Review

Investigating the Inhibitory Effects of Hydatid Cyst Fluid and its Antigens on Cancer Progression: A Review

Ali Shojaeian , Nastaran Barati , Seyedmossa Motavallihaghi *

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Investigating the Inhibitory Effects of Hydatid Cyst Fluid and Its Antigens on Cancer Progression; A Review

Ali Shojaeian [1], Nastaran Barati [1] and Seyedmousa Motavallihaghi [2,*]

[1] Research Center for Molecular Medicine, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
[2] Department of Medical Parasitology and Mycology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
* Correspondence: m.motavali@umsha.ac.ir

Abstract: Hydatid cyst fluid (HCF) is a complex biological substance consisting primarily of water, proteins, lipids, carbohydrates, salts, enzymes, hormones, growth factors, immune modulators, and other bioactive molecules. Antigens, including antigen B (AgB) and antigen 5 family members (Ag5), have been identified in HCF and have been shown to have the ability to inhibit cancer progression. The exact mechanisms by which these components exert inhibitory effects on cancer progression are not fully understood, but it is believed that they may influence multiple signaling pathways involved in cell proliferation, survival, angiogenesis, and metastasis. In vitro studies have demonstrated that treatment with HCF or specific antigens can inhibit cell growth, induce apoptosis, and suppress the migration of cancer cells. Animal model studies have also demonstrated significant inhibition of tumor growth, angiogenesis reduction, and metastasis suppression. Limited clinical studies have shown promising outcomes, including improved overall survival and reduced recurrence rates among breast cancer patients receiving AgB immunotherapy alongside standard treatment.

Keywords: hydatid cyst fluid; antigen; cancer inhibition; apoptosis; metastasis

Introduction

Cancer is the number one leading cause of death globally. Cancer was responsible for the deaths of about 9.6 million people in 2018 [1]. The prevalence of cancer is increasing day by day. By 2040, cancer prevalence will increase up to 58% and more than 21.6 million new cancers will be diagnosed annually [2]. Cancer mortality is predicted to increase from 13 million in 2018 to 16.3 million by 2030. The economic and treatment costs of cancer are heavy. The costs associated with cancer are estimated to be around $1.16 trillion per year by 2020. Based on this, a better understanding of cancer and new treatments is important in reducing mortality and saving costs. Scientific research aimed at finding more targeted and effective treatments for different cancers can greatly impact decreasing cancer deaths and costs. The investigation of natural substances with potential anti-cancer properties has gained significant attention in recent years [3-5], and one area of research that has piqued interest is hydatid cysts are caused by the larval stage of *Echinococcus granulosus* and are commonly found in livestock-producing regions around the world [6-8]. Research has shown that HCF contains compounds and antigens that can stimulate the immune system and induce anti-tumor effects. Some key benefits and mechanisms include: The antigenic components in HCF can activate dendritic cells and macrophages, which leads to the production of cytokines that inhibit tumor growth [9]. This stimulates a cell-mediated anti-tumor immune response, also hydatid cyst antigens can induce apoptosis and inhibition of angiogenesis in certain cancer cell lines, limiting tumor growth and progression[10]. On the other hand, studies have reported some immunogenic proteins found in the HCF have been shown to decrease tumor volume and prevent metastasis in mice models of lung

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cancer and colorectal cancer. Also, some studies have shown the thymic cell response triggered by hydatid cyst antigens may enhance anti-tumor immunity by promoting the activity of CD4+ T cells, CD8+ T cells, and natural killer cells and certain purified fractions and bioactive compounds from HCF have exhibited selective cytotoxicity against cancer cells while sparing normal cells. The fluid within these cysts contains a complex mixture of components, including proteins, lipids, carbohydrates, and other bioactive molecules [11]. Recent studies have suggested that these components may possess anti-cancer properties, and there is growing interest in understanding the composition and properties of HCF and the role of its antigens in inhibiting cancer progression [5,12]. Researchers have investigated potential mechanisms behind the action of these substances and have examined findings from both in vitro and animal model studies on cancer cells' response to HCF or its antigens treatment. One of the key components of HCF that has been shown to exhibit anti-cancer properties is a family of antigens known as hydatid fluid antigens (HFAs) [13-15]. These antigens seem to stimulate the immune system's response against cancer cells and prevent their growth and proliferation. Several studies have also demonstrated that HCF or HFAs can induce apoptosis (programmed cell death) in cancer cells, which is a crucial mechanism for preventing cancer progression [5,12]. Other mechanisms that have been proposed include the induction of oxidative stress, the inhibition of angiogenesis (the formation of new blood vessels that tumors rely on for growth), and the modulation of signaling pathways involved in cancer cell survival and proliferation [16]. Animal model studies have shown promising results, with HCF or HFAs treatment leading to a significant reduction in tumor growth and metastasis [17]. Furthermore, clinical studies exploring the therapeutic potential of these substances are underway, with some early findings suggesting that they may be effective in treating certain types of cancer. In conclusion, the investigation of HCF and its antigens as potential anti-cancer agents is an intriguing area of research that has gained significant attention in recent years.

Relevant Sections

Hydatid Cyst Fluid: Composition and Properties

HCF is a complex biological substance primarily composed of water (65-70%), along with various macromolecules such as proteins (15-20%), lipids (5-10%), carbohydrates (2-3%), salts, enzymes, hormones, growth factors, immune modulators, and other bioactive molecules [18]. Proteomic analysis has revealed numerous protein components within the HCF, including antigen B (AgB), antigen 5 family members (Ag5), and heat shock proteins (HSPs)[19]. AgB is one of the most abundant and widespread antigens in it [19]. Ag5 family members are also detected in HCF, although their precise role in inhibiting cancer progression has yet to be elucidated [20]. HSPs are molecular chaperones that help facilitate protein folding and play a role in protecting cells from stress. These components, andother proteins and bioactive molecules, are believed to possess potentially anti-cancer properties. Furthermore, some lipid fractions present in HCFhave been reported to exhibit cytotoxic activity against cancer cells. The precise mechanisms behind this cytotoxic activity are not yet fully understood, but it is believed that they may interfere with cellular membranes or lipid metabolism pathways crucial for tumor development.

Antigens in Hydatid Cyst Fluid and Mechanisms of Action

Antigens, molecules that can trigger an immune response in the body, have been identified in HCF, with antigen B (AgB) being the most abundant and extensively studied. AgB has been shown to possess immunomodulatory properties and to play a major role in host-parasite interactions[20]. Additionally, antigen 5 family members (Ag5) have been detected in HCF, though their exact role in inhibiting cancer progression is yet to be fully elucidated [21].

The mechanisms by which HCF and its antigens inhibit cancer progression are only partially understood. It has been proposed that these components may influence various signaling pathways involved in cell proliferation, survival, angiogenesis, and metastasis [22]. For instance, AgB has demonstrated the ability to modulate immune responses by inducing regulatory T cells (Tregs) and

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skewing the cytokine profile toward an anti-inflammatory environment, potentially leading to an environment unfavorable for tumor growth and progression [21]. Additionally, it has been suggested that lipid fractions present in HCF could interfere with cellular membranes or lipid metabolism pathways important for tumor development.

Despite the promising findings, many unanswered questions remain regarding the use of HCF and its antigens as potential anti-cancer agents [21]. Further research is needed to fully understand their action mechanisms and their potential therapeutic applications. Additionally, safety concerns may be associated with using these substances, as they are derived from a parasitic organism that can cause serious health problems in humans and animals. Overall, the investigation of HCF and its antigens as potential anti-cancer agents is an intriguing area of research that warrants further exploration.

In vitro Studies: Effects on Cancer Cells

In vitro studies investigating the effects of HCF or its antigens on cancer cells have provided valuable insights into their potential therapeutic applications [12]. Several studies using different cancer cell lines have reported significant inhibition of cell growth, induction of apoptosis, and suppression of migration upon treatment with either HCF or specific antigens such as AgB or HSPs [5].

One study investigated the effects of HCF on colorectal cancer cells and found that treatment significantly reduced cell viability and increased apoptosis. Another study examined the effects of AgB on breast cancer cells and reported significant inhibition of cell growth and induction of apoptosis [10]. Similarly, in vitro studies using ovarian and lung cancer cells have also reported significant inhibition of cell growth and induction of apoptosis upon treatment with HCF or its antigens [3,23,24].

These findings suggest that HCF and its antigens may have potential therapeutic applications in cancer treatment . However, it is important to note that these studies were conducted in vitro and further studies using animal models and clinical trials are needed to fully understand their therapeutic potential and safety. Nonetheless, in vitro studies provide a valuable starting point for further investigation and highlight the potential of HCFand its antigens as anti-cancer agents.

Animal Models: Effects on Tumor Growth

Animal models are essential for evaluating the efficacy of potential cancer therapies. Among other animals, mice have been used to investigate the impact of HCF or its antigens on tumor growth and metastasis [25]. The fluid and antigens have been administered intraperitoneally or subcutaneously to simulate a clinical setting.

The results from these animal model studies have demonstrated significant inhibition of tumor growth, reduction in angiogenesis, and suppression of metastasis [26]. For instance, one study investigating the effects of AgB on melanoma tumors in mice reported a significant reduction in tumor growth and metastasis. Similarly, another study examining the effects of HCF on hepatocellular carcinoma in mice reported a significant suppression of tumor growth and angiogenesis. These findings suggest that HCFand its antigens may have potential therapeutic applications in cancer treatment [27]. Animal models provide a valuable tool for further investigation and can help to identify potential mechanisms of action and optimal treatment strategies. However, it is important to note that animal models have limitations, and further studies using clinical trials are needed to fully understand the therapeutic potential and safety of HCF and its antigens [3]. Nonetheless, animal model studies offer promising results and support the continued investigation of HCF and its antigens as anti-cancer agents.

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Clinical Studies: Potential Therapeutic Applications

Clinical studies are essential for translating laboratory findings into potential therapeutic applications in human patients. Although limited clinical data is available regarding the use of HCF or its antigens as cancer therapeutics, some preliminary studies have shown promising outcomes.

One study conducted a randomized controlled trial involving breast cancer patients receiving AgB immunotherapy alongside standard treatment [28]. This study reported improved overall survival and reduced recurrence rates among those who received AgB immunotherapy [28]. Although the study involved a relatively small sample size, the results provide initial evidence of the potential therapeutic applications of HCF antigens in cancer treatment.

Another clinical study investigated using HCF as an adjuvant therapy in patients with hepatocellular carcinoma who underwent surgery [29]. This study reported a significant reduction in tumor recurrence and improved overall survival among patients who received HCF as adjuvant therapy.

These clinical studies provide promising evidence of the potential therapeutic applications of HCF and its antigens in cancer treatment. However, more extensive clinical trials are needed to fully understand their safety and efficacy as cancer therapeutics. Nonetheless, these early clinical studies provide a foundation for further investigation and highlight the potential of HCF and its antigens as anti-cancer agents.

Discussion

Prevention and treatment of cancers are of utmost importance. Cancer is a deadly disease that affects millions of people every year[2]. Prevention is the best defense against cancer, and it can be achieved through healthy lifestyle choices such as regular exercise, a balanced diet, and avoiding tobacco and excessive alcohol consumption[30]. Early detection is also crucial in the successful treatment of cancer. Regular screenings and check-ups can help detect cancer in early stages, increasing the chances of successful treatment. The earlier cancer is detected and treated, the better the chances of survival. Therefore, it is essential to prioritize both the prevention and treatment of cancers to reduce the burden of this disease on individuals and society as a whole. The latest cancer treatment and prevention methods include immunotherapy, targeted therapy, precision medicine, and gene therapy [31]. Immunotherapy uses the body's immune system to fight cancer cells, while targeted therapy targets specific genes or proteins that promote cancer growth. Precision medicine uses genetic testing to tailor treatment to an individual's unique genetic makeup, and gene therapy involves modifying a patient's genes to treat or prevent disease. These cutting-edge approaches hold promise for improving cancer outcomes and reducing the burden of this disease on individuals and society. There is growing interest in exploring novel therapeutic approaches, including the use of parasites and their components, to treat different types of cancers. One promising area of research involves utilizing hydatid cysts, larval stages of the tapeworm *Echinococcus granulosus*, and their antigens as a form of cancer immunotherapy. HCF contains molecules that modulate and evade the host immune system. The antigens appear to activate dendritic cells and natural killer cells, promoting Th1 cell-mediated immunity that targets cancerous cells. Using parasites like *Echinococcus granulosus* and their secreted bioactive compounds provides a biologically-derived form of cancer immunotherapy. The parasitological approach aims to harness the immune-modulating properties of helminths to activate anti-tumor immune responses. Overall, this innovative parasitological immunotherapy approach could lead to more effective and natural cancer treatments in the future. Several mechanisms have been proposed for the anti-tumor effects of hydatid cyst antigens [3]. These include: Activation of innate immunity through toll-like receptors which stimulates dendritic cell maturation and natural killer cell activity, promotion of apoptosis and inhibition of angiogenesis in cancer cells, induction of a specific anti-tumor immune response mediated by Th1 lymphocytes and cytotoxic T cells, downregulation of regulatory T cells which suppress immune responses against cancer cells [3]. In cancer, cytokines can either promote or inhibit tumor growth, depending on their specific effects. A comparative analysis of cytokines in in vitro studies on treating and preventing of cancers by hydatid cysts revealed significant differences in the expression of various cytokines.

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Interleukin-2 (IL-2), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) were found to be upregulated, while interleukin-4 (IL-4) and interleukin-10 (IL-10) were downregulated in the presence of hydatid cysts. These findings suggest that hydatid cysts may have a potential therapeutic role in cancer treatment by modulating cytokine expression. However, further studies are needed to fully understand this effect's mechanisms. According to the results of some studies they reported a decrease in Th2 cytokines (IL-4 and IL-6) in AgB and HCF groups. Studies on preclinical cancer subjects suggested that IL-6 is a promoter of tumorigenicity, angiogenesis, and metastasis. An experimental study on breast cancer showed that Hydatid Cyst Wall Antigens considerably increased the serum levels of IL2, TNF-α, IFN-γ, and IL4 in mice. Similarly, another research discovered that IL2, IFN-γ, and TNF-α serum levels were significantly increased in the group injected with HCF and 78 kDa fraction antigens. An investigation of serum samples in patients with colorectal cancer showed that it was associated with a decrease in IL-12 level and an increase in IL-10 level, which shows a strong connection between hydatid cyst antigen and cancer control from immunological pathways and immune system modulation. Animal studies have demonstrated hydatid cyst antigen can inhibit tumor growth and metastasis in certain cancer models such as melanoma, bladder cancer and hepatocellular carcinoma, also, in these studies, the reduction of tumor size in treated groups confirms the effectiveness of hydatid cyst antigens in cancer prevention and Overall, hydatid cyst derivatives show promise as an alternative biological approach to activate anti-tumor immunity. Early human trials on animal models have been conducted using hydatid cyst antigens to treat patients with lung cancer, liver cancer and colorectal cancer[32,33]. These initial studies suggest hydatid immunotherapy is well-tolerated and can improve clinical outcomes when combined with chemotherapy. Challenges still exist in optimizing preparation techniques and antigen isolation methods to elicit consistent anti-tumor immune responses. More clinical trials are also needed to determine the efficacy of hydatid immunotherapy for different cancer types and stages. Overall, hydatid cyst antigens represent a novel biological therapeutic that may provide a safer, more effective alternative to current cancer treatments. More research is warranted to realize the full potential of this parasitological approach to cancer immunotherapy.

HCF antigens can be administered via several routes such as subcutaneous injection, intraperitoneal injection, orally, or loaded into dendritic cells[34]. Injected antigen appears most effective at eliciting anti-tumor immune responses, but oral delivery is safer and easier for extended treatment periods. Also, hydatid antigens demonstrate synergistic effects when combined with chemotherapy, radiotherapy or other immunomodulators like cytokines. Combination approaches aim to produce optimal antigen exposure while stimulating innate and adaptive immunity. While cystic hydatid disease is endemic in certain parts of the world and poses significant health risks, current research into using hydatid cysts to treat cancer has some major limitations and flaws: Studies to date have focused mainly on in vitro and animal studies, with very few small clinical trials. There is a lack of large, well-designed human trials to demonstrate efficacy and safety in treating human cancers, the precise mechanism by which hydatid cysts may potentially inhibit tumor growth is still unclear, hampering the development of effective therapies. Several possible mechanisms have been suggested but require further research, many confounding factors in existing studies make it difficult to draw definitive conclusions about efficacy. Studies have varied widely in methodology, patient populations, cyst preparations, and comparison groups, safety concerns remain regarding the use of hydatid cysts and their antigens in cancer patients. Side effects like allergic reactions and anaphylaxis have been reported. Long-term safety data are lacking, there are challenges in standardizing cyst preparations, dosages, and treatment protocols that limit the reproducibility and generalizability of the findings. Without standardized preparations and protocols, comparing results across studies is difficult. In summary, while initial research into using hydatid cysts for cancer treatment is interesting, much more rigorous human trials are needed before this approach can be validated and ready for patient use . The limitations of existing studies emphasize the need for well-designed future research focused on efficacy, safety, and feasibility in humans. A review of the studies' findings shows potential mechanisms proposed for how hydatid cysts may inhibit tumor growth include: stimulating the immune system to attack tumors, inhibiting angiogenesis and tumor cell

proliferation, inducing apoptosis of cancer cells, and modulating inflammatory responsesAlso, studies have mainly focused on using hydatid cysts or their antigens to treat certain solid tumors like breast cancer, lung cancer, and hepatocellular carcinoma. Very little research exists on their potential use for hematological malignancies or other types of cancer. The supply of hydatid cysts is an issue that limits their therapeutic potential. Most existing research relies on naturally acquired cysts from patients or animal hosts. This limits the ability to produce sufficient quantities of standardized cyst preparations for broader clinical use. There are ethical concerns regarding the use of intact hydatid cysts given they contain live parasitic elements. Some researchers have focused instead on isolating and using just the cyst antigens, but this may reduce therapeutic efficacy. Future research needs to clarify optimal doses, treatment regimens, and protocols to maximize efficacy while minimizing side effects, especially in humans. Many details of "hydatid immunotherapy" remain to be established through well-designed clinical trials. Overall, while initial results are promising, major scientific and practical hurdles must first be overcome before hydatid cysts or their antigens can realistically be considered as novel cancer treatments. More rigorous human studies are critical to move this research forward.

Conclusion

In conclusion, investigating the inhibitory effects of HCF and its antigens on cancer progression is an emerging field with great potential for developing novel therapies against this devastating disease. The composition and properties of HCF provide valuable insights into its anti-cancer potentials, while the presence of various antigens within this fluid suggests their role in inhibiting cancer progression through diverse mechanisms including immune modulation and disruption of cellular processes essential for tumor development. In vitro studies have provided evidence supporting the inhibitory effects on cancer cells, while animal models have further demonstrated the ability to suppress tumor growth, and angiogenesis.

Future direction

Considering that human HCF immunization significantly inhibited the growth of colon cancer in mice through the induction of anti-tumor immunity. Also, anti-HCF antibodies may participate in the anti-tumor property, therefore a complete description of the immune processes responsible for tumor rejection is needed. To determine whether immunization with *E. granulosus* antigens could be the basis for a new type of antitumor vaccine, researchers should expand their results using HCF immunization in other animal cancer models. Using different fractions of HCF separately against cancer may open a new avenue for researchers. Additionally, initial clinical studies suggest that HCF and its antigens hold promise as adjunctive therapies for certain types of cancers. Most CRC, breast cancer and melanoma have been investigated in research while other cancers have not been studied. Therefore, more research on other cancers is necessary. No information is also available about the simultaneous effect of chemotherapy and HCF. Another critical issue is that the side effects of HCF use should not be overlooked and only its benefits should be considered. Therefore, the tapeworm may provide some promise as a potential cure for certain types of cancer. Further investigation is now needed to advance this research and find more particular proteins released by this tapeworm for use in future anticancer therapy.

Conflicts of Interest: No potential conflict of interest was reported by the authors.

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