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(REVIEW ARTICLE)

A review: Flavonoid; A Phyto-nutrient and its impact in livestock animal nutrition

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Abstract

Flavonoids, recognized as phyto-nutrients and natural bioactive compounds in animal feed, play a pivotal role in enhancing the quality of animal products and bolstering animal health. Flavonoids cannot be internally synthesized by humans and animals; instead, they are sourced from plants. They are characterized by diverse phenolic structures, and are abundant in a variety of sources such as fruits, vegetables, grains, bark, roots, stems, and flowers. Their multifaceted advantages encompass promoting animal growth, improving the quality of animal products, serving as feed additives, and acting as alternatives to antibiotics in animal production. On average, individuals are estimated to ingest 10–100 mg of flavonoids daily through diverse food items. However, a critical assessment reveals that achieving an optimal dietary intake of flavonoids is challenging due to the vast array of available types, their widespread distribution across various plants, and the varied consumption patterns in both humans and animals, which remain relatively low. Flavonoids exhibit inhibitory effects on both Gram-positive and Gram-negative bacteria, yet the comprehensive mechanisms underlying their antibacterial properties are not fully elucidated. This review explored the impact of flavonoids on diabetes mellitus, their antioxidant effects, and their antimicrobial properties. Finally, the mechanism of operation and the influence of flavonoids on ruminant animal nutrition were also assayed.

Keywords: Flavonoid; Phyto-Nutrient; Nutritional Impact; Ruminant Animal

1. Introduction

In recent times, there has been a growing focus on the presence of natural biologically active substances in animal feeds, aiming to enhance the quality of animal products and promote animal health (Lee *et al*., 2017). Flavonoids, a subgroup of these bioactive substances characterized by diverse phenolic structures, are abundantly found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine (Panche *et al*., 2016). Recognized for their anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties, along with their ability to modulate crucial cellular enzyme functions, flavonoids are now indispensable in various applications, including nutraceuticals, nutrition, pharmaceuticals, medicine, and cosmetics.

The multifaceted benefits of flavonoids extend to promoting animal growth and development, as well as enhancing the quality of animal products (Ahmadipour *et al*., 2017). As an alternative to antibiotics, flavonoids are widely utilized as feed additives in animal production (Lee *et al*., 2017). Research indicates that incorporating flavonoids into ruminant diets can effectively reduce methane production without adversely affecting rumen microbial fermentation, fatty acid production, and the overall performance of beef or dairy cattle. Flavonoids contribute to the improvement of volatile fatty acid production while concurrently reducing rumen ammonia concentration and methane production, desirable alterations in the rumen environment. Consequently, there is significant interest in exploring the potential of these natural bioactive compounds to modify the ruminal microbial ecosystem and induce favorable changes in fermentation

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conditions such as pH, propionate concentration, and protein degradation (Broudiscou *et al*., 2002; Oskoueian *et al*., 2013).

In contemporary ruminant production, flavonoids, alongside other phenolic compounds, are increasingly employed as feed additives, reflecting their widespread acceptance and application (Seradj *et al.,* 2014; Paula *et al.,* 2016). Following absorption, flavonoids are transported to the liver, where they undergo transformation into glucuronide, sulfate, or methyl-conjugate compounds. The abundance of flavonoids, coupled with their low toxicity relative to other plant compounds, allows for their consumption in substantial quantities by both man and animals.

This review aims to;

- Evaluate the effect of flavonoids on diabetes mellitus.
- Examine the antioxidant and anti-microbial effect of flavonoids.
- Determine the impact of flavonoid on ruminant animal nutrition.

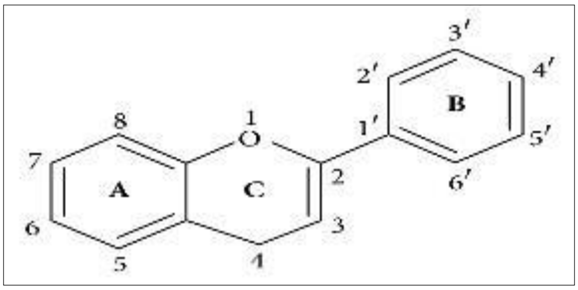

Figure 1 Basic Structure of a flavonoid

2. Sources and effects of processing on flavonoid contents

Flavonoids are present in a diverse array of fruits and vegetables, including cereals and legumes. Within the diet, quercetin and kaempferol stand out as the most prevalent flavonols found in fruits like blueberries, black currants, apples, dark grapes, apricots, onions, berries, broccoli, citrus fruits, cherries, tea, and capers. Leaves of these plants also contain smaller quantities of flavonoids. Notable examples of well-known flavonoids encompass quercetin, kaempferol, catechins, and anthocyanidins, with quercetin being the most abundant in dietary sources. On average, individuals are estimated to consume 10–100 mg of quercetin daily through various food items. These compounds fall within the category of low-molecular-weight phenolic compounds that are extensively distributed across the plant kingdom.

Flavonoids play a crucial role in both human and animal diets. As phytochemicals, they cannot be synthesized by humans and animals (Koes *et al*., 2005), meaning that the flavonoids found in animals originate from plants rather than being produced internally. Among the various classes of flavonoids, flavonols are the most prevalent in foods. These compounds in food are generally associated with several benefits, including a reduced risk of cancer, heart disease, asthma, and stroke.

- Colour
- Taste
- Prevention of fat oxidation
- Protection of vitamins and enzymes (Yao *et al.,* 2004).
- Flavonoids found in the highest amounts in the human diet include;
- Soy isoflavones
- Flavonols
- Flavones.

While catechins are present in most fruits and certain legumes, their concentrations range from 4.5 to 610 mg/kg (Arts *et al*., 2000). The levels of flavonoids can be influenced by the preparation and processing methods employed in food production. A recent investigation, for instance, revealed that orange juices contained soluble flavanones at levels ranging from 81 to 200 mg/L, while the content in the cloud portion was higher at 206–644 mg/L. This suggests that flavanones are more concentrated in the cloud; however, their levels may decrease significantly during processing and storage (Gil-Izquierdo *et al*., 2001). Accurately assessing the average dietary intake of flavonoids proves challenging due to the vast array of available flavonoids, their widespread distribution across various plants, and their diverse consumption patterns in humans (Tomás-Barberán and Clifford, 2000).

Table 1 Subclasses of flavonoids and their occurrence in foods

Flavonoid subclass	**Examples of compounds**	**Food source**	**References**
Flavonol	Kaempferol, quercetin, Myricetin, and tamarixetin	Onion, red wine, olive oil, broccoli apples, cherries, berries, and grape	Stewart, *et al.,* 2000
Flavones	Chrysin,apigenin Rutin,luteolin, glucosidestangeretin	Fruit skins, red wine, buckwheat, red pepper, tomato skin, Parsley, Thyme	Lopez, *et al.,* 2001; Kreft, *et al.,* 1999
Flavonones	Naringin, naringenin, taxifolin, and hesperidin	Citrus fruits, grapefruits, lemons, and oranges	Kreft, *et al.,* 1999
Flavanol	Catechin, epicatechin, epigallocatechin, proanthocyanidins	Apple, tea	Stewart, *et al.,* 2000
Anthocyanidins	Apigenidin, cyaniding, delphinidin, pelargonidin, malvidin	Cherries, easberry, strawberry, and Grapes	Stewart, *et al.,* 2000
Isoflavones	Genistein, daidzein	Soya beans, Legumes	Reinli and Block, 1996.

3. Benefits of flavonoids to livestock animals

3.1. Anti-microbial effect of flavonoids

Flavonoids could exert synergistic antimicrobial effects in the animal's digestive system or in meat when polyphenol administration is combined with low temperatures, low pH, and anaerobic conditions (Ahn *et al*., 2002). Flavonoids have shown inhibitory effects on Gram-positive as well as Gram-negative bacteria (Gadang *et al.,* 2008) and the mechanisms by which flavonoids can act as antibacterial are summarized in:

- Inhibition of nucleic acid synthesis
- Inhibition of cytoplasmic membrane function
- Inhibition of cell division development and differentiation
- Inhibition of energy metabolism
- Inhibition of protein synthesis

Flavonoid demonstrates inhibitory properties against certain pathogens including *E. coli*, *Salmonella typhimurium*, *Campylobacter*, *jejuni*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella enteriditis*, *Shigella flexneri*, *Shigella dysenteriae*, and *Vibrio cholera* (Gadang *et al*., 2008; Hamilton-Miller, 1995). The introduction of a natural flavonoid source, such as citrus fiber, has been shown to reduce counts of aerobic and lactic acid bacteria as well (Viuda-Martos *et al.,* 2010). Moreover, flavonoids can impact methane formation by disrupting or diminishing carbon or electron flow within the microbial food chain. This mechanism prevents the accumulation of hydrogen and promotes an increase in propionate at the expense of acetate and butyrate (Chen and Wolin, 1979).

3.2. Antioxidant effect of flavonoids.

The efficiency of vitamin E as an antioxidant is limited when animals are fed diets rich in polyunsaturated fatty acid such as n−3 (PUFA) (Allard *et al.,* 1997). Moreover, it has a pro-oxidant action when high doses are ingested, or in the absence of other antioxidants able to recycle the oxidized form of vitamin E (Mukai *et al.,* 1993). Hence, possibility of supplementing cattle diets with natural antioxidant compounds, alternative to vitamin E, as a means of improving beef quality requires investigation. Prior and Cao (2000) reported that the antioxidant capacities of many flavonoids are much stronger than those of vitamins C and E and, hence, supplementing ruminants with the compounds may be useful particularly when the animals fed diet rich in polyunsaturated fatty acids such as n-3 fatty acids which are highly susceptible to per oxidation in plasma and tissues (Gladine *et al.,* 2007).

3.2.1. Mode of action

The mechanisms by which the flavonoids can act as antioxidant are based on:

- Direct scavenging of reactive oxygen species (ROS)(Pietta, 2000)
- Activation of antioxidant enzymes (Nijveldt *et al.,*2001)
- Metal chelating activity (Ferrali *et al.,* 1997)
- Reduction of α-tocopheryl radicals (Heim *et al*., 2002)

3.3. Effect of flavonoids on diabetes mellitus

Insulin, recognized as a pivotal metabolic hormone produced in β-cells, plays a crucial role in maintaining glucose homeostasis (Fu *et al.,* 2013). It circulates in the bloodstream, exerting its effects on skeletal myocytes and adipocytes by facilitating glucose uptake through the membrane insertion of insulin-sensitive glucose transporter 4 (GLUT4). This, in turn, stimulates fuel storage in the liver, fat, and skeletal muscle (Amisten *et al*., 2013). The secretion of insulin is highly responsive to fluctuations in blood glucose levels (Tourkey *et al*., 2015). The initiation of insulin secretion in response to glucose occurs with an increase in intracellular ATP levels. Elevated ATP levels prompt the closure of ATP-sensitive K+ channels (KATP), leading to membrane depolarization. This depolarization, in turn, opens voltage-dependent Ca2+ channels, facilitating the influx of extracellular Ca2+ and triggering insulin secretion (Henquin, 2009; Bryan *et al*., 2005).

Meanwhile, silymarin, a flavonoid component derived from Silybum marianum, has been explored for its potential protective effects against apoptotic death of cardiomyocytes associated with diabetes in rats. Treatment with silymarin resulted in a notable reduction in immunoreactions for caspase-3 expression in diabetic rats, similar to the levels observed in the control group. The treated rats exhibited decreased levels of glucose, creatinine, AST, ALT, cholesterol, and triglycerides. Additionally, the diminished levels of insulin in diabetic rats were restored after silymarin treatment, indicating a rejuvenation of pancreatic cell activity (Tuorkey *et al*., 2015).

Furthermore, baicalein, a flavone component and type of flavonoid originally isolated from the roots of Scutellaria baicalensis, was investigated for its protective effects on both insulin deficiency (ID) and insulin resistance (IR) in male Wistar rats induced with fructose. Both ID and IR models resulted in elevated blood pressure, increased vasoconstriction, heightened tumor necrosis factor (TNF), marked leukocyte infiltration in the adventitia, pyknosis of endothelial cells, and substantial collagen deposition. Baicalein ameliorated elevated blood pressure in both models, prevented exaggerated vasoconstriction in the IR model, and improved relaxation in the ID model. Additionally, baicalein reduced TNF levels, inhibited activation, and mitigated histopathological changes in both models.

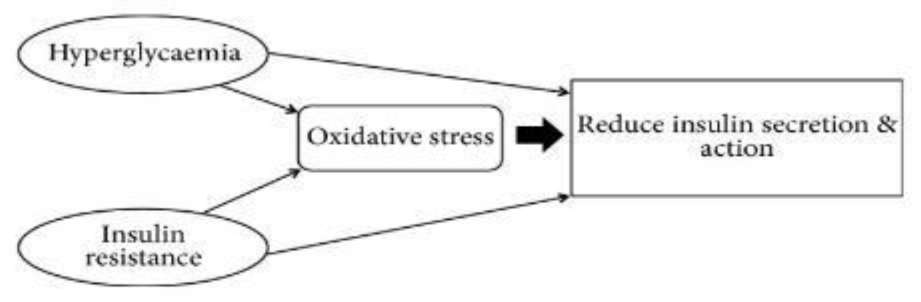

Figure 2 Relationship between hyperglycaemia, insulin resistance, and oxidative stress

3.4. Plants secondary metabolites as feed additive

The term "plant secondary metabolite" (PSM) refers to a category of chemicals found in plants that do not play a role in the primary biochemical processes related to plant growth and reproduction. Instead, these secondary metabolites serve as a protective mechanism for plants against insect predators or herbivores' grazing activities (Hartmann, 2007). Numerous studies have demonstrated the positive impact of PSM, including saponins, tannins, essential oils, organosulphur compounds, and flavonoids, on rumen microbial fermentation and alleviation of nutritional stress factors such as bloat or acidosis (Patra and Saxena, 2010). Additionally, these compounds have shown favorable effects on the productivity and health of animals (Rochfort *et al*., 2008). Wang *et al.* (2013) highlighted the suppressive effect of saponins on lactate-producing bacteria like S. bovis. Amlan and Yu (2012) conducted a review on the antimicrobial properties of essential oils (EO) and found that EO can increase pH values by reducing volatile fatty acid (VFA) production. This implies that EO suppresses fermentation, aligning with the antimicrobial activity of phenolic compounds such as thymol, carvacrol, and eugenol, attributed to the hydroxyl group in their phenolic structure (Burt, 2004).

Thus;

- Phenolic compounds disturb the cytoplasmic membrane
- Disrupting the proton motive force
- Electron flow active transport
- Coagulation of cell contents (Burt, 2004)

Have a broad spectrum of activity against a variety of both Gram-positive and Gram-negative bacteria. (Lambert *et al.,* 2001).

4. Impacts of flavonoids in ruminant animal nutrition

Recent advancements in ruminant nutrition research indicate that enhancing metabolic processes in the rumen for greater efficiency can be achieved through the use of natural feed additives, such as flavonoids (Paula, 2016; Lee *et al*., 2017). Desirable alterations in the rumen ecosystem involve improving volatile fatty acids production while concurrently reducing rumen ammonia and methane concentrations (Oskoueian, 2013; Bodas, 2012). Numerous studies have demonstrated the positive impact of flavonoids and other phenolic compounds, including saponins, tannins, essential oils, and organo-sulfur-containing compounds, on animal productivity, health, rumen fermentation, and the management of nutritional stress such as bloat and acidosis (Rochfort *et al.,* 2006).

Flavonoids, categorized as polyphenolic compounds, exhibit a mode of action similar to monensin and other antibiotics (Cushnie and Lamb, 2011; Yaghoubi *et al.,* 2008). Diets for high grain heifers supplemented with flavonoids demonstrated higher rumen pH values compared to the control group. This observed effect could be attributed to the beneficial impact of flavonoids in enhancing lactate-consuming microorganisms, such as M. elsdenii (Balcells *et al*., 2012

4.1. Control and prevention of acidosis

Acidosis refers to a pathological condition characterized by a decrease in alkali relative to acid (hydrogen ion) content in body fluids (Owens *et al.,* 1998). Rumen lactic acidosis occurs in sheep and cattle that consume substantial amounts of diets rich in quickly fermentable carbohydrates (Nocek, 1997). This leads to the excessive production of volatile fatty acids (VFA) and lactic acid, causing a decrease in rumen pH to non-physiological levels. Simultaneously, it weakens the buffering capacity of the rumen and diminishes the efficiency of rumen flora and fermentation. Lactic acidosis can result in various health issues, including ruminitis, metabolic acidosis, lameness, hepatic abscessation, pneumonia, and even death (Lean *et al*., 2000).

The acidotic process can be categorized into two forms: acute and sub-acute. Acute acidosis occurs with rapid grain overload and may lead to severe consequences such as the death of the animal, severe illness, and liver abscesses. Prolonged problems may cause damage to the ruminal wall, reduced absorption capacity, and depressed feed intake. Sub-acute acidosis is characterized by the prolonged pH drop below 5.0, where lactate-fermenting bacteria metabolize lactate to VFA rapidly. As the pH approaches 5.0 and stays below it for an extended period, the growth of lactate-fermenting bacteria is inhibited, leading to the accumulation of lactate. Sub-acute acidosis has the potential to progress to lactic acidosis if the pH of 5.0 is sustained (Nagaraja and Titgemeyer, 2007).

During an acidosis challenge, the suspension of lactic acid production becomes a critical point. S. bovis titers increase, reaching their maximum coinciding with the highest lactate concentrations. Research indicates that flavonoids, such as naringine, degrade to aglycone, forming naringein in the rumen (Gladine *et al.,* 2007c). Rumen microflora can further break down the aglycone ring into phenylacetic acid, an antimicrobial compound that may inhibit lactic acid-producing bacteria (Winter *et al*., 1989).

4.2. Effect on milk production

The utilization of flavonoids in animal diets can have a dual impact on both the rumen microbial ecosystem and the performance of ruminants. Generally, flavonoids have the potential to modify fermentation characteristics, as documented by various studies (Balcells *et al*., 2012; Ahn, 2002). Furthermore, they can function as antimicrobial agents, reducing the presence of pathogens and methane-producing bacteria. Additionally, flavonoids contribute to enhancing antioxidant content, thereby reducing lipid oxidation and improving the overall quality of milk and meat production (Oskoueian *et al.,* 2013; Seradj *et al*., 2014).

Incorporating moderate levels of flavonoids and polyphenols into the diets of animals, achieved through feeding them with sources rich in flavonoids and phytochemicals, presents a novel approach to increasing the flavonoid and polyphenol content in daily food for consumers (Kalantar *et al.,* 2018). Notably, studies have reported increased milk yield and lactation performance in dairy cows following the administration of silymarin in their feed (10 g/d), primarily composed of flavonolignans (Tedesco *et al*., 2004). It is well-documented that absorbed flavonoids can enter circulation, distributing across tissues and ultimately being excreted through the kidneys (Martin *et al.,* 1982). Another fate for absorbed flavonoids is the mammary gland, where they can be incorporated into the milk of lactating animals (Gonzales *et al*., 2015; Tedesco *et al.,* 2004). Previous research has highlighted the positive impact of various food processing waste and plant-origin by-products on the production and composition of milk (Seradj *et al*., 2014; Lee *et al*., 2017).

4.3. Flavonoids and their impact in rumen modulation

Commonly utilized feed additives in ruminant nutrition play a crucial role in regulating the end products of rumen fermentation, as emphasized by research studies (Oskoueian *et al*., 2013). The consumption of high-concentrate diets can lead to rumen fermentation dysfunctions, such as acidosis or bloat (Lee *et al*., 2017). Although dietary inclusion of monensin/antibiotics has been observed to reduce the incidence of rumen dysfunctions, the use of antibiotics as feed additives has been prohibited by the European Community since January 2006 (Seradj *et al*., 2014). Consequently, numerous alternatives to antibiotic therapies, including flavonoids, have been proposed as feed additives (Balcells *et al.,* 2012; Seradj *et al*., 2014; Lee *et al*., 2017). Given the antimicrobial properties associated with flavonoid extracts, various experiments have explored the impact of these extracts on rumen fermentation (Lee *et al*., 2017). The utilization of mixtures of plant flavonoids in continuous rumen culture systems has been shown to modify fermentation conditions, including pH, propionate proportion, and protein degradation. However, it's important to note that the results of these experiments were not consistently uniform across studies (Oskoueian *et al.,* 2013; Seradj *et al.,* 2014).

4.4. Metabolism and bioavailability of flavonoids in ruminants

Following absorption, flavonoids are transported to the liver, where they undergo conjugation to form compounds such as glucuronide, sulfate, or methyl-conjugates before being excreted through urine or feces (Ahmadipour *et al.,* 2015; Gonzales *et al.,* 2015). The absorption of catechin and epicatechin, as monomeric components of flavanols, is well-established in monogastrics (Kalantar *et al*., 2018). In contrast, ruminants exhibit the ability to derive antioxidant benefits from polymeric proanthocyanidins by metabolizing them into bioavailable compounds, with epicatechin retaining the intact flavonoid-ring structure (Gonzales *et al*., 2015; Spencer *et al.,* 2008). Several factors, including chemical structure, absorption rate, distribution level, and elimination, collectively determine the biological effects of flavonoids (Kalantar *et al.,* 2018; Gonzales *et al.,* 2015). Monogastrics demonstrate higher bioavailability of isoflavones and flavonols compared to other subclasses of flavonoids, while anthocyanins exhibit lower bioavailability in ruminants (Kumar and Pandy, 2013). On the other hand, proanthocyanidins have been observed to have higher bioavailability in ruminants than other subclasses of flavonoids (Kumar and Pandy, 2013; Seradj *et al*., 2014; Lee *et al.,* 2017).

4.5. Diminution of methane production

Efforts to mitigate the impact of methanogenic bacteria in the rumen on global warming have become a significant focus, with a high priority placed on moderating rumen microbial fermentation to reduce methane production through the application of feed additives (Seradj *et al.,* 2014; Bodas *et al*., 2012). The reduction in methane production is considered a valid indicator of inefficiency in rumen microbial fermentation (Oskoueian *et al.,* 2013; Seradj *et al*., 2014). Additionally, alterations in the volatile fatty acid (VFA) profile, such as an enhancement in the molar proportion of propionate at the expense of acetate, contribute to a decrease in CH4 synthesis (Bodas *et al*., 2012). It's noteworthy that methane (CH4) is a potent greenhouse gas with a global warming potential 25 times greater than that of CO2 (Seradj *et al*., 2014; Lee *et al.,* 2017). Previous reports have demonstrated that the addition of plant extracts rich in secondary compounds, including saponins, tannins, essential oils, and flavonoids, can effectively reduce rumen CH4 production (Patra and Saxena, 2010). Seradj *et al.* (2014) specifically showed that incorporating flavonoids like naringin and quercetin into ruminant diets could suppress methane production without influencing rumen microbial fermentation (Kumar and Pandy, 2013).

5. Conclusion

Flavonoids serve as widely utilized feed additives in animal production, primarily due to their antimicrobial and antioxidant properties. They possess the potential to influence rumen microbial activity, bringing about beneficial changes in fermentation conditions, including pH, propionate proportion, and protein degradation. Numerous studies have showcased the positive impact of flavonoids and poly-phenolic compounds on animal productivity, health, rumen fermentation, methane reduction, and the management of nutritional stress, such as bloat and acidosis. This present findings suggest that incorporating flavonoid rich compounds into the diets of ruminant and non-ruminant animals represents a novel approach to enhance flavonoid consumption, thus contributing to an improved performance and well-being of both man and animals.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there is no conflict of interest to be disclosed.

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