

An Analysis of the Mechanism and Clinical Research Progress of Apitherapy in Anti-tumor and Cancer Pain Relief

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Abstract: Existing studies have shown that apitherapy, as a characteristic therapy of traditional Chinese medicine, plays an important role in anti-cancer and relieving cancer pain, thereby prolonging the survival time and improving the quality of life of patients. This paper elucidates the mechanisms of apitherapy in tumor suppression and cancer pain alleviation, based on the current literature and research findings, while also summarizing the regulatory mechanisms of bee acupuncture stings and the anti-tumor and pain-relieving properties of bee venom. The results of this study show that apitherapy, when used alone or combined with other traditional Chinese medicine or Western medicine strategies, shows the same good analgesic effect as analgesics, and the corresponding toxic and side effects are less, and the patients' acceptance is higher, which provides help to improve the quality of life of patients after treatment. Finally, based on the above results, this paper discussed the future prospects of apitherapy in resource utilization, clinical application and professional cooperation.

Keywords: Apitherapy, Melittin, Anti-tumor, Cancer pain, Clinical Progress

1. Introduction

Cancer pain is a sensation resulting from the passage of signals to the nerve center indicating that the place of pain needs repair or modification. Thirty-three to 40% of survivors who have undergone curative cancer therapy endure persistent pain, in contrast to 66% of terminally ill patients with advanced cancer who experience pain, with 55% reporting moderate to severe pain [1]. Modern medicine divides the mechanism of cancer pain into two types: peripheral mechanism and central mechanism. It is generally believed that the peripheral mechanism is related to the local inflammatory response of the tumor, ion channels and pain-related receptors, while the central mechanism involves the sensitization of central neurons, the pain modulation system and the pain transduction pathway [2]. In recent years, the consensus among experts in traditional Chinese medicine has pointed out that "obstruction leads to pain" and "malnutrition leads to pain" are the basic pathogeneses of pain [3]. In the field of traditional medicine and alternative therapies, apitherapy for analgesia, as a treatment with similar analgesic effect and fewer side effects, has attracted wide attention. It has been pointed out that melittin in bee venom has a significant analgesic effect; its inhibitory effect on prostaglandin synthetase is 70 times that of indomethacin, the analgesic intensity is 40% of morphine, and the analgesic duration is longer [4]. Huangdi Neijing recorded that "poisonous bee chelate can cure disease." The Shennong Bencao Jing (Shennong's Classic of Materia Medica) also lists honey as the top quality, which shows that bees and bee products have a long history as a treatment method. Recent

studies on apitherapy have revealed its efficacy in eradicating tumor cells, as well as its potential in cancer prevention and treatment, alleviating cancer-related discomfort, and enhancing patients' quality of life. This article aims to examine the mechanisms and effects of apitherapy in tumor suppression and cancer pain alleviation by reviewing its mechanisms and clinical outcomes while discussing the advantages, challenges, and future prospects of apitherapy, with the hope that it may serve as a clinical reference.

2. Apitherapy Research

Apitherapy integrates the therapeutic properties of bees with the principles of acupuncture. Bee needles are used on acupoints to induce bites, functioning as a form of "acupuncture". Bee venom then infiltrates the human body, functioning as a form of "medicine". Post-acupuncture, the skin exhibited erythema, edema, and increased temperature, akin to "moxibustion". Apitherapy integrates acupuncture, medication, and moxibustion to alleviate symptoms and reduce pain by stimulating the immunological and neurological systems of the human body. Its effect is mostly associated with the mechanism of action of bee stings and bee venom on the human body.

2.1. Effect of Acupuncture

The principles of apitherapy, which are related to acupuncture and moxibustion, exert a triple effect under the action of bee venom. Bee acupuncture, as a special acupuncture device on the skin, is thin and short. It can play the mechanical and physical stimulation effect of traditional "body acupuncture" at acupoints, and relieve cancer pain by regulating pain signal transduction of central and peripheral nerves, inhibiting inflammatory response and affecting the expression of certain transmitters [5].

Some scholars believe that acupuncture analgesia involves the whole nervous system. Acupuncture analgesia is preliminarily processed and interpreted through the spinal cord. The brainstem is responsible for the collation of information. The thalamus, limbic system and its nucleus play a coordinating role between strengthening acupuncture analgesia and controlling analgesia. The cerebral cortex has excitatory, inhibitory and dynamic balance effects on acupuncture analgesia [6]. In the central nervous system, acupuncture can relieve pain by regulating the neuroinflammatory response of the nucleus and restoring neuronal activity. Liu Wenhao et al. discovered that the basolateral amygdala (BLA) plays a role in the molecular mechanism of electroacupuncture (EA) in alleviating cancer pain and depression associated with cancer pain. It is speculated that EA may relieve cancer pain and depression induced by cancer pain by regulating the alleviation of neuroinflammatory response and the recovery of abnormal activity of specific neurons in the BLA [7].

Inflammation plays an important role in pain. TLR9 is widely present in the central nervous system and can regulate downstream inflammatory cytokines, thus playing a role in the process of pain sensitization [8]. Qin Shuanglai et al. used electroacupuncture combined with a pain patch to explore its analgesic effect on bone cancer pain in rats and its effect on the expression of Toll-like receptor 9 (TLR9) in the spinal cord. The experiment found that pain patch and electroacupuncture treatment could reduce the expression of TLR9 and reduce the regulation of pain signals by inflammatory response [8].

Acupuncture can also reduce pain by affecting the expression of certain transmitters. Studies have found that neurotransmitters involved in mediating acupuncture analgesia include opioid peptides, cholecystokinin-8 (CCK-8), 5-hydroxytryptamine (5-HT), norepinephrine (NA) and so on. Among them, three major opioid peptides (β -endorphin, enkephalin and dynorphin) and their receptors are widely distributed in peripheral primary afferent terminals and central nervous system regions related to nociception and pain [9]. Yao Kai et al. investigated the impact of exogenous increases in free

Ca²⁺ concentration within the central gray matter of the midbrain on acupuncture's influence, as evidenced by alterations in pain threshold in rats [10]. The findings indicated that pain stimulation markedly elevated the levels of free Ca²⁺ in the neurons of the central gray matter (PAG) in rats, while acupuncture dramatically diminished these levels, hence producing an analgesic effect.

2.2. Bee Venom and its Pharmacological Effects

Bee venom is a transparent liquid with an aromatic odor secreted by the poison glands of honeybee workers. It has a pungent, bitter taste and acid. Modern studies have found that bee venom contains a variety of peptides, enzymes, amines, acids, amino acids and trace elements, which have anti-tumor, anti-inflammatory, antiviral, and antibacterial effects and blood pressure lowering effects [11]. Peptides constitute a primary component of bee venom, with melittin, melitamin, and degranulated mast cell polypeptide being the principal active peptides present in bee venom [11]. Melittin, comprising about 40% of bee venom, is the primary constituent responsible for its pharmacological and biological effects [12]. Related studies have found that the mechanisms of melittin in relieving cancer pain are mainly reflected in anti-inflammation and nerve block. In addition, melittin also has anti-tumor effects, mainly related to its action on cancer cells to kill them and inhibit proliferation.

2.2.1. Neuroblocking Effects of Melittin on the Nervous System and Anti-inflammatory and Analgesic Mechanisms

Research indicates that both entire bee venom and melittin exhibit selective inhibitory effects on nicotinic cholinergic receptors, which can directly influence the central nervous system via the blood-brain barrier and possess ganglion-blocking properties [13]. Melittin is neurotropic, which has a blocking effect and cholinergic activity on the reticular tissue of the brain and can change the bioelectrical activity of the cortex. In particular, melittin has a selective blocking effect on N-choline receptors, which can block the synaptic excitatory conduction of the central nervous system and show central nicotinic cholinergic receptor blocking effect. At the same time, it can inhibit the conduction of peripheral nerve impulses [14].

Bee venom, similar to acupuncture, possesses anti-inflammatory and analgesic properties. The anti-inflammatory efficacy of melittin has been confirmed in the management of various inflammatory diseases, with its associated mechanisms being intricate and primarily involving multiple inflammatory signaling pathways, including NF- κ B (nuclear factor κ B), MAPK, and JAK/STAT [15]. It has been shown that melittin interacts with sulfhydryl groups in the p50 subunit and I κ B (an inhibitory protein of NF- κ B) kinase structure, thereby hindering I κ B phosphorylation, interfering with NF- κ B DNA binding activity, and blocking p50 nuclear translocation [15-17]. Melittin can also reduce capillary permeability, inhibit leukocyte migration and the synthesis of prostaglandin E₂, and promote the secretion of adrenal cortical hormones [16]. Glucocorticoids in adrenocortical hormones have a powerful anti-inflammatory effect; they can inhibit inflammatory response, reduce redness and heat pain symptoms, and inhibit immune response.

2.2.2. Effect of Bee Venom on Cancer Cells

Melittin acts on cancer cells mainly by killing cells directly, inhibiting cell proliferation and regulating the cell cycle.

From the structure of melittin, it appears that melittin is an amphipathic α -helix composed of 26 amino acids. The first 20 amino acid residues of its N-terminal region are mainly hydrophobic, whereas the six amino acid residues of its C-terminal region are mainly hydrophilic. This structure makes the molecule of melittin hydrophilic at one end and hydrophobic at the other end, thus endowing it with amphiphilic properties [12]. The amphiphilic nature of melittin determines that it

can not only dissolve in water but also bind to membrane and then dissolve cells, so it has certain cytotoxicity.

To investigate the mechanism by which melittin eradicates ovarian cancer cells, Jo et al. administered melittin to these cells and discovered that melittin exerts an anti-cancer effect by upregulating the expression of death receptors and suppressing the JAK2/STAT3 signaling pathway [17]. Wang Qiang et al. found that melittin had an inhibitory effect on the proliferation of bladder cancer T24 cells through experiments, and the content of PCNA (cell proliferation nuclear antigen) in the concentration group treated with melittin decreased significantly [18]. Researchers believe that the proliferation of tumor cells is achieved by abnormal regulation of the cell cycle. Cell cycle regulation encompasses two fundamental control points: the first determines the transition from G1 to S phase, while the second occurs between G2 and M phases, referred to as the G2/M transition point [18]. The findings indicated that the G0/G1 phase in each concentration group was diminished compared to the control group, whereas the S phase was elevated relative to the control group. The G2/M phase in the 10.0 μ g/ml and 100.0 μ g/ml groups exceeded that of the control group. It can be speculated that melittin can affect the proliferation of bladder cancer T24 cells and reduce the number of tumor cells. Through the above experiments, it was found that bee venom has an obvious killing and proliferation inhibition effect on tumor cells, which is helpful to carry out better clinical treatment.

3. Clinical Application of Bee Therapy for Anti-tumor Relief of Cancer Pain

In the experience of apitherapy for cancer treatment, Tian Qingkun et al. used apitherapy and traditional Chinese medicine to treat tonsil cancer and achieved good results in preventing recurrence [19]. The patient had cachexia symptoms such as closed stool, oliguria, inability to get up and move, emaciation, dry and loose skin, etc. After continuous treatment with traditional Chinese medicine and bee acupuncture, the patient ate normally, the clinical symptoms disappeared, and he was able to take part in light physical labor. In the medical case of Liu Lin et al., the clinical management of pain in advanced liver cancer involved the administration of controlled-release morphine sulfate tablets to the patient [20]. After one week, the pain was managed, although the side effects were severe and intolerable. After bee acupuncture treatment, physical examination CT after four diagnoses showed that the liver cancer nodules did not enlarge significantly, and there was no obvious pain in the liver area. Half a year later, the CT scan showed no signs of enlargement or metastasis. Subsequently, the patient was intermittently treated with bee needle stinging and Chinese medicine decoction and survived with the tumor for nearly two years with a good quality of life. When Lu Liguang et al. used apitherapy and neoadjuvant endocrine therapy to treat late-stage prostate cancer, the potential tumor lesions were removed by preoperative adjuvant endocrine therapy plus bee acupuncture, and laparoscopic radical prostatectomy was performed [21]. The postoperative pathology showed that the tumor did not invade the capsule and seminal vesicle, and no cancer was found in the bilateral apex and peripheral resection margin. The patient's tPSA (prostate specific antigen) decreased from 11.06 ng/ml in November 2019 to less than 0.003ng/ml in October 2021. This case shows that for late-stage prostate cancer, perioperative bee acupuncture therapy can strengthen the body and inhibit the tumor before and after the operation, complement the advantages of modern medical treatment, improve the surgical cure rate, and avoid the adverse reactions of endocrine therapy [21].

The above results proved that apitherapy alone or with a traditional Chinese medicine regimen has a clinical effect in the treatment of cancer to prevent recurrence and relieve pain.

By collecting the literature on the clinical effect of apitherapy, it was found that apitherapy, when used alone or combined with other traditional Chinese medicine or western medicine strategies, showed the same good analgesic effect as analgesics, and the corresponding toxic and side effects were less, and the degree of acceptance of patients was higher, which could help improve the quality of life and nutritional status of patients after treatment. In the clinical study of An Xiangzhen et al.,

the treatment group used apitherapy combined with oxycodone sustained-release tablets to treat patients with lung cancer and cancer pain [22]. In comparison to the control group administered just oxycodone sustained-release tablets, the treatment group exhibited an efficacy rate of 82.05%, markedly surpassing the control group's rate of 61.54%. The incidence of burst pain was lower than that of the control group, and the adverse consequences were diminished. The quality of life score in the treatment group rose from 21.28 ± 6.88 to 33.12 ± 7.40 , whereas the control group experienced a rise from 20.67 ± 6.80 to 21.97 ± 7.73 , demonstrating an enhancement in patients' quality of life following the combination therapy. Peng Hui et al. applied apitherapy combined with western medicine to treat cancer pain and randomly divided 60 patients with cancer pain into the treatment group and the control group [15]. Both groups were treated with three-step analgesic drugs recommended by the World Health Organization (WHO), and the treatment cycle was 10 days for a total of 3 courses. The treatment group received bee therapy in conjunction with a three-step analgesic regimen, administered once daily. The findings indicated that the overall effective rate was 96.67% in the treatment group compared to 90.00% in the control group, demonstrating superior efficacy of the treatment group over the control group. The onset of pain in the treatment group occurred more rapidly and lasted longer than in the control group: the minimum onset time in the treatment group was 0.25 hours, the maximum was 2 hours, and the mean was (0.91 ± 0.32) hours. In contrast, the control group had a minimum onset time of 0.5 hours, a maximum of 3.5 hours, and a mean of (1.87 ± 0.47) hours. In the treatment group, the longest duration of pain relief was 9 hours and the shortest was 6 hours, with an average of (7.83 ± 3.46) hours. In the control group, the longest duration of pain relief was 8 hours and the shortest was 4 hours, with an average of (5.71 ± 2.24) hours. Finally, in the analgesic treatment, the incidence of side effects in the treatment group was lower than that in the control group. The above research results show that apitherapy can not only improve the therapeutic effect of western medicine but also reduce the risk of adverse reactions in patients, providing an effective auxiliary means for the treatment of cancer pain.

4. Discussion

Despite its long history and remarkable efficacy, apitherapy still faces several challenges in modern society, mainly related to resource utilization, clinical application, and future collaboration.

First of all, the traditional bee venom collection method is inefficient and the purity is not high, resulting in a low utilization rate of bee venom. Secondly, when carrying out apitherapy, one bee in one acupoint is used, so the use cost of bees is relatively high. Therefore, technicians can reduce the waste of resources by extracting bee venom to make drugs such as bee venom injection. In the process of clinical diagnosis and treatment, it is found that traditional apitherapy often leads to patients' resistance due to obvious pain, allergic reactions, local redness, swelling, itching and pain, which affects patients' compliance and the popularity of bee therapy [20]. The use of painless bee therapy can effectively relieve the pain of traditional bee acupuncture therapy and reduce the occurrence of allergic reactions. In the future, the research of painless bee therapy can be further carried out. Thirdly, the future of apitherapy necessitates interdisciplinary collaboration. The effectiveness of apitherapy for treating rheumatic disorders, arthritis, anti-tumor conditions, and other ailments must be assessed by comprehensive clinical studies, necessitating collaboration among clinical medicine, epidemiology, statistics, and related fields. The development of apitherapy can be advanced solely through collaboration.

5. Conclusion

As a kind of natural therapy, the main mechanisms of apitherapy are the anti-inflammatory and analgesic effects of melittin, nerve blockade, direct killing of cancer cells and inhibition of

proliferation, as well as acupuncture with a bee needle tail hook. It can relieve cancer pain by regulating pain signal transduction in central and peripheral nerves, inhibiting inflammatory response and affecting the expression of some transmitters. In terms of clinical efficacy, the apitherapy has shown good effects in anti-tumor, anti-recurrence, relieving cancer pain and reducing the pain of side effects when used alone or at the same time with traditional Chinese medicine or western medicine strategies, increasing patients' confidence in treatment and yearning for a better life. However, apitherapy also faces some challenges. In terms of resource utilization, the cost of bees is high, so how to reduce resource waste is also the direction of future research. Patients often exhibit a strong resistance to pain acceptance due to the redness and swelling associated with certain allergic reactions, making it challenging for them to endure discomfort. The advancement of painless bee therapy will facilitate more patient acceptance and promote the therapy more effectively. The development of apitherapy in the future is not only the development of a single discipline; promoting more disciplines to understand apitherapy and carrying out disciplinary cooperation can better promote the development and research of apitherapy.

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