APIS

Original Research

Experimental Investigation of the Oncobiological Effects of Apitoxin in a Sarcoma-45 Model

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ABSTRACT

Intensive research is currently being conducted worldwide into novel biologically active compounds and integrative therapeutic approaches for the treatment of malignant diseases. Bee venom (apitoxin) is a natural substance with a complex biological composition containing peptides, enzymes, and other bioactive components. Over recent decades, preclinical studies have increasingly focused on the oncobiological activity of melittin, phospholipase A2, and other peptide components of bee venom.

The aim of the present study was to describe the antitumour effects of bee venom observed in an experimental Sarcoma-45 tumour model and to provide a brief overview of the relevant preclinical literature. Native dried apitoxin obtained by electrical stimulation was administered to rats implanted with Sarcoma-45 tumours using different solvent systems. The control group received no treatment.

Marked tumour regression was observed in the apitoxin-treated groups by days 3–4 of treatment. By day 10, tumour size had decreased to approximately half of the initial volume. The treated animals demonstrated improvement in general condition, increased activity, and improved appetite, whereas the control group exhibited progressive tumour growth and significant mortality.

These findings suggest that the bioactive components of bee venom may influence several biological mechanisms involved in tumour progression and may also affect immunological and inflammatory regulatory pathways. Although further controlled preclinical and clinical studies are required to assess clinical applicability in humans, the available molecular, cellular, and experimental evidence supports further investigation of apitoxin within the field of integrative oncology.

Keywords: apitoxin; bee venom; melittin; integrative oncology; Sarcoma-45; tumour biology; preclinical research; apitherapy; tumour regression; immunomodulation

INTRODUCTION

Intensive research is being conducted worldwide into the development of novel antitumour therapeutic strategies and biologically active compounds. Malignant diseases continue to represent a major global public health burden, with both incidence and mortality rates increasing in many countries (Xia et al., 2022). Large-scale epidemiological studies indicate that the incidence of several malignancies is also increasing among younger age groups (Bleyer & Barr, 2009; André et al., 2025; Sung et al., 2021). Tumour development is a complex multifactorial process resulting from interactions between genetic, epigenetic, environmental, and lifestyle-related factors. Although numerous molecular mechanisms involved in carcinogenesis have been identified, the complete process of tumour formation and the determinants of individual susceptibility remain incompletely understood (Hanahan, 2022; Vineis & Wild, 2014).

Cytotoxic and other systemic oncological therapies used in cancer treatment frequently possess a narrow therapeutic window, and their clinical use may therefore be limited by significant toxicity. Although chemotherapy has improved survival and therapeutic outcomes in many malignant diseases, its administration is

Citation: Ovechkin, V. V. (2026). Experimental investigation of the oncobiological effects of apitoxin in a Sarcoma-45 model. *APIS*, Volume 3 Issue 1. DOI: 10.62949/03917046.5511101

Received: 3. December 2025.

Accepted: 10. June 2026.

Published: 15. June 2026.

commonly associated with immunosuppression, myelosuppression, hepatotoxicity, and impairment of haematopoietic and other physiological regulatory processes (Niraula et al., 2012; Wang et al., 2019).

Although surgery, radiotherapy, and systemic oncological therapies have significantly improved survival outcomes in numerous tumour types, substantial therapeutic challenges remain in advanced and metastatic disease. During antitumour treatment, particular importance is placed on reducing treatment-associated toxicity, preserving quality of life, and supporting and restoring physiological functions throughout the course of therapy (Miller et al., 2022; Sung et al., 2021).

Increasing attention is currently being directed towards integrative oncology approaches, which incorporate various supportive and immunological strategies alongside standard antitumour therapies. These may include selected naturally derived bioactive substances, immunomodulators, and adaptogens intended to support physiological and immunological functions and improve treatment tolerability. Integrative approaches may fulfil different supportive roles during various stages of oncological treatment (WHO, 2013).

One area investigated within integrative oncology is apitherapy, which examines the potential physiological and immunological effects of biologically active substances derived from bee products. Numerous preclinical and experimental studies have investigated the potential antitumour, immunomodulatory, and anti-inflammatory properties of royal jelly, propolis, pollen, and the biologically active components of bee venom. Published findings suggest that these substances may exert both specific and non-specific biological effects; however, their clinical applicability requires further investigation (Cui et al., 2024; Pandey et al., 2023; Rady et al., 2017).

Townsend et al. first identified one of the principal bioactive fatty acids of royal jelly, 10-hydroxy-2-decenoic acid (10-HDA), which demonstrated antitumour activity in experimental leukaemia and ascitic tumour models (Townsend et al., 1959). In subsequent investigations, the authors further analysed the in vitro effects of 10-HDA on tumour cells and compared its biological activity with that of other fatty acids (Townsend et al., 1960).

Later experimental studies evaluated the effects of royal jelly in various tumour models, including Ehrlich and Sarcoma systems. Some studies reported inhibition of tumour progression and effects on survival in experimental cancer models (Tamura et al., 1987).

In our own clinical observations, we investigated the potential effects of royal jelly administration in patients receiving palliative oncological care. Preliminary clinical experience suggested that, in some cases, improvements in quality of life, reduction of pain, enhancement of general condition and functional status, and clinical signs suggestive of tumour regression could be observed. According to our observations, the efficacy of royal jelly appeared more limited in hormone-dependent tumours. However, these observations were not obtained from controlled clinical trials. The primary objective of the present article is therefore not the analysis of human clinical outcomes, but rather the presentation of the effects of apitoxin observed in experimental tumour models.

Investigation of the biologically active components of bee venom has become an area of growing interest in integrative and experimental oncology research. Bee venom (apitoxin) is a secretory product of the venom glands of honeybees and possesses a complex biological composition. It contains proteins, enzymes, peptides, amino acids, biogenic amines (histamine, dopamine, noradrenaline), acetylcholine, lipids, minerals, and other bioactive molecules. Peptides, enzymes, and biogenic amines are considered particularly important contributors to the biological activity of bee venom, and their potential immunological and cellular effects have been examined in numerous preclinical investigations.

Current evidence indicates that melittin, the principal peptide component of bee venom, demonstrates significant cytotoxic activity against several tumour cell types in vitro and in experimental animal models. Reported mechanisms include disruption of tumour cell membranes, induction of apoptosis, and inhibition of certain signalling and proliferation pathways. Nevertheless, the authors emphasise that further studies are required before clinical application in humans can be considered (Pandey et al., 2023).

In the study by Duffy et al. (2020), bee venom and melittin demonstrated rapid and selective cytotoxic effects against highly aggressive breast cancer cell lines, including triple-negative and HER2-positive subtypes. According to the authors, melittin was capable of rapidly disrupting tumour cell membranes and reducing the activity of specific growth factor receptors (Duffy et al., 2020).

According to the review by Cui et al. (2024), melittin and phospholipase A2 are among the most important potential antitumour components of bee venom. The review summarised experimental findings indicating that these substances may induce apoptosis, modulate tumour signalling pathways, and be utilised in various targeted drug delivery systems (Cui et al., 2024).

Rady et al. (2017) identified melittin as one of the most important biologically active components of bee venom, demonstrating antitumour activity in numerous preclinical tumour models. The authors emphasised that one of the principal limitations of therapeutic melittin application is its non-specific cytotoxicity and haemolytic activity, necessitating the development of conjugates and targeted delivery systems (Rady et al., 2017).

Apamin and MCD peptide have primarily been investigated because of their neuroimmunological and membrane-physiological effects, whereas adolapin is mainly known for its anti-inflammatory and analgesic properties. At pres-

ent, only limited preclinical and mechanistic data are available regarding the potential oncobiological relevance of these components. In vitro studies demonstrated that apamin reduced proliferation, migration, and invasive properties of K562 leukaemia cells through inhibition of SK-type calcium-activated potassium channels. These observed effects may be associated with modulation of calcium-dependent signalling and membrane-physiological processes in tumour cells (Vasileva et al., 2023). MCD peptide (mast cell degranulating peptide) is primarily recognised for its mast cell-activating and immunomodulatory properties. Experimental investigations demonstrated enhancement of mast cell degranulation and histamine release, as well as alterations in membrane permeability and inflammatory mediator activity. Its potential oncobiological relevance is mainly being investigated in relation to modulation of immunological and inflammatory processes within the tumour microenvironment (Moreno & Giralt, 2015). Adolapin became known primarily because of its anti-inflammatory and cyclooxygenase-inhibitory activity, which may be relevant to inflammatory regulation within the tumour microenvironment. Melittin remains the most extensively studied component, and its cytotoxic and tumour cell-biological effects have been analysed in greater detail in both in vitro and animal models (Son et al., 2007; Rady et al., 2017; Cui et al., 2024).

Various bioactive components of bee venom may additionally influence immunological, neuroendocrine, and inflammatory regulatory pathways. Experimental studies suggest that bee venom administration may affect the hypothalamic–pituitary–adrenal axis as well as the production of inflammatory mediators and corticosteroid hormones. The immunomodulatory activity of phospholipase A2 and other peptide components has been examined in several preclinical models, particularly with regard to inflammatory and intercellular regulatory processes (Son et al., 2007; Moreno & Giralt, 2015). The precise mechanisms by which bee venom may affect hormone-dependent tumours remain incompletely understood, and further investigations are therefore required.

The present article reports previously unpublished experimental observations performed in 1997 in a Sarcoma-45 animal model and discusses them in the context of current research on the oncobiological effects of bee venom.

MATERIALS AND METHODS

In 1997, laboratory investigations were conducted to study the effects of bee venom on tumour growth in rats implanted with Sarcoma-45 tumours. Native dried bee venom (apitoxin) obtained by electrical stimulation from Carpathian honeybees was used in the experiments. The bee venom was stored in dark glass containers at 4–5 °C. Physiological saline solution and 0.5% novocaine solution were used as solvents.

The study was performed on rats weighing 190–220 g that had been implanted with Sarcoma-45 tumours. Tumour implantation had originally been carried out within an educational experimental programme at the Sverdlovsk Medical Institute. The experimental animals were subsequently made available for additional investigations. A total of 45 animals participated in the present study, with 15 animals in each group. Animals were selected so that tumour size was approximately equivalent between the groups.

The animals were divided into three groups:

1 In the first group, 0.5% novocaine solution was used as the solvent for apitoxin.
2 In the second group, physiological saline solution was used as the solvent.
3 The third control group received no bee venom treatment.

Apitoxin was administered using a gradual dose-escalation protocol over a 10-day period. Treatment was initiated with lower doses, and the administered amount was progressively increased up to a dose equivalent to 5 bee stings. No treatment-related acute toxicity or mortality was observed during dose administration. Tumour regression was observed during the gradual dose-escalation period.

Tumour size was monitored at regular intervals using linear measurements. The study was conducted in accordance with the available experimental animal regulations and institutional practices applicable at that time.

RESULTS

By days 3–4 of treatment, marked tumour regression was observed in both apitoxin-treated groups. No substantial difference in the degree of tumour regression was observed between the solvent systems used (0.5% novocaine and physiological saline solution).

The general condition of the apitoxin-treated animals improved: activity increased, mobility improved, and appetite also showed improvement. By day 10 of treatment, tumour size had decreased to approximately half of the initial volume.

Progressive tumour growth was observed in the control group, and significant mortality occurred during the observation period.

No acute toxicity or immediate severe adverse effects associated with treatment were observed.

Tumour size assessment was performed using linear measurements.

DISCUSSION

Investigation of biologically active natural compounds in tumour biology generally proceeds through sequential stages of research. The initial phase typically involves analysis of cellular and biochemical effects of individual molecules, including their activity on cell membranes, signalling pathways, gene expression, and immunological regulatory mechanisms. These investigations are followed by in vitro tumour models and subsequently by animal studies, which permit analysis of more complex biological effects and organism-level responses.

The molecular and cellular effects of various bioactive components of bee venom — particularly melittin, apamin, and phospholipase A2 — have been examined in numerous preclinical studies over recent decades. The present experimental animal observations demonstrated that natural apitoxin retained its biological activity when administered as a complex natural preparation, and no loss of antitumour activity was observed despite the simultaneous presence of multiple components.

According to the principles of integrative medicine, the primary objective of patient care is improvement of health status, quality of life, and survival outcomes. Accordingly, scientific investigation of any natural or synthetic bioactive substance demonstrating verifiable biological activity and an acceptable safety profile may be considered justified.

Assessment of the clinical applicability of naturally derived bioactive substances is particularly complex. In the case of substances with which humanity has coexisted over long evolutionary periods, and which possess no known severe toxic adverse effects when properly administered — with the exception of allergic reactions — preclinical evidence of safety and efficacy may justify investigation of human clinical application.

In Russia, apitherapy has a longstanding tradition within medical practice and research.

The institutional scientific foundations of Soviet medical apitherapy had already been established by the 1940s. Artemov's monograph on the physiological and therapeutic effects of bee venom (Artemov, 1941) is considered one of the earliest scientific works in this field. During the 1950s, N. P. Ioyrish published several studies concerning the medical application of bee products and the clinical significance of apitherapy. The institutional integration of apitherapy into the Soviet healthcare system is further demonstrated by the fact that, in 1959, the Scientific Medical Council of the USSR Ministry of Health officially approved the clinical instruction for apitherapy using bee venom.

Following completion of medical education and clinical specialisation, physicians may obtain apitherapy qualifications through specialised postgraduate training programmes. Such training is available at several medical institutions, including Ryazan State Medical University, and includes instruction in the physiological, pharmacological, and clinical application of bioactive substances derived from bee products.

Beginning in the 1990s, the author applied the integrative medical use of bee venom in the palliative care of patients with advanced and inoperable malignancies, based upon professional knowledge supported by preclinical and experimental observations, including the author's own animal experiments performed in 1997 and described in the present article. In all cases, treatment was conducted following detailed patient information, voluntary informed consent, and consideration of the ethical principles of the Declaration of Helsinki.

According to the author's clinical experience, apitoxin administration favourably influenced the general condition, quality of life, and symptoms of patients in numerous cases. Nevertheless, systematic clinical investigation and standardised data collection regarding these observations remain important future objectives.

It should also be noted that the review by Li Wanyao (2016) summarised the results of five clinical studies in which bee venom demonstrated oncobiological activity.

CONCLUSION

Based on the present experimental observations, administration of apitoxin in the Sarcoma-45 tumour model was associated with tumour regression, improvement in general condition, and increased activity of treated animals. The findings suggest that the bioactive components of bee venom influenced certain biological mechanisms involved in tumour progression and exerted effects on immunological and inflammatory regulatory processes.

According to the author's clinical experience, bee venom administration in the integrative palliative care of patients with advanced or inoperable malignancies may have been associated with favourable symptomatic and quality-of-life effects. The applied therapeutic approach was based upon the longstanding clinical and postgraduate educational traditions of medical apitherapy in Russia.

Although these observations were not derived from controlled clinical trials, the available molecular, cellular, and experimental findings justify further preclinical and clinical investigation of the bioactive components of bee venom.

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