Advances in the Research of Har-Gabur Fluorescent Carbon Dots for the Treatment of Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a highly aggressive and lethal cancer that often faces problems such as drug resistance and tumor recurrence. Mongolian medicine is an important part of the traditional ethnic medicine of China, and is practiced for thousands of years by the Mongolian people. Har-Gabur (calcined animal feces in traditional medicine) is one of the key components of "Po Pi" (breaking stagnation) therapy with a long history and potential pharmacological activity against hepatic diseases. In recent times, carbon quantum dots (CQDs) have garnered a considerable amount of attention due to their ultrasmall size, high surface area, superb biocompatibility, easy surface functionalization and unique optical properties, making them promising nanoplatforms for various biomedical applications. The review summarizes the chemical composition, pharmacological activity and anti-HCC potential of Har-Gabur and the nanoengineered products, namely fluorescent carbon dots derived from Har-Gabur, aiming to provide insights on new approaches of nanoengineering Mongolian Har-Gabur for HCC treatment, and to give a theoretical basis and research directions to support modernization and application of traditional Mongolian medicine.

Keywords: Carbon Quantum Dots; Har-Gabur Carbon Dots; Mongolian Medicine; Hepatocellular Carcinoma

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumour worldwide. The most recent cancer statistics released by GLOBOCAN estimate that HCC is responsible for around 900,000 new cases each year, and for almost 830,000 deaths, making HCC the sixth most common cancer globally and the third leading cause of cancer-related death [1,2]. The situation is especially dire in China, as liver cancer has become the second most common cause of cancer death, with a total of 367,700 new cases and 316,500 deaths recorded in 2022, according to national health statistics [3]. While there have been strides in HCC screening, diagnosis and systemic therapies, the disease often presents insidiously, is poorly detected, and has high rates of therapeutic resistance, leading to a persistently poor long-term survival, particularly for patients with advanced disease [4,5]. Thus, there is an urgent need in HCC research to find new, effective and low-toxicity treatment modalities.

Although there has been progress in the treatment of HCC, achieving long-term survival remains a challenge. This situation is due to the heterogeneity of tumors and the complex immunosuppressive tumor microenvironment, which leads to drug resistance and a high rate of relapse. Monotherapeutic targeted agents are severely affected by both intratumoral and intertumoral genomic and metabolic heterogeneity and lead to rapid resistance development [6]. Analyses of different regions of the same tumor reveal the non-uniform distribution of driver mutations, making targeted therapy against a given pathway temporary and effective only in a part of the tumor [7]. Additionally, the tumor-immune microenvironment involving tumor-associated macrophages, regulatory T cells, and immune inhibitory cytokines creates a "cold tumor" that dampens the activity of immune effectors, meaning that only certain patients benefit from immunotherapies [8]. This immune evasion is combined with molecular resistance mechanisms, creating insurmountable clinical problems [9].

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Hence, new intervention strategies that can not only overcome tumor heterogeneity but also remodel the immune microenvironment, are paramount in overcoming these barriers.

Recent progress in nanotechnology has accelerated the development of nanomedicine and provided new strategies for cancer diagnosis and treatment. This transformation is driven by the power of nanotechnology that allows manipulation of materials at atomic and molecular levels, and promises an unparalleled level of precision in modulating biomolecules, cells and tissues [10,11]. Nanoparticles have been used widely for the diagnosis and therapy of genetic diseases, auto-immune disorders, malignant tumors and other disorders [12]. Researchers have now begun to explore new approaches for treating liver cancer, and nanotechnology has shown great potential in improving diagnostic accuracy and therapeutic efficacy [13-15]. In the field of diagnosis, nanomaterials, with their high sensitivity and modifiability, have provided powerful tools for the early detection of liver cancer [16]; in the field of treatment, two main therapeutic advantages of the nanoparticle drug delivery platforms are first, that nanoparticles accumulate more in tumors due to their passive and active targeting, which increases the efficacy and reduces systemic toxicity [17] and second, that nanoparticles can carry multimodal therapeutic agents to be co-delivered for synergistic therapeutic effects that overcome drug resistance [18,19].

At the same time, ethnopharmacological exploration has emerged as a key pathway in the discovery of anticancer drugs. The "Pi block" theory or "Po Pi" theory is a basic principle of MM, which considers the formation of "liver masses" as a key pathogenesis of liver diseases. Finally, Har-Gabur (calcined animal feces in traditional Mongolian medicine) is seen as a characteristic MM medicine with characteristics of "breaking stagnation, resolving accumulation and promoting bile flow" [20]. Recently, the hepatoprotective and choleretic effects of Har-Gabur extracts have been confirmed by pharmacological studies, indicating its potential for anti-HCC development [21]. The combination of Har-Gabur and the current nanotechnology, especially the fabrication of carbon quantum dots (CQDs), opens a new interdisciplinary research opportunity for developing effective, targeted and low-toxicity HCC therapeutics.

2. Har-Gabur: From Mongolian "Po Pi" Theory to Modern Pharmacology

2.1 Mongolian Medical Theory and Preparation Methods

Har-Gabur (Mongolian) is also called "Garinaga" and it is first mentioned in a classical Mongolian medicinal book, *Ren Yao Bai Jing Jian* [22]. It is a classic remedy central to the "Po Pi (breaking stagnation)" treatment, which is a therapeutic method of treating hyperplastic obstructive lesions or masses in viscera, body cavities or in superficial tissues which falls under the broad category of "pi syndromes" [23,24]. So, in the context of the MM concept of "pi disease", tumors are classified.

Har-Gabur is considered the master "breaking stagnation" herb due to its strong ability of "calming šira (pathological factor in Mongolian medicine), dissolving sticky obstruction", as well as breaking stagnation and dissipating food stagnation. Its traditional method of manufacture is very important and very precise in order to ensure efficiency. Har-Gabur is not naturally occurring, but is made by a special calcination method in the Mongolian medicine, which is to char dry feces of the wild boar (Sus scrofa Linnaeus) or specific plant stalks in a closed high-temperature system and sublimate, then crystallize on a cooling surface, to produce the medicinal crystals [25]. According to the theory of MM, such a "carbonization-sublimation" process eliminates undesirable harshness and condenses the therapeutic essence, creating ultra-fine particulates that have strong and deep pharmacological activity. Good Har-Gabur is in the form of a lustrous black powder, 2-3 cm in diameter, and has a clear fragrance and a pungent and bitter taste.

Unlike the traditional phytochemicals and medicines of animal origin, Har-Gabur is burnt in this particular stringent way which is followed by a highly remarkable physicochemical change. Interestingly, the resulting material is enriched in carbon containing iron structures [26]. Morphologically and in terms of elemental composition, it is similar to the engineered nanomaterials and can be considered a natural prototype of carbon-based nanomedicine [27]. This view opens up new avenues for the modernization and scientific research of Mongolian traditional medicine.

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2.2 Chemical Composition Elucidation

Har-Gabur's unique preparation engenders a complex chemical matrix rather than a single entity. It is composed of a scaffold made of amorphous carbon with small amounts of organic molecules, trace elements and large amounts of surface functional groups. In recent times, with the development of new analytical methods, the "chemical nature" of its "carbonized preservation of efficacy" principle has continually been revealed.

2.2.1 Backbone and Physical Architecture of Carbonaceous Structure

Har-Gabur is an amorphous carbon framework with a higher proportion of carbon atoms in it making it the main constituent of Har-Gabur. Scanning Electron Microscopy (SEM) analysis shows that it has a loose, porous structure and that the microcrystalline structures resemble irregular graphite [28]. In addition, the X-ray Diffraction (XRD) spectra corroborate that its carbon matrix consists of mainly amorphous character with short-range ordered graphitic microdomains. This highly developed porous morphology provides the tremendous adsorption ability [29] which is consistent with the traditional Mongolian medicine's functions of resolving stagnation and eliminating putrefaction.

The main purpose of the carbonizing by calcining process, which has been traditionally used in the pharmaceutics of Mongolian and Traditional Chinese Medicine [30] is to decrease the toxicity, reduce the irritating effect, and enhance or change the therapeutic properties [31]. Chemically, it is a highly controlled thermochemical process carried out under oxygen-controlled conditions that change the organic matter to carbonaceous substrates loaded with inorganic elements (Fe, Ca, Mg, Zn, etc.) while at the same time creating new microporosity arrangements that have a crucial effect on solubility and pharmacokinetics [32]. Similar materials that have been calcined have been found to have hemostatic, anti-inflammatory and antioxidative bioactivities which have been ratified by contemporary pharmacological assessment [33,34].

From the materials science point of view, the products obtained by calcination in the critical temperature range (400–600°C) are not traditional "carbon" but complex composites consisting of graphitized nanocarbons, carbon quantum dots (CDs), and even metallic nanoparticles [35]. They are nanoscale entities which are hypothesized to be the key pharmacodynamic substrates that mediate the catalytic effect of calcined carbon and its action in regulating intracellular reactive oxygen species (ROS) levels, thus resulting in redox regulation [36].

To sum up, the traditional theory of "preserving properties through calcination" may be reinterpreted in the light of today's science: The preserved and enhanced "properties" of the calcined product are inherent properties of the naturally formed nanomaterials and the process used is "nanoscale fabrication". In this way, traditional carbonized medicines such as Har-Gabur can be regarded as intrinsic nanomedicines with definite redox regulatory activity and thus provide a new theoretical framework for understanding their mechanism of action, which will help to modernize the use of traditional medicines in clinical treatment.

2.2.2 Organic Small Molecule Components

Our previous studies have shown that Har-Gabur, a traditional Mongolian medicinal material, contains not only inert metabolic byproducts but it is also composed of a large number of organic small molecules with well-defined chemical structures. By using LC-MS analysis, several bile acid compounds such as free bile acids and conjugated bile acids were found and quantified in Har-Gabur [37]. Bile acids are steroidal organic molecules with molecular structures decorated with hydroxyl, carboxyl and amide functional groups, providing them with significant biointeractive properties, and hence a key role in a large number of physiological and pathological processes [38]. The chemical properties offer a molecular level basis explaining the pharmacodynamic activities of Har-Gabur.

2.2.3 Spectra of Inorganic Elements and Trace Elements

The inorganic and trace elements are an important part of the material basis of Har-Gabur, and may be very important in the auxiliary or synergistic role of the manifestation of the pharmacological action of Har-Gabur. Using atomic absorption spectroscopy, Zhao Yuying et al. [26] reported a high calcium (Ca) content of 18,570 $\mu g \cdot g^{-1}$ and a zinc (Zn) content of 245 $\mu g \cdot g^{-1}$; Wang Yuguang et al. [39] reported an iron (Fe) content of 87.5 $\mu g \cdot g^{-1}$ using spectrophotometry; and Xu Xiuting et al. [40]

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found a manganese (Mn) content of 9.696 $\mu g \cdot g^{-1}$. These macro- and microelements have well-established in vivo physiological functions: Ca is involved in muscle contraction and biliary motility, Zn and copper (Cu) are essential cofactors for antioxidant enzymes, such as superoxide dismutase (SOD), Fe and Mn are extensively involved in redox reaction, mitochondrial metabolism and catalytic processes of various enzymes. In addition, inorganic constituents like silver (Ag), magnesium (Mg), sodium (Na), cobalt (Co), titanium (Ti) and molybdenum (Mo) have been detected in trace quantities [26] in this functional repertoire, their presence could be the biochemical basis for the traditional uses of Har-Gabur in "hepatoprotection and choleresis" and "dissipating accumulations and resolving nodules". Despite their low levels, they are indicative of the fact that the preparation of Har-Gabur might be a complex process of pyrolysis, redox and mineral mediated reactions. The Mo also serves as a very important cofactor for the enzymes called dehydrogenases such as xanthine oxidase and the Co is a central part of Vitamin B_{12} which is active in regulatory activities in cells. The biological implications indicate that trace elements can have modulatory or synergistic effects on the overall pharmacodynamic profile, despite their low abundance.

When combined with current evidence, the elemental spectrum of Har-Gabur is characterized by high diversity and hierarchical distribution, with abundant elements contributing to the integral structural support of the material and the trace/ultratrace elements contributing to redox homeostasis, enzymatic activity and metabolic signalling pathways that are critical to the manifestation of the effect. Based on the research about its organic composition and adsorption characteristics, the pharmacological mechanism of Har-Gabur should be regarded as a comprehensive effect of multi-component, multi-target and multi-pathway synergism. The elemental profile analysis not only provides a modern scientific basis for its traditional applications such as digestion, anti-masses and protection for liver and bile, but also provides a solid basis for further improvement of preparation methods, research of its pharmacodynamic material basis, establishment of quality control system, etc.

2.2.4 Surface Chemistry and Functional Groups

The surface chemical properties are of fundamental importance for adsorption, molecular recognition and biological interactions. There is evidence that the carbon skeleton created through the carbonization process is not a completely inert structure – some oxygen and nitrogen atoms are still present on the surface as hydroxyl, carboxyl, carbonyl or nitrogen-containing functional groups. These moieties are able to undergo molecular adsorption and interfacial interactions via hydrogen bonding, electrostatic, and coordination, which affect the biological actions of the material [41]. Further, based on previous experimental results, Fourier-transform infrared spectroscopy (FTIR) revealed that the Har-Gabur combustion derived fluorescent carbon dots had two characteristic absorption peaks at 3,467 cm^{-1} and 1,636 cm^{-1}, which are the vibrational modes of hydroxyl groups and amino/carbonyl groups, respectively, demonstrating that there are plenty of oxygen-containing and nitrogen-containing functional groups on the surface of the fluorescent carbon dots. All of these physicochemical characterization evidence support the notion that the carbonized products of the Har-Gabur are not single inert carbon materials but functionalized carbon materials with unique surface chemical activity [27].

Scanning electron microscopy (SEM) revealed that Har-Gabur has a porous, mesh-like structure, similar to porous carbon materials. In addition, adsorption tests with methylene blue as a model molecule revealed that it has a considerable molecular adsorption capacity that increases with decreasing the particle size, suggesting the role played by the pore structure and specific surface area in the adsorption behavior. This type of porous carbonaceous structure is responsible for its physical adsorption properties [28].

As for chemical composition, the multi-batch analysis of samples showed that Har-Gabur has a total nitrogen content of ~2.39% at the elemental level, which supports the potential existence of nitrogenous functional groups or nitrogen doping at the surface. The result does not exclude surface chemical activity, but in combination with the FTIR data, it provides multidimensional evidence of the presence of surface chemical activity [42].

2.3 Progress in the Study of Pharmacological

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Activity

2.3.1 Gastrointestinal Protection and Modulation of the Gut–Liver Axis Related to Hepatocellular Carcinoma

The initiation and development of HCC are tightly linked not only to the chronic liver damage, but also to the function of gastrointestinal tract and the regulatory mechanisms of the gut–liver axis [43]. The liver is a key site in the portal venous system, receiving about 70% of the blood from the gut before it enters systemic circulation and is therefore the first line of defence against substances entering the body from the gut. An intestinal barrier failure allows the portal passage of bacteria and their metabolites, including endotoxins, which constantly activate innate immune reactions, mainly through the Kupffer cells, leading to the production of inflammatory mediators that contribute to hepatocyte damage, regeneration and fibrosis [44]. This chronic inflammatory environment is able to regulate a number of signal transduction pathways, such as NF-κB and STAT3, that favor deregulated hepatocyte growth and resistance to hepatocyte apoptosis that play critical roles in hepatocarcinogenesis [45]. The protective effects of Har-Gabur on gastrointestinal tract have been confirmed in the literature in disease models. It has been shown that treatment with Har-Gabur causes a significant reduction of endotoxin activity with no obvious febrile response using the Limulus Amebocyte Lysate (LAL) assay, which might be due to physical adsorption mechanisms that reduce the biological activity of endotoxins and thus decrease the inflammatory stimuli from gut [29]. A reduction in endotoxin translocation into the portal circulation by improvements in intestinal barrier integrity consequently reduces the inflammatory burden in the liver. Har-Gabur was observed to have a mild modulatory effect on the intestinal smooth muscle function, which was characterized by a decrease in the amplitude of both acetylcholine- and histamine-induced spastic contractions, possibly by modulation of cholinergic and histaminergic pathway signaling. Its suppressive trend was also shown in vivo with regard to the abnormal contraction of small intestinal smooth muscle cells, while high concentrations had slight anti-cholinergic effects, which resulted in intestinal homeostasis, thereby indirectly affecting the balance in the gut-liver axis [46,47]. Har-Gabur was associated with the reduction of pathological damage to the colonic mucosa and modulation of oxidative stress markers such as the increase in glutathione (GSH) and superoxide dismutase (SOD) activities and simultaneous decrease in nitric oxide (NO) and malondialdehyde (MDA) levels in models of inflammatory bowel injury [46]. Such results suggest it could have a protective effect in chronic inflammatory diseases by regulating the intestinal microenvironment by reducing inflammation and enhancing antioxidant defense.

Furthermore, the Mongolian herbal medicine “Ten-Ingredient Har-Gabur Powder” has been extensively used for many gastrointestinal diseases with indications which overlap with those of Helicobacter pylori-associated gastritis and peptic ulcer disease. An in vitro antibacterial study has confirmed the inhibitory growth of H. pylori on the decoction, suggesting that the modification of gastrointestinal microbiota might be an indirect effect of the decoction on hepatocarcinogenic pathways [48]. Further studies indicated that nanostructured carbon entities derived from Har-Gabur can relieve gastric mucosal injury, possibly through the Fas/FasL pathway and the Bax/Bcl-2 pathway in the regulation of apoptosis, which suggested that Har-Gabur's action is not merely physical adsorption, but also involves regulation of cellular signaling networks [49]. These findings strengthen the proposed bioactivity of its carbon based nano structure and offer basic information to investigate its involvement in gut–liver axis in other related pathologies.

2.3.2 Potential Antihepatocarcinoma Activity and Underlying Mechanisms

Chronic inflammation, imbalance of oxidant/antioxidant, immune disorder and alteration of homeostasis of the gut–liver axis all contribute to the basic pathological substrates that underlie the development and progression of hepatocellular carcinoma [50-52]. These interconnected factors drive persistent disturbance of the hepatic microenvironment, leading to continuous damage to the hepatocytes, uncontrolled proliferation and activation of oncogenic signaling pathways.

Given the traditional use of Har-Gabur in gastrointestinal disease, and the current state of knowledge of its pharmacological actions, there is growing evidence of its role in regulating inflammation and maintaining redox homeostasis [46-49]. Previous research showed

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that Har-Gabur reduces inflammatory cytokines and suppresses inflammatory mechanisms in a variety of gastrointestinal injury models. At the same time, it increases the endogenous antioxidant mechanisms (activity of glutathione and superoxide dismutase), thus reducing the accumulation of reactive oxygen species and lipid peroxidation products, which leads to a reduction in systemic oxidative stress [46]. These effects might indirectly affect the hepatic microenvironment, which is important for hepatocarcinogenesis, by its link to chronic inflammation and chronic oxidative stress. However, direct studies of the mechanisms of HCC are relatively limited.

From a cellular fate regulation point of view, similar carbon-based nanobiomaterials and herbal carbonized products have been reported to affect the mitochondrial activities, and intracellular redox state, and are involved in regulating apoptosis related signaling pathways such as alteration in mitochondrial membrane potential and activation of caspase cascades [53]. Post-carbonization Har-Gabur, which has the required carbonaceous structure, is able to participate in such regulatory mechanisms. Its well-known antioxidant activities make it reasonable to believe that Har-Gabur may influence the redox status to impact the viability of the abnormally proliferating cells. It must, however, be emphasized that there is no clear experimental support for the apoptotic or antiproliferative activity on hepatoma cells; and the results so far are inferential.

Changes in the tumor microenvironment such as inflammatory status, extracellular matrix remodeling, and immune cell infiltration play a critical role in tumor invasion and metastasis. Recent research has indicated that some carbon nanomaterials may affect the interaction with the extracellular matrix or reduce local inflammation, which has an impact on the mobility of cancer cells and invasiveness [54,55]. The effects of Har-Gabur on strengthening the barrier function of gastrointestinal mucosa, repairing tissue damage and reducing inflammation suggest that it may indirectly influence the dynamics of the tumor microenvironment by inhibiting the growth of HCC.

Immune regulation is probably a crucial axis of the possible antitumor activity of Har-Gabur. Defective immunosurveillance is a key feature of hepatocarcinogenesis and the gut liver axis is a major player in maintaining hepatic immune homeostasis. It is clear that Har-Gabur has the ability to decrease the burden of endotoxin from the gut, suppress inflammatory responses and regulate gut microecology, which in turn improves the body's immune function[46][47]. Studies on the interaction between carbon-based nanomaterials and immune cells suggest that Har-Gabur may be involved in modulating the tumor immune microenvironment to affect the progression of HCC [56,57]. But the exact molecular events and the cellular targets in which they participate require thorough understanding.

3. Conclusion and Prospect

Har-Gabur is a traditional Mongolian medicinal material, which has been widely and effectively used to treat liver diseases in Mongolian medicine. As nanotechnology has emerged, the preparation of Har-Gabur into carbon quantum dots and incorporation into cutting-edge biomedical systems could open up new opportunities to optimize the therapeutic potential and understand the mechanism of action in the context of the malignancy, recurrence, and drug resistance associated with hepatocellular carcinoma. This interdisciplinary convergence and the spectrum of scientific questions and technological hurdles to be resolved is challenging.

Acknowledgments

This research was financially supported by the Science and Technology Program of Inner Mongolia Autonomous Region (Project No. 2022YFSH0099) and the Department of Science and Technology of Inner Mongolia Autonomous Region (Project No. 2025ZY0082).

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