**Review question / Objective:** Evaluate the potential effect of DHA in regulating cellular antioxidant enzymes and hypothesizes possible molecular scenarios between DHA and Nrf2 in regulating cellular antioxidant defenses.

**Eligibility criteria:** Chosen studies were published between 1998 and 2021 without restriction regarding period or publication status. Exclusion criteria were: (i) titles irrelevant to the research topic; (ii) abstract inappropriate or not related to the research topic; (iii) studies that used n-3 PUFAs rich oils which not allowed to discriminate the effect of DHA from other n-3 PUFAs; (iv) studies that co-administrated DHA with other compounds; (v) studies that used DHA oxidation products to better reflect normal nutritional conditions; (vi) studies or data with inadequate statistical analysis or inappropriate control. Reviews, letters, abstracts, and articles without a complete text in the English language were also excluded.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 June 2023 and was last updated on 05 June 2023 (registration number INPLASY202360017).

**Review Stage at time of this submission:** Completed but not published.

**Conflicts of interest:** None declared.

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**INTRODUCTION**

**Review question / Objective:** Evaluate the potential effect of DHA in regulating cellular antioxidant defenses by DHA supplementation/feeding.

**METHODS**

**Participant or population:** Cultured cells and animal model (mice, rat).
Intervention: Not applicable.

Comparator: Control cells/animals do not receive DHA supplementation/feeding.

Study designs to be included: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).

Eligibility criteria: Chosen studies were published between 1998 and 2021 without restriction regarding period or publication status. Exclusion criteria were: (i) titles irrelevant to the research topic; (ii) abstract inappropriate or not related to the research topic; (iii) studies that used n-3 PUFAs rich oils which not allowed to discriminate the effect of DHA from other n-3 PUFAs; (iv) studies that co-administrated DHA with other compounds; (v) studies that used DHA oxidation products to better reflect normal nutritional conditions (vi) studies or data with inadequate statistical analysis or inappropriate control. Reviews, letters, abstracts, and articles without a complete text in the English language were also excluded.

Information sources: The search was carried out by using the PubMed database in December 2022, and was conducted using the following keywords and Boolean operators: "docosahexaenoic acid" OR "DHA" OR "C22:6" AND "antioxidant" NOT "review".

Main outcome(s): Primary outcomes include the most relevant variables to answer the research question (the modulation of cellular antioxidant defenses by DHA).

Quality assessment / Risk of bias analysis: Not applicable.

Strategy of data synthesis: Data are analyses according to the inclusion and exclusion criteria.

Subgroup analysis: Not present.

Sensitivity analysis: Not applicable.

Country(ies) involved: Italy.

Keywords: Docosahexaenoic acid; antioxidants; Nrf2.

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