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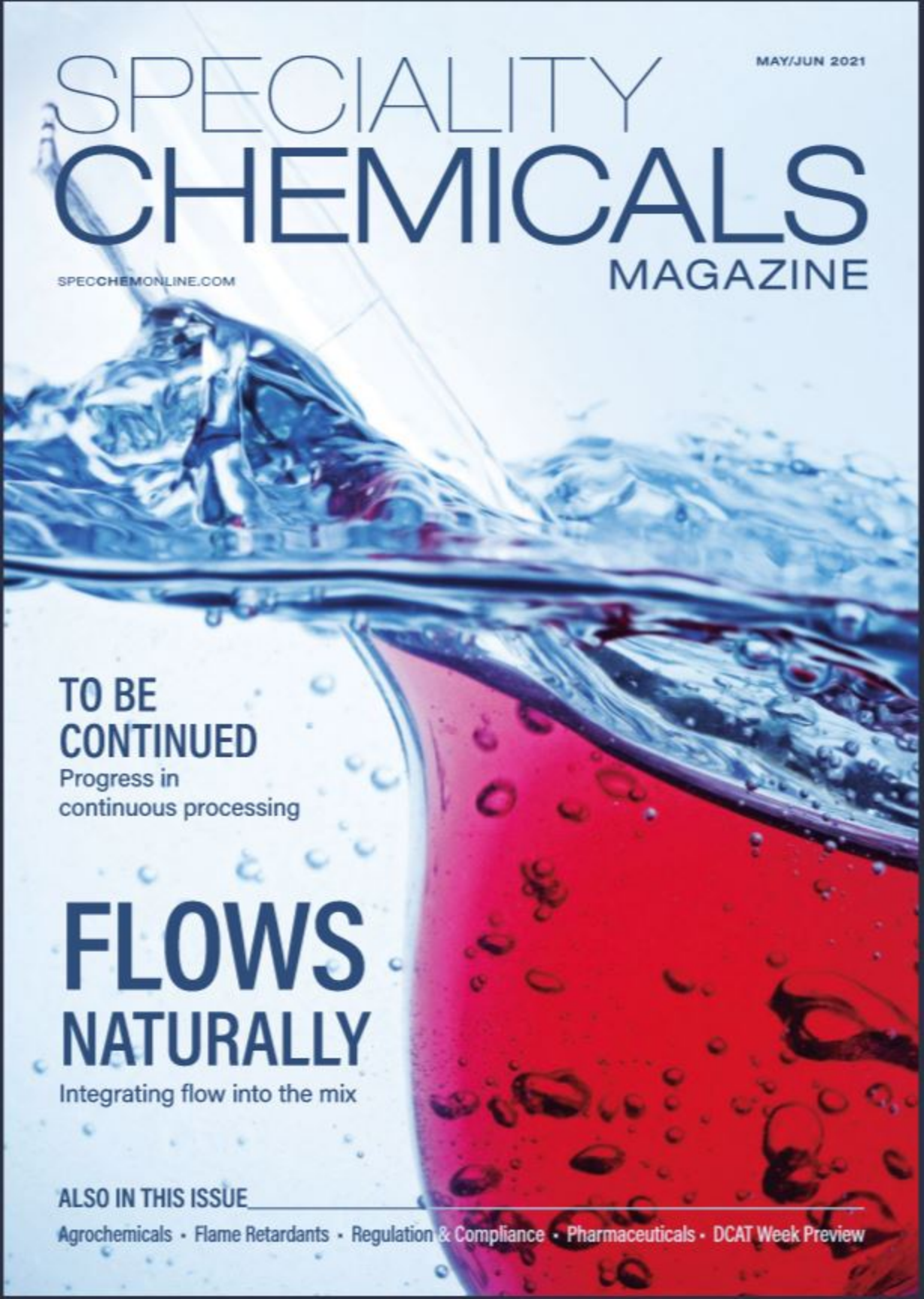

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Progress in continuous processing

FLOWS NATURALLY

Integrating flow into the mix

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Innovation grows **on trees**

A lab-grown tree is the source of both a biofungicide and an adjuvant for a COVID-19 therapy. We spoke with **Gaston Salinas** of **Botanical Solution**

The last few months have seen some major developments for US start-up firm Botanical Solution (BSI). At the end of 2020, it secured $3.3 million from multiple banks and 'angel' investors in a seed round of funding, with a further $6 million round planned shortly.

After several years of partnership in Chile, the company also reached an agreement with Syngenta to commercialise its first product in Peru and Mexico. More significantly still, it made its first moves towards the pharma market.

Co-founder and CEO Gaston Salinas, an industrial engineer by training, spent the early part of his career in his native Chile, working on new product development. He met his business partner, biologist Gustavo Zúñiga, by chance in 2010.

Zúñiga had worked with native plants from the continental and Antarctic regions of Chile and combined biotech with them. Many of these were not easy to source because of their remoteness, so he studied lab-grown versions too.

In the case of *Quillaja saponaria Molina*, he found that those he grew in his own lab generated specific phenolic compounds, different to those they would generate in wild conditions, and that these had fungicidal activity. The technique was patented in the US in 2012 and in Europe in 2013.

"The interesting thing is that in natural conditions, the tree does not produce these compounds spontaneously in sufficient quantities

Salinas

or consistently to curate that biological activity," Salinas says.

"When you grow it *in vitro* and put some stress conditions – varying media culture composition, light exposure and temperature among other factors – they are expressed. We are now extracting these compounds to formulate our first product."

Into commercial production

BSI was founded in Santiago in 2013, thanks to $500,000 in funding from a local venture capital firm who were also one of the largest table grape exporters in Chile. In 2019, it moved to Davis, California, one of the major centres of the biopesticides world.

Botristop, as the biofungicide is known in Chile, is a 10% extract from tissue-cultured *Quillaja saponaria* plants. At 30-60 days of age, these are inoculated into bioreactor systems so that they grow very rapidly and in the right conditions for the secondary metabolites to develop that are responsible for the biological activity.

"Along with supply, consistency in the active ingredients is one of the biggest challenges in botanicals," says Salinas. "We collect materials in our lab every week and whether we grow a milligram, a gram, a kilo or even a tonne of dry material, the chemical composition, batch to batch, is almost identical."

The fresh biomass is reduced to a dry powder to ease the extraction of the active ingredient using natural solvents. Formulation is extremely simple: just add water. A dual mode of action relies on phenolic compounds to give it its fungicide activity to the product, while a systemic acquired response is triggered on plants treated with Botristop.

Botristop was field-tested for several years and proven to be highly efficacious in the prevention and control of *Botrytis cinerea*, especially for conventional growers of blueberries, vines and vegetables. This disease affects the vast majority of high-value crops grown for export in countries like Chile, some of which travel anything up to 90 days to reach their final market. Botristop is also said to be effective against many other fungal diseases.

BSI grows Quillaja Saponaria in vitro

Deal with a giant

At the time that BSI was seeking regulatory clearance in Chile in 2015, Salinas and Zúñiga were travelling every year to Basel for the Annual Biocontrol Industry Meeting, one of the major events in the biologicals field. There, they began conversations with Syngenta, who were seeking partners for growth in Latin America.

By 2018, the two companies had concluded an exclusive distribution agreement and Syngenta launched Botristop in Chile in 2019. New uses, such as sour rot, were approved in 2020 and Botristop now protects about 25,000 hectares across Chile. A rollout is planned in Peru later this year. Launch is also anticipated for Mexico and the US during late 2022.

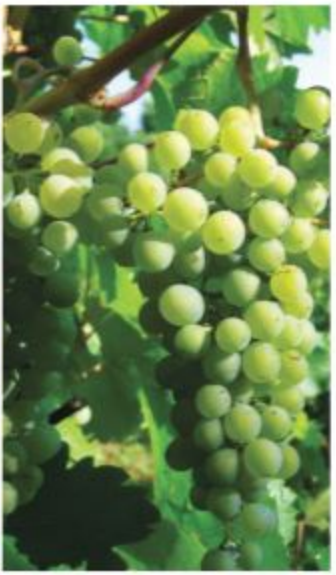
During 2020, the firm also appointed agrochemical industry veteran Marcus Meadows-Smith to its board of directors. "Marcus brings a lot of experience to the company and he also believes we are doing something novel and important," Salinas says.

Meadows-Smith is currently CEO of BioConsortia, which makes microbial crop protection products. Before that, he had headed biopesticide business AgraQuest for four years until Bayer CropScience acquired it for over $400 million and he became head of biologics for Bayer CropScience.

Because of the product's unique modes of action, growers can achieve resistance management and export their produce worldwide, while meeting the strictest MRL guidelines.

With the recent and forthcoming funding rounds, Salinas says, BSI is now at a very important moment in its development. It is transitioning from a single-product company to a portfolio company, while also expanding its footprint throughout Latin and North America.

The company has submitted its registration dossier for Botristop in the US and is thinking about following suit in the EU during 2021. The registration process in the EU can take six to seven years and requires significant financial resources, so, as well as pushing Botristop in existing markets, the new investment will be used to finance new developments.



Botristop is already widely used to protect crops like grapes and lettuce

"We are following two main strategies: the development of novel chemistries from native plants from Chile and other parts of the world, but also producing well-known active ingredients that are expected to be in short supply in the near future," Salinas says.

Pharma potential

Perhaps most importantly, over 24 fractions of saponins are present in *Quillaja saponaria* that have different level of adjuvant activity in both human and animal treatments, mainly vaccines. The most abundant is QS-21, which also has a lower toxicological profile than the others.

QS-21 has been studied for some 30 years. It was first used in a commercial vaccine in 2017, with another for malaria being approved recently. Now, Novavax's vaccine for COVID-19 has been developed, using QS-7 and QS-21 as adjuvants. "More and more, QS-21 is becoming a gold standard in terms of improving the efficacy of modern vaccines," says Salinas.

As a result, shortages of *Quillaja saponaria*–derived products are affecting the pharmaceutical market in the same way as the agrochemical market. In the former case, this is particularly exacerbated by the ever-rising demand caused by the COVID pandemic and other pipeline drugs, plus supply limitations thanks to strict deforestation laws in Chile.

"Global macrotrends in sustainability and carbon sequestration will put under higher scrutiny the exploitation of *Quillaja saponaria* wild forest in Chile to produce sufficient QS-21 in the near future and attempts to produce it synthetically have always been hampered by prohibitive costs," says Salinas. And, because demand is racing ahead of supply, QS-21 from botanical sources is already very costly, typically $400,000-500,000/gram at present.

BSI entered this market space almost by accident, because it was originally intending to focus purely on agrochemicals. The opportunity was sparked by a conversation Salinas had with the CEO of a pharmaceutical producer in Silicon Valley, who asked him about sourcing QS-21 from his plants.

Having no answer to this question, Salinas telephoned Zúñiga, who swiftly ran some internal tests. These found that not only could BSI produce QS-21 in virtually unlimited quantities, its *in vitro* approach yielded over ten times more QS-21 in its starting materials than could be produced from traditional saponins concentrate products based on the bark of old trees.

BSI is now planning to tap into the pharmaceutical market in three stages. First, it confirmed the feasibility of producing QS-21 starting materials in sufficient quantities in its lab in Chile. This year, it is moving from production at milligram-scale to gram-scale. From 2022, it is preparing to move to kilo-scale.

This will be done by working with CMOs initially to remove some of the downstream bottlenecks in GMP production. Some of its next round of finance will be dedicated to pilot production of GMP-grade materials and entering into clinical testing of them, before moving to even larger-scale production. ●

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