Review Article

Flavonoids: Health Promoting Phytochemicals for Animal Production-a Review

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Abstract | Flavonoids are phytochemicals derived from plants that known to possess several surprising health effects. They have been divided into several sub-classes, among those isoflavones (soy flavonoids) and flavanones (citrus flavonoids) have aroused great interest due to their immense availability and multidimensional properties. They exert their effects both as purified molecules and as plant extracts. Their well known properties includes anti-inflammation, antioxidation, antimicrobial, antiallergic and immunomodulation, have indicated both in animal and human models. Their modulatory role in several biological processes has also been identified like oxidation, detoxification of enzymes, apoptosis, host immune system and several others. Their potential to interfere with numerous cellular processes such as protection of genomic vitality suggest that flavonoids may used as dietary compounds for promotion of health and preclusion of several infectious and non-infectious diseases. They are known to enhance the gut morphology and functionality, mucosal and cellular immunity, immune organs size and amelioration of heat stress in farm animals; that suggested them health promoting phytochemicals for animal production.

Keywords | Animal Production, Flavonoids, Antioxidation, Immunomodulation, Gut

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WHAT ARE FLAVONOIDS

Phytochemicals are the substances found naturally in all fruits, vegetables and medicinal plants that, ingested daily or rarely, may exhibit a potential for modulating the human metabolism in a way favorable for the preclusion of chronic and degenerative diseases. These days, many studies are conducted on thousands of phytochemicals that may have important physiological and biochemical effects. Among phytochemicals, several compounds, including flavonoids, polyphenols, stilbenes, carotenoids and anthocyanins, are known to be important for a number of health promoting effects.

Flavonoids have aroused enormous interest in the preceding decade because of their multidimensional health effects on human and animal health, and omnipresence in the plant kingdom. They are called as "functional ingredients" and "health promoting biomolecules" in recent literature due to their potential role in promoting health and preventing chronic degenerative diseases (Nijveldt et al., 2001). These are polyphenolic compounds with a very little molecular weight based on a flavan moiety (i.e., 2-phenyl-benzo-γ-pyrane). The basic structure of bioflavonoids consists of three rings, two benzene rings that linked together through a third heterocyclic oxygen containing pyrane ring (Kuhnau, 1976). Flavonoids have been divided into several sub-classes based on their C-ring structure (Table 1); however, some of them are relatively important due to their universal occurrence in plant-based diets (Middleton et al., 2000). Over 8,000 different flavonoids have been identified, many of which occur in fruits, vegetables, grains, tea, coffee and wine (Croft, 1998).

BIOLOGICAL EFFECTS OF FLAVONOIDS

The flavonoids have shown to possess anti-inflammatory, antioxidant, antibacterial, antiviral, hepatoprotective, antiallergic, antithrombotic, anticarcinogenic and immunomodulator activities in a number of *in vitro* and animal model studies (Cushnie and Lamb, 2005). Their modulatory role in several biological processes has also been identified like oxidation, detoxification of enzymes, apoptosis, host immune system and several others. Their potential to interfere with numerous cellular processes such as protection of genomic vitality suggest that flavonoids may used as dietary compounds for the preclusion of cancer and chronic degenerative diseases (Tapas et al., 2008). Animal studies have declared that, flavonoids cause the inhibition of degranulation of mast cells, basophils and neutrophils. These could protect the rat brain from LPS (lipopolysaccharide) -induced shock through attenuation of lipid peroxidation and nitric oxide generation (Abd El-Gawad et al., 2001). Furthermore, they have shown improved biological actions upon combination with each other that indicates their potential to form synergisms (Alvarez et al., 2008). Research has indicated that plant flavonoids cause the activation of bacterial (Rhizobium) modulated genes involved in the management of nitrogen fixation, which suggests important associations between particular flavonoids and the expression of mammalian genes; however, the real contribution of such compounds in health maintenance and their potential for gene-nutrient interactions are still unclear. Epidemiological studies have also indicated that these phenolic compounds may play an important role in the health and preclusion of chronic dis orders (Nijveldt et al., 2001; Middleton et al., 2000). Recently, interest has been focused mainly on two large groups of flavonoids, i.e., soy flavonoids and citrus flavonoids.

Soy Flavonoids

Among edible plants, legumes, particularly soybean, contains an extensive amount of hormone-like phenolic agents called phytoestrogens. They fall under two main categories i.e., isoflavones (commonly called soy flavonoids) and lignans. Isoflavones, commonly known as soy flavonoids are a large and very distinct subclass of flavonoids family. It has several important members including genistein, daidzen, glyciten etc. Isoflavone are metabolized in the intestine to a biologically active mammalian metabolites with a weak estrogenic activity. These could strongly manipulate the host enzymes, protein synthesis, cell proliferation and differentiation, and angiogenesis (Knight and Eden, 1996; Magee and Rowland, 2004). Like flavonoids they have also antioxidative, anticarcinogenic and antimicrobial properties. They are also known to important for hormone dependent diseases like menopausal symptoms, cardiovascular disease, cancer, and osteoporosis. Substantial epidemiologic evidences have also indicated that high urine or plasma concentrations of isoflavone metabolites have a association with lower risk of cancer and heart diseases (Setchell and Cassidy, 1999).

The chemical structure of isoflavones is markedly similar to mammalian estrogen. On the basis of structure, it is not surprising that isoflavones bind to estrogen receptors; though, their effects are more those of partial estrogen agonists and antagonists. This concept attracts steroid biochemists and endocrinologists for use of isoflavones in hormone-related disorders (Mendelson, 1996). In addition to their classical genomic properties these have many nonclassical actions, including effects on cell signaling pathways and plasma membranes (Setchell, 2001).

Table 1: Main groups of flavonoids, the individual compounds, and food sources

Flavonoids sub-class	Commonly occurring compound	Main food source
Flavones	Apigenin, Sibelin, Chrysin, Rutin, Luteolin	Apple skins, Berries, Broccoli, Celery, Fruit peels, Cranberries, Grapes, Lettuce, Olives, Onions, Parsley
Flavonols	Isorhamnetin, Kaempferol, Myricetin, Quercetin	Nearly ubiquitous in all plant foods
Flavanones	Hesperetin, Fisetin, Narigin, Naringenin, Taxifolin, Neohesperidin, Neoeriocitrin	Citrus fruits and tomatoes
Isoflavones	Daidzein, Genistein, glyciten, Biochanin A, Formononentin	Soybean and soy foods
Flavanol	Catechin, Epicatechin, Epigallocatechin-3-gallate, Epicatechin-3-gallate	Teas, red grapes and red wines
Anthocyanins	Cyanidin, Delphinidin, Petunidin, Pelargonidin, Malvidin, Peonidin	Berries (blueberries, Red grapes, Strawberries)

[1] Anonynmous, (2014)

Citrus Flavonoids

Citrus flavonoids belongs to flavonoid sub-class flavanones. In nature, these are found in glycoside and aglycone forms. Among aglycone forms, quercetin, naringenin and hesperitin are the main flavonoids. Whereas, the glycoside forms can be further classified into rutinosides and neohesperidosides (Djoukeng et al., 2008). Neohesperidosides (e.g., naringin, neohesperidin and neoeriocitrin) contain a sugar neohesperidose (rhamnosyl-a-1, 2 glucose) and they are bitter in taste, while rutinosides (rutin, hesperidin and didymin) contain a disaccharide residue e.g., rutinose (ramnosyl-a-1,6 glucose) which makes them tasteless (Macheix et al., 1990).

Citrus flavonoids fall under the flavonoid subclass of flavanones and usually these are found in diglycoside form, that results the typical taste of citrus fruits (Macheix et al., 1990). Knowledge of citrus fruits is paramount to understand their role in human and animal health and it is well established that some of the nutrients in citrus promote health and provide protection against chronic diseases. Hesperidin, a well known citrus flavonoid is known to be very important for health maintenance. Insufficiency of this compound in the human diet has been linked with abnormal capillary leakiness as well as pain in the extremities causing aches, weakness and leg cramps (Simitzis et al., 2011). Several *in vitro* and *in vivo* experiments have indicate that citrus fruits could exhibit many health promoting activities including inhibition of initiation, promotion and hyperproliferation of cancer cells (De Leo and Del Bosco, 2005; Jayaprakasha et al., 2006). It has been estimated that health promoting effects of citrus juices derived from the interaction of several chemopreventive agents, including flavonoids and isoflavonoids; however studies evaluating the role of pure substances are still required.

INTERACTION OF FLAVONOIDS WITH OTHER COMPOUNDS

Recent literature has indicated that polyphenols and flavonoids could interact synergistically with other compounds like drugs (Alvarez et al., 2008), vitamins (Fujisawa et al., 2006) and with other flavonoids (Mikstacka et al., 2010). However, some of their interactions lead to antagonistic effects. These activity-related interactions (synergism, additive or antagonism) of flavonoids with other compounds and co-antioxidants have not fully elucidated yet, but it is generally recognized that, it depends upon the structures of the compounds and on the micro-environment of the reaction system (Fujisawa et al., 2006). A recent study has suggested that synergistic or antagonistic antioxidative effects depend upon concentration; low concentrations exhibit synergistic antioxidative effects while the high concentration demonstrates additive effects (Mikstacka et al., 2010), however, these observations need to be elucidated further for a firm conclusion. Some other recent studies have reported the synergistic effects of flavonoids for antioxidation (Mikstacka et al., 2010), platelet aggregation (Pignatelli et al., 2000), antimicrobial activity (Alvarez et al., 2008) and for enhanced quality and shelf life of meat (Kamboh and Zhu, 2013a). These studies have opened a new era of research for enhanced effects of phytochemicals and other compounds in reduced cost (in terms of low doses) to improve animal health and production.

GUT MODULATORY ACTIVITY OF FLAVONOIDS

In poultry, at the time of hatching the intestinal morphology is not yet fully developed and undergoes dramatic changes in the post-hatch period. It is estimated that villus surface area (villus height x villus width) increases in all regions until 3 days of age (Lan, 2004). Increased villus height or villus width suggests an increased surface area capable of greater absorption of available nutrients which regulate the nutritional status, improve development and health of the bird. On the other hand, short villi with deeper crypts may lead to deprived nutrient absorption and increased secretion in the gastrointestinal tract, resulting poor growth and performance (Awad et al., 2011). The crypt is known to be a villus factory and a large crypt indicates rapid tissue turnover and a high demand for new tissue. Intestinal epithelial cells originate at the base of the crypts as immature proliferative cells, differentiate and migrate along the villus surface upward to the villus tip, and are finally extruded into the intestinal lumen (Hu and Guo, 2007). Though, the data on the effects of purified flavonoids on histological morphometry of the small intestine is very scarce. But in recent studies, several researchers have reported the gut promotory effects of herbal plants containing adequate amounts of flavonoids in several species of farm animals and poultry; and suggested the antioxidant polyphenols as an important tool to modulate the functional architecture of the small intestine (Awad et al., 2011; Viveros et al., 2011). Some more recent studies have declared that purified flavonoids genistein and hesperidin (Kamboh and Zhu, 2014) and flavonoids-rich fermented Ginkgo biloba leaves (Zhang et al., 2014) could promote the intestinal morphology and absorptive function in growing broilers. Interestingly, while both studies indicated the potential of flavonoids to minimize the deleterious effects of LPS and improved intestinal development in immune-stressed chickens. Likewise, another study suggested the spasmogenic effects of *Berberis lycium* in rabbits and guinea pigs; and suggested its use to modulate gut environment to control diarrhea, intestinal cramps and other gastrointestinal disorders in animals (Shafeeq-ur-Rahaman et al., 2013). The exact mechanism by which these polyphenols modulate the intestinal architecture is not known, but it is hypothesized that morphometric improving effects might be the protective effect of these compounds of pro-apoptotic oxidant stress to gut epithelial cells (Miller et al., 2001) or modulating the intestinal microflora that play an instructive role in the regulation of villus morphology (Hooper et al., 2001).

ANTIOXIDATIVE ACTIVITY OF FLAVONOIDS

All aerobic organisms, including human beings generate free radicals and other reactive oxygen species like hydroxyl radical (OH•), the superoxide radical (O_2•), the nitric oxide radical (NO•) and the lipid peroxyl radical (LOO•) under certain conditions (Rong and Zeyuan, 2004). These are the by-products of normal processing of oxygen in the body that we breathe and the food we eat. Environmental pollutants, industrial chemicals, ultraviolet light and exercise also contribute to the production of free radicals in the body (Mojzisova and Kuchta, 2001). The process by which these radical damage the cellular structures are not fully understood, but it is generally recognized that cellular damages cause a change in the net charge of the cell, thus chang the osmotic pressure of the cell that lead to swelling and ultimate death of cell. Furthermore, free radical attract various inflammatory mediators that lead to inflammation and tissue damage (Nijveldt et al., 2001).

In order to protect from ROS, living organisms endowed with extensive antioxidant defense mechanisms to neutralize the damaging effects of toxic oxygen species. These include enzymes such as superoxide dismutase, glutatione peroxidase and catalase; and some non-enzymatic counterparts like glutathione, ascorbic acid, and α-tocopherol (Mikstacka et al., 2010). However, when the balance between ROS and antioxidants is altered, a state of oxidative stress appeared, that possibly lead to permanent cellular damages. There is growing evidence that oxidative stress is the causative agent in a number of human and animal diseases, such as chronic inflammatory disorders, cancer, atherosclerosis, ischemic injury, aging, and neurodegenerative diseases (Kamboh, 2012). Reparative processes may not completely eliminate the damage of biological macromolecules. A much more effective way is the prevention, such as decreasing of sources that cause free radical formation, and strengthening of the natural antioxidant mechanism by using antioxidative agents. For this reason, special attention is paid to the search of agents with powerful antioxidant potential (Mojzisova and Kuchta, 2001).

The best described property of almost all flavonoids is their antioxidative activity, which reported far exceeds that of well-known antioxidant vitamins (C and E) and carotenoids in *in vitro* and *in vivo* studies (Middleton, 1996). These are known to scavenge or inhibit the production of several kinds of free radicals and reactive oxygen species, which are the major cause of autoimmune and chronic inflammatory diseases in humans and animals like pulmonary hypertension syndrome (also called ascites) of broilers (Iqbal et al., 2002). Studies in broilers have declared that isoflavone and flavanone could improve the plasma antioxidant status of growing chickens (Kamboh and Zhu, 2013b) and also modify the biomarkers of heat-stress towards the positive direction (Kamboh et al., 2013) probably due to their quenching action on free radical and ROS generated by heat stress. Some other studies in laboratory and farm animals have indicated that bioflavonoids could reduce the oxidative stress; thus could improve the performance of farm animals (Abd El-Gawad et al., 2001; Hager-Theodorides et al., 2014).

Flavonoids inhibit oxidation through a variety of mechanisms and their protective effects in biological systems are ascribed to their capacity to transfer free radical electrons, chelate metal catalysts, activate antioxidant enzymes, reduce alpha-tocopherol radicals and inhibit oxidases (Middleton et al., 2000; Nijveldt et al., 2001). Recent work has suggested that the cellular effects of flavonoids may be mediated by their interactions with specific proteins that are central to some intracellular signaling cascades. In particular, flavonoids may act selectively with different components of protein kinase signaling cascades, like asphosphoinositide 3-kinase, protein kinase C, Akt/protein kinase B and etc,. (Hou and Kumamoto, 2010).

IMMUNOMODULATORY ACTIVITY OF FLAVONOIDS

All vertebrates possess the well defined immune system that protect the host from infectious agents present in the environment (e.g., viruses, bacteria, fungi) and from other deleterious insults. Dietary phytochemicals with antioxidant properties such as flavonoids are known to improve the immune response in all taxa of vertebrates. The dietary polyphenols not only stimulate the immune system but also cause the modulation of detoxification enzymes, scavenging of oxidative agents and regulation of gene expression in cells (Catoni et al., 2008). The effect of soy (Sakai and Kogiso, 2008) and citrus fruits (Silalahi, 2002) on the different constituents of humoral and cellular immunity has been reviewed recently. Evidences suggested that epigallocatechin gallate and cyanidin glycosides rich juices could enhance the IL-2 secretion, lymphocyte proliferation and lytic activity of NK cells (Bub et al., 2003). A mini review by Chen and coworkers indicated that intake of flavonoid-enriched purple sweet potato leaves could produce a significant increase in proliferation responsiveness of peripheral blood mononuclear cells with enhanced secretions of immunoreactive IL-2 and IL-4 cytokines. As well, increased lytic activity in NK cells and salivary IgA secretion was also observed (Chen et al., 2005). The mechanisms underlying this phenomenon are not fully understood, but it is generally hypothesized that the intake of antioxidants may reduce the harmful effects of free radicals and ROS on the immune response that results the better performance of the immune system (Sakai and Kogiso, 2008).

Several animal studies also supporting that polyphenols and flavonoids are immune cocktails. In a mice study, it was observed that berry juice could increase the splenic weight and the number of splenic macrophages. There was a corresponding increase in splenic phagocytic cells with increasing doses of juice (Chao et al., 2004). In mouse tumor model, antitumor effects of grape seed proanthocyanidins were observed via the immunomodulatory mechanism. The study suggested that proanthocyanidins could increase the splenic lymphocyte proliferation, CD4+/CD8+ ratio, NK cell cytotoxicity, IFN-γ and IL-2 productions

(Zhang et al., 2005). Plum, a flavonoid-rich fruit (contains 118 to 237 mg/100g) has been documented for its immune enhancing effect. In chicken study challenged with *Eimeria acervulina*, it was observed that plum powder reduced the fecal oocyst shedding, and increased the levels of mRNAs for IL-15 and interferon-γ. Furthermore, chickens fed plum diets exhibited significantly greater spleen cell proliferation (Lee et al., 2007). A recent study has demonstrated that citrus and soy flavonoids could significantly improve the immunity of LPS-challenged broilers. The study suggested the use of plant flavonoids as a feed additive to ameliorate the negative effects of circulatory low dose endotoxaemia on animal production (Kamboh and Zhu, 2014). Another study, addressed the IgY enhancing effects of supplemental quercetin in growing broilers, that obviously indicated the potential of quercetin to promote mucosal immunity (Hager-Theodorides et al., 2014).

CONCLUSION

It has been estimated that free radicals and ROS are involved in the etiology of several human and animal diseases and also responsible for the significant reduction in animal production. Evidences have suggested that phytochemicals especially the flavonoids could reduce the oxidative stress at the cellular level, thus can improve the genomic stability and cellular integrity. These flavonoids also known to improve immunity and gut function that ultimately reduce the risk of infectious diseases and increase animal performance. Moreover, these could produce the syngerisms with each other and other organic and synthetic growth promoters. Hence, these flavonoidal compounds, both in purified and phytoextracts–form could be the potential candidates to improve the production of farm animals.

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