

**MULTIVITAMIN USE AND ITS INFLUENCE ON THE IMMUNE RESPONSE IN
HEALTHY ADULTS: AN ANALYSIS BETWEEN THERAPEUTIC EFFECT AND
PLACEBO RESPONSE**

**USO DE POLIVITAMÍNICOS E SUA INFLUÊNCIA NA RESPOSTA IMUNE EM
ADULTOS SAUDÁVEIS: ANÁLISE ENTRE EFEITO TERAPÊUTICO E
RESPOSTA PLACEBO**

**USO DE MULTIVITAMÍNICOS Y SU INFLUENCIA EN LA RESPUESTA
INMUNITARIA EN ADULTOS SANOS: ANÁLISIS ENTRE EL EFECTO
TERAPÉUTICO Y LA RESPUESTA PLACEBO**

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**Valéria Goulart Viana¹, Fernanda Teixeira Brasil², Janilson Barros de Sá³, Samuel de
Miranda Duque⁴, Gabriella Salomão de Paula⁵, Flávia Alcoforado Nogueira⁶, Lucas
Muniz Baudel⁷, Daniel Gomes Fialho⁸, Vanessa Neglisoli⁹, Isabela Veiga Barbosa¹⁰,
José Henrique Gorgone Zampieri¹¹, Nelson Freire Silva Filho¹², Rúbia Sousa de
Araújo¹³, Midiã Quaresma Quinteiros¹⁴, Guilherme Augusto de Andrade
Paschoalotto¹⁵, Anderson Soeiro Teixeira¹⁶, Victoria Turra Navarro¹⁷, Thelles Lucas
Valério Alves de Souza¹⁸, Gabriel Mendes Horevicht Laporte Mascarenhas¹⁹, Daniel
Alexander Milholo Robles²⁰, Mateus Carlos Braga²¹, Salohá Brazão Rodrigues²²,
Marina Falcão Gurgel Neves²³**

¹ Doctor. Faculdade de Medicina de Itajubá. E-mail: dravaleriagoulart@yahoo.com.br

² Doctor. Universidade Nilton Lins. E-mail: fernandateixeira96@outlook.com

³ Doctor. Universidade de Pernambuco. E-mail: janbupe@gmail.com

⁴ Doctor. Instituto Universitario de Ciencias de la Salud – Fundación Héctor Alejandro Barceló.
E-mail: samuca190342@gmail.com

⁵ Doctor. Pontifícia Universidade Católica de Goiás. E-mail: gabriella_salomao_@hotmail.com

⁶ Postgraduate in ICU. Associação de Medicina Intensiva Brasileira (AMIB). E-mail:
flaviaalnogueira@hotmail.com

⁷ Doctor. Faculdade de Medicina da Universidade de São Paulo (FMUSP). E-mail: baudellucas@gmail.com

⁸ Specialist in Urgent and Emergency Medicine and Intensive Care. Universidade de Mogi das Cruzes.
E-mail: danfialho@hotmail.com

⁹ Specialist in People Management and Business Management. Escola Paulista de Medicina (UNIFESP).
E-mail: vanessaneglisoli@gmail.com

¹⁰ Doctor. Centro Universitário São Camilo. E-mail: isabelaveigab@hotmail.com

¹¹ General Practitioner. Universidade Federal de Pelotas. E-mail: jhgzampieri@gmail.com

¹² Doctor. Universidade Federal de Goiás (UFG). E-mail: nelsonfreire@egresso.ufg.br

¹³ Doctor. mCentro Universitário Barão de Mauá. E-mail: drarubiaraujo@gmail.com

¹⁴ Doctor. Centro Universitário Metropolitano da Amazônia (UNIFAMAZ). E-mail: midy.quaresma@gmail.com

¹⁵ Medical Student. Universidade São Judas, Campus Cubatão. E-mail: guilhermepaschoalotto@gmail.com

¹⁶ Doctor. Universidade Aquino de Bolívia (UDABOL). E-mail: andersonstexx85@gmail.com

¹⁷ Doctor. Centro Universitário Barão de Mauá. E-mail: victoriaturra@outlook.com

¹⁸ Doctor. Faculdade da Saúde e Ecologia Humana (FASEH). E-mail: thellesproducoes@hotmail.com.br

¹⁹ Doctor. Universidade Brasil. E-mail: gabrielhorevicht@hotmail.com

²⁰ Doctor. Centro Universitário FAMESC (UNIFAMESC). E-mail: danielalexanderrobles@hotmail.com

²¹ Medical Student. Universidade Professor Edson Antônio Velano (UNIFENAS), Campus BH
E-mail: mateuscarlos.cdm@gmail.com

²² Doctor. Universidade Nove de Julho (UNINOVE). E-mail: salohab@hotmail.com

²³ Doctor. Faculdade de Medicina Nova Esperança (FAMENE). E-mail: mamafalcao1@gmail.com

ABSTRACT

The use of multivitamin supplements is widespread among healthy adults and supported by the belief that daily intake enhances immune function and prevents infections. However, current scientific evidence indicates that, in the absence of nutritional deficiencies, the therapeutic effects are limited and often confounded by subjective responses associated with the placebo effect. This integrative literature review, conducted through PubMed, Scopus, Web of Science, and SciELO databases from 2015 to 2025, analyzed clinical trials, systematic reviews, and meta-analyses addressing the relationship between multivitamin supplementation and immune response in healthy adults. Findings show that vitamins C, D, A, E, zinc, and selenium are essential for immune integrity, yet supplementation in well-nourished individuals yields no significant physiological improvement. Reported benefits are largely attributed to psychobiological mechanisms of the placebo effect, mediated by positive expectations and activation of neuroendocrine pathways of well-being. It is concluded that multivitamin use should be clinically indicated only in cases of confirmed deficiency, avoiding unnecessary medicalization of healthy behaviors. Future studies should employ rigorous designs to differentiate biological effects from placebo responses and support evidence-based prescription practices.

Keywords: Multivitamins. Immunity. Healthy Adults. Placebo Effect. Supplementation.

RESUMO

O uso de polivitamínicos é amplamente difundido entre adultos saudáveis, sustentado pela crença de que a suplementação diária favorece o fortalecimento imunológico e previne infecções. No entanto, as evidências científicas atuais demonstram que, na ausência de deficiências nutricionais, os efeitos terapêuticos são limitados e frequentemente confundidos com respostas subjetivas associadas ao efeito placebo. Esta revisão integrativa da literatura, conduzida nas bases PubMed, Scopus, Web of Science e SciELO entre 2015 e 2025, analisou ensaios clínicos, revisões sistemáticas e meta-análises sobre a relação entre suplementação multivitamínica e resposta imune em adultos saudáveis. Os resultados indicaram que vitaminas C, D, A, E, zinco e selênio são essenciais à função imunológica, porém a suplementação em indivíduos eutróficos não produz ganhos fisiológicos significativos. A percepção de melhora relatada está associada a mecanismos psicobiológicos do efeito placebo, mediados por expectativas positivas e ativação de circuitos neuroendócrinos de bem-estar. Conclui-se que o uso de polivitamínicos deve ser indicado apenas mediante comprovação de deficiência, evitando-se a medicalização de comportamentos saudáveis. Futuras pesquisas devem empregar delineamentos metodológicos rigorosos para distinguir efeitos biológicos de respostas placebo e orientar prescrições baseadas em evidências.

Palavras-chave: Polivitamínicos. Imunidade. Adultos Saudáveis. Efeito Placebo. Suplementação.

RESUMEN

El uso de multivitamínicos está muy extendido entre adultos sanos, respaldado por la creencia de que la suplementación diaria promueve el fortalecimiento inmunitario y previene infecciones. Sin embargo, la evidencia científica actual muestra que, en ausencia de deficiencias nutricionales, los efectos terapéuticos son limitados y a menudo se confunden con respuestas subjetivas asociadas al efecto placebo. Esta revisión bibliográfica integradora, realizada en PubMed, Scopus, Web of Science y SciELO entre 2015 y 2025,

analizó ensayos clínicos, revisiones sistemáticas y metaanálisis sobre la relación entre la suplementación multivitamínica y la respuesta inmunitaria en adultos sanos. Los resultados indicaron que las vitaminas C, D, A, E, zinc y selenio son esenciales para la función inmunitaria, pero la suplementación en individuos eutróficos no produce mejoras fisiológicas significativas. La percepción de mejoría reportada se asocia con los mecanismos psicobiológicos del efecto placebo, mediados por expectativas positivas y la activación de los circuitos neuroendocrinos del bienestar. Se concluye que el uso de multivitamínicos solo debe indicarse cuando se compruebe una deficiencia, evitando la medicalización de hábitos saludables. Las investigaciones futuras deberían emplear diseños metodológicos rigurosos para distinguir los efectos biológicos de las respuestas placebo y orientar las prescripciones basadas en la evidencia.

Palabras clave: Multivitamínicos. Inmunidad. Adultos Sanos. Efecto Placebo. Suplementación.

1 INTRODUCTION

The use of multivitamins has become a widespread practice among healthy adults, supported by the belief that daily micronutrient supplementation favors immune strengthening and contributes to the prevention of infections. This popular perception, reinforced by marketing strategies and generalized recommendations, has consolidated a consumer culture based more on subjective expectations than on consistent clinical evidence. This phenomenon reflects the contemporary trend towards the medicalization of daily life, in which the concept of health is often associated with the constant consumption of supplements, even in the absence of proven nutritional deficiencies.

Understanding the physiological underpinnings that underpin this practice requires analysis of the immunonutritional mechanisms involved. From a biological standpoint, immunonutrition recognizes that vitamins and minerals play essential roles in maintaining immune homeostasis. Micronutrients such as vitamins A, C, D, and E, as well as zinc and selenium, participate in antioxidant and anti-inflammatory mechanisms, contributing to the integrity of epithelial barriers and to the modulation of cytokine production (Gombart; Pierre; Maggini, 2020). However, although the function of these nutrients is undeniable, recent studies indicate that supplementation in metabolically balanced individuals does not necessarily translate into additional immune benefits, especially when there are no diagnosed nutritional deficiencies (Calder, 2020; Jolliffe et al., 2021).

The scientific literature has shown a growing interest in understanding the interactions between nutritional status and the immune system, especially after the COVID-19 pandemic, which boosted the consumption of supplements, notably vitamins C and D (Carr; Maggini, 2017; Calder, 2020). Despite this, evidence on its immunomodulatory efficacy in healthy adults remains limited, suggesting that the reported effects may be more related to subjective perception of well-being than to measurable physiological modifications.

In this context, the phenomenon of the placebo effect acquires scientific relevance. This effect consists of a psychobiological response mediated by positive expectations regarding the effectiveness of an intervention, even in the absence of an active ingredient (Benedetti, 2014; Kaptchuk et al., 2020). Studies in neuroscience indicate that beliefs and expectations can activate brain reward circuits and release neurotransmitters such as dopamine and endorphins, modulating feelings of energy, disposition, and well-being (Pollo; Benedetti, 2009). Thus, it becomes methodologically challenging to distinguish the actual

physiological effects of supplementation from those resulting from cognitive and emotional mechanisms.

In view of this controversy, it is essential to analyze, in the light of scientific evidence, whether the use of multivitamins in healthy adults exerts a measurable therapeutic effect on the immune response or whether the perceived benefits are predominantly related to placebo responses. In this sense, the present study aims to critically evaluate the influence of multivitamins on the immunity of healthy adults, through an integrative literature review, discussing the available evidence between therapeutic and psychobiological effects, with emphasis on the clinical and ethical implications of the indiscriminate use of supplements.

2 METHODOLOGY

The present study is an **integrative literature review**, elaborated with the objective of gathering, analyzing and synthesizing the available scientific evidence on the use of multivitamins and their influence on the immune response in healthy adults, with emphasis on the distinction between real therapeutic effects and placebo responses. The integrative review was chosen because it allows the inclusion of different methodological designs, clinical trials, observational studies, systematic reviews, and meta-analyses, which allows for a more comprehensive and critical understanding of the phenomenon investigated (Whittemore; Knafl, 2005).

The design followed the steps recommended by Mendes, Silveira and Galvão (2008): (1) identification of the theme and formulation of the guiding question; (2) establishment of inclusion and exclusion criteria; (3) definition of search strategies and selection of data sources; (4) extraction, categorization and analysis of results; and (5) synthesis and presentation of the findings. The research question that guided the study was: *"Does the use of multivitamins exert a measurable influence on the immune response of healthy adults, or do the observed effects stem predominantly from placebo responses?"*

The search was conducted in the **PubMed/MEDLINE, Scopus, Web of Science and SciELO** databases, recognized for the indexing of high-quality scientific publications in the areas of health, biomedicine and nutrition. To ensure methodological traceability and content updating, articles published between **January 2015 and September 2025** were included. The research was carried out independently by two reviewers, in order to minimize selection biases.

The **DeCS/MeSH descriptors** used were combined in Portuguese and English: "multivitamins", "immune system", "placebo effect", "healthy adults", "micronutrients", and "immunomodulation"). To formulate the search strategies, Boolean operators ("AND", "OR") were used in a combined way, resulting in expressions such as: ("*multivitamins*" AND "*immune system*" AND "*healthy adults*") and ("*micronutrients*" AND "*placebo effect*").

Original studies, systematic reviews, and meta-analyses that directly addressed the relationship between multivitamin supplementation and immune response in healthy adults, with or without a placebo control group, were included. Publications in Portuguese, English, and Spanish were accepted, with full text available. Studies **carried out with populations of frail elderly, pregnant women, breastfeeding women, children, professional athletes, patients with chronic diseases, immunosuppressed or users of pharmacological therapies that could interfere with the immune response were excluded, as well as case reports and editorials.**

During the initial screening, titles and abstracts were evaluated for thematic relevance, and duplicate articles or those that did not meet the eligibility criteria were eliminated. Subsequently, the full texts of the selected studies were read in full, and data were extracted regarding the year of publication, country of origin, type of study, sample, mean age of the participants, composition of the supplement, duration of the intervention, immunological outcomes evaluated, and main results. The extracted data were organized in an electronic spreadsheet and analyzed in a descriptive and comparative manner, with categorization in two axes: **proven therapeutic effects** and **responses attributed to the placebo effect.**

The analysis of the results followed an interpretative qualitative approach, seeking to identify convergences and divergences between the findings and to evaluate the methodological robustness of the included studies. The level of evidence was weighted according to the type of research design, prioritizing randomized controlled trials and high-quality systematic reviews, as recommended by the *Oxford Centre for Evidence-Based Medicine* (OCEBM, 2020). The critical evaluation of the articles also considered the risk of bias and the clarity in the description of the randomization, blinding, and placebo control methods, when applicable, following parameters from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2022).

At the end of the process, **27 studies** that met the established criteria were included, **including 14 randomized clinical trials, 6 systematic reviews, and 7 observational studies.** These studies formed the analytical basis of the integrative review and supported

the discussion about the influence of multivitamins on the immune response in healthy adults, as well as the role of placebo in the subjective perception of improvement. The methodological process was conducted in accordance with the ethical principles of transparency and scientific integrity, respecting the international standards of research in human health and nutrition.

3 RESULT AND DISCUSSION

3.1 IMMUNOLOGICAL FUNDAMENTALS AND THE ROLE OF MICRONUTRIENTS

The immune system relies on a complex balance between nutrients, cellular metabolism, and physiological integrity to maintain its protective function. Vitamins and minerals participate directly in the modulation of innate and adaptive immune responses, acting as enzymatic cofactors, antioxidants, and regulators of gene expression of inflammatory mediators. Among the most studied micronutrients, vitamins C, D, A, and E stand out, as well as minerals such as zinc, iron, and selenium, whose deficiency, even in subclinical degrees, is associated with greater susceptibility to infections and exacerbated inflammatory responses (Gombart; Pierre; Maggini, 2020).

Vitamin C (ascorbic acid) plays a fundamental role in antioxidant protection and in the regeneration of other antioxidant molecules, in addition to participating in the proliferation of T and B lymphocytes and phagocytosis (Carr; Maggini, 2017). Its deficiency is related to increased oxidative stress and decreased resistance to respiratory infections. However, systematic reviews indicate that, in individuals without overt nutritional deficiency, vitamin C supplementation does not have a significant impact on the incidence of infectious diseases, although it may slightly reduce the duration and severity of symptoms in some cases (Hemilä; Chalker, 2021).

Vitamin D, in turn, acts on innate and adaptive immunity by binding its active metabolite, 1,25-dihydroxyvitamin D, to the nuclear receptor VDR (Vitamin D Receptor), present in immune cells such as monocytes, macrophages, and T lymphocytes (Calder et al., 2020). This interaction regulates the transcription of genes responsible for the production of antimicrobial peptides, such as cathelicidins and defensins, and modulates the release of pro- and anti-inflammatory cytokines (Aranow, 2011). Observational studies point to an association between adequate serum vitamin D levels and a lower incidence of respiratory infections, although randomized controlled trials show heterogeneous results, especially when applied to populations without baseline deficiency (Jolliffe et al., 2021).

Another essential micronutrient is zinc, whose action is linked to maintaining mucosal integrity, the development of T lymphocytes, and regulating the activity of antioxidant enzymes such as superoxide dismutase (Wessels et al., 2021). Zinc deficiency is recognized to compromise cellular and humoral immunity, increasing the risk of bacterial and viral infections. However, supplementation in eutrophic individuals has not shown consistent results in improving immunological biomarkers, indicating that its effect is more relevant in contexts of deficiency or immunocompromise.

Selenium also has an important immunomodulatory role, integrating selenoproteins with antioxidant and anti-inflammatory activity, such as glutathione peroxidase and thioredoxin reductase. Insufficient selenium levels impair lymphocyte proliferation and antibody production, while adequate selenium replacement can optimize vaccine response and reduce virulence. However, recent reviews highlight that supplementation above physiological needs does not generate additional benefits in the immunocompetence of healthy adults (Calder, 2020).

Taken together, this evidence indicates that micronutrients play indispensable physiological roles in the immune response, but the impact of multivitamin supplementation strongly depends on the individual's previous nutritional status and associated environmental conditions, such as diet, sun exposure, and level of physical activity. When there is a proven deficiency, vitamin-mineral replacement corrects immune dysfunctions; However, in healthy adults with adequate levels of micronutrients, the additional effects on immune function tend to be minimal or nonexistent, which supports the need for a critical evaluation of the real therapeutic benefit of routine supplementation.

3.2 CLINICAL EVIDENCE OF MULTIVITAMIN USE IN HEALTHY ADULTS

The clinical evaluation of the effects of multivitamins on immunity in healthy adults has been the subject of multiple controlled studies, which present heterogeneous and sometimes contradictory results. Although vitamin-mineral supplementation is widely used as a preventive strategy, much of the evidence indicates that its measurable effects on the immune response are limited when there is no underlying nutritional deficiency (Marcos; Nova; Montero, 2018). In well-designed clinical trials, it has been observed that regular consumption of multivitamin supplements can raise serum concentrations of certain micronutrients, such as vitamin C, zinc, and folate, but such increases do not always translate into functional benefits on immunocompetence (Shah et al., 2020).

One of the most cited studies, published in the journal *Nutrients*, evaluated 42 middle-aged and elderly adults who received a daily multivitamin-mineral supplement for 12 weeks. Despite the significant increase in plasma concentrations of vitamins C and D and zinc, no statistically significant changes in phagocytic activity, production of reactive oxygen species or inflammatory response were observed after in vitro immune stimulation. Still, the supplemented group reported lower duration and severity of common cold episodes, which suggests the presence of subjective components or placebo in the perception of benefit (Shah et al., 2020).

Similar results were reported by Ames et al. (2021) in a double-blind trial with 150 healthy adults, in which daily supplementation with multivitamins did not reduce the incidence of respiratory infections, but produced a slight improvement in the feeling of general well-being and vitality scores. In contrast, studies conducted in populations with marginal deficiencies, such as workers exposed to intense physical stress or inadequate diets, have shown a moderate positive effect on antibody production and the reduction of inflammatory markers, reinforcing that clinical benefit strongly depends on baseline nutritional status (Hamer; Witte, 2021).

In a meta-analysis published in the *Cochrane Database of Systematic Reviews*, Huang et al. (2022) evaluated 16 clinical trials involving more than 5,000 adult participants and concluded that there is no consistent evidence that routine use of multivitamins reduces the incidence of infections or improves laboratory parameters of immunity in healthy individuals. The review also highlighted the high degree of heterogeneity between studies, resulting from the different formulations of supplements, doses, treatment durations, and lack of standardization of the outcomes analyzed.

In addition, a large-scale cross-sectional study conducted by Wang et al. (2024), with 4,489 participants from the United States, looked at the association between the use of vitamin supplements and serum inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and lymphocyte count. After adjusting for confounding factors such as age, gender, body mass index, and smoking, no significant difference was observed between users and non-users, indicating that supplementation in well-nourished populations does not significantly impact immune homeostasis.

These results converge with the narrative review by Maggini, Pierre, and Calder (2018), which emphasizes that multivitamin supplementation is only clinically relevant when there are documented nutritional deficiencies or physiological conditions of increased

metabolic demand, such as infections, aging, and chronic oxidative stress. In healthy adults, gains appear to be more related to maintaining optimal micronutrient levels than inducing a superior immune response.

In summary, the clinical literature demonstrates that, although multivitamins can correct subclinical nutritional deficiencies and reduce the subjective perception of fatigue and vulnerability, there is no robust evidence that they promote significant improvement in immune biomarkers in healthy adults. This finding reinforces the importance of differentiating the **real therapeutic effect** from conditioned responses to the **placebo effect**, since the perception of well-being and the positive expectation in relation to supplementation can exert a measurable psychological influence, without necessarily reflecting objective physiological changes.

3.3 THE ROLE OF THE PLACEBO EFFECT AND PSYCHOBIOLOGICAL ASPECTS OF THERAPEUTIC PERCEPTION

A critical review of the literature shows that, in several studies involving healthy adults, multivitamin supplementation is associated with a perceived improvement in well-being, energy, and resistance to infections, even in the absence of significant laboratory or immunological alterations. This phenomenon has been widely interpreted in the light of the **placebo effect**, defined as the physiological or psychological response triggered by the positive expectation in relation to an intervention, regardless of the pharmacological action of the administered agent (Finniss; Kaptchuk; Benedetti, 2010).

The placebo effect involves complex mechanisms that transcend the psychological dimension and reach the neurobiological field. Studies in neuroscience demonstrate that belief in the efficacy of a treatment activates brain circuits related to reward, motivation, and emotional regulation, involving neurotransmitters such as dopamine, serotonin, and endorphins (Benedetti, 2014). This activation can modulate subtle autonomic, endocrine, and immunological responses, affecting the subjective perception of symptoms, such as fatigue and disposition, without significantly altering objective physiological parameters (Enck; Bingel; Schedlowski, 2013).

In the context of multivitamins, placebo can influence both the cognitive assessment of the effects and the subjective feeling of "strengthened immunity". The cultural and media association between vitamins and health reinforces positive expectations that, when internalized, modulate perceptible psychophysiological responses. The literature suggests

that, when the individual believes he or she is adopting a beneficial practice, there is a reduction in cortisol levels and a transient improvement in markers of well-being, a phenomenon interpreted as a psychobiological conditioned response (Pollo; Benedetti, 2009).

In addition, the ritual of daily consumption, opening the package, ingesting the pill and anticipating a result, contributes to consolidating the subjective therapeutic experience, functioning as a positive behavioral reinforcement (Kaptchuk et al., 2020). These symbolic components, although immaterial, can alter bodily and cognitive perceptions, which explains the discrepancy seen in clinical studies in which participants on placebo report improvements comparable to those of groups receiving active supplements.

In fact, the meta-analysis conducted by Price et al. (2018) demonstrated that up to 35% of participants in clinical trials of nutritional supplements report subjective benefits attributable solely to placebo. This percentage tends to be higher in studies involving self-reported outcomes, such as energy, mood, and vitality, precisely the variables most reported in research on multivitamins. In contrast, studies using objective immune biomarkers (cytokines, CRP, lymphocytes) tend to show no significant differences between placebo and supplement (Huang et al., 2022).

From a biopsychosocial perspective, the placebo effect can therefore be understood as an integral part of the total therapeutic response. This means that the subjective perception of improvement, even if not accompanied by physiological changes, represents a legitimate phenomenon of neuroendocrine and psychological self-control. Thus, the distinction between the "real" and the "imagined" in the immunological response induced by multivitamins becomes more diffuse, requiring a scientific approach that recognizes the role of expectations, beliefs, and emotions in health (Colloca; Miller, 2011).

Thus, when evaluating the use of multivitamins in healthy adults, it is essential to consider that a significant part of the effects attributed to supplementation may derive from the placebo response, mediated by cognitive and affective factors. Valuing this component does not imply denying its clinical importance, on the contrary, it reveals the potential of positive expectations in modulating well-being and therapeutic adherence. However, the need to base the prescription of supplements on objective evidence is reinforced, avoiding the medicalization of healthy behaviors and the unnecessary use of compounds without proof of measurable immunological benefit.

4 CONCLUSION

The integrative analysis of the literature shows that the use of multivitamins in healthy adults, although widely disseminated and socially associated with the idea of immune strengthening, lacks robust empirical evidence to prove measurable physiological benefits on the immune response. Most clinical trials demonstrate elevated serum levels of certain micronutrients, such as vitamins C, D, and zinc, without, however, producing significant changes in immunocompetence markers, such as phagocytic activity, cytokine production, lymphocyte count, or inflammatory profiles.

In eutrophic and metabolically balanced individuals, the reported effects seem to be largely due to the correction of marginal deficiencies and the subjective modulation of well-being, a phenomenon widely associated with the **biologically mediated placebo effect**, in which positive expectations and cultural beliefs concretely influence the perception of health, even in the absence of relevant physiological changes. This distinction between actual therapeutic effect and placebo response is essential for the critical interpretation of the evidence and for responsible clinical practice.

From a physiological standpoint, micronutrients are arguably essential to immune integrity. However, indiscriminate supplementation in healthy populations does not demonstrate a relevant functional advantage and can generate a false sense of protection, reinforcing **preventive medicalization** and diverting attention from practices proven to be effective, such as balanced diet, adequate sleep, stress management, and vaccination. From the perspective of public health, the unsupervised consumption of multivitamins represents an ethical and economic challenge, enhanced by marketing strategies that often exceed the consistency of scientific evidence.

It is concluded that multivitamin supplementation should be indicated based on individualized clinical and laboratory evaluation, and is recommended only in situations in which there is a proven deficiency or specific physiological conditions that increase metabolic demand, such as convalescence, aging, or intense physical exertion. For healthy adults, current evidence does not support the routine use of multivitamins as an immune-boosting strategy, reinforcing the importance of evidence-based prescribing practices.

Future research should adopt more rigorous methodological designs, exploring the interaction between **neuroendocrine, immunological, and psychobiological factors** that modulate the placebo effect, in addition to identifying **predictive biomarkers** capable of differentiating subjective responses from real therapeutic effects. Double-blind clinical trials,

with representative samples, standardization of doses, and measurement of objective immunological outcomes, are essential to definitively elucidate the role of multivitamins in the immunity of healthy adults and to consolidate clinical guidelines and public policies based on solid evidence.

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