MARITECH® ORGANIC FUCOIDANS
THE SCIENCE

Dr J. Helen Fitton
Chief Scientist, Marinova Pty Ltd
INTRODUCTION

Fucoidans are non-gelling, fucose-rich sulfated polysaccharides found primarily in brown seaweed. They are highly bioactive compounds that play a pivotal role in protecting seaweed from water-borne pathogens and other environmental challenges. Extensive research has shown that fucoidan extracts impart significant beneficial effects in a wide range of human health settings.

This white paper explores the science behind fucoidan, with a particular focus on the latest research supporting the use of Maritech® fucoidan extracts in immune modulation, gut and digestive health, viral inhibition, anti-inflammation and integrative oncology applications.

CONTENTS

About

The author 3
The company 3
Maritech® fucoidan range 4
Overview 4
Characterisation 5
Pure source 5
Zero-waste manufacturing 5
Maritech® extraction process 6
Bioactivities 8
Overview 8
Anti-cancer 9
Immune modulation 16
Gut and digestive health 18
Viral inhibition 21
Anti-inflammation 22
Regulatory 24
Safety 24
Global acceptance 25
Quality and certifications 25
References 26
Dr Helen Fitton is Marinova’s Chief Scientist and an Adjunct Senior Researcher at the University of Tasmania. With more than 20 years experience in commercially-focussed research and development, Dr Fitton is recognised as a world-leading authority on fucoidan compounds. Her area of expertise lies in polymers for biomedical applications, with a focus on natural polysaccharides from marine macroalgae. Dr Fitton holds a BSc (Hons) in Biochemistry from the University of Manchester, a MSc in Mineralised Tissues from University College London and a PhD in Applied Chemistry from Aston University.

To date, Dr Fitton has been a key contributor to 35 published research papers and 3 book chapters, as well as the reviewer of countless fucoidan and macroalgae-focussed research papers. Dr Fitton has been instrumental in developing Marinova’s portfolio of Maritech® fucoidan extracts and has led the science in creating effective new products for use in a range of nutritional, pharmaceutical, medical device and dermatological applications.

Marinova is a progressive Australian biotechnology company dedicated to the research, development and manufacture of high purity fucoidan extracts for use in pharmaceutical, nutritional and dermatological applications.

With world-class extraction facilities and research laboratories located in Tasmania, Australia, Marinova is recognised globally for its commitment to innovation and expertise in fucoidan science. The company is a GMP, ISO9001 and HACCP accredited manufacturer and the only producer of high purity, certified organic fucoidan. Marinova exports its fucoidan extracts to more than 25 countries across the globe and is the world’s leading fucoidan supplier to research institutions and nutraceutical and pharmaceutical companies.
**MARITECH® FUCOIDAN RANGE**

**Overview**

Maritech® fucoidans are unique, high purity ingredients that are non-toxic and safe for human ingestion. They have been extensively researched and shown to impart a range of beneficial bioactivities. Maritech® fucoidans are particularly well known for their efficacy in anti-cancer, anti-viral, immune modulation, gut health, anti-inflammation and anti-aging applications.

Marinova produces its lead fucoidan ingredients from two species of certified organic, wild grown macroalgae:

*Undaria pinnatifida*: commonly called wakame or mekabu, this is an edible seaweed that grows in the pristine ocean waters of Patagonia and Tasmania. It yields a fucoidan extract which is highly acetylated and rich in galactose.

*Fucus vesiculosus*: commonly called bladderwrack, this species grows in the clear northern hemisphere waters of Nova Scotia and Brittany. It yields a fucoidan extract with a very high fucose content that is not acetylated.

Fucoidans have different chemical structures and bioactivities depending upon the species of seaweed from which they are derived, and the method by which they are extracted. From the *Undaria* and *Fucus* species of seaweeds, Marinova has created a range of high purity fucoidan ingredients, each with distinct benefits and bioactivities.

This range includes highly refined compounds for medical research and pharmaceutical development through to certified organic fucoidan extracts for nutritional and personal care applications. Included in the Maritech® range are extracts that contain both fucoidan and antioxidant-rich algal polyphenols.
MARITECH® FUCOIDAN RANGE

Characterisation

Fucoidans are highly branched, complex polysaccharides of varying size, typically with a high molecular weight. Fucoidans are characterised chemically using validated assays that quantify the sulfation, acetylation, molecular weight and the content of sugars in the carbohydrate "backbone".

Like fucoidan, algal polyphenols are complex structures. The type of polyphenol found in Fucus vesiculosus is a polymeric form of phloroglucinol. The polyphenol content of Maritech® extracts is determined using a validated colorimetric assay.

Pure source

Marinova is a fervent protector of the world’s marine environment and exemplifies sustainable practices in every element of its business. Marinova only sources wild grown, certified organic brown macroalgae from the world’s purest ocean waters. This includes the cool, pristine ocean waters of Patagonia, Nova Scotia, Brittany and Tasmania.

All seaweeds are sourced using best practice environmental standards. The macroalgae used by Marinova is hand-harvested in line with its seasonal growth cycle to minimise disruption to the environment and ensure sustainable growth. Once harvested, the seaweed is immediately dried to retain the natural bioactivity of fucoidan.

Zero-waste manufacturing

Marinova is continuously implementing new initiatives to ensure sustainability and protection of the environment. Since establishing its state-of-the-art extraction facility, the company has succeeded in diverting all seaweed residues away from unproductive landfill and into new, value-added products. Seaweed not utilised for the extraction of high purity fucoidan extracts is sold by Marinova into the gourmet and wholefoods sectors. Both liquid and solid by-products of the extraction process are captured and converted into nutrient-rich organic additives for the horticultural sector. As a result of these initiatives, the company is on the cusp of becoming a legitimate zero-waste manufacturer.
The high purity of Maritech® fucoidan is attributed to the unique, proprietary Maritech® extraction process, developed and used exclusively by Marinova. The aqueous extraction and purification process utilises advanced physical filtration methods to separate and purify fucoidan without the use of harsh organic solvents. This solvent-free technology, and the exceptional quality of the seaweeds, are the reasons that Marinova stands alone as the only manufacturer of certified organic, high purity fucoidan.

The Maritech® process creates efficacious, high purity fucoidan extracts that are:

- Certified organic
- Non-GMO accredited
- Solvent-free
- Kosher and Halal certified
- Nature-identical
- Highly bioavailable

**MARITECH® FUCOIDAN RANGE**

Maritech® extraction process

Wild, certified organic seaweed is hand-harvested from the world’s cleanest ocean waters. Freshly harvested seaweed is immediately air-dried to preserve maximum bioactivity.

**PURE SEAWEED SOURCE**

Advanced filtration systems developed by Marinova capture and purify the fucoidan. All nutrient-rich by-products are then utilised in certified organic horticultural applications.

**PROPRIETARY FILTRATION**

Specialised technologies dehydrate the fucoidan concentrate to create a shelf stable, free-flowing powder. This powdered fucoidan is immediately sealed and stored.

**DEHYDRATION**

Pure water physically separates whole fucoidan compounds from the seaweed matter. No harsh solvents are used, which ensures the natural fucoidan structure is preserved.

**AQUEOUS EXTRACTION**

Purified fucoidan is carefully de-watered at low temperatures to produce a highly concentrated extract.

**CONCENTRATION**

Highly qualified technicians perform multiple tests throughout the entire process of each batch, to ensure only superior quality products are released. Detailed specifications are provided with each product order.

**QUALITY TESTING & RELEASE**
Studies undertaken by Marinova and independent research groups around the world have investigated the efficacy of fucoidan in a diverse range of indications and clinical settings. Marinova has a very active research program. It is continually engaging with leading international universities and research institutions to investigate the beneficial properties of Maritech® fucoidan extracts in various human health settings.

Marinova’s in vitro research, animal studies and human clinical trials are currently focussed on the key health indications below:
Cancer and fucoidan

Fucoidan is particularly well known - and widely utilised - for its anti-cancer properties. Extensive research has been undertaken in this field, demonstrating the potential for fucoidan to be used alongside conventional treatments.\textsuperscript{3,6,7}

In various studies, fucoidan has been found to:

- slow tumour metastasis
- enhance therapeutic effects of conventional therapy
- reduce side effects of chemotherapy
- defend against treatment-related weight loss and muscle loss

Directly affecting cancer cells

Fucoidan can directly affect cancer cells via cellular pathways that involve the activation of NF-κB. This activation is mediated by PI3K/Akt and ERK signaling pathways.\textsuperscript{7}

Recent research indicates that fucoidan may also induce programmed cell death (known as apoptosis) in breast and colon cancer cells by modulating the endoplasmic reticulum stress cascades.\textsuperscript{8}

Maritech\textsuperscript{®} fucoidan has been shown to cause cell cycle arrest in the first growth phase (G1) of a HCT116 human colon cancer cell line.\textsuperscript{9} By halting the cell cycle process in this way, the colon cancer cells are unable to divide and spread.
BIOACTIVITIES

Anti-cancer

Using the immune system
In vitro experiments and animal studies have shown that fucoidan exerts anti-cancer activity by activating immune cells and stimulating the production of anti-cancer cytokines.\(^6\)

Recent research indicates that fucoidan affects macrophages, a type of white blood cell that engulfs and destroys pathogens. In tumours, macrophages can become damaging by secreting chemical messengers, chemokine CCL22, that allow tumours to grow. By suppressing chemokine CCL22, fucoidan is able to switch macrophages back into a ‘healthy’ form.\(^10\) This, in turn, inhibits the migration and growth of cancer cells and the recruitment of CD4+ T lymphocytes.

Blocking chemical messages to cancer
Fucoidan has been shown to effectively block chemical messages to tumours by interfering with the binding between the cellular receptor CXCR4 and chemokine CXCL12 (or SDF-1).\(^11,12\)

In additional research, fucoidan extracts from \textit{Saccharina latissimi} and \textit{Fucus vesiculosus} were shown to bind to CXCL12 and prevent binding to the CXCR4 cellular receptor. In doing so, fucoidan prevented downstream effects, including the secretion of matrix-degrading enzymes necessary for metastasis.\(^13\)

Reducing pre-cursors to cancer
The occurrence of cancer is often linked to chronic inflammation. In pre-clinical studies, Maritech\(^\text{®}\) fucoidan has been shown to significantly reduce gut inflammation and colitis by inhibiting key inflammatory enzymes expressed in the gastrointestinal tract, including COX-1, COX-2 and LOX-15.\(^14\)

In a mouse model, orally ingested Maritech\(^\text{®}\) fucoidan was found to significantly reduce the clinical symptoms, pathology and cytokine elevations of acute colitis.\(^15\) By doing so, Maritech\(^\text{®}\) fucoidan shows promise as a preventative for a number of gastrointestinal disorders and cancers which are closely associated with chronic gastrointestinal inflammation.

In addition, Maritech\(^\text{®}\) fucoidan may play a preventative role in \textit{Helicobacter pylori}-induced diseases and gastric cancer. \textit{Helicobacter pylori} is the primary cause of chronic stomach inflammation, peptic ulcer diseases and gastric cancers in humans. In a cellular model designed to mimic the natural infection of this ulcer-causing bacteria, Maritech\(^\text{®}\) fucoidan effectively dislodged \textit{Helicobacter pylori} from human gastric epithelial cells and reduced adhesion by up to 55%.\(^16\)
Bioactivities

Anti-cancer
BIOACTIVITIES

Anti-cancer

Fucoidan research in various cancer types:
Fucoidan research has demonstrated multi-faceted anti-cancer activity across a wide range of tumour types:

Colorectal cancer
In recent research, fucoidan was shown to inhibit the growth of a colon cancer cell line via inhibition of T-cell originated protein kinase (TOPK). In this study, fucoidan was also orally administered to mice and found to suppress the growth of human colorectal tumours through the same pathway. Results show the potential for fucoidan to be used as a complementary therapy to improve the effectiveness of current cancer treatments. As previously discussed, Maritech® fucoidan has been shown to induce DNA damage and cause cell cycle arrest in the first growth phase of a HCT116 human colon cancer cell line. This action disrupts the ability for the cancer cells to divide and spread.

Lung cancer
In a lung cancer mouse model, fucoidan down-regulated the expression of a number of key markers associated with tumour development, spread and proliferation. These markers included matrix metalloproteinases, NF-κβ and vascular endothelial growth factor. The orally ingested fucoidan was shown to reduce lung masses and lessen weight loss.

Liver cancer
In an in vitro study, fucoidan inhibited the growth of liver cancer cells through the AMPK-associated suppression of fatty acid synthesis and cell cycle G1/S transition. In further in vitro research, fucoidan increased the activity of tumour suppressor proteins p53 and p38 MAPK, which directly inhibits the proliferation of hepatic tumour cells and induces apoptosis.

Breast cancer
Extensive research demonstrates the effects of fucoidan on breast cancer in animal models. Maritech® fucoidan has been shown to significantly improve the effectiveness of tamoxifen, a common chemotherapy used in breast cancer. In a mouse model, orally ingested Maritech® fucoidan reduced breast cancer tumour growth by up to an additional 26% when taken alongside tamoxifen.

Oral cancers
Fucoidan reduced the growth of oral cancer cells and caused cell death in an in vitro study of mucoepidermoid carcinoma, a type of oral cancer. In this research, fucoidan decreased cell proliferation and induced caspase-dependent apoptosis via down-regulation of the extracellular signal-regulated kinase ERK1/2.
**BIOACTIVITIES**

**Anti-cancer**

**Prostate cancer**
Fucoidan has been shown to induce cell death in an *in vitro* study of PC-3 human prostate cancer cells. In the study, fucoidan was shown to activate apoptosis through the use of both intrinsic and extrinsic pathways. Fucoidan has also been found to inhibit growth and induce apoptosis in DU145 human prostate cancer cells involving the PI3K/Akt signaling pathway.

**Ovarian cancer**
Maritech® fucoidan has been shown to decrease the growth of a TOV-112D human ovarian cancer cell line. In a mouse model, the ingestion of Maritech® fucoidan decreased the growth of this tumour line by up to 33%.

**Pancreatic cancer**
Fucoidan decreased the ability for pancreatic cancer cells to secrete matrix-degrading enzymes required to metastasise and spread in an *in vitro* model. In addition, fucoidan was shown to interfere with the binding of chemokines to the cellular receptor CXCR4. Inhibition of CXCR4 has been shown in an animal model to reduce pancreatic tumour growth and metastases. Fucoidan also demonstrated potential to reduce the effects of acute pancreatitis due to its ability to block selectins.

**Cervical cancer**
Maritech® fucoidan has been shown to reduce the growth of a HeLa human cervical cancer cell line. Ingestion of Maritech® fucoidan was found to decrease the growth of this tumour line by up to 70% in a mouse model.
### Anti-cancer

**Maritech® fucoidan and chemotherapy efficacy**

In pre-clinical studies, Maritech® fucoidan has been shown to improve the effectiveness of a number of common chemotherapies. *In vitro* studies showed strong synergistic activity between Maritech® fucoidan and both paclitaxel and tamoxifen, as well as additive activity between Maritech® fucoidan and topotecan.\(^{25}\)

In further pre-clinical research, Maritech® fucoidan has been shown to considerably improve the efficacy of tamoxifen towards breast cancer. In a mouse model, ingestion of Maritech® fucoidan decreased breast cancer tumour growth by up to an additional 26% when taken alongside tamoxifen.\(^{22}\)

**Safety of Maritech® fucoidan with chemotherapy**

It is important for patients and their physicians to be confident that any supplements taken during cancer therapy are safe and do not cause clinically significant adverse effects or interactions. Both *in vitro* tests and human clinical studies have demonstrated the safety of Maritech® fucoidan when used in combination with chemotherapy.

A human clinical study investigated the pharmacokinetics of Maritech® fucoidan on two hormone therapies, tamoxifen and letrozole, commonly used in the treatment of breast cancer.\(^{32}\) Results showed that the ingestion of Maritech® fucoidan caused no adverse effects and no significant changes in steady-state plasma concentrations of letrozole, tamoxifen or tamoxifen metabolites. Additional toxicity monitoring showed that all parameters measured over the study period remained unaffected by fucoidan. These results demonstrate the safety of taking Maritech® fucoidan alongside letrozole and tamoxifen.

A separate *in vitro* study evaluated drug interactions between fucoidan and the chemotherapy drugs paclitaxel, tamoxifen and topotecan in a range of cancer cell lines.\(^{25}\) Five hepatic metabolism phase II pathways involved in chemotherapy action were evaluated — GST, QOR, COMT, UDP and UGT. These key enzyme pathways are required for the effective uptake and action of chemotherapy. Results showed that Maritech® fucoidan did not interfere with these enzyme pathways at physiologically relevant concentrations. These findings demonstrate the safety of fucoidan as an adjunct to cancer therapy.

---

**Improved effectiveness of tamoxifen in ZR-75 human breast cancer tumour**

<table>
<thead>
<tr>
<th>% reduction in tumour size compared to untreated</th>
<th>TAMOXIFEN</th>
<th>TAMOXIFEN + MARITECH® UNDARIA</th>
<th>TAMOXIFEN + MARITECH® FUCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>12.5</td>
<td>25</td>
</tr>
<tr>
<td>12.5</td>
<td></td>
<td>25</td>
<td>37.5</td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>37.5</td>
<td>50</td>
</tr>
</tbody>
</table>

These findings have been echoed in earlier studies, in which fucoidan from the seaweed species *Cladosiphon okamuranus* showed synergistic effects with three chemotherapy agents in breast cancer cell lines.\(^{29}\) In other research, *Undaria pinnatifida* fucoidan was found to increase the efficacy of the cancer drug lapatinib and reduce morbidity in a melanoma model.\(^{30}\) Fucoidan has also greatly increased the efficacy of the chemotherapy drug etoposide in human malignant lymphoid cell lines.\(^{31}\)
BIOACTIVITIES

Anti-cancer

Reducing chemotherapy side-effects
Research shows that fucoidan has the potential to assist in alleviating the following side effects that are common during chemotherapy treatment:

Inflammation
- Raised inflammatory levels are often seen in late stage cancer as a side effect of chemotherapy. In a clinical trial, 4 g of fucoidan was administered daily to 20 patients with advanced cancer. Results showed that fucoidan significantly reduced proinflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) after 2 weeks.33

Fatigue
- In a clinical study involving patients with resectable colon cancer, the daily ingestion of 4.05 g of fucoidan led to a reduction in fatigue and patients were able to tolerate more rounds of chemotherapy.34
- Fucoidan has also been shown to reduce fatigue levels in a mouse model, involving the equivalent of a human dose of 1.5 g of fucoidan per day. In this model, reduced fatigue was associated with increased levels of serum glucose and decreased levels of serum lactate, ammonia and triglyceride levels.

Joint pain
- In an osteoarthritis study, patients who ingested 1 g of Maritech® fucoidan daily achieved a 52% reduction in their osteoarthritis symptoms.36
- In a recent breast cancer study investigating the effects of Maritech® fucoidan on chemotherapy, 20% of patients experienced a reduction in joint pain. This is thought to be associated with a reduction in systemic inflammation.52

Gastrointestinal impairment
- In a colitis mouse model, the oral ingestion of Maritech® fucoidan was shown to be effective in reducing inflammation in the gut.15
- Fucoidan has been shown to be highly effective in restoring mucosal immunity in the gut. As demonstrated in a cyclophosphamide-induced mucositis mouse model, fucoidan enhanced the expression of IgA antibodies (essential for mucosal immune function) and reversed cyclophosphamide-induced damage.37
- In an animal model, fucoidan prevented changes to the levels of gastric hormones gastrin and serotonin – a common side effect of chemotherapy. These findings suggest that fucoidan may assist in maintaining normal gastrointestinal function during cancer treatment.38

Weight loss and muscle wasting
- Fucoidan effectively addressed a reduction in appetite, skeletal muscle atrophy and systemic inflammation in a bladder cancer mouse model.39
- Fucoidan shows promise as a preventative agent for minimising weight loss symptoms and reducing tumour growth during chemotherapy treatment. As demonstrated in a Lewis lung cancer model, fucoidan reduced cachectic symptoms and inhibited the metastasis of lung carcinoma by down-regulating metastatic factors VEGF and matrix metalloprotease enzymes.18
BIOACTIVITIES

Immune modulation

Extensive research undertaken on the immuno-modulatory properties of fucoidan shows a range of beneficial effects including:

- Boosting the immune response
- Activating Natural Killer cells and cytotoxic T cells
- Mobilising stem cells
- Dampening allergic responses

Boosting key immune cells

In a clinical study involving healthy normal subjects, Maritech® fucoidan demonstrated its ability as an immune-priming agent by increasing cytotoxic T cell and Natural Killer cell levels after 3 days. Over the 28 day study period, there was a continual increase in phagocytic activity of monocytes and granulocytes, as well as a reduction in the levels of inflammatory cytokine IL-6. Such an increase in immuno-modulatory activity may be useful as a preventative for infections such as seasonal colds and flu.

In a further study, Maritech® fucoidan extracts significantly enhanced the immune function of cancer-affected mice. The key immune marker Immunoglobulin G (IgG) was significantly modulated, showing a 500% increase relative to controls after 1 week.

Reducing allergic responses

Research has found that fucoidan can reduce allergic responses through oral ingestion and even topical application. In an in vitro study, fucoidan was shown to suppress the production of IgE antibodies from both healthy subjects and subjects with allergic dermatitis.
Immune modulation
BIOACTIVITIES

Gut and digestive health

Maritech® fucoidans are the only high purity, certified organic fucoidans with demonstrated potential in gut and digestive health applications. Comprehensive research suggests a range of gastrointestinal benefits from fucoidan including:

- Protecting gut flora from antibiotics
- Maintaining the balance of good and bad bacteria
- Reducing gut inflammation
- Reducing the growth of yeasts and fungus
- Inhibiting viruses and bacteria
- Protecting against liver disease and fibrosis

**Protecting gut flora from antibiotics**

An unwanted side effect of antibiotic use is the reduction of beneficial bacteria in the gut. Human and animal studies have linked antibiotic-induced changes in the composition of gut flora to a number of negative health outcomes, including obesity and diabetes mellitus.\(^4^5\)

Evidence shows that Maritech® fucoidan has protective effects on beneficial gut bacteria during antibiotic use. Importantly, research also demonstrates that Maritech® fucoidan does not interfere with the treatment action of the antibiotic in fighting harmful bacteria.\(^9\)

In an *in vitro* study involving the common antibiotic gentamicin, Maritech® fucoidan was shown to protect the levels of good *Escherichia coli* bacteria which naturally reside in the human gut.\(^9\) In the same study, Maritech® fucoidan was shown to have no impact on the action of gentamicin against pathogenic *Staphylococcus aureus* bacteria. This study reinforces the protective benefits of fucoidan on good bacteria during antibiotic use, whilst still enabling full antibiotic activity against bad bacteria.

**Reducing gut inflammation and colitis**

In a series of pre-clinical studies, Maritech® fucoidan has been shown to significantly reduce gut inflammation and colitis by inhibiting key inflammatory enzymes expressed in the gastrointestinal tract, including LOX-15, COX-1 and COX-2.\(^1^4\) In a mouse model, Maritech® fucoidan was found to significantly reduce the clinical symptoms, pathology and cytokine elevations of acute colitis.\(^1^5\)

Maritech® fucoidan shows promise as a preventative for a number of gastrointestinal disorders, including cancers which are closely associated with chronic gastrointestinal inflammation.
BIOACTIVITIES

Gut and digestive health

Maintaining the balance of beneficial and harmful bacteria

Recent research has demonstrated that fucoidan can balance the composition of gut flora by promoting the growth of naturally-occurring beneficial bacteria and reducing the growth of harmful bacteria.

In a series of animal studies, dietary fucoidan has been shown to:

- Increase the abundance of beneficial bacteria, *Lactobacillus* and *Ruminococcaceae*, that naturally reside in the gut
- Decrease the abundance of potentially harmful bacteria, *Peptococcus* and *Enterobacteriaceae*, that can grow opportunistically to cause gastrointestinal problems and infections throughout the body
- Significantly decrease the inflammatory response and antigen load of gut microbiota

Together, these results demonstrate the potential for fucoidan to balance the composition of good and bad bacteria in the gut for digestive benefit.

Inhibiting the adhesion of H.pylori and E.coli bacteria

Maritech® fucoidan has been shown to effectively inhibit the adhesion of the pathogenic bacteria, *Helicobacter pylori* and *Escherichia coli* (*E.coli*), to human cells. *Helicobacter pylori* is the primary cause of chronic stomach inflammation, peptic ulcers and gastric cancers.

In a cellular model designed to mimic the natural infection of *Helicobacter pylori*, Maritech® fucoidan dislodged the ulcer-causing bacteria from human gastric epithelial cells and reduced adhesion by up to 55%.16

Maritech® fucoidan also inhibited the adhesion of *E.coli* bacteria to human epithelial cells by up to 72%.14 This study mimicked the adhesion of *E.coli* to epithelial cells that line human oral tracts, genitourinary tract and skin. Pathogenic strains of *E.coli* can cause intestinal infection, diarrhoea, abdominal pain and fever.
Reducing the occurrence of gastric ulcers
Fucoidan has demonstrated effectiveness in healing gastric ulcers and reducing ulcer-induced pain. In a randomised double blind human study, patients who ingested fucoidan in combination with conventional therapy reported a significant improvement in gastric ulcers and abdominal pain.48 Fucoidan has also demonstrated effectiveness in an animal model by reducing the occurrence of aspirin-induced gastric ulcers.49

Inhibiting viral infections
Fucoidan is a highly effective inhibitor of viruses that can infect the gastrointestinal system. In a number of in vitro studies, Maritech® fucoidan has been specifically shown to:
- Inhibit adhesion and block entry of viruses into host cells50
- Directly inhibit multiple strains of influenza which multiply in gut mucosa, including Avian influenza A H5N3 (bird flu)51 and H1N1 (swine flu)52
- Prevent the infection of herpes simplex viruses 1 & 253 which can affect microbial diversity and influence inflammatory bowel disease54

Reducing the growth of yeasts and fungus
Maritech® fucoidan has been shown to effectively inhibit the growth of fungus and yeast strains associated with compromised digestive function.

In an in vitro study, Maritech® fucoidan inhibited the formation of biofilm for the fungus species, Aspergillus brasilienis, and yeast species, Candida albicans.55 Biofilm formation is the process by which microorganisms attach to a surface and cultivate.

Whilst naturally found in the human gastrointestinal tract, Aspergillus brasilienis and Candida albicans species have the ability to overgrow and cause digestive problems, particularly in people who are immunocompromised.

Protecting against liver disease and fibrosis
Research has demonstrated that fucoidan can have a marked protective effect on the liver. Studies have shown that fucoidan not only protects against damage in toxicity models of liver disease, including CCL4 and Con A,56,57 but also in alcohol-induced58 and non-alcohol-induced fibrosis.59,60 In addition, fucoidan has been found to be beneficial in the treatment of patients with chronic hepatitis C, HCV-related cirrhosis and hepatocellular carcinoma.61

BIOACTIVITIES
Gut and digestive health

<table>
<thead>
<tr>
<th>FUCOIDAN µg/mL</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ASPERGILLUS BRASILIENSIS BIOFILM GROWTH</td>
<td>MARITECH® UNDARIA</td>
<td>MARITECH® FUCUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inhibiting viral infections
Fucoidan is a highly effective inhibitor of viruses that can infect the gastrointestinal system. In a number of in vitro studies, Maritech® fucoidan has been specifically shown to:
- Inhibit adhesion and block entry of viruses into host cells50
- Directly inhibit multiple strains of influenza which multiply in gut mucosa, including Avian influenza A H5N3 (bird flu)51 and H1N1 (swine flu)52
- Prevent the infection of herpes simplex viruses 1 & 253 which can affect microbial diversity and influence inflammatory bowel disease54

Reducing the growth of yeasts and fungus
Maritech® fucoidan has been shown to effectively inhibit the growth of fungus and yeast strains associated with compromised digestive function.

In an in vitro study, Maritech® fucoidan inhibited the formation of biofilm for the fungus species, Aspergillus brasilienis, and yeast species, Candida albicans.55 Biofilm formation is the process by which microorganisms attach to a surface and cultivate.

Whilst naturally found in the human gastrointestinal tract, Aspergillus brasilienis and Candida albicans species have the ability to overgrow and cause digestive problems, particularly in people who are immunocompromised.

Protecting against liver disease and fibrosis
Research has demonstrated that fucoidan can have a marked protective effect on the liver. Studies have shown that fucoidan not only protects against damage in toxicity models of liver disease, including CCL4 and Con A,56,57 but also in alcohol-induced58 and non-alcohol-induced fibrosis.59,60 In addition, fucoidan has been found to be beneficial in the treatment of patients with chronic hepatitis C, HCV-related cirrhosis and hepatocellular carcinoma.61
Fucoidan exhibits powerful anti-viral properties, with potential application in a range of therapeutic settings. Research demonstrates that fucoidan can prevent infection by blocking the entry of viruses into cells and inhibiting the adhesion of viruses to host cells.

Influenza
Both in vitro and animal studies have demonstrated the anti-viral activity of fucoidan against influenza viruses. Fucoidan has been proven to inhibit multiple influenza strains, including H1N1 (swine flu),52 Parainfluenza52 and Avian influenza A (bird flu) strains H5N1, H5N3 and H7N2.51,63

Herpes
Maritech® fucoidan has been shown to be a potent inhibitor of clinical strains of the herpes simplex virus by preventing entry into cells. This includes effective inhibition of HSV1 (cold sore virus) and HSV2 (genital herpes) strains.53 Maritech® fucoidan has also been shown to strongly inhibit the activity of herpes viruses HSV1, HSV2 and HCMV on human fibroblast cells.50 Additional research demonstrates that orally ingested fucoidan can protect against the infection of HSV1 as well as increase the production of viral antibodies.64

Other common viruses
Fucoidan has been shown to exhibit anti-viral activity against the measles virus,65 Newcastle virus66 and canine distemper.67 Clinically, fucoidan has also reduced pro-viral loads in patients with human T lymphotropic virus type 1 (HTLV-1)68 and showed benefits for patients with chronic hepatitis C.61
BIOACTIVITIES

Anti-inflammation

Fucoidan is well known - and continues to be studied - for its profound anti-inflammatory properties. Research shows that fucoidan has potential benefits in addressing systemic and local inflammation through its ability to block selectins, reduce cytokine levels and inhibit inflammatory enzymes.

Addressing systemic inflammation

Fucoidan has been shown to inhibit selectins and reduce the potential for systemic inflammation. The selectin blockade mechanism of fucoidan has been widely reported and reviewed.1 Cancer is one condition which uses L-selectins and P-selectins to metastasise to other tissue sites. Fucoidan has been shown in animal studies to inhibit this selectin-induced inflammatory process.69

Reducing gut inflammation and colitis

Maritech® fucoidan has been shown to reduce gut inflammation and colitis by inhibiting key inflammatory enzymes expressed in the gastrointestinal tract, including LOX-15, COX-1 and COX-2.14 In a colitis mouse model, orally-ingested Maritech® fucoidan reduced cumulative histological disease scores of ulcerative colitis by up to 36% and significantly lowered cytokine levels in the colon.15 Weight loss, a common and often undesirable side effect of colitis, was also reduced by more than 50%.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>% change (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1α</td>
<td>-55.9 (0.0002)</td>
</tr>
<tr>
<td>IL-1β</td>
<td>-51.2 (&lt;0.0001)</td>
</tr>
<tr>
<td>IL-10</td>
<td>-62.2 (&lt;0.0001)</td>
</tr>
<tr>
<td>MIP-1α</td>
<td>-46.5 (0.0004)</td>
</tr>
<tr>
<td>MIP-1β</td>
<td>-60.0 (0.0037)</td>
</tr>
<tr>
<td>G-GSF</td>
<td>-80.6 (&lt;0.0001)</td>
</tr>
<tr>
<td>GM-GSF</td>
<td>-51.0 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

Effect of oral fucoidan on colon-derived cytokine levels.

Combating skin inflammation

Fucoidan has been shown to impart anti-inflammatory benefits when applied topically. Research has demonstrated that fucoidan can limit allergy-induced inflammation and can be as effective as cortisone in combatting allergic dermatitis.43

In a series of clinical studies, Maritech® fucoidan was found to significantly reduce erythema and water loss from the skin both before and after exposure to UVA and UVB.70 In vitro models have also shown that Maritech® fucoidan can effectively inhibit glycation and degrading enzymes, elastase and collagenase.71 It can also induce the expression of the ‘anti-aging’ protein SIRT1.14

Improving osteoarthritis symptoms

Maritech® fucoidan has been shown to reduce the symptoms of osteoarthritis in a human clinical study.36 Osteoarthritis is a degenerative disease that involves the painful degradation of joint function. In this study, patients who ingested 1 g daily of Maritech® fucoidan achieved a 52% reduction in osteoarthritis symptoms. Similar results have been demonstrated in an animal model, in which fucoidan inhibited the development of osteoarthritis in rats.72
Anti-inflammation
The safety of fucoidan is widely supported by several lines of evidence including multiple human clinical trials, animal studies and in vitro research. This is unsurprising given the long history of seaweed consumption and use of fucoidan for therapeutic purposes, particularly in Asian cultures. Extensive literature has been published in this area, including 2,500 preclinical in vitro and in vivo studies on seaweed and over 1,600 studies involving fucoidan.

Comprehensive clinical testing and a full safety toxicity dossier confirms that Maritech® fucoidan is safe for human and animal consumption and topical application.25,32,36,41,73,74 Maritech® fucoidan ingredients from the Undaria pinnatifida and Fucus vesiculosus species of seaweed have attained FDA notified GRAS (Generally Recognised As Safe) status. They have been deemed safe for ingestion as a food ingredient at rates of up to 250 mg per day.

A recent preclinical assessment demonstrated that Maritech® fucoidan does not compromise the activity of chemotherapy drugs and is safe to use in a range of cancer treatment regimes.25 The study evaluated drug interactions of fucoidan alone and in combination with chemotherapy drugs paclitaxel, tamoxifen and topotecan. Results showed that Maritech® fucoidan did not interact with key enzyme pathways used by chemotherapy at physiologically relevant concentrations, thereby validating the safety of Maritech® fucoidan as an adjunct to cancer therapy.

Additional research has shown the safety of administering Maritech® fucoidan to breast cancer patients alongside conventional hormone treatments.32 Results found that Maritech® fucoidan caused no adverse effects or significant changes in steady-state plasma concentrations of letrozole, tamoxifen or tamoxifen metabolites. Toxicity monitoring also showed no significant differences in all parameters measured over the study period.

Supporting these clinical observations, Marinova has investigated the effects of Maritech® fucoidan on isolated cells in culture. 100% viability was maintained at very high fucoidan concentrations in a typical cell culture system. Maritech® Undaria pinnatifida fucoidan was found to be non-toxic at 5,175 μg/mL and Maritech® Fucus vesiculosus fucoidan was found to be non-toxic at 632 μg/mL. This extensive portfolio of research attests to the safety and tolerability of Maritech® fucoidan.
Global acceptance

All Maritech® fucoidan extracts have global regulatory and safety acceptance including:
- USA: Generally Recognised as Safe (GRAS)
- Australia: Therapeutic Goods Association (TGA) listable ingredients
- Canada: Health Canada NHP compliant
- Europe: Novel Foods approval
- China: Compliant with Algae Product requirements
- Korea: KFDA (Korea Food and Drug Administration) registered

Quality and certifications

With world-class extraction facilities and research laboratories located in Tasmania, Australia, Marinova manufactures superior fucoidan products under adherence to the most rigorous systems of quality control. The company has vertically integrated operations and a comprehensive certified organic supply chain. Marinova exports its products to more than 25 countries around the globe and is the leading supplier of high purity fucoidan to the research, nutraceutical and pharmaceutical sectors.

Marinova’s solvent-free Maritech® extraction process enables the company to produce and supply high quality fucoidan extracts with the following accreditations:
- Certified organic
- Non-GMO
- Kosher
- Halal
- Made in Australia under GMP
- ISO9001 and HACCP
- Solvent-free
- Safe and non-toxic
REFERENCES
REFERENCES


46. Wang W, Jovel J, Halloran B, Wine E, Patterson J, Ford G, et al. Maritech fucoidans are not intended to treat, cure or prevent any disease or health condition. The statements herein have not been evaluated by the Therapeutic Goods Association, Food and Drug Administration or other regulatory body. Maritech fucoidans are not intended to treat, cure or prevent any disease and recipients of this information must exercise their own judgement in determining the appropriateness for a particular purpose.

© Marinova Pty Ltd 2018. All rights reserved.

Maritech® is a registered trademark of Marinova Pty Ltd.

This paper is intended to provide scientific and educational information only and is not intended to promote or sell any product. The statements herein have not been evaluated by the Therapeutic Goods Association, Food and Drug Administration or other regulatory body. Maritech fucoidans are not intended to treat, cure or prevent any disease and recipients of this information must exercise their own judgement in determining the appropriateness for a particular purpose.