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Efficacy of ω-3 Supplementation in Patients with Psoriasis: A Meta-analysis of Randomized Controlled Trials

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A shortened version of the title: *ω-3 Supplementation on Psoriasis*

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Abstract

Several studies have been conducted with the aim of investigating the effect of ω-3 on different psoriasis indices including Psoriasis Area and Severity Index (PASI) score, erythema, scaling, itching, area involved and infiltration. Nevertheless, a pooled analysis of trials that evaluated these variables has not been conducted. Therefore, the aim of this meta-analysis was to assess the efficacy of ω-3 fatty acids in treating patients with psoriasis. We searched through different electronic, references of retrieved articles and previous related reviews databases up to November 2018. Both combined and stratified analyzes were conducted. A fixed-effects or random-effects model was used to assess the mean effect sizes. An eventual 10 studies involving 560 participants were considered as eligible for inclusion in the present meta-analysis. The meta-analysis indicated a significant reduction in PASI score by −1.58 (95% CI: -2.24, -0.92; $P < 0.001$) in favor of ω-3 PUFA group. The random-effect model showed a statistically significant beneficial effect of ω-3 PUFA supplementation on reducing erythema by -1.66 unit and reducing scaling [WMD: -0.69, 95% CI: -1.26, -0.13, $P = 0.02$). Significant improvements in erythema, itching, and scale were observed in the trials which used the higher-dosage of ω-3 supplementation. The results of current meta-analysis study support the use of ω-3 PUFA supplementation for the improvement of the evaluated parameters in psoriatic patients. However, well-controlled and randomized studies are needed to confirm the veracity of non-significant and/or equivocal findings.

Keywords: psoriasis, polyunsaturated fatty acids, PUFA, meta-analysis

Introduction:

Psoriasis is the most common autoimmune and chronic inflammatory, proliferative skin disorder [1-3]; whilst its' prevalence is asserted to range from 0.1%to 11.8% in various populations, with an average of 2–3%[3]. Psoriatic lesion involves epidermal keratinocytes and leukocyte cells [2], and is characterized, classically, by sharply demarcated, red indurated plaques over the extensor surfaces of the body and scalp, accompanied by silvery white scales [3, 4]. Whilst there exists a component of heritability to psoriasis susceptibility, the inflammatory reaction is modulated by diet, lifestyle and environmental factors, such as infections and stress [1, 2, 5].

Topical medications are the first line treatment approach prescribed for patients with mild to moderate psoriasis [2, 5]. Typical treatments include various compounds, such as; vitamin D analogs, corticosteroids, dithranol, coaltar, and retinoids. However, may confer substantial, negative side-effects, including; hypercalcemia, skin irritation, cloth staining, teratogenicity and causes a burning sensation. The second approach includes systemic treatment methods such as cyclosporine and fumaric acid esters, notwithstanding observed side effects, including; nephrotoxicity, hypertension, slow onset of action, diarrhea, lymphopenia, bone marrow suppression, nausea and hepatic fibrosis [1, 2, 5]. Therefore, given the deleterious side effects associated with traditional psoriatic therapies, it is imperative that contemporary, less injurious, treatments be investigated. Polyunsaturated fatty acids (PUFAs) are among such compounds which are showing potential as a safe, adjunctive treatment for many skin disorders, including psoriasis [1-3, 5, 6]. The abnormal keratinocyte hyperproliferation in psoriasis arises due to the activation of T-cells, which subsequently produces the rich amount of arachidonic acid, leading to the generation of various proinflammatory mediators, including; PGs, LTs, cytokines and

adhesion molecules via MAPK/AP-1, EARK1/2 and protein kinase – C (PKC) activation pathways [1-3, 5].

Omega (ω) - 3 fatty acids (i.e., EPA and DHA) supplementation, in a dose-dependent manner, results in inhibition of various pro-inflammatory mediators and metabolization of EPA and DHA leads to dampening of inflammation and higher resolution of the skin abnormalities[1-3, 5]. These have recently been used alone, or in combination with other drugs, in the treatment of psoriasis, [5].

So far, many studies have been conducted with the aim of investigating the effect of ω-3 on psoriasis. For example, an animal study, conducted by Qin et al, to evaluate the effect of omega 3 on psoriasis [6], and asserted ω-3 to elicit mechanistic influence on psoriasis related inflammation, namely through its down-regulation of T-helper cells, interleukin (IL)-17, IL-22, IL-23, and stimulation of regulatory T-cells [6]. Furthermore, in recent years, many randomized controlled trials have been performed on the efficacy and mechanism of action of ω-3 polyunsaturated fatty acids (n-3 PUFAs) on psoriasis. For example, Upala et al. conducted a systematic review of the effects of n-3 PUFAs on psoriasis [5], and although some studies found that n-3 PUFAs were associated with improvements in the clinical Psoriasis Area and Severity Index (PASI) score, erythema, scaling, itching, area involved and infiltration; numerous studies did not find any reduction in scaling, erythema, area involved or thickness in the treatment group [5]. Therefore, given the potential to aid clinical treatment, yet equivocal nature of findings in the literature, the aim of this meta-analysis was to assess the efficacy of ω-3 fatty acids, as a monotherapy, in treating patients with psoriasis.

Methods and Materials:

Search strategy

The present systematic review and meta-analysis was conducted according to the PRISMA guidelines [7]. We searched through different databases including ISI web of science, Pubmed/Medline™, Scopus™, EMBASE and Cochrane library™ up to November 2018 using the following MeSH and non-MeSH terms in titles and abstracts: ("fish oil" OR "omega 3" OR "ω-3" OR "EPA" OR "DHA" OR "fatty acid") AND ("psoriasis"). Moreover, references of retrieved articles and previous related reviews were also examined to find eligible studies.

Study selection

All published studies were included for meta-analysis if they met the following criteria: 1) Randomized controlled clinical trials with designation of either parallel or cross-over comparing ω-3 PUFA treatment with placebo treatment in patients with psoriasis, 2) providing adequate information upon the baseline and endpoint scores of one of the psoriasis indices, including PASI score (as a tool for measuring the severity and extent of psoriasis by assessing the intensity and affected areas in the head and neck, upper limbs, trunk, and lower limbs), %TBSA (percent total body surface area affected) and subjective reports of disease progression (e.g., erythema, itching, scaling, infiltration and desquamation), with SEM, SD, or 95% CI for intervention and control groups, 3) the study with a proper controlled design where the difference between the intervention and control group was ω-3 PUFA supplementation. We considered the following criteria as the exclusion criteria: 1) non-human studies, 2) lack of a control group for ω-3 supplementation, 3) non-original and/or RCT studies including cohort, case-control, or cross-sectional, reviews, letters, case reports and commentaries.

Quality assessment

The quality of studies were estimated using the Jadad score which includes the following items: (1) randomization (one point for stating random allocation and additional point for describing the method appropriately), (2) blinding (One point for stating that the trial was blinded and additional point for describing the blinding method appropriately; One point was withdrawn if the method of randomization/blinding was inappropriate), and (3) reporting of number and reasons of withdrawals (one point for reporting of number, reasons and fate of dropouts). The possible score varies between 0 and 5, in which a score of ≥3 indicated higher quality studies and a score of less than 3 is considered as the low-quality study [8].

Data extraction

The titles and abstract of included studies were reviewed independently by two authors (M.N) and (M.T). Differing decisions were resolved by consulting a third reviewer (SJ). We retrieved the full-text papers for those that were potentially relevant to the subject of our study in the initial screening. The data extracted from the included trials were: year of study, study design, location of conducted trial, sample size of intervention/control groups, participants characteristics (gender and age), duration of follow up, clinical condition of participants, dosage of intervention supplementation and reported significant outcomes.

If the papers contained inadequate details, we planned to contact the authors to obtain the missing information. Where this was unsuccessful, we planned to calculate the missing data from the raw numbers and P-values reported.

Statistical analysis

variable effects were defined as the weighted mean difference (WMD) with 95% confidence interval (CI) and the corresponding standard deviation (SD) in any of the psoriasis indices values. In case of not reporting the SD values, we calculated the SD from standard errors, P values, 95% CIs, or by converting the median and interquartile range to mean and SE using available formulas. We assessed the I^2 index and $\chi 2$ test on Cochrane's Q statistic to quantify the extent of heterogeneity, in which $P<0.05$ or $I^2>50\%$ was defined as heterogeneous. A random-effects model was used to pool the effect size if significant heterogeneity was indicated between studies. Otherwise, a fixed-effects model was used. We used Funnel plots, Begg's rank correlation test, and Egger's weighted regression test to examine any potential publication biases. To identify any potential heterogeneity source, we conducted sensitivity, stratified and meta-regression analyses in accordance with the Cochrane guidelines [9].

All analyses were performed in Review Manager Software (Review Manager 5.3; Cochrane Collaboration, Oxford, England) and Comprehensive Meta-Analysis (version 3.2; Biostat). A P-value of less than 0.05 was considered as statistically significant.

Results:

Literature search and selection of studies

The flow diagram of study selection was shown in Figure 1. A total number of 87 studies were initially identified after duplicates had been removed. In the next step, 74 more studies were excluded due to the following reasons: experimental studies (in-vitro or non-human trials) (n=61), non-clinical studies (reviews, editorials, letters and case reports) (n=13). Therefore, 13 possibly relevant studies were deemed for full text review. After screening, three articles were excluded because they: 1) did not administer ω-3 as the intervention, or administered as a combined supplementation; 2) insufficient reported data of psoriasis indices in the baseline and the end of follow up. An eventual 10 studies involving 560 participants were considered as eligible for inclusion in the present meta-analysis

Study characteristics and quality assessment

Characteristics of the included studies is presented in Table 1. In total, 10 RCTs [1, 3, 10-17] were included in the meta-analysis, comprising a total of 278 individuals in the intervention group and 282 in the control group. Patients treated in these RCTs had psoriasis [3, 10-17] except for one in which the patients were obese with psoriasis disease[1]. Nine studies were published in English and the remaining one in Polish[3]. Study duration ranged from 4 to 48 weeks with a median of 8 weeks. The dosage of ω-3 supplementation was between 240 mg/day to 3600 mg/day with the median of 1800 mg/day EPA. The studies supplied ω-3 interventions with different forms including EPA [11], EPA and DHA [3, 10, 12-17] and α-linolenic acid (ALA)[1]. All included studies were published between 1988 to 2017 and had been conducted in India (n=1) [3], Spain (n=1) [10], Great Britain (n=1) [11], Norway(n=1) [12], Argentina (n=1) [13], Germany (n=1) [14], Italy (n=1) [1], US (n=2) [15, 16] and Scotland (n=1) [17]. There were no reports of serious adverse effects and only slight abdominal distress was reported in the reviewed papers.

Table 2 presents the results of the study quality assessment. According to the previous studies, which indicated the studies with Jadad score of more than 3 as high quality studies, Most included studies (7 of 10 studies) showed higher quality [1, 11, 12, 14-17] and the remaining 3 studies considered as low methodologic quality [3, 10, 13].

Effect of ω-3 PUFA supplementation on PASI score

Three studies reported data on PASI improvement [1, 3, 10] with no observed heterogeneity among these studies (P = 0.64, I^2 = 0%). The meta-analysis of the included trials indicated a significant reduction in PASI score by −1.58 [95% CI: -2.24, -0.92; Test for overall effect: Z = 4.69 (P < 0.00001)] in favor of ω-3 PUFA group with the standardized mean difference (SMD) and 95% CI of -0.56 [-0.83, -0.28] (Figure 2-a).

Effect of ω-3 PUFA supplementation on erythema

Eight studies had sufficient data for inclusion in meta-analyses erythema [3, 10-16]. There was significant heterogeneity between these studies (P <0.00001, I^2 = 99%). The random-effect model showed a statistically significant beneficial effect of ω-3 PUFA supplementation on reducing erythema by -1.66 unit [(95% CI:-2.52, -0.81; Test for overall effect: Z = 3.82 (P =0.0001]. The pooled SMD and 95% CI were -1.55 [-2.47, -0.62] (Figure 2-b).

Effect of ω-3 PUFA supplementation on itching

Five studies had sufficient data for inclusion in meta-analyses of itching[1, 11, 13, 16, 17]. Significant heterogeneity among trials was observed for itching (P <0.00001, I^2 = 94%). The random-effect model did not indicate any significant pooled WMD favoring ω-3 PUFA

supplement versus control for itching [WMD: 0.25, 95% CI: -0.65, 1.15; Test for overall effect: Z = 0.55 (P = 0.58)] (Figure 2-c).

Effect of ω-3 PUFA supplementation on %TBSA

Four studies had sufficient data for inclusion in meta-analyses of %TBSA with a significant observed heterogeneity among these studies (P <0.00001, I^2 = 99%%)[3, 11, 12, 15]. The random-effect model did not show a significant pooled WMD favoring ω-3 PUFA supplement versus control for %TBSA [WMD: -7.40, 95% CI: -16.75, 1.95; Test for overall effect: Z = 1.55 (P = 0.12)] (Figure 2-d).

Effect of ω-3 PUFA supplementation on scaling

Five studies had sufficient data for inclusion in meta-analyses of scaling [10, 11, 13, 15, 16]. We found a statistically significant heterogeneity among the trials for scaling (P <0.00001, I^2 = 98%). The random-effect model revealed a significant pooled WMD for the efficacy of ω-3 PUFA supplementation on reducing scaling [WMD: -0.69, 95% CI: -1.26, -0.13; Test for overall effect: Z = 2.41 (P = 0.02)] with the pooled SMD of -2.06 [-3.66, -0.46] (Figure 2-e).

Effect of ω-3 PUFA supplementation on desquamation and infiltration

Four and 3 studies had sufficient data for inclusion in meta-analyses of desquamation [3, 12, 14, 16] and infiltration[12, 14, 16], respectively. The observed heterogeneity between studies for both desquamation and infiltration was statistically significant (P <0.00001, I^2 = 97%). The random-effect model did not show a significant net change for the efficacy of ω-3 PUFA supplementation on improving desquamation and infiltration [desquamation WMD: -0.33, 95%

CI: -1.35, 0.69; Test for overall effect: Z = 0.64 (P = 0.52); infiltration WMD: -0.31, 95% CI: -0.82, 0.20; Test for overall effect: Z = 1.19 (P = 0.24)] (Figures 2-f, 2-g).

Subgroup analyses

The results of subgroup analyses are presented in Table 3. To evaluate the influence of ω-3 PUFA supplementation on the complications of psoriasis, included studies were divided into two distinct subgroups according to dosage of supplementation (<1800 vs. ≥1800 mg/day) and duration of study (≤8 vs. >8 weeks). Test of interaction showed significance for the subgroup differences regarding to ω-3 PUFAs' dosage of ≥1800 mg/day. Significant improvements in erythema, itching and scale were observed in the trials which used the higher-dosage of ω-3 supplementation with a significant reduction of heterogeneity in the scale index. Although, the lower-dosage of ω-3 PUFA supplementation and different duration of studies showed significant improvements in some indices, the between study heterogeneities are significant and robust (Table 3).

Sensitivity analysis

Influence analysis was performed to examine the effect of each study on the estimated pooled effect size. Results of systematic removal of each study did not influence the overall weighted mean difference of ω-3 PUFA supplementation on erythema, which ranged from -0.54 (95% CI=-0.95, -0.13) to -1.96 (95% CI=-3.12, -0.80) (Figure 3).

Meta regression

A meta-regression analysis was conducted to investigate the effect of different modulators in determining the heterogeneity of estimates. In accordance with subgroup analysis, higher-dosage

of ω-3 PUFA supplementation and lower duration of supplementation were significantly associated with the improvement in both erythema (dosage of ω-3 PUFA supplementation slope: −0.0007; 95% CI: −0.0005, -0.0006; p<0.001, Figure 4a-1; duration of supplementation slope: 0.05; 95% CI: 0.03, 0.06; p<0.001, Figure 4a-2) and scale complications (dosage of supplementation slope: −0.0004; 95% CI: −0.00053, 0.00032; p<0.001, Figure 4b-1; duration of supplementation slope: 0.05; 95% CI: 0.03, 0.07; p<0.001, Figure 4b-2), whereas lower duration of supplementation were not associated with the improvement in PASI score.

Publication bias

Among the main outcomes, erythema was selected as a representative index for assessing publication bias, as most of the included studies measured erythema as one of the psoriasis complications. Begg's rank correlation (Kendall's Tau with continuity correction: -0.39; z=1.36; two-tailed p= 0.17) and Egger's linear regression test (intercept: -12.7; standard error: 5.25; 95% CI: -25.6, 0.06; t= 2.43, df=6; two-tailed p= 0.06) did not indicate statistically significant publication bias for erythema outcome. This was confirmed according to the symmetric visual inspection of the corresponding funnel plot (Figure 5).

Discussion

Whilst animal studies have routinely purported the therapeutic effect of ω-3 fatty acids on psoriasis, human-based studies are much more equivocal in their conclusions. We therefore sought to conduct a meta-analysis to assess the efficacy of ω-3 fatty acids, as a monotherapy, in treating patients with psoriasis. In accord with the aim of this study, our key findings were that **ω-**3 PUFA supplementation, as a monotherapy, elicited significant reductions in PASI score, erythema, and scaling. Furthermore, our-subgroup analysis highlighted that ω-3 supplementation

with dosages of >1800mg/day and >8weeks in duration were associated with more beneficial outcomes.

The PASI score is a subjective assessment based on estimation by clinicians. Studies have shown that it can be unreliable due to its complex score calculation, it can be difficult to interpret due to its non-linearity and the amount of improvement in the score does not always correspond to clinical relevance. Furthermore, the PASI score does not take into account the disproportionate disease burden reflected in the more visible (hands, feet, nails, face) or covered (genitalia and perianal) body regions, or the impact on patient quality of life. Specifically relating to PASI score, three studies reported such data [1, 3, 10]. ω-3 PUFAs, in general, are considered to modify inflammatory and immune reactions; moreover, ω-3 PUFAs have direct effects on reducing body weight and fat deposition via effects on lipid metabolism-related genes [18] offering a conceivable explanation as to why PASI score may be reduced following a period of supplementation. Of importance is what, practically, demarcates a clinically meaningful improvement. Currently, it is reported that for clinically meaningful improvement in psoriatic patients is at least 50–75% improvement, which has been subsequently translated into 50–75% improvement in the PASI score[19]. Notwithstanding the difficulties in interpreting PASI score, this meta-analysis has highlighted the significant improvements manifest through ω-3 PUFA monotherapy, and therefore warrants consideration in prescribed treatment by clinicians.

The levels of arachidonic acid (AA) and its metabolites, particularly leukotriene B4 (LTB4) and 12-hydroxyeicosatetraenoic acid (12-HETE), are higher in psoriatic plaques than in clinically uninvolved skin [15]. Both LTB4 and 12-HETE are chemotactic for neutrophils, leading to the contemporary use of n-3 PUFAs as an adjunct therapy because their anti-inflammatory and/or

antichemotactic properties seem to induce a protective effect against cutaneous diseases, including psoriasis [17], which has been avowed in the present meta-analysis. Furthermore, Bitteiner [11] assert that since stable plaque psoriasis improves significantly with PUFA supplementation, more profound effects are likely in the inflammatory unstable variants such as erythrodermic psoriasis. This assertion was supported in eight studies included in this meta-analysis [3, 10-16], yielding a statistically significant beneficial effect of ω-3 PUFA supplementation, reducing erythema by -1.66 units. Five studies in this meta-analysis [10, 11, 13, 15, 16] reported that ω-3 PUFA supplementation significantly reduced scaling, and has been suggested that concomitant reduced inflammatory markers in ω-3 PUFA supplementation groups may be mediating such positive changes. Grimminger et al. [14], for example, measured the level of leukotriene B4 and B5, platelet-activating factor (PAF) and 5-HETE. They reported a sharp increase in the generation of LTB5 and 5-HEPE starting from day 3 to day 10 of n-3 PUFA infusion, indicating the reduction of chemotactic and neutrophil activation.

Of note, whilst our meta-analyses highlighted significant improvements in a number of variables, supplementation with ω-3 PUFA did not result in any significant improvements in itching, %TBSA, or desquamation and infiltration. The reason for no significant effect manifest in this meta-analysis stems from the starkly contrasting, and equivocal results in the included studies. Recently, and similarly, Upala et al [5], in their systematic review, noted ω -3 PUFAs were associated with improvements in the PASI score, erythema, scaling, itching, area involved and infiltration; however, some studies did not find reduction in scaling, erythema, area involved or thickness in the treatment group. By conducting the present meta-analysis, we have elucidated the current evidence for the effectiveness of ω-3 PUFA supplementation on PASI score, erythema and scaling; however, it is evident that more well-controlled studies specifically

investigating itching, %TBSA, or desquamation and infiltration are needed to facilitate a more definitive conclusion.

Interestingly, significant improvements in erythema, itching and scale were observed more readily in the trials which used ω-3 supplementation dosages >1800mg/day (Table 3). This finding necessitates further work to ascertain the optimal dosing of ω-3 for it to confer significant benefits.

Strengths and Limitations

The primary strength of this study was that this is the first meta-analysis to assess the impact of ω-3 supplementation on the severity of Psoriasis, manifest in human-based RCTs; and given the potential influence on clinical practice, this is a major finding. The evidence base, prior to this meta-analysis, was bereft of uniformity, and urgently required a summative, quantitative assessment, which we have provided. We demonstrated that there is sufficient evidence for ω-3 supplementation to elicit positive effects on PASI score, erythema and scaling. Another strength of the current meta-analysis is the assimilation of the heterogeneous sample of participants, with a range of demographic status', ethnicities and ages. We were also able to stratify analyses based on both duration of supplementation and dosage, giving clinicians foresight into expected outcomes based on such information.

Notwithstanding, the current study has some limitations worth considering. A large number of included trials were small in sample size, and it has been asserted by Sterne *et al.* that it is probable for studies with small sample sizes to report bigger effect sizes in intervention arms than studies with larger participant pools[20], nevertheless, this was out of the operational control of the meta-analysis. A further limitation of the present study was the paucity of eligible

studies, highlighting the need for more, high-quality RCT's. A further potential limitation is the plethora of controlling treatments administered across the included studies; although our meta-analysis showed, for some variables, ω-3 is significantly better vs. control groups, the controls varied from topical paraffin, talcalcitol, various oils, and medications; conceivably influencing the strength of results found. Therefore, the authors recommend that in addition to further RCTs being conducted, studies should contain at least one standardized control-arm.

Conclusion

The results of current meta-analysis study support the use of ω-3 PUFA supplementation, as a monotherapy, for the improvement of PASI score, erythema and scaling in psoriatic patients. However, the literature base remains equivocal as to whether significant benefits are incurred for itching, %TBSA, or desquamation and infiltration. Therefore, notwithstanding the positive effect elicited by ω -3 PUFA supplementation for some clinically relevant variables, it is evident that more, well-controlled and randomized studies are needed to confirm the veracity of non-significant and/or equivocal findings.

Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

References

1. Guida, B., et al., (2014) *Energy-restricted, n-3 polyunsaturated fatty acids-rich diet improves the clinical response to immuno-modulating drugs in obese patients with plaque-type psoriasis: a randomized control clinical trial.* Clinical Nutrition. **33**(3):399-405.
2. Rahman, M., et al., (2013) *Omega–3 Fatty Acids as Pharmacotherapeutics in Psoriasis: Current Status and Scope of Nanomedicine in its Effective Delivery.* Current drug targets. **14**(6):708-722.
3. Adil, M., P.K. Singh, and K. Maheshwari, (2017) *Clinical evaluation of omega-3 fatty acids in psoriasis.* Dermatology Review/Przeglad Dermatologiczny. **104**(3).

4. Burns, T., *Rook's Textbook of Dermatology. Print and Online Package*. 2010, Wiley-Blackwell.
5. Upala, S., et al., (2017) *Effect of omega-3 fatty acids on disease severity in patients with psoriasis: A systematic review.* International journal of rheumatic diseases. **20**(4):442-450.
6. Qin, S., et al., (2014) *Endogenous n-3 polyunsaturated fatty acids protect against imiquimod-induced psoriasis-like inflammation via the IL-17/IL-23 axis.* Molecular medicine reports. **9**(6):2097-2104.
7. Moher, D., et al., (2009) *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* Ann Intern Med. **151**(4):264-9, w64.
8. Jadad, A.R., et al., (1996) *Assessing the quality of reports of randomized clinical trials: is blinding necessary?* Control Clin Trials. **17**(1):1-12.
9. Gopalakrishnan, S. and P. Ganeshkumar, (2013) *Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare.* J Family Med Prim Care. **2**(1):9-14.
10. Balbás, G.M., M.S. Regaña, and P.U. Millet, (2011) *Study on the use of omega-3 fatty acids as a therapeutic supplement in treatment of psoriasis.* Clinical, cosmetic and investigational dermatology. **4**:73.
11. Bittiner, S., et al., (1988) *A double-blind, randomised, placebo-controlled trial of fish oil in psoriasis.* The Lancet. **331**(8582):378-380.
12. Bjørneboe, A., et al., (1988) *Effect of dietary supplementation with n-3 fatty acids on clinical manifestations of psoriasis.* British Journal of Dermatology. **118**(1):77-83.
13. Escobar, S., et al., (1992) *Topical fish oil in psoriasis—a controlled and blind study.* Clinical and experimental dermatology. **17**(3):159-162.
14. Grimminger, F., et al., (1993) *A double-blind, randomized, placebo-controlled trial of n-3 fatty acid based lipid infusion in acute, extended guttate psoriasis.* The clinical investigator. **71**(8):634-643.
15. Gupta, A., et al., (1989) *Double-blind, placebo-controlled study to evaluate the efficacy of fish oil and low-dose UVB in the treatment of psoriasis.* British Journal of Dermatology. **120**(6):801-807.
16. Soyland, E., et al., (1993) *Effect of dietary supplementation with very-long-chain n-3 fatty acids in patients with psoriasis.* New England Journal of Medicine. **328**(25):1812-1816.
17. Veale, D., et al., (1994) *A double-blind placebo controlled trial of Efamol Marine on skin and joint symptoms of psoriatic arthritis.* Rheumatology. **33**(10):954-958.
18. Mori, T., et al., (2007) *Dietary fish oil upregulates intestinal lipid metabolism and reduces body weight gain in C57BL/6J mice.* The Journal of nutrition. **137**(12):2629-2634.
19. Spuls, P.I., et al., (2010) *How good are clinical severity and outcome measures for psoriasis?: quantitative evaluation in a systematic review.* Journal of Investigative Dermatology. **130**(4):933-943.
20. Sterne, J.A. and M. Egger, (2001) *Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis.* Journal of clinical epidemiology. **54**(10):1046-1055.

Figure 1: *Flow diagram of article selection process*

Figure 2 : *Forest plots of analysis of effect of ω-3 supplementation on psoriasis indices including A)PASI, B) erythema, C) itching, D) %TBSA, E) scale, F) desquamation and G) infiltration. Random effects model was used to pool the mean change of indicators. CI, confidence interval; I-squared inconsistency; Abbreviations: PASI,* Psoriasis *Area Severity Index; %TBSA, percent total body surface area*

Figure 3: *Sensitivity analysis for the effect of ω-3 supplementation on erythema*

Figure 4a: *Meta-regression bubble plots of the association between mean changes in erythema score and 1) dosage of ω-3 supplementation, 2) duration of supplementation.*

Figure 4b: *Meta-regression bubble plots of the association between mean changes in scale score and 1) dosage of ω-3 supplementation, 2) duration of supplementation.*

Figure 5: *Funnel plot detailing publication biases in all included trials.*