Journal of Equine Veterinary Science 69 (2018) 66–77

Contents lists available at ScienceDirect

Journal of Equine Veterinary Science

journal homepage: www.j-evs.com

Review Article

Plant Bioactives and Extracts as Feed Additives in Horse Nutrition

Mona M.M.Y. Elghandour [a], Poonooru Ravi Kanth Reddy [b], Abdelfattah Z.M. Salem [a,*], Punuru Pandu Ranga Reddy [b], Iqbal Hyder [c], Alberto Barbabosa-Pliego [a], Duvvuru Yasaswini [d]

[a] Facultad de Medicina Veterinaria y Zootecnia, Universidad Autónoma del Estado de México, México
[b] Department of Livestock Farm Complex, College of Veterinary Science, Sri Venkateswara Veterinary University, Proddatur, Andhra Pradesh, India
[c] Department of Veterinary Physiology, College of Veterinary Science, Sri Venkateswara Veterinary University, Gannavaram, Andhra Pradesh, India
[d] College of Veterinary Science, Sri Venkateswara Veterinary University, Tirupati, Andhra Pradesh, India

ARTICLE INFO

Article history:
Received 16 May 2018
Received in revised form
5 June 2018
Accepted 12 June 2018
Available online 19 June 2018

Keywords:
Herbal extract
Horse
Anti-inflammatory
Antioxidant
Immunomodulant

ABSTRACT

Despite the extensive availability and use of plant extracts as feed additives in various livestock species, peer-reviewed and scientific evidence of their usage in horses is lacking. This article dealt with the review of reports from recent studies investigating the usage of plant bioactives or extracts in horse nutrition. For the time being, several herbs, either alone or in composites, are being commercialized and openly available in horsemarket stores, which makes it difficult and confusing for horse owners and veterinarians to make a justifiable choice. Usage of ginger extract as a feed additive in sport horses is encourageable as it manages to attain quick recovery after exhaustion in racing and jumping events. Garlic, ginseng, primerose, and rose hip possess potent antioxidative properties, and their supplementation in a regular diet may lessen the chance of occurrence of oxidative stress-related diseases. Owing to their cytoprotective and mucus-stimulatory effects, licorice and Aloe vera extracts have potentiality as feed additives in Standardbred and Thoroughbred racehorses, as they are more prone for equine gastric ulcer syndrome. Echinacea is able to stimulate the equine immunocompetence on addition to the regular diets of equine species. Besides the anti-inflammatory effect, devils claw possess anorexigenic effect, which can limit feed intake, thus keeping the body condition score in check and avoiding obese-related health problems in horses. Regularizing flaxseed meal or its extract as a dietary supplement may support healthy skin and coat condition due to the presence of omega-3 fatty acids as an active component. Aloe vera, well known for cytoprotective and mucus-stimulatory effects, is found to be efficient in protecting the gastrointestinal tract against ulcers or other disorders on administering as a dietary supplement to equines, but the extent of effect depends on the dosage and extent of supplementation. Although, theoretically plant extracts application is safer compared with synthetic antibiotics or drugs, it does not mean they are completely safe, and few considerations should be given for dosage of the drug, period of administration, apart from monitoring parallel drugs given to prevent herb-drug interactions. The plant extracts with potent benefits, and not tested in horses have to be evaluated with a primary objective to verify the negative side effects, if any, followed by standardization of the dosage.

1. Introduction

A feed additive is any ingredient or its constituent, other than regular feed material and premixtures, which are purposefully supplemented to feed or water to achieve, in particular, one or more of the tasks. As per the literature available, no scientific well-proven information was ever quoted on the application of antibiotic growth promoters in horses, but incorporation of antibiotic as a feed additive may be helpful for young foals in combating digestive problems, infectious diseases, and environmental and other stress-

Animal welfare/ethical statement: The research was performed in accordance with the ethical standard laid down in the 1996 declaration of Helsinki and its later amendments.

Conflict of interest statement: There was no conflict of interest.

* Corresponding author at: Abdelfattah Z.M. Salem, Universidad Autónoma del Estado de México, Facultad de Medicina Veterinaria y Zootecnia, 50000 Toluca, Mexico.

E-mail addresses: salem@uaemex.mx, asalem70@yahoo.com (A.Z.M. Salem).

https://doi.org/10.1016/j.jevs.2018.06.004
0737-0806/

related factors [1]. According to the Food and Drug Administration, usage of chlortetracycline at 85 mg per head per day is advisable in horses up to 1 year of age for encouraging the growth and feed efficiency. Few field reports revealed beneficial effects on supplementing antibiotics to horses as a safeguard measure to prevent infectious diseases under stressful conditions, but the effects are of short-term benefit and aftermath consequences are not known [2]. Furthermore, the usage of antibiotics as feed additives is more cautious, as their beneficial effects in other livestock could not be promised in equine species; for an instance, horses are particularly susceptible to ionophore intoxications, which needs still higher doses to exhibit toxicity in cattle and swine. Even though the researchers did not warrant the usage of anabolic steroids as feed additives, they are being used by equine athletes to promote muscle development, appetite, aggressiveness, or other desirable effects [3]. However, as per the NRC (1989) guidelines, usage of anabolic steroids in the diet of healthy, young, and growing horses is not suggested because of their negative effects on the testicular development in males and reproductive function in females [2].

The increased perception of potential negative effects of feeding antibiotic growth promoters and steroids in diets of livestock, irrespective of the species, has ensued in an increased interest in the use of plant extracts or herbs as an alternative source. The global herbal products market size is expected to reach $111 billion by the end of 2023 and is projected to grow with a compound annual growth rate of ~7.2% during 2017–2023. The increase in growth rate is attributed to the increasing preference of consumers toward traditional alternatives for synthetic antibiotics and growth promoters, which are known to have fewer side effects. Nowadays, plant bioactive components or extracts, which are traditionally used against the infections, are being used as feed additives for livestock including cattle, buffaloes, sheep, goat, and poultry. However, the particular herbal extract at a specified dosage fed to any of the aforementioned species cannot be adapted for horses because of the differences in susceptibility levels, pharmacokinetics, and pharmacodynamics compared with other species. As an example, the flavonol quercetin's absorption rate from the gastrointestinal tract in horses is rapid leading to higher amounts of total plasma flavonol levels compared with those in humans, dogs, or pigs [4]. Furthermore, few plant species such as St. John's wort (*Hypericum perforatum*), mistletoe (*Phoradendron flavescens*), cherry trees (*Prunus serotina*), and castor bean (*Ricinus communis*) are considered to be toxic in equines, which can be reviewed as safe to feed other livestock species [5]. In horse marketplaces, various plant extracts and herbal supplements are being sold with claims of well-being and enhanced performance, but scientific evidence for complete biological effects is very limited in equines.

In equines, although, the herbs or their extracts are being used for centuries to improve the performance, their usage, either as an adjunct to drug therapy or unaccompanied, is limited to sporting horses. Besides, as per the regulations of approved national and international equestrian committees, the use of plant extracts in racing contests continues to exist as an ever-debatable and under-researched theme. The phenomenon of disqualifying and elimination of several riders from 2008 Beijing Olympics for using the banned substances illustrates the complications involved in the usage of plant extracts for sporting horses. Furthermore, it is worth mentioning that only a few studies were carried out in equines as experimental animals, and only for a limited number of plant extracts, thus most of the existing evidence on the effects of use of herbal extracts in horses is anecdotal. It has been a traditional practice for horse owners, trainers, breeders, and animal care specialists to use various herbs or their extracts informally either as therapeutic applications or feed additives. Lans et al. (2006) reviewed data on nearly 80 ethnoveterinary plants through key informant interviews; however, their contribution to the existing information on herbal extracts database for equines is not necessarily reliable, as they were based on the personal accounts rather than facts or research [6]. Therefore, a greater understanding and knowledge on utilization of plant extracts in the equines may dispel the concerns over their usage, thus promoting them as feed additives to improve equine health and well being. A survey on US horse owners reported that a total of 58% people are spending $30 or more per horse per month on supplements. Among the respondents, a total of 37% revealed that the supplements are being used as a feed additive to promote overall health and performance, whereas 38% viewed the supplements as a medicine for treating the horse ailments [7]. Although the usage of supplements by horse owners to promote overall performance is as equal as that of treating disorders, almost all the works on herbal extracts in equines were geared toward the therapeutic management of equine disorders rather as feed additives. This article presents a review of the results of various plant extracts utilization in livestock, their properties, and mechanism of action, with special emphasis on the equine research.

2. Plant Herbs or Their Extracts as Feed Additives in Equines

Table 1 reviews the active constituent, mechanism of action, negative effects, and equine research existing for the various herbs or their extracts.

2.1. Garlic

Garlic is known to exert health-promoting effects and documented as an essential ingredient of the human food over 5,000 years ago in India, China, and Greece. The active components include various organosulfur compounds such as alliin, allicin, diallyl sulfide, diallyl disulfide, and diallyl trisulfide (Fig. 1A and B), which can synergistically influence each other. Garlic is one of the most common feed additive used in poultry industry; however, in equines, its usage is primarily limited as an insect repellent followed by the exploitation of its expectorant function to assist disintegration of mucous [29]. Administering a polyherbal composite (Breath) with garlic as a dominant ingredient to horses suffering from a characteristic chronic obstructive pulmonary disease resulted in a decreased rate of respiration without affecting blood hematological and biochemical parameters [30].

Garlic extract decreases the production of reactive oxygen species by influencing both antioxidative enzyme activity and cellular glutathione level besides improving mitochondrial functions [31]. Allicin aids in reducing serum levels of triglycerides, cholesterol, and glucose levels, besides decreasing the hepatic cholesterol storage. Allicin is also known to surge the production of reactive oxygen species and caspase-3 expression and causes DNA fragmentation along with glutathione depletion leading to apoptosis induction in pancreatic tumor cells [32]. Another mechanism stated is that allicin induces the transfer of Baz, a proapoptotic factor, to mitochondria subsequently releasing the cytochrome C from mitochondria to the cytosol, thus triggering apoptosis combined with DNA fragmentation .[33] According to in vitro studies, garlic derivatives reduce the expression of inducible nitric oxide synthase enzyme and therefore contribute to the reduction of peroxynitrite formation and the suppression of oxidative stress in cells [34]. Although garlic supplementation promises improved health benefits, its usage as a feed additive should be monitored carefully as the *ad libitum* feeding or overdosage of garlic is related to Heinz body anemia identified by reduced free hemoglobin, red blood cell count, haptoglobin, and hematocrit in horses [35].

Table 1
Active components, action, negative effects, and equine research on herbs or herbal extracts.

Name of the plant/herb	Source of equine research	Period fed/ administered	Findings of the research work	Active components[a]	Actions[a]	Negative effects[a]
Ginseng (*Panax quinquefolius*, *Panax ginseng*, and *Eleutherococcus senticosus*)	[8]	28 d	Feeding ginseng at 35 mg/kg body weight increased in antibody titer being observed by postvaccination	Ginsenosides, glycosidal saponins, essential oils, and phytosterols	Anti-inflammatory, antioxidant, and antilipidemic	Hypertension, feeding to horses under nonsteroidal anti-inflammatory drugs should be cautiously evaluated.
Ginger (*Zingiber officinale*)	[9]	A week adaptation with 1 d collection for every trial	Feeding ginger extract at 30 g/d reduced the cardiovascular recovery time and increased interferon (IFN)-c and proinflammatory cytokines tumor necrosis factor-1.	Gingerols, Shogaols, Zingerone, and Paradols	Anti-inflammatory, antiulcerogenic, anticarcinogenic antioxidant, and antithrombotic	Caustic effect of ginger extract on the gastrointestinal tract, gastric ulcers, and prolonged bleeding time, platelet dysfunction, and hypertension.
Garlic (*Allium sativum*)	[10]	21 d per trial (crossover manner)	Decreased respiratory rate without affecting blood hematological and biochemical parameters	Organosulfur compounds (alliin, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, gamma-glutamylcysteine	Anti-inflammatory, antioxidant, anticarcinogenic, and immunomodulator	Garlic toxicosis occurs on feeding garlic for chronic periods and increased bleeding tendency.
	[11]	71 d	Experimental horses voluntarily consumed an adequate amount of garlic causing Heinz body anemia.			
Flaxseed (*Linum usitatissimum*)	[12]	18 wk	Feeding 10% flaxseed oil increased serum concentrations of alpha-linolenic acid, eicosa pentanoic acid, and malondialdehyde.	Omega-3 fatty acids, phytoestrogens (secoisolariciresinol diglycoside), flavonoids, and lignans	Anti-inflammatory, antioxidant, and anticholesteremic	Excess doses may lead to bloating, gas, abdominal pain, constipation, diarrhea, stomach ache, and nausea.
	[13]	42 d	Supplementation reduced the inflammation, altered the fatty acid profile of hair, and decreased the lesional area of the skin test response of atopic horses.			
	[14]	16 wk	Feeding flaxseed at 0.1% body weight increased the serum alpha-linoleic acid concentration without affecting serum chemistry and prostaglandin concentration.			
	[15]	90 d	Feeding flaxseed meal (~38 g of n-3 fatty acid) improved the muscle deposition of alpha-linolenic acid, eicosa pentanoic acid, and docosa-hexanoic acid			
	[16]	90 d	Feeding flaxseed meal (~38 g of n-3 fatty acid), improved the alpha-linolenic acid concentration in serum and synovial fluid without any differences in eicosa pentanoic acid and docosahexaenoic acid concentration.			
Echinacea (*Echinacea angustifolia, Echinacea purpurea, Echinacea pallida*)	[17]	42 d	Feeding 1,000 mg standardized extract increased the lymphocyte count and caused neutrophil mobilization, increase in hemoglobin and erythrocyte count over time.	Polysaccharides, glycoproteins, cichoric acid, and alkamides.	Anti-inflammatory, antioxidant, immunomodulator, and hematinic agent	Excess doses may lead to dizziness, insomnia, gastrointestinal tract problems, and fever.
Evening primrose (*Oenothera biennis*)	[18]	8 wk	Feeding primrose oil at 150 mL/d reduced lipid peroxidation, decreased lipolysis without altering the muscle homeostasis.	Linoleic, gamma-linoleic, palmic, and oleic fatty acids	Antioxidant and antilipidemic	Excess doses may lead to stomach upset, nausea, and diarrhea.
Lavender (*Lavandula angustifolia*)	[19]	A week adaptation with 15 min exposure for every trial	Aromatherapy: 20% mixture of water and 100% pure lavender essential oil—decreased heart rate and respiratory rate	Alpha-pinene, limonene, cis-ocimene, 1,8-cineole, 3-octanone, linalyl acetate, linalool, trans-ocimene, lavendulyl acetate, and camphor.	Stress-relieving, antioxidant, and antibacterial	Excess doses may lead to increased appetite, and constipation.
	[20]	Adaptation followed by 15 min exposure for every trial	Aromatherapy: 20% mixture of water and 100% pure lavender essential oil—decreased the cortisol content			

Rose hip (*Rosa canina*)	[21]	90 d	Top dressing daily diet with 210 gm of rose hip powder increased serum vitamin C within 2 h.	Galactolipid, natural vitamin C and E.	Anti-inflammatory and antioxidative.	Excess doses may lead to heart pain, insomnia, and gastrointestinal tract disorders.
	[22]	90 d	Top dressing daily diet with 25 or 50 gm of rose hip powder increased serum Vitamin-C on long-term basis.			
Aloe vera (*Aloe barbadensis*)	[23]	28 d	Feeding Aloe vera inner leaf gel at 17.8 mg/kg B. wt. was effective in decreasing the equine squamous gastric disease (ESGD).	Polysaccharides (acemannan), anthraquinones, saccharides, and salicylic acid.	Anti-inflammatory, antioxidative, cytoprotective, and mucus-stimulatory.	May stimulate uterine contractions in pregnant mares.
Devil's claw (*Harpagophytum procumbens*)	[24]	28 d	Feeding devil's claw in combination with dandelion, stinging nettle, burdock, and comfrey mixture reduced the PGE2 production in arthritic joints.	Iridoid glycosides (harpagoside), sugars, triterpenoids, phytosterol, and aromatic acids	Anti-inflammatory, and anorexigenic	Excess doses may lead to hypertension, mild gastrointestinal complaints, and diarrhea.
Cranberry (*Vaccinium macrocarpon*)	[9]	A week adaptation with 1 d collection for every trial	Feeding cranberry extract at 30 g/d reduced the upregulation and expression of tumor necrosis factor alpha mRNA, a major mediator of inflammation.	Organic acids (salicylate), vitamin C, flavonoids, anthocyanidins, catechins, and triterpenoids	Anti-inflammatory and antioxidant	Excess doses may lead to mild stomach upset and diarrhea.
Valerian (*Valeriana fauriei, Valeriana wallichii, Valeriana edulis, Valeriana officinalis*)	NR[b]	NR[b]	NR[b]	Sesquiterpenes, valepotriates, valerenic acid, alkaloids, gamma amino butyric acid (GABA), and tyrosine.	Sedative and anxiolytic	Excess doses cause drowsiness and idiosyncrasies may lead to hepatotoxicity.
Yucca (*Yucca schidigera*)	NR[b]	NR[b]	NR[b]	Saponins (spirostanosides), resveratrol, stilbenes (yuccaoles A, B, C, D, and E).	Anti-inflammatory, antioxidant, antiprotozoal, antihyperuricemic.	Excess doses may lead to gastrointestinal tract disorders, and loose stools.
Milk thistle (*Silybum marianum*)	[25]	48 h	In vitro laminitis model of the horse: extract at 1000 μg/mL neutralized endotoxins and reduced lipopolysaccharide-induced lamellar separation	Silymarin and silibinin	Anti-inflammatory and antioxidant	—
Herbal composite	[26]	21 d for each trial	Feeding dried composite of five herbs *viz*. devil's claw, stinging nettle, dandelion, comfrey, and burdock revealed chondroprotective properties in IL-1-stimulated cartilage.	Iridoid glycosides, polysaccharides, phenolic steroids, triterpenoids, allantoin, polysaccharides, inulin, and phenolics	Anti-inflammatory, analgesic, and chondroprotective.	It is not known the extent of contribution of individual phytochemical in the amalgamation for the effect.
	[8]	21 d for each trial	Feeding herbal composite constituting garlic, boneset, fennel, licorice, white horehound, aniseed, hyssop, and thyme reduced elevated respiratory rate.	Organosulfur compounds, gamma-glutamylcysteine	Anti-inflammatory and analgesic.	
	[27]	30 d	Feeding herbal mixture containing fleawort, Aloe vera, fenugreek, licorice extracts at 85 g/d reduced the number and severity of ulcerative lesions in horses affected by Equine Gastric Ulcer Syndrome.	Acemannan, anthraquinones, saccharides, and salicylic acid.	Anti-inflammatory, antioxidative, cytoprotective, and mucus-stimulatory.	

[a] Information compiled from [8-12,14-27].
[b] NR—No research was ever conducted in horses.

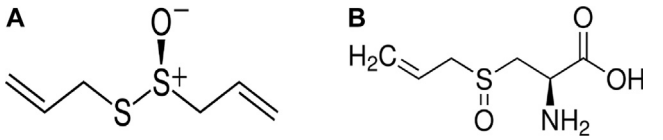

Fig. 1. Active components of garlic extract. (A) Allicin [28]. (B) Alliin [28].

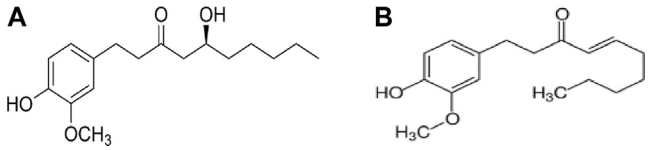

Fig. 3. Active components of ginger extract. (A) Gingerol [40]. (B) Shogaol [40].

2.2. Ginseng

Ginseng is one of the commonest supplements available in equine market, which is traded for use in stress amelioration, improving the performance, and stimulating the immune system [29]. Among various ginseng species, the American ginseng (*Panax quinquefolius*), Asian ginseng (*Panax ginseng*), and Siberian ginseng (*Eleutherococcus senticosus*) are of primary interest. The bioactive constituents of all species comprise ginsenosides, glycosidal saponins, phytosterols, essential oils, peptides, amino acids, vitamins, and minerals (Fig. 2). The ginsenosides predominantly possess antioxidant properties that care for the immune and nerve cells' membranes.

Dietary ginseng, at a daily dose of 35 mg/kg BW for 2 weeks before and 2 weeks after parenteral equine herpesvirus-1 vaccination, significantly improved the magnitude of the antibody response in horses apart from the positively influenced serum electrolyte balance [8]. The ginseng extract exerts an inhibitory effect on proinflammatory cytokines, IL-6 and IL-1b gene expression, COX-2 expression, and increases the expression of MHC class II, which may enhance the differentiation and proliferation of lymphocytes [37]. Orally administered ginseng-water extract showed antileukemia activity through DC11c+ cell-mediated antitumor immunity [33]. More recently, it has been proven that heated ginseng decreases the plasma adipokine levels by promoting the lipolysis and inhibiting excessive lipogenesis in obesity-induced hyperlipidemia condition [38]. Furthermore, it is essential to remember that the use of ginseng in horses under nonsteroidal anti-inflammatory drugs (NSAIDs) should be cautiously evaluated due to their potentiality to interact with each other [39].

2.3. Ginger

Ginger is classified by the Food and Drug Administration as a safe food additive, which is regularly used for the treatment of asthma, diabetes, nausea, and pain in tropical countries. The active constituents' *viz*. gingerols, shogaols, zingerone, and paradols (Fig. 3A and B) possess potent anti-inflammatory properties through inhibiting the cyclooxygenase 1 and 2, blocking leukotriene production, and negatively affecting the cytokine genes [11]. Ginger extract and its main constituents, gingerol and shogaol, markedly enhanced the cytoplasm vacuolization and activated AMP-activated protein kinase, a positive regulator of autophagy, revealing its strong anticancer activity [41].

Nine horses were used in a crossover design to study the post-exercise effects of ginger extract at 30 g/day, supplemented by water an hour before testing. Ginger extract reduced the recovery time for VO_2 (time to recover from the peak observed at fatigue to a postexercise plateau) without affecting the other physiological responses, which is a beneficial tool for horses competing in racing or jumping events. Furthermore, the extract caused a tendency of increased proinflammatory cytokines tumor necrosis factor-1, interferon (IFN)-c and creatine kinase with a single dose of ginger extract; however, the increased kinase levels were related to the gastrointestinal tract irritation with caustic effect of ginger extract [9].

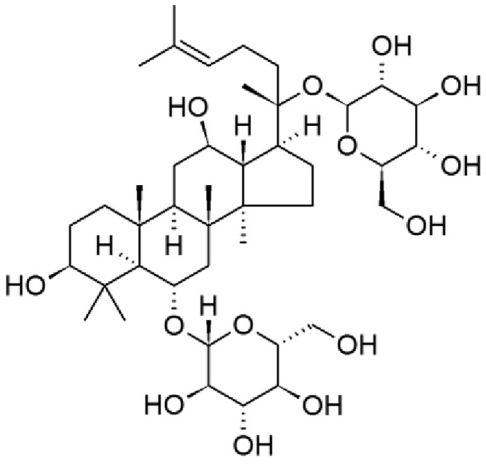

Fig. 2. Active component of ginseng extract (ginsenoside) [36].

2.4. Primrose

The essential oil of primerose constitutes primarily unsaturated fatty acids *viz*. linoleic acid (74.6%), gamma-linolenic acid (9.6%), palmic acid (6.6%), and oleic acid (6.1%) (Fig. 4A and B). Cyclooxygenase and lipoxygenase enzymes use these FAs as substrates, converting them into local hormones (eicosanoids), which further affect a sort of metabolic functions of the organism such as inflammation, vasodilation, vasoconstriction, bleeding, platelets aggregation, immune functions or blood pressure [43]. Primerose oil is also known to contain various potent antioxidants such as gallic acid, alpha-tocopherol, catechin, and epicatechin [42]. In an investigation, Granica et al. (2013) reported that primerose extract displayed anti-inflammatory activity by inhibiting lipoxygenase and hyaluronidase enzymes in a dose-dependent manner, and related the specific effect to the presence of oenothein-B content [44]. An 8-week experiment performed by Mikesova et al. (2014) in 10 healthy horses by supplementing evening primerose oil at 150 mL/day increased the total antioxidant reactivity and reduced the thiobarbituric acid reacting substances revealing an overall reduced lipid peroxidation. The supplementation also decreased lipolysis without disturbing the muscle homeostasis [18].

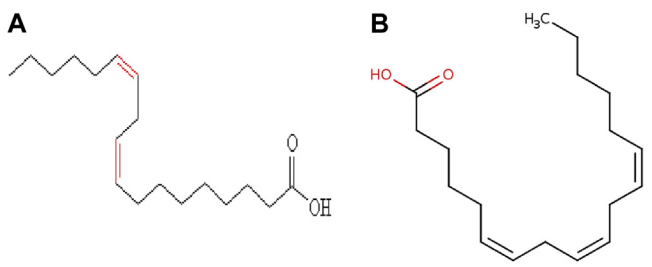

Fig. 4. Active components of primerose extract. (A) Linoleic acid [42]. (B) Gamma-linolenic acid [42].

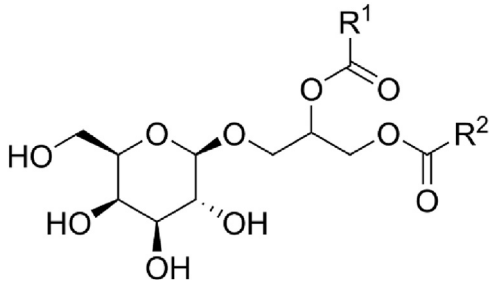

Fig. 5. Active component of rose hip extract (galactolipid) [45].

2.5. Rose Hip

The rose hip powder possesses the fruit including all the seeds and entire shell. The active ingredients of rose hip powder (Fig. 5) comprise an anti-inflammatory substance belonging to the galactolipid family, vitamin C, and E. Winther et al. (2010) top dressed the rose hip powder at 250 g (standardized for 1,000 mg vitamin C) onto the standardized daily diet of 2–3 years trotter for a 3-month period and stated that rose hip extract improves vitamin C status and is effective as an anti-inflammatory and antioxidative agent in horses. They suggested that some “cofactors” or “carriers” within the matrix of rose hip powder might have facilitated the absorption of vitamin C from the gastrointestinal tract [21]. In a secondary study by the same authors, the prolonged effects of the rose hip powder were tested at low doses by feeding rose hip powder at 25 or 50 g (standardized for 125 or 250 mg vitamin C) for a period of 3 months. It was revealed that the rose hip powder at even low doses were sufficient to increase serum vitamin C concentration and decrease the release of oxidative anions [22]. In horse, oxidative stress is more commonly occurred during exercise, and is involved in the etiology of various equine disorders such as recurrent airway obstruction, joint disease and muscle damage, and exercise-induced pulmonary hemorrhage, which may be prevented by supplementing rose hip powder in the regular ration as a feed additive.

2.6. Yucca

Yucca is a commonly sold herb for horses to reduce pain without any gastric side effects, and to ease discomfort due to arthritis, bone and joint problems, and soft tissue swelling. Saponins (mostly steroidal saponin) (Fig. 6) contribute to a large extent (about 10% of stem) among the active components of Yucca, followed by polyphenols such as resveratrol and yuccaols A–E [47]. The examination of physical data and spectroscopic analysis of Yucca extract revealed the presence of particular spirostanol saponins, which were stated to have broad bioactivities, such as anti-inflammatory, antiproliferative, antibacterial, anti-HIV, antifungi, and antihyperuricemic activities [46]. Apart from the production

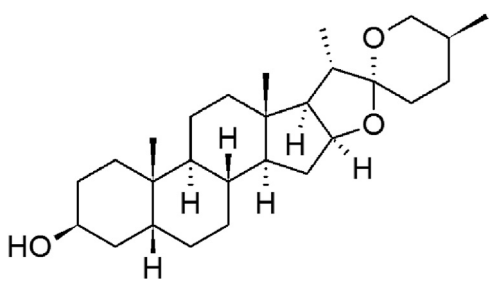

Fig. 6. Active component of yucca extract (steroidal saponin) [46].

perspective, Yucca extract has received much attention in the manure deodorization and gas mitigation programs of livestock rearing [48]. Incorporation of Yucca extract at 100 mg/kg diet enhanced the IL-6 and IFN-c concentration, and antibody titers against Newcastle disease virus in both grower and finisher period of broilers [49]. Feeding Yucca extract in combination with microbial preparation (probiotics) shows synergistic action further resulting in best results [50].

2.7. Echinacea

Despite not approved as a drug by the Food and Drug Administration, Echinacea is the third most sold herb in the United States, and its extract is being marketed for management of upper respiratory tract infections in humans. The equine industry usually uses Echinacea as an immune booster to complement a healthy immune system. The three species used most frequently in dietary supplements are *Echinacea purpurea*, *Echinacea pallida,* and *Echinacea angustifolia,* offered as capsules and teas. The principal active components of Echinacea include caffeic acid derivatives (cichoric acid, caftaric acid, echinacoside, caffeic acid, chlorogenic acid, and chlorogenic acid) polysaccharides, and alkamides (Fig. 7A and B). In a double-blind, placebo-controlled, crossover trial, O'Neill et al. (2002a) investigated the effect of standardized Echinacea extract on eight horses. Echinacea treatment increased the lymphocyte counts, improved the phagocytic ability of isolated neutrophils, and stimulated neutrophil migration, thus stimulating the equine immunocompetence. The supplement also acted as a hematinic agent by increasing the hemoglobin levels and total erythrocyte count, which may be related to improve the exercise performance by increased oxygen transport [17]. In a review, Barrett (2003) concluded no adverse effects of either overdoses or drug interactions on feeding Echinacea extract [52]; however, allergic rashes, hypereosinophilia, and autoimmune diseases and leucopenia were encountered with Echinacea usage for more days or with overdosage.

2.8. Valerian

Valerian supplements are usually sold for the treatment of anxiety, stress, and insomnia in humans. In equine industry, the valerian root extract has been sold with a caption, “Equine Calmer”, claiming its effect in relieving nervousness, restlessness, stress, and fear without affecting performance on feeding 15 g per day/horse. They also claim that Valerian eases the cramping associated with hormonal issues and retain a relaxing and calming effect on the gut by slowing down the passage of food through gut. More recently, a pilot survey on the horse owners' perception toward the usage of equine calming products in the north of Scotland revealed the regular use of valerian by few respondents to induce calming effect, thus mitigating the undesirable behavior during diverse situations [53]. Valerian extract contains at least 150 active constituents, the major include valepotriates, which comprise valtrate, volatile oils, valerenic acid, valeranone, and valerenal, alkaloids and lignans (Fig. 8A and B). Valerian causes a sedative effect by acting mainly as a depressant on nervous system followed by muscle relaxant [55]. In a human study, valerian extract at 600 mg/day valued superior to placebo on the Clinical Global Impression scale, with 66% of patients rating valerian effective for sleep as compared with 26% with placebo [56]. Furthermore, the administration of valerian extract at 1,000 mg/kg reduced the sleep latency period in Wistar rats [57].

2.9. Devil's Claw

In humans, devil's claw has been used as a herbal medicine for various fevers, allergies, appetite stimulation, and dyspepsia since

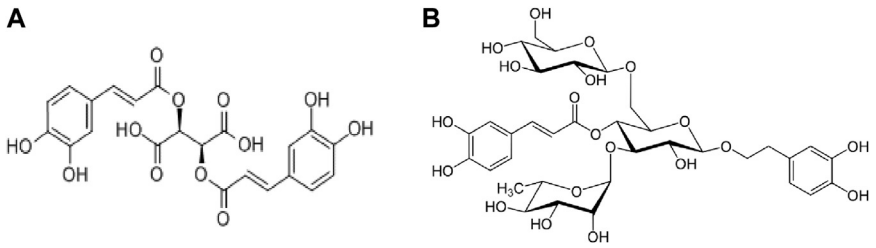

Fig. 7. Active components of Echinacea extract. (A) Cichoric acid [51]. (B) Echinacoside [51].

ancient days; currently, it is more popular as an anti-inflammatory and analgesic agent for osteoarthritis. Among the major elements of the extract (iridoid glycosides, sugars, triterpenoids, phytosterol, and aromatic acids), harpagoside (Fig. 9), a monoterpene iridoid glycoside, exert anti-inflammatory effects by interacting with both lipoxygenase and cyclo-oxygenase mediated pathways, as well as with the release of cytokines and nitric oxide production [58]. Furthermore, a close association between serum harpagoside levels and inhibition of leukotriene biosynthesis was observed in human subjects [59]. Although extrapolation of these results in humans to horses is challenging, the usage of devil's claw in horses is common for pain originating from degenerative joint disease [59]. According to Torres-Fuentes et al. (2014), oral supplementation of devil's claw is efficient for the effective treatment of inflammation, osteoarthritis, rheumatoid arthritis, tendonitis, and dyspepsia [60].

Exposure of C57BL/6 mice to devil's claw root extract demonstrated an increase in cellular calcium influx without inducing subsequent GHS-R1a receptor internalization, indicating full receptor activation and anorexigenic effect [60]. This notion may be applied to limit feed intake and keep the body condition score in check by avoiding an obese condition in sport horses at latency period by using *H. procumbens* extract as a feed additive. Administration of devil's claw was associated with hypertension, possibly as a consequence of the persistent inhibition of endogenous prostaglandins synthesis [61]. Furthermore, Torfs et al. (2008) documented mild gastrointestinal complaints and diarrhea as most common side effects on reviewing all clinical studies on devil's claw extract usage [59]. Excessive dose of devil's claw may also interfere with parallel treatment for cardiac disorders [62].

2.10. Flaxseed

Flaxseed has been used for ages as a dietary supplement for horses because of its high fat content. The active components include omega-3 fatty acids, phytoestrogens (secoisolariciresinol diglycoside), flavonoids, and lignans (Fig. 10A and B). In the recent past, the importance of omega-3 fatty acid supplementation has gained much importance in food industry, especially in designer food production. In this regard, flaxseed can be viewed as a cost-effective and economical way to boost omega-3 fatty acid in the feed. Supplementation of flaxseed oil to horses for 18 weeks did not show any differences in their body weight, plasma fibrinogen levels, blood count, and electrolyte (Na, K, and Cl) concentrations, except for plasma levels of alpha-linolenic acid, eicosa pentanoic acid, and malondialdehyde contents, which could potentially improve the chronic inflammatory disorders such as equine metabolic syndrome, osteoarthritis, and laminitis in horses [12]. In another study, the supplementation of flaxseed (~38 g alpha-linolenic acid) to growing horses leads to higher incorporation of n-3 eicosa pentanoic acid and docosahexaenoic acid in skeletal muscle, which was still higher compared with both control and marine alpha-linolenic acid supplementation [15]. In a similar feeding design, Ross-Jones et al. (2014) estimated the synovial and plasma fatty acid levels for eicosa pentanoic acid and docosahexaenoic acid. Although the plasma levels were higher than control, the levels of eicosa pentanoic acid and docosahexaenoic acid in synovial fluid was far lower than those of marine alpha-linolenic acid supplementation, showing that direct supplementation of these fatty acids is obligatory if the greater levels of those fatty acids are needed in synovial fluid for the management of joint pains [16].

Direct supplementation of eicosa pentanoic acid and docosahexaenoic acid to exercised horse diets were associated with lower plasma glycerol, heart rate, free fatty acids, and cholesterol compared with those fed with corn oil containing diets [64]. Furthermore, the clinical studies revealed that omega-3 fatty acids supplementation aids in improved lung function in the horses suffering from chronic lower airway inflammatory disease. Feeding mares with flaxseed at 0.1% body weight for 16 weeks did not influence progesterone and any of the serum biochemical parameters, except for alpha-linolenic acid concentration, which was higher compared with control [14]. Interestingly, flaxseed usage as a feed additive is identified to play a role in maintaining the health of skin coat apart from treatment of symptoms of dermatitis in

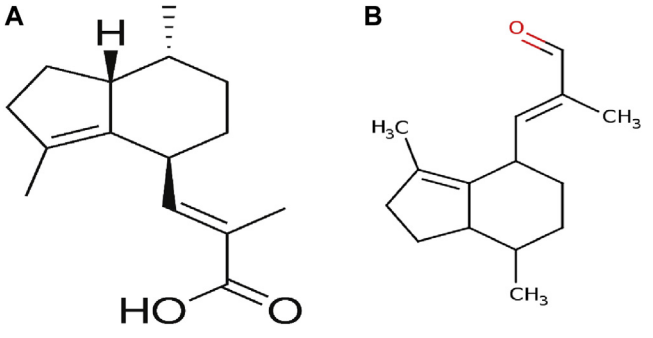

Fig. 8. Active components of valerian extract. (A) Valerenic acid [54]. (B) Valerenal [54].

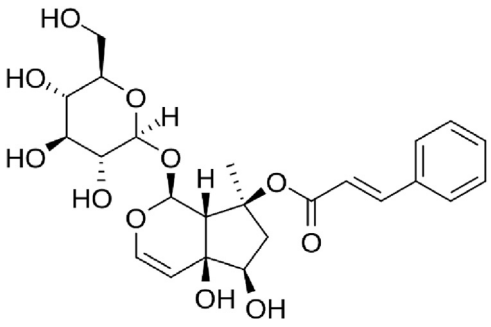

Fig. 9. Active component of devil's claw extract (harpagoside) [33].

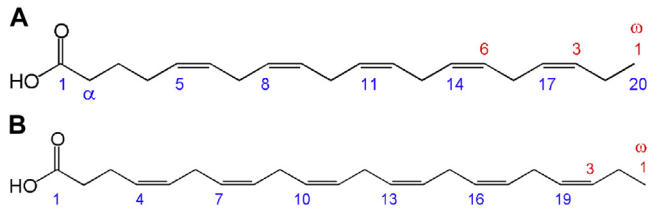

Fig. 10. Active components of flaxseed extract. (A) Eicosapentaenoic acid (EPA) [63]. (B) Docosahexaenoic acid (DHA) [63].

horses, probably, due to modifications in fatty acid profile of the sebum secreted by sebaceous glands [65]. In connection with this, O'Neill et al. (2002b) reported that feeding flaxseed meal significantly reduced the lesional area of skin test response of atopic horses with an altered fatty acidprofile of hair and reduced inflammation in horses, which previously showed a positive skin test for allergy to extract from *Culicoides* sps [13].

2.11. Aloe Vera

Aloe vera, an oldest known natural herb that is used in the field of cosmetology in humans, is also tested to be potent for regulating hoof health and ulcer-related gastric disorders in horses. Aloe vera–based formula was successfully used as emollient on horses' hooves [66]. The extract or gel contains 75 potentially active constituents *viz*. anthraquinones, saccharides, polysaccharides (acemannan), salicylic acids, saponins, vitamins, enzymes, minerals, sugars, lignin, and amino acids [67] (Fig. 11A and B), providing a variety of possible mechanisms including antioxidant activity, anti-inflammatory properties, cytoprotective, and mucus-stimulatory effects. Few studies in monogastric animals specify that the Aloe vera extract can improve the ecosystem of intestinal microflora by decreasing the total *E. coli* count and increasing the Lactobacillus count [69]. More recently, Bush et al. (2018) compared the gastrointestinal tract protective effect of Aloe vera inner leaf gel with omeprazole in 40 horses diagnosed with grade $\geq$2 lesions of the squamous and/or glandular mucosa. Although improvement in lesions was seen, the healing rate was only 17% in Aloe vera group compared with 85% of the omeprazole group; the lower efficacy of extract may be related to the low dosage and short period of exposure (only 28 days) [23]. Aloe vera gel is contraindicated and should not be fed to pregnant mares as it may stimulate uterine contraction, thus increasing the risk of fetal loss [65].

2.12. Other Plant Extracts

A disk diffusion and microdilution methods based in vitro study conducted by using nine essential oils *viz*. cinnamon, peppermint, palmarosa, oregano, Madagascar and Indonesian cloves, niaouli, oregano, sauce thyme, and rosemary, against the *Staphylococcus xylosus* isolates from nasal mucosa of horse revealed a potent antimicrobial activity by all the oils tested, except for rosemary [70]. Owing to their antimicrobial properties, essential oils are traditionally being used to control respiratory and gastrointestinal infections, and nowadays their usage as food additives have been gaining importance in humans. The dried composite of five herbs *viz*. devil's claw, stinging nettle, dandelion, comfrey, and burdock showed a significant protective effect against IL-1–induced glycosaminoglycan (GAG release) and nitric oxide production, suggesting its potentiality as an adjunct to the NSAIDs, but care should be taken regarding the dosage due to the narrow safety margin [26]. Another study conducted by the same author by means of using a herbal composite constituting garlic, boneset, aniseed, white horehound, licorice, fennel, hyssop, and thyme indicated this amalgamation as a possible strategy in safely reducing the elevated respiratory rate in horses suffering from recurrent airway obstruction [8]. Remarkably, the lavender aromatherapy was shown to signal a shift to the sympathetic nervous control from the parasympathetic system, decreased heart rate and respiratory rate [19], and suppressed cortisol levels [20] in horses subjected to stress. The authors stated that lavender usage, being not an illegal substance, in stressed horses is of utmost importance, as there are limited legal medications available for racing horses as per the rules and regulations of Federation Equestre Internationale.

Cranberry extract at 30 g/kg body weight attenuated the upregulation and expression of tumor necrosis factor -α mRNA, a major mediator of inflammation, after a small and intense session of exercise in horses [9]. In a field trial, Luca et al. (2017) fed herbal mixture, constituting fleawort, Aloe vera, fenugreek, and licorice extracts, to the horses diagnosed with equine gastric ulcer syndrome for a period of 30 days. They confirmed that the herbal mixture was effective in reducing both the number and severity of ulcerative lesions, presumably due to the beneficial effects of mucilages in protecting the mucosa from acidity apart from the anti-ulcerogenic activity of the herbs [27]. Although no scientific evidence was found, anecdotal usage of fenugreek in horses seems to be very common for treating various disorders in horses. Meanwhile, Salem et al. (2017) evaluated the effect of different doses of aguamiel (*Agave atrovirens*) sap, having both probiotic and prebiotic characteristics, on in vitro degradation of various forage species. Aguamiel at 34 μg/g enhanced the fermentability of *Caesalpinia coriacea* forage, indicating enhanced feed intake, which was predicted with relation to gas production. Furthermore, the extract at a higher dose (64 μg/g) caused a decreased time for lag phase compared with control suggesting an induced microbial adaptation [71].

Another study was conducted in nine Standardbred mares with a speculation that decaffeinated black tea and orange peel extracts would alter indicators of exercise performance. The extract of

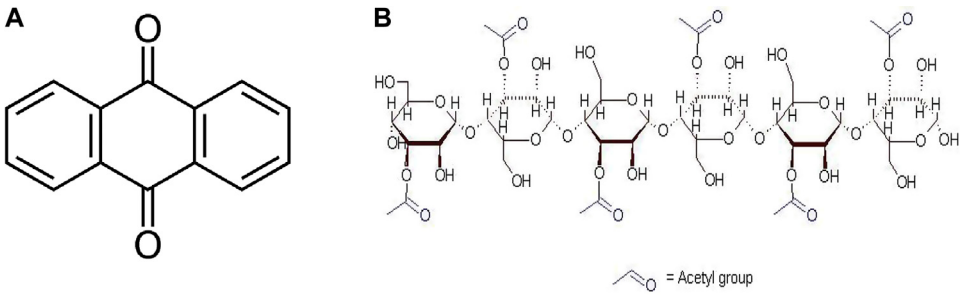

Fig. 11. Active components of flaxseed extract. (A) Anthraquinone [68]. (B) Acemannan [68].

orange peel administered 60 minutes before exercise in horses, which were exercised until fatigue on the treadmill, decreased interferon-γ (IFN-γ) expression and recovery time of cardiovascular parameters because of the anti-inflammatory effect of citrus-derived polymethoxylated flavones. Black tea extract also lessened mRNA expression of tumor necrosis factor-α and IFN-γ due to the tea flavin, a polyphenol having potent inhibition effect on IL-8 gene expression [72]. Furthermore, Bergero (2006) acknowledged ginkgo (*Ginkgo biloba*) extract can ameliorate the performance loss during "sport horse anemia" condition, which decreases oxygen distribution to muscle cells throughout the performance [73]. Torfs et al. (2018) claimed willow (*Salix*) and blackcurrant (*Ribes nigrum*) as phototherapeutic and potential alternatives of NSAID in horses, but yet to be researched completely [59]. Despite lack of any experimental studies in horses, spices such as fenugreek (*Trigonella foenum*), cinnamon (*Cinnamomum zeylanicum*), and turmeric (*Curcuma domestica*) were promoted to use as feed additives in horses as they may provide health benefits other than just increasing the palatability [5]. Parsley (*Petroselinum crispum*) extract, a complex mixture of coumarins, terpenoids, and phenylpropanoids, is another promising feed additive in horses and even has long back history of feeding the whole herb to war horses by warriors [6]. Milk thistle (*Silybum marianum*) extract was able to neutralize endotoxins and reduce lipopolysaccharide-induced lamellar separation in a well-established *in vivo*/*in vitro* laminitis model, presumably due to the antioxidative and anti-inflammatory properties of the active components such as silymarin and silibinin [25]. Furthermore, silymarin may increase the serum levels of glutathione, and also known to use for horses suffering from ragwort poisoning or liver damage [65]. The active principles of various herbs with potentiality to use as feed additives are presented in Fig.12.

Although feeding all the aforementioned herbs or their extracts has their own confines, many herbs growing naturally in hedgerows and pastures provide free access to grazing horses. Hawthorn (*Crataegus*), an antistressor and mild diuretic and known to possess beneficial effects on the cardiovascular system because of the active ingredient vitexin, growing near paddocks seem particularly appetizing to horses. Dandelion, a perennial weed available *ad libitum* in the grazing tracts of horse, is known to possess antidiuretic and hepatoprotective effects [65].

3. Problems Associated with the Utilization of Herbs as Feed Additives in Equines

Most herbs are not scientifically evaluated for their beneficial and adverse effects. The absence of controlled measures either to diagnose or prevent adulteration of herbs or their extracts, in horsemarkets is a considerable problem in exploiting their usage. Adulteration is merely a replacement of various herbs with other unrelated herbal ingredients or incorporation of active components, pathogens, drugs or pollutants.

3.1. Herbs as Feed Additives during Competition

As per the Equine Anti-Doping and Controlled Medication Regulations, any materials, either natural or synthetic, having the potentiality to enhance performance on administering at considerable levels are considered to be banned, have no legitimacy to use, and should not be found in body fluids of sport horses at any level. Scarth et al. (2010) considered that the increased usage of herbal products as feed additives or therapeutic agents may become one of the important threat that greatly influences the future of equine drug metabolism in the area of doping research [75]. However, the UK rules of racing (2010) announced that any feed supplement or medications, including herbal extracts, can be freely fed to horses on training, but the usage should be terminated few days before the sport to prevent their detectability on race

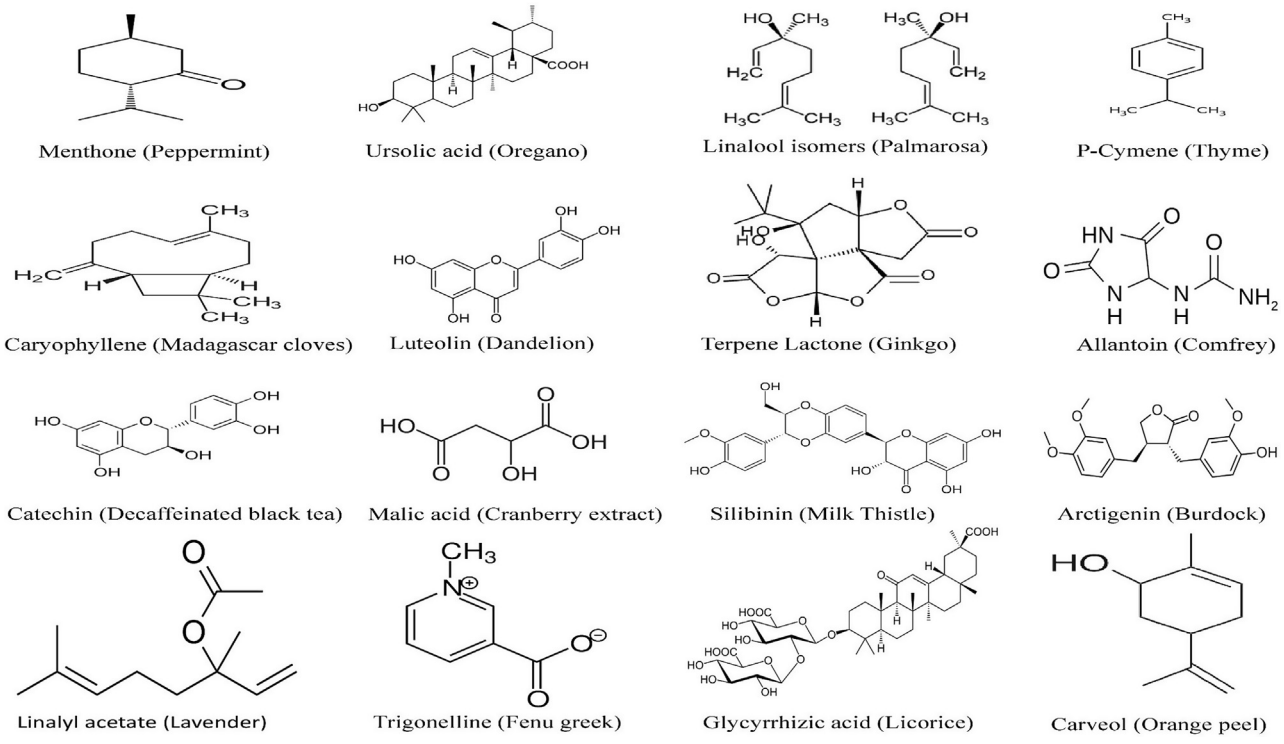

Fig. 12. Chemical structure of active components of few plant herbs to be used as feed additives in equines [74].

days [76]. This thought needs thorough study to know the detection time and withdrawal periods of various herbs, and there is a necessity for developing new approaches for analytical screening by including the principles of the safety of margin, pharmacokinetics, and pharmacodynamics. Furthermore, confusion does exist pertaining to the list of banned substances; although capsaicin, a secondary metabolite of chili pepper with analgesic property, is not listed as class A list of banned substances by Federation Equestre Internationale, its usage was related to disqualifying and elimination of the riders from 2008 Beijing Olympics. Another important consideration is inconsistent regulations regarding the usage of supplements or medicines by the equine regulatory authorities. As an illustration, the usage of phenylbutazone, along with Regumate, Gastroguard, and antibiotics were banned by the German Equestrian Federation, which are still allowed in Federation Equestre Internationale competitions.

3.2. Herb-Drug Interaction

Herb-drug interactions are no more than the drug interactions that occur between conventional drugs and herb extracts because of the interrelationship among normal drug administered and multiple pharmacologically active ingredients in the plant extract. Although most of the herbal extracts are not associated with drug interactions, few are able to cause clinically significant consequences [77]. Extensive reviews on herb-drug interactions were given by Posadzki (2013) [77], Harman (2002) [78], and Izzo et al. (2005) [79]. Furthermore, critical evaluation of causality assessment of various herb-drug interactions in human patients can be found in a review by Awortwe et al. (2018) [80]. The most common interactions with considerable potentiality in equine health and well-being are discussed below.

The herbs containing salicylates *viz*. meadowsweet (*Filipendula ulmaria*), wintergreen (*Gaultheria procumbens*), willow (*Salix alba*), poplar (*Populus tremuloides*), ginseng (*Panax quinquefolius*), licorice (*Glycyrrhiza glabra*), and sage (*Salvia officinalis*) have to be cautiously administered as their interaction with various drugs can create various side effects ranging from mild to severe, depending on the concentration [29]. Feeding devil's claw (*Harpagophytum procumbens*) as a feed additive in horses administered with NSAIDs, antiarrhythmic agents, hypoglycemic medications, anticoagulants, or digoxin, may lead to drug interactions leading to an increased risk of gastrointestinal tract bleeding, hypoglycemia, and arrhythmias [61]. Valerian can interact with alcoholic beverages, barbiturates, benzodiazepines, antihistamines, or anesthetics, and because of these interactions, the same is strictly prohibited to be fed in postsurgical conditions [81]. Two systematic reviews found scientific evidence of Echinacea as a triggering agent of pharmacokinetic drug interactions along with induction of cytochrome P3A enzymes–mediated drug metabolism [82]. Although the overall herb-drug interaction risk for garlic is low, prolonged exposure of concentrated extracts may reduce the efficacy of drugs whose deposition depends on the efflux transporter ABCB1 gene [83]. Furthermore, in equines, feeding excess garlic without a proper check on the levels may lead to Heinz body anemia [35]. Many herbs have been related to the adverse reactions with bronchodilators including cardospermum (*Cardospermum halicacabum*), ginkgo (*Ginkgo biloba*), and St. John's wort (*Hypericum perforatum*) [84].

4. Conclusion

Although the positive results found with all the aforementioned herbs or their extracts as feed additives were mostly in species other than equines, they could also potentially adapted for horses, but with a principal evaluation for suitability of the respective herb at a specified dosage, especially in pregnant and lactating horses. Definitive conclusions can be made on conducting equine-specific studies. Within the equine studies, although few herbs were tested as feed supplements, the outcome and adaptability should be evaluated based on the variations in methods used in the study such as quantity, extraction procedure, form of feeding, and length of the trial period. In addition to alleviating symptoms and treating chronic diseases of horses, these herbal/plant extracts can be used in maintaining health and improving performance by exploiting them as feed additives, if nourished at desired levels, but a large extent of lacunae exist for equines, demanding a vast scope for future studies regarding feed additives application. Exploiting new knowledge of the constituents of various plant extracts, the focus of herbal extract research should shift from currently used therapeutic management to feed additive purpose. Again, the prohibited medications list from the Federation Equestre Internationale has to be taken into account while formulating any herbal-based feed additive for horses at international competitions. Furthermore, natural will not always guarantee safe; hence, the proposal of administration of herbal extracts together with any synthetic drugs should be reconsidered on the background of herb-drug interactions.

References

[1] Jurgens MH. Animal feeding and nutrition. 9th ed. Dubuque, IA: Kendall/Hunt Publishing Co; 2002.
[2] National research council (NRC): nutrient requirements of horses, 5th revised edition. Washington, DC: National Academy Press; 1989.
[3] Soring KH, Hyde WG. Review of anabolic steroid testing in a racing environment. Lexington: American Assoc Equine Pract Proc; 2008. p. 54.
[4] Wein S, Wolffram S. Oral bioavailability of quercetin in horses. J Equine Vet Sci 2013;33:441–5.
[5] Robinson NE, Sprayberry KA. Current therapy in equine medicine 2.Saunders 2009 Elsevier. https://books.google.co.in/books?id=q-26Cz4t-P0C. [Accessed 7 April 2018].
[6] Lans C, Turner N, Brauer G, Lourenco G, Georges K. Ethnoveterinary medicines used for horses in Trinidad and in British Columbia, Canada. J Ethnobiol Ethnomed 2006;2:1–20.
[7] Swirsley NK. Supplement use and perceptions: a survey of U.S. horse owners. A thesis submitted in partial fulfillment of the requirements for the degree of Master of science in horse science equine education. USA: Middle Tennessee State University; 2005.
[8] Pearson W, Omar S, Clarke AF. Low-dose ginseng *(Panax quinquefolium)* modulates the course and magnitude of the antibody response to vaccination against *Equid herpesvirus 1* in horses. Can J Vet Res 2007b;71:213–7.
[9] Liburt NR, McKeever KH, Streltsova JM, Franke WC, Gordon ME, Manso Filho HC, Horohov DW, Rosen RT, Ho CT, Singh AP, Vorsa N. Effects of ginger and cranberry extracts on the physiological response to exercise and markers of inflammation in horses. Comp Excer Phys 2009;6:157–69.
[10] Pearson W. Ethnoveterinary medicine: the science of botanicals in equine health and disease. In: Proceedings of the second annual European equine health and nutrition congress. The Netherlands: Lelystad; 2003. p. 31–40.
[11] Mashhadi NS, Ghiasvand R, Askari G, Hariri M, Darvishi L, Mofid MR. Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity: review of current evidence. Int J Prev Med 2013;4(Suppl 1):S36–42.
[12] Hansen RA, Savage CJ, Reidlinger K, Traub-Dargatz JL, Ogilvie GK, Mitchell D, Fettman MJ. Effects of dietary flaxseed oil supplementation on equine plasma fatty acid concentrations and whole blood platelet aggregation. J Vet Intern Med 2002;16:457–63.
[13] O'Neill W, McKee S, Clarke AF. Immunological and haematinic consequences of feeding a standardized Echinacea (*Echinacea angustifolia*) extract to healthy horses. Equine Vet J 2002;34:222–7.
[14] Swanson TJ, Hammer CJ. Effects of flaxseed supplementation on mare progesterone and blood parameters. Abstracts J Equine Vet Sci 2011;31:230–356.
[15] Hess TM, Rexford JK, Hansen DK, Harris M, Schauermann N, Ross T, Engle TE, Allen KG, Mulligan CM. Effects of two different dietary sources of long chain omega-3, highly unsaturated fatty acids on incorporation into the plasma, red blood cell, and skeletal muscle in horses. J Anim Sci 2012;90:3023–31.
[16] Ross-Jones T, Hess T, Rexford J, Ahrens N, Engle T, Hansen K. Effects of omega-3 long chain polyunsaturated fatty acid supplementation on equine synovial fluid fatty acid composition and prostaglandin E2q. J Equine Vet Sci 2014;34:779–83.
[17] O'Neill W, McKee S, Clarke AF. Flaxseed (*Linum usitatissimum*) supplementation associated with reduced skin test lesional area in horses with Culicoides hypersensitivity. Can J Vet Res 2002a;66:272–7.

[18] Mikesova K, Hartlova H, Zita L, Chmelíkova E, Hulkova M, Rajmon R. Effect of evening primrose oil on biochemical parameters of thoroughbred horses under maximal training conditions. Czech J Anim Sci 2014;59:488–93.
[19] Ferguson E, Kleinman HF, Browning JMS. Effect of lavender aromatherapy on acute-stressed horses clarence. J Equine Vet Sci 2007;33:67–9.
[20] Heitman K, Rabquer B, Heitman E, Streu C, Anderson P. The use of lavender aromatherapy to relieve stress in trailered horses. J Equine Vet Sci 2018;63:8–12.
[21] Winther K, Kharazmi A, Hansen ASV, Falk-Rønne J. A randomised placebo controlled double blind study on the effect of subspecies of rose hip (*Rosa canina*) on the immune system, working capacity and behaviour of horses. In: Ellis AD, Longland AC, Coenen M, Miraglia N, editors. The impact of nutrition on the health AND welfare of horses. EAAP, Vol. 128. Wageningen, The Netherlands: Wageningen Academic Publishers; 2010. p. 283–7.
[22] Winther K, Kharazmi A, Hansen ASV, Falk-Rønne J. The absorption of natural vitamin C in horses and anti-oxidative capacity: a randomised, controlled study on trotters during a three-month intervention period. Comp Exerc Phys 2012;8:195–201.
[23] Bush J, Boom RVD, Franklin SH. Comparison of *aloe vera* and omeprazole for treatment of equine gastric ulcer syndrome. Equine Vet J 2018;50:34–40.
[24] Pearson W, McKee S, Clarke AF. The effect of a proprietary herbal product on equine joint disease. J Nutra Funct Med Foods 1999;2:31–46.
[25] Reisinger N, Schaumberger S, Nagl V, Hessenberger S, Schatzmayr G. Milk thistle extract and silymarin inhibit lipopolysaccharide induced lamellar separation of hoof explants in vitro. Toxins (Basel) 2014;6:2962–74.
[26] Pearson W, Orth MW, Lindinger MI. Differential anti-inflammatory and chondroprotective effects of simulated digests of indomethacin and an herbal composite (MobilityTM) in a cartilage explant model of articular inflammation. J Vet Pharmacol Therap 2007;30:523–33.
[27] Luca S, Enrica Z, Alessia S, Giovanni S, Serena C, Bianca C, Elisabetta F, Francesco F. Efficacy of the administration of a natural feed supplement in the management of equine gastric ulcer syndrome in 7 sport horses: a field trial. Am J Anim Vet Sci 2017;12:104–10.
[28] Block E. Chemistry of garlic and onions. Sci Am 1985;252:94–9.
[29] Williams CA, Lamprecht ED. Some commonly fed herbs and other functional foods in equine nutrition: a review. Vet J 2008;178:21–31.
[30] Pearson W. Ethnoveterinary Medicine: The Science of Botanicals in Equine helath and Disease. Proceedings of the 2nd European Equine Nutrition and Health Congress, March, 19–20, 2004-Lelystad, The Netherlands.
[31] Chmelikova E, Nemecek D, Dvorakova M, Heroutova I, Sedmikova M. Organosulphur garlic compounds influence viability of mammalian cells: a review. Sci Agric Bohem 2018;49:9–16.
[32] Chhabria S, Desai K. Purification and characterisation of alliinase produced by Cupriavidus necator and its application for generation of cytotoxic agent: Allicin. Saudi J Biol Sci 2016. https://doi.org/10.1016/j.sjbs.2016.01.003.
[33] Park J. The garlic preparation as an alternative way for gastroprotection. Gut and Liver 2016;10:321–2.
[34] Majewski M. Allium sativum: facts and myths regarding human health. Rocz Panstw Zakl Hig J 2014;65:1–8.
[35] Pearson W, Boermans HJ, Bettger WJ, McBride BW, Lindinger MI. Association of maximum voluntary dietary intake of freeze-dried garlic with Heinz body anemia in horses. Am J Vet Res 2005;66:457–65.
[36] Kim JH. Pharmacological and medical applications of panax ginseng and ginsenosides: a review for use in cardiovascular diseases. J Ginseng Res 2017;42:264–9.
[37] Kang S, Min H. Ginseng, the 'immunity boost': the effects of panax ginseng on immune system. J Ginseng Res 2012;36:354–68.
[38] Chung SI, Lo LMP, Lee SC. Antihyperlipidemic effects of Korean ginseng in high-fat diet-fed ovariectomized rats. Food Sci Biotechnol 2016;25:1155.
[39] Poppenga RH. Risks associated with the use of herbs and other dietary supplements. Vet Clin North Am Equine Pract 2001;17:455–77.
[40] Rahmani AH, Shabrmi FMA, Aly SM. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. Int J Physiol Pathophysiol Pharmacol 2014;6:125–36.
[41] Akimoto M, Iizuka M, Kanematsu R, Yoshida M, Takenaga K. Anticancer effect of ginger extract against pancreatic cancer cells mainly through reactive oxygen species-mediated autotic cell death. PLoS One 2015;10:e0126605.
[42] Christie WW. The analysis of evening primrose oil. Ind Crop Prod 1999;10:73–83.
[43] Lisiak D, Grzeskowiak E, Borzuta K, Raj S, Janiszewski P, Skiba G. Effects of supplementary vegetable and animal fats on the slaughter values of fatteners, meat quality, and fatty acid profile in pigs. Czech J Anim Sci 2013;11:497–511.
[44] Granica S, Czerwinska ME, Piwowarski JP, Ziaja M, Kiss AK. Chemical composition, antioxidative and anti-inflammatory activity of extracts prepared from aerial parts of *Oenothera biennis* L. and Oenothera paradoxa Hudziok obtained after seeds cultivation. J Agric Food Chem 2013;61:801–10.
[45] Nakamura Y. Galactolipid biosynthesis in flowers. Nakamura Bot Stud 2013;54:29.
[46] Qu L, Wang J, Ruan J, Yao X, Huang P, Wang Y, Yu H, Han L, Zhang J, Wang T. Spirostane-type saponins obtained from yucca schidigera. Molecules 2018;23:1–12.
[47] Williams CA. Specialized dietary supplements. Equine App Clin Nutr 2013:351–66. https://doi.org/10.1016/B978-0-7020-3422-0.00019-5.
[48] Sun DS, Jin X, Shi B, Xu Y, Yan S. Effects of *Yucca schidigera* on gas mitigation in livestock production: a review. Braz Arch Biol Technol 2017;60:1–15.
[49] Sun DS, Shi B, Tong M, Yan S. Improved performance and immunological responses as a result of dietary Yucca schidigera extract supplementation in broilers. Ital J Anim Sci 2017;17:511–7.
[50] Matusiak K, Oleksy M, Borowski S, Nowak A, Korczynski M, Dobrzanski Z, Gutarowska B. The use of yucca schidigera and microbial preparation for poultry manure deodorization and hygienization. J Environ Manage 2016;170:50–9.
[51] Manayi A, Vazirian M, Saeidnia S. Echinacea purpurea: pharmacology, phytochemistry and analysis methods. Plant Rev 2015;9:63–72.
[52] Barrett B. Echinacea: a safety review. HerbalGram 2003;57:36–9.
[53] Ross D, Roberts J. Equine calming products: a short survey into their use, effect and knowledge using a small sample of horse owners in the North of Scotland, UK. J Equine Vet Sci 2018;68:63–7.
[54] Nandhini S, Narayanan KB, Ilango K. Valeriana Officinalis: a review of its traditional uses, phytochemistry and pharmacology. Asian J Pharma Clin Res 2018;11:36–41.
[55] Hattesohl M, Feistel B, Sievers H. Extracts of Valeriana officinalis L. s.I show anxiolytic and antidepressant effects but neither sedative nor myorelaxant properties. Phytomedicine 2008;15:2–15.
[56] Trevena L. Sleepless in Sydney—is valerian an effective alternative to benzodiazepines in the treatment of insomnia? ACP J Club 2004;141:A14–6.
[57] Tokunaga S, Takeda Y, Niimoto T. Effect of valerian extract preparation (BIM) on the sleep-wake cycle in rats. Biol Pharm Bull 2007;30:363–6.
[58] Anauate MC, Torres LM, Mello SBV. Effect of isolated fractions of *Harpagophytum procumbens* D.C. (Devil's claw) on COX-1, COX-2 activity and nitric oxide production on whole-blood assay. Phytother Res 2010;24:1365–9.
[59] Torfs S, Delesalle C, Vanschandevijl K, De Clercq D, Van Loon G, Nollet H, Deprez P. Anti-inflammatory phytotherapeutics: a valuable alternative to NSAID treatment in horses? Vlaams Diergen Tijds 2008;78:161–70.
[60] Torres-Fuentes C, Theeuwes WF, McMullen MK, McMullen AK, Dinan TG. Devil's claw to suppress appetite—ghrelin receptor modulation potential of a *Harpagophytum procumbens* root extract. PLoS One 2014;9:e103118.
[61] Cuspidi C, Sala C, Tadic M, Grassi G, Mancia G. Systemic hypertension induced by harpagophytum procumbens (devil's claw): a case report. J Clin Hypertens (Greenwich) 2015;17:908–10.
[62] Brien S, Lewith GT, Mcgregor G. Devil's claw (*Harpagophytum procumbens*) as a Treatment for Osteoarthritis: a review of efficacy and safety. J Alter Compl Med 2006;12:981–93.
[63] Kajla P, Sharma A, Sood DR. Flaxseed - a potential functional food source. J Food Sci Tech 2015;52:1857–71.
[64] O'Connor C, Lawrence L, St. Lawrence A, Janieki K, Warren L, Hayes S. The effect of dietary fish oil supplementation on exercising horses. J Anim Sci 2004;82:2978–84.
[65] Davies Z. Introduction to horse nutrition. Ames, Iowa, USA: Blackwell Publishing group. 2121 State Avenue; 2009. p. 50014–8300.
[66] Simonato SP, Souza MVD, Diaz MAN, Frassy LN, Pinto JO. Aloe vera-based formula as emollient on horses' hooves. Rev Ceres Viçosa 2013;60:318–23.
[67] Darabighane B, Nahashon SN. A review on effects of aloe vera as a feed additive in broiler chicken diets. Ann Anim Sci 2014;14:491–500.
[68] Foster M, Hunter D, Samman S. Evaluation of the nutritional and metabolic effects of *aloe Vera*. In: Benzie IFF, Wachtel-Galor S, editors. Herbal medicine: biomolecular and clinical aspects. 2nd edition, Chapter 3. Boca Raton (FL): CRC Press/Taylor & Francis; 2011. https://www.ncbi.nlm.nih.gov/books/NBK92765/. [Accessed 9 April 2018].
[69] Darabighane B, Zarei A, Shahneh AZ. The effects of different levels of *aloe vera* gel on ileum microflora population and immune response in broilers: a comparison to antibiotic effects. J Appl Anim Res 2012;40:31–6.
[70] Huerta B, Barrero-Dominguez B, Galan-Relaño A, Tarradas C, Maldonado A, Luque I. Essential oils in the control of infections by staphylococcus xylosus in horses. J Equine Vet Sci 2012;38:19–23.
[71] Salem AZM, Valdez NT, Olurotimi AO, Elghandour MMY, Pliego AB, Coyote RL. Influence of aguamiel (*Agave atrovirens*) as a natural feed additive on cecal fermentation kinetics of some forage species in horse feeding. J Equine Vet Sci 2017;48:103–12.
[72] Streltsova JM, McKeever KH, Liburt NR, Gordon ME, Filho HM, Whorohov D, Rosen RT, Franke W. Effect of orange peel and black tea extracts on markers of performance and cytokine markers of inflammation in horses. Equine Comp Exer Phy 2006;3:121–30.
[73] Bergero D, Valle E. A critical analysis on the use of herbs and herbal extracts in feeding sport horses. Pferdeheilkunde 2006;22:550–7.
[74] National Center for Biotechnology Information (NCBI). PubChem compound database; CID=16666; 64945; 6549; 7463; 5281515; 5280445; 204; 9064; 525; 31553; 64981; 8294; 5570; 16213698; 7438. https://pubchem.ncbi.nlm.nih.gov/compound/16666; 64945; 6549; 7463; 5281515; 5280445; 204; 9064; 525; 31553; 64981; 8294; 5570; 16213698; 7438. [Accessed 31 May 2018].
[75] Scarth P, Teale P, Kuuranne T. Drug metabolism in the horse: a review. Drug Test Anal 2010;3:19–53.
[76] United States equestrian federation. (2017). Drugs & medications, from US Equestrian, Florida. https://www.usef.org/compete/resources-forms/rules regulations/drugs-medications?. [Accessed 1 April 2018].

[77] Posadzki P, Watson L, Ernst E. Herb-drug interactions: an overview of systematic reviews. Br J Clin Pharmacol 2013;75:603–18.
[78] Harman J. The toxicology of herbs in equine practice. Clin Tech Equine Prac 2002;1:74–80.
[79] Izzo AA, Di Carlo G, Borrelli F, Ernst E. Cardiovascular pharmacotherapy and herbal medicines: the risk of drug interaction. Int J Card 2005;98:1–14.
[80] Awortwe C, Makiwane M, Reuter H, Muller C, Louw J, Rosenkranz B. Critical evaluation of causality assessment of herb-drug interactions in patients. Br J Clin Pharmacol 2018;84:679–93.
[81] Sharma M, Jain UK, Patel A, Gupta N. A comprehensive pharmacognostic report on Valerian. Inter J Pharmaceut Sci Res 2010;1:6–40.
[82] Haefeli WE, Carls A. Drug interactions with phytotherapeutics in oncology. Expert Opin Drug Metab Toxicol 2014;10:359–77.
[83] Gurley BJ, Fifer EK, Gardner Z. Pharmacokinetic herb-drug interactions (part 2): drug interactions involving popular botanical dietary supplements and their clinical relevance. Planta Med 2012;78:1490–514.
[84] Pearson W. Concurrent use of veterinary drugs and herbal medicines in racing Standardbreds. Can Vet J 2009;50:1283–5.