

Nisin as a potential anticancer agent

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ABSTRACT

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Cancer treatment has advanced over the last four decades from surgery, chemotherapy, and radiation therapies to a more targeted therapy with less undesirable side effects. Studies on nisin as an anticancer agent in recent years aimed at exploring its potential as an adjuvant therapy due to its claimed selectivity. The aim of this review is to describe the potential use of nisin as an anticancer agent. Nisin has been used against seven different types of cancers. The combination of nisin with a chemotherapeutic agent proofed to be superior to the chemotherapeutic drug used alone. Nisin caused a much lower cytotoxic effect on non-cancerous cells, while inducing apoptosis of cancer cells. This is due to pore on the plasma membrane, allowing influx of calcium, and subsequent series of changes leading to apoptosis. Nisin is a potential therapeutic agent to be used as an adjunct to the current cancer chemotherapy.

Keywords: nisin; bacteriocin; anticancer

1. INTRODUCTION

Cancer cells undergo uncontrolled proliferation due to genetic mutations that results in increased cell growth and decreased death (Meng et al., 2012). Dietary carcinogens, sedentary lifestyle, obesity, smoking, excessive alcohol intake and environmental pollutions are among the modifiable risk factors associated with the development of various cancer types (Stein and Colditz, 2004; Danaei et al., 2005; Blackadar, 2016).

The incidence of cancer is higher in developed nations, however its incidence in developing countries is increasing with significantly expanded mortality (Ghoncheh and Salehiniya, 2016). In 2018, global cancer statistics have estimated 18.1 million new cancer cases, with lung cancer as the most common type, comprising 11.6% of total cancer. It is also the leading cancer diagnosis causing deaths (Bray et al., 2018).

Cancer therapy aims to eliminate malignant cells and prevent recurrences. Many different therapies have been developed and applied on different types and stages of cancer. In addition to standard therapies like surgery, radiotherapy and chemotherapy other types of modalities such as endocrinotherapy, immunotherapy, and targeted therapy have been developed in recent years (Urruticoechea et al., 2010; Falzone et al., 2018). Targeted cancer therapy acts on each cancer's specific mutated genes, proteins, or even the surrounding tissue (tumor environment), which influences the development and survival of cancer (Tsimberidou, 2015; Falzone et al., 2018).

Cancer treatment such as radiotherapy and chemotherapy caused serious side effects due to collateral damage to healthy tissues and the immune system. The typical adverse effects include nausea, vomiting, alopecia, and recurrent infections (Baskar et al., 2012; Schirmacher, 2019). Eradicating or minimizing the side effects without

compromising cancer cell killing using a novel therapy is one of the focuses of cancer research.

Bacteriocins are antimicrobial peptides produced by both Gram positive and negative bacteria. Some of them are used as food preservatives as they were able to annihilate bacteria of the same or closely related strains (Yang et al., 2014). Nisin is the most well-known bacteriocin and has demonstrated to poses anticancer properties in various types of cancers such as the head and neck squamous cell carcinoma, colorectal cancer, breast adenocarcinoma, astrocytoma, neuroblastoma, hepatocellular cancer and melanoma (Ahmadi et al., 2017; Avand et al., 2018; Begde et al., 2011; Joo et al., 2012; Kamarajan et al., 2015; Lewies et al., 2018; Maher and McClean, 2006; Paiva et al., 2012; Preet et al., 2015; Prince et al., 2019; Rana et al., 2019; Zainodini et al., 2018).

This paper aimed to review the mechanism of action and the role of nisin as a potential anticancer drug based on reports in the literature.

2. CONVENTIONAL CANCER THERAPY

2.1 Surgery

Surgery is a very important intervention for localized primary tumors and tumors with regional lymph nodes metastases especially when combined with adjuvant radiotherapy and chemotherapy (Urruticoechea et al., 2010; Tohme et al., 2017). However, surgical resection of tumor can be associated with micrometastasis. In addition, patients are exposed to multiple adverse events, such as the use of general anaesthesia, intraoperative events (such as bleeding or nerve damage), delayed wound healing and subsequent analgesic use for postoperative pain (Horowitz et al., 2015; Climent and Martin, 2018; Tohme et al., 2017). For example, post colectomy for colorectal cancer, the patient may experience complications such as abscess formation, ileus, and leaking anastomosis (Kirchhoff et al., 2010; Climent and Martin, 2018; Valente et al., 2019).

2.2 Radiotherapy

Radiotherapy is another approach used in the treatment of cancer, utilized in more than 60% of cases (Mohan et al., 2019). Exposure to high energy radioactive particles leads to DNA damage followed by cancer cell death (Jackson and Bartek, 2009; Baskar et al., 2012; Jairam et al., 2019). Significant and debilitating complications of radiotherapy are radiation necrosis, radiation-induced neoplasm and infertility (Newhauser et al., 2016; Mohan et al., 2019). In addition, there are organ-specific side effects such as bladder irritation, diarrhea and painful bowel movement (after radiation treatment for colorectal carcinoma), pain at the salivary gland (in thyroid cancer) and urethral strictures (in prostate cancer) (Pilepich et al., 1981, Van Schaeybroeck et al., 2005; Lu et al., 2016).

2.3 Chemotherapy

Chemotherapeutic, the mainstay of cancer treatment, causes DNA damage, leading to cell death and/or inhibition of cell division (Urruticoechea et al., 2010). They can cause numerous mild to life-threatening adverse effects including sepsis, pneumonia, acute kidney injury, anemia, and neutropenia with frequent infections. In addition, the patient

may experience hair loss, nausea and vomiting (Jairam et al., 2019; Schirrmacher, 2019).

Chemotherapeutic drugs target rapidly proliferating cancer cells (Liu et al., 2015). However, they also affect normal cells with such properties, for example bone marrow, hair follicles, epithelium of the gastrointestinal tract and epidermal cells. As a result, patients develop severe side effects such as cytopenia, alopecia, skin itch, nausea, vomiting and diarrhea (Kono et al., 2013; Ghiringhelli and Apetoh, 2015; Liu et al., 2015). Recently, drugs that specifically target cancer cells have been developed, for example, trastuzumab, an anti-human epidermal growth factor receptor 2 (HER2) agent used to treat HER-2 positive breast cancer. Although in theory, this drug should not have affected normal cells, however HER-2 receptors are found in the heart, therefore cardiac toxicity is one of the side effects reported (Suter and Ewer, 2013).

Current standard therapies (surgery, radiotherapy and chemotherapy) are not sufficient to control certain types of cancer. In addition, resistance to chemotherapeutic drugs is becoming a common phenomenon (Housman et al., 2014). The recent reduction of 1.7% in cancer mortality is likely due to improvement in early detection, treatment and decline in smoking (McGuire, 2016). Thus, a novel cancer therapy having less side effects and low susceptibility of resistance is required.

3. NOVEL CANCER THERAPIES

3.1 Biological therapy

Biological therapy utilizes living organisms or their substances to treat diseases. Approximately 50% of agents used in biological therapy are developed based on the human's immune system while the rest are established on the understanding of cellular signaling (Phan, 2014). Table 1 demonstrates the different types of biological therapy.

3.2 Bacteriocins

Bacteriocins are non-immunogenic, biodegradable antimicrobial peptides produced by a certain group of bacteria. As these peptides are directed against bacteria of the same or similar strains, they are predominantly non-toxic to humans and therefore often used as food preservatives, e.g., in milk products. Nisin and other bacteriocins have been reported to possess antimicrobial properties and anticancer properties (Yang et al., 2014; Song et al., 2018).

Bacteriocins are categorized into 3 groups based on their structural and physicochemical properties: class I (<5kDa), II (<10kDa) and III (>30kDa) lantibiotics. (Zacharof and Lovitt, 2012). They are peptides comprising of unusual amino acids synthesized by ribosomes and modified post-translationally (McAuliffe et al., 2001). Class I lantibiotics can either be type A (positively charged) or type B (negatively charged or no net charge). Class II lantibiotics are further classified into class IIa, IIb, or IIc based on the structure. There is no sub-classification of class III lantibiotics (Brotz and Sahl, 2000; Kaur and Kaur, 2015). Among the bacteriocins that have demonstrated an inhibitory role on cancer cells are pyocin, pediocin, microcin and nisin (Cornut et al., 2008; Lundin and Checkoway, 2009; Shaikh et al., 2012; Yates et al., 2012; Boohaker et al., 2012; Yang et al., 2014).

Table 1. Types of biological therapy currently in use for cancer treatment

Biological therapy	Description	References
Monoclonal antibodies therapy	It causes the death of cancer cells by inhibiting cell signaling and/or inducing apoptosis.	Glassman and Balthasar, 2014
Cytokine therapy	Regulation of the immune response, inflammation and hematopoiesis (note -please add how does this related to cancer treatment).	Conlon et al., 2019; Hotte and Koneru, 2009; Marconi et al., 2019
Vaccine therapy	Stimulation of the immune system to produce antibodies against cancer-producing agents, thus preventing the formation of associated cancer.	Bezu et al., 2018; Guo et al., 2013; Rodriguez et al., 2018; Vasquez et al., 2017
Adoptive cell transfer therapy	Development and administration of highly active, tumor-specific lymphocytes to an autologous host.	Dudley and Rosenberg, 2003; Perica et al., 2015; Qian et al., 2014
Oncolytic virotherapy	Use of specific virus to infect and lyse cancer cells.	Fountzilias et al., 2017; Russell et al., 2012
Gene therapy	Induces damage to cancer cell DNA leading to apoptosis.	Brenner et al., 2013; Wirth and Ylä-Herttuala, 2014
Anti-angiogenic therapy	Destroys tumor blood vessels via activation of antiangiogenic factors.	Abdalla et al., 2018; Lupo et al., 2017; Maj et al., 2016; Rajabi and Mousa, 2017
Bacillus Calmette-Guerin (BCG) therapy	Proven to be effective against bladder cancer (add the characteristics of cancer cell killing here-or postulation).	Tomaszewski and Smaldone, 2010
Biochemotherapy	Chemotherapy (single-agent or combination) and interleukin-2 (please elaborate a little more).	Verma et al., 2008
Small molecule therapy	Interacts with surface receptors and intracellular cancer cell targets, inducing cell death. Examples are tyrosine kinase inhibitor (afatinib, bosutinib), EGFR inhibitor (gefitinib, erlotinib), and syrosine kinase inhibitor (lapatinib).	Pathak et al., 2018, Keating, 2014, Cortes et al., 2011, Burris, 2004
Bacteriocin	Anti-microbial peptides produced by certain bacteria recently found to be effective in killing cancer cells.	Ahmadi et al., 2017; Avand et al., 2018; Kamarajan et al., 2015; Paiva et al., 2012; Yang et al., 2014

4. NISIN AS POTENTIAL ANTICANCER AGENT

Nisin is the most common bacteriocin used in the industry and research. It is a class I type A lantibiotic and is a product of *Lactococcus lactis*, a gram-positive lactic acid bacterium. It is composed of 34 amino acids, with a molecular weight of 3.5-kDa. It is cationic and hydrophobic in nature (Brotz and Sahl, 2000; Kaur and Kaur, 2015). Nisin has five internal ring structures involving disulphide bridges with amino and carboxyl end-groups (Figure 1). It has three uncommon amino acids, which are dehydroalanine, lanthionine, and β -methyllanthionine (Williams and Delves-Broughton, 2003).

Identification of at least eight different variants of nisin have been isolated from different microorganisms and sequenced for cross- analysis, which includes nisin A, Z, F, Q, H, U, U2 and P. The most well-known nisin used in cancer research are AP and ZP, in which A and Z are the nisin variants, while the letter 'P' represents a high purity of nisin (95% purity) (Shin et al., 2016).

Nisin is an approved food preservative in over 50 countries worldwide (with coding of E234), including the United States of America and European countries. It is the only bacteriocin endorsed for this use (Brotz and Sahl, 2000). Unlike other bacteriocins, nisin has broad-spectrum antimicrobial effects, able to kill Gram negative bacteria as well as Gram positive ones. (Yang et al., 2014).

It has been demonstrated that nisin interacts with lipid II of the bacterial plasma membrane, resulting in inhibition of cell wall biosynthesis in addition to causing a short-lived pore formation, which led to bacterial death (Christ et al., 2007;

Paiva et al., 2011; Wiedemann et al., 2001; Prince et al., 2016). The effect of nisin on bacteria leads to investigations of its role against cancer cells, in search of a novel therapy.

4.1 Anticancer properties of nisin

The anticancer potential of nisin was first reported in 2006, when it was found that nisin was able to lead to death of two human adenocarcinomas of colon and colorectum, HT29 and Caco-2 cell lines (Maher and McClean, 2006). In 2012, a group of researchers demonstrated that nisin reduced the viability of human breast adenocarcinoma cells (MCF-7 cells) and human liver hepatocellular carcinoma cancer cells (HepG2 cells) (Paiva et al., 2012). Subsequently, nisin was shown to kill SW480 colon cancer cells (Ahmadi et al. (2017).

The mechanism of cell killing has been investigated in several studies. In the 2006 study, in which nisin A was used, it was found to cause a series of cellular effects such as cell polarization and disruption of the epithelial integrity (Maher and McClean, 2006). The cell death was found to be linked to activation of apoptosis. Nisin of A and Z variants have induced apoptosis to both *in vitro* and *in vivo* mice model of head and neck squamous cell carcinoma (HNSCC) (Joo et al., 2012; Kamarajan et al., 2015). The latter study also found that both nisin variants induce endothelial cell apoptosis and inhibit angiogenic sprouting (Kamarajan et al., 2015). Nisin Z was found to affect several mitochondrial mechanisms, leading to oxidative stress-induced apoptosis in A375 melanoma cell lines (Lewies et al., 2018).

Joo et al. (2012) revealed that nisin causes cell cycle arrest in the G2 phase, therefore, resulting in a reduction of HNSCC cell proliferation. The expression of Cdc2, the

principal checkpoint of cell cycle is also decreased, in coherent with the cell cycle arrest (Wang and El-Deiry, 2007; Joo et al., 2012; Kamarajan et al., 2015). Nisin was also found to induce activation of CHAC1, which is a pro-apoptotic cation transport regulator homologue 1 via two mechanisms: oxidation of phospholipids and influx of extracellular calcium. Activation of CHAC1 leads to a series of events, eventually leading to apoptosis. CHAC1, which is found in the cytoplasm, is also involved in the ATF4-ATF3-CHOP signaling pathway that has a role in cell death (Mungrue et al., 2009; Kumar et al., 2012; Liu et al., 2012; Joo et al., 2012; Edagawa et al., 2014; Kamarajan et al., 2015; Liu et al., 2016). More recent study discovered changes in the ratio of BAX/BCL-2 in both mRNA and protein level, suggesting that the apoptosis that occurred via one of the intrinsic pathways (Ahmadi et al., 2017).

There were at least two studies have investigated the effect of a combination of nisin and a chemotherapeutic drug compared to chemotherapy alone. Preet et al. (2015) demonstrated that combination of nisin and doxorubicin is more effective in treating skin cancer in a mice model compared to doxorubicin alone. A subsequent study in 2019 demonstrated that nisin augmented the anticancer effect of 5-fluorouracil both *in vitro* and *in vivo*. The combination therapy potentiates apoptosis, anti-angiogenesis and reduces cell proliferation (Rana et al., 2019). The summary of the anticancer effects of nisin is shown in Table 2.

4.2 Selectivity of nisin's anticancer

Nisin has been reported to exhibit selective cancer cell killing while preserving normal cells. This selective action is associated with three factors related to the surface of the cancer cells. Firstly, the bi-layered phospholipid membrane of the cancer cells has lost their symmetrical nature, which is resulted in it being the negatively charged (Cornut et al., 2008). Nisin is composed of cationic polypeptides, which preferably interact with the negatively charged plasma membranes of cancer cell compared to the neutral or positively charged normal, non-cancerous cells (Hoskin and Ramamoorthy, 2008; Schweizer, 2009; Riedl et al., 2011b).

Secondly, the cancer cell plasma membrane is more fluid compared to normal cells. This results in instability of the cell membrane, causing a higher affinity of the bacteriocins to the cancer cells (Kaur and Kaur, 2015; Garg et al., 2015; Zalba and ten Hagen, 2017). Alteration of the lipid in the plasma membrane varies across different malignancies, among which are the phosphatidic acid (PA), phosphatidylinositol (PI), phosphatidylglycerol (PG), phosphatidylserine (PS) with cholesterol as the key regulator of membrane fluidity (Szlasa et al., 2020). This characteristic has led several researches producing specially-modulated lipid-based anticancer drug carriers (Bompard et al. 2020, Okamoto et al., 2019).

Lastly, the presence of numerous microvilli on cancer cell surface membrane increases the area for nisin interaction (Kaur and Kaur, 2015; Riedl et al., 2011a). A study by Chan et al. (1998) has revealed that the cytolytic effect of a peptide called cecropin B is more prominent on cancer cells (KG-1 leukaemia and Ags stomach carcinoma) in comparison to the normal cells. The data obtained was then correlated with the scanning electron microscopic study, which revealed dense population of irregular microvilli in cancer cells surface. This is the likely explanation for the stronger bacteriocin-plasma membrane interaction in cancer cells.

As observed in its antimicrobial activity, nisin interacts with the anionic nature of phospholipid heads of the cancer cell plasma membrane. Consequently, it mediates reorganization of the membrane, leading to formation of short-lived pores, permitting the influx of calcium ions into the cytoplasm. Others have reported that nisin insert itself into the plasma membrane, polymerizes and produces pores, which allow calcium influx and cytoplasmic content efflux (Martín et al., 2015). The increased concentration of intracellular calcium then activated calpain, a calcium-dependent protease, which is responsible for plasma membrane and cellular substrate degradation. This is one of the principal processes, which later leads to the breakdown of the cellular architecture and ultimately apoptosis (Maher and McClean, 2006; Joo et al., 2012; Preet et al., 2015).

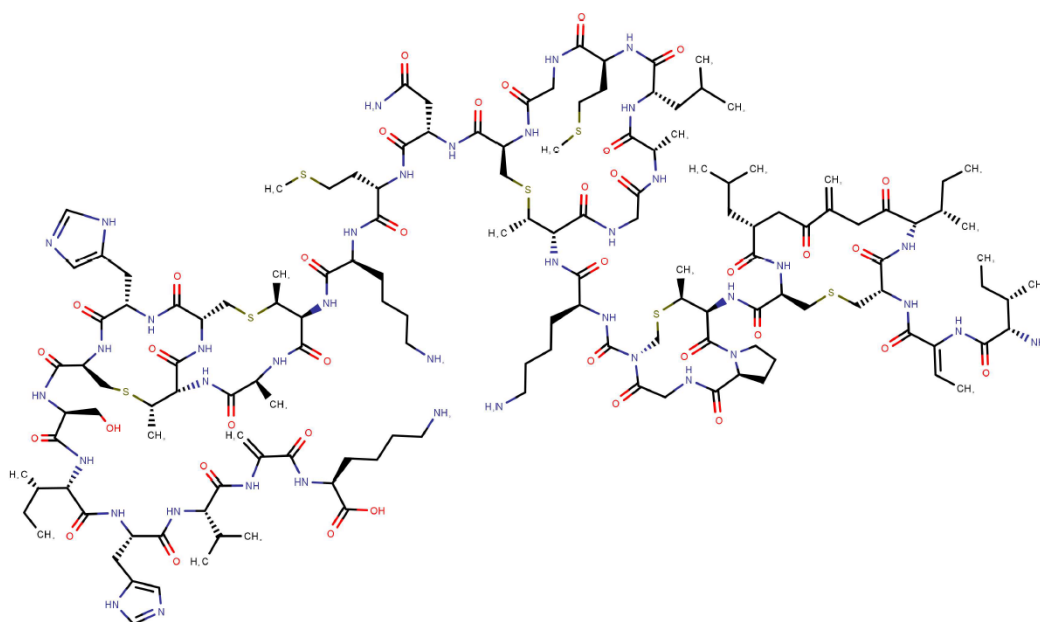


Figure 1. Chemical structure of nisin

Plasma membrane organization, resulting from interaction between nisin and the negatively charged phospholipids, increases fluidization in one of the regions of the membrane called L_d region. Subsequently, more fluidization takes place, potentiating calcium influx (Lewies et al., 2018). Figure 2 depicts the fluidization process and fusion of nisin with the raft-like domain, which is induced by nisin interaction.

Following the rapid entry of calcium ions into the cancer cells, along with the concurrent release of cytochrome C, an apoptosome was produced, activating

several caspases and nucleases, eventually culminating in cancer cell death. It was found that increase in the dose of nisin treatment is proportionately associated with level of caspase 8, indicating the bacteriocin role in activation of the caspase (Yates et al., 2012; Zacharof and Lovitt, 2012). An increase in the intra-cytoplasmic calcium concentration activates the intrinsic apoptosis pathway as shown in Figure 3 (Pinton et al., 2008).

The hypothesized pro-apoptotic and anti-mitotic mechanisms of nisin against the cancer cells based on the existing literatures can be summarized via Figure 4.

Table 2. Effects of nisin on cancer cell lines

Cell type	Type of nisin used	Results	Reference
MCF-7 (human breast adenocarcinoma)	Not mentioned	IC ₅₀ =279.39 μ M	Paiva et al., 2012
HepG2 (human liver cancer)	Not mentioned	IC ₅₀ =289.30 μ M	Paiva et al., 2012
SW480 (colon cancer)	Not mentioned	Significant cytotoxic seen at 15 to 79.22% cell death at 1000 to 4000 μ g/mL of nisin	Ahmadi et al., 2017
HT29 and Caco-2 (colon adenocarcinoma)	Nisin A	HT29: IC ₅₀ =89.9 μ M Caco-2: IC ₅₀ =115 μ M	Maher and McClean, 2006
UM-SCC-17B and HSC-3 (Head & neck squamous cell carcinoma)	Low content nisin (2.5%) & nisin AP & ZP (95%)	UM-SCC: Nisin (2.5%); IC ₅₀ >400 μ g/mL Nisin AP (95%); IC ₅₀ between 200 and 400 μ g/mL Nisin ZP (95%); IC ₅₀ <200 μ g/mL HSC-3 Nisin (2.5%); IC ₅₀ >400 μ g/mL Nisin AP (95%); IC ₅₀ ~200 μ g/mL Nisin ZP (95%)<200 μ g/mL	Kamarajan et al., 2015
SW1088 (astrocytoma)	Not mentioned	The results of IC ₅₀ are as follows: 24 h = 50 μ g/mL 48 h = 75 μ g/mL 72 h = 50 μ g/mL	Zainodini et al., 2018
IMR-32 (neuroblastoma)	Not mentioned	Increasing molarity of nisin from 0 to 25 μ M reduced cell viability.	Prince et al., 2019
A375 (human skin carcinoma)	Nisin (2.5%)	IC ₅₀ nisin=32 μ g/mL IC ₅₀ 5-FU=16 μ g/mL IC ₅₀ nisin+5-F =2 μ g/mL+2 μ g/mL	Rana et al., 2019

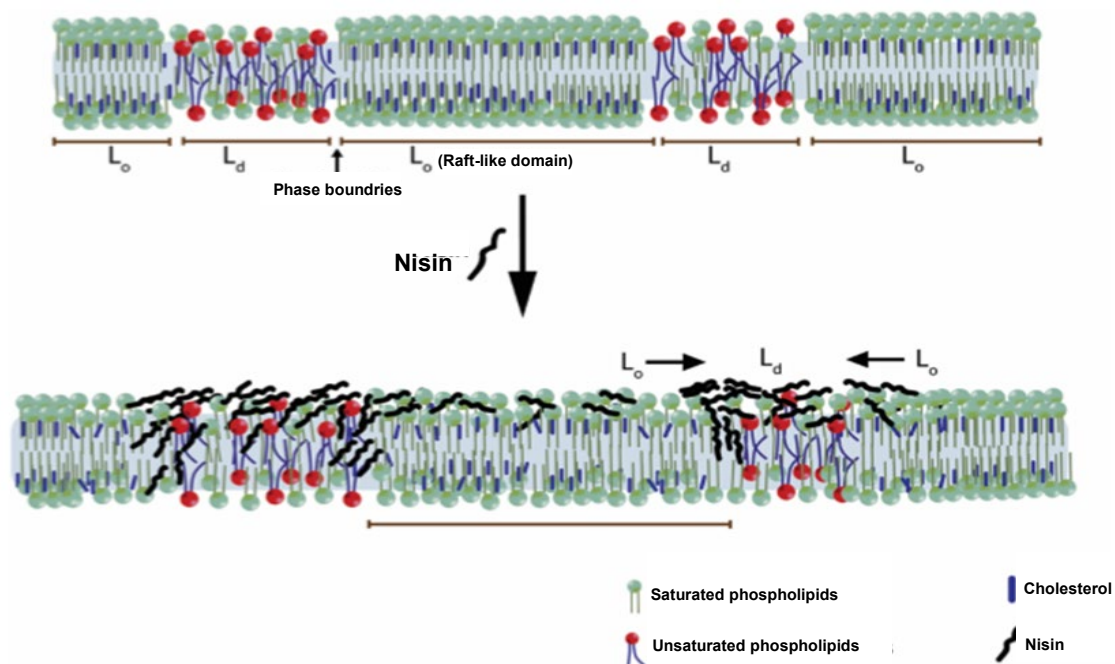


Figure 2. Schematic diagram of nisin induced plasma membrane fluidization and fusion of raft-like domains (Lewies et al., 2018)

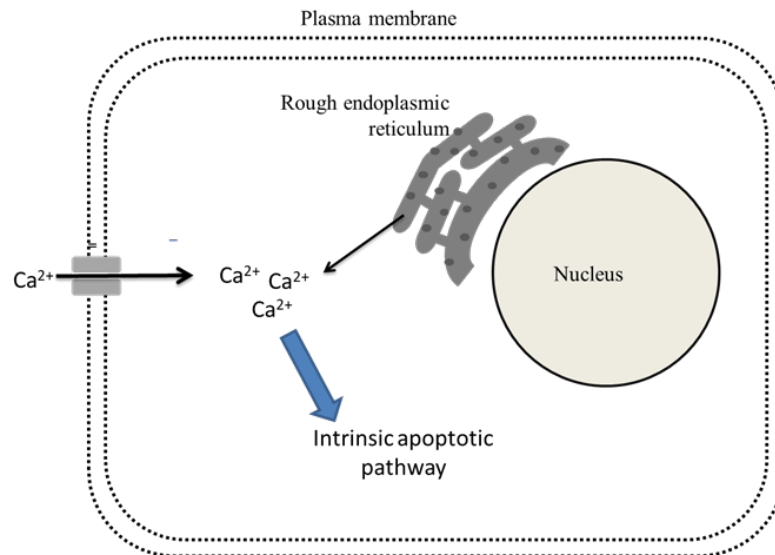


Figure 3. Influx of calcium and release of calcium from rough endoplasmic reticulum activates intrinsic apoptotic pathway

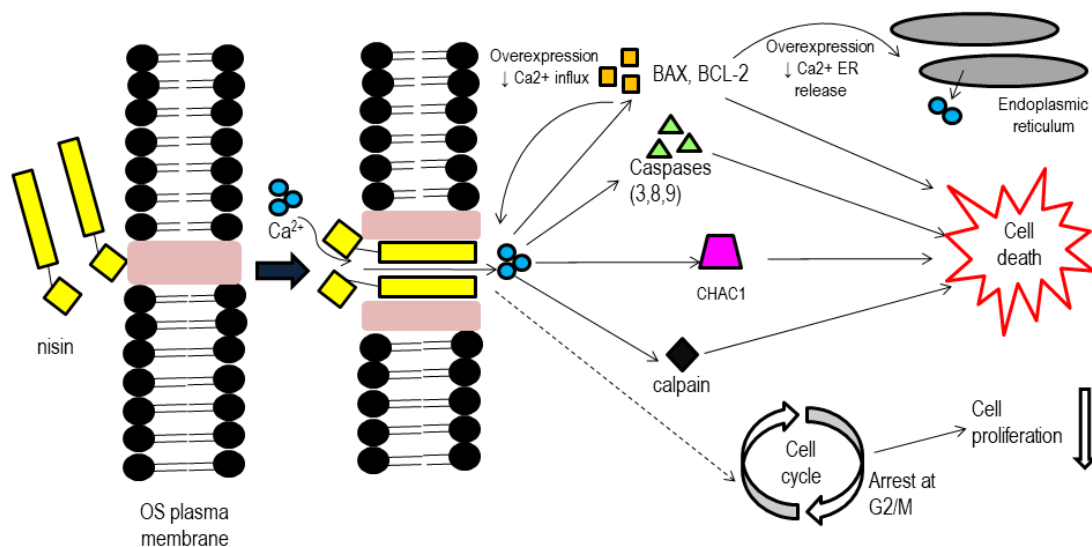


Figure 4. Summary of the hypothesized molecular mechanism for the anticancer effect of nisin against cancer cells

4. CONCLUSION

Nisin, a lantibiotic produced by *Lactococcus lactis*, is a potential adjuvant cancer agent. It has a selective action on cancer cells is due to its electrical property. Nisin reduces cell proliferation via cell cycle arrest and activation of apoptosis. However, the mechanism leading to apoptosis is still poorly described and requires further investigations. Nisin is cheap and easily available with no reported adverse effects, thus offer a good alternative to the current therapy.

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