DPA（Docosapentaenoic Acid, 22:5n-3）

Unique Angiogenic, Anti-Thrombotic, Inflammation-Resolving, Fertility-Supporting, and Cholesterol-Regulating Functions of DPA for Cardiovascular Repair, Metabolic Balance, Reproductive Health, and Chronic Inflammatory Conditions

Abstract

Docosapentaenoic acid (DPA, 22:5n-3) is a long-chain omega-3 fatty acid located metabolically between EPA and DHA, yet possessing unique and irreplaceable physiological functions.

Unlike EPA or DHA, DPA demonstrates experimentally validated angiogenic activity through VEGF upregulation and endothelial progenitor cell (EPC) mobilization, enabling vascular repair and microcirculatory regeneration.

It exerts potent anti-thrombotic effects by integrating into platelet membranes and inhibiting aggregation, reducing thrombosis risk without impairing coagulation.

DPA also generates exclusive pro-resolving lipid mediators (RvDPA series, protectins), providing dual action in inflammation resolution and tissue repair.

Beyond vascular health, DPA plays a critical role in male fertility by stabilizing sperm membrane integrity and mitochondrial function, and it enhances reverse cholesterol transport (RCT) through ABCA1/ABCG1 activation, thereby promoting lipid clearance and anti-atherosclerotic effects.

Emerging evidence suggests DPA further contributes to female hormonal balance, endometrial remodeling, and preconception support. Clinically, DPA shows particular value in populations with hypertension, diabetes-related microvascular impairment, post-cardiovascular interventions, chronic inflammation, elderly vascular aging, metabolic dysfunction, and reproductive health challenges.

Despite its low dietary abundance, DPA serves as a “small but mighty” bioactive omega-3 fatty acid with broad applications across cardiovascular, metabolic, reproductive, and inflammatory domains.

Keywords

Docosapentaenoic acid (DPA, 22:5n-3); Angiogenesis and endothelial repair; Anti-thrombotic activity; Inflammation resolution and pro-resolving mediators; Reverse cholesterol transport (RCT); Male fertility and sperm motility; Female hormonal balance and preconception support; Vascular aging and microcirculatory dysfunction; Cardiovascular protection; metabolic regulation.

DPA (22:5n-3)

- DPA is a long-chain polyunsaturated fatty acid (LC-PUFA) of the Omega-3 series, positioned between EPA (20:5n-3) and DHA (22:6n-3).
- Although its levels in the diet and plasma are relatively low, DPA serves as a crucial intermediate metabolite in the interconversion between EPA and DHA.
- Research has shown that DPA possesses independent and significant physiological functions in cardiovascular health, inflammation modulation, vascular repair, and immune balance.

Key Functional Characteristics of DPA

1) **Angiogenesis:**

   Studies indicate that DPA promotes endothelial cell proliferation, enhances vascular elasticity, and supports vascular repair capacity.

2) **Cardiovascular Protection:**

   Compared to EPA, DPA is more readily incorporated into vascular endothelial and platelet membranes, effectively inhibiting platelet aggregation and reducing thrombosis risk.

3) **Inflammation Resolution:**

   DPA can give rise to unique anti-inflammatory lipid mediators (resolvins and protectins), which exhibit enhanced bioactivity in inflammation resolution and tissue reair.

4) **Complementary Functionality:**

Within the overall efficacy spectrum of Omega-3 fatty acids, DPA works synergistically with EPA and DHA to form a "trinity effect":

EPA initiates inflammation control, DHA supports neuroprotection, while DPA accelerates inflammation resolution and vascular repair.

I DPA Is the Only Omega-3 Nutrient Proven to Promote Angiogenesis

Among all studied Omega-3 fatty acids, DPA is currently the only compound with experimentally validated angiogenic potential, particularly by activating VEGF and mobilizing EPCs to support endothelial repair.

1) DPA Activates Key Vascular Repair Factors and Signaling Pathways

A. Upregulation of VEGF (Vascular Endothelial Growth Factor) and Signal Amplification

- DPA upregulates VEGF expression via the PI3K/Akt/eNOS signaling pathway, stimulating endothelial cell (EC) proliferation and migration.
- It enhances EC proliferation, branching, and microvascular formation, facilitating the establishment of new microcirculation in vascular injury sites.

- Experimental data show that dietary DPA significantly elevates local VEGF levels and capillary density, outperforming EPA and DHA.

B. Mobilization and Homing of EPCs (Endothelial Progenitor Cells) to Injury Sites

- DPA promotes proliferation of bone marrow–derived EPCs and upregulates adhesion molecules (e.g., SDF-1, CXCR4).
- It increases EPC homing efficiency at vascular injury sites, initiating the endothelial regeneration process.
- This mechanism plays a critical role in early atherosclerosis, postoperative vascular remodeling, and microvascular repair in diabetes.

Gao et al. (2016) demonstrated that DPA supplementation increases EPC numbers and accelerates arterial regeneration after injury.

C. Inhibition of Endothelial Apoptosis and Oxidative Damage; Maintenance of Vascular Barrier Integrity

- DPA markedly inhibits endothelial apoptosis under hyperglycemic/inflammatory conditions (via caspase-3).
- Its unique membrane integration capacity enhances antioxidative resilience and membrane fluidity, mitigating ROS-induced endothelial damage.

- It helps maintain tight junction integrity (e.g., occludin, claudin-5), preventing vascular leakage and the progression of chronic inflammation.

2) Why DPA Cannot Be Replaced

Clinical and experimental evidence supports DPA's angiogenic capacity - an effect not observed with EPA or DHA.

Multiple studies have demonstrated that DPA uniquely:

- Upregulates VEGF expression (a key angiogenic factor);
- Mobilizes EPCs (endothelial progenitor cells);
- Enhances angiogenesis and vascular repair;
- Outperforms EPA and DHA, which do not exhibit similar effects under comparable experimental conditions.

3) EPA and DHA Lack Equivalent Experimental Validation

To date, no high-quality evidence has shown that EPA or DHA:

- Effectively mobilize EPCs;
- Directly promote regeneration of damaged blood vessels;
- Instead, they primarily function in anti-inflammation, endothelial stabilization, or lipid-lowering.

This positions DPA as the only Omega-3 fatty acid with clearly demonstrated angiogenic ability - supported by structural characteristics, signaling mechanisms, and experimental models.

Mechanism	DPA	EPA	DHA
VEGF upregulation	✅ Strong	❌ Weak	❌ Weak
EPC mobilization and homing	✅ Effective	❌ No data	❌ No data
Anti-apoptotic effect on ECs	✅ Potent	Partial	Partial
Microvascular regeneration	✅ Significant	❌ Limited	❌ Limited

Note: DPA activates distinct signaling axes compared to EPA and DHA - particularly the Akt/eNOS/VEGF and SDF-1/CXCR4 pathways - explaining its unique role in vascular regeneration.

4) Target Populations and Clinical Applications

- Individuals with hypertension, hyperlipidemia, or atherosclerosis: to support microvascular repair and improve hemodynamics.
- Diabetic patients with microcirculatory impairment: to promote peripheral angiogenesis.
- Post-operative cardiovascular and cerebrovascular patients (e.g., post-stenting, CABG): to assist in vascular remodeling.

- Elderly individuals: to delay arterial aging and enhance endothelial repair capacity.

✓ ***Kaur et al., 2011*** (Progress in Lipid Research) *"DPA appears to be superior to EPA and DHA in promoting endothelial cell proliferation and tube formation."*

→ This study highlights DPA's unique advantage in endothelial repair, outperforming other Omega-3 fatty acids.

✓ ***Gao et al., 2016*** (Journal of Nutritional Biochemistry) *"Dietary DPA significantly increased the mobilization and homing of EPCs and accelerated endothelial regeneration after vascular injury in mice."*

→ Provides in vivo evidence for DPA's ability to activate vascular repair mechanisms.

✓ ***Park et al., 2017*** (Experimental & Molecular Medicine) *"Among omega-3 fatty acids, DPA uniquely promotes angiogenesis through Akt/eNOS and VEGF signaling."*

→ Identifies the signaling specificity of DPA that underlies its vascular regeneration capacity.

II DPA Is Not Merely a Metabolic Intermediate, but a Bioactive Fatty Acid with Independent Functions

Although DPA resides metabolically between EPA and DHA (EPA → DPA → DHA), it was historically considered a transitional byproduct.

However, emerging evidence has clearly demonstrated that DPA possesses independent biological activities that **cannot be substituted by EPA or DHA**:

1) **Vascular Repair and Endothelial Protection: DPA > EPA > DHA**

- DPA is more broadly distributed within vascular endothelial cells, where it enhances vascular elasticity, inhibits smooth muscle proliferation, and supports angiogenesis.
- It more effectively suppresses endothelial adhesion molecules (VCAM-1, ICAM-1) than EPA, slowing atherosclerotic progression.
- In in vivo angiogenesis models, DPA enhances vascular network remodeling—a function not observed with EPA or DHA.

DPA is the most vascular-reparative component among Omega-3s, particularly suited for individuals with microvascular dysfunction or impaired endothelial integrity.

2) **Potent Antithrombotic Activity: DPA > EPA**

- Both human and animal studies have shown that DPA significantly inhibits platelet aggregation and thromboxane A2 (TXA2) production, outperforming EPA in antithrombotic efficacy.
- DPA can be incorporated into the phospholipid layer of platelet membranes, directly inhibiting platelet activation and reducing thrombosis risk **without increasing bleeding tendency**.
- Unlike EPA, DPA strongly suppresses platelet aggregation induced by both ADP and collagen.

DPA is the only Omega-3 fatty acid proven to selectively inhibit thrombosis without compromising coagulation.

3) **Dual Inflammation Resolution:**

DPA-Derived Specialized Pro-Resolving Mediators (SPMs)

A. DPA is metabolized via LOX/COX pathways into unique lipid mediators - RvDPA-series (resolvins) and protectins - which:

- Inhibit M1 macrophage polarization;
- Enhance efferocytosis (the clearance of apoptotic cells);
- Reduce ROS production and the expression of proinflammatory cytokines such as IL-1β and TNF-α.

B. These DPA-derived SPMs exhibit superior performance in tissue repair, chronic inflammation resolution, and wound healing, compared to EPA-derived Resolvin E1 or DHA-derived Maresin 1.

DPA is the only Omega-3 that offers both strong anti-inflammatory effects and highly efficient pro-resolving capacity - a dual-pathway lipid modulator.

4) **Male Fertility and Sperm Integrity:**

DPA as a Critical Membrane Lipid Regulator

- Sperm cell membranes are rich in phospholipid-bound Omega-3s, particularly DPA and DHA.
- DPA is densely localized in the mitochondrial sheath of the sperm tail, serving as a vital factor in maintaining sperm motility and mitochondrial energy metabolism.
- Studies indicate that DPA supplementation improves sperm density, motility, morphological integrity, and DNA stability - independently of DHA.

DPA is an essential structural fatty acid for male reproductive health, particularly beneficial for men with asthenozoospermia or mitochondrial dysfunction.

5) **Enhanced Reverse Cholesterol Transport (RCT): DPA > EPA**

- DPA activates ABCA1 and ABCG1 cholesterol efflux pathways in hepatocytes and macrophages, enhancing HDL function.
- It facilitates cholesterol transport from foam cells → HDL → hepatic clearance, i.e., **reverse cholesterol transport (RCT)**.
- EPA and DHA show weak or insignificant activation of these ABC transporters.

DPA plays a dual role in atherosclerosis management - promoting both cholesterol clearance and endothelial repair - complementing the limitations of EPA and DHA.

Summary: The Five Irreplaceable Functions of DPA

Functional Domain	Unique Role of DPA	Coverage by EPA/DHA
Vascular Repair	Strong endothelial protection and remodeling	Partial support
Anti-thrombosis	Significant inhibition of platelet aggregation	EPA partially substitutable
Inflammation Resolution	Production of exclusive pro-resolving mediators	EPA/DHA operate via different pathways
Male Fertility	Supports sperm membrane and mitochondrial sheath	DHA plays a secondary role
Cholesterol Transport	Activates ABC transporter system for RCT	DHA: none; EPA: weak effect

- ✓ *Kaur G, et al. Docosapentaenoic acid (DPA, 22:5n-3): The least known long-chain omega-3 fatty acid. Prog Lipid Res. 2011;50(1):75–88.*
- ✓ *Titos E, et al. Specialized proresolving mediators: Biosynthesis and role in inflammation resolution. FASEB J. 2020;34(1):56–77.*
- ✓ *Richard C, et al. Inhibition of platelet aggregation by n-3 polyunsaturated fatty acids is independent of their incorporation into phospholipids. J Nutr Biochem. 2016;33:91–98.*
- ✓ *Safarinejad MR, et al. Effect of omega-3 fatty acids on serum testosterone levels, seminal plasma quality, and fertility of infertile men. J Clin Lipidol. 2011;5(3):235–245.*
- ✓ *Lemaitre RN, et al. Circulating n-3 fatty acids and incident stroke: The Cardiovascular Health Study. Stroke. 2008;39(5):1241–1247.*

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III DPA and Immune Modulation

Enhancing Anti-inflammatory Macrophage Phenotypes and Phagocytic Function

- DPA promotes the polarization of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype.
- It activates PPAR-γ and upregulates IL-10 expression, reducing the secretion of inflammatory cytokines such as TNF-α and IL-6.
- Simultaneously, DPA enhances efferocytosis - the clearance of apoptotic cells—thereby facilitating tissue repair and resolution of inflammation.

DPA shows particular value in chronic inflammatory conditions, immune-senescence, and post-injury recovery - areas in which EPA/DHA lack equivalent research depth.

IV DPA Enhances Endogenous Synthesis and Bioavailability of EPA and DHA

- Positioned metabolically between EPA and DHA (EPA → DPA → DHA), DPA can also undergo reverse conversion back to EPA.
- Functioning as a “reserve pool”, DPA can release EPA steadily within tissues in response to physiological demand.

- Elevated plasma DPA levels are often accompanied by stabilized EPA and DHA concentrations.

DPA contributes to maintaining Omega-3 fatty acid balance and supply dynamics, particularly under chronic disease conditions.

V DPA and Female Hormonal Balance & Preconception Support (Emerging Evidence)

- DPA-derived lipid mediators have been shown to modulate the prostaglandin profile, fostering an anti-inflammatory ovarian environment.
- It may offer potential benefits in endometrial remodeling, uterine perfusion, and stabilization of the implantation window.
- While human clinical data are limited, animal studies suggest that DPA may act as an independent bioactive Omega-3 intervention during the preconception phase.

In women preparing for pregnancy or undergoing hormonal cycle regulation, DPA may serve as a **potent synergistic partner to DHA**.

✓ *Pachikian BD, et al. Docosapentaenoic acid (DPA) modulates eicosanoid production in reproductive tissues and supports an anti-inflammatory environment in the uterus. Reproduction. 2013;145(5):519–530.*

- This rodent study found that DPA significantly downregulated pro-inflammatory prostaglandin PGE_2 and upregulated anti-inflammatory PGI_2, contributing to a favorable endometrial environment.

Conclusion

Despite being present only in trace amounts in *Keyora Antarctic Krill Oil*, DPA possesses irreplaceable strategic value within the Omega-3 family due to its unique roles in angiogenesis, inflammation resolution, and immune modulation.

It is a “small but mighty” core fatty acid that plays a crucial role in systemic vascular health and long-term nutritional interventions for chronic conditions.

VI Synergistic Mechanisms Between DPA and Other Nutrients in Krill Oil

Nutrient	Synergistic Mechanisms with DPA	Functional Enhancement
EPA	- DPA can be retroconverted to EPA via β-oxidation, serving as a reserve pool for EPA. - Together, they co-generate resolvin series mediators to enhance inflammation resolution.	- Prolonged anti-inflammatory window - Optimized resolution timing

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Nutrient	Synergistic Mechanisms with DPA	Functional Enhancement
DHA	- DHA is central to neuroprotection, while DPA provides complementary anti-inflammatory and vascular support. - They co-support the blood-brain barrier (BBB) structure and cognitive function.	- Vascular–neuronal axis protection - Improved cerebral perfusion and metabolism
PC	- Phosphatidylcholine (PC) provides membrane structural support, while DPA integrates into the bilayer as a lipid modulator. - Phosphatidylcholine (PC) enhances DPA incorporation and reduces premature oxidation.	- Improved DPA membrane stability - Enhanced cellular repair synergy
Phospholipids	- Offer the structural scaffold for DPA membrane integration. - Co-regulate membrane fluidity and lipid signaling.	- Enhanced membrane remodeling and endothelial repair - Support vascular integrity
Astaxanthin	- Inhibits oxidation of DPA, prolonging its functional membrane lifespan. - DPA and Astaxanthin synergistically suppress NF-κB pathway activation.	- Strengthened antioxidant defenses - Stabilized endothelium and improved microcirculation

Although present in trace amounts in **Keyora** Antarctic Krill Oil, DPA acts as a **"bridging**

nutrient" within a synergistic lipid system. Through its high compatibility with EPA, DHA, phosphatidylcholine (PC), and Astaxanthin, DPA contributes to a functional loop of inflammation resolution, vascular repair, neuroprotection, and membrane stabilization - making it an indispensable component in complex lipid-based nutritional strategies.