Review

Traditional Uses, Origins, Chemistry and Pharmacology of Bombyx batryticatus: A Review

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Abstract: Bombyx batryticatus (B. batryticatus), a well-known traditional animal Chinese medicine, has been commonly used in China for thousands of years. The present paper reviewed advances in traditional uses, origin, chemical constituents, pharmacology and toxicity studies of B. batryticatus. The aim of the paper is to provide more comprehensive references for modern B. batryticatus study and application. In Traditional Chinese Medicine (TCM) culture, drugs containing B. batryticatus have been used to treat convulsions, headaches, skin prurigo, scrofula, tonsillitis and fever. Many studies indicate B. batryticatus contains various compounds, including protein and peptides, fatty acids, flavonoids, nucleosides, steroids, coumarin, polysaccharide and others. Numerous investigations also have shown that extracts and compounds from B. batryticatus exert a wide spectrum of pharmacological effects both in vivo and in vitro, including effects on the nervous system, anticoagulant effects, antitumor effects, antibacterial and antifungal effects, antioxidant effects, hypoglycemic effects, as well as other effects. However, further studies should be undertaken to investigate bioactive compounds (especially proteins and peptides), toxic constituents, using forms and the quality evaluation and control of B. batryticatus. Furthermore, it will be interesting to study the mechanism of biological activities and structure-function relationships of bioactive constituents in B. batryticatus.

Keywords: Bombyx batryticatus; traditional uses; origin; chemical constituents; pharmacology; toxicity

1. Introduction

Bombyx batryticatus (B. batryticatus) is the dried larva of Bombyx mori L. (silkworm of 4–5 instars) infected by Beauveria bassiana (Bals.) Vuill [1]. It is one of the most popular traditional Chinese medicines, called “Jiangcan” in Chinese vernacular and has been used in China for thousands of years. In addition, it is also widely used in Korea and Japan [2]. B. batryticatus is derived from silkworm spontaneously infected by Beauveria bassiana originally [3]. Currently, it is mainly produced through artificial breeding techniques by artificial inoculation of Beauveria bassiana [4].

B. batryticatus, as a common animal medicine in traditional Chinese, Korean, and Japanese medicine systems, has been utilized to treat convulsions, epilepsy, cough, asthma, headaches, skin prurigo, scrofula, tonsillitis, urticarial, parotitis and purpura [2,5,6]. Modern investigations have demonstrated that B. batryticatus possesses various pharmacological activities, including effects...
on nervous system (anticonvulsant effects, antiepileptic effects, and neurotrophic effects), anticoagulant effects, antitumor effects, antibacterial and antifungal effects, antioxidant effects, hypoglycemic effects, as well as other effects [7–9]. In addition, it is reported that *B. batryticatus* contains many different constituents including proteins, peptides, fatty acids, flavonoids, nucleosides, steroids, coumarin, polysaccharide and others [7–10].

In the current review, the advances in traditional uses, origins, chemistry, pharmacology and toxicity of *B. batryticatus* are systematically reviewed. Additionally, the directions and perspectives for future study on *B. batryticatus* are also discussed in the paper.

2. Traditional Usages

*B. batryticatus* has been used as a traditional medicine for many centuries in China based on its wide spectrum of biological and pharmacological activities. Traditionally, *B. batryticatus* has commonly been used to treat liver wind with phlegm, convulsion, acute panic of child, tetanus, stroke, fever, headache, sore throat, itchy rubella, as well as mumps [1]. *B. batryticatus* listed firstly in “*Sheng Nong’s herbal classic*”, a famous monograph of Traditional Chinese Medicine (TCM) during the Han Dynasty more than 1000 years ago, and it was described to be useful for the treatment of convulsions of child and skin whitening. Based on “*Ming Yi Bie Lu*” (Liang Dynasty), the main function of *B. batryticatus* was to treat postpartum pain and morbid leucorrhea in women. According to “*Yao Xing Lun*” (Tang Dynasty), *B. batryticatus* was used for the treatment of sweating and uterine bleeding. Subsequently, in “*Xin Xiu Ben Cao*” (Tang Dynasty), another famous TCM monograph, *B. batryticatus* was described as a treatment for furuncle. In addition, according to “*Ben Cao Gang Mu*” (Ming Dynasty), *B. batryticatus* could treat liver wind with phlegm, headache, and furuncle. Later, in “*Yu Qiu Yao Jie*” (Qing Dynasty), *B. batryticatus* was used to treat headache, thoracic obstruction and rubella. In TCM culture, *B. batryticatus* is salty in taste, even in nature and attributive to the liver, lung and stomach meridians [1].

As an animal traditional Chinese medicine, *B. batryticatus* has a little stench smell. In addition, it is reported that *B. batryticatus* has strong side effects on the gastrointestinal tract, and improper use can cause severe allergic reactions [11–13]. Therefore, to alleviate its stench smell and alleviate side effects, *B. batryticatus* is commonly processed by stir-frying with bran to a yellowish color [11–13]. In addition, the raw *B. batryticatus* and stir-fried *B. batryticatus* are the most common clinically used forms [1]. Although *B. batryticatus* is widely used in TCM, there are limited researches on its side effects and safety evaluations. The Chinese Pharmacopoeia recommends a dose of 5–10 g for *B. batryticatus* [1].

Currently, *B. batryticatus* is a well-known TCM that is used as the main forms of powders, decoctions or infusions for the treatments of convulsion, epilepsy, apoplexy, fever, cough with sputum and other diseases [5,14]. “Chinese Pharmacopoeia”, “Guo Jia Zhong Cheng Yao Biao Zhun”, “Zhong Yao Cheng Fang Zhi Ji”, and “Xin Yao Zuan Zheng Biao Zhen” revealed 175 prescriptions of Chinese patent drug containing *B. batryticatus*. The present paper summaries prescriptions of Chinese patent drug and decoctions which *B. batryticatus* is the main drug (Table 1).
Table 1. The traditional and clinical uses of *B. batryticatus* in China.

| Preparation Name | Main Compositions | Traditional and Clinical Uses | References |
|------------------|-------------------|------------------------------|------------|
| Qi Zhen Pills    | Bombyx Batryticatus, Scorpio, Moschus Artifactus, Cinnabaris, Realgar, Arisaema Cum Bile, Bambusae Concretio Silicea, Crotonis Semen Pulveratum | Relieving convulsion, eliminating sputum, promoting digestion and laxativing, curing acute infantile convulsions, irritability and constipation | “Chinese Pharmacopoeia (2015)”, vol. 1 ⁴ |
| Zhong Feng Hui Chun Pills (Tablets) | Bombyx Batryticatus, Angelicae Sinensis Radix, Carthami Flos, Salviae Miltiorrhizae, Lonicerae Japonicae Caulis, Pheretima, Lycopodii Herba, Scolopendra, Scorpio, Bungarus Parvus | Promoting blood circulation and relaxing tendons, treating apoplexy | “Chinese Pharmacopoeia (2015)”, vol. 1 ⁴ |
| Ru Bi San Jie Capsules | Bombyx Batryticatus, Prunellae Spica, Bupleuri Radix, Rosae Rugosae Flos, Angelicae Sinensis Radix, Ostreae Concha | Activating blood circulation and softening hardness, curing cyclomastopathy | “Chinese Pharmacopoeia (2015)”, vol. 1 ⁴ |
| Bao Ying Powder | Bombyx Batryticatus, Arisaema Cum Bile, Uncariae Ramulus Cum Uncis, Bovis Calculus Artifactus, Scorpio, Margaritifera, Moschus, Typhoni Rhizoma, Gastrodiae Rhizoma, Cicadae Periostraucum, Succinum, Sapochnikoviae Radix, Concretio Silica Praeparata, Cinnabaris | Eliminating sputum, relieving convulsion and clearing heat, curing infantile convulsions, fever, excessive phlegm and cough | “Zhong Yao Cheng Fang Zhi Ji”, vol. 6 ⁴ |
| Li Yan Ling Pills | Bombyx Batryticatus, Manis Squama, Eupolyphaga Stelephaga, Ostreae Concha, Scrophulariae Radix | Activating blood circulation and relaxing tendons, relieving sore throat and pain. | “Zhong Yao Cheng Fang Zhi Ji”, vol. 8 ⁴ |
| Li Yan Jie Du Granule | Bombyx Batryticatus, Isatidis Radix, Lonicerae Japonicae Flos, Forsythiae Fructus, Menthae Haplocalycis Herba, Arctii Fructus, Cretagii Fructus, Platycodon Radix, Isatidis Folium, Scrophulariae Radix, Scutellariae Radix, Rehmanniae Radix, Trichosanthis Radix, Rhei Radix et Rhizoma, Fritillariae Thunbergii Bulbus, Ophiopogonis Radix | Relieving sore throat and clearing heat, curing amygdalitis, pharyngitis and mumps | “Chinese Pharmacopoeia (2015)”, vol. 1 ⁴ |
| Jia Wei She Dan Chen Pi Pills | Bombyx Batryticatus, Fel Serpentis Siccum, Citri Reticulatae Pericarpium, Pheretima, Cinnabaris, Succinum | Dispelling wind, eliminating sputum and relieving convulsion, treating fever, cough and psychosis | “Zhong Yao Cheng Fang Zhi Ji”, vol. 15 ⁴ |
| Yi Xian Pills | Bombyx Batryticatus, Typhoni Rhizoma, Pinelliae Rhizoma, Scolopendra, Alumen, Cinnabaris | Dispelling wind, eliminating sputum and relieving convulsion, curing epilepsy | “Chinese Pharmacopoeia (2015)”, vol. 1 ⁴ |
| Qian Jin Powder | Bombyx Batryticatus, Scorpio, Bovis Calculus Artifactus, Cinnabaris, Borneolum Syntheticum, Coptidis Rhizoma, Arisaema Cum Bile, Gastrodiae Rhizoma, Glycyrrhizae Radix Et Rhizoma | Clearing heat and relieving convulsion, treating fever and twitch of child | “Zhong Yao Cheng Fang Zhi Ji”, vol. 9 ⁴ |
| Fu Fang Qian Zheng Gao | Bombyx Batryticatus, Typhoni Rhizoma, Pheretima, Scorpio, Chuanxiong Rhizoma, Angelicae Dahuricae Radix, Angelicae Siniensis Radix, Paonieae Radix Rubra, Sapochnikoviae Radix, Zingiberis Rhizoma Recens, Camphor, Borneolum Syntheticum, Menthol, Thymol | Dispelling wind, activating blood, relaxing tendons and curing apoplexy | “Chinese Pharmacopoeia (2015)”, vol. 1 ⁴ |
| Tai Ji Sheng Jiang Pills | Bombyx Batryticatus, Cicadae Periostracum, Curcumae Longae Rhizoma, Rhei Radix et Rhizoma, Borneolum Syntheticum, Arisaema Cum Bile, | Dispelling wind, clearing heat, eliminating sputum and relieving convulsion, curing fever, twitch, heat phlegm and constipation | “Zhong Yao Cheng Fang Zhi Ji”, vol. 2 ⁴ |
| Wa Wu Ning | Bombyx Batryticatus, Atractylodis Macrocephalae Rhizoma, Bambusae Concretio Silicea, Uncariae Ramulus Cum Uncis, Glycyrrhizae Radix et Rhizoma, Menthae Haplocalycis Herba, Cinnabaris, Codonopsis Radix, Succinum | Treating cold, fever, spasm, vomiting | “Zhong Yao Cheng Fang Zhi Ji”, vol. 2 ⁴ |
| Preparation Name       | Main Compositions                                                                                       | Traditional and Clinical Uses                                                                 | References                        |
|------------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------|
| Niou Huang Xiao Er Powder | Bombyx Batrytacatus, Uncariae Ramulus Cum Uncis, Gastrodiae Rhizoma, Scorpio, Picrorrhizae Rhizoma, Rhei Radix Et Rhizoma, Arisaema Cum Bile, Fritillariae Thunbergii Bulbus, Bambusae Concretio Silicea, Pinelliae Rhizoma, Citri Exocarpium Rubrum, Talcum, Bovis Calculus Artificatus, Cinnabaris, Moschus Artificatus, Borneolum Syntheticum | Clearing heat, relieving convulsion, eliminating sputum, and dispelling wind, curing cough with sputum and abdominal pain of child | “Zhong Yao Cheng Fang Zhi Ji”, vol. 4 |
| Xiao Er Jing Feng Powder | Bombyx Batrytacatus, Scorpio, Realgar, Cinnabaris, Glycyrrhizae Radix Et Rhizoma                        | Relieving convulsion, dispelling wind and treating spasm and coma of child                      | “Chinese Pharmacopoeia (2015)”, vol. 1 |
| Xiao Er Liang You Powder | Bombyx Batrytacatus, Menthae Haplocalyces Herba, Gastrodiae Rhizoma, Uncariae Ram, Las Cum Uncis, Scorpio, Cicadae Periostracum, Bambusae Concretio Silicea, Cinnabaris, Bovis Calculus, Realgar, Succinum | Relieving convulsion, dispelling wind and eliminating sputum, curing infantile convulsions and cough with sputum. | “Zhong Yao Cheng Fang Zhi Ji”, vol. 2 |
| Jing Feng Pills        | Bombyx Batrytacatus, Gastrodiae Rhizoma, Atractodis Rhizoma, Rhei Radix Et Rhizoma, Angelicae Dahuricae Radix, Realgar, Arisaema Cum Bile, Bambusae Concretio Silicea, Bufonis Venenum, Asari Radix et Rhizoma, Scorpio, Cinnabaris | Clearing heat, relieving convulsion and eliminating sputum, treating convulsions, spasm and cough with sputum of child | “Zhong Yao Cheng Fang Zhi Ji”, vol. 4 |
| Niou Huang Qian Jin Powder | Bombyx Batrytacatus, Scorpion, Bovis Calculus, Cinnabaris, Borneolum Syntheticum, Coptidis Rhizoma, Arisaema Cum Bile, Gastrodiae Rhizoma, Glycyrrhizae Radix Et Rhizoma | Clearing heat and relieving convulsion, curing convulsions, high fever, spasm and cough with sputum of child | “Chinese Pharmacopoeia (2015)”, vol. 1 |
| Niou Huang Xiao Er Powder | Bombyx Batrytacatus, Arisaema Cum Bile, Pherekitma, Uncariae Ramulus Cum Uncis, Aquilariae Lignum Resinatum, Houttuyniae Herba, Bovis Calculus, Borneolum Syntheticum, Margaritiera | Clearing heat, relieving convulsion, dispelling wind and eliminating sputum                      | “Zhong Yao Cheng Fang Zhi Ji”, vol. 4 |
| Niou Huang Bao Long Pills | Bombyx Batrytacatus, Bevis Calculus, Arisaema Cum Bile, Bambusae Concretio Silicea, Portia, Succinum, Moschus Artificatus, Scorpio, Realgar, Cinnabaris | Clearing heat, relieving convulsion, dispelling wind and eliminating sputum                      | “Chinese Pharmacopoeia (2015)”, vol. 1 |
| Dian Xian Kang Capsules | Bombyx Batrytacatus, Gastrodiae Rhizoma, Acorii Tatarinowii Rhizoma, Arisaema Cum Bile, Fritillariae Cirrhosae Bulbus, Salviae Miltiorrhizae, Radix et Rhizoma, Polysiatae Radix, Scorpio, Ophiopogonis Radix, Lophatheri Herba, Zingiberis Rhizoma Recens, Succinum, Ginseng Radix et Rhizoma, Bovis Calculus Artificatus | Relieving convulsion, dispelling wind, and dissipating sputum for resuscitation, treating epilepsy, spasm and vomiting | “Chinese Pharmacopoeia (2015)”, vol. 1 |
| Shu Mian Tablets (Capsules) | Bombyx Batrytacatus, Ziziphi Spinosae Semen, Albiziae Cortex, Bupleuri Radix, Paonieae Radix Alba, Cicadae Periostracum, Albiziae Flos, Junci Medulla | Soothing the liver and calming the heart and tranquillizing the mind, curing insomnia and dizziness | “Xin Yao Zhuan Zheng Biao Zhen”, vol. 81 (33) |
| Jin Sang Qing Yin Pills | Bombyx Batrytacatus, Scrophulariae Radix, Rehmanniae Radix, Ophiopogonis Radix, Scutellariae Radix, Moutan Cortex, Paonieae Radix Rubra, Fritillariae Cirrhosae Bulbus, Alismatis Rhizoma, Coicos Semen, Dendrobii Caulis, Menthae Haplocalyces Herba, Sterculiae Lyciophorae Semen, Cicadae Periostracum, Orosyli Semen, Glycyrrhizae Radix et Rhizoma | Soothing the liver and calming the heart and tranquillizing the mind, curing insomnia          | “Zhong Yao Cheng Fang Zhi Ji”, vol. 18 |
| Jin Su Dan             | Bombyx Batrytacatus, Arisaema Cum Bile, Scorpio, Aconiti Coriani Radix, Haematitum, Moschus, Gastrodiae Rhizoma, Borneolum Syntheticum, Olibanum | Dispelling wind and dissipating sputum, and relieving convulsion, treating spasms of child      | “Zhong Yao Cheng Fang Zhi Ji”, vol. 6 |
| She Xiang Kang Shuang Capsules | Bombyx Batrytacatus, Moschus Artificatus, Saigae Tataricas Corum, Scorpio, Zaoxys, Himudo, Chuanxiong Rhizoma, Gastrodiae Rhizoma, Rhei Radix Et Rhizoma, Carthami Flos, Arisaema Cum Bile, Spatholobi Caulis, Paonieae Radix Rubra, Puerariae Thornei Radix, Rehmanniae Radix, Asimigali Radix, Lonicerae Japonicae Caulis, Angelicae Sinensis Radix, Trachospermum Caulis Et Foliwm, Pherekitma, Siegesbeckiae Herba | Promoting blood circulation to remove meridian obstruction, treating apoplexy               | “Chinese Pharmacopoeia (2015)”, vol. 1 |
| Preparation Name | Main Compositions | Traditional and Clinical Uses                                                                 | References |
|------------------|-------------------|------------------------------------------------------------------------------------------------|------------|
| **Ling Zhu Powder** | Bombyx Batryticatus, Saigae Tataricae Cornu, Shiunongxingzhengzhufen, Bovis Calculus, Cinnabaris, Succinum, Arisaema Cum Bile, Borneolum Syntheticum, Acori Tatarinowii Rhizoma Oil | Clearing heat, and relieving convulsion, curing fever, cough with sputum | “Zhong Yao Cheng Fang Zhi Ji”, vol. 5^c |
| **Dian Xian Ping Tablets** | Bombyx Batryticatus, Acori Tatarinowii Rhizoma, Scorpio, Scolopendra, Gypsum Fibrosum, Paonae Radix Alba, Magnesium, Ostrue Concha, Gleditisiae Fructus Abnormalis, Bupureli Radix | Dissipating sputum to induce resuscitation, clearing heat and relieving convulsion, treating epilepsy | “Guo Jia Zhong Cheng Yao Biao Zhun” vol. of Brain Meridian Limb b |
| **Xiao Er Qing Re Zhen Jing Powder** | Bombyx Batryticatus, Coptidis Rhizoma, Arisaema Cum Bile, Bambusae Concreto Silicea, Scorpio, Glycyrrhizae Radix et Rhizoma, Bovis Calculus, Cinnabaris, Borneolum Syntheticum | Clearing heat, and relieving convulsion, curing convulsion, spasms and cough with sputum of child | “Zhong Yao Cheng Fang Zhi Ji”, vol. 4^c |
| **Xiao Er Hua Tang Pills** | Bombyx Batryticatus, Bambusae Concreto Silicea, Trichosanthis Radix, Fritillariae Cirrhosa Bulbus, Arisaematis Rhizoma Preparatum, Gastrodiae Rhizoma, Menthae Haplocalycis Herba, Platycodonis Radix, Pinelliae Rhizoma, Acori Tatarinowii Rhizoma, Citri Reticulate Pericarpium, Cinnabaris | Dispelling wind and dissipating sputum, treating cold, cough with sputum and fever of child | “Zhong Yao Cheng Fang Zhi Ji”, vol. 15^c |
| **Ding Chu Hua Feng Pills** | Bombyx Batryticatus, Scorpio, Cicadae Periostracum, Saposnokiviae Radix, Notopertygii Rhizoma Et Radix, Ephedrae Herba, Platycodonis Radix, Pinelliae Rhizoma, Coptidis Rhizoma, Rhei Radix Et Rhizoma, Glycyrrhizae Radix et Rhizoma, Bovis Calculus Artificialis, Cinnabaris, Moschus, Borneolum Syntheticum | Clearing heat, relieving convulsion, dispelling wind and dissipating sputum, curing convulsion, excessive phlegm and spasm of child | “Zhong Yao Cheng Fang Zhi Ji”, vol. 1^c |
| **Wu she chan yi decoction** | Bombyx Batryticatus, Zaocys, Cicadae Periostracum, Vespaee Nidus, Scandentis Hebra, Dictamni Cortex | Treating acute or chronic eczema | [15] |
| **Bombyx Batryticas, Ephedrae Herba, Armeniacae Semen Amarum, Zingiberis Rhizoma, Spirodelae Herba, Dictamni Cortex, Moutan Cortex, Citri Reticulate Pericarpium, Paeniae Radix Rubra, Glycyrrhizae Radix et Rhizoma** | Treating urticaria | [16] |
| **Shu feng huo xue decoction** | Bombyx Batryticatus, Rehmanniae Radix, Kochiae Fructus, Dictamni Cortex, Angelicae Sinensis Radix, Cicadae Periostracum, Xanthii Fructus, Polygoni Multiflori Radix, Praeparata, Loniceras Japonicae Flos | Treating papular pruritus | [17] |
| **Xiao feng powder** | Bombyx Batryticatus, Sophorae Flavescentis Radix, Dictamni Cortex, Rehmanniae Radix, Schizophorogete Herba, Saposnokiviae Radix, Cicadae Periostracum, Atractylodis Rhizoma, Smilacis Glabrae Rhizoma, Clematis Armandii Caulis, Angelicae Sinensis Radix | Curing urticaria | [18] |
| **Sheng jiang powder** | Bombyx Batryticatus, Cicadae Periostracum, Curcumae Longae Rhizoma, Rhei Radix et Rhizoma | Treating urticarial and pruritus | [19] |
| **Bombyx Batryticatus, Rhei Radix et Rhizoma, Cicadae Periostracum, Lyciae Cortex** | Treating diabetes and pruritus | [20] |
| **Wu she san chong decoction** | Bombyx Batryticatus, Zaocys, Scorpio, Scolopendra, Spargani Rhizoma, Curcumae Rhizoma, Manis Squama, Cocis Semen, Smilacis Glabrae Rhizoma, Saposnokiviae Radix, Bupleuri Radix, Tribuli Fructus, Astragali Radix, Rehmanniae Radix, Glycyrrhizae Radix Et Rhizoma | Curing prurigo nodularis | [21] |
| **Jiang can formula** | Bombyx Batryticatus, Viulae Herba, Taraxaci Herba, Lonicerae Japonicae Flos, Astmgi Radix, Paeniae Radix Rubra, | Treating pediatric multiple furuncles | [22] |
| Preparation Name | Main Compositions | Traditional and Clinical Uses | References |
|------------------|-------------------|-------------------------------|------------|
| Xiao ban decoction | Bombyx Batryticatus, Angelicae Dahuricae Radix, Angelicae Sinensis Radix, Chuanxiong Rhizoma, Moutan Cortex, Carthami Flos, Bupleuri Radix, Atractylodis Macrocephalae Rhizoma, Poria, Rehmanniae Radix, Rehmanniae Radix Praeparata, Dioscoreae Rhizoma, Epimedi Foli, Crataegi Fructus, Glycyrrhizae Radix Et Rhizoma | Treating pediatric multiple furuncle | [23] |
| Xiao ban plaster | Bombyx Batryticatus, Angelicae Dahuricae Radix, Atractylodis, Macrocephalae Rhizoma, Kaempferia Galanga, Carthami Flos, Margarita | Treating chloasma | [23] |
| Decoction 1 | Bombyx Batryticatus, Cnnumomi Mmulus, Paeoniae Radix Alba, Cicadae Periostracum, Astmgali Radix, Atractylodis Macrocephalae Rhizoma, Saposhnikoviae Radix, Glycyrrhizae Radix et Rhizoma, Zangiberi Rhizoma Recens, Jujubae Fructus | Treating rhinallergosis | [24] |
| Decoction 2 | Bombyx Batryticatus, Notoginseng Radix et Rhizoma, Arctii Fructus | Treating verruca plana | [25] |
| Decoction 3 | Bombyx Batryticatus, Cicadae Periostracum, Treating intractable albuminuria and nephropathy | [26,27] |
| Decoction 4 | Bombyx Batryticatus, Lonicerae Japonicae Caulis, Bupleuri Radix, Fritillariae Thunbergii Bulbus, Meretricis Concha, Cyclinae Concha, Cicadae Periostracum, Scorpio, Phereutima, Hirudo, Coicis Semen, Bambusae Caulis In Taenias, Sargassum, Scrophulariae Radix, Paeoniae Radix Rubra, Glycyrrhizae Radix et Rhizoma, Cyathulae Radix, Chaenomelis Fructus, Gypsum Fibrosum, Lycii Cortex | Treating leg pain of the old | [28] |
| Decoction 5 | Bombyx Batryticatus, Lonicerae Japonicae Caulis, Paeoniae Radix Alba, Glycyrrhizae Radix et Rhizoma, Scorpio, Phereutima, Scolopendra, Cicadae Periostracum, Chaenomelis Fructus | Curing trigeminal neuralgia | [28] |
| Decoction 6 | Bombyx Batryticatus, Siphonostegiae Herba, Sparrniasae Tuberculatae Herba, Glechoma Herba, Artemisiae Argyi Folium, Croci Stigma | Treating localized sclerderma | [28] |
| Decoction 7 | Bombyx Batryticatus, Astmgali Radix, Atractylodis Rhizoma, Atractylodis, Macrocephalae Radizoma, Poria, Paeoniae Radix Rubra, Spatholob Caulis, Scolopendra, Cicadae Periostracum, Chaenomelis Fructus, Glycerizae Radix et Rhizoma Praeparata Cum Melle | Treating dermatomyositis | [28] |
| Decoction 8 | Bombyx Batryticatus, Spatholob Caulis, Violae Herba, Rhei Radix et Rhizoma, Angelicae Sinensis Radix, Bupleuri Radix, Paeoniae Radix Alba, Auranti Fructus Immaturus, Cicadae Periostracum, Scolopendra, Coicis Semen, Coganargiope, Glycyrrhizae Radix et Rhizoma | Curing chronic appendicitis | [28] |
| Tian jiang ge gou decoction | Bombyx Batryticatus, Gastrodiae Rhizoma, Puerariae Lobamle Radix, Uncariae Ramulus Cum Uncis, Poria, Pinelliae Rhizoma Praeparatum, Glycyrrhizae Radix et Rhizoma | Relieving convulsion, dispelling wind and treating tremor syndrome | [29] |
| Chu bi decoction | Bombyx Batryticatus, Scorpio, Schizonepetae Herba, Saposhnikoviae Radix, Notopterygi Rhizoma Et Radix, Angelicae Pubescentis Radix, Glycyrrhizae Radix et Rhizoma | Treating arthromyodynia | [29] |
Table 1. Cont.

| Preparation Name          | Main Compositions                                                                 | Traditional and Clinical Uses                                      | References |
|---------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------|------------|
| Xiao yin decoction        | Bombyx Batryticatus, Sargassum, Laminariae Thallus Eckloniae Thallus, Prunellae   | Treating goiter                                                    | [29]       |
|                           | Spica, Bambusa Caulis In Taenias, Pinelliae Rhizoma, Sepiae Endoconcha, Glycyrrhizae Radix Et Rhizoma |                                                                     |            |
| Xiao yong decoction       | Bombyx Batryticatus, Violae Herba, Taraxaci Herba, Forsythiae Fructus, Chrysanthemi Flos, | Curing multiple furuncle                                          | [29]       |
|                           | Morii Folium, Paeoniae Radix Rubra, Scutellariae Radix, Glycyrrhizae Radix et Rhizoma |                                                                     |            |
| Cai ge jie ji jia wei decoction | Bombyx Batryticatus, Bupleuri Radix, Puerariae Lobamle Radix, Angelicae Dahuricae Radix, Gypsum Fibrosum, Notopterygi Rhizoma et Radix, Scutellariae Radix, Platycodonis Radix, Cicadae Periostracum, Rhei Radix Et Rhizoma, Isatidis Folium, Magnoliae Officinalis Cortex | Dispelling wind and clearing heat and treating fever and cold    | [30]       |
| Wen dan jia wei decoction | Bombyx Batryticatus, Bambusa Caulis In Taenias, Pinelliae Rhizoma Ptaeparatum, Cum Alumine, Arisaema Cum Bile, Scutellariae Radix, Ginkgo Folium, Prunellae Spica, Sargassum, Chuanxiong Rhizoma, Ostreae Concha, Alismatis Rhizoma, Fritillariae Thunbergii Bulbus, Cyathulae Radix, Bambusaec Concreto Silicea | Treating hypertension                                             | [31]       |

a Cited from “Chinese Pharmacopoeia”; b Cited from “Guo Jia Zhong Cheng Yao Biao Zhun”; c Cited from “Zhong Yao Cheng Fang Zhi Ji”; d Cited from “Xin Yao Zhuan Zheng Biao Zhun”.

3. Origin

*B. batryticatus* (Figure 1), derived from silkworm spontaneously infected by *Beauveria bassiana*, is the by-product of sericulture, which was described in “*Sheng Nong’s herbal classic*” (Han Dynasty), “*Xin Xiu Ben Cao*” (Tang Dynasty), “*Zheng Lei Ben Cao*” (Song dynasty), “*Tang Ye Ben Cao*” (Yuan dynasty) and “*Ben Cao Pin Hui Jing Yao*” (Ming dynasty). Dictionary of Chinese Pharmacy by Chen (2010) revealed the formation of *B. batryticatus* that before silkworm became moth, it was infected by *Beauveria bassiana* and eventually died [32]. In addition, the lethal mechanism is that when spore of *Beauveria bassiana* infected silkworm, it can secrete chitinase, then dissolve the epidermis and body wall of silkworm and invade into its body, continuously reproduce and eventually cause the death of silkworm. After silkworm is infected by *Beauveria bassiana*, it becomes stiff and its surface covered with white conidias of *Beauveria bassiana* [33].

![Figure 1](image-url)

**Figure 1.** Silkworms (A); Silkworms infected by *Beauveria bassiana* (B); Bombyx batryticatus (*B. batryticatus*) (C); Stir-fried *B. batryticatus* (D).

With development of prevention technology of silkworm diseases, the source of *B. batryticatus* was significantly deficient. Thus, for meeting the market demands, its artificial breeding techniques, namely artificial inoculation of *Beauveria bassiana*, have received more attention and obtained certain development in recent years [4]. The detailed procedure of artificial breeding of *B. batryticatus* is as follows: *Beauveria bassiana* is mixed with warm water and sprayed on silkworms of 4–5 instars; after inoculation for 15–20 min, silkworms are fed with mulberry leaves, and fed every 5.0–6.0 h until they become stiff and white; finally, stiff silkworms are mixed with lime and dried in a ventilated place. The temperature and humidity of the feeding room should be set at 24.0–26.0 °C and 90.0%, respectively [14].

It was recorded that *B. batryticatus* firstly appeared in Yu county, Henan province in Qin and Han Dynasties [3]. During Tang and Song Dynasties, Henan and Shandong were main producing regions of *B. batryticatus* recorded in “*Ben Cao Tu Jing* and *Zheng Lei Ben Cao*”. Later, during Ming and Qing Dynasties, its main regions moved to south area, such as Jiangsu and Zhejiang, which was recorded in “*Ben Cao Chong Yuan*”. Subsequently, Sichuan and Guangdong became the main producing regions of *B. batryticatus*. Currently, the main regions of *B. batryticatus* bred artificially are Sichuan, Jiangsu,
Zhejiang, Guangdong, Shandong and Guangxi in China, and the quality of B. batryticatus in Sichuan is considered to be the best [34].

4. Chemistry

There are various chemical constituents in B. batryticatus, including protein and peptides, fatty acids, flavonoids, nucleosides, steroids, coumarin, polysaccharide and others. In this section, the major chemical constituents and structures of B. batryticatus are presented (Table 2 and Figure 2).

Figure 2. Cont.
Figure 2. Cont.
Figure 2. Chemical structures of compounds isolated from *B. batryticatus*.

4.1. Proteins and Peptides

As a traditional animal medicine, the main chemical constituents in *B. batryticatus* are proteins. It is reported that the content of proteins in *B. batryticatus* varies in the range within 43.9–74.3% [45,55]. Currently, some research on peptides in *B. batryticatus* have been reported. BB octapeptide is a novel platelet aggregation inhibitory peptide isolated from *B. batryticatus*, and its molecular mass and the

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**Figure 2.** Chemical structures of compounds isolated from *B. batryticatus*. 

- **29**: Ergost-6,22-dien-3β,5α,8α-triol
- **30**: Daucosterol
- **31**: β-sitosterol
- **32**: 6,9-epoxyergosta-7,22-dien-3-ol
- **33**: 6-methoxy-7-O-β-D-(4′-methoxy)-glucopyranosyl coumarin
- **34**: Nicotinamide
- **35**: D-mannitol
- **36**: Ammonium oxalate
- **37**: Aurantiamide
- **38**: (+)-pinoresinol
- **39**: Butyl-2-pyrrolidone-5-carboxylate
- **40**: Isololiolid
- **41**: (+)-mediresinol
- **42**: Methyl 4-hydroxyphenylacetate
### Table 2. Chemical constituents isolated from *B. batryticatus*.

| Classification       | Chemical Component | Molecular Formula | Characteristic Signals or IUPAC Name | References |
|----------------------|--------------------|-------------------|-------------------------------------|------------|
| Peptide              |                    |                   |                                     |            |
| BB octapeptide       |                    |                   | The molecular mass is 885.0 Da, and the amino acid sequence is Asp-Pro-Asp-Ala-Asp-Ile-Leu-Gln | [35]       |
| Beuvericin (1)       |                    | C_{10}H_{16}O_{2}N_{2} | (S,4R,9S,12R,15S,18S)-3,9,15-Trisubstituted-6,12,18-trisopropyl-1,10,16-trimethyl-1,7,13-trixia-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexone | [36–38]    |
| Cyclo(D)-Pro-(D)-Val |                    | C_{10}H_{16}O_{2}N_{2} |                                     | [39]       |
| Cyclo(S)-Pro-(R)-Leu |                    | C_{10}H_{16}O_{2}N_{2} |                                     | [39]       |
| Cyclo(D)-Pro-(D)-Ile |                    | C_{10}H_{16}O_{2}N_{2} |                                     | [39]       |
| Cyclo(D)-Pro-(D)-Phe |                    | C_{10}H_{16}O_{2}N_{2} |                                     | [39]       |
| Cyclo-(Ala-Pro)      |                    | C_{10}H_{16}O_{2}N_{2} |                                     | [36]       |
| ACIBB                |                    |                   |                                     | [40]       |
| Enzymolysis polypeptides by pepsin |                    |                   | The molecular mass were 500.0–1000.0 Da, and the number of amino acid was less than 10 | [41]       |
| Homoarginine (2)     |                    | C_{16}H_{32}O_{2}N_{2} | N^6-Carboxyimido-l-lysine | [42]       |
| Meso-erythritol (3)  |                    | C_{6}H_{12}O_{3} | 1,2,3,4-Butanetetrol | [43]       |
| Citric acid (4)      |                    | C_{6}H_{8}O_{7} | Acide citrique | [44]       |
| Decanoic acid (5)    |                    | C_{10}H_{20}O_{2} | Decanoic acid | [45]       |
| Stearic acid (6)     |                    | C_{14}H_{28}O_{2} | Octadecanoic acid | [45]       |
| Palmitic acid (7)    |                    | C_{16}H_{32}O_{2} | Hexadecanoic acid | [43]       |
| (4E,25,3R)-2-N-octadecanoyl-4-tetradecasphinganine (8) | C_{32}H_{60}NO_{3} | N-(25,3R,4E)-1,3-Dihydroxy-4-tetradecen-2-yloanodiamide | [46]       |
| (4E,6,25,3R)-2-N-eicosanoyl-6,6-tetradecasphingadienine (9) | C_{34}H_{60}NO_{3} | N-(25,3R,6E,6)-1,3-Dihydroxy-6,6-tetradecadien-2-yloanosamide | [46]       |
| (4F,25,3R)-2-N-eicosanoyl-4-tetradecasphingamine (10) | C_{34}H_{60}NO_{3} | N-(25,3R,4F,6E)-1,3-Dihydroxy-4-tetradecen-2-yloanosamide | [46]       |
| (4F,6,25,3R)-2-N-docosanoyl-4,6-tetradecasphingadienine (11) | C_{36}H_{60}NO_{3} | N-(25,3R,4F,6E)-1,3-Dihydroxy-4,6-tetradecadien-2-yloanosamide | [46]       |
| 1,2-di-O-hexadecanoyl-sn-glycero-3-phosphorylcholin (12) | C_{40}H_{68}NO_{3}P | 1,2-di-O-hexadecanoyl-sn-glycero-3-phosphorylcholin | [47]       |
| 1-O-(9Z-octadecenoyl)-2-O-(8Z,11Z-octadecadienoyl)-sn-glycero-3-phosphorylcholin (13) | C_{40}H_{72}NO_{3}P | 1-O-(9Z-octadecenoyl)-2-O-(8Z,11Z-octadecadienoyl)-sn-glycero-3-phosphorylcholin | [47]       |
| 1,2-di-O-9Z-octadecenoyl-sn-glycero-3-phosphorylcholin (14) | C_{41}H_{74}NO_{3}P | 1,2-di-O-9Z-octadecenoyl-sn-glycero-3-phosphorylcholin | [47]       |
| Flavonoids           |                    |                   |                                     |            |
| Quercetin (15)       |                    | C_{15}H_{10}O_{7} | 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one | [36,48]    |
| Kaempferol (16)      |                    | C_{15}H_{12}O_{6} | 3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one | [36,48]    |
| Quercetin-7-O-β-D-4-O-methylglucopyranoside (17) | C_{22}H_{20}O_{12} |  — |  | [2,36] |
| Kaempferol-7-O-β-D-4-O-methylglucopyranoside (18) | C_{22}H_{20}O_{12} |  — |  | [2,36] |
| Nucleosides          |                    |                   |                                     |            |
| Uracil (19)          |                    | C_{4}H_{4}N_{2}O_{2} | 2,4(1H,3H)-Pyrimidinedione | [43,49]    |
| Uridine (20)         |                    | C_{5}H_{4}N_{2}O_{6} | 4-Hydroxy-1-(β-D-ribofuranosyl)-2(1H)-pyrimidinone | [49]       |
| Hypoxanthine (21)    |                    | C_{5}H_{4}N_{2}O | 3,9-Dihydro-6H-purin-6-one | [49]       |
| Xanthine (22)        |                    | C_{5}H_{4}N_{2}O_{2} | Xanthine | [49]       |
| Cytidine (23)        |                    | C_{5}H_{4}N_{2}O_{3} | 4-Imino-1-(β-D-ribofuranosyl)-1,4-dihydro-2-pyrimidinol | [47]       |
| Adenine (24)         |                    | C_{5}H_{5}N_{5} | 1H-Purin-6-amine | [47]       |
Table 2. Cont.

| Classification | Chemical Component | Molecular Formula | Characteristic Signals or IUPAC Name | References |
|----------------|-------------------|------------------|-------------------------------------|------------|
| Steroids       | 5α,6α-Epoxy-(22E,24R)-ergosta-8(14),22-diene-3β,7α-diol | C₂₇H₄₄O₃ | —                                 | [50]       |
|                | 7α-Methoxy-(22E,24R)-5α,6α-epoxyergosta-8(14),22-diene-3β-ol | C₂₀H₄₆O₃ | 7α-Methoxy-(22E,24R)-5α,6α-epoxyergosta-8(14),22-diene-3β-ol | [50]       |
|                | (22E,24R)-Ergosta-5,7,22-Trien-3β-ol | C₂₀H₄₄O₂ | (22E,24R)-Ergosta-5,7,22-Trien-3β-ol | [50]       |
|                | Stigmasta-7,22-diene-3β,5α,6α-triol (28) | C₂₀H₄₆O₃ | Stigmasta-7,22-diene-3β,5α,6α-triol | [50]       |
|                | Ergost-6,22-dien-3β,5α,6α-triol (29) | C₂₀H₄₆O₂ | Ergost-6,22-dien-3β,5α,6α-triol | [43]       |
|                | Dauosterol (30) | C₂₀H₄₆O₂ | (3β)-Stigmast-5-en-3-yl-β-D-glucopyranoside | [37,43]    |
|                | β-Sitosterol (31) | C₂₀H₄₆O₂ | (3β)-Stigmast-5-en-3-ol | [37,42]    |
|                | 6,9-Epoxyergosta-7,22-dien-3-ol (32) | C₂₀H₄₆O₂ | (22E)-6,9-Epoxyergosta-7,22-dien-3-ol | [37]       |
| Oligosaccharides | BBPW-2 | — | Consisting of β-D-(1 → 2,6)-glucopyranose and β-D-(1 → 2,6)-mannosyl units serving as the backbone, α-D-(1 → 2)-galactopyranose and α-D-(1 → 3)-mannosyl units as branches, and α-D-Manp and β-D-Glcp as terminals | [52]       |
| Other compounds | Nicotinamide (34) | C₆H₁₀N₂O | 6-Aminonicotinamide | [47]       |
|                | D-Mannitol (35) | C₆H₁₂O₅ | d-Mannitol | [43]       |
|                | Ammonium oxalate (36) | C₆H₁₂O₄ | Diammonium oxalate | [53,54]    |
|                | Aurantiamide (37) | C₂₂H₂₆N₂O₄ | Na-Benzoyl-N-{[(2S,1-hydroxy-3-phenyl-2-propanyl)-l-phenylalaninamide | [39]       |
|                | (+)-Pinoresinol (38) | C₂₁H₂₂O₄ | 4,4′-[15,3αR,4,5,6αR]-Tetrahydro-1H,3H-furo[3,4-c]furan-1,4-diyl bis(2-methoxyphenol) | [39]       |
|                | Butyl-2-pyrrolidin-5-carboxylate (39) | C₁₄H₁₇NO₃ | butyl 5-oxo-pyrrolidine-2-carboxylate | [39]       |
|                | Isololiolide (40) | C₁₁H₁₆O₃ | (6S,5aS)-6-hydroxy-4,4,7a-trimethyl-6,7-dihydro-4H-1-benzofuran-2-one | [39]       |
|                | (+)-Medioresinol (41) | C₂₁H₂₃O₇ | 4-[15,3αR,4,5,6αR]-4-(4-Hydroxy-3-methoxyphenyl) tetrahydro-1H,3H-furo[3,4-c][furan-1-yl]-2,6-dimethoxyphenol | [39]       |
|                | Methyl 4-hydroxyphenylacetate (42) | C₆H₁₀O₃ | Methyl(4-hydroxyphenyl)acetate | [39]       |

4.1. Proteins and Peptides

As a traditional animal medicine, the main chemical constituents in *B. batryticatus* are proteins. It is reported that the content of proteins in *B. batryticatus* varies in the range within 43.9–74.3% [45,55]. Currently, some research on peptides in *B. batryticatus* have been reported. BB octapeptide is a novel platelet aggregation inhibitory peptide isolated from *B. batryticatus*, and its molecular mass and the amino acid sequence are 885.0 Da and Asp-Pro-Asp-Ala-Asp-Ile-Leu-Gln, respectively [35]. Beauvericin (1), a cyclic three carbohydrate peptide, was identified from *B. batryticatus* [36–38]. Cyclo(D)-Pro-(D)-Val, Cyclo(S)-Pro-(R)-Leu, Cyclo(D)-Pro-(D)-Ile, Cyclo(D)-Pro-(D)-Phe and Cyclo-(Ala-Pro), belonging to dipeptide, were also isolated from *B. batryticatus* [36,39]. In 2004, ACIBB were isolated from *B. batryticatus*, whose molecular mass is 1200.0 Da, and it consisted of 7 kinds of amino acids [40]. Later, homoarginine (2) was identified from *B. batryticatus* by Cheng et al. [2013a] [41]. Finally, enzymolysis
polypeptides by pepsin is studied by Li et al. (2017), and the molecular mass and amino acid number of enzymolysis polypeptide were about 500.0–1000.0 Da and less than 10, respectively [42].

4.2. Fatty Acids

Some studies have been carried out to investigate the fatty acids and their derivatives in *B. batryticatus*. Five fatty acids were isolated from *B. batryticatus*: meso-erythritol (3), citric acid (4), decanoic acid (5), stearic acid (6) and palmitic acid (7) [43–45]. Seven derivatives of fatty acids in *B. batryticatus* were identified: (4E,2S,3R)-2-N-octadecanoyl-4-tetradeascaphingineine (8), (4E,6E,2S,3R)-2-N-eicosanoyl-4,6-tetradeascaphingadiene (9), (4E,2S,3R)-2-N-docosanoyl-4,6-tetradeascaphingadiene (10), (4E,6E,2S,3R)-2-N-docosanoyl-4-tetradeascaphingenine (11), 1,2-di-O-hexadecanoyl-sn-glycero-3-phosphorylcholin (12), 1-O-(9Z-octadecenoyl)-2-O-(8Z,11Z-octadecadienoyl)-sn-glycero-3-phosphorylcholin (13) and 1,2-di-O-9Z-octadecenoyl-sn-glycero-3-phosphorylcholin (14) [46,47].

4.3. Flavonoids

Flavonoids are common constituents of numerous Chinese medicinal materials. To date, only four flavonoids from *B. batryticatus* have been reported. In 2009, quercetin (15) and kaempferol (16) were detected in RP-HPLC method and the contents were 0.2 and 0.6 mg/g, respectively [48]. Later, quercetin-7-β-D-4-O-methylglucopyranoside (17) and kaempferol-7-β-D-4-O-methylglucopyranoside (18) were isolated from *B. batryticatus* [2,36].

4.4. Nucleosides

In 1996, four nucleotides were detected in *B. batryticatus* by Li et al. (1996) through HPLC method, including uracil (19), uridine (20), hypoxanthine (21) and xanthine (22), and among them, uracil content was highest [47]. Later, in 2003, uracil (19), cytidine (23) and adenine (24) were isolated from *B. batryticatus* by Kwon et al. (2003b) [49].

4.5. Steroids

Currently, researchers have found and identified many steroids in *B. batryticatus*. Up to now, eight steroids have been identified from *B. batryticatus*: 5α,6α-epoxy-(22E,24R)-ergosta-8(14),22-diene-3β,7α-diol (25), 7α-methoxy-(22E,24R)-5α,6α-epoxyergosta-8(14),22-diene-3β-ol (26), (22E,24R)-ergosta-5,7,22-trien-3β-ol (27), stigmasta-7,22-diene-3β,5α,6α-triol (28), ergost-6,22-dien-3β,5α,8α-triol (29), daucosterol (30), β-sitosterol (31) and 6,9-epoxyergosta-7,22-dien-3-ol (32) [37,43,50].

4.6. Coumarin

Limited investigations have been carried out to study the coumarin in *B. batryticatus*. To date, only one coumarin was isolated from *B. batryticatus*: 6-methoxy-7-O-β-D-(4′-methoxy)-glucopyranosyl coumarin (33) [51].

4.7. Polysaccharide

One study of Ying et al. (2015) showed that polysaccharide yield of *B. batryticatus* was about 4.4% and it possessed good antioxidant activity [56]. In addition, BBPW-2 was isolated from *B. batryticatus* and its characteristic was analyzed by Jiang et al. (2014). The results demonstrated that BBPW-2 consisted of β-D-(1 → 2,6)-glucopyranose and β-D-(1 → 2,6)-mannosyl units serving as the backbone, α-D-(1 → 2)-galactopyranose and α-D-(1 → 3)-mannosyl units as branches, and α-D-Manp and β-D-Glc as terminals [52].
4.8. Trace Elements

18 trace elements have been found in *B. batryticatus*, including Al, Fe, Ca, Mg, P, B, Ba, Cu, Cr, La, Mn, Ni, Pb, Sr, Ti, U, Y and Zn. Among them, the contents of Al, Fe, Zn, La and Mn were relatively high [57].

4.9. Other Compounds

In addition to the compounds above, some other compounds are also isolated from *B. batryticatus*. In 2003, nicotinamide (34) was reported to be isolated from *B. batryticatus* [47]. Then, D-mannitol (35) was identified from *B. batryticatus* by Yin et al. (2004a) [43]. Furthermore, it is reported that ammonium oxalate (36) was isolated from *B. batryticatus*. [53,54]. Later, in 2015, the following compounds were also found and identified from *B. batryticatus*: aurantiamide (37), (+)-pinoresinol (38), butyl-2-pyrrolidone-5-carboxylate (39), isololiolide (40), (+)-medioresinol (41) and methyl 4-hydroxyphenylacetate (42) were isolated from *B. batryticatus* [39].

5. Pharmacology

5.1. Effects on Nervous System

The characteristic pharmacological activity of *B. batryticatus* is the effects on nervous system, including anticonvulsant and antiepileptic effects, hypnotic effects, neurotrophic effects and others. The beauvericin can significantly prolong latent period of nikethamide-induced and isoniazid-induced convulsion in mice (125.0 and 250.0 mg/kg, s.c.) [58,59]. In addition, β-sitosterol and ergost-6,22-dien-3,5,8-triol were demonstrated to obviously prolong latent period of isoniazid-induced convulsion in mice (125.0 mg/kg, s.c.) [59]. Chloroform fraction of ethanol extract of *B. batryticatus* at dose of 20.0 g/kg showed significant effect on nikethamide-induced convulsion in mice [60]. The results obtained by Yao et al. demonstrated that ethanol extracts of *B. batryticatus* possessed significantly antiepileptic effects on epileptic mice induced by maximal electroshock seizure (MES) and metrazol (MET) in dose-dependent and time-dependent manners [61]. Later, another interesting study reported that ammonium oxalate (30.0 and 60.0 mg/kg) also can inhibit epileptic discharge frequency, amplitude, time and pyramidal cell necrosis in hippocampus region of epileptic rats induced by penicillin [62].

In 2003, it was reported that ethanol extracts of *B. batryticatus* had a significant hypnotic effect on mice (25.0 g/kg, p.o. or 12.5 g/kg, s.c.) and rabbits [63]. The extracts (extracted by water and precipitated by ethanol) of *B. batryticatus* (20.0 g/kg, p.o.) were found to exhibit sedation effect on mice through inhibiting its spontaneous activity [64].

In vitro, some compounds (10.0 µM) isolated from *B. batryticatus* were found to exert notable neurotrophic effect by stimulation of NGF (nerve growth factor) synthesis in astrocytes, including (4E,2S,3R)-2-N-octadecanoyl-4-tetradecasphinghenine, (4E,6E,2S,3R)-2-N-eicosanoyl-4, 6-tetradecasphingadienine, (4E,2S,3R)-2-N-eicosanoyl-4-tetradecasphingine, (4E,6E,2S,3R)-2-N-docosanoyl-4,6-tetradecasphingadienine, 1-O-(9Z-octadecenoyl)-2-O-(8Z,11Z-octadecadienoyl)-sn-glycero-3-phosphorylcholine, 1,2-Di-O-hexadecanoyl-sn-glycero-3-phosphorylcholine and 1,2-Di-O-9Z-octadecenoyl-sn-glycero-3-phosphorylcholin [46,47]. Moreover, Bombycis corpus extract (BCE) had a powerful ameliorating effect on neurotoxicity induced by Amyloid-β (Aβ)25–35 in human neuronal cells dose-dependently at the lowest dose of 1.0 µg/mL, and also effectively attenuated the neurotoxic action of NMDA (Nmethyl-D-aspartic acid) [65]. In 2001, another study reported that water extracts of *B. batryticatus* (1.0 × 10⁻⁷–1.0 × 10⁻⁶ g/mL) also had significant protective effect against Aβ(25–35) peptide-induced cytotoxicity dose-dependently via inhibiting lipid peroxidation and protecting antioxidative enzymes [66].
5.2. Anticoagulant Effect

Anticoagulant effect is another characteristic pharmacological activity of *B. batryticatus*. In 2014, it was reported that BB octapeptide, a novel peptide, can inhibit rabbit platelet aggregation induced by collagen and epinephrine in vitro, with the IC$_{50}$ values of 91.1 and 104.5 µM, respectively [35]. In addition, BB octapeptide also significantly prevented paralysis and death in pulmonary thromboembolism model at doses of 10.0, 30.0 and 50.0 mg/kg, and significantly reduced ferric chloride-induced thrombus formation in rats (5.0, 10.0 and 20.0 mg/kg) [35]. One investigation by Wang et al. (1989) revealed that water extracts of *B. batryticatus* (20.0 mg/mL) could inhibit blood coagulation [67]. Zhao et al. (2005) demonstrated that increasing total concentration of ammonium oxalate in water extracts of *B. batryticatus* (33.7–42.3 mg/mL) can prolong TT (thrombase time) [68]. ACIBBB (9.0, 18.0 and 36.0 mg/kg, i.v.), belonging to peptide, can significantly inhibit venous thrombosis in rats dose-dependently, by decreasing the contents of Fbg (fibrinogen) and PLg (plasminogen), increasing the activities of tPA (tissue plasminogen activator) and AT-III (antithrombin-III), as well as prolonging APTT (activated partial thromboplastin time), PT (prothrombin time) and TT [69]. Similarly to ACIBBB, water extracts of *B. batryticatus* (350.0 mg/kg, i.v.) also possessed fibrinolytic activity and inhibited venous thrombosis [70]. Injection of *B. batryticatus* (150.0 mg/L) was reported that can also inhibit venous thrombosis through increasing tPA activity and decreasing PAI-1 activity [71].

5.3. Antitumor Effect

Numerous studies have been conducted on antitumor effects of *B. batryticatus* in recent years. *B. batryticatus* possesses significant anti-proliferative effects on human cancer cell lines, such as cervical cancer, liver cancer and gastric cancer [8]. In 2011, it was reported that ethanol extracts of *B. batryticatus* possessed significant anti-cervical cancer effect against HeLa cells at concentrations of 3.0–11.0 mg/mL, and anticancer mechanisms may be associated with induction of apoptosis by down-regulating the expression of Bcl-2 [72]. Another study reported that flavonoids isolated from *B. batryticatus* (50.0–500.0 µg/mL) also showed strong anti-cervical cancer activities through suppressing proliferation of HeLa cells in a concentration-dependent manner [73]. Later, an oligosaccharide BBPW-2 in *B. batryticatus* was demonstrated to have notable anti-cervical cancer (HeLa), anti-liver cancer (HepG2) and anti-breast cancer (MCF-7) activities above the dose of 1.0 mg/mL, and the action mechanism was that BBPW-2-induced cellcycle disruption in the G0/G1 and G2/M phases of early and late apoptotic as well as necrotic cells [52]. In addition, ethanol extract of *B. batryticatus* also had significant anti-cervical cancer activity against HeLa cells with IC$_{50}$ value of 1.7 mg/mL by inducing apoptosis via the regulation of the Bcl-2 and Bax [74]. Recently, it has been reported that ethanol extract of *B. batryticatus* can induce apoptosis of human gastric cancer cells SGC-7901 through upregulating expressions of Bax and P21 and downregulating Bc1-2 expressions with IC$_{50}$ value of 3.2 mg/mL [75]. Another investigation demonstrated that ergosterol, β-Sitosterol and palmitic acid isolated from *B. batryticatus* exerted significant anti-melanoma activities at the lowest concentrations of 0.1, 0.1 and 0.3 mmol/L, respectively [76].

5.4. Antibacterial and Antifungal Effects

The study of Xiang et al. (2010) revealed that ethanol extracts of *B. batryticatus* possessed antibacterial effect on *Escherichia coli* with MIC (minimal inhibitory concentration) value of 0.6 mg/mL [77]. Another interesting study reported that ethanol extracts of *B. batryticatus* also showed notable antifungal effects on *Colletotrichum gloeosporioides*, *Valsa mali* and leaf cast of *Pericarpium Zanthoxyli* dose-dependently with EC$_{50}$ values of $4.8 \times 10^{-2}$, $9.9 \times 10^{-2}$ and $7.8 \times 10^{-2}$ g/mL, respectively [78].
5.5. Effects on Viruses

In 2016, one study demonstrated that the supernatant (after ethanol extraction and water precipitation) of *B. batryticatus* possessed antiviral effects against RSV viruses, and the EC$_{50}$ value was $2.7 \times 10^{-2}$ g/mL [79]. Interestingly, the research of Zhang et al. (2014) indicated that ethanol extracts of *B. batryticatus* can significantly increase the virulence of HearNPV via inhibition of the ALP (alkaline phosphatase) activity at concentrations of 40.0–80.0 µg/mL [80].

5.6. Antioxidant Effect

Reactive oxygen species (ROS) is one of main causes of various types of diseases. In addition, recently, increasing studies have been performed on the antioxidant effect of *B. batryticatus*. In 2013, the study of Jiang et al. (2013) demonstrated that flavonoids isolated from *B. batryticatus* had strong abilities to scavenge DPPH radicals and hydroxyl radicals at concentrations of $5.0 \times 10^{-3}$–0.1 mg/mL and 0.1–0.4 mg/mL, respectively [73]. Another investigation reported that methanol extract of *B. batryticatus* possessed notable DPPH radical scavenging, ferric ion-scavenging and lipoxygenase-scavenging activities at the lowest concentrations of 2.0, 8.0 and 4.0 mg/mL, respectively [81]. Later, polysaccharides isolated from *B. batryticatus* possessed a powerful hydroxyl radical-scavenging effect and reducing power at concentrations of $2.5 \times 10^{-2}$–0.3 mg/mL [56]. In addition, water extracts of *B. batryticatus* ($1.0 \times 10^{-7}$–1.0 $\times 10^{-6}$) were reported to possess notable antioxidant effects through inhibiting lipid peroxidation and enhancing SOD activity [66].

5.7. Other Pharmacological Effects

Increasing investigations suggest that *B. batryticatus* possesses a wide range of other biological activities, such as hypoglycemic effects, anti-fertility effects, improving immune function effects and others. It was reported that flavonoids isolated from *B. batryticatus* can significantly promote proliferation of HEK293 normal human embryo kidney cell lines at concentrations of 50.0–500.0 µg/mL [73]. The study of Zhao et al. (2014) demonstrated that methanol extracts of *B. batryticatus* can inhibit tyrosinase activity at concentrations of 5.0, 10.0, 20.0, 40.0 and 80.0 mg/mL [81]. Another investigation revealed that powder of *B. batryticatus* presented notable hypoglycemic effects in clinical use at the dose of 15.0 g/day for 2 months (p.o.) [82,83]. Additionally, powder of *B. batryticatus* was also reported to relieve headache caused by disturbing-up of liver Yang at a dose of 18.0 g/day for 3 days (p.o.) in clinic [84]. In 2002, one interesting study indicated that water extracts of *B. batryticatus* exerted significant anti-fertility effect on mice, and the results showed that water extracts can significantly reduce the weight of ovary, uterus and pregnancy rate in female mice, and increase the weight of testes and seminal vesicles in male mice [85]. Furthermore, another study reported that polysaccharide isolated from *B. batryticatus* can significantly improve immune function via increasing the immune organ weights, improving phagocyte phagocytosis and lymphocyte transformation rate [86].

5.8. Summary of Pharmacological Effects

*B. batryticatus* possesses a wide spectrum of pharmacological effects, including effects on the nervous system, anticoagulant effects, antitumor effects, antibacterial and antifungal effects, effects on viruses and antioxidant effects, etc. (Table 4). These pharmacological effects show that the extracts and the compounds from *B. batryticatus* can used to prevent or treat certain diseases, in particular convulsions, epilepsy, thrombus and cancer. However, there is not enough systematic data on chemical compounds of *B. batryticatus* and their pharmacological effects.
Table 3. Pharmacological effects of *B. batryticatus*.

| Pharmacological Effects | Detail | Extracts/Compounds | Minimal Active Concentration/Dose | In Vitro/In Vivo | Reference |
|-------------------------|--------|--------------------|-----------------------------------|------------------|-----------|
| Anticonvulsant effect   |        |                    |                                   |                  |           |
|                         |        | Beauvericin         | 125.0 mg/kg (s.c.) in vivo         |                  | [58,59]   |
|                         |        | β-Sitosterol        | 125.0 mg/kg (s.c.) in vivo         |                  | [59]      |
|                         |        | Ergost-6,22-dien-3,5,8-triol | 125.0 mg/kg (s.c.) in vivo     |                  | [59]      |
|                         |        | Chloroform fraction of alcohol extract | 20.0 g/kg (p.o.) in vivo |                  | [60]      |
| Antiepileptic effect    |        | Ethanol extracts    | ED_{50} = 18.7 g/kg (p.o.) in vivo |                  | [61]      |
|                         |        | Ammonium oxalate    | 30.0 mg/kg (i.v.) in vivo          |                  | [62]      |
| Hypnotic effect         |        | Ethanol extracts    | 25.0 g/kg (p.o.) or 12.5 g/kg (s.c.) in vivo |                  | [63]      |
| Inhibiting spontaneous activity |    | Water extraction and ethanol precipitation extract | 2.0 g/kg (p.o.) in vivo |                  | [64]      |
| Neurotrophic effect     |        | (4E,25,3R)-2'-N-octadecanoyl-4-tetradecasphingenine | 10.0 µM in vitro |                  | [46]      |
|                         |        | (4E,6,25,3R)-2'-N-eicosanoyl-4,6-tetradecasphingadienine | 10.0 µM in vitro |                  | [46]      |
|                         |        | (4E,25,3R)-2'-N-eicosanoyl-4-tetradecasphingenine | 10.0 µM in vitro |                  | [46]      |
|                         |        | 1-O-(9Z-octadecenoyl)-2-O-(8Z,11Z-octadecadienoyl)-sn-glycero-3-phosphorylcholine | 10.0 µM in vitro |                  | [47]      |
|                         |        | 1,2-Di-O-hexadecanoyl-sn-glycero-3-phosphorylcholine | 10.0 µM in vitro |                  | [47]      |
|                         |        | 1,2-Di-O-9Z-octadecenoyl-sn-glycero-3-phosphorylcholine | 10.0 µM in vitro |                  | [47]      |
| Preventing Aβ25-35 induced neurotoxicity | | BCE | 1.0 µg/mL in vitro |                  | [65]      |
| Anticoagulant effect    |        | BB octapeptide      | IC_{50} = 91.1 µM and 104.5, respectively in vitro |                  | [35]      |
|                         |        | BB octapeptide      | 10.0 mg/kg (i.v.) in vivo          |                  | [35]      |
|                         |        | BB octapeptide      | 10.0 mg/kg (i.v.) in vivo          |                  | [35]      |
|                         |        | BB octapeptide      | 5.0 mg/kg (i.v.) in vivo           |                  | [35]      |
|                         |        | Water extracts      | 20.0 mg/mL in vitro               |                  | [67]      |
|                         |        | Increasing whole the concentration of ammonium oxalate in water extracts | 33.7 mg/mL in vitro |                  | [68]      |
|                         |        | AC1BB               | 9.0 mg/kg (i.v.) in vivo           |                  | [69]      |
|                         |        | Water extracts      | 350.0 mg/kg (i.v.) in vivo         |                  | [70]      |
|                         |        | Injection           | 150.0 mg/L in vitro               |                  | [71]      |
| Anticancer            |        | Ethanol extracts    | 3.0 mg/mL in vitro               |                  | [72]      |
| Anti-cervical cancer (HeLa) |   | Flavonoids          | 50.0 µg/mL in vitro              |                  | [73]      |
|                         |        | BBPW-2              | 1.0 mg/mL in vitro               |                  | [52]      |
|                         |        | ethanol extracts    | IC_{50} = 1.6 mg/mL in vitro     |                  | [74]      |
| Anti-liver cancer (HePG2) |     | BBPW-2              | 1.0 mg/mL in vitro               |                  | [52]      |
| Anti-breast cancer (MCF-7) |     | BBPW-2              | 1.0 mg/mL in vitro               |                  | [52]      |
| Anti-gastric cancer (SGC-7901) |   | ethanol extracts    | IC_{50} = 3.2 mg/mL in vitro     |                  | [75]      |
| Anti-melanoma activity |        | Ergosterol          | 0.1 mmol/L in vitro              |                  | [76]      |
|                         |        | β-Sitosterol        | 0.1 mmol/L in vitro              |                  | [76]      |
|                         |        | Palmitic acid       | 0.3 mmol/L in vitro              |                  | [76]      |
Table 4. Cont.

| Pharmacological Effects | Detail | Extracts/Compounds | Minimal Active Concentration/Dose | In Vitro/In Vivo | Reference |
|-------------------------|--------|--------------------|----------------------------------|-----------------|-----------|
| Antibacterial and antifungal effects | Anti-Escherichia coli | Ethanol extracts | MIC = 0.6 mg/mL | in vitro | [77] |
| Anti-colloteluticum gloeoporioides | Ethanol extracts | EC₅₀ = 4.8 × 10⁻² g/mL | in vitro | [78] |
| Anti-valsa mali | Ethanol extracts | EC₅₀ = 9.9 × 10⁻² g/mL | in vitro | [78] |
| Anti-leaf cast of Pericarpium Zanthoxyli | Ethanol extracts | EC₅₀ = 7.8 × 10⁻² g/mL | in vitro | [78] |
| Effect on viruses | Antiviral effect against RSV viruses | Ethanol extraction and water precipitation supernatant | EC₅₀ = 2.7 × 10⁻² g/mL | in vitro | [79] |
| Increasing the virulence of HearNPV | Ethanol extracts | 40.0 µg/mL | in vitro | [80] |
| Antioxidant effect | Scavenging DPPH | Flavonoids | 5.0 × 10⁻³ mg/mL | in vitro | [73] |
| | | Methanol extract | 2.0 mg/mL | | [81] |
| | Scavenging hydroxyl radicals | Flavonoids | 0.1 mg/mL | in vitro | [73] |
| | | Polysaccharide | 2.5 × 10⁻² mg/mL | in vitro | [56] |
| | | Methanol extract | 4.0 mg/mL | in vitro | [81] |
| | Scavenging ferric ion | Polysaccharide | 2.5 × 10⁻² mg/mL | in vitro | [56] |
| | | Methanol extract | 8.0 mg/mL | in vitro | [81] |
| | Scavenging lipoxygenase | Methanol extract | 4.0 mg/mL | in vitro | [81] |
| | Inhibiting lipid peroxidation | Water extracts | 2.0 × 10⁻³ g/mL | in vitro | [66] |
| | Enhancing SOD activity | Water extracts | 2.0 × 10⁻² g/mL | in vitro | [66] |
| Other pharmacological effects | Promoting proliferation of HEK293 cell | Flavonoids | 50.0 µg/mL | in vitro | [73] |
| | Inhibiting tyrosinase activity | Methanol extract | 5.0 mg/mL | in vitro | [81] |
| | Hypoglycemic effect | Crude powder | 15.0 g/day (p.o., for 2 months) | in vivo | [82,83] |
| | Relieving headache | Crude powder | 18.0 g/day (p.o., for 3 days) | in vivo | [84] |
| | Anti-fertility effect | Water extracts | 5.0 g/kg (p.o.) | in vivo | [85] |
| | Improving immune function | Polysaccharide | 100.0 mg/kg (p.o.) | in vivo | [86] |

6. Toxicity

Throughout its long history, B. batryticatus has been generally considered to be a safe TCM in China [5,14]. However, recent poisoning accidents of B. batryticatus were reported by numerous investigations, which is not consistent with traditional understanding of B. batryticatus safety. Cheng (2007), Gao (2011), Li et al. (2011a), Liu et al. (2013) reported 46, 216, 425, 248 clinical cases about poisoning accidents of B. batryticatus, respectively [87–89]. Based on the literature, it can be found that occurrences of poisoning accidents for B. batryticatus mainly result from the following reasons: overdose and misuse of B. batryticatus, and quality problems caused by non-standard procedure of production and processing [87–95]. Furthermore, as a traditional animal medicine, B. batryticatus is easily contaminated by aflatoxin, which is regarded as carcinogenic or a teratogenic toxic substance in the procedure of processing, storage and transportation [96]. Therefore, it is urgent and important to standardize methods of production and processing and select the proper doses according to the using form of B. batryticatus to avoid adverse reactions and even poisoning.

It was reported that metabolism of ammonium oxalate in the body can produce ammonia easily, and high content of ammonium oxalate may cause blood ammonia poisoning [97]. The content of ammonium oxalate in B. batryticatus is in the range of 5.0–13.0% [53,54]. Thus, overdosing B. batryticatus can possibly cause poisoning. Additionally, toxins secreted by Beauveria bassiana when using infected silkworm, such as beauvericin, chitosan, chitinase and cellulase, can induce cell death procedurally [9]. Currently, the recognized cause of adverse reactions of B. batryticatus is an allergic reaction. Some allogeneic proteins in B. batryticatus, can cause sensitization, immune response and
even cause metabolic disorder and dysfunction of central nervous system [97]. One investigation demonstrated that proteins secreted by Beauveria bassiana can cause adverse effects on mice [97]. However, to date the specific constituents causing adverse reactions or poisoning have not been clarified in B. batryticatus. Thus, further studies should be carried out to confirm which constituents are causing side effects or poisoning in B. batryticatus and explore corresponding content ranges.

7. Future Perspectives and Conclusions

B. batryticatus is one of the most important and frequently used traditional animal medicines, which has been used to treat convulsions, cough, asthma, headaches, skin prurigo, scrofula, tonsillitis and other diseases in China. Recently, B. batryticatus has received increasing attention. However, certain aspects still need to be further studied and explored.

There is limited research on bioactive compounds and the mechanism of biological activities of B. batryticatus. Thus, it is essential to strengthen research on bioactive compounds, action mechanisms of the bioactive compounds and their structure-function relationships in B. batryticatus. Current investigations of B. batryticatus mainly focus on its small molecule compounds, but rarely investigate its macromolecular compounds. In addition, as an animal Chinese medicine, the main chemical constituents in B. batryticatus are proteins. Therefore, future investigations of B. batryticatus could be concentrated on its macromolecular compounds, particularly its proteins and peptides. In addition, mechanisms of biological activities of B. batryticatus should be further explored with techniques of modern molecular biology and pharmacology.

Many monographs of TCM record that powder of B. batryticatus is used directly in a total of 65 prescriptions where B. batryticatus is as the main drug [5,14]. However, in the Pharmacopoeia of the People’s Republic of China of all editions except 1963 edition, the only using form of B. batryticatus is decoction. Therefore, further studies should be done to explore which using form (decoction or powder) of B. batryticatus is more reasonable and scientific. Furthermore, based on scientific using form of B. batryticatus, further studies should be done to analyze reasons of adverse reaction or poisoning caused by B. batryticatus and then to establish its safety evaluation system.

Lack of standardized methods of production and processing is another issue of B. batryticatus. In the process of production, lime is often used to dry silkworm infected by Beauveria bassiana to avoid contamination by miscellaneous bacteria, but lime lacks quality standard and contains a high content of heavy metal and other toxic substances, which seriously affects the quality and safety of B. batryticatus [4]. When B. batryticatus is processed by stir-frying with bran to a yellowish color, processing degree is mainly evaluated by experience of pharmaceutical worker, which lacks quantifiable indices and is not objective. Thus, it is crucial to standardize the procedure of production and processing using modern technologies for ensuring quality of B. batryticatus.

Additionally, as an animal medicine containing complicated compounds, quality evaluation and control of B. batryticatus remains challenging for modern researchers. Currently, quality criteria of B. batryticatus in the Pharmacopoeia of the People’s Republic of China only includes a description, microscopic identification, check (impurity, contents of water, total ash, acid insoluble ash and aflatoxin) and extract [1], which is inadequate to reflect the holistic quality of B. batryticatus. Therefore, it is urgent and important to establish suitable quality evaluation and control systems that can reflect the holistic quality of B. batryticatus, such as the fingerprint of the protein or peptide.

In conclusion, this paper provides a comprehensive overview on the traditional uses, chemistry, pharmacology and toxicity of B. batryticatus. In addition, this review also provides some trends and perspectives for the future development of B. batryticatus.

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