Promising Intervention Approaches to Potentially Resolve Neuroinflammation And Steroid Hormones Alterations in Alzheimer’s Disease and Its Neuropsychiatric Symptoms

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MATERIAL AND METHODS

1. Search strategy

We searched the electronic databases PubMed and Google scholar databases. The research was conducted with no restrictions on language. In PubMed, we used the search terms “natural compounds” OR “nutraceuticals” OR “phytochemicals” AND “Alzheimer’s Disease” OR “Alzheimer” OR “Alzheimer’s”. We selected articles that met the following inclusion criteria: (a) only reviews; (b) each study performed on human, animal models, in vitro approaches.

Starting from 1,832 records without time restriction, this research produced over 119 reviews on the topic in the last two years 2019-2020 (Table 1S).

2. Search strategy and selection criteria for meta-analyses

We searched the electronic databases PubMed, Google scholar, Cochrane Library databases. The research was conducted up to December 2020, with no restrictions on language, date, or study setting. In PubMed, we used the search terms “ozone therapy” OR “oxygen ozone therapy” AND “NF-κB” OR “inflammation” OR “anti-inflammatory” OR “cytokines” OR “interleukins” OR “inflammasome” OR “NLPR3” OR “NLR family pyrin domain containing 3” OR “TLR4” OR “Toll-like receptor 4” OR “Interleukin 17α” OR “IL 17α”.

Only the keyword “ozone therapy” in Pubmed produces 3,770 articles.

Inclusion and exclusion criteria

We selected articles that met the following inclusion criteria: (a) each type of pathology; (b) each study performed on animal models studies; (c) in vitro studies on cells; (d) studies on human; (e) each study performed on peripheral levels (protein); (f) each study performed on expression mRNA levels. The meta-analytic analyses were conducted where data were available before and after the O₃ treatments. We excluded: (a) studies regarding ozone as air pollutant or ozone-induced toxicity; (b) genetic studies on ozone exposition; (c) reviews, commentaries on the topic.

Data extraction for meta-analyses

CS and CB independently extracted the following data: authors of the studies, biomarkers, model, sample size (N), experiments, treatments, and dosages (Table 2S).

Statistical analyses

Review Manager was used to perform the meta-analysis (RevMan Version 5.1.6; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). We used the random-effects model to generate a pooled effect size and 95% confidence interval (CI) from individual study effect sizes (the standardized mean difference using the inverse variance methods). The significance of the pooled effect sizes was determined by z-tests. Between-study heterogeneity was assessed using a χ² test of goodness of fit test and the I² statistic. We used a P-value < 0.05 to indicate statistical significance.

For multiple corrections, we applied the Bonferroni correction: 0.05/number of the biomarkers analysed.

Supplementary Table 1. List of 119 reviews on the “Natural Compounds” and “Alzheimer’s Disease” in the last two years 2019-2020.

A. 2020 year

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Supplementary Table 2. Summary of studies included in the meta-analyses.

| References | markers | Models | N  | Experiments                                                        | Treatments                        |
|------------|---------|--------|----|-------------------------------------------------------------------|-----------------------------------|
| [1]        | NF-κB/p65 | Rats   | 36 | Ischemia/Reperfusion (I/R) injury; Preconditioning with Ozone (O3) | Rectal insufflations, 50μg/ml, 15 treatments, one a day. |
| [2]        | NF-κB/p65 | Rats   | 30 | Adenine diet and/or Ozone (O3)                                   | Rectal insufflations, 50μg/ml, 4 weeks, one a day. |
| [3]        | NF-κB/p65 | Rats   | 18 | Adenine diet and/or Ozone (O3)                                   | Rectal insufflations, 50μg/ml, 4 weeks, one a day. |
| [4]        | IL-17α   | Mice   | 32 | Dexamethasone injury;                                             | Twice a week for 6 weeks.          |
| [5]        | NF-κB/p65 | Rats   | 30 | Nephrectomy injury; Preconditioning with Ozone (O3)              | Rectal insufflations, 50μg/ml, 10 weeks, one a day. |
| [6]        | NF-κB/p65 | Rats   | 40 | NCLDH injury; Preconditioning with Ozone (O3)                     | Intrathecal administration of 10, 20, or 30 μg/mL Ozone (O3) |
| [7]        | NF-κB/p65 | Rats   | 54 | Radiculoneuritis rat model; Preconditioning with Ozone (O3)       | Epidurally administration, 30 μg/ml, 3 days. |
| [8]        | IL-17α   | Rats   | 18 | Ischemia/Reperfusion (I/R) injury; Preconditioning with Ozone (O3) | Rectal insufflations, 100μg/ml, 10 days, one a day. |
| [9]        | IL-17α   | Human  | 40 | Multiple sclerosis                                                | Autohemotherapy method, 25 μg/ml, twice weekly for 6 months. |

NF-κB/p65 (nuclear factor kappa-light-chain-enhancer of activated B cells); IL-17α (pro-inflammatory Interleukin 17), NLRP3 Inflammasome (NLR Family Pyrin Domain Containing 3); N= sample size
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