Anagenix.

Feiolix.

Proposed Mechanisms of Action

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Summary

Feiolix is an aromatic whole feijoa fruit powder with a robust profile of classic vitamins and soluble and insoluble dietary fibre. The unique profile of hydrolysable tannins, flavanols, and abscisic acid collectively perform the following functions:

- stabilize blood glucose/increase glucose uptake by cells through multiple hormone pathways,
- regulate metabolism by downregulating inflammation in the central nervous system and periphery,
- increase satiety through improved leptin signaling,
- and modulate glucagon signaling which improves muscular absorption of glucose.

Beneficial components

Dietary fibre

Dietary fibre travels to the colon where it becomes a substrate (a source of carbon) for carbohydrate degrading species of the gut microbiome. Carbohydrate degraders are largely considered to be beneficial symbionts to humans, as they produce short chain fatty acids which have a broad range of benefits to human health.

- *Pectin* is a complex type of polysaccharide in plant cell walls. Pectin has been shown to bind to cholesterol in the gastrointestinal tract and slow glucose absorption by trapping simpler carbohydrates.

- *Xylans & Xyloglucans* are hemicelluloses that occur in the primary cell wall of plants. Humans do not produce enzymes capable of utilizing xyloglucans, but members of the core gut microbiome do. Dietary xyloglucan consumption supports populations of specific species of Bacteroides, such as *Bacteroides ovatus*, which is associated with improved health and lower BMI (Larsbrink, 2014; Kasai, 2015). Many species of Bacteroides participate in the production of the short-chain fatty acid (SCFA) propionate. Propionate increases norepinephrine release by the sympathetic nervous system, which increases glucagon, and the adipokine fatty acid-binding protein (Fabp4), which jointly induce liver glycogenolysis and compensatory insulinemia (Tirosh 2019).

Bioactive compounds from feijoa

Ellagitannins are a class of hydrolysable tannins. Tannins are large polyphenols in plants which provide that bitter, astringent taste and dry mouthfeel. The inclusion of the feijoa skin in Feiolix increases the concentration of ellagitannins over those found just in the flesh of the fruit. The feijoa tannins, ellagitannins, are converted to ellagic acid which are further transformed by members of the gut microbiota into urolithins. Different structures (A, B, C, D) of urolithins are produced by different species unique to each individual, each with similar

bioactivity. Urolithins are more bioavailable than their ellagitannin or ellagic acid precursors (Kang 2016).

Flavanols are a class of polyphenols. They are the building blocks of the larger tannins. The specific type of flavanols in Feiolix are catechins, which have been most extensively researched in the context of green teas.

Abscisic Acid (ABA) is a universal signaling molecule. ABA is best known as a plant hormone involved in ripening and the separation of fruit from stem. ABA is also expressed in mammalian pancreatic β-cells and other tissues in low concentrations.

Biological targets

LANCL2- lanthionine synthetase C-like 2 receptors are the natural receptors for ABA in mammalian cells. Binding of ABA to LANCL2 activates a G-protein coupled response resulting in nuclear translocation and enrichment. This ABA mediated translocation and enrichment is at the basis of multiple intracellular pathways modulating gene expression involved in glucose uptake and utilization, and fatty acid utilization.

PPARγ - Peroxisome Proliferator Activated Receptor gamma (γ) is a nuclear receptor with broad regulatory functions in the expression of inflammatory and adipogenesis genes. ABA decreases macrophage infiltration into white adipose tissue through a LANCL2 and PPARγ dependent mechanism.

NFκB - Nuclear Factor kappa-light-chain-enhancer of activated B cells is a large class of transcription factors that regulate inflammatory signaling pathways. NFkB induces brain inflammation, particularly of the hypothalamus, which leads to central neuroendocrine and neural dysregulation (Cai 2012). The receptor activator of NF-kB ligand (RANKL) is a member of the tumor necrosis factor superfamily and is a potent activator of NF-kB. High serum concentrations of RANKL are correlated with type 2 diabetes mellitus (T2DM).

GLP-1- Glucagon Like Peptide 1 is an incretin hormone produced by the endocrine cells in the gut and has widespread activity in nearly all cell types in the body. Increased circulating GLP-1 is beneficial. GLP-1 agonists and mimetics are useful in treating inflammatory metabolic, cardiovascular, and digestive diseases.

GLUT-4 – Glucose transporter type 4 is a member of the glucose transporter family which takes up glucose by cardiac and skeletal muscle, adipose tissue (both brown and white) and the brain. GLUT-4 translocation to the surface of the cell where it can act is mediated by the B2-adrenoceptor activated mTORC2 (rapamycin complex 2) pathway (Sato, 2014), which relies on cAMP accumulation in cells by way of G-proteins.

L-type Ca2+ channels on β cells of the pancreas are involved in the depolarization of the β cells of the islets of Langerhans in the pancreas. These channels are also a target of calcium antagonist drugs (dihydropyridines) and are activated by urolithins (Bayle 2019).

Pathways of action

Insulin promotes glucose absorption by skeletal muscle and adipocytes, thereby reducing blood glucose levels and making glucose accessible for utilization or storage. Insulin functions by binding to a glycoprotein receptor, consisting of a hormone specific binding site on the alpha subunit, and insulin stimulated tyrosine-specific protein kinase.

Urolithins improve insulin secretion (Bayle 2019)
Urolithins bind to L-type calcium channels on β-cell islets of the pancreas assisting in the influx of calcium when glucose is bound, subsequent depolarization of the cell interior, and consequential release of insulin.

ABA improves insulin secretion (Bruzzone 2008)
ABA binds to the LANCL2 receptors on the β-cell islets of the pancreas triggering a signalling cascade that sequentially involves a G protein, cAMP overproduction, protein kinase A-mediated activation of the ADP-ribosyl cyclase CD38, and cyclic ADP-ribose overproduction. This sequence prompts β cells to produce and secrete insulin at lower blood glucose levels, thus reducing the size of the spike in post-prandial blood glucose.

GLP-1 secretion from L cells is stimulated by ABA (Bruzzone 2015).
This is part of a feedback loop in which ABA stimulates GLP-1 secretion, and GLP-1 stimulates ABA (mammalian) secretion from β cells of the pancreas. Increased GLP-1 stimulates glucose uptake by skeletal muscles, in a glucose-independent manner, similar to insulin.

Muscular absorption of glucose from blood stimulated by ABA (Sato 2019, Magnone 2020, Leber 2020)
ABA binding to the LANCL2 receptors stimulates the absorption of glucose from the blood stream by stimulating GLUT4 receptor expression in an insulin-independent manner on adipocytes and skeletal muscle cells. Increased expression of GLUT4 transporters results in increased glucose absorption from the blood stream into cells. Increased glucose in skeletal muscle cells leads to increased utilization by the mitochondria and increased thermogenesis.

ABA increases expression of relevant genes (Leber 2020)
ABA increases expression of glycogen synthase which increases the rate of glycogen synthesis when synergized with insulin.

- ABA increases expression of glucose resulting in increased glucose oxidation (glucose utilization).
- ABA increases expression of fatty acid metabolism genes resulting in increased fatty acid oxidation (fat utilization).
- ABA increases expression of mitochondrial metabolism genes resulting in increased metabolic flexibility in some muscle cells.

Systemic inhibition of NF-κB mediated inflammation from PPARγ inhibition (Guri 2008)

Protein Kinase A (PKA), which accumulates in cells in response to ABA binding to LANCL2 receptors, activates both PPARγ and NF-kB. However, the activation of PPARγ inhibits NF-kB and NFATc1 as part of a self-regulatory bifurcating pathway.

Recognition of satiety and regulation of metabolism from the central nervous system via NF-kB inhibition and reduced inflammation in the nuclear cortex of the hypothalamus.

Normally, insulin signaling in the arcuate nucleus cells of the hypothalamus is improved by the binding of leptins, a hormone that regulates appetite through satiety. Leptin-induced insulin sensitivity acts through the canonical wnt pathway. This in turn improves systemic responses to blood glucose. However, in chronic inflammatory conditions such as T2DM, the Wnt pathway is blocked by NF-kB, and insulin sensitivity is lost, resulting in loss of appetite control, greater glucose consumption, and greater quantities of insulin required to achieve the same blood- glucose-controlling response, which ultimately leads to the systemic insulin insensitivity and uncontrolled blood glucose characteristic of T2DM.

The anti-inflammatory properties of Feiolix inhibit NF-kB-mediated blocking of the Wnt pathway, returning appetite and insulin sensitivity in the brain and periphery to normal.

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