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BEEVENOMASAN ANTICANCERAGENT

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Abstract: There has been a great deal of study conducted on the medicinal potential of melittin and bee venom in treating tumours. However, non-specific cytotoxicity and hemolytic activity have posed problems for their clinical utilisation. Several research groups have used optimisation techniques to solve these problems. Gene therapy and the creation of recombinant immunotoxins containing MEL or MEL nanoparticles are two of these tactics. These methods primarily aim to target tumour cells in order to reduce cytotoxicity and improve the overall anticancer efficacy and therapeutic potential of melittin and bee venom. The optimal solutions that have been presented have demonstrated immense promise in surmounting the challenges linked to nonspecific toxicity. Preclinical research has presented positive results using gene therapy, recombinant immunotoxins, and MEL nanoparticles. The current understanding of the anticancer effects of bee venom and its main ingredient, MEL, on numerous types of tumour cells is compiled in this thorough study. The review also aims to clarify the possible anticancer processes that underlie the results that have been seen. This compilation of data offers an invaluable overview of the developments and learnings made in using MEL and bee venom's anticancer characteristics for focused and efficient tumour treatment. In tumour cells, melittin (MEL) has a variety of impacts on cellular processes such as angiogenesis, apoptosis, metastasis, and regulation of the cell cycle. MEL mediates anticancer activities that entail intricate interactions between several signal molecules and regulatory pathways. The paragraph also summarizes current research developments aimed at ensuring effective MEL peptide delivery. The focus on ways to deliver presents fresh perspectives and promising avenues for the in vivo use of MEL in cancer therapy. All things considered, the sentence summarizes the complex effects of MEL on cancer cells and highlights the developing approaches for maximizing its therapeutic potential.

KEYWORDS : TUMORS , BEE VENOM , ANTICANCER

INTRODUCTION : cancer as an intricate step in the emergence and spread of neoplasms Both the number of cancer patients and the death rate associated with it have significantly increased during the previous several decades[1]. There were 8.2 million cancer-related deaths and 14.1 million new cases in 2012 alone. Due to the forecast based on worldwide demographic factors, by 2025 there would be more than 20 million new cases of cancer yearly. The increasing incidence and mortality rates, along with the increased worldwide burden of cancer, highlight the urgent need for groundbreaking innovations in cancer

therapies[2]. Even with great advancements of conventional chemotherapeutic medications, treatment-related side effects and cancer cell resistance continued to be major obstacles. This calls for a paradigm change in the direction of the creation of novel therapeutics and agents. Within this framework, the purpose of our study is to investigate and evaluate new developments and research aimed at augmenting the effectiveness of traditional chemotherapy medications[3]. We hope to shed light on new directions that might greatly increase the efficacy of cancer therapy by combining the most recent research." the rising interest in using substances that are natural, especially biotoxins, for the treatment of cancer. Biotoxins are recognised as important biological resources that are produced and released by an organism's venom glands[4]. These toxins have several components that are pharmacologically active and may have therapeutic advantage. Animal venoms and toxins, including those from snakes, bees (BV), scorpions, sea anemones, and other animals, have been shown through years of thorough research to exhibit good anticancer activity against a variety of cancers[5]. This result provides a viable option in studying natural sources for future cancer therapies and highlights the significance of additional exploration into the therapeutic features associated with biotoxins. The capability of natural sources— especially biotoxins— to yield new molecules with significant anticancer properties that act via many different tumour mechanisms. The many components found in these natural sources have an impact on how cancer develops and spreads. The diversity of poisons and venoms is emphasised as a useful resource that provides a wealth of structural templates that may be applied to the creation of new anticancer drugs[6]. This highlights the potential of biotoxins as viable contenders for the development of pharmaceuticals used in cancer treatment . the importance of more study in this field and says that investigating the wide range of natural substances may give novel techniques to combat cancer[7].

Within the field of cancer research, bee venom (BV) and melittin (MEL), its main component, have become highly examined subjects. The effects of these drugs on different aspects of tumours have been well studied. Notably, they have showed the capacity to keep the development and proliferation of cancer cells[8]. In addition, study has indicated that they have a role in triggering apoptosis, which is a needed programmed cell death that preserves cellular homeostasis. Furthermore, BV and melittin showed effectiveness in preventing tumour spread, a crucial step in the progression of cancer[9]. All of the data point to the possibility that bee venom—and especially its primary ingredient, melittin—could prove to be a highly effective cancer treatment substitute. The observed effects on cancer cells are complex and include growth inhibition, induction of apoptosis, and reduction of metastasis[10]. These findings highlight the potential therapeutic use of both BV and melittin in treating many aspects of cancer pathogenesis. The various ways that BV and melittin show promise as prospects for the creation of cutting-edge cancer treatment approaches are summarised in this paragraph[11].

In this study, we present a summary of recent research on the molecular processes and anticancer features of bee venom (BV) and its main ingredient, melittin (MEL). The goal of this thorough analysis is to provide insightful information for next preclinical studies and potential clinical uses[12]. Several studies show how BV and melittin can stop the growth of cancer cells in a variety of ways. In particular, it has been established that these elements promote apoptosis, impede invasion, and decrease tumour spread[13]. The focus of this study is on the regulatory effect on important cellular variables, including angiogenesis factors, caspases, Ca2+ concentration, extracellular matrix (ECM) degradation enzymes, death receptors (DRs), and other signal pathways[14]. The combined data from all of these studies highlights the many biochemical pathways via which BV and its primary constituent elicit anticancer effects. By understanding these pathways, this work seeks to contribute to the basis for further inquiry in preclinical and clinical research, perhaps opening the way for the development of successful therapies in the battle against cancer[15].

In order to better understand the efficacy and possible therapeutic processes by which bee venom (BV) and/or its components might prevent cancer, this paper is going to supply readers with insights from a variety of experimental and preclinical research examinations[16]. The report aims to clarify the preventative characteristics of BV and its constituents in relation to cancer by integrating these research findings. The investigation also discusses the main difficulties in using melittin (MEL) as a cancer therapy[17]. The purpose of bringing those challenges to light is to raise awareness of potential roadblocks that scientists and doctors could run across while using MEL as a medicinal agent[18]. The research also presents comparable optimization solutions meant to overcome these obstacles. This dual emphasis on problems and benefits, as well as optimisation techniques, offers a thorough picture of the state of the art

when it comes to using BV and MEL for cancer prevention and therapy[19]. The research investigation also discusses the main difficulties in using melittin (MEL) as a cancer therapy. The purpose of coming those challenges to light is to raise awareness of potential roadblocks that scientists and doctors could come across while using MEL as a medical agent[20]. The research also presents comparable optimization answers meant to overcome these obstacles. This dual emphasis on problems and benefits, as well as optimisation approaches, offers a thorough picture of the state of the art when it comes to using BV and MEL for cancer prevention and therapy[21].

Anticancer effect of bee venom :

A plant that produces poison, Apismellifera is the source of bee venom. It is a complex combination comprising multiple peptides, enzymes, and other chemicals, totaling at least eighteen bioactive components. The venom of honeybees contains several noteworthy peptides, such as mast cell-degranulating peptide, melittin, apamin, and adolapin. Phospholipase A2 and hyaluronidase are just two of several amines and non-peptide substances that are also present[22]. Because of its varied composition, bee venom is a topic of interest in many different kinds of sectors, including science and medicine, due to its unique biological activity. Traditional medicine has historically employed bee venom (BV) to cure a variety of illnesses[23]. This has been the case, especially in Asian nations. A major use of BV is the treatment of inflammatory illnesses of the skin, rheumatism, arthritis, and chronic pain. The wide range of biological and pharmacological actions of BV is a foundation for its use in conventional medicine[24]. This historical example demonstrates how certain traditional and cultural healing approaches recognised the medicinal potential of bee venom in alleviating painful and inflammatory illnesses[25].

Concurrently, quite a bit of earlier research has demonstrated the phenomenal antitumor properties of bee venom (BV) on a range of human cancer cell types. Hepatocellular carcinoma, prostate cancer, melanoma, lung cancer, breast cancer, ovarian cancer, bladder cancer, and leukaemia are only a few of the many cancer types studied by these research[26]. The wide spectrum of tumours that BV hits highlights its potential as a viable option for the creation of cutting-edge anticancer treatments. The mounting data from these discoveries adds to our understanding of BV's potential defence towards different types of cancers. According to study, bee venom (BV) induces apoptosis, this effectively prevents cancer cells from proliferating. Results from Moon's experiment demonstrate that BV dramatically causes human leukemic cells to undergo apoptosis[27]. Caspases are activated to cause this induction, and important regulatory components which includes Bcl-2, extracellular regulated protein kinases (ERK), and protein kinase B (Akt) are down-regulated to do this [28]. Furthermore, additional research, for example that done by [Author's Name], showed that BV causes lung cancer cells to undergo apoptosis via a distinct mechanism. In this instance, nuclear factor kappa B (NF-κB) inactivation and the stimulation of death receptors' (DRs') expression cause apoptosis. These results highlight the adaptability of BV in focusing on diverse signalling pathways to cause apoptosis in distinct . bee venom (BV) promotes apoptosis in human melanoma cells through a unique mechanism. In this instance, a caspase-independent mechanism triggers the induction of apoptosis, which is dependent on calcium[29]. Increases in calcium concentrations, the production of reactive oxygen species (ROS), and the release of endonuclease and apoptosis-induced factors (AIF) are the distinctive features of the process. This indicates a diverse collection of caspase-dependent pathways seen in other cancer cell types, and a distinctive array of molecular processes mediated by BV in melanoma cells[30]. Gaining an understanding of these various steps will help us better understand the complex anticancer effects of BV on numerous types of cancer cells.

Research has investigated how bee venom (BV) inhibits human ovarian cancer A2780cp cells. These experiments have showed that BV supports apoptosis in A2780cp cells. Additionally, researchers found that combining BV with the traditional chemotherapy drug cisplatin created a synergistic impact[31]. It was discovered that the cytotoxic effects of cisplatin and BV on ovarian cancer A2780cp cells were magnified. These data show a possible cooperative and complementary effect between BV and cisplatin, paving the path for further study of combinations of drugs in the treatment of ovarian cancer[32]. Human non-small cell lung cancer (NSCLC) cell lines reveal a synergistic anticancer impact when (BV) and immune cells NK-92MI are mixed[33]. The inactivation of nuclear factor kappa B (NF-κB) and the death receptor (DR)-induced apoptotic pathway interact to produce this result. In addition to in vitro study, a number of in vivo

investigations have bolstered the antitumor efficaciousness of BV[34]. For example, it has been demonstrated that BV implementation. efficiently inhibits the development of solid tumours. In one instance, relative tumour inhibition of 52.8% appeared in mouse B16 melanomas after receiving 3 mg/kg of BV[35]. These results show the promise of BV as a viable therapeutic method for cancer therapy, backed by both in vitro and in vivo data. This is especially true when combined with immune cells.

Anticancer effect of melittin :

Melittin, which makes up a significant 40–60% of the venom's dry weight and fulfils a vital biological role, is noteworthy as the main active ingredient in bee venom. This substance, which consists of 26 amino acids, is classified as a linear, cationic, and amphiphilic peptide. Melittin has six positive charges at physiological pH, which contributes to its special structural and electrostatic characteristics[36]. Melittin's unique properties, namely its amphiphilic nature and positive charge, are essential to its functioning in a variety of physiological circumstances and make it an essential component in the biological processes connected with bee venom[37]. Melittin's molecular weight is 2847.5 Da, and its chemical formula is $C_{131}H_{226}N_{26}O_{32}$. An abundance of research on melittin demonstrates a wide range of biological duties, such as antiviral, antibacterial, antifungal, and antiparasitic qualities. Apart from these features, a significant amount of study has focused on investigating melittin's anticancer effects and therapeutic potential in the treatment of cancer[38]. Due to its many biological actions, this complex peptide from bee venom continues to be studied and researched, with an emphasis on possible applications in cancer treatment[39]. Hait et al. first demonstrated the anticancer action of melittin (MEL) in 1985. In the study they conducted, they showed that melittin functions as a calmodulin inhibitor to impede the division of human leukaemia cells[40]. This crucial discovery opened the door for more investigations, which have led to several studies examining the pharmacological and biological properties of melittin. With ongoing research focused at elucidating melittin's mechanisms of action and therapeutic possibilities in the context of cancer treatment, our awareness of the compound's potential as an anticancer agent has grown over time[41,42].

Melittin's (MEL) antibiotic, antiviral, antifungal, and anticancer activities are based on its strong membrane-perturbing action. Phospholipid bilayers are disrupted by this peptide's easy adherence to negatively charged membrane surfaces. This disruptive effect might manifest itself in several ways, such as the emergence of ion channels or transmembrane holes. Melittin also has the ability to change the integrity of lipids by acting as a surfactant. The loss of atomic ions and molecules as well as an increase in membrane permeability are the outcomes of this membrane-perturbing activity[43]. Melittin's broad biological activities are largely attributed to its capability to impact membrane architecture, which also makes it a useful and adaptable agent for a range of therapeutic applications[44].

The composition of lipid membranes, including features like packing density and electric charge, could affect the activity of melittin (MEL). Frequently used as an antimicrobial peptide, MEL has a well-defined procedure on the plasma membrane. In a research done by Lee et al., MEL suggested a dual antibacterial action against Candida albicans. By rupturing the target microorganism's membranes, this procedure induced apoptosis via the mitochondria/caspasedependent pathway. The dual action of MEL on membrane rupture and apoptosis induction highlights how adaptable it is in delivering antimicrobial effects on certain bacteria[45]. The intricacy and versatility of melittin's biological activities are further highlighted by the way membrane compositions affect its effect. Purifying the membranes of both prokaryotic and eukaryotic cells is the capacity of melittin (MEL), a non-selective cytolytic peptide. The utilisation of this non-selective action is complicated by the possibility of severe toxicity responses, such as hemolysis, from the intravenous infusion[46]. Despite the potential for nonspecific cellular lytic action, MEL seems to cause greater damage to tumour cell membranes compared to normal cells. The greater membrane potential of tumour cells is thought to be relevant for this selective influence on tumour cell membranes. The distinct impact on tumour cells emphasisesmelittin's possible therapeutic use in focusing on cancer cells while providing the smallest possible amount of damage to healthy cells[47].

The more beneficial binding of melittin (MEL) to the comparatively lots negative charges in target tumour cells' membranes as opposed to healthy cells is helped by MEL's positive charges. It is beneficial to minimise harm to normal cells with this selective interaction with tumour cell membranes. Moreover, cancer cells are less likely to gain chemoresistance as a result of MEL's distinct mode of action[48]. MEL targets the entire structure of cell membranes, contrasted to traditional chemotherapeutics that target

rapidly dividing cells and promote DNA damage-induced death without distinguish between normal and malignant cells. Moreover, an enhanced effect has been seen when mixing MEL with chemotherapy medications[49]. In addition to rupturing tumour cell membranes, MEL also permeates the cytoplasm by means of endocytosis, impacting a range of intracellular targets. Its dual action, which targets intracellular components alongside the membrane, increases its effectiveness[50]. Consequently, MEL presents itself as an interesting cancer chemotherapeutic agent capable of treating many cancer types. Because of its several mechanisms of action, synergistic effects, and capacity to specifically target cancer cells, melittin is a future research option for cancer treatment[51].

mechanisms of anticancer effect of melittin :

The intricate interactions of several elements in the initiation and evolution of cancer has afforded melittin (MEL) a plethora of chances for tumour medical treatment. A number of studies conducted both in vitro and in vivo have consistently shown that MEL affects malignant cells' biological activities in a variety of ways[52]. The consequences include modulating cell cycle regulation, angiogenesis, metastasis, apoptosis, and proliferation. The ways that different signal pathways, genes, and chemicals are activated or modulated by MEL highlights its multifaceted effects on cancer cells. It's significant to note that these controls differ based on the particular kind of cancer cell being studied[53]. The variety of cellular reactions to melittin points to the drug's potential as a flexible therapeutic agent that may be adapted to target the unique traits and weaknesses of various cancer cell types[54]. Because of the wide variety of benefits reported in these trials, melittin is a prospective option in the ongoing search for efficient therapies for different kinds of cancer. Multiple investigations have been conducted on the cellular processes behind melittin's (MEL) anticancer activities. Several investigations have repeatedly proven that MEL's anticancer actions result in the extermination of cancer cells through a variety of pathways[55]. These mechanisms include a variety of biological functions intended to impede the growth and survival of cancer cells.

Plenty of research on MEL indicate that it may be useful in causing cancer cells to die via a variety of mechanisms. Recognising these pathways is crucial in the advancement of MEL as a viable therapeutic peptide intended for the therapy of cancer[56]. The mounting data from those studies highlights melittin's potential as a desired option in the search for efficient and focused cancer therapy.

Induction of apoptosis

Research on the management of apoptosis in malignant cells has emerged as a major area of interest for cancer researchers, with significant implications for slowing the spread of the disease. Research indicates that chemotherapeutic drugs with apoptotic-inducing properties are vital for inhibiting the growth of tumours[57]. Different from necrosis, apoptosis is a process of planned cell death that may be brought on by any number of internal and external stimuli. Numerous morphological and biochemical alterations are involved, such as chromatin pyknosis, cell shrinkage, and the development of apoptotic bodies. Numerous types of proteins and intracellular signalling pathways have been linked to the apoptotic process[58]. These comprise the NF-κB pathway, the mitochondrial-dependent pathway, the Bcl-2 protein family, ion channels, caspases, and mitogen-activated protein kinases (MAPK) cascade proteins. The coordinated action of these variables aids in the controlled destruction of cells, a process that, if thrown off balance, can result in aberrant cell survival and aid in the initiation and spread of cancer[59]. It is essential for understanding the complexities of apoptosis control in order to design specific treatments that aim to cause malignant cells to undergo programmed cell death[60]. Stimuli pertaining to the mitochondria start the intrinsic route, often referred to as the mitochondrial pathway. This mechanism, which eventually culminates in the activation of caspases, involves the release of cytochrome c, endonuclease G, or apoptosis-induced factors (AIF)[61]. The Bcl-2 protein family is mostly responsible for controlling the processes involved in intrinsic apoptosis. This family includes anti-apoptotic proteins like Bcl-2, Bcl-XL, and BAG as well as pro-apoptotic proteins like Bax, Bak, and Bad[62]. nevertheless extracellular signalling plays a major role in mediating the extrinsic route. Initiator caspases are recruited and many intermediate molecules are activated as a result of ligand-transmembrane receptor interactions. These pathways are examples of separate but related processes that can cause apoptosis. recognising the state of balance and interplay between intrinsic and extrinsic pathways is crucial in deciphering the intricate control of programmed cell death and in formulating focused treatment approaches within the framework of cancer research[63]. Both the intrinsic and extrinsic apoptotic strategies eventually lead to the same execution

pathway, which is started by caspase-3 cleavage. Caspases are essential to the apoptotic process; caspase-3, caspase-6, and caspase-7 have been identified as vital apoptosis executors[64]. Numerous investigations have shown that apoptosis triggered by melittin (MEL) is linked to a variety of cellular modifications. Several noteworthy observations have been published in relation to MEL-induced apoptosis. These include elevated intracellular Ca2+ concentrations, increased death receptor (DR) expression, activation of the mitochondria-mediated apoptosis pathway, activation of the unfolded protein response (UPR) pathway mediated by inositol-requiring protein-α (IRE-α), and inactivation of the Aktsignalling pathway and NF-κB pathway. These molecular alterations point to a complex effect of MEL on the signalling pathways inside cells that control apoptosis[65]. Clarifying these pathways and how MEL modifies them is essential to understanding the mechanisms behind its anticancer actions.

Inhibition of tumor metastasis and invasion :

A significant process by which cancer cells travel to various tissues from their original location is called malignant metastasis. Presently, a major factor in the low survival rates of cancer patients is the difficulty in managing metastasis and avoiding recurrence upon cancer resection[66]. The intricate process of cancer metastasis comprises a number of several molecules, such as adhesion molecules, extracellular matrix (ECM) degrading enzymes, and angiogenesisrelated proteins. Rearranging these molecules in conjunction with other matrix components is essential to inhibiting the growth of tumor cells[67]. Many investigations have demonstrated a tight relationship between the inhibition of tumour invasion and metastasis and melittin's (MEL) anti-tumor action. Learning more of the pathways via which MEL affects these processes might help develop treatment approaches to prevent tumours and enhance the prognosis of cancer patients.

Understanding the biological mechanisms behind melittin's (MEL) ability to prevent the spread of liver cancer cells, namely hepatocellular carcinoma (HCC) cells, has been made achievable by Liu and associates[68]. According to their research, MEL inhibits the growth of tumours by suppressing C3 botulinum toxin substrate 1 (Rac1). Rac1 is recognised to have a vital role in tumour cell motility and invasion. Furthermore, studies have demonstrated that the inhibitory effects of MEL on metastasis are accompanied by the down-regulation of c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK)[69]. Crucially, the researchers found that in HCC cells with a higher potential for cancer metastases, MEL more strongly reduced cell motility. Corroborating the in vitro results, MEL revealed considerable suppression of cell motility and reduction of lung metastasis in an HCC orthotopic transplantation model[70]. These results give important new understandings of the precise molecular processes via which MEL may prevent liver cancer cells from metastasizing, potentially opening up new therapy alternatives to address this vital stage of the disease's development[71]. One important enzyme that helps facilitate the breakdown of the extracellular matrix (ECM) and is essential for the migration of cancer cells is matrix metalloproteinase-9 (MMP-9). The activity of MMP-9 can be controlled by a lot transcription factors, including NF-κB and activator protein-1 (AP-1). The capacity of melittin (MEL) to inhibit the migration of human aortic cells was described in a research. The down-regulation of MMP-9 expression and activity has been linked to MEL's inhibitory effect on cell migration[72]. The NF-κB pathway and the suppression of ERK/p38 MAP kinase phosphorylation were connected to this down-regulation. These findings mean that MEL may interfere with the migration of cells by regulating the activity of MMP-9 and associated signalling pathways, giving possible mechanisms via which MEL contributes to anti-metastatic effects.

Melittin (MEL) has been demonstrated through another investigation to inhibit the motility and invasion of breast cancer cells generated by epidermal growth factor (EGF). Certain signalling pathways were found to be modulates, which resulted in the inhibitory effects. MEL targeted focal adhesion kinase (FAK) phosphorylation and matrix metalloproteinase-9 (MMP-9) expression. The phosphatidylinositol 3-kinase/protein kinase B (PI3 K/Akt)/mammalian target of rapamycin (mTOR) pathway was inhibited as part of the mechanism of action[73]. Through disruption of this route, MEL showed that it might hinder the cellular functions related to invasion and motility, offering more proof of its potential as a suppressant of breast cancer cell metastasis. Research has indicated that the expression of matrix metalloproteinase-9 (MMP-9) is required for melittin (MEL) to prevent cell invasion. Specifically, in renal cancer Caki-1 cells, the anti-metastatic effects of MEL were connected to the inactivation of transcription factors activator protein-1 (AP-1) and nuclear factor-kappa B (NF-κB)[74]. These data combined show that MEL has

considerable potential as an anti-metastasis and invasion agent in the treatment of cancer. MEL may play a therapeutic function in preventing the spread of cancer cells, as evidenced by its capacity to alter important biological processes linked to invasion.

Cell cycle arrest :

One of the hallmarks of cancers is the disturbance of the cell cycle. The normal course of cell division is ensured by a number of checkpoints in the cell cycle, including G1-S and G2-M. One of the hallmarks of cancer is uncontrolled cell growth, which can result from dysregulation of various checkpoints. Therapeutic approaches to stop the growth of tumours have demonstrated promise in the form of agents that target particular cell cycle checkpoints[75]. The ordinary regulatory processes that govern the cell cycle are frequently upset in cancer cells, enabling cells to elude checkpoints and carry on proliferating uncontrolled. By blocking the unrestricted growth of cancer cells, therapeutic medicines that target these checkpoints attempt to restore appropriate cell cycle regulation[76]. With the aim of creating potent medications that precisely target the alterations in cell cycle regulation seen in malignant cells, these strategies constitute an important field of study in cancer therapy.

Melittin (MEL) has been shown in several experiments to have the capacity to impede the development of cancer cells by altering the course of the cell cycle[77]. Controlling the orderly passage of cells through several stages, such as G1 (gap 1), S (synthesis), G2 (gap 2), and M (mitosis), is the closely controlled process known as the cell cycle[78]. Maintaining regular cellular processes and avoiding unchecked cell proliferation depend on proper management of the cell cycle. MEL looks like to have an impact with the way cancer cells proceed through the cell cycle, perhaps leading to cell cycle arrest at certain points. One of the ways that MEL shows its anti-proliferative and growth-inhibitory capabilities in cancer cells is through this cell cycle modification[79]. Gaining knowledge of MEL's precise effects on the cell cycle might help to better understand how it might be used as a therapeutic drug to slow the growing number of cancer cells.

Enhancing efficacy, selectivity, and specificity of melittin :

Indeed, melittin (MEL) has shown promise as an anticancer drug in a number of animal investigations; however, the substantial adverse effects, most notably hemolysis, make it difficult to administer MEL at large dosages in vivo[80]. This problem limits the in vivo utilisation of MEL for cancer therapies by impeding its intravenous delivery. Researchers have looked at optimisation techniques to improve MEL's therapeutic results and increase its selectivity in delivering the drug to malignant cells in response to this constraint[81].

Several optimization strategies have been employed to address the cytotoxicity of MEL while enhancing its antitumor effects and therapeutic capabilities. Some of these strategies include:

Gene Therapy: Distributing MEL to cancer cells in a particular way via gene therapy techniques

Artificial Immunotoxin Including MEL: Creating immunotoxins that selectively target cancer cells by including MEL.

Nanoparticle Delivery: By using nanoparticles as MEL carriers, off-target effects can be minimised and tailored delivery to cancer cells is possible.

Melittin in composition of immunoconjugates for immunotherapy :

Tumor-specific monoclonal antibodies (MAbs) linked with poisons, medications, or radionuclides are known as

immunoconjugates, and they have grown into a potential approach in chemotherapy for cancer. These immunoconjugates' primary benefit is their capacity to confer tumour cell selectivity while reducing harm to healthy tissues. The unique capacity of monoclonal antibodies to identify and bind to certain cell surface phenotypes seen on tumour cells is used to accomplish this specificity[82].

The ability of immunoconjugates to precisely locate cancer cells is the key to their effectiveness. Through the use of monoclonal antibodies' unique binding characteristics, these conjugates possess the capacity to precisely target tumour cells. This focused strategy lowers the threat of negative effects on healthy tissues while simultaneously increasing the therapeutic payload's efficacy. To summarise, immunoconjugates are a promising new therapy option for cancer that offers a customised, targeted approach that may lead to

better treatment results with less side effects than typical systemic medicines[83]. Immunoconjugates are a potential development in the search for more precise and potent cancer treatments because of their capacity to explore cell surface characteristics and attach to tumour cells preferentially.

Synergistic effect of melittin :

Combining some chemotherapeutic medicines with melittin (MEL) has been shown to be equipped with synergistic effects, which raises the possibility of increased efficacy in treating drug-resistant human malignancies. In particular, research like that performed by Wang et al. has shown that MEL can make hepatocellular carcinoma (HCC) cells more susceptible to apoptosis produced by TNF-related apoptosis-inducing ligand (TRAIL)[84]. This finding suggests that treating TRAIL-resistant human tumours with a combination of MEL and TRAIL reagents may be beneficial. It is important that the synergistic effects linked to MEL are peculiar to specific chemotherapy, namely those that are associated with the TRAIL-induced apoptotic pathway. While MEL has shown the capacity to improve the efficiency of TRAIL-induced apoptosis, it may not necessarily quicken cell death due to other chemotherapeutic agents that function through distinct apoptotic pathways. Treatment with BV) enhanced the lethality of bleomycin and prevented human cervical cancer cells from healing from damage caused by bleomycin[85]. This implies that bleomycin (BV) and its primary constituent melittin (MEL) may both be helpful in increasing the cytotoxicity of the anticancer drug. have shown more proof of MEL's beneficial interaction with other chemotherapeutic drugs, such as docetaxel (TXT), cisplatin (DDP), and 5-fluorouracil (5-Fu), on human gastric cancer cells. The downregulation of genes related to chemotherapeutic drugs may be responsible for this synergistic the impact[86]. Interesting results have been noticed in experiments investigating the apoptotic impact of melittin (MEL) in conjunction with irradiation (IR). The mice in the combined therapy group displayed a higher rate of apoptosis, which delayed the formation of the lesions. More specifically, with an enhancement factor of 1.75, the tumour doubling time was extended from 4.88 to 10.67 days[87]. This indicates that esophageal squamous cell carcinoma (ESCC) cells were more radiosensitive both in vitro and in vivo when MEL was injected intraperitoneally (i.p.)[88]. The noted raised radiosensitivity suggests that using MEL in conjunction with radiation may be a viable tactic to raise radiotherapy's performance in treating ESCC[89]. These results further encourage the exploration of new strategies to improve the therapeutic results of cancer treatment, especially when natural substances such as MEL are combined with traditional treatment procedures.

Conclusion :

The clinical application of melittin (MEL) and bee venom has been limited by non-specific cytotoxicity and hemolytic activity, which have been major obstacles in the considerable study on their medicinal potential in treating tumours. However, other methods for optimisation have been investigated by different research groups to address these problems, including as gene therapy, recombinant immunotoxins, and MEL nanoparticles.

By focusing on cancer cells, these optimisation strategies seek to increase the treatment's specificity while lowering cytotoxicity and enhancing its overall anticancer efficiency. These optimised efforts have shown encouraging findings that indicate considerable potential in dealing with non-specific toxicity-related challenges. Positive results have been shown in preclinical tests using MEL nanoparticles, recombinant immunotoxins, and gene therapy. This thorough analysis compiles the most recent research on the antitumor effects of bee venom and its main component, MEL, on a variety of tumour cell types. likewise the paper explores the complex processes that underlie these anticancer effects.

Interestingly, MEL has a number of effects on angiogenesis, apoptosis, metastasis, and cell cycle control, among other biological processes within tumour cells. These anticancer structures entail intricate relationships between different regulatory pathways and signal molecules. In order to wrap up, the review summarises the most recent happenings in MEL peptide delivery optimisation, offering fresh insights and advocating approaches for the in vivo use of MEL in cancer therapy.

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