

A Review on Wasp Venom as a Chemotherapeutic Agent in Different Types of Cancer

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ABSTRACT

Cancer is the most leading cause of the death. Only few treatment options are available for treating the cancer such as radiation therapy, chemotherapy, and surgery. These treatment options can either used as single or combination therapies. Explorations of new drugs have been advanced to combat difficulties to treat cancers. New drug developments from natural biological resources are available all over the world. There are several active principles that are produced by different animals, plants and microorganisms that have been used in the development of novel drugs to combat diseases one of which is having great potential as anti-tumor agents. Wasp venom is a new productive solution that helps in treating cancers. Venoms of wasps are multifaceted mixtures of pharmacologically and biochemically functional elements like biogenic amines, peptides and proteins have been studied. Mastoparan is a selective and potent anticancer peptide. Researchers have developed a novel therapy using peptides derived from wasp venom that binds to several amino acids and show potential in cancer treatment. These peptides form pores on the cell plasma membrane and get penetrate the cell, resulting in lysis and finally causing to death. Numerous bioactive constituents were recognized from wasp venom. These peptides exhibited anticancer, antimicrobial activities against bacteria and fungi. This paper delves into recent progress in bioactive peptides and examines the prospects of utilizing wasp venom as a chemotherapeutic agent for treating variety of cancers.

Keywords: Melanoma cancer, Colorectal cancer, Breast cancer, Lung cancer, Wasp venom, Mastoparan.

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INTRODUCTION

Cancer ranks among the most prevalent diseases, and it is the second leading cause of the death (World Health Organization Cancer <https://www.who.int/news-room/fact-sheets/detail/cancer-2022> Google Scholar - Yahoo India Search Results, n.d.). There are different sorts of cancers such as skin cancer, malignant melanoma, breast cancer, lung cancer, and colorectal cancer. Skin cancer is utmost common malignant disease (Bastos *et al.*, 2024). From past 5 years death rates of cancer have been decreased by 1.8% in men's and 1.4% in women's is observed. Despite this progress, cancer leftovers a significant health concern, being the second leading cause of death. Only few treatment options are available for treating cancer such as radiation therapy,

chemotherapy, surgery these treatment options can either be used as single or combination therapies (Knight *et al.*, 2021; Roy and Li, 2016). These few treatment options underscore the urgent need for improvements in cancer screening, diagnosis and treatment. Anti-Cancer Peptides (ACPs) present a promising, yet underutilized, resource that could serve as effective adjunctive therapies in cancer treatment (Siegel *et al.*, 2015). A variety of novel treatments are under investigation and clinical trials. Explorations of new drugs have been advanced to combat difficulties to treat cancers. Wasp venom is a new productive solution that helps in treating cancers and that can impact biological system in many ways like cell lysis, hemolysis, rhabdomyolysis etc., (Zhong *et al.*, 2021a). Mastoparan is a selective and potent anticancer peptide that is rich in hydrophobic and basic residues that favours electrostatic interactions and this peptide insertion into membrane interact directly with G-proteins and causing the membrane destabilization and lysis (Brigatte *et al.*, 2011; Higashijima *et al.*, 1988; Knight *et al.*, 2021; Leite *et al.*, 2011; Rotem *et al.*, 2006).



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WASP VENOM

Vespid wasps (Family: Vespidae) have a global distribution and occur in over 5000 species worldwide. Wasp venom contains a broad spectrum of chemical constituents such as proteins, peptides (ex: mastoparan) and enzymes like hyaluronidase, phospholipases). The separated moieties from the venom had revealed several beneficiary activities like antimicrobial activity, anticancer activity, and anti-inflammatory activity. However, the levels of these peptides are scarce. Solid phase Peptides Synthesis (SPSS) is used in the design and development of such molecules. Through this technology several peptides and their analogues have been synthesised such as antimicrobial peptides such as mastoparan, anoplin, decoralin, polybia-MP-1, Polybia- CP, polydim-1 and agelaia-MP. Antimicrobial and anticancer properties were noted for the synthetic peptides.

BIOLOGICAL PROPERTIES OF WASP VENOM

Numerous studies on wasp venom and its mechanism of action have been conducted over the past 50 years. Nevertheless, additional experiments are required to bridge knowledge gaps and establish quality control measures to better understand the biological properties of wasp venom shown in Figure 1. According to this study the biological properties of wasp venoms are listed as anticoagulant, antiinflammation, antineoplastic and antimicrobial. The separation and characterization of venom components are dynamic for comprehending the envenoming process. These steps help to identify specific toxins, their mode of action, and their effects on biological systems. By thoroughly analysing these components, researchers can develop targeted treatments and antidotes, ultimately improving clinical outcomes for acerbating cases (Figure).

Bioactive peptides from wasp venom: Unveiling pharmacological and medical prospects

Considering the intricacy and range of venom components it stands as a promising source for novel therapeutic molecules. As we know, substantial numbers of modern-day treatments are derived from natural products. Therapeutic potentials like toxins which include catatonic peptides namely mastoparan and its analogues that show important potency as antimicrobial and antineoplastic agents. Even though some of the potent therapeutic molecules are discovered, there is a need to explore vespa toxins further. Figure 2 shows the pharmacological properties of bioactive peptides in wasp venom.

COMPONENTS OF WASP VENOM

Wasp venom is composed of a diverse array of biomolecules that have therapeutic potential, playing key roles in vital activities essential for the wasp's survival. Wasp venom contains small peptides, proteins and small molecules as represented in Figure 3. Small peptides like neurotoxic peptides, kinins, mastoparans

and chemotactic peptides. Whereas proteins like hyaluronidase, phospholipase and antigen. Many neurotoxins had been isolated from wasp venom some of them like bradykinin related to peptides, pompilidotoxins, philanthotoxins, and microbracotoxin.

WASP VENOM IN DIFFERENT TYPES OF CANCER

Wasp Venom in Colorectal Cancer

Colorectal cancer, one of the third typical type with high mortality rate (Sung *et al.*, 2021). Only 5% of the patients are responsive to the existing therapy (ex: FOLFOX-a combination drug; used as first line treatment for the colorectal rectal cancer). Mutations in the tumor genes and the development of new antigens create barriers for potent immunotherapy of colorectal cancer. Oncolytic approach is a better healing approach by inducing antigenic substances, but it has been restricted due to its structural instability, unwanted toxicity when taken systemically. To overcome this, according to the wasp venom peptide an optimised oncolytic peptide MP9 had been developed by integrating four functional motifs (Lu *et al.*, 2022). There are two different toxins of *Polybia mastoparan* (Polybia-MP-II and Polybia-MP-III) which is mentioned in the Table 1, and their activities are analysed by performing Mast cell degranulation, release of LDH from mast cells, hemolysis, and antimicrobial activity (de Souza *et al.*, 2009). Polybia peptide is related to antibiotic peptide evolving from *Polybia paulista*. It has been also noticed that Polybia-MP has cell selectivity (Wang *et al.*, 2008b). Mastoparan acts on mitochondrial membrane to regulate the tumor cell cytotoxicity. The study suggested that administration of mastoparan via peritumoral way increases the survival (Moreno and Giralt, 2015b).

Wasp Venom in Breast Cancer

Breast cancer is the utmost occurrence cancer in women. The anticancer therapy which is existing developing resistance. The main difficulty is development of resistance to therapeutic strategies; therefore, development of new therapeutic strategies provides more effective anticancer treatment (Hassan *et al.*, 2010). About 1 in 8 U.S. women (around 12%) will be diagnosed with invasive breast cancer at some point in their lifetime. The main treatment options include Surgery, chemotherapy, radiotherapy, and hormone manipulation for breast cancer. Here in this study, we demonstrate that both a natural Antimicrobial Peptide (AMP) derived from wasp venom as well as its synthetic variants designed via the peptide design, exhibits effective activity counter to cancer cells (Torres *et al.*, 2018). In the study of cancer, wasp venom as an anticancer agent shows promising results. Chattergellus-CP1 shows cytotoxicity depending on the concentration (Soares *et al.*, 2022b). Natural products like toxins can damage other living organisms in the concept of neoplastic diseases, they also trigger apoptosis in cancer cells (Kwon *et al.*, 2022).

In this follow up, venoms of different arthropods have been proved for potential anticancer substances. Chlortoxin, a scorpion toxin that is active against glioblastoma commonly found in brain cancer, Melittin that is obtained from different bee species that activity against gastric and liver cancer cell lines (Kong *et al.*, 2016; Mansour *et al.*, 2021). Wasp venom is composed of different combinations of biologically active components (Moreno and Giralt, 2015), they have antimicrobial, anti-inflammatory, and antitumor activity (El-Wahed *et al.*, 2021). They yield excellent outcomes. The surface of the cancer cell membrane has negatively charged molecules. To exploit the negatively charged membrane, it can be targeted with positively charged molecules, and this is based on electrostatic interaction of the peptides (Chiangjong *et al.*, 2020; Deslouches and Peter Di, 2017). Mastoparan, a wasp venom peptide robust anti-neoplastic effects against leukemia, myeloma and breast cancer and it is also active against

drug-resistant cells that had arisen during anticancer treatment of patients and delicately growing cancer cells (Hilchie *et al.*, 2016). There are some Anticancer Peptides (ACP) that can be applied as new adjuvant therapy. Direct acting anti-cancer peptides can totally remove primary tumors without affecting the healthy cells or tissues (Hansel *et al.*, 2007). The major reason for developing these ACPs is noted to be that the existing ACPs are toxic towards the normal cells. Therefore, the novel Anti-Cancer Peptide had been developing to kill the selective cancer cells (Hilchie *et al.*, 2011; Hilchie *et al.*, 2013). Mastoparan peptide has been observed to be a lethal to leukaemia, myeloma, breast cancer cells and also moving to multidrug resistant cancer cells. By subsequent analysis Mastoparan has shown toxicity towards human Tcell Acute Lymphoblastic Leukemia, Acute Monocytic Leukemia, Myeloma cells, Breast cancer cells, 4T1 mouse mammary carcinoma cells, prostate, cervical and ovarian cancer cells. To identify its

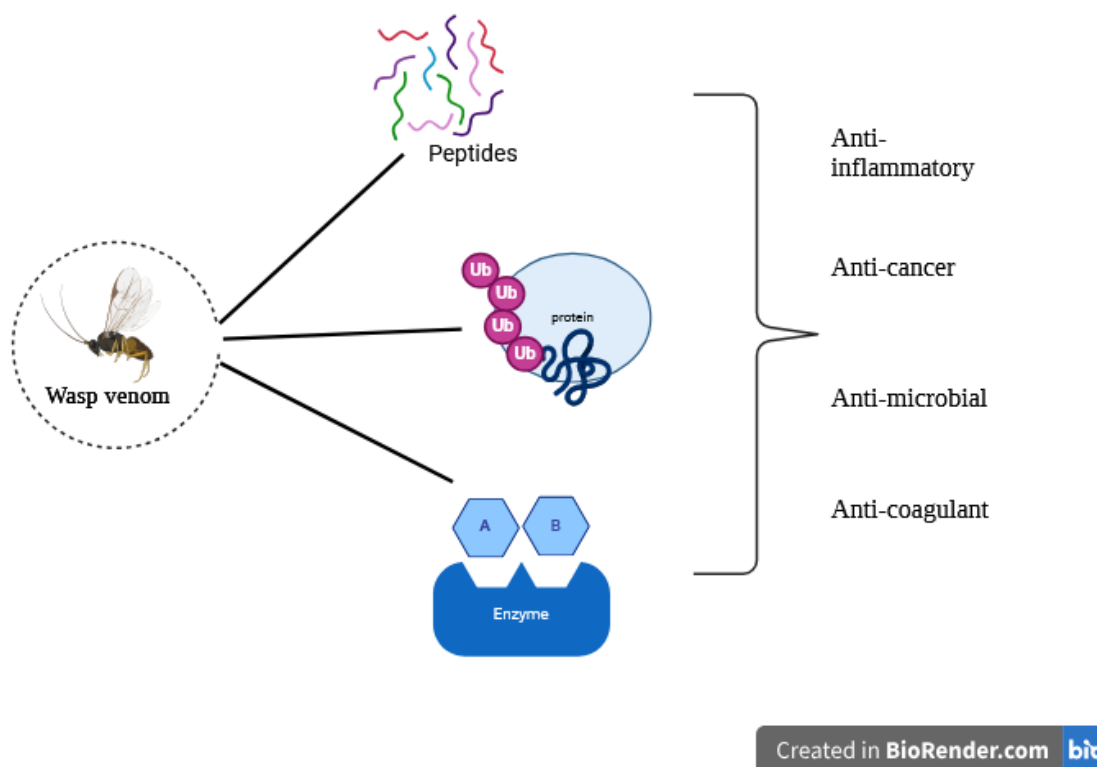


Figure 1: Biological properties of wasp venom.

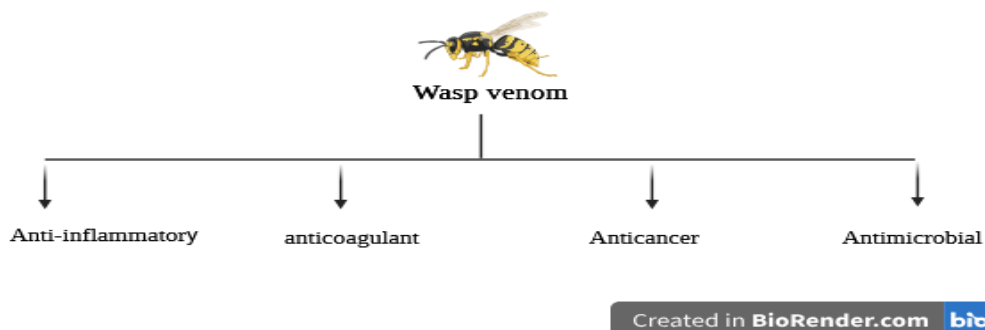


Figure 2: Pharmacological properties of bioactive peptides in wasp venom.

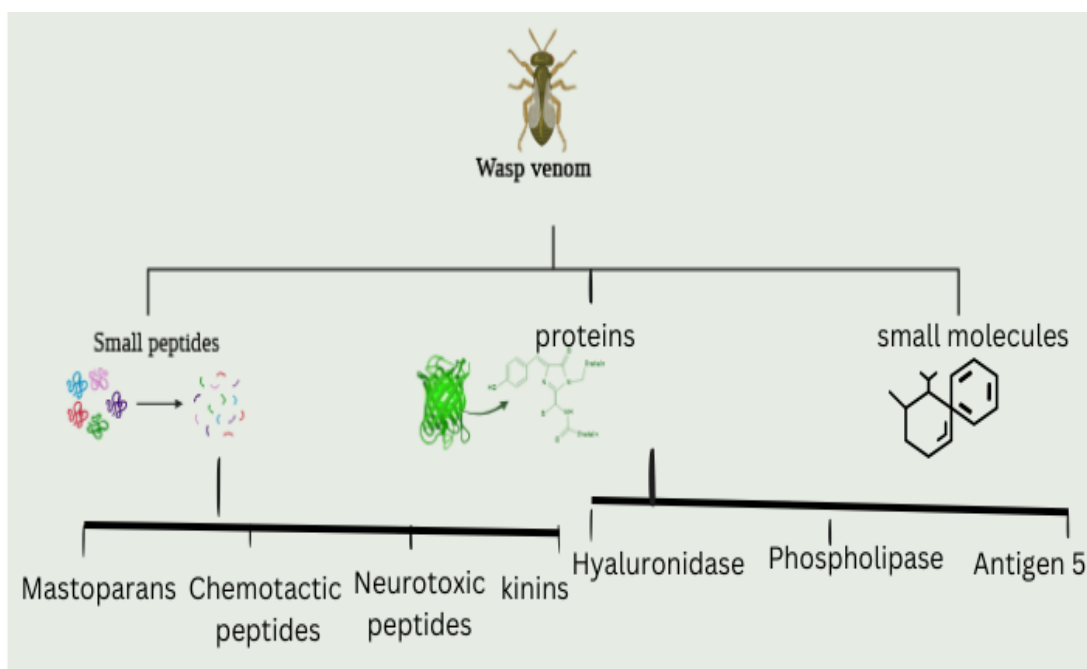


Figure 3: Components of wasp venom.

Table 1: Comparison of different types of bee sources and the peptide involved that shows anticancer property.

Types of cancer	Bee sources	Peptide	Activity	References
Bladder and Prostate cancer	Polybiapaulista	Polybia MPI	Cytotoxicity against leukemic T lymphocytes	(de Souza et al., 2009; Wang et al., 2008)
Bladder and Prostate cancer	Protopolybiaexigua	Mastoporan-1	Inhibition Toll-like receptor 4 (TLR4) mRNA, suppressionTNF-α and interleukin-6 (IL-6)	(Moreno & Giralt, 2015)
Breast cancer	Chartergellus communis	Chartergellus-CPI	significant decrease of cells at the G0/G1 phase from 52.8% to 36.2%	(Soares et al., 2022)
Breast cancer	bee venom	Melittin (combining melittin with plasma-treated phosphate-buffered saline (PT-PBS)	nonspecific cytotoxicity and hemolysis	(Kwon et al., 2022)
Lung cancer	Sigma-Aldrich (St. Louis, MO, USA)	mastoparan	membranolytic anti-tumor activity	(Alhakamy et al., 2021)
Lung cancer	ALS-MP nanoconjugates based on the Box-Behnken experimental design	Alendronate sodium (ALS)-mastoparan peptide (MP)		(Alhakamy et al., 2022)

therapeutic potential mouse model of mammary carcinoma was used. It had been treated with gemcitabine along with mastoparan, by considering the tumor size they had concluded the synergistic interaction between mastoparan and gemcitabine.

Wasp Venom in Lung Cancer

Lung cancer has low life expectancy. There is a study of development of nanoformulation of Fluvastatin with mastoparan. Mastoparan is a peptide that is found in the wasp venom and has anti-tumor

activity. It has been conjugated with a substance called galanin in order to design a cell penetrating peptide. Now a days the targeting of drugs only to the tumor cells has emerged as the best approach, as they reduce the systemic toxicity of antineoplastic drugs (Ray *et al.*, 2010; Sawant *et al.*, 2013). Nanocomplex is to improve cytotoxicity (Hussain *et al.*, 2020). In this they had two major perspectives to be followed. Firstly, the chemical nature of compounds for conjugation and secondly anti-tumor activity against the tumor cells (Alhakamy *et al.*, 2021). Fluvastatin also has

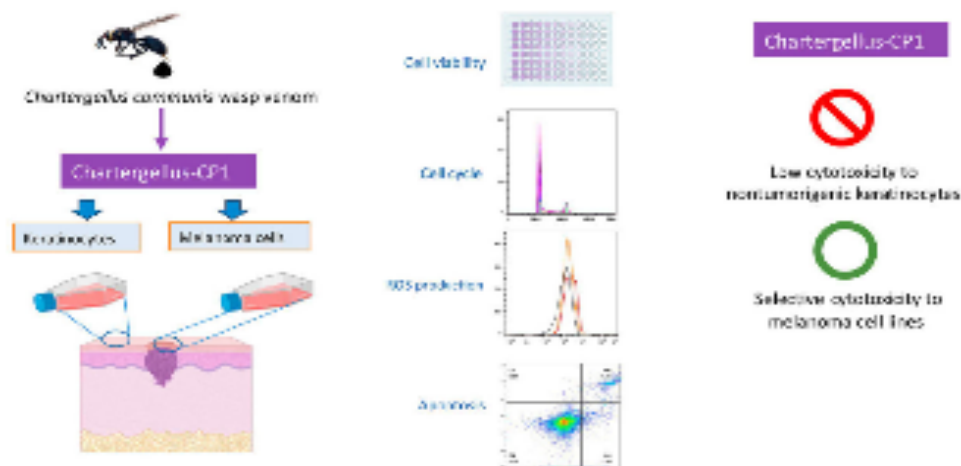
Cytotoxic effects of *Chartergellus communis* wasp venom peptide against melanoma cells

Figure 4: Cytotoxic impacts on melanoma cells (Bastos *et al.*, 2024).

the same activity of suppression of tumor cells. Development of nanocomplex Fluvastatin with Mastoparan have apoptic activity (Alhakamy *et al.*, 2021). This advancement in nanotechnology helps in delivering the chemotherapeutic agents at the targeted sites shows higher level of activity (Alhakamy *et al.*, 2022).

Wasp Venom in Skin Cancer (malignant melanoma)

Malignant Melanoma is a multifactorial disease due to UV exposure, environment and hereditary (Melanoma: Epidemiology, Risk Factors, Pathogenesis, Diagnosis and Classification - PubMed, n.d.). The rising incidence of cancer leads to the development of innovative compounds for better effective treatment. This research study had been stimulated to face hard to treat cancer (Zhong *et al.*, 2021b). The antitumor potential of venom has been highlighted through different examples. (Hammouda *et al.*, 2016). Wasp venoms can exert numerous effects on biological systems like cytolytic activity, rhabdomyolysis etc., (Lopes *et al.*, 2017). These cytolytic effects were analysed that includes cell cycle dynamics, ROS production and cell death (Bastos *et al.*, 2024). Throughout the complex compounds of wasp venoms, the bioactive peptides mastoparans and chemotactic peptides are significant (Souza *et al.*, 2005). This Chemotactic modulation has been used to improve cancer chemotherapy (Li *et al.*, 2005). The antitumor potential of wasp venom is well documented in the cited literature (Silva *et al.*, 2018; Azevedo *et al.*, 2015; Perez-Riverol *et al.*, 2017; Soares *et al.*, 2022; Torres *et al.*, 2018a, 2018b, 2020; Wang *et al.*, 2008, 2009; Wu *et al.*, 2018; Zhang *et al.*, 2010; Wu *et al.*, 2021).

CONCLUSION

Here we reviewed the current understanding of wasp venom as treatment of cancer. Through this review we emphasized that wasp venom is used to treat different kinds of cancer namely

breast cancer, colorectal cancer, skin cancer and lung cancer. Venoms of different arthropods have been proved for potential anticancer substances and concluded that Wasp venom is a new productive solution that helps in treating cancers. Wasp venoms hold significant therapeutic potential due to the bioactive peptides and proteins they contain, which have various medical applications. Each sting delivers a diverse array of chemical compounds, making wasp venom challenging yet promising therapeutic targets. By understanding the bioactivity of wasp venom molecules, we can enhance their medical applications. Moreover, a deeper comprehension of the structure, function, physiochemical properties, and pathology of these peptide and protein components is vital for rising more effective treatments for wasp venom will undoubtedly reveal new biological functions and lead to advancements in research, diagnosis and treatment eventually benefiting human health.

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ABBREVIATIONS

ACPs: Anti-cancer peptides; **SPSS:** Solid phase peptides synthesis; **AMP:** Antimicrobial peptide; **TLR4:** Toll-like receptor 4; **IL-6:** Interleukin-6; **ALS-MP:** Alendronate sodium-Mastoparan peptide; **PT-PBS:** Plasma-treated-Phosphate-buffered saline.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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