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Bowel Regularity with Actazin[®]

ACTAZIN[®]

SCIENCE PERFECTED IN MARKET[®]


Anagenix.

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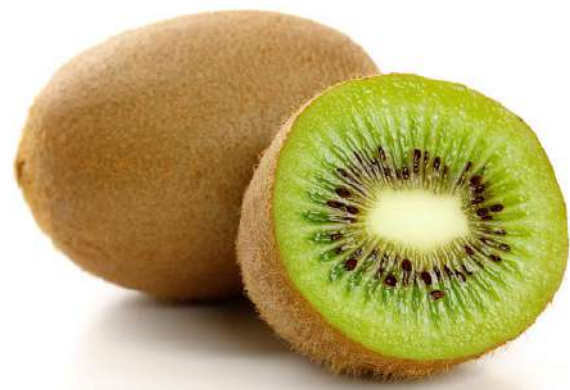
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EXECUTIVE SUMMARY

To help customers with formulation ideas on which health claims can potentially be made, Anagenix has researched various ingredients which may be used in combination with Actazin® for digestive health.

The ingredients investigated (see table below) have approved health claims relating to digestive health in some markets, mainly EU.

INGREDIENT CATEGORY	INGREDIENT	USE/HEALTH BENEFIT
Natural laxative plants	Prunes	• Contributes to normal bowel function. • EU health claim.
	Figs	• Remedy for mild constipation (bulking laxative). • Health claim in South Korea for fig paste.
	Fennel	• For treatment of mild GI complaints, including bloating and flatulence. • EU health claim.
	Mallow	• For the relief of mild discomfort of the stomach and gut. • EU health claim, based on traditional use.
	Polypody rhizome	• For short term use in cases of occasional constipation. • EU health claim, based on traditional use.
	Native chicory inulin	• Contributes to normal bowel function by increasing stool frequency. • EU health claim.
	Castor oil	• For short term use as a laxative for occasional constipation. • EU health claim.
Dietary fibres	Psyllium	• For the treatment of habitual constipation. • EU health claim. • Bulking agent
	Wheat bran fibre	• Contributes to an increase in faecal bulk. • EU health claim. • Bulking agent
	Oat grain fibre	• Contributes to an increase in faecal bulk. • EU health claim. • Bulking agent
	Rye fibre	• Contributes to an increase in faecal bulk. • EU health claim. • Bulking agent



INGREDIENT CATEGORY	INGREDIENT	USE/HEALTH BENEFIT
Natural stimulant laxatives (anthraquinones)	Rhubarb	• Rhubarb root for short term treatment of occasional constipation. • EU health claim.
	Aloe	• For short term treatment of occasional constipation. • EU health claim. • No longer recognised by US FDA as an OTC.
	Senna	• Pods: used for occasional constipation and bowel cleaning. • Leaf: for short-term treatment of occasional constipation. • EU health claim.
	Cascara	• For short term treatment of occasional constipation. • EU health claim.
	Frangula	• For short term treatment of occasional constipation. • EU health claim.
Synthetic laxatives	Lactulose	• For the treatment of habitual constipation. • EU health claim. • Bulking agent
	Polydextrose	• Contributes to an increase in faecal bulk. • EU health claim. • Bulking agent
Sugar alcohols	Sorbitol	• No EU health claim for gut health. • Osmotic laxative
	Lactitol	• Contributes to normal bowel function by increasing stool frequency. • Osmotic laxative

Of the ingredients investigated, several were found to have potential for formulating with Actazin® and the key information on these are outlined below.

Formulation Ideas For Constipation



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Actazin® + Prunes (*Prunus domestica* L.) – For Normal Bowel Function

Approved health claim Prunes/dried plums have an EU health claim: maintenance of normal bowel function¹.

- To obtain effect, 100 g prunes should be consumed daily.

Rationale for formulating with Actazin®

- Strong evidence from clinical data: 100 g/d prunes resulted in a statistically significant increase in stool weight (Tinker et al., 1991). 80 g/d prunes also significantly increased stool weight (mean + 22.2g/d, p=0.026), frequency (6.8 bowel movements/wk, p=0.023) and Bifidobacterium species (p=0.046) (Lever et al., 2019).
- Prunes have shown superior laxative capability compared to psyllium (Attaluri et al., 2011).
- Sorbitol (14.7g/100g in prunes) acts as an osmotic laxative. Osmotic laxatives are relatively safe and can be taken daily.
- In a 4-week study, kiwifruit exerted greatest effects on stool frequency in first 2 weeks of treatment, while prunes led to a slower but sustained increase in stool frequency over the 4-week treatment period (Chey et al., 2020).
- Kiwifruit was well-tolerated with the least side effects and highest rate of satisfaction by participants.

Mechanism of action Osmotic laxative²

Sorbitol (14.7g/100g) is a sugar alcohol in prunes that acts as an osmotic laxative due to its humectant quality (ability to bind water). Unabsorbed sorbitol draws water into

the intestinal lumen by osmotic gradient, thus increasing intraluminal pressure, and distends the intestine to stimulate a contractile response; overall accelerating colon transit and causing stool softening effects.

- Note: consumption of 40g/d sorbitol led to rapid expulsion of liquid stools, due to rapid change in viscosity; and increased severity of abdominal pain (McRorie et al., 2000).
- Sorbitol is a FODMAP and may cause adverse effects in susceptible populations.

Fibre supplementation (prunes 6.1g/100 g)³

Prunes, like kiwifruit and Actazin, contain both soluble and insoluble dietary fibre.

- Soluble fibre is readily fermented by the colonic microbiota, leading to increased microbial biomass and fermentation by-products, consequently increasing stool weight.
- Insoluble fibres resist colonic fermentation. They act as bulking agents, increasing both size and weight of food remnants, partly by binding water. This may lead contribute to faecal bulking and reduced gut transit time.

Polyphenols for peristalsis

Chlorogenic acid, a polyphenol present in both prunes and kiwifruit, may increase serotonin biosynthesis in enterochromaffin cells in the colon⁴ to increase peristalsis and aid bowel function⁵.



Dosage

INGREDIENT	MINIMUM DOSAGE FOR EFFICACY	REFERENCE	DOSAGE STATED IN CLAIM (IF APPLICABLE)
Prunes	80 g/d	(Lever et al., 2019)	100 g/d
Kiwifruit	600 mg/d	Ansell et al (2015)	

Existing products

Prunelax Ciruelax® ⁶

Prunelax – prunes + senna tablets for alleviation of occasional constipation and helping to maintain bowel regularity.

- Each tablet contains 62.5 mg prunes, 480 mg senna leaves, 90 mg Alexandrian senna pods – to take 2 to 3 tablets before bedtime.

Nu-Lax Natural Laxative Tablets with Senna & Prunes⁷

Nu-Lax – prunes + senna leaves; laxative tablets for quick, overnight relief and promotes regularity, making stools easier to pass.

- Each tablet contains 1 mg prunes extract, 90 mg Senna alexandrian extract, 15 mg sennoside B, senna pods.

Fiberex Fiber®⁸

Llorens Pharmaceutical (USA) – 15 g soluble dietary fibre (from polydextrose) + fructose-obligosaccharides (FOS) + natural prune concentrate for chronic constipation.

- Other ingredients: Purified water, potassium sorbate (to preserve freshness), sodium benzoate (to preserve freshness), malic acid, caramel color, sucralose.

1. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2712>
2. <https://linkinghub.elsevier.com/retrieve/pii/S0016508595904484>
3. <https://www.sciencedirect.com/science/article/pii/S0261561418300037>
4. <https://www.sciencedirect.com/science/article/abs/pii/S0378874119322032>
5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1574906/>
6. Prunelax Ciruelax Regular Strength Tablets | Natural-Origin Laxative
7. Nu-Lax Natural Laxative Tablets - Senna & Prune | Nu-Lax (nu-lax.com)
8. Fiberex Fiber – Llorens Pharm

Actazin® + Psyllium (Ispaghula)

– For Habitual Constipation

(As well as IBS Symptoms)



Approved health claim

Psyllium husk has an EU health claim:

- used for the treatment of habitual constipation⁹ and in conditions where softening of stools is desirable to reduce pain when they are passed, such as anal fissures, haemorrhoids and after surgery to the anus or rectum.
- used in people where an increase in the daily intake of dietary fibre may be advisable such as patients with irritable bowel syndrome who are suffering from constipation or in combination with diet in patients with hypercholesterolaemia.
- To be used without further processing or as preparations obtained by powdering the seed coats.

Rationale for formulating with Actazin®

- Dietary fiber supplements such as psyllium are quite unpalatable and need to be combined with flavorings and then dissolved in water to be ingested – so combination with kiwifruit may be more palatable.
- **Strong evidence from clinical data:**
 - o Psyllium husk (5.1 g) twice daily increased stool frequency, and stool weight in patients with Parkinson's disease and constipation (Ashraf et al., 1995), and

- has great laxative efficacy in patients with chronic constipation (McRorie et al., 1998).
 - o For IBS: Psyllium (3.5 g) 2 or 3 times per day significantly diminished abdominal pain in patients suffering from IBS (Dettmar & Sykes, 1998), and psyllium husk 6 g daily reduced pain episodes (mean reduction in pain 8.2 ± 1.2) when given to children with IBS (Shulman et al., 2017).
- Kiwifruit fibre is completely fermented by the microflora, playing a significant role in modulation of the microflora. In contrast, psyllium husk fibre resists fermentation, and increases fecal bulk and colonic transit; acting in different regions of the colon – driving different functionalities that target separate gastrointestinal features, can potentially maximise symptom improvement.
- Greater effect on stool weight and consistency (higher % bound water) than wheat bran (Stevens et al., 1988). The American College of Gastroenterology recommends psyllium over wheat bran for controlling overall symptoms in irritable bowel syndrome (IBS)¹⁰, as wheat bran and other fibers do not produce high-viscosity gel similar to psyllium.

Mechanism of action

Note: psyllium must be taken with adequate fluid, as lack of water increase bloating and can increase incidence of bowel obstruction¹¹.

Fibre supplementation & faecal bulking

- Psyllium is composed of 70% soluble and 30% insoluble fibre. Most of the laxative benefits of psyllium attributed to its high content of arabinoxylans; which is soluble, has high water-holding capacity, low fermentability and produce a high viscosity gel (gel-forming).
- Kiwifruit contains non-digestible oligosaccharides and insoluble fibre that are unaltered through the small intestine to the colon, where they have a dual function as a prebiotic to stimulate growth of the gut microflora (hence is fermented to SCFAs of butyrate, acetate, and propionate) and as fibre to bulk the stool.

Stool softening – high water-holding capacity

Psyllium fibre and kiwifruit fibre¹², have high water-holding capacity. In turn, this increases stool water content which

results in bulky/soft/easy-to-pass stools (stool normalising effect), promoting laxation and alleviation of constipation (Belorio & Gómez, 2020).

Increased transit + lubricant layer – gel-forming capability

Mucilage in psyllium (composed of arabinoxylans) forms a gel when in contact with water – swelling factor >9 for entire seed, and >40 for seed husk (Gill et al., 2020). As it passes through the digestive tract and arrives in the large bowel, it acts as an effective stool bulking agent; increasing the intraluminal diameter and consequently lowering the bowel wall tension needed to generate propulsive contractions. In turn, causing more mass movements which increase the rate of luminal transit & frequency of defecation. It also forms a lubricant layer that coats the intestinal tract and facilitates transit.

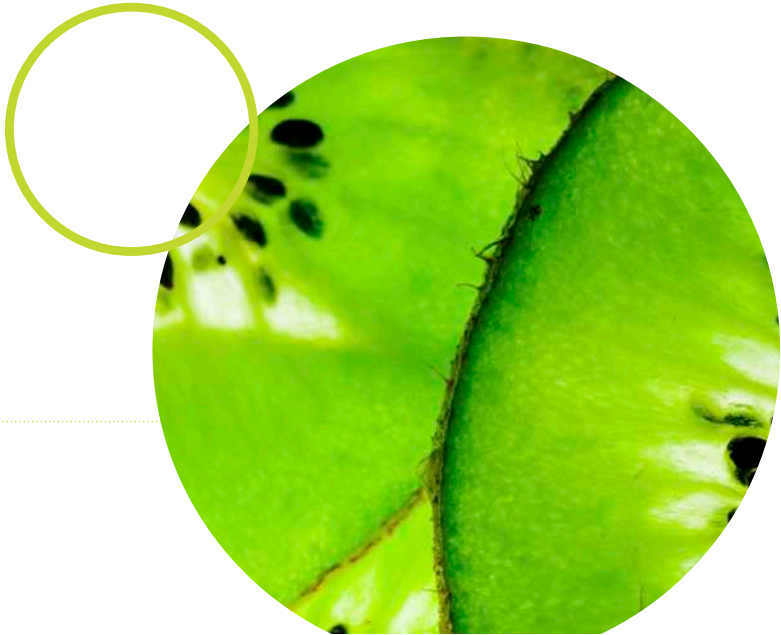
Existing products

Metamucil

Psyllium husk to promote digestive health and regularity.

Dosage

INGREDIENT	MINIMUM DOSAGE FOR EFFICACY	REFERENCE	DOSAGE STATED IN CLAIM (IF APPLICABLE)
Psyllium	6 g/d for reducing IBS symptoms	(Shulman et al., 2017)	
	10.2 g/d for constipation	(Ashraf et al., 1995)	
Kiwifruit	600 mg/d	Ansell et al (2015)	



9. constipation not caused by a physical change to an organ
10. <https://gi.org/wp-content/uploads/2018/07/IBS-Monograph-2018.pdf>

11. <https://www.mdpi.com/2072-6643/11/5/1130>
12. Amount of water that is bound to insoluble fiber and is not separated from fiber from centrifugation.

Actazin® + Mallow Flower (Osmotic Laxative)

Approved health claim

Mallow has an EU health claim:

- mallow leaf (AND flower) can be used to treat irritation of the mouth or throat and associated dry cough, it can also be used to relieve mild discomfort of the stomach and gut.

Rationale for formulating with Actazin®

- Mallow used by Sanofi in combination with Actazin® (Phytoxil Transit)
- Mallow flower (*Malva sylvestris* flos) consists of the whole or fragmented dried flower of *Malva sylvestris* L. or its cultivated varieties. The leaves, (*Malva folium*) lowers and aerial parts of the *Malva sylvestris* L. plant are used as laxative in humans and animals.
- Conditions of use: adults and adolescents over the age of 12 years.
- There are no published clinical studies on *Malva folium* or *Malva sylvestris* flos where the active substances of the medicinal product have been in medicinal use within the EU for at least ten years.
- However, the traditional medicinal use of mallow flowers and leaves has been documented in several medicinal handbooks with indications consistent with the existing pertinent pharmacological experiments performed in vitro and in vivo and it is substantiated by the presence of medicinal products on the European market

- Therefore, the traditional use of mallow fulfils the requirement for at least 30 years of medicinal use at a specified strength and specified posology, according to Directive 2001/83/EC as amended.

Mechanism of action

- Mucilages in mallow flower have a laxative activity. Among dicotyledonous plants, the order Malvales possesses the most abundant deposits of mucilages - found mainly in leaves (6.0-7.2%), flowers (3.8-7.3%) and roots (7.5%).
- Mucilage consists mainly of glucuronic acid, galacturonic acid, rhamnose, galactose, fructose, glucose, sucrose and trehalose. The amount of uronic acids, galacturonic and glucuronic acid in *Malva sylvestris* is much higher in flowers (22.8%) than in leaves (8.2%).
- After hydrolysis, it may act like hydrophilic laxatives, softening wetting agents, as well as osmotic laxatives.
- The monosaccharide sugar products of mucilage hydrolysis can be converted to acids (e.g. lactic acid) by the gut bacteria. These acids **lower the pH** and help in balancing intestinal microflora and normalising intestinal transit (Elsagh et al., 2015). Elsagh et al (2015) suggests that *Malva sylvestris* L. extract has **acetylcholinesterase (AChE) inhibitory effects**, which may contribute to laxative effects. Acetylcholine is one of the main neurotransmitters controlling the gut motility.



NOTES:



**For more information,
please contact Chris Johnson**

Mobile: +64 21 724 008 | Email: chris.johnson@anagenix.com



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