cantharidinate (**60**), and sodium demethylcantharidate (**61**). These derivatives have shown promising anticancer activity with markedly reduced side effects and have been approved in

China for treating various solid tumors [102], illustrating the ongoing efforts to harness cantharidin's therapeutic potential while minimizing its adverse effects.

Digestive disease drugs

Silibinin

The therapeutic use of Silybi Fructus, notably for "flank pain", has historical roots, with further research validating their effectiveness in treating liver disorders. Silibinin (**62**), a principal flavonolignan from *Silybum marianum*, recognized for its broad pharmacological spectrum, including hepatoprotective, anti-inflammatory, antioxidant, and cardioprotective effects [103]. Notably, early clinical trials in Austria highlighted silibinin's potential to significantly enhance survival rates among patients with alcoholic cirrhosis when compared to placebo recipients. However, the oral bioavailability of silibinin is limited; less than half of the administered dose is absorbed, with only about 10% reaching the hepatic and intestinal circulation to manifest therapeutic actions, primarily due to its poor water solubility [104]. Advancements in drug formulation led to the development of a fat-soluble injectable form, the silibinin phosphatidylcholine complex salt, by Italian researchers. This innovation markedly improved silibinin's bioavailability and was patented in Europe in 1985 [105]. The World Health Organization officially recognized silymarin, a related compound, for its hepatoprotective activity in the 1970s [106]. Injectable forms of silibinin have expanded to include various salts such as glucosamine salts, sodium diaminosuccinate salt, and phosphates, enhancing its application scope. Oral formulations remain widely used, consisting mainly of tablets and capsules, such as Silymarin tablets, Yixin Tablets, and silibinin lecithin complex hard capsules. These developments underscore the continued evolution and application of silibinin in therapeutic practices, particularly for liver health.

Glycyrrhizic acid

Glycyrrhizae Radix Et Rhizoma, a herb extensively used in traditional Chinese medicine, houses glycyrrhizic acid as its main bioactive constituent. Classified as a triterpenoid saponin, glycyrrhizic acid (**63**) is renowned for its diverse pharmacological effects, including anti-inflammatory, hepatoprotective, antioxidant, antiviral, and immunomodulatory properties [107,108]. Introduced by a Japanese pharmaceutical company, glycyrrhizin gained approval in Japan in 1979 as an effective treatment for chronic hepatitis, particularly when used in conjunction with glycine and cysteine to diminish plasma aminotransferase levels. Building on this foundation, Chinese researchers have developed various glycyrrhizin formulations, such as diammonium glycyrrhizinate injections and enteric capsules, as well as magnesium isoglycyrrhizinate injections, focusing on enhancing the safety and efficacy of these preparations. Further research has broadened our understanding of glycyrrhizic acid's therapeutic potential, revealing its benefits in treating not only hepatitis but also conditions such as dermatitis, pemphigus, and gastric ulcers. These findings underscore the versatility of glycyrrhizic acid as a valuable pharmacological agent across a spectrum of medical applications, highlighting its importance in both traditional and modern therapeutic practices [109].

Metabolic diseases drugs

Metformin

In the late 19th century, *Galega officinalis*, known for its use in Europe for diabetes treatment, led to the isolation of galegine, a compound found to significantly lower blood glucose levels. However, its clinical application was hindered by its short duration of action in the body [110]. Inspired by galegine, Slotta *et al*., in 1929, synthesized a series of biguanide compounds, including metformin (**64**) [111], which marked a significant advancement in diabetes treatment. Dr. Sterne was a pioneer in using metformin clinically, demonstrating its efficacy in reducing insulin requirements in diabetes mellitus patients. Metformin tablets were first approved in England in 1958 for type 2 diabetes mellitus treatment and later gained FDA approval in the United States in 1995 [112]. Following the British Prospective Diabetes Study, metformin has been recognized as the first-line pharmacological treatment for type 2 diabetes and remains widely used today. The introduction of an extended-release metformin tablet in the United States in 2000 further diversified the treatment options, alongside the development of various metformin combinations with other hypoglycemic agents. Metformin's hypoglycemic effect is attributed to multiple mechanisms, including the inhibition of the adenylate cyclase pathway, leading to reduced ATP utilization, and the activation of the 5'-AMP-activated kinase (AMPK), which increases AMP levels and inhibits glucose production pathways. It also activates the AMPK signaling pathway, reducing lipid and cholesterol synthesis [113]. Recent findings by Chinese researchers have identified that metformin also exerts its hypoglycemic activity by targeting the presenilin enhancer 2 to mediate AMPK activation [114], shedding light on its complex mechanism of action. This underscores the continuous exploration and understanding of metformin's pharmacological effects and its pivotal role in managing type 2 diabetes.

Colchicine

Colchicine (**65**), an alkaloid extracted from *Colchicum autumnale*, has been recognized for its medicinal properties in treating pain and inflammation since ancient times. Recent clinical research has further established colchicine's significant anti-inflammatory effects, expanding its use to treat conditions such as acute gout, familial Mediterranean fever (FMF), calcium pyrophosphate deposition disease, and systemic sclerosis. Moreover, colchicine's therapeutic scope has broadened to include applications in anti-infective treatments, anticancer therapies, cardiovascular medicine, immunology, and neurodegenerative disease research [115]. Although colchicine has been available in the US market since 1961, it only received formal FDA approval in 2009 for oral tablets designed to prevent or manage gout flare-ups and FMF [116]. The growing body of evidence linking chronic inflammation to cardiovascular disease has spurred interest in colchicine's

potential as a therapeutic agent. A pivotal phase III clinical trial highlighted colchicine's capacity to reduce the risk of heart disease by 31% in patients with atherosclerotic cardiovascular disease, prompting the FDA to approve its use for this condition [117]. This approval positioned colchicine as the first non-steroidal anti-inflammatory drug (NSAID) endorsed by the FDA for managing cardiovascular disease. Colchicine's mechanism involves binding to microtubule proteins to prevent their aggregation, affecting cell proliferation and migration and potentially leading to cell death. Furthermore, it suppresses the expression and release of pro-inflammatory cytokines, illustrating its profound anti-inflammatory capabilities. This dual action—both at the cellular level and through cytokine modulation [118]—underscores colchicine's importance in treating a diverse array of diseases by targeting the underlying inflammatory processes.

Discussion and Perspective

The history of drug development from NPs traces its roots back to 1804 when Friedrich Sertürner isolated morphine from opium, marking a significant milestone in pain management [119]. Since then, the clinical application of NP-derived drugs has seen exponential growth, contributing immensely to human health and well-being. Today, NPs remain a critical resource for new drug discovery, highlighting the necessity for a comprehensive analysis of their benefits and challenges in drug development, alongside strategies to enhance research and development in this field.

Drug development based on NPs presents several advantages, stemming from their origins in enzyme-catalyzed biosynthetic processes within living organisms. These advantages include enhanced biocompatibility, the potential for diversified chemical structural modifications, and access to a wider chemical space. As a result, NPs are predisposed to effectively interact with biological targets, exhibiting significant biological activity. Additionally, NPs are subject to natural selection and evolution in their environments, which equips them with exceptional adaptability and survivability traits. This evolutionary refinement often translates into a superior safety profile when compared to chemically synthesized compounds, as NPs have co-evolved alongside biological systems. The rich tradition of Traditional Chinese Medicine (TCM), with its extensive historical record of medicinal practices, further underscores the potential of NPs. TCM provides a fertile ground for the discovery of clinically valuable compounds that are both safe and effective, having been utilized and refined over centuries. This historical and practical context enhances the likelihood of identifying NPs with therapeutic benefits, making them a valuable resource in the ongoing search for new and effective drugs.

Many limitations have an impact on the drug development based on NPs. Most NPs exhibit colorful biological activities, but few of them have strong bioactivity due to the limitations of the constituent elements, C, H, and O, which are not dominant elements for biological activities, except alkaloids. Though extensive research has been conducted on NPs worldwide, leading to the discovery and development of various drugs, it remains hard issues to identify compounds with medicinal value from the fixed chemical components present in nature, particularly from herbs. Moreover, discovering potent active ingredients from micro or trace components is theoretically possible but presents challenges in their development into novel drugs. Additionally, properties, such as solubility, bioavailability, and pharmacokinetics, along with other factors, significantly influence the draggability of NPs. Ensuring an adequate supply of sample sources also poses a crucial consideration in drug development and production; however, this aspect does not favor NPs.

It is encouraging to see that there are sustained interests in innovative drug discovery and development based on NPs. The greatest advantage of NPs lies in the diversity of their chemical structures, which determines the variety of their target actions and plays a crucial role in the development of First-in-class drugs. In future research, interdisciplinary collaboration between NP chemistry, medicinal chemistry, pharmacology, chemical biology, and other related fields should be emphasized to enhance the success rate of new drug discovery based on NPs. For instance, chemical biology can be employed to harness the intricate chemical architecture of NPs for the exploration of novel targets. In-depth biological investigations can facilitate the identification and subsequent screening of active natural compounds possessing innovative chemical structures. Structural modification serves as a pivotal approach to improve drug-like properties by utilizing bioisosterism, scaffold hopping, and prodrug methods to modify the structure of NPs. Additionally, emerging technologies, including artificial intelligence, bioinformatics, nanobiotechnology, and antibody-coupled drug design, can be employed to introduce pharmacophores and heteroatoms into these compounds to enhance the bioactivities and reduce toxicity levels. Furthermore, attention should be given to improving the solubility, bioavailability, and pharmacokinetic properties through various strategies. Solutions involving semi-synthetic methods, total synthetic approaches, and biosynthesis can be applied to address challenges associated with sourcing new drug candidates effectively. The advancement of multidisciplinary collaboration and the comprehensive integration of novel technologies will enhance research on the pharmacokinetics of NPs, address existing limitations in their drug development, and facilitate the approval and clinical application of a greater number of natural product-based drugs. Consequently, NPs are produced to assume an increasingly pivotal role in promoting health and well-being among individuals in China and worldwide.

Supplementary Information

An index form for all drugs can be obtained by sending E-mail to the corresponding author.

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