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Impact of berberine on human gut bacteria

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Introduction

A recently published paper in *Nature* [1] stated that 27% of 835 non-antimicrobial drugs have a significative impact on gut microbiota. It is likely that a similar or greater proportion of botanicals have comparable effects. For instance, we know that curcumin increases the abundance of butyrate-producing bacteria and faecal butyrate level [2]. This could explain why, despite its very poor oral bioavailability, curcumin acts as an anti-inflammatory agent and why it is a promising therapeutic option for the treatment of inflammatory bowel disease. Berberine is another excellent example of a botanical which acts by modulating the microbiota. Knowledge of the mechanism by which berberine modulates the microbiota could lead to better understanding of the role of berberine in metabolic diseases.

Berberine

Berberine is an intensely yellow, bitter isoquinolone alkaloid found in several plants, including *Berberis aristata* and *Berberis vulgaris*. The impact of berberine on glucose and lipid metabolism has been extensively studied. It has a very low oral bioavailability of approximately 1% due to its poor solubility and the presence of P-glycoprotein (P-gp) in the human intestine, which expels, through an ATP-consuming process, the alkaloid into the gut lumen [3]. The co-administration of P-gp inhibitors, such as silymarin, enhances the effect of berberine [4].

Glucose regulation by berberine

AMPK plays a key role in regulating cellular and whole-body energy homeostasis. As shown in Figure 1, berberine's effects on glucose metabolism are partially due to its activation of AMPK [5]. In a mouse model of diabetes, berberine was shown to modulate the expression of genes that promote the catabolism of high-energy intermediates and to promote glucose uptake through a mechanism distinct from that of insulin. Insulin increases cellular glucose uptake by promoting glucose transporter type 4 (GLUT4) expression on the cell surface through the activation of phosphatidylinositol 3-kinase. In contrast, berberine appeared to induce glucose transport by enhancing GLUT1 gene expression [6]. These effects are mediated by the activation of AMPK, which coordinates both short- and long-term metabolic changes, leading to an improvement in energy production and a reduction in energy storage. Specifically, AMPK activation leads to an increase in the uptake of glucose from the blood to target organs. Other studies have highlighted complex I, the largest

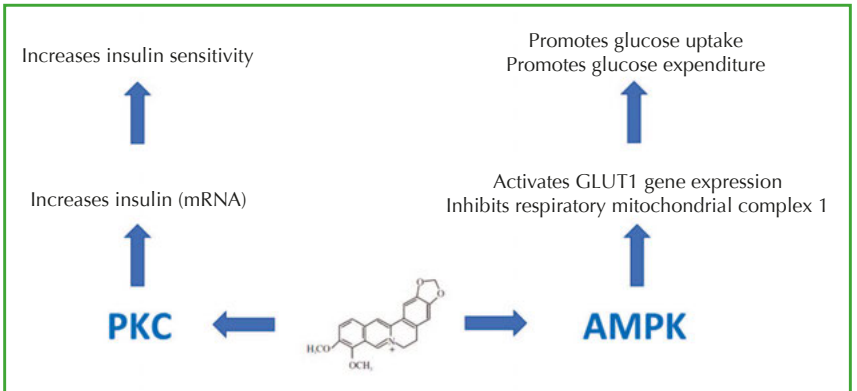

Figure 1 - Effect of berberine on glucose metabolism

enzyme complex of the mitochondrial respiratory chain, as a major target for berberine [7]. Berberine activates AMPK and induces glycolysis, resulting in lowered insulin resistance and decreased oxygen respiration [8]. Another mechanism underlying the action of berberine on insulin sensitivity is its ability to increase insulin receptor (InsR) expression in a dose- and time-dependent manner, thereby promoting cellular glucose uptake in the presence of insulin. Berberine induces InsR gene expression via transcriptional regulation through protein kinase C (PKC). In a mouse model of type 2 diabetes, berberine lowered fasting blood glucose and fasting serum insulin. It increased insulin sensitivity and elevated InsR mRNA, as well as PKC activity in the liver. As expected, berberine did not lower blood glucose in type 1 diabetic mice, because of insulin deficiency [9]. These results were consistent with those of a double-blind, placebo-controlled trial in which berberine administration lowered fasting and postprandial plasma glucose levels, with a slight reduction in postprandial insulin and body weight in patients with type 2 diabetes [10]. Berberine was also shown to lower fasting blood glucose, haemoglobin A1c and insulin levels in patients with type 2 diabetes to levels similar to those seen following metformin and rosiglitazone administration, confirming the upregulation of InsR [11].

Lipid regulation by berberine

Berberine has been shown to reduce plasma cholesterol and triglyceride (TG) levels in both human and animal trials. The mechanism of action appears to be downregulation of low-density lipoprotein cholesterol (LDL-C) by upregulation of LDL receptor (LDLR) expression. This mechanism differs from that of statins but is comparable in effect [12]. In addition to upregulating LDLR expression, berberine reduces cholesterol levels by inhibiting cholesterol absorption and promoting its excretion. Berberine administration (50–150 mg/kg) to atherogenic rats reduced total cholesterol (TC) by 29%–33% and non–high-density lipoprotein (non-HDL) by 31%–41%. It also reduced the absorption rate of fractional dietary cholesterol by 40%–51% [13]. These findings point to the connection between plasma TC or non-HDL levels and cholesterol absorption rates, owing to the decrease in enterocyte cholesterol uptake and secretion. Berberine's lipid-lowering effect is also likely due to the promotion of cholesterol excretion from the liver into bile. This was demonstrated in a study of hyperlipidaemic hamsters treated with either 50 or 100 mg/kg berberine. A gradual decrease in liver cholesterol levels and an increase in bile cholesterol levels was observed at both doses [14]. In a very interesting experiment using hyperlipidaemic hamsters, Wang *et al* demonstrated that berberine and plant sterols/stanols worked synergistically to inhibit cholesterol absorption more effectively than the two actives alone [15]. Finally, the hypolipidaemic action of berberine appears to be also mediated by its role in PCSK9 up-modulation [16]. This clearly explains the effective hypolipidaemic action exerted by the association of berberine with statins or monacolins, the latter being well-known PCSK9 down-modulators [17, 18].

The berberine paradox: a link with *Akkermansia*

Although the gut absorption rate of berberine is about 9% [19] and systemic oral bioavailability is about 1% [20], the glycaemic effects are stronger than the lipid effects [21]. As shown in Figure 2, since more berberine seems to reach the liver than other peripheral organs, the opposite result should be expected. A possible explanation for this paradox is the effect of berberine on the microbiota, which is somewhat similar to that of metformin [22]. As with metformin,

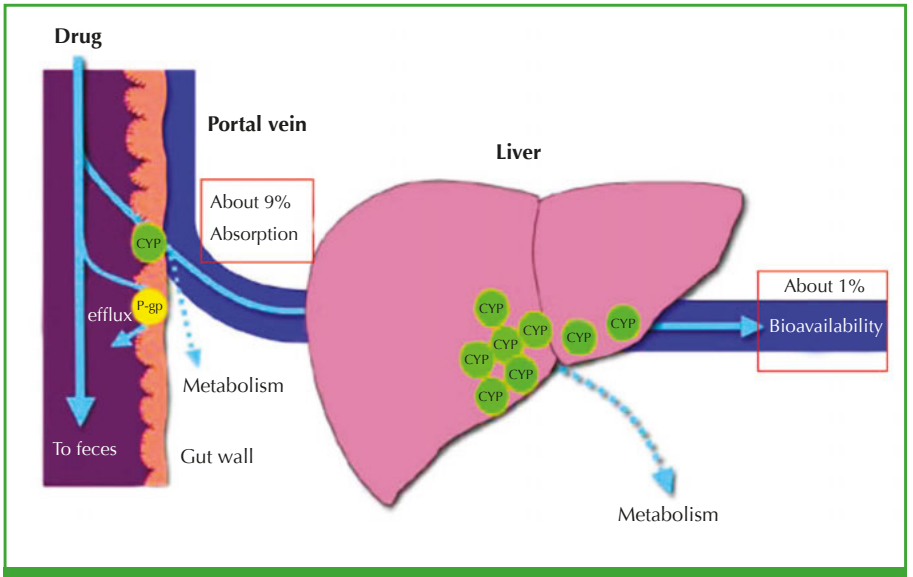

Figure 2 - Berberine pharmacokinetics

berberine increases the quantity in the gut of *Akkermansia muciniphila*, a Gram-negative bacterium belonging to the Verrucomicrobia phylum [23] responsible for mucus thickness in the adult gut. Indeed, *A. muciniphila* colonization is inversely associated with obesity, diabetes, cardiometabolic diseases and low-grade inflammation. In addition to numerous observed correlations, a large body of evidence has also demonstrated a causal beneficial impact of this bacterium in various preclinical models of metabolic disorders [24]. The assumption is that these disorders are associated with altered gut barrier function due to an impaired mucus stratum, which could lead to increased plasma LPS levels, eventually triggering low-grade inflammation and metabolic disorders. The greater the amount of *Akkermansia*, the more mucin is produced and released (Figure 3) and the more mucus thickness is increased, thereby improving metabolic disorders by reducing LPS permeation [25]. A decrease in LPS gut permeation results in reduced TNF-α-mediated inflammation and then, for instance, type 2 diabetes. Other microbes may also be involved in such mechanisms. *Bifidobacterium* is a Gram-positive genus of bacteria also stated to antagonize LPS-mediated inflammation. As also described for *Akkermansia*, Chen *et al* have reported an increase in the *Bifidobacterium* population in the gut after administration of berberine [26] in patients with type 2 diabetes. The administration of oral berberine could therefore increase the *Akkermansia* and *Bifidobacterium* populations, thus reducing gut inflammation (caused mainly by LPS) and counteracting metabolic diseases such as diabetes.

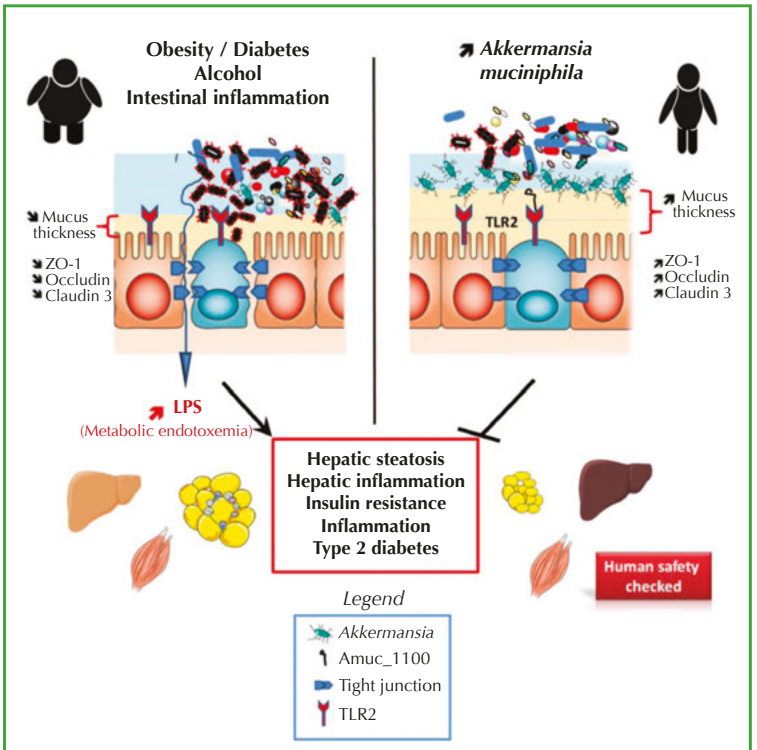

Figure 3 - Correlation between *Akkermansia* and gut mucus thickness

Conclusions

We have described a new way of thinking about drugs and botanicals which interact with the microbiota before they affect the human host. Modulation of the microbiota could partially explain the beneficial role exerted by a particular active such as berberine. In addition to working as a direct anti-hyperglycaemic drug, berberine seems to modulate gut microbiota by increasing the populations of both *Akkermansia* and *Bifidobacterium* which are both described as modulating gut-mediated metabolic inflammation. A new era of understanding actives maybe about to begin.

Conflict of interest

Francesco Di Pierro is owner of Velleja Research.

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