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THE RESVERATROL EFFECTS ON HUMAN HEALTH: THE BRAZILIAN OVERVIEW: AN INTEGRATIVE LITERATURE REVIEW

*¹Cesar Augusto Marton, ²Mariane Moreira Ramiro do Carmo and ³Romano Deluque Júnior

¹Graduating in Psychology at Universidade para o Desenvolvimento do Estado e da Região do Pantanal (UNIDERP), Graduating at Nutrition at Faculdade Mato Grosso do Sul (FACSUL), Graduating at Gerontology at Centro Universitário Claretiano. Researcher on Issues such as men's health and longevity

²Nutritionist, Phd in Health with emphasis on Metabolism and Nutrition at Universidade Federal do Mato Grosso do Sul (UFMS), Master in Biotechnology Applied to Health at Universidade Católica Dom Bosco (UCDB)

³Psychologist, Master student of the Postgraduate Program in Psychology at Universidade Católica Dom Bosco (UCDB), Researcher on Issues such as Prejudice and Democracy, Graduating in Law

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*Corresponding author:

Cesar Augusto Marton

ABSTRACT

The purpose of the present study is to interrogate for the panorama regarding the effects of resveratrol in human health that have been established by the latest research within the Brazilian territory. To achieve this goal, we used a literature review in the form of an Integrative Review that could demonstrate these designs. We raise the following question: what aspects and designs regarding the effect of Resveratrol supplementation on human health have appeared in research in the field of health, and what notes have these researches made to emerge within the national scenario? After applying the inclusion and exclusion criteria, 7 papers were selected to compose the corpus of the present review, and their information was categorized, evaluated and synthesized. The analysis categories are presented as follows: year of publication, magazine or periodical, Brazilian State where the research was carried out, area of activity of the authors, methodological designs, sample characteristics, ethical procedures, results, and main conclusions.

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INTRODUCTION

Resveratrol (RESV) is a phenolic compound found in plants such as grapes and peanuts (ALBERTONI; SCHOR, 2015b), as well as in its products and derivatives such as red wine (ALBERTONI; SCHOR, 2015b; SÉFORA-SOUZA; by ANGELIS-PEREIRA, 2013). It has been the object of study worldwide due to its properties and benefits to human health (ALBERTONI; SCHOR, 2015a; SCOTT et al., 2012). It is therefore believed that resveratrol has antinephrolytic, anti-diabetes, anti-cancer, anti-inflammatory, antioxidant, anti-inflammatory, cardioprotective, chemopreventive and neuroprotective properties (TIMMERS et al. 2011). Its effects on the aging process have been studied since the 90s (FERRO; de SOUZA, 2011), and several studies show that it has been gaining importance as it contributes to delaying aging and

preventing various pathologies (XIA, DENG, GUO et al., 2010; BARGER, KAYO, VANN et al., 2008). Thus, it is possible for resveratrol to emerge as an ally that helps, not only in prolonging human life but also as a preventive agent for certain diseases associated with age. This study aims to interrogate the panorama regarding the effects of resveratrol on human health that have been established by the latest research within the Brazilian territory. To achieve this goal, we used a literature review in the form of an Integrative Review that could demonstrate these designs.

MATERIALS AND METHODS

Literature Review: An integrative review aims to raise empirical or theoretical research and, from them, it is possible to verify not only the general conclusion lines regarding a

certain theme but also, how this same theme has been treated by the literature. In this sense, it is reported as a research method since 1980 (MENDES, PEREIRA & GALVÃO, 2008), has the important function of "gathering and synthesizing research results on a delimited theme or issue, in a systematic and orderly way" (p. 759), as well as to contribute to the general understanding of the investigated topic. The integrative review as a research method allows the elaboration of a synthesis about the investigative status of a given question, and can, with this, help the production and direction of new research in the area, as well as point out gaps that need to be filled with new studies. (MENDES, PEREIRA & GALVÃO, 2008). As specificity of the integrative review under other research methods, such as qualitative review, meta-analysis and systematic review, there is the possibility of integrating different theoretical and empirical research (quantitative or qualitative) on a given topic (SOARES *et al.*, 2013), with the ultimate goal of rigorously synthesizing "findings from primary studies developed through various research designs" (p.336). From the perspective of health care and care, the integrative review can help to understand phenomena already studied on subjects related to the theme, in order to present the state in which the research on this respective phenomenon is. The integrative review can also contribute to new theoretical developments, as well as assist in the creation of health practices and public policies. The study presented here proposes to question the state of the following question: what aspects and designs regarding the effect of Resveratrol supplementation on human health have appeared in research in the field of health, and what notes have these researches made to emerge within the national scenario?

Study Designs: For our study, the following databases were consulted: PePSIC (Electronic Journals of Psychology), SciELO (Scientific Electronic Library Online), LILACS (Latin American and Caribbean Literature in Health Sciences), and MEDLINE (Medical Literature Analysis and Retrieval System Online). The inclusion criteria adopted were: 1) Brazilian productions, made on Brazilian soil and by Brazilian authors; 2) complete articles indexed in journals; 3) published between 2009 and 2019; 4) published in Portuguese, Spanish, French or English; 5) studies whose scope is the effects of resveratrol supplementation on human health. No geographical limits have been established on the instruments of publication, in order to also include in the results, works done by Brazilians and published abroad. Once the above criteria were established, all the studies that matched were selected. Test cell studies have been included as long as using human cells. Such an approach is purposefully broad, thus including theoretical studies, literature reviews, empirical (quantitative, qualitative or mixed), as well as other formats, however, works in the form of complete theses, such as undergraduate, master's, and doctorate degrees were excluded. No exclusion had been made based on the area of study, or by the approach adopted, in order to obtain the following exclusion criteria were: 1) productions published in a different timeframe than intended; 2) diverse production of complete articles properly indexed; 3) different theme than intended; 4) productions with a similar theme, but which contemplated the effects of resveratrol in a secondary or superficial way; 5) articles that focused on the effects of resveratrol in non-human animals; 6) articles made by foreigners or by Brazilians outside Brazil.

Procedures: The search process with the descriptor "resveratrol" occurred in October 2019 and yielded the

following results: 1) SciELO - 53 results; 2) LILACS - 72 results; and finally, 3) MEDLINE - 9711 results. Due to the high number of studies found in the MEDLINE indexer, a second descriptor was chosen, thus, it was used in this database "resveratrol" AND "brazil", which yielded a total of 34 studies. Thus, 159 works totaled. Then, the titles and abstracts were read to proceed to the respective selection, according to the criteria already presented. Once the inclusion and exclusion criteria were applied, the refined results were as follows: 1) SciELO - 3 results; 2) LILACS - 5 results; and 3) MEDLINE - 2 results, totaling 10 works. There were 3 repeated works indexed in more than one search engine, so they were excluded. Finally, discounting the repetitions, there were 7 works selected to compose the corpus of the present review, with their information categorized, evaluated and synthesized. The analysis categories are presented as follows: year of publication, magazine or periodical, Brazilian State where the research was carried out, area of activity of the authors, methodological designs, sample characteristics, ethical procedures, results, and main conclusions.

RESULTS

The studies were captured on a national / Brazilian scale, in this sense, all studies that met the inclusion and exclusion criteria were selected. No exclusion due to the linguistic component was made. Seven studies were selected (N = 7). Of them, 2 studies were published in 2018 (n = 2), one in 2016 (n = 1), 2 in 2015 (n = 2), one in 2013 (n = 1), and finally, one in 2011 (n = 1). As for the area of concentration of the authors, the results show that most research in the area is carried out by nutrition professionals/courses (n = 3). Two of the studies were developed by medical schools and courses (n = 2), 1 study by a postgraduate program in science (n = 1), and finally, another by an aging science program (n = 1). Regarding the researcher's institutional link, several studies were obtained whose authors were linked to more than one institution: 2 studies were produced exclusively by the Federal University of São Paulo - UNIFESP (n = 2); a study was also produced by UNIFESP but in association with the Centro Universitário São Camilo (n = 1); 2 studies were produced by the University of São Paulo - USP, but in association, respectively with the Federal University of Lavras (n = 1), and with the Energy and Nuclear Research Institute - IPEN and Hospital Israelita Albert Einstein (n = 1). Finally, a study was produced by the Federal Institute of Southeast Minas Gerais - IFMG (n = 1), and the last one by Universidade São Judas Tadeu - USJT. All studies were produced in the southeast region.

There were 4 studies published in English (n = 4) and 3 studies published in Portuguese (n = 3). The following journals published, respectively, one study each: Brazilian Journal of Medical and Biological Research; Brazilian Journal of Nephrology; Integrative Cancer Biology & Research; MedicalExpress; J. Morphol. Sci.; Rev of the Society of Cardiology of the State of SP; and Revista Brasileira de Plantas Mediciniais. In all, 24 authors produced a total of 7 studies, resulting in an average of 3.4 authors per study. As for the authors who signed more than one study, only Guilherme Albertoni and Nestor Schor appear with 2 publications each, all the other authors signed only one study each. As for the methodological designs, 4 studies were obtained in the format of literature reviews (n = 4); 2 studies in test cells (n = 2), and finally, one study used tests in humans (n = 1).

DISCUSSION

Albertoni and Schor (2015a) carried out a research with test cells whose purpose was to verify the effects of resveratrol on the impacts of uric acid (UA) on increases in Angiotensin (AII), Endothelin (ET-1), and ions Calcium [CA²⁺] in immortalized human mesangial cells. In the study, it was found that the administration of 12.5 micrometers of resveratrol (μM) did to reduce the production of AII and ET-1 in the analyzed mesangial cells. Resveratrol also inhibited the increase in [CA²⁺] in these same cells. In another study, Albertoni and Schor (2015b) carried out a literature review in order to relate the effects of resveratrol on kidney diseases. The authors reaffirmed, based on the results obtained, the benefits of resveratrol for cardiovascular health. Also based on the results obtained, it was concluded that resveratrol can assist in the repair of kidney injuries in animal models, which include diabetic nephropathy, hyperuricemia, drug-induced injury, aldosterone-induced injury, ischemia-reperfusion injury, injuries related to sepsis, and finally, endothelial dysfunction. In addition, corroborating the aforementioned study by the same authors, it can be seen that resveratrol can prevent the increase in vasoconstrictors such as Angiotensin (AII) and Endothelin (ET-1). Moreno *et al.* (2018) conducted a test cell test. Different doses of radiation were administered to human lung mucoepidermoid carcinoma cells in the presence of 0, 12, 30, and 60 micrometers (μM) of resveratrol concentration. In the study, the authors did not find benefits of resveratrol for cell protection in case of administration of irradiation doses at doses of 0.8, 5 and 10 Gy. When 30 (μM) of resveratrol were administered, the results were an increase in injured cells after 24 hours of radiation loads. Thus, although there are studies that indicate the radioprotective potential of resveratrol, in the study in question, this characteristic cannot be verified. Silva-e-Oliveira *et al.* (2016) conducted a survey with hypertensive people that involved a resveratrol group (n = 11) and a placebo group (n = 10). The participants were analyzed for 30 days, in which the Heart Rate Variability Parameters (HRVP) were measured before and during a standardized exercise on a treadmill. After the referred study was completed, no change in the HRVP parameters between the Resveratrol Group and the Placebo Group can be seen. Although the literature indicates the beneficial potential of resveratrol in cardiovascular pathologies, the results did not converge to that end. Ferro and de Souza (2011) developed a literature review study without restriction on descriptors. Using the Pubmed and Medline databases, the authors found that resveratrol presents itself as a potent nutraceutical to delay aging and prevent disease, including a sirtuin activator. According to the results obtained in that study, resveratrol still acts as a preventive for oxidation of LDL cholesterol. However, the study concludes that the functionality of resveratrol must be analyzed on a case-by-case basis and in tissue by tissue, given that the responses are different for each type of cellular condition. Vatauvuk-Serrati *et al.* (2018) presented a synthesis of 15 studies that made up the corpus of their literature review. Selected studies assessed endothelial function, glycemic profile, inflammatory profile, lipoproteins, as well as the safety of resveratrol consumption by the elderly. According to the selected studies, resveratrol supplementation proved to be safe in the elderly and beneficial mainly for endothelial function in different populations, having a positive effect also on the glycemic profile of patients with insulin resistance and inflammation.

For last, Séfora-Souza and de Angelis-Pereira (2013) presented a literature review that, corroborating with Ferro and de Souza (2011), found the antioxidant function of resveratrol compared to LDL. The study also shows that the phenolic compounds present in grapes can be complexed with metals such as iron and zinc, and thus increase the antioxidant activity of plasma. The benefits of wine consumption for the prevention and treatment of cardiovascular diseases were widely confirmed by the referred study.

Conclusion

Considering the research conducted here, it was found that, once the aforementioned inclusion and exclusion criteria were established, the results were very few. However, we chose here a cut that privileged the effects of resveratrol on human health, thus, several studies that were willing to address the topic in tests with animals or animal cells were not selected. The national reality on the subject seems to be taking its first steps towards a robust relationship with that topic, however, the studies that made up the corpus of this article were presented with excellent quality, both in terms of methodological aspects, as well as in the composition of the theoretical body used. The vast majority of studies were of literature reviews (n = 4), which can denote the difficulties of the national scene in terms of funding and the possibilities of research with human beings and laboratories. Of the researches that used test cells, one managed to demonstrate the beneficial effects of resveratrol on cellular health, while in the other, the results varied from unchanged to the increase in lesions in cells affected by radiation.

In general, the beneficial effects of resveratrol on men's health were widely endorsed in the present study. Specifically, the focus was on cardiovascular health and its benefits in the field of nephrology. From the analyzed studies, it was possible to perceive two lines of action: one related to studies aimed at perceiving the effects of resveratrol on specific human health functions; and others, especially some literature reviews, which attempted to encompass the effects of resveratrol on human health in a more comprehensive and generalized perspective. Finally, the benefits of resveratrol stands out in almost all the selected studies. Many of these studies suggest the need to research the theme with greater specificity so that the effects, in this case of resveratrol, can be better understood and delimited. In general, it can be said that research on Brazilian soil is found, in quantitative terms (it should be noted) and in terms of access to resources, one notch below those carried out in other more developed countries in terms of research, so much so that both studies that made use of test cells, did so in a technological partnership with foreign institutes.

Study Limitations: As it is a study of national nuances, it is not possible to emerge a global outline regarding the understandings about the effects of resveratrol on human health. However, our intention lies in trying to demonstrate how research on the subject in Brazil is progressing.

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Table 1. Search and Selection Process

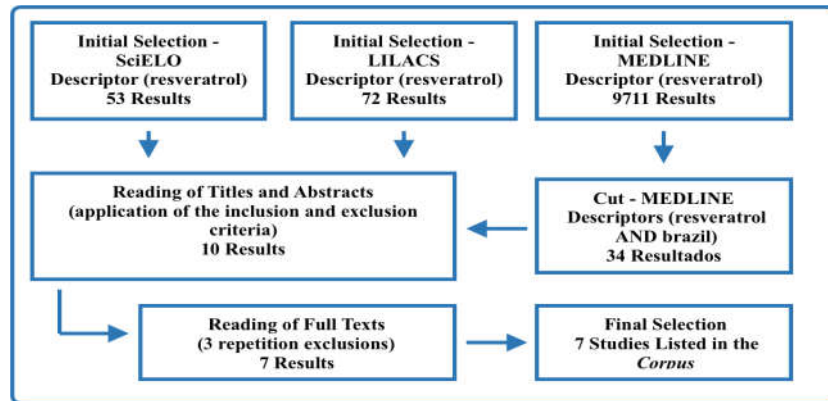


Table 2. Citation; year of publication; journal; concentration area of the authors; institutional bond; methodological designs; and main results and conclusions

Nº	Citation and Year of Publication	Journal / Author's Focus Area	Institutional Bond	Methodological Designs	Main Results and Conclusions
1	Albertoni; Schor, 2015a	Brazilian Journal of Medical and Biological Research/ Medicine	Universidade Federal de São Paulo - UNIFESP	For testing, immortalized human mesangial cells (ihMCs) were used.	Resveratrol may minimize the impact of Uric Acid (AU) on increases in Angiotensin (AII), Endothelin (ET-1) and Calcium ions [CA2 +] in the tested mesangial cells, suggesting that it may prevent the effects of soluble substances (Au) in the mesangial cells of living people.
2	Albertoni; Schor, 2015b	Revista Brasileira de Nefrologia / Medicine	Universidade Federal de São Paulo - UNIFESP	This is a literature review study whose aim is to relate the effects of resveratrol (RESV) on kidney diseases.	Numerous studies have shown that polyphenols promote cardiovascular health and can repair various types of kidney damage in animal models, including diabetic nephropathy, hyperuricemia, drug-induced injury, aldosterone-induced injury, ischemia-reperfusion injury, sepsis-related injuries, and endothelial dysfunction. Besides, RESV can prevent the increase of vasoconstrictors, such as angiotensin II (AII) and endothelin-1 (ET-1), as well as intracellular calcium, in mesangial cells. Together, these results suggest an important role for RESV as a complementary therapy in the prevention of kidney injuries.

.....Continue

3	Moreno et al. 2018	Integrative Cancer Biology & Research / Sciences	Instituto de Pesquisas Energéticas e Nucleares - IPEN / Universidade de São Paulo - USP / Hosp. Isr. Albert Einstein	Radiation doses were administered to human lung mucocarcinoma cells in the presence of 0, 12, 30, and 60 micrometers (μM) of resveratrol concentration.	It was observed that when cells of mucocarcinoma (NCI-H292) are exposed to resveratrol at a concentration of 30 μM before irradiation at doses of 0.8, 5 and 10 Gy, there is an increase in injured cells, observed 24h after irradiation. Thus, it is suggested that, although there are studies that indicate the radioprotective potential of resveratrol in various types of cancer cells, in the cells analyzed in the present study, the effects varied from, without alteration to the increase of injured cells.
4	Silva-e-Oliveira et al. 2016	MedicalExpress / Nutrition	Instituto Federal Sudeste de Minas Gerais - IFMG	Twenty-one hypertensive volunteers of both sexes were supplemented with resveratrol (n=11) or placebo (n=10) for 30 days. Heart rate variability (VBC) parameters were measured before and during a standardized treadmill exercise.	Although resveratrol has been listed since the '90s as an aid in the treatment of cardiovascular pathologies, in that study there were no anthropometric changes between the resveratrol group and the placebo group other than the difference in body mass index. The parameters of VBC evaluated also did not differ between both groups.
5	Ferro; de Souza, 2011	J. Morphol. Sci. / Sciences of Aging	Universidade São Judas Ta deu - USJT	It is a study of literature review without restricted use of descriptors. In the study, the Pubmed and Medline databases were used with the following search engines: resveratrol AND cell aging.	The vast majority of studies have shown that resveratrol is a potent nutraceutical to prevent disease and slow aging, including an activator of sirtuins. In any case, almost all authors who work with sirtuins and aging claim that the molecular mechanism of how sirtuins slow aging and improve the life span is still unclear. Thus, further studies are needed to affirm a plausible answer to this question.
6	Vatavuk-Serrati et al. 2018	Rev da Sociedade de Cardiologia do Estado de SP / Nutrition	Centro Universitário São Camilo / Universidade Federal de São Paulo - UNIFESP	This is a review of the recent literature on resveratrol supplementation in humans and its effects on risk factors for the development of cardiovascular diseases. We included 15 studies that evaluated endothelial function, glycemic profile, inflammatory profile, lipoproteins, as well as the safety of consumption by the elderly	According to the selected studies, resveratrol supplementation was shown to be safe in the elderly and beneficial mainly for endothelial function in different populations, also having a positive effect on the glycemic profile of patients with insulin resistance and inflammation. - a significant reduction in the intestinal and hepatic production of the APO B-48 and APO B-100 lipoproteins. Due to all these aspects, resveratrol supplementation can play a protective role against the development of cardiovascular diseases.
7	Séfora-Souza; de Angelis-Pereira, 2013	Revista Brasileira de Plantas Mediciniais / Nutrition	Universidade de São Paulo - USP / Universidade Federal de Lavras - UFLA	This is a literature review study conducted by searching the PubMed and ScienceDirect databases using the following descriptors: red wine, grape, polyphenols, resveratrol, atherosclerosis, oxidized LDL, inflammation, oxidative stress, NF- κ B, AP-1, Nrf2, SIRT-1, MicroRNA.	The selected studies indicate that phenolic compounds present in grapes can complex with metals (such as iron and copper) that cause lipid peroxidation, increase the antioxidant activity of the plasma, associated with LDL-c increasing its resistance to oxidation, preserve the activity of the para oxonase enzyme, neutralize free radicals, and activate transcription factors such as Nrf2, which increases the expression of genes that encode proteins important in antioxidant defense, such as superoxide dismutase and glutathione peroxidase.
