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Anti-Nutritional Factors in Animal Feedstuffs: A Review

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ABSTRACT

Plants naturally co-exist with their predators and have therefore developed certain defense mechanisms against them. These include production of secondary metabolites, which are not directly involved in their growth processes (as opposed to primary metabolites), but act as deterrents to their predators. Some of these metabolites, known as anti-nutritional factors, affect the nutritive value of forages and feedstuffs, and hence animals (including humans) that feed on them. Although they are generally not lethal, their effects may be contrary to optimum nutrition, making them undesirable for human and animal nutrition as they may interfere with feed utilization, health and productivity of animals. Their wide distribution in plants is determined by age, cultivar, geographic distribution, and storage condition after harvesting. Certain characteristics which they possess, together with other reasons make them to be found at some levels in almost all plants and plant products used as animal feedstuffs. The major classes of anti-nutritional factors include glycosides, alkaloids, protease inhibitors, amylase inhibitors, phenolic compounds, phytohaemagglutinins, phytates, terpenes/ triterpenes, non-protein amino acids, oxalates, and glucosinolates. The varied chemical structure and composition of these metabolites which are diverse in their abundance in different plants and their products, result in an array of direct and indirect effects which impinge on animal productivity and health. They occur in various quantities in plants, with alkaloids as the most abundant in higher plants. Alkaloids are among the most important drugs used by human beings and have also been adjudged to be the most useful and most dangerous products of nature. The effects of these anti-nutrients may be physical such as alopecia or physiological such as disruption of metabolic reactions and synthesis of important biochemical components of tissues. Their structures, occurrence, effects, and other related issues are reviewed herein.

Keywords: Secondary metabolites, Anti-nutritional factors, Animal Feedstuffs, Molecular and Cellular Targets, Phytoanticipins and Phytoalexins.

INTRODUCTION

Plants have developed defense mechanisms for their survival due to their co-evolution with their predators (insects, fungi, and grazing animals), including production of secondary metabolites, (SM) which are not directly involved in their growth processes, but act as deterrents to attack by their predators [1]. These compounds, commonly referred to as anti-nutritional factors, (ANFs) also affect animals (including humans) and the nutritive value of forages and feedstuffs. They are natural components or chemical compounds of plants, which present biological activity but no nutritional properties, and in fact, some of them may be undesirable for human and animal nutrition [2]. Staessen [3] stated that the anti-nutritional activity of a compound is not an intrinsic characteristic of the compound, rather it is determined by the digestive process of the animal by which it is ingested. This had been confirmed by [4],

who noted that trypsin inhibitors are degraded in the rumen of ruminant animals, whereas they are regarded as ANFs in monogastric animals.

According to [5] anti-nutritional factors are those substances generated in natural feedstuffs by the normal metabolism of species and by different mechanisms, e.g. inactivation of some nutrients, diminution of digestive process or metabolic utilization of feed, which exert effects contrary to optimum nutrition. The ANFs may therefore, be regarded as a class of compounds, which are generally not lethal but reduce animal productivity and may cause toxicity during periods of scarcity or confinement when feed rich in these substances are consumed by animals in large quantities [6]. They also noted that they are substances, which by themselves or through their metabolic products, may interfere with feed utilization and affect the health and productivity of animals. Consequently, as opposed to primary metabolites, they do not have any direct role in functions related to growth and development such as photosynthesis, respiration, solute transport, translocation, protein synthesis, nutrient assimilation, differentiation, or the formation of carbohydrates, proteins, and lipids [7]. He also noted that they differ from primary metabolites (amino acids, nucleotides, sugars) in having a restricted distribution in the plant kingdom whereas primary metabolites are found throughout the plant kingdom.

Anti-nutritional factors are widely distributed in most plants [8]. Yang and Lin [9] reported that the age, cultivar, geographic locality of a plant or the storage condition after harvest could significantly affect its anti-nutritional content. Usually, varying concentrations and combinations of these toxic principles and anti-nutritional factors are present in animal feedstuffs. Generally, anti-nutrients can be natural or synthetic compounds that interfere with the digestion, absorption, metabolism and assimilation of nutrients by animals, with a concomitant reduction in feed intake and/or feed conversion.

Characteristics of plant secondary metabolites

Plant secondary metabolites are natural products that are synthesized by secondary metabolism. Basically, they are substances manufactured by plants to make them competitive in their own environment [10]. However, their general characteristics include the following:

They are:

i.) products of secondary metabolism,
ii.) found in virtually all plants to some degree,
iii.) common in tropical forages, and
iv.) play defensive roles to plants

It is for these and other reasons that anti-nutrients are found at some level in almost all plants and plant products used as animal feedstuffs.

Roles of plant secondary metabolites

Heterotrophic animals and most micro-organisms depend on autotrophic plant materials for energy, since only such plants are photosynthetic. In order to survive, plants have had to develop defence strategies against these organisms, as well as other plants that compete for light, space and nutrients. They do so by producing secondary metabolites and several macromolecules, which apart from their function in physiology or structural maintenance, serve for defence against microbes and herbivorous animals. These compounds, also called allelochemicals, exhibit both defence and signal functions [11-13]. Experimental, toxicological and circumstantial evidence clearly indicate that secondary metabolites and other allelochemicals are toxic or deterrent to insects and vertebrates, as well as have functions that are vital for the fitness of the plants producing them [14]. Therefore, their structures have been shaped during evolution to closely interact with molecular targets in cells and tissues or other physiological features in animals or

microorganisms. These metabolites are known to specifically modulate corresponding molecular and cellular targets, which could be neurotransmitter receptors and transmembrane transporters, enzymes which degrade neurotransmitters, hormone receptors, ion channels, ion pumps, or elements of the cytoskeleton, in animals or humans [12, 15-17]. Their structures may resemble endogenous substrates, hormones or neurotransmitters and can thus mimic a response at the corresponding molecular targets. Consequently, there is hardly a target in animals or microorganisms for which a natural product does not exist, since plants provide a wide array of bioactive substances [18]. It is on this premise that so many natural products can be used in diverse ways in biotechnology, pharmacy, medicine and agriculture.

Secondary metabolites are always produced as mixtures of several substances, usually from different classes, e.g. polyphenolics are often accompanied by terpenoids, indicating that their activities could be additive or synergistic [19]. Therefore, they perform many functions that enable most plants to withstand various threats from herbivores, microbes and the physical environment. According to [7, 19], they may be constitutive or stored in inactive forms in plant parts (phytoanticipins) or induced against or in response to microbial or insect attacks (phytoalexins). Their main roles as highlighted by [17, 20, 21] include the following:

i.) defence against herbivores (insects and vertebrates),
ii.) defence against fungi and bacteria,
iii.) defence against viruses,
iv.) defence against other plants competing for light, water and nutrients,
v.) protection against the damaging effect of U-V light,
vi.) signal compounds to attract pollinating and seed-dispersing animals,
vii.) signals for communication between plants and symbiotic microorganisms, and
viii.) ix) they may play nutritional roles during germination of seeds.

The increased interest in phytochemicals in animal diets has been prompted by the ban on 'in feed' antibiotics, the removal of animal proteins from animal diets and thus the increased variety and inclusion levels of vegetable protein sources [17]. Extensive studies have been conducted on them because of the adverse effects that they have when ingested by animals, although they also have some beneficial effects in animals and human beings [22-25).

Classes of anti-nutritional factors

The anti-nutritional factors in plants may be classified on the basis of their chemical structure, the specific actions they bring about or their biosynthetic origin [4]. This classification does not encompass all the known groups of anti-nutritional factors, but it presents the classes of those frequently found in human foods and animal feedstuffs. According to [26], anti-nutritional factors found in animal feedstuffs may be classified based of their effects on the nutritional value of feedstuffs, and on the biological response to them in the animal into the following categories:

i.) Factors with a depressive effect on protein digestion and on the utilization of protein, such as protease inhibitors, phenolic compounds such as tannins, and glycosides such as saponins;
ii.) Factors that affect mineral utilization, which include phytates;
iii.) Factors that stimulate the immune system and may cause a damaging hypersensitivity reaction, such as antigenic proteins;
iv.) Factors with a negative effect on the digestion of carbohydrates, such as amylase inhibitors, phenolic compounds and flatulence factors.

However, the major classes of anti-nutritional factors found in animal feedstuffs include glycosides (primarily cyanogenic and cardiac glycosides), alkaloids, protease inhibitors, amylase inhibitors, phenolic compounds,

phytohaemagglutinins, phytates, terpenes/triterpenes, glucosinolates, oxalates, and non-protein amino acids [5, 27-29].

Glycosides: Glycosides have been recognized as organic compounds of plant origin or a heteromolecule made up of one or more sugars in combination with a non-sugar moiety such as an alcohol, a phenol, or a complex molecule such as a steroid nucleus [30-32]. Many plants store them in inactive forms which become activated by hydrolyzing enzymes [33]. In general, they perform many important functions in living things but are also used as medications. The two groups which are of particular physiological importance to animals are: cyanogenic glycosides and cardiac glycosides, because of the potential risks they pose to humans and animals that consume them [34].

Cyanogenic Glycosides (CGs): They are a group of natural nitrile containing plant secondary metabolites that release hydrogen cyanide (cyanogenesis) due to enzymatic breakdown [34, 35]. These compounds abound in 100 families and at least 2000 species of plants [29, 34], many of which are used as food. Many economically important plants are highly cyanogenic such as apples, plums, cherries, almonds, cashew, cassava, cocoyam, rubber, sorghum), barley, white clover, etc. [35-38]. There are about 25 identified cyanogenic glycosides out of which amygdalin is the most common in fruits [34].

Cyanogenic glycosides are not toxic on their own but are hydrolyzed when plant cell structures are disrupted such as chewing by herbivores, grinding, pounding and grating, presence of water during soaking and fermentation, thereby bringing cyanogens in contact with hydrolyzing enzymes [39-40]. Cyanogenesis is the ability of some plants to synthesise cyanogenic glycosides, which when enzymatically hydrolyzed, release cyanohydric acid or hydrocyanic acid (HCN) also known as prussic acid [41]. In cassava two types of cyanogenic glycosides are produced - linamarin (93%) and lotaustralin (7%) [42]. The variation in concentration of cyanogenic glycosides in plants is determined by age, variety, genetic factors, location, soil types and environmental conditions [43].

The main biological function of CGs is to defend plants against distinct animals (attacks by insects and herbivores) [44]. However, cyanogenic glycosides have been implicated in the etiology of several chronic diseases, debilitating irreversible neurological conditions, and death [34, 45]. Therefore, its control, reduction and possible elimination in such plants are paramount in animal feeding and in food safety [45].

Cardiac glycosides: Cardiac glycosides are a unique group of plant secondary metabolites comprising the most drug-like molecules, which are divided into two main classes in plants - cardenolides and bufadienolides, with the latter being confined to the angiosperms [46]. They occur in small amounts in the seeds, vacuoles, stems, roots and bark of flowering and non-flowering plants. According to [47], the most commercially important sources of cardiac glycosides are *Digitalis purpurea, D. lanata, Strophanthus gratus,* and *S. Kombe*. Cardiac glycosides are C_{23} and C_{24} steroids with the ability to exert specific powerful action on the cardiac muscles, but are also responsible for the poisoning of livestock [46].

Alkaloids: Alkaloids are traditionally defined as basic (alkali-like) nitrogen-containing organic constituents that occur mainly in plants [48]. They can also be defined as a group of biologically active and heterocyclic chemical compounds containing nitrogen and may have some pharmacological activity, and in many cases, medicinal or ecological use [49]. They were initially considered to be exclusive to plants, but many types have been isolated from amphibians [50]. Over

10,000 alkaloids are known with narcotine as the first one to be discovered [29]. Alkaloids are common in the Angiosperms or are most abundant in 25% of higher plants (mono- and dicotyledons), but rare in lower plants, although there are exceptions [27, 29]. The highest alkaloid concentrations are believed to occur in the ovules, seeds, and immature fruits of plants [51]. Hegnauer [52] defined alkaloid plants as those species which contain more than 0.01% of alkaloids. Alkaloids can be classified in terms of their, biological and ecological activity, chemical structures, and biosynthetic pathway [27, 29]. Structurally, they are divided according to their shapes and origins into true alkaloids, protoalkaloids, and pseudoalkaloids. According to [29] alkaloids are historically and contemporaneously the only molecules of natural origin with highly important benefits and diagnostic uses. He further noted that they are the most useful and also the most dangerous products of nature. They are among the most important drugs in human history [53].

Biologically, the most important points about them are that they are active at different cellular levels of organisms, and they are involved in the biological processes of plants, animals and micro-organisms [27]. In nature, it is difficult to generalize the effects of alkaloids present in feeds but they are considered to play very important roles in plant–animal interactions. Pollinators and grazing animals are exposed to a wide range of alkaloids since they subsist on plants, and they act as both attractants and deterrents to herbivorous animals, being more toxic to vertebrates than invertebrates [54]. The main role of alkaloids in plants revolves around defense against herbivores and predators by toxicity, anti-nutritive, and repellent substances [53]. They are naturally non-toxic in plant vacuoles where they are stored but become toxic when they are discharged and undergo changes in their chemical configurations and biological activities on the basis of changes in P^H in different cells and tissues [27]. Some of their main effects according to [44, 53, 55-57] include the following:

i.) Reduced palatability and act as feeding deterrents by bitterness e.g. quinine,
ii.) Disruption of protein function following ingestion and metabolism, and nervous system alteration,
iii.) Alkaloid toxicity involves neurotoxicity or cell signaling disruption, thereby affecting different metabolic systems in animals using different toxic mechanisms,
iv.) Significant financial losses are usually experienced in livestock production due to alkaloid toxicity,
v.) v) Musculo-skeletal deformities, muscle weakness, frequent urination and defecation, ataxia, collapse and death by respiratory failure in livestock, and
vi.) Multiple congenital deformities in pigs, goats, cattle and sheep.

Protease Inhibitors: Generally, enzyme inhibitors are substances that reduce the rate of an enzyme catalyzed reaction [4]. Proteases are a group of enzymes responsible for protein digestion, whose actions can be inhibited by protease inhibitors. Fan and Guo-Jiang [58] classified digestive proteases into four major groups: serine proteases, cysteine proteases, metaloproteases and acid proteases. It has been well noted that they occur in abundance in leguminous species [59, 60].

Protease inhibitors act via the formation of a proteinaceous or non-proteinaceous enzyme– inhibitory molecule complex [60]. They are known to bind an enzyme through a reactive or inhibitory site, thereby preventing the enzyme from binding to the substrate [61-63]. These result in inability of the enzyme-inhibitor complex to ensure substrate hydrolysis due to decreased catalytic potential [60]. Profound interference with several physiological and biological processes ensue, such as inflammation, blood clotting, apoptosis, hormonal actions, etc. [64]. Serine proteases are trypsin and chymotrypsin, which are involved in protein digestion in humans and

animals. Trypsin and chymotrypsin inhibitors impair protein digestion with a resultant anti-nutritional effect and a concomitant deleterious effect on growth [60]. These, including pancreatic hyptertrophy, have been observed by [65].

Amylase Inhibitors: Another group of enzyme inhibitors found in plants are those that slow down the rate of carbohydrate digestion, known as amylase inhibitors. The two major amylases in monogastric animals are α-glucosidase and α-amylase. They are found in the brush boarder of the small intestine where they act on oligosaccharides and disaccharides, to form absorbance monosaccharides[66,67]. Other compounds, such as phenolic compounds e.g. flavonoids and tannins, and terpenoids exhibit α-amylase inhibitory tendencies [28]. Studies have revealed the existence of a large number of plant α-amylase inhibitors [68, 69], such as in *Cajanus cajan, camelina, amaranthus, bougainvillea, guava, etc.* [70-72]. Amylase inhibitors delay carbohydrate digestion with a consequent reduction in glucose absorption and are therefore anti-hyperglycaemic [67, 73, 74]. According to [28] such compounds have demonstrated activities consistent with their possible use as antidiabetic drugs. However, they can have a growth inhibitory effect in animals by reducing energy for metabolic processes e.g. arcabose [28, 67].

Phenolic Compounds: These are a class of naturally occurring plant secondary metabolites broadly divided into phenolic acids and polyphenols [75]. They are common in fruits, vegetables, cereals, and beverages [76]. Scalbert *et al.* [77] identified the main classes as phenolic acids, flavonoids, stillbenes and lignans. Pandey and Rizvi [76] also noted that polyphenols and other food phenolics have become the subject of increasing scientific interest owing to their possible beneficial effects on human and animal health. In their opinion, flavonoids are the most studied class of polyphenolics out of the over 8000 polyphenolic compounds identified in plants. The major types of phenolic compounds identified in herbs include phenolic acids, flavonoids, tannins, coumarins, lignans, quinones, stilbenes, and curcuminoids [78]. However, the most important dietary phenolic compounds are phenolic acids, flavonoids, and tannins [79]. Phenolic compounds possess antioxidant potentials which are attributed to their capacity to scavenge free radicals, donate hydrogen atoms and electrons, or chelate metal cations [80-82]. In general, they are involved in defense against ultraviolet rays of the sun or aggression by pathogens [83]. However, they may be implicated in bitterness, odour, flavour, astringency, and oxidative stability of foods [76]. The presence of tannins is believed to be responsible for the astringent taste of some leaves and fruits [84]. They also noted that hydrolysable tannins can affect monogastrics by reducing growth rates, protein utilization and causing damage to the mucosa of the digestive tract, thereby increasing the excretion of protein and amino acids.

Haemagglutinins: Haemagglutinins, also known as lectins, are natural proteins present in both plant and animal tissues possessing the ability to agglutinate erythrocytes [85]. They also lyse erythrocytes via their lectin activity [86]. They are also called phytohaemagglutinins because they were originally found in plant extracts, which gave rise to the conception that they are almost exclusively plant proteins [85, 87]. Lectins and hemagglutinins are proteins/glycoproteins, which have at least one non-catalytic domain that exhibits reversible binding to specific monosaccharides or oligosaccharides [88]. They are known to bind carbohydrates and the name haemagglutinin is actually used when the sugar specificity is unknown. Initially lectin refers to the ability of some carbohydrate–binding proteins to selectively agglutininate erythrocytes of a particular human blood

group [89]. Therefore, they opined that agglutinins may be more correct because the term lectin was widely applied to all proteins with more general agglutination behaviour and hence the ability of the carbohydrate-binding proteins to agglutinate erythrocytes or other cells. They are ubiquitous in nature, found in various families of plants, and hence are consumed in appreciable amounts daily by both animals and human beings [90].

According to [89] there are three major classes of lectins based on their overall structure namely, merolectins, hololectins, and chimerolectins. They may be natural purified or recombinant lectins. Three major groups of natural lectins are plant, animal, and mushroom lectins [88]. Ramteke *et al.* [91] identified the following features of lectins amongst others. They are:

i.) present in legumes,
ii.) found in both plant and animal tissues,
iii.) toxic and combine with glycoprotein components of red blood cells to cause their agglutination,
iv.) resistant to digestion by pancreatic enzymes, and
v.) resistant to dry heat but are moist-heat (steam) labile.

Lectins are present in the seeds of a number of legume species consumed by humans and animals. Hill [92] recognized kidney bean (*Phaseolus vulgaris*) as the main legume species high in lectins, which are also found in *P. coceineus* and *P. acuitifolius*. Some legumes exhibit zero lectin activity, namely, Soya bean, Cowpea, Mung bean, Garden pea, Pigeon pea, Chick pea, etc.

Lectins are involved in establishing the symbiotic relationship between legumes and nitrogen-fixing bacteria (*Rhizobium leguminosarum*) [85, 89]. According to [85], two proposals were made in the 1970s on the roles of plant lectins in protection and symbiosis, namely,

i.) They are involved in the association between leguminous plants and their symbiotic nitrogen fixing bacteria [93, 94], and
ii.) Lectins protect plants against phytopathogenic micro-organisms, insects and predatory animals [95, 96].

Although lectins are toxic, they do not completely protect plant parts or their seeds from consumption, and the reaction of avoidance by the animal may be beneficial for the survival of the species [89]. In a review of anti-nutritional properties of lectins, [90] opined that they survive digestion in the gastrointestinal tract, and cause series of harmful local and systemic interactions, which present them as anti-nutritive and/or toxic substances. According to them, locally, they can affect the turnover and loss of gut epithelial cells and damage luminal epithelial membranes, interfere with digestion and absorption of nutrients, stimulate shifts in the bacterial flora and modulate the immune state of the digestive tract, as well as intestinal and systemic metabolism. The main effect of lectins on humans and animals occurs through their interference with digestion in the small intestine. They cause rapid body weight loss in animals while the weight of the small intestine increased [92]. He therefore, proposed that lectin-containing seeds should be processed by heat treatment before being fed to monogastric animals.

Phytate: According to [97, 98], phytate, which is widely distributed in all seeds and possibly all plant cells, is the salt of phytic acid consisting of an inositol ring and at least one phosphate group. The biosynthesis of phytate is initiated just after flowering and continuous accumulation occurs from development to seed maturity and desiccation [98]. They are abundant mainly in the protein-aleurone layer in cereals, except in maize in which it is abundant in the embryo [99, 100]. As much as 80% of total seed phosphorus is in the form of phytic acid, making it a primary storage compound of phosphate as energy source and antioxidant for the geminating seeds [101, 102].

Phytate is sometimes considered as an anti-nutritional factor because it is implicated in

the impaired absorption of minerals [2]. The presence of phytate in diets is of major concern due to its negative effect on mineral uptake which makes bone mineral deficient. It capable of chelating metal cations, primarily iron, zinc, calcium, as well as proteins and digestive enzymes, such as pepsin, amylase, and trypsin [101]. Therefore, dietary phytate has received much attention as an antinutrient, since the chelating effects of phosphate groups cause phytic acid to bind to mineral cations, especially Zn^{2+} and Cu^{2+} [98]. Mineral deficiencies in bones and malnutrition are known consequences of a homogenous and high dietary phytate or phytic acid acting as antimetabolites [102, 103]. Bohn *et al.* [98] reported that the capability of phytic acid to bind minerals makes it an anti-nutritional factor because the solubility of the phytic acid:metal complexes are low at the P^H of the major part of the small intestine. They also reported that in monogastric animals, phosphorus in the form of phytic acid is largely unavailable as a nutritional factor because insufficient degradation capabilities in the gastrointestinal tract prevent the bioavailability of phosphorus. Therefore, pig and poultry feeds are traditionally supplemented with inorganic phosphate to meet their optimal requirements for growth.

Different processing strategies have been tried with the use of phytic acid hydrolyzing enzymes adjudged to be most beneficial. Such phytases have been used as feed additives with multiple benefits such as increasing mineral, phosphorus and energy uptake. In pigs, yeast phytase were found to be resistant to denaturation in a grain-based diet mixed with rice leaves [104]. Consequently, degradation of phytic acid and the release of phosphorus and minerals have been of great interest to human and animal nutritionists as well as ecologists [98].

Terpenes/Terpenoids: Terpenes are a collection of organic compounds primarily synthesized by plants as their secondary metabolites, usually with strong aroma, and produced in part for defense or to help them deter insects and parasitic micro-organisms [105-107]. They are also produced by animals, microbes, insects, plant pathogens, endophytes and marine organisms [108], and are present as miscellaneous lipids in all living organisms and natural products [109-110].

They occur in all plants and represent the largest class of and most structurally diverse plant natural products or secondary metabolites - over 55,000 isolated members, with wide applications [111, 112]. The structures of terpenes are built from five carbon isoprene or isopentane units assembled in thousands of combinations [108, 111]. Each isoprene unit has the molecular formular C_5H_8. According to [108], the classes of terpenes based on the number of isoprene units are:

i.) Hemiterpenes: one (1) isoprene unit or five (5) carbon atoms, which is not usually considered to be a terpene, but may form oxygen-containing derivatives such as prenol and isovaleric acid [113].

ii.) Monoterpenes: two (2) isoprene units or ten (10) carbon atoms.

iii.) Sesquiterpenes: three (3) isoprene units or fifteen (15) carbon atoms.

iv.) Diterpenes: four (4) isoprene units or twenty (20) carbon atoms.

v.) Sesterpenes: five (5) isoprene units or twenty five (25) carbon atoms.

vi.) Triterpenes: usually contain six (6) isoprene units or thirty (30) carbon atoms.

vii.) Sesquarterpenes: contain seven (7) isoprene units or thirty five (35) carbon atoms.

viii.) Tetraterpenes: contain eight (8) isoprene units or fourty (40) carbon atoms.

ix.) Polyterpenes: contain ten (10) or more isoprene units or fifty (50) or more carbon atoms. (However, [114] identified terpenes with greater than 8 isoprene units as polyterpenes, with the general formular $(C_5H_8)_n$.

Terpenes are more commonly found in corniferous species but they are also found in other plant phyla such as angiosperms [115]. Generally, the plant surface structures

such as stem, bark, leaves, and fruits are the main sources of terpenes [116]. Terpenoids is a broader term covering modified terpenes either by oxidation, reduction or rearrangement of the carbon frame [108], and is synonymous with terpenes [117]. They are synthesized by plants in response to herbivory and stress, and are also emitted by flowers to attract pollinating insects [101]. Furthermore, attack by herbivorous insects induce the release of terpenes which serve as attractants of predatory species or parasites and facilitate the location of the attacked plants [118-122]. Terpenes are known to inhibit the growth of rumen microorganisms, which are important for the breakdown of cellulose [14]. Terpenes also influence ungulate herbivory on other plants and may serve as a basis for balancing the diets of ruminants. Sheep are known to tolerate terpenes if they consume more grains [123]. They are also believed to play anti-feedant roles [124]. In general, they have diverse biological, pharmacological, and therapeutic effects.

Glucosinolates: These constitute a group of secondary metabolites of plants of the family brassicaceae (cruciferae) within the order brassicales (previously known as capparales), which embrace the mustard and cabbage family [125-127]. They are a family of more than 120 plant compounds consisting of sulphur and nitrogen containing phytochemicals (thioglycosides) derived from several amino acids and occurring naturally as potassium or sulphate salts [128]. Glucosinolates and their miscellaneous breakdown products are generally known as mustard oil glucosides or thioglucosides [129]. The most common glucosinolates in dietary crucifers are glucobrassicin, glucoraphanin, or progoitrin. They are also found in at least 500 species of non-cruciferous plants [128].

In the producing plants, glucosinolates constitute part of an innate defense system [126, 129]. They are widely distributed in plant tissues/parts (seeds, leaves, root, stems, bark), with the highest concentration in seeds [128] and youngest tissues [130]. Glocosinolate-containing plants have always made major contribution in human and farm animals' diets, such as cabbage, swede/turnip, raddish, brocole, roped/ cangla, and crops and crop residues used as animal feedstuffs such as canola/rapeseed and its cake, kale, turnip, etc. [131]. The plant content of glucosinolates depends on a variety of conditions such as a soil fertility, environmental factors, pathogenic challenge, and plant growth regulators [128, 132].

On their own, they are relatively biologically inactive but upon tissue disruption they are hydrolyzed to produce many structurally diverse products with different biological activities [131]. When plant tissues are damaged by herbivory, contact between glucosinolates and the myrosinase (sequestered in different compartments) is established resulting in hydrolysis and the formation of thiocyanates, nitrites and elemental sulphur [128, 129]. These compounds are toxic to humans and farm animals, and impair iodine uptake and synthesis of thyroid hormones, resulting in hypothyroidism and enlargement of the thyroid gland (goitre) [133]. In swine and poultry goiterous swelling of the neck is not apparent [134]. Bischoff [135, 136] highlighted some of their beneficial effects as regulatory functions in inflammation, stress response, phase 1 metabolism, and antioxidant activities, as well as direct antimicrobial properties. He also noted that high levels of glucosinolates in livestock rations may result in reduced feed intake and growth, gastrointestinal irritation, goiter, anemia, and hepatic and renal lesions. Adverse effects in monogastric animals include; reduced egg production and plasma urate levels in layers [137]; decreased feed intake and significant reduction in weight gain in broiler chicks [138], reduction in litter size, delayed sexual maturity, impaired conception rates, decrease in litter weight and hypothyroidism in pigs and piglets [139], etc. However,

[140] highlighted reduced palatability, decreased growth and production as the major deleterious effects of glucosinolates ingestion in animals.

Oxalates: Chemically, oxalates are salts of oxalic acid, an organic acid occurring in both plants and animals, and generally accumulates as a metabolic end product in the form of a free acid [141]. They occur naturally in relatively small amounts in many plants where they are synthesized by incomplete oxidation of carbohydrates [142]. The highest levels of oxalates are found in amaranth, cocoyam, spinach, sorrel (oxalis), rhubarb and purslaine [143]. According to him, they are also present in high levels in cocoa, potatoes, almonds, cashews, peanuts, beans, sweet potato, beetroot, and raw carrots, with differences in levels among plants being probably due to differences in growth conditions, cultivars, and plant part used. The distribution within plants is also uneven as [144] observed that it is highest in the leaves followed by the seeds and stems. This had also been confirmed for amaranth, spinach and beetroot [145, 146]. High levels have also been observed in cocoyam, yam, and sweet potato [147, 148].

High levels of oxalates in some tropical plants have generated some concern. Oxalates are readily absorbed after ingestion but cannot be metabolized in mammals and are primarily eliminated through renal excretion. Bioavailability of oxalates in foods and feeds exert a negative effect on calcium and iron absorption [149]. The adverse effects of oxalates should therefore be considered in terms of oxalate:calcium ratio, with 9:4 as the optimal limit [143]. Oxalates can have harmful effects on human and animal health by reducing calcium absorption and aiding the formation of kidney stones [150].

Non-Protein Amino Acids (NPAAs): Amino acids are the building blocks of proteins and there are thousands of them in nature, out of which only twenty are directly involved in protein structure [151]. All other amino acids other than the twenty incorporated in proteins are known as non-protein amino acids [151, 152]. Over 900 NPAAs have been reported in a variety of plants, which they are mainly found in the seeds of legumes [153], although they also occur in their leaves.

At least 20 non-protein amino acids are known to be toxic to humans and livestock [154]. This has been confirmed by Bell [155], who reported that an NPAA, indospicine, is hepatotoxic to sheep, cows and rabbits, and has caused abortions in pregnant animals. Another one – mimosine, is associated with alopecia on the tail, ear, face and umbilical sheath in cattle and sheep fed large amounts of Leucanea, which is known to be rich in mimosine [156]. In pregnant gilts it is linked with high incidence of resorption of foetuses and limb deformities in others. In monogastric animals, they can cause productive abnormalities and limb deformities (pigs), and residual effects in tissues (chickens). Basic processes such as protein synthesis, urea synthesis and neurotransmission may be disrupted [155].

An overview of modes of action of anti-nutritional factors in animals

Plant secondary metabolites, some of which act as anti-nutritional factors, are well known for their toxic and hallucinogenic properties [15, 16]. Wink and Schimmer [14] noted that although the structures of many of these anti-nutritional factors are well known, there is fragmented and incomplete knowledge of their molecular modes of action. Such knowledge is, however, necessary to understand the functions of anti-nutritional factors in the producing organism, and for the rational utilization of their modes of action in animals that ingest them. As previously noted, several authors have confirmed that they specifically modulate corresponding molecular and cellular targets. The ability of their structures to interact with many different molecular and cellular targets, and

thus mimic a response at the corresponding molecular target is known as "evolutionary molecular modelling" [17].

The potential targets in animals include mercapto or sulfhydryl groups (SH) of proteins, amino group (NH_2), and amino acids of proteins, although they can modulate any cellular target [14]. Thus, plants produce a wide range of bioactive substances, and many of these substances are already in widespread use in biotechnology, pharmacy, medicine and agriculture [17]. Anti-nutritional factors are multi-target substances, produced as a mixture of different classes, making it more difficult for herbivores and microbes to resist them [157, 158]. Furthermore, the activity of individual metabolites in the mixtures may be additive or apparently synergistic [159-161]. Anti-nutritional factors have a wide range of biological activities, from their biochemistry and functions, as components of feedstuffs that animals eat or can eat. This gives room for considerable interactions between ingested anti-nutritional factors and tissues, enzymes and other compounds within the animal [17]. They also noted that the interactions during absorption, deposition, metabolism, and excretion are highly dependent on the physico-chemical attributes of the compounds involved and their susceptibility to transformation.

Upon ingestion of plant secondary metabolites by humans and animals, the following physico-chemical factors exert profound influence on them: molecular size and architecture; pH of the environment; hydrophilicity; lipophilicity; charge and polarity; ability to form micelles; solubility. [17, 20]. Following the modulation of molecular targets, there is a negative influence on its communication with other components of the cellular network, especially proteins (crosstalk between proteins), elements of signal transduction, or membrane functions. Consequently, the metabolism and function of the whole organism, starting from cells to tissues, organs, and systems, is affected.

CONCLUSION

The scientific evidences reviewed herein reveal certain critical issues about plant secondary metabolites that are anti-nutritional factors in animal feedstuffs. They are integral parts of plants and their products, occurring naturally in all parts of plants as a defense mechanism against their natural predators. Primarily, they are generated in natural feedstuffs by the normal metabolism of species and by different mechanisms and exert effects contrary to optimum nutrition. Apart from their function in physiology or structural maintenance, they serve for defence against microbes and herbivorous animals, and specifically modulate corresponding molecular and cellular targets in animals and humans. They exist as mixtures of diverse metabolites, with additive or synergistic activities that may be beneficial or harmful to animals and human beings. In animal feedstuffs, they may affect protein digestion and utilization, and mineral utilization, stimulate the immune system and may cause a damaging hypersensitivity reaction, or exert negative effect on carbohydrate digestion. The classes they belong to may be: glycosides, alkaloids, protease inhibitors, amylase inhibitors, phenolic compounds, phytohaemagglutinins, phytates, terpenes/triterpenes, glucosinolates, oxalates, and non-protein amino acids. The wide array of effects they exert find diverse uses in in biotechnology, pharmacy, medicine and agriculture, since there is hardly a target in animals or microorganisms for which a natural product does not exist. Amongst them, alkaloids with highly important beneficial and diagnostic uses, are also adjudged to be the most useful and the most dangerous products of nature. Anti-nutritional factors act via their ability to interact with diverse molecular and cellular targets, by mimicking responses at molecular targets, a phenomenon known as "evolutionary molecular modelling." Their potential targets are mercapto or sulfhydryl groups

(SH) of proteins, amino groups (NH_2), and amino acids of proteins, although they can modulate any cellular target in animals. Upon ingestion, their actions depend on molecular size and architecture; pH of the environment; hydrophilicity; lipophilicity; charge and polarity; ability to form micelles; solubility. By the concept of crosstalk between proteins, they affect the metabolism and functioning of the whole organism, starting from cells to tissues, organs and systems.

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REFERENCES

1. Rao SBN, Prasad KS, Rajendran D. Recent advances in amelioration of anti-nutritional factors in livestock feed stuffs. In: Animal Nutrition & Reproductive Physiology: Recent concepts. Sampath KT, Jyotirmoy G, Raghavendra B. (Eds). Delhi, India, Satish Serial Publishing House. 2013. p.655-678.
2. Trugo LC, Baer EV, Baer DV. Lupin Breeding. Elsevier Ltd. 2004. 2:174 - 182.
3. Staessen T. Anti-nutritional factors in the water extract of five protein sources. M. Sc. dissertation. 2014. Department of Aquaculture, Faculty of Bioscience Engineering, Universiteit Gent, China.
4. Emire SA, Jha YK, Mekam F. Role of anti-nutritional factors in food industry. Beverage and Food World. 2013; 2:23-28.
5. Kumar R. Anti-nutritional factors, the potential for toxicity and methods to alleviate them. In: Legumes trees and other fodder crops as sources of proteins for livestock. Speedy A, Pugliese P. (Eds). Proceedings of the FAO expert consultation held at the Malaysian Agricultural Research and Development Institute (MARDI) 1991 October 14-18; Kuala Lumpur, Malaysia. www.fao.org.
6. Cheeke PR. Natural toxicants in feeds, forages, and poisonous plants. 2nd ed. Danville Ilinois: Interstate Publishers, Inc. 1998. pp 479.
7. Dey D. Role of secondary metabolites in plant defense. Innovative Farming. 2016; 1(4): 115-118.
8. Medoua NG, Mbome IL, Agbor-Egbe T. *et al*. Anti-nutritional factors changes occurring in trifoliate yam (*Dioscorea dumentorum*) tubers after harvest. Food Chemistry. 2007; 102: 716-720.
9. Yang DJ, Lin JT. Effects of different storage conditions on steroidal saponins in yam (*Dioscorea pseudojaponica Yamamoto*) tubers. Food Chemistry. 2008; 110:670-677.
10. Teoh ES. Secondary Metabolites of Plants. Medicinal Orchids of Asia. 2015; 5:59-73.
11. Bernays EA, Chapman RF. Host-plant selection by phytophagous insects. New York: Chapman & Hall. 1994. p. 14-54
12. Wink M. Importance of plant secondary metabolites for protection against insects and microbial infections. In: Naturally Occurring Bioactive Compounds: A New and Safe Alternative for Control of Pests and Diseases. Carpinella C, Rai M. (Eds), Amsterdam: Elsevier. 2007. p. 251–68.
13. Wink M. Plant secondary metabolism: diversity, function and its evolution. Natural Products Communications. 2008; 3:1205-1216.
14. Wink M, Schimmer O. Molecular modes of action of defensive secondary metabolites. In: Functions of Plant Secondary Metabolites and Their Exploitation in Biotechnology. Michael Wink (ed). Annual Plant Reviews. 2009; 39:21-161.
15. Van Wyk BE, Wink M. (Eds). Phytomedicines, herbal drugs, and poisons. Chicago: University of Chicago Press. 2015. pp 479
16. Wink M, Van Wyk BE. Mind-Altering and Poisonous Plants of the World. Portland: Timber Press. 2008. pp 464.
17. Acamovic T, Brooker JD. Biochemistry of plant secondary metabolites and their effects in animals. Proceedings of the Nutrition Society, Scottish section and British Society of Animal Science. 2005; 64:403-412.
18. Efferth T, Fu Y, Zu Y, *et al*. Molecular target-guided tumor therapy with natural products derived from Traditional Chinese Medicine. Current Medicinal Chemistry. 2007; 14:2024-2032.
19. Zaynab M, Fatima M, Abbas S, *et al*. Role of secondary metabolites in plant

defense against pathogens. Microbial Pathogenesis. 2018; 124:198-202.
20. Harborne JB. Twenty-five years of chemical ecology. Natural Product Reports. 2001; 18: 361-379.
21. Ralphs MH, Gardner DR, Pfister JA. Toxophenology and grazing risk models of tall larkspur. In: Poisonous Plants and Related Toxins. Acamovic T, Stewart CS, Pennycott TW (Eds). Wallingford, Oxon.: CAB International. 2004. p 575-581
22. Acamovic T, Stewart CS, Pennycott TW. (Eds). Poisonous Plants and Related Toxins. Wallingford, Oxon., CAB International. 2004. p
23. Cross DE, Hillman K, Fenlon D, *et al*. Antibacterial properties of phytochemicals in aromatic plants in poultry diets. In: Poisonous Plants and Related Toxins. Acamovic T, Stewart CS, Pennycott TW (Eds). Wallingford, Oxon.: CAB International. 2004. p 175-180.
24. James LF, Panter KE, Gaffield W, *et al*. Poisonous plant research: Biomedical applications. In: Poisonous Plants and Related Toxins. Acamovic T, Stewart CS, Pennycott TW (Eds). Wallingford, Oxon., CAB International. 2004. pp 361-376.
25. Bento MHL, Acamovic T, Makkar HPS. The influence of tannin, pectin and polyethylene glycol on attachment of ^{15}N-labelled rumen microorganisms to cellulose. Animal Feed Science and Technology. 2005; 122(1-2):41-47.
26. Huisman J, Tolman GH. Antinutritional factors in the plant proteins of diets for non-ruminants. Recent developments in pig nutrition. 2001; 3:261-291.
27. Aniszewski T. Alkaloids – Secrets of Life: Alkaloid Chemistry, Biological Significance, Applications and Ecological Role. The Netherlands, Elsevier Amsterdam. 2007. p
28. De Sales PM, de Souza PM, Simeoni LA, *et al*. α-Amylase inhibitors: A review of raw material and isolated compounds from plant source. Journal of Pharmacy and Pharmaceutical Science. 2012; 15(1) 141-183.
29. Patel V, Patel R. The active constituents of herbs and their plant chemistry, extraction and identification methods: Review article. Journal of Chemical and Pharmaceutical Research. 2016; 8(4):1423-1443.
30. Hollman A. Plants and cardiac glycosides. British Heart Journal. 1985; 54: 258-61.
31. Alamgir ANM. Secondary metabolites: Secondary metabolic product consisting of C and H; C, H, and O; N, S, and P elements; and O/N heterocycles. In: Therapeutic use of medicinal plants and their extracts. Volume 2. Progress in Drug Research. Volume 74. Springer, Cham. 2018. pp 165-309.
32. Kandar CC. Secondary metabolites from plant sources. In: Bioctive natural products for pharmaceutical applications. Advanced Structured Materials. Volume 140. Springer, Cham. 2021. pp 239-377.
33. Brito-Arias M. N-Glycosides. In: Synthesis and Characterization of Glycosides. (2nd ed.). Switzerland, Springer International Publishing. 2022. pp 229-284.
34. Bolarinwa IF, Oke MO, Olaniyan SA *et al*. A review of cyanogenic glycosides in edible plants. Toxicology - New aspects to this scientific conundrum. 2016. pp 179-191.
35. Kwok J. 2008. Cyanide poisoning and cassava. Food safety focus. 19th issue 2008 February. Incident focus. http://www.cfs.gov.hk/english/multimedia
36. Francisco IA, Pinotti MHP. Cyanogenic glycosides in plants. Brazilian Archives of Biology and Technology. 2000; 43(5):487-492.
37. Haque MR, Bradbury JH. Total cyanide determination of plants and foods using the picrate and acid hydrolysis method. Food Chemistry. 2002; 77:107-114
38. Codex Committee on Contaminants in Foods. Discussion paper on cyanogenic glycosides. CX/CF 09/3/11. FAO/WHO, Rome. 2008.
39. Cooke RD, Maduagwu EN. The effect of simple processing on the cyanide content of cassava chips. Journal of Food Technology. 1985; 13:299-306.
40. CFS (Centre for Food Safety). Natural toxins in food plants. Risk assessment studies. Food and Environmental Hygiene Department, the Government of the Hong Kong Special Administrative Region. 2007. Report No. 27.
41. Harborne JB. Plant toxins and their effects on animals. In: Introduction to Ecological Biochemistry. London: Academic Press. 1993. p.71-103.
42. Gleadow RM, Moller BL. Cyanogenic glycosides: synthesis, physiology, and

phenotypic plasticity. Annual Review of Plant Biology. 2014; 65:155-85.
43. Rawat K, Nirmala C, Bisht MS. Processing techniques for reduction of cyanogenic glycosides from bamboo shoots. In10th World Bamboo Congress, Korea. 2015 Sep 17. pp. 1-12.
44. Vetter J, Gopalakrishnakone P, Carlini CR, *et al*. Plant cyanogenic glycosides. Plant Toxins. The Netherlands, Springer Nature. 2017. pp 287-317.
45. FAO/WHO. WHO Food Additive Series: 65. Safety evaluation of certain additives and contaminants. Prepared by the 74th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2012. Geneva, World Health Organisation.
46. Morsy N. Cardiac glycosides in medicinal plants. In: Aromatic and medicinal plants-back to nature. El-Shemy HA (Ed). Croatia, InTech. 2017. pp 288. doi.org/10.5772/65963
47. Cressey P, Saunders D. Determination of presence of cyanogenic residues in apple juices in Australia and New Zealand. Institute of Environmental Science & a Review of Cyanogenic Glycosides in Edible Plants. http://dx.doi.org/10.5772/64886 187. Research Limited contracted by the New Zealand Ministry for Primary Industries. 2012. Unpublished Report FW12032.
48. Fester K. Plant alkaloids. In: Encyclopaedia of life sciences. Chichester, John Wiley and Sons Ltd. 2018. doi:10:9780203743218
49. Aniszewski T. The biological basis of quinolizidine alkaloids. Science of Legumes. 1994; 1:1-24.
50. Daly JW, Spande TF, Garraffo HM. Alkaloids from amphibian skin: A tabulation of over eight-hundred compounds. Journal of Natural Products. 2005; 68:1556-1575.
51. Sengupta G, Gaurav A, Tiwari S. Substituting medicinal plants through drug synthesis. In: Synthesis of Medicinal Agents from Plants. Elsevier Ltd. 2018. pp 47-74.
52. Hegnauer R. Biochemistry, distribution and taxonomic relevance of higher plant alkaloids. Phytochemistry. 1988; 27:2423-2427.
53. Matsuura HN, Fett-Neto A). Plant alkaloids: Main Features, Toxicity, and mechanisms of action. Plant Toxins. 2015; 2(7):1- 5.
54. Aniszewski T. Ekologiczna Rola Alkaloidow Łubinowych. In: Postpy w badaniach łubinu. Frencel I, Gulewicz K. (Eds). Pozna´n: Polskie Towarzystwo Łubinowe, Instytut Chemii Bioorganicznej Polskiej Akademii Nauk. 1995. pp. 9-31.
55. Roberts MF. Introduction. In: Alkaloids, biochemistry, ecology and medicinal applications. Roberts, MF Wink M (Eds) New York: Plenum Publishing Corporation. 1998. pp 486.
56. Schnitzius JM, Hill NS, Thompson CS, *et al*. Semi-quantitative determination of ergot alkaloids in seed, straw, and digested samples using a competitive enzyme-linked immunosorbent assay. Journal of Veterinary Diagnostic Investigation. 2001; 13:230-237
57. Mithofer A, Boland W. Plant defense against herbivores: Chemical aspects. Annual Reviews in Plant Biology. 2012; 63:431-50.
58. Fan S, Guo-Jiang, W. Characteristics of plant proteinase inhibitors and their applications in combating phytophagous insects. Botanical Bulletin of Academia Sinica. 2005; 46(1): 273-292.
59. Udedibie ABI. In search of food: FUTO and the nutritional challenges of Canavalia seeds. 6th Inaugural Lecture, Federal University of Technology, Owerri, Nigeria. 2003. pp 48.
60. Paiva PM, Pontual EV, Coelho LC, Napoleao TH. Protease inhibitors from plants: Biotechnological insights with emphasis on their effects on microbial pathogens. Microbial pathogens and strategies for combating them: Science, Technology and Education. 2013.1:641-649.
61. Bode W, Huber R. Natural protein proteinase inhibitors and their interaction with proteinases. European Journal of Biochemistry. 1992; 204:433-451.
62. Turk B, Turk D, Salvesen GS. Regulating Cysteine Protease Activity: Essential Role of Protease Inhibitors as Guardians and Regulators. Current Pharmaceutical Design. 2002; 8:1623-1637.
63. Oliva MLV, Silva MCC, Sallai RC, *et al*. A novel subclassification for Kunitz proteinase inhibitors from leguminous seeds. Biochemistry. 2010; 92:1667-1673.
64. Habib H, Fazili KM. Plant protease inhibitors: a defense strategy in plants. Biotechnology and Molecular Biology Reviews. 2007; 2:68-85.

65. Liener IE. Antinutritional factors in legume seeds: state of the art. In: International Workshop on Antinutritional Factors (ANF) in Legume Seeds, Wageningen, Netherlands. Huisman J, Van der Poel AFB, Liener IE (eds). 1988. pp. 6-13.
66. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes. Journal of the American Medical Association. 2002; 287: 360-372.
67. Van de Laar FA, Lucassen PLBJ, Akkermans RP, *et al*. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews. 2005; Issue 2. Art. No.: CD003639.
68. Kobayashi K, Baba E, Fushiya S, *et al*. Screening of mongolian plants for influence on amylase activity in mouse plasma and gastrointestinal tube. Biological and Pharmacological Bulletin. 2003; 26(7):1045-1048.
69. Sunmonu TO, Lewu FB. Phytochemical Analysis, in vitro Antioxidant Activity and Inhibition of Key Diabetic Enzymes by Selected Nigerian Medicinal Plants with Antidiabetic Potential. Indian Journal of Pharmaceutical Education and Research. 2019; 53(2):250-60.
70. Conforti F, Statti G, Loizzo MR, *et al*. In vitro antioxidant effect and inhibition of α-Amylase of two varieties of *Amaranthus caudatus* seeds. Biological and Pharmacological Bulletin. 2005; 28:1098-1102.
71. Funke I, Melzing MF. Traditionally used plants in diabetes therapy-phytotherapeutics as inhibitors of a-amylase activity. Revista Brasileira de Farmacognosia. 2006; 16:1-5.
72. Bhat M, Zinjarde SS, Bhargava SY, *et al*. Antidiabetic Indian plants: A good source of potent amylase inhibitors. Evidence Based Complementary Alternative Medicine. 2011; 2011:1-6.
73. Cheng AYY, Fantus IG. Oral antihyperglycemic therapy for type 2 *Diabetes mellitus*. Canadian Medical Association Journal. 2005; 172:213-226.
74. Mentreddy SR. Medicinal plant species with potential antidiabetic properties. Journal of the Science of Food and Agriculture. 2007; 87: 743-750.
75. Minatel IO, Borges CV, Ferreira MI, *et al*. Phenolic compounds: Functional properties, impact of processing and bioavailability. In: Phenolic Compounds - Biological Activity. Soto-Hernandez M, Palma-Tenango M, Garcia-Mateos MDR (Eds). [Internet]. London: IntechOpen. Cited 2023 January 13. Available from: https://www.intechopen.com/books/5609. 2017. pp 1-24.
76. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxidative Medicine and Cellular Longevity. 2009; 2(5): 270-278.
77. Scalbert A, Manach C, Morand C. Dietary polyphenols and the prevention of diseases. Critical Reviews in Food Science and Nutrition. 2005; 45:287-306.
78. Cai Y, Luo Q, Sun M, *et al*. Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. Life Sciences. 2004; 74(17):2157-2184.
79. King A, Young G. Characteristics and occurrence of phenolic phytochemicals. Journal of American Diet Association. 1999; 99(2):213-218.
80. Khan AG, Kuek TM, Chaudhury TM, *et al*. Role of plants, mycorrhizae and phytochelators in heavy metal contaminated land remediation. Chemosphere. 2000; 41:197-207.
81. Zheng W, Wang SY. Antioxidant activity and phenolic compounds in selected herbs. Journal of Agricultural and Food Chemistry. 2001; 49(11):5165-5170.
82. Michalak A. Phenolic compounds and their antioxidant activity in plants growing under heavy metal stress. Polish Journal of Environmental Studies. 2006; 15(4):523-530.
83. Urcan DE, Pop N, Rolle L *et al*. Importance of grape phenols in the human diet. Journal of Horticulture, Forestry and Biotechnology. 2016; 20(1):46-50.
84. Shahin H, Naser M, Behrad E, *et al*. Plants and secondary metabolites (Tannins): A Review. International Journal of Forest, Soil and Erosion. 2011; 1(1):47-53.
85. Sharon N, Lis H. History of lectins: from hemagglutinins to biological recognition molecules. Glycobiology. 2004; 14(11):53R-62R.
86. Kilpatrick DC. Animal lectins: A historical introduction and overview. Bioechemica et Biophysica Acta (BBA) – General Subjects. 2002; 157292-15793):187-197.

87. Kaltner H, Caballero GG, Ludwig AK, et al. From glycophenotyping by (plant) lectin histochemistry to defining functionality of glycans by pairing with endogenous lectins. Histochemistry and Cell Biology. 2018; 149:547-568.
88. Lam SK, Ng TZ. Lectins: production and practical applications. Applied Microbiology and Biotechnology. 2011; 89:145-155.
89. Peumans WJ, Van Damme EJM. Plant Lectins: Versatile Proteins with Important Perspectives in Biotechnology. Biotechnology and Genetic Engineering Reviews. 1998; 15(1):199-228
90. Vasconcelos I, Oliveira J. Anti-nutritional properties of plant lectins. Toxicon. 2004; 44:385-403.
91. Ramteke R, Doneria R, Gendley MK. Anti-nutritional factors in feed and fodder used for livestock and poultry feeding. Acta Scientific Nutritional Health. 2019; 3(5):39-48.
92. Hill GD. Plant Anti-nutritional Factors/Characteristics. Lincoln University, Elsevier Science Ltd. 2003. Pp. 4578-4586.
93. Hamblin J, Kent SP. Possible role of phytohaemagglutinin in *Phaseolus vulgaris* L. Nature New Biology. 1973; 245:28-30.
94. Bohlool BB, Schmidt EL. Lectins: a possible basis for specificity in the *Rhizobium*-legume root module symbiosis. Science. 1974; 188:269-271.
95. Sa RA, Gomes FS, Napoleao TH, *et al*. Antibacterial and antifungal activities of *Myracrodruon urundeuva* heartwood. Wood Science and Technology. 2009; 43:85-95.
96. Garderes J, Bourguet-Kondracki M, Hamer B, *et al*. Porifera Lectins: Diversity, Physiological Roles and Biotechnological Potential. Marine Drugs. 2015; 13:5059-5101.
97. Frolich W. Bioavailability of micronutrients in a fibre-rich diet, especially related to minerals. European Journal of Clinical Nutrition. 1995; 49:S116-S122.
98. Bohn L, Meyer AS, Rasmussen SK. Phytate: Impact on environment and human nutrition. A challenge for molecular breeding. Journal of Zhejiang University Science B. 2008; 9(3):165-191.
99. Chen Z, Zha B, Wang L, *et al*) Dissociation of aleurone cell cluster from wheat bran by centrifugal impact milling. Food Research International. 2013; 54(1):63-71.
100. Humer E, Schwarz C, Schedle K. Phytate in pig and poultry nutrition. Journal of Animal Physiology and Animal Nutrition. 2014; 9(2015):605-625.
101. Feyera M. Review of some cereal and legume based composite biscuits. International Journal of Agricultural Science and Food Technology. 2020; Available at https//www.peertechzpublications.com/articles/IJASFT-6-162.php#
102. Raboy V. Myo-Inositol-1,2,3,4,5,6-hexakisphosphate. Phytochemistry. 2003; 64:1033- 1043.
103. Reinhold JG. Problems in mineral nutrition: A global perspective. In: Trace minerals in foods. CRC Press. 2020. p 1-55
104. Hamada A, Yamaguchi K, Harada M, *et al*. Recombinant, rice produced yeast phytase shows the ability to hydrolyze phytate derived from seed-based feed, and extreme stability during ensilage treatment. Bioscience, Biotechnology and Biochemistry. 2006; 70(6):1524-1527.
105. Pichersky, E., Noel, J. P. & Dudareva, N. (2006). Biosynthesis of plant volatiles: Nature's diversity and ingenuity. Science. 311(5762):808-811.
106. Molina G, Pessoa MG, Pimentel MR, Pelissari FM, Bicas JL, Pastore GM. Production of natural flavor compounds using monoterpenes as substrates. New developments in terpene research, 1ed edn. New York, Nova Publishers. 2014:1-24.
107. Adedeji AA, Babalola OO. Secondary metabolites as plant defensive strategy: a large role for small molecules in the near root region. Planta. 2020; 252:61.
108. Perveen S. Introductory Chapter: Terpenes and Terpenoids. In S. Perveen, & A. M. Al-Taweel (Eds). Terpenes and Terpenoids-Recent Advances. IntechOpen. 2021. Available from https://doi.org/10.5772/intechopen.98261
109. Rao AVSSR. A textbook of Biochemistry. 9th Ed. New Delhi, India: UBS Publishers Distributors. 2002. p 49.
110. Morrison, RT & Boyd, RN. Organic chemistry (6th Edition). New Jersey, USA: Pearson Prentice Hall Publishers. 2006. p 457
111. Maimone T, Baran P. Modern synthetic efforts toward biologically active

terpenes. Nature Chemical Biology. 2007; 3:396-407.
112. Ogbonna MJ, Opara EU. Pathogen penetration into the host plant tissues: Challenges and Obstacles - An Overview. Scholars Journal of Agriculture and Veterinary Sciences. 2017; 4(5):175-185.
113. Wikipedia. Terpene. Wikipedia Foundation Incorporated; 2022. Updated 2022 November 30; cited 2022 December 30. Available from https://en.wikipedia.org/wiki/Terpene.
114. Eastman RH, Kluger RH. Isoprenoid. Encyclopedia Britannica. Updated 2018 April 11. Available from https://www.britannican.com/science/isoprenoid.
115. Zwenger S, Basu C. Plant terpenoids: Applications and future potentials. Biotechnology and Molecular Biology Reviews. 2008; 3(1):001-007.
116. Gotfredsen E. Liber Herbarum II: The incomplete reference-guide to herbal medicine. 2009. Available from https://www.liberherbarum.com/.
117. Thimmappa R, Geisler K, Louveau T, *et al*. Triterpene biosynthesis in plants. Annual Review of Plant Biology. 2014; 65:225-257. Available from www.annualreviews.org.
118. Kessler A, Baldwin IT. Defensive function of herbivore induced plant volatile emissions in nature. Science. 2001; 291:2141-2144.
119. Kappers IF, Aharoni A, Van Herpen T, *et al*. Genetic Engineering of terpenoid metabolism attracts bodyguards to Arabodopsis. Science. 2005; 309:2070-2072.
120. Heil M. Indirect defence via tritrophic interactions. New Phytologist. 2008; 178:41-61
121. McCormick AC, Unsicker SB, Gershenzon J. The specificity of herbivore-induced plant volatiles in attracting herbivore enemies. Trends in Plant Science. 2012; 17(5):303-310.
122. Block AK, Vaughan MM, Schmelz EA, *et al*. Biosynthesis and function of terpenoid defense compounds in maize (*Zea mays*). Planta. 2019; 249(1):21-30.
123. Villalba JJ, Provenza FD, Olson KC. Terpenes and carbohydrate source influence rumen fermentation, digestibility, intake, and preference in sheep. Journal of Animal Science, 2006; 84: 2463-2473.
124. Davis EM, Croteau R. Cyclization enzymes in the biosynthesis of monoterpenes, sesquiterpenes, and diterpenes. Biosynthesis. Topics in Current Chemistry. 2000; 209:53-95.
125. Tian Q, Roselot RA, Schwartz SJ. Quantitative determination of intact glucosinolates in broccoli, broccoli sprouts, Brussels sprouts, and cauliflower by high performance liquid chromatography-electrospray ionization-tandem mass spectrometry. Analytical Biochemistry. 2005; 343:93-99.
126. Kliebenstein DJ, Kroymann J, Mitchell-Olds T. The glucosinolate-myrosinase system in an ecological and evolutionary context. Current Opinions in Plant Biology. 2005; 8(3): 264-271.
127. Frohne D, Pfander HJ. Poisonous Plants. A handbook for Doctors, Pharmacists, Toxicologists and Biologists. Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft mbH. 2005. pp 450-.
128. Bartnik M, Facey PC. Glycosides. In: Pharmacognosy: Fundamentals, Applications and Strategies. Badal S, Delgoda R (Eds). 2017. Elsevier Inc. pp 101-161.
129. EFSA (European Food Safety Authority). Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the European Commission on glucosinolates as undesirable substances in animal feed. The EFSA Journal. 2008; 590:1-76.
130. Rask L, Andreasson E, Ekbom B, *et al*. Myrosinase: Gene family evolution herbivore defense in Brassicaceae. Plant Molecular Biology. 2000; 42:93-113.
131. Blazevic I, Mastelic J. Glucosinolate degradation products and other bound and free volatiles in the leaves and roots of radish (*Raphanus sativus* L.). Food Chemistry. 2009; 113: 96-102.
132. Holst B, Fenwick GR, Benjamin C. Glucosinolates: In Encyclopeadia of Food Sciences and Nutrition. Oxford, Academic Press. 2003; p. 2922-2930.
133. Blazevic I, Montaut S, Burcul F, et al. Glucosinolates: Novel sources and biological potential. In: Glucosinolates. Merillon JM, Ramawat K (Eds). Reference Series in Phytochemistry. Switzerland: Springer, Cham. 2017. pp 3-60.

134. Halkier BA, Gershenzon J. Biology and biochemistry of glucosinolates. Annual Review of Plant Biology. 2006; 57(1):303-333.
135. Schone F, Rajendran R. Iodine in farm animals. In: Comprehensive Handbook of Iodine: Nutritional, Physiological, Biochemical, Pathological and Therapeutic aspects. Preedy, VR, Burrow GN, Watson RR (Eds). Academic Press. 2009; pp 151-170.
136. Bischoff KL. Glucosinolates. In: Nutraceuticals. Academic Press. 2016. pp 551-554.
137. Bischoff KL. Glucosinolates and organosulphur compounds. Nutraceuticals in Veterinary Medicine. 2019; 1:113-119.
138. Martland MF, Butler EJ, Fenwick GR. Rapseed induced liver haemorrhage reticulosis and biochemical changes in laying hens: the effects of feeding high and low glucosinolate meals. Research in Verterinary Science. 1984; 63:293-309.
139. Ryhanen EL, Perttila S, Tupasela T, *et al*. Effect of *Camelina sativa* expeller cake on performance and meat quality of broilers. Journal of the Science of Food and Agriculture. 2007; 87(8):1489-1494.
140. Schone F, Leiterer M, Hartung H, *et al*. Rapeseed glucosinolates and iodine in sows affect the milk iodinie concentration and the iodine status of piglets. British Journal of Nutrition. 2001; 85:659-670.
141. Tripathi MK, Mishra AS. Glucosinolates in animal nutrition: A review. Animal Feed Science and Technology. 2007; 132(1-2):1-27.
142. Abratt VR, Reid RD. Oxalate-degrading bacteria of the human gut as probiotics in the management of kidney stone disease. Advances in Applied Microbiology. 2010; 72:63-87
143. Savage GP. Oxalates in human foods. Proceedings of the Nutrition Society of New Zealand. 2002; 27:4-24.
144. Osweiler GD, Carson TL, Buck WB, *et al*. Clinical and diagnostic veterinary toxicology. 3rd Ed. USA; Kendall/Hunt Publishing Company. 1985. pp 711-475.
145. Concon JM. Food Toxicology – Principles and Concepts. New York, Marcel Dekker. 1998. pp 416-419.
146. Bressani R. Amaranth. In: Encyclopaedia of Food Science, Food Technology and Nutrition. London, Academic Press. 1993. pp 135-140.
147. Holloway WD, Argall ME, Jealous WT, *et al*. Organic acids and calcium oxalate in tropical crops. Journal of Agriculture and Food Chemistry, 1989; 37:337-341.
148. Mosha TC, Gaga HE, Pace RD, *et al.* Effect of blanching on the content of antinutritional factors in selected vegetables. Plant Foods Human Nutrition. (Formerly Qualitas Planturum). 1995; 47(4):361-367
149. Heaney RP, Weaver CM, Recker RR. Calcium absorbability from spinach. American Journal of Chemical Nutrition. 998; 47:707-709.
150. Noonan S, Savage G. Oxalate content of foods and its effect on humans. Asia Pacific Journal of Clinical Nutrition. 1999; 8:64-74.
151. Vranova V, Rejsek K, Formanek P. Non-protein amino acids: Plant, soil and ecosystem interactions. Plant Soil. 2011; 342:31-48.
152. Ambrogelly A, Palioura S, Soll D. Natural expansion of the genetic code. Nature Chemical Biology. 2007; 3 (1):29-35.
153. Yamane H, Konno K, Sabelis M, *et al*. Chemical defence and toxins of plants. In: Comprehensive natural products II Chemistry and Biology Vol. 4: Chemical Ecology. Ben H, Liu LM (Eds). Elservier Science. 2010. pp 339-385.
154. Hegarty MP. Toxic amino acids of plant origin. In: Effects of poisonous plants on livestock. Keeler RF, Van Kampen KR, James LF (Eds). New York, Academic Press. 1978. pp 575-585.
155. Bell EA. Non-protein amino acids of plants: significance in medicine, nutrition, and agriculture. Journal of Agriculture and Food Chemistry. 2003; 51:2854-2865.
156. Xuan TD, Elzaawely AA, Deba F, *et al*. Mimosine in *Leucaena* as a potent bio-herbicide. Agronomy and Sustainable Development. 2006. 26:89-97.
157. Robins C, Brooker JD. The effects of Acacia aneura feeding on abomasal and intestinal structure and function in sheep. Animal Feed Science and Technology. 2005; 121(1-2): 205-215.
158. Eid SY, El-Readi MZ, Eldin EE, *et al*. Influence of combinations of digitonin with selected phenolics, terpenoids, and alkaloids on the expression and activity of P

glycoprotein in leukemia and colon cancer cells. Phytomedicine. 2013; 21:47-61.
159. Hellmann JK, Munter S, Wink M, *et al*. Synergistic and additive effects of epigallocatechin gallate and digitonin on *Plasmodium* sporozoite survival and motility. PLoS ONE, 2010; 5:e8682.
160. Hamoud R, Reichling J, Wink M. Synergistic antibacterial activity of the alkaloid sanguinarine with EDTA and antibiotic streptomycin against multidrug resistant bacteria. Journal of Pharmacy and Pharmacology. 2015; 67:264-273.
161. Wink M. Current understanding of modes of action of multicompetent bioactive phytochemicals: Potentials for nutraceuticals and antimicrobials. Annual Review of Food Science and Technology. 2022; 13(1):337-359.

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