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Impact of Methicillin-Resistant *Staphylococcus Aureus* (MRSA) in livestock farming, animal products and its mitigation strategies with medicinal plants: A brief review

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ABSTRACT

Methicillin-resistant Staphylococcus aureus (MRSA) is any strain of S. aureus that has developed multiple drug resistance to antibiotics. MRSA could be a highly pathogenic strain of bacteria causing thousands of deaths in humans. Detection of MRSA in foodstuffs of animal origin has been widely reported and has raised public health concerns about the transmission of MRSA from foodstuffs of animal origin to humans. There are many reports of MRSA infections originating from dairy cow's milk, milk products, and livestock along with MRSA transmission between farmers working in livestock farms including people working within the dairy industry. Significant differences in the spread of cases of MRSA infection originating from milk and milk products are reported among various countries around the world. This difference could also be caused by different livestock production management systems in numerous countries within the world. Animal products contaminated with MRSA are going to be a possible transmission of MRSA to humans causing serious health problems leading to tremendous public health concerns. The milking process administered by farmers and the processing of milk for milk products are often risk factors for the transmission of MRSA to humans. Contamination of MRSA in milk and milk products and other animal products could be a major reason for the malady. Several antibiotics of choice are often employed in treating patients who experience poisoning with milk and milk products like fluoroquinolone, tetracyclines, lincosamide, and trimethoprim-sulfamethoxazole. Adherence to good hygiene practices during milking, processing, and handling of dairy cattle can significantly minimize MRSA contamination of milk and dairy products. The objective of this review is to summarize the risk factors for the occurrence and spread of MRSA in dairy herds and to identify the respective knowledge gaps. This review focuses on common causes of MRSA infection and used antibiotics combined with herbal extracts against MRSA and the corresponding mechanisms. Through systematic analysis, we found that herbal extracts combined with antibiotics, such as β-lactams, quinolones, aminoglycosides, tetracyclines, and glycopeptides, could greatly enhance the antibacterial effects of the antibiotics, reduce the dosage and toxic side effects, and reverse MRSA resistance. Therefore, it can be concluded that herbal extracts combined with antibiotics may be a promising strategy to combat MRSA. This review provides a novel idea for overcoming antibiotic resistance.

Keywords: *Dairy products, MRSA, Public health, Antibiotic, Herbal Extract, Mastitis, I. Helenium, Livestock*

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a group of Gram-positive bacteria that are genetically distinct from other strains of *Staphylococcus aureus*. MRSA is responsible for several difficult-to-treat infections in humans. It caused more than 100,000 deaths attributable to antimicrobial resistance in 2019. MRSA is any strain of *S. aureus* that has developed (through natural selection) or acquired (through horizontal gene transfer) a multiple-drug resistance to beta-lactam antibiotics. Beta-lactam (β-lactam) antibiotics are a broad-spectrum group that includes some penams (penicillin derivatives such as methicillin and oxacillin) and cephems such as cephalosporins. Strains unable to resist these antibiotics are classified as methicillin-susceptible *S. aureus* or MSSA.MRSA is common in hospitals, prisons, and nursing homes, where people with open wounds, invasive devices such as catheters, and weakened immune systems are at greater risk of healthcare-associated infection. MRSA began as a hospital-acquired infection but has become community-acquired, as well as livestock-acquired. The terms HA-MRSA (healthcare-associated or hospital-acquired MRSA), CA-MRSA (community-associated MRSA), and LA-MRSA (livestock-associated MRSA) reflect this. Detection of MRSA in foodstuffs of animal origin has been widely reported and has raised public health concerns about the transmission of MRSA from foodstuffs of animal origin to humans [1,2]. There are many reports of MRSA infections originating from dairy cow's milk, milk products, and meats, and MRSA transmission between farmers working in livestock farms including people working within the dairy industry. Significant differences in the spread of cases of MRSA infection originating from milk and milk products are reported among various countries around the world [3]. This difference could also be caused by different livestock production management systems in numerous countries within the world. Milk and milk products contaminated with MRSA are going to be a possible transmission of MRSA transmission when consumed by humans and might be a controversy for public health [4,5,6]. The milking process administered by farmers and also the processing of milk for milk products are often risk factors for transmission of MRSA to humans. Contamination of milk and milk products by MRSA could be a major reason for malady[7].

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Several antibiotics of choice are often employed in treating patients who experience poisoning with milk and milk products like fluoroquinolone, tetracyclines, lincosamide, and trimethoprim-sulfamethoxazole. Adherence to good hygiene practices during milking, processing, and handling of dairy cattle can significantly minimize MRSA contamination of milk and dairy products.

History of MRSA infection in animals

In 1972, MRSA was found in milk from Belgian cows with mastitis. MRSA has since been reported in many diverse species, including dogs, cats, sheep, chickens, horses, rabbits, seals and birds.

ETIOLOGY OF MRSA

The start of methicillin-resistant Staphylococcus aureus (MRSA) began in 1961 in the UK, one year after methicillin antibiotics were introduced into clinical practice to treat cases of penicillin-resistant Staphylococcus aureus infection within the early 90s MRSA began to become a heavy health threat within the U K and also the U S . Resistance is encoded by a mobile genetic element, referred to as staphylococcal chromosomal cassette mec (SCCmec), carrying the genes encoding mecA and mecC, both of which encode penicillin-binding protein 2a (PBP2a). B-lactam antibiotics bind to PBP, acting within the synthesis of cytomembrane peptidoglycan, which causes bacterial cells to lysis. But PBP2a incorporates a low affinity for β- lactam antibiotics, so peptidoglycan synthesis activity continues in MRSA strains, despite the presence of varied β-lactam inhibitor combinations. The mecA coding gene is identified in one amongst eleven SCCmec (I-XI) types, which carry 5 differing types of mec-coding gene complexes, like mecA and their regulatory genes mecR1 and mecI, and eight differing types of the ccr gene complex. MRSA was obtained from the combination of the SCCmec element carrying the mecA gene encoding the methicillin-sensitive Staphylococcus aureus. a brand new MRSA coding gene named mecC (originally named mecALGA251) by the International Social Unit (IWG) was discovered within the SCCmec element classification, which was isolated for the first time from a sample of dairy cattle milk within the UK in 2011 and this mecC coding gene was also isolated from human clinical samples in Denmark, Scotland, and therefore the UK in 2014.

Staphylococcus aureus is considered a contagious mastitis pathogen that enters the mammary gland through the teat canal. In most cases, there is one predominant *S. aureus* strain that affects multiple cows and spreads from cow to cow within dairy herds [7,8]. Thus, the primary risk period for *S. aureus* transmission is during the milking process. The usual routes of transmission are milkers' hands, udder cloths, and milking equipment such as seat liners.

The overall prevalence of mastitis pathogens is extremely variable and differs between herds and regions. To date, the foremost common pathogens causing clinical mastitis seem to be environmental streptococci and coliform bacteria followed by S. aureus [9-12]. In some studies, S. aureus remains the foremost prevalent pathogen isolated from mastitis milk samples [13].

Consequently, culling might be the only chance to remove MRSA from dairy herds. In addition, MRSA in dairy cows is of human health concern since people working on dairy farms were shown to carry similar MRSA strains as their cows. MRSA transmission from cows to consumers of milk seems unlikely due to commonly practiced heat treatment.

However, the consumption of raw milk is a possible source of infection [14-20]. This might be an issue since many dairy farmers and their families consume raw milk and the number of raw milk vending machines is increasing[21,22]. Thus, MRSA in dairy herds represents a possible health hazard for both humans and cattle.

MANAGEMENTAL EFFECT ON MRSA IN DAIRY FARM

Poor management of dairy farms and inappropriate use of antibiotics can increase the incidence of MRSA in cow's milk. Earlier studies have reported cases of hospital-related MRSA infection (Hospital acquired Methicillin-resistant Staphylococcus aureus / HA-MRSA) and Community-acquired Methicillin-resistant Staphylococcus aureus (CA-MRSA) infections. Recent studies have found another group of MRSA, namely MRSA related to livestock (Livestock associated with Methicillin-resistant Staphylococcus aureus / LA-MRSA). LA-MRSA colonization of dairy cows has been shown to be a risk factor for veterinarians, breeders, employees of the dairy processing industry, and people in close contact with dairy cows [23-30].

LA-MRSA infections in humans, originating from milk and milk products, can include skin and soft tissue infections starting from mild to severe. Expression of methicillin-resistant Staphylococcus aureus may complicate antibiotic treatment. The prevalence of LA-MRSA must be done from the start before the transmission of food from animal origin to humans can eventually become a threat to human health. Studies on the spread of MRSA that are sourced from foodstuffs of animal origin like milk and dairy products can limit the threat of MRSA infection cases to human health.

LA-MRSA infections in humans, originating from milk and milk products, can include skin and soft tissue infections starting from mild to severe[31,32]. Expression of methicillin-resistant Staphylococcus aureus may complicate antibiotic treatment. The prevalence of LA-MRSA has to be done from the start before the transmission of food from animal origin to humans can eventually become a threat to human health. Methicillin-resistant Staphylococcus aureus (MRSA) Expression of resistance to penicillinase-stable antibiotics penicillinase, commonly remarked as “methicillin resistance” or “oxacillin resistance”, in staphylococcus aureus bacteria is manifested as bacteria that are immune to all β-lactam class antibiotic agents including carbapenems and cephalosporins[33].

Prevalence and Epidemiology of MRSA in Dairy Herds

The detection of *S. aureus* in dairy cows is demanding due to its intermittent shedding patterns in milk (34-36]. Comparison of MRSA prevalence studies is additionally challenging because of differences in types of samples, inoculum volumes, (pre-) enrichment, and detection methods. MRSA prevalence (*mecA*/*mecC*) in bulk tank milk (BTM) has been previously reported to range from 0% to 20%. A study from Sicily found a significantly higher MRSA prevalence of 43.8% in BTM from dairy farms [37-40]. This high prevalence was presumably caused by the preselection of dairy farms that had tested positive for MRSA in previous years. The majority of studies (76%) are from Europe. MRSA prevalence was significantly lower in BTM samples from the United States with ~0.3% (3/980) [41,42]. Compared with Europe, MRSA prevalence was also lower in pig herds from the United States [43-45] The MRSA prevalence within individual dairy herds prevalence of MRSA was 39.7% (31/78) in Japan, 44% (11/25) in Sweden, and 60% (n = 33/55) in a herd from Italy[46].

MRSA in food of animal origin

Many researchers who have reported finding MRSA in foodstuff of animal origin around the world have found varying prevalence in beef, lamb, chicken, pork, rabbit, wild boar, eggs, milk, dairy products, and fish. In addition, it is important to emphasize that the MRSA strains found in humans have also been found in food, due to the contamination of food consumed by humans. It also depends on the epidemiological factors of the geographic area of each country, about 0.7-1.5%ofhumans in the world have been infected with MRSA.

MRSA IN MILK

The incidence of MRSA infection from cow isolates with mastitis has been widely studied and also the prevalence rate remains low. Following the primary reports of MRSA from cows with mastitis [47-51], sporadic cases of MRSA infection in dairy cows are detected among Staphylococcus aureus isolates from dairy cows with subclinical mastitis and clinical mastitis. in an exceeding study conducted in Korea [52], MRSA of cow's milk was found with an isolation ratio of 0.18%. during a report on farming in Belgium, the very best percentage of MRSA identification was found in breastfeeding dairy cows at 15% [53-56], these cows did have a previous history of MRSA infection. Until now, the prevalence of MRSA identification in dairy cows with mastitis continues to be low, considering the period since MRSA was first discovered in dairy cows and shut contact with farmers with dairy cows' udders. during a study in Germany, the very best proportion of positive MRSA samples was found within the nose swabs of calves, namely 45%, and therefore the lowest proportion of positive samples of MRSA in bulk tank milk was 4.1%, most of the MRSA isolates came from the spa type t011 and t034 belonging to the CC398 clonal complex [57-60]. The invention of LA- -MRSA CC398 in tank milk proved that MRSA was colonized in dairy cows' udders and is a possible explanation for subclinical mastitis cases in dairy cows[61]. Close contact between dairy cows and humans can cause strain transfer between dairy cows and humans through milk production. in an exceeding study in Hungary, identical MRSA isolates were found.

Risk Factors for the Occurrence of MRSA in Dairy Herds

Improper milking hygiene: Proper milking hygiene and particularly the employment of postmilking teat disinfectants are important control strategies for S. aureus mastitis [62-65]. within the past several decades, progressive use of milking hygiene procedures and other recommendations from the National Mastitis Council 5- and 10-point plan have led to a discount in the prevalence of contagious mastitis pathogens in many countries[66-69].

A recent case study from Brazil reported a high MRSA prevalence (12.2%) in mastitis milk samples from one herd [70]. The authors observed an absence of pre- and post-dipping procedures, udder towels were used on quite one cow, and also the use of gloves was inappropriate. On the farm with the very best overall MRSA prevalence [70] in Italy, milkers weren't using gloves in an exceedingly study from Sicily, the milking hygiene score was negatively correlated with MRSA prevalence. The authors concluded that improper milking hygiene procedures are also a risk factor for MRSA transmission within dairy herds [71-75].

Transmission of MRSA

MRSA strains can spread from animals to humans and from humans to animals.

MRSA transmission usually occurs through direct contact, often through contact with animals or those that are infected or colonized with MRSA [76-79] the extent of spread of MRSA within the general population usually varies depending on the geographical conditions of every country [80-82] within the hospital, patients who are infected and colonized with MRSA are going to be the most reservoir of transmission of MRSA, which is sometimes easily spread from patient to patient by hand touch [80]. The route of transmission of MRSA is also almost like that of other strains of Staphylococcus aureus, but there could also be differences in the efficiency of host colonization after exposure. There are many other factors within the transmission of MRSA transmission like through contaminated surrounding air, saliva splashes, and nasal discharge. Animals also act as reservoirs for MRSA transmission and might transmit MRSA to humans and other animals. Several styles of MRSA exhibit host specificity and are widely in contact with certain geographic areas. Therefore, MRSA transmission is more frequently related to animals than to humans. LA-MRSA CC398 is the sort of MRSA that's most related to intensive-reared animal-based food-producing livestock, especially dairy cows. Although LA-MRSA CC398 was found to colonize livestock without causing clinical symptoms, it could cause clinical infection with MRSA in animals. LAMRSA CC398 colonization has been found in many breeders, members of the family of farmers, employees of the food processing industry, and veterinarians. The spread of MRSA may also occur in personnel and other animals including cats, dogs, and horses, between pets, in veterinary hospitals, and in households. In some cases, pets can act as a source of MRSA infection in humans. Foodstuffs of animal origin including milk and milk products contaminated with MRSA and also the handling process that contaminates MRSA in milk and milk products are potential transmission transmissions. within the case of patients hospitalized thanks to illness, MRSA contamination can spread MRSA to other patients or healthcare workers. Reports within the Netherlands, MRSA cases associated with contaminated milk infected 27 patients and 14 hospital workers and caused 5 deaths. an individual who consumed milk and milk products was found to own colonized the MRSA strains just like the MRSA strains found in milk and milk product samples. Contaminated milk and milk products may result in cases of septicemia because of MRSA, which may then be passed on to other patients within the hospital. transmission mechanism that's contaminated with MRSA also plays a vital role in the spread of MRSA. Given the abundance of evidence for the presence of MRSA strains in dairy cows, it'll raise public concern about MRSA contaminants found in milk and dairy products. However, there's no detailed description of the direct association of MRSA in animal and human foodstuffs, although there are reports of increased MRSA contamination in milk and milk products, furthermore because of the incidence of MRSA infection within the community. Further investigations are needed to see the the true role of milk and dairy products in animal-to-human transmission of MRSA transmission. Another aspect of MRSA that contaminates milk and dairy products is that MRSA often carries enterotoxin (SE) genes like SEA, SEB, SEC, and SED which are often the explanation for malady.

Effect of medicinal plants as a therapeutic option for MRSA

Natural products including medicinal plants have contributed immensely to human health, well-being, and the development of novel drugs. They are useful natural blueprints for the development of new drugs to be used for the treatment of disease (commonly in developing countries and Europe).

Medicinal plants can be valuable therapeutic resources. In numerous developing countries, including Nigeria, 80% of patients use homemade phytomedicines to treat infectious diseases. Despite the availability of modern medicine in some communities, the use of medicinal plants has remained high due to their efficacy, popularity, and low cost. They also represent sources of potentially important new pharmaceutical substances since all the plant's parts are utilized in traditional treatment and can, therefore, act as lead compounds. The applications of phytomedicines for human well-being and as blueprints for developing novel useful drugs have drastically increased worldwide in recent years. The emergence of multidrug-resistant infectious agents associated with over- and inappropriate use of antibiotics has necessitated the World Health Organization (WHO) to acknowledge and pronounce the urgent need to develop novel antimicrobials and/or new approaches to tackle the menace caused by them around the globe; these have subsequently led to the resuscitation of the interest in medicinal plants... The most common bacteria that have been used in susceptibility tests with numerous medicinal plants include *Staphylococcus aureus,* methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Pseudomonas aeruginosa Helicobacter pylori,* etc. Presently, numerous studies have reported the antibacterial activity of many plant extracts against MRSA. Earlier studies found fifty-one (51) plants with anti-MRSA activities from thirty-five (35) families were mentioned. The minimum inhibitory concentrations (MIC) values of the plants on the tested MRSA strains were between 1.25 µg/ml to 6.30 mg/ml. Twenty-nine of the plants had MIC values < 1.0 mg/ml while the remaining twenty-two MIC values were > 1.0 mg/ml but < 8.0 mg/ml. Extracts exhibiting activities with MIC values below 8 mg/ml are widely accepted to possess some antimicrobial activity while those with values below 1 mg/ml are considered noteworthy. However, most of the plants in this review were not tested on *S. aureus* strains with reduced vancomycin susceptibility.

The solvents used for the medicinal plant extraction in this review were ethanol and methanol. This is probably because alcoholic extracts have higher antimicrobial activity than aqueous extracts. It has been reported that ethanolic extracts have higher antimicrobial activity than aqueous extracts because of the presence of higher amounts of polyphenols. They are more efficient in cell walls and seed degradation causing polyphenols to be released from cells. Also, the enzyme polyphenol oxidase degrades polyphenols in water extracts but is inactive in methanol and ethanol. Moreover, water is a better medium for the growth of microorganisms than ethanol. Although, methanol is more polar than ethanol it is not frequently used for plant extraction due to its cytotoxic nature which may give incorrect results.

Extracts of medicinal plants are rich in phytochemicals. Phytochemicals or secondary metabolites are natural protective agents biosynthesized by plants against external stress and pathogenic attack. They are crucial for plant defenses and survival. They have been divided into several categories: phenolics, alkaloids, steroids, terpenes, saponins, etc. They exhibit other bioactivities such as antimutagenic, anticarcinogenic, antioxidant, antimicrobial, and anti-inflammatory properties and are therefore responsible for the medicinal potential of plants.

Herbal medicines have gained popularity throughout the world as alternative therapeutics for controlling common infections.

The emergence of multiple drug-resistant strains of bacteria and the high cost of synthetic compounds has directed researchers to look for new therapeutic agents including medicinal plants. Many laboratories are currently involved in documenting the application of medicinal plants against infectious and noninfectious diseases through in vitro and in vivo systems. Earlier studies have described in vitro anti-MRSA potential of 29 herbs, of which *Althaea officinalis*, *Ziziphusjujuba*, *Cordia latifolia* , and *Thymus vulgaris* were found superior in controlling MRSA. MRSA is a super-drug-resistant bacterium. Developing new drugs or therapeutic strategies against MRSA is urgently needed. Increasing evidence has shown that herbal extracts and antibiotics can have synergistic effects against MRSA. Elecampane (*Inula helenium L.*) is an herb originating from Europe and parts of Asia. Most commonly, elecampane is used to move phlegm which causes respiratory issues, and eliminate intestinal bacteria to improve stomach issues. The root and sometimes the rhizomes from two- to three-year-old elecampane plants are used in herbal medicine and formed into teas, tinctures, medicinal honey, syrup, capsules, extracts, or sweet confections. Elecampane is also used to provide flavor in foods and beverages and to lend fragrance to beauty products. This herb contains a large amount of the prebiotic soluble fiber inulin, which supports a healthy intestinal tract. Dietary inulin is found in many foods (including whole wheat, onions, and garlic) and is said to slow digestive metabolism and reduce blood glucose spikes in people with diabetes. Inulin from chicory root is now being added to many foods to boost their soluble fiber content.

Because of its carminative, anti-spasmodic, anti-inflammatory, and antimicrobial properties, Elecampane is also can be used to soothe nausea, flatulence, and diarrhea. Elecampane also contains the phytochemicals alantolactone and iso-alantolactone, which are said to address worms such as hookworm, roundworm, threadworm, and whipworm, which can also cause digestive issues.

Soothe Pain and Inflammation

Some herbal medicine practitioners say elecampane could be used to easepain stemming from lung diseases such as asthma, bronchitis, and whooping cough. Since elecampane is said to prevent coughing, this herb may also relieve symptoms of tuberculosis. Elecampane is said to loosen phlegm in these situations so a person will cough and expel it from the body. Studies have also found sesquiterpene lactone compounds in the herb have an anti-inflammatory effect.

Fight Bacteria

Elecampane has astringent and antimicrobial properties, which may act against bacterial infection. Elecampane has also been said to promote sweating in individuals who are attempting to rid their bodies of bacteria or a virus. While a 2009 study found the antimicrobial compounds of elecampane as a potential treatment against Methicillin-resistant Staphylococcus aureus (MRSA),as many herbs do, elecampane may interfere with normal levels of blood pressure. Elecampane often causes drowsiness due to its ability to affect the central nervous system.

Conclusion

The risk factors for the transmission of MRSA into dairy herds are direct or indirect contact with pigs and humans carrying MRSA. Moreover, improper milking hygiene procedures enhance the spread of MRSA within herds as is well known for MSSA.

There is some evidence that conventional dairy farms and farms with a larger herd size are more often affected by MRSA. The association of antimicrobial exposure and MRSA prevalence in dairy herds needs to be further investigated. High amounts of β-lactam antibiotics have been used for dry cow treatment and mastitis therapy on dairy farms. Nevertheless, MRSA prevalence is low in dairy cows. Furthermore, it is not known whether additional risk factors for *S. aureus* transmission in dairy herds differ from those of MRSA. A higher somatic cell count in milk is probably not a reliable indicator for the occurrence of MRSA in dairy herds. The risk of food-borne zoonotic MRSA infections through consumption of milk seems to be low. Milk is usually heat treated before marketing and consumption and MRSA prevalence is low in milk from dairy cows. However, MRSA prevalence should be carefully monitored, since some studies suggest increasing levels of resistance. Therefore, segregation and culling of infected cows often remain the only option for removing MRSA from dairy herds. In conclusion, we stress the need for continuous MRSA monitoring in dairy herds and the development of MRSA prevention strategies.

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