International Journal of Agriculture Innovations and Research
Volume 8, Issue 4, ISSN (Online) 2319-1473
Manuscript Processing Details (dd/mm/yyyy):
Received: 19/01/2020 | Accepted on: 03/02/2020 | Published: 19/02/2020

An Augmented Review about Anti-Nutrients and Toxins of Feed Stuff and their Control Strategies, a Step toward Sustainable Resource Utilization

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Abstract **– Human population is multiplying rapidly (estimated to be 6.8 billion) and is expected to reach 9 billion by 2040. Animal production is one of the most active and well organized sectors to serve the humanity to fulfill food demand of growing human population. Hence, plants are main producers in the food chain and animal feed is based on plants feed stuff, whereas, agricultural land area is abruptly shrinking from the few last decades which has resulted in a decrease in agriculture production. This raised the fear of shortage of animal feed resources for future. Different crops and crops by-products are commonly used in animals feed to provide balanced nutrition. However presence of anti-nutrients limits the utilization of these feeds stuff due to which feeds/rations have to be over-formulated to fulfill the requirement of animals which cause a rise in feed costs. The feed costs more than 70% of entire production cost. Therefore sustainable use of resources and adding nonconventional feed stuff in animal feed is demand of the time for economical cum efficient production to save the future generations. For efficiently utilization of these conventional and nonconventional feed resources the anti-nutrients present in these feeds must be explored and nullified. Therefore, the intent of the present article is to provide the detailed information about the different toxic/anti-nutritional factors found in various conventional and non-conventional feed ingredients used in animals feed.**

Keywords **– Animal, Nutrition, Anti-Nutritional Factors, Toxins, Production, Sustainable.**

I. INTRODUCTION

Pakistan is an agricultural based state and Livestock plays an important role in its economy. Most of the population of the country dependent on poultry, livestock, dairy and fishery to fulfill the protein need. Livestock animals are our ‘‘bread and butter’’ and most important species on our earth serving the human. Pakistan is the 4th largest producer of milk and approximately 40 million rural populations of the country dependent on livestock sector. Livestock contributes 11.4% GDP of Pakistan and 53.2% share to GDP of agriculture of the country (GOP, 2018). Animal production is one of the most active and a well organized sector which is a source of employment and is playing a pivotal role in eliminating poverty throughout the world (Abbas, 2020). Human population is multiplying rapidly (estimated to be 6.8 billion) and is estimated to reach about 9 billion by 2040. The speedy growth of humans needs continuous higher production to ensure food supply, whereas agricultural land area which is prime and basic source of food production is abruptly shrinking due to unwise establishment of housing societies and unproductive uses of land (Abbas, 2020). Question arises from where the food will come for this huge population. Although today are discussions /debates about the Internet of things and artificial Intelligence (AI) through advanced sensor technologies to be employed in agriculture practices for the sustainable food production with potential to produce 30times more feed as compared to conventional agricultural operations (McClements,2019a;2019b; Srinu and Baskaran, 2018; Banovic *et al.,* 2018; Parodi *et al.,* 2018; Nemenyi, 2018; Medina *et al.* 2018). However, these are not permanent and safe solution; moreover, ethics does not support such type of practices.

Yet, exploiting the natural resources to their full potential and sustainable use of resources may play a pivotal

role to fulfill the food demand of this huge population. For the purpose of increased animal's production per unit of natural resources, scientists have developed excellent producers by exploiting good genes and excel feed formulation. Our feed resources are full of significant nutrients; however the bioavailability of these essential nutrients is not being fully exploited due to presence of some toxic material present in these (Younas and Yaqoob, 2005). The problem of feeding such forages and crops and most of the unconventional feed sources is that they have varying levels of anti-nutrient substances which cause toxicity in animals (Smith, 2013). However, exploitation of available conventional as well as unconventional feedstuffs to their full potential will increase productivity with minimum loss of ecological diversity. These toxic compounds when consumed in significant quantities, they not merely render the other essential nutrients unutilized but also cause detrimental effects on productive/reproductive performance and health of animals. Removing/nullifying these anti-nutrient and toxic substances in feed stuffs can tremendously increase the potential for utilization of diets, decrease feeding cost, also helpful to reduce environmental pollution. Various methods (physical and chemical treatment etc.) have been tried to triumph over the harmful effect of these anti-nutritional/toxic factors before feeding such feed stuff (Wadhwan, 2014; Jones and Mangan, 1977). Adding enzymes, autoclaving, germination, sprouting, extruding (combination of high temperature and pressure), blanching (mild temp at 75-95°C), soaking (Exposure to water and salt solutions), roasting (dry heating at 120-250°C) fermentation, using PEG (Ben *et al.,* 2000; Makkar, 2003; Ben Saleem *et al.,* 2004; Salem *et al.,* 2007; Jones and Mangan, 1977), thiols, sulphites and copper salts, supplements, urea (Russel and Lolley, 1989) or biological treatment with fungi (Hassan, 2006; 2009) may prove helpful to lower the anti-nutrient contents of ration. Therefore the intent of this review article is to provide awareness about various anti-nutrient substances of feed stuff and techniques to reduce the content of these anti-nutrient/toxic factors for sustainable animal production.

Anti-Nutrient Substances

Compound/substances which work to decrease nutrient ingestion, digestion, absorption and/or consumption and may cause other undesirable effect are known as anti-nutrients or anti-nutritional factors (Cheeke and Shull, 1985; Akande *et al.,* 2010). These include protease inhibitors, amylase inhibitor, phenolic compounds, tannins, cyanogenetic glycosides and saponins (Jenkins and Atwal, 1994). It also includes gossypol, glucosinolates, chlorogenic acid, phytates, and oxlate, dietary fibers, biogenic amines, toxic amino acids including mimosin, djenkolic acids and canavanine (Kitagawa and Tomiyama, 1929; Rosenthal, 1982.; D'Mello, 1982; Enwere, 1998; D'Mello, 2000; Luo *et al.,* 2000; Tadele, 2015) have their own mechanism to prevent the utilization of nutrients. Mimosine can act as an amino acid and may disrupt either catalytic, transaminases process and/or can form complex with metals such as Zinc to render these unavailable (Hegarty, 1987).

These are secondary plant metabolites (Habtamu and Nigussie, 2014; D'Mello, 2000) cause a decrease in growth, production performance and health of animals via different mechanisms such as reduction in protein digestibility, binding to various nutrients and/ or destructing the intestinal wall, disturbing the digestive physiology and efficiency. Anti-nutrients cause nutritional deficiencies by interfering the consumption of essential nutrients during ingestion, digestion and/or absorption. Antiproteins, antiminerals, antivitamins.

II. PROTEINS

Protease Inhibitors

Protease inhibitors are protein which restrains the protein digesting enzymes by binding to the active sites of these enzymes by one-to-one molar ratio (Liener, 1976; Liener and Kakade, 1980). These are found in raw legume seeds (especially soybean) and cereal grains including paddy, sorghum, wheat and potato meals. These are polypeptides which inhibit the actions of Trypsin, Pepsin and other Proteases in the gut (Cheeke and Shull, 1985). These inhibitors cause indigestion, increased bile output and pancreatic hypertrophy (Chunmei *et al.,* 2010; Liener, 1976) and hyperactivity (McDonald *et al.,* 1995) resulting in increased production of Trypsin and Chymotrypsin in mono-gastric animals (Cheeke and Shull, 1985; Akande *et al.,*2010). Presence of protease inhibitors in animal feed results in reduced feed intake, growth, performance (McDonald *et al.,* 1995), also declines the egg production, cause abnormal yolk color and mottling of the yolk (Leeson and Summer, 2001).Protease inhibitors can easily be inactivated by wet heating (Liener, 1995). Autoclaving for 20 minutes at 115°C and/or 40 minutes at 107°C to 108°C is sufficient to denature these proteins. Former soaking in water for 12 to 24 hours is proved more beneficial, moreover, boiling at 100°C for 15 to 30 minutes is enough to get better the nutritional worth of soaked soybeans.

Amylase inhibitors (starch blockers) present in legumes prevents the release of simple sugars and absorption by the body (Choudhury *et al.,* 1996). Pigeon pea has been reported to have these proteins. Amylase inhibitors are reported to prevent the action of bovine pancreatic amylase, however it cannot work on endogenous amylase, bacterial Amylase and fungal Amylase.

Lectins

Haemagglutinins are glycol-proteins which cause agglutination of RBCs (Leeson and Summers, 2001). These are found in more than 800 varieties of the legume family. One of example is lectins that have vastly specific binding sites for carbohydrates membrane receptors (Pusztai, 1989). Most of the lectins are glycoproteins (Bender, 1983) which interferes the absorption and transportation of carbohydrates and other essential nutrients (Santiago *et al.,* 1993). Lectins are found in legumes such as castor bean. Jequirity bean peanut, soybean, jack bean, also found in maize barley, potato meal, banana meal and mango meal. Lectins of barley and corn are almost nontoxic whereas lectins of caster (ricin) seed and lectin of jequirity (abrin) bean are most toxic (Chahal *et al.,* 2008; Leeson and Summer, 2001). Ingestion of castor seed may cause feed refusal, excessive salivation, violent purgation, bloody diarrhea, trembling and in-coordination, depression, weakness, abnormal feathering, dehydration, vent pasting and mortality (Leeson and Summer, 2001). Soybean agglutinins (SBA) may cause atrophy of microvilli, increase in relative weight of small intestine, degeneration of kidneys and liver (Leeson and Summer, 2001). These tends to directly bind with the intestinal mucosa (Almeida *et al.,* 1991) therefore, presence of haemagglutinins in diet cause disrupt in small intestinal metabolism (Santiago *et al.,* 1993), death of intestinal epithelium cells by binding their ribosomes, injure small intestinal villi (Leeson and Summer, 2001) due to capability to bind with brush border surfaces in the distal part of small intestine (Oliveira *et al.,* 1989).

Heat cooking can decrease the toxicity of lectins, however, lower dry temperature or inadequate cooking is not sufficient. For complete detoxification steam cooking or wet heating is required (Ayyagari *et al.,* 1989; Almeida *et al.,* 1991).

Toxicdipeptides

Toxicdipeptides are related to poultry feed (Leeson and Summer, 2001). Two most commonly occurred toxic

dipeptides are gizzerosine (animal origin) and linatine (plat origin). Gizzerosine is present in some fish meal and tends to cause gizzrd erosion and black vomiting in poultry birds (Diaz and Sugahara, 1995). Linatineis found in linseed meal and flaxed seed meal. It is an antagonist of Pyridoxal Phosphate (vitamin B6) and may cause anorexia, convulsions, poor growth and perosis in poultry birds (Leeson and Summers, 2001).

Toxic Amino Acids

Toxic amino acids are non-protein amino acids including mimosin, djenkolic acids and canavanine (Kitagawa and Tomiyama, 1929; Rosenthal, 1982.; D'Mello, 1982; Enwere, 1998; D'Mello, 2000; Luo *et al.,* 2000) have their own mechanisms in inhibiting the utilization of nutrients. Canavanine is present in jack bean, creeping indigo and sesbania seeds (Belmar and Morris, 1994). Indospicin is another arginine analogue found in creeping indigo (Pass *et al.,* 1996). *Leucaena leucocephala* is reported to depress the performance of poultry because of presence of mimosine (Khanada *et al.,* 1998). β-aminopropionitril (BAPN) present in sweet pea, flat pea, sigletary pea, caley pea; β-cyano-L-Alanine (BCA) present in common vetch, hairy vetch and narrow leaf vetch. Another toxic amino acid is β-N-Oxalylamino-L- alanine (BOAA). These toxic amino acids affect the connective tissues and nervous system and may cause Skelton deformities, enlarge hock joints, curled toe, leg paralysis, ataxia, abnormal embryonic development, egg deformities and aortic rupture (Marsh and Gallis, 1994; Chowdhary and Davis, 1995; Leeson and Summers, 2001).Milk vetch contains Seleno-amino acids are sulfur containing amino acids which may cause selenium toxicity (Leeson and Summers, 2001).

III. Fatty Acids

A number of natural occurring fatty acids have propene ring in their chemical structure (Caligiani and Veronica, 2018). Sterculic acid' was first isolated from the seed oil of *Sterculia foetida*, afterwards 'malvalic acid' was isolated. These fatty acids are found in seeds of various oils producing plant families of the order Malvales and are found in leaves, roots and shoots. Cyclopropene fatty acids (CFAs) are strenuous impurity in cottonseed oil, *Gossypium hirsutum*, and kapok (*Ceiba pentandra)* and they ought to be aloof by strong refining processes before the oil can be used in animal feed (see below). The cyclopropene ring is highly reactive. It reacts rapidly with thiol groups and other sulfur containing compound and produces unwanted biological effects by accumulation of saturated fatty acids and altering the permeability of vitelline membrane of egg due to which iron from yolk diffuse to albumen where it binds to ovotransferrin and causes pink discoloration of albumen. On the other hand ovotransferrin diffuses to yolk and causes brownish-salmond discoloration of yolk. The affected eggs have a rubbery like consistency along with pink discoloration of white of the egg.

Yet, these acids also prevent de-saturation for the period of production of fatty acids and pheromone hormones in insects/arthropods therefore can shield plants against insect attack.

Erusic acid is another fatty acid which is cardio-toxic and is most commonly found in brassica family (Leeson and Summer, 2001).Presence of erusic acid in diet may cause adverse effect on performance and digestibility of nutrients especially apparent digestibility of individual fatty acids and total lipids (Sim *et al.,* 1985; Leslie *et al.,* 1973).

Chlorogenic acid is tannin like substances present in Sunflower meal. It inhibits the function of gastrointestinal enzymes included trypsin, chymotrypsin, lipase and amylase (Cheeke and Shull, 1985). Chlorogenic acid is a precursor of ortho-Quinone that forms through the act of polyphenol oxidase (plant enzyme). These chemical

compounds subsequently react with the polymerize lysine at some stage in processing process and/or in the gastrointestinal tract. Adverse effect of Chlorogenic acid can be prohibited by dietary supplementation with methyl donating compounds such as choline and methionine or using aqueous extraction (Dominguez *et al.,* 1996).

IV. PHENOLIC COMPOUNDS

These are largely distributed throughout the plant tissues. Some of the pheolic compounds are simple essential metabolite whereas others have complex structure (Leeson and Summer, 2001). Phenolic compounds include polymeric phenols such as tannins, free phenol acids, gossypol and sinapine. Free phenolic acids are benzoic acid based and cinamic acid based compounds, however, benzoic acid based phenolic compounds are largely distributed in nature. Simple type includes proto-catechuic, gallic, p-hydroxybenzoic, synergic and venillic acids whereas cinamic acid based are mostly found as ester with quinic acid or sugar. Chlorogenic acid present in sunflower is an example of cinamic acid phenolic.

Tannins

Tannins are water soluble phenolic compounds of higher molecular weight (more than 500 Daltons) which are notorious to form protein-tannin insoluble complexes (Habtamu and Nigussie, 2014). These are heterogeneous group of largely distributed substances found in forage legumes, trees and shrubs (Kumar and Vaithiyanathan, 1990; D'Mello, 2000; Leeson and Summer, 2001; Min *et al.,* 2003; Dube *et al.,* 2001; Jain *et al.,* 2009). Tannins tends to precipitate protein from aqueous solution (Leeson and Summer, 2001; Jain *et al.,* 2009; Akande *et al.,* 2010). These can be differentiated on the basis of degradation behavior and botanical distribution, namely condensed tannins (CT) and hydrolyzable tannins (HT). CTs strongly reduce digestibility of nutrients than hydrolysable tannins. These are gallic, digallic, and ellagicacid esters of glucose or quinic acid. Tannic acid (gallotannic acid or gallotannin) is an example of this group. Tannic acid is common gallotannin which contain 8 to 10 moles of gallic acid per mole of glucose (Leeson and Summer, 2001).Tannic acid is reported to severely affect the liver, i.e., liver necrosis and fatty liver. Heavy molecules cause more pronounced effects as compared to light weight molecules (Yacout, 2016). CTs are flavonoids and are polymers of leucoanthocyanidins. These form strong H bonds with different nutrients ultimately inhibits the digestive enzymes to work properly (Helsper *et al.,* 1993) including Trypsin, Lipase and Amylase (Kumar and Singh, 1984) and rumen microbial activity (Kumar and Singh, 1984). It is commonly found in Sorghum, millet, white barley, triticale, pea, faba beans, tea, coffee and grapes.

A level of 2-4% of dry matter enhance utilization of nitrogen due to increased bypass protein, whereas, concentrations more than 7% generally reduce utilization of nutrient (Yacout, 2016). Tannins are present in the neutral detergent fibers and acid detergent fibers bound to the cell wall and cell protein causing a decrease in digestibility of nutrients (Reed *et al.,* 1984), leg abnormalities (Elkin *et al.,* 1978), reduce palatability of feed and feed consumption, reduces growth rate, performance. These are reported to decrease absorption of essential minerals such as iron (Butler, 1989; Roeder, 1995) and vitamin B12 (Liener and Kakade, 1980). Devastating effect of tannins can be nullified by dietary supplementation of DL Methionine and/or adding tannin binding agents such as polyvinylpyrrolidone (PVP) and gelatin (Leeson and Summer, 2001). However, tannins may also have some beneficial effect on animal health as these can be used as an anti-oxidant, free-radical, anti- bacterial, anti-diarrhea, scavenging and anti-proliferative activity in liver cells.

Gossypol

Gossypol is yellow pigment phenolic compound, a complex of esters and ethers of different carbohydrates present in pigment glands of plants mostly in genus gossypium, family Malvaceae. It may be present as a free form or in abound form. Free gossypol contains both aldehyde and phenolic group, therefore more reactive and toxic (Leeson and Summer, 2001). Bound gossypol is not absorbed ad is non-toxic. Gossypol is found in higher concentrations in cottonseed, safflower. This anti-nutrient is existed in three tautomeric forms (phenolic quinoid tautomer, aldehyde and hemiacetal). Gossypol makes insoluble chelates with several necessary elements such as iron and amino acids hence reduces the availability of these nutrients also prevents the activity of important enzymes (Church, 1991; Robinson, 1991). Presence of gossypol in feed reduces appetite and production performance of animals, cause contraception and infertility in animals (Leeson and Summer, 2001), leg weakness, olive green discoloration of yolk, decrease O_2 carrying capacity of haemoglobin (Hb), lower Hb to RBC (red blood cells) ratio and lower serum protein concentration. Dietary intake of gossypol may also cause diarrhea, oedema in body cavities, liver discoloration, and degeneration of myocardium, liver and spleen (Church, 1991; McDonald *et al.,* 1995; Olomu, 1995). Processing and addition of iron 1:1 ratio can remove 80 to 99% of the gossypol; moreover high protein contents of meal are also helpful to reduce gossypol effect (Leeson and Summer, 2001).

Brassica and Crambe species of plant also contain the choline ester of the sinapic acid, a bitter component known as sinapine. Sinapine cause fishy taints in brown shelled eggs. Higher sinapine contents of canola meal may reduce its inclusion level in the ration (Leeson and Summer, 2001). Other natural phenolic compounds of feed stuff are photodynamic phenols which include hypricin and fagopyrin. These agents cause photosensitiza- - tion in the skin and produce lesions erythema, edema, serum exudation, skin necrosis, scab formation and blisters on the beak, feet and eye in poultry (Leeson and Summer, 2001).

V. GLYCOSIDES

Glycosides are molecules in which a sugar moity (glycon part) is bound to another functional group (aglycon part) by a glycosidic bond. Glycosides play various significant roles in life. Some glycosides are as such toxic such as cardiac glycosides whilst others release toxic substances (aglycon part) when hydrolyze such as cyanogenic glycosides. These are present in many plant species mostly concerning in animal nutrition.

Cyanogens

Cyanogens are found in approximately more than 2000 species of plant kingdom (Leeson and Summer, 2001; Vetter 2000) including the Rosaceae, Graminae Araceae and Leguminosae (Bora 2014). Some legumes like linseed (*Linum usitatissmium*), lima bean, kidney bean, cassava root (*Manihot esculenta*), white clover (*Trifolium repens*), red gram and some species of *Lotus* contain cyanogenic glycosides in reasonable amount. It is also found in lesser quantity in almonds (*Amygdalus communis*), peaches (*Prunus persica*), apples (*Malus sylvestris*) and apricots (*Prunus armeniaca*). These compounds release Hydrogen Cyanide (HCN) along with glucose and beznaldehyde on hydrolysis (Purseglove, 1991; Gleadow and Woodrow 2002; Zagrobelny *et al.* 2004; Akande *et al.,* 2010). Released hydrogen cyanide rapidly absorbed through the intestine and being a weak acid, it dissociates in to H^+ and CN^- the blood. CN^- is ligand to hem of iron which reacts with cytochrome oxidase in the mitochondria to form a stable complex thus blocks the respiratory chain. Resultantly hemoglobin fails to release O_2 to electron

transport system, stops ATP formation and leads to celluar hypoxia and ultimately death (Leeson and Summer, 2001; Zagrobelny *et al.* 2004). Non-lethal doses of cyanide are detoxified by enzyme rhodanese which transfer sulpher from various donors to cyanide to convert it in to thiocyanate. Which is goitrogenic (Leeson and Summer, 2001). HCN is very toxic even a minute intake to animals it can cause dys-functioning of the central nervous system (CNS), respiratory failure, cardiac arrest, goitrogenic toxicity andgrowth depression (Montgomery, 1969; D'Mello, 2000; Sarah robson, 2007). However cooking the ground meal in water liberates volatile HCN. Other examples of toxic glycocides are Linamarin, Dhurrin and Cyanogens.

Glucosinolates

Glucosinolates/goitrogenic compounds which ability to increase the size of the thyroid gland, have been found in legumes (soybean and groundnut) and cruciferous species including mustard rapeseed, cramb seeds, brassica seeds, horseradish, brussel sprouts, cabbage, broccoli, turnip and kale (Leeson and Summer, 2001; Akande *et al.,* 2010). These compounds on hydrolysis by enzyme myrosinase yield, thiocyanate, isothiocynates and oxazolifinethione (Leeson and summer, 2001). Glucosinolates have been reported to decline productive and reproductive performance (Olomu, 1995), prevent the uptake of iodine, enlargement of thyroid, inhibit the synthesis and secretion of the thyroid hormones thus considered goitrogens (Olomu, 1995). Glucosinolates which produce nitrile upon hydrolysis are more toxic and are considered as nephrotoxic as well as hepatotoxic. There is no effective method to nullify the glucosinolate contents of feed ingredients (Leeson ad Summer, 2001), however, effect can effectively be counteracted by supplementation of iodine as compared to heat treatment (Liener, 1975).

Saponins

Saponins are a diverse group of naturally existing foam-producing triterpene (aglycon part) or steroidal (aglycon part) glycosides with properties resembling to that of soap and detergent that found in a vast range of plants species (Price *et al.,* 1987) i.e. pulses and legume seeds including guar, kidney bean, navy bean, mung-bean, peanut, lupin, lentilchickpea, soybean, groundnut, sunflower, rapeseed, alfalfa and sugarbeet (Jain et al 2009; Jenkins and Atwal,1994; Price *et al.,* 1987). High concentration is found in alfalfa, soybean and chick pea (Leeson and Summer, 2001). Saponins are bitter in taste and can affect metabolism in many ways such as erythrocyte haemolysis, hypoglycemic and hypocholesterolemic effect (Esenwah and Ikenebomeh 2008; Umaru et al 2007) due to reduction in absorption of glucose and cholesterol through intra-lumenal physicochemical interaction also reduce the uptake of many other nutrients (dietary lipids, bile acids, cholesterol, vitamin A, vitamin E) by binding the cells of small intestine (Cheeke, 1971; Johnson *et al.,* 1986; Jenkins and Atwal, 1994; Milgate, 1995; Esenwah and Ikenebomeh, 2008). Saponins are reported to reduce microbial fermentation and synthesis in rumen, thus, depresses the performance and growth rates in livestock and poultry species (Leeson and Summer, 2001; Jenkins and Atwal,1994;Lu and Jorgensen, 1987; Cheeke, 1971), may also cause bloat in ruminants (Cheeke, 1971). They also can inhibit enzymes function and can re-strain smooth muscle function. The adverse effect of saponins can reduced by Sprouting and roasting (Shi *et al.,* 2004). However, Saponins has also beneficial medicinal and pharmacological effect and are being used as anti-microbial, antibacterial, anti-protozoal and insecticidal actions (Avato *et al.,* 2006; Habtamu and Ngusse, 2014).

Hemolytic Glycosides

Faba bean contain pyrimidine B- glucosides i.e. Vicine and Convicine (Lattanzio *et al.,* 1983). Convicine and

Vicine are inactive compound in the body, however these are hydrolyzed by the gut anaerobic microflora to a enormously reacting free radical compound, the (aglycone) divicine and isouramil (Leeson and Summer, 2001; Mager *et al.,* 1969). Upon hydrolysis, the glycon part of the molecule splits off and divicine is absorbed through the intestinal epithelium and taken up in the blood (Leeson and Summer, 2001; *Luzzatto and Arese, 2018; Baker, 1984).* Divicine and isouramil are noxious in individuals/animals who suffer a genetically loss of glucose 6 phosphate dehydrogenase (G6PD), the enzyme of glycolysis and have a powerful oxidizing ability for glutathione (Mager *et al.,* 1965). The deficiency of G6PD results in lack of glutathione in RBCs (*Luzzatto and Arese, 2018)* which may implicates oxidative stress on RBCs and hemolytic anemia, called favism (Mager *et al.,* 1969). A sudden attack of favism results in jaundice, abdominal pain, pale appearance of face, dark urine and in most cases fever (*Luzzatto and Arese,2018).*Indications of The β-glycosidic bond between glycon and the "OH" group at Carbon 5 on the pyrimidine ring are hydrolyzed torelease vicine, divicine (Rizzello *et al.,* 2016). Vicine in the of diet of animals lead to reduced production performance, anoxia (Arbid *et al.,* 2013), reduced haemoglobin (Hb) levels, decreased fertility, enlarged liver, higher concentration of glutathione in liver and higher level of plasma lipid (Leeson and Summer, 2001; Jezierny *et al.,* 2010). Poultry that had ingested vicine showed a significant decrease in performance and lower Hemoglobin level (Pulkkinen *et al.,* 2016; Leeson and Summer, 2001) whilst the others did not (Farran *et al.,* 2002).

VI. ALKALOIDS

Alkaloids

Alkaloids are nitrogen containing organic compounds of secondary plant metabolites (Orekhov, 1955; Hesse and Manfred, 2002; Aniszewski and Tadeusz, 2007; Azzeme and Zaman, 2019) which cause gastrointestinal and neurological disorders in animals (Aletor, 1993). Several related compounds with neutral and even weakly acidic properties are also included in this group (Manske, 1965; IUPAC, 1997; Lewis, 1998).

These are colorless and bitter in taste, insoluble in water, basic in nature and can form salts with acids (Leeson and Summer, 2001; Rhoades and David, 1979) the glycol-alkaloids, chaconine and solanine present in Solanum spp and potato (Aletor, 1993; saito *et al.,* 1990) are toxic to fungal species and human being. Seeds from *Amsinckia*, *Crotalaria*, and *Heliotropium* spp, are usually found adulterated in grains during harvesting, therefore may cause toxicity in cattle, small ruminants, horses, and poultry.

Many Alkaloids, however, have found to use in wide range of traditional or modern medicine including antiasthma, anticancer, anti-plasmodium (Kittakoop *et al.,* 2014), cholinomimetic (Russo *et al.,* 2013) anti arrhythmical (irregular heart beat), vasodilatory, analgetic/ anodyne (Raymond *et al.,* 2010) antibacterial/ antibiotic (Cushnie *et al.,* 2014) and anti-hyperglycemic physiochemical actions (Qiu *et al.,* 2014), whereas, some alkaloids have psychedelic/ hallucinogenic and stimulation/ induction activities e.g. cocaine, caffeine, nicotine (Robbers *et al.,* 1996). Some plant alkaloids are reported to cause infertility (Olayemi, 2010; Kiranmayi 2014). Tropane, Piperidine and phyrrolizidine are most toxic alkaloids related to poultry nutrition (Leeson and Summer, 2001).

Pyrrolizidine

Pyrrolizidine alkaloidosis is a chronic toxic found in plants of genera *Crotalaria*, *Senecio*, *Cynoglossum*, *Heliotropium*, *Amsinckia*, *Echium* and *Trichodesma*. The plants mainly concerned include groundsel (*S.*

riddellii, *S. longilobus*), ragwort (*S. jacobea*), yellow tarweed (*A. intermedia*), rattlepods (*Crotalaria spectabilis)* and seeds of rattle weed (*Crotalaria retusa*). These alkaloids are metabolized in the liver and bio-activated to high active compound ”pyrroles” by cytochrome P450 enzyme, however, this bio-activation may also occurs in, epithelial tissues, vascular tissues, heart, kidneys, lungs and gut and other organ/system where P450 enzyme is present (Leeson and Summer, 2001). Pyrrols are powerful alkylating agents which cause cytotoxic effect on target site, mainly the nuclei of hepatocytes which results in hepatic failure. These toxic pyrroles cross-link DNA strands thereby inhibiting the cell replication; also connect DNA with nucleo- proteins such as actin. Such types of molecular modifications are assumed to produce the cyto-toxic, antimitotic, and macrocytic effect which are characteristic of pyrrolizidine alkalosis.

In poultry pyrrolizidine alkaloidosis toxicity caused by ingestion of *senecio* and *crotaleria spp. crotaleria spectabilis* (rattlebox). Rattlebox have yellow flower hummingbird like shape. Post mortem of birds died by *crotaleria spectabilis* toxicity showed hemorrhages in liver, lungs and pericardium, reduced liver size and ascites. An acute intoxication shows enlarged, mottled friable, yellow/brown/red liver and distended gall bladder having clear green bile (Leeson and Summer, 2001). Chronic toxicity causes irregular size and shape of liver lobes and/or atrophy of liver with hepatic fibrosis, enlarged kidneys and splenomegaly and ascites. Early signs of toxicity include anorexia, inactivity, depression and growth retardation (Leeson and Summer, 2001).

Piperidine

Piperidine is colorless liquid organic compound (heterocyclic amines) with an objectionable odor (Frank, 1947; Vitaku *et al.,* 2014). The name Piperidine is derived from the genus name *Piper* or pepper (Senning, 2006; Pianaro, *et al.,* 2012). Piperine gives black pepper its spicy taste. Most important Piperidine alkaloids are coniine from poison hemlock (*Conium maculantum*), that was used to put great scholar Socrates to death (Thomas, 1949). Pyridine can be reduced to piperidine using a Birch reduction using sodium in ethanol (*Marvel and Lazier, 1941).* Poison hemlock has its eight derivatives however coniine and gama conicein are most prominent. Clinical signs of toxicity include tremor, flaccid paralysis, hypermetria, depression, seiures, opisthotonus and mortality. Postmortem examination reveals enteritis and liver congestion. Animal ingested poison hemlock is serious concern to human health and should not be allowed for human consumption (Leeson and Summer, 2001).

Piperidine has been obtained from black pepper (Spath, 1935), *Psilocaulon absimile* (Aizoaceae) (Rimington 1934) and *Petrosimonia monandra* (Juraschewski, 1939).Other examples of piperine toxins are the fire ant toxin solenopsin (Arbiser, *et al.,* 2007) and the nicotine analog anabasine of tree tobacco.

Datura also known as devil's trumpets is a genus (comprised of 9 species) belonging to the family Solanaceae (Leeson and Summer, 2001) include approximately 1600 species commonly known as daturas producing nodding seed capsules. These species are distributed to temperate, subtropical and dry regions of the world (Karinho-Betancour *et al.,* 2015). Daturas belong to the distinctive "witches' weeds" including deadly nightshade (*Arropa beladona*), henbane (*Hyocyamus niger*), and *Mandragora officinarum* (mandrake). All component (parts) of the plants may be toxic, however, roots, seeds and flowers of all species of Datura contain tropane alkaloids such as scopolamine and atropine which are poisonous and can cause psychosis, respiratory, depression, hallucinations, arrhythmias and even death (Adams and Garcia, 2005 Leeson and Summer, 2001;

Preissel and Preissel, 2002). In *Datura stramoniun* atropine whilst in *Datura ferox* scopolamine is the major alkaloid (Leeson and Summer, 2001). In subcontinent it was used in Ayurveda as a medicine and a poison. Seeds of datura and jimson-weed are found as contaminant in soyabean meal, in seed meal, sorghum, wheat and corn (Leeson and Summer, 2001; Preissel and Preissel, 2002). In poultry relatively higher level (3% or more) of dietary inclusion of jimsonweed decreased the growth rate without causing toxic effects. However, results of the research revealed that jimson weed seeds at 1% dietary can safely be used in poultry feed (Day and Dilworth, 1984).Egg weight, shell thickness and body weight of layers did not affect by all dietary levels of alkaloid (Kavatsis *et al.,* 1993; 1994).

Datura ingesting in adolescents and young adults has been reported critical to cause many tragic incidents ofserious illness in recent past (*Goetz et al.,* 2003; Leinwand, 2006). A number of reports of death has been describe in literature due to ingesting of *Datura stramonium* and *Datura ferox* (*Michalodimitrakis, M.; Koutselinis, A. (1984; Boumba et al., 2004 ; Steenkamp et al., 2014)*. Particularly Children are at higher risk to atropine intoxication (*Taha, and Mahdi, 1984; Djibo and Bouzou, 2000)*.

VII. Other Anti-Nutritional Factors

Anti-Minerals

These are mostly non-starch polysaccharides (NSPs) components of small intestine such as silicates, phytates and oxalates (Leeson and Summer, 2001). Anti-mineral substances interfere with the utilization of essential minerals. These are found in most of the plant foods, therefore, anemia and other essential mineral deficiency diseases are more common in vegetarian communities of the world (Erdman, 1979). These are present in vegetables, legumes, fruits, and cereal grains. Anti-metals Oxalate (COOH–HOOC) is regarded as an anti-nutrient as it reduces calcium absorption (Olomu. 1995) resulting in to hypocalcemia, tetany, poor bones growth, poor egg shell, vascular necrosis and haemorhages (Rahman and Kawamura, 2011; Leeson and Summer, 2001; Holmes *et al.,* 2001). It is present in numerous plant species in significant amounts especially in Araceae family (Leeson and Summer, 2001) also found in significant amount in sesame, rhubarb (McDonald *et al.,* 1995), locust bean (Alabi *et al.,* 2005), pigeon pea (Olomu. 1995), grains and grasses infected by *Aspergillus niger* (Leeson and Summer, 2001). This strong acid interference the digestion of protein, absorption of essential minerals such as calcium even may also induce toxic effects (Akande *et al.,* 2010). Soluble oxalates are absorbed into the systemic circulation where these can easily bind with serum calcium forming insoluble calcium oxalate crystals hence can develop the threat of increasing kidney stones which induce acute renal failure (Adrenyl *et al.,* 2009; Leeson and Summer, 2001). Oxalic acid contents of the can be reduced by increasing the harvesting intervals of fodder/grass (Smitha *et al.,* 2013).

Phytates

Phytates are hexphosphoric ester of myo-inositol present in considerable quantity in ingredients of high fiber containing legumes, palm kernel seeds and cereal grains (Matyka *et al.,* 1993; Osho, 1993; Ravindran *et al.,* 1995; Khare, 2000; Leeson and Summer, 2001). This strong acid binds proteins and minerals like calcium, iron, phosphorus, magnesium, copper, molybdenum and zinc and makes these unavailable (Nelson *et al.,* 1968; Erdman, 1979; Khare, 2000; Walter *et al.,* 2002). Phytate also reported to interfere the function of Trypsin, Chymotrypsin, Amylase, Lipase, Amylase and Tyrosinase (Khare, 2000). To reduce phytate activity in

monogastric animals, phytase enzyme is added in the feed. The enzyme catalyzes the dephosphorylation of phytate.

Dietary Fiber

Dietary fiber ornon-starch polysaccharides (NSPs) are derivative of plant cell walls include pectic substances, alginates, celluloses, hemicelluloses, lignin, plant gums, algal polysaccharides, and mucilages, dietary fiber can bind with amino acids, proteins, and even sugars. NSPs (Beta-glucans and arabinoxylans) have sugars excluding glucose or have link other than ordinary linkage in sugar i.e. in cellulose ß-(1→4) different orientation prevents the action of enzyme for digestion. Some non-digestible oligosaccharides such as raffinose and stachyose pass through intestine to lower digestive tract where cause bacterial growth and fermentation (Leeson and Summer, 2001).

Dietary fibers do not cause signs of over toxicity, however these negatively affect digestion in monogastric animals by increasing the viscosity of digesta, therefore, decrease the efficiency of digestive enzymes as a result reduce the performance of animals. Colon cancer (Ferguson and Harris, 1999). Adverse effect of dietary fibers can be avoided by adding B-glucanase and pentosanases in the diet of monogastric animals (Cambell and Bedford, 1992).

A variety of plants contain anti vitamin factors especially leguminous plants. Anti-vitamin E such as tocopherol oxidase and antivitamin B12 is reported in soybean meal (Hill 2003). Some plants and mushrooms have pyridoxine antagonists, ascorbic acid oxidase, antithiamines and anti-vitamin B6 agents. Anti-thiamine agents can be distinct as thiaminases, tannins, and catechols which may lead to serious neurotoxic effects due to thiamine deficiency. Thiaminases (enzymes) are antithiamine factors which cleave thiamine at the methylene link. Antithiamines are present in many fish species, saltwater species, freshwater and in some species of crabs however, antithiamine factors are also of plant origin. Cooking destroys thiaminases in fish meal and other sources.

VIII. Detoxification Strategies

Numerous methods are tried to triumph over the harmful effect of anti-nutritional factors. Legumes are usually cooked to inactivate lectine and protease inhibitors. Enzyme inhibitors and lectins can be denatured by heat treatment. Lower molecular weight substances are seeped out into cooking water to be deteriorated. Oxalates can be eliminates by cooking and de-hulling. Other methods of detoxification include postharvest processing, chemical detoxification, genetic engineering and through genetic modification of crops.

These methods involved germination (Singh *et al.,* 2014), making hay, silage with inoculants, acid or alkali treatment (Bora, 2014), using PEG (Ben *et al.,* 2000; Salem *et al.,* 2007) urea (Russel and Lolley, 1989) or biological treatment with fungi (Hassan, 2006; 2009) which have been proved to either take off or minimize and/ or lower anti-nutritional factors concentration. Adding Phytase enzyme and/ or germination or fermentation can lower the phytate content of ration. Sprouting has been renowned to be a useful treatment to eliminate Saponins. Soaking may prove helpful to decrease the Trypsin inhibitor activity. Extruding products produce their own friction and heat to denature of haem-agglutinins and other anti-nutrients. Cyanogenic glycosides, saponins, terpenoids and alkaloids can be eliminated by autoclaving.

Phenolic compounds such as tannins can be prevented by de-hulling the seeds. It is investigated that alkali tre-

-atment includes polyethylene glycol (PEG), which is a tannins-binding agent (Jones WT, Mangan , 1977) was revealed to be a potent compound for isolating the effect of tannins on different digestive function (Barry *et al.,* 1986; Mkkar *et al.,* 1995) But its use is not economical. Though the inclusion of polyethylene glycol (PEG) to inactivate tannins is pretty helpful, however, a success of its implementation relies on the cost: benefit ratio (Makkar, 2003; Ben Saleem *et al.,* 2004). Feeding animals with 1% urea (Russsell and Olley 1989) deactivates the tannins. Detoxification strategy of various anti-nutrients is discussed in table 2.

Table 1. Different anti-nutrients and their effect (Khan, 2000).

Anti-nutrients	**Mode of action**
Glucosinolates	Interfere with the utilization of other nutrients
Amylase /trysin /chymotrypsin inhibitor	Interfere with the digestion of various feedstuffs
Saponins	Interfere with the digestion of various feedstuffs
Linatine, oxalates, tannins	Prevent absorption of calcium, iron and other nutrients. Oxalates also cause kidney stone formation.
Lipoxygenase, phytate	Interfere with the metabolism of essential minerals and various nutrients
Cyanogenetic glycosides, erusic acid, cyclopropene FA, Haemaglutinins	Directly toxic

Table 2. Potential anti-nutrients in feed stuff and their control strategies.

Cottonseed meal	**Gossypol, CFA, tannins**	**Heat treatment, addition of iron salts 1:4,**
Rapeseed meal, cabbage, turnip, mustard green	Erusic acid, glucosinolates. Tannins, pectins	Formaldehyde and/or alkali or acid treatment with Ca(OH)2 . Treatment with Polyethylene glycol (PEG) and polyvinyl pyroldone (PVP) or treatment organic solvents like acetone, acids H2 O2
Soybean meal	protease /trysin inhibitor, saponin Anti-vitaminB_{12} factor, trace mineral binding factor	Heat treatment
Linseed meal	HCN	Alkali treatment
Sesame meal	Phytates, oxalates and chlorogenic acid	phytase enzymes, heat trt.
Rice bran, rice polish	Phytates, trysin inhibitor, free fatty acids	Autoclaving/boiling/antioxidants
Triticale	Chymotrypsin /trysin inhibitor	Heat treatment
Sorghum	Tannins	Water/chemical treatment, Treatment with Polyethylene glycol (PEG) and polyvinyl pyroldone (PVP) or treatment organic solvents like acetone, acids H2 O2
Wheat	Pentosans	Xylanase enzymes
Barley	B glucans	Water treatment / B glucanase enzyme
Chunnies	Antitryptic inhibitor	Heat treatment.

sugar beat	Saponins	Repeated washing with water and feeding phytosrerols
Lucern	saponins	Repeated washing with water and feeding phytosrerols
Sudan grass, Johnson grass, pearl millet, oats	Nitrates, cyanogens	Cutting the mature grass, drying and ensilaging
Safflower meal	Phenolic glucosides	Detoxified by solvents.
Subabul	Mimosin	Supplementation with amino acids or with metal ions i.e. Zn, Al and Fe.
Castor seed	Haemaggutinin	Cooking with 2 % Na OH
Sunflower meal	Chlorogenic acid High in fiber	Low temp. processing Addition of methionine & choline
Salseed meal	tannins	1% urea
Rubber seed meal	HCN	drying and ensilaging
Cassava meal	HCN	Cutting at maturity, Post-harvest wilting, drying and ensilaging
Ground nut cake, corn	Mycotoxins, Aflatoxins	HSAS, zeolite, PEG or probiotics like *Sacharomyces cerevisiae*.

IX. Conclusion

Presence of various anti-nutritional substances in animal's feed ingredients is a main restraint to utilize these feed resources for their full potential. In Pakistan where there is scarcity of fodders, exploiting the full potential of unconventional and available conventional feed ingredients may helpful to decrease animal production cost. However, different anti-nutrients present in these feed stuffs should be reduced to take advantage of their maximum utilization. For this, information regarding the correct estimation of the type/nature and level of the anti-nutrients present in the feed stuffs is essential. Famers should be trained about different facets of anti-nutrients, their effects and control/reducing measures by conducting seminars, workshops and awareness campaigns at national level for better and healthier production.

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