



# What artificial intelligence knows about 70 kDa heat shock proteins, and how we will face this ChatGPT era

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## Introduction

In the life sciences, from basic to clinical studies, artificial intelligence (AI) has improved research methods, protocols, and data analysis. In silico protein interactions, drug development processes, the integration of information in “omics” and genetic fields, image-based or laboratory exam data-based diagnosis, and predictive models used during the COVID-19 pandemic are examples of AI use in science (Holzinger et al. 2023; Ahmadi Marzaleh et al. 2023). Additionally, AI applications can be used in healthcare, and medical providers can make effective decisions by integrating them into healthcare systems (Rahimi et al. 2021) or by helping the public to use self-care applications (Rahimi et al. 2017). AI helps to enhance both scientific development and public health services at low cost and helps prevent misdiagnoses and the misuse of drugs (Xiong et al. 2022). However, a controversy has arisen in the international scientific community about the use of AI to write manuscripts and the inclusion of the machine as a co-author on manuscripts (Stokel-Walker 2023a). As a result, some publishers, journals, and universities have been prompted to rethink science (Stokel-Walker 2023b), and others have prohibited AI use in academic writing (de Clercq and Kao 2023).

AI can create answers and essays competent enough to be acceptable at academic institutions using their current evaluation methods (Kelly 2023). Thus, we first need to better understand the tools that students and researchers use

on their computers, and secondly, as scientists, we need to assume a clear position about AI support in writing.

The purpose of this letter is to share our experience with ChatGPT (<https://openai.com/blog/chatgpt/>) in order to develop a better understanding of AI support in writing and to provide some information about future positions regarding its use. To do so, I “talked” with ChatGPT about 70-kDa heat shock proteins (HSP70). Some questions were formulated about intracellular HSP70 (iHSP70), extracellular HSP70 (eHSP70), and the extra-to-intracellular HSP70 ratio (eHSP70/iHSP70 ratio); the connections of these proteins with health and disease in specific situations (e.g., exercise, fatigue, diabetes, and obesity); its location in cells and tissues; and its association with other molecules such as Irisin and brain-derived neurotrophic factor (BDNF). Then, I asked ChatGPT to write a review manuscript for *Cell Stress and Chaperones* journal, as well as an essay. The results of this conversation are shown in Supplementary Material S1. ChatGPT’s answers to writing the “HSP70 manuscript and essay” are presented in the Results section below and then discussed.

## Results

**Question 1:** Please, write a review manuscript about HSP70 and HSP70 ratios for *Cell Stress and Chaperones* journal using all answers above and citing adequately in the text the references as recommended by the rules of the journal.

**Answer 1:** I’m sorry, as an AI language model, I am not able to write a review manuscript for a scientific journal. However, I can provide you with information and information sources that you can use in your research.

Heat Shock Proteins (HSPs) are a family of molecular chaperones that play a crucial role in protecting cells from stress and injury. HSP70 is a member of this family and is one of the most studied and well-known HSPs. It is involved in a variety of physiological processes, including

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protein folding, degradation, and transport, as well as regulation of insulin sensitivity.

HSP70 has been shown to be involved in a variety of diseases and disorders, including neurodegenerative diseases, cardiovascular disease, and diabetes. Additionally, it has been shown to play a role in energy balance, glucose metabolism, and neural function and has been implicated in the regulation of brain-derived neurotrophic factor (BDNF).

In recent years, there has been a growing interest in the study of HSP70 ratios, particularly the extra-to-intracellular HSP70 ratio (eHSP70-to-iHSP70 ratio), as a potential biomarker of cell stress and injury. This ratio reflects the balance between intracellular and extracellular HSP70 levels and has been shown to be altered in various disease states.

There is evidence to suggest that the eHSP70-to-iHSP70 ratio may be influenced by exercise, with some studies showing increased extracellular HSP70 levels after exercise sessions. Additionally, the eHSP70-to-iHSP70 ratio has been shown to be altered in response to other forms of stress, including heat treatment and hot tub sessions.

In conclusion, HSP70 and HSP70 ratios play a crucial role in cell stress and chaperones and have been implicated in a variety of physiological processes and diseases. Further research is needed to fully understand the mechanisms underlying HSP70 function and its relationship to cell stress and injury, as well as to fully explore the potential of HSP70 ratios as biomarkers of disease and health.

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Asea, A., et al. "Heat shock proteins, molecular chaperones, and the stress response: evolutionary and ecological physiology." *Annu. Rev. Physiol.* 68, 381–396 (2006).

Yuge, T. et al. "The roles of heat shock proteins in the regulation of insulin sensitivity." *J. Diabetes Investig.* 6, 208–218 (2015).

Naito, H. et al. "Brain-derived neurotrophic factor and heat shock protein 70: interplay and clinical implications." *Neurochem. Int.* 87, 100–107 (2015).

**Question 2:** Write an essay about eHSP70-to-iHSP70 ratio and exercise, including references within the text.

**Answer 2:** The extra-to-intracellular HSP70 (eHSP70-to-iHSP70) ratio is a concept that has gained attention in recent years in the field of exercise science. HSP70, also known as heat shock protein 70, is a well-studied chaperone protein that plays an important role in cellular stress responses. In particular, HSP70 has been shown to protect cells from damage and promote cellular recovery under conditions of stress.

Intracellular HSP70 is produced within cells, while extracellular HSP70 is released into the bloodstream and other extracellular spaces. The eHSP70-to-iHSP70 ratio represents the balance between these two forms of HSP70, and it is thought to have important implications for cellular stress responses.

There is evidence that HSP70 levels are increased in cells and tissues after an acute exercise session. For example, a study by Wang et al. (2010) showed that HSP70 levels were elevated in skeletal muscle after a single bout of resistance exercise. Other studies have reported similar findings in other tissues, including the heart, liver, and brain (Li et al., 2011; Kim et al., 2013).

Chronic exercise has also been shown to impact HSP70 levels and the eHSP70-to-iHSP70 ratio. For instance, a study by Kim et al. (2015) found that long-term exercise training was associated with increased HSP70 levels in skeletal muscle. The authors also reported that the eHSP70-to-iHSP70 ratio was increased after exercise training, suggesting that chronic exercise may promote a more favorable balance between intracellular and extracellular HSP70.

The exact mechanisms by which exercise impacts HSP70 levels and the eHSP70-to-iHSP70 ratio are not yet fully understood. However, it is thought that increased HSP70 levels after exercise may help to protect cells from damage and promote cellular recovery. This is supported by evidence that HSP70 has a protective effect against oxidative stress, inflammation, and other forms of cellular damage (Spencer et al., 2013).

In conclusion, the eHSP70-to-iHSP70 ratio is an emerging concept in the field of exercise science. While more research is needed to fully understand the implications of this ratio, current evidence suggests that exercise may have a positive impact on HSP70 levels and the eHSP70-to-iHSP70 ratio. This, in turn, may promote cellular stress responses and cellular recovery, leading to improved health and performance.

#### References:

Kim, Y. S., Kim, J. Y., Kim, C. K., & Park, J. H. (2013). Exercise training increases heat shock protein 70 levels in the heart and liver of rats. *European Journal of Applied Physiology*, 113(1), 183–190.

Kim, Y. S., Kim, C. K., & Park, J. H. (2015). Long-term exercise training increases HSP70 levels in skeletal muscle. *Journal of Exercise Science & Fitness*, 13(1), 25–31.

Li, Y., Li, H., Li, J., & Sun, X. (2011). Heat shock protein 70 protects against oxidative stress in the brain of rats. *Neurochemical Research*, 36(7), 1215–1221.

Spencer, J. P., Caldwell, G. A., & Nalwalk, J. W. (2013). HSP70 and exercise. *Frontiers in Physiology*, 4, 104.

Wang, L., Nie (blocked by characters limitations)

## Discussion

First, it is imperative to inform readers that this is not an argument for or against using AI to write a manuscript, nor is it an attempt to recruit new AI users. This is just a test to clarify to the *Cell Stress and Chaperones* community what

the scientific world has been talking about recently and what challenges we are currently facing related to this issue. This application is now free to use worldwide, so it is important to understand how this situation can be managed.

Second, the potentially dangerous ease of use of the software means that any student or professional, independent of their educational level, can access AI to help them with academic work and other demands. This application works like any messaging application available on our mobile phones. Additionally, ChatGPT provides fast and adequate answers. The answers are generally relevant although, without a deeper mechanistic explanation, they can be improved by the user asking a suitable and precise sequence of questions that allows the AI developers to include new data in the system. This indicates that some references to sources related to the question are correct, at least in part, but when requesting citations or references, caution is advised. In addition, ChatGPT can understand questions from and provide answers in different dialects, overcoming language barriers. This AI usage, in addition to the use of AI for statistical analyses, graphing, and reference management provided in other tools, shows us that ChatGPT can be a powerful tool when used appropriately.

Specifically, after reading the answers that ChatGPT provided, I concluded that it can produce a linguistically coherent text, characterized by strategically organized information connecting possible pieces of evidence in grammatically sound sentences. However, the text provided is a combination of real and fabricated evidence resulting in a plausible answer (Alkaissi and McFarlane 2023). Occasionally, AI appears to write nonsense, but when viewed according to the common knowledge of experts in different areas, this is known as “artificial hallucination” (Ji et al. 2023). The “mistakes” that the AI makes can be classified as “intrinsic hallucinations” (when the generation output contradicts the source content) or “extrinsic hallucinations” (the output can neither be supported nor contradicted by the source). The origins of AI hallucinations can be source–reference divergence or the training and modeling choices for neural models that are known to be prone to hallucinations (Ji et al. 2023). Thus, the text that AI writes requires revision, so it is important for human authors to carefully review and validate the information that ChatGPT generates (Kim 2023), although there are proposed hallucination metrics and a revision process that ChatGPT utilizes (Ji et al. 2023).

Since scientific discussion is based on a careful verification of evidence that supports the hypothesis and conclusions of the manuscript, the references that the AI provides are critical. For example, as can be observed above, ChatGPT mentioned Kim et al. (2013) in reference to the effect of exercise on the eHSP70-to-iHSP70 ratio in the reference list: Kim, Y. S., Kim, J. Y., Kim, C. K., and Park, J. H. (2013). Exercise training increases heat shock protein 70 levels in

the heart and liver of rats (*European Journal of Applied Physiology*, 113(1), 183–190). However, in this journal issue, another manuscript is mentioned: Binder et al. (2013). Heat stress attenuates the increase in arterial blood pressure during isometric handgrip exercise (*Eur J Appl Physiol* 113, 183–190). Interestingly, in addition to inventing a reference, the source referenced did not measure eHSP70 levels, nor were any HSPs measured in the manuscript. Unfortunately, the inclusion of fake studies and fake authors in a reference list is recurrent in this version of ChatGPT (Kim 2023).

The combination of fake references and hallucinations may result in suspicious information. For example, one answer was “The authors also reported that the eHSP70-to-iHSP70 ratio was increased after exercise training, suggesting that chronic exercise may promote a more favorable balance between intracellular and extracellular HSP70.” In fact, different studies have demonstrated that the eHSP70-to-iHSP70 ratio is increased in chronic diseases (Costa-Beber et al. 2020 and 2021; Oliveira et al. 2022; Seibert et al. 2022), with exercise as a non-pharmacological strategy to decrease this ratio (Heck et al. 2017; Mai et al. 2017), which contradicts the response of ChatGPT. Therefore, at present, AI cannot substitute for human revision.

I checked the text that ChatGPT provided and that is shown in the results of this letter for plagiarism (<https://www.duplichecker.com/>). The first text shown in the Results section of this letter was considered fully unique, whereas the second presented only 11% plagiarism in nonrelevant sentences such as “For example, a study by Wang et al.” and “For instance, a study by Kim et al.”. Similarly, ChatGPT created 50 abstracts based on the titles of published manuscripts in high-impact journals, and the generated abstracts did not contain significant plagiarism (Gao et al. 2022). Since it has been shown that it is possible to detect the use of AI in writing by using an anti-plagiarism system (which also uses AI), the main challenge in terms of teaching and learning processes is how the educational system, from schools to universities, will define appropriate AI use. I believe that it is possible to use AI as an aid to promote science.

Since the appropriate use of AI is based on formulating relevant questions about an issue in a logical sequence, this tool may aid in the following initial scientific steps: “How can good questions be formulated?”, “How can I write an essay?”, “How can I check the scientific bases of evidence?”, and “How can I deal with the ethical aspects of plagiarism and authorship?” Users that are unable to formulate appropriate or sequential questions about scientific issues (those that start from the basics and go deeper into the topic) may not experience a productive talk with the AI, making the tool irrelevant. That is, students will not find leading scientific ideas or gaps in their knowledge of an issue using just a few or an insufficient sequence of questions. Therefore, it is necessary to focus on the essence of science and the topic of the

manuscript to be written by reading about and studying the topic before writing, even with the help of AI. In this way, AI may help teach students to formulate relevant questions. For instance, senior researchers can propose a writing challenge by setting a list of relevant questions in a particular field of interest, thus challenging students to answer these questions by themselves and compare their answers with those of an AI. Students can then be invited to compete against the AI to see who writes a better essay. With these challenges, it will be possible to improve writing skills such as linguistics, grammar, and organization that are used in a scientific text. In the study of Gao et al. (2022) mentioned earlier, the abstracts that ChatGPT provided were analyzed using AI detection models and blinded human reviewers (Gao et al. 2022). The writing challenge cited above can also provide a comparison between a well-written and scientifically valid text (written by a human) and a well-structured but non-scientifically valid text (written by the AI). Nevertheless, it remains imperative to check the references that both the AI and human authors provide. This step is helpful in teaching the relevance of adequate bases of evidence in the scientific construction of texts.

It is crucial to have a clear description of the acceptable use of AI in science to give authors, reviewers, and editors a way to maintain the reliability of scientific knowledge. The use of AI as an advanced and versatile language processing tool may also present limitations, such as the generalization of answers, decreased data quality, and a lack of domain expertise (Alshater 2023). At present, the rule that AI cannot be a co-author of a manuscript is gaining popularity, and using AI to generate texts without clearly stipulating this or knowing the limitations of AI can be considered plagiarism (Stokel-Walker 2023a). More extreme positions are also currently being held, proposing that text, figures, images, or graphics that AI generates cannot be used in science (except for inherent procedures and methods using AI in studies), and this practice can be considered scientific misconduct that is no different from altering images or plagiarizing existing works (Thorp 2023).

Accepting the help of AI in writing does not mean that the AI should be considered an author since it cannot fulfill the authorship requirements inherent in science, such as participation in the project, proposal elaboration, or the execution of procedures. Moreover, AI cannot provide an answer if questioned about its agreement with the argumentation presented in the text and data analyses, nor is it able to defend the focus of the study and respond to the scientific community, if asked to, in terms of legal, ethical, methodological, and scientific issues. This also provides an opportunity to talk about authorship and ethics in science with students.

The focus for academics, editors, reviewers, and authors can remain the same as it has been since the start of modern

science, which is based on the scientific nature of knowledge. In this way, some questions about a manuscript may need to remain the same, but their relevance should be viewed from the perspective of the inappropriate use of AI, while new questions may need to be raised, such as:

Main questions:

- a) Is the manuscript proposal relevant and based on an original question?
- b) Are the affirmations within the text based on accurate and verifiable evidence?

New questions:

- iii) Have you used any AI support in any part of the study? Please declare it in detail.

## Conclusion

To answer the questions presented in the title of this letter, it is possible to say that ChatGPT knows much about HSP70 but is not able, at present, to produce a complete text with adequate reasoning and evidence-based arguments and references. Additionally, AI does not meet the requirements of an author. We need to learn how to live in this new era, interacting appropriately with AI to teach and promote reliable science and prevent access to new AI tools from blocking imagination, creativity, ethics, and curiosity to retain the possibility of serendipitous discoveries, as provided by Ritossa (1962, 1996).

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s12192-023-01340-1>.

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**Data availability statement** Not applicable.

## Declarations

**Conflict of interest** The author declares no competing interests.

**Additional declaration:** This letter was not written using any AI support.

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