Sustainable Agriculture Reviews 57

Vinod Kumar Yata
Ashok Kumar Mohanty
Eric Lichtfouse *Editors*

Sustainable Agriculture Reviews 57

Animal Biotechnology for Livestock Production 2

Springer

Sustainable Agriculture Reviews

Volume 57

Sustainable agriculture is a rapidly growing field aiming at producing food and energy in a sustainable way for humans and their children. Sustainable agriculture is a discipline that addresses current issues such as climate change, increasing food and fuel prices, poor-nation starvation, rich-nation obesity, water pollution, soil erosion, fertility loss, pest control, and biodiversity depletion.

Novel, environmentally-friendly solutions are proposed based on integrated knowledge from sciences as diverse as agronomy, soil science, molecular biology, chemistry, toxicology, ecology, economy, and social sciences. Indeed, sustainable agriculture decipher mechanisms of processes that occur from the molecular level to the farming system to the global level at time scales ranging from seconds to centuries. For that, scientists use the system approach that involves studying components and interactions of a whole system to address scientific, economic and social issues. In that respect, sustainable agriculture is not a classical, narrow science. Instead of solving problems using the classical painkiller approach that treats only negative impacts, sustainable agriculture treats problem sources.

Because most actual society issues are now intertwined, global, and fast-developing, sustainable agriculture will bring solutions to build a safer world. This book series gathers review articles that analyze current agricultural issues and knowledge, then propose alternative solutions. It will therefore help all scientists, decision-makers, professors, farmers and politicians who wish to build a safe agriculture, energy and food system for future generations.

Vinod Kumar Yata
Ashok Kumar Mohanty • Eric Lichtfouse
Editors

Sustainable Agriculture Reviews 57

Animal Biotechnology for Livestock Production 2

Springer

Editors
Vinod Kumar Yata
Animal Biotechnology Centre
ICAR-National Dairy Research Institute
Karnal, India

Ashok Kumar Mohanty
ICAR-Indian Veterinary Research Institute
Mukteswar, India

Eric Lichtfouse
Aix-Marseille University, CNRS, IRD,
INRAE, Coll France, CEREGE
Aix-en-Provence, France

ISSN 2210-4410 ISSN 2210-4429 (electronic)
Sustainable Agriculture Reviews
ISBN 978-3-031-07495-0 ISBN 978-3-031-07496-7 (eBook)
https://doi.org/10.1007/978-3-031-07496-7

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

This book is the second volume of *Animal Biotechnology in Livestock Production*, published in the book series entitled Sustainable Agriculture Reviews. Biotechnology has shown its impact in livestock production, and it will continue to be excel in coming years. This second volume of the book presents the essential concepts and in-depth analysis on animal reproduction and breeding methods.

Chapter 1 focusses the discussion on effects of sexual steroids on stress response and welfare of female ruminants. This chapter also discusses how the behavior and welfare of farm animals could be affected with the application of reproductive biotechnologies.

Chapter 2 provides valuable information on kidney diseases. This chapter includes the discussions on topics such as pathophysiology, molecular biomarkers, and proteomics of kidney diseases.

Chapter 3 covers the updated information on production of genetically modified pigs with the use of CRISPR/Cas9. This chapter focusses the discussion on the production of genetically modified pigs along with pros and cons.

Chapter 4 summarizes various types of anti-nutritional factors and their beneficial and deleterious effects on livestock. This chapter provides information on common factors such as enzymes and chemical compounds found in plant materials used for animal feed.

Chapter 5 summarizes the genetic engineering tools in livestock production. This chapter provides the updated information on biotechnological methods such as molecular gene cloning, diagnostics, vaccines, microarray, marker assisted selection (MAS) in animal breeding, genome editors, role of biotechnology in animal nutrition, artificial insemination, cloning and transgenic animals in livestock production, embryo transfer technology (ETT), and embryo sexing and sperm sexing.

Chapter 6 focuses the discussion on role of specific minerals in female animal reproduction. This chapter covers the discussion on biochemical, enzymatic, and endocrine actions of macromineral (calcium, phosphorus, and magnesium) and micromineral (copper, zinc, and manganese) ions along the hypothalamo-pituitary-ovarian axis.

Chapter 7 discusses genetic selection of livestock such as cattle, sheep, goat, buffalo, and poultry. This chapter also provides a brief overview on statistical models for genomic prediction and whole sequence data.

Dairy cattle production at ICAR-National Dairy Research Institute, India

This book serves as an important reference source for professionals and academicians working in the research area of livestock production. We would like to thank all the authors for their contribution and cooperation. We would like to thank the director of the Indian Council of Agricultural Research (ICAR)-National Dairy Research Institute (NDRI), Karnal, India, for providing institutional support. We would like to extend our thanks to the staff of Springer Nature for their support in publication of this book. We would like to acknowledge the Department of Biotechnology, Government of India, for providing financial support from "DBT-RA Program in Biotechnology & Life Sciences."

Karnal, India Vinod Kumar Yata

Mukteswar, India Ashok Kumar Mohanty

Aix-en-Provence, France Eric Lichtfouse

Contents

About the Editors

Vinod Kumar Yata is an interdisciplinary researcher working at the National Dairy Research Institute, Karnal, India. Previously, he worked as an assistant professor in the Department of Biotechnology, Dr. B R Ambedkar National Institute of Technology Jalandhar, Punjab, India. He received his PhD in biotechnology from the Indian Institute of Technology Guwahati. He specializes in interdisciplinary research which includes nanotechnology, microfluidics, animal biotechnology, cancer biology, and bioinformatics. He has developed a microfluidic device for the separation of live and motile spermatozoa form cattle semen samples. His research interests have been focused on the development of nanocarriers, understanding prodrug enzyme therapy, and targeted drug delivery. He elucidated the structural features and binding interactions of several biomolecules by in silico methods. Vinod has published four books as an editor and one book as an author with Springer Nature. He has published several research papers in peer-reviewed international journals and presented papers at several international conferences.

Ashok Kumar Mohanty is an eminent scientist in animal biotechnology and is currently serving as joint director of ICAR-Indian Veterinary Research Institute, Mukteswar, Uttarakhand, India. His group is involved in various basic and applied research related to animal production systems. His research group has made pioneering contributions to the field of animal biotechnology, with emphasis on gene cloning, expression and functional characterization of animal proteins, proteomics in animal production, cell and molecular biology, and structural biology of proteins. His group has developed a buffalo mammary epithelial cell line for the first time which can be used as a model system to understand lactation biology in animals as well as humans. His team has also developed a pregnancy diagnostic kit for the early detection of pregnancy in cattle and buffalo. His group is also extensively involved in developing low-cost technology for semen sexing in cattle. Ashok has organized a number of national and international workshops and international conferences. He is a recipient of several awards, including DBT Overseas Associateship by the Ministry of Science & Technology, Govt. of India., and Jawaharlal Nehru Award (gold medal) by the Indian Council of Agricultural Research (ICAR), New Delhi, for outstanding postgraduate research in the field of animal biotechnology. He is a fellow of the National Academy of Dairy Sciences (NADS), India, executive member of the Proteomics Society of India, and associate fellow of the National Academy of Veterinary Science, India. He has supervised more than 50 graduates, PhD students, and postdocs. Ashok has published more than 200 peer-reviewed research and review papers. He has also authored eight book chapters in the areas of animal and food biotechnology published by national and international publishers.

Eric Lichtfouse is Professor of Environmental Sciences and Scientific Writing at Aix Marseille University, Xi'an Jiaotong University, and the University of Shanghai for Science and Technology. He has invented carbon-13 dating, a molecular-level method allowing to study the dynamics of organic compounds in temporal pools of complex environmental media. He has discovered temporal pools of individual substances in complex media such as soils. He is chief editor and founder of the journal *Environmental Chemistry Letters* and the book series Sustainable Agriculture Reviews and Environmental Chemistry for a Sustainable World. He is the author of the book *Scientific Writing for Impact Factor Journals*. Eric has awards in analytical chemistry and scientific editing.

Contributors

Salma H. Abu Hafsa Livestock Research Department, Arid Lands Cultivation Research Institute, City of Scientific Research and Technological Applications, Alexandria, Egypt

Alberto Barbabosa-Pliego Facultad de Medicina Veterinaria y Zootecnia, Universidad Autónoma del Estado de México, Toluca, Mexico

Suresh H. Basagoudanavar ICAR-Indian Veterinary Research Institute, Bengaluru, Karnataka, India

Subhasmita Behera ICAR-Indian Veterinary Research Institute, Bengaluru, Karnataka, India

Garima Dadhich Pharmacology and Toxicology Laboratory, Dietetics and Nutrition Technology Division, CSIR-Institute of Himalayan Bioresource Technology, Palampur, India

Mona M. M. Y. Elghandour Facultad de Medicina Veterinaria y Zootecnia, Universidad Autónoma del Estado de México, Toluca, Mexico

Aline Freitas-de-Melo Departamento de Biociencias Veterinarias, Facultad de Veterinaria, Universidad de la República, Montevideo, Uruguay

J. Gadea Physiology of Reproduction Group, Department of Physiology, Universidad de Murcia, Murcia, Spain
Instituto Murciano de Investigación Biosanitaria, IMIB-Arrixaca-UMU, Murcia, Spain

P. S. P. Gupta ICAR-National Institute of Animal Nutrition and Physiology, Bangalore, India

Ayman A. Hassan Animal Production Research Institute, Agricultural Research Centre, Dokki, Gizza, Egypt

Mustafa Hassan Jan ICAR-Central Institute for Research on Buffaloes, Sub-Campus, Nabha, Punjab, India

Shikha Kapil University Institute of Biotechnology, Chandigarh University, Mohali, Punjab, India

Rajiv Kumar Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh, India
Biotechnology Division, CSIR-Institute of Himalayan Bioresource Technology, Palampur, India

Miguel Mellado Department of Animal Nutrition, Autonomous Agrarian University Antonio Narro, Saltillo, Mexico

S. Mondal ICAR-National Institute of Animal Nutrition and Physiology, Bangalore, India

S. Nandi ICAR-National Institute of Animal Nutrition and Physiology, Bangalore, India

S. Navarro-Serna Physiology of Reproduction Group, Department of Physiology, Universidad de Murcia, Murcia, Spain
Instituto Murciano de Investigación Biosanitaria, IMIB-Arrixaca-UMU, Murcia, Spain

J. Parrington Department of Pharmacology, University of Oxford, Oxford, UK

Vikram Patial Pharmacology and Toxicology Laboratory, Dietetics and Nutrition Technology Division, CSIR-Institute of Himalayan Bioresource Technology, Palampur, India
Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh, India

C. Piñeiro-Silva Physiology of Reproduction Group, Department of Physiology, Universidad de Murcia, Murcia, Spain

Madhu Ramesh JNCASR, Jakkur, Bengaluru, Karnataka, India

H. B. Ranjitha ICAR-Indian Veterinary Research Institute, Bengaluru, Karnataka, India

R. Romar Physiology of Reproduction Group, Department of Physiology, Universidad de Murcia, Murcia, Spain
Instituto Murciano de Investigación Biosanitaria, IMIB-Arrixaca-UMU, Murcia, Spain

Abdelfattah Z. M. Salem Facultad de Medicina Veterinaria y Zootecnia, Universidad Autónoma del Estado de México, Toluca, Mexico

Anjum Sherasiya Veterinary World, Wankaner, Gujarat, India

Harpreet Singh Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, Haryana, India

S. K. Tripathi ICAR-National Institute of Animal Nutrition and Physiology, Bangalore, India

Rodolfo Ungerfeld Departamento de Biociencias Veterinarias, Facultad de Veterinaria, Universidad de la República, Montevideo, Uruguay

Dhanesh ValiyaValappil ICAR-Indian Veterinary Research Institute, Bengaluru, Karnataka, India

Chapter 4
Dietary Anti-nutritional Factors and Their Roles in Livestock Nutrition

Salma H. Abu Hafsa, Ayman A. Hassan, Mona M. M. Y. Elghandour, Alberto Barbabosa-Pliego, Miguel Mellado, and Abdelfattah Z. M. Salem

Abstract Nutrition is widely recognized as one of the chief factors driving profitability, efficiency, and development of livestock production. Plant-derived feedstuffs are high in macronutrients and micronutrients, but they also possess anti-nutritional factors (ANFs). Anti-nutritional factors are secondary compounds that lower the nutrient content of forages and reduce forage feed intake by livestock. Protease inhibitors, amylase inhibitors, lectins, tannins, mimosine, phytic acid, gossypol, oxalates, cyanogens, saponins, nitrates, alkaloids, and anti-vitamins are some of the most common ANFs found in livestock feed. The ANFs block or interfere with how the animal's body absorbs other nutrients, resulting in reduced bioavailability of various legumes and cereal components. Thus, ANFs may cause micronutrient malnutrition and mineral deficiencies. Different traditional techniques and methods are used alone or in combination to reduce the ANFs content in livestock feed, such as fermentation, germination, debarking, sterilization, steam sterilization, and soaking. The majority of ANFs found in livestock feeds offer potential health advantages or risks for livestock.

Keywords Plant-based diet · Anti-nutrients · Potential health benefits · Adverse health effects · Livestock

S. H. Abu Hafsa
Livestock Research Department, Arid Lands Cultivation Research Institute, City of Scientific Research and Technological Applications, Alexandria, Egypt
e-mail: hashim_salma@yahoo.com

A. A. Hassan
Animal Production Research Institute, Agricultural Research Centre, Dokki, Gizza, Egypt
e-mail: aymanan19@hotmail.com

Mona M. M. Y. Elghandour · A. Barbabosa-Pliego · A. Z. M. Salem (✉)
Facultad de Medicina Veterinaria y Zootecnia, Universidad Autónoma del Estado de México, Toluca, Mexico
e-mail: mmohamede@uaemex.mx; salem@uaemex.mx

M. Mellado
Department of Animal Nutrition, Autonomous Agrarian University Antonio Narro, Saltillo, Mexico

V. K. Yata et al. (eds.), *Sustainable Agriculture Reviews 57*, Sustainable Agriculture Reviews 57, https://doi.org/10.1007/978-3-031-07496-7_4

4.1 Introduction

Plants grown as animal feed are the basic feedstuff that provides nutrients to animals. Various shrubs, cereals, legumes, roughs, trees, herbs, and other non-conventional feeds for animals contain anti-nutritional factors (ANFs). These ANFs limit the usefulness of edible leaves, twigs, and pods of shrubs and trees as livestock feed. The ANFs are substances that, either by themselves or through their metabolic products, interfere with feed absorption and utilization, reduce nutrient intake and digestion, affect animal health and reproduction, or may produce other adverse effects (Akande et al. 2010). When consumed by animals in quantities above a critical threshold, even at a minimum level, ANFs reduce animal productivity, reproduction efficiency, and the quality of their products (milk, meat, and eggs) and cause toxicity. There is a wide distribution of non-lethal toxic factors throughout the plant kingdom, especially in plants used as animal feed (Igile 1996; D'Mello 2000). Several ANFs with potential toxicity for farm animals have been identified and are either heat-labile or heat-stable. These factors include protease inhibitors, amylase inhibitors, lectins, tannins, mimosine, phytic acid, gossypol, oxalates, cyanogens, saponins, nitrates, alkaloids, and anti-vitamin agents. These ANFs, found in plant-derived feeds, cause nutritional and animal health problems. Recently, the knowledge that these factors produce toxins and elicit beneficial biological responses has led to numerous investigations regarding their possible physiological implications in different biological systems (Igile 1996). Some of these factors are known as 'secondary metabolites,' which are widely applied in nutrition and as pharmacologically active agents as antioxidants and reduce inflammation (Soetan 2008; Petroski and Minich 2020). Proper precautions, including physical, chemical, and biotechnical treatments, and the quantities and methods of use can aid in destroying or reducing the ANF content in unconventional feeds before feeding to livestock and may help to overcome the deleterious actions of ANFs and to make them useful for livestock (Amaefule and Onwudike 2000; Balogun 2013).

4.2 Anti-nutritional Factors

Anti-nutritional factors (ANFs) are chemicals that interfere with the absorption and utilisation of feed and affect animal productivity and health by themselves or their metabolic products. ANFs are also referred to as anti-nutrients, secondary substances, or plant secondary metabolites. Many ANFs with potential toxicity for livestock have been identified and can be either heat-labile or heat-stable (Table 4.1).

Table 4.1 Heat-labile and/or heat-stable types of anti-nutritional factors in livestock feed

Heat-stable anti-nutritional factors	Heat-labile anti-nutritional factors
Maintained at high temperature Phytic acid, polyphenolic compounds (such as condensed tannins), Alkaloids, Saponins, and non-protein amino acids (Mimosine), etc.	Sensitive to standard temperature and lost at high temperature Lectins, Cyanogenic Glycosides, and Protease inhibitors, etc.

Adapted from Felix and Mello (2000)

4.3 Classification of Anti-nutritional Factors

Anti-nutritional factors (ANFs) in plants can be classified based on their chemical composition, properties, mechanisms of action (Aletor and Adeogun 1995), effects on the nutritional value of feedstuffs, and biological effects on the overall animal health (Huisman and Tolman 2001). ANFs which are frequently found in animal feed can be grouped as follows:

The major ANFs commonly found in plant-derived feedstuffs used in animal feed are summarised in Tables 4.2 and 4.3.

4.3.1 Direct and Indirect Factors Affect on Protein Digestion and Metabolism

4.3.1.1 Enzyme Inhibitors

Protease Inhibitors

Proteinases are enzymes that have diverse effects in improving the functional and nutritional properties of different protein molecules (Salas et al. 2018; Samtiya et al. 2020). Protease inhibitors are natural plant inhibitors. They have been amply studied due to their proteolytic action (reduces enzyme activity by protein–protein interactions), inflammatory response, ability to coagulate blood, and role in numerous hormone processing pathways (Gomes et al. 2011). They are widely distributed within the plant kingdom. For instance, protease inhibitors are present in seeds of most leguminous crops, and their presence prevents the utilization of the seeds as livestock feed, which may lead to reduced mineral bioavailability as well as reduced digestion and nutrient absorption (Bajpai et al. 2005; Yasmin et al. 2008) (Table 4.6). Compared with legumes, cereals contain much less of these digestive inhibitors, particularly those that act against proteases and amylases (Nikmaram et al. 2017). Protease inhibitors are concentrated in the outer portion of cereal cotyledons, which are the most common areas containing anti-nutritional factors in plants, and they can inhibit the activity of proteolytic enzymes secreted in the digestive system of animals (Nørgaard et al. 2019) by blocking the active site of the enzymes through a catalytic means. The N- and C-terminal and the exposed protease inhibitors are

Table 4.2 Classification of major anti-nutritional factors present in the plant-derived feedstuffs used in livestock feed

Anti-nutritional factors	Plant-derived nutrient source	Means of alleviation
Interaction with protein nutrition		
Enzyme inhibitors	Soybean, sunflower oil cake, rapeseed meal, lupin seed meal, sesame meal, pea seed meal, Jatropha kernel meal, Rapeseed, mustard oil cake	Heat, autoclaving, boiling, soaking
Lectins (Heamagglutinins)	Soybean, pea seed meal, Jatropha kernel meal	Heat, autoclaving
Saponins	Peas, Jatropha kernel meal, sunflower oil cake, lupin seed meal, pea seed meal	Soaking,
Tannins	Sorghum, mustard oil Cake, Jatropha kernel meal, pea seed meal, Rapeseed, mustard oil cake	Soaking, germination followed by dehulling, genetic modification
Mimosine	*Leucaena leucocephala*	Heat and chemical treatments, supplementation with amino acids or with metal ions
Interaction with mineralavailability		
Phytic acid	Soybean, pea seed meal, cottonseed meal, Jatropha kernel meal, sesame meal, Rapeseed, mustard oil cake	Supplementation, use of phytase, roasting, soaking, autoclaving, fermentation, germination, genetic modification
Oxalic acid	Leaf proteins	Heat treatment, Boiling
Gossypol	Cottonseed meal	Genetic modification, fermentation, use of iron salts
Interaction with vitamin availability		
Cyanogens,	Cassava, sorghum, pea seed meal	Heat treatment, boiling, simmering, blanching
Alkaloids	Lupin seed meal	Heat treatment, soaking
Antivitamins	Cottonseed meal, soybean meal, pea seed meal	Heat treatment

Francis et al. (2001)

often considered structural features necessary for inhibiting enzyme activity (Otlewski et al. 2005). They bind proteases, which resist digestion in the small intestine; thus, ensuring their removal through excretion (Fig. 4.1). Because of their protein-particular nature, protease inhibitors can be easily denatured by heat treatment, although some residual activity may remain in commercially produced products. The anti-nutrient activity of protease inhibitors is related to growth suppression and pancreatic hypertrophy (Chunmei et al. 2010). There are two types of protease inhibitors, the Kunitz inhibitor (inhibits trypsin only) and the Bowman-Burk inhibitor (inhibits trypsin and chymotrypsin) (Ramteke et al. 2019), commonly found in soybeans and cannot be quickly inactivated by heat treatment due to the presence of disulfide bridges (Liu 1997; Van Der Ven et al. 2005). The trypsin inhibitor in

Table 4.3 The types of anti-nutritional factors in forage crops

Anti-nutritional substances	Crops/species
Non-protein amino acids	
Mimosine	*Leucaena leucocephala*
Indospecine	*Indigofera spicta*
Glycosides	
Cyanogens	*Acacia giraffae* *Acacia sieberiana* *Acacia Cunninghamii* *Barteria fistulosa* *Bambusa bambos* *Manihot esculenta*
Saponins	*Albizia stipulate* *Sesbania sesban* *Bassia latifolia*
Phytohemagglutinins	
Ricin	*Bauhinia purpurea* *Robinia pseudoacacia*
Robin	*Ricinus communis*
Polyphenolic compounds	
Tannins	All vascular plants
Lignins	All vascular plants
Alkaloids	
N-methyl-B-phen	*Acacia berlandieri*
Ethylamine	*Sesbania vesiceria*
Sesbanine	*Sesbania punicea* *Sesbania drummondii*
Triterpenes	
Azadirachtin	*Azadirachta indica*
Limonin	*Azadirachta indica*
Oxalate	*Acacia aneura*

soybean interferes with methionine availability from raw soybean and forms non-digestible complexes with dietary protein in the gastrointestinal tract (Ramteke et al. 2019). These complexes are not digestible even in large amounts of digestive enzymes (Thakur et al. 2019). Chicks fed raw soybeans develop pancreatic hypertrophy, but this is not observed in pigs and calves (Ramteke et al. 2019). The presence of trypsin inhibitors in the diet creates an irreversible condition known as the enzyme-trypsin inhibitor complex, which leads to a reduction of trypsin in the intestine and a decrease in protein digestion, slowing down the animal growth. Several enzyme inhibitors are found in plant-derived feeds, but those that affect trypsin and α-amylase activity are the two main types found in all cereals and legume-based feeds. The factors controlling the destruction of protease inhibitors are heat treatment, duration of heating, particle size, and moisture level (Vaz Patto et al. 2015).

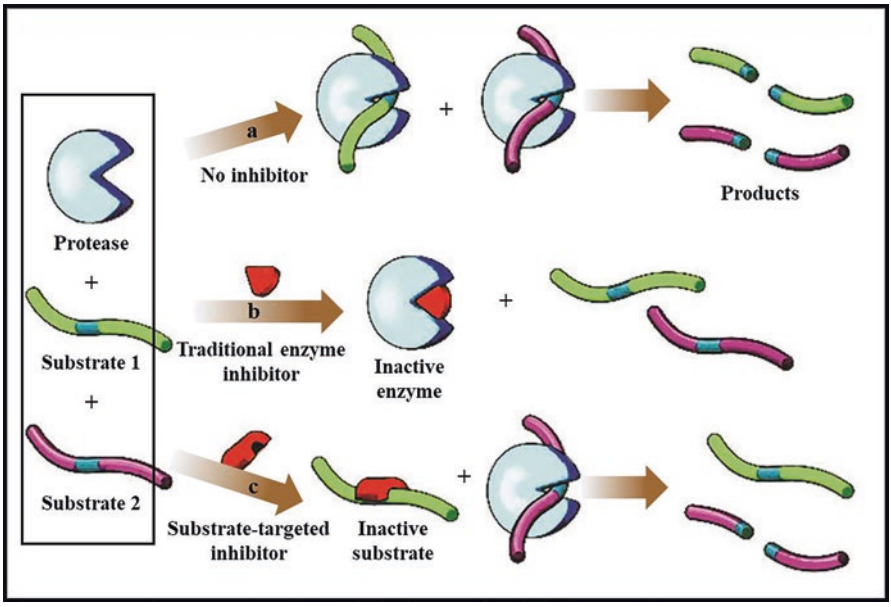

Fig. 4.1 Potential Target molecules of protease inhibitors

Amylase Inhibitors

α-amylase regulates the breakdown of carbohydrates, such as the breakdown of polysaccharides into oligosaccharides. Amylase inhibitors are known as starch blockers because they contain substances that prevent the absorption of dietary starches. Therefore, α-amylase inhibitors increase the time for carbohydrate absorption by delaying carbohydrate digestion, thus decreasing the rate of glucose absorption and affecting the average postprandial plasma glucose concentration (Bhutkar and Bhise 2012). These inhibitors are heat-labile and are active in the pH range of 4.5–9.5 (Marshall and Lauda 2007). Amylase inhibitors do not inhibit bacterial, fungal, or endogenous amylase but can inhibit bovine pancreatic amylase. This inhibitor's instability in the gastrointestinal tract leads to reduced insulin responses and increased caloric production from food when the inhibitor is used in starch blocking tablets (Giri and Kachole 1998).

4.3.1.2 Lectins (Haemagglutinins)

Lectins are sugar-binding proteins that readily bind to red blood cells to cause agglutination and are found in most plants, especially seeds such as grains and beans, tubers like potatoes, and raw meat (Hamid et al. 2013). Grains and legumes generally contain lectins, which are glycoproteins. Lectin activity has been determined in more than 800 legumes; 2–10% of the total legume seed proteins are

lectins in soybean and ricin (castor bean), the latter is toxic and causes severe inflammation in the intestine, kidney, thyroid gland, etc. (Ramteke et al. 2019). In addition, the transport and hydrolytic functions of intestinal cells can be impaired by the consumption of foods containing lectins (Krupa 2008). Lectins impair the absorption of nutrients by binding directly to the intestinal mucosa, interacting with enterocytes, and resulting in severe intestinal damage, which disrupts digestion, causes nutrient deficiencies and epithelial lesions within the intestine, and allows bacterial populations to come in contact with the bloodstream (Muramoto 2017) (Fig. 4.2). In a study by Bardocz et al. (1995), the epithelium had an increased density of goblet cells and a marked decrease or absence of absorptive vacuoles; the microvilli of the intestinal cells were shortened with an increase in microvillar

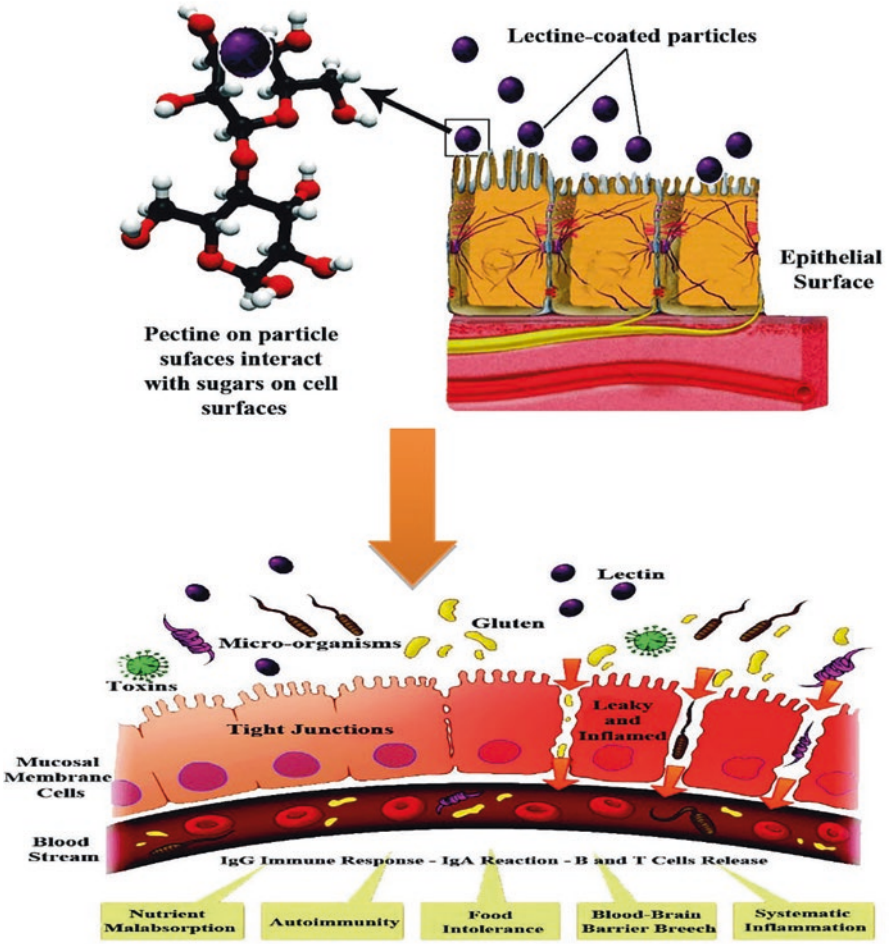

Fig. 4.2 Binding of particle-lectin conjugates with sugar residues of the cell membrane

vesicle formation and the number of intestinal crypt cells. The increase in the density of the goblet cells may have been due to the production of hypertrophic mucus in the intestine as a result of the irritation by lectins; thus, preventing the absorption of digestion end products in the small intestine. Lectins may also have resisted digestion through pancreatic juice (Ramteke et al. 2019). Lectins from soybeans, known as soybean agglutinins, impair animal growth, cause enlargement of the small intestine, damage the small intestine's epithelium, and stimulate hypertrophy and pancreas hyperplasia (Grant 1991) (Table 4.6). Lectins also bind with the glycoprotein components of erythrocytes, causing cell agglutination. Lectins have some interesting chemical and biological properties, such as interacting with specific blood groups, performing various mitotic division functions, destroying cancer cells, and having toxic effects in some animals. Since they bind with different sugar groups, lectins that attach to the intestinal wall may vary depending on sugar type. Dietary lectins are important because they are resistant to digestion and are not hydrolyzed in the intestine (Fig. 4.2). Although lectins are proteins, they are partially resistant to proteolytic degradation in the intestine. Soybean lectins can bind to brush border surfaces, particularly in the small intestine's distal part (Grant 1991; Dublecz 2011). Lectins selectively bind carbohydrates and, most importantly, the carbohydrate moieties of glycoproteins present on most animal cell surfaces. Lectins act as protein antigens that simultaneously bind to surface glycoproteins or glycolipids in red blood cells and immune factors, causing haemagglutination and anemia (Sauvion et al. 2004). They are present in small amounts in 30% of foods and in higher quantities in whole-grain diets. Haemagglutination of red blood cells is commonly used to measure lectin activity (Dublecz 2011; Fereidoon 2014). Consumption of feed-containing lectins may result in endogenous loss of nitrogen and reduced protein utilization. Undigested and unabsorbed proteins and carbohydrates in the small intestine reach the colon, where the bacterial flora ferments them into short-chain fatty acids and gases. These may, in turn, contribute to some digestive symptoms related to the intake of raw beans or purified lectins. The gastrointestinal mucosal disruption caused by lectins may allow bacteria and their endotoxins to enter the bloodstream and cause toxicity. Lectins can also be absorbed directly and cause systemic effects such as increased protein catabolism, breakdown of stored fats and glycogen, and mineral metabolism disturbances (Fereidoon 2014).

4.3.1.3 Tannins

Tannins are astringent and bitter plant polyphenols with molecular weights higher than 500 Da. One of the properties of these compounds is their ability to precipitate proteins and various other organic compounds, including amino acids and alkaloids. Tannins are secondary compounds found in plants' leaves, fruits, and bark (Timotheo and Lauer 2018). They are also found in cereals such as sorghum (containing up to 5% condensed tannin) and barley (Serrano et al. 2009; Morzelle et al. 2019), food crops and legumes such as lima beans, fava beans, sunflower seed meal, and rapeseed, in the foliage of many trees and shrubs, and many seeds and agro-industrial

by-products (Dube et al. 2001) (Table 4.4). Tannins usually affect protein digestion by forming reversible and non-reversible tannin-protein complexes between the hydroxyl group of tannins and the carbonyl group of proteins, reducing essential amino acids (Lampart-Szczapa et al. 2003; Patra and Saxena 2010; Raes et al. 2014). In nature, there are two types of tannins: hydrolyzable (e.g., gallotannins and ellagitannins) and condensed (e.g., proanthocyanidins) (Patel et al. 2013) (Fig. 4.3). The two types differ in their molecular weight, structure, and nutritional and toxic effects on herbivorous animals, especially in ruminants that ingest tannin-rich forages (Fig. 4.3).

Condensed tannins (CT) are the most common type of tannins present in legumes, seeds, trees, and stems (Barry and McNabb 1999). They are extensively distributed in legume pasture species, several Acacia species, seeds, and other plant species (Degan et al. 1995). The CT consists of flavonoid units (flavan-3-ol) linked by carbon–carbon bonds, which influence its physical and biological properties (Hassanpour et al. 2011). The complexity of CT relies on flavonoid units that vary

Table 4.4 Distribution of tannins in selected feedstuffs

Feed ingredients	Tannin concentration (%)[a]	References
Sorghum grain (white)	0.55	Gowda et al. (1994)
Sorghum grain (yellow)	0.2–2.0	Fuller et al. (1996)
Sorghum grain (red)	1.54–7.44	Medugu et al. (2010)
Sunflower cake	2.36	Jacob et al. (1996)
Sesame seed cake	2.15	Jacob et al. (1996)
Mango seed kernel	5.47	Diarra et al. (2008)
Mango seed kernel	0.08–0.10	Bala et al. (2013)
Soybean meal	2.47	Jacob et al. (1996)
Pigeon pea	4.3–11.4	Jambunathan et al. (1988)
Chick pea	1.9–6.1	Jambunathan et al. (1988)
Mucuna beans	0.80	Akinmutimi (2007)

[a]Dry matter basis

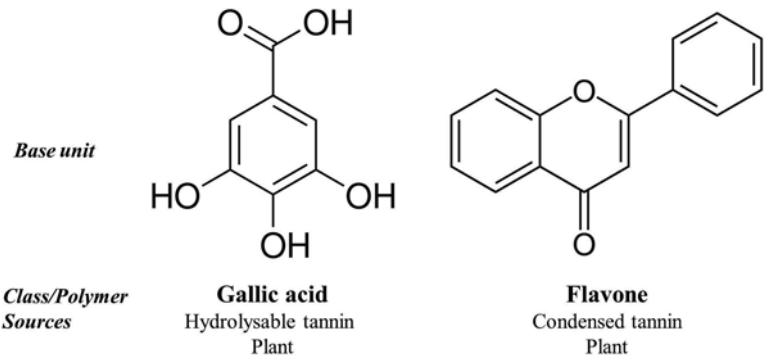

Fig. 4.3 Types of tannins and their primary structures

between components and within sites to form interflavan bonds. Hydrolyzable tannins (HT) are usually found at lower concentrations in plants than CT, and they are further divided into taragallotannins (gallic and quinic acid) and caffetannins (caffeic and quinic acid) (Mangan 1988). The HT are easily hydrolyzed during the digestion process by tanninase enzymes that engage in ester-bond hydrolysis. They can form compounds such as pyrogallol, which is toxic to ruminants. Poisonous compounds from more than 20% HT in the diet can cause kidney damage, proximal tubular necrosis, liver necrosis, lesions related to haemorrhagic gastroenteritis, and high mortality in sheep and cattle (Reed 1995). Previous studies have shown that cattle and sheep are sensitive to these tannins, while goats are resistant (D'Mello 2000; Bhattarai et al. 2016; Smeriglio et al. 2017). Tannins mainly accumulate on the seed coat of legumes; when ingested, they form protein-containing complexes that disrupt various digestive enzymes and reduce protein digestion (Joye 2019). In non-ruminants, HT can reduce growth rates, protein utilization, cause damage to the mucosa of the digestive tract and increase the excretion of protein and amino acids (Hassanpour et al. 2011). CT strongly reduces hydrolyzable tannin's digestibility, while HT causes varied toxic manifestations due to hydrolysis in the rumen (Akande et al. 2010). Tannins are the most common anti-nutritional factors found in plants. Their anti-nutritional effects depend on their chemical structure and concentration. They can inhibit trypsin, chymotrypsin, amylase, and lipase activities, reduce dietary protein quality, and interfere with dietary iron absorption (Lumen and Salamat 1980; Rao and Desothale 1998). Tannins also form insoluble complexes with proteins, which may explain the anti-nutritional effects of feeds containing tannins (Gemede and Ratta 2014) (Table 4.6). Tannins interfere with digestion by displaying anti-amylase activity and forming a complex with vitamin B (Liener 1980). Other adverse nutritional effects of tannins include intestinal damage and a possible carcinogenic effect, depression of feed intake, growth rate, feed efficiency, and microbial enzyme activities, including cellulose and intestinal digestion, as well as increased endogenous protein excretion, digestive tract malfunctioning, and toxicity of absorbed tannins or their metabolites. Tannins may form small digestive complexes with the feed antagonistic to arginine, interfere with RNA proteins, bind and inhibit endogenous proteins such as digestive enzymes, make proteins partially unavailable, and increase faecal nitrogen (Kumar and Singh 1984) (Fig. 4.4). Tannin-protein complexes include both hydrogen bonding and hydrophobic interactions. The protein–tannin complex's precipitation depends on the pH, molecular size, and ionic strength of tannins (Fig. 4.5). Both protein precipitation and incorporation of tannins in the precipitate increase as the tannins' molecular weight exceeds 5000 Da, and the tannins become insoluble and lose their ability to precipitate protein. The degree of polymerization then becomes necessary to assess the role of tannins in ruminant nutrition. CTs are responsible for the test-linked trypsin inhibitor activity of fava beans (Helsper et al. 1993).

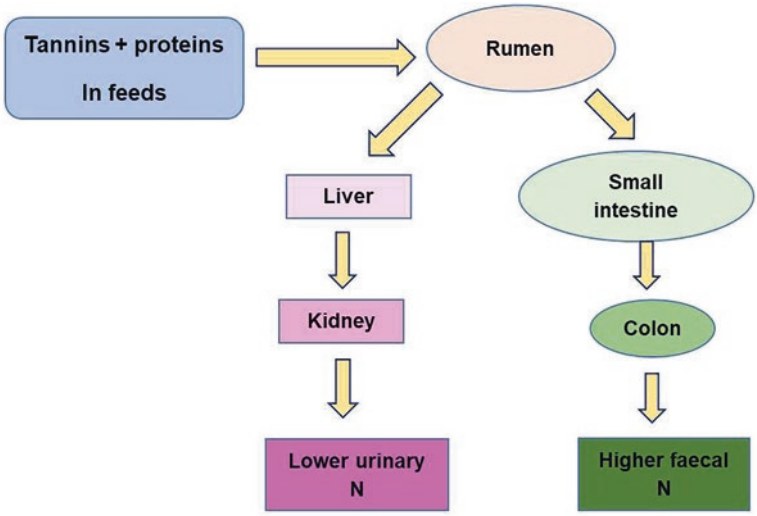

Fig. 4.4 Tannins that bind to dietary protein increase the nitrogen flux from the rumen to the small intestine

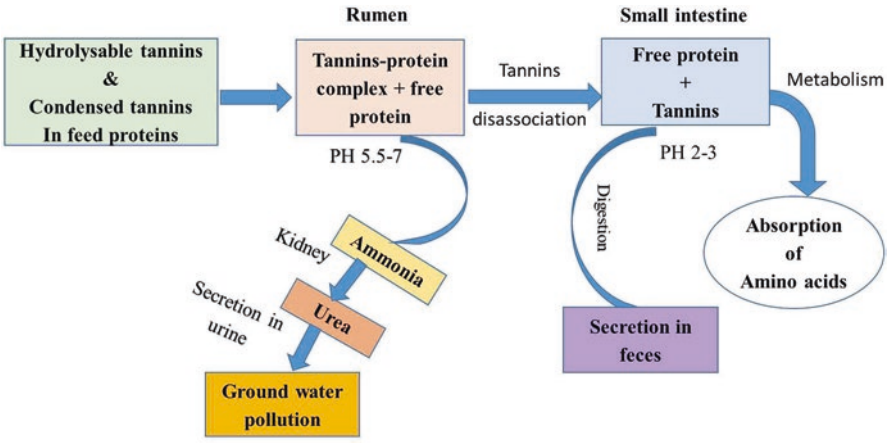

Fig. 4.5 Protection of feed proteins through tannin-protein complexes

4.3.1.4 Non-protein Amino Acids

Mimosine

Mimosine is a non-protein amino acid that is structurally similar to tyrosine. It is present in *Leucaena leucocephala*, in which the leaf mimosine level is approximately 2–6% and varies depending on season and maturity of leaves and stems. The main clinical symptoms of toxicity in non-ruminants include poor growth,

reproductive problems, eye cataracts, and alopecia. When *L. leucocephala* is used as a feed meal for poultry, rabbit, or pigs, more than 5–10% of the meal generally causes poor growth and reproduction. In ruminants, mimosine toxicity causes poor body growth, poor wool development, depressed serum thyroxine levels, goiters, alopecia, dullness, swollen and raw coronets above the hooves, lesions in the mouth and oesophagus, and lameness (Table 4.6). Symptoms may be due to the mimosine metabolite in the rumen or 3,4-dihydroxypyridine.

Additionally, Jones et al. (1989) observed a diminished calving percentage in cows fed *L. leucocephala*. The problems caused by mimosine can be solved by genetically selecting *Leucaena* species with low mimosine content, but it has been noted that the low-mimosine species are unproductive and have low vigor; this problem can be solved by producing feed containing *Leucaena* mixed with other forages and concentrates. Hiremat (1981) suggested that the use of *Leucaena* as fodder can be limited to 50% of green forage for goats and 30% for cattle and buffalo. This strategy results in better livestock growth and production.

4.3.2 Factors Interfering with Minerals Utilisation

4.3.2.1 Phytic Acid

Phytic acid, also known as inositol hexakisphosphate, occurs naturally as phytate in feedstuffs of plant origin, and it acts as a storage form of phosphorus (Bedford 2000) (Fig. 4.6). Phytic acid is a phosphorus-containing compound that binds to

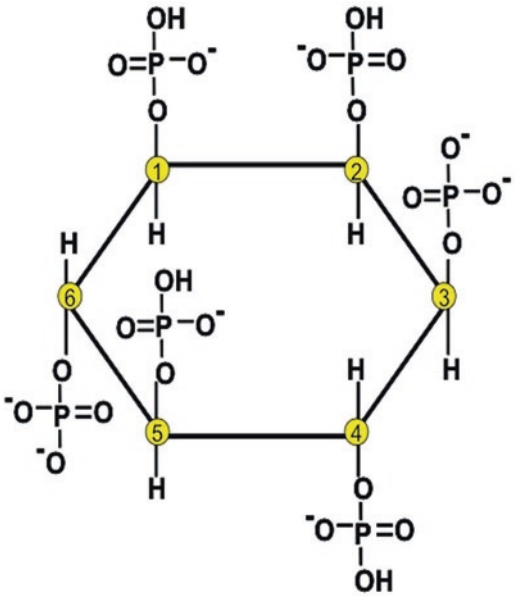

Fig. 4.6 Phytic acid and its basic structure

minerals and inhibits mineral absorption, resulting in decreased bioavailability of essential minerals, eventually turning them into insoluble compounds that are less readily absorbed and digested in the small intestine (Desphande and Cheryan 1984; Lott et al. 2000; Raboy 2000). Phytic acid is a ubiquitous secondary compound ranging from 0.1% to 6.0% among plant species, especially seeds, legumes, and cereals (Lolas 1976; García-Estepa et al. 1999; Lori et al. 2001; Loewus 2002; Margier et al. 2018). Phytic acid is primarily present as a salt of the mono- and divalent cations K^+, Mg^{2+}, and Ca^{2+}, and it accumulates in seeds during ripening (Maenz 2001).

Phytic acid is generally a negatively charged structure that binds to positively charged metal ions such as zinc, calcium, magnesium, and iron to form complexes and reduce these ions' bioavailability through lowered absorption rates. Phytic acid is one of the most effective anti-nutrients in animal feeds due to its chelating property. Its presence causes mineral ion deficiency in animal and human nutrition (Walter et al. 2002; Bora 2014; Grace et al. 2017) (Table 4.6). Since phytic acid, one of the strongest ANFs in plant feedstuffs, accumulates in seed storage sites, behaves as a chelating ligand with minerals and forms complex salt phytates; and can act as potent chelators that form protein and mineral-phytic acid complexes in a reduced bioavailability of protein and minerals (Erdman 1979). Most of the phosphorus contained within phytic acid is unavailable mainly to non-ruminants due to the absence of phytase in these animals' gastrointestinal tract (GIT). In chickens, there is a significant inverse relationship between phytic acid availability and the availability of phosphorus, magnesium, zinc, and calcium in feedstuffs, such as rapeseed, palm kernel seed, soybean meal, and cottonseed meal. Phytic acid, a highly negatively charged ion, works in a broad pH range and binds nutritionally important divalent cations in the diet such as iron, zinc, copper, magnesium, calcium, and molybdenum and endogenous GIT secretions such as digestive enzymes and mucins. This binding leads to the formation of insoluble complexes that are not readily absorbed by the GIT and increase the endogenous secretion of nutrients (Frontela et al. 2008; Woyengo and Nyachoti 2013) (Fig. 4.7). It also inhibits the action of GI tyrosinase, trypsin, pepsin, lipase, and amylase. Phytic acid is poorly hydrolyzed by non-ruminants (Woyengo and Nyachoti 2011, 2013). Most poultry does not have endogenous enzymes to break down phytate and release nutrients; thus, phytate transits undigested through the GIT (Fig. 4.8). This is also why high proportions of valuable nutrients from plant sources are not utilized by non-ruminants and are wasted in the excreta (Mueller 2001). Phosphorus bound to phytate is not bioavailable to non-ruminants. Ruminants, such as sheep and cows, chew, swallow, and then regurgitate their food; this regurgitated food is known as cud and is chewed a second time. Due to the phytase activity of rumen microorganisms, these animals can separate and process phosphorus into phytates (Haese 2017).

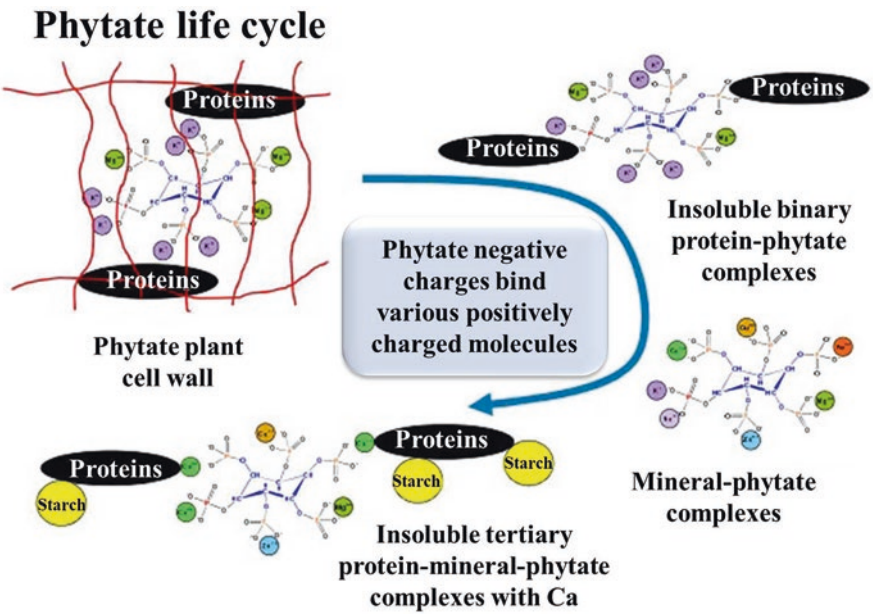

Fig. 4.7 Phytate life cycle

4.3.2.2 Gossypol

Gossypol is a phenolic compound with a yellow pigment, which is a complex of esters and ethers of various carbohydrates found in the pigment glands of plants of the genus Gossypium, family Malvaceae. It is present in two forms: free gossypol or bound form (Abbas 2020). Free gossypol contains aldehyde and phenolic groups, making it more reactive and toxic (Leeson and Summer 2001) (Fig. 4.9). Bound gossypol (BG) is not absorbed and is non-toxic. Gossypol is found in higher concentrations in cotton seeds (0.4–2.4%), and the average content of free gossypol in cottonseed meal is 0.01% (Liener 1980). Whole cotton seeds contain the highest amount of free gossypol. Cottonseed meal is a by-product of extracting cottonseed oil from whole seeds. Different extraction techniques significantly impact on the amount of free gossypol contained in cottonseed meal. The screw-press method uses heat that increases protein binding, thus converting more free gossypol (toxic form) into BG (non-toxic). Solvent extraction is widely used because more oil can be extracted. However, because heat is not used in solvent extraction, the amount of free gossypol content in cottonseed meal is approximately ten times higher than that in cottonseed meal processed by the screw-press method. This can be a considerable difference if there is much gossypol in the seed. This switch to solvent extraction explains the increase in gossypol toxicity in the past decades (Morgan 1989). Free gossypol is the most common anti-nutritional factor in cottonseed meal, primarily affecting the heart, liver, reproductive tract, and kidneys (Nagalakshmi et al. 2007). During cotton seed oil extraction, free gossypol binds to the epsilon amino group of

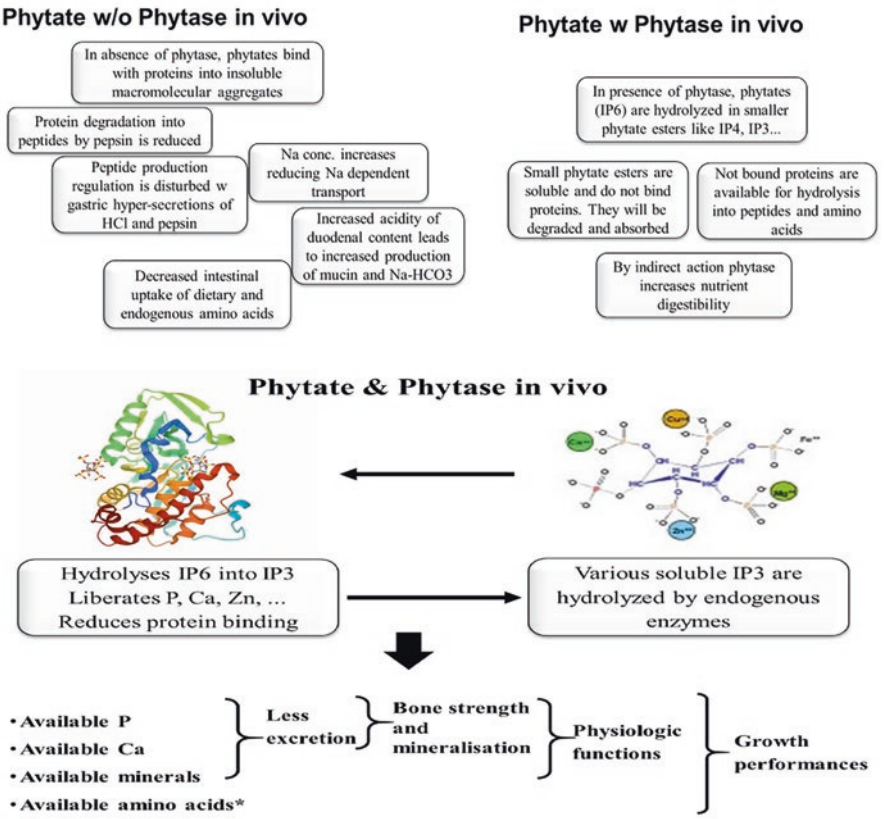

Fig. 4.8 Phytate with/without phytase in vivo

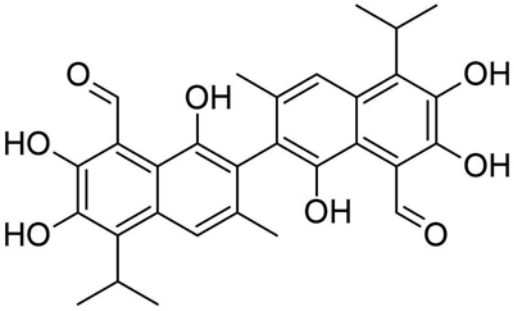

Fig. 4.9 Gossypol and its basic structure

lysine, resulting in BG, which reduces lysine availability to animals. The amount of free gossypol in cottonseed meal can be variable. Many factors influence its content, such as cotton plant species, climatic and soil conditions, oil extraction methods, kernel to husk ratio, and seed coat (Nagalakshmi et al. 2007). This makes it impossible to know how much free gossypol the cottonseed meal contains without testing

it. Hence, the quality of cottonseed meal is restricted by the free gossypol, its unbalanced digestible amino acid, and its high fluctuation in free gossypol concentration. Moreover, methionine, lysine, threonine, and valine deficiency in cottonseed meal protein causes a decrease in its digestibility, probably due to high cell wall components, which provokes a faster digestion passage rate due to gossypol binding to the soluble protein (Nagalakshmi et al. 2007). Gossypol makes an insoluble chelate with many essential elements such as iron and amino acids, hence reducing these nutrients' availability (Church 1991; Robinson 1991). Gossypol may reduce protein digestibility by binding to the free epsilon amino group of lysine during heat treatment, and the gossypol protein complex formed in cottonseed meal may render the adjacent peptides unavailable for proteolytic action. Gossypol inhibits the activity of important enzymes by binding to their free epsilon amino groups (Sharma et al. 1978). Non-ruminants have long been known to be susceptible to gossypol toxicity. Ruminants such as cattle and sheep can tolerate higher free gossypol levels because gossypol binds to proteins in the rumen. However, young calves and lambs are pretty susceptible to gossypol toxicosis. Although they are ruminants, their rumen is not fully functional and cannot bind as much free gossypol as the rumen of adult animals. General signs of gossypol toxicity are reduced appetite and the productive performance of animals, and causes contraception and infertility in animals (Leeson and Summer 2001), inhibition of haemoglobin synthesis by iron-binding, inhibition of respiratory enzymes resulting in difficulty breathing and cardiac arrhythmias (Ferguson et al. 1959; Skutches et al. 1973), reduction in the oxygen-carrying capacity of hemoglobin, and a decrease in the ratio of hemoglobin to red blood cells and decreased serum protein concentration. Dietary gossypol may also cause diarrhea, oedema of the body cavities, liver discoloration, and degeneration of myocardium, liver, and spleen (Church 1991; Olomu 1995). In poultry, free gossypol reduces production performance and causes leg weakness (Lordelo et al. 2007) and egg yolk mottling (i.e., olive green discoloration of yolk) (Davis et al. 2002) due to the interaction between gossypol and yolk iron, and may also harm blood biochemistry variables (Adeyemo 2008) (Table 4.6). Cotton seeds are rich in gossypol and can thus produce severe toxicity to farm animals; however, the cumulative effects of dietary gossypol and toxicity can occur after an ingestion period of 1–3 months (Patton et al. 1985; Kerr 1989; Soto-Blanco 2008; Gadelha et al. 2011). Gossypol toxicity has been reported in many species, including broiler chicks (Henry et al. 2001), pigs (Haschek et al. 1989), goats (East et al. 1994), and sheep (Morgan et al. 1988). Non-ruminants are more susceptible to gossypol toxicity than ruminants (Alexander et al. 2008; Kenar 2006; Randel et al. 1992; Zhang et al. 2007). Moreover, young ruminants are more sensitive to gossypol than adult ruminants (Soto-Blanco 2008) because gossypol is not bound during rumen fermentation, as it is in animals with fully functional rumen. However, if gossypol intake overwhelms the rumen's detoxification capacity, free gossypol may be absorbed in hazardous concentrations even in adult ruminants (Willard et al. 1995). The rate of gossypol absorption is inversely proportional to the amount of iron in the diet (Haschek et al.

1989); thus, dietary supplementation with ferrous sulfate inhibits free gossypol (Barraza et al. 1991). In ruminants, microbial fermentation in the rumen binds dietary free gossypol with proteins (Schneider et al. 2002). However, it is unknown whether the intestine can absorb the BG form or if microorganisms can release free gossypol from the bound form, as absorbed gossypol accumulates in the liver (Lindsey et al. 1980) and kidneys (Kim et al. 1996). The primary route of gossypol excretion is through the bile; it is then eliminated through faeces after conjugation with glucuronides and sulfates (Abou-Donia et al. 1989). Small amounts of gossypol are also excreted in expired air (Soto-Blanco 2008), and some gossypol is excreted in the milk (Lindsey et al. 1980).

4.3.2.3 Oxalates

Oxalate (oxalic acid) is a substance that can form insoluble salts with minerals such as Ca, K, Na, Mg, and Fe. These compounds are found in small amounts in both plants and mammals (Petroski and Minich 2020). Under normal conditions, oxalate is confined to separate compartments, but when it is processed and or digested, it comes into contact with the nutrients in the digestive system (Noonan and Savage 1999). When released, it binds with nutrients, rendering them unavailable to the body. If feed with excessive amounts of oxalic acid is consumed regularly, a nutritional deficiency is likely and severe irritation of the gut lining (Liebman and Al-Wahsh 2011). Strong bonds are formed between oxalic acid and many other minerals, such as Ca, K, Na, and Mg (Fig. 4.10). These chemical combinations lead to the formation of oxalate salts found in plants' soluble and insoluble forms. Soluble salts are formed when oxalate binds to Mg, Na, and K, while insoluble salts are produced when oxalate binds to Fe and Ca. Oxalate affects Ca and Mg metabolism and interacts with proteins to form complexes that inhibit digestion. The high content of soluble oxalate content prevents the absorption of soluble Ca ions, as oxalate binds to Ca ions to form insoluble Ca-oxalate complexes (Hamid et al. 2017). This renders Ca unavailable for maintaining healthy bones, as a cofactor in enzymatic reactions, the transmission of nerve impulses, and as a clotting factor in the blood (Table 4.6). Ca loss leads to bone deterioration, impaired blood clotting, and a disturbance in the absorbed Ca:P ratio, which leads to bone mineral mobilization to alleviate hypocalcemia; therefore, prolonged mobilization of bone minerals

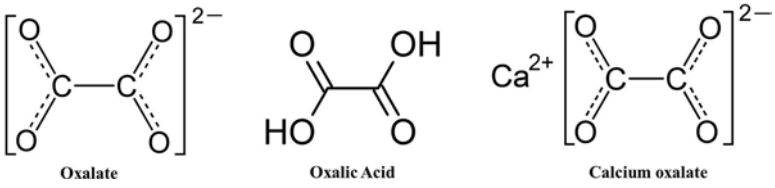

Fig. 4.10 Show the different chemical structure between oxalate, oxalic acid and calcium oxalate

leads to osteodystrophy fibrosa or hyperparathyroidism (Rahman and Kawamura 2011). In ruminants, oxalate is marginally significant as ANF because rumen microflora efficiently metabolize soluble oxalates (Gemede and Ratta 2014) and, to a lesser extent, even insoluble Ca-oxalate. If large quantities of oxalate-rich plants are ingested, the rumen is overwhelmed and cannot metabolize oxalates, poisoning the animal. A soluble oxalate level of 2% or more in forage grasses may cause severe poisoning in ruminants, but in non-ruminants, a level <0.5% is safe. However, these proposed safe levels of soluble oxalate should be considered preliminary (Rahman et al. 2013). Various tropical grasses, including pangola and buffel grasses, kikuyu-grass, and *Setaria* grasses, contain soluble oxalates in sufficient concentrations to induce Ca deficiency in grazing animals. Young plants contain more oxalate than older ones (Jones and Ford 1972). There is a rapid rise in oxalate content during the early stages of growth, followed by a decrease as the plant matures (Davis 1981). The highest oxalate content in grasses occurs during rapid growth, reaching concentrations up to 6% of the dry weight (Cheeke 1996). Additionally, oxalate content can be manipulated by varying the harvesting interval, decreasing with an increased harvest interval (Rahman et al. 2009; Patel et al. 2013).

4.3.3 Anti-vitamins

Some anti-vitamin factors are found in plants, especially leguminous plants. Anti-vitamins are organic compounds that destroy specific vitamins, combine and form non-absorbable complexes, or interfere with digestive and/or metabolic functions (Ramteke et al. 2019) (Table 4.6). Antivitamin A in raw soybeans contains lipoxygenase enzymes that oxidize carotene, a precursor of vitamin A. Heating soybeans can destroy it for 5 min at atmospheric pressure. Antivitamin D is a rachitogenic factor in isolated soy protein (unheated). It interferes with the absorption of Ca and P in pigs and chicks, and it is destroyed by autoclaving. Antivitamin E is present in soybeans and alfalfa, and it causes muscle dystrophy and liver necrosis in lambs and chicks by reducing plasma vitamin E. It is similarly destroyed by autoclaving. Antivitamin K in sweet clover causes a fatal haemorrhagic condition in cattle known as sweet clover disease. Dicoumarol reduces the levels of prothrombin in the blood and affects blood clotting. Other anti-vitamins include anti-thiamine, also called thiaminase, which is found in cotton seeds, linseed, mustard seed, and mung bean, and anti-niacin, which is found in sorghum, maize, and wheat bran and causes perosis (chondrodystrophy) and growth depression. Additionally, anti-pyridoxine, also called linatine, has been identified as 1-amino-D-proline, and is naturally occurring with glutamic acid as a peptide, and can be destroyed after water treatment and autoclaving. Finally, anti-vitamin B12 is found in raw soybeans (Ramteke et al. 2019).

4.3.4 Miscellaneous

4.3.4.1 Cyanogens

When consumed, several plant species produce hydrogen cyanide from cyanogenic glycosides, which are sugar glycosides or polysaccharides that combine with cyanide and contain aglycone (Fig. 4.11). More than 2500 plant species have been reported to contain cyanogenic glucosides, including important staple foods such as sorghum, cassava, white clover, and linseed (Rosling 1987; Vennesland et al. 1982). Cyanogenic glucosides, or cyanoglycosides, represent approximately 90% of the broadest group of plant toxins known as cyanogens. The main feature of these toxins is cyanogenes, the formation of free hydrogen cyanide, which binds to cyanohydrins that have been stabilized by glycosylation (binding of polysaccharides) to form cyanogenic glycosides. In addition, cyanogenic glucosides are classified as phytoanticipins. Their function in plants depends on activation by glucosidases to release toxic volatile hydrogen cyanide and aldehydes or ketones to repel herbivory and pathogens (Zagrobelny et al. 2004). Hydrogen cyanide inhibits the cytochrome oxidase enzyme in the mitochondria of cells by binding to the Fe^{3+}/Fe^{2+} present in the enzyme, resulting in decreased tissue O_2 utilization, causing increased levels of blood glucose and lactic acid, and reducing the ATP/ADP ratio, indicating a shift from aerobic to anaerobic metabolism.

Moreover, many enzyme systems inhibit growth by interfering with certain essential amino acids and utilizing associated nutrients (Table 4.6) and causing severe poisoning, neuropathy, and death (Osuntokun 1972). Cyanide activates the glycogenolysis process and converts glucose in the pentose phosphate pathway, which reduces the rate of glycolysis and inhibits the tricarboxylic acid cycle. Cyanide then reduces the energy availability in all cells, but its effect is immediate on the respiratory system and heart. Since cyanide is highly toxic, it inhibits cytochrome oxidase, which is the last step in electron transport, thus inhibiting ATP synthesis. The most obvious symptom is death, but before dying, symptoms include faster and deeper respiration, a faster irregular and weaker pulse, salivation and frothing mouth, muscular spasms, dilation of the pupils, and bright red mucous membranes. The potential toxicity of cyanogen depends mainly on the potential concentration of hydrogen cyanide that may be released upon consumption. When

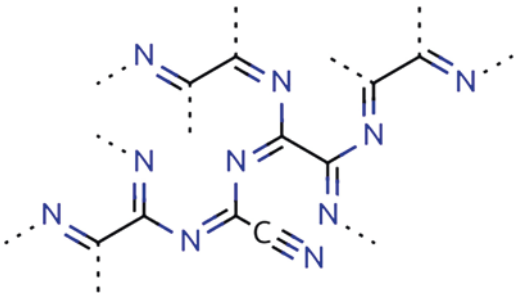

Fig. 4.11 Cyanogens and their basic structure

a cyanogenic plant is consumed, β-glycosidase is released during digestion and follows the known cyanide metabolic pathways and toxicokinetic processes in animals and humans (Oke 1979, 1980); it remains active until inactivated by a low gastric pH. After the catabolic intracellular enzyme β-glucosidase is released upon contact with glycosides, this enzyme breaks down cyanogenic glycosides releasing hydrogen cyanide, glucose, ketones, or benzaldehydes (Gonzales and Sabatini 1989; Rosling 1987; WHO 2010). The hydrolytic reaction can occur in the rumen by microbial activity. Hence, ruminants are more susceptible to cyanide toxicity than non-ruminants (Patel et al. 2013). After its absorption, cyanide is rapidly distributed in the animal body through the blood. It is known to combine with Fe in both methemoglobin and haemoglobin found in red blood cells, leading to an increased cyanide concentration in red blood cells compared with that of plasma. Cyanide is detoxified in the liver by the enzyme rhodanese, forming thiocyanate, which is excreted in the urine (Oke 1979, 1980). There is a range for the lethal dose of hydrogen cyanide in animals for various species (0.66–15 mg/kg body weight). For cattle and sheep, the range is 2.0–4.0 mg/kg body weight (Robson 2007).

Furthermore, a level greater than 50 mg/kg is harmful to poultry (Udedibie et al. 2004). Decreased growth and egg production rates have been observed in hens offered fed containing cyanide (Okafor and Okorie 2006), and the acute toxicity of hydrogen cyanide in rabbits occurs at 0.66 mg/kg body weight (EPA 1990). The presence of cyanogens in feed can also deplete sulfur-containing amino acids in birds, resulting in reduced protein synthesis and growth since an adequate amount of amino acids is one of the basic requirements for protein synthesis. The need to supplement cassava feed with methionine and cysteine (sulfur-containing amino acids) has been demonstrated for non-ruminant species (Maner and Gomez 1973).

4.3.4.2 Saponins

Saponins are a heterogeneous group of foam-producing triterpenes or steroidal glycosides that are widely distributed in nature, occurring primarily in the plant kingdom, including in pulses (chickpeas, beans, lentils, among others), oilseeds, groundnuts, lupin beans, sunflower, and alfalfa, with minor levels in other legumes such as soybeans, rapeseed, and various varieties of peas. The name ‘saponin’ is derived from the Latin word *sapo,* meaning ‘soap’ because saponin molecules form soap-like foams when shaken in water (Fig. 4.12). Saponins consist of non-polar aglycones coupled with one or more monosaccharide moieties (Oleszek 2002). This combination of polar and non-polar structural elements in their molecules explains their soap-like behavior in aqueous solutions. The structural complexity of saponins results in physical, chemical, and biological properties such as sweetness and bitterness, foaming and emulsifying, pharmacological and medicinal, hemolytic, antimicrobial, insecticidal and molluscicidal activities (Sparg et al. 2004; Gemede and Ratta 2014). Saponins have been recognized as ANF constituents because of their

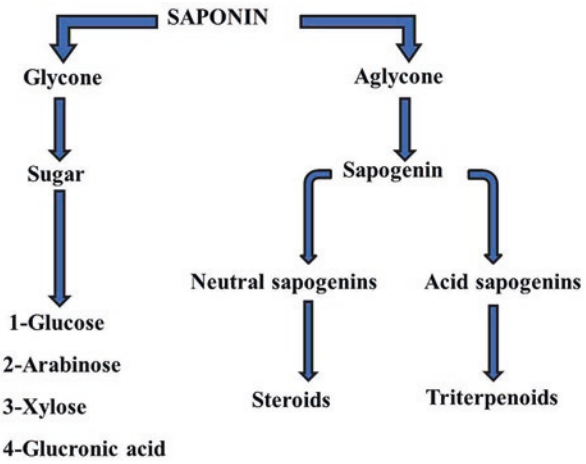

Fig. 4.12 Pathways of saponins synthesis

adverse health effects, including impaired growth and reduced feed intake owing to bitterness and throat irritation that they cause (Shi et al. 2004). Dietary saponins are poorly absorbed because they can form complexes with sterols, leading to harmful biological effects in the digestive system (Cheeke 1996). Saponins increase the permeability of intestinal mucosal cells, prevent active mucosal transport, and facilitate the uptake of substances that are not customarily absorbed (Johnson et al. 1986). In addition, they reduce the bioavailability of nutrients, decrease enzyme activity, and affect protein digestibility by inhibiting various digestive enzymes such as trypsin and chymotrypsin (Simee 2011). Saponins reduce the absorption of certain nutrients, including glucose and cholesterol, in the gut through an intra-lumenal physicochemical interaction (Table 4.6); hence, the effects of hypocholesterolaemia have been reported (Umaru et al. 2007). Additionally, saponins can form complexes with dietary Fe, rendering it unavailable for absorption (Southon et al. 1988). In fact, saponins have lytic action (the specific ability to form pores in membranes) on erythrocyte membranes, causing hemolysis in red blood cells (Seeman 1974). Since they reduce the surface tension of blood in cold-blooded animals, saponins have a highly toxic effect. They reduce growth performance in both poultry and swine. In chickens, saponins reduce growth and feed efficiency and interfere with the absorption of dietary lipids, vitamin A, and vitamin E (Jenkins and Atwal 1994). Compared with non-ruminants, poultry is more sensitive to saponins. Saponins increase the digestibility of carbohydrate-rich foods through a detergent-like activity that reduces viscosity, preventing the regular blocking action of such foods in the intestine. In general, saponins are of minor concern in non-ruminants because they are only present at low levels in common feedstuffs (Dublecz 2011).

4.3.4.3 Nitrates

Nitrates are ANF whose toxicity is associated with consumption of plants with high levels of nitrates, which causes health problems similar to bloating, sweet clover poisoning, or grass/winter tetany. Nitrate accumulates in plants damaged by frost, hail, drought, or even sudden cold and cloudy weather conditions. Also, high nitrates occur in forages subjected to excessive fertilization (Basso and Ritchie 2005). Affected plants must be grazed or harvested to avoid an adverse effect on livestock, especially ruminants. Nitrate toxicity is caused by excess nitrates in feeds, leading to a dangerous condition in ruminants due to a lack of O_2 in the bloodstream; death may result if not treated immediately. It is possible to treat nitrate toxicity, but it is challenging to identify animals with symptoms of this condition. Some forages such as Sudan grass, pearl millet (Andrews and Kumar 1992), and oats can accumulate nitrates at potentially toxic levels. Most nitrate is accumulated in the stem, followed by leaves, and very little in grains (Singh et al. 2000). Nitrate toxicity occurs mainly in ruminants when animals consume feed containing excess nitrate (NO_3^-), which is converted into nitrite (NO_2^-) by rumen bacteria (Fig. 4.13). Then, NO_2^- crosses the rumen wall and enters the bloodstream, where it combines with hemoglobin to form methemoglobin, which hampers the ability of red blood cells to carry O_2 into body tissues. NO_3^- at low levels in forages is converted into ammonia by bacteria in the rumen (Lee and Beauchemin 2014). This process is one of detoxification because NO_2^- is ten times more toxic than NO_3^-. This detoxification process occurs more slowly than the conversion of NO_3^- into NO_2^-. When microbes that convert NO_2^- to ammonia are overwhelmed by high NO_2^- levels in the rumen, toxicity will occur. NO_3^- and NO_2^- pass through the rumen wall and interfere with Fe ions in the red blood cells, and the ferrous Fe of hemoglobin turns into the ferric form; thus, forming methemoglobin. This metalloprotein, in which the iron in the heme group is in the Fe^{3+} (ferric) state, not the Fe^{2+} (ferrous), does not have the same O_2 carrying capacity as hemoglobin. So the tissues do not get enough O_2 and, thus, suffer from O_2 deprivation (Fig. 4.14). The blood turns to bluish chocolate-brown color rather than the usual bright red. An animal that dies from NO_3^- (NO_2^-) poisoning actually dies from a lack of O_2 (asphyxiation) (Benjamin 2006) (Table 4.6). When forages contain an unusually high level of nitrate, animals cannot complete the conversion process, consequently accumulating the nitrite (Table 4.5). A positive feedback loop occurs if the animals consistently have access to a high-nitrate

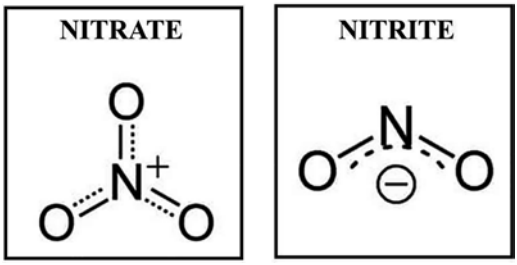

Fig. 4.13 Show the different chemical structures between nitrate and nitrite

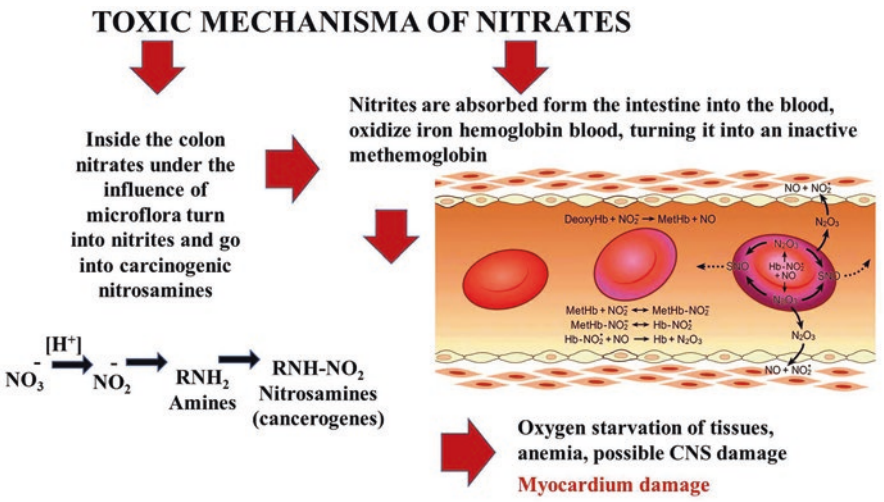

Fig. 4.14 Mechanism of nitrate toxicity

Table 4.5 Level of nitrate in forage (as DM basis) and potential effects on animals

Nitrate content (ppm)	Effect on animals
0–1000	This level is considered safe to feed under all conditions
1000–1500	This level should be safe to feed to non-pregnant animals under all conditions. It may be best to limit its use to pregnant animals to 50% of the total ration
1500–2000	Feeds are fed safely if limited to 50% of the ration
2000–3500	Feeds should be limited to 35–40% of the ration. Feeds containing over 2000 ppm nitrate- nitrogen should not be used for pregnant animals
3500–4000	Feeds should be limited to 25% of the ration. Do not use it for pregnant animals
> 4000	Feeds containing over 4000 ppm are potentially toxic. Do not feed

Adapted from Andrae (2008)

feed. While NO_3^- in the bloodstream, which does not initially cause toxicity problems, can be recycled back into the rumen via saliva or intestinal secretions and converted into NO_2^-. High-nitrate feed exacerbates the problems because NO_3^- is constantly being flooded into the system and either rapidly turns into NO_2^- in the rumen or enters the bloodstream to be recycled back into the rumen and reabsorbed into the blood as NO_2^-. The rate and quantity of forage consumption, type of forage, energy level, or diet adequacy are the factors that affect the severity of nitrate poisoning. Sheep, goats, and other ruminants are likely to suffer from NO_3^- toxicity as cattle. Sheep are the least sensitive to NO_3^- toxicity compared with cattle, which are the most sensitive. Sheep convert methemoglobin to hemoglobin and NO_2^- to ammonia more efficiently than cattle; therefore they can be safely fed feeds with a higher NO_3^- content (Benjamin 2006). Non-ruminants are unlikely to be affected by nitrate poisoning because NO_3^- is primarily converted into NO_2^- in the intestine,

Table 4.6 Deleterious and beneficial effects of some anti-nutrients on livestock

Anti-nutritional factors	Deleterious effects	Beneficial effects
Enzyme's inhibitors	Reduce protein digestion and absorption Disturb digestive functions Reduce bioavailability of minerals Decrease the growth Cause diarrhea or excessive gas Pancreatic hypertrophy Animal growth depression	Decrease the incidences of pancreatic cancer Act as anti-carcinogenic agents
Lectins (Haemagglutinins)	Impair animal growth Caused damage to the epithelium of the small intestine Reduced nutrient absorption Cause damage to the gastrointestinal tract Cause endogenous loss of nitrogen and protein utilization Increased protein catabolism, Breakdown of stored fats and glycogen Disturbance in mineral metabolism Stimulate hypertrophy and hyperplasia of the pancreas Cause hemagglutination and anemia Allow bacteria and their endotoxins to enter the bloodstream and cause a toxic response	
Tannins	Decreased growth rate Decrease bioavailability of amino acids Reduce protein digestibility Decreased palatability and feed intake A less digestible complex with dietary proteins Inhibit the endogenous protein such as digestive enzymes Interfere with dietary iron absorption Have the ability to complex with vitamin B	Show antioxidant, antibacterial, anti-diarrhea, free-radical scavenging, anti-proliferative activity Reduce protein degradation during ensilage Increase protein utilization efficiency Reduce parasite burden on gastrointestinal tract Prevent bloating Reduce N emissions into the environment Reduce methane emissions Increase animal product quality Improve live weight gain, reproductive efficiency, and wool production in sheep Increase amino acids absorption in the small intestine

(continued)

Table 4.6 (continued)

Anti-nutritional factors	Deleterious effects	Beneficial effects
Mimosine	Act as an amino acid Lead to inactivation of the catalytic, transaminases, Complicated with metal such as zinc Cause poor body growth, poor wool development Depress serum thyroxine level and goiter alopecia, dullness, swollen and raw coronets above the hooves, lesions of the mouth and esophagus, and lameness	
Phytic acid	Chelating of mineral cofactors or interacting with a protein Reduce mineral bioavailability and inhibit their absorption Inhibit the action of gastrointestinal tyrosinase, pepsin, trypsin, amylase, and lipase	A powerful natural antioxidant Reducing lipid peroxidation Reduce cholesterol Protect against cancer Against foodborne pathogen Coronary heart disease
Gossypol	Reduce protein digestion Reduce the availability of lysine to the non-ruminants Decreased appetite, weight gain, leg weakness, egg production, and egg size, decreased egg hatchability, caused egg yolk mottling, olive-green discoloration of egg yolk in poultry Decrease hemoglobin, total red blood cell count, protein and albumin to globulin ratio in blood serum	
Oxalates	Form insoluble calcium oxalate Negatively affect the absorption and utilization of calcium in the animal body Cause severe irritation to the lining of the gut	
Cyanogens	Depress growth Interfering with essential amino acids and utilization of nutrients Inhibit many enzyme systems Cause severe toxicity, neuropathy, and death Reduce energy availability in all cells Inhibit cytochrome oxidase Depression in birds growth and small eggs production Deplete the sulfur-containing amino acids for birds resulting in reduced protein synthesis Respiratory inhibitors	

(continued)

Table 4.6 (continued)

Anti-nutritional factors	Deleterious effects	Beneficial effects
Saponins	Reduce growth rate, bloat (ruminants) Reduce the absorption of nutrients (monosaccharide, glucose, and lipids) Hemolysis in erythrocytes Low blood and liver cholesterol Inhibition of smooth muscle activity Alter the integrity of intestinal epithelial cells Inhibit microbial fermentation and synthesis in the rumen	Antibacterial and antiprotozoal, antioxidants, antitumor property Lowering cholesterol Immune potentiating Bind ammonia and hydrogen sulfide, thus improving air quality in poultry houses Reduced risk of coronary heart diseases Form of first collagen that has a role in the wound-healing process (hydrocarbon ointment)
Nitrate	Nitrite poisoning Convert haemoglobin in the blood to methaemoglobin (blood turns to a chocolate brown color) Animal death from asphyxiation	
Alkaloids	Cause gastrointestinal and neurological disorders Cause infertility	
Anti-vitamins	From non-absorbable complexes Interfere with digestive and/or metabolic functions Anti-vitamin A Anti-vitamin D interferes with the absorption of calcium and phosphorous in chicks and pigs, Anti-vitamin E causing liver necrosis and muscle dystrophy in chicks and lambs Anti-vitamin K causes a fatal haemorrhagic condition in cattle (known as sweet clover disease) Anti-niacin causes Perosis and growth depression	

closer to the end of the digestive system, thus reducing the chance for NO_2^- being absorbed into the bloodstream. However, NO_3^- poisoning in non-ruminants is still possible, but it is not as severe as in ruminants (Okafor and Okorie 2006). In ruminants, NO_3^- toxicity is most commonly reported in ruminants grazing fresh herbage. Due to insufficient data on nitrite levels in the most common livestock diet feeds, reliable exposure estimates can be calculated. The highest estimated dietary exposure of cattle to NO_3^- from feed was for beef cattle fed a grass silage-based diet (53 mg/kg body weight/day). For sheep and goats, the categories 'lactating sheep' and 'goats for fattening' had the highest estimates of exposure to NO_3^- from the

silage-based diet, at 46 and 60 mg/kg body weight/day, respectively. In non-ruminants, exposure estimates are low (from the average upper limit 5.6 mg/kg body weight/day in laying hens). However, this may be underestimated due to the lack of data on key ingredients in their diets (EFSA 2020). Risks of nitrate poisoning exist, mainly when animals are not accustomed to consuming nitrate-containing feeds. When animals are introduced to these feeds slowly over time, they can slowly adapt to a feed intake with at least 1% nitrates; it is important to note that this introduction must be prolonged for feeds high in nitrates. Acute toxicity signs and symptoms include a rapid and weak heartbeat, an abnormal body temperature, muscle tremors, weakness, and ataxia. Additionally, brown/bluish-grey mucous membranes, excessive salivation, lacrimation, labored and rapid breathing, frequent urination, vomiting (more common in non-ruminants), diarrhea or scouring, and an inability to get back up from laying down are all common symptoms. Death follows within a few hours of feeding cattle with a nitrate-rich forage. Animals die from asphyxiation due to a lack of O_2 in the body tissues. Subacute nitrate poisoning often corresponds to decreased weight, decreased feed intake, decreased milk production, increased susceptibility to infections and diseases, and reproductive problems such as silent heats and reduced fertility (Lee and Beauchemin 2014).

4.3.4.4 Alkaloids

Alkaloids are common groups of chemical compounds synthesised by plants from amino acids. They are generally found as salts such as malic, oxalic, citric, or tartaric acids (Yilkal 2015), which are small organic molecules found in 15–20% of all plants. Usually, alkaloids consist of several carbon rings with side chains replaced by one or more carbon or nitrogen atoms. Decarboxylation of amino acids produces amines that react with amine oxides to form aldehydes. The distinctive heterocyclic ring in alkaloids undergoes Mannich-type condensation of aldehyde and amine groups (Felix and Mello 2000; Yilkal 2015). The chemical type of their nitrogen ring provides how the alkaloids are sub-classified; for example, glycoalkaloids (aglycone fraction) glycosylated with a carbohydrate moiety are formed as metabolic by-products. Plants repel insects and herbivores with alkaloids due to their potential toxicity and bitter taste (Fereidoon 2012, 2014; Yilkal 2015). Lupins contain high alkaloids, specifically quinolizidine alkaloids, while soybeans and linseed may be contaminated by *Datura stramonium*. Linseed also contains scopolamine and hyoscyamine alkaloids (Dublecz 2011).

Potato tubers naturally contain the two toxic and bitter glycoalkaloids, a-solanine, and a-chaconine. The levels are usually low and have no adverse effects on food safety or culinary quality. However, consumption of potato tubers that are unusually high in glycoalkaloids has sometimes been associated with severe toxicity, including gastrointestinal and neurological disturbances, and the disruption or inappropriate augmentation of electrochemical transmission (Fernando et al. 2012). In tubers, glycoalkaloid levels are inheritable and vary significantly between different species. Environmental factors to which tubers are exposed during germination, growth,

harvest, and storage may further affect glycoalkaloid levels (Jadhav et al. 2009). Indeed, the physiological effects of alkaloids on humans and animals are quite evident (Gemede and Ratta 2014). Consuming a high dose of tropane alkaloids accelerates the heartbeat, causes paralysis and fatality. Ingesting a high dose of tryptamine alkaloids causes a staggering gait and death (Fernando et al. 2012; Gemede and Ratta 2014). Alkaloids are oxidized in the liver to produce metabolites, such as dehydrosparteine, responsible for the observed toxicity. The level of toxicity is affected by the alkaloid composition. There is a high degree of variation in the ability of different animal species to deal with these compounds. Toxicity by alkaloids and their metabolites is mainly mediated through the nervous system, although they also stimulate the liver cells to absorb copper, resulting in copper toxicity. Pigs appear to be more sensitive to alkaloids than poultry. Glycoalkaloids significantly inhibit cholinesterase, and this also causes symptoms of neurological disorders. Alkaloids cause gastro intestinal and neurological disorders (Aletor 1993; Stegelmeier et al. 2020). Coumarins, which are feed components, have been associated with hemorrhagic disease in cattle that consume spoiled sweet clover. Alkaline pH conditions generally improve glycoalkaloid absorption, as binding to sterols in cell membranes leads to extra disruption. Nicotine (tobacco), cocaine (leaves of coca plant), caffeine, quinine (cinchona bark), morphine (dried latex of opium poppy), and solanine (unripe potatoes and potato sprouts), and strychnine are well-known examples of alkaloids. Pyrrolizidine alkaloid toxicity causes liver damage in chickens that initially might not show any clinical signs. The symptoms may appear very vague and are often confused with other diseases. Toxicity occurs in chickens of all ages and breeds, but not all flock members show signs of liver damage. Clinical symptoms of pyrrolizidine alkaloid poisoning include loss of appetite, lethargy, neurobehavioral abnormalities, and excessive drinking.

4.4 Mechanism of ANFs Toxicity

Protease inhibitors reduce protein digestion, so when legumes are eaten either raw or without being properly cooked, they disturb digestive functions and cause diarrhea or excessive gas (Thakur et al. 2019). Feeding animals with raw soybean or isolated soybean inhibitors causes a pancreatic enlargement in susceptible animals, which can be characterized histologically as hypertrophy (i.e., an increase in the size of pancreatic acinar cells) (Friedman and Brandon 2001); this is accompanied by an increase in the secretion of digestive enzymes including trypsin, chymotrypsin, and elastase. This supports the hypothesis that the growth inhibition caused by trypsin inhibitors results from an endogenous loss of amino acids in the form of enzymes secreted by a hyperactive pancreas. Pancreatic enzymes, such as trypsin and chymotrypsin, are particularly rich in sulfur-containing amino acids. Hence, the outcome of pancreatic hyperactivity is converting these amino acids from body tissue protein synthesis to the synthesis of these enzymes, which are subsequently lost in feces (Friedman and Brandon 2001). Trypsin inhibitor-induced pancreatic

hypertrophy/hyperplasia observed in susceptible animal species has been explained by an adverse reaction mechanism where enzyme secretion is inversely related to the level of trypsin present in the small intestine (Liener 1994). Therefore, when the level of active trypsin in the gut is reduced due to the inhibitor's presence, the pancreas compensates by producing more enzymes. Mimosine's function is unclear, but it may act as an amino acid, lead to inactivation of the catalyst (transaminase), or bind to a mineral such as zinc (Hiremat 1981). To overcome the mimosine problem, *Leucaena leucocephala* should be restricted to 50% green forage for goats and 30% for cattle and buffalo (Hegarty 1987). The effects of tannins come from their ability to form strong H-bonds with nutrients, resulting in the inhibition of digestive enzymes and microbial activity in the rumen (Kumar and Singh 1984). These effects can be significantly increased with an increase in tannin molecules. It is well known that tannins are potential protein precipitants (Ahmed et al. 1991) and reduce animal protein digestibility (Salunkhe et al. 1990; Jansman 1993). The increase in faecal nitrogen associated with the ingestion of tannin-containing feed is largely due to interactions between tannin and dietary proteins or tannin and digestive enzymes, or both (Jansman 1993; Kelln et al. 2021). In a study by Ahmed et al. (1991), diets containing tannins, mostly hydrolyzable gallotannins, were fed to broilers at 13.5, 25, and 50 g/kg to verify their effects on enzymes in the pancreas, intestinal lumen, and intestinal mucosa. Pancreatic weight showed a significant increase with an increased dietary tannin level. The activities of trypsin and α-amylase in the pancreas of birds fed the highest level of tannins were more than double those of birds fed a tannin-free diet. In the intestinal lumen, the inhibition of trypsin activity increases with an increase in dietary tannin level. Likewise, dipeptidase and sucrose α-glucosidase were inhibited by tannins in the intestinal mucosa. Protein digestion and bird growth were negatively affected by tannin-containing diets. Similarly, feeding pigs with fava bean hulls high in tannins significantly reduced aminopeptidase activity in the jejunal mucosal homogenates in young piglets (Van Leeuwen et al. 1995). Low aminopeptidase activity was associated with decreased protein digestibility. Pancreatic enlargement caused by diets containing tannins may be mediated by hormones transported in the blood (Ahmed et al. 1991). The pancreatic enlargement caused by dietary tannins has also been reported in response to dietary trypsin inhibitors (Liener 1994). This might indicate a common mode of action for these ANFs, at least on the cellular level. The consumption of tannin-rich sorghum, CT, which has been isolated and purified from sorghum, or tannic acid, increase the size of the parotid glands, synthesis and secretion of proline-rich proteins (Mehansho et al. 1992), and the synthesis of proline-rich proteins secreted with saliva and associated with dietary tannins in the oral cavity to protect dietary protein. The association of tannins with dietary and endogenous proteins, such as digestive enzymes and proteins located on the luminal side of the intestine, has been used to explain the reduced digestion of protein in diets containing tannins (Jansman et al. 1994). There is no clear evidence for systemic effects in animals after they have been intensively fed with CT. It is hypothesized that CTs are resistant to intestinal degradation and are poorly absorbed due to forming a less digestible compound with dietary proteins. They may bind and inhibit endogenous proteins, including digestive enzymes.

These compounds are astringent and negatively affect animal feed intake (Patel et al. 2013). CT concentration above 4% of diet is toxic to ruminants because they are resistant to microbial attack and are harmful to various microorganisms (Waghorn 2008), resulting in reduced palatability, feed intake, growth rate, utilization, and iron absorption (Roeder 1995). Phytate can adversely affect digestive enzyme activity by chelating mineral cofactors or interacting with proteins at an acidic or alkaline pH (Ryden and Selvendran 1993; Khare 2000). For full activity, some digestive enzymes require metal cofactors, such as calcium, zinc, copper, magnesium, iron, and molybdenum. For example, these enzymes include α-amylase, carboxypeptidases, aminopeptidases, and alkaline phosphatase. Phytate binding to proteins may directly form phytate-protein complexes or indirectly form phytate-cation-protein complexes. These processes may differ according to pH, time, and relative concentrations (Ryden and Selvendran 1993). At the low pH in the stomach, the positively charged side-groups of protein essential amino acids can bind to the negatively charged phytate due to strong electrostatic interactions (Cheryan 1980; Deshpande and Cheryan 1984). Above its isoelectric point, the protein carries a net negative charge. A multivalent cation bridge (which includes calcium) appears to be involved in the complex formation between phytate and proteins. Phytate–cation–protein interactions are expected to be predominant at high pH in the small intestine (Selle et al. 2000). Another indirect mechanism for phytate inhibition of digestive enzyme activity measured in vitro has been proposed to include complex interactions between phytate, digestive enzymes, and other proteins present in solution (Li et al. 1993). These interactions also inhibit the action of gastrointestinal tyrosinase, pepsin, trypsin, amylase, and lipase (Khare 2000). Oxalic acid binds with calcium to form insoluble calcium oxalate, which negatively affects the absorption and utilization of calcium in the bodies of animals (Akande et al. 2010). Gossypol binds to proteins and/or to a group of free essential amino acids. In particular, gossypol binds to lysine in cottonseed meal, resulting in BG, which is less toxic to non-ruminants than is free gossypol. The free and BG content in the meal varies with the cultivar and the type of treatment. Gossypol reduces protein digestion in two ways. First, by binding to free epsilon amino group of lysine during heat treatment and the gossypol-protein complex formed in the meal makes the adjacent peptides unavailable for proteolytic action. Second, gossypol may directly affect certain enzymes in the gastrointestinal tract, such as pepsinogen, pepsin, and trypsin, by binding to the free epsilon amino groups (Sharma et al. 1978). Gossypol toxicity in poultry results in decreased appetite, weight loss, leg weakness, reduced egg production, and egg size, egg yolk discoloration, and decreased egg hatchability, hemoglobin, total red blood cell count, protein, and albumin-to-globulin ratio in blood serum (Waldroup and Goodner 1973; Suryawanshi et al. 1993). Saponins decrease the absorption of certain nutrients, including monosaccharides, glucose, and cholesterol in the gut through intraluminal physical and chemical interactions; thus, they have been reported to have hypocholesterolemic effects (Umaru et al. 2007). Additionally, saponins have distinctive foaming properties, as observed in white clover and alfalfa. Saponins can negatively affect animal performance and metabolism in several ways: hemolysis in erythrocytes, low blood and liver cholesterol, reduced

growth rate and bloat in ruminants, inhibition of enzyme and smooth muscle activity, reduced absorption of nutrients, and inhibition of microbial fermentation and synthesis in the rumen (Akande et al. 2010). However, saponins have diverse biological effects due to structural differences in sapogenin fractions. Finally, some plant alkaloids have been reported to cause digestive and nervous disorders and infertility (Aletor 1993; Olayemi 2010), while glycoalkaloids (solanine and chaconine), found in potatoes and *Solanum* spp. (Saito et al. 1990; Aletor and Adeogun 1995) are toxic to humans (Table 4.6).

4.5 Methods of Reducing the Deleterious Effects of ANFs

The abundance of ANFs and consequent toxic effects in the plant-based diets of animals is a cause for concern, and ways to reduce their levels should be explored (Soetan and Oyewole 2009). Removing undesirable components is essential for improving a plant-based diet's nutritional quality and effectively utilizing its full potential as a feed source for livestock. It is widely accepted that simple and inexpensive processing techniques effectively achieve desirable changes in feed ingredient composition (Akande and Fabiyi 2010). Uhegbu et al. (2009) reported the effects of several methods tested to overcome ANFs and their harmful effects in various browses, grains, seeds, and agro-industrial by-products. These methods include mechanical or physical techniques (e.g., processing, wilting, and ensiling) and biological or chemical techniques (e.g., treatment with alkalis, organic solvents, and precipitants). In general, of the different processing methods that are used to reduce levels of various ANFs (soaking, boiling, and toasting) (Balogun 2013), soaking is one of the most common methods to lower trypsin inhibitors (from 13.8 to 9.4 TIU/100 g), phytates (from 0.18% to 0.09%), tannins (from 0.23% to 0.09%), saponins (from 0.42% to 0.24%), hydrogen cyanide (from 8.6% to 5.7%), and alkaloids (from 0.34% to 0.28%) -(Nwosu 2010). Boiling, simmering, and blanching reduce the cyanide content in *Moringa oleifera* leaves by 88%, 81%, and 62%, respectively (Sallau et al. 2012). Owing to the water solubility of oxalates, wet treatment methods such as boiling and steaming produce the highest oxalate reduction (Mada et al. 2012; Petroski and Minich 2020). Autoclaving seeds for 20 min reduce phytic acid by 24.7%, while roasting can reduce phytic acid content by 23.1–28.6% (Embaby 2011). Amaefule and Onwudike (2000) and Kankuka et al. (2000) reported that cooking legumes improve their nutritional value by destroying most ANFs and improving protein and energy availability. Autoclave treatment or boiling also reduces the content of protease inhibitors. Ramteke et al. (2019) reported that the trypsin inhibitor activity of soybean meal was destroyed by autoclaving under specific conditions (i.e., 5, 10, and 15 psi for 45, 30, and 20 min, respectively) or by exposure to steam for 60 min. Likewise, a longer boiling time (40 min), autoclaving (20 min), and microwaving (12 min) cause complete disruption of trypsin inhibitor activities (Sallau et al. 2012). Although lectins are usually degradable, their stability varies among plant species, as many lectins are resistant to dry heat inhibition and

require moisture for destruction (Boehm and Huck 2009; Ramteke et al. 2019) or can quickly disintegrate by hydrothermal treatment (100 °C for 10 min) or autoclaving (Grant 1991). Physical treatments such as heat and chemical treatments or supplementation with amino acids or mineral ions such as Zn, Fe, and Al reduce mimosine's toxicity (Hiremat 1981). Other processing methods, like germination followed by dehulling, reduce tannins by 43–52% and phytic acid by 47–52% (Ghavidel and Prakash 2006). Polyethylene glycol is the most frequently used reagent to neutralize the secondary compounds in tannin-rich diets for animals. It can be used in various ways, such as applied in concentrate or feed blocks, sprayed on feed, or dissolved in water. Additionally, polyethylene glycol is an effective supplement for increasing feed intake, digestion, daily weight gain, and the synchronized, fractionated, and balanced supply of essential nutrients for rumen microflora and host animals fed on diets rich in tannins (Mueller 2001; Patel et al. 2013). Fermentation can reduce some anti-nutrients in feed, such as phytic acid and tannins (Sarangthem and Singh 2013; Singh et al. 2017). This method could also improve the nutritional value of cottonseed meal and increase the lysine and methionine content of cottonseed meal when fermented with Aspergillus oryzae NRRL 506 *Aspergillus Janus* NRRL 1935 for 48 h (Nagalakshmi et al. 2007). One of the recent trends in reducing free gossypol content in cottonseed meal is to produce varieties of cotton plants through genetic modification; however, other cotton seed processing methods such as pelleting, extrusion, cooking, and $Ca(OH)_2$ can be used to improve the nutritional value of cottonseed meal for poultry (Nagalakshmi et al. 2007). Treatment with iron 1: 1 ratio can remove 80–99% of gossypol; moreover, high protein content in the meal is also helpful in reducing the effect of gossypol (Leeson and Summer 2001). Moreover, using exogenous phytases to enhance phosphorous digestibility is now common practice where animal agriculture's contribution to environmental pollution is of concern. The phytase enzyme releases phosphorus, bound minerals, and amino acids from phytate, increasing nutrient utilization. Evidence indicates that phytases enhance ileal amino acids, which increase the body's nitrogen, calcium, and phosphorus retention and increase fecal energy digestibility in poultry (Woyengo and Nyachoti 2011). The use of gamma irradiation to reduce anti-nutrients in canola meal causes a significant increase in its nutritional value for broilers (Gharaghani et al. 2008). Finally, the use of the electron beam radiation method reduces hydrocyanic, phytic, and tannic acids.

4.6 Beneficial Effects of Anti-nutritional Factors

The potential beneficial effects of protease inhibitors remain unclear. However, a decrease in the incidence of pancreatic cancer has been observed in a population where the consumption of soybean and its products was high (Giri and Kachole 1998) (Table 4.6). Additionally, protease inhibitors have been associated with pancreatic cancer in animal studies, and they may act as anti-carcinogenic agents (Chunmei et al. 2010). It is not necessary to completely eliminate anti-nutritional

factors from plant-based diets such as that of *Moringa oleifera* leaves because low amounts of ANFs, such as tannins and hydrolyzable phenols, may act as antioxidants in animal feed and may not only help improve meat quality but also reduce methane emissions (Su and Chen 2020) and gastrointestinal nematodes (Naumann et al. 2017) from ruminants. The benefits of tannins in animal feed and health include increased protein utilization efficiency, amino acid absorption (Hervás et al. 2003), antioxidants, antibacterial and anti-diarrhoeal effects, free-radical scavenging, and anti-proliferative activity (Corder 2006). Also, tannins reduce the impact of gastrointestinal parasitism, protein degradation during ensilage (Reed et al. 1990), prevent bloating, increase animal product quality, reduce N emission to the environment and promote rumen defaunation as a CH_4 mitigation strategy (Animut et al. 2008; Boadi et al. 2004), and reduce methane emissions from rumen fermentation (Waghorn 2008) (Table 4.6). CTs help to improve weight gain, reproductive efficiency, and wool production in sheep, reduces the effect of gastrointestinal parasitism, and lessens methane emissions from rumen fermentation (Waghorn 2008), allows dietary protein to bypass the rumen for digestion in the lower gastrointestinal tract (Hassanpour et al. 2011), and shows a bacteriostatic effect on *Salmonella enteritidis* infection in broiler chickens and can reduce excretion of these bacteria (Redondo et al. 2013a). Both HT and CT have antimicrobial activity against *Campylobacter jejuni* (Anderson et al. 2012; Gutierrez-Banuelos et al. 2011). The *in vivo* effects of tannins in the necrotic enteritis model reduce the incidence and severity of gross lesions and improve broilers' productive performance (Redondo et al. 2013b). Tannic acid can treat diarrhea because it causes constipation without inflammation (Phytolab 2007).

Phytic acid has been suggested as a store of cations, high-energy phosphoryl groups, and free iron chelates, making phytic acid a potent natural antioxidant (Mueller 2001). In addition, phytic acid can reduce cholesterol and protect against iron-induced intestinal cancer. Furthermore, phytic acid exhibits natural antioxidant properties, providing other benefits such as reducing lipid peroxidation (Table 4.6). Of the many plant compounds, saponins have beneficial biological effects, including antibacterial, antiprotozoal (Avato et al. 2006), antioxidant, antitumor, cholesterol-lowering, immune-potentiating, and anticancer (Blumert and Liu 2003) effects. Furthermore, saponins reduce the risk of coronary heart diseases (Ferri 2009) and the probability of forming collagen, a protein with a role in wound healing that can also be used as a hydrocarbon ointment. Saponins attract considerable interest due to their beneficial effects in the poultry industry; they can bind ammonia and hydrogen sulfide, thus improving air quality in poultry houses (Tab*le* 4.6).

4.7 Conclusions

Anti-nutritional factors (ANFs) in plant-based protein diets for livestock may reduce their full utilization. Thus, to justify the nutritional value of any plant-based protein source, it is imperative to appropriately assess the nature, type, and concentration of

the ANFs present in the diet and the bioavailability of the required nutrients. Basic information about the most common factors found in plants used for animal feed includes protease inhibitors, amylase inhibitors, lectins, tannins, mimosine, phytic acid, gossypol oxalates, cyanogens, saponins, nitrates, alkaloids, and anti-vitamin agents. These ANFs interfere with the nutritional value of feed by reducing digestion, absorption, and utilization of proteins and minerals that cause toxicity and lead to undesirable effects on animal health if their consumption is excessive. However, these ANFs may have beneficial health effects if they are present in low amounts. Risk factors associated with ANFs include a lack of knowledge on tolerance levels of these compounds in livestock, limited information on the degree of variability of individual risk, and lack of knowledge regarding the influence of environmental factors on the detoxification capacity of livestock feed. Thus, using appropriate and effective techniques and methods alone or in combinations can help eliminate or reduce the harmful effects of these ANFs in plant-based diets and, therefore, improve their nutritional value. Several strategies are used to counteract the effects of ANFs, including physical and chemical treatments, supplementation with enzymes, amino acids or mineral ions, germination, fermentation, and genetic modification.

References

Abbas G (2020) An augmented review about anti-nutrients and toxins of feedstuff and their control strategies, a step toward sustainable resource utilization. Int J Agric Innov Res 8:2319–1473

Abou-Donia MB, Othman MA, Obih P (1989) Interspecies comparison of pharmacokinetic profile and bioavailability of (±)-gossypol in male Fischer-344 rats and male B6C3F mice. Toxicology 55:37–51. https://doi.org/10.1016/0300-483x(89)90173-x

Adeyemo GO (2008) Effects of cottonseed cake-based diets on haematology and serum biochemistry of egg-type chickens. Int J Poult Sci 7:23–27

Ahmed AE, Smithard R, Ellis M (1991) Activities of enzymes of the pancreas, and the lumen and mucosa of the small intestine in growing broiler cockerels fed on tannin-containing diets. Br J Nutr 65:189–197. https://doi.org/10.1079/bjn19910080

Akande KE, Fabiyi EF (2010) Effect of processing methods on some anti-nutritional factors in legume seeds for poultry feeding. Int J Poultry Sci 9:996–1001. https://doi.org/10.3923/ijps.2010.996.1001

Akande KE, Doma UD, Agu HO, Adamu HM (2010) Major anti-nutrients found in plant protein sources: their effect on nutrition. Pak J Nutr 9:827–832. https://doi.org/10.3923/pjn.2010.827.832

Akinmutimi AH (2007) Effect of cooking periods on the nutrient composition of velvet beans (*Mucuna pruscens*). In: Proceeding of the 32nd annual conference of the Nigerian society for animal production march 18th–21st. University of Calabar, Calabar, pp 223–236

Aletor VA (1993) Allelochemicals in plant foods and feeding Stuffs. Part I. Nutritional, biochemical and physiopathological aspects in animal production. Vet Hum Toxicol 35:57–67

Aletor VA, Adeogun OA (1995) Nutrient and anti-nutrient components of some tropical leafy vegetables. Food Chem 53:375–379. https://doi.org/10.1016/0308-8146(95)99830-S

Alexander J, Benford D, Cockburn A et al (2008) Gossypol as undesirable substance in animal feed. EFSA J 908:1–55. https://doi.org/10.2903/j.efsa.2009.908

Amaefule KU, Onwudike OC (2000) Comparative evaluation of the processing methods of pigeon pea seeds (*Cajanus cajan*) as protein source for broilers. J Sustain Agric Environ 1:134–136
Anderson RC, Vodovnik M, Min BR, Pinchak WE, Krueger NA, Harvey RB et al (2012) Bactericidal effect of hydrolysable and condensed tannin extracts on Campylobacter jejuni *in vitro*. Folia Microbiol 57:253–258. https://doi.org/10.1007/s12223-012-0119-4
Andrae J (2008) Preventing prussic acid poisoning, Forage Leaflet, 13. Clemson University
Andrews DJ, Kumar KA (1992) Pearl millet for food, feed and forage. Adv Agron 48:89–139. https://doi.org/10.1016/S0065-2113(08)60936-0
Animut G, Puchala R, Goetsch AL, Patra AK, Sahlu T, Varel VH, Wells J (2008) Methane emission by goats consuming diets with different levels of condensed tannins from lespedeza. Anim Feed Sci Technol 144: 212–227
Avato P, Bucci R, Tava A, Vitali C, Rosato A, Bialy Z, Jurzysta M (2006) Antimicrobial activity of saponins from *Medicago* spp.: Structure-activity relationship. Phytother Res 20:454–457. https://doi.org/10.1002/ptr.1876
Bala SM, Ameh DA, Omage JJ, Bugaje SM, Makeri MU, Dikko H, Usman MS (2013) Influence of processing method on the nutrients and antinutrients content of kernels of three nigerian local mango (mangifera indica l.) varieties. Journal of Applied Agricultural Research 5:203–213
Bajpai S, Sharma A, Gupta MN (2005) Removal and recovery of antinutritional factors from soybean flour. Food Chem 89:497–501. https://doi.org/10.1016/j.foodchem.2004.02.055
Balogun BI (2013) Evaluation of the nutritional potentials of fermented oil beans seed Pentaclethra macrophyllah Benth. PAT Nsuka J 9:73–87
Bardocz S, Grant G, Ewen SW, Duguid TJ, Brown DS, Englyst K, Pusztai A (1995) Reversible effect of phytohaemagglutinin on the growth and metabolism of rat gastrointestinal tract. Gut 37:353–360. https://doi.org/10.1136/gut.37.3.353
Barry TN, McNabb WC (1999) The implications of condensed tannins on the nutritive value of temperate forages fed to ruminants. Br J Nutr 81:263–272
Barraza ML, Coppock CE, Brooks KN, Wilks DL, Saunders RG, Latimer GW Jr (1991) Iron sulfate and feed pelleting to detoxify free gossypol in cottonseed diets for dairy cattle. J Dairy Sci 74:3457–3467. https://doi.org/10.3168/jds.S0022-0302(91)78536-6
Basso B, Ritchie JT (2005) Impact of compost, manure and inorganic fertilizer on nitrate leaching and yield for a 6-year maize–alfalfa rotation in Michigan. Agric Ecosyst Environ 108:329–341. https://doi.org/10.1016/j.agee.2005.01.011
Bedford MR (2000) Exogenous enzymes in monogastric nutrition their current value and future benefits. Anim Feed Sci Technol 86:113
Benjamin DN (2006) Effect of fertilizer application and cutting interval on nitrate accumulation in bermudagrass. M.Sc. (Agri.), Thesis, University Tennesse, Martin, TN
Bhattarai S, Coulman B, Biligetu B (2016) Sainfoin (*Onobrychis viciifolia* Scop.): renewed interest as a forage legume for western Canada. Can J Plant Sci 96:748–756. https://doi.org/10.1139/cjps-2015-0378
Bhutkar MA, Bhise SB (2012) *In vitro* assay of alpha amylase inhibitory activity of some indigenous plants. Int J Chem Sci 10:457–462. https://doi.org/10.31031/MAPP.2018.01.000518
Blumert M, Liu J (2003) Jiaogulan (*Gynostemma pentaphyllum*), China's Immortality Herb, 3rd edn. Torchlight
Boadi D, Benchaar C, Chiquette J, Massé D (2004) Mitigation strategies to reduce enteric methane emissions from dairy cows: update review. Can J Anim Sci 84:319–335
Boehm S, Huck S (2009) Presynaptic inhibition by concanavalin: are alphalatrotoxin receptors involved in action potential-dependent transmitter release? J Neurochem 71:2421–2430
Bora P (2014) Anti-nutritional factors in foods and their effects. J Acad Ind Res 3:285–290
Cheeke PR (1996) Biological effects of feed commercial use and forage saponins and their impact on animal production. In: Saponins used in food and agriculture. Plenum Press, New York, pp 377–386. https://doi.org/10.1007/978-1-4613-0413-5_32
Cheryan M (1980) Phytic acid interactions in food systems. CRC Crit Rev Food Sci Nutr 13:297–335. https://doi.org/10.1080/10408398009527293

Chunmei G, Hongbin P, Zewei S, Guixin Q (2010) Effect of soybean variety on anti-nutritional factors content, and growth performance and nutrients metabolism in rat. Int J Mol Sci 11:1048–1056. https://doi.org/10.3390/ijms11031048

Church DC (1991) Livestock feeds and feeding, 3rd edn. Prentice Hall Incorporation, New Jersey, p 546

Corder R (2006) Tannins in some European Reds have Greater Protective Effects on Heart than Other Red Wines. Nature Online Advance Edition. News Release, Queen Mary University of London. http://www.cbsnews.com/stories/2006/11/29/health/webind/main2215429.html

D'Mello JPF (2000) Anti-nutritional factors and mycotoxins. In: Farm animal metabolism and Soybeans. CAB International, Wallingford, pp 383–403. https://doi.org/10.1079/9780851993782.0383

Davis AM (1981) The oxalate, tannin, c rude fiber, and crude protein composition of young plants of some Atriplex species. J Range Manag 34:329–331. https://doi.org/10.2307/3897862

Davis AJ, Lordelo MM, Dale N (2002) The use of cottonseed meal with or without added soapstock in laying hen diets. J Appl Poult Res 11:127–133. https://doi.org/10.1093/JAPR/11.2.127

Deshpande SS, Cheryan M (1984) Effects of Phytic acid, divalent cations, and their interactions on α-amylase activity. J Food Sci 49:516–524. https://doi.org/10.1111/j.1365-2621.1984.tb12456.x

Degan AA, Becker K, Makkar HPS, Borowy N (1995) Acacia saligna as fodder tree for desert livestock and the interaction of its tannins with fiber fractions. J Sci Food Agric 68:65–71

Diarra SS, Usman BA, Kwari ID, Yisa A (2008) Effect of processing methods on the antinutrional factor and the nutritional composition of sesame seed. Sahel J Vet Sci 7:16–20. https://www.ajol.info/index.php/sjvs/article/view/41483

Dube JS, Reed JD, Ndlovu LR (2001) Proanthocyanidins and other phenolics in Acacia leaves of Southern Africa. Anim Feed Sci Technol 91: 59–67. https://doi.org/https://doi.org/10.1016/S0377-8401(01)00229-2

Dublecz K (2011) Animal nutrition. http://www.tankonyvtar.hu/en/tartalom/tamop425/0010_1A_Book_angol_04_takarmanyozastan/index.html

East NE, Anderson M, Lowenstine LJ (1994) Apparent gossypol-induced toxicosis in adult dairy goats. J Am Vet Med Assoc 204:642–643

EFSA CONTAM Panel, Schrenk D, Bignami M, Bodin L, Chipman JK, del Mazo J, Grasl Kraupp B, Hoogenboom LR, Leblanc JC, Nebbia CS, Nielsen E, Ntzani E, Petersen A, Sand S, Schwerdtle T, Vleminckx C, Wallace H, Bampidis V, Cottrill B, Frutos MJ, Fürst P, Parker A, Christodoulidou A, Gergelova P, Hogstrand C (2020) Risk assessment of nitrate and nitrite in feed. EFSA J 18:6290, 110 pp. https://doi.org/10.2903/j.efsa.2020.6290

Embaby HE-S (2011) Effect of heat treatments on certain Antinutrients and in vitro protein digestibility of Peanut and sesame seeds. Food Sci Technol Res 17:31–38. https://doi.org/10.3136/fstr.17.31

EPA (1990) Summary review of health effects associated with hydrogen cyanide, Health Issue Assessment Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment Office of Research and Development, US Environmental Protection Agency Research Triangle Park, North Carolina, USA

Erdman JW (1979) Oilseed phytates: Nutritional implications. J Am Oil Chem Soc 56: 736–741. https://doi.org/https://doi.org/10.1007/BF02663052

Felix JP, Mello D (2000) Farm animal metabolism and nutrition. CABI

Fereidoon S (2012) Antinutrients and Phytochemicals in Food. Developed from a symposium sponsored by the division of agricultural and food chemistry at the 210th National Meeting of the American Chemical Society, Chicago, Illinoi. ACS symposium series, ISSN 0097-6156; 2

Fereidoon S (2014) Beneficial health effects and drawbacks of Antinutrients and phytochemicals in foods. Appl Microbiol Biotechnol 97:45–55

Ferguson TM, Couch JR, Rigdon RH (1959) Histopathology of animal reactions to pigment compounds-chickens. In: Proceedings of the conference on chemistry structure and reactions of gossypol and non-gossypol pigments of cottonseed. National Cottonseed Products Association, Memphis, pp 131–141

Fernando R, Pinto MDP, Pathmeswaran A (2012) Goitrogenic food and prevalence of goitre in Sri Lanka. J Food Sci 41:1076–1081. https://doi.org/10.5923/j.ijim.20120102.02

Ferri M (2009) Binahong (*Anredera cordifolia*) Sebagai Obat. Bull Warta 15(1)., April 2009. Penelitian dan Pengembangan Tanaman Industri. Badan Penelitian dan Pengembangan Pertanian

Francis G, Makkar HPS, Becker K (2001) Antinutritional factors present in plant-derived alternate fish feed ingredients and their effects in fish. Aquaculture 199:197–227. https://doi.org/10.1016/S0044-8486(01)00526-9

Friedman M, Brandon DL (2001) Nutritional and health benefits of soy proteins. J Agric Food Chem 49:1069–1086. https://doi.org/10.1021/jf0009246

Frontela C, Garcıa-Alonso FJ, Ros G, Martınez C (2008) Phytic acid and inositol phosphates in raw flours and infant cereals: The effect of processing. J Food Compos Anal 21:343–350

Fuller JB, Patterson CEP, Hester K, Stringer DY (1996) A quantitative review of research on charismatic leadership. Psychol Rep 78:271–287. https://doi.org/10.2466/pr0.1996.78.1.271

Gadelha ICN, do Nascimento Rangel AH, Silva AR, Soto-Blanco B (2011) Efeitos do gossipol na reprodução animal. Acta Vet Bras 5:129–135. https://doi.org/10.21708/avb.2011.5.2.2343

García-Estepa RM, Guerra-Hernández E, García-Villanova B (1999) Phytic acid content in milled cereal products and breads. Food Res Int 32:217–221. https://doi.org/10.1016/S0963-9969(99)00092-7

Gemede HF, Ratta N (2014) Antinutritional factors in plant foods: potential health benefits and adverse effects. Int J Nutr Food Sci 3:284–289. https://doi.org/10.11648/j.ijnfs.20140304.18

Ghavidel RA, Prakash J (2006) Effect of germination and dehulling on functional properties of legume flours. J Sci Food Agric 86:1189–1195. https://doi.org/10.1002/jsfa.2460

Gharaghani H, Zaghari M, Shahhoseini G, Moravej H (2008) Effect of gamma irradiation on antinutritional factors and nutritional value of canola meal for broiler chickens. Asia Aust J Anim Sci 21:1479–1485

Giri AP, Kachole MS (1998) Amylase inhibitors of pigeon pea (*Cajanus cajan*) seeds. Phytochemistry 47:197–202. https://doi.org/10.1016/s0031-9422(97)00570-0

Gomes MTR, Oliva ML, Lopes MTP, Salas CE (2011) Plant proteinases and inhibitors: an overview of biological function and pharmacological activity. Curr Protein Pept Sci 12:417–436. https://doi.org/10.2174/138920311796391089

Gonzales I, Sabatini S (1989) Cyanide poisoning: pathophysiology and current approaches to therapy. Int J Artif Organs 12:347–355. PMID: 2674018

Gowda NKS, Katiyar RC, Sastry VRB (1994) Detoxified Mahua (*Bassia latifolia*) seed cake as protein source for high growth potential animals. Indian J Anim Nutr 11:1–6

Grace ZH, Sudipta S, Das B, Hoang ML, Karbaschi MR, Alexander AT, Williams B, Sagadevan G, Mundree SG (2017) Finger on pulse: iron pumping into chickpea. Front Plant Sci:1–17. https://doi.org/10.3389/fpls.2017.01755

Grant G (1991) Lectins. In: D'Mello JPF, Duffus CM (eds) Toxic substances in crop plants. The Royal Society of Chemistry, pp 49–67. https://www.worldcat.org/title/toxic-substances-in-crop-plants/oclc/28224827

Gutierrez-Banuelos H, Pinchak WE, Min BR, Carstens GE, Anderson RC, Tedeschi LO et al (2011) Effects of feed-supplementation and hide-spray application of two sources of tannins on enteric and hide bacteria of feed lot cattle. J Environ Sci Health B Pest Food Contamin Agric Wastes 46:360–365. https://doi.org/10.1080/03601234.2011.559419

Haese EB (2017) Studies on the extent of ruminal degradation of phytate from different feedstuffs. Thesis PhD in Agricultural Science, Faculty of Agricultural Science, Weingarten, Germany. http://opus.uni-hohenheim.de/volltexte/2017/1343/

Hassanpour S, Maheri-Sis N, Eshratkhah B, Mehmandar FB (2011) Plants and secondary metabolites (Tannins): A Review. International Journal of Forest, Soil and Erosion 1(1):47–53

Helsper JPFG, Kolodziej H, Hoogendijk JM, van Norel A (1993) Characterization and trypsin inhibitor activity of proanthocyanidins from Vicia faba. Phytochemistry 34:1255–1260

Hamid R, Masood A, Wani IH, Rafiq S (2013) Lectins: proteins with diverse applications. J Appl Pharm Sci 3:S93–S103. https://doi.org/10.7324/JAPS.2013.34.S18

Hamid, Thakur NS, Kumar P (2017) Anti-nutritional factors, their adverse effects and need for adequate processing to reduce them in food. Agric Int 4:56–60. https://doi.org/10.5958/2454-8634.2017.00013.4

Haschek WM, Beasley VR, Buck WB, Finnell JH (1989) Cottonseed meal (gossypol) toxicosis in a swine herd. J Am Vet Med Assoc 195:613–615

Hassanpour S, Maheri-Sis N, Eshratkhah B, Mehmandar FB (2011) Plants and secondary metabolites (Tannins): a review. Int J For Soil Eros 1:47–53

Hegarty (1987) Toxic amino acids of plant origin. In: Effect of poisonous plants on livestock. Academic

Henry MH, Pesti GM, Brown TP (2001) Pathology and histopathology of gossypol toxicity in broiler chicks. Avian Dis 45:598–604. PMID: 11569732

Hervás G, Frutos P, Giráldez FJ, Mantecón AR, Álvarez Del Pino MC (2003) Effect of different doses of quebracho tannins extract on rumen fermentation in ewes. Anim Feed Sci Technol 109:65–78. https://doi.org/10.1016/S0377-8401(03)00208-6

Hiremat NB (1981) Subabul (*Leucaena leucocephala*)- a wonder plant. Indian Dairy Man 33:351–356. https://agris.fao.org/agris-search/search.do?recordID=US201302634066

Huisman J, Tolman GH (2001) Antinutritional factors in the plant proteins of diets for non-ruminants. In: Recent developments in pig nutrition. Netherlands, 3. Elsevier, pp 261–291. https://www.cabdirect.org/cabdirect/abstract/20013120943

Igile GO (1996) Phytochemical and Biological studies on some constituents of *Vernonia amygdalina* (compositae) leaves. Ph.D thesis, Department of Biochemistry, University of Ibadan, Nigeria

Jacob JP, Mitaru BN, Mbugua PN, Blair R (1996) The effect of substituting Kenyan serena sorghum for maize in broiler starter diets with different dietary crude protein and methionine levels. Anim Feed Sci Technol 61:27–39. https://doi.org/10.1016/0377-8401(96)00955-8

Jadhav SJ, Sharma RP, Salunke DK (2009) Naturally occurring toxic alkaloids in foods. CRC Crit Rev Toxicol 9:21–104

Jambunathan R, Singh U, Subramanian V (1988) Grain quality of sorghum, pearl millet, pigeon pea and chick pea. In: Achaya KT (ed) Interfaces between Agriculture, Nutrition and Food Science. Proceedings, workshop on Hyberabad, India, November, 10–12th 1981, Food and Nutrition Bulletin supplement, 9, Tokyo, pp 47–50

Jansman AJM (1993) Tannins in feedstuffs for simple-stomached animals. Nutr Res Rev 6:209–236. https://doi.org/10.1079/NRR19930013

Jansman AJM, Frohlich AA, Marquardt RR (1994) Production of proline-rich proteins by the parotid glands of rats is enhanced by feeding diets containing tannins from faba beans (*Vicia faba L.*). J Nutr 124:249–258. https://doi.org/10.1093/jn/124.2.249

Jenkins KJ, Atwal AS (1994) Effects of dietary saponins on fecal bile acids and neutral sterols, and availability of vitamins A and E in the chick. J Nutr Biochem 5:134–138. https://doi.org/10.1016/0955-2863(94)90084-1

Johnson IT, Gee JM, Price K, Curl C, Fenwick GR (1986) Influence of saponins on gut permeability and active nutrient transport in vitro. J Nutr 116:2270–2277. https://doi.org/10.1093/jn/116.11.2270

Jones RJ, Ford CW (1972) Some factors affecting the oxalate content of the tropical grass (*Setaria sphacelata*). Aust J Exp Agric Anim Hus 12:400–406

Jones RM, McLennan MW, Dowsett KF (1989) The effect of *Leucaena leucocephla* on the beef cattle reproduction of beef cattle grazing leucaena-grass pastures (reduced calving rates) 23, 108–114. https://agris.fao.org/agris-search/search.do?recordID=AU9000106

Joye I (2019) Protein digestibility of cereal products. Foods 8:199. https://doi.org/10.3390/foods8060199

Kankuka FG, Balogun TF, Yaakugh IDI (2000) Effect of duration of cooking of full fat soybean on dry matter digestibility and energy utilization by young pigs. In: Ukachukwu SN,

Ibeawuchi JA, Ibe SN, Ezekwe AG, Abasiekong SF (eds). Proceedings of Annual Conference of the Nigerian Society for Animal Production. Umudike, Abia State, pp 191–193. 19 – 23rd March, 2000

Kelln BM, Penner GB, Acharya SN, McAllister TA, Lardner HA (2021) Impact of condensed tannin-containing legumes on ruminal fermentation, nutrition, and performance in ruminants: a review. Can J Anim Sci 101:210–223. https://doi.org/10.1139/cjas-2020-0096

Kenar JA (2006) Reaction chemistry of gossypol and its derivatives. J Am Oil Chem Soc 83:269–302. https://doi.org/10.1007/s11746-006-1203-1

Kerr LA (1989) Gossypol toxicosis in cattle. Compend Contin Educ Pract Vet 11:1139–1146

Khare SK (2000) Application of immobilized enzymes in soybean processing. In: The Third International Soybean Processing and Utilization Conference (ISPCRC III): 2000 of the Innovation Era for Soybeans. 15–20, October, 2000, Tsukuba, Ibaraka, Japan, pp 381–382

Kim HL, Calhoun MC, Stipanovic RD (1996) Accumulation of gossypol enantiomers in ovine tissues. Comp Biochem Physiol B: Biochem Mol Biol 113:417–420. https://doi.org/10.1016/0305-0491(95)02061-6

Krupa U (2008) Main nutritional and antinutritional compounds of bean seeds-a review. Polish J Food Nutr Sci 58:149–155. https://agris.fao.org/agrissearch/search.do?recordID=PL2008000713

Kumar R, Singh M (1984) Tannins their adverse role in ruminant nutrition. J Agric Food Chem 32:447–453. https://doi.org/10.1021/jf00123a006

Lampart-Szczapa E, Siger A, Trojanowska K, Nogala-Kalucka M, Malecka M, Pacholek B (2003) Chemical composition and antibacterial activities of lupin seeds extracts. Food Nahrung 47:286–290. https://doi.org/10.1002/food.200390068

Lee C, Beauchemin KA (2014) A review of feeding supplementary nitrate to ruminant animals: nitrate toxicity, methane emissions, and production performance. Can J Anim Sci 94:557–570

Leeson S, Summers JD (2001) Scott's nutrition of the chicken, 4th edn. University Books, Guelph

Li Z, Alli I, Kermasha S (1993) In-vitro α-amylase inhibitor activity-phytate relationships in proteins from Phaseolus beans. Food Res Int 26:195–201. https://doi.org/10.1016/0963-9969(93)90053-L

Liebman M, Al-Wahsh IA (2011) Probiotics and other key determinants of dietary oxalate absorption. Adv Nutr 2:254–260. https://doi.org/10.3945/an.111.000414

Liener IE (1980) In: Summerfield RJ, Bunting AH (eds) Advances in legume science. Academic, New York/London

Liener IE (1994) Implications of antinutritional components in soybean foods. Crit Rev Food Sci Nutr 34:31–67. https://doi.org/10.1080/10408399409527649

Lindsey TO, Hawkins GE, Guthrie LD (1980) Physiological responses of lactating cows to gossypol from cottonseed meal rations. J Dairy Sci 63:562–573. https://doi.org/10.3168/jds.S0022-0302(80)82972-9

Liu K (1997) Chemistry and nutritional value of soybean components. In: Soybeans. Springer, Boston, pp 25–113

Lolas GM (1976) The phytic acid-total phosphorus relationship in barley, oats, soybeans, and wheat. Cereal Chem 53:867–871. https://agris.fao.org/agrissearch/search.do?recordID=US19770146612

Lordelo MM, Calhoun MC, Dale NM, Dowd MK, Davis AJ (2007) Relative toxicity of gossypol enantiomers in laying and broiler breeder hens. Poult Sci 86:582–590. https://doi.org/10.1093/ps/86.3.582

Loewus FA (2002) Biosynthesis of phytate in food grains and seeds. In: Reddy NR, Sather SK (eds) Food Phytate. CRC Press, Boca Raton, Florida, pp 53–61

Lori O, Thava V, James HH (2001) Phytic acid. Food Rev Int 17: 419–431. https://doi.org/10.1081/FRI-100108531

Lott JN, Ockenden I, Raboy V, Batten GD (2000) Phytic acid and phosphorus in crop seeds and fruits: a global estimate. Seed Sci Res 10:11–33. https://doi.org/10.1017/S0960258500000039

Lumen BD, Salamat LA (1980) Trypsin inhibitor activity in winged beans (Psophocarpus tetragnolobus) and the posible role of tannins. J Agric Food Chem 28:533–536

Mada SB, Garba A, Mohammed A, Muhammad A, Olagunju A, Mohammed HA (2012) Effects of boiling and roasting on antinutrients and proximate composition of local and some selected improved varieties of *Arachis hypogaea* L (Groundnut). Int J Food Nutr Saf 1:45–53. Corpus ID: 100127073

Maenz DD (2001) Enzymatic characteristics of phytases as they relate to their use in animal feeds. In: Bedford MR, Partridge GG (eds) Enzymes in Farm Animal Nutrition. CABI, Wallingford, UK, pp 61–84

Maner HJ, Gomez G (1973) Chronic cassava toxicity. In: Proceedings of an interdisciplinary workshop, London January, 29–30

Mangan JL (1988) Nutritional effects of tannins in animal feeds. Nutr. Res. Reviews 1:209–231

Margier M, Georgé S, Hafnaoui N, Remond D, Nowicki M, Du Chaffaut L, Amiot MJ, Reboul E (2018) Nutritional composition and bioactive content of legumes: characterization of pulses frequently consumed in France and effect of the cooking method. Nutrients 10:1668. https://doi.org/10.3390/nu10111668

Marshall JJ, Lauda CM (2007) Purification and properties of Phaseolus vulgaris. J Biol Chem 250:8030–8037

Medugu CI, Kwari ID, Igwebuike J, Nkama I, Mohammed ID, Hamaker B (2010) Performance and economics of production of broiler chickens fed sorghum or millet as replacement for maize in the semi-arid zone of Nigeria. Agric Biol J N Am 1:321–325

Mehansho H, Asquith TN, Butler LG, Rogler JC, Carlson DM (1992) Tannin-mediated induction of proline-rich protein-synthesis. J Agric Food Chem 40:93–97

Min BR, Barry TN, Attwood GT, McNabb WC (2003) The effect of condensed tannins on the nutrition and health of ruminants fed fresh temperate forages: a review. Anim Feed Sci Technol 106:1–4

Morgan SE (1989) Gossypol as a toxicant in livestock. In: Burrows GE (ed) Vet Clin North Am Food Anim Pract 5: 251–263

Morgan S, Stair EL, Martin T, Edwards WC, Morgan GL (1988) Clinical, clinicopathologic, pathologic, and toxicologic alterations associated with gossypol toxicosis in feeder lambs. Am J Vet Res 49:493–499. PMID: 3377308

Morzelle MC, Salgado JM, Massarioli AP, Bachiega P, de Oliveira Rios A, Alencar SM et al (2019) Potential benefits of phenolics from pomegranate pulp and peel in Alzheimer's disease: antioxidant activity and inhibition of acetylcholinesterase. J Food Bioact 5:136–141. https://doi.org/10.31665/JFB.2019.5181

Mueller I (2001) Analysis of hydrolysable tannins. Anim Feed Sci Technol 91:3–20. https://doi.org/10.1016/S0377-8401(01)00227-9

Muramoto K (2017) Lectins as bioactive proteins in foods and feeds. Food Sci Technol Res 23:487–494. https://doi.org/10.3136/fstr.23.487

Nagalakshmi D, Rama RSV, Panda AK, Sastry VRB (2007) Cottonseed meal in poultry diets: a review. J Poult Sci 44:119–134. https://doi.org/10.2141/jpsa.44.119

Naumann HD, Tedeschi LO, Zeller WE, Huntley NF (2017) The role of condensed tannins in ruminant animal production: advances, limitations and future directions. Rev Bras Zoot 46:929–949

Nikmaram N, Leong SY, Koubaa M, Zhu Z, Barba FJ, Greiner R et al (2017) Effect of extrusion on the anti-nutritional factors of food products: an overview. Food Control 79:62–73. https://doi.org/10.1016/j.foodcont.2017.03.027

Noonan SC, Savage GP (1999) Oxalate content of foods and its effect on humans. Asia Pac J Clin Nutr 8:64–67. PMID: 24393738

Nørgaard JV, Malla N, Dionisio G, Madsen CK, Pettersson D, Lærke HN et al (2019) Exogenous xylanase or protease for pigs fed barley cultivars with high or low enzyme inhibitors. Anim Feed Sci Technol 248:59–66. https://doi.org/10.1016/j.anifeedsci.2018.12.005

Nwosu JN (2010) Effect of soaking, blanching and cooking on the anti-nutritional properties of asparagus bean (Vigna Sesquipedis) flour Obizoba C, J, Atii JV 1991. Effects of soaking, sprouting,fermentation and cooking on nutrient composition and some antinutritional factors of sorghum (Guinesia) seeds. Plant Foods Hum Nutr 41:203–212

Okafor PN, Okorie CN (2006) Determination of Cyanide, Nitrate and Nitrite, contents of poultry feeds of four top animal feed companies in Nigeria. J Food Technol 4:225–228. https://medwelljournals.com/abstract/?doi=jftech.2006.225.228

Oke OL (1979) Some aspects of the role of cyanogenic glucosides in nutrition. World Rev Nutr Diet 33:70–103. https://doi.org/10.1159/000402550

Oke O (1980) Toxicity of cyanogenic glycosides. Food Chem 6:97–109. https://doi.org/10.1016/0308-8146(80)90025-4

Olayemi FO (2010) A review on some causes of male infertility. Afr J Biotechnol 9:2834–2842. https://doi.org/10.5897/AJB2010.000-3110

Oleszek W (2002) Chromatographic determination of plant saponins. J Chromatogr 967:147–162. https://doi.org/10.1016/s0021-9673(01)01556-4

Olomu JM (1995) Non-ruminant animal nutrition: principles and practice. Jachem Publication, Benin City, p 320

Osuntokun BO (1972) The effects of malnutrition on the development of cognitive functions of the nervous system in childhood. Trop Geogr Med 24:295–310

Otlewski J, Jelen F, Zakrzewska M, Oleksy A (2005) The many faces of protease–protein inhibitor interaction. EMBO J 24:1303–1310. https://doi.org/10.1038/sj.emboj.7600611

Patel PAS, Alagundagi SC, Salakinkop SR (2013) The anti-nutritional factors in forages – a review. Curr Biotica 6:516–526

Patra AK, Saxena J (2010) A new perspective on the use of plant secondary metabolites to inhibit methanogenesis in the rumen. Phytochem 71:198–1222. https://doi.org/10.1016/j.phytochem.

Patton CS, Legendre AM, Gompf RE, Walker MA (1985) Heart failure caused by gossypol poisoning in two dogs. J Am Vet Med Assoc 187:625–627. PMID: 4086371

Petroski W, Minich DM (2020) Is there such a thing as anti-nutrients? A narrative review of perceived problematic plant compounds. Nutrients 12:2929. https://doi.org/10.3390/nu12102929

Phytolab (2007) Phytochemicals Polyphenols–Tannic Acid. Retrieved July 6, 2007 from http://www.Phytochemicalsinfolphytochemicals/tannic-acid.phD

Raboy V (2000) Low-phytic-acid grains. Food Nutr Bull 21:423–427. https://doi.org/10.1177/156482650002100416

Raes K, Knockaert D, Struijs K, Van Camp J (2014) Role of processing on bioaccessibility of minerals: influence of localization of minerals and antinutritional factors in the plant. Trends Food Sci Technol 37:32–41. https://doi.org/10.1016/j.tifs.2014.02.002

Rahman MM, Kawamura O (2011) Oxalate accumulation in forage plants: some agronomic, climatic and genetic aspects. Asian Aust J Anim Sci 24:439–448. https://doi.org/10.5713/ajas.2011.10208

Rahman KSM, Pasirayi G, Auger V, Ali Z (2009) Development of a simple and low cost microbioreactor for high-throughput bioprocessing. Biotechnol Lett 31:209–214. https://doi.org/10.1007/s10529-008-9853-8

Rahman MM, Abdullah RB, Wan Khadijah WE (2013) A review of oxalate poisoning in domestic animals: tolerance and performance aspects. J Anim Physiol Anim Nutr 97:605–614. https://doi.org/10.1111/j.1439-0396.2012.01309.x

Ramteke R, Doneria R, Gendley MK (2019) Antinutritional factors in feed and fodder used for livestock and poultry feeding. Acta Sci Nutr Health 3:39–48

Randel RD, Chase CC Jr, Wyse SJ (1992) Effects of gossypol and cottonseed products on reproduction of mammals. J Anim Sci 70:1628–1638. https://doi.org/10.2527/1992.7051628x

Rao P, Desothale YG (1998) Tannin content of pulses varietal difference and effects of germination and cooking. J Sci Food Agric 33:1013–1015

Redondo LM, Fernandez Miyakawa ME, Fortunato R, Salvat A, Chacana P (2013a) Eficacia de aditivos alimentarios basados en extractos vegetales para disminuir la excreción de *Salmonella enteritidis* en pollitos BB. II Seminario Internacional de Salmonelosis aviar. Medellin, Colombia

Redondo LM, Redondo EA, Delgado F, La Sala L, Pereyra A, Garbaccio S et al (2013b) Control of Clostridium perfringens necrotic enteritis by tannins added to the diet. In: Proceedings of the 8th international conference on the molecular biology and pathogenesis of the Clostridia (ClostPath 8), vol 5, Palm Cove

Reed JD (1995) Nutritional toxicology of tannins and related polyphenols in forage legumes. J Anim Sci 73:1516–1528. https://doi.org/10.2527/1995.7351516x
Reed JD, Solar H, Wood Ward A (1990) Foder tree and straw diets for sheep: intake, growth, digestibility and the effect of phenolics on nitrogen utilization. Anim Feed Sci Technol 30:39–50. https://hdl.handle.net/10568/28206
Robinson EH (1991) Improvement of cottonseed meal protein with supplemental lysine in feeds for channel catfish. J Appl Aquac 1:1–14. https://doi.org/10.1300/J028v01n02_01
Robson S (2007) Prussic acid poisoning in Livestock. www.dpi.nsw.gov.au/ Prime facts
Roeder E (1995) Medicinal plants in China containing pyrrolizidine alkaloids. Pharmazie 50:83–98. PMID: 7700976
Rosling H (1987) Cassava toxicity and food security: a review of health effects of cyanide exposure from cassava and of ways to prevent these effects. Uppsala. UNICEF/African Household Food Security Programme, 40p. https://agris.fao.org/agris-search/search.do?recordID=SE881037988
Ryden P, Selvendran RR (1993) In: Macrae R, Robinson RK, Sadler MJ (eds) Encyclopedia of food science, food technology, and nutrition. Academic, San Diego, pp 3582–3587
Saito K, Horie M, Hoshino Y et al (1990) High performance liquid chromatographic determination of glycoalkaloids in potato products. J Chromatogr 508:141–147. https://doi.org/10.1016/S0021-9673(00)91247-0
Salas CE, Dittz D, Torres MJ (2018) Plant proteolytic enzymes: their role as natural pharmacophores. In: Biotechnological applications of plant proteolytic enzymes. Springer, Cham, pp 107–127
Sallau AB, Mada SB, Ibrahim S, Ibrahim U (2012) Effect of boiling, simmering and blanching on the anti-nutritional content of Moringa oleifera leaves. Int J Food Nutr Saf 2:1–6. Corpus ID: 56219382
Salunkhe DK, Chavan JK, Kadam SS (1990) Dietary tannins: consequences and remedies. CRC Press, Boca Raton
Samtiya M, Rotimi EA, Dhewa T (2020) Plant food anti-nutritional factors and their reduction strategies: an overview. Food Prod Process Nutr. https://doi.org/10.1186/s43014-020-0020-5
Sarangthem K, Singh TN (2013) Fermentation decreases the anti-nutritional content in bamboo shoots. Int J Curr Microbiol Appl Sci 2:361–369. Corpus ID: 62835452
Sauvion N, Nardon C, Febvay G, Gatehouse AM, Rahbe Y (2004) Binding of the insecticidal lectin concanavalin a in pea aphid, Acyrthosiphon pisum (Harris) and induced effects on the structure of midgut epithelial cells. J Insect Physiol 50:1137–1150
Schneider IC, Ames ML, Rasmussen MA, Reilly PJ (2002) Fermentation of cottonseed and other feedstuffs in cattle rumen fluid. J Agric Food Chem 50:2267–2273
Seeman P (1974) Ultrastructure of membrane lesions in immune lysis, osmotic lysis and drug-induced lysis. Fed Proc 33:2116–2124. PMID: 4607618
Selle PH, Ravindran V, Caldwell RA, Bryden WL (2000) Phytate and phytase: consequences for protein utilization. Nutr Res Rev 13:255–278. https://doi.org/10.1079/095442200108729098
Serrano J, Puupponen-Pimiä R, Dauer A, Aura AM, Saura-Calixto F (2009) Tannins: current knowledge of food sources, intake, bioavailability and biological effects. Mol Nutr Food Res 53:S310–S329. https://doi.org/10.1002/mnfr.200900039
Sharma NK, Lodhi GN, Ichhponani JS (1978) Comparative feeding value of expeller processed undecorticated and decorticated cottonseed cakes for growing chicks. J Agric Sci 91:531–541. https://doi.org/10.1017/S0021859600059906
Shi J, Arunasalam K, Yeung D, Kakuda Y, Mittal G (2004 Spring) Jiang Y (2004) Saponins from edible legumes: chemistry, processing, and health benefits. J Med Food. 7:67–78. https://doi.org/10.1089/109662004322984734
Simee W (2011) Isolation and determination of antinutritional compounds from root to shells of peanut (Arachis Hypogaea). J Disper Sci Technol 28:341–347
Singh A, Tiwana US, Tiwana MS, Puri KP (2000) Effect of application method of level of nitrogen fertilizer on nitrate content in oat fodder. Indian J Anim Nutr 17:315–319

Singh A, Gupta S, Kaur R, Gupta HR (2017) Process optimization for antinutrient minimization of millets. Asian J Dairy Food Res 36:322–326. https://doi.org/10.18805/ajdfr.DR-1215
Skutches CL, Herman DL, Smith FH (1973) Effect of intravenous gossypol injection on iron utilization in swine. J Nutr 103:851–855. https://doi.org/10.1093/jn/103.6.851
Smeriglio A, Barreca D, Bellocco E, Trombetta D (2017) Proanthocyanidins and hydrolysable tannins: occurrence, dietary intake and pharmacological effects. Br J Pharmacol 174:1244–1262. https://doi.org/10.1111/bph.13630
Soetan KO (2008) Pharmacological and other beneficial effects of antinutriional factors in plants. –a review. Afr J Biotechnol 7:4713–4721. https://doi.org/10.5897/AJB08.024
Soetan KO, Oyewole OE (2009) The need for adequate processing to reduce the anti-nutritional factors in plants used as human foods and animal feeds: a review. Afr J Food Sci 3:223–232
Soto-Blanco B (2008) Gossipol effatores antinutricionais da soja. In: Spinosa HS, Górniak SL, Neto JP (eds) Toxicologia aplicada à medicina veterinária. Manole, Barueri, pp 531–545
Southon S, Johnson IT, Gee JM, Prince KR (1988) The effect of Gypsophylla saponins in the diet on mineral status and plasma cholesterol concentration in the rat. Br J Nutr 59:49–55
Sparg SG, Light ME, Van Staden J (2004) Biological activities and distribution of plant saponins. J Ethnopharmacol 94:219–243. https://doi.org/10.1016/j.jep.2004.05.016
Stegelmeier BL, Davis TZ, Clayton MJ (2020) Neurotoxic plants that poison livestock. Vet Clin N Am Food Anim Pract 36:673–688
Su B, Chen X (2020) Current status and potential of Moringa Oleifera leaf as an alternative protein source for animal feeds, review article. Front Vet Sci. https://doi.org/10.3389/fvets.2020.00053
Suryawanshi SN, Bhandarkar AG, Bhagwat SS (1993) Pathological investigations of acute cottonseed cake toxicity in rabbit and chicken. Livestock Advisor 18:30–32
Thakur A, Sharma V, Thakur A (2019) An overview of anti-nutritional factors in food. Int J Chem Stud 7:2472–2479
Timotheo CA, Lauer CM (2018) Toxicity of vegetable tannin extract from Acacia mearnsii in Saccharomyces cerevisiae. Int J Environ Sci Technol 15:659–664. https://agris.fao.org/agris-search/search.do?recordID=US201800213215
Udedibie ASI, Anyaegbu BC, Onyeckwu GC, Egbuokporo OC (2004) Effects of feeding different levels of fermented and unfermented cassava tuber meals on the performance of broilers. Niger J Anim Prod 31:211–219. https://doi.org/10.51791/njap.v31i2.1816
Uhegbu FO, Onwuchekwa CC, Emeka O, Iweala EJ, Kanu I (2009) Effect of processing methods on nutritive and antinutritive properties of seeds of *Brachystegia eurycoma* and *Detarium microcarpum* from Nigeria. Pak J Nutr 8:316–320. https://doi.org/10.3923/pjn.2009.316.320
Umaru HA, Adamu R, Dahiru D, Nadro MS (2007) Levels of antinutritional factors in some wild edible fruits of northern Nigeria. Afr J Biotechnol 6:1935–1938. https://doi.org/10.5897/AJB2007.000-2294
Van Der Ven C, Matser AM, Van den Berg RW (2005) Inactivation of soybean trypsin inhibitors and lipoxygenase by high-pressure processing. J Agric Food Chem 53:1087–1092. https://doi.org/10.1021/jf048577d
Van Leeuwen PV, Jansman AJM, Wiebenga J, Koninkx JFJG, Mouwen JMVM (1995) Dietary effects of faba bean (Vicia faba L.) tannins on the morphology and function of the small intestinal mucosa of weaned pigs. Br J Nutr 73:31–39. https://doi.org/10.1079/BJN19950006
Vaz Patto MC, Amarowicz R, Aryee AN, Boye JI, Chung HJ, Martín-Cabrejas MA et al (2015) Achievements and challenges in improving the nutritional quality of food legumes. Crit Rev Plant Sci 34:105–143. https://doi.org/10.1080/07352689.2014.897907
Vennesland B, Castric PA, Conn EE, Solomonson LP, Volini M, Westley J (1982) Cyanide metabolism. Fed Proc 41:2639–2648
Waghorn G (2008) Beneficial and detrimental effects of dietary condensed tannins for sustainable sheep and goat production—Progress and challenges. Anim Feed Sci Technol 147:116–139. https://doi.org/10.1016/j.anifeedsci.2007.09.013
Waldroup PW, Goodner TO (1973) Tolerance levels of free gossypol in layer diets as influenced by iron: gossypol ratios. Poult Sci 52:20–28. https://doi.org/10.3382/ps.0520020

Walter HL, Fanny L, Charles C, Christian R (2002) Minerals and phytic acid interaction: is it a real problem for human nutrition. Int J Food Sci Technol 37:727–739. https://doi.org/10.1046/j.1365-2621.2002.00618.x

WHO, World Health Organization (2010) Toxicological evaluation of certain food additives and naturally occurring toxicants, WHO Food Additive Series: 30. World Health Organization, Geneva. 9241660325_eng.pdf (10.55Mb)

Willard ST, Neuendorff DA, Lewis AW, Randel RD (1995) Effects of free gossypol in the diet of pregnant and postpartum Brahman cows on calf development and cow performance. J Anim Sci 73:496–507. https://doi.org/10.2527/1995.732496x

Woyengo TA, Nyachoti CM (2011) Supplementation of phytase and carbohydrases to diets for poultry: a review. Can J Anim Sci 91:177–192. https://doi.org/10.4141/cjas10081

Woyengo TA, Nyachoti CM (2013) Review: Antinutritional effects of phytic acid in diets for pigs and poultry – current knowledge and directions for future research. Can J Anim Sci 93:9–21. https://doi.org/10.4141/cjas2012-017

Yasmin A, Zeb A, Khalil AW, Paracha GMUD, Khattak AB (2008) Effect of processing on anti-nutritional factors of red kidney bean (*Phaseolus vulgaris*) grains. Food Bioproc Technol 1:415–419. https://doi.org/10.1007/s11947-008-0125-3

Yilkal T (2015) Important anti-nutritional substances and inherent toxicants of feeds. Food Sci Qual Manag 36:40–47. Corpus ID: 56333400

Zagrobelny M, Bak S, Rasmussen AV, Jorgensen B, Naumann CM, Moller BL (2004) Cyanogenic glucosides and plant insect interactions. Phytochemistry 65:293–306. https://doi.org/10.1016/j.phytochem.2003.10.016

Zhang WJ, Xu ZR, Pan XL, Yan XH, Wang YB (2007) Advances in gossypol toxicity and processing effects of whole cottonseed in dairy cows feeding. Livest Sci 111:1–9. https://doi.org/10.1016/j.livsci.2007.03.006