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The Application of Coral in Traditional Medicine and Its Chemical Composition, Pharmacology, Toxicology, and Clinical Research

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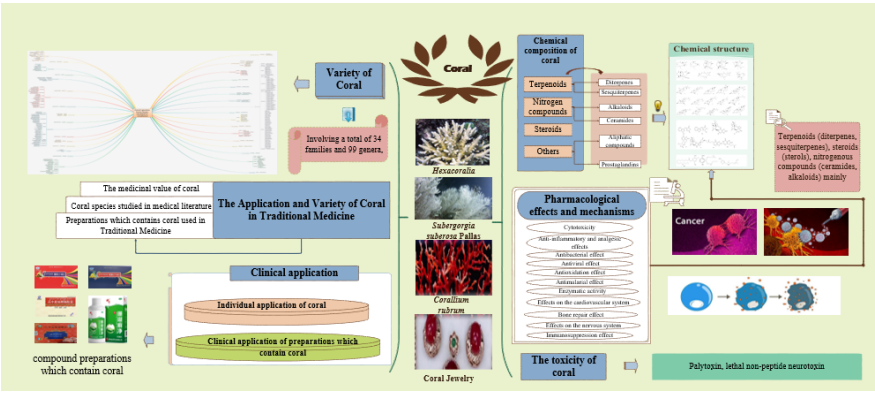
Abstract

This reviews the variety, chemical composition, pharmacological effects, toxicology, and clinical research of coral used in traditional medicine in the past two decades. At present, there are 56 formulas such as traditional Chinese medicine, Tibetan medicine, Mongolian medicine, and Uyghur medicine. 34 families and 99 genera of corals are involved in medical research, with the Alcyconiidae family and Sarcophyton genus being the main research object. The compounds extrate from coral includ terpenoids, steroids, nitrogen-containing compounds and others. The biological activities of coral include cytotoxicity, anti-inflammatory and analgesic, antibacterial, antiviral, immunosuppressive, antioxidant, neurological, and other aspects, and a detailed summary of its related mechanisms or target targets is provided. Coral toxicity mostly occurs in the marine ornamental soft coral Zoanthidae genus, with Palytoxin as the main toxic component. At the same time, non peptide neurotoxins are extracted from aquatic corals. The compatibility of coral related preparations did not show significant acute toxicity, but if used for a long time, it will still cause toxicity to the liver, kidneys, lungs and others in a dose-dependent manner. In clinical applications, individual application of coral is often used as a substitute for orthopedic materials to treat bone diseases. Secondly, it mainly appears in the form of compound preparations which contain coral, such as Ershiwuwei Shanhu Pills, which are widely used in neurological diseases such as migraine, epilepsy. This article is expected to provide some reference for the research of coral chemical composition, biological activity, chemical ecology and the discovery of marine drug lead compound.



1 Introduction

The marine biological resources are abundant, and coral is one of the most common organisms in the ocean. It is a lower-level invertebrate of the ocean, belonging to the phylum Coelenterata and the class Coralis. It

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mainly lives in tropical oceans, with a wide variety and distribution. There are over 6100 species of coral worldwide, and 719 species in China (LI, 2010b),Corals can be divided into*Hexacorallia* and*Octocorallia* (Xu, 2016). Corals are known as "sea flowers" and are a type of aquatic coelenterate. Its population is dendritic, branching and spreading like fans, with very fine branches. On its surface, there are many hydra bodies, called anthozoan polyp. The body is hemispherical in shape, with 8 feathered tentacles on top. The tentacles have a mouth in the center, and the insect body can secrete limestone to form bones. The white one is better than snow, the red one is like blood, the green one is like jade, and the yellow one is like gold. It naturally grows in the sea, with strange shapes and unparalleled beauty(Group, 1996). The main component of coral is calcium carbonate, which also contains a series of elements such as iron, manganese, copper, and strontium, as well as chitin and organic acids. Corals are commonly white, while gemstone grade corals are red, pink, and orange red, with a small amount of black and blue. The color is caused by containing about 1% iron oxide and organic matter. With red as the top grade, red coral is as red as fire, known as the "fire tree" in ancient times. Its origin is in the deep sea of the Mediterranean and Atlantic oceans, and it is mainly used for jewelry products, with the largest being used for carving figures, flowers and birds, and other handicrafts(Wen, 2007). Indians and Tibetans use coral as a mascot for worship, often used to make Buddhist beads and decorate deities. In the West, coral is listed as one of the three major organic gemstones, while in the East, it has been regarded as a symbol of auspiciousness and happiness since ancient times. It represents nobility and power, and is a symbol of happiness and eternity(Wen, 2007). The ancient Romans believed that coral had functions such as disaster prevention, intelligence, hemostasis, and heat dissipation, which continued until this century(Hong, 2009).

Corals are distributed in the South China Sea, North China Sea, and East China Sea, among which the South China Sea is located in a tropical and subtropical zone and contains abundant coral biological resources. Since the 1980s, chemists have conducted in-depth research on corals in the South China Sea. At the beginning of the 20th century, the utilization of coral resources mainly included: human bone substitutes. Feed calcium filler. A good source of calcium supply for the human body(Huang, Zhang, Zhang, Lin & Liu, 1997). With the rapid development of modern separation and identification methods and the increasing maturity of biotechnology, a large number of active substances have been isolated from marine organisms(Zhang, 2013a) such as salicin with antibacterial activity and alkaloids with cytotoxic activity , which have been isolated from the *Sinularia suberosa* on the side of the South China Sea(Qi, Zhang, Li & Li, 2005),and anti-tumor alkaloids have been obtained from the *E.curvata* on the side of the South China Sea(Zhang, 2012b). With the deepening of chemical research on natural products of soft coral and Gorgonian, thousands of compounds with dozens of structural skeletons have been discovered, mainly involving steroids, terpenoids, nitrogen-containing compounds, long-chain fatty acids, and long-chain alcohols. The diverse structures, unique molecular frameworks, and significant pharmacological activities of coral secondary metabolites fully demonstrate their potential medicinal value(Shao et al., 2009b; Zhang, Guo & Gu, 2006).

In the late 1960s, American scholars and others discovered prostaglandin precursors with unique structures and strong physiological activity from Gorgonian, which further promoted the research of coral chemistry,The pharmacological activity of coral is gradually being explored, mainly manifested in various aspects such as anti-tumor, anticancer, antioxidant, and anti cardiovascular and cerebrovascular system diseases。 These pharmacological effects are mostly exerted by a single active substance extracted from coral bodies, while coral's own bones are mostly used as materials for bone transplantation and other applications(Wang, Wang, Han, Liu & Zhen, 2002). In fact, coral, as a medicinal material, has been recorded in detail in the *The Compendium of Materia Medica* (1578 AD). It has a sweet taste, flat. and has the effects of improve eyesight, tranquilizing mind and stop epilepsia. It is mainly used to treat corneal opacitycorneal opacity, dissipate blood stasis, and powder can stop epistaxis. In clinical, coral is also used in various compound preparations, such as Ershiwuwei Shanhu Pills and Shanhu qishiwei pill, which have the effects of inducing resuscitation, dredging meridians, and relieving pain。 It is used for "albichoriasis ", unconsciousness, body numbness, dizziness, brain pain, irregular blood pressure, headache, epilepsy and various neuropathic pain. *The Compendium of Materia Medica* (1578 AD) records that corals are non-toxic, but according to literature reports, corals can release toxins, which are the second largest known deadly gas in the world, ultimately

leading to toxic reactions such as muscle pain, four limb weakness, and fainting. On the contrary, in compound use, short-term use does not produce acute toxic reactions, but long-term use can cause damage to the liver, kidneys, and other organs.

This reviews the traditional medicine of coral and its application in chemical composition, pharmacology, toxicology and clinical research in the past two decades, with a view to providing meaningful research data for the comprehensive development of marine biological resources, the discovery of drug lead compound, the chemical ecology research of marine invertebrates, and even the determination of organic synthetic chemical target compounds.

2.The Application and Variety of Coral in Traditional Medicine

2.1 Coral species studied in medical literature

Tang Sujing wrote in the*Newly Revised Materia Medica* in 659 AD, which recorded that*Corallium rubrum* (Linnaeus), also known as red coral, Hong shan, Huo shu, and *Corallium japonicum* , belongs to the genus *Corallium* in the family*Coralliaceae* . In addition, *Corallium japonicum* Kishinouye was included in the genus *Corallium* in the family*Coralliaceae* in the *National Compilation of Chinese Herbal Medicine* (Second Edition). As Mongolian medicine Zhuru, Ulan Shuru and Shuru are recorded. *Fossilia Corrallium* is recorded as a Uyghur medicine in the *Dictionary of Chinese ethnic medicine* and is mostly distributed in the Baihe Mahle River. It is commonly used to treat diarrhea, gastrointestinal bleeding, and neurasthenia. The *Dictionary of Traditional Chinese Medicine*also records *Corallium japonicum*Kishinouye, which is recorded as*Coralliumkonojoi* with the same name in the *Chinese Traditional Chinese Medicine Resources* . In addition, there are *Corallium secundum* Dana, *Corallisum elatius* Ridley. The *Records of Chinese Traditional Chinese Medicine Resources (Part 2)* also records six species of coral, namely *Porites nigrescens* Dana in the*Poritidae* family Coral, *Porites*genus.*Antipathes sp* , *Antipathes sp* and National first-class protected wild animal *Corallisum japonicum*Kishinouye、*Corallisum elatius* Ridley and *Corallisum konojoi* Kishinouye are also recorded. In the past two decades, most of the coral species that have been studied in medicine belong to the*Alcyoniidae* and *gorgonacea* , and*scleractinia* . After sorting, it was found that red coral is mostly used in medical records. Modern research on coral species is diverse, involving a total of 34 families and 99 genera,*Alcyoniidae, Nephtheidae, Plexauridae, Gorgoniidae, Xeniidae, Elisellidae, Briareidae, Subergogiidae, Clavulariidae* family corals are more common, *Sarcophyton* and*Sinularia* are research hotspots in *Alcyconiidae* , followed by *Dendronephthya* , *Litophyton* , and *Lemnalia* corals in the *Nephtheidae* family, followed closely by*Echinogorgia* , *Plexauridae* , and *Eunicea* corals in the *Plexauridae* family, as shown in Figure 1.

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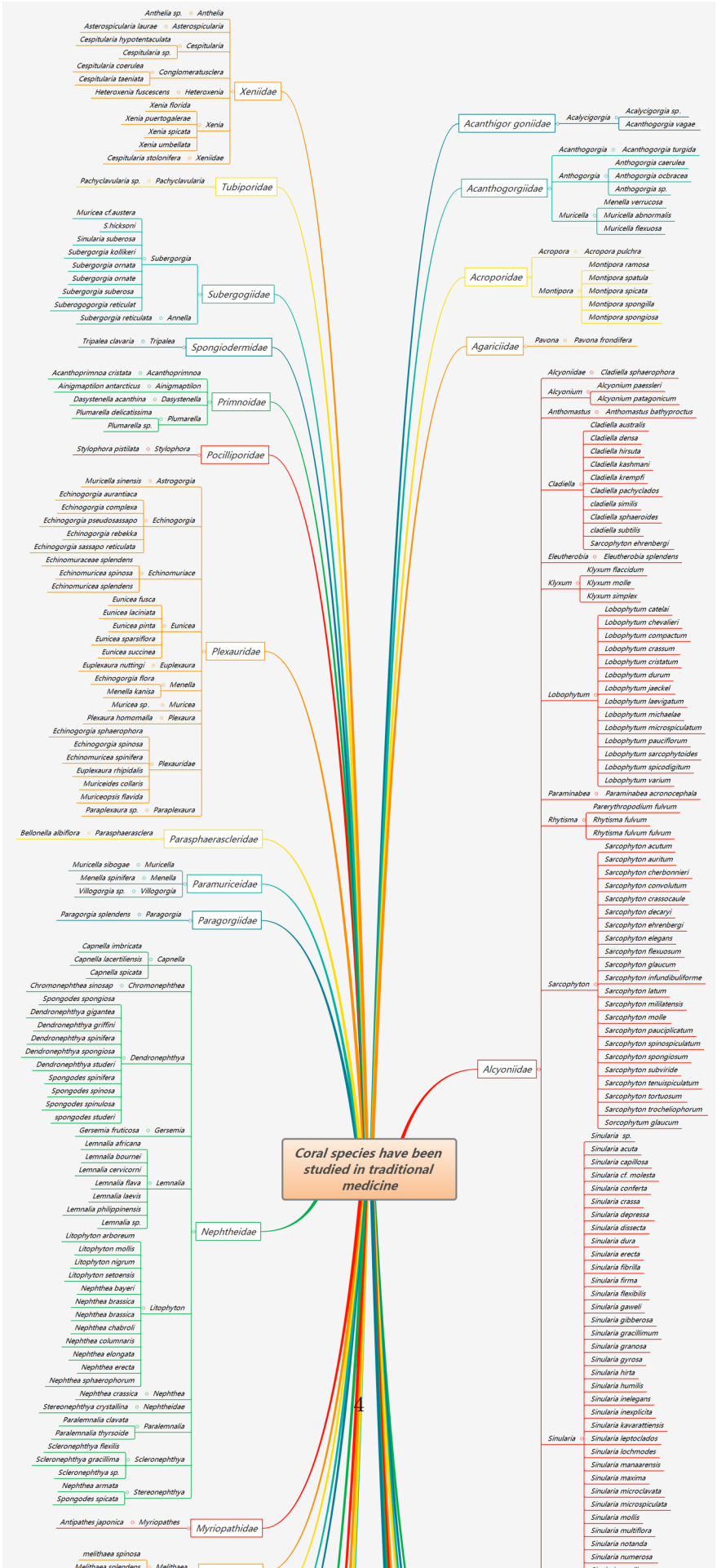

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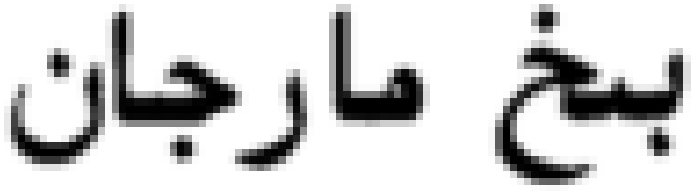
Figure 1 Coral species studied in medical literature

2.2The medicinal value of coral

The records of coral can be traced back to the Three Kingdoms period (226-231 AD). Kangtai and Zhu Ying of the Eastern Wu Dynasty mentioned in their *Biography of Fu Nan* : "In the rising sea, the coral reef falls, and there is a rock at the bottom of the reef, and the coral grows on it(Cao, 2012). Coral is used as medicinal materials were first recorded in the *Newly Revised Materia Medica*(659 AD), which describes coral as "sweet, flat, non-toxic, mainly used for blood retention, corneal opacitycorneal opacity, and powder can stop epistaxis. It grew in the South China Sea, resembling jade red, with many pores in the middle and some without pores. It also came from Persia and Lion Kingdom." *The "General Introduction to the Essential Prescriptions of Zengguang and Zhiju* " (1208 AD) records that coral has the effect of removing corneal opacitycorneal opacity and stoping epistaxis, *Yue Hau zi* (908-923 AD) describes that coral can tranquilize mind, stop epilepsia, *Oversea Materia Medica* (907-960 AD) records that coral is the main cause of blood stasis and wind epilepsy, The classic work*Compendium of Materia Medica* (1578 AD) points out that coral has the effect of dropping and removing flying silk, *Materia Medica Yanyi* (1116 AD) records that coral can be used to remove corneal opacitycorneal opacity, *Compendium of Selected Essentials of Materia Medica* (1644-1911 AD) describes that coral is mainly used for corneal opacitycorneal opacity, blood stasis, epistaxis, it can improve eyesight, tranquilize mind, stop epilepsia, and drop and remove flying silk, In the *second edition of the National Compilation of Chinese Herbal Medicine (Volume 2)* (compiled by the Compilation Team of the*National Compilation of Chinese Herbal Medicine* , 1996) records that coral is also known as red coral, with a sweet and flat; It has the effect of tranquilizing mind, stoping epilepsia, improving eyesight, and is mainly used for treating convulsions, stopping epilepsy, and removing corneal opacitycorneal opacity. Traditional Chinese medicine books such as *Taiping Holy Prescriptions for Universal Relief* (992 AD), *Fangmai Zhengzong*(1749 AD), *Peng Family Miao Prescription* , and *Aquatic Product Nutrition and Medicinal Manual* all contain prescriptions made from red coral, which can remove children's corneal opacitycorneal opacity, dizziness, epilepsia or palpitations, heart and lung congestion, persistent vomiting and bleeding, and water and fire burns(Lai, Bao & Bao, 2016)。



Tibetans, Mongols and Uygurs also often use coral as a medicinal material for compatibility treatment. The coral Tibetan medicine, named Qiwuru (**byu-ru /)** , also known as Pazhuma, has the effects of Clearing meridian and liver heat and detoxifying various toxins. It is mainly used to treat encephalopathy, liver disease, various fevers, and poisoning. The Mongolian medicine is named Shuru(shirU), also known as Zhuru and Ulan Shuru. It has the effects of clearing heat, detoxifying, and tranquilizing mind. It mainly treats liver heat, meridian heat, gathering disease, toxic heat, stroke, and albichoriasis. The Uyghur medicine is named Bihe Marjiang(), also known as Busai, and has the effects of eliminating dampness and astringing sores, clearing heat and inflammation, dispersing and consolidating tooth qi, refreshing the heart and pleasing the mind, stopping bleeding, stopping diarrhea, and stopping bleeding. It is mainly used to treat damp heat or blood related diseases. Li Xin(Li, 2015) et al. found through experimental research that Mongolian Jiegu Medicine Water Pills have good therapeutic effects on fractures. A'naer Vigills has the functions of clearing heat, eliminating dampness, and relieving itching. It has been used for various symptoms such as itching, redness, swelling, and excessive vaginal discharge in women caused by bacterial and fungal vaginitis. It is a commonly used Uyghur medicine preparation in clinical practice(Chen, 2011). Ershiwuwei Shanhu Pills

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can intervene in the treatment of neurological diseases such as Alzheimer's disease, cerebral infarction, and migraine(Jiaojia et al., 2022; Zhou, Liu, Mei & Chen, 2019; Zhu et al., 2020).

The use of coral in modern medicine is no longer limited to red coral. Jiang Mei (Jiang, 2013)conducted an extraction experiment on the active ingredients of *Dichotella gemmacea* , and found that some of its diterpenoid compounds showed cytotoxicity to human lung pancreatic cancer cells (A549) and human osteosarcoma cells (MG63), and some of the compounds had antibacterial activity, Wu Rongcui(Wu, 2013) studied the *Echinogorgia flora* and found that its sesquiterpene active ingredients showed weak anti influenza virus activity. Mahmoud Amany Hamouda(Mahmoud et al., 2022) showed that the steroids and sesquiterpene of red sea soft corals showed obvious activity on A549, MCF-7 and HepG2 cell lines. The chemical components in*scleractinia* (Zhao, Zhang & Yan, 2016) exhibit good biological activities such as cytotoxicity, antibacterial, insecticidal, and toxic fish. At present, the corals used as medicinal materials mainly include soft corals, gorgonian, stone corals, and red corals(Ai, Chen & Qi, 2006). Stone corals have received little attention from chemists because they are mainly composed of calcareous bones, and the scarcity of red coral resources also limits their utilization. So active soft corals and gorgonian have become the first choice for coral reef benthic research, and are increasingly becoming hot biological species in modern marine natural product research(Xue, 2014).

2.3 Preparations which contains coral used in Traditional Medicine

Coral is used as medicinal materials has a long history in China. Ancient Chinese ancestors recognized the medicinal value of coral. Coral is mainly used in traditional Chinese medicine, Tibetan medicine, and Mongolian medicine, but the specific variety of coral is not clearly specified in the prescription. Red coral is mainly used as medicine, and the method of medicine is to take the original medicinal material, remove impurities, wash, grind into fine powder, and then fly it into extremely fine powder, dry it. The compatibility of its medication is shown in Table 1. It is mainly used to treat nervous system disease, chronic ulcers and various heat syndromes. Traditional Chinese medicine often plays a role in clearing heat, mainly treating eye diseases such as chest and hypochondriac swelling and pain caused by dampness and heat in the liver and gallbladder. Tibetan medicine is used to treat headache, epilepsy and various neuropathic pain caused by albichoriasis. Mongolian medicine has a wide range of treatments, including various new and old fractures, soft tissue injuries, femoral head necrosis, and various edema in addition to traditional Chinese medicine and Tibetan medicine. There are also records in Uyghur medicine that treat various bacterial, fungal, trichomonal vulvitis, and vaginitis caused by itching, redness, and swelling of the genital area in women, as well as excessive vaginal discharge.

Table 1 Preparations which contains coral used in traditional medicine(Lai, Bao & Bao, 2016)

The name of the preparation	Systems of traditional medicine	Indications
Teling Yanyao	Traditional Chinese Medicine	Swelling and pain of e
Jinniu Yangao	Traditional Chinese Medicine	Epidemic hemorrhagic
Jinniu Yanyao	Traditional Chinese Medicine	Epidemic hemorrhagic
Babao Boyun San	Traditional Chinese Medicine	Swelling and pain of e
Babao Guangming Powder	Traditional Chinese Medicine	Swelling and pain of e
Babao Ruiren plaster	Traditional Chinese Medicine	Corneal opacity and x
Babao Yanyao	Traditional Chinese Medicine	Epidemic hemorrhagic
Babao Yanyao	Traditional Chinese Medicine	Epidemic hemorrhagic
Pai Feng Yun plaster	Traditional Chinese Medicine	Corneal opacity, epide
Panyi Zijin plaster	Traditional Chinese Medicine	All kinds of acute con
Dajin Pill	Traditional Chinese Medicine	Sputum fire burnt dia
Dianyan Qibao Powder	Traditional Chinese Medicine	Wind heat rush up, ac
Fo Bao Dan (Saizhen Powder)	Traditional Chinese Medicine	Throat poisoning, thr
Gengong Pest Eliminating Pill	Traditional Chinese Medicine	All symptoms of diph

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The name of the preparation	Systems of traditional medicine	Indications
Hongding eye medicine	Traditional Chinese Medicine	hyperemia of bulbar c
Wiping teeth white quartz powder (white quartz powder)	Traditional Chinese Medicine	Teeth are bright white
Keliang Eye Medicine	Traditional Chinese Medicine	Swelling and pain of e
Luma Baoyuan Pill	Traditional Chinese Medicine	Supporting Yang and
Qibao Powder	Traditional Chinese Medicine	Corneal opacity
Zhenzhu San	Traditional Chinese Medicine	Corneal opacity
Qishiwei Songshi Pills	Tibetan Medicine	Chest and hypochond
Sanshiyiwei Songshi Pills	Tibetan Medicine	Acute and chronic hep
Sishierwei Shugan capsules	Tibetan Medicine	Damp heat in the live
SareShisanweiPengniao Pills	Tibetan Medicine	Apoplexy, Oral and ey
Ershiwuwei Songshi Pills	Tibetan Medicine	Liver depression and c
Ershiwuwei Shanhu Pills	Tibetan Medicine	”Albichoriasis”, Uncon
Ershiwuwei Shanhu capsules	Tibetan Medicine	“Albichoriasis”, Uncon
Hupo Powder	Tibetan Medicine	The eyes are old and
Ruyi Zhenzhu Powder	Tibetan Medicine	Plague beats, the hea
Ershisanwei chen Powder	Tibetan Medicine	Cough gray phlegm, r
Shibawei Jiangjun Powder	Tibetan Medicine	Albichoriasis
Jing ying Wan	Tibetan Medicine	Albichoriasis, hiraousu
Sishiwei Jiangjun Powder	Tibetan Medicine	Various poisoning
Mingmu pills	Tibetan Medicine	Various febrile liver di
SareShisanweiPengniao Pills	Tibetan Medicine	Ocular deviation, num
Sishibawei Jiedu Powder	Tibetan Medicine	Poisons such as self po
Shibawei Xijiao Powder	Tibetan Medicine	Albichoriasis
Coral Bone Joining Pill (Sunrise Tu Uril)	Mongolian Medicine	Various new and old f
Jiuwei Hailuo Powder	Mongolian Medicine	Panic, palpitations, fe
Shisanwei Ying pill	Mongolian Medicine	Albichoriasis, cerebral
Zhachong Shisanwei Pill	Mongolian Medicine	Hemiplegia, left paral
Ershiwei Huangjin Powder	Mongolian Medicine	Albichoriasis
Bianbao Pills	Mongolian Medicine	Various edema
Lianchuang Powder	Mongolian Medicine	All kinds of long-term
Shiwei Baohui Powder	Mongolian Medicine	Various edema
Shiqiwei Jinhui Pills	Mongolian Medicine	Scrofula, black Hiraou
Shibaweiguan Pills	Mongolian Medicine	Wind cold dampness,
Jiuwei Xionghuang Powder	Mongolian Medicine	Seasonal heat, plague
Sishiwei Chenxiang Powder	Mongolian Medicine	Spermatorrhea
Ershiwuwei Songshi Pills	Mongolian Medicine/Tibetan Medicine	Various liver diseases
Shiwuwei Zhenzhu Powder	Mongolian Medicine/Tibetan Medicine	In an abject state of r
Shiwuweirupeng Pills	Mongolian Medicine/Tibetan Medicine	Rheumatoid disease
Shanhu qishiwei pill	Mongolian Medicine/Tibetan Medicine	Cerebral thrombosis,
A’naer Vigills	Uyghur Medicine	Various bacterial, fung
GangKangMuKuLi Tablets	Uyghur Medicine	Hemorrhoids, clunial
Poison Symptom Drug Powde	——	Various poison formul

Chemical composition of coral

In recent years, Chinese scholars have made important contributions to the research of international marine natural products. In 1980, Su Jingyu first isolated two new types of diterpenoid dimers with double fourteen membered cyclic carbon frameworks from soft corals(Xue, 2014). In 1969, Weinheimer et al. first discov-

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ered abundant and highly active prostaglandin like compounds from gorgonian(Weinheimer & Washecheck, 1969). These research results have aroused great interest in the study of coral chemical composition. After decades of research exploration and development, a large number of structurally novel and biologically active compounds have been discovered and determined from coral. Such as terpenoids, alkaloids, steroids, macrolides, quinones, polyethers, flavonoids, and peptides, each type of compound contains many compounds with different structures(Li, 2012a). Below is an explanation of the chemical composition based on different structural types.

3.1 Terpenoids

Terpenoids are the most abundant and diverse class of compounds in coral, and new skeleton terpenoids are constantly being discovered. Its pharmacological screening shows strong biological activity(Liu, 2017; Zhang & Guo, 2003). Therefore, the isolation and identification of terpenoids has always been the focus and hotspot of coral chemistry research. After sorting out and analyzing the literature, it was found that the terpenoid compounds are mainly sesquiterpene and diterpenes, in addition to semiterpenoids and triterpenes.

3.1.1 Sesquiterpenes

Sesquiterpene are important terpenoids, which are widely distributed in terrestrial fungi, higher plants, insects and marine organisms such as soft corals. In addition to the earlier discovery of guaiacane and furan sesquiterpene, sesquiterpene also contain africanne, capnellane and illudalane(He, 2013). In 2002, Wang(Wang, Ahmed, Kuo & Sheu, 2002) isolated subergorgiol and 2β-acetyl subergorgic acid with a unique angular triquetane structure from the Taiwanese soft coral *S. suberosa* , in which subergorgiol exhibited moderate cytotoxicity against HeLa tumor cells. The semi-inhibitory concentration values were 20.8 and 30.6 μM, respectively, and showed moderate cytotoxic menecubebane B and the known compound analogue against Eca9706 and HeLa cell lines were isolated from the gorgonian*Menella sp.* . In the coming year, Ninh Thi Ngoc(Ngoc et al., 2017b) extracted and identified four sesquiterpenes nanolobatols A and B, sinularianins B and D in the Vietnamese soft coral *Sinularia nanolobata* . sinularianins B and D was similarly extracted in*Sinularia sp.* (Chao, Hsieh, Chen, Lu & Sheu, 2006; Yang et al., 2013). A novel chlorine-containing carbon-deficient sesquiterpene was isolated from Taiwan gorgonian and this compound showed inhibitory effects on Gram-negative bacteria(Sung, Chuang, Kuo, Fan & Hu, 2007). See Figure 2 for details.

3.1.2 Diterpenes

Many diterpenes show strong biological activities, so diterpenoids have remained a focus and hot spot for research in the past few years. Diterpenes are the most abundant and diverse structural types in corals, and the most common and diverse diterpene is cembrane, which is characterized by an isopropyl and three methyl substitutions in the tetradecane ring, and also includes eunjcellin, casbane, biflorane, briarellin, dolabellane, lobane, sarcodictyins, and xenia(Shao et al., 2009a). Li Jinfeng(Li, Yao, Zeng & Guo, 2022) extracted 20 sissonane type diterpenes from *Sarcophyton glaucum* . *Sinularia* family is rich in diterpenes. Eighteen sissonane type diterpenes sinuflexibilins A-F, 18 cembrane type diterpenes(Jiang, Ru, Yao, Miao & Guo, 2019; Yin et al., 2013),2 sinulins C and D etc(Qin et al., 2018). were isolated from the extract of CH2Cl2/EtOH of *Sinularia sp.* . Some of the compounds exhibit some degree of cytotoxicity against A549 and HL-60 or exert anti-inflammatory effects through iNOS and COX-2 expression, etc(Chao et al., 2011a). Su-Hui WANG(Wang et al., 2010) first discovered a new chlorinated briarane (fragilide J) and two chlorinated briaranes (robustolide L and robustolide H) from*Junceella fragilis* and *Ellisella robusta.*Ten sissonane diterpenes were isolated from soft coral *Sinularia flexibilis* samples by Jiao-Jiao Xu, and the inhibitory activity of each monomer compound on LPS-induced NO release from RAW264.7 cells was examined by Griess method at non-cytotoxic doses, and the results showed that the compounds had some inhibitory effect on NO production(Xu, 2016).

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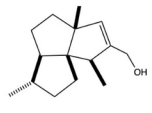
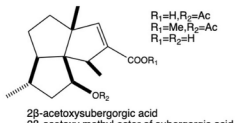
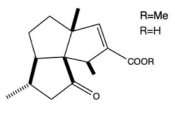


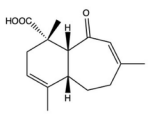
subergorgiol



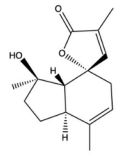
2β-acetoxysubergorgic acid
2β-acetoxy methyl ester of subergorgic acid
2β-hydroxysubergorgic acid



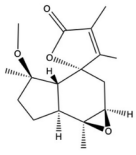
subergorgic acid methyl ester
subergorgic acid



Sinularianins A



Sinularianins B



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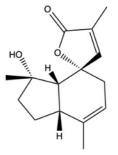
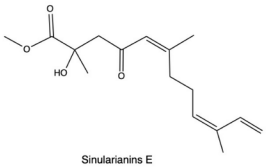
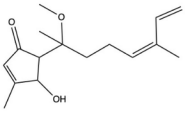


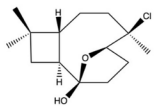
Sinularianins D



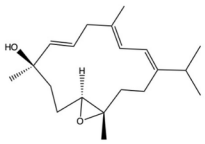
Sinularianins E



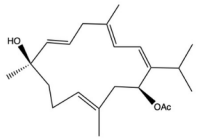
Sinularianins F



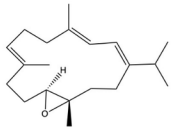
Rumphellatin A



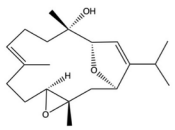
15-dehydroxy-sarcophytol D



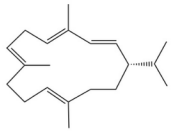
ximaoglaucumin C



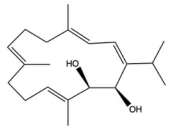
(11S,12S,1E,3E,7E)-11,12
-epoxycembra-1,3,7-triene



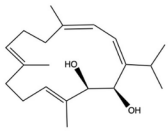
sarcophytol W



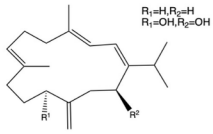
cembrene



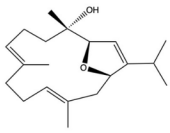
sarcophytol B



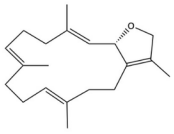
sarcophytol J



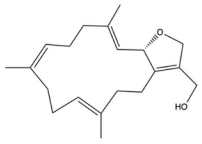
pentaene-cembrene
sarcophytol E



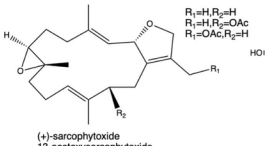
(+)-marasol



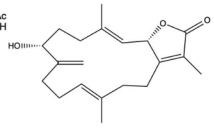
(2S)-sarcophytoninsarcophytoxide



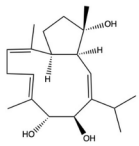
(-)-17-hydroxydeepoxysarcophytoxide



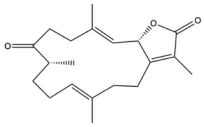
(+)-sarcophytoxide
13-acetoxysarcophytoxide
bophynin B



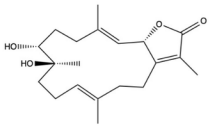
16-oxosarcophytoxide E



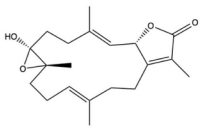
trocheliophol L



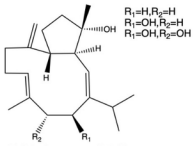
sarcophinone



7a-8β-dihydroxydeepoxysarcophine



(+)-sarcophine



14-dehydroxy-sarcophytol L
sarcophytol L
13a-hydroxy-sarcophytol L

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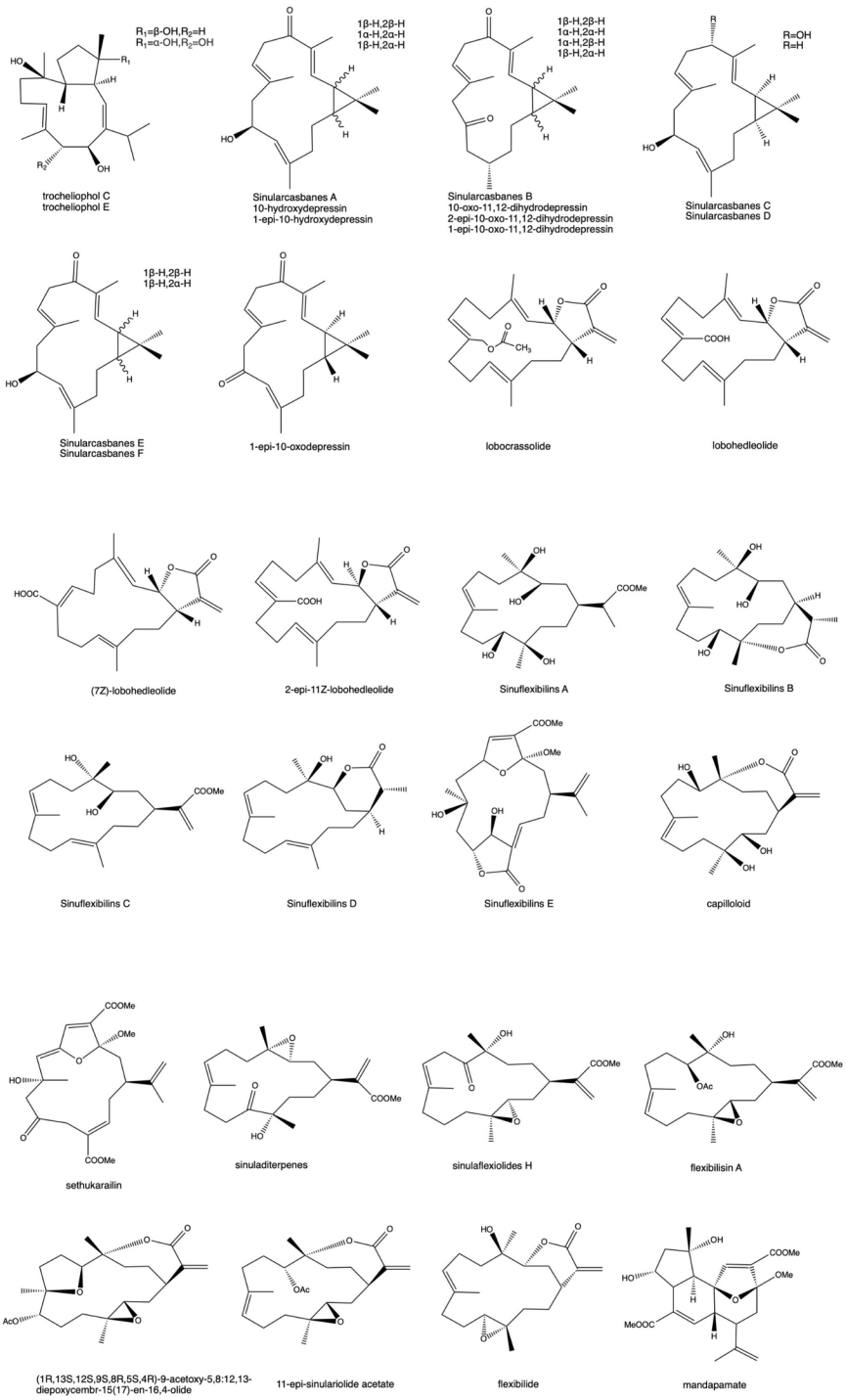

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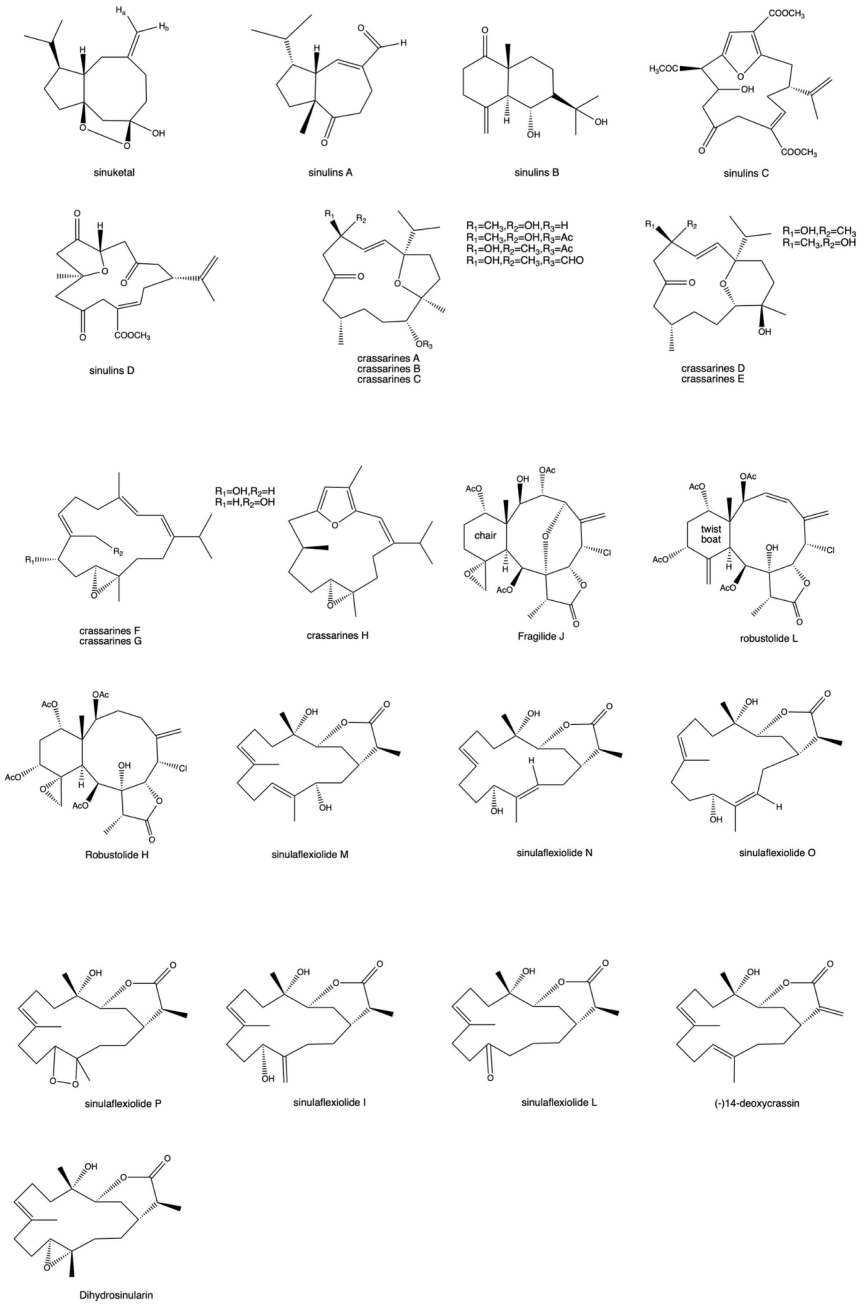
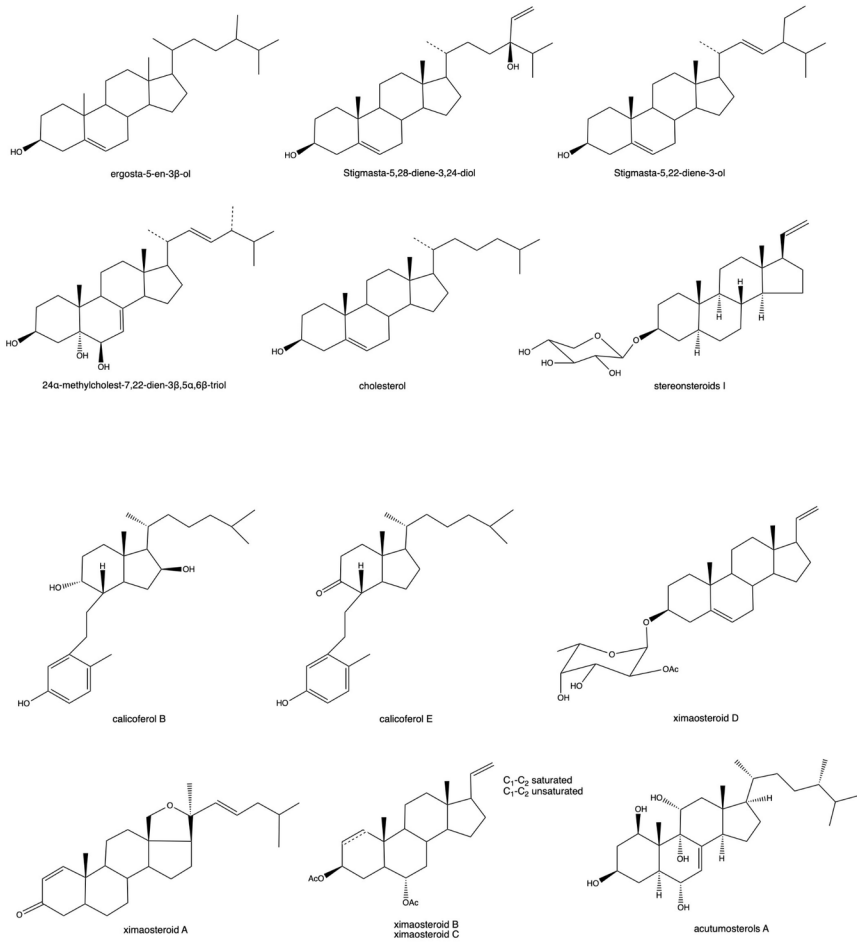


Figure 2 Some pharmacologically active terpenoids extracted from coral

3.2 Steroids

As shown in Figure 3. Steroids are a class of biologically active compounds in corals, mainly the main types such as pregnane, cholestane and ergosterone. It has received a lot of attention due to its structural diversity and remarkable biological activity(Liu, 2017). There are abundant sterols in corals, and the structure is more complex due to the diversification of sterol side chain structure and the different degrees of oxidation(Ai, Chen & Qi, 2006). It was reported that seven new cleaved ring sterols with $C_{9,11}$ break and C_{22}

hydroxylation were isolated for the first time from *Tripalea clavaria* collected from the South Atlantic Ocean in 2006, as determined by wave spectroscopy and Mosher method, and further studies showed that some of their substances had some inhibitory activity against *Staphylococcusaureus* . Four bioactive sterols with anti-inflammatory, antibacterial, antioxidant, antitumor and antitubercular properties were isolated from *Junceella fragilis*from Sanya, Hainan(wen, Qi & Zhang, 2007), and subsequently two sterols were isolated from the extract of CH_2Cl_2/EtOH of this coral(Qi, Zhang, Huang, Xiao, Huang & Li, 2004). For The first time, two B-ring open-loop sterols were isolated from the Chinese small pointed gorgonian *M. sinensis* (Verril1) from The South China Sea. In the bioactivity screening, calicoferol E was found to show inhibitory activity against protein tyrosine phospholipase 1B (PTP1B) with an IC50 value of 27.28 μM(Yan, Guo & Zhu, 2005).



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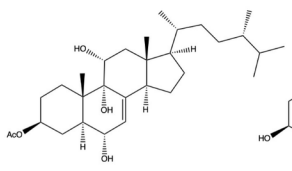
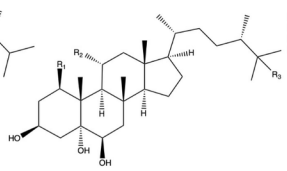
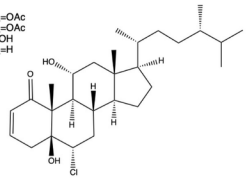


Hirsutosterol E

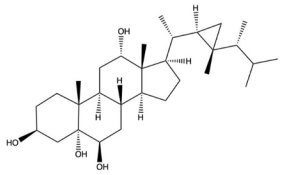


R_1=H, R_2=OH,R_3=OAc
R_1=OH, R_2=H,R_3=OAc
R_1=H, R_2=H,R_3=OH
R_1=H, R_2=OH,R_3=H

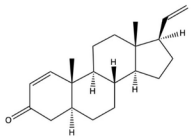
acutumosterols B
(24S)-24-methylcholestan-1β,3β,5α,6β,25-pentaol 25-monoacetate
(24S)-ergostane-3β,5α,6β,25-tetraol
Sarcoaldosterol B



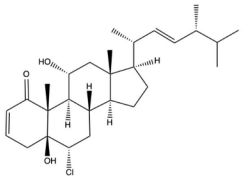
yonarasterols H



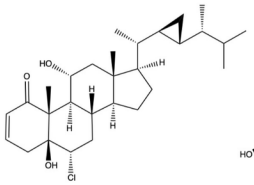
Lobophysterol D



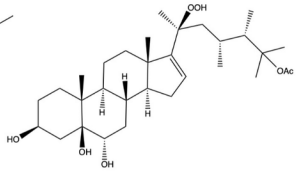
5α-pregna-1,20-dien-3-one



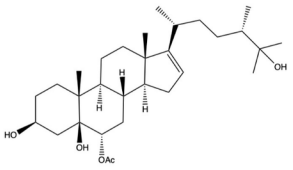
yonarasterols G



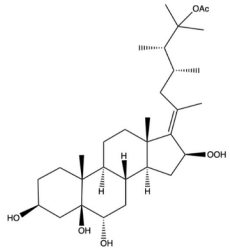
yonarasterols I

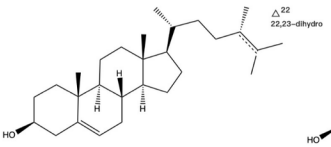


michosterols A

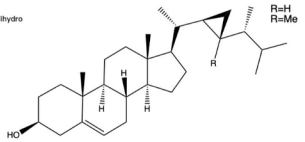


michosterols C

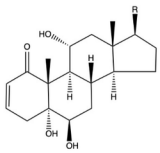


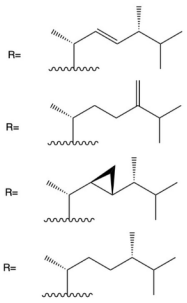


brassicasterol
24S-methylcholesterol

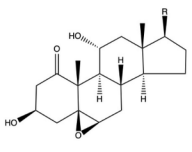


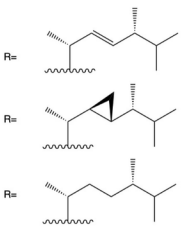
23-demethylgorgosterol
gosterol





stoloniferones H
stoloniferones I
stoloniferones J
stoloniferones K





stoloniferones L
stoloniferones M
stoloniferones N

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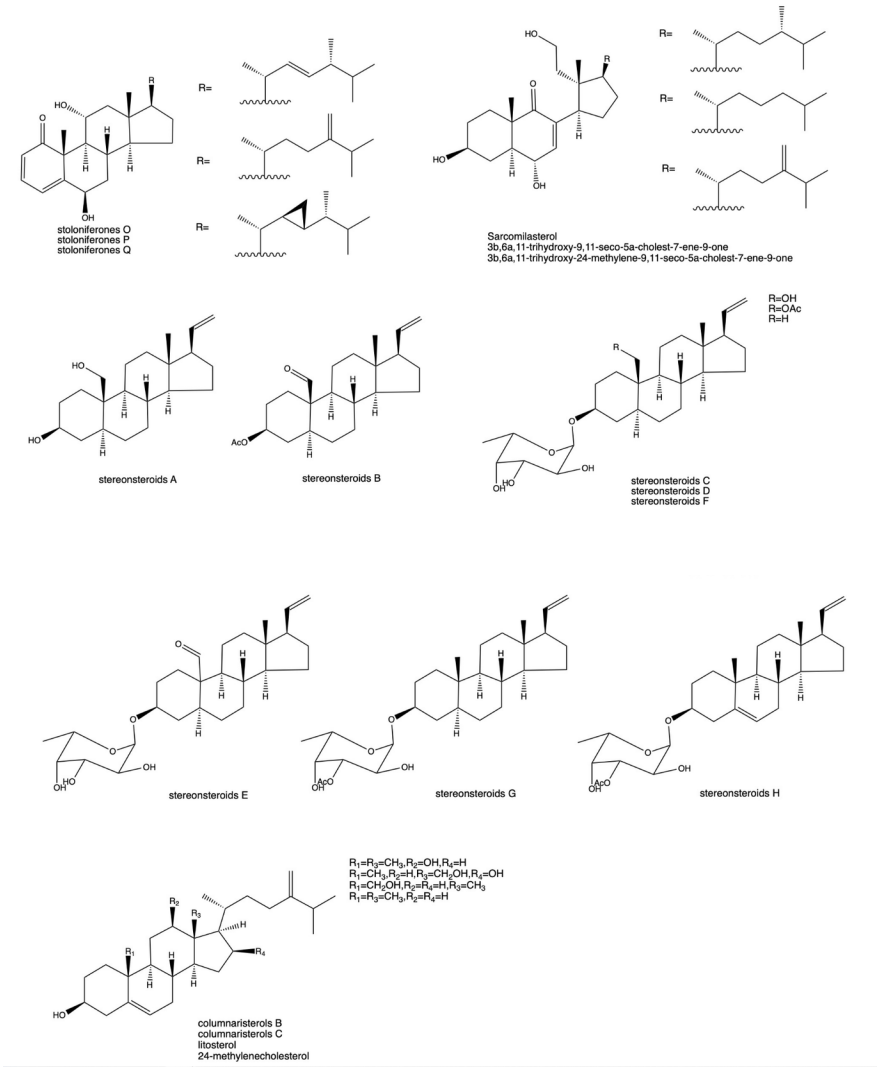
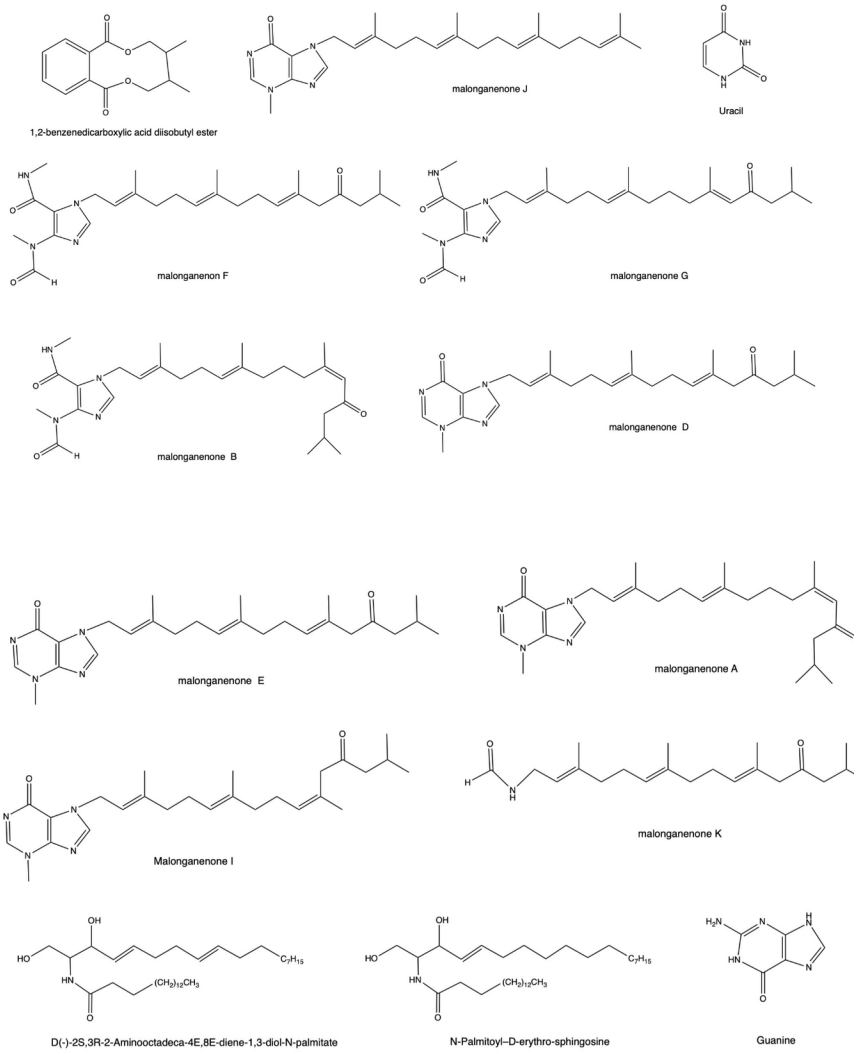


Figure 3 Some pharmacologically active steroids extracted from coral

3.3 Nitrogen compounds

The nitrogenous compounds in corals are mainly ceramides, alkaloids (deoxythymidine, thymine, methyluracil and urea). They generally have antifungal, antibacterial and cytotoxic activities. It has been shown that it can also inhibit acetylcholestan-converting protease, thus providing an alternative lead compound for the development of therapeutic drugs for atherosclerosis and other cardiovascular diseases(Ai, Chen & Qi, 2006). Jinrong Zhang(Zhang, 2012b) isolated 16 alkaloids (9 diterpene alkaloids, including 3 new diterpene alkaloid compounds) and 5 ceramides from *E. robusta* and *E. curvata*of the gorgonian. A preliminary evaluation of the antitumor activity at the cellular level was carried out, from which four diterpene alkaloids were screened to show strong cytotoxicity against both HeLa and K562 cancer cells, and the enzyme activity inhibition was evaluated by enzyme-linked immunosorbent assay (ELISA). The activity results showed that the diterpene alkaloid malonganenone D had a strong inhibitory effect on the enzymatic activity of c-Met. Isolation of the ceramide N-1-Hydroxymethyl-2-hydroxy-(E, E)-3, 7-heptadecadienylhexadecanoamide(Liu, Xu, Guo & LI, 2001), thymine, uracil from *Acropora pulchra* (brook)(Xu, Yang, Guo & Liu, 2003). In addition from

different corals such as *Litophyton arboreum* (Abou El-Kassem, Hawas, El-Desouky & Al-Farawati, 2018), *Junceella juncea Pallas* (Krishna, Muralidhar, Kumar, Rao & Rao, 2004) *Lobophytum chevalieri* (Li, Di & Long, 1989) have bioactive ceramides. The structure diagram is shown specifically in Figure 4.



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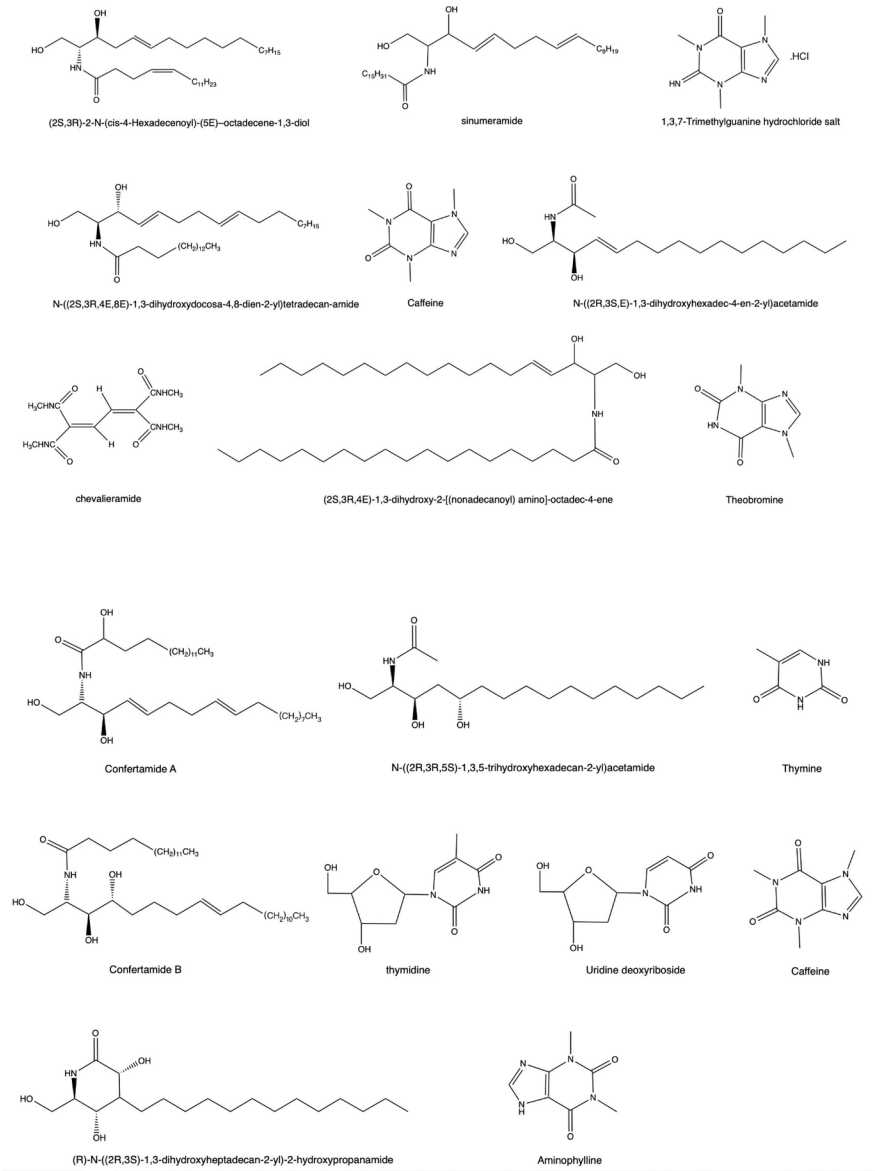
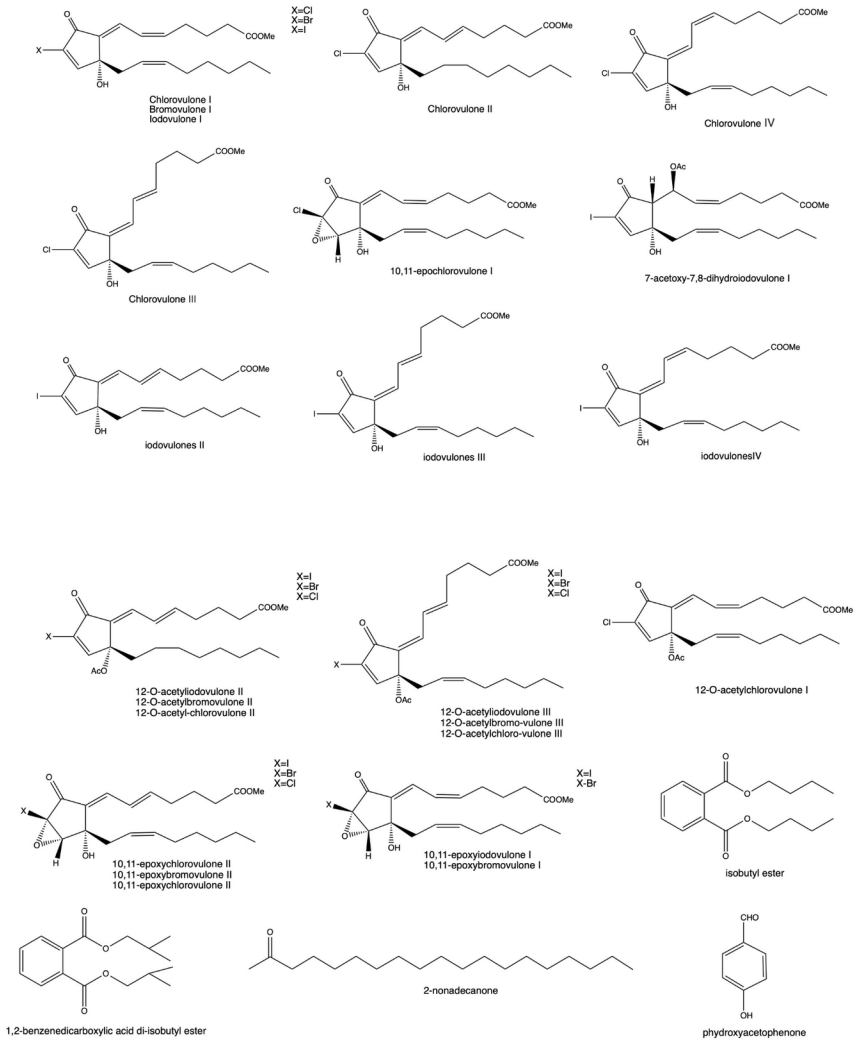


Figure 4 Some pharmacologically active nitrogen compounds extracted from coral

3.4 Others

As shown in Figure 5. Aliphatic compounds (long-chain fatty acids, long-chain aliphatic alcohols whose aldehydes and esters they form, etc.) and prostaglandins were also extracted from different corals(Hurtado, Castellanos, Coy-Barrera & Tello, 2020; Reina, Ramos, Castellanos, Aragón & Ospina, 2013; Watanabe, Sekine & Iguchi, 2003). According to literature records, a large amount of batyl alcohol has the pharmacological effect of raising leucocyte, which is extracted from coral and has been widely used in clinical practice(Ma, 2008; Sun, 2012; Xue, Guan, Yu, Li, Tang & Li, 2014; Zhao et al., 2011). Kinzo Watanabe(Watanabe, Sekine & Iguchi, 2003) tested 15 new halogenated prostaglandins isolated from the Okinawan soft coral *Clavularia viridis.* Among them, 3 new members of iodovulone, 7members of 12-O-acetyliodovulones, 12-O-acetylbromovulones, and 12-O-acetylchlorovulones, and the rest are 10,11-epoxy congeners of iodovulone,

bromovulone, and chlorovulone ◦ A simple compound, p-hydroxybenzaldehyde was, obtained from crude extracts of*Sinularia dissecta* (Jin, 2005)*, Muriceides collaris* (Zhu, Li, Tang & Li, 2013). In addition, some simple aldehydes were isolated from *Antipathes dichotoma pallas* (Ge, Gao, Wang, Wen & Qi, 2010)*, Sinularia notanda* (Xu, Tang, Li & Li, 2017)*, scleronephthya sp.* (Huo et al., 2011)*, Dichotella gemmacea (valenciennes)* (Liu, 2008)*, Dendronephthya sp* (Li, 2004). *and Hicksonella guishanensis*Zou(Yu, Yan, Hou & Guo, 2004). P-Hydroxybenzoic acid can be extracted from both *suberogogorgia reticulat* (Xie, Lin, Long, He & Gao, 2013) and red coral(Lai, 2017). Zou Xue(Zou, 2015) sorted out olefins from the crude extract of *Sinularia sp.* Subsequently, Li Rui(Li, 2012a) extracted ketones and alcohols from this coral. Esters are also contained in this coral such as methyl arachidonic acid(Liang, Li, Zheng, Yao & Guo, 2017), dibutyl phthalate, diisobutyl(Wang et al., 2009), 1,2-benzenedicarboxylate(Lv, Chi, Dai & Deng, 2012), etc.



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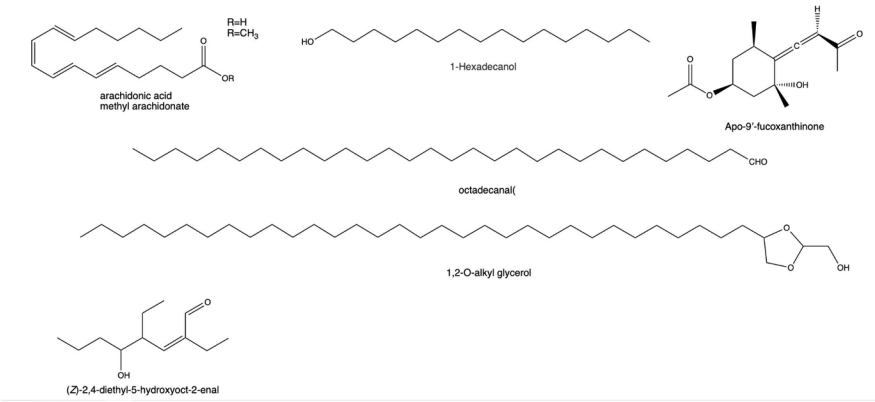

Figure 4 Some pharmacologically active other compound extracted from coral

Pharmacological effects and mechanisms

According to the literature, many structurally active unique secondary metabolites such as terpenoids, steroids, ceramides, prostaglandins, etc. have been extracted from corals and their significant pharmacological activities such as cytotoxic and antiviral activities have been widely noticed and studied by natural product chemists and other researchers. Meanwhile, the pharmacological activities of coral bone powder and various coral preparations in cardiovascular system etc. have been explored. This article focuses on their cytotoxic effects on a variety of tumor cells and cancer cells, their restorative effects on bone injury diseases and their biological activities such as antioxidant, anti-inflammatory analgesic and anti-viral on tissues of the nervous system and respiratory system, and they also have significant therapeutic effects in diseases of the nervous system(Li, 2000).

4.1 Bone repair effect

The key to the treatment of bone defects is the suitability of the repair material. Autologous bone grafts cannot meet clinical needs for various reasons, and allogeneic and xenogeneic bones are limited in clinical application due to their antigenic nature(Zhou et al., 1993). The microstructure of coral and skeleton is also very close, specifically in its internal structure. Corals are divided into pinnate, laminate, branching and pith-like structures depending on the arrangement of the calcification centers. According to the skeleton body whether the tiny tube traffic, and divided into interlocking, interoperable. Depending on whether the microscopic tubes in the skeleton are in traffic or not, they are divided into interlocking and interoperable. The interconnected coral skeleton has longitudinally and horizontally arranged tiny tubes with pore diameters of 0.05-2.0 mm. regardless of the section, these pores are interconnected. Coral artificial bone is widely valued as a promising material for bone repair(Issahakian & Ouhayoun, 1989; Roux, Brasnu, Loty, George & Guillemin, 1988). Animal experiments have shown that the horned honeycomb coral (favites) artificial bone has good biocompatibility and osteocompatibility. When it is implanted in the mandible, femoral cortical defect site after 8 months can be repaired, the final complete repair(S., Ren & Li, 1997). Zhou Zongyu(Zhou et al., 1993) used Hainan Cheng Huang Bin Coral (Hainan Coral, Porites Iutea; HNC) composite implant material as the material graft side mandibular defect model affirmed that the coral group had new bone tissue formation, wrapped with phenanthrene fibrous tissue, followed by its better bone repair effect when used with BMG, reflected in additional or with the bone bed was osseous healing, bone marrow cavity formation and clear visualization of the Harvard system of new bone tissue. Lai-Ying(Lai, 2017) concluded that red coral can promote fracture healing and shorten the fracture healing period. According to the literature(Dagli, Akalin, Bilgili, Seckin & Ensari, 1997; Souyris, Pellequer, Payrot & Servera, 1985; Zhou, 2014), coral can

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also be used to correct saddle nose deformities, oral implants, skull injuries or post-operative repairs and other orthopedic disorders.

In addition, coral transplants in the human body is not caused by rejection, in the coral of the countless fine pores will gradually grow microscopic blood vessels and synthesis of living cells of bone(Ma, 1994). Guillemin et al. showed that the resorption process of corals starts with the growth of granulation tissue and blood vessels from the bone marrow into the coral. The coral is then progressively resorbed by many osteoclasts near its edges, while the woven bone formed with osteoclasts gradually grows into the resorbed void, and finally the woven bone is transformed into typical plate-like bone by the Harvard system(Guillemin, Meunier, Dallant, Christel, Pouliquen & Sedel, 1989; Lu & Chen, 1994).

Chemical components extracted from corals also play a role in bone injury diseases. yen-You Lin isolated Ya-s11 (9 mg/kg) from the Taiwanese soft coral *Sinularia querciformis* not only attenuated aia-induced ankle joint pathological changes, but also significantly reduced the expression of osteoclast-related proteins(Lin et al., 2013b).

4.2 Cytotoxicity

See Table 2 for details. Studies in the literature in the last two decades have found that those extracted from coral have good cytotoxicity, which are mainly diterpenes, sesquiterpenes, sterols, and a small number of alkaloids, prostaglandins, and esters active substances also have some biological activity. These compounds are mostly from corals of the genus *Sinularia* , *Lobophytum* ,*Sarcophyton* , family *Alcyoniidae* . Corals of the family*Gorgoniidae* are also used as a source of active natural substances. Tumor cells such as A549, HL-60, MCF-7, colon cancer cells, K562 and HeLa were the hot spots of research, followed by HepG2, Hep3B, MDA-MB-231, P-388, HT-29, MCF-7, Sup-T1, U937 and other cells. In 2020, researchers evaluated(Shaaban, Yassin & Soltan, 2021) evaluated the in vitro anticancer properties of hydroazulenes, an extract of the soft coral*Sarcophyton glaucum* , on colon (Caco-2) and breast (MCF-7) cell lines by MTT assays, and showed that its anti-proliferative or anti-angiogenic effects were ultimately achieved by inhibiting the migration of MCF-7 cells and significant inactivation of VEGFR2 enzymes. Interestingly the growth inhibitory concentrations of 5α-3β,6α,11-trihydroxy-24-methyl-9,11-seco-5a-cholest-7-en-9-one were 0.62 and 2.3 mM, but there was no toxicity to RPE-1 cells when the concentration was highly 10 mM. The team also studied for the first time the sterol 10- epicubebol methyl ether was studied for the first time for its anticancer properties. The first study of *Sarcophyton acutum* extract activity by Sabry A. H. Zidan showed that polyhydroxylated steroids compounds had significant HepG2 cell line (semi-inhibitory concentration 17.2 ± 1.5 μg/mL), MCF-7 (semi-inhibitory concentration 33.2 and 25.1 mM) cytotoxicity(Abdelkarem et al., 2021; Zidan, Abdelhamid, Al-Hammady, Fouad, Matsunami & Orabi, 2020), and the side chains of polyhydroxylated sterols play an important role in the cytotoxic activity of such sterols. The researchers also demonstrated by SRB method that gorgonian of *Euplexaura rhipidalis* has a significant apoptosis-inducing effect on both A549 and HepG2 cells(Gong, Yuan, TAng, Zhang & Lan, 2017), that prostaglandins with hydroxyl and carboxylic acids have good properties as cytotoxic agents, and that they may have potential inhibitory effects on certain types of cancer(Hurtado, Castellanos, Coy-Barrera & Tello, 2020). In fact, more than a decade ago, studies showed that the structure of compounds could influence cytotoxicity. A sterol compound that is cytotoxic if C-12 or C-22 free hydroxyl group is important for enhancing cytotoxic activity against HeLa cell lines. In addition, the introduction of hydroxyl groups at C-20 decreased the inhibitory potency against HeLa cell lines, while the presence of acetoxy groups at C-18 seemed to enhance the cytotoxic activity(Zhang, Liao, Wang, Deng & Xu, 2013).

Table 2Classification statistics table for cytotoxicity of active substances extracted from the coral

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Active ingredient	Source	Activities	Concentration	Target cell	Reference
Sesquiterpenoids	*Muriceides Collaris*	——	50 μg/mL (Y)	P388, BEL-7402	(Shi, 2009)
Sesquiterpenoids	*Litophyton arboreum*	——	4.32±0.13-44.52±0.5 μM (IC_{50})	MCF-7	(Abou El-Kassem, Hawas, El-Desouky & Al-Farawati, 2018)
Sesquiterpenoids	*Xenia sp.*	——	5.89-6.45 μM (IC_{50})	STI	(Phan, Kamada, Ishii, Hamada & Vairappan, 2019)
Sesquiterpenoids	*Lemnalia sp.*	——	15.9 μM (IC_{50})	CCRF-CEM	(Yan et al., 2021)
Sesquiterpenoids	*Sarcophyton glaucum*	——	18.8±0.07, 19.9±0.02(HEPG2), 9.9 ±0.03, 2.4±0.04, 3.2±0.02(MCF-7), 29.4 ±0.03, 19.4±0.02, 25.8±0.03(HCT116) μM (IC_{50})	HepG2, MCF-7 and HCT116	(Abdel-Lateff, Alarif, Ayyad, Al-Lihaibi & Basaif, 2015)
Sesquiterpenoids	*Muriceides Collaris*	——	50 μmol/L (Y)	HL-60, HeLa	(Zhu, Li, Tang & Li, 2013)
Sesquiterpenoids	*Sinularia kavarattiensis*	Antiproliferation	17.5, 16.8 μM (IC_{50})	Leukemia and prostate cancer	(Rajaram et al., 2013)
Sesquiterpenoids	*Sinularia scabra.*	——	9.6-13.8 μg/mL (ED_{50})	MCF-7, WiDr, Daoy, HEp2	(Su et al., 2012)
Sesquiterpenoids	*Sinularia cf. molesta*	——	5.26, 8.37 μM (IC_{50})	HeLa, HCT-116	(Chu et al., 2018)
Sesquiterpenoids	*Sinularia sp.*	Cells that inhibit apoptotic proteins and trigger apoptosis by regulating Nrf2-ARE signaling	61.22, 43.73 μM (Y)	HCT116	(Taira, Miyazato & Ueda, 2018)
Sesquiterpenoids, Steroids	*A. Ocbracea*	——	3.70-29.03 μg/mL (IC_{50})	HepG2, Hep3B, MCF-7/ADR, PC-3, HT-116, Caski	(Sun, 2012)
Sesquiterpenoids, lactone	*Melithaea sp.*	——	50 μg/mL (Y)	K562, P388, Hela	(Su, 2011)

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Active ingredient	Source	Activities	Concentration	Target cell	Reference
Diterpene	*Nephthea sp.*	——	37 μg/mL (IC_{50})	MCF-7	(Hegazy et al., 2016)
Diterpene	*Lobophytum sp.*	——	4.52-6.62 μM (IC_{50})	HT-29, Capan-1, A549, SNU-398	(Li et al., 2020)
Diterpene	*Sinularia flflexibilis*	——	6.9-26.7 μM (IC_{50})	P-388, K-562, HT-29	(Wu et al., 2018)
Diterpene	*Lobophytum sp.*	——	1.8-8.2 μM (IC_{50})	A549, HT-29	(Nguyen et al., 2010)
Diterpene	*Cladiella sp.*	——	4.7, 10.2 μM (IC_{50})	CCRF-CEM	(Chen et al., 2010)
Diterpene	*Cladiella sp.*	——	2.0-31.1 μg/mL (IC_{50})	DLD-1, HL-60	(Chen et al., 2011b)
Diterpene	*Lobophytum laevigatum*	Inhibition of transcriptional activity	9.0 $\pm$ 0.8-38.8 $\pm$3.8 μM (IC_{50})	HL-60, A549, HCT-116, MCF-7	(Quang et al., 2011a)
Diterpene	*Asterospicularia laurae*	——	1.3-19.41 μM (IC_{50})	Molt 4, K562, Sup-T1, U937	(Su et al., 2021)
Diterpene	*Dichotella gemmacea*	——	11.4-72.0 μM (IC_{50})	A549, MG63	(Li et al., 2016)
Diterpene	*Cladiella krempfi*	——	8.5$\pm$1.0-18.1$\pm$1.5 μg/mL (ED_{50})	H1299, BT483	(Tai, Su, Huang, Wen, Dai & Sheu, 2011)
Diterpene	*Sinularia triangular*	Antiproliferation	26.0-37.1 μM (ED_{50})	CCRF-CEM, DLD-1	(Su & Wen, 2011)
Diterpene	*Cespitularia taeniata*	——	0.3, 6.7, 8.7 μM (IC_{50})	Medulloblastoma and colon adenocarcinoma cancer cells	(Lin, Wang, Chen, Kuo & Shen, 2014)
Diterpene	*Sinularia gibberosa*	Anti invasion, anti metastasis	4-8 μM (Y)	HA22T, RT4 and T24 human bladder cancer, HCC	(Wu, Wei, Dai, Su, Tseng & Tsai, 2020)
Diterpene	*Nephthea sp.*	——	25, 70, 40, 125 μg/mL (IC_{50})	Hela/MCF-7	(Ishii, Kamada & Vairappan, 2016)
Diterpene	*Lobophytum sp.*	——	5.99-10.83 μM (IC_{50})	HeLa, A459, B16-F10, and RAW 264.7	(Roy, Roy & Ueda, 2019)
Diterpene	*Klyxum flflaccidum*	——	16.5-49.4 μM (IC_{50})	HT-29 A549 K562 P388	(Ahmed, Tsai, Huang, Wang & Sheu, 2017)
Diterpene	*Lobophytum crassum*	——	1.2-2.5 μg/mL (IC_{50})	Ca9-22	(Chao, Wen, Wu, Yeh & Sheu, 2008)
Diterpene	*Sinularia humilis*	——	12.5 μM (IC_{50})	HT-29	(Li et al., 2022)

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Active ingredient	Source	Activities	Concentration	Target cell	Reference
Diterpene	*Lobophytum sp.*	——	1.2-8.6 μg/mL (IC_{50})	SGC7901, A549, MCF7, HCT116, B16	(Zhao et al., 2013b)
Diterpene	*Sarcophyton elegans*	——	10 μM (Y)	MDA-MB-231	(Liu et al., 2015)
Diterpene	*Sinularia microclavata*	——	5.0, 20.0(KB, MCF), 0.5(A-549) μg/mL (IC_{50})	KB, MCF, A-549	(Zhang et al., 2005a)
Diterpene	*Lobophytum michaelae*	——	0.3-61.5 μM/mL (ED_{50})	HT-29, P-388	(Wang & Duh, 2012)
Diterpene	*Nephthea sp. and Sarcophyton cherbonnieri*	Apoptosis	0.15-8.6 μg/mL (GI_{50})	HM02 HepG2 MCF7	(Gross, Kehraus, Nett, König, Beil & Wright, 2003)
Diterpene	*Sinularia flexibilis*	——	0.16-32.4 μg/mL (ED_{50})	A549, HT-29, KB, and P-388	(Duh, Wang, Tseng, Sheu & Chiang, 1998)
Diterpene	*Pseudopterogorgia acerosa*	——	1.25->8.10 μM (GI_{50})	DU-145 LN-caP IGROV IGROV-ET SK-BR3 SK-MEL-28 A549 PANC1 HT29 HT29-KF LOVO LOVO-DOX HELA HELA-APL	(Montalvo, Amade, Funel-Le Bon, Fernández & Reyes, 2006)
Diterpene	*Sinularia gibberosa*	——	18.7, 19.5, 11.0 μg/mL (IC_{50})	HepG2, A549	(Chen et al., 2009)
Diterpene	*Sinularia flexibilis*	——	0.7-16.0 μg/mL (ED_{50})	KB, A-549, HT-29, P388	(Hsieh, Chang, McPhail, Lee & Wu, 2003)
Diterpene	*Clavularia inflata*	——	0.052-27.3 μg/mL (ED_{50})	A549 HT-29 P-388	(Duh, Chia, Wang, Chen, El-Gamal & Dai, 2001)
Diterpene	*Lobophytum sp.*	Apoptosis	3.7(HT-29), 5.1(A549), 6.6(SNU-C5) μM (IC_{50})	HT-29, A549, SNU-C5	(Hong et al., 2012)
Diterpene	*sinularia sp.*	——	7.98-17.23 μM (IC_{50})	HCT-116	(Xu, 2013)

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Active ingredient	**Source**	**Activities**	**Concentration**	**Target cell**	**Reference**
Diterpene	*Dichotella gemmacea*	——	3.8-112.3μg/mL (IC_{50})	A549, MG63	(Jiang, 2013)
Diterpene	*Sarcophyton latum*	——	50 μg/mL (Y)	P388, A549, BEL-7402	(Wang, 2008)
Diterpene	*Sinularia dura*	Antiproliferation, anti invasion	20-30	Highly malignant+-SA breast epithelial cells, PC-3M-CT+	(Radwan et al., 2008)
Diterpene	*Sarcophyton trocheliophrum*	——	10 μmol/L (Y)	A-549, HL-60	(He, 2013)
Diterpene	*Lobophytum sp.*	——	1.83-44.69 μg/mL (IC_{50})	B16F10, HeLa, HepG2	(Lang, 2013)
Diterpene	*Lobophytum sp.*	——	50 μg/mL (Y)	P388, Hela	(Fernando et al., 2017)
Diterpene	*Cladiella krempfi.*	——	6.7±0.7-19.2±4.0 μg/mL (IC_{50})	A549, BT483, H1299, HepG2, SAS	(Tai et al., 2013)
Diterpene	*Sinularia sp.*	Apoptosis	——	HL-60	(Kamada, Kang, Phan, Zanil, Jeon & Vairappan, 2018)
Diterpene	*sinularia sp.*	——	0.0039 μg/mL	HL-60, PC-3MIE8, BGC-823	(Li, 2004)
Diterpene	*Dichotella gemmacea*	——	10.6-70.0 μM (IC_{50})	A549, HL-60, K562	(Sun, 2012)
Diterpene	*Cladiella*	Directly affecting tumor growth and angiogenesis	1.6(MDA-MB-231 cell)/>10 μM (IC_{50})	EGF-dependent cancers	(Mohyeldin, Akl, Siddique, Hassan & El Sayed, 2017)
Diterpene	*Sarcophyton mililatensis*	——	0.78-1.26 μM (IC_{50})	HL-60, A549	(Li, 2018)
Diterpene	*Clavularia sp.*	——	50 μM (Y)	K562, HL-60, HeLa, A549	(Xue, 2014)
Diterpene	*sinularia sp.*	——	2.32-8.97 μM (IC_{50})	K563	(Zou, 2015)
Diterpene	*Anthoptilum grandiflorum*	Killed the NT2 cells, Antiproliferation	——	NT2	(Thomas, Sanchez, Kee, Wilson & Baker, 2019)
Diterpene	*Sarcophyton crassocaule*	——	2.0, 1.2, 2.6, 3.2 μM (ED_{50})	MCF-7, WiDr, HEp-2 and Daoy can cer cell lines	(Lin et al., 2010)

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Active ingredient	**Source**	**Activities**	**Concentration**	**Target cell**	**Reference**
Diterpene	*Briareum sp.*	reduced the expression of COX-2	5-30 μM (IC_{50})	Caco-2 cells	(Joyner et al., 2011)
Diterpene	*Dichotella gemmacea*	Antiproliferation	5.0-78.5 μM (IC_{50})	A-549, MG63	(Li et al., 2013)
Diterpene	*Pseudopterogorgia kallos.*	——	<0.01, 0.51 μM (GI_{50})	EKVX nonsmall cell lung cancer, CAKI-1 renal cancer	(Marrero et al., 2004)
Diterpene	*Lobophytum crassum*	Inhibition of transcriptional activity	6.30 $\pm$0.42-6.63 $\pm$ 0.11 μM (IC_{50})	HepG2	(Thao et al., 2014a)
Xenicane	*Protodendron repens*	——	0.2-6.3 μM (GI_{50})	MDAMB-231, HT-29, NSLC A-549	(Urda, Fernández, Pérez, Rodríguez, Jiménez & Cuevas, 2017)
Terpenoids	*Sarcophyton sp.*	——	6.4-33.7 μM (IC_{50})	P338, A549, HL-60, K562	(Gong, 2014)
Terpenoids	*Sarcophyton tortuosum*	——	3.5-24.7 μg/mL (IC_{50})	Human nasophyringeal carcinoma CNE-2 cell line, P-388	(Zeng et al., 2004)
Terpenoids	*Sinularia sp.*	Inhibitory activity	6.5-33 μM (IC_{50})	E3-ubiquitin ligase casitas B-lineage lymphoma proto-oncogene B (Cbl-b)	(Jiang et al., 2021)
Terpenoids	*Sarcophyton sp.*	——	6.03$\pm$1.93, 6.70$\pm$1.06 μM (IC_{50})	Canpan-1	(Lu, 2020)
Diterpene, steroids	*sinularia dissecta*	——	2.54-100 μg/mL (IC_{50})	PC-3MIE8, A549	(Jin, 2005)
Diterpene, steroids	*Lobophytum compactum*	——	17.80 $\pm$ 1.43-59.06 $\pm$ 2.31 μM (IC_{50})	A549, HL-60	(Chau et al., 2011)
Diterpenoid lactone, Steroids	*Sinularia polydactyla*	——	1.0, 6.1, 8.2 μg/mL (IC_{50})	HepG2, Hep2, HCT	(Aboutabl el et al., 2013)
Steroids	*Sinularia gibberosa*	Antiproliferation	6.8-10.0 μM (ED_{50})	Hepa59T/VGH	(Ahmed, Dai, Kuo & Sheu, 2003)

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Active ingredient	Source	Activities	Concentration	Target cell	Reference
Steroids	*Sarcophyton glaucum*	Antiproliferation	0.62, 2.3 μM (IC_{50})	Caco-2, MCF-7	(Shaaban, Yassin & Soltan, 2021)
Steroids	*Sinularia erecta*	——	15.57±5.26-40.55±7.51 μM (IC_{50})	A549, HT-29, SNU-398 and Capan-1	(Liu et al., 2020)
Steroids	*Verrucella corona*	——	12.32±1.47 -33.77±1.28 μM (IC_{50})	LNCaP, HepG2, KB, MCF-7, SK-Mel2, HL-60, LU-1, SW480	(Nam et al., 2018)
Steroids	*Sinularia leptoclados*	——	13.45±1.81 -29.01±3.21 μM (IC_{50})	HepG2, SW480, HL-60, MCF7 LU-1 SK-Mel2 LNCaP	(Ngoc et al., 2017a)
Steroids	*Heteroxenia fuscescens*	——	33.2, 25.1 μM (IC_{50})	MCF-7	(Abdelkarem et al., 2021)
Steroids	*Nephthea erecta*	Apoptosis, increase caspases activity	20, 40 μM (Y)	H1688, H146 lung cancer	(Chung et al., 2017)
Steroids	*sinularia suberosa*	——	5.5-6.5 μM (IC_{50})	K562, MDA-MB-231	(Zhang, 2013a)
Steroids	——	——	21.56-40.04 μM (IC_{50})	HT-29, SNU-398, Capan-1	(Zhang, 2019)
Steroids	*Rumphella aggregata*	——	10 μg/mL (Y)	K562	(Liu, Li, Tang & Li, 2012)
Steroids	*Nephthea sp.*	——	7.51 ± 0.22-18.72 ± 0.78 μg/mL (IC_{50})	HeLa	(Zhang, Liao, Wang, Deng & Xu, 2013)
Steroids	*Pacifigorgia senta*	——	7.0-29.7 μM (IC_{50})	HepG2, Hep3B, MCF-7/ADR, PC-3, HCT-116	(Chen, Han, Zhang & Wang, 2016)
Steroids	*Paragorgia sp.*	Antiproliferation	3.0-90 μM (GI_{50})	A-549, HT-29, MDA-MB 231	(Poza, Fernández, Reyes, Rodríguez & Jiménez, 2008)
Steroids	*Clavularia viridis*	——	0.1-6.8 μg/mL (IC_{50})	HT-29, P-388	(Duh, Lo, Wang & Dai, 2007)
Steroids	*Stereonephthya crystalliana*	——	1.6-13.3 μg/mL (ED_{50})	HT-29, P-388	(Wang, Dai & Duh, 2006)
Steroids	*Sinularia sp.*	——	0.69, 4.03, 1.79 μM (IC_{50})	HL-60	(Li, Chen, Yao & Guo, 2018)

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Active ingredient	Source	Activities	Concentration	Target cell	Reference
Steroids	*Menella kanisa*	Antiproliferation	11.0±4.2-257.2 ± 20.7 μM (IC_{50})	A549, MG-63	(Wang et al., 2013a)
Steroids	*Subergorgia suberosa*	——	15.1 μM (IC_{50})	HeLa	(Zhang, Liu, Zhong, Liao & Xu, 2015)
Steroids	*Sinularia polydactyla*	Anti migration, neuroprotective activity on nerve cells	10,20	HeLa, MCF7, SH-SY5Y	(Tammam et al., 2020)
Steroids	*Sinularia brassica*	——	1.17 ± 0.42-92.53 ± 1.68 μM (IC_{50})	A-549, HeLa, PANC-1	(Tran et al., 2017)
Steroids	*Scleronephthya gracillimum*	——	23.3, 21.9, 24.3 μM (IC_{50})	HepG2, A549, MDA-MB-231	(Fang et al., 2013)
Steroids	*Carijoa sp.*	——	9.33, 11.02, 18.68 μM (IC_{50})	Bel-7402	(Zhao, Shao, Li, Han, Cao & Wang, 2013)
Steroids	*Sarcophyton sp.*	——	6.4-10.3 μM (IC_{50})	HL-60, HeLa, K562	(Gong et al., 2013)
Steroids	*Sinularia sp.*	——	8.36-37.30 μM (IC_{50})	HepG2, HeLa	(Sun et al., 2016)
Steroids	*Sarcophyton sp.*	——	5.25, 12.30, 4.95, 4.10(K562), 7.30, 6.20(A549) μg/mL (IC_{50})	K562, A549	(Sun, Fu, Li, Xing & Wang, 2013)
Steroids	*Subergorgia suberosa.*	Inhibiting activity	5.5, 6.2, 6.5 μM (IC_{50})	K562, MDA-MB-231	(Zhang et al., 2013)
Steroids	*Klyxum flaccidum*	——	12..7-15.5 μM (IC_{50})	HT-29, P388 and K562	(Tseng et al., 2016)
Steroids	*Nephthea chabrolii*	——	1.1, 1.2, 1.0 μg/mL (ED_{50})	P-388, A-549, HT-29	(Shang-Kwei, Wang, Shyh-Yueh, Puu, Chang-Yih & drugs, 2013)
Steroids	*Lobophytum laevigatum.*	Apoptosis, antiproliferation	3.2-18.1 μM (IC_{50})	HCT-116, A549, HL-60	(Quang et al., 2011b)
Steroids	*Nephthea sp.*	——	9.9*10-7-98.5*10-4 M Y	HL-60, A-549	(Ma, 2008)
Steroids	*Lobophytum sp.*	——	21.56-38.83 and 40.04 μM (IC_{50})	HT-29, SNU-398, Capan-1	(Zhang, Liang, Miao, Wu & Guo, 2019)
Steroids	*Litophyton mollis*	——	10 μM (IC_{50})	K562, PBMCs	(Zovko Končić et al., 2016)

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Active ingredient	Source	Activities	Concentration	Target cell	Reference
Steroids	*Nephthea erecta*	——	6.5–14.0 μM (IC_{50})	K562, Molt-4, Sup-T1, U937	(Tsai, Huang, Chou, Shih, Chiang & Su, 2016)
Steroids	*Lobophytum michaelae*	——	14.9±5.7 μg/mL (IC_{50})	A549	(Huang et al., 2018)
Steroids	*Verrucella corona*	——	12.32±1.47 -33.77±1.28 μM (IC_{50})	LNCaP, HepG2, KB,MCF-7,SK-Mel2,HL-60,LU-1, andSW480	(Nam et al., 2018)
Steroids	*Sinularia microspiculata*	——	72.32± 1.30-89.02± 9.93 μM (IC_{50})	HL-60, SK-Mel2	(Thanh et al., 2016)
Steroids	*Sarcophyton acutum*	——	17.2±1.5, 24.8 ± 2.8–57.2 ± 5.2 μg/mL (IC_{50})	HepG2, MCF-7, A549	(Zidan, Abdelhamid, Al-Hammady, Fouad, Matsunami & Orabi, 2020)
Steroids		The ability to induce autophagy	20 μM (Y)	MCF-7	(Weng et al., 2018)
Steroids	*Cladiella hirsuta*	——	8.2-42.0 μM (IC_{50})	HepG2, HepG3B, MDA-MB-23, Ca9-22	(Chen et al., 2011a)
Steroids	*Sinularia variabilis*	Apoptosis	——	MCF-7, MDA-MB-231	(Mohammadi Pour, Yegdaneh, Aghaei, Ali, Khan & Ghanadian, 2022)
Steroids	*Spongodes sp.*	——	0.14, 5, 3.8 μg/mL (IC_{50})	BEL-7402, A-549, HT-29, P388	(Yan, Lin, Ding & Guo, 2007)
Steroids	*sinularia acuta*	——	7.28-44.82 μM (IC_{50})	HL-60, K562, HeLa	(Zhang, 2014)
Steroids	*Carijoa sp.*	——	9.33-18.68 μM (IC_{50})	Bel-7404	(Zhao, 2013)
Steroids	*Sarcophyton sp.*	——	-——	K562	(Sun, 2012)
Steroids	*sinularia sp.*	——	1.79, 4.03 μM (IC_{50})	HL-60	(Li, 2018)
Steroids	*sinularia sp.*	Antiproliferation	1.61, 3.26 μmol/l (IC_{50})	HL-60	(Li, Yao, Liang & Guo, 2018)

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Active ingredient	**Source**	**Activities**	**Concentration**	**Target cell**	**Reference**
Steroids	*Sinularia sp.*	Apoptosis	10.14-41.71 μM (IC_{50})	MDA-MB-436, A549, Hep3B, HT-29 and H157	(Jiang, Ru, Huan, Miao & Guo, 2019)
Steroids	*Subergorgia suberosa*	——	1.09-6.22 μM (IC_{50})	K562,	(Liu, 2014)
Steroids, Ceramide	*Cespitularia stolonifera*	——	23.0-1574.0 μg/mL (IC_{50})	A549, MCF-7	(Elshamy, El-Kashak, Abdallah, Farrag & Nassar, 2017)
Alkaloid	*E. Robusta E. curvata*	——	0.35-58.01 μM (IC_{50})	Hela, K562	(Zhang, 2012b)
Alkaloid	*Menella kanisa*	Inhibiting activity , Antiproliferation	13.3, 55.0 μg/mol (IC_{50})	Osteosarcoma cells	(Yao et al., 2015)
Alkaloid	*Muriceides Collaris*	——	5.08-8.37 μM (IC_{50})	K562, HeLa	(Zhu, 2013)
Alkaloid	*Scleronephthya sp.*	Anti metastasis	5.3±0.2-12.4±0.2 μM (IC_{50})	A549, B16	(Cheng et al., 2017)
Prostanoids	*soft coral Clavularia viridis*	Apoptosis	0.12-11.7 μM (IC_{50})	Prostate cancerPC-3 cells	(Chiang et al., 2006)
Prostanoids	*Clavularia viridis*	Antiproliferation	0.5-7.9 μM (IC_{50})	PC-3, HT29	(Shen, Cheng, Lin, Guh, Teng & Ko, 2004)
Prostanoids	*Plexaura homomalla*	Inhibiting the expression of related enzymes	16.46, 25.20 μg/mo (IC_{50})	MDA-MB-213, A549	(Hurtado, Castellanos, Coy-Barrera & Tello, 2020)
Ester	*Sinularia flflexibilis*	Antiproliferation	10 mg/kg (Y)	Small cell lung cancer	(Lin et al., 2013b)
Ester	*Cladiella kashmani*	Anti invasion, anti metastasis	1, 2.5, 5, 10 μM (Y)	T24 human bladder cancer cells	(Wu, Su, Dai, Su & Liu, 2019)
Ester	*Paraminabea acronocephala*	——	0.5-2.2 μM (IC_{50})	HepG2, Hep3B, MDA-MB-231, MCF-7, A-549	(Chao et al., 2011b)
Ester	*Lobophytum durum*	——	3.8 μg/mL (ED_{50})	P-388	(Cheng, Chen, Chen, Wang & Duh, 2011)
Ester	*Sinularia flflexibilis*	Anti invasion, anti metastasis	——	Gastric cancer	(Wu, Lin, Din, Su & Liu, 2019)
Ester	*Stragulum bicolor*	Apoptosis	0.18, 4.3 μM (IC_{50})	A2058	(Nuzzo et al., 2019)

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Active ingredient	**Source**	**Activities**	**Concentration**	**Target cell**	**Reference**
Sinulariolide	*Sinularia flexibilis*	Antiproliferation, Apoptosis	15 μM (Y)	Bladder carcinoma cell, TSGH cells	(Neoh et al., 2012)
Alkane	*Montipora sp.*	——	1.40-29.16 μg/mL (ED_{50})	A549, SK-OV-3, SK-MEL-2, XF498, HCT15	(Alam, Bae, Hong, Lee, Im & Jung, 2001)
Aromatic compounds	*Scleronephthya gracillimum*	——	2.86-7.51μg/mL μM (IC_{50})	Hela, P388 HepG2, Hep3B, HT-116	(Han, 2011)
Oligopeptides	*Sarcophyton glaucum*	——	8.6, 4.9, 5.6 mmol/L (EC_{50})	HeLa	(Quah et al., 2019)
EPA	*Eunicea succinea*	——	5.1-6.9 μmol/L (IC_{50})	Malignant glioma U87-MG and U373-MG cells	(Iwamaru et al., 2007)
Lobophorin	*Lophelia pertusa*	——	6.3±8.2, 23.0±8.9, 34.0±85.1 μM (IC_{50})	MiaPaca-2, MCF-7, THLE-2	(Braña et al., 2017)
Tetraprenylbenzoquinone	*Sinularia capillosa*	——	9.8, 12.7 μM (ED_{50})	P-388	(Cheng, Huang, Wang, Wen, Chen & Duh, 2010)
Durumolide	*Sinularia polydactyla*	——	1.0-8.2μg/mL (IC_{50})	HepG2, Hep2, HCT	(Aboutabl el et al., 2013)
Biscembranoids	*Sarcophyton pauciplicatum*	——	7.93±2.08 -94.18±3.02 μM (IC_{50})	LNCaP MCF7 KB HepG2, SK-Mel2 HL-60 SW480 LU-1	(Nam et al., 2015)
Tryptamine derivatives	*Eunicella granulata*	——	1.7-12.7 μM (GI_{50})	DU-145 LN-caP SK-OV-3, IGROV IGROV-ET SK-BR3 SK-MEL-28 A549 K-562, PANC1 HT29 LOVO LOVO-DOX HELA HELA-APL	(Reyes, Martín & Fernandez, 2006)
Tetracyclic biscembranes	*Sarcophyton glaucum*	——	13.3-58.0 μM (IC_{50})	HL-60	(Iwagawa et al., 2009)

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Active ingredient	Source	Activities	Concentration	Target cell	Reference
Sinularin	*Sinularia flexibilis*	Increasing G2/M cell cycle arrest, inducing apoptosis, and activating DNA damage responses	17.5 ± 6.7, 9.4 ± 2.3(HEPG2), 43.2 ± 8.1, 33.9 ± 8.6 μM(Hep3B) μM (IC_{50})	HepG2, Hep3B	(Chung, Lin, Su, Chen, Lin & Chan, 2017)
13-acetoxysarcocrassolide	*Sarcophyton crassocaule*	Apoptosis	1, 1.5 μg/mL (Y)	BFTC,	(Su et al., 2011)
Flaccidoxide-13-acetate	*Sinularia gibberosa*	Apoptosis	20 μM (Y)	RT4 and T24 human bladder cancer cells	(Wu, Su, Dai, Su & Liu, 2019)
Glycolipids	*Lobophytum crassum*	——	9.2-15.0 μg/mL (IC_{50})	HepG2, Hep3B, MDA-MB-231, Ca9-22	(Chao, Huang, Wu, Lu, Dai & Sheu, 2007)
Crude extract	*sinularia cf. molesta*	——	50 μg/mL (Y)	K562, HL-60	(Jiang, 2015)
——	*Muricella sibogae*	——	1, 10, 50 μg/mL (Y)	P388, BEL-7402	(LI, 2010b)
——	*Cladiella australis, Clavularia viridis and Klyxum simplex*	Apoptosis	31.5±1.5-53.8±2.1 μg/ml (IC_{50})	Squamous Cell Carcinoma Cells	(Liang et al., 2008)
——	*Carotalcyon sp.*	Antiproliferation, Apoptosis	0.7±0.4-250.9±92.1 μg/mL (IC_{50})	HGUE-C-1, HT-29, SW-480	(Ruiz-Torres et al., 2019)
——	*Euplexaura rhipidalis*	Apoptosis	<10 μg/ml (IC_{50})	A549, HepG2	(Gong, Yuan, TAng, Zhang & Lan, 2017)
——	*Sinularia maxima*	Inhibition of transcriptional activity	15.81±2.29-29.10 ± 1.54 μM (IC_{50})	HepG2	(Thao et al., 2014b)

4.3 Anti-inflammatory and analgesic effects

Inflammatory processes usually constitute the initial activation of the mammalian immune system and the body's normal defense or protective mechanisms against microbial infections or stimuli or tissue/organ damage. There is growing evidence of a critical link between inflammation and the chronic promotion/progression of various human diseases, including atherosclerosis, diabetes, arthritis, inflammatory bowel disease, cancer, and Alzheimer's disease(Wei, Sung, Duh, Chen, Sheu & Yang, 2013). Different types of cells such as monocytes/macrophages, neutrophils and lymphocytes are involved in the inflammatory process(Serhan & Savill, 2005). Several marine biology and chemistry researchers have systematically screened the in vitro anti-inflammatory activity of several marine natural products isolated from corals, and lipopolysaccharide-

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stimulated mouse macrophage models have been widely used as a system for assessing the anti-inflammatory activity of secondary metabolites of marine and terrestrial origin(Lin et al., 2015). Yen-You Lin's study showed that the diterpene compound excavatolide B from gorgonian of *Briareum excavatum* produced potent anti-inflammatory activity in vitro and in vivo, and the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) mRNA expression was significantly inhibited. Gyrosanols A and gyrosanols B show significant anti-inflammatory activity by reducing COX-2 protein levels in RAW 264.7 macrophages(Cheng et al., 2010a). Hsin-Pai Lee(Lee et al., 2013) found that soft coral-derived Lemnalol attenuated monosodium urate induced gouty arthritis in rats by inhibiting leukocyte infiltration and expression of iNOS and COX-2 proteins, among others.

The inflammatory process also involves the peripheral and central nervous system (CNS) and is thought to be involved in the pathogenesis of neuropathic pain(Ellis & Bennett, 2013). Nan-Fu Chen investigated flexibilide extracted from cultured soft coral as a possible drug for neuropathic pain, and its anti-neuritis and analgesic mechanism of action may be related to spinal TGF-β1(Chen et al., 2014). The sphingosine derivative obtained from soft corals also has anti-inflammatory and analgesic effects(Radhika, Rao, Archana & Nalamolu, 2005). After compiling nearly 100 literatures, it was found that the anti-inflammatory activity of coral extracts is mainly diterpene compounds, followed by sterols, prostaglandins and alkaloids have also been reported. Its anti-inflammatory activity is mainly mediated by inhibition of lipopolysaccharide-induced expression of iNOS and COX-2 in mouse macrophages (RAW264.7) or by inhibition of superoxide anion, release from human neutrophils FMLP/CB and elastin, as detailed in Table 3.

Table 3 Classification statistics table for anti-inflammatory and analgesic effects of active substances extracted from the coral

Active ingredient	Source	Activities	Concentration
Sesquiterpenoids	*Sinularia tumulosa*	I	2.6-7.5μM (IC_{50})
Sesquiterpenoids	*Anthogorgia sp.*	N, A	27.81μg/mL (IC_{50})
Sesquiterpenoids	*Sinularia scabra.*	I	10 μM (Y)
Diterpene	*Lobophytum crassum*	I, C	10 μM (Y)
Diterpene	*Cladiella krempfi.*	I, C	10 μM (Y)
Diterpene	*Briareum sp.*	C	5-30 μM (Y)
Diterpene	*Lobophytum sp.*	N	5,10,25 μM (Y)
Diterpene	*Klyxum flflaccidum*	N	50, 46.7, 47.0 (IC_{50})
Diterpene	*Sinularia flflexibilis*	S, E	10.8 ± 0.38 and 11.0 ± 1.52 μ
Diterpene	*Cladiella krempfi*	I	10 μM (Y)
Diterpene	*Sinularia triangular*	I, C	10 μM (Y)
Diterpene	*Lobophytum laevigatum*	I, C	0.1-10 Y
Diterpene	*Sarcophyton glaucum*	A	20 μmol/L (Y)
Diterpene	*Sinularia flexibilis*	N	10 μM (Y)
Diterpene	*Briareum excavatum*	I, C	10 μM (Y)
Diterpene	*Briareum sp.*	I	10 μM (Y)
Diterpene	*Briareum sp.*	I, C	10 μM (Y)
Diterpene	*Lobophytum crassum*	N	2.4±0.21-16.6_x0007_ 1.70 (IC_5
Diterpene	*Lobophytum varium*	S, E	10 μM (Y)
Diterpene	*Lobophytum crassum*	N	50 μg/mL (Y)
Diterpene	*Sinularia gyrosa*	C	10 μM (Y)
Diterpene	*Lobophytum durum*	I, C	10 μM (Y)
Diterpene	*Sinularia querciformis and Sinularia granosa*	I, C	10 μM (Y)
Diterpene	*Cladiella sp.*	S, E	10 μM (Y)
Diterpene	*Cladiella sp.*	S, E	8.1±0.3-49.4±0.2 (IC_{50}/Inh)
Diterpene	*Klyxum simplex*	I, C	10 μM (Y)
Diterpene	*Lobophytum sp.*	N	3.2-9.4 μM (IC_{50})

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Active ingredient	Source	Activities	Concentration
Diterpene	*Sinularia gyrosa*	C	10 μM (Y)
Diterpene	*Sarcophyton cherbonnieri*	S, E	30 μM (Y)
Diterpene	*Lobophytum crassum*	I, C	6.30 ± 0.42-6.63 ± 0.11 μM (I
Diterpene	*Sarcophyton glaucum*	A	10 μM (Y)
Diterpene	*Junceella fragilis*	I	10 μM (Y)
Diterpene	*Nephthea columnaris*	I, C	9.80 μg/mL (IC_{50})
Diterpene	*Lobophytum durum*	I	10 μM (Y)
Diterpene	*Sinularia maxima*	I	4.35±0.12-59.77±2.34 μM (IC_5
Diterpene	*Sinularia maxima*	I	0.1, 1.0 and 10 μM Y
Diterpene	*Lobophytum pauciflorum*	N	2.8 μM (IC_{50})
Diterpene	*Sinularia crassa*	I, C	10 μM (Y)
Diterpene	*Lobophytum sarcophytoides*	N	7.1-32.1 μM (IC_{50})
Diterpene	*Klyxum molle*	I, C	10 μM (Y)
Diterpene	*Sarcophyton ehrenbergi*	I	7.2-38.6 μM (IC_{50})
Diterpene	*Briareum excavatum*	I, C	1-50 μM (Y)
Diterpene	*Sinularia crassa and Lobophytum*	——	10 mg/kg (Y)
Diterpene	*Sinularia nanolobata*	N, A	20 μM (Y)
Diterpene	*Cladiella sp*	S, E	1.97±2.44-41.08±3.26μg/mL (
Cembranoid	*Sarcophyton crassocaule*	I, C	10 μM (Y)
Cembranoid	*Sinularia sp.*	I	¡6.25 μg/ml (Y)
Norditerpenoids	*Sinularia maxima*	I	5.30 ± 0.21-69.85 ±4.11 μM (I
Norditerpenoids	*Sinularia numerosa*	I	10 μM (Y)
Norditerpenoids	*Sinularia siaesensis*	A	20μM Y
Norditerpenoids	*Sinularia maxima*	I	23.52 ± 1.37,69.85 ± 4.11 μM
Norditerpenoids	*Sinularia sp.*	N, I	33 μg/ml (Y)
Norditerpene	*Sinularia gyrosa*	I	10 μM (Y)
Nanolobatolide	*Sinularia nanolobata*	I	10 μM (Y)
Diterpene, Sesquiterpenoids	*Cespitularia sp.*	I, C, N	100 μM (Y)
Steroids	*Nephthea chabroli*	I, C	10 μM (Y)
Steroids	*Sinularia crassa*	I, C	10 μM (Y)
Steroids	*Klyxum flflaccidum*	S, E	4.40 ± 0.19, 5.64 ± 0.41 (IC_{50}
Steroids	*Nephthea chabroli*	I, C	10 μM (Y)
Steroids	*Scleronephthya gracillimum*	I, C	10 μM (Y)
Steroids	*Clavularia viridis*	I, C	10 μM (Y)
Steroids	*Dendronephthya griffifini*	I, C	10 μM (Y)
Steroids	*Echinomuricea sp.*	S, E	1.13±0.55-95.54±6.17μM (IC_{50}
Steroids	*Dendronephthya gigantea*	I, C, S, E N	4.33 ± 0.50 μg/mL (IC_{50})
Steroids	*Pinnigorgia sp.*	I, C	10 μM (Y)
Crude extract	*Nephthea Sp.*	C	33.72-46.75μg/mL (IC_{50})
Flexibilisquinone	*Sinularia flexibilis*	I, C	5–20 μM (Y)
tocopherol-derived	*Cladiella hirsuta*	S, E	3.7 ± 0.3-4.1 ± 1.1 μM (IC_{50})
EGFR	——	C, I	10μM (Y)
Lemnalol	——	I, C	30 mg/kg (Y)
Lemnalol	*Lemnalia cervicorni*	A	0.05-10μg (Y)
Lemnalol	*Lemnalia cervicorni*	I, C	15 mg/kg (Y)
Quinones	*Sinularia flexibilis*	I, C	5-20 μM (Y)
Glycoside	*Pseuadopterogorgia elisabethae*	——	1-4 μM (IC_{50})
Briarane	*Junceella fragilis*	E	10 μg/mL (Y)
Isosarcophine	*Sarcophyton cherbonnieri*	S, E	30 μM (Y)
Tetraprenylbenzoquinone	*Sinularia capillosa*	I, C	10 μM (Y)

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Active ingredient	Source	Activities	Concentration
Withanolide	*Paraminabea acronocephala*	I, C	10 μM (Y)
Capnellene	*Capnella imbricate*	C	6.21±2.5 and 17.9±2.9 μM (IC
Bicyclogermacrenes	*Capnella sp.*	I, N	10, 20 μM (Y)
Isoprenoids	*Sinularia erecta*	S, E	0.9 ± 0.1-8.5 ± 0.3 μM (IC_{50})
Prostaglandin	*Plexaura homomalla*	V, E	100 μM (Y)

*Inhibition of iNOS (I), COX-2 (C), superoxide anion (S), N(N0), A(Astrocytes) and elastase (E).

4.4 Antiviral effect

Viruses are infectious entities that use the cellular biosynthetic machinery to replicate their own nucleic acids and synthesize the proteins encoded by their nucleic acids, and finally assemble into complete, infectious viral particles. In most cases, viruses can cause disease and even death in infected hosts(Li, Liu & Wang, 2022). Almost all clinical and public health outbreaks over the decades have been caused by emerging viruses, including coronavirus (SARS), which causes severe acute respiratory distress syndrome, influenza A virus subtype H1N1 (IAV-H1N1), which caused an influenza pandemic in 2009, human cytomegalovirus (HCMV), which can cause visceral disease, and the SARS CoV-2 outbreak, which is a widespread outbreak worldwide in 2019(Chen, Sun, Wang, Ao & Song, 2023). The widespread outbreak of the virus not only poses a great threat to the lives and health of people across the country, but also severely hinders global economic development. Marine organisms have been shown to be a rich source of antiviral drugs(Cao et al., 2014). Chun-Kuang demonstrated that lobohedleolide isolated from the Taiwanese soft coral *Lobophytum crassum* significantly reduced HCV replication in replicon cells and JFH-1-infected systems with EC50 values of 10 ± 0.56 and 22 ± 0.75 μM at non-toxic concentrations, respectively. Their study also concluded that the inhibitory effect on HCV replication was due to the inhibition of HCV-induced cyclooxygenase-2 (COX-2) expression(Lin et al., 2018). Specific types of steroids first shown to be active against influenza viruses by Kai-Kai Gong et al(Gong et al., 2013). The antiviral effect of coral is mainly achieved through the inhibition of viral replication and expression of antigens. As summarized coral mainly has antiviral activity against pathogens such as HCMV and H1N1, and secondly some studies have also found some antiviral activity against pathogens such as HBV and HCV. See Table 4 for details.

Table 4 Classification statistics table for antiviral effects of active substances extracted from the coral

Active ingredient	Source	Virus	Concentration
Sesquiterpenoids	*Muriceides collaris*	H1N1	50 μM (Y)
Sesquiterpenoids	*Lemnalia sp.*	H1N1	1.1, 7.1μM (IC_{50})
Sesquiterpenoids	*Lemnalia sp.*	H1N1	5.9 μM (IC_{50})
Sesquiterpenoids	*Echinogorgia flora*	H1NI	50 μM (Y)
Diterpene	*Sinularia gyrosa*	HCMV	2.6, 3.7 μM (IC_{50})
Diterpene	*Junceella fragilis*	HBeAg	0.89-6.47 μM (IC_{50})
Diterpene	*Ellisella sp.*	HBV, HBeAg	10 μM (Y)
Diterpene	*Clavularia sp.*	H1N1	50 μM (Y)
Diterpene	*Lobophytum durum*	HCMV	5.2 μg/mL (IC_{50})
Norditerpenoids	*Sinularia gyrosa*	HCMV	1.9 μg/mL (IC_{50})
Steroids	*Echinogorgia rebekka*	Respiratory syncytial virus	0.19 μM (IC_{50})
Steroids	*Sarcophyton sp.*	H1NI	19.6-36.7 μg/mL (IC_{50})
Steroids	*Sarcophyton sp.*	H1N1-IAV	19.6 and 36.7 μM (IC_{50})
Steroids	*Subergorgia suberosa*	H1N1	35.64-50.95 μM (IC_{50})
Marine endophytic Streptomyces species	*Sarcophyton convolutum*	H1N1、HCV	——

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Active ingredient	Source	Virus	Concentration
Lobohedleolide	*Lobophytum crassum*	HCV	10±0.56 - 22±0.75 μM
Tetraprenylbenzoquinone	*Sinularia capillosa*	HCMV	——

4.5 Antibacterial effect

See Table 5 for details. According to the literature, the antimicrobial activity of coral is mainly in terms of activity against bacteria (gram-negative and gram-positive bacteria, etc.) and fungi. Its antibacterial active substances are mainly terpene components extracted from coral, with sesquiterpenes and diterpenes as the first, followed by steroidal active substances. Back in 1997, Badria's team conducted antibacterial tests on Sarcophytolide extracted from soft corals using reagents such as dimethyl sulfoxide and showed that the compound had broad activity against *Staphylococcus aureus* , *Pseudomonas aeruginosa* , *Candida albicans* and *Staphylococcus brevis* . Mohamed N. Gomaa not only tested the antibacterial activity of the soft coral of *Sarcophyton* genus, but also compared the differences in the antibacterial activity of different extracts. The results showed that hexane extract had a strong antibacterial effect. The antibacterial activity of nerve sphingolipids and sterols in the *Antipathes dichotoma* was also obtained by disc diffusion technique(Al-Lihaibi, Ayyad, Shaher & Alarif, 2010). The diterpenoids isolated from *Lemnalia sp.* also showed antibacterial activity with MICs of 4-64 μg/mL for *Bacillus subtilis* and*Staphylococcus aureus* (Yan et al., 2021). The antibacterial mechanism has not been specifically reported.

Table 5 Classification statistics table for antibacterial effects of active substances extracted from the coral

Active ingredient	Source	Strain
Sesquiterpenoids	*Anthogorgia sp.*	*S. aureus*
Sesquiterpenoids	*Muriceides Collaris*	*vibrio anguillarum, vibriio harveyi, vibrio alginolgticus*
Sesquiterpenoids	*Litophyton arboreum*	*Bacillus cereus*
Sesquiterpenoids	*Paralemnalia thyrsoide*	*Staphylococcus aureus, Escherichia coli, Candida albicans*
Sesquiterpenoids	*Lemnalia sp.*	*Bacillus subtilis*
Sesquiterpenoids	*Xenia sp.*	*Lagenidium thermophilum*
Diterpene	*Junceella juncea*	*Fungi: Aspergillus niger, Candida albicans and Penicillu*
Diterpene	*Lobophytum pauciflorum*	*S. aureus, S. pneumoniae*
Diterpene	*Dichotella gemmacea*	*Staphylococcus albus, Staphylococcus aureus*
Diterpene	*Lobophytum sp.*	*S. aureus, S. pneumoniae.*
Diterpene	*Lemnalia sp.*	*Bacillus subtilis and Staphylococcus aureus*
Diterpene	*Dichotella gemmacea*	*Gram-positive bacterium Bacillus megaterium and Gram-*
Diterpene	——	*T. brucei, L. donovani.*
Diterpene	*Nephthea sp.*	*Staphylococcus aureus, Escherichia col*
Terpenoids	*Sarcophyton trocheliophorum*	*Gram-positive and Gram-negative bacteria*
Steroids	*Sarcophyton sp.*	*Escherichia coli, Bacillus megaterium, Microbotryum vio*
Steroids	*Carijoa sp.*	*Pseudomonas putida, Bacillus cereus, Tetragenococcus ha*
Steroids	*Sarcophyton sp.*	*Staphylococcus albus*
Steroids	*Carijoa sp.*	Pseudomona puido
Diterpene and Steroidal saponin	*Dichotella gemmacea*	*Bacillus megaterium, Botrytis cinerea*
Polyphenol	*Talaromyces sp.*	*E. coli, MRSA, S. aureus and E. faecalis*
Lobophorin	*Lophelia pertusa*	*pathogenic Gram-positive bacteria such as Staphylococcus*
BCE	*Sarcophyton sp.*	*pathogenic Gram-positive bacteria such as Staphylococcus*
——	*Xenia sp.*	*Lagenidium thermophilum*
——	*Nephthea sp.*	*L. thermophilum*
——	*Muricella sibogae*	*vibrio anguillarum*

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Active ingredient	Source	Strain
——	*Sinularia polydactyla*	*Gram-positive bacteria: Bacillus subtilis, Bacillus megate*

4.6 Antioxidation effect

Altered oxidative status may have peroxidative effects on lipids, proteins and RNA and regulate cellular responses, signal transduction and and metabolism, thereby impairing their biological functions. At present, few reports on the antioxidant effect of coral can be retrieved, and the antioxidant effect mostly works through free radical scavenging, oxidative free radicals and lipid peroxidation, generally common free radicals include $^{-}$OH, O^{2-}, DPPH, ABTS^{-+}. The coral derivatives sinularin and dihydrosinularin showed general radical scavenging activity against the free radicals 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and hydroxyl (-OH), as well as induction of Fe^{+3} reduction and Fe^{+2} chelating ability, all of which enhanced their antioxidant activity. It was shown that sinularin exhibited higher antioxidant properties compared to dihydrosinularin. Further ATP assays showed that the different antioxidant properties contributed to the anti-proliferative effect on different cancer cells as well(Wang et al., 2021). The in vitro antioxidant results of the active ingredients BCE (alkanes, terpenoids, esters, fatty acids and aromatic compounds) extracted from black horn coral proved that some of them have scavenging effect on DPPH- and OH-. The in vivo antioxidant effect shows that it not only has a morphological protective effect on lung tissue, but also can effectively increase the SOD activity in vivo and reduce the MDA content, thus reducing the damage to lung tissue caused by the large amount of oxygen free radicals in tobacco(Bai, 2011). See Table 6 for details.

Table 6 Classification statistics table for antioxidation effects of active substances extracted from the coral

Active ingredient	Source	Mechanism	Concentr
Sesquiterpenoids	*Sinularia sp.*	Oxidative free radical absorption	5.36 units
Steroids	——	Lipid peroxidation (Vit C/Fe^{2+}excited)	7.6, 30.6, 1
Pseudopterin I	*S. suberosa*	Free radical scavenging: ·OH、O^{2-}·、DPPH	0.1006, 0.1
Pseudopterin II	*S. suberosa*	Free radical scavenging:·OH、O^{2-}·、DPPH	0.2509, 0.2
Cladiellin A	*Cladiella sp.*	Oxidative free radical absorption	3.151, 4.78
Sinularin	——	Free radical scavenging: DPPH, ABTS*+, and *OH	250-400 μM
Dihydrosinularin	——	Free radical scavenging: DPPH, ABTS*+, and *OH	200-400 μM
Lobocompactols A	*Lobophytum compactum*	Oxidative free radical absorption	1.4 and 1.3
Lobocompactols B	*Lobophytum compactum*	Oxidative free radical absorption	1.4 and 1.3
BCE	——	Free radical scavenging: DPPH, *OH and Lipid peroxidation	——

4.7 Antimalarial effect

Malaria, caused by Plasmodium vivax, poses a major health threat to much of the world's population(Thao et al., 2015). Various marine natural products with anti-protozoal activity have been reported in the literature(Mohyeldin, Akl, Siddique, Hassan & El Sayed, 2017; Sanchez et al., 2013; Watts, Tenney & Crews, 2010). Nguyen Phuong Thao(Thao et al., 2015) identified laevigatol A in Vietnamese soft corals, which showed inhibition of Plasmodium falciparum (Pf) NF54 strain when its $IC_{50} < 5.0$ μM. Sesquiterpene extracts of the octocoral coral *Eunicea sp.* (*Plexauridae* :*Octocoralia* : Cnidaria) were tested for their antimalarial activity against chloroquine-resistant strains of Plasmodium falciparum by inserting fluorochromes into the parasite DNA. The results showed a significant inhibition of Plasmodium falciparum growth by the compounds(Garzón, Rodríguez, Sánchez & Ortega-Barria, 2005). Claudia A Ospina's team(Ospina, Rodríguez,

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Sánchez, Ortega-Barria, Capson & Mayer, 2005) also found an interesting experiment in which caucanolide A, a diterpene compound extracted from anise coral, exhibited significant in vitro antiplasmodial activity against Plasmodium falciparum W2 at an IC_{50} of 17 μg/mL, and caucanolide D was equally effective at an IC_{50} of 15 μg/mL.

4.8 Immunosuppression effect

According to incomplete statistics, terpenoids and sterols active substances extracted mainly from the soft coral *Sinularia scabra* ,*Sinularia polydactyla* , Sinularia sp., *Libertasomyces sp.*and gorgonian *Verrucella umbraculum* have immunosuppressive effects in vitro. Yi-Zhe Sun(Sun et al., 2017) reported for the first time the immunomodulatory activity of new polyketide and trans-fused decane ring system-like metabolites by inducing the proliferation of CD3+ T cells. Further structure-activity analysis revealed a key role of the Δ7 and terminal OH groups in the regulation of CD3+ T cell proliferation. In 2018(Yang, Liang, Li, Tang & Guo, 2020), the sterol compound yalongsterol A , 5α,8α-epidioxy-24-methyl-cholesta-6,24(28)-dien-3β-ol (22E,24S)-5α,8α-epidioxy-24-methylcholesta-6,22 -dien-3β-ol exhibited moderate immunosuppressive activity against T and/or B lymphocytes with semi-inhibitory concentration values of 19.30-59.49 μM. Subsequently, Wan-Xiang Cui showed that polycyclic furanobutenolide derived norditerpenoids exhibited strong inhibitory effects on cona-induced T lymphocyte and/or lps-induced B lymphocyte proliferation(Cui et al., 2020). Diterpenoids of different membrane types isolated from the South Sea soft coral *Sinularia scabra* have the same biological activity(Yang et al., 2019). In a recent report, metabolites of the 9,10-secosteroids structure from the South Sea gorgonian *Verrucella umbraculum* show immunomodulatory activity by inhibiting the differentiation of CD4+ T lymphocytes(Li, Sun, Tang, Su, Zheng & Zhang, 2021).

4.9 Enzymatic activity

See Table 7 for details. In summary, reports on coral enzyme activity are rare, but from the collected literature it can be obtained that some terpene masses isolated from coral have enzyme inhibitory activity, in addition some steroids, polyketides and alkaloids active substances may also have enzyme activity. With the in-depth research and increasing understanding of enzymes, they have played an increasingly significant role in the regulation of diseases, not only for the adjuvant treatment of important organs such as brain, heart, liver and kidney, but also in the use of tumors with remarkable results. The diterpenes sinupol and sinulacetate both exhibit good inhibitory activity against protein tyrosine phosphatase 1B (PTP1B), which in turn is a potential drug target for the treatment of type II diabetes and obesity(Ye, Zhu, Gu, Li, Zhu & Guo, 2018). Cespine diterpenes isolated from the soft coral*Sinularia crassa* in The South China Sea for antidiabetic treatment as alpha-glucosidase inhibitors. This provides a different way of thinking for developing new drugs(Wu, Wang, Jiang & Guo, 2020).

Table 7 Classification statistics table for enzymatic activity of active substances extracted from the coral

Active ingredient	Source	Related active substances
Sesquiterpenoids	*Sinularia cf. molesta*	PTP1B
Diterpene	*Sarcophyton trocheliophorum*	PTP1B
Diterpene	*Sinularia crassa*	α-glucosidase
Diterpene	*Sinularia polydactyla*	PTP1B
Diterpene	*Sarcophyton glaucum*	Cytochrome P450 1A
Diterpene	*Sarcophyton glaucum*	Glutathione *S*-transferases(GST), quinone reductase(QR), epoxide h
Diterpene	*Sarcophyton trocheliophrum*	Acetylcholinesterase
Diterpenoid alkaloids	*E. Robusta, E. curvata*	Tyrosine kinase c-Met
Steroids	*Sinularia dissecta*	COX-2 cyclooxygenase-2
Prostaglandin	*Plexaura homomalla*	P38α-kinase, Src-kinase, topoisomerase IIα

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4.10 Effects on the nervous system

The neuroprotective effects of coral are manifested in two ways. On the one hand, there are anticonvulsant and antiepileptic effects. As early as 1984, preliminary pharmacological experimental studies on the soft coral *Lemnalia exilis* showed that its extract had a significant antispasmodic effect on the guinea pig isolated ileum(Fang & Zhang, 1984). Nermeen A. Eltahawy measured the anticonvulsant activity of ceramide isolated from the Red Sea soft coral *Sarcophytonauritum*using a pentylenetetrazol (PTZ)-induced seizure model, and the mechanism may be the modulation of CNS inhibitory activity through GABA and serotonin receptors(Eltahawy et al., 2015). Some sterols also exhibited neuroprotective activity against neuron-like SH-SY5Y cells(Tammam et al., 2020). On the other hand, it has a sedative-hypnotic effect(Liao, Haung & Liu, 1992). Finally, the coral derivative excavatolide-B can enhance long-term induction by suppressing the delayed rectifier potassium current, which has the effect of lowering the action potential onset threshold and ultimately enhancing situational memory retrieval in mice, resulting in enhanced memory extraction.

The effects of formulated preparations about coral on the nervous system have also been documented. First of all, Ershiwuwei Shanhu Pill can prolong the latency period of epileptic seizures, shorten the duration of epileptic seizures, reduce the level of epileptic seizures, decrease the number of clonic seizures and suppress epileptic discharges. And at a certain dose, its effect was significantly better than that of the positive control drug sodium valproate group(Luo, 2012; Luo et al., 2013). Secondly, Li Peng explored the protective effects of Ershiwuwei Shanahu Pill on senescent hippocampal cells. The drug inhibited D-lactose-induced neuronal degeneration and excessive activation of astrocytes, thereby reducing neuronal and astrocyte damage(LI et al., 2014). Finally, Ershiwuwei Shanhu capsules have the effect of increasing adenosine levels in secondary spinal cord injury, thus increasing the ability of nerve cells to repair themselves(Jiao, Yao, Zhou & Luo, 2013).

4.11 Effects on the cardiovascular system

In 1984, Fang Zhensheng(Fang & Zhang, 1984) found by research that soft coral extract has high physiological activity on cardiovascular system, the extract of soft coral can not only delay the time of arrhythmia in isolated heart of rats, and shorten the duration of arrhythmia, but also can make rabbit heart coronary flow increase and heart rate slow down. In Lai-Ying's study, it was also pointed out that red coral could regulate TXB_2/6-keto-$PGF_{1\alpha}$ levels, as well as reduce plasma PF_4/β-TG levels and lower plasma ET-1 levels in rats with blood stasis model, ultimately reducing vascular injury in rats(Lai, 2017). 15-hydroxy-tetracosa-6,9,12,16,18-pentaenoic acid and sesquiterpenes isolated from the soft coral *Sinularia numerosa* and *Lemnalia sp.* exhibit anti-tubulinogenic and pro-angiogenic activities, respectively, in a dose-dependent manner(Wang et al., 2020; Yamashita, Nakao, Matsunaga, Oikawa, Imahara & Fusetani, 2009; Yao, Vidor, Foss & Chang, 2007).

4.12 Others effect

First, antihypertensive effect. The diterpene glucoside of soft coral isolated from *Cespitularia turgida* in South China Sea has significant acute antihypertensive effect, and it has obvious quantity-effect relationship, and its antihypertensive effect has no rapid tolerance phenomenon, and it has little effect on heart rate at the same time of antihypertensive. Second, hypolipidemic effect. The formulated preparation of coral, Shanhu qishiwei Pill, may reduce blood lipid levels in HLP model rats by inhibiting LKB1/AMPK signaling pathway(Chun, Wei, Zhu, Wu & Dawa, 2022). Third, anti-ulcer activity was demonstrated by Abdelsamed I. Elshamy et al. in a rat ulcer model induced by ethanol and acetic acid(Elshamy, El-Kashak, Abdallah, Farrag & Nassar, 2017)..

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The toxicity of coral

Many corals, such as animal corals, also known as soft corals, are very popular in aquariums (home or public) because of their appreciation value and low maintenance costs. The soft corals *Palythoa* ,*Protopalythoa* , *Zoanthus* and *Parazoanthus* in the genus *Zoanthidae* contain a highly toxic and potentially lethal compound, Palytoxin(Hoffmann et al., 2008). Therefore, the toxic component of coral is mainly Palytoxin. Ciminillo extracted palytoxin and 42-hydroxy palytoxin at levels up to 509 μg-23 μg per 0.5 g of*zoanthid* (Ciminiello, Dell'Aversano, Dello Iacovo, Fattorusso, Forino & Tartaglione, 2011). Palytoxin is both a potent vasoconstrictor and its neurotoxicity and cardiotoxicity are primarily due to dysregulation of the transmembrane pump Na/Katp enzyme, which can lead to serious human disease, causing gastrointestinal symptoms, myalgia, muscle spasms, respiratory and cardiac problems, and even death(Wieringa, Bertholee, Ter Horst, van den Brand, Haringman & Ciminiello, 2014). The toxin is heating resistant and conventional boiling inactivation operations are not effective against it. Reports of human exposure to Palytoxin consumption have described significant morbidity and mortality(Sud, Su, Greller, Majlesi & Gupta, 2013).

Palytoxin exposure and the production of toxic components through corals is primarily associated with toxin poisoning from inhalation of toxin-dissolved water aerosols during cleaning, scrubbing or eradication of corals in home/public aquariums. Thus, aquarium store staff and home aquarium hobbyists face a consequent elevated risk of exposure. In the data we collected, people as young as 80 years old and children exposed to Palytoxin nebulized from coral had immediate symptoms such as cough, dyspnea, chest pain, myalgia, tachycardia and gastrointestinal symptoms, and in severe cases, acute reactions such as burning or stinging and erythema. Coral injuries may also have complications such as foreign body reactions, bacterial infections or local eczema reactions(Na, Lee, Baek, Roh & Lee, 2008). Examples of poisoning due to prolonged and unprotected exposure to corals have also been reported(Hoffmann et al., 2008; Smith, Taylor & Fanning, 2003). A patient who placed his right hand on a *zoanthid* colony while cleaning a seawater aquarium at home developed myalgia, symptoms of general weakness of the four branches, and subsequently even signs of poisoning such as speech impairment, dull eyes and fainting. And the degree of poisoning is closely related to the contact time, contact distance and contact method. Subsequently, corneal toxicity due to exposure to*zoanthid* corals has been documented. Seven patients presented with corneal manifestations ranging from superficial punctate epithelial lesions to bilateral corneal melting and subsequent perforation, with some patients presenting with progressive corneal melting even requiring therapeutic penetrating corneal transplantation. Fortunately, more than half of these case reports show that short-term minor injuries are reversible with medication or emergency measures, with only a few disabilities, or a significant reduction in quality of life due to sequelae(Chang, Deeds & Spaeth, 2020).

In 2014, water extracts from water corals were first reported to contain a lethal non-peptide neurotoxin(García-Arredondo, Rojas-Molina, Bah, Ibarra-Alvarado, Gallegos-Corona & García-Servín, 2015). The investigators gave intravenously 5.3 μg protein/g body weight of the extract to mice, which caused violent convulsions and death in the range of 1 min, and histopathological damage to the kidneys and lungs at doses below the LD_{50} ($LD_{50} = 4.62$ μg protein/g body weight). After incubation under heat denaturing conditions, this histopathological damage was completely eliminated. However, the denatured extracts maintained their lethal effect. Secondly, in the process of the research of anti-neurotoxic active ingredients of the side flat soft willow coral, it was found that the extraction of alkali water insoluble part of *sinularia suberosa* can make the animal produce the whole body soft, heavy limb tremor, turn positive reflex disappeared and other reactions(Liao, Haung & Liu, 1992)

As medicine, coral is often used in combination. Ershiwuwei Shanhu Pill and others are the classic Tibetan remedies composed of coral. In the acute toxicity test of Ershiwuwei Shanhu Pill, there were no obvious acute toxic reactions, but in the subacute toxicity test, toxic damage to liver, kidney and lung pathological sections were observed(Liu et al., 2016). If rats on long-term doses of Ershiwuwei Shanhu Pill have some accumulation of copper, mercury and lead in the internal organs. It also causes a few rats to develop symptoms of the vegetative nervous system such as increased salivary gland secretion(LI, 2011). It can cause toxic reactions, manifested in immune function and liver, kidney and lung tissue are affected and damaged to varying degrees,

the main toxic target organs are liver, kidney and lung, and shows a certain dose dependence(Liu et al., 2016). However, because of the complexity of its components, the specific toxic substances remain to be investigated.

Clinical application

6.1 Individual application of coral

Coral's good stability, easy to take and low price make it the main material in orthopedic diseases. In addition, coral contains 12 kinds of trace elements: Zn0.05, Cu0.6, Pb0.0025, Ni0.004, Ti0.005, Mn0.004, Fe0.7, Al0.35, Mg3, Si>1.0, Sr0.1, and most of these trace elements are indispensable to the human body(Wang, Wang, Han, Liu & Zhen, 2002). Xiao Zongmiao(Xiao, Wang & Li, 2005) had systematically reported the treatment of black horn coral for bone injury diseases, after taking the medicine for 5-7 days in mild cases and 1-2 months in severe cases, the patients' clinical symptoms were basically relieved and X-ray films also showed that the bone changes were basically corrected or in a stable state. In the clinical method of immediate implant placement, artificial coral bone powder particles were placed in the bone defect area near the crest of the alveolar fossa, where significant osteogenesis was observed after 6 months. The gingival texture and color were better than before the restoration(Zhou, 2014).

Coral clinical applications are detailed in Table 8, it is often processed into powder punch or with direct use of its bones to treat bone injury diseases. It is also very effective in the treatment of cerebral vascular sclerosis and coronary artery sclerosis, etc(Yuan, 1991). It was reported that in 1990, the School of Medicine of Kyoto University in Japan extracted a substance from the coral of the cockle, and used one hundredth of a gram of it to mix into 1000 mL of compound saline for injection or infusion. In difficult cases, it is also often used in combination with restorative dental tablets, etc. However, how coral works is still unknown to us, in the available literature, it has been reported that it may be related to the absorption of coral by osteoclast-associated proteins(Lin et al., 2013b) and bone marrow granulation tissue and blood vessels(Guillemin, Meunier, Dallant, Christel, Pouliquen & Sedel, 1989). But it is also only a vague term, and a clearer and more explicit mechanism has to be studied.

Table 8 Classification statistics table for individual application of coral

Disease	Pharmaceutical preparations	Experimental subjects	Research design	Groups and number of people	Groups and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
				Treatment group	Control group	Treatment group	Control group		

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Groups and number of people	Groups and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Bone defects and non union	Deer horn coral skeleton	35 cases: 32 males, 2 females	Randomized controlled trials	35 cases: 32 males, 2 females	——	Coral bone particles are disinfected under high pressure and placed at the desired bone graft site in the human body	——	——	——

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Groups and number of people	Groups and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Avascular necrosis of the femoral head, bone hyperplasia, spinal and lumbar lesions	Black horned coral skeleton	23 cases: 14 males, 9 females	Randomized controlled trials	23 cases: 14 males, 9 females	——	Crush the black horn coral and add softener to form a powder, and take it in an herbal soup	——	1 dose per day for 20-30 days	One case died of cerebrovascular accidental death, and the other 22 cases were examined 1˜2 months after taking the medicine. The clinical symptoms were basically disappeared or relieved, especially the osteoporosis was basically corrected or stabilized

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Groups and number of people	Groups and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Patients with residual roots of anterior teeth and premolars	Coral bone powder	34 cases: 19 males, 15 females	Randomized controlled trials	34 cases: 19 males, 15 females	——	Artificial coral bone powder particles are implanted and undergo secondary repair surgery through porcelain crowns six months later	——	1 year	34 patients had significant bone formation in their alveolar ridges before the second stage surgery. After the second stage repair, they recovered normally and the texture and color of the gums were better than before the repair

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Groups and number of people	Groups and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Extraction of molars	Coral bone powder	45 cases: 23 males, 22 females	Randomized controlled trials	20 cases: 10 males1, 10 females	25cases: 13 males, 12 females	Fill the extraction socket with coral bone powder, and perform restoration operations such as filling the amount flush with the top of the adjacent alveolar ridge	Conventional biting gauze roll for about 30 minutes	6 months	The gingiva on the buccal and lingual sides of the experimental group were smooth and continuous, forming a plateau shape, and the alveolar bone was plump; The height and width of the alveolar bone in the control group were significantly reduced, and the buccal lingual side of the occlusal surface was significantly sunken, resulting in a narrow and elongated alveolar bone. After 6 months of tooth

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Groups and number of people	Groups and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Nasal deformity	Black horned coral skeleton	20 cases: 12 males, 8 females8	Randomized controlled trials	20 cases: 12 males, 8 females	——	External nose shaping technology, implanting appropriately carved coral blocks into the nasal cone	——	——	18 patients recovered smoothly, 1 had an unexpected fracture, and 1 had an infection
Delayed sternal closure	coral hydroxyapatite	1 male	Randomized controlled trials	1 case: male	——	——	——	——	——

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Groups and number of people	Groups and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Cranial injury or postoperative repair	Coral fragments	72 cases	Randomized controlled trials	72 cases	——	——	——	17 months	50% of cases have coral skeletons almost completely absorbed; Another 50% of cases have partial absorption. The absorption of coral structures in larger implants does not exceed 40% of their volume, and no infectious complications have been found

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Groups and number of people	Groups and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Craniofacial bone contour defect	Coral fragments	36 cases: 13.39%males, 22.61%females	Randomized controlled trials	——	——	——	——	12-3 6months	Except for 5 clinically significant material absorption sites (incomplete absorption), the enhancement effect of other patients is very stable

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Groups and number of people	Groups and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Cervical adjacent segment degenerative disease	——	52 cases: 37 males, 15 females	Randomized controlled trials	52 cases: 37 males, 15 females	——	11 patients underwent anterior cervical discectomy and fusion (ACDF), 24 patients underwent anterior cervical discectomy and fusion (ACCF), and 4 patients underwent cervical disc replacement (CDA). The median time interval between the first and second surgeries was 74 months	Thirteen patients underwent their first SLAC surgery. The median time interval between the first and second surgeries is 33 months (21-59 months)	——	——

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Groups and number of people	Groups and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Cerebrovascular Sclerosis Coronary arteriosclerosis and heart disease	Cockscomb Coral Extract	——	Randomized controlled trials	——	——	One part per million of this substance is refined and mixed into 1,000 ml of compounded saline for injection or infusion to patients with significant therapeutic effects.	——	——	——

6.2 Clinical application of preparations which contain coral

In clinical practice, the compound prescription of coral is mainly composed of Ershiwuwei Shanhu Pills, Ershiwuwei Shanhu capsules, and also includes Shanhu Qishiwei pills. Ershiwuwei Shanhu Pills is a Traditional famous party and proved recipe for Tibetan medicine to treat albichoriasis and epilepsy. It uses coral as the monarch drug, together with pearl, *Terminalia chebula* and so on. It has the effects of inducing resuscitation, dredging meridians, relieving pain. It is mainly used to treat "albichoriasis", Unconsciousness, body numbness, dizziness, brain pain, irregular blood pressure, headache, epilepsy and various neuropathic pain. According to the collected literature, it was found that clinically, Erxuanwei Coral Pill has satisfactory efficacy in the treatment of neurological diseases (epilepsy, primary headache, etc.), cardiovascular diseases (cerebral infarction, hypertension, etc.) and orthopedic system (neurogenic cervical spondylosis, lumbar myofasciitis). In acute and severe cases, the combination of drugs is often used clinically to bring about a synergistic effect to bring about relief. See Table 8 for details.

6.2.1 Clinical application of nervous system disease

Neurological disorders consist of two main areas. On the one hand, it is manifested in the treatment of epilepsy disorders. Epilepsy is a chronic disease of sudden, transient, recurrent central nervous system malfunction caused by abnormal over-discharge of neurons in the brain(Xu, Abulikemu & Zhuang, 2009). Ershiwuwei Shanhu Pills can cause a significant reduction in the number of seizures, shorten the duration of

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seizures, improve the type of seizures, reduce the symptoms of headache after seizures, and reduce the degree of cognitive impairment, with significant anti-seizure and anticonvulsant effects. Clinically, 112 patients were randomly divided into a treatment group and a control group, and the treatment group was given Twenty-five Coral Pills while the control group was treated with Western standardized AEDs, and the results showed that the total effective rate of the treatment group was 91.07%, while the control group was only 67.86%(Wang, Zhao, Wang, Wu, Zhang & Gao, 2014). In the treatment of patients with epileptic tonic-clonic seizures, the total effective rate of the treatment group (taking Ershiweuwei Shanhu Pills alone) was 88.23%(Wang, Zhao, Zhao, Chen & Gao, 2013). The effects of combination drug treatment regimens have also been reported. Patients were treated orally with Ershiwuwei Shanhu Pills on top of oral levetiracetam tablets or carbamazepine, and the results showed that the therapeutic effect was much higher than that of conventional Western medical treatment, and it reduced serum IL-2, TNF-α, sICAM-1, IL-6, and CRP levels. It can be seen that the combination of drugs has better clinical efficacy in the treatment of epilepsy, while improving the immune function of patients and reducing the inflammatory response(Huang & Zhao, 2017; Yuan, Ji, Xing & Zuo, 2018).

Migraine, tension headache and intractable headache are common clinical primary headache disorders and another aspect of neurological disorders. 63 patients with migraine were randomly divided into taking Ershiwuwei Shanhu Capsules or Nao Zhen Ning, and after 30 days, 30 out of 33 patients taking Ershiwuwei Shanhu Capsules were effective, with a total effective rate of 90.9%, and 22 out of 30 patients taking Nao Zhen Ning were effective, with a total effective rate of only 73.3%(Renwang & Renqing, 2010). 110 patients were selected for the study, and the efficiency of the treatment group (taking Ershiwuwei Shanhu Pills alone) was 94.55%, which was significantly higher than the total efficiency of the control group (taking flunarizine hydrochloride capsules combined with amitriptyline hydrochloride tablets), which was 74.55%. Meanwhile, clinical efficacy observation shows that Ershiwuwei Shanhu Pills can improve the clinical efficacy of headache by reducing the abnormal blood flow condition(Wang, Zhao, Wang & Gao, 2013). In addition to medication, acupuncture can also be combined with treatment. 110 patients were randomly divided into two groups, the control group was treated with acupuncture and the observation group was treated with Ershiwuwei Shanhu Pills on this basis, the results showed that the total effective rate was 80% in the acupuncture group, but 94.5% in the observation group. Further study found that β-EP, NO and 5-HT levels were higher than the acupuncture group and ET levels were lower than the acupuncture group, suggesting that Ershiwuwei Shanhu Pills can improve neuro-endocrine factors and regulate cerebral blood flow rate in migraine patients, thus contributing to the improvement of migraine symptoms(Gu, 2014). As early as 2000, a study found that Ershiwuwei Shanhu Pills combined with acupuncture could treat intractable headaches(Bai & You, 2000). Modern research has shown that Ershiwuwei Shanhu Pills not only dilate blood vessels and improve the effect of microcirculation in the brain, but also effectively improve the symptoms of vascular smooth muscle spasm in order to restore local central cerebral area blood perfusion and thus relieve headache symptoms(Li, 2007; Yang, 2010).

6.2.2 Clinical application of cardiovascular and cerebrovascular diseases

In cardiovascular system diseases, it is effective in treating post-stroke headache and cerebral infarction related conditions. 64 patients with post-stroke headache were studied, and after 4 weeks of treatment, it was observed that the efficiency of the treatment group with the addition of Ershiwuewei Shanhu capsules to the conventional medical treatment was 93.75%, which was significantly higher than that of the control group with the conventional medical treatment of 56.25%. The patient's headache level is reduced, the number of attacks is significantly reduced and the duration of headache is significantly shortened during the treatment period(Shi & Zheng, 2018). In a study by Dongmei Guan, it was shown that the clinical efficacy of Ershiwuewei Shanhu capsules given to patients with post-stroke headache was higher than that of the reference group. The pharmacological analysis showed that the mechanism was similar to that of primary headache, and both acted by dilating blood vessels, regulating cerebral blood flow, and improving neurological function(Wang & Li, 2014; Yang et al., 2015).

Aspects of cerebral infarction disease, 90 patients were randomly divided into the control group and the

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observation group, and were given Huoxue TongmaiPian and Ershiwuewei Shanhu Pills, respectively. The results showed that the efficacy of Erxuoyi Coral Pill was better and its clinical application was more valuable(Zeng, 2019). On the basis of the study that Ershiwuewei Shanhu Pill can significantly reduce infarct foci in rats with focal cerebral ischemia, researchers randomly selected 60 patients and tested their blood lipid, uric acid, homocysteine and other levels, and the results showed that the treatment group had elevated levels of glutamate transaminase, glutamic oxalacetic transaminase and other enzymes, which clearly demonstrated the efficacy of Ershiwuewei Shanhu Pills in treating cerebral infarction, but there is a certain effect on heart, liver and kidney function, and the mechanism may be related to its regulation of blood lipid(Zhu et al., 2020). Although aspirin can improve the hypercoagulable state of blood, the drug alone is not effective. Patients with acute cerebral infarction were observed by using Ershiwuewei Shanhu Pills combined with aspirin, and the control group used aspirin combined with atorvastatin, and the results showed that both MMSE scores increased, NIHSS scores, FIB, D-dimer, and platelet aggregation index decreased, and the changes were large in the observation group(Tao, Huang & Luo, 2022). Pharmacological studies have further shown that Ershiwuewei Shanhu Pills can inhibit cerebral thrombosis, reduce the area of cerebral infarction, reduce brain tissue edema, and dilate cerebral blood vessels, improve cerebral blood circulation and brain tissue metabolism, which coexist with the antithrombotic effect of aspirin to improve the therapeutic effect and have higher clinical use value(Tan, 2020). The total effective rate of Shanhu Qishiwei Pills with Heart Failure Combination for the treatment of persistent heart failure also reached 88% while no significant toxic side effects were found(He, Song & Xiong, 2007).

Ershiwuewei Shanhu Pills cured 26 cases of hypertension out of 30 cases, with a total efficiency of 96.7%. The pharmacological study proved that the whole formula has lowered blood viscosity, reduced water retention in the body and changed blood rheology. It has a significant effect on lowering blood pressure and has a long-lasting and stable effect on lowering blood pressure, which is more effective for unstable hypertension(Li, 2010a). In additional, combination treatment regimens not only improve treatment efficiency, but also have better results in terms of treatment safety. The total effective rate of Ershiwuewei Shanhu Pills combined with diphenhydramine drugs in the treatment of hypertensive patients was as high as 95.56%, which was much higher than that of patients taking only diphenhydramine drugs, whose effective rate was only 77.78%(LI & Liu, 2021).

6.2.3 Clinical application of orthopedic system diseases

The same as the application of coral single medicine, its compound prescription is also effective in orthopedic system diseases, and has better efficacy in the clinical treatment of neurogenic cervical spondylosis, lumbar myofasciitis, and traumatic synovitis of knee join(Jiao, Yao, Zhou & Luo, 2013; Li, Wang, Huang & Luo, 2013)t. In 65 clinical cases of neurogenic cervical spondylosis, after taking Ershiwuewei Shanhu Pills orally and combining with acupuncture according to the condition for one course of treatment, the pain symptoms were significantly reduced, and after two courses, the symptoms disappeared completely, and no recurrence was seen so far(Zhang & Zhang, 2011). Ershiwuewei Shanhu Pills have also been used in combination with conventional Western medical treatment. The researchers randomly assigned 84 patients to the control group to receive flunarizine hydrochloride capsules orally and the observation group to add Ershiwuewei Shanhu capsules on top of the control group. The results showed that the observation group could increase the patients' plasma neurohypophyseal concentration, reduce pain and improve blood flow velocity in the vertebral and basilar arteries, with a final total effective rate of 90.48%, significantly higher than the 69.05% of the control group(Ren, Wang, Ma, Gao & Zhou, 2015). A patient with lumbar myofasciitis was treated with oral and external application of Ershiwuewei Shanhu Pills for 20 days, and all the symptoms were removed, and no recurrence was seen after one year of follow-up(Li, 2006).

6.2.4 Clinical applications of other diseases

In addition, Twenty-Five Flavored Coral Pills have shown clinical return in trauma, herpes zoster and respiratory system. 17 patients with lumbar, hand and foot sprains and smash injuries were cured within 7 days by using Coral Ershiwuewei Shanhu Pills alone, both internally and externally on the affected area(Yang,

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2003). In clinical practice, the efficacy of Ershiwuewei Shanhu Pills in clearing heat and detoxifying,clearing and moistening the lung was taken as the monarch drug, together with Chouluo Gengsheng Powder, to treat 54 cases of lung fever patients, all of which obtained satisfactory results(Yang, 2003). Acyclovir is also used clinically in combination with Ershiwuewei Shanhu Pills to treat herpes zoster, a neuropathic pain caused by damage after the activation of the herpes zoster virus, which belongs to the Tibetan medical term "albichoriasis"(Zhang, 2012a). Therefore, the treatment of neuralgia of herpes zoster with Ershiwuewei Shanhu Pills has its unique effects and efficacy. Shanhu Qishiwei Pills is also one of the common classical compound prescriptions containing coral, and is used to treat cerebral hemorrhage, limb paralysis, epilepsy and various neuritis. In 4 patients with cerebral hemorrhage, headache and vomiting were relieved after taking Shanhu Qishiwei Pills once a day for 20 days, and round-like hypodense foci were seen in the skull. At the same time, no other adverse effects were observed(Bian, 2012). Although the compound prescriptions are diverse and the ingredients that exert their medicinal effects may be multiple, there is no denying the synergistic effect of the coral in treating the symptoms of the disease and improving the efficacy of the treatment.

In clinical practice, we use one side to treat multiple diseases, identify the syndrome accurately, and use the right medicine for the syndrome. The conventional Western medical treatment package includes symptomatic treatment such as improving the patient's hemodynamics and pain relief, but the efficacy is not significant(Ren, Wang, Ma, Gao & Zhou, 2015). In conclusion, the therapeutic rate of combined drugs is much higher than that of single or compound drugs, and it can even produce additional therapeutic effects, so it has a higher promotion value and is an effective solution worth promoting in the clinic.

Table 9 Classification statistics table for clinical application of preparations which contain coral

Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
				Treatment group	Control group	Treatment group	Control group		

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Cervical spondylosis of vertebral artery type	Ershiwuwei Shanhu Capsules Combined with Western Medicine	84 cases: 54 males, 30 females	Randomized controlled trials	42 cases: 28 males, 14 females	42 cases: 26 males, 16 females	On the basis of the control group, add 2 capsules of Ershiwuwei Shanhus of coral each time, with a specification of 0.5g per capsule, once a day	Routine treatment of western medicine: oral fluranazine hydrochloride capsules every 10mg, once a day, before sleep, and chiropractic treatment	30 days	Observation group: 22 cases were cured, 10 cases were significantly improved, 6 cases were effective, and 4 cases were ineffective, with a total effective rate of 90.48%; Control group: 14 cases were cured, 6 cases were significantly improved, 9 cases were effective, and 13 cases were ineffective, with a total effective rate of 69.05%; The pain score decreased after treatment, and the decrease in the observation group

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Cervical spondylosis of vertebral artery type	Ershiwuwei Shanhu Capsules	90 cases	Randomized controlled trials	45 cases	45 cases	On the basis of the control group, orally take 2 capsules of Ershiwuwei Shanhus of coral capsules per day for 20 days as a course of treatment	Chiropractic treatment [Spinal neurobiomechanical reduction method (founded by Luo Xiaoyang), once every 3-4 days, with 5 times as a course of treatment	——	After treatment, the two subgroups showed improvements in relieving neck and arm pain, neck tenderness, cervical mobility, and upper limb numbness compared to before treatment, with the combined treatment group showing more significant improvemen

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Cervical spondylosis	Ershiwuwei Shanhu Pills	65 cases: 23 males, 42 females	Randomized controlled trials	65 cases: 23 males, 42 females	——	Twenty-five flavor coral pills, taken orally, at the same time, according to the condition and combined with acupuncture and moxibustion treatment, a course of 10 days, generally 2-3 courses	——	20-30 days	444 cases recovered without any clinical symptoms, 15 cases were effective, and 6 cases were ineffective. The total effective rate is over 90%

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Lumbar fasciitis	Ershiwuwei Shanhu Pills	150 cases: 98 males, 52 females	Randomized controlled trials	150 cases: 98 males, 52 females	——	Take Ershiwuwei Shanhued Coral Pills, 4 pills per dose, 1 dose per day, with warm water-soaked powder and medication residue on an empty stomach.	——	21 days	Cure 30 people by 20%; Improved 108 people by 72%; 11 people had no significant changes, accounting for 7.3%; One person has not recovered, accounting for 0.6%, indicating aggravation.
Epilepsy	Ershiwuwei Shanhu Pills	136 cases: 62 males, 74 females	Randomized controlled trials	68 cases: 32 males, 36 females	68 cases: 30 males, 38 females	Oral administration of Ershiwuwei Shanhus of coral pills, 1 g each time, once a day, with warm water for delivery	Taking epilepsia drugs, including 20 cases treated with single drug, 38 cases treated with dual drug, and 10 cases treated with combination of three drugs	2 months	The total effective rate of the treatment group who only took Ershiwuwei Shanhus of coral pills was significantly higher than that of the control group

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Epilepsy	Ershiwuwei Shanhu Pills	112 cases: 65 males, 47 females	Randomized controlled trials	56 cases: 34 males, 22 females	56 cases: 31 males, 25 females	Oral Tibetan Medicine Ershiwuwei Shanhu Pills for Treatment, 1g/time, 1 time/day, delivered with warm water	Oral administration of sodium valproate tablets, 0.2-0.4g/time, 3 times/day, or additional administration of topiramate tablets (25-200mg/time, 2 times/day) or phenytoin sodium Tablets (50-100mg/time, 2-3 times/day)	2 months	The total effective rate of the Ershiwuwei Shanhus coral pill group was 91.07%, while the total effective rate of the control group was 67.86%

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Epileptic tonic clonic seizures	Ershiwuwei Shanhu Pills	102 cases: 62 males, 40 females	Randomized controlled trials	51 cases: 32 males, 19 females	51 cases: 30 males, 21 females	Oral administration of Ershiwuwei Shanhus of coral pills, 1 g each time, once a day, with warm water for delivery	Sodium valproate tablets, 0.2-0.4g/time, 3 times/day, or topiramate tablets (25-200mg/time, 2 times/day) or phenytoin tablets (50-100mg/time, 2-3 times/day	2 months	The total effective rate of the treatment group was 88.23%, while the total effective rate of the control group was 68.62%. Compared with before treatment, the epilepsy symptom scores of both groups were significantly reduced after treatment. Compared with the control group, the symptom scores of the treatment group were significantly reduced

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Epilepsy	Ershiwuwei Shanhu Pills Combined with Carbamazepine	82 cases	Randomized controlled trials	41 cases	41 cases	On the basis of the control group, oral administration of Ershiwuwei Shanhus of coral pills, 1 pill/time, 1 dose/day	Take orally carbamazepine tablet, the initial dose is 0.2 g/time, twice a day. After one week of continuous treatment, adjust the dose, increase 0.1 g per week, to 0.4 g per time, twice a day	2 months	After treatment, the total effective rates of the control group and the treatment group were 80.95% and 95.24%, respectively. The HAD scores of both groups were significantly reduced, while MoCA was significantly increased. The number of epileptic seizures in both groups of patients was significantly lower than before

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Epilepsy	Ershiwuwei Shanhu Pills Combined with Levofloxacin Tablets	60 cases	Randomized controlled trials	30 cases	30 cases	On the basis of treatment in the control group, oral administration of Ershiwuwei Shanhus of coral pills, 1 g/time, 1 time/day	Oral administration of levetiracetam tablets after meals, starting at a dose of 500 mg/time, twice a day, and adding to 1000 mg/time, twice a day after one week	3 months	The total effective rates of the control group and the treatment group were 73.33% and 93.33% respectively, and the levels of inflammatory factors in the treatment group were significantly lower than those in the control group. After treatment, the frequency of seizures in both groups was significantly reduced, and the fre-

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Epilepsy	Combined use of Ershiwuwei Shanhus of coral pills	176 cases: males: females=2:1	Randomized controlled trials	——	——	The addition group of Wuwei Coral Pills was composed of carbamazepine, valproic acid, and Xilishu	Valproic acid added with Shunqi Anshen Wan	1 year	Three compatibility schemes of Ershiwuwei Shanhus coral pills (three groups of Ershiwuwei Shanhus coral pill addition group) have a significant effect on reducing the frequency of seizures, alleviating the degree of epileptic discharge, and improving the degree of headache and cognitive impairment after seizures in symptomatic epilepsy; Among them, the combination of Ershiwuwei Shanhus of coral pill and sodium

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Primary headache	Ershiwuwei Shanhu Capsules Combined with Cowpox Vaccine	67 cases: 26 males, 41 fmales	Randomized controlled trials	30 cases: 12 males, 18females	37 cases: 14 males, 23 females	Ershiwuwei Shanhu Capsules, 4 capsules per day, intravenously administered with a dose of 3ml of rabbit skin extract caused by cowpox vaccine, added to 5% glucose injection (250ml) once a day	Conventional western medicine treatment, oral fluranolol cinnarizine 1 capsule per night, intravenous drip of venoruton 250ml, once a day	2 weeks	Observation group: 18 cases showed significant effect, 10 cases were effective, and 2 cases were ineffective, with a total effective rate of 93.3%; Control group: 16 cases showed significant effect, 14 cases were effective, and 7 cases were ineffective, with a total effective rate of 81.1%; The headache relief rate in the study group was higher than that in the control group

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Migraine	Ershiwuwei Shanhu Pills	50 cases: 13 males, 37 females	Randomized controlled trials	30 cases: 8 males, 22 females	20 cases: 5 males, 15 females	Ershiwuwei Shanhued Coral Pills, 4 pills per time, once a day	Sibeline 10mg, once a day; 10mg of oryzanol, three times a day; Qiye Shen'an Tablets 100mg, three times a day	4 weeks	The total effective rate of the treatment group was 93.33%. The total effective rate of the control group is 75%

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Migraine	Ershiwuwei Shanhu Pills	40 cases: 12 males, 28 females	Randomized controlled trials	40 cases: 12 males, 28 females	——	Ershiwuwei Shanhued Coral Pills, 4 at a time, once a day	——	1 month	12 cases were cured, accounting for 30.0%; 17 cases showed significant effect, accounting for 42.5%; 8 cases were effective, accounting for 20.0%; Three cases were ineffective, accounting for 7.5% of the total. Total effective rate 92.5%

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Migraine	Ershiwuwei Shanhu Pills	480 cases: 211 males, 269 females	Randomized controlled trials	235 cases: 111 males, 124 females	245 cases: 100 males, 145 females	Ershiwuwei Shanhu Pills 3 tablets/1, 2 times/d, swallowed in installments	Ershiwuwei Shanhu Pills 4 tablets/1, 1 time/day, taken by soaking in hot water	4 weeks	The cure rate in the conventional dose group was 115/245 cases, while the cure rate in the high-dose group was 148/235 cases
Migraine	Ershiwuwei Shanhu Pills in combination with Flunarizine	112 cases: 49 males, 63 females	Randomized controlled trials	56 cases: 26 males, 30 females	56 cases: 23 males, 33 females	Twenty-five flavor coral pills, 4 pills each time (0.25 g each), once a day, fluranine cinnarizine capsules 5 mg, taken daily before sleep	Flunarizine 5 mg, taken daily before bed	4 weeks	After treatment, the peak systolic period in the treatment group improved significantly compared to before treatment

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Migraine	Ershiwuwei Shanhu Pills Combined with Sibeline	158 cases: 56 males, 102 females	Randomized controlled trials	84 cases: 27 males, 57 females	74 cases: 29 males, 45 females	Ershiwuwei Shanhued Coral Pills, taken orally in warm water every morning, 4 capsules per dose; Sibeline, take 1 capsule before bedtime every night	On the basis of conventional medication treatment, sibirin is administered orally, taking 1 capsule before bedtime every night	4 weeks	The observation group significantly alleviated the level of anxiety or depression in patients, with better results than the control group

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Migraine	Ershiwuwei Shanhu Pills combined with acupuncture and moxibustion	110 cases: 37 males, 73 females	Randomized controlled trials	55 cases: 20 males, 35 females	55 cases: 17 males, 38 females	Acupuncture and moxibustion treatment and taking Ershiwuwei Shanhu pills, 1g/time, once a day.	Acupuncture and moxibustion: Baihui, Shenting (the affected side), Benshen (the affected side), Dagu (the affected side), Waiguan (both sides), Fengchi (both sides), Jiaosun (both sides), Qiuxu (both sides), plus or minus hyperactivity of liver yang plus Taichong, interline, blood deficiency plus blood sea, Sanyinjiao, phlegm plus Tongli, Fenglong, kidney deficiency plus Guanyuan, Taixi, blood stasis	5 weeks	The total effective rate of clinical efficacy in the observation group was 94 5%, 80% in the acupuncture and moxibustion group, and the observation group is superior to the acupuncture and moxibustion group

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Stubborn headache	Ershiwuwei Shanhu Pills	128 cases: 78 males, 50 females	Randomized controlled trials	64 cases: 40 males, 24 females	64 cases: 38 males, 26 females	Ershiwuwei Shanhued Coral Pills, 1 g each time, once a day, taken with warm water	Oral Zhengtian Pills, 1 bag (6 g) each time, 3 times a day, discontinue other medications and painkillers 1 week before and during treatment	8 weeks	The frequency, intensity, and duration of pain in the treatment group were significantly lower than those in the control group; The total effective rate of the treatment group was 93.75%. The total effective rate of the control group is 81.25%

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Stubborn headache	Ershiwuwei Shanhu Pills	8 0cases: 47 males, 33 females	Randomized controlled trials	40 cases: 26 males, 14 females	40 cases: 21 males, 19 females	Ershiwuwei Shanhu Pills, taken in boiling water, 1g once, twice a day	Take Zhengtian Pills orally, once in the morning, once in the morning, once in the evening, and take one bag each time; Take amitriptyline hydrochloride tablets in combination, once in the morning and once in the evening, taking 2 tablets each time	1 month	After treatment, the pain intensity and duration of the control group patients were higher than those of the observation group patients, with a total effective rate of 72.5% in the control group and 92.5% in the observation group

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Stubborn headache	Ershiwuwei Shanhu Pills combined with acupuncture and moxibustion	8 cases: 2 males 6 females	Randomized controlled trials	8 cases: 2 males, 6 females	——	0.6g per pill, once a day, one pill per time. Take one pill at night and soak it overnight with a little saffron and bear bile, then take it at dawn the next day. Acupuncture should be done once a day for the initial treatment, which can be combined with moxibustion. Change to acupuncture and moxibustion every other day after pain relief	——	——	——

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Tension headache	Ershiwuwei Shanhu Pills	120 cases: 43 males, 67 females	Randomized controlled trials	55 cases: 22 males, 33 females	55 cases, 21 males, 34 females	4 pills (1g) each time, once a day, ground and taken with warm water	Flunarizine hydrochloride capsules, 5mg each time, twice a day	4 weeks	The total efficacy of the treatment group was 54.55%, while the control group was 29.09%

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Tension headache	Ershiwuwei Shanhu Pills	70 cases	Randomized controlled trials	35 cases	35 cases	Ershiwuwei Shanhu Pills 1g, oral once a day	Amitriptyline tablets, 25mg, taken orally 3 times a day	28 days	The total effective rate of the Ershiwuwei Shanhus coral pill treatment group was 82.86%, while the total effective rate of the amitriptyline control group was 80.00%; The total effective rate of traditional Chinese medicine syndrome in the treatment group was 88.57%, while in the control group it was 82.86%; The

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Tension headache	Delixin and Ershiwuwei Shanhu Pills United	160 cases: 58 males, 102 females	Randomized controlled trials	80 cases: 31 males, 49 females	80 cases: 27 males, 53 females	Dailixin takes 1 tablet orally in the morning and 1 tablet orally in the middle of the day, and 4 capsules of Jinzhu Yalong Ershiwuwei Shanhu Pills are taken orally once in the morning	Take 1 tablet of sibirin every night before going to bed, and add symptomatic medications (such as general painkillers, nourishing blood and clearing brain granules, Tongtian oral liquid, etc.)	2 weeks	Among the 80 cases in the treatment group, 80 cases were effective with a total effective rate of 100%, while in the control group, 22 cases were effective with a total effective rate of 85%

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Chronic tension-type headache	Ershiwuwei Shanhu Pills Combined with Low Dose Trazodone Hydrochloride Tablets	120 cases: 26 males, 94 females	Randomized controlled trials	60 cases: 11 males, 49 females	60 cases: 15 males, 45 females	Ershiwuwei Shanhu Pills 1 g, once a day (taken in hot water), Trazodone Hydrochloride Tablets 25 mg, once a night	Amitriptyline hydrochloride tablets 25 mg, once per night, gradually increased according to patient tolerance ([?] 75 mg per day)	3 months	The total effective rate of the treatment group was 81.67%, which was better than the control group's total effective rate of 73.33%; VAS score; Both HAMD and HAMA scores decreased, and the observation group was better than the control group

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Frequent episodes of tension type headache	Ershiwuwei Shanhu Pills Combined with Low Dose Amitriptyline	240 cases: 92 males, 148 females	Randomized controlled trials	120 cases: 47 males, 73 females	120 cases, 45 males, 75 females	Take 4 capsules (1.0 g) of Ershiwuwei Shanhu pills orally and soak them in water once a day; Amitriptyline tablets 12.5 mg. Twice daily	Amitriptyline tablets 25 mg, twice daily	12 weeks	The total effective rate of the treatment group was 93.33%. The total effective rate of the control group was 73.33%. The therapeutic effect of the treatment group was better than that of the control group

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Angioneurotic headache	Combination of Ershiwuwei Shanhu Pills and Nursing Intervention	60 cases: 37 males, 23 females	Randomized controlled trials	30 cases: 19 males, 11 females	30 cases: 18 males, 12 females	Take 2 Tibetan medicine Ershiwuwei Shanhu pills once a day, orally before meals; Nursing interventions	Zhennaoling treatment: 4 capsules of Zhennaoling each time, three times a day, in the morning, middle, and evening, taken orally	30 days	Among the study group of patients, there were 12 controlled cases, 7 significantly effective cases, 8 effective cases, and 3 ineffective cases, with a total effective rate of 90.00%; In the control group, 8 patients were under control, 6 were significantly effective, 5 were effective, and 11 were ineffective, with a total effective rate of 63.33%

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Angioneurotic headache	Ershiwuwei Shanhu Pills Combined with Nursing Intervention	80 cases: 43 males, 37 females	Randomized controlled trials	40 cases: 22 males, 18 females	40 cases: 21 males, 19 females	Ershiwuwei Shanhu Pills, combined with nursing interventions for treatment, dosage is 2 capsules, once a day, administered orally before meals	The dosage of aspirin enteric coated tablets is 30 mg, 3 times a day, administered orally; The dosage of nimodipine is 30 mg, 3 times a day, administered orally	30 days	Observation group: Among the 40 cases, 28 were significantly effective, 11 were effective, and 1 was ineffective, with a total effective rate of 97.5%; Control group: Among the 40 cases, 21 were significantly effective, 10 were effective, and 9 were ineffective, with a total effective rate of 77.5%

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Angioneurotic headache	Ershiwuwei Shanhu Pills	63 cases	Randomized controlled trials	33 cases	30 cases	33 cases 30 cases Ershiwuwei Shanhu capsules, 2 capsules (0.5g/capsule), once a day	Zhennaoling, 4 capsules (0.3g/capsule), 3 times daily	30 days	30 cases in the treatment group were effective, with a total effective rate of 90.9%, and 22 cases in the control group were effective, with a total effective rate of 73.3%

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Post stroke headache	Ershiwuwei Shanhu Capsules	70 cases: 47 males, 23 females	Randomized controlled trials	35 cases: 25 males, 10 females	35 cases: 22 males, 13 females	Tibetan Medicine Ershiwuwei Shanhu Capsules, 2 capsules/time	Routine medical symptomatic treatment should be carried out with antiplatelet aggregation, analgesia, nutritional nerve, and softening vascular drugs	8 weeks	The frequency of headaches in both groups was lower than before treatment, and the duration of pain was shorter than before treatment. The frequency of headaches in the Tibetan medicine group was lower than that in the reference group, and the duration of pain was shorter than that in the reference group

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Post stroke headache	Ershiwuwei Shanhu Capsules	64 cases: 33 males, 31 females	Randomized controlled trials	32 cases: 18 males, 14 females	32 cases: 15 males, 17 females	Twenty-five coral capsules, 0.5 g pellets at 1 time / D and 2 pellets / time, were given orally on the basis of routine internal medicine treatment	It is given routine medical treatment, which includes nourishment of nerves, invigorating blood circulation and eliminating stasis, anti platelet aggregation, anti atherosclerosis and pain relief	4 weeks	The effective rate of the treatment group was 93.75%, while the control group was 56.25%

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Headache	Ershiwuwei Shanhu Capsules Combined with Danzhen Headache Capsules	76 cases: 35 males, 41 females	Randomized controlled trials	38 cases: 17 males, 21 females	38 cases: 18 males, 20 females	Combination therapy of Tibetan medicine, oral administration of twenty-five coral capsules and Danzhen headache capsules, the former 4 capsules once daily and the latter 2 capsules three times daily	To be treated with conventional western medicine, take Flunarizine or Thagrelate orally, the former takes one capsule every night, the latter three times a day, the dose is 100mg	1 month	In the treatment group of 38 patients, 10 were cured, 19 were significantly improved, 7 were effective, and 2 were ineffective. The total effective rate of treatment was 94.7%; In the control group of 38 patients, 6 were cured, 15 were significantly improved, 10 were effective, and 7 were ineffective. The total effective rate of treatment was 81.6%

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Vertigo	Ershiwuwei Shanhu Pills	160 cases: 88 males, 72 females	Randomized controlled trials	100 cases: 56 males, 44 females	60 cases: 32 males, 28 females	Boiled blister suit, 1 g once, 1 day	Gastrodia elata Blume capsules, 4 capsules at 1 time, 3 times at 1 day	1 month	The total effective rate of the treatment group was 85.00%. After ridit analysis of the comparison results between the two groups, the therapeutic effect of the treatment group was significantly better than that of the control group

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Acute cerebral infarction	Ershiwuwei Shanhu Pills	60 cases: 32 males, 28 males	Randomized controlled trials	30 cases: 19 males, 11 females	30 cases: 13 males, 17 females	On the basis of the control group, add 1g of Ershiwuwei Shanhu pills once a day	spirin 100mg, once daily; Clopidogrel Hydrogen Sulfate Tablets 75mg, once daily; Atorvastatin calcium tablets 40mg, once daily; Ligustrazine 120mg, once daily; Cytidine sodium 0.5g, once daily; Edaravone 30mg, twice daily	——	In the control group, there were 9 cases with a decrease in NIH SS score, 4 cases with an increase, and 17 cases with no change in NIHSS score; In the treatment group, 21 cases decreased, 2 cases increased, and 7 cases remained unchanged in the NIHSS score; Compared with the control group, the NIHSS score significantly decreased after treatment

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Disease	Pharmaceutical preparations	Experimental subjects	Research design	Group and number of people	Group and number of people	Therapeutic method	Therapeutic method	Course of treatment	Curative effect
Acute cerebral infarction	Ershiwuwei Shanhu Pills Combined with Aspirin	80 cases: 43 males, 37 fmales	Randomized controlled trials	40 cases: 22 males, 18 females	40 cases: 21 males, 19 females	On the basis of the control group, Ershiwuwei Shanhus of coral pills were given 1 g/time, 1 time/day	Take atorvastatin tablets orally before bedtime, 20 mg/dose, once a day; Oral aspirin enteric coated tablets 100 mg/time, once a day.	60 days	Both groups showed an increase in MMSE scores, a decrease in NIHSS scores, FIB, D-dimer, and platelet aggregation index, with significant changes observed in the observation group

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Cerebral infarction	Ershiwuwei Shanhu Pills	60 cases: 38 males, 22 fmales	Randomized controlled trials	30 cases	30 cases	Ershiwuwei Shanhu Pills, 2 capsules each time, 2 times a day, taken orally; Or once a day, 4 capsules each time, taken orally	Huoxue Tongmai tablets, 4 tablets each time, 3 times a day, taken orally.	20 days	Among the 30 cases in the treatment group, 6 were basically cured, 13 were significantly improved, 10 were improved, and 1 was ineffective, with a total effective rate of 96.7%; Among the 30 cases in the control group, 1 case was basically cured, 8 cases were significantly improved, 12 cases were improved, and 9 cases were ineffective. The total effective rate was 70.0%

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Cerebral infarction	Ershiwuwei Shanhu Pills	90 cases: 52 males, 38 females	Randomized controlled trials	45 cases: 27 males, 18 females	45cases: 25males, 20females	Cerebral Infarction Tibetan Medicine Ershiwuwei Shanhued Coral Pills, 2 capsules each time, 2 times a day, taken orally	Huoxue Tongmai tablets, 2 capsules each time, 2 times a day, taken orally.	20 days	Observation group: Among 45 cases, 30 were significantly effective, 13 were effective, and 2 were ineffective, with a total effective rate of 95.56%; Control group: Among 45 cases, 13 were significantly effective, 19 were effective, and 13 were ineffective, with a total effective rate of 71.11%; After treatment, the NIHSS scores of both groups decreased, and the NIHSS scores of the observation group were significantly lower than

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Cerebral hemorrhage	Shanhu Qishiwei Pills	4 cases	Randomized controlled trials	——	——	Coral Seventy Flavored Pills, 1 pill per day	——	20days	The patient's symptoms have decreased. CT scan shows circular low-density lesions visible in the intracranial region. After being discharged from the hospital, the patient took 70 flavors of coral under guidance, and their symptoms have improved significantly so far without any other adverse reactions.

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Refractory heart failure	Heart failure mixture combined with Shanhu Qishiwei Pills	150 cases: 90 males, 60 females	Randomized controlled trials	100 cases	50 cases	Conventional anti heart failure treatment should, in principle, discontinue the use of Western medicine to dilate the coronary artery and improve myocardial ischemia. In severe cases, basic Western medicine treatment such as cardiotonic, diuretic, and vasodilation should be given. At the same time, one pair of heart failure mixture was given daily, and 500ml of juice was taken by frying twice in water. The	Routine anti heart failure treatment	1 month	Among the 100 cases in the treatment group, 56 were significantly effective, 32 were effective, and 12 were ineffective, with a total effective rate of 88%; Among the 50 cases in the control group, 20 were significantly effective, 18 were effective, and 12 were ineffective, with a total effective rate of 76%

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Hypertension	Ershiwuwei Shanhu Pills	30 cases: 16 males, 14 females	Randomized controlled trials	30 cases: 16 males, 14 females	——	Soak in water in the morning and take it every night while sleeping, once a day	——	1 month	26 cases were cured, accounting for 86.7%; 3 cases showed significant effect, accounting for 10.0%; 1 case was ineffective, accounting for 3.3%; Total effective rate 96.7%

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Hypertension	Ershiwuwei Shanhu Pills in Combination with Dipine Drugs	90cases	Randomized controlled trials	45 cases	45 cases	Combined Tibetan Medicine Ershiwuwei Shanhu Pills, taken orally with warm water on an empty stomach, 1 capsule/time, 1 dose/day, 30 days as a course of treatment	Treatment with dipines	3 days	The effective rate of the treatment group (95.56%, 43/45) is higher than that of the control group (77.78%, 35/45), and the systolic and diastolic blood pressure after treatment in both groups are lower than before treatment, and the reduction in the treatment group is more significant

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Cough with lung heat	Ershiwuwei Shanhu Pills	54 cases: 33 males, 21 females	Randomized controlled trials	——	——	Coral Ershiwuwei Shanhu Pills 1/2, 3 times before meals, powder, 3 times after meals	——	15 days	15 days of recovery

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Waist, hand, and foot injuries	Ershiwuwei Shanhu Pills	17 cases: 11 males, 6 females	Randomized controlled trials	——	——	Take Coral Ershiwuwei Shanhu Pills orally, 3 times a day, 1 pill each time, chew carefully and take with boiling water. Take the medicine half an hour before meals. For external use, use 6 pills of coral Ershiwuwei Shanhus as the end, soak in 3 liang of Baijiu, half an hour later, apply externally to the affected part, 3-4 times a day, with moderate force	——	7 days	17 cases all recovered

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Discussion

Coral as an important marine biological resource, species resources are extremely confusing and complex. In the qing dynasty, where the second grade civil and military officials top wear, are made of red coral, become a symbol of official status. India and Tibet, people use coral as an auspicious object to worship Buddha, mostly used to make Buddhist beads, decorate the statue of the deity in the temple(Hong, 2009). In the ancient records have also long recorded coral applications in medicine, but a blemish in an otherwise perfect thing is that only a few pointed out that coral in the medicine as a combination of coral species for the use of red coral. But red coral is just a broad range, there are many species such as *Corallium japonicum* Kishinouye,*Corallium secundum* Dana and *Corallisum elatius* Ridley, etc. It is known that *Corallium japonicum* Kishinouye (trade name: Aka) is mostly used in compounding. Arca is expensive, but no reports have been retrieved on whether other red corals can be substituted. In addition, the corals studied in modern pharmaceutical research involve a total of 34 families and 99 genera of corals, dominated by the families*Alcyoniidae* , *Nephtheidae* , and *Plexauridae* . Coral species are confusing and complex, sorting out their resource species not only helps us to distinguish corals, but also lays the foundation for developing new drugs and further research on corals.

Coral has a long history of medicinal value, with the effect of removing corneal opacitycorneal opacity, improving eyesight, tranquilize mind, promoting wound healing and stopping bleeding. Modern pharmacological studies have also gradually verified the medicinal value of coral and its mechanism of action. First of all, coral contains a large amount of calcium carbonate and a small amount of organic matter, which has much in common with human bones. Coral transplantation in the human body is not cause rejection, in the coral of the countless fine pores will gradually grow microscopic blood vessels and synthesis of living cells of bone. Numerous literature reports that coral has become an alternative material to bone, often used in the field of maxillofacial surgery, orthopedics(Guillemin, Meunier, Dallant, Christel, Pouliquen & Sedel, 1989; Lai, 2017; Zhu, 2001). Secondly, active ingredients such as terpenoids (diterpenes, sesquiterpenes) and steroids extracted from coral have obvious pharmacological activities such as antiviral, antibacterial, antioxidant and antimalarial. In addition, some of the active ingredients not only show good enzyme inhibition activity, but also have obvious anticonvulsant, antiepileptic and sedative-hypnotic effects in the nervous system; in the cardiovascular system, they show anti-tubular formation activity and pro-angiogenic activity, and have a certain amount-effect relationship. The antihypertensive, hypolipidemic, (Chun, Wei, Zhu, Wu & Dawa, 2022)anti-ulcer(Elshamy, El-Kashak, Abdallah, Farrag & Nassar, 2017) activities have also been relevantly verified. It was found that most of these chemical components were extracted from corals of the *Alcyoniidae* and*Gorgonidae* , and the components extracted from a particular coral may have multiple uses. In conclusion, the study of active ingredients in corals becomes the cornerstone of subsequent pharmacological studies, and exploring the mechanism of action of active substances can be the research direction. In order to provide a basis for the elucidation of pharmacological effects and the design of clinical experiments(Wang, 2015).

Coral has various pharmacological activities, among which cytotoxic and anti-inflammatory and analgesic pharmacological effects are more prominent among the many pharmacological activities of coral. A549, HL-60, MCF-7, colon cancer cells, K562, HeLa and other tumor cells are hot spots for research. Scholars have mostly evaluated the inhibitory and apoptotic effects of different concentrations of active ingredients on different cells by MTT assay and SRB method. Studies have also shown that cytotoxicity can be influenced by compound structure. For example, prostaglandins with hydroxyl groups have good inhibitory properties(Hurtado, Castellanos, Coy-Barrera & Tello, 2020), sterols introduced with hydroxyl groups decrease the inhibitory potency against HeLa cell lines, while acetyl groups increase the cytotoxic activity. Pro-inflammatory enzymes, in particular inducible nitric oxide synthase (iNOS) for nitric oxide production and prostaglandin-producing cyclooxygenase (COX-2), play a central role in inflammatory mechanisms(Wei, Sung, Duh, Chen, Sheu & Yang, 2013). In addition, glial cells and elastin are also a mechanism of action. At present, the pharmacological experiments of coral, although the identification of its active ingredients, but in the extraction method, extraction conditions have not been reported, so the joint use of related

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techniques, such as ICP-MS, LC-MS, etc. to explore the best extraction of the active ingredients of coral becomes a breakthrough for future experiments. Most of the results of pharmacological studies are derived from cellular or animal models and do not fully prove their effectiveness, so more clinical trials are needed to confirm(Zhang, Mao, Ge & TANG, 2015).

Clinically, coral is often processed into powder for punching or used directly with its bones to treat bone diseases, in addition to showing good therapeutic effects in the treatment of epilepsy, primary headache, migraine, cerebral infarction, hypertension, neurogenic cervical spondylosis, lumbar myofasciitis, etc. In the face of complex diseases, it is difficult to obtain the desired effect of a single drug, so coral is often used in combination with other drugs to treat the disease, which has satisfactory results in clinical applications. At a certain efficacy, compound prescriptions contain coral exhibit the same effects as when the coral is used alone. However, due to the large number of herbs contained in the compound, the role played by coral in it is unclear, the effect may be weakened, the effect may be synergistically enhanced, or another effect may be stimulated, and its mechanism of action is not yet clear, and further research is needed.

Although coral toxicity is not included in the *Pharmacopoeia of the People's Republic of China* , it has been found in studies that coral toxicity is mostly found in marine ornamental soft corals of the genus*Zoanthidae* . Palytoxin is the main toxic component. The next also contains non-peptide neurotoxins extracted from water coral, all of which have toxic effects on the skin, cornea, etc. Short-term minor injuries are reversible with medication or emergency measures, with only a few disabilities, or a significant decrease in quality of life due to sequelae. No significant acute toxicity was seen in coral-related compound preparations, but if applied for a long time, toxicity to the liver, kidneys, lungs and other internal organs can still occur in a dose-dependent relationship. The toxicity of coral is not yet generalized because of the complexity and diversity of its species. Coral insects are toxic, but due to the special nature of coral, whether the coral is toxic after calcification has yet to be studied.

The pharmacokinetic study of coral is not yet reported in the literature, and it is not clear how the absorption, distribution, metabolism and excretion as well as the blood concentration of coral changes over time after administration in the body. In terms of absorption, the utilization of coral is not high, its often in the form of powder into the body, which greatly increases the contact area between the drug and the body, where the black horn coral for the treatment of bone diseases is the most significant. In addition, diluted coral extracts have been derived as new drugs for the treatment of diseases that. In conclusion, the form of coral taking should not be limited to powder or acting as an orthopedic material, but the development of its active ingredients is not a research strategy and prospect. It provides different ideas for the development of new drugs.

The organic components in corals are more studied, while other components such as trace elements are less studied. Coral as mineral medicine should strengthen the exploration and development of other components such as trace elements to pave the way for improving its quality standards and research on the basis of medicinal substances. In addition, the pharmacological effects of coral are numerous and extensive, but there is a lack of research on its mechanism of action, which should be focused on deepening to the genetic and molecular level in the future to make it better applied in practice. Toxicological studies have also come to the forefront. The limited clinical trials are not perfect in quality, but still have some reference value, and more scientific and representative clinical trials are needed in the future. Coral is currently used in several different fields, such as medical and apparel(Zhang, 2013b), with more areas still under development. Its value in medical care is particularly significant and needs more attention and extensive research.

Conclusion

It is well-known that marine invertebrates, a rich potential source of drug precursors, have been a popular avenue for the international search for drugs or drug precursors in the past decades. In the last two decades, coral chemistry and pharmacology research has made some achievements and discovered some new com-

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pounds with unique structures and strong physiological activities, but the corals that have been utilized are limited to only a small number and species of families. This article provides the first comprehensive account of six aspects of the medicinal history, species, chemical composition, pharmacological activity, toxicology and clinical application of coral in China. Coral as a natural mineral medicine, its active ingredients not only small amount of mixed, difficult to extract, in the identification of the composition is also very difficult. However, the pharmacological effects of most of the components isolated from coral have been developed, although they mostly reside in superficial areas, which shows that there is a long way to go in the study of the mechanism. Toxicological studies have shown that corals of the genus *Zoanthidae* cause toxic reactions in people through contact and inhalation, but can be treated with pharmacological relief. In terms of clinical application, coral is mostly used in combination with other drugs to treat diseases, with limited cases of coral alone, which may lead to an inability to substantively prove the effectiveness of coral, but is still informative. In conclusion, the pharmacological studies of coral are mostly about the monomer extracted from coral, while the clinical studies are more about the compound prescription applications of coral, which are less related. It is foreseeable that through more extensive and in-depth research on the active ingredients of coral and its mechanism of action, more remarkable achievements will be obtained and new ideas will be provided for the development of new drugs. This is both a pressure, a challenge and an opportunity for us(Ai, Chen & Qi, 2006).

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Authors' contributions

Mengtian Han is responsible for collecting data and writing this article, Zhongyuan Wang is responsible for the chemical composition structure graphics and pharmacological activity content improvement and Yiye Li is responsible for the translation and finishing of the clinical application section. Zhang Wang directs the writing of the article and functions as our corresponding author.

Conflicts of Interest

All authors have no conflict of interest to disclose.

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