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SUMARIO • SUMMARY • RESUMO

Editorial

From the Editorial Board of the journal MLS Health and Nutritional Research in the transfer of scientific knowledge in the field of health, nutrition and food. We encourage you to continue sending us your articles in order to contribute to the advancement of knowledge.

The first article addresses "Immunonutrition for patients undergoing elective head and neck cancer surgery vs. Standard enteral nutrition". Squamous cell carcinoma of the head and neck is the 6th most common head and neck carcinoma in the world. In this review we aim to examine the scientific evidence on the effects of enteral immunonutrition vs. Standard formulas.

The following article discusses the "Relationship between meal timing, body composition and weight loss" Weight gain among the world's population is a relevant issue in recent years.

Nutritional approaches that take into account the timing and frequency of meals may be of interest in improving body composition and weight. To know if there is a relationship between the number and timing of meals, body composition and weight loss.

From the field of community nutrition "Epidemiological surveillance of anisakiasis in Falcón state, Venezuela". Anisakiasis is a zoonotic disease of worldwide importance, caused by parasites of the Anisakidae family, and is unknown in Falcón and Venezuela. This research was developed with the purpose of establishing an epidemiological surveillance system for anisakiasis in the state of Falcón.

The following article "Benefits of insect consumption as a food source on human health". The exponential demographic increase and the lack of resources are forcing the population to look for healthier and more appealing alternatives for their diet. The objective of this review is to demonstrate that the consumption of insects, as a food supplement in the regular diet of humans, provides health benefits.

Related to "Revalorization of a food waste for oil extraction and microencapsulation: pumpkin seed (cucurbita maxima duchesne ex lam)". Food systems generate a significant amount of food waste, such as pumpkin seeds that are discarded before the pulp is consumed. They are a source of nutrients that can be used to improve the human diet.

Finally, "Effect of the Mediterranean diet in the prevention of preeclampsia". Preeclampsia is a complication with a notorious prevalence nowadays that could be prevented through a healthy lifestyle, in this case, a Mediterranean diet.

Editor-in-Chief

Dr. Iñaki Elío Pascual

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IMMUNONUTRITION FOR PATIENTS UNDERGOING ELECTIVE HEAD AND NECK CANCER SURGERY VS. STANDARD ENTERAL NUTRITION

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Summary. The purpose of this literature review was to examine the most recent scientific evidence on the effect and real benefits of enteral immunonutrition in postoperative recovery compared to standard formulas in patients with head and neck cancer undergoing elective surgery. The main bibliographic sources of high scientific impact have been rescued from databases such as Medline, PubMed, Cochrane Library, Elsevier, Scielo and major medical oncological societies such as: SEOM, NIH and clinical guidelines such as ESPEN. There is great heterogeneity among the results examined in the different reviews and meta-analyses on the effect of immunonutrition on postoperative complications. Overall, the findings indicate a benefit in the use of immunonutrition, however, for head and neck cancer they are based on poor quality evidence due to numerous limitations, so the scientific community has not yet found a common consensus. More prolific research could confirm such results with greater benefits for patient survival and, consequently, a shorter hospital stay, which would burden less on the costs of the healthcare system.

Key words: Head and neck cancer, enteral immunonutrition in cancer, *arginine, fatty acids ω-3*.

INMUNONUTRICIÓN PARA PACIENTES SOMETIDOS A CIRUGÍA ELECTIVA DE CÁNCER DE CABEZA Y CUELLO VS NUTRICIÓN ENTERAL ESTÁNDAR

Resumen. La finalidad de esta revisión bibliográfica ha sido examinar la evidencia científica más reciente sobre el efecto y los reales beneficios, en la recuperación postoperatoria, de la inmunonutrición enteral respecto a las fórmulas estándar, en pacientes que padecen cáncer de cabeza y cuello, sometidos a cirugía electiva. Las principales fuentes bibliográficas de elevado impacto científico, se han rescatado a partir de bases de datos como Medline, PubMed, Biblioteca Cochrane, Elsevier, Scielo y principales sociedades médicas oncológicas como: SEOM, NIH y guías clínicas como ESPEN. Existe una gran heterogeneidad entre los resultados examinados de las diferentes revisiones y metaanálisis, sobre el efecto de la inmunonutrición en las complicaciones postoperatorias. En general, los hallazgos indican un beneficio en

el uso de la inmunonutrición, sin embargo, para el cáncer de cabeza y cuello se basan en evidencia de calidad deficiente por numerosas limitaciones, por lo que la comunidad científica no ha encontrado todavía un consenso común. Una investigación más prolífica podría confirmar tales resultados con mayores beneficios para la supervivencia del paciente y, consecuentemente, una menor estancia hospitalaria, que gravaría menos en los costes del sistema sanitario.

Palabras clave: Cáncer de cabeza y cuello, inmunonutrición enteral en el cáncer, *arginina, ácidos grasos ω-3*.

Introduction

Head and neck squamous cell carcinoma [HNSCC] is the 6th most common cancer in the world. It is very heterogeneous due to the multiplicity of sites and tissues involved, such as epithelial cells of the oropharynx, larynx/hypopharynx, nasal cavity, glands and upper aerodigestive tract (Fig 1). It has a very high incidence, is lethal, aggressive, recurrent with metastases, has a high morbimortality due to postoperative complications and is responsible for approximately 1-2% of all cancer deaths [(1-4)].

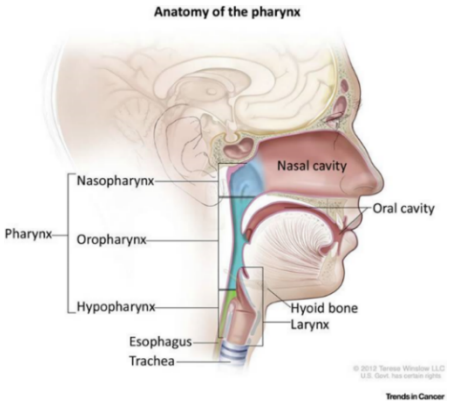

Figure 1. *Localization of cancer of the head and neck. Horton JD 2019* [(4)]

Notwithstanding technological advances over the last 50 years, both in specific treatments and surgical techniques, its overall survival rate remains constant at around 63-66%.

Its risk factors are tobacco, alcohol and *Human Papilloma* Virus (HPV). Its prevalence is higher in the male sex, specifically in Spain it is 10:1 for men, although in recent years, due to the increase in smoking and alcoholism in women, this ratio is being modified [(5)].

During the development and evolution of CECyC, the immune system plays a fundamental role, through the synergistic action of an innate and an adaptive response. Exposure to tumor cells increases the secretion of proinflammatory cytokines, the interleukins (IL-1β, IL-6, TNF-α) and anti-inflammatory cytokines (IL-2, IL-4, IL-10), the latter of which may be affected by poor nutritional status, as is common in the oncology patient or by neoplasia. This condition results in a suppression of the immune system, by a variation of immunocompetent cells, by a dysregulation in the production of pro-inflammatory cytokines and by a consequent intensification of the inflammatory state. The alteration in the antitumor response allows, therefore, the free development of the neoplasm. [(6, 7)]

The combination of the same neoplasm and its specific treatments, consisting of chemo-radiotherapy (CRT) and surgery, has a devastating synergistic effect on the organism, which determines a toxic state with important secondary effects on the integrity of the local tissues The microvascular damage resulting from radiotherapy produces tissue hypoxia, together with fibrosis, as a result of a reparative process due to alteration of the fibroblasts. These factors predispose the patient to local wound infections and complications, the appearance of fistulas and impaired healing, in addition to general

infections and complications (urinary, respiratory). With a cascade mechanism, the clinical picture is critical because of the numerous postoperative complications that lead to high morbidity and mortality (Fig. 2). [8]

Current scientific research is directed towards the use in nutritional support of immunomodulatory enteral formulas (INM) enriched with *arginine, fatty acids ω-3*, , nucleotides, etc. These immunonutrients, with both nutritional and pharmacological action, modulating the inflammatory/immune response could prevent the appearance of complications in the surgical patient and represent a new strategy, more effective than the standard normo or hypercaloric and normo or hyperproteic polymeric formula, to contain the neoplasia and improve the quality of life [12-15] (Table 1).

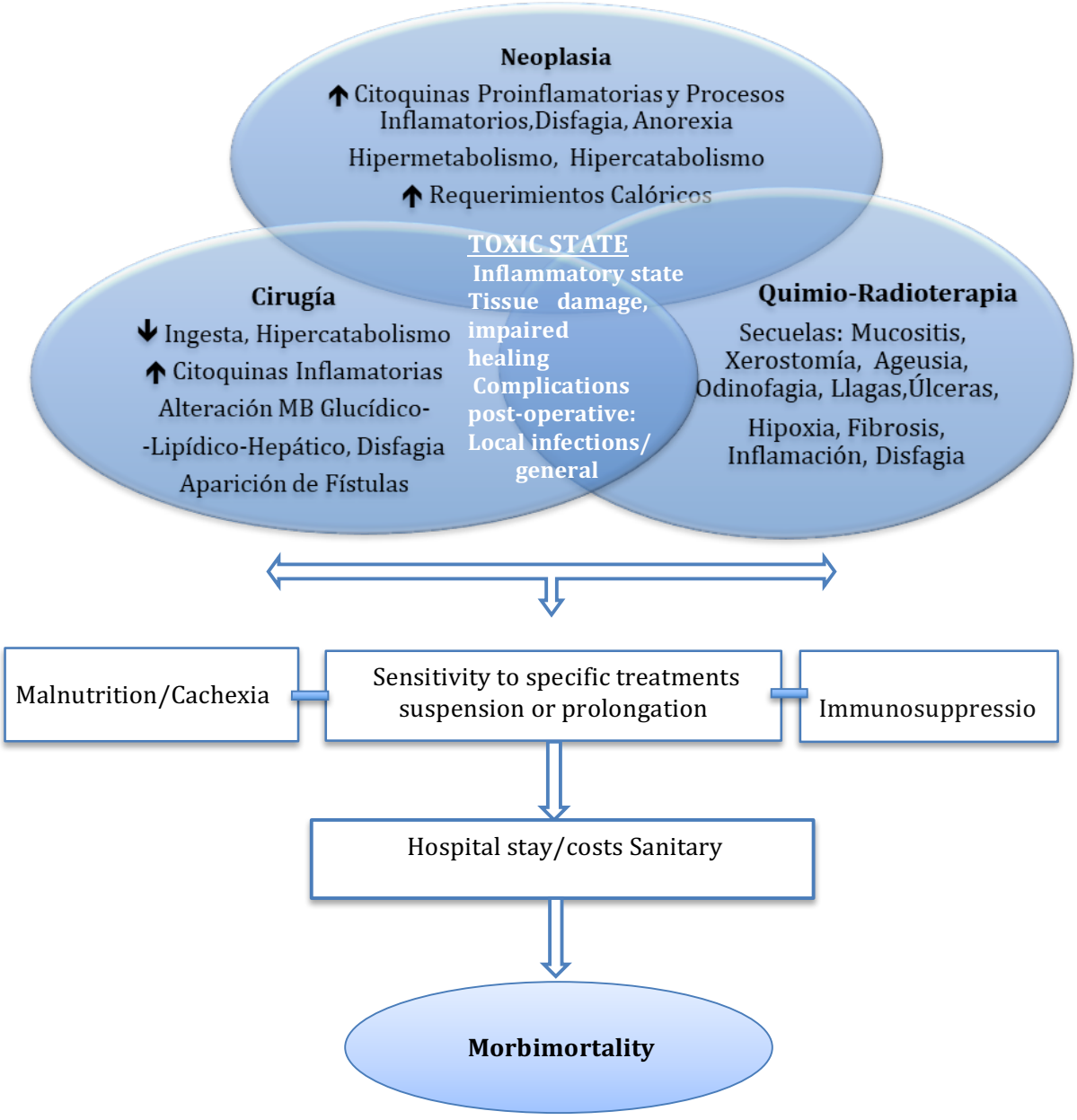

Figure 2. *Synergistic effect between neoplasia, chemoradiotherapy (CRT) and surgery* [3, 5-11, 16-20, 21-24].

The effect of these immunonutrients is coadjuvant: in the reduction of tissue sclerosis, suppressing excessive collagen deposition and in the improvement of wound healing; in the reduction of inflammation and risk of infection; in reducing esophagitis, diarrhea and weight loss related to toxic effect; in reducing the incidence, severity and occurrence of mucositis during chemotherapy, in the improvement of weight, lean body mass and fat in neoplasms (3, 5-11, 16-20) [3, 5-11, 16-20, 21-24].
It is noted that nutritional optimization represents treatment compliance, improved clinical outcomes and patient rehabilitation [12,15].

Table 1

Most commonly used pharmaconutrients and their action

Immunonutrients	Main mechanisms of action
Glutamine	Improves T-lymphocyte response, B-lymphocyte and macrophage function. Improves the function of the intestinal mucosa. Decreases the rate of infections. Decreases hospital stay.
Arginine	Increases T-lymphocyte response. Increases cytokine levels in blood. Increases insulin, prolactin and glucagon secretion.
Fatty acids ω-3	Increases circulating levels of Ig and INF-ɣ. Improves neutrophil function. Increases the percentage of T helper lymphocytes
Nucleotides	Promote DNA and RNA synthesis Improves macrophage activity and lymphocyte function.

Adapted from *Gómez Candela C* et al. (2021) [25]

The possible beneficial effects of immunonutrition in oncological pathologies have been investigated for 30 years. However, it is since 2000 that research activity has intensified. *Gianotti* et al. (2002) [26] were among the pioneers , with a randomized clinical trial in which they evaluated the effect of pre- and perioperative INM compared to the control group with the traditional formula in patients undergoing gastrointestinal surgery. They observed a lower incidence of postoperative infectious complications and a shorter hospital stay (HME) in the two groups with administration.

In addition to determining the clinical benefits, one of the crucial points of the research, is to define the most effective dose, duration and timing of pre-, post- or peri-operative administration of immunonutrients (INM).

Another determining factor to know the real efficacy of each of the immunonutrients is to examine them in isolation, because in a combination of ingredients,

as found in the most common commercial formulas, what is observed is a synergistic effect [(14)].

Mueller et al. (2019) [(27)] and *Aeberhard C* et al. (2018) [(28)] observed, in two very similar studies, lower incidence of postoperative infectious complications and as a consequence a strong reduction of the mean hospital stay (MHS), which actually seemed very excessive in correlation with the preceding data, in the subgroup of intervention with preoperative INM, previous radiotherapy and extensive surgery.

Beneficial effects of INM, both pre- and perioperatively administered, were confirmed in the most current meta-analysis of 24 randomized clinical trials (RCTs) published by *Buzquurz F* et al. (2020) [(29)], an intense reduction in general and wound infections was observed, however, no impact, in contrast, on mortality. Through a postoperative administration of INM and to better understand the effect, *Casas-Rodera P*. et al. (2008) [(30)] compared two different INM formulations, in two groups, one with isolated arginine, the other with the *arginine*triad, ω *-3*nucleotides and in the control group the standard formula. No major significant differences or clinical benefits were observed between the two MRI intervention groups.

A 3.5-day reduction in hospital stay was found as a result of postoperative MRI administration in the systematic review by *Stableforth WD* et al. (2009) [(31)]. This decrease was not very clear because it was not associated with any other clinical benefit.

Vidal-Casariego A. et al. (2014) [(32)] confirmed in a systematic review- meta-analysis, notwithstanding numerous limitations concerning trials, the beneficial effect of both peri- and postoperative-only MRI, associating it with a significant reduction in the occurrence of fistulas and hospital stay.

Identical to *Casas-Rodera P* et al. (2008) [(30)], *Barajas-Galindo DE* et al. (2020) [(21)] who, in a retrospective observational study, did not confirm beneficial effects of postoperative MRI in malnourished patients, but rather related the appearance of fistulas to the degree of malnutrition of the patient.

The first authors to evaluate perioperative supplementation of INM were *Synderman CH* et al. (1999) [(33)] administered a higher dose of *arginine* than all other studies (18.7 g of *arginine* 5 days before and 12.5 g 8 days after the intervention). In a trial of high methodological quality they observed the reduction of infections, however, they did not point out any impact on the reduction of hospital stay.

Felekis D et al. (2010) [(34)], like other previous authors, following a perioperative MRI procedure, observed a significant reduction in postoperative complications exclusively in the normo-nourished subgroup. Results supported by *Turnock A*. et al. (2013) [(7)] a few years later.

Howes N et al. (2018) [(35)], published a systematic review, collected in the *Cochrane database,* of 19 RCTs, comparing peri- and postoperative NMI. Despite the large number of participants, 1099 in total, the sample size was very limited, ranging from 8 to 209 subjects. In this case, there was no significant evidence that immunonutrition had any real effect on wound infection, postoperative complications, hospital stay, mortality, etc.

The main objective of this review was to analyze the scientific evidence on the validity, effectiveness and real benefit of INM, evaluating the reduction of clinical parameters such as: local/general infections, occurrence of fistulas, mean hospital stay

(MSH) and mortality. It will also be convenient to determine the most effective time of administration of the immuno-formula.

Method

A bibliographic review was carried out on the use of immuno-nutrition in the CECyC in the last 20 years, consulting the most important and relevant sources of scientific literature. Research in this area is so limited and muddied, therefore, in order to examine the evolution over time of the studies and gather more information, no restriction or filter of seniority of the last 5 years has been imposed on the provider's search. The preferred elements have been systematic reviews and meta-analyses with a minimum Impact Factor (IF) > 1.5. The literature search began in January 2022 and ended in April 2022. Article eligibility criteria were established (Tables 2 and 3). All trials met the inclusion criteria, except for two trials with specific prior radiotherapy (RT) treatment, included to look at deviation during treatment and to have a broader overview of the question, until the most recent systematic review/meta-analysis in August 2018.

Table 2

Criteria for selection of articles from the bibliography

Criteria for inclusion of articles
- Randomized controlled trials, systematic reviews and meta-analyses in humans.
- Publications in English and/or Spanish.
- Patients ≥ 18 years old diagnosed with head and neck and undergoing elective major surgery.
- Any nutritional status: at risk of malnutrition, malnourished or normo-nourished.
- Full text" articles or with limited access, consulted through the *sci-hub*web page.
- Intervention group: enteral formula enriched with immunonutrients.
- Supplementation with arginine-fatty acids ω-3 - RNA in isolation or as a set (oral/enteral Impact® formula).
- Control group: enteral formula with traditional nutritional supplementation.
- Timing of MRI intervention: pre, post and perioperative.
- Postoperative recovery after immunonutrition.
- Studies that will evaluate as outcomes general and wound post-surgical infectious complications, occurrence of fistulas, EMH (mean hospital stay) and survival.

Table 3.

Criteria for selection of articles from the bibliography

Article exclusion criteria

- Non-random EC.
- Low level and low IF scientific journals.
- Patients aged ≤ 18 years.
-Articles with patients who did not suffer from head and neck cancer and who were not undergoing elective surgery.
- Studies that, in addition to surgery, included previous chemotherapy treatments previous.
- Parenteral nutrition.
- Studies with different INM of the arginine-fatty acid triad ω-3 - RNA.
- Studies with the use of a placebo in the control group.

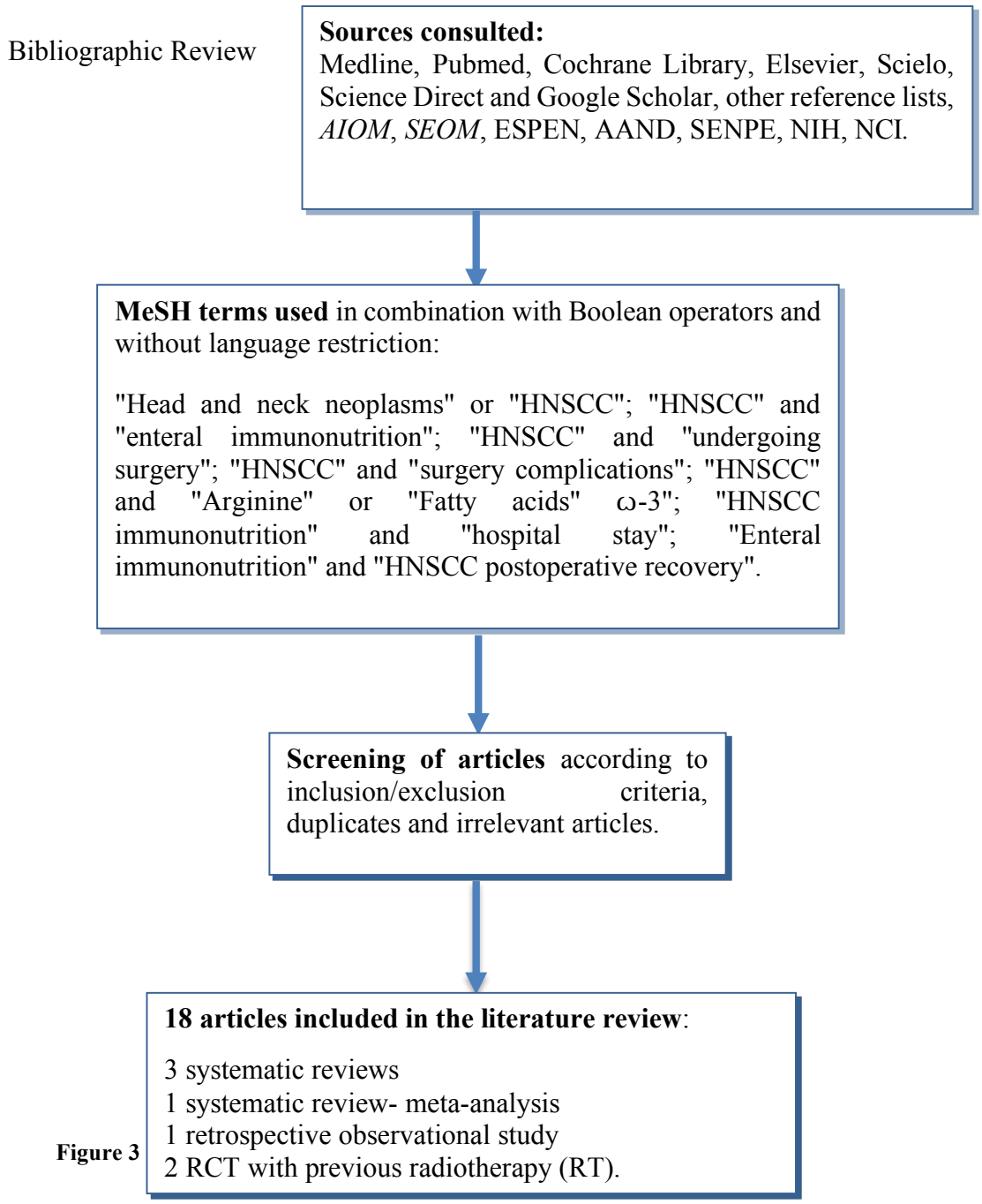

Figure 3

Flow chart of the literature review

Results

The reduction in hospital stay of 3.5 days, observed in the postoperative MRI intervention group, in the review by *Stableforth* et al. (2009) [31]) was considered very unclear and was not associated with other clinical benefits. The increase in CD4 and CD4/CD8 lymphocytes determined in only one trial [36] did not, however, correspond to a reduction in hospital stay (HME). A very contrasting analogous result, following postoperative MRI, was observed by *Synderman CH* et al. (1999) [33]. In the intervention group they evaluated an incongruent decrease in HME corresponding to an increase in both wound infection and fistula occurrence. Increase that the authors related to the surgical technique, to the severity of the pathology and to the nutritional status, or even hypothesized that the cause of this result was due to some adverse effect of the INM (as in septicemic patients) that detrimentally altered the inflammatory response [33].

In spite of the postoperative administration of a formula with a high dose of *arginine*, neither *Barajas Galindo* et al. (2020) [21] found clinical benefits, however, they observed a higher incidence of fistulas in severely malnourished patients in both groups (Table 4), a result related to a low intake of formula received. In addition, hospital stay was not correlated with immunonutrition, on the contrary, with the presence of fistulas that depend on malnutrition.

Vidal Casariego et al. (2014) [32] in contrast (Table 5) in a meta-analysis review confirmed the benefit of postoperative MRI, despite numerous study limitations. They determined a significant reduction of fistulas [37] in addition to a reduction of fistulas and EMH in another trial [38], consolidating the fistula-EMH relationship. No effect on wound infection or other complications, however, was determined.

In contrast to the previous result, in the same review by *Stableforth* et al. (2009) [31] and *Riso S* et al**.** (2000) [36] confirmed that INM administered postoperatively in malnourished patients significantly improved the main postoperative complications and EMH, but did not improve the occurrence of fistula, which had the same incidence in the two groups (Table 4). This could mean, therefore, that INM has no effect on the fistula or that EMH does not depend only on the fistula, a hypothesis that was confirmed by *Luis DA et al*. (2010) [39] in the systematic review by *Casas Rodera* et al. (2012) [40] in a trial with comparison of a high *arginine* dose with another with its half in the two groups, however the limitations were not reported, the blinding was very unclear and the inter-trial variability was, as in other reviews, very high (Table 5).

Both *Aeberhard* C et al. (2018) [28] [28] as *Mueller SA* et al. (2019) [27] observed as a result of a preoperative administration of INM, with prior radiotherapy (RT), a sharp decrease in fistula incidence and an even higher reduction of EMH (from 17 to only 6 days) in high-compliance subgroups. However, they linked the sharp reduction in EMH to the *Swiss DRG 2012* discharge optimization process that penalizes a prolonged stay. They therefore confirmed, in agreement with *Barajas Galindo* et al. (2020) [21], that fistula and HME are dependent on malnutrition, also stressing the importance of high compliance, in addition to the presence of *arginine* (Table 6).

Howes N et al. (2018) [35], have published, in the *Cochrane*database, the most relevant and recent review on immunomodulatory supplementation in patients with CECyC undergoing elective surgery (Table 7); 19 RCTs in total (post and perioperative INM, excluding 3 trial administering other types of immunonutrients). The different

timing of administration did not produce significant differences in the findings, however, it was observed that INM given only postoperatively (evaluated in 10 RCTs, n = 747) could reduce the risk of fistula incidence by 50%. EMH was reduced in 8 of 10 studies in which it was analyzed (n = 757) without being able to confirm this finding due to lack of evidence, because INM had no effect on wound infection and on overall complications. Even less was reported any effect of immunonutrients on mortality [(35)].

Tabla 4 Características de los ensayos clínicos aleatorizados (ECA) con empleo de INM postoperatoria vs nutrición estándar

Autores Tipo de estudio	n Inm/ Est.	Momento de administración INM	Tipología Fórmulas INM/Est.	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Stableforth 2009 [(31)] Rev. Sist. 10 ECA	Tot. 605	Inm Postoper.	Impact® Enteral:Argi nina+ ác. grasos ω-3, ARN Estándar Nutrison Intensive®	Peso, complic. clínicas, parám. bioq., EMH, calidad de vida, tolerancia a fórmula, fuerza de agarre.	↓ EMH se observó en 6 estudios (3,5 días en media), sin otro beneficio clínico que lo explicara ↓ Fístula en 3 ECA, ↓ Infecc. herida en 2 ECA ↑ mejor respuesta inmunol. en sólo 1 ECA, pero sin reducc. de EMH. En 1 ECA ↑Fístula + Infecc. herida con una incongruente ↓ de EMH	ECA muy pequeños. Había poca evidencia de heterogeneidad. Datos insuf. para excluir efecto de INM. Muy ≠ las intervenciones, la duración, el tipo y estadio de los tumores. Comparación INM perioper. vs NO+ postoperatoria. Falta de datos sobre tolerancia a la fórmula. Limitaciones metodológicas. Sólo la mitad de los estudios informaron del doble cegamiento [(31)].

Autores Tipo de estudio	n Inm/ Est.	Momento de administración INM	Tipología Fórmulas INM/Est	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Barajas Galindo 2020 [(21)] Estudio Obs. Retrosp.	Tot 135 INM 68 EST 67	Inm Postoper.	Impact® [Polim +arg+ ác. g.ω3 + RNA] Ingesta de arginina= 21,5g	Fístulas, EMH, reingresos y la mortalidad a 90 días	Ningún resultado significativo, con elevada dosis de arginina, después de ajustes. Fístula: > incidencia en desnutridos de ambos grupos. Posible relación entre: Desnutrición -fístula - EMH	Estudio retrospectivo, pacientes de ≠ épocas y probablemente ≠ técnicas quirúrgicas. Bajo cumplimiento de la ingesta media en el 20,6% de los participantes. No inclusión de datos sobre la tolerancia al alimento (diarrea) o análisis sobre la rentabilidad [(21)].

Origen: Datos recopilados de Stableforth 2009 [(31)], Barajas Galindo 2020 [(21)] n = muestra; Inm = Fórmulas Inmunomoduladoras; Est.= Fórmula Estánd

Tabla 5 Características de los ECA con empleo de INM peri/postoperatoria vs nutrición estándar

Autores Tipo de estudio	n Inm/ Est.	Momento de administrac. Inm	Tipología Fórmulas Inm/Est.	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Casas Rodera 2012 [40] Rev. Sist. 14 ECA	Tot. 836 INM 436 EST 400	Inm Peri/Postoper.	-Polim+arginina -Impact® [Polim +arg+ ác. g.ω3 + RNA]	Complic. inf herida, EMH, parám bioq. tolerancia a fórmula.	↓ EMH En 6 ECA ↓ Fístula en 5 ECA, ↓ Infecc. herida En 2 ECA ↓Complicac.post. en 2 ECA En 1 ECA ↑Fístula e Infecc. herida No ≠ en marcadores nutricionales e inmunológicos EMH no depende solo de la fistula	No reportadas las limitaciones de estudios. Cegamiento poco claro Elevada heterogeneidad entre ensayos [40].

Autores Tipo de estudio	n Inm/ Est.	Momento de administrac. Inm	Tipología Fórmulas Inm/Est.	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Vidal-Casariego A. 2014 [32] Rev. Sist./Metaan 6 ECA doble ciego	Tot.397 INM 20 EST 187	Inm Peri/ Postoper.	-Polim+arginina -Impact® [Polim +arg+ ác. g.ω3 + RNA]	Fístulas, inf. de heridas y generales EMH	Beneficio de INM postoperatoria ↓ EMH y Fístulas en 1 ECA ↓ Fístula en 2 ECA No ≠ en complic infecciosas, ni en tolerancia a INM. Posible relación Fistula-EMH	Elevada variabilidad entre los ECA por ≠ de tipología del cáncer, bajo nº de ECA y baja calidad de algunos, déficit en el método de aleatorizado y de cegamiento de las intervenciones. Tamaño de muestra pequeño, bajo poder estadístico, no hubo heterogeneidad estadística entre los ECA. Comparación de ≠ momento de administración vs nutrición estándar y ≠ dosis de arginina 12-20 g/L empleada, fórmula INM especificada en sólo 3 ECA. Estado nutricional muy ≠ en el reclutamiento [32].

Origen: Datos recopilados de *Casas Rodera* 2012 [40] *Vidal-Casariego A.* 2014 [32] n= muestra; Inm = Fórmulas Inmunomoduladoras; Est.= Fórmula Estándar

Tabla 6 Características de los EC, con radioterapia previa, incluidos en la revisión bibliográfica sobre el empleo de INM preoperatoria vs nutrición estándar

Autores Tipo de estudio	n Inm/ Est.	Momento de administrac. Inm	Tipología Fórmulas Inm/Est.	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Aeberhard C 2018 [23] ECA no aleatorizado + Radioterapia previa	Tot 411 INM 202 EST 209	Inm Preoperat	Oral Impact® [dosis diaria arg. = 11,3g; ω-3= 3g	Complicaciones quir. EMH, mortalidad y fistula en pacientes sometidos a C(RT) previa y cirugía	↓ Fístula en grupo INM ↓EMH resultado sólido- después de ajuste multivar. Beneficios significativos en subgrupo de alto cumplimiento (al menos 75% de la ingesta prescrita) y con RCT y cirug. extensa No ≠ en complicaciones gener. Relación entre: Desnutrición - Fistula - EMH	Estudio no aleatorio, carácter retrospectivo de la recogida de datos. ≠ en cuanto a variables sociodemográficas, sitio, estadio tumoral y tipo de cirugía entre los 2 grupos y con RCT previa. Proceso de alta hospitalaria especifico ***Swiss DRG 2012*** ha podido influir en EMH (por penalizar una estancia prolongada) [23].

Autores Tipo de estudio	n Inm/ Est.	Momento de administrac. Inm	Tipología Fórmulas Inm/Est.	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Mueller SA 2019 [22] ECA + Radioterapia previa	96 INM 51 EST 45	Inm Preoperat.	Oral Impact® Arginina + ác. grasos ω-3, ARN oral /enteral	Complicaciones de la herida en general. EMH en pacientes sometidos a (RCT) y cirugía	↓ Complic. generales de la herida ↓ EMH reducción muy intensa (de 17 a 6 días) en pacientes de alto cumplimiento Relación entre: Desnutrición - Fistula - EMH	Tamaño pequeño de la muestra. Carácter retrospectivo del ECA. Probable sesgo por la optimización del proceso de alta hospitalaria SwissDRG en 2012 [22].

Origen: Datos recopilados de Aeberhard C, 2018 [23], Mueller SA, 2019 [2][2] n= muestra; Inm = Fórmulas Inmunomoduladoras; Est.= Fórmula Estándar

Tabla 7 Características de los ECA con empleo de INM peri/postoperatoria vs nutrición estándar [35]

Autores Tipo de estudio	n Inm/ Est.	Momento de administración Inm	Tipología Fórmulas Inm/Est.	Objetivos	Resultados en grupo de intervención Inm	Limitaciones
Howes N, 2018 [35] Revisión Sistem. 19 ECA 2 ECA excluidos por ≠ fórmulas INM	Tot. 1099	19 ECA: -10 ECA postop - 9 ECA periop	- Polimér.+ arginina Impact® - Polimér + arginina Nutrison intensive® - Impact Recover®+ arg+ glutam. ARN	1º EMH infección de la herida, formación de fístulas, tolerancia a la fórmula INM 2º: mortalidad por infecciones y complicaciones	Fístula ↓ del 50% de incidencia con INM postoperatoria. Evaluado en 10 ECA (n=747). ↓ EMH: Se redujo en 10 ECA (n=757) con reducción de 2,5 días, sin encontrar pruebas; Infección herida: evaluada en 12 ECA (n=812). No evidencia de un efecto de la INM sobre la infección de la herida Mortalidad: Se evaluó en 14 ECA (n= 776). Complicaciones generales: No se reportaron con frecuencia complicaciones infecciosas generales. INM puede tener poco o ningún efecto sobre heridas, mortalidad y EMH	Según la calificación GRADE: ↓ EMH evidencia baja ↓ Infección de la herida y mortalidad con evidencia muy baja. Estudios y el tamaño de muestra pequeño (12/19 ECA con n < de 25 participantes), IC muy amplio en torno a estimaciones del efecto, descripción muy insuficiente del método para evaluar los resultados (evaluación de la herida y efectos adversos). Resultados incompletos y no confiables. Elevada heterogeneidad en dosis, tipología de la fórmula y duración de administración INM (de 5 a 14 días preoperatoria y de 5 a 22 ± 12 días perioperatoria). Elevada variabilidad entre estudios [35].

Origen: Datos recopilados de *Howes N, 2018* [35] n = muestra; Inm = Fórmulas Inmunomoduladoras; Est.= Fórmula Estándar

Discussion and conclusions

The use of immunonutrients as a new strategy to contain head and neck cancer neoplasia in patients undergoing elective surgery presents considerable perplexities. There is an inconsistency between the use of immuno-modulating formulas and the results, which are very contrasting, scarce and incomplete due to lack of evidence and a high number of limitations. It is not possible to confirm the strength of the evidence of its real benefits. Evidence so necessary in order to evaluate the cost-effectiveness of this intervention and to decide whether it is convenient to sustain the huge daily cost of drug-nutrition, versus a possible reduction of treatments, of a patient's hospitalization and an improvement in his or her quality of life, which is clinically and economically important [35].

Casas-Rodera P. et al. [30], in their trial demonstrated that the immunonutrient triad had no greater potential than the administration of arginine alone. More determinant in the postoperative recovery of the patient was, according to the authors, the nutritional status and the surgical technique, with respect to the impact that INM could have.

According to the *GRADE* (Grade of Recommendation, Assessment, Development, and Evaluation) rating of the evidence of effect on the actual benefit of immunonutrition, in the review by *Howes N* et al. (2018) [35]), ranged from low (for reduction of EMH and fistula occurrence) to very low (for reduction of wound infection and mortality), attributable to a high number of limitations that analogously characterize most clinical trials evaluated in this setting and are summarized in Table 8. Numerous biases attributed to the very wide confidence interval, to the high heterogeneity, revealed in the type of formula, with *arginine* administered alone or in a set of immunonutrients and corresponding doses, methodology and scientific quality of the studies, which varied from low to very low according to the *Grade System*rating.

Limitations, in addition, on the representativeness of the sample, such as its size and the age of the individuals. There was a large difference in the mean age of the participants in the different studies, which ranged from 47 to 66 years, however, in the trial by *Turnock A* et al. (2013) [7] ranged from 28 to 68 years in the intervention group and from 17 to 79 years in the control group. Likewise, women were underrepresented in

the vast majority of the trials, as CCSCC is a predominantly male type of cancer, currently with a reversal of the trend due to an increase in smoking among women; the ratio of men to women in the trials was 65: 7.

A limitation present in many trials is the lack of communication or the coexistence of different nutritional states at the time of recruitment, which complicates, therefore, the comparison of effects and results. Knowing the previous nutritional status could be the main condition for the subsequent development of fistula or other complications, which highlights the importance of nutritional assessment prior to surgery in patients with head and neck tumors [16, 41].

The *American Academy of Nutrition and Dietetics* (*AAND 2019***)** speaks out *in favor of fatty acids ω-3*, *when dietary intake is inadequate, to stabilize body weight and limit body weight loss*, with recommendation grade: strong; imperative and with grade C for S&C cancer [42].

The *Australian Guidelines* (2020) [43] with grade C state that drug-nutrition, in the preoperative period, has no benefit compared to conventional nutrition, however, it is suggested in the postoperative period to reduce the average hospital stay (with grade B recommendation), without having a clear mechanism and evidence on the reduction of complications and infections. Its use should last at least 7 days (grade C).

The *European Society for Clinical Nutrition and Metabolism Guidelines (ESPEN,* 2017), on the other hand, suggest the use of fatty acids ω-3 with low level of evidence and grade of recommendation in patients with advanced cancer, undergoing chemotherapy and at risk of malnutrition. There is still insufficient evidence to recommend its use in ECCC [42, 43].

Definitely, it is not possible to trust the results and neither is it possible to attribute them with certainty to immunomodulatory formulas, since they are scarce, contrasting and with a low or very low level of evidence, which shows that this subject is still under development. Scientists do not yet agree on a common consensus on the real efficacy of immunomodulatory enteral formulas administered preoperatively in ECCC. [27,28].

However, according to some studies, administered postoperatively, they could reduce the average hospital stay, because they are probably related to a lower incidence of fistulas, although the mechanism is not very clear because it has not yet been demonstrated [21,31,35]. It is also considered that perioperative supplementation of fatty acids ω-3 may be desirable in malnourished cancer patients or those at risk of malnutrition exclusively for the maintenance of lean mass and weight [44].

Table 9. *Main limitations and sources of clinical heterogeneity in the trials evaluated*

Category	Item	Specification
Study variables	Methodology	Retrospective studies with lack of access to data, low methodological rigor and quality, variability between studies, incomplete and contrasting results, very wide confidence interval (CI) including null value, insufficient communication of methodology and blinding.
	Sample	Non-representative: due to a very wide age range, disproportionate ratio between the sexes of the participants, inappropriate size of the study population, and high heterogeneity of the variables among the participants.
Nutritional intervention	INM Formula	≠ INM formula typology: nutrients administered in isolation or in a triad (nucleotides, arginine, ω−3). ≠ Timing of formula administration: pre, post or perioperative, differences also in the comparison between perioperative administration in the intervention group vs standard postoperative in the control group. ≠ Duration of treatment. ≠ Formulation mode of administration: oral/enteral. ≠ Immunonutrient doses among trials in the same literature review.
Patient	Neoplasia	≠ Typology and clinical stage of the neoplasm considered. Lack of data communication. ≠ Typology of surgery. ≠ Patient severity.
	Nutritional status	≠ Nutritional status among participants [well nourished, moderately/severely malnourished]. ≠ Nutritional status assessment tool used (NRS 2002, VGS−GP, MUST, MNA). ≠ Average intake of each individual participating in the trial or lack of data on the volume received with respect to the indicated volume.
	Follow-up and discharge hospital	≠ Criteria for hospital discharge. Different duration of follow−up of a participant: until hospital discharge, after 30 days or for a few months.
Determinations	Nutritional Assessment Tool	≠ Nutritional status assessment tool used in the studies (NRS 2002, VGS−GP, MUST, MNA).
	Biochemical parameters	≠ Analytical parameters used to assess inflammatory status, immune response or

		nutritional status and also determined at different times.

Table adapted from *Gómez Candela C,* 2021 [34]. Data collected from references [21-23, 31, 32, 32, 35, 40]

A high percentage of oncology patients, between 35% and 66% approximately, present pathology-related malnutrition at the time of diagnosis [20]. Although it is not yet possible to propose exact and clear recommendations on the use of immunonutrients, the strength of research in this area is the attention and importance given to the need for the attention and importance given to the need for screening and evaluation of the nutritional status of the oncological patient undergoing surgery. In addition to the need to examine the volume of formula intake in relation to the amount of formula supplied, since a relationship has been observed between malnutrition and the appearance of fistulas and, consequently, an increase in hospital stay supplied, since a relationship has been observed between malnutrition and the appearance of fistulas and, consequently, an increase in hospital stay. The aim is to achieve early nutritional treatment that is adequate to their needs, in order to avoid malnutrition, which is associated with a worse clinical prognosis that compromises patient survival [45, 46] and is a burden on health care costs.

Recommendations for future research

Among the recommendations, the main one is the design of an "*ad hoc"* study with high methodological quality, low variability, a very narrow confidence interval and adequate blinding. A prospective nature will be necessary to avoid unavailability of necessary data. Thus, a representative sample with an appropriate size, fair sex ratio and adequate age range. The effect of each isolated immunonutrient will be evaluated, thus avoiding masking. In addition, it will be essential to standardize in the assays parameters such as nutritional status and the tool for its evaluation, immunological/biochemical parameters and the specific time of their determination, as well as the type of formula used, dosage, time and duration of its administration. On the other hand, *follow-up*time, hospital discharge criteria and, finally, the type of cancer, surgery, clinical stage and severity of the participants will be standardized.

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RELATIONSHIP BETWEEN MEAL TIMING, BODY COMPOSITION AND WEIGHT LOSS

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Summary. Weight gain among the world's population has been a relevant issue in recent years. Nutritional approaches that take into account the timing and frequency of meals may be of interest in improving body composition and weight. The objective is to know if there is a relationship between the number and timing of meals, body composition and weight loss. A bibliographic review was carried out, scientific articles were selected and consulted, both studies and reviews, official websites and relevant documents. A total of 12 studies published in the last 5 years belonging to the Pubmed and Scielo databases were taken into account and analyzed in depth. In addition, the use of the Google search engine was employed for official pages, Both the timing of meals and the frequency at which they are eaten or the macronutrients they ingest are effective dietary-nutritional strategies for body composition and weight modification. More current research is needed, especially in the area of meal frequency to demonstrate effects on body composition, however, it can be concluded that both consideration of macronutrient intake and food timing are possible competent nutritional approach strategies for body composition and weight change.

Key words: Chrononutrition, meal timing, meal frequency, body balance and macronutrients.

RELACIÓN ENTRE EL HORARIO DE COMIDAS, LA COMPOSICIÓN CORPORAL Y PÉRDIDA DE PESO

Resumen. El aumento de peso entre la población mundial es un tema relevante en estos últimos años. Abordajes nutricionales que tengan en cuenta los horarios de las comidas, así como su frecuencia pueden ser interesantes a la hora de mejorar la composición corporal de la población y el peso. El objetivo es conocer si existe relación entre el número y el horario de las comidas, la composición corporal y la pérdida de peso. Se realizó una revisión bibliográfica, fueron seleccionados y consultados artículos científicos, tanto estudios como revisiones, webs oficiales y documentos relevantes. Se tuvieron en cuenta un total de 12 estudios publicados en los últimos 5 años pertenecientes a la base de datos Pubmed y Scielo, los cuales fueron analizados en profundidad. Además, se empleó el uso del buscador de Google para páginas oficiales, Tanto el horario de las comidas como la frecuencia en la que estas se realizan o los macronutrientes que

ingieren son estrategias dietético-nutricionales efectivas para la modificación de la composición corporal y del peso. Se necesitan un mayor número de investigaciones actuales, sobre todo en el ámbito de la frecuencia de las comidas para demostrar los efectos sobre la composición corporal, sin embargo, se puede concluir que tanto tener en cuenta los macronutrientes que se ingieren como el timing alimentario, son posibles estrategias de abordaje nutricional competentes para el cambio de composición y peso corporal.

Palabras clave: Crononutrición, horario de las comidas, frecuencia de las comidas, balance corporal y macronutrientes.

Introduction

The relationship between our internal state and the environment, as well as the way in which the latter affects us was first named by Jean-Jacques d'Ortus de Mairan in the eighteenth century (1,2). Chronobiology (CB) progressed and was studied in humans for the first time in the 20th century, after which the terms circadian, CB, chronodisruption (CD) and chrononutrition (CN) were invented (1,3,4).

The term BC according to the US National Institute of Health (NIH) (3)refers to the study of physical, mental or behavioral fluctuations that occur within twenty-four hours. Circadian rhythms play a fundamental role in the organism in aspects such as the optimization of nutrients and energy that the body uses for the actions of routine life(5,6). This is shaped and modified by external, non-modifiable signals, such as light and dark times, and environmental signals, or modifiable signals such as dietary pattern or intake (3,6–8). When there is an alteration, maintained over time, of the rhythms and both biological and physiological aspects are modified, the so-called CD is produced (4,5,9–11).

It is not known whether, taking all of the above into account, there are times of the day when, although the net energy load is the same, there is a greater predisposition to weight loss (12–14). It should be noted that the global percentage of people suffering from obesity continues to increase every year (12,15,16).

General Objective:

- To know the relationship between the number and timing of meals and their effect on body composition.

Specific objectives:

- Determine if there are recommendations regarding meal times to promote weight loss.
- Assess how the number of meals influences weight gain or loss.

Chronobiology

The concept of "clock" in this branch of physiology was inspired by Kramer to refer to the compensation made by birds with the sun. The term is currently used to explain the relationship between nature and the internal rhythm that humans present (1,17).

Due to the importance that these circadian rhythms, together with the seasons of the year, have on the organism; living beings, including humans, have been trying to adapt to all the changes that have been occurring. One of the most drastic changes is industrialization, since the number of hours that people spend exposed to artificial lights has increased and, consequently, the incidence of natural light has decreased (1,6,17).

Chronobiology and nutrition

The organ par excellence in charge of the regulatory processes of hunger and satiety in the body is the hypothalamus. Thanks to the latter, with the help of hormones,

peptides and other molecules and nutrients such as glucose or fatty acids, humans are able to distinguish times when they need a caloric intake from those when they do not (8,17).

Many hormones are currently known to be involved in the processes of hunger and satiety, of which three stand out as they have been extensively studied. On the one hand, leptin, secreted by adipocytes when fat levels are increased and responsible for the feeling of satiety. Ghrelin, which is responsible for providing the sensation of hunger and thus inciting food intake, is also important (8,17,18). Thirdly, neuropeptide Y (NPY) is related to the regulation of intake and is responsible, together with ghrelin, for increasing appetite by inciting the initiation of food consumption. The concentrations of these hormones appear to oscillate depending on the time of day, affecting the way in which food is absorbed (6,17,18).

The way in which food assimilation processes could be modified is by modulation of the hypothalamus, pineal gland and thus the CNS. In addition, molecules such as glucose, which is controlled by the hormone insulin and this, in turn, by the CNS, see their absorption modified and slower as the day progresses (11,18,19).

As science has progressed, new concepts have emerged. Due to the need to unify the concepts of circadian rhythms, BC and food, the concepts of CN arise, which refers to the study of nutrients as well as the variability of use throughout the day, and the concept of chronodiet, which is explained as the study to know what are the best times to consume one or other foods (17,20–22).

BC, as mentioned above, refers to the study of changes (physical, mental or behavioral) that occur over the course of a day (17,18). Over time, the human body has seen changes in the way it feeds itself. This change generates DC but, contrary to what one might think, it has not generated alterations in the genes, so that the body has not "adapted" to new habits imposed by the human being himself, such as *social jet lag* (a practice carried out especially in young people with study and nightlife), shift work, high exposure to artificial lights, etc. On the other hand, the epigenetic scope could be affected by this factor, which could lead to changes in gene expression (3,6,17,23).

However, there are other factors that can cause a DC in the body, such as irregular sleep, drastic temperature changes, very frequent meals or a low physical activity routine; these types of practices can be related to changes in the weight of people, especially an increase in weight (6,8,17,18,24).

It was thought that even aspects such as the season of the year could affect weight gain by causing CD, the current evidence does not associate a decrease or increase in weight to these seasonal changes, although the food consumption that the population ingests is different, for the evidence to be firm a greater number of studies are needed (25,26).

Meal times and frequency

Frequency of meals

Meal frequency refers to the number of times meals are eaten during a 24-hour period. The number of intakes during a day has a strong cultural basis, although aspects such as epidemiological studies and scientific evidence provided throughout history have also led to slight modifications in human habits (17,19).

Throughout history, it has been investigated whether food frequency has an effect on human weight. At the beginning of the research, around 1964 and 1965, it was said that a greater number of meals was associated with greater weight loss, with the recommendation being to eat between five and six meals a day. It was also observed that a smaller number of meals per day was associated with a greater predisposition to develop heart disease (7,13,19).

In 1989, the *"Nibbling versus gorging"* study(27) study continues to support the theory that a greater frequency in the number of meals has benefits in terms of lipid profile with a decrease in LDL and total cholesterol.

Research continued and, in 2001, the first evidence began to show that people who ate one or two meals a day were able to lose more weight compared to those who ate three to six meals a day (7,19). From about 2010 onwards, there is a greater variety in the results, some associating a greater loss with a lower frequency of meals and others, on the other hand, with a higher frequency of meals (8,19,28).

In some studies, a lower number of meals was associated with an increased risk of developing some pathologies or Non-Communicable Diseases (NCDs) such as increased risk of cardiovascular pathologies, obesity and lipid profile problems (7,12,29,30). While the randomized crossover study by Belinova L. et al (31) relates lower meal consumption with stabilization of hormone levels (mainly leptin and ghrelin) and thus lower weight gain and development of DM2.

In another study, the frequency of main meals is not mentioned as a promoter of obesity, but rather the number of snacks eaten, suggesting in this case a lower number of snacks as the day progresses (32).

The scientific evidence focuses more strongly on meal timing and less on meal frequency, since the timing of meals has a greater impact on potential CD (8,17).

Food timing

Mealtimes, as well as the number of meals, are closely linked to cultural and family traditions and psychological factors, as shown in Figure 1. (19,33). The timing of intakes has begun to be a predictor of health and a risk factor for the development of NCDs such as obesity (33,34).

Figure 1

Determinants for the food schedule (34)

In the last 5 years, *food timing* has been a topic of study for researchers. There are a variety of results, some of the latest (7,35)there are a variety of results, some of the latest showing that an earlier mealtime window benefits weight loss compared to those who start later. This result is intended to argue that the time at which meals are taken has an effect on body weight (35).

A review, including observational, randomized crossover and longitudinal studies, examines the causal relationship (36)including observational, randomized crossover and longitudinal studies, analyzes the causal relationship between the timing of food consumption, the development of NCDs and weight loss. In this article, the timing of meals was investigated and it was concluded that eating after three o'clock in the afternoon could be a factor that generates weight gain. In addition, taking into account the macronutrients ingested in them could also contribute to greater difficulty in weight loss. The review cites a cultural association (modifiable) with dinner and a more genetic association with the time at which breakfast is eaten, the latter being a possible factor in weight loss (36).

In the case of the studies by Richter et al. (37) and Engin (18)the former a randomized clinical trial and the latter a review including mainly observational studies, concluded that an intake of calories earlier in the day is more important than total calorie intake per se. In both studies, even an increase in the amount of food eaten at dinner was associated with an increased risk of CD and thus of developing metabolic syndrome and/or obesity (18,37). Other interesting aspects mentioned are the association of caloric restriction with CNS activation and the alteration or modification of the timing of intakes with the activation of peripheral clocks (18,37).

Similar results were obtained by Shaw et al. (13)basolo et al. (15)and Dashti et al. (34)in these studies, the first two systematic reviews and the last one a cohort study, a possible improvement in weight loss was seen when the main intake was in the first hours of the day, although without very significant differences in the first two. It is believed that eating in a disorderly manner, without clear schedules and without having any routine can affect the total energy expended and cause changes in appetite and hormones (13).

Some studies make associations between mealtime and peaks in the levels of different hormones. For example, when a peak of melatonin is found in the blood, the amount of food consumed is reduced, with the aim of reducing appetite and thus weight gain. This peak usually coincides, as explained above, with the hours close to bedtime and sunlight disappears (29).

The effect of meal frequency and timing on body weight has also been studied jointly (38). The conclusions reached tilt the balance towards the fact that the time of meals has a greater impact than the frequency of meals on the modification of body weight, with the predominant theory being that if meals are eaten early in the day, they have a preventive effect on weight gain. Despite these results, it is believed that meal frequency may have greater relevance if changes are added as the years go by (8,38).

On the other side of the coin are studies in which there is no significant evidence between eating schedule and weight loss (12,39–41). failing to see a clear association between increased food consumption in the evening, weight gain and the occurrence of NCDs in people with obesity (40). Individual variation among the population, known to be a very heterogeneous group, means that no relevant associations can be observed in terms of greater resistance to weight loss in people who consume greater amounts in the morning versus at night (12,40).

The adaptations that the human body generates during caloric restriction regardless of meal timing make weight loss in obsessive patients more complicated (40). Energy deficit, for some studies, is the sole determinant of weight loss, regardless of other factors such as fasting range or diet quality (41).

Chronotypes

Circadian rhythms are defined in humans by means of the chronotype. This term is defined as the characteristics that an individual possesses in relation to circadian rhythms, which are marked by the schedules and habits of sleep, physical activity, energy, etc. (42,43). The chronotype as such reflects differences in the organism's preference for the time of day's activities.

In humans, chronotype is classified into three broad categories: morning chronotype, evening chronotype and neutral chronotype (39,42–45).

First, the morning chronotype, also known as the morning type, is reflected in people who are more active, both energetically and mentally, in the early hours of the day (39,42,43). Secondly, there are the evening types, the names of chronotype owl or E (evening type) also define them. They are people who have their peak mental and energetic activity in the afternoon (42,43). The last chronotype type is the neutral one, also known as intermediate. They account for 60% of the world's population and are characterized by having no problem adapting to timetables (42,43). From these three types of chronotypes, there are hybrids among them, with different names and characteristics that derive from the main chronotypes (42). As a result of the study of the human chronotype, in the results obtained, differences have been observed in terms of characteristics (such as habits and personality) and other factors such as dietary pattern or the quality of sleep of people depending on their chronotype (39,42,44).

At the beginning, the literature on weight loss and chronotype was practically null, since chronotype was not taken into account as a relevant factor for weight loss and body composition. After a few years, studies began to assess the need to include the chronotype of individuals, as it is believed that it can influence the food metabolism and the eating pattern that is carried out (19,39,42,43).

Currently, it is believed that due to the imposition of both social and work schedules, people with a chronotype E are more vulnerable to the development of NCDs such as obesity and DM2, as well as poorer blood glucose control (43,45).

One of the last studies that have been carried out about the food intake, chronotype and body composition (39)the study concludes that people with a morning chronotype are more likely to gain weight if they eat most of their meals in the afternoon and those with an evening chronotype are more likely to gain weight if they eat most of their meals in the morning.

Method

The present article consists of a bibliographic review of scientific articles to determine whether the timing and/or frequency of meals is related to the decrease in body weight.

For its realization, we proceeded to search for scientific articles on the area to be treated, with preference given to those carried out on human beings. Since not all articles contained information on both issues (frequency and schedule), isolated searches were also conducted in order to find further evidence. For the development of the work, which began on November 5, 2021 and ended on March 29, 2022, publications and books of

interest were consulted, as well as relevant international organizations in reference to the topic of chronobiology and human health. In addition, it was taken into account that the items had an age, except in specific cases, of 5 years, i.e. the range used was from 2017 to 2022. Among the criteria for inclusion of the articles, the impact factor of the journals in which they were published was taken into account, all of them being of scientific relevance and in the first or second quartile. Aspects such as the authors' writing or relevance in the field of research were also taken into account.

The databases used for the bibliographic search are explained below.

1. Pubmed: The start date of the search began on November 5, 2021 and ended on March 29, 2022. As keywords used to search for articles, the following were used:

- *Chronobiology "Cronobiology"*. This search yielded a total of 1989 documents related not only to this term but also to others such as "circadian rhythms". For the screening of the articles, the established inclusion criteria were taken into account, although it is true that since the purpose of this search was to find the origins of this part of science, as well as the history in this respect, after this search, the bibliography of the articles was searched until the first author was found. Therefore, 4 articles were selected that were useful for the literature review process.
- *Food timing and weight balance*: Forty-six articles were obtained, of which 25 were used for the literature review.
- *Food frequency and weight balance"*: A total of 346 articles were found in the search, of which 8 articles were selected at the end, although in the previous search articles were found that dealt with the topic together.
- *Macronutrients and weight balance "Macronutrients and weight balance"*. With these keywords, 646 results were obtained, of which only 6 were used.
- *Human chronotype and weight loss "Human chronotype and weight loss"*. A total of 12 results were obtained for this search, 4 of which were used for this work.

The exclusion criteria mentioned above were applied in these searches.

2. Scielo: The start date of the search began on December 07, 2021 and ended on March 29, 2022. As keywords, the following terms were used in English:

- *Chronobiology "Cronobiology":* A total of 55 articles were obtained, of which only 1 was used.
- *Food frequency and weight loss:* Four articles were obtained, which were not used for the literature review.
- *Meal timing and weight loss "Food timing and weight loss":* Thirty-eight articles were obtained. One article was used, since two others had already been previously selected in Pubmed.

Finally, a total of 49 articles were used for the literature review.

Discussion and conclusions

Chronobiology can be a new aid in the treatment of the population in weight loss and modification of body composition, thus providing evidence to the population with both normal weight and overweight and obesity on the best nutritional approach (19,32).

In reference to meal timing, 10 articles specifically and directly address the possible relationship between meal times and changes in body composition or weight loss. Depending on the study model, 3 are reviews and the rest are experimental, including 3 cohort studies and 4 cross-sectional or randomized crossover studies (8,12,29–32,34,35,46,47). In relation to weight loss and changes in body composition, five of the eight (29,30,32,34,35) studies concluded that there were changes and improvements in weight loss if the timing of meals was taken into account, while the other two concluded that the timing of meals did not affect the body modification of individuals.

Some authors linked this increased predisposition to weight gain to circadian rhythms and hormones released in the body (29,32,34), while others did not investigate this part of physiology but did look at changes in insulin resistance throughout the day (30,35). The parameters to be taken into account in all studies are weight or BMI, some also take into account other hormonal parameters or sleep (29,30,34).

With the results obtained from the articles and systematic reviews, the evidence suggests that meal times do relate to greater or lesser

weight loss.

Regarding the frequency at which meals are taken and the modification of body composition of individuals, 4 articles talked specifically about this aspect, divided according to their approach into 1 systematic review, 1 cross-sectional study, 1 cohort study and 1 randomized crossover study, the last three shown in Table 1 (19,31,38,41).

All of them propose a lower frequency in the number of meals, either so that the hormonal part is modified and regulated (31) as well as for the simple fact that a smaller number of meals implies a lower caloric intake in general (38,41). Like the articles, the review also concludes that a frequency of 2 or 3 meals per day along with the timing and composition of the meals may be a good approach to weight loss. In order to reach these conclusions, some of the studies looked at parameters such as BMI, weight, amount of macronutrients, and even hours of sleep in one of them (38,41). In the case of Belinova L. et al (31) blood markers GLP-1, GIP, PP,PYY, leptin, ghrelin and amylin are used.

The influence of macronutrients is another aspect to take into account when it comes to human body modification. Within the articles that talk about this topic, there are 3, 1 of them is an observational study, a cohort study and a review with meta-analysis (32,48,49).

As for the results obtained in them, the study Xiao et al. (49)it was observed that a distribution of meals, with a higher percentage of consumption centered in the morning, benefited a lower BMI and therefore weight loss and a lower percentage of fat. Regarding macronutrient distribution, the consumption of a higher amount of HC and protein close to bedtime, especially in people with evening chronotypes, increases the chances of obesity.

Although conclusions are drawn in the research, some of the studies see the need for more research in the area in order to reach reliable and scientifically sound conclusions about whether meal timing is associated with improved weight loss or weight gain

(7,12,15,34,40,47). In addition, other factors such as the quantity and quality of sleep and the microbiota should also be investigated as elements that affect weight loss. These factors may not only affect weight loss in situ, but may also have a synergistic effect with the other concepts explained above, such as the case of feeding schedules or frequency (19,24).

Scientific evidence suggests that the timing of meals influences the weight of patients as well as possible variations in body composition, and factors such as chronotype modify the assimilation of nutrients and thus the total energy balance. The frequency of meals, although not as recently studied as the timing, is also relevant in the nutritional approach of patients, and the literature shows that a smaller number of meals can be a good nutritional approach for weight loss and reduction of the fat percentage.

Reference	Type of study	Population	Features	Parameters	Results
Kahleova H. et al. 2017. (38)	Cohort study	50.660 subjects	Weight loss was observed in people who consumed 1 or 2 meals per day compared to those who consumed 3 meals per day.	BMI, age, amount of macronutrients in the diet, as well as hours of sleep, sex, and aspects related to alcohol and tobacco consumption were taken into account.	Eating less often, not snacking between meals, eating breakfast as a small meal first thing in the morning can be an effective strategy for weight loss.
Belinova L. et al. 2017. (31)	Randomized crossover study	54 patients with DM2	Patients between 30 and 70 years of age diagnosed with DM2 diagnosed more than one year ago, who were administered a hypocaloric diet for 12 weeks.	Observation of GLP-1, GIP, PP, PYY, leptin, ghrelin and amylin markers.	For patients who present with DM2 as well as overweight, a two-meal-a-day nutritional approach may be more effective for weight loss.
Zeballos E. et al. 2020. (41)	Cross-sectional study	23488 subjects	Adults over 18 years of age who will submit two records 24h.	Caloric count according to whether subjects did not eat breakfast, lunch or dinner	The elimination of the evening meal results in a decrease in caloric intake and thus greater weight loss, but there is also a loss in nutritional variety (especially if breakfast is skipped) which could negatively affect health.

Even taking all these results into account, a greater number of supporting studies are needed to obtain more current scientific evidence.

After reading the articles, some limitations could be taken into account for the elaboration of future research, the following points are proposed:

- The studies do not take into account the time of the year at the time of the intervention, taking into account the solar time at the time of the studies could be a good approach, since summer and winter time advance or delay the day by one hour; therefore, the circadian rhythm may be altered. Meal times such as

breakfast and dinner are most likely to be affected by light/dark times causing some meals to be eaten at night.

- In the studies in which the time is taken into account, other relevant factors such as the inclusion in the study of the distribution of macronutrients and chronotypes are not taken into account in order to know if, taking into account all these parameters, the time can influence the body composition of the subjects.
- Finally, no specific methodology has been created in which all the studies observe the same parameters and thus a comparison can be made and conclusions reached with greater reliability.

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EPIDEMIOLOGICAL SURVEILLANCE OF ANISAKIASIS IN THE STATE OF FALCON, VENEZUELA

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Abstract: Anisakiasis is a zoonotic disease of worldwide importance, caused by parasites of the *Anisakidae*family, and is unknown in Falcón and Venezuela. This research was developed with the purpose of establishing an epidemiological surveillance system for anisakiasis in the state of Falcón, by means of a descriptive and transversal observational study, through the documentary analysis of periodical publications, epidemiological yearbooks and continuous statistics of official organisms; within the regional research lines: Health promotion and disease prevention. The information collected was systematized by searching, selecting, organizing and arranging the sources of information, integrated for analysis and establishment of central ideas, where it was demonstrated that the genus *Contracaecum* sp parasitizes 100% of the fish of the families *Mugilidae* and *Gerreidae* and 6% of the genus *Pseudoterranova* sp parasitizes the family *Gerreidae*, in the Médano Blanco fishing zone, Falcón state. Parasites located in the digestive cavity migrating to muscles represent a parasite load of 16 to 21 parasites per specimen, where 64% of fishermen and consumers were unaware of the parasite and its hygienic control measures. Imminent risk was detected and an epidemiological surveillance program was designed to address the threat. This research generated surveillance schemes, health promotion and protection guidelines, applicable through health education, in order to provide knowledge of the health risks derived from the capture, marketing and consumption of parasitized seafood products, in order to guarantee safe food for the population.

Key words: Gastric anisakiasis, Zoonosis, epidemiological surveillance, health promotion.

VIGILANCIA EPIDEMIOLÓGICA DE LA ANISAKIASIS EN EL ESTADO FALCÓN, VENEZUELA

Resumen: La anisakiasis es una enfermedad zoonótica de importancia mundial, causada por parásitos de la familia *Anisakidae*, es desconocida en Falcón y en Venezuela. Se desarrolló esta investigación con el propósito de establecer un sistema de vigilancia epidemiológica para la anisakiasis en el estado Falcón, mediante la realización de un estudio observacional descriptivo y transversal, a través del análisis documental de publicaciones periódicas, anuarios epidemiológicos y estadísticas continúas de organismos oficiales; dentro de las líneas de investigación regionales: Promoción de salud y Prevención de enfermedades. La información recopilada fue sistematizada a *MLS Health&NutritionResearch*

partir de la búsqueda, selección, organización y disposición de las fuentes de información, integradas para su análisis y establecimiento de ideas centrales, donde se demostró que el género *Contracaecum* sp parasita en un 100% al pescado de la familias *Mugilidae* y *Gerreidae* y el 6% de género *Pseudoterranova* sp a la familia *Gerreidae*, en la zona pesquera Médano Blanco, estado Falcón. Los parásitos ubicados en la cavidad digestiva migrando a músculos, representan una carga parasitaria de 16 a 21 parásitos por espécimen, donde el 64% de pescadores y consumidores desconocía el parásito y sus medidas higiénicas de control. Se detectó riesgo inminente y se diseñó un programa de vigilancia epidemiológica para hacer frente a la amenaza. Esta investigación generó esquemas de vigilancia, lineamientos de promoción y protección de la salud, aplicables mediante educación sanitaria, con el fin de aportar conocimientos de los riesgos sanitarios derivados de la captura, comercialización y consumo de productos marinos parasitados, en función de garantizar a la población alimentos seguros.

Palabras clave: Anisakiasis gástrica, Zoonosis, vigilancia epidemiológica, promoción de salud.

Introduction

Anisakiasis is a zoonotic disease transmitted to humans through the ingestion of raw or undercooked fish containing L3 larvae (infective stage) of the parasites of the *Anisakidae*family, species: *Anisakis simplex, contracaecum and pseudoterranova*. This ichthyozoonosis is unknown in Falcón state and in Venezuela (1- 4). In a study carried out with the purpose of evaluating the knowledge of fishermen in the Médano Blanco fishing zone, Falcón state, about *Anisakidae* parasites and the manifestation of gastric or respiratory symptoms related to anisakiasis, it was found that fishermen had never received courses on hygienic handling of fish, health agencies do not inspect the work, fish are marketed without a sanitary permit, fish are eviscerated and the remains are discarded into the environment, fish are not refrigerated, they do not know details of the parasite even when they have seen it, and they also pointed out that gastric and respiratory symptoms are common in children and adults (2,4,5).

The nematode parasites of the *Anisakidae* family in fresh fish sold for human consumption in Caracas were studied, concluding that they were located mainly in the mesentery and viscera; the prevalence and intensity of parasitization were high in all samples, with no relation to geographic origin, which allows concluding that the intermediate and definitive hosts of this parasitosis are permanently present along the Venezuelan coast, where the identification of several species of *Anisakidae*parasites has been reported, as well as their presence in the fishing areas of the eastern and western states of the country (6-9).

Diagnostic methods have been evaluated interdisciplinary with emphasis on the use of the endoscope as medical equipment for the diagnosis and treatment of digestive anisakiasis, the researchers conclude that it is necessary to establish alliances with biomedical engineering, to promote innovations and necessary steps with the endoscope and its implements, as a diagnostic resource and for the extraction of parasite larvae from the organism of patients; considering necessary the organization and development of networks of interdisciplinary professionals in favor of health, leading to materialize solutions to anisakiasis in the Venezuelan and Latin American context (5,10,11).

The high prevalence of the parasite demonstrated in previous studies, constitutes a risk for public health, of generating gastric or gastro-allergic anisakiasis; on the other hand, underlying absence of diagnosis and, lack of association of the specific symptoms characteristic of the disease, enabling silent diseases in consumers of parasitized fish, which consequently made them accidental hosts of the parasite, affected by its detritus, when the fish is marketed in presentations of: wheels, fillets, shredded or salted; which consequence, brings importance

to consider anisakiasis an increasing disease, both in the Venezuelan and Colombian Caribbean, where there are no known reported cases; even so, epidemiological alarms should be activated (12-15).

On the western coast of the Isthmus of Medanos, Miranda and Falcon municipalities, Falcon state in Venezuela and on the Atlantic coast (Bay of Cartagena) in Colombia, there persist predisposing factors typical of the evolutionary cycle of the parasite, which guarantee its presence, coupled with a high parasite load per specimen, circumstances that argue and conceptualize the problem. The high prevalence of *Anisakidae* parasites, detected in the Médano Blanco fishing zone, as well as in the coasts of the eastern states of the country, reveal the imminent high risk for the population to suffer from the disease transmitted by the ingestion of parasitized fish, which justifies proposing a system of epidemiological surveillance of anisakiasis, to guarantee the protection of public health through health promotion mechanisms (16-18).

Large aquatic mammals, which move long distances between oceans and seas, lead the evolutionary cycle of the *Anisakis* parasite and are responsible for the arrival of this parasite, discovered in Japan in approximately 1950, in South America; its presence is located in the Venezuelan and Colombian Caribbean; in the same way, it has been found in fishing areas of the Pacific Ocean: Peru, Chile and Argentina, where the problem can be aggravated due to poor sanitary handling of the contents of the digestive cavity when fish and marine products are eviscerated, which strengthens the existence of an endemic parasitic condition caused by *Anisakidae* nematodes in populations consuming parasitized fish, crustaceans and cephalopods (19 -22).

The lack of official notification and the absence of diagnostic mechanisms reflect a precarious health condition in the face of an emerging zoonotic pathology, of which there would be no record in the annals of local, regional and national epidemiology; without specific treatment, other than the supportive treatment to overcome symptoms similar to an infection or food poisoning, whose natural history is not identified. These tangible shortcomings in the lack of systematized and well-argued information on anisakiasis in Venezuela, which can be extrapolated to South America, constitute a threat to any progress that may have been made in the field of public health (23-26).

Establishing an epidemiological surveillance model of anisakiasis in Falcón state, as a health promotion strategy, is considered an essential function of public health, under the guidelines or methodologies proposed by the Pan American Health Organization and the World Health Organization, systematizing and documenting these research experiences on the risks of anisakiasis in the population, providing valuable information that can contribute to improving local conditions and relations between fishermen's families and consumers, promoting the modification of their practices in the capture of fish, handling on board or on the shore, evisceration, and sanitization of fish in the marketing mechanisms that lead to improving the health and quality of life of the population (27-31).

The parasites of the Anisakidae family are whitish, round, unsegmented worms, known as nematodes, with specific organs such as cuticular teeth, excretory pores and esophagus, which help in their identification. In general when the fisherman markets fish without the proper sanitary permit, in areas near his home, becoming part of a last link in the epidemiological chain, to place in circulation anisakis parasites, responsible for a large number of people (children, adolescents and adults), present symptoms associated with anisakiasis such as: diarrhea, nausea vomiting, epigastralgia and respiratory problems of allergic type, which bulge

the casuistry of the health dispensing center in the marsh down sector of the city of Santa Ana de Coro (13,14,30-32).

It has been argued that the prevalence of the parasite is influenced by factors such as: fishing areas located to the west, which may represent a greater or lesser infestation of fish; local culinary customs, such as the way of cooking fish, which may vary from a moderate heat grill, to a high temperature and longer frying; also marinating, smoking and salting without subsequent cooking (14,33). It is considered a parasitosis of increasing incidence in the world (4 cases/100,000 inhabitants/year) and in Japan, due to social and behavioral factors, i.e., eating habits of consuming raw fish, a very high prevalence (2000 cases/year) is recorded, accounting for 95% of the world's cases. In European countries such as: Spain, France, Holland and Germany, anisakiasis has been found to be only 3.5% prevalent on average (33,34).

There is little knowledge of the mechanisms for health promotion, supported by epidemiological surveillance systems, in terms of fishermen and consumers, providing knowledge of the priorities to be taken into account for action, forming the human and institutional capacity required to develop, implement, monitor and evaluate health promotion activities at local and national level, identifying and selecting the mechanisms to control anisakiasis, as well as good fish handling and marketing practices to protect health. Theoretically, epidemiological surveillance has been understood as the systematic and continuous collection of data about a specific health problem, such as anisakiasis, its analysis, interpretation and use in the planning, implementation and evaluation of a health program aimed at addressing the threat (35,36).

It should be differentiated that the term epidemiological surveillance encompasses a series of different techniques and methodological strategies such as: health surveys; where we find individual and collective purposes. The former are related to the person under surveillance and the latter to the social group to which they refer. In practical terms, they can be attributed the same importance; however, the impact of each of them in the field of prevention can be considered different (36). For this reason, three main actions of epidemiological surveillance are known, when related to the individual: Health impacts detected at an early stage. Identification of sensitive groups at risk for the disease. The adaptation of individuals according to the activity they perform, when we relate it to the collectivity (36,37).

Knowledge of the health situation regarding anisakiasis will make it possible to plan preventive action in accordance with the priorities for action and the actions to be taken, always evaluating preventive measures and the difficulties encountered that serve as a warning, which is why it is necessary to assume that the conception of epidemiological surveillance is mediated by two dimensions: one strategic and the other tactical. The strategic dimension is focused on the continuous observation of trends in the medium and long term of the objectives, purposes and guidelines, aimed at increasing the health of the population, in their immediate and medium terms, aimed at characterizing the state of health, since it is nourished by the different subsystems of registration and notification of health problems and related conditions, events or factors (33,34,38,39).

The tactical dimension has to do with the alertness responsible for detecting sudden changes in health conditions and related events or factors. It should include new and specific data, issues not foreseen or, on the contrary, subject to a very close observation; also, potential damages or information on absent or empty phenomena, but of great importance for health, should be contemplated. The action-alert subsystems and the direct information system should be the mechanisms for carrying out epidemiological surveillance integrated into the global

prevention plan. In Venezuela, the presence of *Anisakidae* parasites in fish products should be controlled with prophylaxis, hygienic measures in the handling of fish on board and at the shore, as well as guiding the population to consume cooked fish or fish previously frozen at -20°C for 48 to 72 hours (34,38,39).

In the sanitary legislation of some countries, preventive measures have been established in order to reduce the incidence of anisakiasis. When the focus is directed towards prospective sanitary control measures or preventive control considerations, the establishment of a plan for safe food requirements based on hazard analysis and critical control points (HACCP), which is well established in food quality management, is considered. This plan will always consist of a package of written documents based on food safety principles, containing: risk analysis; preventive controls; programs to be implemented in the supply chain; delineation of procedures to be followed for monitoring, corrective actions and verification procedures (35 - 37).

Obligations must be established under regulatory jurisdiction (standards and decrees) for fish, in terms of fishing, handling on board or on shore, and conservation mechanisms until sale; a strategy that generally gives rise to a manual of good manufacturing practices, with risk analysis and preventive controls based on the regulation of seafood for human consumption, based on a Manual of Safe Manufacture, processing, packaging and storage of seafood products for human consumption, taking as an example the guidelines established in the document Health in the Americas. Establishing these regulations requires that the activities be deployed within a qualified control program (with trained personnel) who will subsequently receive comprehensive training in the development and application of preventive controls in accordance with current food law (36,37).

The aforementioned organizations point out that HACCP can be applied throughout the food chain from the production or capture zone, handling and storage on board or on shore in the case of artisanal fishing, evisceration, refrigerated/frozen transport to table service; with the objective of producing safe food that will not cause harm or damage to the consuming public. Potential hazards, whether biological (parasites) or chemical (allergic), and methods to eliminate, control or reduce them to an acceptable level should be identified (8,13,36)

This research was developed with the following general objectives of: Establish an epidemiological surveillance program for anisakiasis in the state of Falcón. Specific: 1.Describe the status of parasites of the family *Anisakidae* and anisakiasis through a systematic search for information. 2. Identify the elements of the epidemiological surveillance program through specific activities to be carried out and promotion actions. 3. Design an epidemiological surveillance program for anisakiasis by establishing the structures that integrate it, its attributes and evaluation measures.

Method

A descriptive and cross-sectional observational study was carried out through the documentary analysis of periodical publications, epidemiological yearbooks and continuous statistics from official organizations, which was submitted for evaluation and approved by the Bioethics Committee of the Health Sciences Area of the UNEFM (40). This doctoral research project adhered to the lines of research: Health Promotion and Disease Prevention (41). The information gathered was systematized from the search, selection, organization and disposition of the information sources, integrated for its analysis corresponding to the hermeneutic dimension, which allowed building ideas and consolidating knowledge of what has been done

or needs to be done in order to meet the guidelines and requirements of an epidemiological surveillance program for anisakiasis in the state of Falcón (36-39).

Results

The presence of Anisakidae parasite genera identified in fish from the Médano Blanco fishing zone, Falcón state, can be seen in Table 1, the number and percentage of parasites found in fish of the *Mugilidae* and *Gerreidae*families belonged to the genera *Contracaecum* sp and *Pseudoterranova* sp; it is also evident that the number of parasites of the *Contracaecum* sp genus behaves in a similar way in the *Mugilidae* and *Gerreidae*families, i.e., very high. The genus Pseudoterranova sp, is considered low, being present only in the family Gerreidae

Table 1

Number and percentage of parasites of the family Anisakidae, identified in fish of the families Mugilidae and Gerreidae, in the Médano Blanco fishing zone, Falcón state, belonging to the genera Contracaecum and Pseudoterranova.

Family/Fish	*Anisakidae* Genus	Number of parasites	% of parasites
Mugilidae	*Contracaecum* sp	414	100%
Gerreidae	*Contracaecum* sp	336	94%
Gerreidae	*Pseudoterranova* sp	21	6%

Taken from (4, 11, 13).

Table 2 shows the anatomical location of the parasites of the family *Anisakidae,* identified in fish of the families *Mugilidae and Gerreidae*. In the family Mugilidae (Mugil lisa and Mugil curema) the prevalence of parasites in the liver and hemal canal is high, and they were not detected migrating to the muscle; however, in the genus Eugerres sp, the prevalence of parasites is very high in the liver and hemal canal and they were already present in the muscle.

Table 2

Anatomical localization of parasites of the family Anisakidae found in the digestive cavity, muscles and hemal canal of fish of the species Mugil lisa or Mugil curema and Eugerres sp, in the Médano Blanco fishing zone, Falcón state, Venezuela.

Species/fish	Liver	Liver	Muscle	Hemal canal
Mugil lisa or *Mugil curema*	119	0	295	
Eugerres sp	106	38	213	

Total 225 38 508

Taken from (4, 11, 13).

The parasite load or parasitization index by fish species is presented in Table 3, which also shows the maximum, minimum and average parasite load for the species *Mugil lisa* or *Mugil curema* and *Eugerres* sp. In the species *Mugil lisa* and *Mugil curema* the average parasitization index is higher than in the genus *Eugerres sp.*

Table 3

Parasite load per specimen of parasites of the family Anisakidae in species: Mugil lisa or Mugil curema and Eugerres sp in the fishing area of Médano Blanco, Falcón state, Venezuela

Species/fish Maximum Minimum Average Average Parasite load

Mugil lisa or *Mugil curema* 21 0 9,2 21+- 9,2 p/u

Eugerres sp 16 1 7,9 16+- 7,9 p/u

Taken from (4, 11, 13).

Legend: p/u: Parasites per unit or specimen.

Fish for consumption, product of the slaughter in Médano Blanco, Falcón state, constitute the vehicle for the arrival of the parasite to humans, highlighting that the fish correspond to the *Mugilidae* family*(Mugil lisa* or *Mugil curema*: lisa, taina and candilete) in 30%, to the *Gerreidae* family*(Eugerres* sp, known as mojarra) 26%. Among the others we find: snapper, carite, corocoro, shrimp and prawns, 44% (5, 11). The situation of danger for the consumer of suffering from anisakiasis is represented by the fact that 64% of fishermen and consumers do not know hygienic practices applicable to fishery products, only 36% know and follow hygienic habits (12, 13, 15).

The progress of mankind and the improvement of the quality of life have seen in epidemiological surveillance programs a basic function of public health that has as elements: Entry of data collected on the prevalence of the *Anisakidae* parasite and the characteristic symptoms of anisakiasis. Data processing for analysis and interpretation. Output of the proposal and execution of actions understood as dissemination and communication. Feedback: evaluation of the results and of the system. Follow the steps to design the surveillance system. Definition and importance of anisakiasis as a disease to be monitored (31-33).

Consideration of the elements of the system for the collection of information on the disease and the analysis and interpretation of the data. Verify the actions that will be developed to maintain anisakiasis surveillance and finally evaluate the surveillance system and the program (31-33).

In the design of the characteristics of the epidemiological surveillance program for anisakiasis in the state of Falcon, it was proposed to use as a source of data for surveillance, the routine and mandatory notification of events of interest collected by the health dispensing centers, dependent on the Secretariat of Health of the state of Falcon, as well as the Venezuelan Institute of Social Security (IVSS) and the Institute of Social Welfare and Assistance for the Ministry of Education Personnel (IPASME), in order to establish the necessary connections with the trained personnel working in the agencies of the National Health System in an integrated manner (32-35).

The proposed surveillance system consisted of: The general subsystem, where the information received weekly, quarterly or yearly is consolidated, related to the component of diagnosis and clinical surveillance on anisakiasis, as well as the parasites of the *Anisakidae*family, prevalent in the Médano Blanco fishing zone in Falcón state. The specific subsystem, where information on the diagnosis of anisakiasis will be registered, according to the symptoms of the disease, studies by endoscopy, laboratory surveillance by serology. Each subsystem will have its own objectives and will require specific information, statistical data processing and epidemiological surveillance strategies (34,37).

The modeled surveillance system has the following attributes: Sensitivity: ability to correctly detect cases of anisakiasis or the determined risk factor, with predictive-positive value to the condition under surveillance. Specificity: ability to correctly identify individuals who are not sick with anisakiasis or the risk factor under surveillance (31-34). The ability to detect false positives or inaccuracies in detection. Flexibility: ability to accommodate new requirements within the system itself**.** Acceptability: Level of acceptance of the activity by the people who manage and coordinate the system, as well as by those who generate the information. Simplicity: Degree of simplicity of a system to interact in an agile and efficient way with the environment, without losing quality in its actions. Representativeness: to describe as accurately as possible the occurrence of a health event in the community, according to its distribution in time, place and person. Timeliness: which reflects the speed in time that elapses between the different steps of the surveillance system (occurrence-detection-notification-action (31,34).

Levels of organization of the surveillance system will be: Local Level: constituted by the health team in contact with the population. They generate the data and the epidemiological record. There may be a departmental level. Epidemiological surveillance is triggered: Observation, Alert, Alarm and Control. Local level responsibilities: Perform the control and analysis of primary data. Timely detection of the occurrence of the disease in the community. Immediately initiate control actions according to specific regulations. Request support from the higher level if necessary. Report cases to the next higher level. Report on the control actions carried out to the next higher level. Participate in training programs related to surveillance. Promote and execute social communication strategies. Preparation of the Epidemiological Bulletin (34,36,37).

Provincial level: integrated by the Directorate of Epidemiology. Receives the information generated by the local or departmental level, where it is analyzed and consolidated to be sent to the higher level. They can collaborate with the local and departmental level in different training actions or interventions when events occur (36,39).

Responsibilities of the Provincial Level: Program, coordinate and supervise Epidemiological Surveillance activities in their area. Promote the training of the human resources of the Epidemiological Surveillance System under its control (36,39).

Conduct appropriate epidemiological investigations. Receive, consolidate, process, analyze and continuously disseminate the jurisdiction's information. To prepare and disseminate epidemiological information at the provincial level. Promote the use of different data sources to identify risk factors. Actively participate in the design of social communication strategies. Coordinate activities with national and jurisdictional reference institutions. Raise the alert and coordinate the necessary intervention actions when the event exceeds the possibilities of action at the local and/or regional level. Participate in the formulation of health plans and programs. Participate in the organization of the provision of health services in their area. Refer the information, according to standards, to the higher level (34,36,37).

National level: Defined in the Organizational Chart of the Ministry of the People's Power for Health (MPPPS), as the Epidemiology Directorate. They receive information from the preceding levels, consolidate, analyze and send it to international organizations. Its function is mainly normative and according to its levels and responsibilities. Activities: All levels will carry out their epidemiological surveillance activities such as: monitoring, evaluating and consolidating information from the levels, formulating recommendations for disseminating information based on indicators and attributes (35-37).

Discussion

When contrasting the results presented and described with the different authors cited, we find that they fully agree (1,11-13,15) that the situation of danger for the consumer of suffering from anisakiasis is represented by the high prevalence detected in the fishing zone; added to the fact that 64% of fishermen and consumers do not know hygienic practices applicable to fish products, only 36% know and follow hygienic habits (1,11-13,15).

There was also agreement among authors, who identified that the safety of the fish that will reach the consumer depends on the handling on board or at the shore, because the time it takes for the preventive measures or hygienic practices of evisceration and washing allow the *Anisakidae* parasite to migrate from the digestive cavity or mesentery to the muscle and hemal canal, making its removal difficult and the greater amount of detritus (1 - 5,11,12,15,18,19).

The genus *Contracaecumsp*predominates in the parasitization of fish of the family *Mugilidae*, while the genus *Pseudoterranovasp*predominates for the family *Gerreidae*, in percentages above those found on the coasts of the eastern states of Venezuela, as reported by (4,6-11,13). Epidemiological research carried out in the Médano Blanco fishing zone provides information that indicates that the prevalence of *Anisakidae* parasites in fish has been increasing and in the last report reached 97% for the genus *Contracaecumsp*and 3% for *Pseudoterranovasp*(4,5,11,13,14,15,19-22).

The studies carried out in the Médano Blanco fishing zone showed that 64% of the fishermen involved in the fishing operation do not know about hygienic habits that could affect fish safety; even worse, they do not have any knowledge about parasitosis, nor do they have, nor have they ever processed the sanitary permit, where it is mandatory to comply with the course for food handlers, given by the competent sanitary authority in Falcón state, which trains them for the hygienic handling of food, specifically fish and marine products, which allows the commercialization of fish in better conditions of safety and healthiness. It is important to highlight that only 36% knew and followed hygienic habits (1, 2, 9, 21, 36, 37, 39).

Elements of the anisakiasis epidemiological surveillance program

The management of frequent parasites and their evolution, within a safe food plan, has been analyzed by the authors (22-27), who understand that the knowledge of the prioritized actions should be selected to act, forming the human and institutional capacity required to develop, implement, monitor and evaluate the health promotion activities established at the local and national level, within the anisakiasis surveillance program. It should identify and select control mechanisms, as well as good fish handling and marketing practices to protect health (22-27).

The health situation on anisakiasis, according to the interpretation of (28-32), based on new data on the hosts, in relation to the diagnosis and control of anisakiasis, will guide the planning of preventive actions, always verifying the difficulties encountered that serve as an alert; to highlight the sudden changes that could occur with cases of anisakiasis and the events or factors related to it, where we would be applying the tactical dimension of epidemiological surveillance. The strategic dimension will be implemented through continuous observation of trends in the medium and long term according to objectives, purposes and guidelines, aimed at increasing the health of the population, in the immediate and medium terms, aimed at characterizing the state of health (28-32).

The alert-action subsystems and the direct information system will execute the epidemiological surveillance integrated to the global prevention plan, to help maintain the surveillance of anisakiasis and the evaluation of the surveillance program, in the Venezuelan health system, opinion consubstantiated by (33-35). The role that civil society should play in the presence of *Anisakidae* parasites in fishery products should not be discarded and, consequently, their control with prophylaxis, hygienic measures in the handling of fish on board and at the shore; as well as orienting the population with consumption habits of cooked fish, or fish previously frozen at -20°C for 48 to 72 hours (33-35,37,38).

Conclusions

The situation currently detected in this research shows that there are no changes or improvements that allow us to argue that the risk to public health represented by the *Anisakidae* parasites in the fishing zone in question is decreasing, justifying the need for action by the competent health agencies, the epidemiological surveillance measures, involving the fisherman, attributing to him the responsibility that also assists him in this problem

Risk analysis and control of critical points in food processing, as in this case seafood, constitute a technology applicable from the production area, acting with monitoring and verification actions throughout the production chain, up to the consumer's table, including environmental management of the contents of the digestive cavity during evisceration, which requires its disposal in a safer place, ensuring that it will not be food again for plankton organisms or other fish, where it would be favoring the colonization of the parasite in the fishing area.

The lack of knowledge of the parasite by fishermen and fisherwomen, as well as of habits or hygienic practices in the handling of fish, merit health education activities to overcome this risk and engage in the process of contribution and generation of continuous learning about the *Aniskidae* parasites and the parasitic disease they trigger, as a basis for collective action, where the community assumes participation in the epidemiological surveillance program of anisakiasis

The importance of Falcon State in the western axis, as the first productive state among the main fishing areas of Venezuela, warns of the need for greater concern for the safety of the fish that is marketed, in order to guarantee safe food to the population, based on the legal strengths attributed to it by the existing sanitary legislation on food sovereignty and safety in Venezuela.

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BENEFITS OF INSECT CONSUMPTION AS A FOOD SOURCE ON HUMAN HEALTH: A LITERATURE REVIEW

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Summary. The exponential demographic increase and the lack of resources are forcing the population to look for healthier and more appealing alternatives for their diet. The objective of this review is to demonstrate that the consumption of insects, as a food supplement in the regular diet of humans, provides health benefits. A bibliographic review of articles with a consolidated scientific basis was carried out by consulting the databases "Cochraine", "Pubmed", "Science direct", "Dialnet" and "Medline plus", with a date restriction of 5-10 years, in Spanish and English. Gray literature such as dissertations, projects, master's theses, among others, has also been included. As for the study, no limitations have been made. Insects have the capacity to offer health benefits to people due to their high nutritional value, the bioactivity of their components and even to increase environmental sustainability. The type of insect, its diet, its habitat... They will determine its composition and, consequently, its nutritional benefits. As a result, there is a great deal of research demonstrating such benefits to a greater or lesser extent, although, due to their novelty and precariousness, much research is needed.

Key words: Edible insects. Entomophagy. Nutritional value. Bioactive compounds. Human health.

BENEFICIOS DEL CONSUMO DE INSECTOS COMO FUENTE DE ALIMENTO EN LA SALUD HUMANA: UNA REVISIÓN BIBLIOGRÁFICA

Resumen. El aumento demográfico de forma exponencial y la falta de recursos obliga a la población a buscar alternativas más saludables y sugerentes para su alimentación. El objetivo de esta revisión es demostrar que el consumo de insectos, como complemento alimenticio en la dieta habitual de los seres humanos, aporta beneficios a la salud. Se realizó una revisión bibliográfica de artículos con base científica consolidada consultando las bases de datos “Cochraine”, “Pubmed”, “Science direct”, “Dialnet” y “Medline plus”, con restricción de fecha de 5-10 años, en español y en inglés. También se ha incluido literatura gris como tesinas, proyectos, trabajos de fin de máster, entre otros. En cuanto al estudio, no se han hecho ningún tipo de limitaciones. Los insectos tienen la capacidad de ofrecer beneficios a la salud de las personas por su alto valor nutricional, la bioactividad de sus

componentes e inclusive, por aumentar la sostenibilidad medioambiental. El tipo de insecto, su alimentación, su hábitat... Van a determinar su composición y, por consiguiente, sus beneficios nutricionales. A consecuencia de esto, existen numerosas investigaciones en las que se demuestran tales beneficios en mayor o menor medida aunque, debido a su novedad y a su precariedad, se necesita mucha investigación al respecto.

Palabras clave: Insectos comestibles. Entomofagia. Valor nutricional. Compuestos bioactivos. Salud humana.

Introduction

Food consumption and demand is increasing unlimitedly worldwide. Due to a lack of resources, people are increasingly forced to opt for highly processed alternatives whose safety is not assured. Due to the exponential growth of the human population and the lack of extensions such as agricultural areas, it is necessary to introduce another type of food to complement the dietary pattern of the population, insects. This type of invertebrate animal is one of the most diverse groups of animals found on the planet. With more than 1 million described species, they can be considered the most abundant animal population, accounting for about 90% of the existing life forms (1).

Edible insects are found in countless habitats, however, some species are in danger of extinction due to deforestation, anthropogenic factors, pollution, etc. Both their distribution and availability are affected by climate change (2).

Resources are limited and, with it, food, feed and fuel. Insects are an important and interesting food source due to their high content of macro and micronutrients, and their capacity to be used as an ingredient in other products, increasing their nutritional value and collaborating in more ecological productions. The Food and Agriculture Organization of the United Nations (FAO) states that it is necessary to increase food production in order to avoid nutritional problems such as malnutrition and undernutrition, among others (3).

The use of insects as a food source is an interesting and innovative strategy because, among the many benefits they can offer us, these animals have a high feed conversion rate (for 2kg of feed, insects gain 1 kg of weight; on the other hand, cattle would need 8 kg of insects to gain 1 kg of weight), they give off less greenhouse gas (GHG) and ammonia than cattle, they are pollinating animals, they need less water to survive, they improve soil fertility, contribute to pest control and even act as aids to the subsistence of certain populations, improving the health of both favored and disadvantaged people (4).

We can affirm that insects, apart from being sustainable, have a positive influence on people's health (3,4). New studies and research advocate the consumption of edible insects, as long as they are regulated by law, as they offer high nutritional quality and numerous health benefits (5).

The main objective of this review is to demonstrate through their composition, bioactive compounds, food safety and consumer acceptability, among others, that the consumption of insects provides benefits to human health.

Method

In order to carry out the bibliographic search, several studies were analyzed, which were mainly focused on insects as a new food to be incorporated to enrich the Western diet, as long as they are safe for human consumption and are legally permitted in Europe. Clinical studies, review articles, online books, guides, dictionaries... were included. Among many other scientific sources. Gray literature such as dissertations, projects, master's theses, among others, has also been included. The search began in November 2021 and ended in April 2022.

The following is a more detailed explanation of how this literature search was carried out using some key words in the following open access databases (Cochrane, Pubmed, Science direct, Dialnet, Medline plus): ("Edible Insects" [in title and abstract] or "Entomophagy" [in title and abstract]), ("Insect Nutritional Value" [in title and abstract] or "Insect Proteins" [in title and abstract] or "Insect Lipids" [in title and abstract]), ("Edible Insect Ecology" [in title and abstract] or "Insect Sustainability" [in title and abstract]) and ("Insect Food Safety" [in title and abstract] or "Insect Allergies" [in title and abstract]).

Once the search had been carried out and the titles and abstracts of each article had been obtained, the following inclusion criteria were applied: the articles should be articles on insects suitable for human consumption, especially those that are safe for consumption and permitted in Europe; the articles should be in indexed journals with an IF≥1.5; and the articles should be from the last 5-10 years.

As for the exclusion criteria, they are simply those that do not meet the inclusion criteria without any other type of limitation. Consequently, 86 articles were selected and included in the review.

Results

Nutritional value

The nutritional value of these invertebrates is highly variable, since it depends on the species, the metamorphic stage in which it is found, its habitat, its diet, its processing and preparation, and even the analytical techniques and methods used in its measurement (2). Broadly speaking, all food-grade insects are a valuable source of energy, protein, fat, fiber and micronutrients, according to the nutritional quality index (NQI) (6)and we can therefore consider them as an interesting food to incorporate into our diet (7).

Focusing on the insects legally permitted by the European Union, we will divide them into two orders; coleoptera (*Tenebrio molitor*) and orthoptera (*Locusta migratoria and Acheta domesticus*).

The mealworm (*Tenebrio molitor*) is a beetle that is usually consumed in its larval stage. It is used as food for reptiles and birds, although it is becoming increasingly popular for human consumption due to the high protein and lipid content needed for energy production during the metamorphic process (8).

The domestic cricket (*Acheta domesticus*) and the migratory locust (*Locusta migratoria*) are Orthoptera whose breeding is mainly intended as animal feed, although their interest in human consumption is increasingly being encouraged due to their high nutritional value, their low fat content compared to the *Tenebrio molitor* and their high fiber (chitin) content thanks to their exoskeleton (9, 10) (9, 10).

As far as nutritional composition is concerned, the 3 species are rich in proteins and fats, although the mineral and vitamin content differs among them (11-13) (Table 1).

Table 1

Nutritional composition of Tenebrio molitor, Acheta domesticus and Locusta migratoria (6, 11-13). Own elaboration.

Species dried of insects	**Value energy (Kcal/100g)**	**Proteins (g/100g of dry matter)**	**Fats (g/100g of subject dry)**	**Carbohydrates carbon (g/100g of dry matter)**	**Minerals (mg/100g of dry matter)**	**Vitamins (µg or mg /100g of dry matter)**
Acheta domesticus (adult common cricket)	153	20,5	TOTALS (5.06) PUFA (2.43) SFA (2.28)	1-4	Ca (99.6) Cu (0.62) Faith (5,46-8,83) Mg (55.1) P (299,3) Na (163-178) K (347-390) Zn (6.71-11) Mn (1.15)	A (6.53 µg) E (2.26 mg) B1 (0.04 mg) B2 (3.41 mg) B3 / PP (3.84 mg) B6 (0.23 mg) B12 (0.53 µg) C (3 mg)
Locusta Migratoria (lobster migratory adult**)**	400-500	40-60	TOTALS (4.3) PUFA (3.75) SFA (3.5)	0,1-2	Faith (8-20)	Provitamin A (958.44 µg/100g) Vitamin C (102.17mg/100g)
Tenebrio molitor (mealworm, larva**)**	178	24,13	TOTALS (6.14) PUFA (5.85) SFA (2.32)	1-6	Ca (24.2) Cu (0.75) Fe (2.87) Mg (69) P (295) Na (66) K (368) Zn (4.86) Mn (0.46)	A (<30 µg) E (<0.34 mg) B1 (0.1 mg) B2 (0.85 mg) B3 / PP (5,64 mg) B6 (0.81 mg) B12 (0.56 µg) C (5.4 mg)

Proteins (PP)

The biological value of the proteins found in these animals is high, especially in Orthoptera. Protein content varies according to family, species, sex, etc. and is usually expressed as a function of dry matter. Their digestibility is very variable depending on the species, this is due in part to the nitrogenous substances they contain bound to the chitin. This means that, if their nitrogen composition differs from their actual protein composition, it does not mean that a higher amount of nitrogenous substances results in a higher bioavailability (14).

Insects are rich in phenylalanine, tyrosine, lysine, threonine and tryptophan. This composition varies according to the insect's diet (natural or feed-based). It is worth mentioning leucine, since it is a limiting amino acid in this type of food source (6) (6). In the case of orthoptera, the protein content is higher than in goat meat, chicken or pork, although their digestibility is lower(11, 14).

An alternative to food shortages for obtaining high quality proteins would be to obtain them from some species of insects whose amino acid composition is optimal. Proteins found in the mealworm, Tenebrio molitor, have been shown to have a high quality protein composition (15).

It should always be noted that there is a difference between the recommended level of amino acids and the minimum required intake level of each amino acid. The PDCAAS (Protein Digestibility-Corrected Amino Acid Score) and DIAAS (Digestible Indispensable Amino Acid Index) approach to assess the quality of insect proteins can be compared with the usual peptide sources in the Western population (Table 2)

Protein hydrolysates have functional properties, including nutritional properties. These properties can be seen in flours such as the defatted and native caterpillar larvae (Imbrasia oyemensis), although their solubility is low due to their isoelectric point. The hydrolyzed protein fraction has a much higher solubility of 80%. All this would be interesting in terms of the anabolic capacities of insect meals and their possibility of increasing the postprandial availability of amino acids in the blood (16).

The use of insect protein preparations in gluten-free diets is an interesting alternative to conventional ingredients because the extraction of gluten from bakery products results in low gas retention in the fermentation process. This problem can be corrected through the addition of previously defatted insect flours, such as those of crickets, which provide gluten-free proteins (17) (17).

Table 2

Comparison of the different essential amino acids found in Tenebrio molitor and Acheta domesticus with different meat products(mg/100 g of edible portion) (6).

	Essential amino acids								
Species	**ILE**	**LEU**	**LYS**	**MTH**	**TRYP**	**PHE**	**HIS**	**THRE**	**VAL**
Acheta domesticus A	940	2050	1100	300	130	650	480	740	1070
Acheta domesticus L	710	1270	1090	274	144	587	450	680	1050
Tenebrio molitor A	1030	1960	1050	300	260	620	680	810	1500
Tenebrio molitor L	835	1400	1070	400	216	654	559	770	1280
Leg of lamb	773	1195	1267	381	196	621	425	727	785
leg of veal	826	1293	1349	413	174	660	551	688	853
Horsemeat	1457	2129	2240	627	226	853	627	874	1122
Pork shoulder	821	1432	1483	487	235	699	584	966	927
Beef tenderloin	997	1680	1844	560	232	911	706	951	1038
Rabbit carcass	825	1277	1462	452	186	771	426	717	851
Goose channel	264	493	515	144	84	254	162	268	287
Duck carcass	391	611	686	214	95	329	250	370	479

Note: The abbreviations for the column headings are as follows: ILE: isoleucine, LEU: leucine, LYS: lysine,

Turkey breast	915	1419	2015	522	248	703	537	994	953
Turkey thigh	797	1233	1758	452	217	607	468	865	826
Chicken breast	1251	1579	2022	631	360	772	941	911	1345
Chicken thigh	982	1240	1590	497	283	606	739	715	1057

MTH: methionine, CYS: cystine, PHE: phenylalanine, TYR: tyrosine, THRE: threonine, TRYP: tryptophan, VAL: valine, A: adult insect, L: larval form.

Carbohydrates (HC)

HC is the least predominant macronutrient, accounting for 15-50% in orders such as Coleoptera and Orthoptera (18). Among them, Chitin and Threalose stand out.

In arthropods we can find chitin, a natural polysaccharide considered the second most abundant biopolymer in nature after cellulose. It is known that insects, such as crickets, have a fat-reducing effect thanks to chitin, making those animals that consume them thinner than others that consume other types of feed or food lacking chitin (19). However, chitin reduces the digestibility of insects as it is a non-digestible fiber even though the enzyme chitinase is found in our gastric juices. This is because in the European population, this protein is inactive. Due to the binding of the nitrogen chains with it, in order to obtain quality protein, it is necessary to eliminate the chitin, for example, through the lyophilization process (12).

Through the deacetylation partial deacetylation of this substance, chitosan is obtained, which is used commercially as a high-fiber supplement (19). Chitosan is often used as an additive for ruminants (thus reducing methane emissions) and for plants (activating their defenses against pathogens), among numerous other health benefits. In humans, consumption of food sources such as cricket powder increases the probiotic Bifidobacterium animalis 5.7-fold, endowing chitosan with pharmacological, antimicrobial, antiviral, anticoagulant, antihypertensive, hypolipidemic and hypercholesterolemic properties (20-24).

On the other hand, we find a disaccharide discovered in the 19th century by Berthelot in the eggs of beetles of the genus Larinus, which he called trehalose. This substance, also called mycose, is formed by two glucoses allowing the preservation of cellular structures such as membranes and proteins. It is also interesting when consuming products that cannot be obtained fresh due to their distant origin, drying them with trehalose and then rehydrating them and serving them as fresh (25).

Currently, it is known that this compound is distributed in nature from microorganisms such as bacteria, to insects, fungi and plants, even in numerous foods such as honey and fermented foods such as beer, wine or vinegar. In addition, some living organisms contain functional genes capable of encoding the trehalase enzyme that degrades this compound. Among them we find Homo sapiens capable of synthesizing it in the kidney, where osmoregulation in which trehalose

plays a fundamental role is continuously taking place (25, 26). Several clinical studies point out that trehalose intolerances or mushroom intolerances are very rare and well known, in fact they are much lower compared to those caused by lactase deficiency with dairy intake (26).

Recent studies have affirmed that the use of trehalose as an artificial sweetener offers both physiological and cardiometabolic benefits; it promotes weight loss, improves glycemic control and even reduces insulin resistance. Its use could help reduce the risk of obesity and type 2 diabetes (27).

Fats (LIP)

It is the second most abundant fraction in insects after protein, especially in the larval stage. The lipid content they usually have is high, and in some of them it is even higher than the daily foods in our diet (meat, fish, milk or eggs) (24). In Orthoptera (*Acheta domesticus* and *Locusta migratoria*) it usually oscillates around 13%, while in Coleoptera (*Tenebrio molitor*) it is around 33% (11,28) (11,28).

Commonly, some species, such as crickets, contain high levels of Om3 and Om6 in a 3:1 ratio, compared to some of the terrestrial mammals and freshwater fish. It is true that animals living in salty aquatic environments tend to have higher levels of Om3 than those exposed to salty water (13) (13).

Antinutrients

Antinutrients are natural or synthetic compounds that interfere with nutrient absorption (29). Among those that can be found in insects, we highlight toxins, phytates, tannins, phenols, hydrocyanides (HCN), oxalates and phytic acid (30). Some of these substances also offer beneficial health effects such as phytates, tannins and phenols for their antioxidant properties (31) (31)although the latter can interfere with iron absorption and generate anemia (32). It should be noted that in order to truly exert an anti-nutritional effect, these compounds must be present in sufficient quantities. In the case of insects, their levels are very low and are therefore considered safe and nutritionally acceptable (33) (33).

Antimicrobial peptides

AMPs or antimicrobial peptides are small polypeptides (30-60 amino acids) found in insects. They are encoded by genes and are created in cells by a structure called a ribosome. Among the most outstanding are lebocins, attacins, cecropins, defensins.... Among many others rich in moricins, prolines and gloverines. The use of AMPs as antimicrobial substances has been extensively studied, in fact, it has been shown that peptides rich in proline (abaecin) and rich in glycine (hime-noptaecin) combined have bactericidal effect (34). In these animals, AMPs can be classified into cysteine-rich peptides, proline-rich peptides, glycine-rich peptides and α-helical peptides, which can be effective in the fight against *Escherichia coli* to *Listeria monocytogenes* (35).

It is true that the largest reservoir of antimicrobial peptides is found in the different and unexplored insect species that can be useful as an alternative to conventional antibiotics, facing the pathogenicity of multiresistant microorganisms (36) (36).

Antioxidant compounds

Humans undergo a biochemical process essential for life called oxidation. Sometimes it is produced excessively and generates what is known as oxidative stress, which, together with free radicals, damages the body's cells. To combat this stress, we need the help of compounds called antioxidants that inhibit and/or reduce this process (37).

Some insect species possess these compounds, and insect protein hydrolysates and flours have been shown to be promising antioxidants in terms of free radical scavenging and reducing power (38) (38). In the following study, antioxidant activity was calculated using extracts of freeze-dried larvae of Tenebrio molitor. It has been shown that extracts of raw larvae dried with infrared, microwave or high frequency indicate higher amounts of compounds and antioxidant capacity than those dried in an oven (39) (39). The mechanisms through which protein hydrolysates exert antioxidant activity are not fully understood, but it is known that both the type of amino acids that compose them and their sequence are essential for their antioxidant activity (40, 41) (40, 41).

The ability of insects to inhibit pancreatic lipase has also been demonstrated, in fact, this study states that extracts of *Tenebrio molitor* compared to *Acheta domesticus* have greater antioxidant activity, and thus a greater ability to inhibit pancreatic lipase (42).

Others

Numerous studies in obese mice fed with powdered *Tenebrio molitor* larvae have revealed their reducing power on type II diabetes and the accumulation of lipids and triglycerides in adipocytes (43) (43). In turn, the role of wax moth, silkworm and yellow worm in reducing hypertension (HTN) in mice, through inhibition of angiotensin (ACE), is speculated (44) (44).

Security

Nowadays, insects can be a risk, in terms of food safety, through 4 ways; the toxicity of the insect itself; the acquisition of harmful substances or pathogens; because of the production cycle; or, simply, as a consequence of an allergic reaction to them. Therefore, the need for good hygienic practices and HACCP in the case of being a producer of edible insects is established, especially in more developed countries with stricter regulations as in Europe (11).

The European Commission requires a science-based authority such as EFSA to assess the safety of edible insects before adopting the above-mentioned regulation. This agency evaluated microbiological, parasitic, environmental, chemical, allergy and intolerance risks. All of these are both in the consumer and in the animals, since they consume them whole or through feed containing them. The evaluation was carried out at all metamorphic stages of insects, including rearing, production and final consumption of insects, concluding that in the recommended quantities, the insects approved by EU legislation are safe for human consumption (7).

Consumer attitude

People develop in geographic areas and cultures that shape our preferences and tastes when it comes to food choices. Our childhood marks unique eating pleasures that provide us with security and stability, rather than nutritional quality (1).

In the world there are an infinite number of food patterns and technological progress allows us to reach and diversify our diet in such a way that we adopt new experiences and flavors to our palates (45,46). The population that, in addition to its usual diet, is insectivorous, i.e. feeds on insects, is increasingly more abundant than many people think (Figure 1) (47).

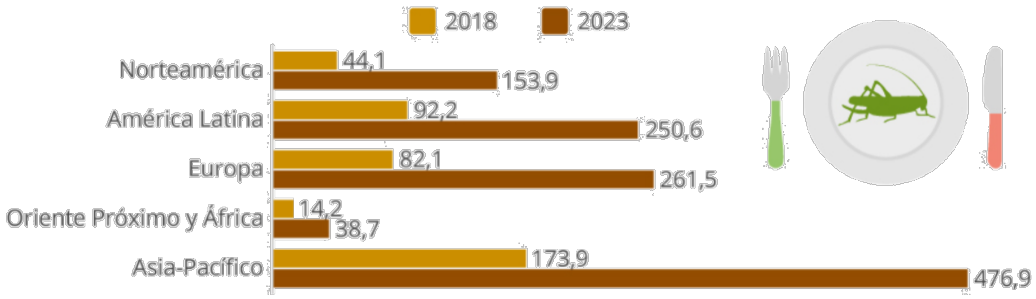

Figure 1: Edible insects market volume (47).

The acceptance of entomophagy is influenced, among many things, by price, taste, availability... (48). We must be aware that, directly or indirectly, humans practice entomophagy within the food chain, through the consumption of birds, livestock or fish whose diet is based on insects (41) (41). There are some questionnaires to determine the acceptance of different consumers towards these invertebrates such as: the food neophobia scale and the insect phobia scale (Table 3) (49).

Table 3

Food Neophobia Scale (FNS) and Insect Phobia Scale (IPS) (49).

Number	Statement	Median	IQR
1	I am constantly trying new and different foods (R).	3	2
2	I don't trust new foods.	3	2
3	If I don't know what a food is, I don't try it.	4	3
4	I like foods from different cultures (R).	2	3
5	Ethnic food seems too weird to eat.	2	2
6	At dinners, I will try new foods (R).	2	2
7	I'm afraid to eat things I've never eaten before.	3	3
8	I am very particular about the foods I eat.	4	3
9	I will eat almost anything (R).	2	2
10	I like to try new ethnic restaurants (R).	2	3

Note: R, inverse coding and IQR, interquartile range

Number	Statement
1	The idea of eating insects makes me repulsed/repulsed.
2	The consumption of insects is not socially acceptable.
3	I'm afraid that insect-based foods have an unpleasant taste.
4	I'm afraid that insect-based foods have an unpleasant consistency.
5	I think insect-based foods have poor hygiene.
6	I believe that eating insects is not suitable for our diet.

At the same time, it is worth noting the existence of aversions to these products for purely cultural reasons, for example, the consumption of the sea lobster (*Palinurus elephas*) is considered a delicacy in the West despite being in the phylum arthropods along with insects, arachnids and myriapods (50) (50). To increase their acceptance, insects are being used as ingredients in many preparations such as breads, hamburgers and tortillas (47). Other strategies to address consumer concerns include: providing more information on the benefits of insect consumption (51, 52), insect banquets where insects are offered for tasting, the use of role models such as top chefs, or the promotion of their environmental benefits (53).

Discussion and conclusions

From the literature search, 10 articles of experimental studies were selected and divided according to the study model used (Figure 2).

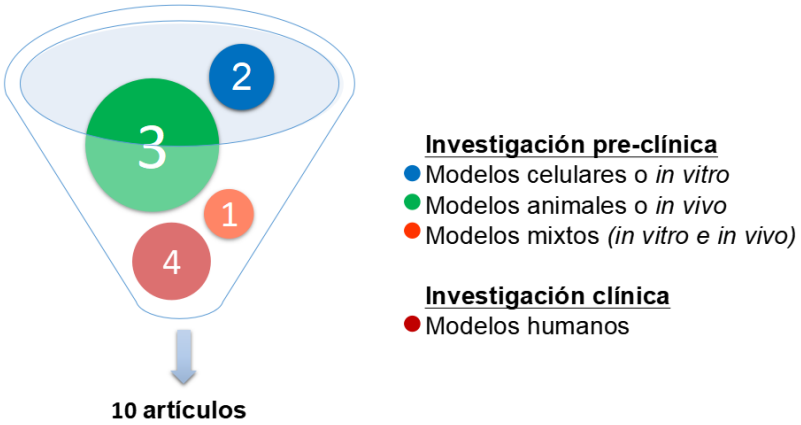

Figure 2: Classification of the different experimental studies according to the study model used (15, 18, 19, 24, 27, 39, 41, 42, 49, 51). Own elaboration.

Regarding the consumption of insects and their nutritional value, 5 review articles (6, 11, 13, 14, 29) incorporated in the work propose edible insects as an interesting part to adopt in the food chain of human beings due to their high nutritional value. We have also included 3 experimental articles on this subject. Based on the experimental model used, we can divide these studies into: 1 clinical study (humans) (15) and 1 experimental study in animals or *in vivo* (insects) (18).

In relation to the consumption and nutritional value of insects, Orkusz A (6) and Payne CLR et al (29) state that insects have a high nutritional value, as do meat products, since they are rich in macro and micronutrients, some of which are essential, although few data are available on vitamin content. Adult forms of insects contain the highest protein content, followed by larvae. On the other hand, according to Van Luis A (11), females have more lipid content than males. It is true that the nutritional composition of these animals stands out for containing Om3/Om6, iron, zinc and proteins of high biological value that provide significant health benefits, and can alleviate malnutrition in countries with nutritional deficiencies, in war conflicts, in droughts, etc., or be used as an extra contribution to improve the health status of people (13,14). Hermans WJH et al conducted a study in humans in which it was demonstrated that protein derivatives of mealworm have, after ingestion, the same capacity for amino acid release into the blood, rate of protein synthesis and digestibility as those derived from dairy products. Today, the main disadvantage is that they are products with very high prices due to their low production (15). On the other hand, Adámková A et al (18) analyzed other nutrients such as fat and chitin in the domestic cricket as well as in the common mealworm and the giant mealworm, concluding that the cricket had more chitin than the worms and the latter had more fat, being higher in the giant mealworm (35%) than in the common mealworm (31%).

Referring to these substances such as chitin, trehalose, antimicrobial peptides and antioxidant compounds, among others, based on the experimental model used we can divide the experimental studies on the subject into: 1 clinical study (humans) (27), 2 experimental studies in animals or *in vivo* (insects) (19, 39), 1 mixed experimental study (*in vivo and in vitro*) (42) and 2 *in vitro* studies (24, 41). Five relevant review articles have also been included (21, 23, 26, 34, 43).

Several researches relate chitin with a fat mass reducing effect in broilers due to its performance as dietary fiber, in fact Lokman IH et al (19) revealed that chitin from cricket at 0.5 g/kg significantly improved growth performance and organ characteristics, and reduced fat accumulation in broilers with respect to a basal diet, in turn, according to Tripathi K et al (21) it improves the composition of the microbiota among many other interesting effects explained above as antihypertensive and hypocholesterolemic, however, Betchem G et al (23) and Di Mattia C et al (24) state that due to their difficult digestion they are used as ingredients in pharmaceuticals, cell cultures, engineering, etc, rather than as a food ingredient. As for another carbohydrate such as trehalose, Ahmed A et al (26) have observed, apart from its participation in kidney osmoregulation, that its consumption as an artificial sweetener offers the capacity to control blood glucose, decreasing the prevalence of obesity and type II diabetes. Although Yoshizane C et al (27) state that studies in prediabetic and type 2 diabetic patients are needed to confirm this.

Other bioactive compounds to be highlighted are antimicrobial peptides and antioxidant compounds. As for peptides, Jantzen da Silva Lucas et al (34) have shown that they have an effect mainly in reducing the levels of *Listeria monocytogenes* and *E. coli*. It should be noted that peptides have other properties such as their high emulsifying or foaming capacity, which makes them ideal for use as a food ingredient, giving products high nutritional value and better organoleptic characteristics (39). The antioxidant compounds of the edible insect extracts *Acheta domesticus* and *Tenebrio molitor,* in relation to their antioxidant capacity and their possible effects on pancreatic lipase inhibition according to Navarro Del Hierro J et al, both showed antioxidant capacity, but in the case of pancreatic lipase inhibition those of *Tenebrio molitor* were the most effective (41).

In relation to other benefits that insects can provide, Seo M et al (42) have shown that *Tenebrio molitor* larvae powder influences adipogenesis and metabolic syndrome by attenuating body weight gain in obese mice. This leads us to affirm its potential as a therapeutic agent in the treatment of obesity in humans. In turn, Cito A et al (43) support the ACE inhibitory effect of bioactive peptides from insect protein hydrolysates for the treatment of hypertension.

Regarding consumer attitudes toward entomophagy, 2 reviews (48, 50) and 2 human clinical trials (49, 51) show that one of the major, if not the major, impediments to increasing insect consumption on a large scale is the strong rejection or reluctance toward insects as food. Numerous studies have attempted to find out how to achieve greater public acceptance of entomophagy, beyond demonstrating its potential health benefits.

In the review conducted by House J (48) in the Netherlands, the acceptance of insect-based convenience foods by diners was critically evaluated, concluding that attention should not be based on their acceptance but on the evaluation of social, practical and contextual factors that determine it. In the case of Italy, Moruzzo R et al (49) conducted a study through 420 questionnaires introducing an experimental scale specific to insects and one referring to neophobia, whose results were inconclusive due to the lack of specific scales to determine "insect phobia". On the other hand, Toti et al (50) showed that the Italian diet is still clearly influenced by local tradition and its psychological motivation needs to be increased. In contrast, a substantial proportion of Americans (72%) and Indians (74%) were at least willing to consider eating some type of insect-based food, especially by men, although disgust appears to be the most common reaction of both groups to the prospect of eating insects, as noted by Ruby MB et al (51).

Further research is needed to assess the effect of cultural variations among the population of different countries, especially in Europe, on food neophobia and acceptance of insects. This is because the potential success of a strategy in one country may not be suitable for others.

With all this we can conclude that insects contain proteins of high biological value and bioactive peptides which are a key complement to the usual dietary pattern of the population, enriching their diet and providing anabolic and antimicrobial effects, among others. Some extracts extracted from some insects, such as *Acheta domesticus* and *Tenebrio molitor,* have antioxidant activity, as do potato hydrolysates. In addition, mealworm has possible effects on pancreatic lipase inhibition. On the other hand, they also contain interesting carbohydrates such as trehalose, whose use as an artificial sweetener could improve glycemic control and even reduce insulin resistance in people who suffer from it. Fiber such as chitin, found in small invertebrates with an exoskeleton, although difficult to digest, has been attributed possible effects as a regulator of adipogenesis and, together with one of its components, chitosan, may contribute to improving the composition of the microbiota, among other effects such as antihypertensives, anticoagulants and antivirals. In terms of lipid content, insects stand out for their composition of Om3 and 6 fatty acids essential for humans, even at the same level as those found in fish, especially freshwater fish. It has been shown that, together with proteins, fat is the main component to be taken into account to avoid malnutrition, undernutrition and starvation, especially in underdeveloped countries.

Thus, it can be concluded that all these substances together confer on insects the ability to provide health benefits to humans and even safeguard food safety, enhance environmental sustainability, optimize agriculture and enrich existing food products.

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REVALORIZATION OF A FOOD WASTE FOR OIL EXTRACTION AND MICROENCAPSULATION: SQUASH SEED *(CUCURBITA MAXIMA DUCHESNE EX LAM)*

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Abstract. Food systems generate a significant amount of food waste, such as pumpkin seeds that are discarded before the pulp is consumed. They are a source of nutrients that can be used to improve human nutrition. The objective of this study was to extract, characterize and microencapsulate oil from peeled and unpeeled discarded pumpkin seeds. Five methods of oil extraction were tested and fatty acid profile was determined. The oil was microencapsulated by spray drying using gum arabic and maltodextrin as wall materials and the microcapsules were characterized. Finally, storage stability was evaluated for a period of 40 days. Peeled pumpkin seeds showed higher fat content (52.33%). Solvent-assisted extraction was effective for oil extraction. The extracted oil showed high contents of linoleic acid (62.98%) and oleic acid (17.69%). The encapsulation efficiency after spray drying was over 90%. The microcapsules were 5-20 μm in size, with spherical and concave shapes, with smooth surface, without pores or cracks, which allowed keeping the active principle inside the capsule and increasing stability. Both pumpkin seed oil and microcapsules were stable against oxidation during storage. The oil presented good nutritional characteristics with a high content of monounsaturated and polyunsaturated fatty acids. The gum arabic-maltodextrin system was effective for microencapsulation with favorable morphological characteristics.

Key words: oil; pumpkin; extraction, microencapsulation; seeds.

REVALORIZACIÓN DE UN RESIDUO ALIMENTARIO PARA LA EXTRACCIÓN Y MICROENCAPSULACIÓN DE ACEITE: SEMILLA DE CALABAZA (*CUCURBITA MAXIMA DUCHESNE EX LAM*)

Resumen. Los sistemas alimentarios generan una cantidad importante de desperdicios alimentarios, como las semillas de calabaza que son descartadas antes del consumo de la pulpa. Éstas son fuente de nutrientes que pueden utilizarse para mejorar la alimentación humana. El objetivo de este estudio fue extraer, caracterizar y microencapsular el aceite de semillas de calabaza descartadas peladas y sin pelar. Se probaron cinco métodos para extraer el aceite y se determinó perfil de ácidos grasos. El aceite se microencapsuló mediante secado por aspersión usando goma arábiga y maltodextrina como materiales de pared y se caracterizó las microcápsulas. Finalmente se evaluó estabilidad al almacenamiento durante un periodo de tiempo de 40 días. Las semillas de calabaza peladas mostraron mayor contenido de grasas (52,33%). La extracción asistida por solvente resultó efectiva para la extracción de aceite. El aceite extraído mostró altos contenidos de ácido linoleico (62,98%) y oleico (17,69%). La eficiencia de encapsulación después del secado por atomización fue superior al 90%. Las microcápsulas tenían un tamaño de 5-20 μm, con formas esféricas y cóncavas, con superficie lisa, sin poros ni grietas, lo que permitió mantener el principio activo dentro de la capsula y aumentar la estabilidad. Tanto el aceite de semilla de calabaza como las microcápsulas se mantuvieron estables frente a la oxidación durante el almacenamiento. El aceite presentó buenas características nutricionales con altos contenidos ácidos grasos monoinsaturados y poliinsaturados. El sistema goma arábiga-maltodextrina resultó eficaz para la microencapsulación con características morfológicas favorables.

Palabras clave: aceite; calabaza; extracción, microencapsulación; semillas.

Introduction

At present, food systems generate significant food losses and waste that are discarded at the different links of the food chain for different reasons, which can be the result of both human action and external factors; environmental or crop factors [(1)].

Reducing food loss and waste (FWL) is an urgent necessity and consumers are one of the fundamental pillars to contribute to this cause, since for every product that is discarded, nutrients, water and energy are wasted, causing not only environmental deterioration but also great economic losses [(2)]. According to research by the Food and Agriculture Organization of the United Nations (FAO), 842 million people in the world suffer from hunger and 30% of the

food produced is lost or wasted, that is, around 1.3 billion tons, equivalent to one third of world production [3].

The pumpkin or squash is one of the species that make up the Cucurbitaceae family, represented by about 120 genera and 800 species. The genus Cucurbita is native to the American continent. It includes about 27 species that can be annual or perennial and are cultivated mainly for the consumption of their fruits at the mature or immature stage, but other parts of the plant such as seeds, leaves and flowers are also consumed [4].

Pumpkin seeds are discarded as vegetable waste before consumption and contain significant amounts of nutritional compounds such as lipids and proteins [5], which provide up to 80-85% of the dry weight of the embryo [4]. They are composed of 40 to 52% oil, of which 29% is oleic acid and 51.9% linoleic acid; they also contain proteins, minerals (magnesium, phosphorus, copper, potassiumiron, zinc, manganese), β-carotene and γ-tocopherol [6].

Oilseeds are used as raw material to obtain edible oils because they accumulate lipids, proteins and carbohydrates as reserve substances [7]. The main characteristic of the cells of these seeds is the existence of cellular organelles called lipid and protein bodies, which contain, respectively, most of the oil and proteins of the grain [8]. Lipid bodies (also called oleosomes or spherosomes) are the site of lipid storage, which are immersed in a cytoplasmic network composed of protein and their frequent size ranges from 1 to 2 μm ([8, 9]. Cell walls are composed of cellulose, hemicellulose, lignin and pectin; and their rupture during the different extraction processes (organic solvents, supercritical fluids, pressing and hydrolytic enzymes) exposes the oil located inside the cell and facilitates the filtration of the solvent, within which the lipids can diffuse [8].

Vegetable oils provide essential fatty acids that the body cannot synthesize and must be ingested with food, such as linoleic and linolenic acid (intake range between 2.5 and 9% of energy), which influence the prevalence and severity of chronic noncommunicable diseases such as diabetes, cancer, heart disease and age-related functional decline [10,11].

Studies on the chemical composition of pumpkin seed oil, from different origins and varieties, describe the presence of four fatty acids in significant amounts, such as linoleic, oleic, palmitic and stearic acids [6, 12, 13, 14], the first two of which are widely recognized for their health benefits [15].

Microencapsulation is a technology that allows the encapsulation of active ingredients (core or central materials) covered by a polymeric wall with hydrophobic and/or hydrophilic properties (encapsulation or wall material). The resulting products are referred to as microparticles [16]with sizes ranging from 1 to 1000 μm ([17]. The food industry applies it for its multiple benefits: it provides protection against factors such as heat, air, light, humidity and oxygen, prevents volatilization and extends the shelf life of oils and essential fatty acids, improves the flavor, aroma, stability, nutritional value and appearance of the processed food, allows the transformation of liquid active substances into solids, facilitates their handling in the industry, provides resistance to processing, storage, transport and marketing, allows controlling the release of microencapsulated substances and facilitates their inclusion as an ingredient in the food industry [16, 18, 19, 20].

Several studies conducted on pumpkin seed oil concluded that its physicochemical characteristics are suitable for use in food or as a raw material in products with various industrial uses [5, 10, 21, 22, 23]. On the other hand, research based on the microencapsulation of oil by spray drying, infer that the use of the polymeric mixture of gum arabic-maltodextrin is appropriate for effectively masking the oil and obtaining microparticles with desirable morphological characteristics that avoid direct contact with oxygen, thus preventing its degradation and

extending its shelf life, in addition to guaranteeing an encapsulation efficiency of over 90% and a loss by desiccation of less than 10% [24, 25].

A report by the Commission for Environmental Cooperation on the characterization and management of food loss and waste in North America prioritizes the reduction of ADP at source and food recovery over recycling and final waste disposal at the post-harvest, processing, distribution, sales, food preparation and catering stages [26]. For this reason, the present research was developed with the objective of extracting, characterizing and microencapsulating pumpkin seed oil recovered from a food service that produces this type of waste on a daily basis, valuing its nutritional properties by reincorporating it into the production cycle as a potential ingredient for the formulation of food products.

Method

An experimental study was proposed.

The seeds of 45 pumpkins were collected from the Student Canteen of the National University of Salta, Argentina. They were washed with cold water [27] and rubbed with a polypropylene mesh (1 mm) to remove pulp remains. Drying of whole seeds (with shells) was carried out in an oven at 40 ± 1 °C with forced air for 16 hours until a humidity of 5.7 ± 1.9% was reached [21]. Those with no surface damage and with the presence of pulp to the touch [27] were selected, vacuum packed in airtight "BoiZip" bags and stored refrigerated at a temperature of 4 ± 2 °C.

The chemical composition of shelled (SCC) and unshelled (SSC) seeds was determined: moisture by drying in an oven at a temperature of 105 ± 1 °C, carbohydrates by Felhing Cause Bonnas method, proteins by Kjeldhal method, fats by Soxhlet method, ashes by calcination in a muffle at a temperature of 600 ± 5 °C, all according to official methods [28].

The oil extraction process was standardized using various methods, in order to select the one that meets the objectives and is effective and efficient for the purposes of the work: EA1 using a hand press and exerting manual pressure on each of the unshelled seeds; EA2 through a hydraulic press and using a stainless steel pillbox as a receptacle, pressure was exerted on the whole seeds (uncrushed) with and without shells, applying a force of 4 to 5 tons; EA3 with a hydraulic press, using two superimposed stainless steel plates, pressure was exerted on the unshelled seeds (placed between the two receptacles) with a force of 4 to 5 tons; EA4 using a homemade press, seeds with and without shells (whole and crushed) were placed in the container intended for this purpose and pressure was exerted manually and EA5 by maceration with organic solvent, adapted to the processes used by Betancurt [23] and González and Yánez [29]. The husk was removed manually, the seeds were crushed in an Arcano stainless steel grinder, model FW 100, 460 W at 24000 rpm and passed through a mortar until a fine paste was obtained. Extraction was performed by mixing with organic solvent in a 1:2 ratio (sample:hexane) [23]. The mixture was allowed to stand for 48 hours under refrigeration with intermittent stirring on a Stir Decalab 2000 rpm magnetic stirrer. Finally, it was centrifuged in a "DAMON/IEC" refrigerated centrifuge for 15 minutes, speed 4 to separate the oil; the solvent was evaporated in a Lavarota 4000 rotary evaporator at 60 - 70 °C at a pressure between 300 - 400 mmHg and stored in amber glass bottles under refrigeration (4 ± 2 °C) [29].

The determination of fatty acids was carried out according to the official method of the AOAC 996.01-1996 [30] starting from a methylation, 3 g of oil obtained by the EA5 method was

placed in a balloon and 10 ml of methanolic solution of NaOH 0.5M was added, it was taken to reflux for 10 minutes. 10 ml of boron trifluoride was added and continued to reflux for 5 minutes. Finally, 10 ml of heptane was added and left for 1 min. The balloon was removed and once cooled, the contents were transferred to centrifuge tubes with the addition of 5 ml of saturated NaCl solution. It was centrifuged for 10 minutes and the top layer was collected for analysis. These were injected into a Clarus 680 gas chromatograph coupled to a Clarus 600 mass spectrometer, Elite-Wax 30 m capillary column, using hydrogen as carrier gas, which were prepared according to the FAMEs method [(30)]. The reading was performed in triplicate and the data were reported as percentages of relative area. The results were expressed in g of fatty acid/100 g of oil through the following calculation:

[(Ai) x (P13:0)/ (A13:0) x (Ri)]

Ai = maximum area of the sample of individual fatty acids as methyl esters

P13:0 = sample weight (mg)

A13:0 = area of the peak of the internal standard

Ri = response factor for each fatty acid.

Microencapsulation was carried out by spray drying. The emulsion was formulated with the following proportions: gum arabic 24%, maltodextrin 12%, oil 18% and the volume was completed with distilled water [(31)]. Homogenization was carried out with a hand blender for 5 minutes and with Ultra Turrax model K41, TRI-R for 5 more minutes until a homogeneous mixture was obtained without phase separation [(24)].

An emulsion stability test was performed according to Carneiro et al. [(32)]: 50 ml of sample was placed in a test tube and stored at room temperature (21 ± 1 ºC) for 24 hours, then the volume of phase separation was measured and the stability was expressed in percentage of separation through the following formula:

$$\%\ \text{Separación} = \left(\frac{\text{E1}}{\text{H0}}\right) \text{x } 100$$

E1: upper phase measurement after 24 hours

H0: initial emulsion value

Mini Spray Dryer Buchi B - 290 equipment was used with a spraying system with a 1.5 mm diameter nozzle. The emulsion was atomized inside a hot air stream with inlet and outlet temperatures of 150 and 100 ± 1 °C respectively [(25)], pumping 25% and air flow 30 - 40 m3/h. The microcapsules were stored in 200 ml amber glass containers with lids at room temperature (21 ± 1 ºC) for 40 days for subsequent measurement of oxidative stability.

The characterization of the microcapsules to evaluate their quality was carried out through the following determinations:

- Free or surface oil: 1 g of the microcapsules was weighed and 8 ml of hexane was added. It was shaken manually for 4 minutes and passed through filter paper into a previously treated and weighed beaker. It was evaporated in an oven at 60 °C to dryness and the free oil content was determined by gravimetric method [(32)].

$$\%\ \text{Aceite libre} = \left(\frac{\text{V1} - \text{V2}}{\text{g muestra}}\right) \text{x } 100$$

V1: beaker with sample after the oven

V2: beaker without sample after treatment

- Total oil: 0.5 g of powder was weighed, 4 ml of double-distilled water was added and stirred manually until dissolved. Hexane/isopropanol (3:1 v/v) was added and stirred manually for 5 min. It was transferred to centrifuge tube and centrifuged for 15 minutes. The clear phase was transferred to a previously treated and weighed beaker. It was evaporated in an oven at 60 °C to dryness and the amount of extracted oil was determined gravimetrically [33].

$$\% \text{ Aceite total} = \left(\frac{V1 - V2}{\text{g muestra}}\right) \text{x } 100$$

V1: beaker with sample after the oven

V2: beaker without sample after treatment

- Encapsulation efficiency (EE): was calculated by applying the following equation [32]:

$$\% \text{ EE} = \left(\frac{AT - AS}{AT}\right) \text{x } 100$$

AT: is the total amount of oil contained in the capsule

AS: surface oil

- Payload: was calculated by taking the mass ratio of the encapsulated oil to the total mass of the powder [34].

$$\% \text{ Carga útil} = \left(\frac{MA}{MP}\right) \text{x } 100$$

MA (mass of oil): quantity of oil in grams.

MP (powder mass): quantity of microcapsules in grams

- Microcapsule morphology: the size and geometrical shape of the microcapsules were observed in Jeol scanning electron microscope (SEM) (JSM 6480 LV, Tokyo, Japan), with an accelerating voltage of 15 Kv, including secondary and backscattered electron probes, working with high and low vacuum. The most representative SEM micrograph was selected for presentation [24].

To determine the storage stability of the oil and microcapsules, the samples were packed in amber glass containers at room temperature (21 ± 1° C) and in darkness in a closed place, in order to analyze the changes produced in the oil and microcapsules during a period of 40 days of storage. Then, through the peroxide index (PI) and the thiobarbituric acid test (TBA), the alterations that occurred during the course of time were analyzed.

Method 965.33 [30]was adapted to determine the PI by applying the following procedure:

1 g of oil was weighed into a 250 ml glass-stoppered erlenmeyer, 30 ml of solvent (3 parts glacial acetic acid and 2 parts chloroform) was added and shaken manually for 1 min. Subsequently, 5 ml of the saturated potassium iodide solution was added and allowed to stand for 1 min in the dark with occasional stirring. Then, 50 ml of water was added to stop the reaction and prior to titration, 5 ml of the 1% starch solution was added. It was titrated with 0.01N sodium thiosulfate until final titration. Simultaneously a blank was performed where the

sodium thiosulfate consumption was < 0.2 ml. It was calculated by applying the following equation

$$\text{IP} = \frac{\text{S x N x 1000}}{\text{g muestra}}$$

S: sodium thiosulphate expenditure in ml corrected with blank
N: normality of Sodium thiosulfate

The determination of ATB was carried out by applying the following procedure: 3 g of oil was weighed in a beaker and 10 ml of hexane was added. It was then transferred to a decanting vial and 10 ml of the thiobarbituric acid reagent (dissolved in 50% glacial acetic acid) was added, shaken manually for 5 minutes and allowed to stand until the phases separated. The lower part was collected in a test tube (the lower part is the part containing the malonaldehyde) and placed in a boiling bath for 10 minutes. After this time it was cooled in a cold water bath to room temperature and after 5 minutes the absorbance was read at 530 nm in a spectrophotometer. The value was expressed in mg MDA/kg [35].

$$\text{MDA} = \frac{\text{A530 x 3 x k ext. x 0,926}}{\text{g muestra}}$$

Results are presented as mean ± standard deviation. To find significant differences between the analyses, the Student's t-test for independent samples ($p < 0.05$) was used and the calculation was performed using InfoStat v statistical software. 2016p.

Results

The final moisture content of all whole seeds after oven treatment was 5.33 ± 0.99%. The results of chemical determinations of pumpkin seeds with (SCC) and without (SSC) shell are shown in Table 1.

Table 1
Chemical analysis of shelled and unshelled pumpkin seeds (Cucurbita maxima Duchesne ex. Lam.)

Parameters (100 g)	**SCC**			**SSC**		
Humidity (%)	5,00[a]	±	0,00	4,50b	±	0,00
Carbohydrates (g)	10,26a	±	0,15	7,36b	±	0,43
Protein (g)	37,10a	±	0,74	34,13b	±	0,74
Fats (g)	40,39a	±	0,53	52,33b	±	0,58
Ash (g)	3,62a	±	0,25	4,17a	±	0,29

Different letters between rows indicate significant differences ($p < 0.05$) .

Table 2 summarizes the qualitative characteristics of each method used for oil extraction.

Table 2

Qualitative characteristics of extraction methods

EA1	EA2	EA3	EA4	EA5
				
Difficulty in oil collection Losses and decrease in yield Large amount of remnant in the used containers				Efficient oil collection Lower loss Minor remainder Lower cost for higher yield (31.86 ± 3.98%).

Figure 1 shows the oil resulting from extraction.

Figure 1
Pumpkin seed oil (Cucurbita maxima Duchesne ex Lam)

The presence of four fatty acids was observed in the oil extracted by the EA5 method: linoleic acid (18:2) 62.98 ± 2.47%, oleic (18:1) 17.69 ± 0.64%, palmitic 12.06 ± 1.03% and stearic 6.02 ± 0.90%.

The emulsion prepared for microencapsulation 24 hours after homogenization was kinetically stable (0% phase separation). The percentage loading of gum arabic improved the stability of the encapsulation and the maltodextrin contributed to the formation of a fine, uniformly colored powder as shown in Figure 2.

Figure 2
Pumpkin seed oil microcapsules (Cucurbita maxima Duchesne ex Lam)

The parameters applied to characterize the microcapsules and the results obtained are shown in Table 3.

Table 3
Characterization of pumpkin seed oil microcapsules

Parameters	**Value**		
Free oil (%)	2,33	±	0,57
Total oil (%)	25,33	±	1,15
EE (%)	90,71	±	2,77
Payload (%)	20,59	±	1,15

The morphological characteristics of the microcapsules presented different sizes ranging from 5 to 20 µm, with spherical and concave shapes, smooth surface, without pores or cracks as shown in Figure 3.

Figure 3
Morphological characteristics of microcapsules

The results of the IP and ATB storage stability tests on the oil and microcapsules are shown in Figure 4.

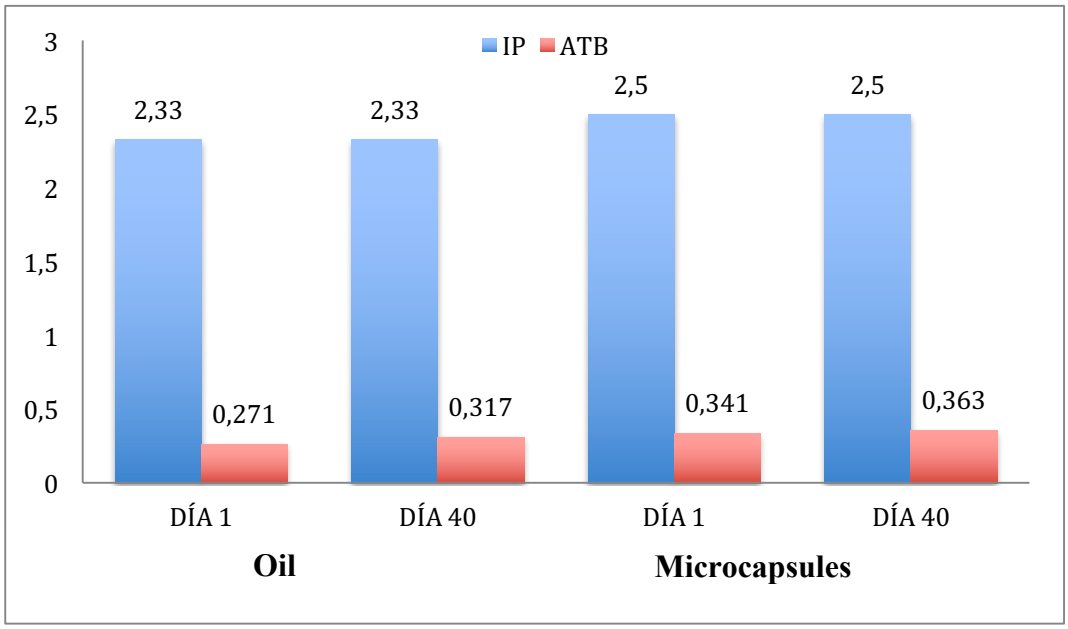

Figure 4
Storage stability of pumpkin (Cucurbita maxima Duchesne ex Lam.) seed oil and microcapsules

The PI in the oil sample was 2.33 ± 0.57 mEq O2/kg on days 1 and 40, a value that remained stable throughout the storage period and without significant statistical differences ($p < 0.05$). The ATB test yielded results of 0.271 ± 0.01 and 0.317 ± 0.01 MDA/kg respectively ($p < 0.05$). In the microcapsules, the PI value was 2.50 ± 0.71mEq O2/kg on day 1 and 40, a behavior similar to that of the oil sample and without significant statistical differences ($p < 0.05$). The ATB result was 0.341 ± 0.01 and 0.363 ± 0.01 MDA/kg respectively ($p < 0.05$).

Discussion and conclusions

The final moisture content of all seeds was adequate to inhibit the growth of microorganisms and inactivate enzymes that could cause seed deterioration [36].

The chemical composition values compared to those reported by Kipping et al. [15] were: moisture similar to that found of 5.58% SCC and 4.45% SSC; carbohydrates higher than 5.57% and 6.99% in SCC and SSC respectively, this difference could be associated with the presence of fiber in them, the method applied for their determination and the variety of the species used [37]; protein and fat values were higher than 28.92% SCC and 24.36% SSC and 35% SCC and 49% SSC respectively, obtained by Kipping et al. [15].

The fat concentration of the present study, compared to other vegetable oils, are similar to those of sunflower 43 - 51.1% [38] and rapeseed 40 - 48% and higher than those of corn 33%, safflower 30 - 35% and soybean 18 - 22% [37], a characteristic that makes the raw material used a potential and valuable source for extraction.

The literature reports differences in ash content of 1.43% SCC and 5.37% SSC [23], 5.3% SCC [37] and 3.95% SSC [39]. Differences in composition could be attributed to species variety, climate, cultivation practices, soil composition, and maturity of the vegetable at harvest [33,37].

Methods EA1, EA2, EA3 and EA4 could generate higher costs if they are to be implemented on a pilot or industrial scale for oil extraction. The extraction percentage obtained by the EA5 method exceeds that reported in the literature with 5 and 9% [14, 23]. The use of hexane as solvent provided good oil solubility and easy separation of the oil in the evaporation process. The green color, similar to olive oil, could be attributed to the presence of chlorophyll in the seeds of pumpkin *C. maxima Duchesne ex Lam.*

Regarding the fatty acid profile, the linoleic acid content (62.98 ± 2.47%) was higher than that reported by Kipping et al. [15] of 51.87%. This fatty acid is considered essential together with linolenic acid, since its formation in the body is not possible and the balance between the two is crucial in the regulation of inflammatory processes such as metabolic syndrome, diabetes and obesity [11]. The oleic acid value (17.69 ± 0.64%) was lower than those found by other authors of 29.04% [15], 31.34% and 32.40% [39]. This could be attributed to the variety and the species [5, 37]; and be compensated by the higher linoleic content in the seeds studied compared to the literature cited. The consumption of this monounsaturated fatty acid prevents and reduces the risk of coronary accidents and metabolic diseases [11]. Palmitic acid content (12.06 ± 1.03%) was similar to that reported by Kipping et al. [15] of 11.64% and lower than those of Kim et al. [40] of 13.14 and 14.07%. Although this saturated fatty acid does not have a beneficial effect on the body, its concentration is low, and with regular consumption of this oil, it would not exceed 10% of the recommended daily energy [11]. With respect to stearic acid (6.02 ± 0.90), it was lower than the 7% [15], 7.33% and 4.67% [40]observed in the literature. The differences could be attributed to genetic diversity [37].

The stability of the emulsion could be attributed to the emulsifying capacity of the wall materials used, which kept the mixture invariable [24, 32].

Free oil was similar to that reported by López et al. [24] of 2.3%, which also establishes a limit of 10% for this parameter. The low percentage could be attributed to the role played by gum arabic and maltodextrin in containing the active ingredient inside the capsule [33].

The proportion of total oil is related to %EE, and these were higher than those achieved by Klinkesorn et al. [33] of 18.37% and 86.94%, respectively. According to Barbosa et al. [41] the more stable the emulsion is from the beginning, the higher the %EE; this characteristic can be attributed to the process of elaboration of the mixture and to the gum arabic-maltodextrin system that maintained the stability of the preparation prior to spray drying [24].

The payload (amount of powder resulting after drying) suggests that the product yield was lower than reported by other authors of 63.2% [31], 82.1% [25] and 97.4% [24]; which could be attributed to particle deposits around the spray lid and on the chamber wall of the equipment used, inlet temperature, polymer concentration and the sprayer model used [42].

According to different authors, the characteristics obtained by SEM are advantageous, since they prevent degradation and extend the shelf life of the encapsulates [24, 25].

Fat oxidation is one of the main causes of food spoilage. According to Jiménez [35], the increase in ATB could be related to the initiation of the formation of carboxylic compounds resulting from the degradation of fatty acids or peroxides; however, the figures obtained do not exceed the reference value of 0.7 to 1 mg MDA/kg.

The storage stability values of the oil and the microcapsules show that both samples tend to behave in a stable manner, with no evidence of oxidation according to the results obtained. In the oil, it could be attributed to the presence of natural antioxidants such as tocopherols (non-glyceride components of great importance in vegetable oils) responsible for oxidative stability during processing and storage [21, 39, 36, 43]; and in the microcapsules, to the polymers used as wall material (gum arabic and maltodextrin) and to the %EE obtained, which provided protection and preserved the particles adequately.

The results of this work show that it was feasible to reuse a waste product, such as *Cucurbita maxima Duchesne ex Lam*. pumpkin seeds, for the extraction of oil with good nutritional characteristics, especially linoleic and oleic acid. It was possible to microencapsulate the oil by spray drying and the gum arabic-maltodextrin system allowed obtaining stable and homogeneous emulsions, with a high percentage of encapsulation efficiency. The extracted oil and the microcapsules remained stable during 40 days of storage, showing no evidence of deterioration caused by oxidation phenomena.

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List of symbols and abbreviations

%EE: Encapsulation efficiency percentage
AOAC: Association of Official Agricultural Chemists
ATB: Thiobarbituric acid
EA1: Oil extraction with hand press
EA2: Oil extraction with hydraulic press + pill dispenser
EA3: Oil extraction with hydraulic press + plates
EA4: Oil extraction with home-made presses
EA5: Oil extraction by maceration with organic solvent
FAMEs: Fatty acid methyl esters
FAO: Food and Agriculture Organization of the United Nations
IP: Peroxide value
MDA: Malonaldehyde
NaOH: Sodium hydroxide
NaCl: Sodium chloride
SCC: Shelled seeds
SEM: Scanning Electron Microscope
SSC: Shelled seeds
PDA: Food loss and waste

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EFFECT OF THE MEDITERRANEAN DIET ON THE PREVENTION OF PREECLAMPSIA

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Summary. Introduction: Preeclampsia is a complication with a notorious prevalence nowadays that can be prevented through a healthy lifestyle, in this case, a Mediterranean diet. Objectives: To demonstrate whether an adequate Mediterranean diet can improve maternal health status, in particular, preeclampsia. Material and methods: A literature review was conducted. Eighty-nine bibliographic references were used, using 23 articles taken from Medline, Pubmed and Scielo for the discussion of these concepts, studying 15 of these in depth. Results and discussion: Most of the studies discussed encourage the use of the Mediterranean diet to avoid complications in pregnancy, although most of them have numerous limitations. The role of omega-3 fatty acids, or some micronutrients such as calcium, phosphorus and vitamin D do have a high evidence of benefits in the prevention of pregnancy complications. Conclusions: The Mediterranean diet seems to have ideal health characteristics and can be recommended to pregnant women to prevent preeclampsia and other complications. Even so, more research is needed. What is clear is the importance of a varied and balanced diet.

Key words: Mediterranean diet, preeclampsia, benefits, complications, complications

EFECTO DE LA DIETA MEDITERRÁNEA EN LA PREVENCIÓN DE LA PREECLAMPSIA

Resumen. Introducción: La preeclampsia es una complicación con una prevalencia notoria hoy en día que puede ser prevenida mediante un estilo de vida saludable, en este caso, con una dieta mediterránea. Objetivos: Demostrar si una dieta mediterránea adecuada consigue mejorar el estado de salud materno, en concreto, la preeclampsia. Material y métodos: Se realizó una revisión bibliográfica. Se utilizaron 89 referencias bibliográficas, utilizando 23 artículos sacados de Medline, Pubmed y Scielo para la discusión de estos conceptos, estudiando 15 de estos en profundidad. Resultados y discusión: La mayoría de los estudios discutidos fomentan el uso de la dieta mediterránea para evitar complicaciones en el embarazo,

aunque la gran parte de ellos con numerosas limitaciones. El papel de los ácidos grasos omega 3, o algunos micronutrientes como el calcio, fósforo y vitamina D sí que tienen una alta evidencia de beneficios en la prevención de las complicaciones en el embarazo. Conclusiones: La dieta mediterránea parece tener características idóneas para la salud, pudiéndose recomendar a las gestantes para evitar la preeclampsia y otras complicaciones. Aun así, se requiere más investigación. Lo que se tiene claro es la importancia de una alimentación variada y equilibrada.

Palabras clave: Dieta mediterránea, preeclampsia, beneficios, complicaciones

Introduction

Complications in pregnancy today are still very common, despite having more knowledge compared to past generations. Preeclampsia is one of the major complications that occur in pregnant women and should therefore be investigated (1). There is evidence that itis a problem, above all, in low-income countries with a much improved quality of life (2), like most diseases and complications, with high rates in African-American women with subsequent death of both the fetus and the mother (3). Likewise, the World Health Organization (WHO) estimated that developing countries have a 7 times higher risk of suffering from preeclampsia and it ranges between 2%-10% incidence among pregnancies (5). Another observational study carried out at the Guillermo Díaz de la Vega Regional Hospital, with 1692 participants, shows that 57 pregnant women suffered from preeclampsia during the study, that is, with a prevalence of 3.7%, and this number may be higher in underdeveloped countries (4).

Increasingly, studies and reviews support nutritional treatment as a tool to avoid complications, based on a varied, healthy and balanced diet (6). It could be said that it can be a key tool for both prevention and treatment of its complications. However, this is still under investigation. The Mediterranean diet can be highlighted as a key factor in the control of preeclampsia. Many studies advocate its use for blood pressure reduction, although without specifying the nutritional treatment used (7). Although it may seem that the Mediterranean diet is already well studied, for the moment, there is no scientific clarity on the relationship of this diet and preeclampsia, it is not known exactly if there is a direct benefit due to the Mediterranean diet or to specific components that could also be obtained with other nutritional approaches

The Mediterranean diet has been modified by cultural factors, both in terms of food types and quantities. This is quite a serious problem because of the creation of diet variants that have actually changed from the original diet. In view of the above, this study will address a literature review that will try to clarify whether an adequate Mediterranean diet with a specific nutritional plan is really beneficial enough to prevent or treat preeclampsia, since in recent years its prevalence is increasing markedly and it is urgent to seek measures to solve it.

1.1 Target

The general objective of this study is to review the existing literature in order to clarify whether an adequate Mediterranean diet can improve maternal health, particularly preeclampsia. In addition, a series of specific objectives are established:

1.2 Define preeclampsia, its complications and nutritional treatment.

1.3 To establish the pathophysiological mechanisms that cause preeclampsia

1.4 To establish the relationship of micronutrients with preeclampsia

1.5 To explain the role of the Mediterranean diet on preeclampsia and determine its effectiveness

1.2 Preeclampsia. Definition

Preeclampsia, also known as EPH-Gestosis, is a very common complication of pregnancy characterized by (2):

- Edemas
- Arterial hypertension
- Proteinuria

These would be the most common conditions, although there may be other problems such as:

- Functional alteration in organs
- Alteration in the growth of the fetus

The trigger for this syndrome is the release of anti-angiogenic markers, causing oxidative stress and a morphological and functional alteration in cells, mainly uterine cells. Among these factors, the most studied are tyrosine kinase-1 (sFlt-1), soluble endoglobin (sEng), placental growth factor (PIGF) and vascular endothelial growth factor (VEGF).

A randomized control trial, conducted in Ireland, does not support the incorporation of a PIGF test for the detection or screening of premature preeclampsia, but does not deny its benefits (8). In an ideal or adequate pregnancy, there is a balance between angiogenesis processes (formation of blood vessels) and anti-angiogenic processes (destruction of blood vessels) (9,10).

- According to their severity we can differentiate (11):
- Preeclampsia without severity. It is characterized by a systolic pressure greater than 130 mmHG and a diastolic pressure equal to or greater than 90 mmHG, with proteinuria (excessive protein in urine) but without organ involvement.

Preeclampsia with severity. It is characterized by systolic hypertension equal to or greater than 160 mmHG and diastolic pressure equal to or greater than 110 mmHG, with proteinuria and organ involvement.

Table 1

Classification of preeclampsia according to severity. Own elaboration. (11)

Type	Pressure	Proteinuria	Organ involvement
No gravity	Systolic=>130mm HG Diastolic=>90mm HG	Yes	No
With gravity	Systolic=>160mm HG Diastolic=>110mm HG	Yes	Yes

1.3 Risk factors, complications and symptoms

Risk factors for preeclampsia are still under discussion, with some being considered certain for this complication.

- Age. Late ages in pregnancy have been associated with an increased risk of preeclampsia. Even so, there are studies (12) that support a high probability of preeclampsia in young women.
- Obesity. It increases VEGF/Flt 1, reducing angiogenesis, thereby producing placental insufficiency and hypoxia (13).

It appears that pregestational BMI may indicate an increased risk of preeclampsia. A person with a high BMI is apparently more likely to have this complication, although as we know the reliability of the BMI is limited depending on the person and their physiological situation. There are studies that do not relate BMI to preeclampsia, as is the case of the meta-analysis and systematic review by Morteza Motedayen et al (14), which found that the mean BMI between women with preeclampsia and healthy women was practically the same.

- Race. African-American women, for example, are at higher risk. In a study conducted at the Hospital General Guasmo Sur in the Guayas Province (country) (15), by means of specific inclusion and exclusion criteria, several characteristics were related to the prevention of preeclampsia. The results showed an increase in the incidence of this disease in black women, which is the first risk factor according to this study.
- First pregnancy. The first pregnancy causes a higher probability of preeclampsia (16).
- Family factors. There is research supporting the relationship of familial inheritance with preeclampsia. Women with mothers who have had preeclampsia have a higher risk of having this syndrome (16).

Figure 1
Distribution of factors associated with preeclampsia (16)

Preeclampsia can cause problems in both the mother and the fetus.

HELPP syndrome

One of the most common complications following preeclampsia is HELLP syndrome. A disease that causes liver damage and the fracture and rupture of red blood cells (16). An in-depth literature review by Sunita Dubey and Jyotsna Rani (17) concludes that liver damage should be significantly related to hypertensive women, even more so if they suffer from some type of epigastric pain or other symptoms such as pallor or skin discoloration. It is vitally important to monitor both during the gestational and postpartum periods. In addition, laparoscopy and blood transfusions are used as treatment in the case of very advanced stages.

Table 2 below shows the classification of Hellp syndrome according to the Mississippi and Tennessee classification:

Table 2

Class	Mississippi Classification	Tennessee Classification
1	Platelets ≤ 50.000mL LDH >600 IU/L AST or ALT ≥70 IU/L	Platelets ≤ 100,000mL LDH ≥ 600 IU/L AST or ALT ≥70 IU/L
2	Platelets > 50,000mL and ≤ 100.000mL LDH >600 IU/L AST or ALT ≥70 IU/L	
3	Platelets > 100,000mL and ≤ 150.000mL LDH >600 IU/L AST or ALT ≥40 IU/L	

Severity classification of HELLP syndrome according to the Mississippi criteria (18)

Eclampsia

Eclampsia is a complication that is often accompanied by preeclampsia. It is the occurrence of seizures or coma during pregnancy after the 20th week of gestation, delivery or in the first hours of the puerperium unrelated to neurological conditions. How to prevent eclampsia in women with preeclampsia through serum magnesium levels is being investigated. A randomized clinical trial conducted by Pascoal (19) divided 62 women into two groups according to the amount of magnesium sulfate administered (1 or 2 g). The results gave an insignificant difference between the 2 groups and also the group with the administration of 1 gram had fewer side effects. There is not much knowledge, at present, on this aspect.

Consequences on the fetus

In the case of the fetus it can occur (20):

- Low birth weight, due to the lack of oxygen and nutrients reaching the baby, resulting in slow growth of the baby.
- Premature birth. Very common in pregnant women who are forced to give birth because of the risk that can occur in both her and her baby.
- Placental abruption. Before giving birth, in many cases, the placenta detaches from the uterus resulting in a lack of oxygen and nutrients. A very common symptom is vaginal bleeding, which usually occurs in mid-pregnancy.
- Kidney failure. Changes in blood flow and glomerular filtration appear to occur in patients with preeclampsia, as well as osmoregulatory and morphological changes of the kidney (21).

Depression

Recent research links possible depression after having suffered from preeclampsia. It is related in a dependent manner and, therefore, care should be taken and care should be taken to try to prevent this type of disorder. A systematic review of 13 studies (22), 8 of which related depression to preeclampsia, showed a possible relationship in most of them. More studies would be needed in this regard, concluding the review by writing that not only is it a risk factor, but it also aggravates the symptoms of this disease in the postpartum period. These hypotheses may be true due to the existence of other articles such as a retrospective cohort study in Edinburgh (23), which concludes a higher rate of postpartum depression after severe preeclampsia (30.77% vs. 14.58%) among preeclamptic women and a control group of women.

Preeclampsia may be asymptomatic, although this is not common. The first sign of preeclampsia is usually increased blood pressure and this can occur slowly or suddenly (the latter is usually less common) (24).

Some of the main symptoms are:

- Nausea
- Reduced urine production
- Low platelet levels
- Changes in vision
- Hypoxia
- Headaches

1.4 Nutritional treatment

There is much controversy about the nutritional treatment that should be used for the prevention of preeclampsia and, progressively, multiple studies are coming to light covering this aspect as they have begun to realize the role of nutrition in this condition. In contrast, there are still recent studies that support the lack of relationship between dietary habits and the prevention of preeclampsia, as in the case of a study at the Faculty of Medical Sciences at the University of Guayaquil (Ecuador) (25), in which they conclude that there is an insufficient relationship between dietary habits and preeclampsia. For this purpose, they made diagrams showing the consumption of

different types of food in the pregestational stage and in the pregnancy period, where a clear relationship between both aspects could not be drawn.

- Macronutrients

Dairy products are essential to prevent preeclampsia, without abusing them due to the possible accumulation of saturated fats. Its recommendation is mainly due to fat-soluble vitamins such as vitamin A and vitamin D (25). Fruits and vegetables are extremely important foods for pregnant women because of their fiber intake and because they prevent fluid retention, which can lead to fatal consequences in women (25). As for proteins, they should be of high biological value, not abusing red meat and alternating the consumption of poultry and fish. Oily fish is included for its properties such as omega 3, fats with anti-inflammatory properties (26).

With regard to carbohydrates, it is taken for granted that simple carbohydrates with a high glycemic value, such as industrial pastries, should be excluded from the diet of pregnant women due to the innumerable list of unfavorable consequences they can have. These macronutrients are of great importance for pregnant women. In fact, an analytical case-control study in a hospital in Lima (Peru) in 2019 (26) reflected increased preeclampsia in those who consumed fewer carbohydrates.

As for fats, as will be discussed later, their use as a preventive factor is currently being studied, with some positive and others somewhat contradictory results. Foods should be chosen with an optimum quality and simple cooking methods, avoiding, for example, frying. In high quantities, fats can cause cardiometabolic problems. In fact, a cross-sectional study at the Hospital de Ginecología y Obstetricia del Instituto Materno Infantil del Estado de México (27) shows who have higher cholesterol and triglyceride levels than normotensive individuals without preeclampsia. They conclude by suggesting a lipid profile for women in the gestational period and postpartum.

Referring to the previous study on carbohydrates, they also analyze the role of lipids. Women diagnosed with preeclampsia ingested higher amounts of lipids than the others. Even so, it should be studied in more depth, due to the recent publication of several studies defending the use of fatty acids in this syndrome. According to the study in the Perinatal Perinatal Peruvian journal (26), the risk of preeclampsia is related to carbohydrate consumption in 43.94% with respect to the sample of 102 participants, so it is not really clear the role of carbohydrate specifically for this complication. On the other hand, lipid intake was related to preeclampsia. An intake of more than 1743 kcal of lipids was associated with a 68.97% increase in the chances of contracting preeclampsia; in contrast, 17.81% had no apparent effect on this complication. Both studies were performed with a 95% confidence interval.

- Micronutrients

Folic acid: it appears that the risk of preeclampsia is reduced with folic acid supplementation. A folate deficiency can induce cell apoptosis, invading the trophoblast and synergistically impairing placental development. The beneficial action of folic acid has been seen with multivitamin supplementation, that is, together with the administration of other vitamins rather than with the administration of this vitamin alone. More studies are needed, but it seems that it may prevent the risk of preeclampsia (28).

Table 3

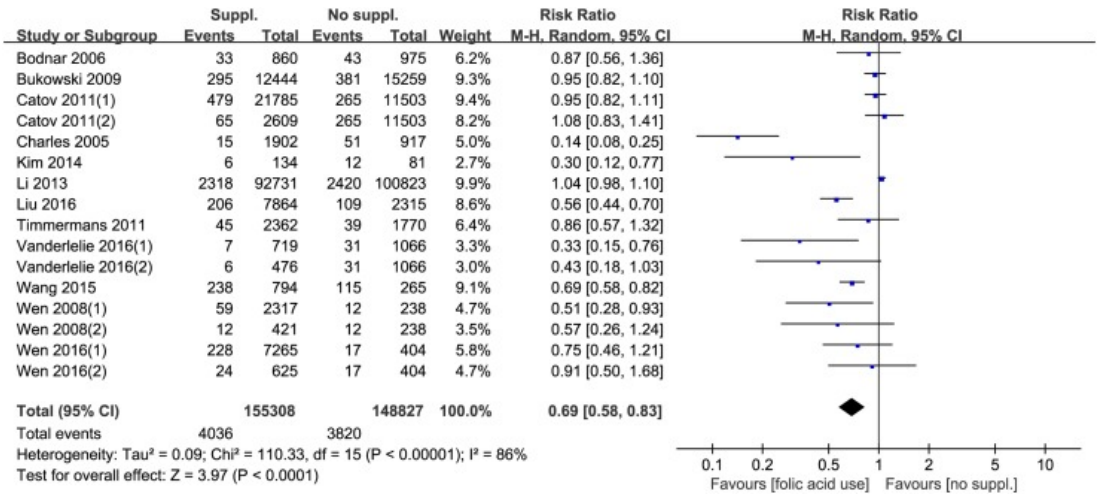

Table showing the relationship of preeclampsia risk with folic acid supplementation in a systematic review published in 2018. The RR (Risk Ratio) of 0.69 indicates a decreased risk with folic acid supplementation (28)

Vitamin D: studies have recently been published on vitamin D, a vitamin found mainly in oils, some types of fish, eggs, etc., and its relationship with the prevention of preeclampsia. More evidence is still lacking as it is a relatively new object of study, but everything points to a good correlation with this disease. Vitamin D could be a regulator of blood pressure through the renin-angiotensin system. Research should focus on the appropriate and recommended dose to serve as an incentive for this syndrome. What I have just mentioned is the conclusion of a randomized clinical trial in which a dose of 400 IU and 4000 IU is given to women with vitamin D deficiency and women without deficiency, respectively, with greater benefits in the second group (29). Another important factor could be calcium for the prevention of preeclampsia. Intakes of approximately 1.2-1.5g of calcium per day may reduce the risk of preeclampsia, as supported by numerous reviews (30).

A meta-analysis relating vitamin D, calcium and supplementation of the two together could be found (31) which is summarized in the following Table 4:

Table 4

Rango etario (años)	Instituto de Medicina de Estados Unidos			Sociedad de Endocrinología para pacientes con riesgo de deficiencia	
	EAR: Requerimiento promedio estimado (µg / UI)	DRI: Ingestas dietética de referencia (µg / UI)	UL: Nivel máximo de ingesta tolerable (µg / UI)	Requerimiento diario (UI)	Consumo tolerable (UI)
14 - 18	10 / 400	15 / 600	100 / 4.000	600 a 1.000	4.000
19 - 30	10 / 400	15 / 600	100 / 4.000	1.500 a 2.000	10.000
31 - 50	10 / 400	15 / 600	100 / 4.000	1.500 a 2.000	10.000

Interpretación niveles séricos de vitamina D Estado	Unidades convencionales (ng/ml)	Sistema internacional de unidades (nmol/ l)
Deficiencia	<20	<50
Insuficiencia	21 a 29	52,5 a 72,5
Suficiencia	>30	>75
Toxicidad asociada a hipercalcemia	>150	>375

The recommended intakes of Vitamin D according to the age of the pregnant women are shown (31)

As a conclusion, vitamin D could be preferred because it is a precursor for the maintenance of calcium homeostasis, in addition to being a potent suppressor of renin formation, which is involved in blood pressure (32). Even so, the exact amounts to be

used are still not known and, therefore, much research remains to be done in this regard, adding that there are studies in which vitamin D and preeclampsia have not been assigned any type of relationship (33).

Copper, magnesium and selenium: other micronutrients, such as copper, selenium and magnesium, were found to be decreased in a randomized cross-sectional study in pregnant women in southeastern Nigeria, there are more studies linking these micronutrients, but further research is still needed to draw a clear conclusion (34). It seems that it is not so important the type of diet as to have an adequate and balanced level of the different micro and macronutrients, rather than the choice of a specific type of food, being able to be flexible.

1.5 Mediterranean diet

The Mediterranean diet (35) is a dietary pattern with multiple proven benefits from countries such as Cyprus, Croatia, Spain, Italy, Morocco and others nearby. It is characterized by the presence of the following foods: high amounts of vegetables, fish, monounsaturated fats (olive oil), fruits, dairy products, meats and avoiding processed products, refined flours, sugars and saturated fats as much as possible. It should be noted that the composition of this diet has changed over the years.

According to the WHO (36) it is an exemplary type of diet if it is carried out together with the execution of physical exercise and the avoidance of unhealthy habits such as tobacco or alcohol. For UNESCO (36) it is declared Intangible Heritage of Humanity, recommending its type of food and, in addition, emphasizing its sustainability, which we will discuss later in a later section. The U.S. Department of Health (37) specified that 3⁄4 parts of the population did not have conducive and adequate dietary habits to maintain an adequate cardiometabolic status, having micronutrient deficiencies and excess fats and proteins of low biological value.

Table 5

Fruits	1-2 meals
Vegetables	>2 meals
Cereals	1-2 servings/meal
Dairy	2 servings per day
Nuts, seeds and legumes	Nuts and seeds 2 or 3 servings per day Legumes >= 2 servings per week
Beef,pork,ham,lamb	Red meat <2 servings
Fish, Seafood	>= 2 servings per week
Sweets	<= 2 servings per week
Olive oil	1-2 servings per meal
Others	Eggs 2-4 servings per week Potatoes <= 3 servings per week
Alcohol	Wine in moderation

Number of servings per week of the different foods used in the Mediterranean diet. (38)

Inconveniences at the health level

In specific cases, some variations may occur in biochemical parameters and in the anthropometry of the people who are prepared to follow this type of diet (39).

Weight gain can be very common when using multiple sources of fats, so if special care is not taken it can lead to this consequence. A large percentage of studies agree that, with proper nutritional planning, the Mediterranean diet helps to lose weight and thus to improve different biochemical parameters.

In a randomized controlled trial conducted for the CARDIVEG (Cardiovascular Prevention with Vegetarian Diet) project (40), 2 groups were compared: ovo-lactovegetarian diet and Mediterranean diet in overweight people. The conclusive results were a weight reduction with the two types of diet, in the case of the Mediterranean diet the triglyceride levels decreased more in comparison with the ovo-lactovegetarian diet and in the case of the ovo-lactovegetarian diet the decrease in cholesterol was greater. Recent research (41) is focusing on linking the obesity-associated gene (FTO) to the Mediterranean diet but the results are inconclusive. That said, women should have an adequate weight before and during gestation to avoid associated comorbidities.

Deficiency of some micronutrients, such as calcium or iron, may be present in various cases. The daily consumption of dairy products in Spain is usually below the recommended level. According to AECOSAN (42) (Spanish Agency of Consumption, Food Safety and Nutrition), the ideal would be the consumption of 2-3 servings of dairy products per day, giving great importance to the growth period in children and pregnant women.

Table 6

Dairy consumption recommended by the Department of Agriculture, MyPlace Initiative

	Daily recommendation		**Equivalences in Spain**
Toddlers	2-3 years	2 cups	480 ml = 2.4 servings
	4-8 years	2 ½ cups	600 ml = 3 servings
Girls	9-13 years	3 cups	720 ml = 3.6 servings
	14-18 years	3 cups	720 ml = 3.6 servings
Children	9-13 years	3 cups	720 ml = 3.6 servings
	14-18 years	3 cups	720 ml = 3.6 servings
Women	19-30 years	3 cups	720 ml = 3.6 servings
	31-50 years	3 cups	
	51+ years	3 cups	720 ml = 3.6 servings
			720 ml = 3.6 servings
Men	19-30 years	3 cups	720 ml = 3.6 servings
	31-50 years	3 cups	
	51+ years	3 cups	720 ml = 3.6 servings
			720 ml = 3.6 servings

Recommended daily intake of dairy products at different stages of life (43)

Dairy product supplementation has resulted in significant changes in several cardiovascular and anthropometric aspects as well as in more specific variants such as mood and cognitive functions (44).

In the case of iron, deficiencies are possible if the person's diet is not purely Mediterranean in nature, because he/she should not be deficient in this mineral. In fact, clinical trials in the elderly, such as a one-year randomized trial conducted in Europe through the (NU-AGE) program (45), find that iron status did not change significantly, but did not drop either, and markers of iron status improved considerably.

The culture of alcohol, specifically wine, in this diet, has always been a very controversial issue that has grown in recent years. It is supported that moderate alcohol consumption has a positive effect on the incidence of coronary heart disease. Daily doses of 10 to 30 grams of alcohol are associated with a lower risk of this type of disease. Doses of more than 30 grams of alcohol already have a negative effect according to the WHO (46).

Focus on cardiovascular health

Leland Allbaugh and Ancel Keys (47) with their Seven Countries study showed that populations eating a Mediterranean diet had lower mortality rates compared to other diets, such as those of Nordic countries. This research marked a before and after and, progressively, clinical trials and cohort studies were carried out to confirm these facts.

What has been seen, additionally, with other diets such as low-fat diets, is a decrease in high blood pressure, positive glucose levels and thus a lower predisposition to suffer from Diabetes Mellitus type 2. As for the lipid profile, the results are more diverse, with improvements in cholesterol and inflammatory markers (48).

In an uncontrolled intervention study carried out in a hospital in Barcelona (49) on patients with ischemic heart disease, in which it was proposed to increase their adherence to a Mediterranean diet in order to verify the changes produced, beneficial results were obtained both in adiposity and cardiovascular health, with an associated improvement of around 20% with respect to cardiovascular risk over the next 5 years. Some of its limitations were: a sample size that was not very significant after the rejection of the participants to the study and the loss of some of them during the course of the study, in addition to the absence of a control group.

In contrast, in a study conducted through the PREDIMED (Prevention with Mediterranean diet) model (50), a prevention trial was conducted on 7,403 participants who were randomly divided into 3 groups. The groups were assigned according to the type of diet: Mediterranean diet with EVOO (extra virgin olive oil), Mediterranean diet with nuts and a control diet. The follow-up period was long and the conclusions were that the use of the Mediterranean diet for the prevention of heart failure could not be stated with certainty (51).

Time is a very important factor and the longer the time, the greater the probability of being able to draw more accurate and objective conclusions. Such is the case of a study carried out in America on firefighters who were assigned to a Mediterranean diet intervention for certain periods of time and it was possible to observe the improvement (although not massive) of cardiovascular and biochemical parameters when this dietary pattern was administered for a longer period of time (52).

Environmental sustainability

Global concern for environmental care has become increasingly evident in the wake of climate events around the world. The Mediterranean diet should be understood as a cultural model, as well as an ecological model (53). In recent years, especially in the last decade, the sustainability of this diet has been studied in depth (54).

The project of Sáez-Almendros S et al (55) aimed to analyze the sustainability of the Mediterranean diet in the Spanish population through: greenhouse gas emissions, agricultural land use, energy consumption and water consumption. Meat and dairy were the major contributors to environmental footprints but their damage to the environment was very small compared to Western diets. The methodology was based on calculating the composition of each food pattern and the footprints of each food.

Spain would reduce all of the above, while a Western diet would increase the parameters by (12% to 72%). The consumption of food in this diet does not mean that undesirable changes in the environment do not occur, but what is evidenced is that it is much less harmful than other types of diets. Various investigations seem to be clear that the reduction of meat and the increase of other products, such as dairy products, eggs, fish and vegetables, help significantly to make a more sustainable diet (56).

Possible beneficial effects of the Mediterranean diet in the prevention of preeclampsia.

Controversy in nutritional topics is the order of the day, as new inventions are discovered or previously established theories are rejected. The same thing happens with preeclampsia. A considerable number of articles of different types (reviews, randomized and controlled trials, books, papers, etc.) show benefits in the use of the Mediterranean diet in the prevention of preeclampsia (57).

Overall positive relationship

In this clinical trial (58), a study was made of the complications that 3 types of diet, including the Mediterranean diet, can cause in pregnancy. Its consumption can be related to a lower risk of hypertension and preeclampsia. It is true that after this intervention some women were diagnosed with preeclampsia, although it is possible that they were already diagnosed with this syndrome before pregnancy, which could constitute a bias in the results.

The review of Argyro Singelaki et al (59), with a massive investigation of articles, concludes that the accompaniment of a diet (most of the studies with a standardized Mediterranean diet) with the accompaniment of physical exercise is a possible preventive method for gestational diseases and complications.

A study in Norway by Assaf Balut (60) review shows that a Mediterranean diet has a lower incidence of preeclampsia in pregnant women, focusing on the importance of adherence to the Mediterranean diet in the pregestational period.

Soltani S et al (61) in their prospective observational study of 812 pregnant women, collecting information through a consumption frequency questionnaire, concluded, objectively, as the results showed, that women with a Western dietary pattern compared to a healthy pattern (as close as possible to the Mediterranean diet) had a more significant association with the possible occurrence of preeclampsia.

Premature infant death, in recent years, has been and is one of the most numerous complications in pregnancy. Nutritional treatment appears to be a key part of preventing these events. In an observational cohort study of women who had delivered preterm, it was observed that women with low adherence to the Mediterranean diet had higher rates of overweight and preeclampsia (62). In contrast, the articles continue to support the idea of a positive relationship between the Mediterranean pattern and preeclampsia, but do not relate it to obesity or hypertension (63).

Therefore, the role of nutrition in the life of the pregnant woman seems to be an important factor, and the Mediterranean diet could be an example of an adequate dietary treatment for an adequate development of the pregnancy and to avoid hypertensive disorders (64). Even so, further studies are required.

Fruit and vegetable consumption and the prevention of preeclampsia

The Mediterranean diet, in its essence, is characterized by an abundant consumption of fruits and vegetables.

In a systematic review and meta-analysis conducted on hypertension in Ethiopia (65), alcohol consumption and urinary tract infection during pregnancy significantly increased the risk of developing hypertensive disorders of pregnancy. In contrast, pregnant women who obtain nutritional counseling during the prenatal period and consume fruits and vegetables during pregnancy reduce the risk of developing hypertensive disorders of pregnancy and the risk of preeclampsia. These hypotheses are supported by more studies (66, 67).

In the randomized clinical trial conducted at the Carlos III Institute (68), the Mediterranean dietary pattern profile (a Mediterranean diet supplemented with EVOO and pistachios) gave satisfactory results in terms of a lower risk of gestational diabetes, prematurity, urinary tract infections and preeclampsia, compared to a standard diet. Olive oil is the distinctive product of the Mediterranean diet, as are fruits and vegetables (69) that accompany practically all meals in this diet, associating their consumption with lower probabilities of preeclampsia. Some reviews (70) sought to study the effect of fruits and vegetables in pregnant women through vegetable diets and the Mediterranean diet due to its high consumption of these foods, resulting in this dietary pattern being favorable for preventing weight gain and preventing preeclampsia in pregnant women, as well as allergies and dermatitis in infants.

Role of fats (omega 3 acids)

Omega-3 acids have been studied for their anti-inflammatory and cardiometabolic role in pregnant women. This is particularly important because of the correlation between the Mediterranean diet and this type of fatty acids.

In a meta-analysis published in 2018 (71), through a search in the Cochrane library, it is found that certain studies express the possible reduction of preeclampsia with omega-3 fatty acids, specifically 20 trials supported this hypothesis with a sample size between all of them of about 8,000 participants, even so, they rated it as evidence of a medium quality in terms of reliability.

A review article, published in January 2020 by Bakouei F et al (72), on omega-3 fatty acid intake and its relationship to pregnancy, spoke extensively of omega-3 fatty acid supplementation and increased intake for the prevention of preeclampsia and hypertension, indicating which trials and which meta-analyses supported that

hypertension and the rate of preeclampsia were not significantly reduced in the groups supplemented with omega-3 in high-risk and low-risk pregnancies, mentioning as a possible limitation the size of the sample and the number of trials performed. This last point is a major drawback when it comes to evidencing the role of fatty acids as high quality information, as positive results are being seen, but more support is needed through further research (57).

To finish with fatty acids, it is worth mentioning that both the quality and quantity of these biomolecules is very important. A high amount can lead to complications. A cross-sectional study in which women were recruited by the Department of Obstetrics and Gynecology at the Medical College of Nevada (U.S.A.) and the Department of Obstetrics and Gynecology at the University of Nevada, Nevada School of Medicine (U.S.A.) was conducted. (73), showed that a 1g increase in fat intake compared to the usual recommendations resulted in gestational weight gain and increased metabolic complications in pregnancy.

Inconveniences and limitations of the Mediterranean diet in the prevention of preeclampsia

In the section on the Mediterranean diet and disadvantages, there is a paragraph dedicated to calcium and its possible deficiency with this type of diet. As already known, the role of calcium in pregnant women is very important to avoid risks to the fetus and the mother herself, affects bone health and is associated with restricted fetal growth and low birth weight. Evidence shows that adequate consumption of dairy products, with a moderate fat content, reduces systolic blood pressure and points to a consequent reduction in preeclampsia (74). Within dairy consumption, milk, especially, would be one of the best dairy products to consume (67). On the other hand, prospective cohort studies, such as that of Carla Assaf Balut (75), see no improvement with low-fat treatment with dairy during pregnancy.

Low levels of calcium in the diet (less than 700 mg) increase the risk of preeclampsia; supplementation of calcium in the diet could reduce the risk by 30% to 50%. WHO (76) recommended that women take calcium supplements to prevent preeclampsia. In-depth reviews on calcium supplementation in periconceptional and conceptional situations, such as the one by Najate Achamrah et al (77), support its supplementation in case the levels of this micronutrient are below the needs of pregnant women.

Regarding supplementation, there is no clear and sufficient evidence on the necessary doses to advise its use. Further research is needed to see if supplementation before and during the first trimester of pregnancy is appropriate to abolish pregnancy complications, including preeclampsia. Likewise, with the systematic review of Hofmeyr GJ et al. conducted in South Africa (78), doses equal to or more than 1 g per day of calcium during the first part of pregnancy could reduce the risks of preeclampsia in pregnant women with diets low in calcium (common in the Mediterranean diet).

As for alcohol, it has always been characteristic of the Mediterranean diet, especially years ago when the effects of excessive consumption were not known. In randomized clinical trials, such as that of Iwama N et al (79) in Japan, the percentage of women who consumed alcohol were at increased risk of preeclampsia and hypertensive disorders. It is important to note that these results were seen with the consumption of more than 150 grams of ethanol per day, an amount well above the current recommendations. Therefore, if it is not consumed in excess, apparently there should not be too many complications

(80). Evidently, the risk will be higher compared to pregnant women who do not consume any alcohol (81).

Among the benefits of the Mediterranean diet with the prevention of preeclampsia, some studies have shown the pros of this pattern with the corresponding disease. There are meta-analyses, such as that of Traoré SS et al (82), which after study analysis support the benefit of the diet, but without knowing by what mechanism or what nutritional factors are most involved, comparing a healthy dietary pattern (where the Mediterranean diet is found) and the Western dietary pattern. Reijnders IF et al (83) in a meta-analysis of observational studies, study proper nutrition and the changes that occur, noting the importance to be given at all stages of pregnancy.An expert review by Marshall NE et al (84) focuses on nutrition before pregnancy, supporting proper nutrition during the periconceptional period as a prevalent factor in complications. Durán A, De la Torre Ng, Assaf Balut C et al (85) also study the Mediterranean dietary pattern and its association with hypertension and preeclampsia. It seems not to have results very much in favor of this relationship.

There are also reviews, such as that of Balut (86), highlighting his projects and research in the periconceptional period with a Mediterranean dietary pattern. Its purpose is to get answers about gestational diabetes, but at the end of the day preeclampsia is present because it is usually a very common complication of diabetes. More studies have been published relating adherence to gestational hypertension and, therefore, to preeclampsia, such as the cross-sectional study of 218 women in the Canary Islands (87). The adherence of their diets to the Mediterranean diet was classified using the PREDIMED model, dividing it into high, medium and low, without showing too many differences.

A meta-analysis by Rogozinska E et al (88) attributes lifestyle changes (here diet would be included), emphasizing the role of physical activity, nutrition would not be the strong point of this study, relating it very little to these complications. Finally, the final search in this section was a randomized clinical trial in 5 maternity units in England (89) to people with metabolic risk factors, giving participants a Mediterranean-style diet. The results were not very positive with respect to the decrease in maternal complications, in general.

Method

This work consists of a bibliographic review, in which, through the support of books, databases, documents, etc., it has been possible to investigate the relationship between the Mediterranean diet and preeclampsia. The search conducted included research studying both the beneficial and harmful or even non-existent relationship of the role of the Mediterranean diet in the prevention of preeclampsia. An attempt was made to prioritize the choice of clinical trials, but the lack of such trials made it necessary to resort to systematic reviews and other articles.

Specific inclusion and exclusion criteria were used: the inclusion criteria used were: studies from indexed journals, an impact factor >1.5, recent research studies (5 years maximum), pregnant women, and articles mostly in English (75%) and the rest in Spanish (25%). The exclusion criteria used include titles that are not related to the topic to be studied, studies with insignificant or non-representative samples, and studies that, although the title may seem appropriate, the information may not be adequate.

The search for items and other complications began in February 2022 and ended in April 2022. The main databases used were:

1 Pubmed. Keywords were used in the title and abstract. The Boolean operator "and" was used. Together with Google Academic were the most used databases. About 30 articles from this platform are used.

2 Sciencedirect. Keywords were used in the title and abstract. The Boolean operator "and" was used. About 10 articles from this platform are used.

3 Google Scholar. Keywords were used in the title and abstract. The Boolean operator "and" was used. About 25 articles from this platform are used.

4 Scielo. Keywords were used in the title and abstract. The Boolean operator "and" was used. About 5 items from this platform are used.

5 Other sources:

6 Internet. A search was carried out, mostly in the initial part of the TFG, in health pages with a notorious quality and evidence.

7 Books. 2 books used from the library of the Universidad Europea del Atlántico.

The key words used in this search are very numerous, so the articles used from each database have been mentioned in a general way; moreover, the key words used differ according to the section of the work in question.

Table 7

Part of the work	Search strategy	Number of items used	Number of items found	Database and other sources used
Introduction	Preeclampsia, Mediterranean diet and prevention as key words. Using the "and" and 5 years old at the most.	7	350	Pubmed, Science Direct, and various web pages such as WHO
Preeclampsia	Preeclampsia, symptoms, risk factors and nutritional treatment as key words. Using the "and" and 5 years old at the most.	27	130	Pubmed, Science Direct, Scielo, various websites and book
Mediterranean diet	Mediterranean diet, sustainability, cardiovascular effect and prevention as key words. Using the "and" and 5 years old at the most.	22	380	Pubmed, Science Direct, Scielo, various websites and books.
Relationship between Mediterranean diet and preeclampsia	Preeclampsia, Mediterranean diet, advantages and disadvantages as key words. Using the "and" and 5 years old at the most.	23	84	Pubmed, Science Direct, Scielo

Search strategy according to the part of the job. Own elaboration

Discussion and results

In reference to the efficacy of the Mediterranean diet and the prevention of preeclampsia, there are not many studies that directly relate these concepts, but rather it is more of a secondary objective or result that comes from the study carried out, generally focused on another issue. The studies mentioned above (58-86) support the Mediterranean dietary pattern to not only avoid complications such as preeclampsia, but most of the problems that can take root in this period of gestation. But most of these studies need further investigation (59, 60, 64, 83, 86).

Table 8

Authors	Type of study	Efficacy with the Mediterranean diet
Li M, Grewal J, Hinkle SN, Yisahak SF (58)	Randomized clinical trial 24h reminder at 16-22 weeks and 24-29 weeks.	A healthier diet, including the Mediterranean diet (Med Diet), was associated with lower risks of GDM, hypertension and preeclampsia.
Syngelaki A, Sequeira Campos M, Roberge S et al (59)	Bibliographic review through Pubmed,Embase,Cinahl,Web of Science and Cochrane. In the end, 23 trials were selected.	Diet and exercise may improve parameters such as preeclampsia, but more studies are needed.
Assaf Balut (60)	Research Project of the Faculty of Medicine of the Complutense University of Madrid. Bibliographic review.	Obese people with a poor diet are more likely to have complications in pregnancy and a healthy diet (Mediterranean diet) decreases the risk.
Soltani S, Aminianfar A, Hajianfar H et al (61)	In this prospective cohort study, 812 pregnant women aged 20 to 40 years who were in their first trimester were recruited and followed up until 24 to 28 weeks of gestation. The dietary intake of the study subjects was examined using a semiquantitative food frequency questionnaire (FFQ).	The comparison between a healthy diet (as close as possible to the Mediterranean diet) and a Western diet has the benefit of fewer complications (preeclampsia) with respect to the Western diet.
Parlapani E, Agakidis, C, Karagiozoglou-Lampoudi T, et al (62)	Prospective cohort study of 82 pregnant women. A consumption frequency questionnaire was completed and their adherence to the Mediterranean diet was attached.	Women with low adherence to the Mediterranean diet were more likely to have higher rates of complications such as preeclampsia and gestational diabetes. He hypothesizes that it may help prevent it, but it is not obvious.
Minhas A, Hong X, Wang X, Mueller NT. (63)	Cohort trial conducted in Boston on 8507 women of whom 849 developed preeclampsia. Frequency of consumption questionnaires were carried out and different notes on clinical information were taken.	The conclusions are that the Mediterranean style is associated with a lower risk of preeclampsia, but hypertension and obesity are not associated with preeclampsia.
Kibret KT, Chojenta C, Gresham E, et al (64)	It is a systematic review and meta-analysis. A search was conducted in seven databases. The selection of articles was made by 2 reviewers.	Significantly fewer preeclampsia complications were associated with a healthy dietary pattern diet.
Traore SS, Bo Y, Amoah AN, et al (82)	Meta-analysis of observational studies. Literature was searched in Pubmed, Cochrane Library and Web of Science. The choice was made by 2 authors, selecting a total of 12 articles out of 25 observed studies	A healthy dietary pattern (Mediterranean diet) may reduce the risk of preeclampsia, but it would be useful to observe the period of administration as they mention the lack of changes during the 1st and 2nd trimester.

Reijnders IF, Mulders AGMGJ, van der Windt M, et al (83)	Systematic review with a search in Pubmed, Cochrane,Web of Science and Google Scholar on lifestyle, tobacco, alcohol, caffeine, nutrition etc.).	An intake following a Mediterranean dietary pattern during the first trimester improves complications during the second and third trimester of pregnancy. More research is needed.
Marshall NE, Abrams B, Barbour LA, et al (84)	Expert review	They focus on the importance of a proper Mediterranean diet before pregnancy to avoid later complications.
Carla Assaf Balut,Alfonso Luis Calle Pascual (86)	Systematic review of several studies on pregnancy complications.	Diverse results on preeclampsia. The articles that were studied in this review gave much importance to the pre-pregnancy period, numerous review articles support the positive effect of the Mediterranean diet especially olive oil and nuts.

Table with the articles that positively relate the Mediterranean diet with preeclampsia. Own elaboration. (58-64, 82-84, 86)

Studies have been found that support the benefit of this diet with preeclampsia such as those included in Table 8, but without specifying what may be the key factor causing this (83). What can be observed, after studying the articles, is a general inability to explain the reasons for these benefits, even though in most cases their effectiveness is demonstrated with data. Therefore, the role, for example, of fats and fruits and vegetables (typical foods of this diet), their characteristics may be beneficial for this, as well as the role of alcohol and calcium and their possible relationship with preeclampsia, were mentioned in the state of the question.

Meta-analysis of maternal patterns and preeclampsia (82) found a relationship between these concepts with an odd ratio (concept used to determine the relationship of 2 variables in statistics) of 0.009, which is a significant result; or the meta-analysis of Kibret KT et al (63), which found a reduction in preeclampsia with higher consumption of fruits and legumes and an odd ratio of 0.0178, and with even lower values in the reduction of other complications such as gestational diabetes. Not only meta-analyses or reviews, but also clinical trials with a fairly large sample size (58), which are the ideal studies in the health area, obtained an odd ratio value of 0.03 in this case. It is also worth mentioning the existence of articles such as the expert review (84), which concludes that a diet guided by a Mediterranean pattern has a lower probability of suffering preeclampsia (based on 4 articles); or others such as the prospective study by Parlapani E, Agakidis, C, Karagiozoglou-Lampoudi T, et al (82) pointing to the Mediterranean diet as an independent and significant predictor of preeclampsia.

Even so, studies such as that of Parlapani E et al (83) did not find significance in high-risk individuals such as hypertensive and obese persons, conclusions in which Minhas A et al (63) also agree; while others, such as the research project of Balut (60), found improvement with diet, precisely in obese persons (P=0.0134).

Of vital importance, and still under investigation, is the timing or time period in which diet is effective in the prevention of preeclampsia. There are studies that endorse the periconceptional moment as the key to avoid it, without seeing changes in the diet during pregnancy. As mentioned in the systematic review by Reijnders IF et al (83), future

research should focus on the periconceptional period, thus observing its subsequent impact on pregnancy. Adequate nutrition in the 2nd and 3rd trimester reduces complications, associating less resistance of the uterine and umbilical arteries; and works such as an expert review by Marshall NE et al (84) advocate a healthy dietary pattern consumption before pregnancy, in addition to monitoring and screening methods before pregnancy for the prevention of preeclampsia.These are not the only studies that endorse the timing of study as a key factor. In the gestational period, it appears that low adherence to a DietMed (Mediterranean diet) pattern is not associated with pregnancy-induced hypertension or preeclampsia (85).

Other studies, such as the review by Minhas A et al (63), do not relate obesity to preeclampsia, a conclusion that is surprising, since reviews such as that of Assaf Balut (60), conducted in obese people, had significant rates of developing preeclampsia. After all, a diet is mainly related to health, but this is also reflected in the physical condition of the person at a visual level. These variations are curious since more than one study supports an adequate state of health, precisely before pregnancy, to achieve a lower probability of complications (82,84).

Table 9

Authors	Type of study	Effectiveness of the Mediterranean diet
Durán A, De la Torre Ng, Assaf Balut C et al (85)	Prospective single-group intervention study. A total of 1066 were initially recruited, leaving 932 women for the study. Blood tests, anthropometric measurements and nutritional intervention were taken.	In the gestational period, it appears that low adherence to a DietMed pattern is not associated with pregnancy-induced hypertension or preeclampsia.
Tomaino L, Reyes Suárez D, Reyes Domínguez et al (87)	A retrospective cross-sectional study was conducted on a sample of 218 women and their newborns at the Hospital Insular Materno Infantil de Gran Canaria (HIMIGC), Spain. The anthropometric characteristics of the mother were evaluated and adherence to the Mediterranean diet was based on the PREDIMED survey.	No significant results were seen with adherence to the Mediterranean diet in gestational hypertension and preeclampsia.
Rogozińska E, Marlin N, Jackson L, et al (88)	Bibliographic review with searches in MEDLINE, EMBASE and COCHRANE. They focused on the evaluation of weight gain with adverse outcomes through appropriate dietary intervention.	The effect of diet and lifestyle during pregnancy did not show conclusive results in avoiding gestational complications.
H. Al Wattar B, Dodds J, Placzek A, et al (89)	Multicenter randomized trial in 5 maternity units in different hospitals in England. A control group and a Mediterranean diet intervention group were assigned to 593 women.	No changes were seen in the rates of complications such as preeclampsia, small fetus or admission to the neonatal care unit.

Table on articles that do not positively relate the Mediterranean diet to preeclampsia. Own elaboration. (85,87 ,88 ,89)

There are 4 studies that support the lack of efficacy of the Mediterranean diet (1 cross-sectional study, 1 clinical trial, 1 systematic review and 1 prospective study). Findings, such as that of Rogozińska EE et al (88), relate adequate diet and active lifestyle to gestational weight, but not to complications such as hypertension, preeclampsia, or diabetes. On the other hand, Durán A et al (85), in their prospective study did not see

differences in hypertension or preeclampsia in diets with low adherence to the Mediterranean diet (odd ratio of 0.8), in contrast to gestational diabetes in which they see significance, with olive oil fats as a possible trigger. The others do not put much emphasis on preeclampsia as they cover many outcomes in the study, but in the overall results a nonsignificant difference can be observed with the Mediterranean diet (87, 89).

In the multicenter trial conducted in England (89), not only were no differences seen with preeclampsia, but no differences were seen with any other complication, except for gestational weight (odd ratio = 0.54) and gestational diabetes (odd ratio = 0.67), with no significant results. Negative results were also found in the case of the cross-sectional study carried out at the Hospital in the Canary Islands (87). Adherence to the Mediterranean diet with the risk of preeclampsia was not significant with a value of (p=0.2); even higher values were found in the review by Rogozinska et al (88) with values of (p=0.96-1.16).

More than the type of diet, much importance is given to specific micronutrients to prevent preeclampsia. After an in-depth study, it appears that folic acid and vitamin D are very important in controlling this disease. Folic acid, a major constituent of fruits and vegetables, plays a very important role in preeclamptic cells (29). Their role seems to go further and they find improvements in the prevention of urinary tract infections, fetal maldevelopment and prevention of some allergies (66-71).

With vitamin D and calcium there is sufficient certainty, through numerous studies, of their benefits in pregnant women to prevent bone weakness, fetal alterations and hypertensive disorders, among others (68, 75-77). What would remain to be resolved would be whether supplementation is necessary, as stated by the WHO (77), or whether it is only necessary in the case of not ingesting adequate amounts daily for different reasons, and thus what daily amounts would be necessary (78) and whether they should be increased or not (30).

We must not forget to mention the role of EVOO (Extra Virgin Olive Oil), a differentiating attribute of the Mediterranean diet. It seems that omega-3 fatty acid has great benefits in preeclampsia, but more research is still needed to know the adequate doses and studies with more precise methodologies (58, 72-74). Lastly, and no less characteristic of the Mediterranean diet, alcohol should be considered. Its consumption can cause complications for the woman and the baby. In the recommended daily amounts there would be no major inconvenience, but if consumption could be avoided it would be best (79-81).

Studies such as that of Mengying Li et al (58) or the prospective study by Soltani et al (61) use a 24-hour recall, which may lead to an inadequate relationship between what is consumed and what is captured in these recalls. The MEDAS protocol, used to assess adherence to the Mediterranean diet, as mentioned in the prospective study carried out in the Hospital Canario (87), does not provide exhaustive information on the quality of the diet and the calories it provides.

The existence of clinical trials has been somewhat scarce, only 2 trials (58.89) with some scientific evidence. Trials are very scarce in this area and have limitations such as small sample numbers or a methodology that could be improved. It would be necessary to add the commitment of the participants, as is the case of the randomized clinical trial by Traoré SS, Bo Y, Amoah AN et al (88), in which they mention that they only knew the dietary intake of about 40% of the study population. In general, both clinical trials

and cohort or intervention studies have a considerable sample size, giving rise to greater evidence and objectivity when assessing the results (58, 61-63, 85, 89).

Another limitation that can be added in the discussion of these studies is the different pathological situation of the persons studied. The project carried out by Balut (60) focused on obese people; the study by Soltani S, Aminianfar A, Hajianfar H et al (61) excluding women smokers; the multicenter clinical trial carried out in 5 maternal units in England (89) on women with cardiovascular conditions and, in addition, of different races and other pathologies such as obesity; or the prospective study by Durán de La Torre (85) with diabetic people. These differences in the way research is conducted can be a key factor in relating the different results that are produced.

The type of diet and its characteristics are a subject of discussion in the literature. In fact, some of the researches speak of a healthy dietary pattern (62, 64, 82), mentioning the properties of the diet very similar to the Mediterranean diet, but without dubbing it with the name "Mediterranean diet". Neither are the same amounts and portions of food used, so it is difficult to objectively compare studies, for example, using a diet heavily focused on EVOO and nut consumption (89). While others, directly (60, 88), focus on the concept of diet, in general, without specifying.

To conclude with the limitations, the studies presented may not have the fame or prestige that other journals or databases may have. For example, the study by Assaf Balut (60) conducted by the Universidad Complutense de Madrid, or the randomized clinical trial by Mengying et al (58) conducted by a small group of people who did not have a transcendental background in this field, which does not mean that their results should be belittled or treated as invalid. Some of the articles found belong to final degree works, university works or, for example, works from different hospitals, as in the case of the Hospital del Sur de Guayas (Peru) (15).

Summarizing, of all the articles that directly relate the concepts of preeclampsia and Mediterranean diet, 4 studies are found that do not support or do not support these concepts and would be (85, 87-89), while the studies that support their benefit, in total 11, would be (58-64, 82-84, 86).

Conclusions

To conclude, emphasizing the studies that relate preeclampsia to the Mediterranean diet, there is a greater number of articles that directly support this relationship. In general terms, the Mediterranean diet can be recommended to avoid complications in pregnancy, such as preeclampsia. It is true, as has been mentioned in the discussion, that there is a lack of articles specifying the mechanisms that produce these benefits in the prevention of preeclampsia, as well as the lack of certainty of its benefit in healthy individuals only, or also in individuals with pathologies.

Processed foods, excessive fats, refined sugars and other unhealthy products are not suitable for this stage of life or any other, due to their pro-inflammatory effects, as well as metabolic and cardiovascular disorders. In this study, an attempt has been made to clarify the objectives that were proposed at the beginning. All the general aspects related to preeclampsia have been discussed, both complications and pathophysiological mechanisms, as well as the role of nutrition in the disease. As with the Mediterranean diet, its characteristics, its cardiovascular approach and its relationship with preeclampsia have been studied. Complications from preeclampsia can be very dangerous for maternal and fetal health, explaining the optimal nutrients for the prevention of preeclampsia.

After a thorough search, we can conclude the importance of certain macro and micronutrients, which can also be provided by diets other than the Mediterranean diet. It is easier to focus on a micro or macronutrient than on a diet in general, because it is much more difficult to draw conclusions as to what has been the triggering factor due to the diversity of variables to be taken into account if we consider a diet in a broad sense. Consequently, we do not claim that this is the ideal and only dietary pattern to be used in pregnancy, since studies have shown that using other types of diets there is also an improvement.

It should be emphasized, as mentioned in the status of the question, that preeclampsia and its development is multifactorial and that an adequate diet can interfere in one way or another depending on the race, the number of pregnancies of the pregnant woman and other characteristics. Finding good studies, as well as conducting them, is a very complicated task due to the many variables to be taken into account. An adequate state of health will help most of the time to minimize the risk of all kinds of diseases, in particular, food and, in this case, the Mediterranean diet, can abolish cardiovascular and metabolic complications.

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