Rice Field Snail Shell Anticancer Properties_Final

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Rice Field Snail Shell Anticancer Properties: An Exploration Opinion

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Notes to Reviewers

This article is an opinion article that has a word limit and the number of images/tables, I hope this adjustment can be understood during the peer-collaborative-review process by the peer-reviewers.

1. Introduction

Molluscs, especially Gastropods, including land, freshwater, and sea snails, are commonly used as traditional medicine and cost-effective food resource (Sundalian, M. et al., 2021). Snail meat has beneficial nutritional values as it is high in protein and low in fat (Ulagesan, S. and Kim, H.J., 2018). Hence markets around Asia, such as Indonesia, China, Taiwan, Japan, and Hongkong, frequently process snail meat into food (Needham, S. and Funge-Smith.,2015). A type of freshwater snail, *Pila ampullacea*, is a native mollusk easily found in Southeast Asian rice fields and lakes. Like its fellow gastropods, it contains high nutritional values (100 mg meat: ±209 kcal calories, ± 18 g protein, 12 mg zinc, 102 mg iron, and 812 mg calcium) (Nurhasan, M. et al., 2010). Although conventionally consumed as food, *Pila ampullacea* is also recognized as a crop pest (Broto, R.T. et al., 2020). As their rising consumption, snail shells are less explored functionally become animal feed material, accessories, and waste products with low economic value (Sundalian, M. et al., 2021).

Calcium carbonate constitutes 87-96% of the total weight of freshwater snail shells (Parveen et al., 2020). High dietary calcium intake is clinically protective against multiple chronic diseases, including lowering the risks of developing cancer (Li, Q. et al., 2017; Peterlik, M. et al., 2009). Calcium carbonate is also the primary material used to synthesize Hydroxyapatite, a biocompatible material with high binding activity to proteins and genetic materials. Nanoparticle hydroxyapatite showed the anti-proliferative potential of cancer cells *in vitro* and *in vivo* (Kargozar, S. et al., 2020; Zhao, H. et al., 2018). Various studies have shown that snail shells also contain bioactive compounds like chitin, the primary chitosan material, that offer antipathogenic, antioxidant properties and pharmaceutical additive potential (Jatto, O.E. et al., 2010; Abd El-Hack. M.E. et al., 2020). Furthermore, chitin and its derivatives were found to have a significant immunomodulating response against cancer and antitumor activity through the downregulation of tumor angiogenesis factors, apoptotic effects stimulation, and decreased cell adhesion (Satitsri, S. and Muanprasat, C., 2020). However, the bioactive component's profile of snail shells is partially influenced by their habitat, surrounding environment, mineral content, and microorganisms (Sundalian, M. et al., 2021). Therefore, this article aims to summarize the recent findings on potential anticancer properties, specifically of rice field snail shells.

2. Rice Snail in General

Freshwater snails (*Pila ampullacea*) belong to a genus of large aquatic snails and the family of Ampullariidae (Ihsani, I. et al., 2020). Besides, rice fields can generally be found in ponds, marshes, and lakes. It has a morphology similar to a golden snail (*Pomacea canaliculata*) but a darker green to black spiral-shaped shell. Its approximate height is around 100 mm, with a width

of up to 100 mm (Broto, R.T. et al., 2020). *Pila ampullacea*, also named apple snail, is often regarded as a crop pest with potential damage of 10-40% to wetland agricultural goods, especially rice (Fatimah, I. et al., 2018). *Pila ampullacea* feeds on aquatic plants such as lettuce; however, during its starvation phase, it can consume decaying animals (Lamkom, T. and Phosri D., 2017). Rice snail is considered to be a potential functional food ingredient due to its high protein and calcium with low fat and phosphorus content, which can offer metabolic advantages such as augmenting weight loss and reducing cardiometabolic risks (Widiany, F.L. et al., 2021; Wycherley, T.P. et al., 2012). *Pila ampullacea* has also been processed into various types of food and formulations, such as baby porridge, liquid food formula, crackers, and flavor enhancers (Ihsani, I. et al., 2020; Broto, R.T. et al., 2020; Fatimah, I. et al., 2018). Furthermore, high scavenging activity towards free radicals was found in snail extract, potentially due to its amino acid characteristics (Ulagesan, Kuppusamy, & Kim, 2018).

3. Anticancer Properties of Rice Snail Shell

The shell extract snail has been studied for its antioxidant property and influence on the Caco-2 cancer cell line (Matusiewicz et al., 2018). Interestingly, even though the antioxidant activity of the shell extract was higher than other parts of the snail, the shell extract didn't display a significant reduction in cancer cell line viability, which the presence of Fe might influence. However, proximate analysis of many snail species shells revealed that snail shells contain low iron and zinc but high calcium and magnesium (Nkansah, Agyei, & Opoku, 2021). Calcium and magnesium intakes were associated with the incidence of cancers and patients' survivability (Gong et al., 2022; Shah et al., 2020). Matusiewicz et al., (2018) identified myristic acid in the shell extract, a medium-chain fatty acid that can cause cancer cell death (Park et al., 2020). Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) was also successfully synthesized from the rice field snail shell (Charlena, Suparto, & Putri, 2015).

Additionally, hydroxyapatite which is highly contained in snail shells exhibited anticancer properties, explained mainly by endocytosis in cancer cells and cellular protein synthesis suppression (Tang, W. et al., 2014; Han et al., 2014). Direct injection of hydroxyapatite nanoparticles into a transplanted tumor formed by human hepatocarcinoma cells *in vivo* showed a 50% reduction of tumor size with two times the antiproliferative effect on cancer cells compared to healthy ones (Han et al., 2014). Hydroxyapatite nanoparticles exert their effects by localizing around the endoplasmic reticulum of the cancer cells, where they impede the translation process by competitively binding to the ribosome, preventing mRNA from bonding with it; this causes GO/G1 phase arrest in the cell cycle (Ignjatović, N.L. et.al, 2016). Further study also showed the snail shell caused significant inhibitory effects against several cancer cell lines (SKOV-3, MCF-7,

MDA-MB-231, and HepG2), in which the antiproliferative effect against SKO-V-3 (human ovarian cancer) cells was comparable to cisplatin as its positive control (Alburae, N.A. et al., 2020). Another similar study showed laminated hydroxyapatite (L-HAp) significantly decreased the migration ability of human breast cancer MDA-MB-231 cells by blocking integrin β-1 phosphorylation which mediates the adhesion of cancer cells (Jin. J. et al., 2014).

Snail shell also contains calcium carbonate (87-96% of shell weight) (Parveen et al., 2020). Interventions using calcium carbonate showed the capability of calcium carbonate to prevent recurrent adenomas in colorectal cancer patients (Chu et al., 2011). On the other side, calcium carbonate has been studied as a targeted drug or gene delivery strategy for malignant tissues and cells (Dizaj et al., 2019) and as a compartment of the cancer imaging system (Huang et al., 2020). Surprisingly, snail shells – in the form of powder – exhibited wound-healing properties (Andrade et al., 2018), reflecting the anti-inflammatory activity of the shells. This regulation of the inflammatory process may be beneficial in treating cancer since inflammation and wound healing share "similar" mechanisms and hallmarks to cancer (MacCarthy-Morrogh & Martin, 2020). Snail shell's functionality as metal adsorbent due to their chitin, chitosan, and hydroxyapatite content has been studied (Asimeng et al., 2022; Bambaeero & Bazargan-Lari, 2021; Foroutan et al., 2019), indicating their potential to prevent cancer caused by carcinogenic metal toxicity (Kim, Kim, & Seo, 2015). Moreover, chitosan derivatives are also known for their anti-inflammatory, antioxidant, and anticancer properties (Kim, 2018).

4. Future Applications and Implications

Snail meat is the only part of snails that has been utilized in various food products to increase their protein and calorie content which can alleviate malnutrition (Adeyeye et al., 2020; Ghosh, Jung, & Meyer-Rochow, 2017). The snail shells were mostly underutilized and ended up as waste. Snail shell powder has only been used as a calcium source in the diets of broilers, small animals, and cattle (Tchakounte et al., 2019). However, snail shell remains interesting to be utilized as food, supplement, or drug component. Incorporating snail shell powder into a diet may be a novel form of mineral fortification. For example, a snail shell can be ground into a powder that can be added to daily food or beverages. Dietary intake of chitosan – present in the snail shells – may promote cellular immunity, which is strongly linked to cancer development (Carroll et al., 2016). Snail shells can be innovated into a bone health supplement since snail shells are rich in calcium and magnesium. The rich calcium carbonate in snail shells may also be incorporated with other compounds, such as tocopheryl polyethylene glycol succinate and curcumin (Guan et al., 2021), to create a more potent drug that can overcome cancer drug resistance and reverse tumor immunosuppression.

5. Discussions

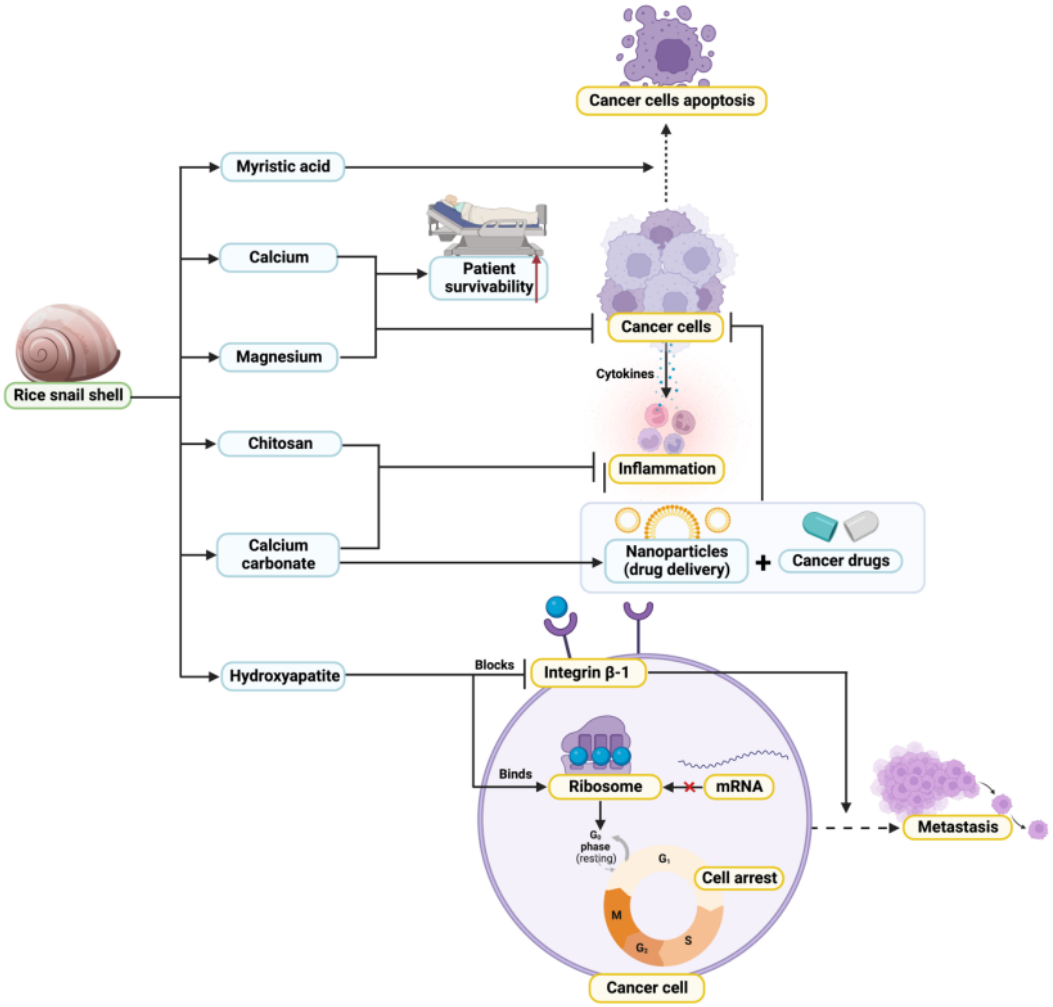

Figure 1. Possible mechanistic of anticancer properties of Rice snail shell.

According to previous reports, it has been summarized that snail shells are a rich source of calcium (Ca). Ca is the vital element which needs the body for functioning and is only taken by the body through dietary sources (Figure 1). It also plays a vital role in the mineralization of the skeleton and possesses a broad range of functioning (Peacock, 2010), such as anti-cancerous activity. Previous mice study also suggested that rich calcium dietary intake could help to reduce colon cancer (Yang et al. 2008). A recent meta-analysis study indicated that higher Ca dietary intake could lower esophageal cancer risks (Li et al., 2017). The latest study found that snails contain $CaCO_3$ crystals in their shell with diverse shell surface functional groups (Figure 1)

(Parveen et al., 2020). $CaCO_3$ is one of the essential components for the synthesis of hydroxyapatite where hydroxyapatite nanoparticles are used for cancer treatment (Figure 1). So, the overall opinion of this article is that snail shells may be the potential to help reduce cancer concerns (Figure 1). But it is only an exploration opinion, so large studies on *in vivo* and *in vitro* trials must be needed to conclude that snail shells have anti-cancerous properties.

6. Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7. Author Contributions

JJIR, SL, WBG, ISW, VMY, TWY, NS, MS, and FN: Contributed to the conceptualization with the design of the critical opinion study, firstly drafted the manuscript, edited-revised, and approved the final version of the submitted manuscript. All authors and contributors contributed to the opinion article and approved the submitted version.

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10. Data Availability Statement

There is no data related to this opinion article. The data is only sourced from the literature that has been listed in this article.

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