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Livestock welfare and production: stress control via phytogenics

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Abstract

A supply that meets the demand is one of the key factors in any industry. Therefore, various attempts have been made in livestockindustryto satisfy the demand. Basically, livestock population has been substantially increased, and the methods such as breeding and use of antibiotic and inorganic feed additives have been employed to improve productivity. Such methods have resulted in unprecedented increase in productivity of the modernlivestockindustry although they are not likely to satisfy the steep increase in livestock demand in the future. Moreover, these methods have resulted in various problems with respect to antibiotic-resistant bacteria, environmental pollution, and livestockstress andwelfare. As a potential solution to these problems, phytogenic feed additives have received attention. Phytogenics have been used for medicinal purposes, and as each plant species exhibits diverse and unique efficacy, they are argued as the optimal material to replace the conventional methods inlivestock husbandryagainst various livestock stresses.

Keywords: livestock, stress, animal welfare, phytogenics

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1. INTRODUCTION

Livestock husbandry is known to have begun around 11,000 years ago[1], which is 1/30 of the time since the beginning of mankind; *Homo sapiens* appeared approximately 300,000 years ago[2]. The population of livestock increased as humans flourished and agriculture and livestock industries advanced[3].

Due to the industrial revolution during the 19th century, the human population surged to 1.17 billion, but the supply of food was not sufficient to meet the increased demand[4]. Then, at the end of the 19th century, Fritz Haber and Carl Bosch developed the technology of nitrogen fertilizer production that led to exponential increase in crop production and the subsequent increase in livestock population[5]. In the 20th century, based on the discovery of penicillin by Alexander Fleming and advancement in medical science, human population increased by over twofolds. Currently, at a phase less than 20% of the 21st century, the population has already increased by three times compared with that of the 20th century. By the2050 years, human population is expected to reach approximately 10 billion to face a critical moment in history once again[6-8].Every second, various animals are sacrificed as food source globally. According to the Food and Agriculture Organization (FAO), in 2003, approximately 52 billion livestock were slaughtered, and the steep increase in human population is expected to require approximately 100 billion livestock by 2050 [7].

To satisfy the huge demand, livestock breeding has gradually started to resemble a factory and rely on overcrowding, producing livestock population seven to ten times the human population. Therefore, cultivation of crop also has increased, and currently, the supply of crops, such as beans and corns, to livestock exceeds the supply to humans, as they are the crops most heavily used as livestock feed. The rapid population growth of humans and livestock accompanies the problems of food supply, environmental pollution, and livestock welfare. According to the Food and Agriculture Organization (FAO), among the lands that occupy 29% of the Earth’s surface, only 71% has been shown to be habitable, and only 1% of these habitable lands is occupied by cities, while more than 50% is devoted to agriculture and livestock industries. The livestock industry occupies 77% of those lands; in other words, the area of land used for livestock is approximately 40 times that used for cities[9].Although such a large proportion of land has been shown to be used for livestock, the conditions for livestock husbandry are deteriorating in most animal farms. The extreme overcrowding of animals caused by housing as many animals as possible in the limited area of land making animals to spend their life in a space where they cannot even move freely. Moreover, the large areas of pasture used in livestock husbandry are turning into desolate lands[10, 11], and the livestock produce80% of the greenhouse gases agriculturally, thereby accelerating environmental pollution and global warming [12].

The limitations of increasing the population of livestock to satisfy the demand have become clear today, and there is a need for ways to improve productivity rather than population. The most common traditional method of increasing productivity is breeding, which requires a long period to acquire dominant traits through several generations, and it is expected to face challenges in meeting the surging demand.

Recent attempts of using gene editing techniques have enabled faster acquisition of dominant traits than breeding; nonetheless, consumers have been avoided because of the lack of complete validation of stability [13]. Both breeding and gene editing are difficult to respond to various stresses that occur suddenly in the livestock husbandry, and they can be susceptible to disease by reduced genetic diversity [14]. In addition, growth promoting hormone (GPH) and antibiotics have been used, but serious problems have been reported both in the environment and in the human body due to component residues and antibiotic resistant bacteria (ARB) [15] . However, after the ban on the use of growth promoting antibiotics (GPA), livestock mortality and the incidence of various disease incidence also increased in livestock farms [15].

In this milieu, the market for feed additives for GPA and GPH substitution has grown significantly [16]. Vitamins, nutrients, antioxidants, and probiotics have been used as feedstock additives for Livestock, and phytogenic functional feed additives (PFAs) using plant have been attracting attention as a broad utility value [17]. Currently, medicinal plants are estimated to be about 35,000 [18], and PFAs can have various effects such as anti-inflammation, antioxidant, anti-microbial, and growth promoting depending on the plant's active substance [19].Therefore, PFAs are one of the most likely methods to replace GPA and GPH in response to various stresses in cattle breeding [17, 19]. In addition, it can act as prebiotics or regulate the growth and activity of specific microorganisms, which can be a solution to environmental pollution problems by reducing pollutant production such as nitrogen and gas from livestock [20].

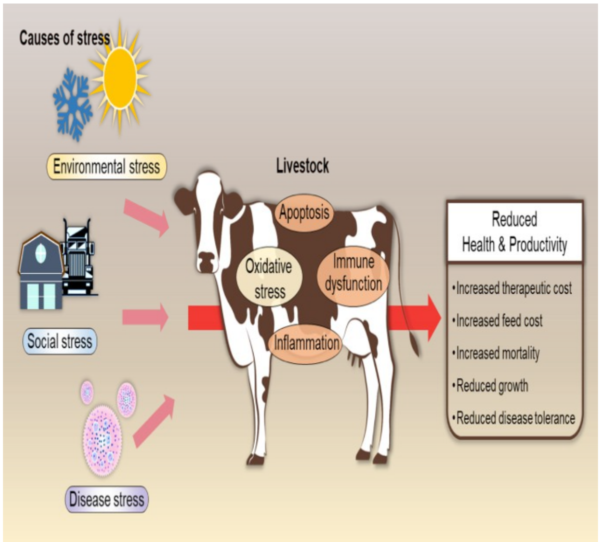
Thus, in this chapter, the various stresses livestock experience and the traditional methods to improve livestock productivity will be compared. Furthermore, the potential benefits of using PFAs will be discussed.

2. Stress in livestock husbandry

In the modern livestock industry, the livestock spend their entire life in a narrow cage without having to search for food as they are provided the feed. Such living conditions lower the immunity and disease resistance of livestock to fall below those of wild animals[21].The increased crowding during breeding and various related factors cause livestock homeostasis to lose balance, thereby, increasing livestock stress. Stress can be broadly divided into three categories: social stress[22] caused by factors such as change in habitat and isolation; environmental stress[23] caused by temperature, noise, humidity, and air quality; disease-related stress. Among them, social stress is receiving more emphasis in livestock industry, and correlation between livestockdisease and productivity has been reported[22]. Studies on environmental stress began during the early 20th century to prove its effects on livestock adaptability, productivity, and disease, while suggesting various potential solutions[24]. Nonetheless, in small- and medium-sized farms, where it is difficult to control the environment, and in the developing countries, the methods so far have not produced appropriate responses to environmental stresses, which are faced with growing challenges due to rapidly changing environment.

Livestock stress exerts negative effects on immunity, disease resistance, various metabolic processes, feed intake, and reproductive capacity of livestock. Thus, increasing the susceptibility to disease stress, ultimately, deteriorating livestock quality and productivity (Fig.2.1.). Livestock stress induces the secretion of cortisol from the adrenal cortex, and although cortisol might facilitate blood glucose and energy metabolism to benefit the livestock, excessive cortisol secretion due to persistent stress might lower their immunity and disease resistance. Besides cortisol, increase in various stress factors, such as reactive oxygen species (ROS), might negatively affect livestock health and productivity. Livestock stress has long been a major problem in livestock industry, but a novel solution is still required. Therefore, the cause and mechanism behind the development of livestock stress should be understood first.

Fig.2.1. Stress and livestock health



2.1. Social stress

Humans are social animals prone to social stress caused by relationship with other animals and the environment, and studies have reported correlations between social stress and various diseases ranging from a mere headache to severe conditions, such as cancer. However, studies have not focused intensively on social stress in animals. The recent increase in the number of companion animals and people's interest in animal welfare have led to studies on social stress in livestock, and the cause-and-effect relationship between social stress and livestock productivity has steadily been identified[22]. Similar to humans, livestock are also exposed to social stress caused by changes in group members, solitude, overcrowding, and transportation. Social stress can be manifested through various symptoms, and in the modern society, hormonal imbalance has been pointed out as the main cause. In particular, cortisol, the stress-inducing hormone, and oxytocin, the stress-buffering hormone, are regarded as the two crucial social stress-regulating hormones[25].

Social stress in livestock can be subdivided into: stress due to space, stress between one animal and another, and stress between livestock and humans. When an animal is isolated in a space that is either too small or large in relation to its radius of activity or when it is placed in an exceedingly poor breeding condition, the animal might suffer social stress due to space. Further, the stress between one animal and another may be induced upon separation of the young from its mother, pecking order, competition for food, and formation or separation of a group. Finally, the social stress caused by humans can have a large effect on livestock, and it is often due to unwanted contact or transportation. The transportation of livestock induces social stress through noise, vibration, and change in environment. The mammalian ear comprises three structures: the outer ear collects sound and the middle ear vibrates and transfers the sound wave to the inner ear where it is conveyed by neurons to the cerebellum to complete the process of hearing[26]. Although the structures are similar, the hearing ability differs according to species, and livestock have far more sensitive hearing than humans despite less ability of sight. They can perceive sounds that humans cannot hear, and what may not be a noise to humans can be felt as a noise by livestock. In particular, the first noise a live stock experiences might induce fear in the animal and hence become a social stress[27]. The livestock are more sensitive to high frequency waves than humans; an adult human can hear sounds of frequency between 20 Hz and 20 kHz on an average, whereas, the livestock such as cattle and porcine can hear sounds of up to 37–45 kHz[28, 29]. As a social stress, noise can facilitate the secretion of stress hormones that can induce abnormal behavior in livestock as well as cardiovascular dysfunction, oxidative stress, and inflammation. As it might also affect the reproductive capacity of an animal, noise can have deteriorating effects on livestock welfare, health, and productivity[30].

Social stress can be prevented by providing adequate breeding space, allowing grazing, supplying high quality feed, and blocking the source of noise. However, in the developing countries or in animal farms close to cities, such solutions are difficult to implement wing to the problems associated with cost and space. Thus, a way to enhance stress resistance in livestock by regulating their stress hormones is required.

2.2. Temperature stress

Both high and low temperatures can have negative effect on livestock productivity[31, 32]. Most livestock animals maintain slightly higher body temperature than humans (36.5–37°C);porcine maintains 38.7–40°C[33], poultry 40.6–41.7°C[34], and cattle 38.6 °C[35].This makes them more susceptible to cold; therefore, the breeding temperature should be maintained higher than the surrounding environment. Furthermore, as most livestock animals lack organs such as sweat glands to maintain body temperature, their heat stress tolerance is weak [36]. Thus, temperature control is crucial in livestock husbandry, but it is faced with challenges due to the recent global warming and abnormal climate causing steep changes in temperature. In particular, the developing countries in tropical regions, such as Africa and South America, have suffered severe damages due to heat stress[37].

Heat stress is regulated by factors such as ambient temperature, radiant heat, humidity, wind speed, and the contact between livestock animals. The higher the temperature, humidity, and the contact between livestock animals, and the lower the wind speed, the greater the heat stress[38]. Heat stress decreases livestock feed intake, and excess and persistent heat stress induces energy depletion and the subsequent decrease in growth, breeding, and milk yield of an animal[39]. In addition, increased body temperature reduces the blood flow into organs, causing organ dysfunction while inducing decreased immune function and inflammation. Through this process, heat stress can have serious effect on livestock health and productivity. In the USA, a developed country with the world's largest livestock industry, heat stress has been estimated to cause a loss of approximately 2.4 billion USD each year across all animal industry, and the loss is expected to increase with the increase in temperature[40]. To solve the problem, suggestions have been made to build shades in breeding farms or to lower the temperature and promote air circulation[39].However, it is difficult to lower the temperature in the developing countries in tropical regions and in large pasture farms in the USA owing to the problems associated with cost.

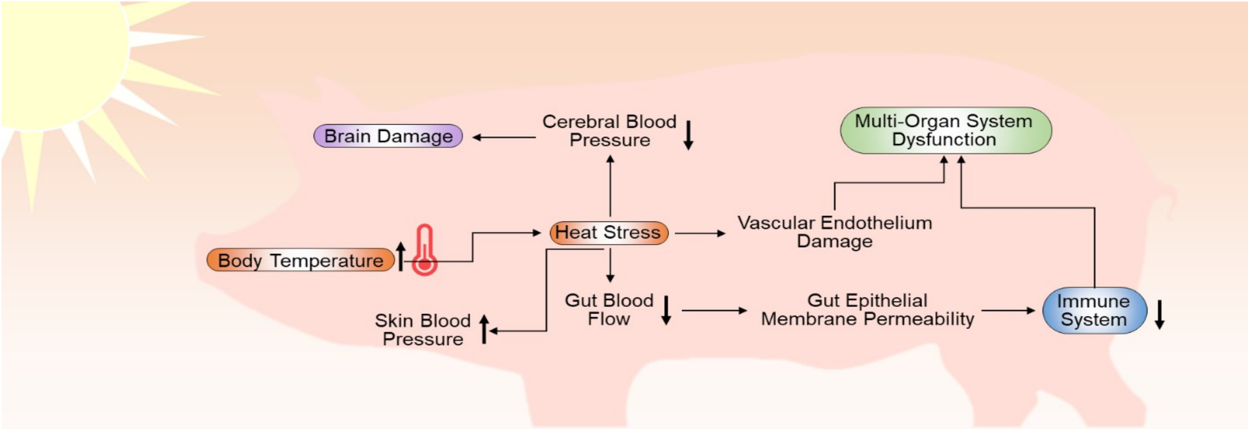


Fig.2.2. Symptoms caused by heat-stress.

The symptoms caused by heat stress were once considered to be due to decreased feed intake, and attempts were made to solve the problem by providing high-nutrient feed.However, recent studies have showed that, although livestock lowers energy metabolism involving lipids, proteins, and carbohydrates to increase the body temperature and inhibit the production of ROS to minimize heat stress regardless of feed intake, persistent heat stress induces energy depletion and oxidative stress leading to cell death [41]. Thus, a method to enhance heat stress tolerance in livestock to promote energy metabolism and reduceoxidative stress has attracted attention in order to regulatelivestock heat stress. Therefore, an increasing number of studies are focusing onheat shock proteins (HSPs) as heat stress tolerance regulator.

The HSPs are chaperon proteins that promote the refolding of damaged proteins, whose expression is induced byheat or other forms of shock. The discovery was made in the mid20th century, and it has been shown that heat stress or ROS production due to heat stress activates the heat shock factor (HSF), which induces the expression of HSPs. Among the HSPs, HSP70 and HSP90can activate anti-inflammatory metabolism inmammals andlivestock to protect them against cell damage [42, 43]. Thus, it is possible to enhance heat stress tolerance by regulating the expression and activity of HSF and HSPs in livestock under heat stress conditions.

2.3. Oxidative stress and inflammation

Oxidative stress occurs when intracellular ROSincreases excessively or when antioxidant metabolismis inhibited, altering homeostasis [44].The ROS are defined as reactive chemical species containing oxygen, and they are produced naturally at a constant amount in most organisms during aerobic respiration[45]. In mammals, the highest quantity of ROS is produced during mitochondrial metabolism. Although ROSperform useful functions related toimmune response, signaling, and transcription factors, excessive production and the resulting high reactivity converts the ROS into oxidants in the body, which function as toxic substances inducing aging, inflammation, and cell death [45]. ROS-induced oxidative stress destroys the lipid chains and increases cell membrane permeablility [46], while causing amino acid modification, enzyme in activation, and proteolysis[46]. It also mediates the oxidation of deoxyribose in DNA, separates the strands, removes the nucleotides, and damages the DNA bases[46]. Reactive oxygen species might also accumulate excessively in the mitochondrial membrane to cause abnormal mitochondrial functions[47]. The body's defense against such extensive damages caused by ROS is called antioxidant network. The antioxidant network, in the order of anti-inflammatory strength, comprises anti-inflammatory enzymes including superoxide dismutase (SOD), glutathine peroxidase (GPx), and catalase (CAT), and organic compounds, such as glutathione (GST), coenzyme q10 (CoQ10), and vitamins (E, A, and C)[48]. In plants, diverse secondary metabolites that are not found in animals may be produced[49].

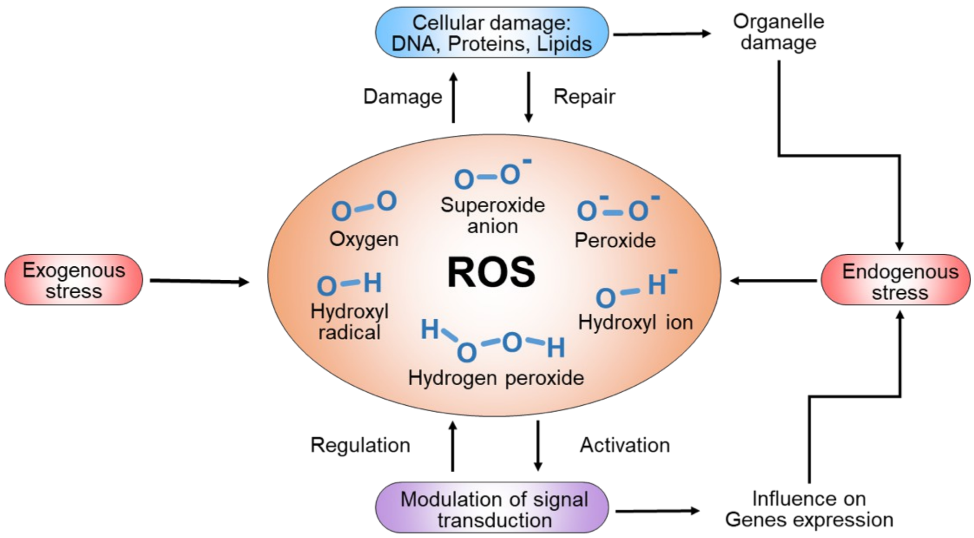


Fig.2.3. Reactive oxygen species and oxidative stress.

The control of oxidative stress in livestock is also crucial as it might arise from all forms of stress—social, environmental, and disease stresses. In humans, increased oxidative stress might cause structural damages at the cellular level as well as functional disorders that induce the pathogenesis of various metabolic diseases, such as diabetes, hypertension, aging, and cancer[50]. In livestock, oxidative stress might also cause various diseases and lower productivity. In dairy cattle, repeated gestation and lactation for milk production and breeding consumes a considerable amount of energy, which increases metabolism and ROS accumulation. Thus, oxidative stress in dairy cattle weakens immunity and causes mastitis, which deteriorate dairy cattle health, milk quality, and productivity[51]. In race horse, oxidative stress is caused by strenuous exercise causing muscle injury, vasoconstriction, and arthritis that have adverse effects on health and athletic performance[52].

2.4. Overcrowding and disease stress

Overcrowding and diseases are considered the most serious problems in the modern livestock industry. Increased livestock population within a limited space inevitably results in crowding, causing various side effects related to livestock health, welfare, and productivity[53]. Overcrowding is a major cause of livestock social stress and can reduce the immunity of livestock [22], leading to increased susceptibility to disease and increased transmission of epidemics, which is a major problem in modern livestock farming (Fig.2.4.) [54, 55].

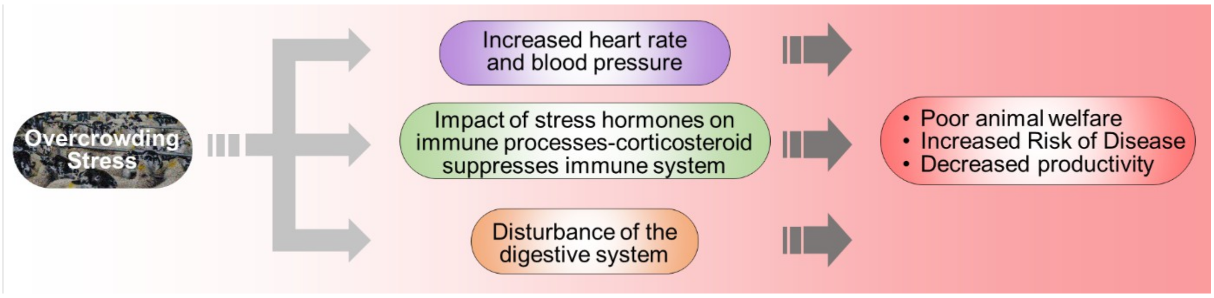


Fig.2.4. Stress caused by overcrowding.

Livestock diseases include the infectious diseases caused by parasites, viruses, and bacteria, metabolic diseases, and hereditary diseases. The infections caused by parasites most frequently occur in chicken, and there are two cases: one is that of external parasites and the other of internal parasites. External parasites live on the skin where they cause damages to the skin and sometimes hematuria. Internal parasites such as roundworm and tapeworm usually live in the stomach, liver, and lungs where they cause more severe symptoms than that by the external parasites, such as reduced feed efficiency or organ dysfunction [56].

Recently, infectious diseases have caused the greatest damage. Unlike before, migration is becoming more active around the world and disease is easily transferred [57].Wild species have stronger immunity than livestock, which does not easily cause epidemic symptoms, but it can lead to serious infectious diseases if transferred to livestock [58].In particular, in animal farms, the highest amount of damages is caused byinfectious diseases, and as their transportation across the world has become more frequent than that in the past, the diseases are also more easily transferred. The wild species possess stronger immunity than thelivestock,therefore, they do not easily exhibit the symptoms ofinfectious diseases; however, if those diseases are transferred to livestock, it might result in serious infections (Table 2.1) [58].

Table 2.1 Common diseases, their causes and symptoms in livestock

Species	Major causes	Diseases	Symptoms
Poultries	*Poxviridae*, *Avipoxirus*	Fowl pox	Blisters, scabs, difficulty breathing
	Clostridium botulinum	Botulism	Anorexia, vomiting, diarrhea, muscle paralysis
	Pasteurella multocida	Fowl cholera	Loss of appetite, difficulty breathing, diarrhea, pneumonia
	Influenza virus	Avian influenza	Fever, increased death rate
Cattles	*Bacillus anthracis*	Anthrax	Dyspnea, convulsions, fever, bleeding
	Clostridium chauvoei	Blackleg	High fever, swelling
	Brucella abortus	Brucellosis	Arthritis, decreased milk production
	Physical damage, infection	Mastitis	Breast tissue damage, fever
Porcine	*Aphthovirus*	Foot-and-mouth disease	Fever, water blister, increased mortality
	Staphylococcus hyicus	Exudative epidermitis	Black spot, greasy skin
	Coronavirus, *Mycoplasma hyopneumoniae*	Porcine respiratory disease complex	Coughing, fever, anorexia, purple skin
	Porcine parvovirus	Porcine parvovirus infection	Leukopenia, maternal reproductive failure

Even in poultries, avian influenza (AI) is considered a very serious infectious disease. The early symptoms of AI virus infection are so mild that they often remain unnoticed. The infection is highly contagious and rapidly spreads throughout the farm. After several months, when the virus is completely activated, it can cause the death of the animal within 48 h[59]. Furthermore, H5N1 type AI is known to infect humans, which poses a major problem topublic health[60]. In hooded animals includingporcine, cattle, sheep and goats, the foot-and-mouth disease (FMD) causes the highest damage. The FMD virus was the first animal pathogenic virus to be identified, and it is highly contagious. Foot-and-mouth disease causes symptoms of high fever and blister formation, while inducing weight loss and reduced milk quantity[61].

Among the diseases caused by bacterial infection, brucellosis causes a serious damage. Various wild animals are infected with *Brucella*, and when livestock are infected, the symptoms are weight loss and reduced milk quantity. An infected pregnant cow might give birth to a calf with physical disability.Moreover, infection to humans is possible depending on the strain of bacteria, which requires attention[62].

3. Techniques and trends in livestock productivity enhancement

The life of several people, from homes to enterprises and from developing countries to developed countries, depends on the livestock industry. Thus, various attempts have been made to improve livestock productivity[63]. The fundamental concepts in promoting the modern livestock productivity are less feed and faster growth. Therefore, genetic techniques have been used internally[64], whereas, drugs such as growth promoters and antibioticsare used externally[65, 66].The corresponding increase in the density of livestock further propels the rapid increase in productivity. Nonetheless, damages caused by animal stress, animal welfare, and environmental pollution have also markedly increased, implying a need for novel ways to improve techniques that promote livestock productivity.

3.1.Genetic technology

Early humans acquired meat through foraging and hunting that required tremendous efforts, and therefore, only a few could consume meat[67].However, the emergence of livestock and the advancement of industry and technology allowed the mass-production and supply of meat, unlike that in the past. As meat availability increased, the demand for meat surged, turning small animal farms into large, high-density farms in an effort to meet the increased demand[1].Even withhigher livestock population, the demand for meat continued to soar, and when it became difficult to further increase the livestock population due to space constraints, studies on ways to improve livestock productivity became more active. Among the diverse approaches to improve productivity is the method of enhanced transduction through breeding, whereby different individuals with excellent traits are crossed to produce an individual with even more excellent traits[64].

Breeding was the method that allowed increased reproduction, faster growth, and more fluent management. The representative case of enhanced transduction through breeding would be the common image that people conjure with porcine—a pink, chubby animal with little hair. However, has this always been the image of porcine since its discovery? The porcine today has the appearance of livestock porcine produced by breeding that has continued over centuries[68, 69].

The early breeding techniques involved the selection of individuals with excellent traits and repeated cross breeding, in the late 19th century, when Gregor Johann Mendel proposed the genetic law, the interest in breeding techniques increased and laying the foundation for modern breeding systems (Table 3.1) [70]. Today, as the function of each gene is known and genetic analysis has become more convenient, a method of breeding based on genetically analyzing animals have been made available.

However, since the 21st century, the importance of animal rights has been emphasized worldwide, and the side effects of breeding have become clear.

The lifespan of most chickens is as short as seven years and as long as 13 years; however, most chickens are slaughtered around day 30 of their lives in modern farm. This early slaughter was made possible by the growth of livestock growth through breeding. Chicken weighed 565 days in 1957, but only a half-century later in 2005, it increased to 4,202g, more than four times higher than in the past, with less use of feed and faster growth, resulting in rapid growth in productivity (Fig.3.1.) [71].

Table 3.1 Modern livestock breeding systems

In Breeding	
Close breeding	Breeding between brothers, sister, and parents
Line breeding	Repeated breeding from one ancestor
Out Breeding	
Pure breeding	Mating of female and male in same breeds
Cross breeding	Mating of different breeds
Line crossing	Mating between different inbreed strains
Out crossing	Mating between purebred without common ancestors in the same breed to the 6th generation
Granding up	Way to increase the number of exotic species, repetitive breeds of the offspring born with a few exotic species.
Species hybridization	Make hybrid breeds by mating among different breeds

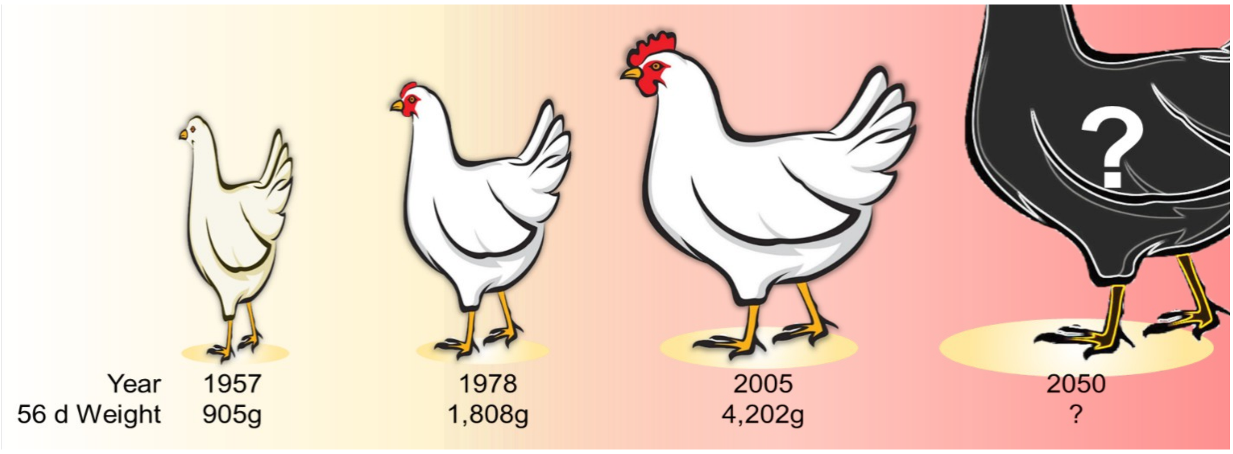


Fig.3.1. Development of broiler chicken.

Source: [71]

Most livestock species today are the result of breeding that is widely accepted as the most basic and reliable method established as a successful way to supply livestock to consumers. However, is breeding, where dominant species are selected and maintained to produce even more dominant species, a righteous method? Consider the example of companion dogs, a common example of breeding in daily life. It is known that the husbandry of dogs, an animal most intimate to humans, began approximately35,000 years ago[72].The wolves became domesticated, friendly to people, easy to follow, and the original wolf features almost disappeared. Through breeding, various kinds of paper have been born and are being cultivated. And in fact for decades, wild foxes have been experimented to domesticate, and like pet dogs, ears and followers have emerged [75]. Through this breeding, the production of livestock as a food source could be increased and the animal companion of wild animals could be possible. However, repetitive inbreeding to produce pure hematoma reduced the genetic diversity of the livestock and made it susceptible to disease. In dogs, the risk of genetic diseases such as heart and oculomotor was increased [14, 73, 74].

Despite these problems, traditional breeding continues to improve productivity. However, breeding is achieved through interbreeding between individuals, and repeated interbreeding is necessary in order to obtain superior traits. However, the development of the Gene editing technique in the 21st century seems to overcome limitations and disadvantages of conventional breeding [75]. The discovery ofclustered regularly interspaced short palindromic repeats (CRISPRs) thirty years ago has brought revolutionary changes in all aspects of biotechnology today, it has been used in many fields because it is more convenient, accurate, and less costly than previous generation genetic editing technologies [76]. The genome editing technology based on CRISPR was first applied to agricultural products, and the representative genetically modified (GM) corn allowed a groundbreaking increase in productivity through improved disease resistance as well as growth promotion[76]. Nuclear factor YB expression can be regulated to improve resistance to drought[77]and genes producing natural pesticides can be introduced. Moreover, a diverse range of improved breeds have been developed, such as rice with increased content of desired vitamins or other nutrients (Table 3.2) [78].

Table 3.2 Genome editing in agricultural production

Species	Target gene	Advantages
Corn	*Nuclear factor Y, subunit B1*	Drought tolerance, corn yields on water-limited acres [77]
Rice	*Gn1a*, *DEP1*, *GS3*, and *IPA1*	Rice yield[79]
Cotton	*Dehydration-responsive element-binding protein*	Cold tolerance[80]
Corn	Acetolactate Synthase 1	Herbicide tolerance[81]

Source: [78]

The use of such gene editing techniques that improve the productivity and supply of livestock to consumers at a low cost was expected to provide a solution to countries with problems of food shortage and famine[78]. However, the newly developed foods using gene editing techniques are being developed and commercialized at a worrying rate without considering the opinion of consumers. Some are of the opinion that it is too early to consume these foods as their stability has not been verified and others are of the opinion that these foods as a revolutionary solution to the problems associated with food. Although numerous animal experiments to verify the stability have been carried out, most consumers are not ready to accept the results[82]. It has been shown that the general consumers, compared with the opinion of professionals in the field of genetic engineering, view the use of gene editing techniques in food production more dangerous[83].However, despite such views, people are consuming the genetically modified organisms (GMOs) without being aware. For example, consuming a product that has not been labeled a GMO plant might have been grown using GMO fertilizer, and the livestock might also be fed the GMO plant. As such information is currently not available to the consumers, there is growing anxiety.

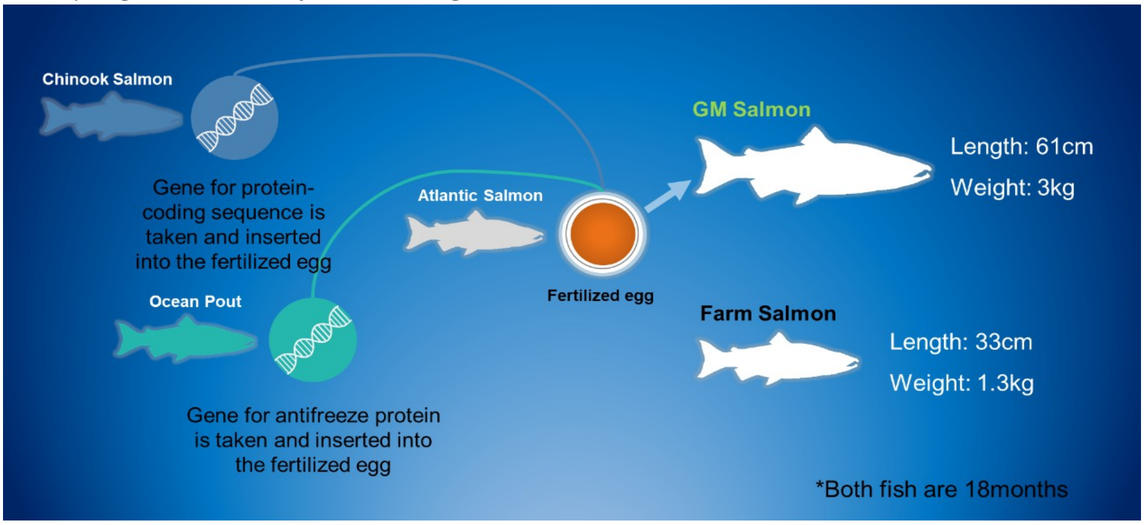


Fig.3.2. Genetically modified salmon

Recently, some countries have started trading genetically modified livestock. According to "The Guardian", in Canada, GM salmons, whose rate of growth is two times higher than that of common salmons, were put on the market, and consumers were unable to distinguish between salmon that was a natural breed and genetically engineered one (Fig.3.2.). Thus, in some countries, any trade of GM livestock is prohibited until a method that allows consumers to identify GM foods has been developed. Due to the ongoing debate on potential hazards of GM foods preventing the consumers from accepting the GM livestock, a longer time is necessary until the commercialization of GM livestock.

3.2. Antibiotics

Antibiotics are substances that microorganisms possess to resist one another, and when they were discovered and isolated by humans, they were adapted to the 'antibiotics' for human use today[84]. The early antibiotics were a blessing to mankind. They were applied to diverse areas related to human life, such as hospitals, foods, and transportation, and not long before, antibiotics began to be used in agriculture and livestock industry (Table 3.3). In the 1940s, when the first antibiotics were developed and mixed with feed, and then provided to porcine and poultry, it resulted in their rapid growth. This led to an exponentially increased use of antibiotics.

Table 3.3 Potential effects of antibiotics for the livestock and farm

Level of aggregations	Factors	Advantages
Livestock	Average daily yield	Increase weight in short time
	Feed efficiency	Reduce feed required
	Mortality rate of young animals	Lower mortality rate
Farm	Costs of antibiotics for treating	Reduce the therapeutic cost
	Feed costs	Increase feed efficiency
	Labor costs	Reduce the time to care the animals

Currently, a large quantity of antibiotics is being used as a way to promote livestock growth easily and cost-efficiently due to the lack of a reliable alternative. Over 50% of the total amount of antibiotics used in most countries today is accounted by those used in the livestock industry, and in the USA, more than 80% of the antibiotics is currently used for livestock, mostly to promote their growth [65]. However, recently, global efforts have been made to reduce the use of antibiotics that might be a solution to treat diseases and promote growth. The world is facing the problem of indiscreet use of antibiotics, and the largest proportion of which is occupied by the antibiotics used for growth enhancement in livestock.

Antibiotics resistant bacteria were found in about 10 years after the first development and introduction of Antibiotics. According to the World Health Organization (WHO), resistant bacteria have been developed against almost all commercial antibiotics nowadays, and the number of antibiotics resistant bacteria is increasing every year, necessitating the reduction of antibiotics use. In this situation, the use of livestock antibiotics, which account for more than half of the antibiotic use, has been pointed out as a major problem (REF). In China, the country with the second largest porcine production in the world and the largest porcine consumption, there is a lack of appropriate regulations on the use of antibiotics in livestock and the management has been poor. The results of polymerase chain reaction array to test antibiotic-resistance genes in a porcine farm in China revealed the resistance to almost all antibiotics, except vancomycin, and as much as 1000 times more antibiotic-resistance genes were detected in the feces and soil, compared with that in the farms that did not use antibiotics [85]. As shown, the antibiotics consumed by livestock can be released into the environment via excretion, producing antibiotic-resistant bacteria. Furthermore, the antibiotics consumed by livestock can reach humans via meat consumption, which poses a serious problem (Fig.3.4.). The EU has banned the use of antibiotics for the promotion of livestock growth since 2006 to address these ARB problems, but there is no clear alternative to antibiotics, leading to an increase in mortality and disease ratesHowever, the evidence thatantibiotics directly influence the metabolism in livestock to promote growth is not clear, and currently, it is considered a result of reduced livestock stress asantibiotics mediate feed decomposition and suppress inflammation in the body[86].

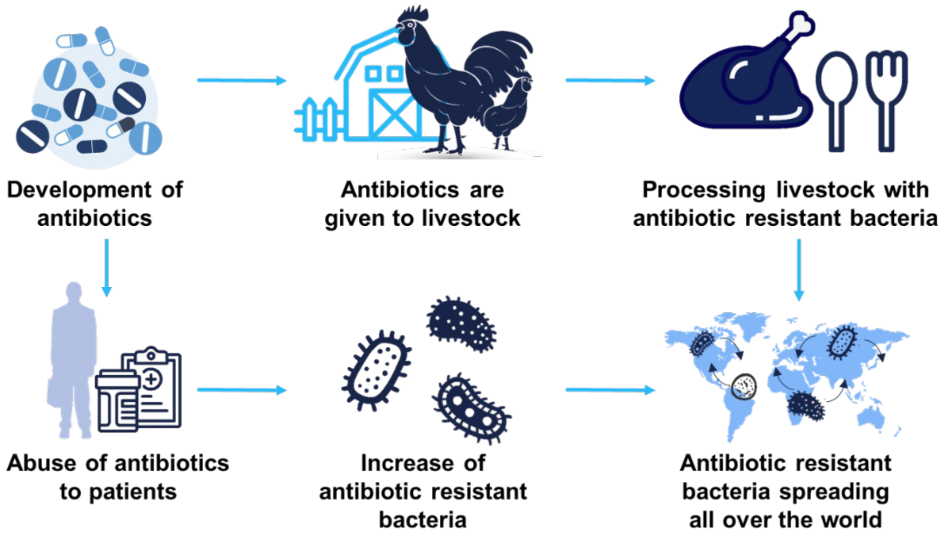


Fig.3.4. Spread of antibiotics resistance

Source: [86]

3.3. Feed additives

For livestock, the main focus is on growth promotion. The antibiotics and growth promoters used to improvelivestockproductivity are a type oflivestockfeed additives. Nonetheless, countries have banned the use ofantibiotics andgrowth promoters due to raised problems, and consumers tend to avoid them as well.

Therefore, preference and consumption of feed additives such as vitamins, amino acids and minerals are increasing. Recently, functional feed additives with functionalities such as antioxidants and feed enzymes have been used (Table 3.4) [16].Due to the increased use of feed additives, the world feed additive market size will reach 18,590 UD $ in 2016, with a 50% increase over the next 10 years to reach US $ 27,820 [16].

Table 3.4 Common feed additives at farm.

Type	Classification
Amino acids	Lysine,Methionine, Threonine, Tryptophan
Antioxidants	Butylated hydroxyanisole, Butylated hydroxytoluene,Ethoxyquin
Feed enzymes	Non-starch polysaccharides,Phytase,Protease, Xylanase
Feed acidifiers	Formic acid,Butyric acid,Fumaric aicd
Vitamins	Water soluble,Fat soluble
Minerals	Zinc,Iron,Maganese,Copper
Antibiotics	Tetracycline,Penicillin

Data was modified from the report on “Allied Market Research”, Source: [16]

3.4. Probiotics

Probiotics broadly refers to the microorganisms with efficacy that benefits the health of host, such as humans and animals, and more specifically refers to the microorganisms that produce lactic acid to help create a favorable environment in the intestines. Since Louis Pasteur identified fermentation mediated by bacteria and yeast, several studies have focused on probiotics [87]. A recent study found a correlation between obesity and gut microbiota, suggesting that probiotics may have more versatile effects than previously thought, and this stimulated an exponential increase in studies on gut microbiota. Projects were developed to identify the total microorganism in the human body, and studies are currently analyzing the entire gut microbiota in livestock. Through diverse studies, the gut microbiota has been found to influence not only the feed intake efficiency but also immunity and growth, which emphasized them further. Although the common probiotic products have been developed in the form of yoghurt, milk, or tablets, numerous recent attempts applying probiotics to livestock feed additives have led to their commercialization. Currently, their effects on improving feed in take efficiency and weight gain are being verified[88].

4. Phytogenic feed additives for livestock welfare and productivity

Plants provide all the essential elements, including food, clothing, and shelter, to humans, and an inextricable relation has been maintained between plants and humans since their appearance[89]. Plants provide additional health benefits to humans, and their influence has been substantial. The use of medicinal plants is thought to have begun around the time when human race appeared, and the oldest recorded evidence was discovered in Nagpur, India approximately 5,000 years ago. Before the 50th century, hundreds of different species of medicinal plants were analyzed and their efficacy documented[90]. The plants were mainly used in the form of powder, extract, or tea, and during the early 18th and 19th century, the advancement in plant chemistry allowed the isolation of active ingredients in plants and their subsequent use in the development of plant-derived drugs. Nevertheless, natural substances seemed to be forgotten with the rapid development of chemical synthetic methods. The drugs so produced before the 20th century lacked verification of efficacy or stability, and when the US FDA was established in the 20th century and reinforced the drug stability verification, the risks of chemically synthesized goods became known to the public, therefore, studies on natural substances began to increase once again.

Modern science uncovered several effects and active ingredients of medicinal plants, and the most important components were identified as the plant secondary metabolites (PSMs).The secondary metabolites are produced to help the organism to adapt to and resist environment stress although not essential in maintaining life[91, 92]. Plants mostly rely on photosynthesis for metabolism, and during this process, after both primary and secondary metabolisms, the PSMs, also known as polyphenols, are produced (Fig.4.1.). To be specific, the carbohydrates generated by photosynthesis enter the pentose phosphate pathway and shikimate pathway to form an aromatic structure, which enters the phenyl propanoid pathway to produce phenolic compounds. The key to the functionality of PFAs are the phenolic compounds among the finally produced PSMs.

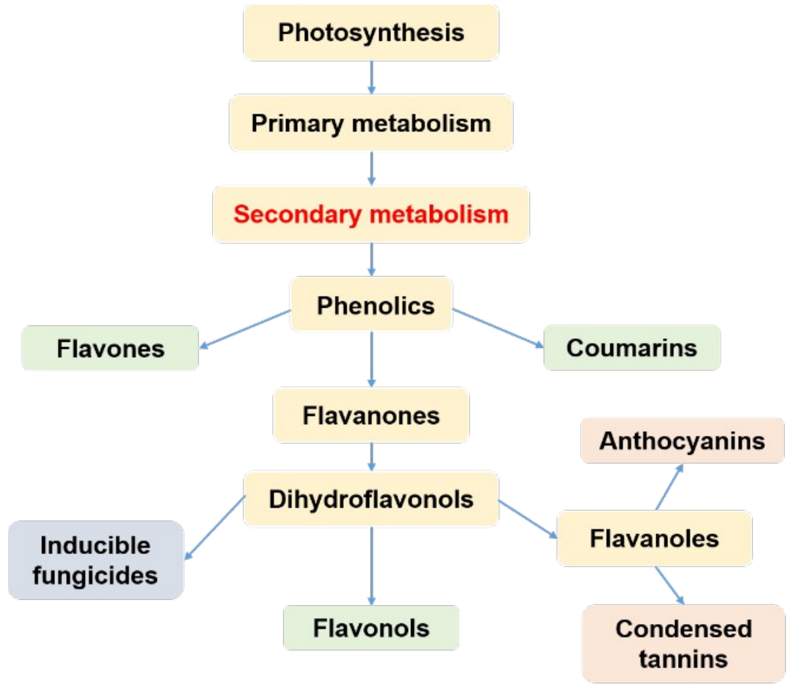


Fig.4.1. Synthetic pathways of PSMs

Phenol (carbolic acid) is an aromatic compound that can be extracted from coal or oil and a powerful toxic substance with a lethal dose of3–30g. Although it used as a disinfectant, nowadays, it is mostly employed as a synthetic intermediate. The acquisition of two or more phenol groups leads to polyphenols, transforming a toxic substance into an excellent health supplement. So far, thousands of plant-derived polyphenols have been identified, most of which have complex structures that pose challenges to chemical synthesis and thus rely on plant extraction. The most well-known polyphenols are curcumin in turmeric, resveratrol in grapes, catechin in green tea, and tannin in chocolates. The individual mechanisms of action of polyphenols differ; however, most of them exhibit powerful anti-oxidant and anti-inflammation effects.

Polyphenols are broadly categorized into phenolic acid, flavonoids, stilbenes, and lignans, depending on the number of rings and the binding structure. Furthermore, the polyphenols produced by individual plants differ according to species, and among them, flavonoids are the most widely detected in edible plants and are most specifically categorized. The widely known catechins and isoflavones found in leguminous plants are also flavonoids (Table 4.1.) [93].

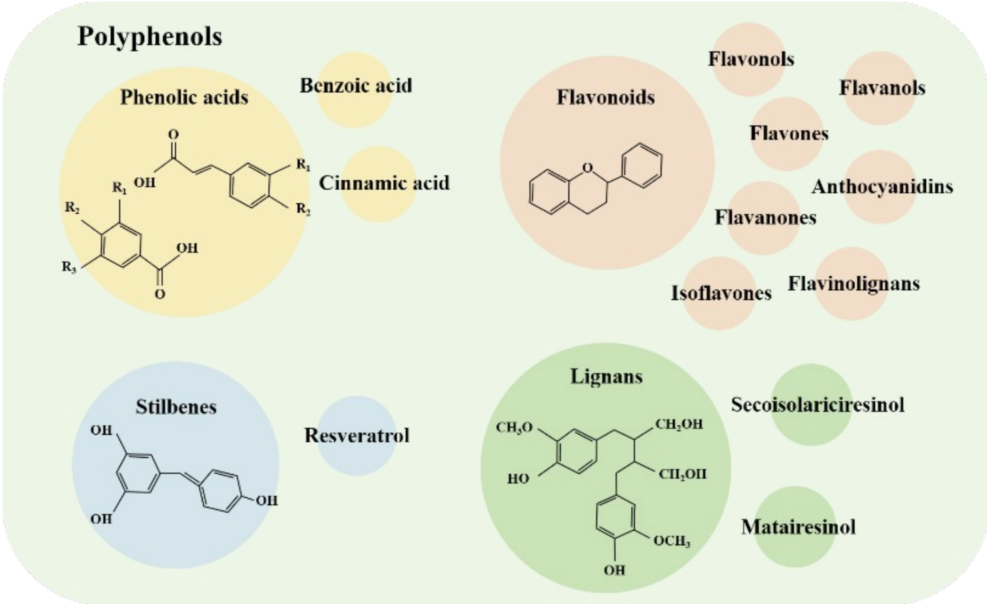


Fig.4.2. Types of polyphenols

The PSMs comprising such diverse polyphenols can be categorized under different purposes: the resistance and protection against environmental factors, reproduction, and nutrient absorption and storage[92]. Through these abilities, the PSMs greatly enhance the resistance of plants to environmental stress, whereas, in animals including humans and livestock, the PSMs enhance the resistance to stress or disease by regulating geneexpression, protein synthesis, and various metabolic pathways. The effects of PSMs vary from anti-oxidant, anti-inflammation, and anticancer effects to improve cardiovascular diseases and regulate cholesterol. Although studies on PSMs began in the $18^{th}$to 19^{th} century, the exact mechanisms could not be identified, and there were doubts on their *in vivo* efficacy despite their verified *in vitro* efficacy. On the contrary, numerous recent studies have elucidated the precise mechanisms of action and the *in vivo* efficacy of plantextracts and PSMs, encouraging research and development on them as a material that can be applied in diverse fields, such as foods, pharmaceuticals, and feed additives (Table 4.1).

Table 4.1 Commercialized PFAs materials

Phytogenics	Main ingredients	Effects
Garlic	Alliin, allicin, allyl disulfide	Antioxidant, anti-inflammation, promote blood circulation, antibiotics, antimicrobial [94]
Corn	Beta-sitosterol	Antioxidant, anti-inflammation, anti-cancer, growth promotion [95, 96]
Pepper	Piperine	Antioxidant, digestion enhancement [97]
Soapwort	Saponins	Antioxidant, gall secretion enhancement, improve nutrient absorption [98, 99]

Source: [93]

4.1. PFAs as prebiotics

The gut microbiota can be regulated by the nutrients that reach the intestines, antibiotics, and infection; however, it is most strongly influenced by the ingested food in both livestock and humans. The use of probioticsis a method to improve intestinal health by transplanting beneficial microorganisms to the gut via oral administration. However, the microorganisms introduced to the gut from an external environment cannot settle for a long time and there for econtinuous intake is required. One way to solve this problem is to use prebiotics. Prebiotics is a fairly recent idea, suggested in 1995 by Gibson and Roberfroid, who defined them as non-digestible food such as fibers and oligosaccharides that can selectively stimulate the microorganisms in human intestines[100]. The intake of prebiotics promotes the growth and activity of the beneficial gut microorganisms bifido bacteria and lactobacilli, thereby, increasing their occupancy to promote intestinal health, reduce pathogenic microbes through competition, and stabilize the gut microbiota [101]. Additionally, dietary fibers exhibit various other effects such as facilitate the secretion of digestive enzymes directly to the gut, stabilize feces formation, and treat metabolic diseases, such as obesity[100, 102].

Nonetheless, within a short time since 1995, the definition and scope of prebiotics rapidly changed. The scope now includes dietary fibers and compounds, and three conditions have been suggested to define prebiotics [103].

(1) The substrate should not be digested in the stomach or small intestine.

(2) It should selectively activate the beneficial symbiotic bacteria.

(3) The fermentation of substrate should produce beneficial effects on the lumen and whole body of host.

Within only a few years, the areas in which prebiotics can be applied have rapidly expanded, and polyphenols have also been pointed out as a potential material for prebiotics. Despite their diverse bioactivity in the body, only 5%–10% of the ingested polyphenols in the diet are absorbed in the small intestine, and the remaining 90%–95% are either accumulated in the large intestine or excreted. The accumulated polyphenols may be digested by the enzymes secreted by the gut microbiota or act as prebiotics influencing their activity (Fig.4.3.) [104].

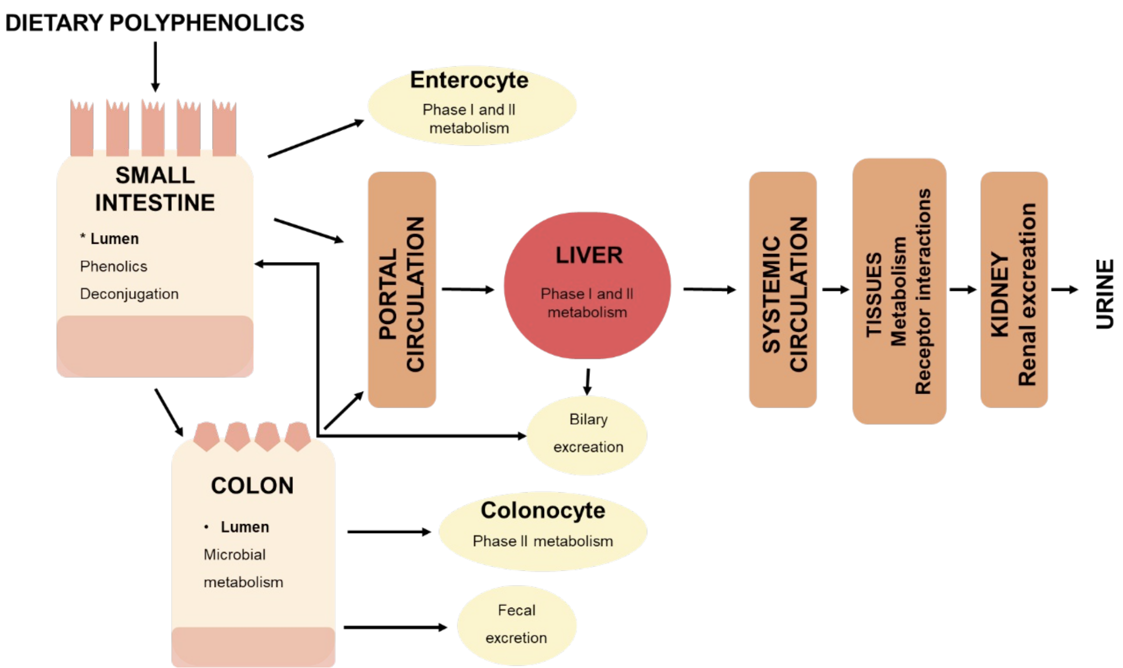


Fig.4.3. Dietary polyphenols as prebiotics

Source: [104]

In a study by Queipo-Ortuño, María Isabel, et al., in which the effects of red wine polyphenols on the gut microbiota in male subjects were investigated, various polyphenols, including malvidin-3-glucoside (antocyanin), quercetin (flavonol), trans-piceid (stilbene), catechin, and resveratrol, were identified, whose ingestion exerted definite effects on the human gut microbiota within a short time. Although the effects onlactobacilli could not be verified, the number of beneficial microorganisms, bacteroides and *Bifidobacterium*, was shown to have substantially increased [102].

Despite the drawback that humans can absorb only less than 10% of the ingested polyphenols, the polyphenols are capable of moving in to the large intestines and colon, where they can regulate the growth of gut microbiota. Thus, taking a leap from being originally defined as non-digestible fibers, polyphenols are capable of actively interacting with the gut microbiota and undergo metabolism to increase the activity of microbes or decrease the number of toxic microorganisms through antimicrobial activity, like probiotics; when used with probiotics, polyphenols are expected to produce complementary effects.

Asantibiotics were banned from being used as feed additives for livestock, there is an urgent need for novel alternatives; the polyphenols have shown a significant potential as an alternative to prebiotics and antibiotics based on their ability to promote the activity of beneficial microorganisms and inhibit the activity of harmful microorganisms. The effects of probiotics in livestock have already been verified, leading to the development of various feed additives; however, the problems such as sepsis, shelf-life, and microbial mutation should be addressed. Currently, the US FDA does not approve the term prebiotics, and the ability of prebiotics in regulating the microorganisms is not yet regarded as a health improving effect but as a process accompanying changes in sugar or cholesterol concentration. Thus, a longer period of time is necessary for the establishment of prebiotic effect of PFAs based on the polyphenols [105, 106].

5. Future perspectives

The livestock industry has grown in line with the advancement of humans since approximately 11,000 years ago when livestock husbandry began. To meet the surging demand for livestock, the early response was to simply increase livestock population; however, the constraints of limited space and the problems of food and environment have led to the search for alternative ways.

Diverse attempts have been made to improve livestock productivity although subsequent problems ensued. Breeding is a method to produce an enhanced trait by crossing the individuals with dominant traits, which has been used since approximately 10,000 years ago. Nonetheless, as it takes a long time to produce an enhanced trait, the method is likely to face difficulties in rapidly responding to the increase in demand. Furthermore, a dominant trait in livestock breeding may indicate a breed with high productivity but it indicates a breed with beautiful appearance and friendliness toward humans with respect to companion animals. In other words, as the criteria for a dominant trait is devised by humans, problems may arise when the criteria contrast the health and welfare of livestock. In the case of GM foods, based on the gene editing techniques that have attracted recent interest, animals and plants with improved resistance to diseases and high productivity have been produced through genemutation. However, the method also entails several problems, which should be resolved before they can be made commercially available. There are three major problems. First, the problem of safety arises from the short time between the present and the time for the development of GM foods, which has not allowed sufficient scientific evidence to accumulate to verify the safety. Thus, continuing research is required for providing evidence for the safety of GM foods. Second, the awareness of consumers on GM foods;it is another problem that requires considerable time and effort. An example is GM tomato developed in 1994; although it was developed by simple deactivation of genes related to the softening of fruit during distribution, the mere fact that gene mutation is involved caused a strong aversion from the consumers and disappeared from the markets. The final problem is that of ecological disturbance caused by GM food crops. Genetically modified foods have comparatively stronger resistance to diseases and environment and therefore they are expected to survive the competition with other foods. This would lead to the unification of plant breeds, and the reduced variety would consequently cause devastating effects on their survival upon an infection. As such, GM foods are facing various problems and a lot of time and effort are needed before they are made commercially available.

One way to resolve such problems is by the use of PFAs. In previous sections, different types of stress and their effect on the modern livestock breeding conditions have been reviewed. Several studies have confirmed thatstress control is a factor that can substantially improve live stock productivity. Notably, when appropriate nutrients for a given phase of growth are provided, productivity was shown to increase significantly. Through a long period of time devoted to the research on plants, the PFAs have been shown to exhibit relatively high safety, and they are expected to provide multi-level solutions to the various current problems of the plant-derived bioactive substances. The recently reinforced restrictions on antibiotic use have elicited the growth of market for alternatives to growth promoters and antibiotics, and PFAs that rely on the efficacy of novel plant materials in stress control and growth promotion are likely to lead to promising alternatives that will attract attention in the market. The PFAs also have problems related to the PSMs at the heart of their efficacy, as PSMs vary in their specific content of bioactive substances depending on the cultivation conditions of the source plant. To resolve this problem, the key bioactive substances and markers should be determined for each plant source of the PFAs, by which thorough quality control should also be performed.

The PFAs may not be the ultimate solution to the various current problems including livestock stress due to overcrowding, livestock welfare, and environmental pollution caused by increased livestock population. Nevertheless, it is certainly a step forward in the present state.

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