

From Ancient Medical Thought to Modern Health Systems: The Modern Translation of the "Fighting Poison with Poison" Principle in Cancer Therapy

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Abstract. "Using poison to fight poison" is an important principle in traditional Chinese medicine for treating intractable diseases. It uses the therapeutic effects of toxic medicinal agents and provides a unique strategy for modern antitumor drug development. This review examines the theoretical basis and modern development of "using poison to fight poison." Three representative toxic drugs, arsenic trioxide (ATO), cantharidin and norcantharidin, and bufalin, are discussed. Their pharmacological origins, antitumor molecular mechanisms, clinical applications, and approaches to toxicity control are systematically reviewed. Studies have shown that ATO promotes differentiation and apoptosis of acute promyelocytic leukemia cells by targeting the PML-RAR α fusion protein; cantharidin and its structurally modified products mainly inhibit tumor cell proliferation and induce apoptosis through multi-target regulation; and bufalin exhibits broad anti-tumor activity by affecting multiple signaling pathways such as PI3K/Akt and MAPK. However, current research is still mainly based on basic and preclinical evidence, and there is still a lack of therapeutic window, toxicity evaluation, and high-quality clinical evidence. Future research should strengthen research on precision drug administration, toxicity monitoring, drug delivery, and randomized controlled trials to promote the transformation of traditional theories into a standardized, precise, and internationalized modern cancer treatment model.

Keywords: Fighting poison with poison, cancer therapy, arsenic trioxide, cantharidin, bufalin

1. Introduction

Malignant tumors constitute a major public-health challenge worldwide. According to GLOBOCAN 2022 estimates released by the International Agency for Research on Cancer, approximately 20 million new cancer cases and 9.7 million cancer deaths occurred globally in 2022 [1]; in China, an estimated 4.825 million new cases and 2.574 million deaths were recorded in the same year, accounting for roughly 24.2% and 26.4% of the global totals [2]. Although surgery, radiotherapy, chemotherapy, molecular targeted therapy, and immunotherapy form the main framework of cancer treatment, chemotherapy-induced adverse reactions, tumor drug resistance, and high costs still markedly limit therapeutic efficacy and accessibility. Against this background, mining highly

effective and low-toxicity antitumor resources from traditional medicine has become an important direction of global drug development, and the use of toxic Chinese medicinals guided by the principle of "fighting poison with poison" is its most representative application.

"Fighting poison with poison" refers to the therapeutic rule of using the toxicity of medicinal agents to expel endogenous "pathogenic toxins." Its theoretical roots can be traced to the doctrine of "attacking pathogens with toxic drugs" in Huangdi Neijing (Yellow Emperor's Inner Classic), and Shennong Bencao Jing (Shennong's Classic of Materia Medica) explicitly recognized the dual nature of toxic drugs, in which efficacy and toxicity coexist. Modern science has gradually revealed that its rationality lies in dose-dependent bidirectional effects and molecular targeting: the same toxic constituent can induce either tumor-cell differentiation or apoptosis at different concentrations, and its selective action on defined molecular targets constitutes the molecular basis of "attacking poison" [3-5]. Nevertheless, conspicuous gaps remain: most toxic medicinals have narrow therapeutic windows and lack systematic dose-toxicity evaluation; existing mechanistic evidence derives mainly from in vitro and animal studies, and high-quality clinical evidence is insufficient [6]; and the translational pathway between traditional empirical terminology and the discourse of modern precision medicine has not been systematically mapped.

In view of this, focusing on cancer therapy, this review selects three representative toxic medicinals for which modern research is relatively mature - arsenic, Mylabris (blister beetle), and Venenum Bufonis (toad venom) - and systematically reviews the theoretical origins, scientific connotations, and practice lineage of this principle. Their translational pathways are analyzed across molecular mechanisms, clinical evidence, and toxicity control, followed by a discussion of the paradigm shift of this principle and its value and challenges within global health systems.

2. Theoretical origins and scientific connotations of "fighting poison with poison"

2.1. Theoretical origins and historical practice

The principle of "fighting poison with poison" is rooted in the TCM tradition of analogical reasoning (qu xiang bi lei) [7]. Ge Hong's Zhouhou Beiji Fang recorded the application of rabid-dog brain tissue to prevent rabies, and variolation in the Ming and Qing dynasties embodied the same idea of stimulating host defense with attenuated pathogens; both are embryonic forms of active immunization. For tumor-like illnesses, conceptualized as "accumulations" and "malignant sores," ancient physicians extensively employed toxic medicinals: Bencao Gangmu records that arsenic "treats abdominal accumulations and erodes necrotic tissue"; Mylabris was indicated for abdominal masses; and Shennong Bencao Jingshu states that "the ancients used it precisely in the sense of fighting poison with poison." These records constitute the historical empirical basis for applying this principle to cancer.

2.2. Modern scientific connotations

From a modern scientific perspective, the rationality of "fighting poison with poison" rests on three pillars. The first is dose-determinism: hormesis in toxicology demonstrates that the boundary between "poison" and "medicine" depends on dose and administration. The second is molecular targeting: toxic constituents selectively act on aberrantly activated signaling pathways in tumor cells while exerting relatively controllable effects on normal tissues. The third is controllable detoxification: processing (paozhi), compatibility, structural modification, and formulation

improvement can reduce toxicity while preserving efficacy. Together, these three pillars provide the theoretical foundation of the analytical framework of this review.

2.3. Lineage of ancient and modern practice

Over more than two millennia, the application spectrum of "fighting poison with poison" has spanned infectious-disease prevention and the treatment of tumor-like illnesses (Table 1) - from rabid-dog brain application and variolation to the modern rediscovery of the arsenic-containing compound "Ailing-1" for leukemia in the 1970s. This lineage indicates that the principle is not an isolated empirical fragment but a dynamic body of knowledge that has been repeatedly tested, screened, and rediscovered.

Table 1. Representative ancient and modern practices of the "fighting poison with poison" principle

Era and source	Agent or method	Indication	Rationale and modern interpretation
Jin dynasty, Ge Hong, Zhouhou Beiji Fang	Topical application of rabid-dog brain tissue	Rabies	Attenuated pathogenic material stimulates host defense; an embryonic form of active immunization
Ming-Qing dynasties, Douzhen Dinglun and others	Variolation (insufflation of ground dried scabs)	Smallpox	Attenuated antigens induce specific immunity; inspired modern vaccinology
Shennong Bencao Jing	Mylabris (listed as lower grade)	Abdominal masses, malignant sores	Using toxic drugs to attack "accumulations"; the origin of its antitumor application
Bencao Gangmu	Arsenic	Abdominal accumulations, necrotic tissue, abscesses	"Treating accumulations and eroding necrotic tissue": the putrefaction-attacking use of a mineral poison
Bencao Gangmu	Venenum Bufonis	Severe abscesses and all malignant swellings	An animal toxin that resolves toxicity, relieves pain, and attacks malignant sores
1970s, clinical team in Harbin	"Ailing-1" (arsenic-containing compound)	Acute promyelocytic leukemia	Modern rediscovery of a folk remedy; initiated the translational path of arsenicals against leukemia

3. Modern translation of the principle in cancer therapy

The modern translation of toxic medicinals is essentially a systematic reshaping of four links: material basis, mechanism of action, clinical evidence, and safety control. This section examines three representative medicinals - arsenic, Mylabris, and Venenum Bufonis, of mineral, insect, and animal origin respectively - followed by a brief account of other toxic medicinals; Table 2 compares their pharmacological origins, core mechanisms, major toxicities, and detoxification strategies.

3.1. Arsenic (arsenic trioxide): from a folk remedy to the global standard therapy for APL

Arsenic (Pishuang) is extremely hot in nature and highly toxic; Bencao Gangmu records that it "treats abdominal accumulations and erodes necrotic tissue." In the 1970s, the arsenic-containing compound "Ailing-1" was rediscovered from folk remedies and showed definite efficacy against acute promyelocytic leukemia (APL). In the 1990s, Chen and colleagues verified this efficacy at the molecular level [8]: arsenic trioxide (ATO) directly binds the PML moiety of the PML-RARalpha fusion protein, promotes its SUMOylation, and drives its ubiquitin-proteasome degradation, releasing the differentiation block of myeloid cells; arsenicals restored complete remission in relapsed or refractory APL. ATO was subsequently purified, its direct target dissected, its dose-effect relationship quantified, and the regimen validated in multicenter trials.

The molecular hallmark of APL is the t(15;17) chromosomal translocation, which generates the PML-RARalpha fusion protein that blocks myeloid differentiation. The core mechanism of ATO is targeted degradation of this fusion protein, displaying a striking dose-dependent bidirectional effect: at low concentrations (0.1-0.5 micromol/L), ATO promotes SUMOylation of the PML domain and RNF4-mediated ubiquitin-proteasome degradation of the fusion protein, inducing leukemic-cell differentiation; at high concentrations (0.5-2.0 micromol/L), it induces reactive oxygen species and activates the mitochondrial caspase-9/3 apoptotic pathway to kill tumor cells directly [3]. One molecule, two fates - a molecular footnote to "the dose makes the poison."

Regarding clinical evidence, the Italian multicenter randomized APL0406 trial showed that ATO plus all-trans retinoic acid (ATRA) achieved a complete remission rate of 100% in newly diagnosed APL, with 2-year event-free survival of 97% versus 86% and 2-year overall survival of 99% versus 91% compared with ATRA plus chemotherapy, establishing the chemotherapy-free targeted regimen as first-line therapy [9] (Figure 1). The oral Realgar-Indigo naturalis formula (compound Huangdai tablets) proved non-inferior to intravenous ATO, moving APL treatment to home-based oral therapy [10], and the AAML1331 study validated arsenic-containing regimens in pediatric APL [11]. ATO has been included in the WHO Model List of Essential Medicines [12, 13].

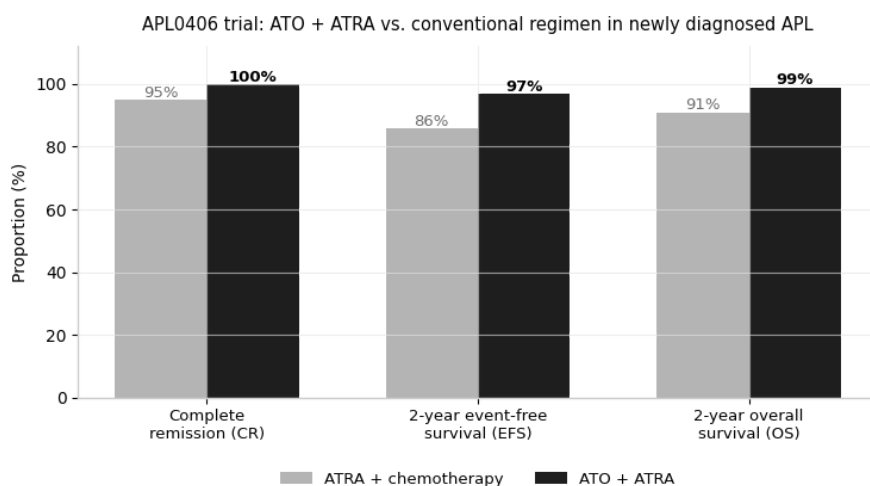


Figure 1. Efficacy comparison between the ATO+ATRA regimen and the conventional regimen in the APL0406 trial [9]

Meanwhile, the toxicity of arsenic must not be overlooked: an oral dose of 5-50 mg causes acute poisoning in adults and 0.1-0.2 g is lethal, while chronic poisoning damages the liver, kidneys, and

peripheral nerves; ATO therapy may also cause QT-interval prolongation, differentiation syndrome, and hepatic impairment. The proximity of toxic and therapeutic doses dictates that modern translation rely on precision dosing, therapeutic drug monitoring with electrocardiographic surveillance, and standardized clinical pathways.

3.2. Cantharidin and norcantharidin: a paradigm of structural detoxification

Mylabris (blister beetle) is highly toxic and was listed as a lower-grade medicinal in Shennong Bencao Jing; Shennong Bencao Jingshu states explicitly that "the ancients used it precisely in the sense of fighting poison with poison." Its active constituent, cantharidin, is a monoterpene toxin that inhibits protein phosphatases PP1 and PP2A.

Modern research has characterized the multi-target anti-hepatocellular-carcinoma profile of cantharidin, involving TP53, PTEN, and PI3K/Akt signaling [4]. To address its severe toxicity, the demethylated derivative norcantharidin (NCTD) was developed, which markedly reduces urinary toxicity while retaining antitumor activity and has been clinically approved in China since the 1980s [14]. NCTD induces mitotic arrest, apoptosis, and autophagic death in hepatocellular carcinoma cells and inhibits metastasis through repression of c-Met/mTOR and JAK/STAT3 signaling, reversal of RASSF1A methylation silencing, and activation of TRAIL-R2/DR5 signaling [6]; it can also reverse multidrug resistance, offering rationales for combination therapy [14]. In terms of toxicity, oral cantharidin can cause severe gastrointestinal ulceration, urinary-tract injury, and hepatorenal impairment. In vivo toxicity profiling of NCTD indicates persistent dose-related toxicity dominated by liver injury [15], and, notably, most mechanistic evidence derives from in vitro studies, with high-quality clinical evidence clearly insufficient [6].

3.3. Venenum Bufonis (bufalin): broad-spectrum antitumor activity versus cardiotoxicity

Venenum Bufonis (toad venom, Chansu) is toxic and resolves toxins, relieves pain, and opens the orifices; Bencao Gangmu records that it "treats severe back abscesses and all malignant swellings." Bufalin, its principal active monomer, is a steroidal lactone structurally analogous to cardiac glycosides. Modern studies show that bufalin combines Na⁺/K⁺-ATPase inhibition with multi-target antitumor activity, displaying broad-spectrum suppression in models of hepatocellular carcinoma, cholangiocarcinoma, colorectal cancer, breast cancer, glioblastoma, and other malignancies [16]: in intrahepatic cholangiocarcinoma it targets CAMKK2 to block the Wnt/beta-catenin pathway [17]; in colorectal cancer it degrades SRC-3 via the SRC-3/MIF pathway [18]; it also induces cell-cycle arrest, inhibits angiogenesis, and reverses multidrug resistance [16].

Regarding toxicity, cardiotoxicity is most prominent: bufalin inhibits myocardial Na⁺/K⁺-ATPase and can cause arrhythmia or even cardiac arrest, and its narrow therapeutic window is the core bottleneck restricting clinical translation. Nanocarriers and exosome-based delivery are being explored to enhance tumor targeting and widen the therapeutic window [5]. Taken together, the translational practice of the three representative medicinals reveals common patterns: a clearly defined material basis is the starting point, mechanistic dissection is the key, structural modification and formulation innovation provide detoxification pathways, and high-quality clinical evidence is the final threshold (Table 2).

Table 2. Modern translation of three representative toxic-TCM-derived antitumor agents

Source material	Active constituent	Main antitumor indications	Core mechanisms	Major toxicities	Detoxification and translation strategies
Arsenic (mineral)	Arsenic trioxide (ATO)	Acute promyelocytic leukemia	Targeted degradation of the PML-RARalpha fusion protein; differentiation induction at low concentrations and apoptosis induction at high concentrations	Acute arsenic poisoning; QT prolongation, differentiation syndrome, hepatorenal impairment	Precision dosing with therapeutic drug monitoring; intravenous formulation and oral compound (Realgar-Indigo naturalis formula)
Mylabris (insect)	Cantharidin / norcantharidin (NCTD)	Primary hepatocellular carcinoma and other solid tumors	Inhibition of PP1/PP2A; repression of PI3K/Akt, c-Met/mTOR, and JAK/STAT3 pathways; reversal of RASSF1A methylation	Gastrointestinal ulceration, urinary-tract injury, hepatorenal toxicity	Demethylated structural modification (NCTD); nano-lipid-carrier delivery
Venenum Bufonis (animal)	Bufalin	Broad spectrum across multiple cancer types	Inhibition of Na ⁺ /K ⁺ -ATPase; apoptosis induction and cell-cycle arrest; targeting of CAMKK2/Wnt/beta-catenin and SRC-3/MIF pathways	Cardiotoxicity (arrhythmia), gastrointestinal reactions, hepatorenal accumulation	Nano- and exosome-based delivery systems; dose-window control with cardiac monitoring

3.4. Translational exploration of other toxic Chinese medicines

Beyond the three medicinals above, realgar acts synergistically with ATO in targeting PML-RARalpha, and the water-soluble triptolide prodrug Minnelide has entered clinical studies for indications such as pancreatic cancer [19]. These explorations show that the modern translation of "fighting poison with poison" has evolved into a systematic endeavor spanning structural chemistry, pharmacology, pharmaceuticals, and evidence-based medicine.

4. Discussion: paradigm shift and remaining challenges

Across the four dimensions of dose, mechanism, formulation, and evidence, "fighting poison with poison" is shifting from an empirical-medical term to a precision-medicine paradigm. Empirical dosing has given way to pharmacokinetically guided precision dosing, exemplified by the standard ATO regimen with concentration monitoring [10]; phenomenological efficacy has been resolved into molecular events - PML-RAR α degradation by ATO, PP1/PP2A inhibition by cantharidin, and the actions of bufalin on Na⁺/K⁺-ATPase and CAMKK2 [3, 17] - which guided the structural design of norcantharidin [14]; crude preparations are being replaced by modern delivery systems such as the prodrug Minnelide and nano- or exosome-based carriers [5, 6, 19]; and anecdotal experience has been upgraded to evidence-based proof through multicenter randomized trials [8, 9]. Within global health systems, the low-cost, orally administrable ATO-ATRA regimen - now on the WHO Model List of Essential Medicines [13] - contributes to health equity in high-burden, resource-limited settings [2, 10] and exemplifies the productive integration of Chinese and Western medical paradigms [20].

Remaining challenges are substantial: first, narrow therapeutic windows and dose-control difficulties are widespread, with toxic doses of arsenic, cantharidin, and bufalin all lying close to therapeutic doses [3, 14, 16]; second, most constituents other than ATO lack support from randomized controlled trials [6, 16]; third, quality standardization and regulatory systems for toxic medicinals remain inadequate, as differences in raw-material sources and processing techniques affect compositional stability; and fourth, the alignment between traditional terminology and modern medical discourse still requires standardization. Confronting these challenges squarely is a prerequisite for the standardization and internationalization of "fighting poison with poison."

5. Conclusion

Focusing on cancer therapy, this review has traced the translational pathway of the "fighting poison with poison" principle from an ancient empirical term to a modern therapeutic paradigm. The analysis shows that its scientific validity lies not in "poison" itself but in the controllability of dose, target, and evidence: arsenic trioxide has turned acute promyelocytic leukemia into a curable disease through targeted degradation of the PML-RAR α fusion protein; structural modification of cantharidin has spawned the less toxic norcantharidin; and the multi-target antitumor mechanisms of bufalin have been progressively dissected. Once translated into molecular language and subjected to evidence-based scrutiny, traditional experience can be integrated into modern precision medicine and global health systems, offering a replicable paradigm for discovering antitumor drugs from natural toxins. Given that existing mechanistic evidence remains primarily preclinical, future research should prioritize precision dosing and toxicity monitoring, high-quality randomized controlled trials, and quality standardization, promoting the standardization and internationalization of this principle in cancer treatment.

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