



Review Article

# Functional activity and mechanisms of common marine traditional Chinese medicine

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Received: 5 June 2024 / Revised: 6 September 2024 / Accepted: 6 September 2024

**Abstract:** In recent years, the research of marine drugs has become a global hot spot, and marine traditional Chinese medicine (MTCM) is an important part of traditional Chinese medicine. To promote the development and application of MTCM, this review collected 10 kinds of MTCM from the Pharmacopoeia of the People's Republic of China, analyzed and expounded their pharmacological effects. The pharmacological effects of MTCM are mainly anti-inflammation, antioxidation and anticancer, and could be used for the treatment of diabetes, atherosclerosis and other diseases. Modern pharmacological studies have confirmed that the pharmacological effects of MTCM are consistent with those recorded in ancient books, *Ostreae Concha* and *Laminaria Thallus*, as MTCM, have been listed as medicinal and edible substances in China. However, MTCM is facing problems such as lack of quality standards and resource destruction. Therefore, it is necessary to summarize the pharmacological effects and use methods of MTCM, to provide reference for the application and resource development of MTCM.

**Keywords:** marine; traditional Chinese medicine; activity; mechanism

**Citation:** Lu X. W., Qin S., Wang Q., et al. Functional activity and mechanisms of common marine traditional Chinese medicine. *Food & Medicine Homology*, 2025, 2: 9420075. <https://doi.org/10.26599/FMH.2025.9420075>

## 1 Introduction

Marine traditional Chinese medicine (MTCM) is an important part of traditional Chinese medicine. Under the guidance of traditional Chinese medicine theory, MTCM refers to drugs derived from marine sources (including seawater itself, coastal beaches, wetlands and saline soil areas outside the sea) for the prevention, diagnosis and treatment of diseases<sup>[1]</sup>. Marine drugs have become a hot spot in global drug research and development. In 2017 alone, 1490 new compounds from the marine were reported. Currently, 49 active substances in the ocean have been approved for marketing or clinical use in China and internationally. China has a coastline of approximately  $1.8 \times 10^4$  km and a sea area of approximately  $4.7 \times 10^6$  km<sup>2</sup>, in recent years. China has accelerated the development and utilization of MTCM, in which drugs such as sodium alginate diester, glycosyl ester and squalene have been approved for listing<sup>[2]</sup>.

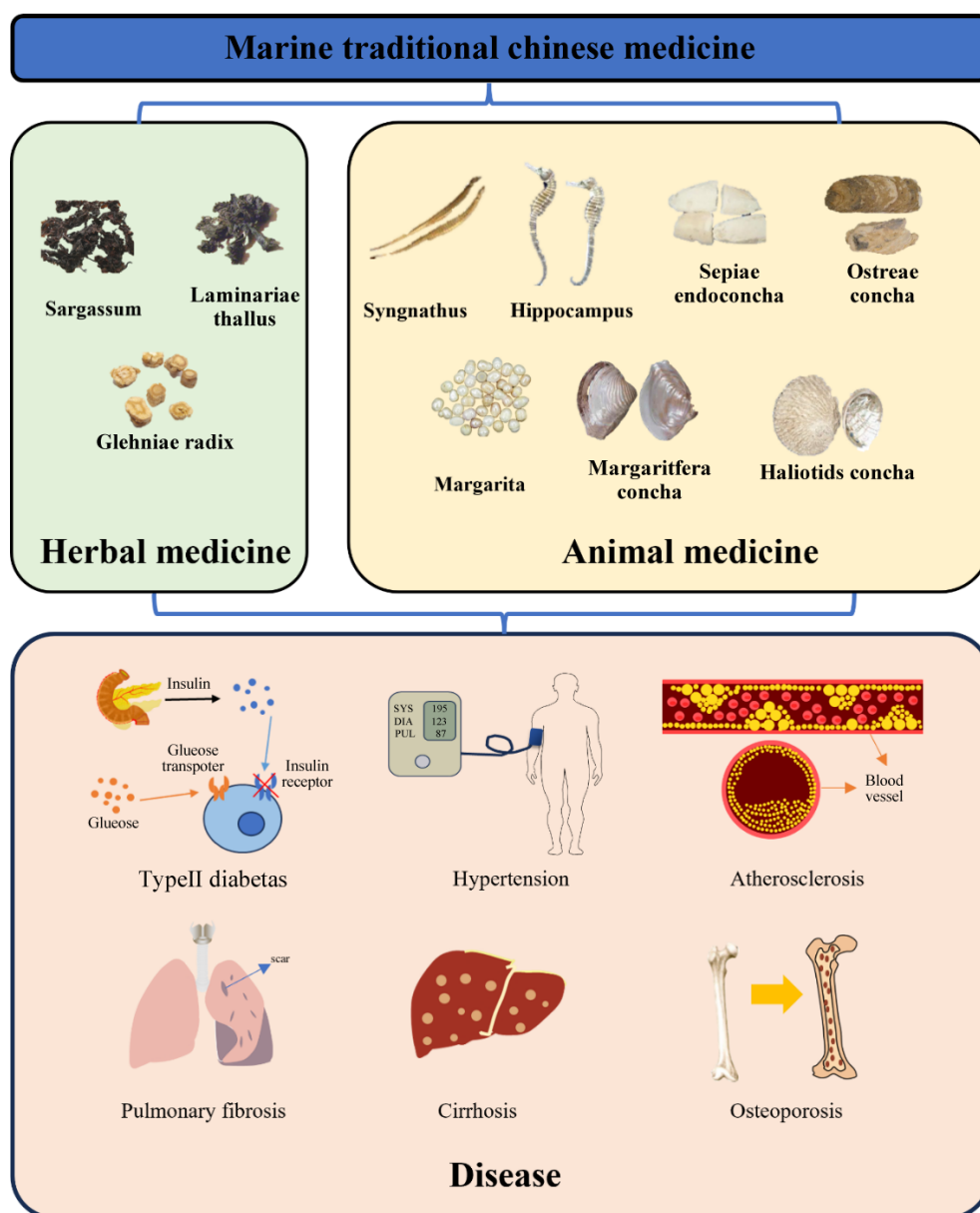
Records related to MTCM can be traced back to the Spring and Autumn and Warring States periods. 'Shennong's Herbal Classic' is the earliest existing monograph of traditional Chinese medicine in China. The recorded MTCM includes seaweed, oysters, squid bones, etc. There are 190 kinds of MTCM recorded in 'Compendium of Materia Medica', involving 116 species; Zhonghua Haiyang Bencao, edited by Guan Huashi, published in 2009, included 613 MTCM, involving 1,479 species. The records

of the use of MTCM can be traced back to 2,500 years ago. In this paper, 10 kinds of common MTCM were collected, such as sargassum, laminariae thallus, *Glehniae Radix*, hippocampus, syngnathus, *Sepiae Endoconcha*, *ostreae concha*, margarita, *margaitifera conch* and *haliotids concha*. Under the guidance of traditional Chinese medicine theory, these MTCMs can be used to treat diseases such as type 2 diabetes, hypertension, atherosclerosis, pulmonary fibrosis, hepatitis and bone hyperplasia (Fig. 1) in China as being used as homology of medicine and food.

Currently, there is no systematic literature on the pharmacological effects of MTCM. Therefore, it is necessary to sort out the pharmacological effects of MTCM. This paper reviews the pharmacological effects of MTCM to provide a reference for the further development of traditional Chinese medicine resources.

## 2 Herbal MTCM

Herbal medicines of MTCM include *Sargassum*, *Laminariae Thallus* and *Glehniae Radix*. these herbal medicines often have antioxidation, anti-inflammation, antitumor, hypoglycemic, and other effects and can be used for the prevention and treatment of atherosclerosis, hyperglycemia, nervous system diseases, and other diseases (Table 1).



**Figure 1** Marine traditional Chinese medicine and its application.

## 2.1 *Sargassum*

*Sargassum* is the dried algae of *Sargassum pallidum* (Turn.) C. Ag or *Sargassum fusiforme* (Harv.) Setch.<sup>[37]</sup>. In recent years, research on the chemical composition of *sargassum* mainly focuses on *sargassum* polysaccharides. The improvement of the quality standard of *sargassum* mainly depends on the improvement of polysaccharide detection technology. Currently, the commonly used polysaccharide detection methods mainly include phenol-sulfuric acid method and anthrone-sulfuric acid method. The common principle is that after the polysaccharide is hydrolyzed by sulfuric acid, it forms a colored complex with phenol or anthrone to measure the polysaccharide content<sup>[38]</sup>. Modern pharmacological studies have confirmed that *sargassum* polysaccharides have antioxidant, anti-inflammatory, and anti-cancer effects<sup>[39]</sup>. Wan *et al.*<sup>[40]</sup> compared hot water extraction, acid-assisted extraction, alkali-assisted extraction, ultrasonic-assisted extraction, microwave-assisted extraction and hydrogen peroxide/ascorbic acid assisted extraction, the results showed that the yield of polysaccharide prepared by hydrogen

peroxide/ascorbic acid assisted extraction method was the highest. The reason is that the hydrogen peroxide/ascorbic acid system can produce more hydroxyl radicals, which leads to the cleavage of glycosidic bonds and the degradation of polysaccharides. *In vitro* experiments confirmed that the polysaccharide had good antioxidant activity.

Fang *et al.*<sup>[41]</sup> found that *sargassum* polysaccharide dose-dependently scavenged  $\cdot\text{OH}^-$  and oxyradical ( $\text{O}_2^-$ ). When the polysaccharide concentration was 200  $\mu\text{g/mL}$ , the scavenging rate of  $\cdot\text{OH}^-$  was 26%, and the scavenging rate of  $\text{O}_2^-$  was 80%. In addition, *sargassum* polysaccharide showed some inhibitory effect on lipovitellin. Therefore, *sargassum* polysaccharide is expected to be developed as an antioxidant. A study by Li *et al.*<sup>[42]</sup> demonstrated that *sargassum* polysaccharides could promote the expression of immune factors (iNOS) and TNF- $\alpha$  and inhibit the proliferation of A549 lung cancer cells. This suggests that *sargassum* polysaccharide not only has immune-enhancing activity but also some antitumor activity. Ding *et al.*<sup>[43]</sup> showed that *Sargassum fusiforme* polysaccharide could inhibit the proliferative

Table 1 Traditional Chinese herbal medicine from the marine

| Herbal medicine       | Pharmacological effects                            | Action mechanism                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Reference |
|-----------------------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Sargassum             | Antioxidation                                      | Scavenging of superoxide radicals 1,1-diphenyl-2-picrylhydrazyl (DPPH).                                                                                                                                                                                                                                                                                                                                                                                                                                          | [3]       |
|                       | Anticancer                                         | Sargassum polysaccharide can increase the levels of tumor necrosis factor- $\alpha$ (TNF- $\alpha$ ), interleukin (IL)-1, nitric oxide (NO) and immunoglobulin M in serum (IgM), increase the expression of B-cell lymphoma-2 (Bax), decrease the expression of B-cell lymphoma-2 (Bcl-2), inhibit the proliferation of tumor cells and promote the apoptosis of tumor cells.                                                                                                                                    | [4, 5]    |
|                       | Hypolipidemic activity                             | Inhibition of triglyceride and free fatty acid levels in cells; regulate fat production, decomposition and free fatty acid oxidation.                                                                                                                                                                                                                                                                                                                                                                            | [6, 7]    |
|                       | Immunoregulation                                   | The number of lymphocytes, bone marrow mononuclear cells and goblet cells in the intestine increased.                                                                                                                                                                                                                                                                                                                                                                                                            | [8]       |
|                       | Anti-inflammation                                  | Decreased the expression of IL-1 $\beta$ , IL-8 and TNF- $\alpha$ , increased the expression of mucin-2, tight junction protein ZO-1 and occludin; regulating gut microbiota composition.                                                                                                                                                                                                                                                                                                                        | [9, 10]   |
|                       | Anti-virus                                         | Inhibition of viral replication <i>in vitro</i> and <i>in vivo</i> .                                                                                                                                                                                                                                                                                                                                                                                                                                             | [11, 12]  |
|                       | Hypoglycemic                                       | Reduce fasting blood glucose, triglycerides, total cholesterol (TC), increase high-density lipoprotein cholesterol (HDL-c), improve glucose tolerance; increase benign bacteria in the intestine and reduce harmful bacteria; reduced branched chain amino acids and aromatic amino acids in the colon                                                                                                                                                                                                           | [13, 14]  |
|                       | Anti-viral                                         | Upregulation of IRF3 signaling-mediated interferon $\alpha$ (IFN- $\alpha$ )                                                                                                                                                                                                                                                                                                                                                                                                                                     | [15, 16]  |
|                       | Anti-coagulation                                   | Inhibition of intrinsic factor Xase, prolong the activated partial thromboplastin time (APTT).                                                                                                                                                                                                                                                                                                                                                                                                                   | [17]      |
|                       | Anti-atherosclerosis                               | Regulating autophagy-mediated macrophage polarization alleviates lipid deposition, reduces the expression of M1 macrophage markers, and increases the expression of M2 macrophages.                                                                                                                                                                                                                                                                                                                              | [18, 19]  |
| Laminariae<br>Thallus | prevent podocyte epithelial-mesenchymal transition | Inhibition of transforming growth factor- $\beta$ (TGF- $\beta$ ) induced suppressor of mothers against decapentaplegic (Smad)-3, Smad-4 and p38MAPK activation, upregulation of epithelial markers (Nephrin, WT-1, podocin), downregulation of mesenchymal markers (alpha-smooth muscle actin( $\alpha$ -SMA), fibronectin 1(FN-1)) expression.                                                                                                                                                                 | [20]      |
|                       | Anticancer                                         | Inhibition of activation of beta-catenin/transcription factor-4 (TCF4) pathway activation, inhibited the protein expression of Ki67 and proliferating cell nuclear antigen (PCNA), downregulated the expression of Bcl-2 while upregulated the expression of Bax, cl-caspase-3, and cl-caspase-9, upregulated the expression of E-cadherin, downregulated the expression of vascular endothelial growth factor (VEGF) and N-cadherin, and downregulated beta-catenin, TCF4, and c-Myc protein expression levels. | [21, 22]  |
|                       | Anti-obesity                                       | Reduce liver fat accumulation, reduce TC and Low-Density Lipoprotein levels, increase HDL, lipids metabolism enzyme (LPL), Uncoupling Protein 2, peroxisome proliferators-activated receptor (PPAR)- $\alpha$ levels; reduce the levels of inflammatory factors TNF- $\alpha$ and IL-6 in the intestine; increased the abundance of probiotics in the intestine                                                                                                                                                  | [23]      |
|                       | Anti-type 2 diabetes                               | Lower blood sugar, relieve insulin resistance; increase the abundance of beneficial bacteria in the intestine and reduce the abundance of harmful bacteria; increased the content of moderate bioactive substances in the intestine.                                                                                                                                                                                                                                                                             | [24, 25]  |
|                       | Anti-hypertension                                  | Binds to the angiotensin converting enzyme (ACE) active site through hydrogen bonding, forming a very stable complex structure to inactivate the ACE.                                                                                                                                                                                                                                                                                                                                                            | [26, 27]  |
|                       | Anti-allergic reaction                             | Reduced histamine and IL-4 levels, increased interferon (IFN)- $\gamma$ levels, increased the number of Treg cells in the tissue, and inhibited Th0 cell differentiation.                                                                                                                                                                                                                                                                                                                                        | [28, 29]  |
|                       | Antibacterial                                      | Inhibit the growth of the growth of <i>Fusarium solani</i> , <i>Fusarium seminudum</i> , <i>Fusarium oxysporum</i> , <i>Aspergillus parasiticus</i> and <i>Aspergillus flavus</i> .                                                                                                                                                                                                                                                                                                                              | [30]      |
|                       | Immunoregulation                                   | The killing rate of natural killer cells and the transformation function of T lymphocytes in spleen were enhanced, and the contents of immunoglobulin M (IgM) and immunoglobulin G (IgG) in serum were increased.                                                                                                                                                                                                                                                                                                | [31]      |
|                       | Antioxidation                                      | Scavenging of DPPH radical and hydroxyl ( $\cdot\text{OH}$ ) radical.                                                                                                                                                                                                                                                                                                                                                                                                                                            | [32, 33]  |
|                       | Anticancer                                         | Induce cell arrest in S and G2/M phase, inhibit cell proliferation and migration; downregulation of PCNA expression induced apoptosis.                                                                                                                                                                                                                                                                                                                                                                           | [34]      |
| Glehniae<br>Radix     | Anti-inflammation                                  | Inhibit the expression of inflammatory factors (IL-2, etc.).                                                                                                                                                                                                                                                                                                                                                                                                                                                     | [35, 36]  |

activity of HEL cells, and the inhibitory effect was proportional to the dose. polysaccharide (100  $\mu\text{g/mL}$ ) reduced the viability of HEL cells from 100% to 40%.

## 2.2 Laminariae Thallus

The medicinal part of the *Laminaria Thallus* is the dried leafy body of *Laminaria japonica* Aresch. or *Ecklonia kurome* Okam.<sup>[37]</sup> *Laminaria thallus* is rich in iodine and polysaccharide compounds. Generally, iodine is determined by potassium iodate method, the pharmacopoeia stipulates that iodine in dried *Laminaria japonica* is not less than 0.35%, and iodine in *Laminaria thallus* is not less than 0.20%. Polysaccharides were measured using anthrone-sulfuric acid method. The polysaccharide content in kelp were measured by fucose, not less than 2.0%.

The *Laminariae thallus* is known as an iodine-rich herb because of its high iodine content and can be used to treat Graves' disease

and hyperthyroidism<sup>[44]</sup>. Aoe *et al.*<sup>[45]</sup> studied the effect of *Laminariae thallus* on the body composition of overweight subjects. The results showed that the body fat percentage of overweight men who consumed low iodine *Laminaria thallus* powder decreased significantly, and had no effect on thyroid secretion. Li *et al.*<sup>[46]</sup> compared the three methods of hot water extraction, ultrasound-assisted extraction, and enzyme-assisted extraction. The results showed that hot water extraction caused the least structural damage to the polysaccharide, and the polysaccharide extracted by this method had a uniform smooth, sheet structure. The polysaccharide can inhibit the migration of tumor cells and promote tumor cell apoptosis. The antioxidant activity of *Laminariae thallus* polyphenols was investigated by Shi *et al.*<sup>[47]</sup>. *Laminariae thallus* polyphenols (200  $\mu\text{g/mL}$ ) showed a scavenging rate of 79.53% for DPPH radicals, 95.25% for  $\cdot\text{OH}$  and 69.83% for  $\text{O}_2^-$ , indicating that *Laminariae thallus* polyphenols

have antioxidant activity. In addition, *laminariae thallus* was able to inhibit the growth and reproduction of *Escherichia coli*, *Bacillus subtilis*, and *Staphylococcus aureus*, indicating that *laminariae thallus* polyphenols showed some inhibitory effects on gram-negative bacteria. China's first self-developed marine drug, Polysaccharide Sulfate, is a drug with anticoagulant and antithrombotic activity developed from fucoidan, an extract of brown algae.

### 2.3 Glehniae Radix

The medicinal part of Glehniae Radix is the dry root of *Glehnia littoralis* Fr. Schmidt ex Miq.<sup>[37]</sup>. Glehniae Radix has active ingredients such as polysaccharides and flavonoids, which have various effects, such as immune regulation, antioxidation, antitumor and anti-inflammation<sup>[48]</sup>. Yu *et al.*<sup>[49]</sup> obtained the polysaccharide of Glehniae Radix by water extraction, alcohol precipitation and anion exchange column separation and purification. Compared with the blank control group, Glehniae Radix polysaccharides promoted the proliferation of RAW264.7 cells and mouse spleen lymphocytes and then played an immunoregulatory role. Xu *et al.*<sup>[50]</sup> used the ethanol reflux method to obtain the extract of Glehniae Radix and extracted it with petroleum ether, ethyl acetate, *n*-butanol, and water to obtain four extracts with different polarities. The content of total flavonoids was determined by the sodium nitrite-aluminum nitrate-sodium hydroxide method, and the scavenging ability of different extracts to DPPH and 2, 2'-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) free radicals was determined. The results demonstrated that the highest content of total flavonoids in the ethyl acetate phase was 494 mg/g. Additionally, the ethyl acetate phase showed the strongest scavenging ability against DPPH free radicals and ABTS free radicals, outperforming the positive control drug, vitamin C. It was confirmed that the extract in the ethyl acetate phase had good antioxidant capacity, though whether this was due to flavonoids was not confirmed. Du *et al.*<sup>[35]</sup> obtained a homogeneous polysaccharide composed solely of glucose after hot water extraction, ethanol precipitation, and column chromatography. *In vitro* studies confirmed that the polysaccharide has immunomodulatory, anti-inflammatory, and anti-tumor activities.

## 3 Animal MTCM

Marine sources of animal medicine packages, which include the hippocampus and syngnathus. These MTCMs are rich in polysaccharides and polypeptides, which have anti-inflammation, antioxidation, anticancer, bone-filling and other effects. Mineral Chinese medicines are mostly derived from the inner shell of cartilaginous animals or the shell of shellfish animals. The efficacy of mineral medicine is mainly to treat gastrointestinal diseases and to have a tranquilizing effect. (Table 2).

### 3.1 Hippocampus

The source of the hippocampus is the dried body of *Hippocampus kelloggi* Jordan et Snyder, *Hippocampus histrix* Kaup, *Hippocampus kuda* Bleeker, *Hippocampus trimaculatus* Leach, and *Hippocampus japonicus* Kaup<sup>[37]</sup>. Proteins, peptides and steroids in the hippocampus have anti-inflammatory, antioxidant, and anti-aging effects<sup>[89]</sup>.

Wang *et al.*<sup>[90]</sup> found that hippocampal active protein could downregulate the mRNA levels of inflammatory factors such as TNF- $\alpha$ , IL-6 and IL-1 in RAW264.7 macrophages induced by

LPS, indicating that hippocampal active protein had an anti-inflammatory effect. Chen *et al.*<sup>[91]</sup> separated and purified the freeze-dried powder of the linear hippocampus using the wet natural sedimentation method to obtain four polypeptide components with different molecular weight segments. The antioxidant activity of these components was studied *in vitro*. The results indicated that the scavenging rates of the 0.43-1.09 kDa and 1.09-2.08 kDa hippocampal polypeptide components against O<sub>2</sub><sup>-</sup> were 67.35% and 61.73%, respectively. These components showed better antioxidant activity than other molecular weight hippocampal polypeptide.

### 3.2 Syngnathus

The source of syngnathus is the dried body of *Solenognathus hardwickii*, *Syngnathoides biaculeatus* or *Syngnathus acus* Linnaeus<sup>[37]</sup>. Syngnathus is rich in protein and trace elements such as Zn, Mn and Cu. The syngnathus protein has an antitumor effect.

Liu *et al.*<sup>[92]</sup> treated HeLa cervical cancer cells with syngnathus protein with a molecular weight of 33 kDa. The results showed that syngnathus protein had a significant inhibitory effect on the proliferation of HeLa cells. The early apoptosis rate with 4 mg/mL syngnathus protein was 61.56  $\pm$  1.09%, and the late apoptosis rate was 14.60  $\pm$  0.03. In contrast, the early apoptosis rate of the blank control group was 9.82  $\pm$  0.18%, and the late apoptosis rate was 1.12  $\pm$  0.09%. Syngnathus protein significantly inhibited the proliferation of HeLa cells. Studies by Cai *et al.*<sup>[56]</sup> showed that sea dragon polypeptides can promote protein expression in AMPK/PGC-1 $\alpha$  and Keap1/NRF2 pathways, regulate intestinal microecological balance, and thus exert anti-fatigue effects.

### 3.3 Sepiae Endoconcha

Sepiae Endoconcha is the dry inner shell of *Sepiella maindroni* de Rochebrune or *Sepia esculenta* Hoyle<sup>[37]</sup>. Sepiae Endoconcha is rich in calcium carbonate, amino acids, polysaccharides, chitosan, and trace elements such as Na, Fe, Mn, and Si. These substances have the pharmacological effects such as protecting the gastric mucosa, improving hypocalcemia, promoting hemostasis, and bone filling<sup>[93]</sup>. The main component of cuttlebone is calcium carbonate. The determination method of calcium carbonate content is heating cuttlebone powder, using calcein and ethylenediamine tetraacetic acid disodium to titrate. The pharmacopoeia standards stipulates that the content of calcium carbonate should be no less than 86.0%.

Qiu *et al.*<sup>[62]</sup> used a rat model of acute gastric mucosal injury to study the protective effect of Sepiae Endoconcha on gastric mucosa. The results showed that Sepiae Endoconcha could prevent indomethacin-induced acute gastric mucosal injury in rats. The mechanism may involve increasing serum EGF secretion and PEG2 synthesis, reducing lipid peroxidation, and increase SOD activity. Jin *et al.*<sup>[94]</sup> measured that 1 g of Sepiae Endoconcha could neutralize 0.109 mol/L of artificial gastric acid in 140-145 mL by the acid-base neutralization method. Sepiae Endoconcha showed no toxicity or side effects, indicating its potential use as a natural gastric acid drug. Gao *et al.*<sup>[95]</sup> established a fracture model of rat tibia by drilling holes and the expression of type I, II and III procollagen mRNA, TGF- $\beta$ 1 mRNA, bone morphogenetic protein-2 (BMP-2) mRNA, and VEGF mRNA was observed. The results confirmed that Sepiae Endoconcha can play a role in angiogenesis and bone healing by upregulating the levels of type I and III procollagen mRNA and BMP-2 mRNA. The above studies

Table 2 Traditional Chinese animal medicine from the marine

| Herbal medicine      | Pharmacological effects                         | Action mechanism                                                                                                                                                                                                                                                                                                                                                                            | Reference |
|----------------------|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Hippocampus          | Anti-inflammation                               | Downregulation of iNOS expression and decreased the concentration of NO. Inhibition of p65, inhibitor of nuclear factor kappa-B (IκB), extracellular regulated protein kinases (ERK) phosphorylation; reduce the secretion of TNF-α; inhibition of nuclear factor kappa-B (NF-κB) DNA activity.<br>Reduce the expression of creatine, creatine kinase, lactate                              | [51]      |
|                      | Anti-fatigue                                    | dehydrogenase, L-lactate, citrate; increased serum glucose, free fatty acids, hepatic glycogen, adenosine triphosphate, succinate dehydrogenase production; improving mitochondrial function and protecting muscle fibers through the mitogen-activated protein kinase (AMPK)/ PPAR (peroxisome proliferator-activated receptor-gamma)-gamma coactivator-1alpha (PGC-1α) signaling pathway. | [52]      |
|                      | Antioxidation                                   | Reduce intracellular reactive oxygen species (ROS) levels, scavenging peroxy radicals.                                                                                                                                                                                                                                                                                                      | [53]      |
|                      | Anticancer                                      | Downregulation of dihydrotestosterone-induced androgen receptor and androgen receptor expression. Induce cancer cell apoptosis and inhibit migration.                                                                                                                                                                                                                                       | [54]      |
|                      | Antitumor                                       | Induce cancer cell apoptosis and increase the expression of pro-apoptotic proteins (Bax, p53); stimulate lymphocyte division, improve immune system function. Inhibits the growth of cancer cells and induces apoptosis of cancer cells.                                                                                                                                                    | [55]      |
| Syngnathus           | Anti-fatigue                                    | Inhibit oxidative stress; improve mitochondrial function, increase adenosine triphosphate (ATP) production; regulating gastrointestinal microecological balance.                                                                                                                                                                                                                            | [56]      |
|                      | Immunoregulation                                | Stimulate lymphocyte proliferation, increase the expression of IL-2 and TNF, improve immunity.                                                                                                                                                                                                                                                                                              | [57]      |
|                      | Bone healing                                    | Increased the number of osteoblasts, osteoclasts, woven bone, lamellar bone, havers system, and bone repair.                                                                                                                                                                                                                                                                                | [58, 59]  |
| Sepiae               | Antibiosis                                      | Inhibit the growth of <i>Vibrio harveyi</i> , <i>Vibrio alginolyticus</i> and <i>Staphylococcus aureus</i>                                                                                                                                                                                                                                                                                  | [60]      |
| Endoconcha           | Gastric protection                              | Increased the secretion of epidermal growth factor (EGF) and the synthesis of prostaglandin E2 (PEG2) in serum, decreased lipid peroxidation and increased superoxide dismutase (SOD) activity.                                                                                                                                                                                             | [61, 62]  |
|                      | Hemostasis                                      | Reduce APTT, prothrombin time; prothrombin promotes the formation of coagulation factors and kallikrein during the formation of thrombin.                                                                                                                                                                                                                                                   | [63, 64]  |
|                      | Anti-osteoporosis                               | Enhanced the proliferation, differentiation and formation of bone nodules of primary osteoblasts.                                                                                                                                                                                                                                                                                           | [65]      |
|                      | Anticancer                                      | Inhibition of cell proliferation, cell cycle arrest in G0/G1 phase; the expression of oncogenes such as c-myc and mutant p53 (MTp53) decreased. The expression of tumor suppressor genes such as cyclin-dependent kinase inhibitor p21 (WAF1/CIP1) and retinoblastoma protein (Rb) was enhanced.                                                                                            | [66, 67]  |
| Ostreae concha       | Immunoregulation                                | Repair the damage of spleen and thymus tissue morphology, enhance the level of serum hemolysin, increase the concentration of IL-2, interferon-γ and immunoglobulin.                                                                                                                                                                                                                        | [68]      |
|                      | Reduce reproductive damage related to autophagy | Reduce intracellular ROS levels and malondialdehyde (MDA) content. Reducing oxidative stress; increase testosterone levels; regulate cell autophagy.                                                                                                                                                                                                                                        | [69]      |
|                      | Hypolipidemic                                   | Inhibition of lipid metabolism synthesis gene expression, inhibition of lipid biosynthesis and accumulation; reducing cholesterol synthesis and increasing the conversion of cholesterol to bile acid; promote the discharge of fatty acids.                                                                                                                                                | [70]      |
|                      | Hypoglycemic                                    | Inhibition of α-glucosidase activity.                                                                                                                                                                                                                                                                                                                                                       | [70]      |
| Margarita            | Wound repair and regeneration                   | Increase the proliferation and migration of skin cells, enhance the biomechanical strength of healed skin; improve the formation and regular deposition of collagen, enhance skin angiogenesis.                                                                                                                                                                                             | [71, 72]  |
|                      | Tranquilization                                 | The abnormal gene expression caused by insufficient sleep was corrected by retrograde endocannabinoid signaling pathway, and the protein interaction.                                                                                                                                                                                                                                       | [73, 74]  |
|                      | Anti-photoaging property                        | Upregulated the activity of catalase (CAT), glutathione peroxidase (GSH-Px) and SOD, decreased the level of MDA, and inhibited the production of IL-1β, IL-6, Prostaglandin E2, TNF-α and Cyclooxygenase-2.                                                                                                                                                                                 | [75]      |
|                      | Inhibiting granulosa cell apoptosis             | Inhibit the expression of cleaved-caspase3 and Bax through MAPK pathway.                                                                                                                                                                                                                                                                                                                    | [76]      |
| Margaritifera concha | Antioxidation                                   | Scavenging hydroxyl radicals; inhibition of tyrosinase activity.                                                                                                                                                                                                                                                                                                                            | [77, 78]  |
|                      | Antihypertensive                                | Competitive inhibition of angiotensin I converting enzyme activity                                                                                                                                                                                                                                                                                                                          | [79]      |
|                      | Tranquilization                                 | Increase the expression of 5-hydroxytryptamine (HT) <sub>1A</sub> receptor and decrease the expression of 5-HT 2A receptor. Restoring the normal expression of brain-derived neurotrophic factor (BDNF).                                                                                                                                                                                    | [80]      |
|                      | Osteogenic                                      | Promote osteoblast proliferation and inhibit osteoclast formation; accelerate preosteoblast differentiation and extracellular matrix mineralization; prevent bone loss.                                                                                                                                                                                                                     | [81, 82]  |
|                      | Proangiogenic                                   | Add/synergize with growth factors in cells to increase cell differentiation and functional properties.                                                                                                                                                                                                                                                                                      | [83]      |
| Haliotids Concha     | Antioxidation                                   | Scavenging superoxide free radicals.                                                                                                                                                                                                                                                                                                                                                        | [84]      |
|                      | Antihypertensive                                | Downregulate plasma norepinephrine, epinephrine, angiotensin II, aldosterone levels; upregulate plasma NO levels                                                                                                                                                                                                                                                                            | [85]      |
|                      | Repair effect on the ocular surface             | Protect conjunctival goblet cells, inhibit ocular surface cell apoptosis, and inhibit ocular surface CD4 <sup>+</sup> T cells.                                                                                                                                                                                                                                                              | [86]      |
|                      | Anti-inflammation                               | Inhibition of iNOS expression and removal of neutrophils by phagocytosis. Induces the secretion of transforming growth factor beta1 (TGF-β1), converting collagen during the tissue remodeling phase.                                                                                                                                                                                       | [87]      |
|                      | Osteogenic                                      | Promote the proliferation and differentiation of osteoblasts and promote bone remodeling.                                                                                                                                                                                                                                                                                                   | [88]      |

have shown that *Sepiae Endoconcha* has therapeutic effects on gastric mucosal injury and bone healing.

### 3.4 Ostreae Concha

*Ostreae concha* is the shell of *Ostrea gigas* Thunberg, *Ostrea*

*talienwhanensis* Crosse, and *Ostrea rivularis* Gould<sup>[37]</sup>. *Ostreae concha* are rich in peptides, polysaccharides, amino acids, taurine and other active substances, which have antitumor, hypoglycemic, immunoregulatory and other functions<sup>[96]</sup>. The main component in *ostreae concha* is calcium carbonate. According to the

pharmacopoeia, the content of calcium carbonate in oysters is not less than 94.0%.

Xu *et al.*<sup>[97]</sup> used cyclophosphamide (CTX)-induced immunocompromised female ICR mice as a model to observe the effects of different doses of ostreae concha peptides on immune function in mice. The results showed that the ostreae concha peptide could improve the atrophy and cell reduction of immune organs in CTX-induced immunosuppressed mice. The mechanism may be related to regulating the distribution of T lymphocytes in immunosuppressed mice, regulating the secretion of interleukin 5 (IL-5) and interleukin 7 (IL-7), and restoring the normal proliferation of bone marrow. To explore the protective effect of oyster polysaccharides on acute alcoholic liver injury, Hou *et al.*<sup>[98]</sup> found that oyster polysaccharides can reduce the activity of alanine aminotransferase and aspartate aminotransferase in the serum of mice with liver injury caused by ethanol gavage, increase the levels of SOD and alcohol dehydrogenase, improve the antioxidant capacity of liver cells, and reduce the damage of alcohol to the liver. The mechanism by which oyster polysaccharides protect against liver injury may be by improving the antioxidant capacity of hepatocytes, protecting the structural integrity and function of hepatocytes, and antagonizing alcohol damage to hepatocytes.

### 3.5 Margarita

Margarita are calcium carbonate-containing mineral beads formed by the stimulation of bivalves such as the pearl shell animal *Pteria martensii* (Dunker), *Hyriopsis cumingii* (Lea), or *Crustaria plicata* (Leach)<sup>[37]</sup>. Margarita is rich in calcium carbonate, amino acids, trace elements, and a variety of proteins. It has conglutinant, anticonvulsant and other activities, and it is often used to treat recurrent aphthous ulcers, gastric ulcers, duodenal ulcers and other diseases.

By comparing the protein release of pearl powder with 544 nm, 2 mm and 67 mm margarita sizes and the healing effect on rat skin wounds, Chen<sup>[71]</sup> showed that with the decrease in margarita powder, the protein release increased, which promoted the growth and reproduction of fibroblasts, increased skin tensile strength, promoted the formation of new blood vessels, and improved the wound healing rate. Nanosized margarita powder has the best effect on improving the tensile strength of the wound, which can increase the tensile strength of the wound to 15 N. The skin tensile strength of ordinary pearl powder and micron-sized pearl powder is between 10-15 N, and that of the blank control group is less than 5 N. Zhang *et al.*<sup>[74]</sup> studied the anticonvulsant and sedative effects of pearls. The results showed that the water-soluble protein extracted from pearls could reduce 5-HT in brain tissue from 0.55 ng/mL to 0.4 ng/mL. After freeze-drying with dilute hydrochloric acid, the protein reduced the 5-HT level to 0.3 ng/mL. Both water-soluble protein and acid-soluble protein could restore  $\gamma$ -aminobutyric acid from 1.5 ng/mL to 2.7 ng/mL.

### 3.6 Margaritfera Concha

Margaritfera concha is the shell of the aforementioned pearl. Margaritfera concha consists of calcium carbonate, which induces skeletogenesis in vertebrates. Jean-Daniel<sup>[99]</sup> compared the osseointegration and erosion of pearl-layer screws with titanium screws *in vivo* in rats implanted with mother-of-pearl screws in the right condyle and titanium screws in the left condyle after anesthesia and showed that the volume of pearl-layer screws decreased over time, with a large difference between pearl screws

and titanium screws at 6 months and no significant difference by 12 months. There was no significant difference at 12 months. The erosion of the pearl screws occurred only within the diaphysis, and the screw portion outside the diaphysis did not change, suggesting that the pearl layer screws are only resorbed when in contact with the bone marrow. Therefore, the pearl layer screws can be used as a bone graft substitute under partial conditions and avoid the step of surgical removal of the device after bone healing. Yamagami *et al.*<sup>[100]</sup> treated rats to study the effect of margarit concha powder on scopolamine-induced memory impairment by the Y-maze experiment, Barnes maze experiment and object recognition test. It was found that mother-of-pearl extract could improve scopolamine-induced memory impairment in mice. For further study, a sulfated polysaccharide was extracted from margarit concha, which was found to mediate its anti-amnesic effects by preventing oxidative stress and inflammation and increasing the expression levels of BDNF and nerve growth factor.

### 3.7 Haliotids Concha

Haliotids Concha is the shell of *Haliotis diversicolor* Reeve, *Haliotis discus hannai* Ito, *Haliotis ovina* Gmelin, *Haliotis ruber* (Leach), *Haliotis asinina* Linnaeus, and *Haliotis laevigata* (Donovan)<sup>[37]</sup>. Modern studies have shown that haliotids concha have pharmacological effects, such as antihypertensive, antibacterial, and neutralizing effects on gastric acid. The pharmacopoeia stipulates that the calcium carbonate content of this product is not less than 95.0%.

Wan<sup>[86]</sup> used haliotids concha powder in a dry environment and scopolamine-induced immunodeficient dry eye mice to observe the therapeutic effect of haliotid concha on dry eye and study its mechanism. Haliotid concha achieved a damage repair effect on the ocular surface by protecting conjunctival cupped cells, inhibiting apoptosis of ocular surface cells, and suppressing ocular surface CD4<sup>+</sup> T cells to reduce dry eye. Wang *et al.*<sup>[84]</sup> extracted a heteropolysaccharide from the shell of *Haliotis discus hannai* Ito, which has significant superoxide radical scavenging ability. Liu *et al.*<sup>[101]</sup> confirmed that the haliotid concha has a strong and lasting hypotensive effect, can inhibit the growth of *Pseudomonas aeruginosa* and has a bacteriostatic effect.

## 4 Prospects

As research on MTCM pharmacology deepens, the efficacy of MTCM has been gradually confirmed. The ancient books shows that sargassum has the function of clearing phlegm and softening hardness. It can be used to treat diseases such as gall tumors and scrofula. Now it is mainly used to treat diseases such as goiter, thyroid tumors and lymphatic tuberculosis. These diseases are the same as those recorded in ancient books<sup>[102]</sup>. The Sepiae Endoconcha has the effects of astringing hemostasis, astringing essence and stopping belt, relieving acid, relieving pain, astringing dampness and astringing sores. It can be used to treat diseases such as uterine bleeding, pannus and sores. Modern clinical application follows the application of Sepiae Endoconcha in ancient books, which is mostly used to neutralize gastric acid, protect mucosa and stop bleeding<sup>[103, 104]</sup>.

MTCM has the characteristics of complex pharmacological effects, multiple components and targets. These characteristics make it difficult to systematically study the targets and mechanisms of MTCM, in recent years, technologies such as network pharmacology and big data have developed rapidly, which have had a significant impact on MTCM research. They are

widely used in the screening of active ingredients, the positioning of action targets, and the interpretation of the mechanism of multicomponent, multitarget and multi-pathway MTCM. Therefore, the establishment of the chemical molecular database of MTCM, the active ingredient-gene database of marine, and the active ingredient-target database of marines is helpful to provide the basis for the study of the targets and mechanisms of MTCM *in vivo* by using network pharmacology.

As the marine economy has developed by leaps and bounds, the unreasonable development of resources and environmental damage have threatened the sustainable development of MTCM resources, and frequent human activities and dense populations have brought great challenges to the protection and development of MTCM resources. For example, mangroves, which are typical coastal plants and can be used as MTCM resources, have great development potential as MTCM. However, mangroves are facing problems such as area reduction, habitat degradation and biodiversity reduction, making them protected species in China. Therefore, it will be an important measure for the sustainable development of MTCM resources to establish a germplasm bank of MTCM resources, strengthen the system construction of rare and endangered MTCM resources and protect wild MTCM resources.

The complexity of MTCM and its preparation components, the instability and trace of secondary metabolites lead to the uncertainty of the efficacy of most traditional Chinese medicines. At the same time, the detection of one or several components of a traditional Chinese medicine cannot reflect the overall efficacy of traditional Chinese medicine, resulting in the lack of quality standards for MTCM. With the development of science and technology, the technologies for drug identification are becoming more and more perfect. The quality control standards of traditional Chinese medicine in 'Pharmacopoeia' are becoming more and more complete, including chromatography including thin layer chromatography and high-performance liquid chromatography, ultraviolet spectrophotometry and other spectroscopy, DNA barcoding technology and inductively coupled plasma mass spectrometry. In addition, the fingerprint of traditional Chinese medicine is widely used in the quality control of MTCM in recent years because it can comprehensively reflect the types and contents of medicinal materials.

In this paper, only a small part of MTCM resources was listed. Although the types of MTCM have increased rapidly in recent years, the newly added drugs have not been clinically applied due to the lack of records of efficacy and toxicity and incomplete information on functional indications. Therefore, it is necessary to systematically sort out and excavate the research system and evaluate the drug efficacy and toxicity of MTCM, which is conducive to overcoming the problems of drug efficacy and toxicity evaluation and quality control of MTCM and expanding the clinical application of MTCM.

## 5 Conclusion

MTCM has many activities such as anti-inflammatory, anti-oxidation and anti-tumor. Therefore, accelerating the industrialization of MTCM and contributing a force to the construction of healthy China will help promote MTCM to the world. China has a long cultural history and rich resources in MTCM. However, due to the imperfect information of MTCM, the industrialization of MTCM is restricted. However, with the continuous improvement of the status of traditional Chinese

medicine industry in the economic society and the growing health needs of the people, the people's recognition of traditional Chinese medicine is increasing, and the products related to MTCM are gradually infiltrated into people's daily life. Although the development and utilization of MTCM mostly stay in food and health products, with the progress of science and technology and the support of national policies, the level of MTCM industry will be continuously improved. So as to promote the common development of traditional marine Chinese medicine and healthy China.

## Conflicts of interest

The authors declare that there are no conflict of interest in this work. Chenyang Lu is an associate editor of Food & Medicine Homology, but was not involved in the processing, peer review or decision making of this article.

## Acknowledgments

This work was supported by the National Key Research and Development Program of China (Grant number 2021YFC2103900).

## Authors' contributions

All authors contributed to the study conception and design. Xianwen Lu performed the original draft; Song Qin, Qi Wang and Chenyang Lu performed the review and editing; Wenjun Li performed the funding acquisition.

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