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Review Article

INTERACTIONS OF PLANT BIOACTIVES WITH NUTRIENT TRANSPORT SYSTEMS IN GUT OF LIVESTOCK

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Research on natural plant secondary compounds (PSC) has gained widespread impetus for use as feed additives to improve production performance, welfare and health of livestock and poultry due to their antimicrobial, antioxidant, immunostimulatory and other beneficial biological effects. Moreover, various PSC are usually present in regular diets of animals and humans. Dietary PSC may regulate absorption of nutrients, minerals and ammonia via transcellular and paracellular routes in the gastrointestinal (GI) tract influencing nutrient transporter gene expression and molecular structures of tight junctions. Some PSC stimulate nutrient absorption, while other PSC may impair transport mechanisms in the intestine interacting with nutrient transporters of enterocytes and tight junction motifs and their regulatory proteins. One challenging aspect is to select an effective dose at which a specific PSC could improve GI nutrient absorption while preserving or improving other beneficial biological effects. The optimum doses and precise molecular mechanisms for PSC are yet to be identified to understand discrepant observations among different studies and to improve the targeted biotechnological and pharmaceutical uses of PSC in farm animals. This review discusses the effects of different PSC on nutrient transport and permeability of GI epithelia and their mechanism of actions focusing mainly on livestock species.

Key words: Gastrointestinal tract, Ion channel, Nutrient absorption, Permeability, Plant secondary compound

Herbs or their plant secondary compounds (PSC) have gained extensive research interests in recent years for use in livestock and poultry as an alternative to antibiotic feed additives (Windisch *et al.*, 2008; Patra and Saxena, 2009a,b; Pathak *et al.*, 2016; Chowdhury *et al.*, 2018). Many PSC are also normally present in diets of animals and humans. Several medicinal plants or plant-derived natural bioactive molecules

had been used for millennia for prevention and cure of many diseases, which are widely explored recently as antimicrobial agents and potent drug substances (Patra, 2012; Gechev *et al.*, 2014; Atanasov *et al.*, 2015). There are more than 350,000 PSC identified in several broad classified groups including alkaloids, glucosinolates, saponins, terpenes, flavonoids and phenylpropanoids (Wink, 2003; Patra and Saxena, 2010; Patra, 2012). Only few of them have been evaluated for their antimicrobial actions, stimulating effects on the digestive enzyme secretion, modulatory effects on ruminal microbial fermentation, antioxidant properties and various pharmacological effects in livestock animals (Windisch *et al.*, 2008; Patra and Saxena, 2010, 2011; Patra and Yu, 2015; Sar *et al.*, 2015; Kumar *et al.*, 2017.)

Dietary PSC can also modulate the gastrointestinal (GI) integrity and health, and consequently modulate the nutrient transport and barrier functions in the GI tract (Patra *et al.*, 2018a). The GI tract is inhabited by several trillion of commensal microbes in animals and humans, and they take part in the molecular crosstalk with the GI epithelial signaling pathways influencing GI health and barrier function (Wells *et al.*, 2010; Ulluwishewa *et al.*, 2011). Although the PSC are specifically applied to inhibit the growth of pathogenic microbiota in the GI tract, they may impart in many other beneficial biological roles. In fact, many PSC have shown promising in livestock animals to improve growth performance, to inhibit growth of pathogenic microorganisms in the intestine, to boost immunity, and to mitigate methane production and to improve quality of livestock-derived food products, which have been reviewed elsewhere (Windisch *et al.*, 2008; Patra, 2014; Patra and Saxena, 2010; Kumar and Patra, 2017; Alagawany *et al.*, 2018). Dietary PSC may potentially regulate nutrient transport mechanisms in the GI tract. The present review delineates the effects of different PSC on nutrient transport and their molecular mechanisms in the GI tract of farm animals.

Physiology of nutrient transport systems in gut

The mucosal surface of the GI tract is lined by a single layer of tightly connected columnar epithelial cells that segregate lamina propria from the intestinal lumen (Ulluwishewa *et al.*, 2011). The intestinal epithelial cells are primarily composed of over 80% absorptive enterocytes along with goblet, Paneth and enteroendocrine cells (Ulluwishewa *et al.*, 2011; Peterson and Artis, 2014). The mucosa performs nutrient absorption and waste secretion, and forms a highly dynamic barrier between the adverse external milieu of the lumen and the internal submucosal tissue in the intestine (Turner, 2009; Ulluwishewa *et al.*, 2011). This function requires a selectively permeable barrier permitting the passage of nutrients, ions, minerals, water and preferred antigens, but restricting the entry of pathogens (bacteria, viruses and antigenic substances) and toxins, consequently modulating the epithelial nutrient transport and barrier function in the intestine (Ulluwishewa *et al.*, 2011).

Epithelial cells of the GI tract are tightly fastened at paracellular interfaces by intercellular junctional complexes, which are essential for regulation of paracellular permeability and preservation of barrier function (Turner, 2009; Ulluwishewa *et al.*, 2011; Suzuki and Hara, 2011; Kosiñska and Andlauer, 2013). The intercellular junctional complexes, which are comprised of different protein motifs including tight junction (TJ), adherens junctions, gap junctions and desmosomes, maintain paracellular permeability interacting with cellular cytoskeleton (Turner, 2009; Ulluwishewa *et al.*, 2011). The molecular structures of the junctional assembly are greatly dynamic, which are continually modified by various regulatory proteins depending upon the interactions with outside luminal stimuli including pathogenic and commensal microbiota, toxins and food residues (Ulluwishewa *et al.*, 2011).

There are two pathways by which nutrients and other solutes can pass through the epithelial membrane: (1) the paracellular pathway, where passive diffusion of solutes occurs through water-filled pores of the TJ between the cells, and (2) the transcellular pathway, where nutrients essentially penetrate the enterocyte cell membranes. The TJ regulate passive movement of hydrophilic solutes including microorganisms, toxins and antigenic substances across the GI epithelium through the paracellular pathway (Ulluwishewa *et al.*, 2011). Paracellular permeability has to be specifically regulated allowing nutrient movements while excluding the entry of pathogenic microorganisms and antigenic substances through the tight junctions. The absorption of nutrients through paracellular route is considered to be passive for hydrophilic solutes that cannot be transported via transcellular pathways, and thus requires increased TJ permeability, a high concentration of intralumenal nutrients, and a sufficient osmotic gradient to drive flow of fluid. However, the surface area for paracellular pores is very less constituting of 0.01%-0.1% of the total intestinal membrane surface area (Nellans, 1991). The transcellular pathway allows movements of molecules both passively and actively across the epithelial cell membranes, usually using specific transport or channel proteins (Turner, 2009). The transcellular transport is needed for efficient absorption and secretion of nutrients and ions and additionally creates a transepithelial concentration gradient to induce paracellular transport of nutrients, electrolytes and water passively (Clayburgh *et al.*, 2006; Turner, 2009). Transcellular active nutrient absorption is mediated by transporter proteins expressed on enterocytes.

There are many transporter proteins for different nutrient absorption in different animals. For example, glucose absorption across the apical surface of the enterocytes is mediated primarily by the Na^+-dependent glucose (also transports galactose) transporter 1 (SGLT1; a major intestinal glucose transporter) that is encoded by *SLC5A1* gene, whereas glucose and fructose

transport across the basolateral side of enterocytes and into the blood circulation is mainly mediated by the facilitated transporter Na^+-independent glucose transporter 2 (GLUT2), which is encoded by *SLC2A2* (Röder *et al.*, 2014; Williams *et al.*, 2017). GLUT2 transporter is also localized at apical side of enterocytes and can also transport fructose, galactose, mannose and glucosamine. Fructose can also be transported by GLUT5 at the apical side of the cells.

Amino acids are absorbed in their free forms by different specific amino acid transporters or as di- and tripeptides by the peptide transporter (e.g., PEPT1) in different animals and humans. Amino acid transporters usually have substrate specificities. For instance, absorption of basic amino acids is mediated by BAT and Na^+-independent cationic and zwiterionic amino acid transporter ($b^{o,+}AT$), Na^+-independent cationic amino acid transporter 1 (CAT1) and CAT2, Na^+-independent cationic and Na^+-dependent neutral amino acid transporter 1 (y^+LAT1) and y^+LAT2 transporters, neutral amino acids by B^oAT and LAT1, and anionic amino acids by excitatory amino acid transporter 3 (EAAT3) and there are some overlaps in substrate specificities in these transporters (Gilbert *et al.*, 2008; Mastrototaro *et al.*, 2016).

Effect of PSC on nutrient transport proteins

Various PSC interact with nutrient transporters that may be stimulated or inhibited resulting in modulations of absorption of nutrients and drugs across GI tracts. The influences of PSC on transcellular nutrient transport mechanisms in the GI tract in farm animals are scanty. In a study with nematode (*Ascaris suum*) infected pigs, cinnamaldehyde was added to a diet at 1 g/Kg diet or orally dosed with 1 g/d on 11 and 13 day post-infection (Williams *et al.*, 2017). Cinnamaldehyde supplemented with the diet, but not oral dosing of cinnamaldehyde, increased mRNA expressions of *SLC5A1* and tended to increase the expression of *SLC2A2*. A recent nutrient uptake measurement study in Ussing chambers using epithelia obtained from sheep supplemented with menthol-based PSC (at 80 and 160 mg/d) showed that Na^+-independent glucose and methionine uptakes were increased from the rumen, but not from the intestine of sheep receiving the menthol-based PSC; whereas menthol did not affect Na^+-dependent uptakes of glucose and methionine from rumen and intestine (Patra *et al.*, 2018b). Genistein (a isoflavone present in soyabean) added to milk replacer (fed to piglet at dose rate of 360 mL/Kg body weight) at 1 or 14 mg/L did not influence glucose or glutamine absorption in jejunum and ileum of piglets, which was measured by the change in short-circuit current (I_{sc}) induced by the addition of either 10 mM of glucose or glutamine to the luminal buffer in Ussing chambers (Chen *et al.*, 2005). Genistein, however, reduced enterocyte proliferation and migration in the small intestine (Chen *et al.*, 2005). Zhang *et al.* (2013) conducted a study to investigate the fermented or

non-fermented *Ginkgo biloba* leaves on *SGLT1* expression in duodenum with or without exposure to lipopolysaccharide (a stimulator of the intestinal immune system and present in the membrane of all gram-negative bacteria) in broiler chickens. Ginko leaves are rich sources of bioactive flavonoids, polysaccharides and terpenoids. Expression of *SGLT1* was not affected by fermented or unfermented *G. biloba* leaves in broiler chickens without lipopolysaccharide-challenge, but fermented leaves decreased the *SGLT1* expressions in lipopolysaccharide-challenged chickens compared with the control or non-fermented leaves (Zhang *et al.*, 2013). From the overall results of this study, it was suggested that dietary fermented *Ginko* leaves may be useful for chickens, especially in the presence of stress, which can be partially ascribed to the immunomodulatory effect of flavonoids and polysaccharides of fermented leaves on maintaining Th1/Th2 balance in response to extracellular pathogens (Zhang *et al.*, 2013).

In contrast to the stimulating effects on nutrient transporters, some PSC may inhibit the active transport of nutrients. Polyphenols are known to interact directly with glucose transporters to regulate the rate of glucose absorption. With *in vitro* cell culture study, for example, an anthocyanin (a flavonoid compound)-rich berry-extract (0.125%, w/v) reduced sodium-dependent as well as sodium-independent (facilitated uptake) glucose uptake by human intestinal Caco-2 cells, which was accompanied by down-regulation of *SGLT1* mRNA and *GLUT2* mRNA expression (Alzaid *et al.*, 2013). Capsaicin decreased Na^+-dependent methionine uptake in rat intestinal epithelial cells (IEC-6) *in vitro*, which was reported due to downregulation of sodium-coupled neutral amino acid transporter 2 *(SNAT-2)* mRNA levels and its SNAT2 protein at the apical membrane (Talukdar *et al.*, 2016). Tomato seed saponin, tomatoside A (10 ìM for 3 h) reduced glucose transport by 46% in human intestinal Caco-2 cells, which was supported by decreased expression of *GLUT2*, but there was no change in the expression of *SGLT1* (Li *et al.*, 2018). In this study, lower glucose uptake by tomatoside A was ameliorated by a protein kinase C inhibitor suggesting suppressed *GLUT2* expression via PKC signaling in Caco-2 cells.

Green tea polyphenols competitively inhibited the *SGLT1* transport protein with greater inhibitory effects of epicatechin gallate in small intestinal brush-border membrane vesicles of rabbits (Kobayashi *et al.*, 2000). In an Ussing chamber study using jejunal and ileal epithelia of pigs, a non-flavonoid polyphenol *trans*-resveratrol (0.3 mM) and ε-viniferin (0.3 mM) reduced glucose uptake (Guschlbauer *et al.*, 2013). In a further detailed study, apical addition of *trans*-resveratrol (0.3 mM) decreased Na^+-dependent glucose and alanine transport in the jejunum and ileum of pigs which was associated with phosphorylation of *SGLT1* and kinases because resveratrol increased the phosphorylation of *SGLT1*, protein kinase A substrates and AMP-

activated protein kinase (Klinger and Breves, 2018). SGLT1, PEPT1 and phosphorylated Na^+/H^+-exchanger 3 did not change due to resveratrol in this study. Authors suggested that greater cAMP levels are likely a part of the mechanisms affecting the nutrient transport. Quercetin-3-O-glucoside decreased Na-dependent glucose uptake in a dose dependent and competitive manner, but did not affect L-leucine uptake into porcine jejunal brush border vesicles, which suggested a specific inhibition of SGLT1 by the quercetin glucoside (Ader *et al.*, 2001; Cermak *et al.*, 2004). In addition, quercetin-3-O-glucoside also reduced the Na-independent glucose uptake. Among other flavonoids tested (quercetin-4-O-glucoside,-3-O-galactoside, -3-O-glucorhamnoside and aglycone quercetin, naringenin-7-O-glucoside, genistein-7-O-glucoside and cyanidin-3,5-O-diglucoside), only quercetin-4-O-glucoside inhibited Na-dependent glucose uptake into vesicles in this study (Cermak *et al.*, 2004). Thus, dietary quercetin monoglucosides are competitive inhibitor to intestinal nutrient transporters such as SGLT1, possibly interacting the glucose moiety with the sugar binding site of the transporter (Cermak *et al.*, 2004; Guschlbauer *et al.*, 2013). In ruminants, quercetin glucoside may be deglycosylated by ruminal microorganisms, which would then show less inhibitory effect on glucose uptake in rumen and intestine. Nevertheless, flavonoid aglycones may also showed inhibitory effect on GLUT2 transporter as shown in a Caco-2E cell culture study (Kwon *et al.*, 2007). Dietary PSC may also interact with mineral absorption in the intestine. As for example, oral administration of quercetin to rats decreased iron absorption in the duodenal mucosa and also the mRNA expression levels of iron transporters such as divalent metal transporter 1 (DMT1) and ferroportin (Lesjak *et al.*, 2018). When interpreting the negative effects of resveratrol and quercetin on specific nutrient transport functions, it needs to be considered that resveratrol otherwise improved overall gut functionality by upregulating tight junction gene expression, reducing heat shock protein gene expression and permeability in heat-stressed broiler chickens (Liu *et al.*, 2016; Zhang *et al.*, 2017). Thus, the selection of a PSC for practical use in feed and pharmaceutical industries should thus consider the whole portfolio of expectable effects (Patra *et al.*, 2018a).

Effect of PSC on permeability of nutrients

As pointed out before, permeability of the paracellular pathways is highly regulated by the TJ, which comprises of many proteins including claudins, occludin, and cadherins (Turner, 2009). Tight junctions are also controlled by other peripheral proteins (i.e., zona occludens), actomyosin ring and regulatory protein kinases (Turner, 2009; Ulluwishewa *et al.*, 2011). Many studies have shown that PSC affect claudins, occludin, zona occludens and various regulatory kinases (Patra *et al.*, 2018a), which can modify TJ functions and in turn permeability of nutrient via paracellular route (Suzuki, 2013). The transepithelial

electrical resistance (TEER) in Ussing chamber studies indicates mainly paracellular permeability to ions with higher TEER values being associated with decreased GI permeability (Wijtten *et al.*, 2011). Feeding of broiler chickens with dietary thyme essential oil (0.5 g/Kg diet for 35 days) increased TEER values in the intestine (Placha *et al.*, 2014). Placha *et al.* (2015) observed that lower concentrations of sage essential oil (0.1 and 0.25 g/Kg) increased TEER values while high concentration (0.5 and 1 g/Kg diet) had opposite effect, which suggests that an optimum dose is important to obtain targeted effects.

In passive transcellular transports, solutes penetrate the apical membrane, which is followed by diffusion through the cytoplasm of the cell interior and the solute exits through the basolateral membrane of enterocytes. There is very less study how PSC affect passive transcellular transports. In a study by Sun *et al.* (2015), an essential oil mixture (60 mg/Kg diet for 24 days) containing thymol (25%) and carvacrol (25%) was fed and the authors investigated the transcellular permeability to propranolol in mucosal-to-serosal direction, while permeability to rhodamine 123 was assessed in serosal-to-mucosal direction. This mixture reduced the increase of passive transcellular permeability to propranolol (mucosal-to-serosal) caused by *C. perfringens* infection. However, no effect on the transcellular flux of the P-glycoprotein substrate rhodamine 123 (serosal-to-mucosal) was noted (Sun *et al.*, 2015).

Several studies have also investigated the effects of PSC when applied acutely to tissues or cells. In an Ussing chamber study, short circuit current (I_{sc}) indicates an active ion transport and provides an evidence of electrolyte-dependent absorption of glucose and amino acid in the GI tract (Wijtten *et al.*, 2011). In the Ussing chamber study of Boudry and Perrier (2008), thymol or cinnamaldehyde added to the mucosal compartment increased I_{sc} in the jejunal mucosa of piglets in a dose-dependent manner with doses ranging 10 to 100 µM indicating increased ion transport due to these essential oil, but TEER values were not affected. It was also noted that thymol effect on I_{sc} was inhibited in low Cl^- buffer and HCO_3^--free buffer and abolished in low Cl^-/HCO_3^--free buffer (Boudry and Perrier, 2008). Genistein did not influence carbachol or serotonin-induced Cl^- secretion in jejunum and ileum of piglets as measured by the change in I_{sc} induced by the addition of either 0.1 mM of carbachol or serotonin to the serosal buffer in Ussing chambers (Chen *et al.*, 2005).

Effect of PSC on ion channels

A number of transient receptor potential (TRP) channels (e.g., TRPM6, TRPM7, TRPV3, TRPV4 and TRPA1) are expressed in ruminal and intestinal epithelia of cattle and sheep (Rosendahl *et al.*, 2016; Schrapers *et al.*, 2018). These TRP channels are involved in transport of mono and divalent cations across epithelia of rumen and intestine. For example, NH_4^+, Na^+, K^+ and Ca^{2+} are transported across ruminal

epithelia through cation-selective TRPV3 and TRPA1 channels (Rosendahl *et al.*, 2016; Schrapers *et al.*, 2018). Evidence also suggests that TRPV5 and TRPV6 are involved in intestinal transport of Ca^{2+} (Dimke *et al.*, 2011) and TRPM6 and TRPM7 are involved in intestinal and ruminal transport of Mg^{2+} (Dimke *et al.*, 2011; Martens *et al.*, 2018).

There is growing evidence that PSC can modulate TRP channels. For instance, Rosendahl *et al.* (2016) investigated the effects of cinnamaldehyde, menthol, thymol, and capsaicin on ruminal TRP channels and uptake of NH_4^+ in the ruminal epithelium. In ovine epithelia, menthol added apically in Ussing chamber at 10 and 100 µM reduced Ca^{2+} flux from serosal to mucosal side (efflux), but tended to increase Ca^{2+} flux from mucosal to serosal side (influx) with net absorption of Ca^{2+}. Menthol at high concentration (1000 µM) did not influence influx of Ca^{2+}; but increased efflux with a net decline of Ca^{2+} absorption (Rosendahl *et al.*, 2016). Thymol at low concentrations (10 and 100 µM) had no noticeable effects on influx, efflux or net flux of Ca^{2+}, but at high concentration (1000 µM) increased both influx and efflux with net decline of Ca^{2+} absorption. In this study, menthol (200 and 1000 µM) increased the uptake of NH_4^+, but cinnamaldehyde (1000 µM) and capsaicin (100 µM) decreased NH_4^+uptake; whereas thymol (200 and 1000 µM) did not affect NH_4^+ uptake in bovine ruminal epithelia (Rosendahl *et al.*, 2016). In a patch-clamp technique study using bovine TRPV3-overexpressed HEK-293 cells, apical application of menthol, thymol and carvacrol at 1000 µM enhanced whole cell currents mediated by Na^+, NH_4^+ and K^+, with an increase in intracellular Ca^{2+} concentration in response to menthol (Schrapers *et al.*, 2018). Together, these results suggest that some essential oils could modulate activity of TRP channels acting as either agonists or antagonists depending upon concentrations and type of PSC, which consequently may affect the fluxes of various mono- or -divalent cations across the intestinal and ruminal epithelium.

Conclusions

Numerous PSC have been investigated for their use as feed additives, but only few of them have been evaluated for nutrient transport functions in the GI tract of farm animals. Dietary PSC may inhibit pathogenic microorganisms in the intestine, and improve GI epithelial barrier, they could simultaneously regulate nutrient absorption from rumen and intestine both positively and negatively depending upon the type of PSC and their doses. Therefore, there are challenges to select an effective dose at which a specific PSC could inhibit pathogenic microbial growth considerably while preserving or improving GI functions including nutrient and ion transports. A precise mechanism and an exact target site of action of the PSC at the molecular levels need to be unraveled to better understand the transport functions in the rumen and intestine for their applications in livestock feed formulation.

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