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Chapter 5 Cordyceps as an Herbal Drug

Bao-qin Lin and Shao-ping Li.

5.1. INTRODUCTION

Cordyceps is the composite of a genus of fungus that grows on the larva of insects. To date, more than 350 *Cordyceps-related* species have been found worldwide based on fungus and/or insect host. However, since 1964, only *Cordyceps sinensis* has been recorded officially as an herbal drug in Chinese pharmacopoeia. *C. sinensis*, known as *Dongchongxiacao* (winter-worm summer-grass) in Chinese, is one of the most famous traditional Chinese medicines and medicinal mushrooms. The fungus attacks the larva of some species of insects (Fam. *Hepialidae*), and converts each larva to a sclerotium, from which the fruiting body grows (Figure 5.1).

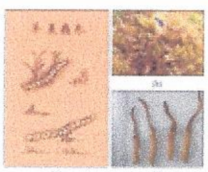

FIGURE 5.1

(See color insert.) (a) *Cordyceps sinensis*, illustrated in the book *Ben Cao Bei Yao* by Wang Ang, which was published in 1694; (b) *C. sinensis* found in the soil (arrowhead indicates *C. sinensis*); and (c) collected as raw materials.

According to the theory of Chinese medicine, *C. sinensis* is sweet in taste and neutral in nature, and it can replenish the kidney, soothe the lung, stop bleeding, and eliminate phlegm. The fungus *C. sinensis* has been used for the treatment of fatigue, cough, hyposexuality, asthenia after severe illness, renal dysfunction, and renal failure (State Pharmacopoeia Commission of PRC 2005). In China, it is found in the soil of prairies at elevations of 3500–5000 m, mainly in the provinces of Qinghai, Tibet, Sichuan, Yunnan, and Gansu. In China, *C. sinensis* has been known and used as a remedy for more than 300 years. It was first recorded in *Ben Cao Bei Yao* by Wang Ang in 1694, and the Italian scholar Saccardo named the *Cordyceps* found in China officially as *Cordyceps sinensis* (Berk.) Sacc. in 1878; this nomenclature has been used ever since.

The ecosystem of *C. sinensis* has been terribly affected by the restriction of habitat and over-exploration. Although the Ordinance of Resources Protection on Wild Herbal Medicine was issued in 1987, the yield of natural *C. sinensis* is still decreasing. It was reported based on a survey conducted during June–July 2007 that the yield of natural *C. sinensis* decreased by more than 90% in the last 25 years. The price rocketed to more than 200,000 Renminbi (RMB)/kg (approximately US$25,000) in 2007 (Feng, Yang, and Li 2008), and its usage was limited during the past decade by its limited supply.

Due to the rarity and outstanding curative effects of *C. sinensis*, some natural substitutes such as *C. militaris, C. liangshanensis, C. gunnii*, and *C. cicadicola* have been sold in markets (Yang et

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Review

Deer antler base as a traditional Chinese medicine: A review of its traditional uses, chemistry and pharmacology

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abstract

Ethnopharmacological relevance: Deer antler base (Cervus, Lu Jiao Pan 鹿角盘) has been recorded in the Chinese medical classics Shen Nong Ben Cao Jing (神农本草经) 2000 years ago and is believed to nourish the Yin, tonify the kidney, invigorate the spleen, strengthen bones and muscles, and promote blood flow. In China, deer antler base has been extensively used in traditional Chinese medicine (TCM) to treat a variety of diseases including mammary hyperplasia, mastitis, uterine fibroids, malignant sores and children's mumps.

Aim of the review: We provide an up-to-date and comprehensive overview of the traditional uses, chemistry, pharmacology, toxicology and clinical trials of deer antler base in order to explore its therapeutic potentials and future research needs.

Background and methods: The pharmacological value of deer antler base was ignored for many years while researchers concentrated on the pharmacological value of velvet antler. However, more recently, scientists have carried out a great number of chemical, pharmacological and clinical studies on deer antler base. The present review covers the literature available from 1980 to 2012. All relevant information on deer antler base was collected from ancient Chinese herbal classics, pharmacopoeias, formularies, scientific journals, books, theses and reports via a library and electronic search by using PubMed, Google Scholar, Web of Science, Science Direct, and CNKI (in Chinese).

Key findings: Both in vitro and in vivo pharmacological studies have demonstrated that deer antler base possess immunomodulatory, anti-cancer, anti-fatigue, anti-osteoporosis, anti-inflammatory, analgesic, anti-bacterial, anti-viral, anti-stress, anti-oxidant, hypoglycemic, hematopoietic modulatory activities and the therapeutic effect on mammary hyperplasia. Although the mechanism of actions is still not clear, the pharmacological activities could be mainly attributed to the major bioactive compounds amino acids, polypeptides and proteins. Based on animal studies and clinical trials, deer antler base causes no severe side effects.

Conclusions: Deer antler base has emerged as a good source of traditional medicine. However, further investigations are needed to explore individual bioactive compounds responsible for these in vitro and in vivo pharmacological effects and its mechanism of actions. Further safety assessments and clinical trials in humans need to be performed before it can be integrated into medicinal practices. The present review has provided preliminary information for further studies and commercial exploitations of deer antler base.

Contents

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1. Introduction

The natural products with some health claim are a rapidly growing segment of the market in industrialized countries (Heinrich et al., 2006). Natural products such as green medicines are considered healthier and safer than synthetic ones (Parvath and Brindha, 2003). The use of natural products in traditional and local medicines has been of increasing concern, such as Rehmannia glutinosa, Aristolochia, Garcinia mangostana and Artemisia dracunculus (Zhang et al., 2008; Heinrich et al., 2009; Obolskiy et al., 2009, 2011). Growing research is being conducted worldwide with respect to plant based medicines neglecting the other two components of traditional medicine, i.e. mineral and animal based medicines (Wilson et al., 2011). Therefore, some scientists have devoted themselves to study the animal based medicine in recent years, such as Gekko swinhonis Guenther and Eupolyphaga sinensis Walker (Chen et al., 2010; Ge et al., 2012). As a traditional animal based medicine, velvet antler has been used in the East for over 2000 years to prevent or treat various diseases, including cardiovascular disease, gynecological problems, immunological deficiencies, blood cancers, tissue repair and health promotion (Hong, 1996; Wang, 1996; Huang, 1997; Sun, 2007).

China is a major deer raising country, behind only the former Soviet Union and New Zealand (Hou et al., 2003). China also is home to a tremendous diversity of deer species with 21 species of deer, nearly half of the world's total, found in China (Ohtaishi and Gao, 1990). There are eight subspecies of red deer in China, and deer farming has now been extended to include some of these subspecies of red deer (Hou et al., 2003). Natural populations of sika deer are now distributed over northeastern Asia from the Ussuri region of Russia to China, North Vietnam, Taiwan, and Japan (Tamate et al., 1998). Although commercial hunting of wild sika deer was restricted by China Veterinary Association, a lot of domesticated sika deer as a new livestock are now incorporated into animal husbandry management (Song et al., 2005). And the most successful and largest sika deer farming area in the world is in Jilin province of China (Fig. 1) (Zhang et al., 2011). Velvet antler (120–150 t/yr), the major product of farmed sika deer, is harvested by using anesthetic agents to alleviate the pain of deer (Han, 1998). It is mainly consumed in China whereas a small amount exported to South Korea, Japan and other countries (Liu et al., 2011; Chen, 2012).

Sika deer (Cervus nippon Temminck) and red deer (Cervus elaphus Linnaeus), the major two deer species in China, belong to the genus Cervus in the family Cervidae. Deer antler base, commonly known as Lu Jiao Pan (鹿角盘), Lu Hua Pan (鹿花盘) and Zhen Zhu Pan (珍珠盘) in Chinese, is the ossified and rudimental antler of the male sika deer and red deer after sawing off the velvet antler, which then falls off by itself in the following year when the new velvet antler begins to germinate at incredible speed (Figs. 2 and 3) (Gao, 1996; Qian et al., 2009; Li et al., 2011). Since deer antler base is produced naturally by the deer without any pain every year, it can be obtained at a relatively low cost (Qian et al., 2009). Over the past few decades, people have paid attention only to the nutritional and medicinal value of velvet antler, while ignoring the medicinal value of deer antler base for a long time (Wang and Gao, 1999; Zhang et al., 2011). And deer antler base is very hard and not easily crushed, therefore it is difficult to extract and separate its active components. As a result, much less research has been devoted to the use of deer antler base than to velvet antler (Qiu et al., 2007). However, the use of deer antler base as a folk remedy has a long history and achieved desirable results (Zhang and Wang, 1980; Wang 1987; Wang et al., 2007).

Recently, many investigations have been undertaken to determine the chemical constituents as well as the pharmacological and clinical effects of deer antler base. A growing number of papers have been published in this area but no review papers are available. Therefore, this paper was initiated to review the traditional uses, chemistry,

Fig. 1. Sika deer (Cervus nippon Temminck) farming in China.

Fig. 2. The cycle of sika deer (Cervus nippon Temminck) velvet antler production: (A) velvet antler; (B) sawing off the velvet antler; (C) deer antler base and (D) new velvet antler.

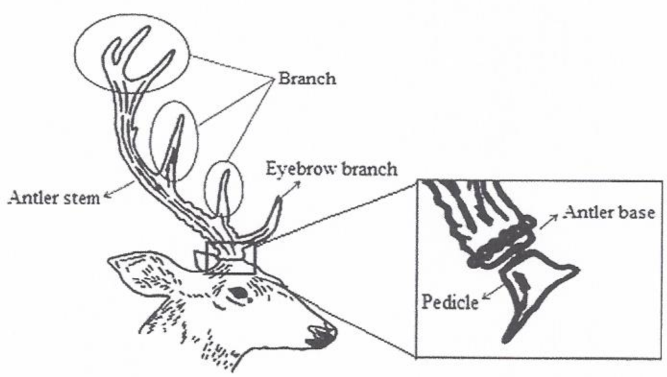

Fig. 3. Line drawing of sika deer antler base (Cervus nippon Temminck).

pharmacology and clinical trials of deer antler base. It is hoped that the work presented here will encourage more research on the pharmacological effects and provide further insight into the mechanisms associated with the therapeutic effects of deer antler base.

2. Local and traditional uses

Deer antler base, obtained from the sika deer and red deer, has been recorded in the Chinese medical classics Shen Nong Ben Cao Jing (神农本草经) 2000 years ago and is believed to nourish the Yin, tonify the kidney, invigorate the spleen, strengthen bones and muscles, and promote blood flow. In China, deer antler base has been used in traditional Chinese medicine and has been proven to possess remarkably therapeutic activities in mammary hyperplasia, mastitis, uterine fibroids, malignant sores, children's mumps and other diseases (Zhang and Wang, 1980; Wang 1987; Qiu et al., 2007; Wang et al., 2007). Now, both velvet antler and deer antler base from the sika deer and red deer are designated as medicinal antlers in the Chinese Pharmacopoeia (The State Committee of Pharmacopoeia, 2005).

In China, deer antler base is held in such high regard that it is not only used as a medicine to cure some diseases but also as a supplement to prevent disease and strengthen the body. Generally, deer antler base is macerated in wine or decocted with water for oral consumption (The State Committee of Pharmacopoeia, 2005). To increase its effect, deer antler base was often used with other traditional medicines, such as Panax ginseng, Cornu Cervi Pantotrichum, Colla Corii Asini, Ziziphus jujube, Fructus Lycii, Herba Taraxaci, Semen Coicis, Glycyrrhizae uralensis, Radix Bupleuri, Radix Pseudostellariae, Angelica sinensis, Paeonia lactiflora, Rhizoma Sparganii, Rhizoma Curcumae, Fossilia Ossis Mastodi, Fritillaria thunbergii, Epimedium, Polygala arillata, Cucumis sativus, Eupolyphaga sinensis Walker, Pheretima, Gekko swinhonis Guenther, Commiphora myrrha, Ginsenosides, Flos Lonicerae, Flos Chrysanthemi, Flos Sophorae, Pyrite and even with the meat of deer hooves and deer placenta ointment. Recently, more convenient forms have been developed for consumption, such as tablets, capsules, granules, and ointments. Moreover, it is noteworthy that most of the local products have been applied for patents and are believed to be useful for treating many diseases as shown in Table 1.

3. Processing

In China, deer antler base has traditionally been prepared by decocting in water. In this method, deer antler base was cut into

Table 1
The popular traditional food therapy or medicated diet of deer antler base.

Local names	Prescription	Uses recorded	Formulation/ mode of usage	Reference
Lujiaopan soup 鹿角盘口服液	Deer antler base	Mammary hyperplasia, mastitis	Decoctions	Wang (1987)
Lujiaojing soup 鹿角精口服液	Deer antler base, Colla Corii Asini, Fructus Lycii, Ginsenosides, Royal jelly	Mastitis, mammary hyperplasia, uterine fibroids, sterility, menoxenia, osteodynia, chilly, tuberculosis, hepatitis	Decoctions	Zhang et al. (2005)
Lutai soup 鹿胎口服液	Deer placenta ointment, deer antler base, Semen Coicis, Ziziphus jujube, Glycyrrhizae uralensis, Radix Pseudostellariae, Cucumis sativus, honey	Immune dysfunction, acratia, dizziness and tinnitus	Decoctions	Wu et al. (2001)
Banlongpan capsules 斑龙盘胶囊	Deer antler base	Immune dysfunction	Capsules	Dong et al. (1993)
Lujiaopan capsules 鹿角盘软胶囊	Deer antler base, Panax ginseng, Cornu Cervi Pantotrichum, Herba Taraxaci	Mastitis, osteoporosis, immune dysfunction	Capsules	Zhang et al. (2005)
Fufang Lujiaopan capsules 复方鹿角盘胶囊	Deer antler base, Radix Bupleuri, Paeonia lactiflora, Rhizoma Sparganii, Rhizoma Curcumae, Fritillaria thunbergii, Epimedium, Angelica sinensis	Mammary hyperplasia, mastitis	Capsules	Zhao et al. (2010a)
Lujiaopan chewable tablets 鹿角盘咀嚼片	Deer antler base, sucrose, starch, tea flavor additives, polyethylene glycol 6000	Immune dysfunction, amnesia, osteoporosis, mammary hyperplasia, mastitis	Tablets	Wu et al. (2010), Zhang et al. (2010), Xu and Jin (2009a)
Lujiaopan effervescent tablets 鹿角盘泡腾片	Deer antler base, sodium bicarbonate, citric acid, microcrystalline cellulose, xylitol, polyvinylpyrrolidone, magnesium stearate, lemon flavor additives	Immune dysfunction, amnesia, osteoporosis, mammary hyperplasia, mastitis	Tablets	Wu et al. (2010), Zhang et al. (2010), Xu and Jin (2009b)
Lujiaopan granules 鹿角盘颗粒剂	Deer antler base, stevia rebaudiana, dextrin	Immune dysfunction, amnesia, osteoporosis, mammary hyperplasia, mastitis	Granules	Wu et al. (2010), Zhang et al. (2010), Xu and Jin (2009c)
Surong lujiaopanjing granules 速溶鹿角盘晶冲剂	Deer antler base, wine	Immune dysfunction, osteoporosis	Granules	Fan (1997)
Pangengushen granules 盘根骨神散	Deer antler base, Polygala arillata, Fossilia Ossis Mastodi, Cucumis sativus, Eupolyphaga sinensis Walker, Pheretima, Gekko swinhonis Guenther, Commiphora myrrha, Pyrite	Fracture healing, osteoporosis, menopausal syndrome, immune dysfunction	Granules	Zhai (1993)
Gouqizibu ointment 枸杞滋补膏	Deer antler base, Fructus Lycii, Angelica sinensis, honey	Impotence, prospermia, spermatorrhea, azoospermia, gynecological diseases, menopausal syndrome	Medicated diet	Wang (2004a)
Functional foods 功能性食品	Deer antler base, deer hooves meat, Flos Chrysanthemi, Flos Lonicerae, Flos Sophorae	Mammary hyperplasia, mastitis, breast cancer	Medicated diet	Zheng and Zhang (2006)

thin slices and placed in boiling water and decocted repeatedly to get a glue solution. The glue solution was filtered and combined using a little potassium alum powder, then decocted and concentrated with a slow cooking fire (while adding the appropriate amounts of soybean oil, rock sugar and rice wine) to a thick paste, condensed naturally and then cut into small pieces. The finished product, known as antler glue (Colla Cornus Cervi), is a translucent yellow-brown or reddish brown color with high collagen content. The remaining gray bone residue, which contains no colloid, is named unglued antler powder (Cornu Cervi Degelatinatum) (Ma and Wang, 2000). The antler glue processed by this method has an anti-fatigue effect and greater efficacy for improving immunity and protecting gastric mucosa (Bao et al., 1995; Wu et al., 2007). Another product, unglued antler powder, is claimed to have a good therapeutic effect on acute mastitis and postpartum chapped nipple (Zhou et al., 2000; Gao and Gao, 2004). The antler glue pill was made from antler glue, unglued antler powder and other traditional Chinese medicines and has been proven to have a role in the prevention and treatment of osteoporosis (Wang and Li, 2003).

4. Chemical constituents

With advances in analytical techniques, although the chemical constituents in deer antler base have not been well studied, multiple classes of chemical constituents including amino acids, proteins, lipids and polysaccharides have been isolated and identified in different investigations. And several kinds of mineral elements are detected in deer antler base like Ca, P, Na, K, Mg, etc. Table 2 provides the details of the chemical constituents present in deer antler base.

Although deer antler base and velvet antler have the similar chemical constituents (Liu et al., 2010a), the content of them presented obvious differences (Yao et al., 2002; Li et al., 2007a). A comparison of the proportion of chemical constituents in deer antler base and velvet antler is summarized in Table 3.

4.1. Inorganic substances and minerals

Deer antler base contains 58.14% inorganic substances (Tian, 2011). Deer antler base contains many different inorganic substances and the content of these may change with the age of the deer producing the deer antler base. The content of inorganic substances is closely related to the pharmacological effects of this Chinese medicine (Li et al., 2011).

Nowadays, 12 kinds of mineral elements are detected in deer antler base by atomic absorption spectrometry, including Ca, P, Mg, Na, K, Fe, Mn, Zn, Al, Sr, Ba and Cu (Table 2). Zhang et al. found that the content of Ca, P, K, Zn and Al increased with the age of the deer, but the content of Fe was unaffected by the animal's age (Zhang et al., 2005). In contrast, Liu et al. reported that in sika deer less than 5 years old, the content of Zn in deer antler base decreased with age while the content of Cu and Fe increased (Liu et al., 2010b). These contrary results suggest that the regulatory mechanisms in deer antler base causing changes in mineral elements as the deer ages require further study.

Table 2
Summary of the chemical constituents present in deer antler base.

No.	Class	Chemical constituents	Reference
1	Mineral elements	Calcium (Ca)	Yao et al. (2002), Zhang et al. (2005), Tian and Hu (2010), Tian (2011)
2		Phosphorus (P)	
3		Sodium (Na)	Zhang et al. (2005), Tian and Hu (2010), Tian (2011)
4		Potassium (K)	
5		Magnesium (Mg)	
6		Iron (Fe)	Zhang et al. (2005), Liu et al. (2010b), Tian and Hu (2010), Tian (2011)
7		Zinc (Zn)	
8		Manganese (Mn)	
9		Aluminum (Al)	Zhang et al. (2005)
10		Strontium (Sr)	
11		Barium (Ba)	
12		Copper (Cu)	Liu et al. (2010b)
13	Amino acids	Lysine (Lys)	Wang (1987), Wang and Gao (1999), Su et al. (2001), Zhang et al. (2005), Li et al. (2007a), Tian and Hu (2010)
14		Arginine (Arg)	
15		Histidine (His)	
16		Glutamic acid (Glu)	
17		Proline (Pro)	
18		Aspartic acid (Asp)	
19		Serine (Ser)	
20		Threonine (Thr)	
21		Glycine (Gly)	
22		Alanine (Ala)	
23		Isoleucine (Ile)	
24		Leucine (Leu)	
25		Phenylalanine (Phe)	
26		Methionine (Met)	Wang (1987), Wang and Gao (1999), Su et al. (2001), Li et al. (2007a), Tian and Hu (2010)
27		Tyrosine (Tyr)	
28		Valine (Val)	Su et al. (2001), Zhang et al. (2005), Li et al. (2007a), Tian and Hu (2010)
29		Cysteine (Cys)	Su et al. (2001)
30		Hydroxyproline (Hyp)	Zhang et al. (2005)
31		Tryptophan (Trp)	
32	Proteins	65.57, 28.18, 21.27, 16.79, and 13.79 kDa polypeptides or proteins	Su et al. (2001)
33		10□110 kDa polypeptides or proteins	Tang et al. (2008)
34		20.1□31 kDa proteins	Qiu et al. (2007)
35		8□15 kDa polypeptides	Wang et al. (2008)
36		b-3 subtype of hemoglobin Antimicrobial peptide Peptidoglycan recognition protein b-c subtype of hemoglobin Pre-pro serum albumin	Huang et al. (2010a)
37		Crude proteins (32.80%) Water-soluble proteins (8.29%)	Tian (2011)
38	Polysaccharides	Total sugar (1.682%) Reducing sugar (0.575%) Soluble sugar (1.143%)	Tian (2011)
39	Lipids	Crude fat (1.91%) Free fatty acids (0.067%) Phospholipids (0.3%)	Tian (2011)
40		Cholesterol (0.224 mg/g)	Wang and Zhao (2009)

The content of Ca and P in deer antler base is very high which is consistent with its ossi□cation. Deer antler base contains 10.70% Ca and 11.23% P (Tian and Hu, 2010; Tian, 2011). The levels of Ca and P in deer antler base are signi□cantly higher than those of the two-branched and three-branched velvet antler ($P<0.05$) (Table 3), and the calcium□phosphorus ratio of deer antler base is greater than 1:1, which is easy for human body to absorb (Yao et al., 2002).

4.2. Amino acids, polypeptides and proteins

Deer antler base is rich in amino acids, polypeptides and proteins and these are considered to be the most prominent bioactive components in deer antler base (Zhang et al., 2005, 2011). Till date, 19 kinds of amino acids have been isolated and identi□ed in different studies (Table 2). In 1987, Wang used a decocting method to extract the colloidal substances from deer antler base and isolated the active low molecular polypeptides composed of 16 different amino acids using dialysis and hyper-□ltration (Wang, 1987). Su et al. extracted the total proteins from deer antler base by means of salt extraction, thermal denaturation and gel □ltration and determined the content of amino acids using an amino-acid analyzer. Their results revealed 17 amino acids in the protein component of deer antler base with the content of glycine, glutamic acid and proline being higher than the other amino acids (Su et al., 2001). Zhang et al. detected 16 amino acids

Table 3
Comparisons of the proportion of chemical constituents present in deer antler base and velvet antler.

Class	Chemical constituents	Average mass percentage			Reference
		Deer antler base	Two-branch of velvet antler	Three-branch of velvet antler	
Mineral elements	Calcium (Ca)	7.71	7.32	7.06	Yao et al. (2002)
	Phosphorus (P)	7.47	6.09	5.76	
	Ca/P	15.18	13.41	12.82	
Amino acids	Aspartic acid (Asp)	1.92	3.63	4.02	Li et al. (2007a)
	Threonine (Thr)	4.61	1.55	2.09	
	Serine (Ser)	0.88	1.79	1.94	
	Glutamic acid (Glu)	3.63	4.98	5.43	
	Glycine (Gly)	6.81	6.35	7.57	
	Alanine (Ala)	2.93	3.76	4.12	
	Valine (Val)	1.05	2.08	2.69	
	Methionine (Met)	0.38	0.56	0.61	
	Leucine (Leu)	0.53	2.73	2.86	
	Isoleucine (Ile)	1.20	1.02	0.95	
	Tyrosine (Tyr)	0.59	1.14	1.36	
	Phenylalanine (Phe)	1.04	2.05	2.21	
	Lysine (Lys)	1.45	2.86	2.65	
	Histidine (His)	0.34	0.89	0.92	
	Arginine (Arg)	2.38	4.56	4.23	
	Proline (Pro)	3.76	4.52	4.92	
	Total	33.50	44.47	48.57	

in deer antler base, eight of which are essential for the human body. Among them, the basic amino acids tryptophan, lysine, histidine and arginine had a total content of 231 mg/g with lysine in the greatest content (190 mg/g). The remaining amino acids are acidic and neutral amino acids, which had a total content of 242.17 mg/g with glycine in the greatest content (75.60 mg/g) (Zhang et al., 2005). In addition, Li et al. (2007a) compared the amino acid content in different products from sika deer and found that the total mass percentage of 16 kinds of amino acids in deer antler base (33.50%) was lower than velvet antler (44.47% and 48.57%; Table 3).

Several studies have focused on the proteins and polypeptides in deer antler base. It has been found that deer antler base contains 32.80% crude proteins and 8.29% water-soluble proteins (Tian, 2011). Moreover, the proteins of deer antler base are mostly acidic proteins (Yao et al., 2010). Su et al. extracted the total proteins from deer antler base by means of salt extraction, thermal denaturation and gel filtration. Five bands were determined by SDS-PAGE and the molecular weights of these bands were 65.57, 28.18, 21.27, 16.79, and 13.79 kDa (Su et al., 2001). Tang et al. used ammonium sulfate precipitation and other methods to extract the total proteins from deer antler base and showed that the protein content accounted for 88% of the crude proteins as measured by a BCA™ protein kit. SDS-PAGE showed 11 bands of water-soluble proteins in deer antler base with molecular weights ranging from 110 to 10 kDa (Tang et al., 2008). Other researchers used ultra-fine grinding technology to crush deer antler base, and after leaching, salting out, enzymatic hydrolysis and molecular sieve chromatography, they purified the proteins. The molecular weights of these proteins were between 20.1 and 31 kDa, whereas those of the polypeptides were between 8 and 15 kDa (Qiu et al., 2007; Wang et al., 2008). Recently, five different proteins were identified from the soluble proteins of deer antler base including the b-3 subtype of hemoglobin, anti-microbial peptide, peptidoglycan recognition protein, b-c subtype of hemoglobin and pre-pro serum albumin (Huang et al., 2010a).

4.3. Lipids and polysaccharides

Tian (2011) evaluated the crude fat content of deer antler base using the Soxhlet extraction method and also determined the content of free fatty acids and phospholipids using sodium hydroxide titration and spectrophotometry, respectively. These results showed that deer antler base contains 1.91% crude fat, 0.067% free fatty acids and 0.3% phospholipids. Additionally, Wang and Zhao (2009) used the HPLC method to determine the cholesterol content of deer antler base and found it to be approximately 0.224 mg/g. However, few studies of the lipids in deer antler base have been conducted. In particular, there is a lack of information on the content of unsaturated fatty acids with strong biological activity.

Natural polysaccharides are a class of nontoxic macromolecules with polymeric carbohydrate structures and physiological activities, which are receiving more and more attention in the development of new drugs and health products (Li et al., 2011; Liu et al., 2012). The content of reducing sugar, total sugar and solubility sugar were measured using the 3,5-dinitrosalicylic acid and phenol sulfuric acid method. It was found that deer antler base contains 1.682% total sugar, 0.575% reducing sugar and 1.143% soluble sugar (Tian, 2011).

In summary, although multiple classes of chemical constituents including mineral elements, amino acids, proteins, lipids and polysaccharides have been identified, further studies are needed to explore the other chemical constituents of deer antler base. In addition, deer antler base and velvet antler have similar chemical constituents, it is difficult to distinguish between them using common analytical methods. Therefore, it is highly desirable to find an effective method to distinguish these two products.

5. Pharmacological properties

In recent decades, there have been a number of reports on the pharmacological functions and activities of deer antler base and its active principles on the immune system, blood system, bone metabolism, glucose metabolism, mammary tissue and its anti-cancer, anti-fatigue, anti-inflammatory, analgesic, anti-bacterial, anti-viral, anti-stress, anti-oxidant effects. Consequently, deer antler base has enormous potential for research and exploitation. An overview on the current status of modern pharmacological evaluations is summarized in Table 4.

Table 4
A summary of the studies conducted on the pharmacological effects of deer antler base.

No.	Property/ condition	Formulation/extract/dosage	Model	Mode of action	Effect	Reference
1	Mammary tissue	Deer antler base injection (6 g/kg/day, i.p., for 10 days) and deer antler base polypeptides (20 mg/kg/day, i.p., for 10 days)	Mice (in vivo)	The number, diameter and height of hyperplastic mammary gland in estradiol valerate-induced mammary hyperplasia mice	Antagonism	Chen et al. (1987, 1989)
				The atrophic number of hyperplastic mammary gland in estradiol valerate-induced mammary hyperplasia mice	Stimulatory	
		Deer antler base polypeptides (1, 2 g/kg/day, i.g., for 30 days)	Rats (in vivo)	The level of estradiol in estradiol valerate-induced mammary hyperplasia rats model	Antagonism	Wang et al. (2007, 2008)
		Compound deer antler base capsules (13 g/kg/day, i.p., for 30 days)	Mice (in vivo)	The levels of progesterone or follicle-stimulating hormone in benzoic acid estradiol-induced mammary hyperplasia mice	Stimulatory	Zhao (2008)
				The uterine weight and uterine index, the levels of estradiol or luteinizing hormone and the expression of estrogen receptor protein	Antagonism	
		Compound deer antler base capsules (13 g/kg/day, i.p., for 30 days)	Mice (in vivo)	The level of follicle-stimulating hormone in benzoic acid estradiol-induced mammary hyperplasia mice	Stimulatory	Zhao et al. (2010a,b)
				The uterine weight and uterine index, the level of luteinizing hormone and the morphological parameters of breast tissue	Antagonism	
2	Immune system	Deer antler base injection (6, 17 g/kg/day, i.p., for 7 days)	Mice (in vivo and in vitro)	Phagocytosis of peritoneal macrophages and the ratio of T/B lymphocytes in normal mice	Stimulatory	Chen et al. (1987, 1989)
		Deer antler base polypeptides (1, 2 g/kg/day, i.g., for 7 days)	Mice (in vivo)	The phagocytic index and phagocytic coefficient of liver and spleen in normal mice	Stimulatory	Wang et al. (2007, 2008)
3	Anti-cancer	Deer antler base injection (30, 86 g/kg/day, i.p., for 10 days)	Mice (in vivo and in vitro)	The body weight and the tumor weight of mice with breast cancer MA-737	Antagonism	Chen et al. (1987, 1989)
				The ratio of T/B lymphocytes in mice with breast cancer MA-737	Stimulatory	
		Water-soluble extract of deer antler base (30, 86 g/kg/day, i.p., for 10 days)	Mice (in vivo and in vitro)	The body weight and the tumor weight of mice with breast cancer MA-737	Antagonism	Wang and Gao (1999)
				The ratio of T/B lymphocytes in mice with breast cancer MA-737	Stimulatory	
4	Anti-fatigue	Deer antler base proteins (40 mg/kg/day, i.g., for 5 days)	Mice (in vivo)	Swimming time and adrenal coefficient	Stimulatory	Su et al. (2001)
		Aqueous extract of deer antler base (100 mg/kg/day, i.g., for 30 days)	Mice (in vivo)	Swimming time, the level of hepatic glycogen	Stimulatory	Niu et al. (2011a)
				The levels of blood lactic acid and serum urea nitrogen	Antagonism	
		Deer antler base collagens (800 mg/kg/day, i.g., for 21 days) and deer antler base proteins (70 mg/kg/day, i.g., for 21 days)	Mice (in vivo)	Swimming time, the lactate dehydrogenase activity, and the level of hepatic glycogen	Stimulatory	Shi et al. (2011)
				The level of serum urea nitrogen	Antagonism	
5	Bone metabolism	Deer antler base collagens (800 mg/kg/day, i.g., for 90 days)	Rats (in vivo)	Bone mineral density, the level of hydroxyproline, bone mechanical indicators (payload maximum, deflection maximum, moment maximum, bone stress and strain), bone formation parameters	Stimulatory	Niu et al. (2012)
				Alkaline phosphatase activity, bone resorption parameters	Antagonism	
		Chloroform-soluble extract of deer antler base	Bone marrow-derived macrophages (in vitro)	The formation and differentiation of osteoclasts, bone-resorbing activity, the formation of actin ring	Antagonism	Li et al. (2007b)
				Osteoclast apoptosis	Stimulatory	
6	Anti-bacterial	Ethanol extract of deer antler base (0.25 g/ml)	Hemolytic streptococcus	Inhibition zone diameter	Stimulatory	Wang et al. (2004)
		Deer antler base proteins (2.8, 11.2 mg/ml)	Escherichia coli, Hemolytic streptococcus	Inhibition zone diameter	Stimulatory	Huang et al. (2010b)
		Deer antler base powder (1%)	Escherichia coli, Staphylococcus aureus	Inhibition zone diameter	Stimulatory	Xiao (2012)

Table 4 (continued)

No.	Property/ condition	Formulation/extract/dosage	Model	Mode of action	Effect	Reference
7	Anti-viral	Deer antler base polysaccharides (2–39 mg/ml)	Bovine kidney cell line (in vitro)	The anti-bovine viral diarrhea virus activity measured by neutral red dye method	Stimulatory	Gao et al. (2010)
8	Anti-inflammatory and analgesia	Deer antler base polypeptides (40 mg/kg/day, i.g., for 8 days)	Mice (in vivo)	The auricular swelling in dimethylbenzene-induced mice	Antagonism	Wang (2004b)
		Deer antler base proteins (20.1–31.0 kDa)	Mice (in vivo)	The paw swelling in formaldehyde-induced mice, the times of writhing reaction in acetic acid-induced mice	Antagonism	Qiu et al. (2007)
		Aqueous extract of deer antler base (100, 200 mg/kg/day, i.p., for 7 days)	Mice (in vivo)	The carrageenan-induced paw swelling and the xylene-induced auricular swelling in mice, and the times of writhing reaction in acetic acid-induced mice	Antagonism	Niu et al. (2011b)
				The pain threshold in hot-plate test	Stimulatory	
9	Glucose metabolism	Deer antler base polypeptides (100 mg/ml)	Mice (in vivo) and Hep G2 cells (in vitro)	Reduction of blood glucose level in KK-Ay mice, and the glucose consumption in Hep G2 cells of insulin resistance	Stimulatory	Huang et al., (2010c)
10	Blood system	Deer antler base collagens (5 g/kg/day, i.g., for 8 days) and deer antler base proteins (40 mg/kg/day, i.g., for 8 days)	Mice (in vivo)	The number of red blood cells, and the content of hemoglobin	Stimulatory	Su et al. (2001)
11	Anti-stress	Deer antler base collagens (5 g/kg/day, i.g., for 4 days) and deer antler base proteins (40 mg/kg/day, i.g., for 4 days)	Mice (in vivo)	The anxiety and fur biting of mice induced by paint	Antagonism	Su et al. (2001)
12	Anti-oxidation	The protein hydrolysate of deer antler base (0.2–1.0 mg/ml)	IC_{50} (in vitro)	The radical scavenging activities of DPPH, $\cdot$OH and $\cdot O^{2-}$	Stimulatory	Yu et al. (2011)

5.1. Therapeutic effect on mammary hyperplasia

Treatment of breast lumps has long been a historical application for deer antler base (Wang et al., 2007). Mammary hyperplasia, also known as mammary dysplasia, is a common female disease (Cardiff and Wellings, 1999). The cause of mammary hyperplasia is closely related to an imbalance of endocrine hormones, especially estrogen and progesterone secreted by the ovary during the luteal phase (Song, 2003). Modern studies have shown that deer antler base could treat mammary hyperplasia and mastitis (Wang, 1987; Qiu et al., 2007).

Intraperitoneal injection (i.p.) of deer antler base injection (6 g/kg/day) or deer antler base polypeptides (20 mg/kg/day) to estradiol valerate-induced mice for 10 days promoted the shrinkage of the hyperplastic mammary gland (Chen et al., 1987, 1989). The mechanism may be related to the improvement of brain dopamine production which then serves to inhibit the secretion of prolactin in the blood (Wang and Gao, 1999; Zhang et al., 2005). In addition, intragastric administration (i.g.) of 1 and 2 g/kg/day of deer antler base polypeptides for 30 days reduced the level of estradiol in rats with mammary hyperplasia (Wang et al., 2008). Zhao found that compound capsules made from deer antler base reduced uterine weight, the levels of estradiol and luteinizing hormone and the protein expression of estrogen receptor, whereas it elevated the levels of progesterone and follicle-stimulating hormone in mice with mammary hyperplasia (Zhao, 2008). In a different experiment, Zhao et al. observed the effect of compound deer antler base capsules on the treatment of mammary hyperplasia in mice established by benzoic acid estradiol. The results showed that 13 g/kg/day of compound deer antler base capsules can restore uterine weight and the uterine index, and regulate the imbalance of sex hormones (luteinizing hormone and follicle-stimulating hormone) to maintain a dynamic balance. At the same time, this substance can also improve the morphological parameters of breast tissue, including the number of acinar and lobular cells, the diameter of the acinar cavity and ductal as well as cytoplasmic areas (Zhao et al., 2010a,b).

Taken together these studies indicate that deer antler base may be an effective drug for curing mammary hyperplasia. However, the individual bioactive compounds and the exact molecular mechanism through which deer antler base functions are still unclear. Other mechanisms such as the modulation of protein function, intracellular cascades and gene expression may also be involved.

5.2. Immunomodulatory effect

It is estimated that a 98% of animal species have acquired "innate immunity" to respond to pathogens that threaten their lives (Rodríguez et al., 2012). The immune system is thought to be a defensive system (Liang et al., 2004). The injection and polypeptides of deer antler base could affect the phagocytic ability of macrophages and regulate immune function. Chen et al. reported that intraperitoneal injection of 6 and 17 g/kg/day of deer antler base to mice over a period of 7 days could significantly increase the phagocytic index of macrophages and the ratio of T/B lymphocytes compared with the control group. The immunomodulatory mechanism may be that deer antler base injection greatly enhanced the phagocytosis of macrophages, promoted the proliferation and differentiation of T and B mouse lymphocytes and increased the activity of both these lymphocytes (Chen et al., 1989). In 2008, Wang et al. used ultra-fine grinding technology to crush deer antler base, and after leaching, salting out, enzymatic hydrolysis and dialysis, they extracted and purified its polypeptides. It was found that 2 g/kg/day of deer antler base polypeptides greatly increased the phagocytic index and phagocytic coefficient of spleen and liver, respectively (Wang et al., 2008). These results indicate that deer antler base and its extracts have a considerable effect on the immune system. Further investigations regarding the effects of deer antler base on other immune organs, immune cells and immune factors are necessary.

5.3. Anti-cancer effect

Many studies have reported that plant based medicines had anti-cancer activity, such as Caragana, Epimedium, Curcuma and Sargassum (Meng et al., 2009; Ma et al., 2011; Li et al., 2012; Liu et al., 2012). In this connection, as an animal based medicine, deer antler base also can efficiently inhibit the growth of breast cancer. For example, intraperitoneal injection of 30 and 86 g/kg/day of deer antler base injection to mice for 10 days followed by injection with 0.2 ml of breast cancer cell suspensions at the right armpit of mice significantly reduced tumor weight compared with the mice injected with cell suspensions only. Moreover, deer antler base injection significantly prevented the depletion of T lymphocytes and increased the ratio of T/B lymphocytes in mice with breast cancer MA-737 (Chen et al., 1989). In a different study, water-soluble extract of deer antler base obviously suppressed the tumor growth, prevented the depletion of T lymphocytes and increased the ratio of T/B lymphocytes in mice with breast cancer MA-737. The mechanism may be that the water-soluble extract of deer antler base promotes a cytotoxic-like effect of lymphokines, removing the hyperplastic and necrotic mammary epithelial cells (Wang and Gao, 1999). In summary, a series of in vivo studies suggest that deer antler base has a beneficial effect on breast cancer. However, it has no effect on the later stages of breast cancer which needs to be investigated further.

5.4. Anti-fatigue effect

Many reports suggested that deer antler base extracts have anti-fatigue effects. Intragastric administration of deer antler base proteins to mice, at a dose of 40 mg/kg/day for 5 days, markedly prolonged the swimming time (from 5.85 ± 1.30 to 10.52 ± 0.80 h, $P < 0.01$) and increased the adrenal coefficients (from 0.07 ± 0.01 to 0.08 ± 0.01 mg·10 g^{-1}, $P < 0.05$) in a forced swim test. These results suggest that the anti-fatigue effect of deer antler base proteins may be related to the enhancement of adrenal function (Su et al., 2001). In a different study, intragastric administration of 100 mg/kg/day aqueous extract of deer antler base to mice for 30 days prolonged the swimming time and decreased the level of blood lactic acid, but there was no significant difference in hepatic glycogen and serum urea nitrogen levels compared with the control group. The results suggest that the aqueous extract of deer antler base efficiently relieved fatigue and enhanced exercise tolerance (Niu et al., 2011a). Furthermore, intragastric administration of deer antler base collagens (800 mg/kg/day) or deer antler base proteins (70 mg/kg/day) to mice for 21 days significantly prolonged the swimming time, improved the activity of lactate dehydrogenase, and decreased serum urea nitrogen but increased hepatic glycogen (Shi et al., 2011). Based on the above results, it can be seen that the collagens and proteins of deer antler base are the major anti-fatigue substances, but further investigations are needed to fully elucidate the exact mechanisms.

5.5. Anti-osteoporosis effect

Niu et al. treated osteoporotic rats caused by bilateral ovariectomy with 800 mg/kg/day of deer antler base collagens for 90 days. The analysis showed that deer antler base collagens obviously increased bone mineral density and the content of hydroxyproline while reducing the content of alkaline phosphatase in serum compared with the sham group. Deer antler base collagens also caused significant differences in bone histomorphometry, such as mean trabecular plate thickness and spacing, trabecular bone volume and mean cortical bone thickness, indicating that deer antler base collagens could increase bone formation parameters, reduce bone resorption parameters, and effectively prevent the loss of bone mass. Moreover, deer antler base collagens significantly improved several bone mechanical indicators, including maximum payload, maximum deflection, bone stress and bone strain, indicating that deer antler base collagens can reduce bone fragility and the incidence of fractures in osteoporotic rats. These results indicate that deer antler base has a satisfactory therapeutic effect on osteoporosis. However, the body weights and organ coefficients of osteoporotic rats treated with 800 mg/kg/day of deer antler base collagens were not statistically significant compared with the sham group indicating that the mechanism of action is likely not through estrogen-like effects or through adjustments in the function of the hypothalamic–pituitary–adrenal axis (Niu et al., 2012).

Osteoclasts are specialized bone-resorbing cells derived from multipotent myeloid progenitor cells. They play a crucial homeostatic role in skeletal modeling and remodeling and destroy bone in many pathologic conditions (Choi et al., 2010; Ma et al., 2011). A previous study showed that the chloroform-soluble extract of deer antler base significantly inhibited the formation of TRAP-positive multinuclear osteoclasts in bone marrow-derived macrophages stimulated by macrophage-colony stimulating factor (M-CSF) plus receptor activator of nuclear factor κB ligand (RANKL). It also significantly inhibited the bone resorptive activity both by inducing osteoclast apoptosis and by disrupting the formation of the actin ring (a marker of activated osteoclasts) in mature osteoclasts. Furthermore, the chloroform-soluble extract of deer antler base suppressed osteoclast differentiation and bone resorption via Akt, ERK and NF-κB signaling pathways (Li et al., 2007b). These results demonstrate that deer antler base may be a useful remedy for the treatment of osteoporosis. Although the active substances have not yet been identified, it is clear that the chloroform-soluble extract of deer antler base contains bioactive substances that inhibit osteoclast differentiation and bone resorption. Therefore, further fractionation and purification of the chloroform-soluble extract of deer antler base is needed to identify the bioactive compound(s).

In conclusion of the effect on bone metabolism, the mechanisms by which deer antler base can act in the prevention and treatment of osteoporosis include the following three points: (1) effectively controls the loss of bone mass; (2) promotes bone formation and inhibits bone absorption; and (3) improves the negative balance of bone metabolism. In TCM, the kidney is believed to be in charge of the bone, and deer antler base was thought to tonify the kidney and strengthen bones and muscles. Now, its efficacy in the prevention and treatment of osteoporosis has been confirmed.

5.6. Anti-bacterial effect

A series of studies have been performed on the effects of deer antler base and its crude extracts on the growth of different bacteria (Hemolytic streptococcus, Staphylococcus aureus and Escherichia coli). The growth of Hemolytic streptococcus was inhibited by 0.25 g/ml ethanol extract of deer antler base (Wang et al., 2004). Recently, Huang et al. extracted proteins from deer antler base and velvet antler according to the method described by Rauscher et al. (2002) and studied the inhibitory effect of deer antler base proteins and velvet antler proteins by the filtering paper method. They found that at a concentration of 11.2 mg/ml, both deer antler base proteins and velvet antler proteins significantly inhibited the growth of Escherichia coli compared with the control group. The protein concentration of deer antler base and velvet antler that markedly inhibited the growth of Hemolytic streptococcus was 2.8 mg/ml, and the inhibition zone diameters were 10 ± 0.5 and 8.0 ± 0.1 mm ($P < 0.01$), respectively. These experiments indicate that deer antler base proteins can inhibit the growth of Escherichia coli and Hemolytic streptococcus, and the anti-bacterial activity of deer antler base proteins was better than velvet antler proteins (Huang et al., 2010b). In a different experiment, Xiao used a double paper plate diffusion method to measure the average diameters of the inhibition zone of deer antler base powder and antibiotics. They observed that the average diameters of the inhibition zone of deer antler base powder on Staphylococcus aureus and Escherichia coli were 14.22 ± 4.49 and 12.22 ± 6.76 mm, while the average diameters of penicillin were 26.22 ± 3.89 and 8.8 ± 1.03 mm, as well as the average diameters of streptomycin were 13.0 ± 4.24 and 18.8 ± 5.59 mm, respectively. These results imply that deer antler base powder has moderate bacteriostatic efficacy compared with penicillin and streptomycin (Xiao, 2012). Therefore, the anti-bacterial effects of this animal based medicine might be a new hot spot for pharmacological studies in the next few years.

5.7. Anti-viral effect

In addition to moderate anti-bacterial effects, deer antler base also has anti-viral effects. Gao et al. used the neutral red dye method to determine the toxicity of deer antler base polysaccharides to MDBK bovine kidney cell line in order to study its anti-bovine viral diarrhea virus activity. The results showed that the effective anti-bovine viral diarrhea virus activity is in the concentration range of 2–39 mg/ml, with a dose–effect relationship. In other words, under a nontoxic range of concentrations, the anti-viral activity improves with increasing concentrations of deer antler base polysaccharides (Gao et al., 2010). Therefore, deer antler base polysaccharides are expected to become a new class of potential anti-viral drug following virus reverse transcriptase activity inhibitors and protease inhibitors, but further studies are needed to explore its mechanisms of action.

5.8. Anti-inflammatory and analgesic effect

Wang studied the anti-inflammatory effect of the deer antler base polypeptides extracted by using 80% methanol and 35–50% ethanol. It was found that deer antler base polypeptides can obviously inhibit dimethylbenzene-induced auricular swelling of mice (Wang, 2004b). Moreover, Qiu et al. demonstrated that 10 and 20 mg/kg/day of deer antler base proteins with molecular weights between 20.1 and 31.0 kDa have significant anti-inflammatory effects on formaldehyde-induced paw swelling and can also reduce the times of writhing reaction in acetic acid-induced mice showing a significant analgesic effect (Qiu et al., 2007). In a different experiment, intraperitoneal injection of aqueous extract of deer antler base, at doses of 100 and 200 mg/kg/day for 7 days, markedly inhibited carrageenan-induced paw swelling and xylene-induced auricular swelling in mice. At the same time, the aqueous extract of deer antler base obviously improved the pain threshold during the hot-plate test and reduced the times of writhing reaction in acetic acid-induced mice, which indicates that it has good anti-inflammatory and analgesic effects (Niu et al., 2011b). As summarized above, the polypeptides and proteins of deer antler base are the major anti-inflammatory substances and display evident anti-inflammatory and analgesic properties in vivo, which validate its traditional use in mastitis and children's mumps. However, the mechanism of action related to multiple inflammation-related proteins and signal pathways should be further investigated with both in vitro and in vivo studies.

5.9. Hypoglycemic effect

Huang et al. extracted and purified deer antler base polypeptides by Resource S, Superdex 75 and inverted HPLC processes. They observed the hypoglycemic effect of deer antler base polypeptides in genetically diabetic mice (Type II, KK-Ay) by single oral administration and studied the effects of deer antler base polypeptides on glucose consumption in human hepatoma Hep G2 cell line of insulin resistance. The results showed that within 24 h of administration, deer antler base polypeptides could reduce the blood glucose levels of KK-Ay mice and the time to reach the highest peak of drug action was 12 h. Additionally, 100 mg/ml of deer antler base polypeptides obviously promoted glucose consumption (4.36 mmol/l) in Hep G2 cells of insulin resistance induced by 0.5 mmol/l insulin which even recovered to normal levels (4.38 mmol/l) (Huang et al., 2010c). Although deer antler base has not traditionally been used to treat hyperglycemia, these results suggest that deer antler base polypeptides could be a potential source of hypoglycemic agents. The outcome of such study may further expand its existing therapeutic potential.

5.10. Hematopoietic modulatory effect

Intragastric administration of deer antler base collagens (5 g/kg/day) or deer antler base proteins (40 mg/kg/day) to mice for 8 days significantly increased the number of red blood cells and the hemoglobin content in treated mice compared with the control group (Su et al., 2001). This indicates that deer antler base collagens and proteins could enhance the body's hematopoietic function. The mechanism may be that deer antler base collagens and proteins promote the hematopoietic system to secrete hematopoietic-related factors, improve the hematopoietic micro-environment and stimulate the proliferation, differentiation and maturation of hematopoietic stem cells, and thus elevate the number of red blood cells and the content of hemoglobin in peripheral blood (Kong et al., 1998). It can be seen that deer antler base has a very clear hematopoietic modulatory activity. However, determining its exact cellular and molecular mechanisms will require further investigation.

5.11. Anti-stress effect

The peculiar smell of paint is a harmful stimulus for mice and could abate the stress function of the neuroendocrine system which could lead to a state of anxiety, and the animal may even bite the fur coated paint. Intragastric administration of deer antler base collagens (5 g/kg/day) or deer antler base proteins (40 mg/kg/day) to mice for 4 days markedly inhibited the state of anxiety and fur biting of mice induced by paint. This indicates that deer antler base collagens and proteins may stimulate the endocrine system, enhance the anti-stress activity for external noxious stimuli, reduce excitability and improve the stress response capacity of mice (Su et al., 2001). These results show that the collagens and proteins of deer antler base are the major anti-stress substances, but the mechanism of action should be further investigated with both in vitro and in vivo studies.

5.12. Anti-oxidation effect

Yu et al. optimized the enzymatic hydrolysis of deer antler base proteins and studied the anti-oxidation activity of the protein hydrolysate. They observed that the effect of the protein hydrolysate of deer antler base was predominant in eliminating free radicals, including 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydroxyl radical (·OH) and superoxide anion (·O^{2-}) with an IC_{50} 1.89, 0.38 and 0.70 mg/ml, respectively. Additionally, within the concentration range of 0.2–1.0 mg/ml, the scavenging activity of the protein hydrolysate of deer antler base for DPPH, ·OH and ·O^{2-} appeared to be enhanced in a dose-dependent manner (Yu et al., 2011). So the protein hydrolysate of deer antler base was effective against oxidation in vitro.

6. Clinical trials

Deer antler base has been used in clinical treatment of various women's diseases for many years. In 1980, Zhang and Wang used deer antler base injection made from the rude extraction of deer antler base and Momordica cochinchinensis to treat 86 cases of mammary hyperplasia, which accounted for 33.7% of clinically cured patients and 87.2% of total efficiency (Zhang and Wang, 1980). A few years later, deer antler base injection was used to treat 146 cases of mammary hyperplasia, which accounted for 32.9%of clinically cured patients and 83.6%of total efficiency. The results showed that deer antler base injection has a good curative effect on mammary hyperplasia and is very effective in the control of early stage breast cancer (Zhang and Wang, 1987). Zhang and Lin adopted traditional deer antler base capsules to treat 120 cases of mammary hyperplasia. Their shortest treatment time was 10 days and the longest was two courses of treatment. They obtained 88 cases of clinically cured patients and their total effective cure rate was 94.2%(Zhang and Lin, 2010).

It is of interest to see some clinical reports about other women's diseases, such as acute mastitis and chapped nipple. Zhou et al. used unglued antler powder (Cornu Cervi Degelatinatum) made from deer antler base to treat 56 cases of acute mastitis, whereby the patient recovered from the disease after being given 15 g of unglued antler powder, orally three times a day over a period of 5 days, which accounted for 93.3% of total efficiency (Zhou et al., 2000). Other researchers used the unglued antler powder to treat 38 cases of postpartum chapped nipple, whereby the patient all recovered from the disease after being given 5 g of unglued antler powder, orally three times a day over a period of 2 days (Gao and Gao, 2004).

Besides various women's diseases, deer antler base has also been used in the clinical treatment of gastric cancer. For example, Han reported a case of gastric cancer treated by deer antler base, whereby the patient recovered from the disease after being given 5 g of deer antler base powder, orally three times a day over a period of 2 years (Han, 1987). Zhang reported another case of gastric cancer treated by deer antler base, whereby the patient with late stage gastric cancer recovered from the disease after being administered 10 g of deer antler base powder, orally three times a day over a period of 2 years (Zhang, 2006). These cases suggest that the active components of deer antler base have an inhibition effect on gastric cancer cells.

In conclusion, the clinical effects of preparations from deer antler base for mammary hyperplasia, acute mastitis, chapped nipple and gastric cancer have been studied. The useful and authoritatively clinical studies were very limited and most of these preparations were made of the rude extraction from deer antler base alone or with other herbals and most of these studies were designed very simply. Therefore, further clinical trials are urgently needed to perform before it can be integrated into medicinal practices.

7. Toxicology

Deer antler base, as a traditional Chinese medicine, has been used for 2000 years in China. Although it is listed as a medicine, investigation of its relative toxicity and safety evaluations have been lacking although no major side effects have yet been discovered. The famous Chinese medicinal books Ben Cao Gang Mu (本草纲目) and Ming Yi Bie Lu (名医别录) unanimously point out that deer antler base is nontoxic. In 1987 and 1989, the safety of deer antler base was evaluated in a series of experiments, including the acute toxicity test, the long-term toxicity test, the stimulated test and the allergic test. The acute toxicity test was conducted using intraperitoneal injection of deer antler base to mice at a dose of 30 g/kg. This dosage was equal to 500 times the normal human dosage in clinical application and no mortality was found within 72 h of treatment. The long-term toxicity test was investigated using intraperitoneal injection of deer antler base to rats at doses of 15 and 30 g/kg/day for 28 days. It was found that deer antler base injection had no effect on blood biochemical parameters and the cellular structure of organs and tissues. The stimulated tests were performed by subcutaneous injection of 0.1 ml (0.37 g) deer antler base to the left ear of rabbits or intramuscular injection of 0.25, 0.5, or 1 ml (3.7 g, equivalent to 30 times the clinical application) deer antler base to the quadriceps muscle of rabbits. No adverse stimulus-response (e.g. edema and hyperemia) was observed. The allergic test was detected by intravenous injection of deer antler base to guinea pigs. The results showed no dyspnea or suffocation (Chen et al., 1987, 1989). In 2010, the acute toxicity of the protein extracts of deer antler base was measured by intragastric administration to mice at a dose of 40 mg/kg/day for 7 days. No significant differences were found in treated mice for any organ parameter analyzed (including pancreas coefficient and kidney coefficient), and no deaths were observed, suggesting that the protein extracts of deer antler base has little or no acute toxicity (Ma and Wang, 2010). In short, no known contraindications for the use of deer antler base have been found.

8. Conclusions

Deer antler base has been widely used in traditional Chinese medicine (TCM) for many centuries and is generally believed to nourish the Yin, tonify the kidney, invigorate the spleen, strengthen bones and muscles, and promote blood flow. Traditional uses include the treatment of mammary hyperplasia, mastitis, uterine fibroids, sterility, menoxenia, amnesia, osteoporosis, immune dysfunction, dizziness and tinnitus, and so on. The recent pharmacological studies have validated the traditional uses of deer antler base.

Both in vitro and in vivo pharmacological studies have demonstrated that deer antler base possess immunomodulatory, anticancer, anti-fatigue, anti-osteoporosis, anti-inflammatory, analgesic, anti-bacterial, anti-viral, anti-stress, anti-oxidant, hypoglycemic, hematopoietic modulatory activities and the therapeutic effect on mammary hyperplasia. It is particularly noteworthy that pharmacological studies and clinical practice provide strong evidence for the effectiveness of deer antler base in treating mammary hyperplasia and mastitis. However, further studies are needed to detailedly illustrate the biochemical and physiological mechanisms associated with the therapeutic effects of deer antler base.

Most of the pharmacological studies were conducted using uncharacterized crude extracts of deer antler base. It is difficult to reproduce the results of these studies and pinpoint the bioactive compounds. Hence, there is a need for chemical standardization and bioactivity-guided identification of bioactive compounds. Among several classes of chemical constituents identified in deer antler base, amino acids, polypeptides and proteins are assumed to be the main bioactive compounds responsible for the majority of its pharmacological effects. However, the vast traditional use and proven pharmacological activities of deer antler base indicates that an immense scope still exists for its chemical exploration. The outcome of such chemical studies may further expand its existing therapeutic potential.

In recent years, chemical and pharmacological studies of deer antler base have received much interest, but the pharmacological studies so far have mostly been performed in vitro and in vivo with animals. Therefore, more clinical studies in humans are urgently needed to confirm the effectiveness of this traditional therapy. Based on this review, it is concluded that there is not sufficient information on the toxicity of deer antler base. Although no major side effects have yet been discovered, extensive research is necessary to confirm the safety of deer antler base before it can be fully integrated into medicinal practice. In addition, taking into account their therapeutic efficiency and economical considerations, the major bioactive compounds of deer antler base might be developed into new drugs for the treatment of difficult and complicated diseases, especially mammary hyperplasia, mastitis, osteoporosis, cancer, immunity-related diseases.

All in all, the collected information reviewed here provides a resource for future studies and commercial exploitations of deer antler base.

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