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REVIEW

Natamycin: a natural preservative for food applications—a review

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Abstract Natamycin is a natural antimicrobial peptide produced by the strains of *Streptomyces natalensis*. It effectively acts as an antifungal preservative on various food products like yogurt, khoa, sausages, juices, wines, etc. Additionally, it has been used as a bio preservative and is listed as generally recognized as a safe ingredient for various food applications. In this review, natamycin properties, production methods, toxicity, and application as a natural preservative in different foods are emphasized. This review also focuses on optimal condition and process control required in natamycin production. The mode of action and inhibitory effect of natamycin on yeast and molds inhibition and its formulation and dosage to preserve various food products, coating, and hurdle applications are summarized. Understanding the scientific factors in natamycin's production process, its toxicity, and its efficiency as a preservative will open its practical application in various food products.

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Keywords Natamycin · Mode of action · Production · Toxicity · Food applications

Abbreviations

MIC	Minimum inhibitory concentration
LD_{50}	Lethal dose$_{50}$
NOAEL	No observed adverse effect level
MN	Micronucleus
MI	Mitotic Index
NDI	Nuclear Division Index

Introduction

Prevention of microbial contamination plays a crucial role in minimizing the economic loss of food due to spoilage. The primary concern with fungal spoilage is mycotoxin production (a secondary metabolite produced by fungi) being fatal and could pose severe health threat to both humans and livestock. The removal of visible mold and yeast superficially from the food products gives no assurance to food product safety. Antifungal Preservatives used for mold and yeast growth prevention were ineffective against the toxic fungal metabolites as toxins are diffused in the food products. Food industries are now shifting from conventional preservatives to natural preservatives due to the increasing demands for biopreservation in terms of safety and efficacy (Galvez et al., 2014). Conventional preservatives (nitrates/nitrites, propyl gallate, sodium benzoate, and sulfites potassium sorbate) carry chemical hazards as residues and also have side effects if consumed more than permitted limits. For instance, nitrates/nitrites are associated with leukemia and stomach cancer, sorbates and sorbic acids are linked to urticaria and contact dermatitis, benzoates causes asthma, allergies, and skin rashes,

etc. (Sharma, 2015). Natural preservatives are isolated from plants, animals, and microbes and their metabolites (Singh et al., 2010). In plants, variation exists due to the non-availability throughout the year, climatic variations, and varietal differences. Microorganisms are the preferred natural source as they can be isolated in the control environment with higher production rates. Biopreservation has increasing attention in recent years in the food industry and consumers. Several antimicrobial peptides/proteins are produced by both Gram-negative and Gram-positive bacteria, during their growth possess antimicrobial activities.

Natamycin is known for its efficacy in controlling fungi growth and pays way to be a preservative in the food industry for more than 30 years (Davidson and Doan, 2020; He et al., 2019). It is a natural preservative derived from a microorganism known as *Streptomyces natalensis*. Food industries utilize natamycin for its preservative effect on food products like cheese, sausages, yogurts, juices, and wines, etc. (Dalhoff and Levy, 2015). It is most commonly preferred over the other preservatives as it is free from odor and color. World Health Organization (WHO), European Food Safety Authority (EFSA), and Food and drug administration (FDA) has listed it as generally recognized as safe (GRAS) status after thorough evaluation, and being considered as a natural preservative by the European Union and labeled with E number (EEC No. 235). In a recent study by Chen et al. (2021) demonstrated that combination of natamycin-fludioxonil or a natamycin-propiconazole were shown to have a synergistic effect resulting in a $> 85.0\%$ reduction of green mold and sour rot thereby managing post-harvest fruit decay of citrus.

Natamycin was reported to be effective against nearly all mold and yeasts (such as *Candida* spp., *Aspergillus* spp., *Cephalosporium* spp., *Fusarium* spp. and *Penicillium* spp.) but proved to be ineffective against bacteria and viruses (Raab, 1972). It is not only certified for safe use in foods but also used for the treatment of fungal infections in humans. Natamycin is the only antifungal medication approved by U.S. Food and Drug Administration (Arora et al., 2011). The objective of this paper to review the mechanism of action, inhibitory effect, Production methods, and toxicity of natamycin in general. Further emphasis on the application of natamycin as an anti-fungal preservative in various food products is also discussed in detail.

Properties of natamycin

Natamycin (also known as pimaricin), is a polyene macrolide antimycotic agent produced by submerged fermentation of strains of *Actinomycetes* such as *S. natalensis* and *Streptomyces chattanogenesis* (Davidson and Doan, 2020). Structurally, natamycin is characterized by a series of conjugated double bonds enclosed in a macrocyclic lactone ring with the number of hydroxyl bonds. The lactone ring consists of 25 carbon atoms. So natamycin is classified as a macrolide antibiotic joined to a mycosamine moiety (3-amino-3,6-dideoxy-D-mannose) by an ether linkage (Raab, 1972). The mycosamine moiety is a six-membered pyranose ring present at the C15 position. Natamycin is also classified as a tetraene antibiotic because it is made up of 4 conjugated double bonds. The combination of mycosamine group and carboxyl moiety is present in the structure of natamycin makes it amphoteric (Bolard, 1986). Chemically, it is 22-(3-amino-3,6-dideoxy-b-D-manno-pyranosol)oxy-1,3,26-trihydroxy-12-methyl-10-oxo-6,11,28-trioxiatri[22.3.1.05.7]ocatosa-8,14,16,18,20-pantanene-25-carboxylic acid (Delves-Broughton et al., 2005).

Natamycin is a white or creamy-white colored powder with a molecular weight of 665.75 g/mol. The empirical formula is $C_{33}H_{47}NO_{13}$ with an isoelectric pH of 6.5 (Brik, 1981). Natamycin shows poor solubility in water ($\sim$ 40 µg/mL), but it is soluble in organic solvents (Davidson and Doan, 2020). The stability of natamycin depends on various factors like solvent used, temperature, pressure pH, light (UV and fluorescent light), temperature, oxidants, and heavy metals, etc. Due to its low solubility in water, natamycin remains on the surface of the food products (specifically used for surface treatment of cheese) instead of migrating inside the food and thereby maintaining its preservative effect optimally. Natamycin showed the highest solubility in 75% aqueous solution of methanol at pH of 2.0, the temperature of 30 °C, and pressure of 1 atm (Zeng et al., 2013). Luo et al. (2008) reported that temperature directly increases natamycin's solubility in isopropanol and methanol. Its solubility in an aqueous solution and its stability can be effectively enhanced by encapsulation of natamycin in a methyl-β-cyclodextrin complex without compromising its antifungal potential (Fang et al., 2019). Natamycin or its suspension remains stable in heat, even after continuous heating at 100 °C for several hours with small degradation of its activity. Complete inactivation of its activity was observed at 121 °C for 30 min (Gao et al., 2010). Natamycin gets destabilized at low pH values and forms mycosamine due to the hydrolysis of the glycosidic bond (Brick, 1976). The lactone ring of natamycin is saponified at high pH, resulting in the formation of biologically inactive natamycoic acid (Brik, 1981). The activity of natamycin solution (50 ppm) could be degraded by exposure with acid (8.62%), alkali (9.18%), and hydrogen peroxide (24.13%) for 4 h (Chaudhari and Chhabra, 2014). An aqueous solution of natamycin (20 mg/L) was degraded entirely by exposure to 1000 lx fluorescent lighting for 24 h at 4 °C. On the other hand, an aqueous solution of natamycin

(20 mg/L) was stable up to 14 days when stored under dark conditions at 4 °C (Koontz et al., 2003).

Cheese is mainly administered with natamycin as a preservative. However, the sensitivity of natamycin may vary its preservative efficiency. In general, cheese is exposed to light during retailing and transportation, leading to the degradation of natamycin, reducing natamycin's preservative effect (Thoma and Kubler, 1998). Exposure of UV light for 99 min and fluorescent light for 10 days may result in the destruction and inactivation of natamycin (Gao et al., 2010). Apart from UV light, natamycin is also sensitive to gamma radiation (Li et al., 2010) and acidic conditions resulting in loss of tetraene structure and gives decomposition products like—mycosamine (major product), aponatamycin, dinatamycinolidediol, etc. (Brick, 1976). Apo-natamycin is made up of natamycin and natamycinolide-moiety with each of the epoxy group (at C4–C5) hydrolyzed.

Historical development

Natamycin was discovered by Struyk in 1955 in Gistbrocades research laboratories. It was isolated from a cultural filtrate of *S. natalensis* in South Africa (Stark, 2003). In 1957, Stryuk revealed his discovery along with the properties of natamycin in Antibiotics Annual (Struyk et al., 1958). Natamycin was initially named pimaricin because the culture of *Streptomyces* was isolated from soil in Pietermaritzburg (Capital and second-largest city in the province of KwaZulu-Natal, South Africa). After some years, World Health Organization (WHO) announced that the name of the preservative should reflect the name of the organism from which it was isolated and, thereafter pimaricin was renamed as natamycin.

In 1959, an antibiotic was isolated from the culture medium of a *Streptomyces* strain. This strain was collected from a soil sample in Chattanooga, Tennessee. As a result, the strain and antibiotic were named *Streptomyces chattanoogensis* and tennecetin (Raab 1972). After analytical studies and biological assay of tennecetin, it was reported that tennectine was similar to the previously known natamycin (Burns, 1959). Therefore, the name tennectin was replaced by natamycin. The Royal Netherlands Fermentation Industries, Ltd., was established as a division of Gistbrocades laboratories, owns the first and second patent by American Cyanamid Corporation. Both patents disclose a similar method for natamycin production. In both cases, butanol was utilized to extract natamycin from culture broth, after acidification to pH 3.0 followed by different steps i.e. precipitation, extractions, and spray drying to get the end product.

On a commercial scale, natamycin is produced by fermenting the culture of either *S. natalensis* or *Streptomyces gilvosporeus* in a medium consisting of a carbon source and a fermentable nitrogen source. The carbon sources can be starch or molasses, whereas corn steep liquor, soya bean meal, and casein can be utilized as a fermentable nitrogen source. Fermentation is done under the conditions of pH 6–8 and at the temperature of 26–30 °C. During fermentation, the contents are agitated mechanically to ensure the homogeneity of the mixture, and antifoaming agents were also added to aid the process. Since natamycin has poor solubility, it accumulates as crystals (0.5–20 μm) and can be separated from the biomass through solvent extraction (Delves-Broughton and Weber, 2011).

Several commercial brands of natamycin are available in the market (Supplementary Table 1). The utilization of natamycin in meat and dairy products is highest in the Asia Pacific followed by Europe that utilizes natamycin, especially for cheese and sausages. As per Mordor Intelligence Report, countries like China and India also witnessing substantial growth rates because of their huge population. The purchasing growth of natamycin is slow compared to the other countries due to the non-clearance from the regulatory bodies. The key market players of natamycin are D and F Control System Inc. USA, Toku-E Company USA, Qingdao FTZ United International Inc China, and DSM Food Specialties Holland (Lule et al., 2016).

Inhibitory effect of natamycin

Natamycin was proved to be beneficial against yeast, filamentous fungal pathogens (Hsiao et al., 2014), molds, and various mycotoxins but inactive against bacteria and viruses. The minimum dosage required for the inhibition of pathogens is termed Minimum Inhibitory Concentration (MIC). In the case of natamycin, the MIC of 0.5–6 μg/mL and 1.0–5.0 μg/mL were sufficient for the inhibition of molds and yeast, respectively (Branen et al., 2005). In the case of *Saccharomyces cerevisiae*, 50 ppm of natamycin was sufficient to reduce the CFU count to less than 10 CFU/mL after 96 h of storage (at an incubation temperature of 25 °C). The antimycotic effect was observed at 20 ppm against *Yarrowia lipolytica*. Natamycin is found to be less sensitive against *Zygpsaccharomyces rouxii* (Resa et al., 2014). Growth of *Aspergillus carbonarius* and Ochratoxin could be inhibited at the concentration of 50–100 ng/mL of natamycin (Medina et al., 2007). Various studies on the inhibitory concentration of natamycin and its sensitivity to yeast and molds are summarized in Table 1.

Table 1 Inhibitory effect of Natamycin towards yeasts and molds

Yeast or mold	Media	Conc. of natamycin (mg/L)	Load reduction	References
Saccharomyces cerevisiae	Whey protein concentrate (16%w/v) based medium	50	Less than 10 CFU/mL	Resa et al. (2013)
Zygosaccharomyces rouxii	Whey protein concentrate (16%w/v) based medium	50	The microbial load was reduced by 1.3 log cycle	
Yarrowia lipolytica	Whey protein concentrate (16%w/v) based medium	50	Less than 10 CFU/mL	
Aspergillus sp., *Penicillium* sp., *Embellisia* sp., *Mucor* sp., *Fusarium* sp., *Rhizoctonia* sp., *A. niger* GIM3.422, *A. oryzae* GIM3.471, *P. brevicompactum* GIM3.494, *M. racemosus* GIM3.87, *Rhizopus arrhizus* GIM3.382	Potato dextrose agar and Murashige and Skoog medium	10	No growth	Pengfei et al. (2013)
A. carbonarious strain (263, 476 and 1102), *A. Niger* IBT 3256, *Geotrichum candidum IL, Geotrichum* sp. Strain AS1,	Grape juice (grape extract—water 20:80 v/v) based medium	0.02	No growth	Medina et al. (2007)
P. commune IBT 3429, *P. roqueforti* IBT PV	Luria–Bertani, nutrient agar, yeast-peptone-dextrose, and Micro Assay Culture Agar	21.6	No growth	Pedersen (1992)

Mode of action

Yeast and Molds are responsible for food spoilage, crop infestation and would cause several infections to immune-compromised individuals. Various antifungal agents such as weak-organic acids, azole derivatives, fluorocytes, allylamines, and polyenes (Brul and Coote 1999; Ghannoum and Rice 1999) were being utilized in food and medical systems for the prevention of fungal growth. However, these antifungal agents are not employed due to their synthetic origin and might cause the problem of microbial and drug resistance.

Every preservative has its mechanism of action through which it kills various spoilage-causing microorganisms and pathogens. Natamycin has a different mode of action against yeast and molds but all these modes are ergosterol dependent. The membrane of a eukaryotic cell made up of lipids, phospholipids, proteins, and sterols are called ergosterol. Sterol plays a crucial role in providing selective binding sites for natamycin. Due to the high affinity for ergosterol, natamycin binds irreversibly with ergosterol in the fungal cell membrane and forms a polyene-sterol complex. This complex alters the permeability of the membrane resulting in the rapid leakage of essential ions and small peptides, resulting in cessation of yeast and mold growth (Munn et al., 1999). The schematic diagram representing the mode of action of natamycin on a fungal cell are illustrated in Fig. 1. Welscher et al. (2008) revealed that natamycin has an affinity of approximately 100 μM for ergosterol and forms a polyene-ergosterol complex which kills the yeast. The formation of the polyene-ergosterol complex is facilitated by a double bond in the B ring of ergosterol. This complex directly blocks the fungal growth without altering the permeability of the membrane.

Yeast requires ergosterol for the fusion of the vacuole membrane (Kato and Wickner 2001). Natamycin interferes with the process of vacuole formation without permeabilization that kills the yeast and molds (Welscher et al., 2010). A study utilized ergosterol and cholesterol as a membrane sterol for the preparation of vesicles in *Achloplasma laidlawii*. The study showed that natamycin interacts with ergosterol more efficiently and results in leakage of potassium ions (maintains plasma membrane potential) in the vesicles of *Achloplasma laidlawii* which leads to cell death (De Kruijff and Demel 1974). Van Leeuwen et al. (2009) elucidated natamycin's mode of action and concluded that endocytosis in germinating conidia of *Penicillium discolor* was inhibited by natamycin without membrane permeabilization.

Production of natamycin

Natamycin is produced in a fermenting medium that contains a pure inoculum of Streptomyces species. Some of commonly used strains are *S. chattanoogensis*, *S. gilvosporeus*, *S. lydicus* and *S. natalensis*. The major bottleneck during the production of natamycin is the optimal medium conditions and process control. The process conditions during the natamycin production should be optimized to

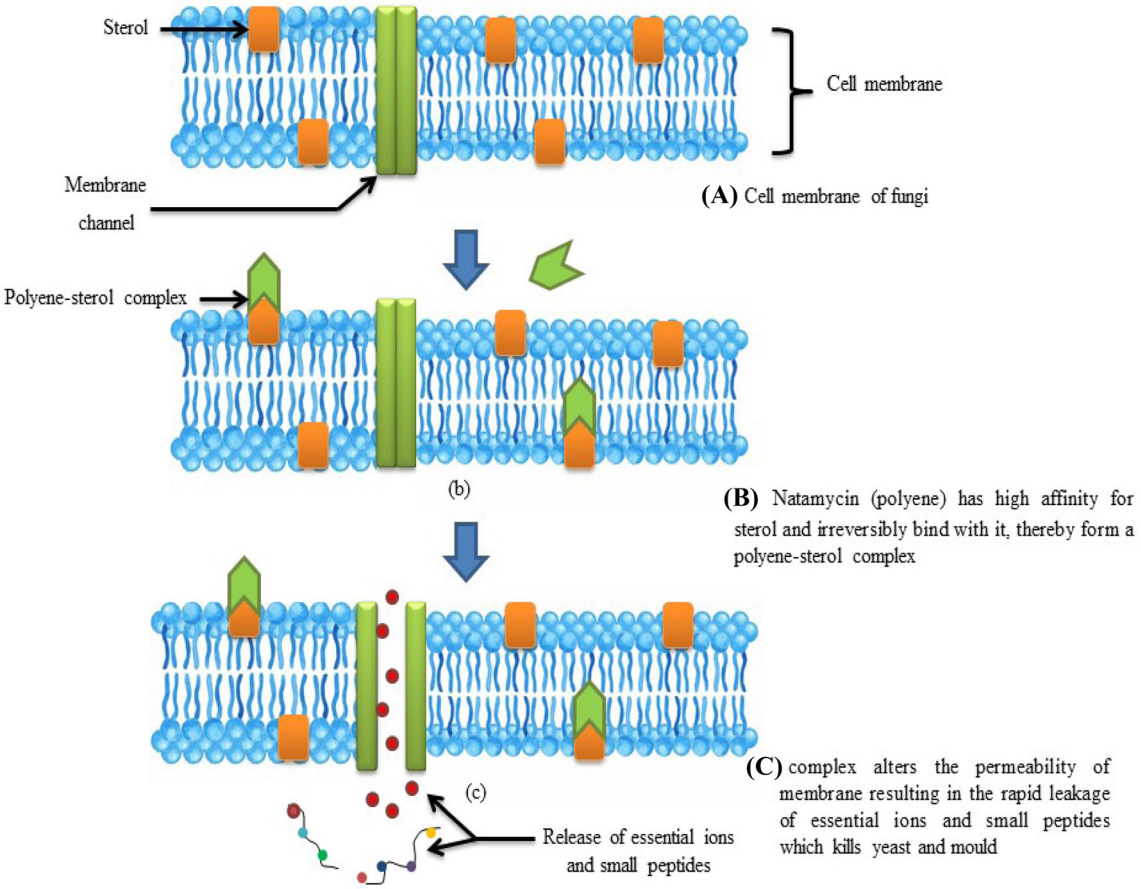

Fig. 1 Mode of action of Natamycin on a fungal cell. (**A**) Presents the schematic diagram of a fungal cell and location of sterol and membrane channels within a cell. (**B**) Affinity of natamycin towards sterol resulting in formation of polyene sterol complex. (**C**) Leakage of membrane channel with loss of ions and peptides from fungal cell

give high yields with good activity against pathogens and mycotoxins. Submerged fermentation is the industrial process for producing natamycin, and many different process strategies has been tried to improve natamycin production including strain improvement, optimization of culture medium, process parameters, carbon source and control of fermentation process. The production process of natamycin depends on fed-batch cultivation The Schematic representation of natamycin Production process are shown in Fig. 2. Fed-batch is characterized by feeding one of the components of the production medium, usually the limiting substrate to avoid problems associated with organic acids secretion (Zeng et al., 2019). Screening and optimization of production medium influence the natamycin production. Process conditions such as agitation, dissolved oxygen, inoculum type and size, carbon source and feed additives impact the natamycin production significantly. (Enhanced Natamycin production by *S. natalensis* in shake-flasks and stirred tank bioreactor under batch and fed-batch conditions). The production of antibiotics is affected by the concentration of dissolved oxygen in the bioreactor. If adequate aeration is not supplied, the dissolved oxygen levels will fall below the critical level for the organism which predominantly affects the antibiotics production (El-Enshasy et al., 2000). Various studies have been made to

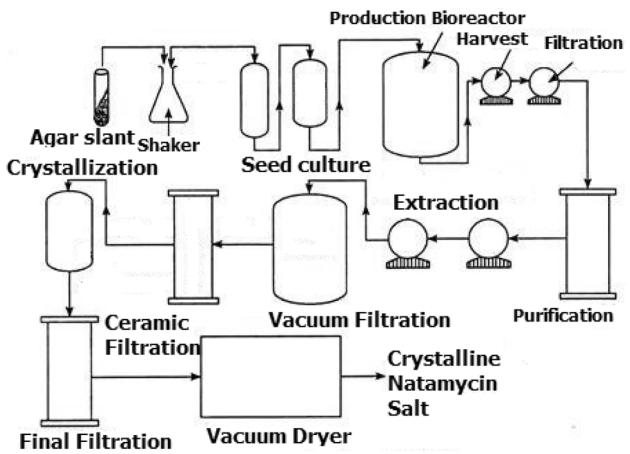

Fig. 2 Process flow diagram for Natamycin production

Table 2 Studies on process optimization for natamycin production

Composition of the media	Culture used for fermentation	Process conditions	Yield (g/L)	Findings	References
Glucose (20 g/L), beef extract (2 g/L), yeast extract (2 g/L), asparagine (0.5 g/L), and potassium dihydrogen phosphate (0.05 g/L)	*S. natalensis* NRLL 2651	Incubation temperature—30 °C, RPM—200, Time—96 h	1.5	Glucose (20 g/L) supplemented with beef (8 g/L) and yeast (2 g/L) extract increased the natamycin yield by two times higher than the initial medium	Farid et al. (2000)
Glucose (38.2 g/L), Yeast extract (3.0 g), soy peptone (15 g)	*S. gilvosporeus*	Incubation temperature—29 °C, RPM—200, Time—96 h, pH—7.8	2.45	Yield was 90% higher than the initial medium	Chen et al. (2008)
Glucose (60 g/L), soybean cake meal (10 g/L), peptone (5 g/L), yeast extract (5 g/L), beef extract (5 g/L), NaCl (2 g/L), CaCO3 (5 g/L), and MgSO4 (1 g/L)	*S. gilvosporeus* LK-196	Fermentation, temperature—28 °C, RPM – 400, Time – 96 h, pH – 6, Dissolved oxygen was more than 30%	3.94	High shear force harmed the mycelia growth as well as reduce the natamycin production Optimal conditions were found to be using glucose as carbon source at pH 6.0 ± 0.2, while maintaining 30% dissolved oxygen level	Liang et al. (2008)
Glucose (20 g/L), beef extract (2 g/L) yeast extract (2.0 g/L) asparagines (0.5 g/L) and KH_2PO_4 (0.05 g/L)	*S. natalensis* NRLL 2651	RPM – 300, pH– 7.0, Acetic and propionic acid (7:1) were added in the culture media	3.98	The addition of carboxylic acid increase the antibiotic yield and reduce the production time from 96 to 84 h The combination of acetic acid and propionic acid showed stimulatory effect on natamycin production Yield was 113% higher than the control sample (without carboxylic acid supplementation)	Elsayed et al. (2013)
Soybean powder (10 g/L), yeast powder (8 g/L), glucose (20 g/L), and calcium carbonate (2 g/L)	*S. natalensis* F4-245	Incubation temperature – 29 °C, RPM – 220, Time – 144 h, Propanol (0.2%) was added at 28 h		Yield was 17% higher than the control (without propanol) Concentration of amino acid and acetyl Co-A increased by adding propanol, that in turn enhanced the natamycin production	Li et al. (2014)
Glucose (20 g/L), Yeast extract (2 g/L), Beef extract (8 g/L), and DL-Asparagine (0.5 g/L)	*Streptomyces natalensis* NRLL 2651	Inoculation temperature – 30 °C, RPM – 600, pH -7.2	1.58 ± 0.032	Continuous fermentation by adding glucose @ 20 g/l with yield 1.6 and 1.72 times yield higher than batch cultivation in bioreactor and shake flask	Elsayed et al. (2019)

optimize the process parameters to increase the yield of natamycin are listed in Table 2.

The purification of natamycin is carried out by separating it from the fermentation broth using Ultrafiltration. The filtrate containing natamycin was dissolved in isopropanol. Flash column chromatography using silica gel was used for the initial purification of natamycin. Silica gel was used as the stationary phase and a mixture of organic solvents was used for the purification of the natamycin. The second level of purification was carried out using Sephadex chromatography. Large scale Sephadex column was used for purification. The active fractions of natamycin were separated by the Sephadex column using gradient elution. A gradient of acetonitrile and potassium phosphate mixture was used as eluent. Natamycin was monitored using a UV absorption wavelength set at 254 nm. The separated fraction contains the active form of natamycin with 99% purity. Natamycin was concentrated using a crystallizer. The final crystalline natamycin product was successfully

obtained (Atta et al. 2012; Manikindi, 2016; Weinstein and Wagman, 2000).

Toxicity of natamycin

In 1957, the first toxicological study of natamycin for rats, mice, and guinea pigs was reported by Struyk. The study reported the LD_{50} of natamycin for guinea pigs as 450 mg/kg (Struyk et al., 1958). Another acute oral toxicity study was performed on rats (both male and female) and male rabbits. After oral administration, the LD_{50} values of natamycin were reported to be 2.73 g/kg, 4.67 g/kg, and 1.42 g/kg for male rats, female rats and male rabbits, respectively (Levinskas et al., 1966).

Three subchronic toxicity studies with natamycin were performed on animals (two studies were performed on rat and one study on dogs). The study performed on rats (fed on 500 mg/kg of natamycin supplemented diet) showed no deviation in hematological, biological factors and organs weight (Hutchison et al., 1966). In another study performed on rats, reduction in mean body weight and mean food intake have been reported (Levinskas et al., 1966). The No Observed Adverse Effect level (NOAEL) of the study was 45 mg/kg bw/day for Beagle dogs exposed to natamycin for 3 months. The natamycin at the levels of 0, 12, and 25 mg/kg bw/day for 3 months exposure resulted in transient diarrhoea and slight reduction in body weight of the dogs (van Eeken et al., 1984). A two year chronic toxicity study was performed on rats and dogs. Rats were exposed to the different levels of natamycin (0, 125, 250, 500 or 1000 mg/kg diet). Reduction in growth rate and food intake was seen only in the highest dose group (1000 mg/kg of natamycin in diet). The NOAEL was reported to be 22.4 mg/kg bw/day. This study also concluded that there was no significant difference between the natamycin treated groups and their respective control groups in terms of numbers and types of tumors (Levinskas et al., 1963, 1966). In the dog, obesity was observed in the group that was fed with highest dose of natamycin (500 mg/kg of natamycin in diet), whereas 6.25 mg/kg bw/day or less dietary levels of natamycin diet did not affect the body weight and hence considered as its NOAEL (Levinskas et al., 1966).

A reproductive study with natamycin was performed on three generations of rat (Cox et al., 1973). An increased number of foetus born dead and decreased number of foetus born alive (surviving at 21 days at F1 generation) was noticed at highest dose group (100 mg/kg bw/day). Natamycin dietary dose of 50 mg/kg bw/day or less did not affect the growth, reproduction, and pathology. The NOAEL of this study was considered to be 50 mg/kg bw/day.

Rasgele and Kaymak (2013) presented a study on cytotoxic and genotoxic effects of natamycin in mice bone marrow. In this study, different doses of natamycin (20, 400 and 800 mg/kg) were intraperitoneally given to the mice (both male and female) for different time periods (6, 12, 24, 48 and 72 h). Chromosomal assay confirmed that natamycin was not clastogenic (a mutagenic agent) and did not increase chromosome aberrations. Natamycin (400 and 800 mg/kg) treatment induced the micronucleus (MN) formation (in 24 and 48 h) in both male and female mice due to which natamycin might be aneugenic. Decrease in mitotic index (MI) and Polychromatic erythrocyte/normochromatic erythrocyte (at all the concentrations of natamycin) ratio were reported, reflecting the cytotoxic effect of natamycin on mice bone marrow.

Natamycin (400 and 800 mg/kg) can alter the serum levels of liver enzymes (alkaline aminotransferase, lactate dehydrogenase and alkaline phosphatase) and cause degenerative disorders in liver of mice (Rasgele and Kaymak, 2013). The effect of different concentrations of natamycin (13, 18, 23 and 28 μg/mL for 24–48 h) on human lymphocytes was studied. The study concluded that natamycin showed cytotoxicty by reducing the replication index (RI), mitotic index (MI) and nuclear division index (NDI) in lymphocytes of humans (Rencuzogullari et al., 2009). In contrast to the previous study, the natamycin was reported to show low toxicity when ingested. In this study, a Langmuir monolayer (contains 25% sterol and mimics a natural cell membrane in mammals) was prepared to examine the effect of natamycin and reported a negligible or low toxic effect of natamycin (Arima et al., 2014).

To assess the long term toxicity effect of natamycin, groups of 35–40 male and female rats were fed with diets containing natamycin at a concentration of 0, 125, 250, 500, or 1000 mg/kg for 2 years. The animals remained in good health, and their survival was unaffected by treatment. Nausea, vomiting, and diarrhea have been observed occasionally after an oral dose of 300–400 mg of natamycin daily; no changes in peripheral blood cells were observed (Anonymous, 1968). A group of 10 patients with systemic mycoses received oral doses of 50–1000 mg/day for 13–180 days. Nausea, vomiting, and diarrhea occurred in those receiving 600–1000 mg/day (Newcomer et al., 1960). No allergic sensitization occurred among 111 patients being treated with natamycin for a variety of conditions (Gruyper, 1961, 1964). No history of allergic reactions was found in 73 workers engaged for an average of 5 years in the manufacture of natamycin. Natamycin is allowed in many countries for application on the surface of cheese, skin, and specific meat products. In South Africa and China, natamycin is allowed to be used in fruit juices. China also uses natamycin for the surface treatment of baked products. Natamycin's application in fish products,

wine, yogurt, and tinned food is only allowed in South Africa. The Food and Drug Administration (FDA) has authorized the use of natamycin in yogurt.

Safety and tolerance

Natamycin was extensively reviewed in 2003 by JECFA, who concluded that the previously established ADI of 0–0.3 mg/kg body weight was satisfactory and the consumption of treated cheese and meats would not exceed this ADI (World Health Organization, 2002). European Union had permitted the use of clarified natamycin in Ripened cheeses and uncut cheese products at the level of 1 mg/dm^2 for external use only (European Union Commission Regulation, 2015). Several potential metabolites of natamycin like aponatamycin, mycosamine hydrochloride, and dinatamycinolidediole were reported to have LD_{50} values of 3200, 3700, and $>$ 4000 mg/kg, respectively.

Applications of natamycin in food preservation

Dairy products

Dairy products are highly susceptible to microbial spoilage due to favorable composition like high water activity, moderate pH, proteins, salts, etc. Several fungi like *Debaryomyces hansenii, Kluyveromyces lactis, Kluyveromyces maxianus, Penicillium breviocompactum, Rhodotorula mucilaginosa*, and *Yarrowia lipolytica* present in the environment can spoil the dairy products (Delavenne et al., 2013). Therefore, preservatives and food additives play a very crucial role in maintaining the quality and enhancing the shelf life of dairy products. Natamycin has been commonly used in dairy products worldwide. Due to its low solubility, it is generally applied on the food products surfaces to enhance their shelf life. An advantage of nataycin over use of sorbates in the limited migration characteristics into the food matrix (Elsser-Gravesen and Elsser-Gravesen et al., 2013). Cheese is the major dairy product where the application of natamycin plays a role for several years. Cheese is susceptible to mold growth due to the large surface area on exposure to the external environment. There are other factors like extra handling while cutting the cheese, contaminated starter culture, and dirty processing machines, making the cheese favorable for microbial contamination or mold growth (Kure et al., 2004). Mold contamination results in the formation of metabolites that could induce undesirable flavors and aroma to it. Production of carcinogenic mycotoxin by molds is the biggest threat for cheesemakers (Dalie et al., 2010). The most concern in soft cheese is fungal growth during their storage. Ombarak and Shelaby (2017) studied the inhibitory action of natamycin at different concentrations (5–20 ppm) on mold growth in Egyptian fresh soft cheese (Tallaga cheese). Natamycin showed the best inhibitory action at 20 ppm with an increased shelf life of cheese up to 4 weeks. The combination of preservatives is an excellent approach to enhance the shelf life as well as the consumer acceptance of the food products. Natamycin and nisin acted synergistically and increased the shelf of Galoytri cheese (traditional Greek cheese) for more than 28 days by inhibiting the yeast and molds (Kallinteri et al., 2013). The application of natamycin on cheese can be done by spraying, dipping, coating emulsions, and direct addition (Elsser-Gravesen and Elsser-Gravesen, 2013). The coating application of natamycin with the carrier as alginate and zein films were studied on shelf life of Kashar cheese by Küçük et al. (2020). They reported that increasing concentrations of natamycin (100, 200, 500, 1000, 2000, 400 ppm) on films showed higher antifungal activity. For the strains of *A niger and P camemberti* alginate films showed greater inhibitory activity than zein fims in terms of compatibility with natamycin. In adddition, comparison with *A niger* greater inhibition zones formed against *P camemberti* indicating its high sensitivity towards natamycin. However, codex standards define the maximum permitted levels of Natamycin in processed cheese, ripened cheese and cheese analogues as 40 mg/kg in US and 20 mg/kg in Germany (Lee and Paik, 2016)

Probiotics are gaining huge popularity in global markets due to their beneficial health effects for their role in colonizing good bacteria in the gut. Although probiotics are reported to be microbiologically safe, they get contaminated with acid-tolerant fungi. Studies showed that plain yogurt treated with natamycin (10 ppm) was reported to have a shelf life up to 40 days as e yeast and mold growth was reduced (3.36 $\pm$ 0.66 log 10 cfu/g) (Sara et al., 2014). Natamycin at the concentration of 8–10 ppm was shown to reduce the yeast counts up to 65.99 % in vanilla-flavored yogurt stored at 5 $\pm$ 1 °C without altering their native sensory attributes (Dzigbordi et al., 2013). Growth of *Mucor circinelloides* (involved in bloating the container) in yogurt was inhibited by applying 8 ppm of natamycin to yogurt (refrigerated at 15 °C) resulted in shelf-life extension of up to 30 days without compromising the sensory aspects. The application of natamycin as an anti-fungal preservative and its effect on shelf life is detailed in Table 3.

Meat and meat products

The primary application of natamycin are indented for surface treatment of fermented sausages. The codex commission has set maximum permitted levels of natamycin in

Table 3 Application of natamycin in various food products

Food product	Natamycin conc	Target micro-organisms	Load reduction/ microbial population	Shelf life achieved days/ storage temp (°C)	Effect on nutritional/sensory properties	References
Vanilla flavor stirred yoghurt	8 ppm	Yeast	Reduces yeast count by 69.36%	35/ 5.5 °C	Minimal changes in physicochemical properties (Ph, total soluble solids, titratable acidity)	Bakar (2011)
Plain yoghurt	10 ppm	Yeast and molds	Yeast and mold counts were reduced to minimum level (3.36 ± 0.66 $\log_{10}$ cfu/g)	40	Sensory properties were remained good upto 40 days	Sara et al. (2014)
Doogh	10 ppm	Coliform, *Escherichia coli*, lactic acid bacteria, coagulase positive *Staphylococci*, yeast and molds	The microbial count was reduced to zero and fungus count was significantly reduced	60/25	NA	Sarabi et al. (2019)
Khoa	0.5%	Yeast and mold	Reduce the yeast and mold count	40/5	Lower extent of lipolysis and proteolysis was observed	Rajarajan et al. (2010)
Orange Lemon	4.5 mg/mL 5 mg/mL	*Penicillium italicum* *Peniillium digitatum*	Reduce the chances of disease from 90 to 100% Reduce the chances of disease from 90 to 100%	14–21 14–21	Reduced the incidence of decay by 40% Reduced the chances of spoilage	Yİğİter et al. (2014)
Muffins Bread Loaves Pan Bread Pan Bread	4 to 5 μg/cm^2 2.5 μg/cm^2 Natamycin (14 ppm) + vinegar Natamycin (14 ppm) + vinegar + cultured wheat flour (2%)	Yeast and mold	Zero mold growth was observed	60 30 15 30	Inhibits the mold growth efficiently	Delves-Broughton et al. (2010)

cured meat, game meats, dried and processed meat as 6 mg/kg with penetration depth of not more 5 mm (Lee and Paik, 2016). Meat Sausages have a larger surface area, thereby acting as a medium for undesirable mold growth. Specifically in case of fermented sausages where ripening casues decrease in various volatile compounds like carbonyl, carboxylic acids, alcohols, phenols, etc. are formed during smoking. These volatiles not only imparts aroma and flavor to sausage but also acts as an antifungal agent (Ledesma et al., 2016). Sausages are also treated with different preservatives like sorbic acid, potassium sorbate, natamycin, etc. to extend the shelf life and minimize the losses by fungal growth. However, Natamycin showed a better antimycotic effect on sausages that were heat-treated and fermented than sorbates (Pipek et al., 2010). A combination of natamycin, sodium lactate, and nisin was used to suppress mold growth on emulsion-type sausages and extend their shelf life (Jingwei and Yunxia, 2009). A dosage of 300 ppm of natamycin reduced the chances of *Aspergillus niger* contamination by 44.80% on minced beef meat and kept the overall acceptability intact for 8 days (Salem et al., 2016). The combination of several

preservatives like nisin, natamycin and polylysine at the concentration of 0.1, 0.05, and 0.1 shows inhibition ration of 95.1% against the spoilage microbes in ham Xuan et al., 2013). Matari et al. (2017) studied the effect of irradiation and natamycin treatment on yeast and mould counts in the 60 samples of fresh minced meat. They found that samples treated with 0.1% of natamycin showed significant decrease in yeast and mould count at 0, 5, 10 and 15 days of storage at 4 °C. Nevertheless, application of natamycin is well known in the poultry feed industry to control the disease caused by Aspergillus without interfering in the growth performance of broiler.

Fruits and vegetables

Postharvest loss due to fungal infection is a severe threat to various agricultural commodities causing significant financial loss. There are two major postharvest fungi namely *Botrytis cinerea* and *Penicillium expansum,* which are involved in grey mold disease that infects strawberries, apples, and grapes, etc., and blue mold disease. Blue mold disease was caused by the production of mycotoxin (patulin) by *Penicillium expansum* (Dean et al., 2012; Williamson et al., 2007). The concentration of 100 mg/L and 200 mg/L of natamycin prevented grey mold disease in grapefruit and blue mold disease in jujube fruit. Natamycin prevents these two diseases by inhibiting spore germination through permeabilization (He et al., 2019). Dipping strawberries in 20 mg/L of natamycin for 5 min can inhibit mold growth, respiration rate, and fruit rot. The postharvest quality of button mushroom (stored at 4 ± 1 °C) was improved by a combined effect of natamycin (0.5 mM) and 100% oxygen (100 mL/min flow rate) in cold storage. This combination effect was shown to inhibit yeast and mold growth besides maintained firmness, delayed browning, cap opening, and reduced respiration rate. This combination also enhanced the mushrooms' shelf life by inhibiting the spoilage enzymes like polyphenol oxidase, peroxidase, and phenylalanine ammonia-lyase (Jiang, 2012).

Fermented olives are highly prone to yeast and mold growth during fermentation if the conditions (temperature, pH, starter culture, time, etc.) are not appropriately maintained. Due to uncontrolled conditions (i.e. traditional fermentation), a fungal layer may be formed on the exposed area of brine in which olives were preserved and might lead to undesirable olive softening (Arroyo-Lopez et al., 2008). Fermentation of black olives in brine (8% w/v) and natamycin (0.01% w/v) medium inhibits yeast and mold without affecting the other desirable bacteria, helps in more vigorous fermentation with delivered a product with high titratable acidity (Hondrodimou et al., 2011). The chances of *Aspergillus ochraceus* growth in the olive paste were inhibited by using a dose of 350 µg/g natamycin. This also reduced the production of penicillic acid to 96% (Gourama and Bullerman, 1988).

Soaking of mulberry in natamycin solution (0.3 g/L) reduced the decay rate (23.3% on the 10th day), malondialdehyde content, phenylalanine ammonia-lyase, and polyphenol oxidase activity throughout storage (Wen et al., 2019). It also reduced the total phenolic, glucose, fructose, and anthocyanin content. Natamycin was also proved to be beneficial in maintaining the total soluble solids, total acids, sucrose levels, color, and firmness of mulberries during storage. This soaking treatment of natamycin enhanced the catalase, superoxide dismutase, and peroxidase in mulberries.

Bakery products

Baked goods are susceptible to spoilage by mold, the pattern, and incidence of which depends on the food's moisture content. Most of the baked items like cake, pastries, bread, and muffins have high water activity (a_w), due to which they get spoil rapidly. The molds that are associated with the spoilage are *Penicillium* (*P. chrysogenum, P. brevicompactum,* and *P. roqueferti*), *Mucor, Aspergillus, Rhizopus, Wallemia, Chrysonilia sitophila,* and *Eurotium* respectively (Saranraj and Geetha 2012).

Although the baking temperatures are sufficient for the inhibition of fungi, their vegetative cells, and mold spores, nevertheless mold spores can recontaminate the baked product during post-processing (Ponte and Tsen, 1987). Several chemical preservatives (sorbate and propionate) are utilized for the inhibition of molds in baked goods. These preservatives are proved to be ineffective at pH 6 (normal pH of baked goods) and give an inappropriate taste to the baked commodities (Seiler, 1964). In addition, several strains of yeast and mold like *Monascus ruber* and *pencillium roqueforti* has degrade sorbate or propionic acid preservatives. Treatment of baked products with natamycin can enhance the shelf life without destroying the taste and other sensory attributes. Moreover, addition of natamycin in dough would inhibit yeast fermentation. Studies on vacuum packed Psyllo (pastry product) by treatment of chitosan and natamycin on shelf life extension by inhibition of spoilage microflora was studied by Tsiraki et al. (2018). They found that Chitosan at 1.5%, w/v and natamycin at 10 mg/L, w/v showed have significant effect on yeast and mould count by extending the shelf life upto 11 days without affecting the sensorial characteristics. The detailed study on application of natamycin on surface of various baked goods were extensively reviewed by Delves-Broughton et al. (2010). USFDA has set permissible levels for addition of natamycin for various bakery products as 14 mg/kg for bread, 20 mg/kg for tortillas, 7 mg/kg for US

Table 4 Effect of composite films and coatings prepared with natamycin over different products

Composition of coating/composite film	Product	Shelf life (days)	Discussion	References
Natamycin (0.05 mg), 0.2 g Tween 80 (Surfactant), 2.75% (Chitosan), Glycerol (25% w/w to chitosan)	Halloumi cheese	35	Coating inhibits yeast and moulds growth No effects on sensory attributes of the product The brine requirement for the cheese reduced from 15 to 10%	Mehyar et al. (2018)
Starch:glycerol:water (2.5:1:46.5), Natamycin (0.027 g), 0.0068 g Nisin (pH 2)	Port salut cheese	8	The film controlled and inhibited the growth of *Saccharomyces cerevisiae and Listeria innocua* respectively	Resa et al. (2016)
Cinnamaldehyde (5%) cross linked with gliadin films, Natamycin (0.5)	Soft sliced cheese	NA	The cross-linking networks increased the migration of natamycin thereby increased the preservative effect Films showed good barrier against oxygen permeation Film provided antimycotic activity against *Penicillium* species, *Alternaria solani*, *Colletotrichum acutatum*	Balaguer et al. (2014)
Tritical flour (4.0 g/mL), Glycerol (30 g/100 g flour), Natamycin (0.08 g/100 mL of film solution)	Soft cheese	14	Filmcontrolled the growth of *Aspergillus niger* and *Candida albicans*	Romero et al. (2016)
Glycerol (0.5 g), Chitosan (0.5 g), Lactic acid (1% v/v), Natamycin (0.5 mg/mL)	Saloio cheese	27	Coating decreased the growth of yeast and mold to 1.1 log (CFU g^{-1}) Increased the O_2 and CO_2 permeability without altering the water vapour permeability	Fajardo et al. (2010)
Starch, glycerol, water (1.8:1:32.5), natamycin (9.25 mg/dm^2)	NA	NA	Film showed fungicidal activity against *Saccharomyces cerevisiae* Contamination was not observed up to 10 days	Resa et al. (2013)
Whey protein isolate (7%), malic acid (3%), sorbitol (1.5%), nisin (50 IU/mL), natamycin (0.002 g/mL), EDTA (0.1% w/v), Tween 80 (0.15% w/v), sucrose monostearate and sucrose distearate (0.075% w/v)	NA	NA	Film showed the inhibitory effect against *L. monocytogenes*, *Ps. aeruginosa, Y. lipolytic*a and *P. commune* and *P. chrysogenum*	Pintado et al. (2010)
Whey protein isolate (10%), glycerol (5% wt/wt), guar gum (0.7% wt/wt), sunflower oil (10% wt/wt), tween 20 (0.2% wt/wt), lactic acid (6 g/L) and natamycin (0.25 g/L)	Semi hard cheese	60	The edible coating decreased the hardness, water loss and color changes The coating did not altered the fat and salt content Edible coating did not allow the growth of pathogens but allowed lactic acid bacteria to grow throughout the storage period	Ramos et al. (2012)
Chitosan (1.5 g), natamycin (5 g), acetic acid (1% w/w), tween 80 (2% v/v)	Ground cherry	50	The activity of superoxide dismutase and ascorbate peroxidase (reactive oxygen species scavenging enzymes) was enhanced which delayed the senescence period The coating reduces the chances of accumulation of malondialdehyde	Hao et al. (2017)

style muffins. Similarly in China, natamycin residue in moon cakes should not exceed 10 mg/kg.

Packaging material

Natamycin has the antimycotic effect that could be utilized as a coating material or incorporated in packaging material to increase food products shelf life. Various researches have conducted studies on natamycin as an antifungal agent to make edible coatings or composite films for food application are enlisted in Table 4. The major concern while making the composite films (or coating) is the low solubility of the natamycin which reduces the antimycotic efficiency of the films (Medina et al., 2019). The inclusion of natamycin in methyl-β-cyclodextrin could increase the solubility of natamycin by inserting the hydrophobic part of natamycin (C16-C26) into the rim formed by the natamycin/methyl-β-cyclodextrin (N/ME-β-CD) complex

(Yang et al., 2019). This also inhibits the *Botrytis cinerea* in cherry tomatoes.

Hurdle effect

Combining various emerging technologies and bacteriocins in a hurdle approach has been reported to enhance microbial inactivation. Leistner (1978), defines the hurdle concept as minimally processing of food by applying several sub-lethal treatments (hurdles) to achieve microbial stability, rather than focusing solely on one lethal preservation method. The combination of these hurdles results in increasing destruction of the microbial cytoplasmic membrane and preventing cell repair of survivors from treatment. A combination of non-thermal food preservation techniques works synergistically in maintaining organoleptic properties and nutritional quality while still ensuring the safety and stability of the food product. Very few studies are reported on the synergistic effect of natamycin with other non-thermal food preservation technologies. In all these studies, the hurdle effect of natamycin and non-thermal technologies were analyzed on different fruit juices. This combined hurdle of non-thermal technologies and natamycin could provide a potential alternative to the beverage industry to prevent microbial spoilage and improve the sensory and nutritional qualities of fruit juice (Yikmiş and Aksu, 2020; McNamee et al., 2010). Yikmiş and Aksu (2020) demonstarted the effect of combination of natamycin at 12.5 ppm and Ultrasound of 80 W, 26 kHz and 60 amplitude for 5 min on the red grape juice. They found that combined treatment was found to be effective in decreasing the growth of *Botrytis cinerea* by 2.4 log (CFU/mL) without significantly changing the sensory characteristics. Similar dosage were employed on fresh pomogranete juice was reported to reduce the yeast and mold counts from 7.15 ± 0.03 log cfu/mL to not detectable levels at 30 days of storage at 4 °C (Yıkmış, 2019). The combination of Pulsed electric field at dosage of 40 kV/cm for 100 µs (flow rate, 16 mL/min) with 10 ppm of natamycin has shown to cause reduction of 4.2 log of *P. fermentans* in orange juice (McNamee et al., 2010).

More research needs to be carried out to successfully optimize non-thermal techniques in combination with appropriate inhibitory levels natamycin for commercial application to achieve safe, quality and wholesome food. The growth of pathogenic mycotoxin-producing molds can cause economic losses as well as impose some severe health threats to human lives. Worldwide, mycotoxins like aflatoxins (B1, B.2, G1, G2 and M1), ochratoxinA, deoxynivalenol, fumonisins, T-2 toxin, HT-2 toxin, zearalenone and patulin are in increasing concern due to their adverse effects on humans and animals. These major issues could be resolved by utilizing natamycin as a natural preservative because it has a long history of safe use in obstructing the fungal growth on food surfaces (like cheese) and beverages. Natamycin has a GRAS status, it is used in combination with non-thermal techniques to achieve a synergistic effect in terms of efficacy of inhibition of mold growth with minimal change in nutrient and organoleptic properties. Recent researches are taking advantage of the antimycotic effect of natamycin to create composite film and coatings to enhance the shelf life of food so that a minimum amount of preservative would be added to a food product. In the future, natamycin can be very advantageous in the field of food nanotechnology for the development of antifungal nanoemulsion, nanogels and coatings for the food applications. Europen Union as stringent regulation with regard to permissible limits of mycotoxin in spices and condiments being exported from various countries. Future insights on application of natamycin to reduce mycotoxin producing fungus in spices and condiments will be highly constructive.

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Conflict of interest All authors declare that they have no conflict of interest.

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