Review Article

Cytotoxic Activity of Nisin on Human Cancer Cell Lines: A Systematic Review

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Received: 21 November, 2021; Accepted: 17 January, 2022

Abstract

Cancer is one of the leading causes of mortality and morbidity worldwide. Nisin consists of various and uncommon amino acids as an antimicrobial protein synthesized by the *Lactobacilli* genus. The current systematic review aimed to evaluate the anticancer activity of Nisin, an antibacterial peptide, on different human cancer cell lines. We searched PubMed/Medline and Embase databases to detect the studies addressing the cytotoxic activity of Nisin on human cancer cell lines. Our study was conducted following the "PRISMA" guideline. Of 202 potentially relevant articles, 15 studies met the inclusion criteria and were included for further analysis. The results revealed that Nisin has different levels of anticancer activity on human cancer cell lines. The outcomes of our review indicate that some cancer cell lines, such as cell skin carcinoma (A431), Melanoma cells (A375), and colorectal cancer cell lines (LS180), are strongly affected by the anticancer properties of Nisin. In contrast, the anticancer effect of Nisin on others like Human promyelocytic leukemia (HL60) is lower. Nisin shows significant anticancer effects in different cancer cell lines. Utilizing Nisin simultaneously with other antitumor agents can enhance its anticancer features and efficacy. Further studies, especially *in vivo* assay and clinical trials, are recommended to achieve more accurate results in this field.

Keywords: Nisin, Cancer treatment, Systematic review, Cytotoxic activity, Cell line

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Please cite this article as Hosseini SS, Hajikhani B, Goudarzi H, Rommasi F, Nasiri MJ. Cytotoxic Activity of Nisin on Human Cancer Cell Lines: A Systematic Review. Novel Biomed. 2022;10(3):184-91.

Introduction

Cancer is one of the leading reasons for mortality and morbidity worldwide. The liver, lung, stomach, colon, and breast malignancies are the most prevalent causes of cancer death[1]. Carcinogenesis can be caused by genetic mutations resulting from heredity or environmental factors[2]. The cancer incidence rate is rising in developing countries due to population growth and other risk factors such as overweighting, smoking, and unhealthy diets[3]. One of the most critical approaches to treating cancer is the chemotherapy method. Chemotherapeutic drugs cannot specifically recognize tumor tissue from healthy tissues; therefore, they simultaneously influence the normal and cancerous cells in the body. They also have toxic impacts on normal cells, which may cause many side effects[3].

In addition, cancer cells have shown a tendency to resist chemotherapy drugs[4], which may decrease the efficacy of standard cancer therapy strategies. On the other hand, it is revealed that various proteins and

peptides can be used to combat cancer5. Probiotics can affect other bacteria and pathogens by synthesizing antibacterial substances, including acids and bacteriocins[6, 7]. One probiotic bacterium is *Lactococcus lactis*, a subspecies of lactic produce Nisin.

Nisin is a protein substance with a low molecular weight (about 3.49 kDa) that contains only 34 amino acids. Nisin is an antibacterial peptide and bacteriocin with antitumor activity confirmed by the Food and Drug Administration (FDA) as a non-toxic food preservative compound for human consumption[8]. This systematic review aimed to investigate the anticancer activity of Nisin as a potential candidate for cancer treatment on diverse cancer cell lines.

Methods

Search strategy: For this study, a relevant database was arranged from July 1, 2000, to July 1, 2020, using

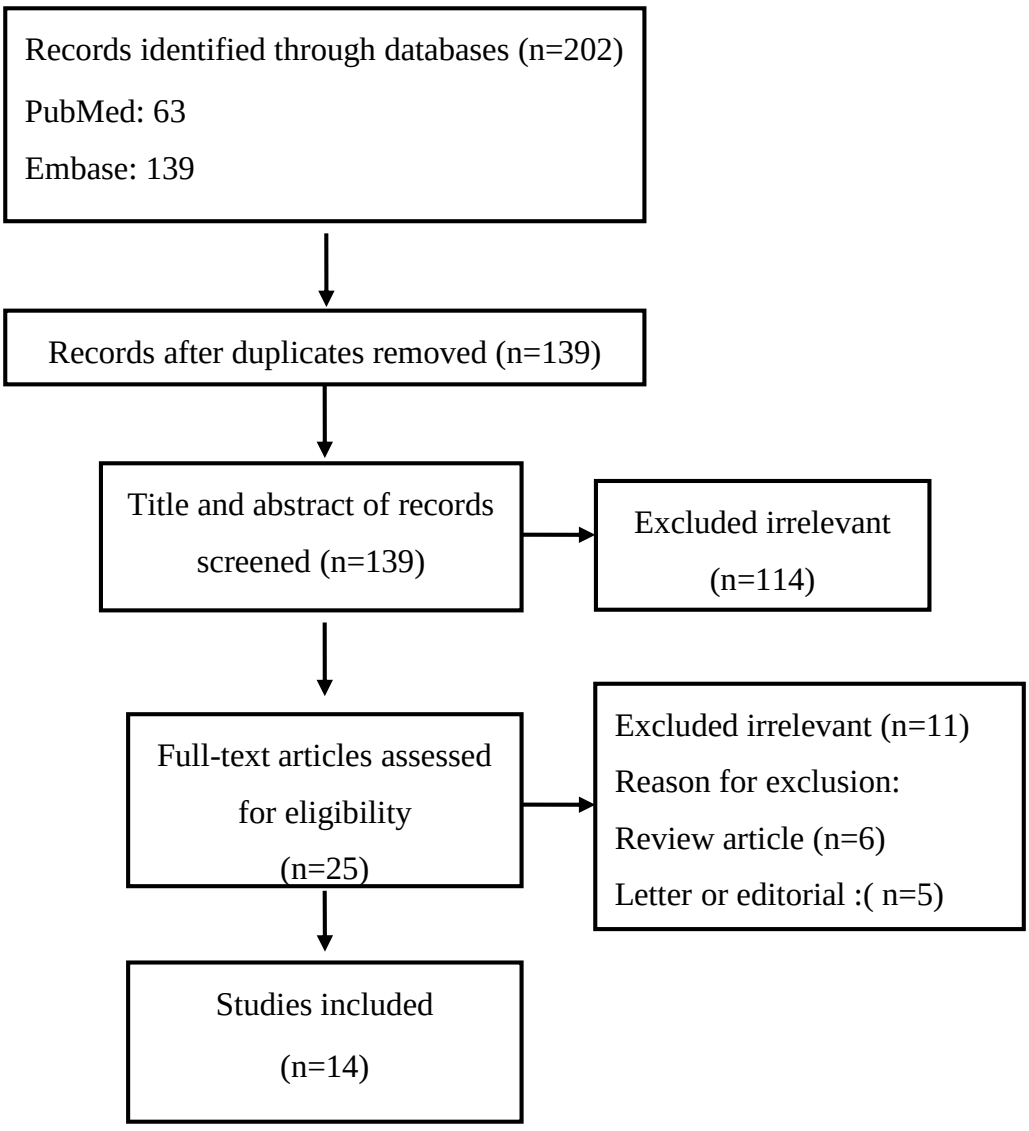

Figure 1. Flow chart of study selection for inclusion in the systematic review.

the PubMed / Medline and Embase databases. The search scope was limited to English articles on the cytotoxic activity of Nisin on human cancer cell lines that confer the present study's data. Utilizing Boolean operators (and, or) following keywords from Medical Subject Headings, titles or abstracts were collected: Cancer, Nisin, and *Lactococcus lactis***.** The research was conducted and reported following the "PRISMA" guidelines[9]**.**

Study selection: The articles and records in the research database are integrated, and duplicate data were removed by exploiting EndNote X7 (Thomson Reuters, New York, NY, USA). Two autonomous reviewers screened the titles and abstracts in terms of relevance.

Two authors regain and review the full text of qualified papers. if articles met the following inclusion criteria, studies were included:

(i) studies in which cancer cell lines were treated with Nisin alone

(ii) studies in which different cancer cell lines were treated with Nisin and other substances.

All of the Letters to the editor, editorials, conference abstracts, and review articles were excluded.

Data extraction: The two reviewers investigated the extracted data from eligible studies and resolved the disagreements by consensus. The extracted data are as follows: first name of the author; year of publication; type of study, Countries in which research has been conducted; kind of cancer cell line; effect of Nisin on cancerous cells, cell viability (%).

Results

Initially, a total of 202 articles were retrieved from databases. Then, 114 articles were excluded according to the title and abstract evaluation. 11 studies were excluded based on the full-text screening in the next step. The inclusion criteria of this article are illustrated in Figure 1.

Eventually, the number of eligible articles in the systematic review reached 15. Characteristics of the selected papers are summarized in Table 1.

Our results demonstrated that Nisin peptide, as bacteriocin produced by the *Lactococcus lactis* subtype, has different anticancer impacts on various human cancer cell lines. The highest anticancer effect of Nisin was on squamous cell skin carcinoma (A431), Melanoma cells (A375), and colorectal cancer cell line (LS180), respectively. Our outcomes exhibit that Nisin has the lowest anticancer influence on Human promyelocytic leukemia (HL60) (Table 2).

Also, the combination of Nisin with other anticancer substances such as magainin, doxorubicin, defensin, nanoparticles, and fluorouracil has higher cytotoxic effects on cancer cell lines than Nisin alone.

The present study also showed that Nisin-Z has a higher cytotoxic effect on cancer cells than Nisin. The expression level of caspase-3 and Bax/Bcl-2 ratio was evaluated in the included studies. The elevated level of caspase-3 and increased Bax/Bcl2 ratio indicate that Nisin can activate the apoptotic pathway in cancer cells and increase cytotoxicity in these cells.

Discussion

Cancer is the second most prominent cause of death globally, and its mortality rate has been steadily rising in recent decades. The World Health Organization (WHO) 2018 reported that approximately 18.1 million new cancer cases were identified in 2018, with about 9.6 million people dying[10]. Surgical resection of the tumor, accompanied by radio- and chemotherapy, is currently the primary treatment option for cancer therapy. Although there have been significant advances in cancer treatment, many existing cancer therapy methods are highly toxic and have harmful side effects for patients[11]. On the other hand, cancer cells develop resistance to current anticancer drugs. As a result, new anticancer agents with low toxicity for normal cells and healthy tissues should be considered. So, there is a lot of interest in developing anticancer therapeutics with a new mechanism of action[12].

Cationic antimicrobial peptides are one form of the studied antimicrobial compound (AMPs). Naturally occurring antimicrobial peptides are likely one of prokaryotic cells' first developed and effective chemical defense mechanisms. These peptides have exerted various biological functions, such as inhibiting membrane protein synthesis, suppressing DNA synthesis, antitumor effects, and antiviral properties, such as tumor cell apoptosis or cytotoxicity[12, 13].

Table 1: Characteristics of included studies.

First Author	Published year	time of study	Country	type of cancer	cancer cell line	Evaluation of Nisin alone	Evaluation of Nisin combined to other substances
Murinda [27]	2003	2002	USA	Human colon	SV40-HC	Yes	No
Cruz-Chamorro [28]	2006	2005	Spain	Human promyelocytic leukemia	HL-60	Yes No	No Nisin With Magainin
Goudarzi-1 [29]	2013	2012	Iran	stomach	AGS	Yes	No
Kamarajan [30]	2015	2015	USA	Head and neck squamous cell carcinoma	HNSCC	Yes	No
Ahmadi [16]	2017	2017	Iran	Colorectal	sw480	Yes	No
Lewies [31]	2017	2017	South Africa	Melanoma cells	A375	Yes Yes	No No
Avand [32]	2018	2017	Iran	Breast cancer	MCF7	No	Nisin With Doxorubicin
Zainodini [33]	2018	2017	Iran	Human Asterocytoma	SW1088	Yes	No
Norouzi [34]	2018	2018	Iran	Colorectal cancer cell line	LS180 SW480 HT29 CACO2	Yes Yes Yes Yes Yes	No No No No No
Goudarzi-2 [35]	2018	2018	Iran	Stomach	AGS	No	Nisin-Loaded Nanoparticles
				Esophageal squamous cell carcinom	KYSE-30	Yes No	No Nisin-Loaded Nanoparticles
				Myelogenous leukemia cell line	k562	Yes No	No Nisin-Loaded Nanoparticles
				Hepatocellular carcinoma	HepG2	Yes No	No Nisin-Loaded Nanoparticles
Prince [36]	2018	2018	India	Neuroblastoma cell line	(IMR-32)	Yes	No
Rana [37]	2019	2019	India	Squamous cell skin carcinoma	A431	Yes No	No Nisin + 5fu
Sasani [38]	2020	2020	Iran	Human colorectal carcinoma	HCT-116 PC-3 HCT-116 PC-3	Yes Yes No No	No No Nisin With Defensin Nisin With Defensin
Hosseini [39]	2020	2019	Iran	Colorectal	sw480	Yes	No

Nisin, one of the natural AMPs, is produced by the *Lactococctheus lactis* subspecies. The bacteriocin mentioned is related to lantibiotics and includes rare amino acids such as lanthionine, didehydroalanine, methyllanthionine, didehydro-aminobutyric acid, which are synthesized during post-translational modifications of protein[14]. This polypeptide is commonly exploited as a food preservative and might serve as a novel potential treatment of some kinds for cancer[8, 15].

Nisin is non-toxic to animals and harmless for humans. The Joint Food and Agriculture Organization (FAO) and WHO confirmed it as a healthy food supplement in 1969[16]. Nisin has been approved in over

50 countries and has impacted the food sector as a natural bio-preservative for various foods. Due to the scientists' high interest in this substance's potential anticancer effects, multiple studies have been conducted on the impact of Nisin on different cancer cells or laboratory animals. In the present article, we collected and reviewed the results of these studies to provide more comprehensive information on the effects of this bacteriocin. Fifteen related articles conducted between 2003 and 2020 were included in the present study. Most of these studies examined the impact of Nisin on different colorectal cancer cell lines. Nine out of 15 included studies were reported from Iran. All selected articles in the present study used the MTT method to evaluate the survival of cancer cells after exposure to Nisin. The results of our systematic review revealed that Nisin exhibits its highest anticancer activity on squamous cell skin carcinoma (A431), Melanoma cells (A375), and colorectal cancer cell line (LS180), respectively, and the lowest effect was observed on Human promyelocytic leukemia (HL60). Depending on the nature of the cancer cell, its receptors, cell cycles, and genes involved in cell growth, the impacts of Nisin can be different on that cancer cell. Based on conducted studies, various mechanisms have been proposed for the anticancer effects of Nisin. Only a few of the research included in this systematic review considered the changes in the expression of genes implicated in apoptosis in cancer cells following Nisin exposure. Their results demonstrate that Nisin can activate the apoptotic pathway in cancer cells by increasing the caspase-3 level and Bax/Bcl2 ratio.

In some cancer cell lines, such as cell carcinoma of the neck and head squamous, Nisin exerts its effects by fragmenting cellular DNA or inducing apoptosis in a concentration-dependent pathway. These effects are partly because of cation transport regulator homolog 1 (CHAC1), a proapoptotic cation transport regulator, and an accompanying CHAC1-independent influx of extracellular calcium[8, 17].

On the other hand, researchers suggested that Nisin could cause an influx of ions by forming pores in the cell membrane via interaction with the negatively charged phospholipid heads[18].

Nisin's selectivity for cancer cells could be explained based on membrane differences. In addition, as we know, the membrane composition and function of different cancer cells and their response to calcium fluxes vary. That's why the ability of Nisin to alter the cell membrane characteristics might influence its predominant effects on some cancer cells, such as squamous cell skin carcinoma, Melanoma cells, and colorectal cancer cell line, as well as its non-cytotoxic outcomes in specific concentrations on normal cells[19, 20]. Tumor cell surfaces have a negative charge because their cell membrane contains more anionic molecules like phosphatidylserine. Opposite ordinary cells have an overall neutral control because the membrane of cells is principally composed of sphingomyelin, phosphatidylethanolamine, and phosphatidylcholine[21, 22]. The selective cytotoxicity of this peptide may be due to electrostatic interactions between the anionic membrane and cationic Nisin of cancer cells. Yet, the precise mechanism of the anticancer effect of Nisin must be interoperated.

Paiva et al. showed that Nisin has a cytotoxic effect on MCF-7 and HepG2 cell lines. Their research demonstrated that the cell viabilities of the two kinds of cell lines at the uppermost Nisin concentration experimented, i.e., 140 mM, were less than 20%. Based on their findings, Nisin exerts its anticancer properties on the cell through shrinkage, condensation, vacuolization of cytoplasm, and lateralization of the nucleus, which eventually leads to cell detachment[23].

Some studies have examined the anticancer effects of Nisin in combination with substances such as nanoparticles, doxorubicin, defensin, or magainin. Preet et al. investigated the synergistic effect of Nisin and doxorubicin combination on the skin of mice carcinoma. They showed that the nisin-doxorubicin mixture decreased the tumor volume by 66.82% compared to the untreated people. This amount was more significant than the effect of each compound alone. These researchers concluded that Nisin could increase the potential of doxorubicin as a chemotherapeutic drug[24]. It was shown that Nisin might increase doxorubicin uptake by cancer cells by destabilizing the cellular membrane or making pores[25].

However, it should be noted that some articles have pointed out that Nisin does not affect cancer cells. For instance, Bede et al., in their research using DNA fragmentation assay, found no apoptosis of both the Jurkat normal and cancer cell lines were observed at

the cytotoxic concentrations[26].

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Table 2: Cytotoxicity properties of Nisin.

First author	Assessment of cytotoxicity	Dose of Nisin tested	Cell viability (%) average of each triplicate experiment as mean ± sd.	Time	Cancer cell line	Evaluation of Nisin alone	Evaluation of Nisin combined to other substances
Murinda	Trypan blue	700 AU/ml	43	16h	SV40-HC	Yes	No
Cruz-Chamorro	MTT	5oμM	95	24h	HL-60	Yes	No
		5oμM(nisin)+50nM (magainin)	25	24 h		No	Nisin with magainin
Goudarzi-1	MTT	450 μM	25	24h	AGS	Yes	No
Kamarajan	MTT	800μg/ml	10	24h	HNSCC	Yes	No
Ahmadi	MTT	4000μg/ml	15	24h	sw480	Yes	No
Lewies	MTT	400μM	8	24h	A375	Yes	No
Avand	MTT	25μg/m	46	48h	MCF7	Yes	No
		10μg/m(nisin) + 6 μg/ml(dox)	15	48h	MCF7	No	Nisin with doxorubicin
Zainodini	MTT	100 μg/Ml	45	24h	SW1088	Yes	No
Norouzi	MTT	400 IU/ml(668 μg/ml)	10	24h	LS180	Yes	No
		600 IU/ml (1002μg/ml)	20	24h	SW480	Yes	No
		800IU/ml (1336μg/ml)	20	24h	HT29	Yes	No
		800 IU/ml (1336μg/ml)	25	24h	CACO2	Yes	No
Goudarzi-2	MTT	450 μM	25	24h	AGS	Yes	No
		450 μM	15	24h	AGS	No	Nisin-loaded nanoparticles
		450 μM	45	24h	KYSE-30	Yes	No
		450 μM	40	24h	KYSE-30	No	Nisin-loaded nanoparticles
		450 μM	30	24h	k562	Yes	No
		450 μM	25	24h	k562	No	Nisin-loaded nanoparticles
		450 μM	25	24h	HepG2	Yes	No
		450 μM	20	24h	HepG2	No	Nisin-loaded nanoparticles
Prince	MTT	25μM	64	24h	(IMR-32)	Yes	No
Rana	MTT	64μg/ml	40	48h	A431	Yes	No
		64μg/ml+ 64 μg/ml	10	48h	A431	No	Nisin + 5fu
Sasani	MTT	75μg/ml	65	24h	HCT-116	Yes	No
		75μg/ml	61	24h	PC-3	Yes	No
		75μg/ml + 15 μg/ml	45	24h	HCT-116	No	Nisin with defensin
		75μg/ml + 15 μg/ml	35	24h	PC-3	No	Nisin with defensin
Hosseini	MTT	1500 μg/ml	38	24h	sw480	Yes	No

Generally, based on our systematic review of available studies performed on anticancer properties of Nisin, it's plausible that this bacteriocin, for some cancer cells, is single or in composition with the rest chemotherapeutic agents, which could be a possible therapy. However, more detailed studies are still mechanisms that cause these effects.

The current systematic review has several limitations. First, because of the role of the Nisin peptide in different cancers, few phenotypic and genotypic studies have been done in this field in the world. Accordingly, we could not investigate Nisin's role in

various cancers. Second, most of the studies were in-vitro, and thus, further animal studies should be done.

Conclusion

Nisin is still in the early phases of development as an anticancer agent. However, few studies have been conducted on Nisin as a promising alternative or adjunctive therapy with anticancer features. The present systematic review indicates the beneficial role of Nisin in the treatment of cancers. However, further studies are necessary to achieve a definitive conclusion.

Acknowledgments

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

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