Advances in the Research of Mongolian Medicine Har-Gabur

Junhua Han[1], Tegexibaiyin Wang[2,*], Qingshan Zhang[1,*]
[1]*Inner Mongolia Minzu University, Tongliao, Inner Mongolia, China*
[2]*Affiliated Hospital of Inner Mongolia Minzu University, Tongliao, Inner Mongolia, China*
**Corresponding Author*

Abstract: As a special medicinal material, Har-Gabur is widely used in Mongolian medicine for treating chronic gastritis, functional dyspepsia, Helicobacter pylori infection and its related diseases, and it has a unique therapeutic effect. With the development of nanomedicine, Har-Gabur has been successfully prepared into fluorescent carbon dots and has become a research hotspot in the biomedical field in recent years. This review summarizes the most recent advances related to its chemical composition, pharmacological activities, clinical use and advances in nanomedicine, with the aim of offering a scientific rationale for the further exploitation of the scientific value of Har-Gabur and of advancing the modernization of Mongolian medicine.

Keywords: Har-Gabur; Chemical Composition; Pharmacological Activity; Fluorescent Nanoparticles

1. Introduction

Mongolian medicine is an invaluable part of traditional Chinese medicine, which is based on the basic concepts of “three roots, seven elements, and three impurities” and advocates comprehensive regulation and well-balanced treatment. It has unique advantages for the treatment of non-curable diseases, chronic diseases and tumors [1,2]. Har-Gabur, derived from animals, is a carbonaceous medicine commonly used in Mongolian medicine with a long history and with a proven efficacy. Historical literature including *Ren Yao Bai Jing Jian* [1] has first recorded Har-Gabur as the completely carbonized faeces of wild boars (Suidae family) and is the representative medicine of the Mongolian concept of “using carbon as medicine, employing toxicity against toxicity, and adsorptive expulsion of pathogens”. It is bitter and pungent, warm and acts upon the stomach, liver and gallbladder meridians, has the core effects of pacifying šira, and digestion and food accumulation resolution, dissolving “sticky” obstruction [3,4]. Har-Gabur is one of the most important ingredients in the treatment of indigestion, šira masses and “sticky” syndromes in clinical practice, and is often used in classic prescriptions, such as Harigabur-10 and Alatan Five-Ingredient Pills [3].

Nanomedicine has recently become a state-of-the-art approach with great promise for improving drug targeting and safety. According to the process recorded in the *Study on Mongolian Medicine Processing* [5] the process of Har-Gabur preparation is: Feces of wild boar are placed in an iron pot, which is then covered with another iron pot placed upside down, and the seam is sealed with yellow earth or salt-laden mud. After the mud is slightly dry, a weight is placed on top to prevent cracking, cooled and pulverized after the impurities contained in the feces are removed. This carbonized form of Har-Gabur, being used as a medicine, is characterized by carbon nanostructures, supplemented with inorganic elements and small amounts of organic components, and is structurally similar to man-made nanomaterials. This similarity puts Har-Gabur as a prototype of natural nanomedicine based on the carbon, which can give new ideas in the research of Mongolian medicine modernization [6].

2. Chemical Constituents of Har-Gabur

Har-Gabur is regarded as one of the key medicinal herbs in traditional treatments for digestive and hepatobiliary diseases in Mongolian medicine and the study of the material basis of the therapeutic effect of Har-Gabur is one of the research focuses. Systematic analyses performed in recent times have pointed out a number of important chemical classes:

2.1 Inorganic Elements

Har-Gabur contains a variety of essential trace and macro elements which are important to control metabolism and maintain physiological balance. Based on its composition (organic carbon, inorganic salts and trace elements), specific extraction and pretreatment methods have been developed. Zhao et al. [7,8] found a rich content of iron (Fe), zinc (Zn), calcium (Ca), potassium (K), manganese (Mn) and magnesium (Mg) and that processing has a strong effect on Fe and Zn concentrations [5]. Further research conducted by Xu et al. [9] and Cui et al. [10] determined the content of trace elements manganese and molybdenum, and found Mo content of 0.474 μg/g [10]. In particular, Peng et al. [11] noted the high concentration of certain heavy metals including lead (Pb), cadmium (Cd), arsenic (As), mercury (Hg), and copper (Cu) ranging from 17.65 to 77.82 mg/kg, thus emphasizing the need for comprehensive safety monitoring in addition to efficacy assessment.

2.2 Organic Components

In addition to the elemental composition, Har-Gabur also has some small molecule organic compounds that are not removed by carbonization, which may amplify the pharmacological effect of Har-Gabur. By using Kjeldahl nitrogen determination method, Xing et al. [12] analyzed 10 batch samples and found that the content of nitrogen in the samples is 2.39% (above the provisional limit of 1.5%), which proved the presence of nitrogenous organics. This finding proposed new quantitative quality control indices.

2.3 Carbonaceous Adsorptive Structure

Ma et al. [13] found that the Har-Gabur has an irregular porous network that is similar to the structure of activated carbon by observation with scanning electron microscopy. Its specific surface area and adsorption capacity are not as good as activated carbon and montmorillonite, but it still has certain physical adsorption properties. This unique microarchitecture is the basis of its “adsorption of toxins” and “clearing febrile toxicosis and jaundice” actions and is a foundational basis for its anti-inflammatory, immunomodulatory and putative antineoplastic effects.

3. Pharmacological Effects of Har-Gabur

3.1 Regulation and Protection of Gastrointestinal Function

The extensive studies showed that Har-Gabur regulated gastrointestinal motility and had a spasmolytic effect on gastrointestinal mucosa and anti-ulcerogenic effect, which were all consistent with the clinical effects of Har-Gabur in the treatment of dyspepsia and mass formation. In a cold stress-induced gastric mucosal injury model, Bai et al. [14] reported that Har-Gabur inhibited the gastric injury with an inhibition rate of 64.5%, and interestingly, it also enhanced the gastric emptying rate compared to the control group by 98.6% and 38.5% in high and low dose groups, respectively. In addition, it helped to improve the passage of activated charcoal through the small intestine by 17.1% and 7.0%. Cai et al. [15] investigated its effects on intestinal smooth muscle receptors, and found that it had little effect on the normal isolated ileal muscle and had a significant inhibitory effect on the histamine-induced spasms (25%, $P<0.05$), while it had a weak inhibitory effect on the acetylcholine-induced contractions (9.7%). Har-Gabur was found to be antimotility in the small intestine in vivo, and high doses were atropine-like. Wang [16] explained the anti-ulcer mechanism on the molecular level, revealing the main components of the carbon nanomaterials (e.g., graphene oxide), which could cause pro-inflammatory M1 polarization in macrophages. But, when administered in combination with curcumin, it is able to suppress the exaggerated inflammation by blocking the TLR4/MyD88/NF-κB signaling pathway and exert therapeutic effects. Lin et al. [17] noticed that when a TNBS-induced colitis rat model was used, the body weight loss was significantly alleviated, the suppression of food intake was significantly reduced and the pathological examination indicated that the congestion, edema and ulceration of the colon were significantly decreased (inhibition rates of 29.0% and 25.8% for congestion and edema/ulceration, respectively). Biochemical assays showed a decrease in white blood cells (WBC), erythrocyte sedimentation rate (ESR) and an increase in the activity of superoxide dismutase (SOD) and a decrease in malondialdehyde (MDA).

3.2 Adsorptive Properties and Antibacterial Activity

Har-Gabur's pharmacodynamics is closely related to its unique physicochemical properties. The strong adsorption capacity of it was validated by Chang et al. [18] which had an average adsorption of 2.85 mg/g toward lemon yellow dye. Ma et al. [14] pointed out its porous structure similar to that of activated carbon, which allows it to adsorb intestinal pigments and toxins. Li et al. [19] showed good endotoxin adsorption (up to 97%) which improved with time and found that the adsorption mechanism was similar but more biocompatible than activated carbon. Wang [16] also demonstrated that Har-Gabur preparations (such as Ten-Ingredient Har-Gabur Powder) inhibit Helicobacter pylori proliferation in a concentration-dependent manner, which further confirmed the clinical effect of Har-Gabur on peptic ulcer.

4. Clinical Application of Har-Gabur

Har-Gabur has consistently shown remarkable therapeutic effects from classical formulations to recent clinical research. It has clinical application mainly in two aspects: using the traditional compound prescriptions in the process of syndrome differentiation and combining with current combination therapy for some diseases.

4.1 Clinical Application in Traditional Mongolian Medicine

Har-Gabur has been one of the key ingredients for the treatment of "heyi", šira diseases and other gastrointestinal disorders for centuries [3]. The use of composite prescriptions containing Har-Gabur is described in detail in the famous Mongolian medical treatises, including *Gan Lu Si Bu* [20] and *Yi Fa Zhi Hai* [21]. It is an indispensable component in many Mongolian patent medicines such as Harigabur-10 (Ten-Ingredient Har-Gabur Powder), Yihe Har-12 and Alatan Aru-5 (Alatan Five-Ingredient Pills) [22]. All these formulas contain Terminalia chebula, pomegranate, Momordica cochinchinensis and Trogopterus dung for potentiation of digestive promotion, dispelling of internal "bada gan (a concept related to phlegm and coldness)", and elimination of šira [23]. According to the traditional Mongolian pharmacology, Har-Gabur has bitter and pungent flavor, warm property and functions of digestion promotion, pacification of šira, dissolution of "sticky" masses and resolving masses. The clinical manifestations include cold-type šira, indigestion, jaundice, stomach šira symptoms and "sticky" ulcers. In Mongolian etiopathogenesis, Har-Gabur is considered to be one of the key ingredients to treat gastrointestinal heat accumulation, food stagnation and hepatobiliary heat syndrome and it is frequently used as first-line prescription in Mongolian medicine for "heyi" and šira syndromes [22,23].

4.2 Clinical Application in Modern Medicine

As evidence-based medicine has progressed, clinical applications of Har-Gabur have been further validated or extended [24]. Combination therapy nowadays is based on the premise of synergism between the multiple targets of different drugs, thus obtaining "1+1>2" therapeutic benefits that exceed those of monotherapies, together with the reduction of the drug dose, the decrease of side effects and the delay of resistance. The efficacy of Har-Gabur containing compounds in clinical studies is confirmed in chronic gastritis, functional dyspepsia, cholelithiasis and Helicobacter pylori infection [25-29]. Modern applications include such combination as Alatan Five-Ingredient Pills for chronic cholecystitis, scleral icterus, hepatobiliary heat syndromes for the resolution of jaundice and for improving bile flow [25]. Combination therapy has shown better results under the right conditions, such as Liu Liangying et al. [26] used Alatan Five-Ingredient Pills combined with pantoprazole for the treatment of chronic superficial gastritis, achieving an 86.32% overall effective rate, which far exceeded that of pantoprazole alone (63.22%). Chen et al. [27] observed the efficacy of Alatan Five-Ingredient Pills combined with mosapride in the treatment of FD was 95.71%, which was significantly higher than the efficacy of mosapride alone (85.71%), and there was also a significant decrease in the number of positive H. pylori and relapses. Deng Taozhi et al. [28] found that combination of Alatan Five-Ingredient Pills and lansoprazole showed 93.12% total response rate in GERD patients compared to 81.25% in patients receiving lansoprazole alone, and that bloating, abdominal pain and constipation were significantly relieved. In clinical studies done in H. pylori associated chronic gastritis (cold šira pattern), the eradication rate of Mongolian medicine was lower (70%) than western triple therapy (80%), but Mongolian medicine did not have any adverse effect or hepatic/renal toxicity and provided better symptom relief (belching, epigastric pain, anorexia), indicating the safety and symptomatic benefits of Mongolian medicine [29]. In summary, Har-Gabur's inclusion in contemporary polypharmacy practices upholds the principles of Mongolian medicine and provides a safe and effective new option for clinical treatment.

5. The Research Progress of Har-Gabur Fluorescent Carbon Dot

Cao et al. [6] discovered that there are some intrinsic carbon nanoparticles of different sizes naturally existing in Har-Gabur. The nanoparticles were fractionated according to different centrifugal speeds, and nanoparticles with smaller diameter (<100 nm) showed a prominent green fluorescence. Interestingly, they were observed to have an inverse relationship between fluorescence intensity/quantum yield and particle size. These nanoparticles exhibited size-dependent antibacterial activity against E. coli and S. aureus with smaller sizes being more effective. Du et al. [30] found that Har-Gabur carbon dots have excellent aqueous solubility and high fluorescence, meaning that they are surface modifiable and can be used as drug delivery vectors. Tegexibaiyin Wang et al. [31] synthesized Har-Gabur fluorescent carbon dots (Har Gabur CDs) with the size of ~4 nm, based on a biomimetic gastrointestinal digestion-simulating synthesis method using the carbonized Har-Gabur derived from the wild boar feces. The carbon dots showed excellent photostability and resistance to photo bleaching. PLL-passivated CDs were found to be efficient at the labeling of HepG2 cells both in vitro and in vivo, and zebrafish exposed for 10 min in water containing CDs showed much stronger fluorescence signals, indicating good potential applications of the CDs as biocompatible fluorescent probes with low cytotoxicity. Collectively, these results support the distinctive optical characteristics and the physicochemical benefits of the Har-Gabur-derived carbon nanomaterials, highlighting their potential in the emerging biomedical field.

6. Conclusion

Mongolian medicine is a part of the traditional medicine of China and has its rich history and theoretical system. In short, Har-Gabur is the perfect example of the combination of ancient Mongolian medical knowledge and modern nanotechnology, bringing to light its distinctive properties that have the potential to reshape the landscape of modern Mongolian pharmaceutical research. Its unique carbonaceous properties can be used to incorporate the time-honored concept of “carbon-based medication” into the new paradigm of nanomedicine, thus providing a solid scientific basis for the transition from “empirical efficacy” to a new era of Mongolian medicine with clearer mechanisms and more reliable clinical effects.

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