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Review Article

A Review on - Transforming Toxins into Treatments: The Revolutionary Role of α-amanitin in Cancer Therapy

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ABSTRACT

Although diagnostic and therapeutic advancements have been made, the global cancer burden continues to grow. The limitations of current chemotherapy, including harm to healthy cells and tumor resistance, highlight the urgent need for innovative pharmaceutical solutions with reduced toxicity and improved efficacy. The discovery of natural anticancer agents, such as α-amanitin toxins derived from Amanita phalloides fungi, has opened up new avenues in cancer therapy since their isolation. Our initial screening revealed that the methanol extract of Amanita spissacea fruiting bodies showed promising cytotoxic activity against human lung cancer cells in a laboratory setting. Despite the notorious toxicity of most Amanitaceae family mushrooms, the chemical composition of A. spissacea remains largely unexplored, with the exception of its amino acid profile. Amanita phalloides extracts show promise in inhibiting tumor cell activity, with potential therapeutic benefits for various cancers & minimal side effects. This review explores the therapeutic applications of α-amanitin toxin in targeting various cancer types, highlighting its potential as a novel anticancer agent.

INTRODUCTION

Cancer is the world's second deadliest disease and one of the toughest to tackle. According to the World Health Organization, the global number of new cancer cases is projected to increase from 9.6 million in 2018 to 21.3 million by 2030, representing a significant rise in cancer incidence worldwide.(4) While many cytotoxic therapies can halt tumor progression, they often come with a high cost to normal cells, putting healthy tissues at risk of severe damage and compromising their integrity.(5)To address this need, researchers have

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turned to mushrooms, specifically α-amanitin, as a potential solution in cancer treatment, and efforts have been made to isolate and harness its therapeutic properties from amanitin-producing fungi.(6)While some Amanita species are edible, mycologists strongly advise against amateur mushroom collectors attempting to harvest them for consumption, recommending instead that only experienced experts handle them.(4) Nevertheless, in certain cultures, Amanita mushrooms are a prized local delicacy during their seasonal availability.(7) The Amanita genus comprises around 900-1000 agaric species, featuring some of the most toxic mushrooms known, as well as a select few that are widely recognized as edible and safe for consumption.(8, 9)

1. **Amanita mushroom**:

Recently, mushroom consumption has gained popularity, likely attributed to their exceptional nutritional value and potential medicinal benefits.(10) The danger of mistakenly picking toxic mushrooms has grown, raising the risk of poisoning.(6)Although cytotoxic therapies can effectively slow or stop tumor growth, their harmful effects on normal cells can put healthy tissues in jeopardy, leading to potentially severe consequences.(4)To address this need, researchers have turned to mushrooms (specifically, α-amanitin) as a potential solution in cancer treatment, and efforts have been made to isolate and harness amanitin from fungi. (11) Amanitins, a subgroup of the amatoxin family, are toxic bicyclic octapeptides with a molecular weight of approximately 900 g/mol, found in specific fungi species. These toxins are primarily associated with three fungal families: Amanita, Galerina, and Lepiota. Notably, the death cap (Amanita phalloides) is the most common cause of fatal poisonings, inducing severe and rapidly life-threatening hepatic damage. (12) The amatoxin family encompasses at least nine compounds, which are categorized into two groups based on their chemical properties: neutral compounds (α-amanitin, γ-amanitin, amaninamide, amanulline, and proamanulline) and acidic compounds (β-amanitin, ε-amanitin, amanine, and amanullinic acid). Notably, the differences in chemical properties between these two groups do not correlate with variations in toxicity. (13,14) The primary toxic compounds found in certain Amanita species are amino acids and cyclopeptides, which are responsible for their deadly effects. Furthermore, isoxazoles, known to induce hallucinogenic symptoms, are also present in some Amanita genera and are considered toxic substances. (15,16) The toxic compounds present in Amanita phalloides, such as α-amanitin, are highly stable and resistant to heat, making them unaffected by cooking or boiling. This means that even if the mushroom is cooked, the toxins remain active and can still cause poisoning.The toxic profile of Amanita phalloides mushrooms is characterized by the presence of two main toxin groups: amatoxins and phallotoxins. Phallotoxins, although toxic, are relatively less harmful due to their instability and rapid breakdown by heat, gastric acid, and digestive enzymes. In contrast, amatoxins are highly stable and resistant to degradation, making them the primary contributors to the mushroom's toxicity, with a potency 10 to 20 times greater than that of phallotoxins. (17,18) Current cell-destructive therapies, including chemotherapy and apoptosis-inducing programs, have limited success in extending patient survival. This is largely due to the tumor cells' ability to develop resistance to multiple treatments and their genetic inability to undergo programmed cell death, or apoptosis. (19) Amanitin inhibits RNAPII, a crucial enzyme overexpressed in tumor cells. This inhibition reduces tumor cell activity by 50% without side effects, allowing the immune system to target and attack cancer cells, and potentially leading to recovery. Amanita therapy shows promise in

controlling various tumor syndromes. (20,21) This review explores the potential of natural treatment approaches for cancer, with a specific focus on the application of amanitin therapy as a novel and innovative strategy.

Figure 1: Amanita Mushroom

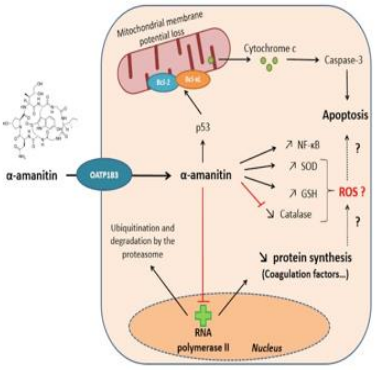

Figure 2: Toxic effects of Amanitins

3. Management of amanita poisoning:

According to the new classification, amatoxins are categorized in the cytotoxic group (1A) due to their mechanism of action, which involves inhibiting RNA polymerase II and disrupting the transcription of DNA into RNA. This interference with messenger RNA leads to the inhibition of protein synthesis, ultimately resulting in cell necrosis.Cells with high protein synthesis rates, like enterocytes, hepatocytes, and proximal renal cells, are the first to be affected by amatoxins.(22,23) No international guidelines exist for Amanita phalloides poisoning, but general treatment principles include stabilizing vital functions, addressing electrolyte imbalances, and administering fresh frozen plasma to manage coagulopathy.(24) High-volume plasma exchange has improved liver transplant-free survival in acute liver failure cases.(25)Potential antidotes tested include hormones, steroids, antioxidants, antihistamines, antibiotics, and flavonoids.Despite the incomplete understanding of the underlying pathophysiology, three primary therapeutic strategies have emerged:

(1) Inhibiting the OATP1B3 transporter with β-lactam core antibiotics

(2) Inducing antioxidant effects with N-acetylcysteine, vitamin C, vitamin E, cimetidine, and α-lipoic acid, and

(3) Combining antioxidant activity with OATP1B3 inhibition using silibinin or silymarin.(26,27,28) Despite the absence of randomized controlled trials, a multidimensional statistical analysis of available studies provides valuable information on patient survival rates associated with various drug classes in the management of Amanita phalloides poisoning. While a high-level evidence-based recommendation cannot be established yet, the observed survival trends support an empirical therapeutic approach. The analysis reveals that silibinin, both alone and in combination with other agents, and N-acetyl-cysteine are associated with significantly improved survival rates, with mortality rates of 5.6% and 6.8%, respectively. Based on these findings, the European Union has approved Legalon® (Rottapharm Madaus, Cologne, Germany), a standardized extract of flavonolignans from milk thistle seeds, for the treatment of Amanita phalloides poisoning, providing a much-needed therapeutic option for this potentially fatal condition. (28,29,30) Recently, a novel antidote, M101, has been developed from the extracellular hemoglobin of the marine worm Arenicola marina. M101 has shown promise in reducing amanitin-induced cell death and mitochondrial reactive oxygen species production in HepaRG cells, a hepatocyte-like cell line. This

breakthrough has led to the filing of a patent for M101 as a potential treatment for amanitin poisoning. (31) While these findings are currently limited to in vitro studies, they offer a promising therapeutic avenue for the treatment of Amanita phalloides poisoning. (32)

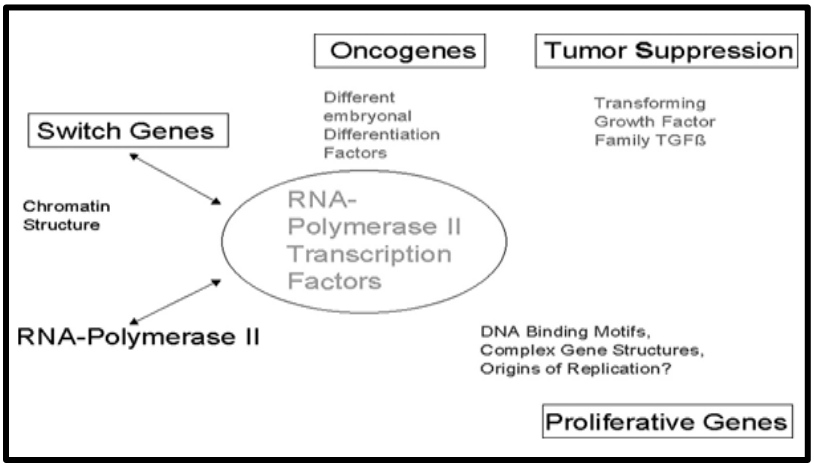

Figure 3. Tumor formation biochemistry (Riede, 2013a). All switch genes acts as transcription factors for RNA polymerase II (RNAP) and cause to be 100 % activity of RNAP in tumor cells. Partial inhibition of activity reduces tumor cell activity with no influencing normal cells.

4. Treatment for cancer:

Over the past few years, research has surged on harnessing fungal toxins as potential cancer treatments through direct tumor injection, with numerous studies exploring this innovative approach. Amanita therapy utilizes diluted extracts of A. phalloides, a centuries-old homoeopathic approach. For 300 years, these dilutions have been employed to alleviate existential anxiety, a hallmark of severe illness. Notably, A. phalloides D2 dilutions (100 ml) inhibit approximately 50% of RNA polymerase (RNAP) molecules across all cells, leading to long-term stabilization with tailored dosing regimens. (33)

Amanita treatment achieves significant stabilization in various tumor conditions:

A. Breast Cancer

Amanitin dilutions from A. phalloides were administered to a patient with mammary duct cancer, demonstrating efficacy in tumor marker detection and halting tumor growth. Previously, the tumor doubling time was three months; however, the patient achieved complete recovery within 18 months, with no adverse effects on liver function or erythrocyte count. (34)

B. Leukemia

Leukemia commonly presents with anemia-like symptoms, resulting from the proliferation of malignant leukocytes that gradually supplant erythropoietic stem cells within the bone marrow, leading to erythrocyte deficiency. (35) Amanitin administration results in decreased circulating leukocytes and enhanced cell lysis, as evidenced by elevated lactate dehydrogenase (LDH) levels. This promotes swift erythrocyte level recovery. In contrast, absent amanitin, LDH values remain within normal ranges, suggesting insufficient immune-mediated tumor cell elimination. (36) Amanitin's cytotoxic effects extend beyond tumor growth inhibition. This lysis suggests amanitin's immunomodulatory potential. Amanitin enhances tumor cell susceptibility to immune attack by altering antigen expression, amanitin boosts anti-tumor immunity. (35) The temporal dynamics of amanitin uptake and cellular response can be divided into two phases:

1. Initial synchronization: Concurrent cell migration and lysis, triggering inflammatory responses.

2. Desynchronization: Cells progress at disparate rates, leading to attenuated clinical symptoms and presentation of general fatigue. Amanita-based therapy exhibits promising results in the treatment and prophylaxis of diverse oncological indications, notably Colon carcinoma, Mammary carcinoma, Hypopharyngeal tumors (tongue root tumors). Amanitin exhibits cytotoxic specificity towards tumor cells, disrupting their activity and triggering lysis and migration. Notably, somatic and immune cells remain unaffected. This selective action underscores the therapeutic potential of A. phalloides-derived homeopathic dilutions in oncology. (37.38)

C. Colon cancer

Colorectal cancer, encompassing both colon and rectal cancer, is a type of malignancy where:

1. Cells in the colon or rectum exhibit abnormal growth
2. Uncontrolled cellular division leads to tumor formation
3. Cancer cells spread (metastasize) to other organs (39)

Several factors contribute to an elevated risk of colorectal cancer:

1. Age: Risk increases with advancing age
2. Ethnicity: African Americans are disproportionately affected
3. Family history: Genetic predisposition plays a role
4. Diet: Low fiber intake increases risk
5. Lifestyle: Sedentary behavior contributes to increased risk

Studies are underway to explore the medicinal properties of a specific mushroom, which has demonstrated: - Anticancer activities, inhibiting tumor growth and proliferation, Immunological enhancements, boosting immune response, Glycemic control, reducing blood glucose levels. These preliminary findings suggest potential therapeutic applications. (40)

Research indicates that medicinal mushrooms: Demonstrate negligible toxicity, Lack harmful side effects, Show promise in improving treatment outcomes. For colorectal cancer, presenting a compelling alternative to conventional synthetic chemotherapies. (41)

Medicinal mushrooms' multifaceted benefits: Antimicrobial: inhibiting microbial growth, Antitumor: suppressing tumor development, Anticancer: preventing cancer progression.

Position them as a viable candidate for chemoprevention, meriting investigation as a standardized pharmaceutical treatment. (42)

D. Thyroid cancer

Thyroid cancer

1. Amanita-based therapy
2. Dietary interventions

Influence thyroid cancer progression.

A 70g/day sugar supplement elevates tumor marker levels, whereas a sugar-free, low-carbohydrate diet yields decreased tumor marker values. Therefore, amanita Therapy as a lifelong treatment is recommended. Scientific Research suggests a balanced cancer- protecting diet. Some Regimens utilize a diet with reduced carbohydrate comprising, unprocessed materials Tumor marker analysis demonstrates sugar's effect on tumor cell activity:

1. Thyroid cancer cells display reduced sensitivity
2. Rectal tumor cells exhibit significant (3-fold) increase

Dietary interventions for cancer protection emphasize:

1. Plant-based foods (vegetables, fruits, wild herbs)
2. Unsaturated fatty acids
3. Plant oils. (43)

E. **Prostate cancer**

Prostate cancer is a prevalent men's health issue, typically affecting those over 50. Diagnosis

involves: Recognizing symptoms, Physical examination, Prostate-Specific Antigen (PSA) test, biopsy (44) Prostate Cancer Screening and Amanita Therapy Men over 50 should undergo prostate cancer screening. Low-dose Amanita phalloides (D2, D4) maintains PSA levels: D4 drops daily, 100ml D2 every 2 months.

In 2010, tumor fear led 3 patients to try Amanita. After 3 years, they felt well and stopped treatment. Ignoring maintenance, PSA levels rose. (45)

Effective management of Amanita's physical symptoms requires strong leadership. Ongoing research will uncover additional benefits of this promising therapeutic approach. (46)

F. Lung cancer

Our initial study on A. spissacea's anticancer potential involved:

1. Preparing a methanol (MeOH) extract from fruiting bodies
2. Investigating cell viability in four human lung cancer cell lines, representing different p53 genetic backgrounds: A549 cells (wild-type p53), H1264 cells (mutated p53), H1299 cells (p53-depleted), Calu-6 cells (p53-depleted).

This research aims to explore A. spissacea's therapeutic potential in lung cancer treatment.

Following MeOH extract treatment, human lung cancer cells exhibited distinct morphological features indicative of apoptosis: Cell rounding and shrinkage, indicative of cellular condensation, Plasma membrane blebbing, suggesting cytoskeletal disruption, Detachment from the substratum, reflecting loss of cell-substrate interactions

These observations suggest the MeOH extract induces programmed cell death in lung cancer cells. (47, 48)

TUNEL assay revealed a substantial increase in apoptotic cells following MeOH extract treatment across all human lung cancer cell lines, compared to DMSO controls. This suggests:

1. MeOH extract's cytotoxicity is primarily apoptosis-driven
2. Pro-apoptotic mechanisms underlie its anticancer efficacy. (2)

5.CONCLUSION:

Amanita therapy, specifically α-amanitin, has garnered attention as a gentle cancer treatment. Research shows:

- No severe side effects or clinical symptoms
- Potential for tumor-specific therapy
- Complementary to conventional treatments (antiandrogen drugs, chemotherapy, radiation, prostatectomy)

This review consolidates knowledge on amanitin toxicity, management, and innovative treatments."

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