Fenoprolic® 70 – A Powerful Alternative to Pycnogenol®

Unlocking the Potential of Pine Bark Extract with a Bioequivalence Study

Executive summary

The following research explores the bioequivalence of Fenoprolic® and Pycnogenol®, two standardized pine bark extracts known for their high levels of oligomeric proanthocyanidins (OPCs) and their associated health benefits, including antioxidant, anti-inflammatory, and cardiovascular support.

While Pycnogenol® has dominated the market due to its established volume of clinical data, Fenoprolic presents a more accessible, affordable alternative. A comparative study using Eurofin's BioMAP® Diversity PLUS® Panel provided an in-depth, unbiased analysis of both extracts across 148 biomarkers in the same human primary cells, revealing practically identical bioactivity profiles despite being extracted from different species of pine trees.

The analysis shows a strong alignment in the biological effects of Fenoprolic® and Pycnogenol®, with comparable activity detected in 41 biomarkers across 9 of the 12 health systems tested. The twin bioactivity profile and the same OPC levels reinforce the case for their bioequivalence and suggest that Fenoprolic® delivers equivalent therapeutic benefits.[1]

As a result, Fenoprolic® emerges as a viable and cost-effective alternative to Pycnogenol®, suitable for diverse health applications in the nutraceutical market.

Harnessing the Health Benefits of Oligomeric Proanthocyanidins (OPCs)

Pine bark extract, especially standardized forms like Fenoprolic[1] and Pycnogenol [2], is valued for its rich content of oligomeric proanthocyanidins (OPCs), bioactive compounds with potent antioxidant and anti-inflammatory properties. These benefits extend to protecting cells from oxidative stress, enhancing cardiovascular health, reducing joint inflammation, improving skin condition, and supporting immune function.

Pine Bark Extract is a potent source of bioactive polyphenols with well-documented health benefits, offering versatile support for various wellness needs. However, its availability of quality material was limited by the complex and costly manufacturing process—until Eevia Health developed Fenoprolic®, a high-quality pine bark extract that delivers the same health benefits at a fraction of the cost. There are cheaper extracts in the market claiming to contain the same or higher level of OPC. However, proper analytical methods reveal that these extracts contain polymerized compounds that produce analytical results, such as OPC, but without bioefficacy.

Bioequivalence in Action: Comparing Fenoprolic® and Pycnogenol®

The research project aimed to evaluate whether Fenoprolic® can match Pycnogenol's® therapeutic claims by comparing their bioactivity and establishing bioequivalence. Using the BioMAP® Diversity PLUS® Panel, the study conducted an in-depth, unbiased assessment of the biological effects of both extracts across multiple human cell models.

Bioequivalence is crucial for validating therapeutic claims and ensuring product efficacy in the nutraceutical industry. It confirms that the two products deliver similar biological effects despite being made from different raw materials.

The BioMAP® Diversity PLUS Panel provides robust evidence to support Fenoprolic's bioequivalence to Pycnogenol, a clinically validated market leader, reinforcing its market credibility

Given Pycnogenol®'s market dominance, driven by its scientific data and aggressive legal actions against competitors, there is a need for accessible alternatives with similar health benefits. **By demonstrating comparable bioactivity between Fenoprolic® and Pycnogenol®, the study justified the use of equivalent health claims for Fenoprolic®, positioning it as an affordable and scientifically validated option in the nutraceutical space.**

[1] ***Fenoprolic®*** *is a trademark owned by Eevia Health Plc, Finland*
[2] ***Pycnogenol®*** *is a trademark owned by Horphag Research, Swizerland*

BioMAP® Diversity PLUS®: Comparative Bioactivity Across 148 Biomarkers

The BioMAP Diversity PLUS Panel offers an unbiased, data-driven method for analyzing the effects of both pharmaceuticals and nutraceuticals on human disease models and translational biomarkers. It uses primary human cell models to replicate the complex biology of various organs, such as the skin, lungs, and immune system. This allows for a more accurate assessment of how products interact across a broad set of biological systems in this project 12 systems.[2]

With 12 cell-based models covering critical biological processes, the BioMAP Diversity PLUS Panel is a versatile tool for evaluating health impacts across various tissue types and conditions.

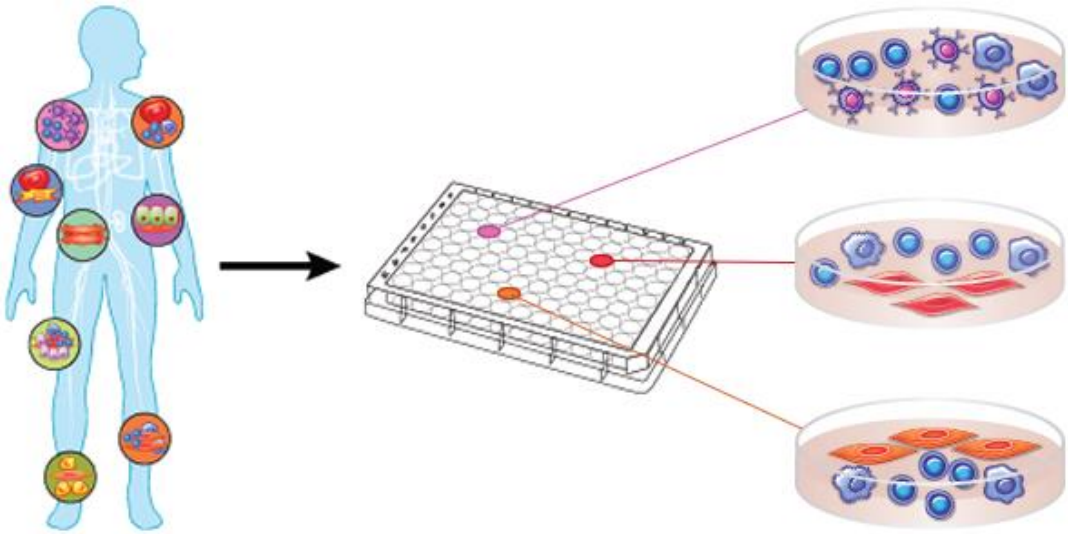


Figure 1: BioMAP Diversity PLUS Platform. Primary cells are extracted from human donors and built into an in vitro model of respective tissues. The platform encompasses 12 systems that simulate various biological processes, including vascular biology, immune response, airway inflammation, and connective tissue health. This setup allows for a comprehensive assessment of how substances interact across multiple physiological environments.3

The BioMAP platform allows researchers to evaluate the performance of health ingredients by comparing them directly with nutraceuticals that have shown benefits in clinical settings. It measures 148 different protein biomarkers—indicators that reveal changes in the body's biological activity—such as cell receptors, cytokines, chemokines, matrix molecules, and enzymes.

When a test substance is applied, it generates a unique BioMAP profile that shows how the body responds to it. This profile is matched against a reference database of over 4,000 substances, including common drugs and chemicals, to find similar activity patterns. **This approach is critical for nutraceutical companies like Eevia Health, providing data-backed insights into how Fenoprolic performs in a side-by-side comparison to Pycnogenol.**

A Head-to-Head Comparison: Fenoprolic® vs. Pycnogenol®

Although Fenoprolic® and Pycnogenol® are distinct extracts derived from different species of pine trees, the BioMAP Diversity PLUS analysis showed remarkably similar results. The study revealed a near-identical profile of activities across the 148 biomarkers examined, with significant similarities in 41 common biomarkers across 9 out of the 12 systems tested (as seen below).[4,5,6]

Additionally, a third-party evaluation found that both extracts contain similar levels of OPCs, the primary bioactive compounds responsible for nearly all the therapeutic effects associated with pine bark extracts. **This consistency in OPC levels aligns with the comparable activity profiles observed in the BioMAP analysis, reinforcing the case for the bioequivalence of Pycnogenol®.**

Bioactivity Profile Comparison:

Fenoprolic® (in red) and Pycnogenol® (in black)

The chart below (Figure 3) illustrates the BioMAP Plot Comparison of the two extracts, highlighting the striking similarities in their biological activities.

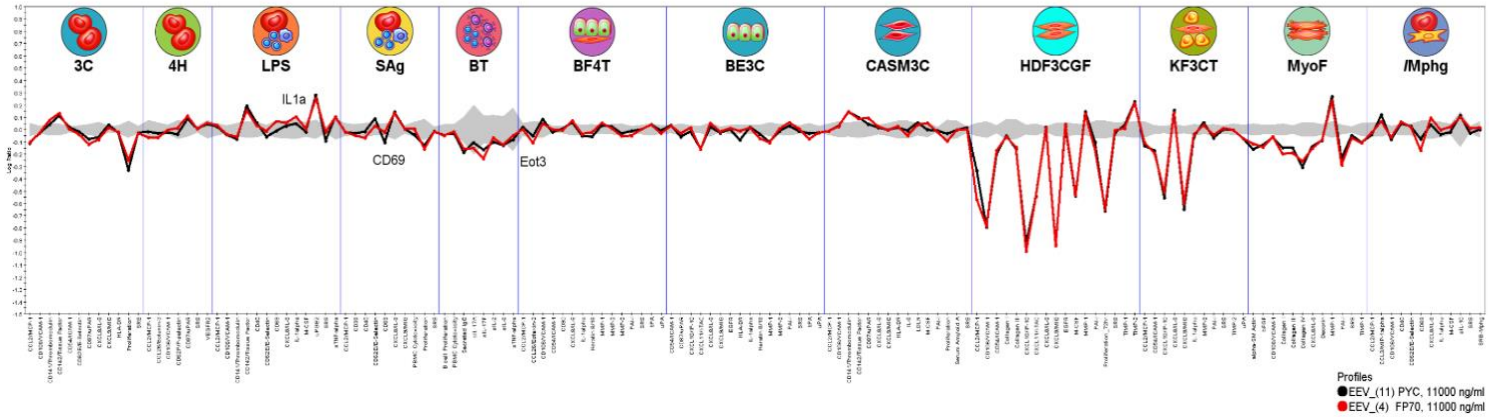


Figure 2: BioMAP Profile Plot Comparison of Fenoprolic® and Pycnogenol®

Key Similarities Between Fenoprolic® and Pycnogenol®

- Inflammation-Related Activities: Both extracts demonstrated significant modulation of key inflammation-related biomarkers, including MCP-1, VCAM-1, ICAM-1, and IL-8, across multiple biological systems, suggesting comparable anti-inflammatory properties.5,7
- Connective Tissue Remodeling: The extracts showed comparable effects on tissue remodeling biomarkers, such as collagen types I, III, IV, and matrix metalloproteinase-1 (MMP-1), indicating shared efficacy in promoting connective tissue health.5
- Immunomodulatory Activities: Similar immunomodulatory effects were observed, including the downregulation of sIL-17F, a cytokine that promotes inflammation, suggesting benefits in regulating immune responses.8
- Vascular Inflammation: Consistent activity patterns were found in biomarkers related to vascular inflammation, such as TNF-α and sPGE2, indicating similar cardiovascular health benefits.7
- Hemostasis: Both Fenoprolic® and Pycnogenol® affected key hemostasis-related biomarkers, including Tissue Factor (TF) and Thrombomodulin, suggesting comparable roles in regulating blood clotting and supporting vascular health.5

Achieving Bioequivalence: What It Means for Fenoprolic®

The BioMAP analysis demonstrates that despite their different origins and production methods, Fenoprolic® and Pycnogenol® exhibit nearly identical bioactivity profiles across various biomarkers. **The striking similarity in their effects on fundamental biological processes and consistent levels of OPCs strongly supports the case for their bioequivalence.** These findings suggest that the two extracts can deliver comparable therapeutic benefits.

While proving equal bioavailability remains challenging due to polyphenols' complex metabolism, the significant similarities in chemical composition reduce the necessity for further bioavailability comparisons. Since bioequivalence is defined by whether the outcomes or biological activities are the same, the BioMAP results already establish that both extracts meet this criterion, making additional bioavailability testing a less critical factor

This evidence positions Fenoprolic® as a compelling and cost-effective alternative to Pycnogenol®, offering comparable benefits for various health formulations.

Chemical composition analysis – small molecular weight polyphenols

One central follow-up point promised in the original article was to investigate the similarity further regarding compound composition with a chemical characterization of the two products, which will be discussed in this chapter.

The two products were submitted to an HPLC and MALDI-TOF chemical characterization panel to elucidate their possible chemical composition differences. In addition to the main active compound class, **oligomeric proanthocyanidins,** three other low molecular weight polyphenolic compound classes**, anthocyanins, hydroxycinnamic acids,** and **flavonols**, were chosen for this comparison.

The Anthocyanin analysis aimed to exclude them and confirm that they were not present in either of the materials. They were indeed not found in either of the products (hence, results omitted from this report).

Some differences were found between the other two low molecular weight chemical classes, Hydroxycinnamic acid and Flavonols. The results of both classes are described in the two tables below. Precise compound identification was not part of the scope of this characterization analysis.

Table 2. Hydroxycinnamic acids.

HYDROXYCINNAMIC ACIDS (mg/g)		
PEAK	**Fenoprolic®**	**Pycnogenol®**
1	0,4	-
2	0,3	0,4
3	0,2	0,8
4	0,3	-
5	-	-
6	0,1	-
7	0,4	0,7
8	-	-
9	-	-
10	-	-
11	-	-
SUM	**1,70**	**1,90**

Table 3. Flavonol content.

FLAVONOLS (mg/g)		
PEAK	**Fenoprolic®**	**Pycnogenol®**
1	0,67	-
2	0,29	-
3	0,18	0,41
4	0,09	-
5	0,88	-
6	0,40	0,44
SUM	**2,51**	**0,85**

The analysis detected 11 peaks coming from compounds that could be assigned to Hydroxycinnamic acids, six of them in high enough concentration for quantification. Fenoprolic® showed a somewhat more diverse composition, but the total amount of Hydroxycinnamic acids was almost the same.

For Flavonols, Fenoprolic® had a considerably more diverse and concentrated Flavonol content, with six (6) different identified peaks compared to two (2) found in Pycnogenol®. However, the absolute concentration of Flavonol compounds found in the products was very low, 0,085–0,251%, which might not be significant enough on a biological scale to establish bioactivity or cause significant differences between the two products.

Even when everything is added together, the three small molecular weight compound classes were found to be present in the products in less than 0.5% of the total composition, which is most likely too little to cause any significant efficacy differences.

Chemical composition analysis – oligomeric proanthocyanidins

In the previous part of this study, Fenoprolic® and Pycnogenol® were analyzed in a third-party laboratory for their respective OPC concentrations. Both products were found to have similar amounts of OPCs in them with the methods tested (DMAC and USP), the results being within 95% of each other with both methods tested. Fenoprolic® had a slightly lower concentration in both cases, most likely coming from the differences in the standardization protocol.

However, to further investigate the chemical characteristics of the most abundant class of polyphenols and the purported active component of both pine bark extracts, oligomeric proanthocyanidins were analyzed with a MALDI-TOF using the Bruker Autoflex MALDI-TOF instrument. Spectra was collected in a mass range of 700 – 3500 Da.

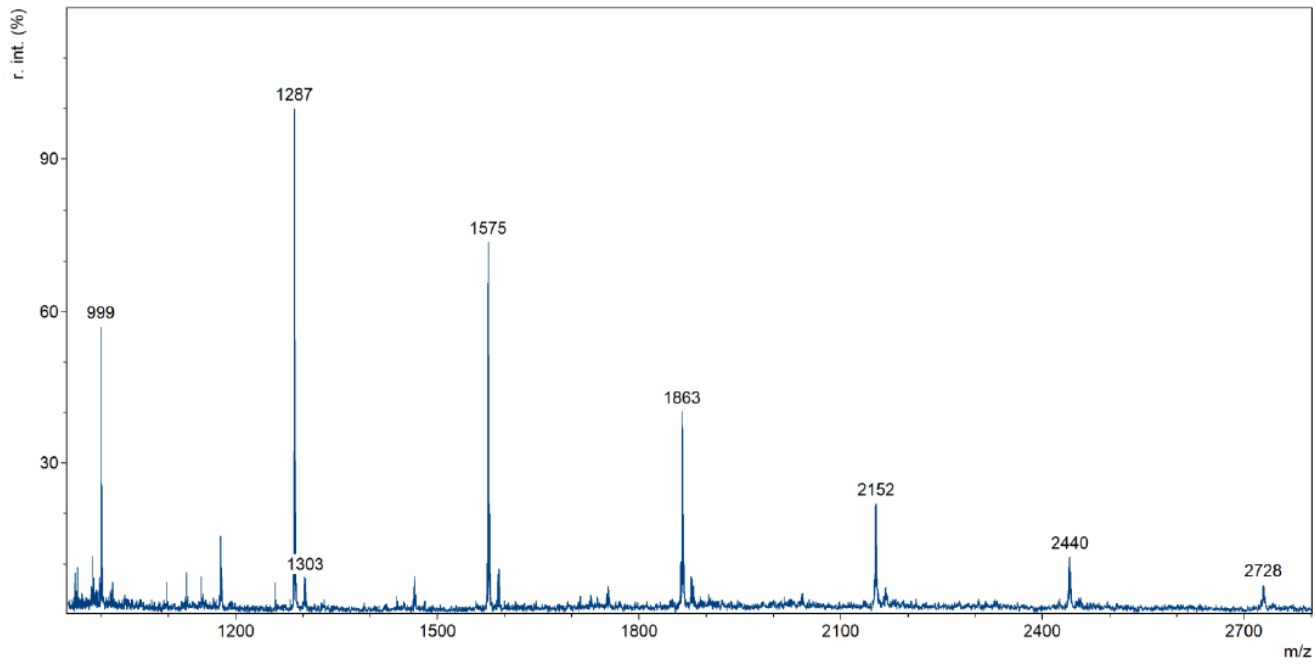


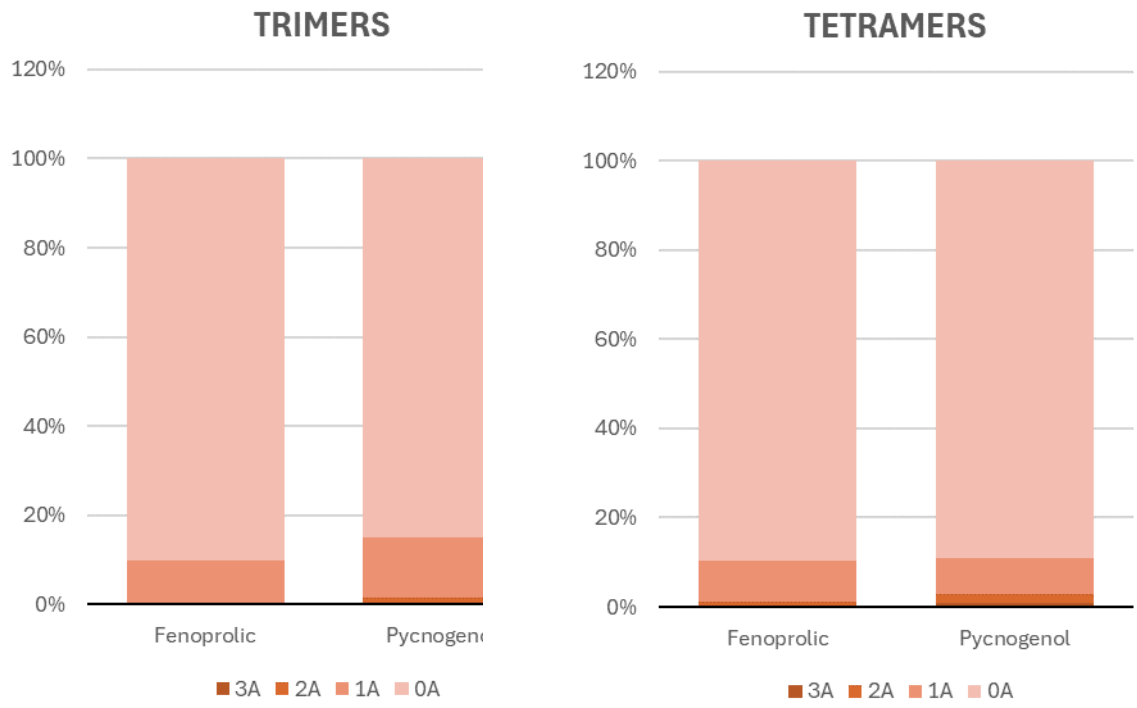
Figure 3. MALDI-TOF spectra of Fenoprolic®, showing the isotope distribution of OPC oligomers of various degrees of polymerization, from trimers (999) all the way up to the nonamers (2728).

Deconvolution of OPC isotope distributions enables the relative ratios (%) of interflavan bonds to be determined at each degree of polymerization from the trimer through the

heptamer. **Each isotope peak represents a specific chemical configuration of an OPC molecule. Hence, with this data, it is possible to see how the absolute OPC concentration compares, how the OPC molecules themselves are built, and what their relative distribution is in the product.**

For the Fenoprolic® and the Pycnogenol® pine bark extracts, the nonamer (9 catechin units long oligopolymer) was the highest observed OPC oligomer. Additionally, OPCs of both products were found to be almost exclusively B-type (0A-type) interflavan bonds. These semiquantitative data can be used not only for comparison purposes but also to establish bioequivalence and to support the authenticity/identification of the proanthocyanidin fraction.

When mean percent rations of interflavan bonds at each degree of polymerization are compared, the products are qualitatively similar across the oligomer space, with the B-type (0A) interflavan bond dominating the profiles.



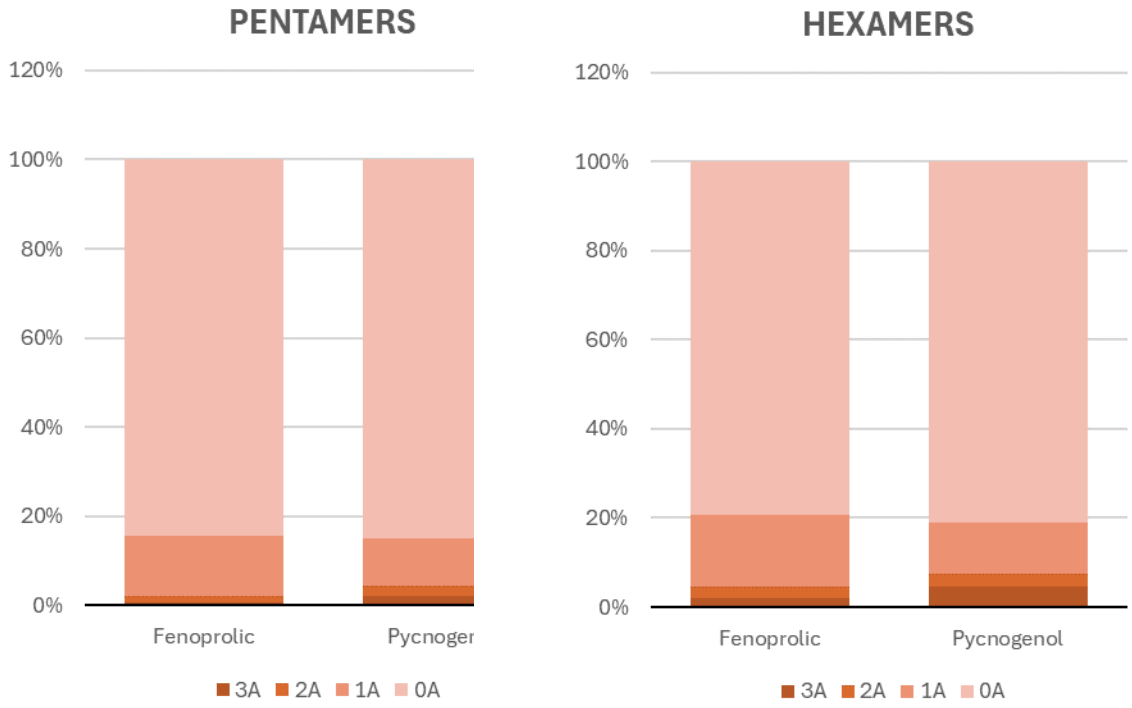
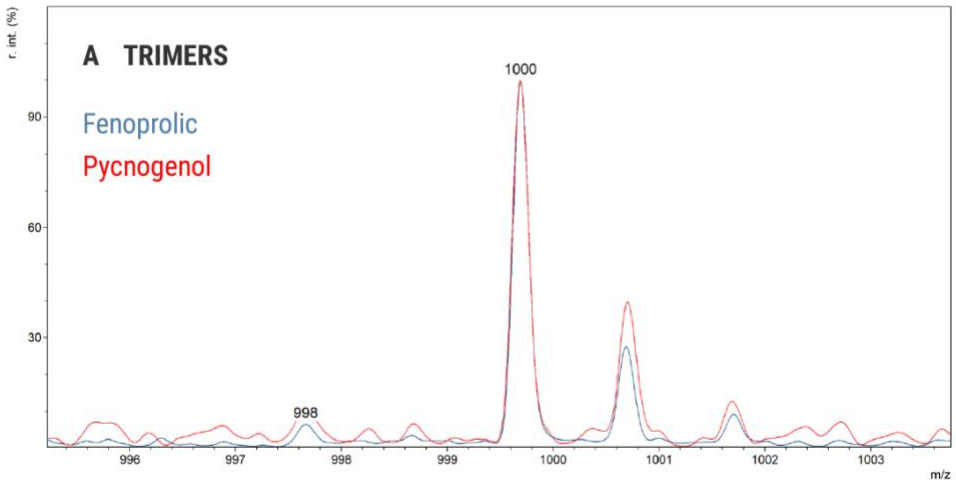


Figure 4. Mean percent ratios of different interflavan bonds at each degree of polymerization from trimers to the hexamers for Fenoprolic® and Pycnogenol®. When the colored bars are similar between the two products, their OPC content in their respective degree of polymerization was of similar chemical configuration.

This similarity can also be observed directly from the MALDI-TOF spectra by zooming in on top of the oligomers and comparing the overlapped and normalized spectra of the two products simultaneously. Interflavan bond distribution and ratios are very similar in all degrees of polymerization.



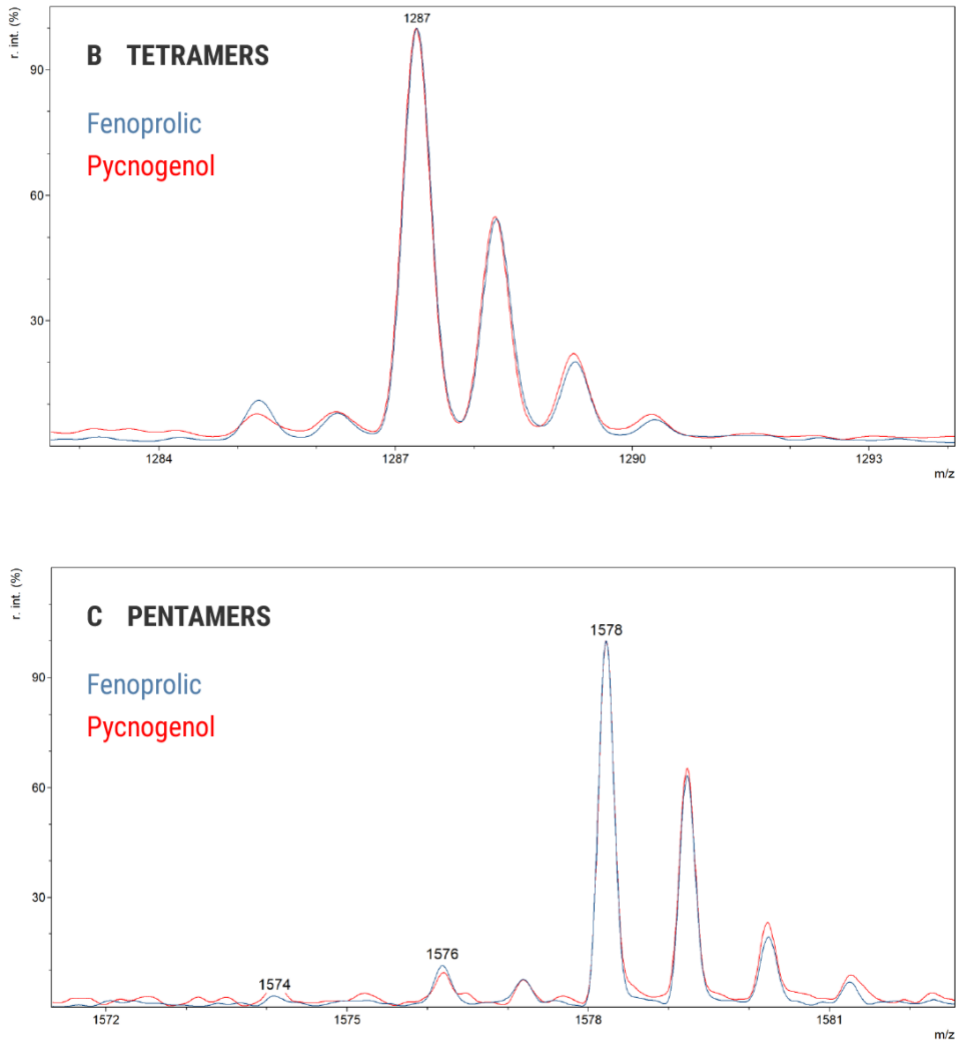


Figure 5. Overlapped MALDI-TOF spectra of Fenoprolic® (blue) and Pycnogenol® (red) oligomeric proanthocyanidins for trimer (A), tetramer (B) and pentamer (C) degree of polymerization. Products exhibit remarkable similarity across all degrees of polymerization.

Discussion and future efforts

This report article was written to follow up on the previously published Research Article, which observed and reported findings of close to identical bioactivity profiles between the two products of Fenoprolic® and Pycnogenol® across the 148 biomarkers studied in the BioMAP panel. One purpose of this whitepaper was to see if further chemical characterization of the two products could help explain the observed bioactivity similarities.

In these reported efforts, Fenoprolic® had a more diverse and over two-fold more concentrated portion in a tiny molecular weight polyphenol class studied the Flavonols. However, the actual concentration was very low for both products, 0.25% and 0.09%. Such a slight difference is most likely not able to contribute much to the overall bioactivity observed so far.

When the main active compound class of both products, oligomeric proanthocyanidins (OPCs), were studied in detail using MALDI-TOF mass spectroscopy, similarities between the two products were once again observed, as the OPC fraction was found to have considerable similarities, not only in polymerization rate but also in cross-linkage features and observed functional group substitutions. The active component of the products was found to consist predominantly of the same kind of OPC molecules, with the same kind of degree of polymerization and interflavan bonds.

The apparent similarity in the active component fraction fits well with the previously discovered identical bioactivity in the BioMAP platform. If over 70% of the product composition predominantly consists of the same kind of active compounds, it's reasonable to expect that the activity of those compounds inside biological systems will be the same as well.

In the pharmaceutical world, two drug products are considered bioequivalent when their bioavailability in both rate and extent after administration are equal, and the degree of their effects concerning both efficacy and safety can be essentially the same or near identical. If two products are confirmed to be bioequivalent, they are expected to work the same.

While the emphasis on bioavailability makes perfect sense in pharmaceuticals – where products are pure chemical compounds – it is not as simple in nutraceuticals and botanical extracts. The typical scenario involving bioequivalence determination between two drugs is conducted between two compounds of identical chemical structure, but in botanical extracts, the bioequivalence must be established between two complex mixtures of compounds.

In a discussion of bioequivalence between Fenoprolic® and Pycnogenol®, both chemical composition and bioactivity have now been studied in a reasonable amount of detail, with both results speaking in favor of bioequivalence. The final challenge would be to demonstrate equal bioavailability, but given the complexity of polyphenol bioavailability and metabolism, that might be a very difficult task to achieve. However, since bioavailability is always an expression of the chemical composition, and that has already been shown to have significant similarities, bioavailability comparison can be considered somewhat redundant at this point. Ultimately, bioequivalence is defined as whether the outcome or activity can be expected to be the same, which was established already with the BioMAP results.

Fenoprolic® 70: The Ultimate Pine Bark Extract

Fenoprolic® is a premium, organic oligomeric proanthocyanidin (OPC) extract made from the bark of Arctic pine trees (Pinus sylvestris), sourced from the pristine forests of Finnish Lapland. Located north of the Arctic Circle, this region's pure and unspoiled nature provides ideal conditions for wild plants to thrive. The area's soil has exceptionally low lead levels, far below those found in other parts of Europe, ensuring the raw materials used for Fenoprolic® are as pure and high-quality as they come.

Standardized to 70 ± 5% procyanidins (USP-NF), Fenoprolic provides a robust and diverse spectrum of bioactive components, including monomeric catechin, lignans, phenolic acids, stilbenes, and flavanonols. **This diversity in oligomeric and polymeric proanthocyanidins sets it apart from other pine bark extracts, delivering a more comprehensive profile of beneficial polyphenols.**

Fenoprolic® effectively promotes gut health, reduces inflammation, and supports tissue remodeling. The health ingredient has demonstrated activities related to immune modulation and hemostasis, making it a versatile choice for diverse health applications. The extract's powerful antioxidant and anti-inflammatory properties further enhance its therapeutic potential, contributing to overall health and well-being.

Why Choose Fenoprolic®? A Look at Purity and Efficacy

Fenoprolic® is produced through a sustainable, water-based multi-step extraction process that employs green chemistry techniques and chromatographic purification to achieve a high concentration of OPCs. Free from excipients, additives, or preservatives, this standardized extract maintains a pure and clean formulation, boasting contaminant levels less than 10% of typical alternatives on the market.

This exceptional purity ensures safer consumption and makes Fenoprolic ideal for individuals with sensitivities or those seeking the highest quality supplements. The lower levels of impurities also mean a more effective product, as the active ingredients are delivered in their most potent form

With 100% traceable and organic-certified raw materials sourced from Arctic pine bark, Fenoprolic® delivers a potent, eco-friendly solution that combines unparalleled purity and environmental responsibility—making it a superior choice for those seeking the health benefits of an all-natural pine bark extract.

Sustainable Sourcing: The Importance of Finnish Lapland

Fenoprolic® sets a new standard for pine bark extracts, combining advanced cold processing and sustainable practices to deliver exceptional purity and nutrient quality. Here is a closer look at what makes this ingredient stand out:

1. **Advanced Cold Processing Technique:** Fenoprolic is produced using a proprietary cold processing method developed by Eevia Health. This method preserves the raw Arctic pine bark's nutrients for maximum health benefits.

2. **High Purity and Low Contaminant Levels:** The extraction process results in a product with contaminant levels less than 10% of those found in typical pine bark extracts. This exceptional purity is achieved because the raw materials have ultra-low starting levels and are processed through a multi-step water-based process and chromatographic purification.

3. **Concentration of Low-Molecular Weight OPCs:** Fenoprolic contains high concentrations of low-molecular-weight oligomeric proanthocyanidins, optimized for better bioavailability, making the health benefits more accessible.

4. **Sustainable and Environmentally Friendly Practices:** The raw materials are 100% traceable and certified organic, sourced from the pristine forests of Finnish Lapland. The manufacturing process adheres to green chemistry principles, minimizing environmental impact while maintaining the highest product quality.

Structure/Function Claims

Fenoprolic is associated with a few key structure-function claims:

1. **Gut barrier integrity:** The proanthocyanidins in Fenoprolic are indicated to have beneficial effects on the digestive system, modulating inflammation in the gut and in improving the mucosa and gut barrier integrity.

2. **Antioxidant Support:** Fenoprolic has strong antioxidant properties, which help protect cells from oxidative damage. It is rich in proanthocyanidins, which are believed to help neutralize free radicals, thus supporting cellular health and reducing oxidative stress.

3. **Cardiovascular Health:** Proanthocyanidins from Fenoprolic may promote healthy circulation and normal blood flow, potentially benefiting heart health and reducing blood pressure

4. **Joint Health:** Fenoprolic has the potential to reduce inflammation and support joint health, particularly in individuals with conditions like osteoarthritis.

5. **Skin Protection:** The extract is believed to enhance skin elasticity, hydration, and overall appearance, while also providing protection against UV damage.

6. **Cognitive Function:** Fenoprolic may support cognitive health and enhance memory and concentration, due to neuroprotective effects.

7. **Immune System Support:** It is also associated with promoting a healthy immune response.

Please note thar regulatory bodies like the FDA have not specifically evaluated or endorsed these claims

Dosage and Formulation Guidelines

Fenoprolic comes as a fine powder that is 99,99% water soluble. It can be applied in multiple dosage forms, including tablets, hard get capsules, and gummies.

The dosage recommendations for Fenoprolic vary based on the intended use and the formulation, for inmstance:

1. **General Health**: Dosage recommendation is 100 to 200 mg per day.

2. **Cardiovascular Support**: Dosages is recommended the range of 100 to 300 mg per day.

3. **Joint Health**: For osteoarthritis, dosages of approximately 150 to 200 mg per day have been commonly used.

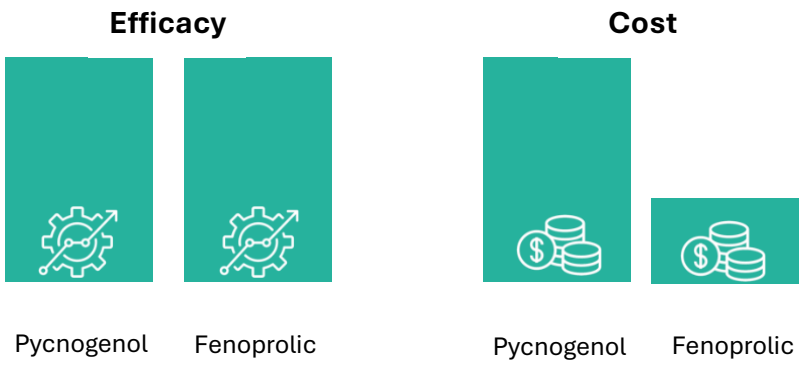
4. **Skin Health**: Dosages can vary, but around 100 to 200 mg daily is often recommended for skin-related benefits.

5. **Cognitive Support**: Some studies suggest dosages in the range of 100 to 300 mg per day for cognitive function.

Safety and Regulatory Compliance

Fenoprolic®'s quality and safety are assured through rigorous third-party evaluations and analytica testing, and made under certifications like ISO 22 000 by DnV, Euroleaf Organic certification from EuroCert (USDA NOP compliand) and Kosher. It has undergone studies using platforms like BioMAP to confirm its biological activity and safety profile.

Comparative Cost Analysis



Eevia Health: A Partner in Sustainable Wellness

Eevia Health is dedicated to addressing health challenges with high-quality, organic plant extracts sourced from the Arctic's pristine forests. Operating near the Arctic Circle, Eevia harnesses resilient botanicals like bilberry, lingonberry, chaga mushroom, and pine bark to create extracts known for their unique bioactive profiles and scientifically supported benefits. These extracts target inflammation, metabolic health, and cognitive function.

Committed to sustainability, Eevia maintains one of the lowest carbon footprints in the industry through an efficient, short value chain and green chemistry practices. Rigorous quality standards and certifications, including ISO 22 000, ensure the safety and purity of its products, positioning Eevia as a leader in sustainable ingredient sourcing.

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