

# TECHNICAL NOTE

Formulations Guide  
for Metabolic Health



*InSea<sup>2</sup>*<sup>®</sup>

# INTRODUCTION

Metabolic health involves supporting five key components within an optimum range: blood glucose, blood pressure, HDL-cholesterol, triglycerides and waist circumference<sup>1</sup>. A healthy diet and regular exercise help maintain metabolic health. Furthermore, several favorable scientific studies support the use of dietary supplements in achieving a healthy metabolism.

This document aims to identify the foundations supporting the development of safe and effective dietary supplements for metabolic health.

## INSULIN AS A KEY TARGET

Healthy insulin signaling is one of the key mechanisms involved in the maintenance of metabolic health. Insulin acts on muscle, fat and liver cells, to help regulate the levels of circulating glucose. However, the effects of insulin extend far beyond, having an impact on circulating HDL and LDL, cholesterol, triglycerides, blood pressure, and fat accumulation<sup>2</sup>.

One of the most effective ways to support insulin function involves keeping post-meal insulin levels to a minimum. This can be achieved using inhibitors of carbohydrate digestion. This mechanism of action has the advantage of slowing glucose uptake before it can reach the bloodstream. Some natural ingredients can block either  $\alpha$ -amylase or  $\alpha$ -glucosidase enzymes, respectively involved in the conversion of dietary starch and disaccharides into glucose, enabling their uptake to the bloodstream. There are also dual inhibitors of  $\alpha$ -amylase and  $\alpha$ -glucosidase, such as brown seaweeds<sup>3</sup> having the important advantage of reducing the glycemic impacts of both starch and disaccharides (such as table sugar) **using a single ingredient**.

# CORE INGREDIENT

Metabolic health products should be focusing on ingredients and combinations that have been validated through human clinical trials only. The core ingredient for metabolic health should ideally optimise insulin function and control blood glucose, as this is the most important pathway toward metabolic health.

The inhibitory activity against  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes of various commercially available extracts is reported in Table 1, with lower IC<sub>50</sub> values indicative of higher inhibition potency.

Table 1: Inhibitory activity of various commercial plant extracts against  $\alpha$ -amylase and  $\alpha$ -glucosidase

EXTRACT	Inhibition IC <sub>50</sub> (µg/ml)	
	$\alpha$ -amylase	$\alpha$ -glucosidase
InSea2 <sup>®</sup> brown seaweed extract	1.0 ± 0.0	0.22 ± 0.01
Other brown seaweed extract	12.8 ± 1.8	1.15 ± 0.13
Cinnamon extract	25.9 ± 1.4	1.51 ± 0.04
Salacia extract	197 ± 25	5.50 ± 0.09
Morus alba extract	No inhibition	21.3 ± 0.9
Phaseolus vulgaris extract	No inhibition	>100

From these results, among brown seaweed extracts, it appears that **InSea2<sup>®</sup>** offers the highest potential for the inhibition of enzymes involved in carbohydrate digestion and assimilation. This ingredient has been evaluated in several human clinical trials. Upon administration of a dose of **250 mg before a standard meal**, InSea2<sup>®</sup> led to a significant 66% decrease in 2h-postprandial glycemia of treated subjects compared to placebo subjects<sup>4</sup>. In another clinical trial, the use of InSea2<sup>®</sup> before a standard meal led to a significant 12% decrease in the postprandial insulin response, while insulin sensitivity (Cederholm index) was improved by 8%<sup>5</sup>.

Once a core ingredient has been selected, additional layers of ingredients may be added to bring synergetic effects or additional benefits in support of metabolic integrity.

## 2<sup>ND</sup> LAYER INGREDIENT

The second layer ingredient should offer a clinical benefit supported by studies in human. These clinical trials should show proven synergies with the core ingredient.

**Chromium** has been a staple ingredient for maintenance of blood glucose since the discovery that diabetic individuals are often chromium deficient. Chromium in fact induces improvement in the phosphorylation of the insulin receptor as well as the signal transduction process leading to an increased expression of glucose transporters at the surface of the cells. Such a mechanism suggests that chromium supplementation may act in a synergetic manner with that of brown seaweeds, by facilitating the removal of glucose once it has reached the bloodstream<sup>6</sup>.

Chromium itself has been clinically-tested in patients affected by insulin and metabolic impairments. In one clinical trial, the use of 400 µg per day of chromium picolinate by T2D patients for 8 weeks showed significant improvements in HOMA-IR (a marker of insulin resistance), total cholesterol and LDL cholesterol<sup>7</sup>. The impact of chromium supplementation in normoglycemic volunteers is however subject to doubts, with some clinical trials showing no effect<sup>8</sup> in this population, while others have yielded conclusive results on lean muscle mass improvement and body weight reduction<sup>9</sup>.

The synergy of chromium with InSea2<sup>®</sup> have been explored in multiple human clinical trials involving prediabetic, T2DM and metabolic syndrome patients. In one trial, Nicolucci *et al.* studied the use of 250 mg of InSea2<sup>®</sup> with 7.5 µg of chromium picolinate in 505 subjects with metabolic syndrome. After 6 months of treatment, body weight was reduced on average by 7.3 kg, waist circumference

by 7.5 cm, fasting blood glucose by 16.3 mg/dL, HbA1c by 0.55%, systolic and diastolic blood pressure by 7.1 mmHg and 4.2 mmHg, respectively, LDL cholesterol by 18.2 mg/dL, and triglycerides by 39 mg/dL. HDL cholesterol was significantly increased by 2.9 mg/dL. The authors concluded that the 10-year risk of cardiovascular events significantly decreased by 1.8%, corresponding to a relative risk reduction of 27.7%<sup>10</sup>.

## 3<sup>RD</sup> LAYER INGREDIENTS

Third layer ingredients are those that offer clinically-proven benefits within the metabolic health area, as well as showing potential synergies with the core ingredient. 3<sup>rd</sup> layer ingredients may serve to bring further brand differentiation or convey additional benefits to a specific target audience.

**Quercetin:** A double-blinded, placebo-controlled, cross-over study showed that 150 mg quercetin per day for six weeks reduced systolic blood pressure (SBP) and oxidized LDL in 93 hypertensive overweight individuals with high cardiovascular disease risk<sup>11</sup>.

**Curcumin:** A randomized, double-blinded, placebo-controlled trial in 60 volunteers with metabolic syndrome showed that curcumin supplementation (500 mg per day) induced a significant decrease in body weight over the placebo group, with a trend toward reduction in waist circumference. Pulse wave velocity, a marker of arterial stiffness, was also beneficially impacted by the supplementation<sup>12</sup>.

**Berberine:** A randomized, double-blind, placebo-controlled clinical trial was carried out in 24 patients with a diagnosis of metabolic syndrome taking 500 mg before each meal. After 12 weeks of treatment, a significant decrease in systolic blood pressure (SBP), triglycerides, glucose and insulin area under the curve was noted<sup>13</sup>.

**Black cumin:** A randomized, double-blinded, placebo-controlled trial was conducted involving 140 women with metabolic syndrome. The results show a significant decrease in fasting blood glucose, total and LDL cholesterol as well as triglycerides following 8 weeks of treatment using a dose of 500 mg per day<sup>14</sup>.

**Resveratrol:** In one recent randomized, double-blinded, placebo-controlled trial, 25 volunteers with metabolic syndrome were put to a lifestyle intervention program including diet and exercise, with 250 mg of resveratrol or a matching placebo for a duration of 3 months. The supplementation with resveratrol improved total cholesterol (TC), HDL cholesterol and VLDL cholesterol over the placebo group<sup>15</sup>.

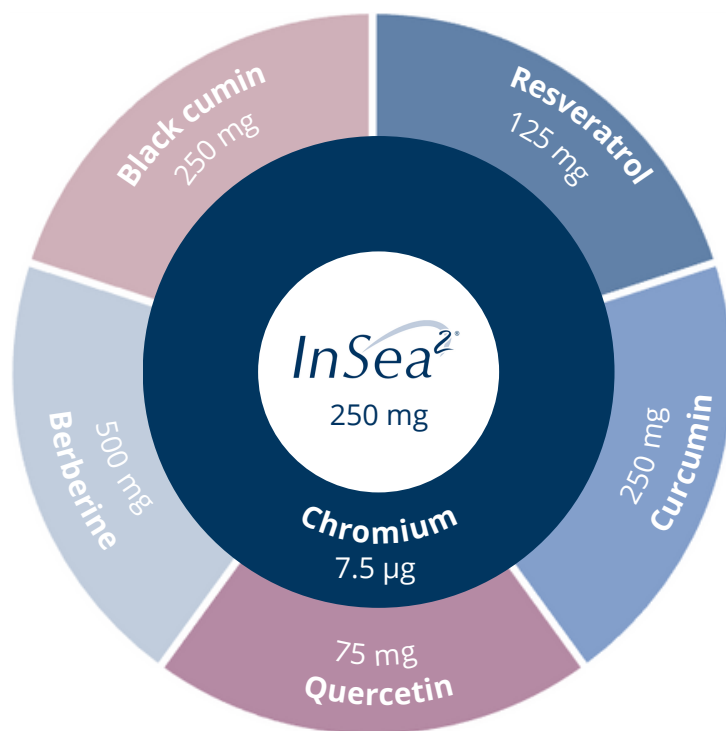


Figure 1: Formulation matrix for metabolic health.  
Recommended use twice a day

## CONCLUSION

With less than 1 in 8 Americans considered metabolically healthy<sup>16</sup>, metabolic health is a promising market segment for innovative dietary supplement formulations. While formed of five distinct components, metabolic health depends heavily on the efficacy of insulin signaling, making this mechanism an essential target for any formulation in that area. Several individual ingredients have already proven their efficacy, among which a combination of brown seaweed extract and chromium picolinate is standing out as a front runner. Additional ingredients, reviewed here, may be considered for differentiation.

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