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EFFECTS OF RESVERATROL ON TUMOR IMMUNITY: REVIEW

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ABSTRACT

The purpose of this review was to relate functional aspects of the immune system to cancer and verify if the use of resveratrol may present any adjuvant strategy. The immune system protects the human body against aggressive agents and presents a complex and integrative form of action involving different immune cells. In the neoplastic context, conventional treatment by chemotherapy and radiotherapy generates many side effects. In the neoplastic context, defective cells that are not recognized by immune system and the conventional treatment by chemotherapy and radiotherapy generates relevant collateral effects. Resveratrol has been described as an important immunomodulator. Thus, we raise the following question: if resveratrol can be used as a coadjuvant on cancer treatment?

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INTRODUCTION

Cancer has been consolidated as a global public health problem (REBECCA, 2017), revealing itself as the second-highest frequency of incidence, frequency of diagnosis and death. Due to the intensive treatment regimens and the surgeries needed to treat this disease, the financial implications of a cancer diagnosis represents a considerable economic burden for the family involved, as well as for health services and society (MCCORMICK, 2018; SUN, 2016). According to the World Health Organization (WHO, 2018), cancer is the second leading cause of death in developed countries, losing only to cardiovascular disease, resulting in an impact of 190,000 deaths per year (Who, 2018; SIM, 2009; INCA, 2020). This disease originates from cells that undergo a genetic alterations sequence, mainly in signaling pathway cells. These changes may be the result of a variety of factors, such as inherited genetic mutations or random errors in DNA replication, such as damage and genetic instability induced by radiation, by chemical substances or by viral infection (SHANMUGAM, 2018; MARELLI, 2018). Cancer is a closely related disease to the immune system. The interaction of cancer with the immune system can occur by the suppressor activity of immune responses or exaggerated activation of some molecular pathways (CHEN, 2017). Therefore, individuals with congenital or acquired deficiencies of the immune system are more inclined to develop the disease (LIPINSKI, 2016).

There are three traditional forms of cancer treatment: surgery, radiotherapy and chemotherapy (INCA, 2020). However, despite the efficacy of the related treatments, these therapeutic modalities also promote several adverse effects, including myelosuppression, nausea, vomiting, diarrhea and alopecia. Due to these collateral effects, there is a need for seeking new alternatives that may help in cancer treatment (MARELLI, 2018). Among the alternatives that purpose to prevent and treat cancer cases, combined with conventional treatment, scientific literature points out that Resveratrol is characterized by an effective strategy, both in prevention and response of the immune system against the tumor, as well as its modulating activity of several pathways involved in cell and offers fewer collateral effects (MUKHERJEE, 2010). Resveratrolis known to reduce the incidence and development of various types of cancer, such as cervical (ZHOU., 2018), pancreatic (ZHAO, 2018), gastric (WU, 2018), breast and colorectal (LUCAS, 2018), as well as thyroid cancer (ZENG, 2018). This review aims to relate functional aspects of the immune system to cancer and its conventional forms of treatment, as well as to verify if the use of Resveratrol can present an accessory strategy. It´s expected that the findings in this research turns out to be a turning point of decision-makers and stimulates the production of deeper knowledge about the pursuit for new alternatives for the treatment of cancer.

METHODS

The literature review was conducted from January to February 2021, seeking to answer the following guiding question: "Can the use of Resveratrol be used as a coadjutant treatment?" The databases used in this systematic review were: Science Direct, NCBI, MEDLINE / PubMed, Scopus, Scielo and One File. The large number of journals found, in immunology justifies this choice. With regards to the search for articles, had been used some keywords combinations, such as "Immunology of Cancer" OR "Resveratrol and cancer" OR "Resveratrol and macrophages" OR "Immune System and Cancer". In this context, filters were used to consider only English-language publications in peer-reviewed journals and made fully available. The selection was made according to the sequence title, abstract and total article, considering revisions and original articles.

RESULTS AND DISCUSSION

The different cells and molecules responsible for immunity constitute the immune system, and their collective and coordinated response to foreign substances are called: immune response (TOTSCH, 2017). The primary function of the immune system is to combat infections and toxic agents caused by pathogens (HALL,2017). It is a complex system maintained by immune cell actions that triggered two types of responses, innate and adaptive, and also by the proteins of the complement system (BARRET, 2014). The innate response is the body's first line of defense mediated by cells such as phagocytes (monocytes, macrophages and neutrophils), natural killer (NK) cells, eosinophils, basophils and mast cells, whereas, second response, acquired or adaptive immunity, is activated by contact with infectious agents and its response to infection increases in magnitude at each successive exposure to the same invader (ABBAS,2010). Furthermore, there are two types of acquired immunity: cellular immunity and humoral immunity, which is mediated by T-lymphocytes (CD4 and CD8) and B-lymphocytes and their antibodies (HALL,2017). These two immune responses communicate to each other, which are mediated by antigen presenting cells (APCs). The APCs cells present the antigen to T and B-lymphocytes, activating specific responses. For example, cancer cells are able to release cytotoxic components by membrane perforating proteins, and the cells that help counteract these effects are NK, macrophages and TCD8 lymphocytes (BARRET, 2014 and TERRA 2012). From these presuppositions, (CHEN, 2017) is discussed the intercourse of cancer with the immune system. According to the author, this interaction occurs by the suppressor activity of immune responses or exaggerated activation of some molecular pathways, also used to negatively control the pathogens, where they induce immunological homeostasis or, in some cases, cause an escape from the detection of tumor activity. Agreeing, (FINN, 2012) states that the immune system exerts great influence on cancer, either by preventing or favouring the onset of these diseases. For this author (FINN, 2012), the immune system has the greatest potential for the specific destruction of tumors with no toxicity to normal tissue, further allowing the formation of long-term memory that can prevent the recurrence of neoplasia. The immune system, by recognizing the presence of tumor cells, may emit a cellular or humoral immune response. In this way, immune cells and molecules produced by them work using various signalling pathways, pleiotropic or redundant, aiming to eradicate the malignity (ZHOU, 2018, ZHAO, 2018). The recognition of tumor antigens involves several cell types and molecules of the immune system. Activated macrophages, NK cells, CD4 + and CD8 + T lymphocytes specific for tumor peptides, as well as high titers of immunoglobulins against a vast repertoire of these antigens, are found in neoplastic tissues (CHEN, 2017). In their studies, Liu and Zeng (2017) described macrophages as potent phagocytes of the innate component of the immune system, acting as the primary defense against tumorigenesis. Data from Woo (2015) reports that tumor-associated macrophages (TAMs) present two phenotypes (M1 and M2), where M1 macrophages produce IL-12 and IL-10 cytokines contributing to tumor growth control and, in turn, M2 macrophages have a pro-tumor profile, induced by various mechanisms, tumor progression. NK cells represent the first line of defense in antitumor immunity and are capable of inducing lysis of cells which exhibit a decrease in MHC class I expression on their surface (CONTRAN, 2013). This is a device widely found in tumor cells as an escape mechanism. The decrease in surface MHC I molecules prevents cells from being recognized and damaged by specific CD8 + T lymphocytes (PECORINO, 2012 and SUVA, 2013). Cytotoxic CD8 + T lymphocytes, along with NK cells, are the main effector cells of tumor cell immunity. They are responsible for the recognition of antigens on the surface of tumor cells induced by a viral infection or by a chemical agent. When active, they perform a direct cytolytic effect against the tumor cell in response to secretion of elevated levels of IFNγ, TNFα, perforins and granzymes (MAEDING, 2016). Through the production of cytokines, CD4 + T lymphocytes play a fundamental role in supporting lymphocyte clonal expansion and in generating an inflammatory response. They have a certain singularity since they are the only ones that express the surface marker of CD4 cells (PECORINO, 2012). Pro-inflammatory antitumor effects of CD4 + T lymphocytes are generally mediated by the T helper (Th) 1 phenotype updated by the secretion of gamma-interferon (IFN) -γ and other pro-inflammatory cytokines. However, Treg cells (CD4 + CD25 +) have an important role in immunological regulation, highlighting the mechanisms of control of the adaptive immune response have a decisive implication in the proper functioning of the immune system. (HAYNES, 2008). The immunosuppressive effects are mainly governed by Treg cells, their growth factors and related cytokines, such as the transforming growth factor (TGF) -β and IL-10; or by IL-4, IL-5-secreting TH2 cells, cell types generally associated with deleterious effects in cancer patients (DESCHOOLMEESTER 2010; GAUR, 2014).

This subset of lymphocytes is highly diversified and its subpopulations exert a variety of functions, able to modulate CD8 cells and B cells to induce their function of cytotoxicity and antibody production, respectively, or on the other hand, induce a tolerogenic immune response (SVAJGER, 2012). Thus, the tumor microenvironment can influence the immune system, tumor cells have the efficacy of deceiving this defense mechanism and evading the antitumor immune response(SARMA, 2011 and FINN, 2012). Consequently, over the years, the academic community has shifted the focus of the investigations of the cancerous cell to the host and alternative that can be efficient for their treatment.In the seek for an effective alternative in the modulation of response in tumor immunity, which provides biological and consequently clinical benefits without causing harmful side effects to the organism, allied to its low cost, phytotherapeutic methods began to be investigated. One of the substances with immunomodulatory potential is Resveratrol (MUKHERJEE, 2010). The resveratrol-3,5,4'-trihydroxy-droxy-stilbene (RESV) is a phytoalexinapoliphenol found in many plants, in its natural form, and some products such as red wine and peanut (SVAJGER, 2012), is composed that this substance has many benefits to the organism. It is chemically composed of two phenolic rings linked by a double bond of styrene to generate the stilbene structure, which may exist as a cis or trans isomer. According to Svajger and Jeras (2012), the pharmacological effects of trans-resveratrol, both in vitro and in vivo, have been intensively studied and attributed to greater potential than cis-resveratrol. The Resveratrol is one of the most important natural stilbenes and has been extensively studied. It has been demonstrated that the substance has health promotion properties, in which stand out the antitumor (WANG, 2010), anti-inflammatory (PATEL, 2011) and antiaging activity and (SOARES-FILHO, 2011).Several recent studies report the potential health benefits and effects on cancer provided by Resveratrol, this study aimed to show this. The anti-cancer property of Resveratrol has been supported by studies indicating its power to inhibit the proliferation of a wide variety of human tumor cells in vitro, leading to numerous preclinical studies in animals to evaluate the potential of Resveratrol for chemo intervention and chemotherapy (SHUKLA, 2011 and KISELEV, 2011). Jang, et al. (1997) demonstrated, for the first time, the preventive effects of Resveratrol on the inhibition of multistage carcinogenesis. Since then, several

studies have been demonstrating the action of this compound under numerous types of cancer in different stages of development. Resveratrol affects all three distinct stages of carcinogenesis (initiation, promotion, and progression) by modulating signal transduction pathways that control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis, and is therefore considered by some such as promising anticancer therapy (KRAFT, 2009). It was afterwards shown that this polyphenolic compound suppresses the proliferation of a wide variety of human tumor cells *in vitro*, which has led to numerous preclinical studies in animals (BAUR, 2006) In vitro data showed that Resveratrol interacts with multiple molecular targets and damaged cells of breast, skin, stomach, colon, esophagus, prostate and pancreas cancer, as well as leukemia (BOOCOCK, 2005).The study of the pharmacokinetics of Resveratrol in humans concluded that even high doses of Resveratrol might be insufficient to reach in vivo necessary concentrations for systemic cancer prevention (NILES, 2006). This information is consistent with the results of animal cancer models, which indicate that the use of Resveratrol is limited by its low systemic bioavailability (CASANOVA, 2012). The strongest evidence for Resveratrol's anticancer action exists for tumors with which it may come into direct contacts, such as tumors of the skin and gastrointestinal tract. For other cancers, the evidence is unclear, even if massive doses of Resveratrol are used (SHUKLA, 2011). Another action attributed to the compound was to enhance the anti-tumor activity of anti-tumor drugs such as melphalan and tamoxifen, both used in the treatment of breast cancer (SHI, 2103; ZHOU, 2011). Concerning in vivo studies, demonstrated that Resveratrol activates caspase-3, a crucial mediator of apoptosis in pancreatic cancer. In this sense Kma (2013) reports that the compound reduced by more than 40% the number of metastases in lung carcinoma models. Little is known about the mechanisms responsible for the antitumor activities exhibited by Resveratrol (FRAZZI, 2014). Among the Resveratrol mechanisms of action, there is the activation of the intrinsic apoptotic pathway, the generation ofreactive oxygen species(EROs) , modulation of the p53 pathway and the activation of the receptor pathway of extrinsic death. This compound can interfere with the mitochondrial respiratory chain, generating an increase in EROs production. According to (FRAZZI and TIGANO, 2014)the redox state of cells plays an important role in many types of apoptosis and the ROS produced at the level of mitochondria may be involved in the death of cells.

CONCLUSION

This study points to Resveratrol as a natural compound that has showed to be effective in inhibiting cell proliferation of different tumor cell lines and preventing tumor development at the different stages of carcinogenesis. Also, it is perceived through the various studies presented here that the compound may be a good complement to chemotherapy or even be an alternative in the development of less aggressive therapies. Despite this, further studies are still needed to clarify and evidence the mechanism of action of the compound to elucidate the antitumor effect of Resveratrol and how this effect varies with tumor type.

The authors declare that there are no conflicts of interest.

REFERENCES

ABBAS AK. Imunologia Básica. 3ª ED, 2010.

Barrett, K. Fisiologia médica de Ganong. 24. ed. Porto Alegre, RS: AMGM. 2014.

Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat. Rev. Drug Discov. 20065: 493–506.

Boocock D.J, FAUST KR. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. Cancer Epidemiol. Biomarkers Prev. 2007, 16: 1246–1252.

Casanova F, Quarti J, Costa DC, Ramos CA, Silva, JL, Fialho E.Resveratrol chemosensitizes breast 144ancer cells to melphalan by cell cycle arrest. *Journal of Cell Biochemistry.* 2012, 113; 8: 2586-96.

Chen, DS.; Mellman, I. Elements of cancer immunity and the cancer-immune set point. Nature. 2017, 18;541(7637):321-330.

Contran, R.S.; Kumar, V.; Collins, T. Pathologic Basis of disease.W.B. Saundens Co. Philadelfia, USA, 2001.- McLeod HL Cancer pharmaco genomics: early promises, but concentred effortneeded. Science.2013, 339: 1563-1566.

Deschoolmeester, V. et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol. 2010, 11:1- 19.

Finn, O J. Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. Annals of Oncology. 2012.v. 23, sup. 8, p. viii6-9.

Frazzi R, Tigano M. The multiple mechanisms of cell death triggered by resveratrol in lymphoma and leukemia. International Journal of Molecular Sciences. 2014, 15; 3: 4977-93.

Gaur, P. et al. Inter-relation of Th1, Th2, Th17 and Treg cytokines in oral cancer patients and their clinical significance. Human Immunol, 2014, 75; 4: 330–337.

Hall and John E. Guyton e Hall: tratado de fisiologia médica. 13. ed. Rio de Janeiro: Elsevier, 2017.

Haynes BF, Soderberg KA, FAUCI AS. Introdução ao sistema imune e complexo gênico principal de histocompatibilidade. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editores. Harrison medicina interna. 17a ed. Rio de Janeiro: McGraw Hill; 2008. p. 2019-53.

Inca. Estimativa 2020: Incidência de Câncer no Brasil, (INCA 2020) INCA (Incidência de Câncer no Brasil), 2021.

Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science, 1997, 275; 5297: 218-20.

Kiselev, KV. Perspectives for production and application of resveratrol. Applied Microbiology and Biotechnology, 2011,90;2: 417-425.

Kma, L. Synergistic effect of resveratrol and radiotherapy in control of cancers. Asian Pacific Journal Cancer Prevention. 2013, 14; 11: 6197-208.

Kraft TE, D Parisotto, Schempp, T. Efferth. Fighting cancer with red wine? Molecular mechanisms of resveratrol. Crit. Rev. Food Sci. Nutr. 2009: 782–799.

Lipinski, KA, Barber, LJ, Davies, MN, Ashenden, M, Sottoriva, A, Gerlinger M. Cancer Evolution and the Limits of Predictability in Precision Cancer Medicine. Trends Cancer. 2016,2 (1):49-63.

Liu and ZENG et al. Rational combination of oncolytic vaccinia virus and PD-L1 blockade works synergistically to enhance therapeutic efficacy. Nature Communications. 2017, 8, n. 1, p.14754-14754, 27.

Lucas J, Hsieh TC, Halicka HD, Darzynkiewicz Z, WU JM. Up-regulation of PDL1 expression by resveratrol and piceatannol in breast and colorectal cancer cells occurs via HDAC3/p300mediated NFκB signaling. Int J Oncol. 2018, 53: 1469–148.

Maeding et al. Boosting Tumor-Specific Immunity Using PDT. Cancers. 2016; 8:10, 91.

Marelli G, Howells A, Lemoine NR, WANG Y. Front Immune.Oncolytic Viral TherapyandtheImmune System: A Double-Edged Sword Against Cancer. 2018, 26; 9:866.

MCCORMICK, P. J. Cancer Tsunami: Emerging Trends, Economic Burden, and Perioperative Implications. Current Anesthesiology Reports. 2018, 8(4), 348–354.

Mukherjee, SJI and DUDLEY EDK. "Dose-dependency of Resveratrol in providing health benefits." Dose-Response.2010 8(4): 478-500.

Niles RM, Cook CP, Meadows GG. Resveratrol is rapidly metabolized in athymic (nu/nu) mice and does not inhibit human melanoma xenograft tumor growth. J. Nutr. 2006, 136: 2542–2456.

Patel KR, Brown VA, Jones DJ, Britton RG, Hemingway D, Miller AS et al. Clinical pharmacology of resveratrol and its metabolites

in colorectal cancer patients. Cancer Research. 2011, 70, n. 19, 7392-9.

Pecorino, L. Molecular biology of cancer. Oxford University Press, 2012; 3, 342.

REBECCA L. SIEGEL, KIMBERLY D. MILLER AHMEDIN JEMAL DVM. Cancer statistics, 2017. Ca Cancer J Clin 2017;67:7–30

Sarma, JV, Ward PA. The complement system. Cell Tissue Research. 2011, 343; 1: 227-35.

Shanmugam MK, Shen H, Tang FR, Arfuso F, RAJESH M, Wang L, Kumar AP, Jinsong B, ET al.Potential role ofgenipin in cancertherapy. Pharmacol Res 2018; 17: 31356-7.

Shi, X. P.; Miao, S.; Wu, Y.; Zhang, X. F.; Ma, H. Z.; Xin, H. L.; Feng, J.; Wen, A. D.; LI, Y. Resveratrol Sensitizes Tamoxifen in Antiestrogen-Resistant Breast Cancer Cells with Epithelial- Mesenchymal Transition Features. International Journal of Molecular Science. 2013,14; 8: 15655-68.

Shukla Y Singh R. Resveratrol and cellular mechanisms of cancer prevention. Ann N Y Acad Sci. 2011, 1215:1-8.

Sim, Dados de declaração de óbito. Brasil. Ministério da Saúde. Departamento de Informação e Informática do SUS. Brasília: DATASUS In, Sistema de informação sobre mortalidade SIM, 2009.

Soares-Filho PR, Castro I, Stahlschmidt A. Efeito do vinho tinto associado ao exercício físico no sistema cardiovascular de ratos espontaneamente hipertensos. Arquivos Brasileiros de Cardiologia. 2011, 96;4, p. 277-83.

SUN HEE RIM, GERY P. GUY JR., K. ROBIN YABROFF, KATHLEEN A. MCGRAW & DONATUS U. The impact of chronic conditions on the economic burden of cancer survivorship: a systematic review. Expert Review of Pharmacoeconomics & Outcomes Research. 2016, 16:5, 579-589.

Suva, ML. Epigenetic reprogramming in câncer. Science. 2013, 339: 1567-1570.

Svajger, U, Jeras M. Anti-inflammatory effects of resveratrol and its potential use in therapy of immune-mediated diseases. International Reviews of Immunology. 2012, 31; 202–22.

Terra, R. Efeitos do exercício no sistema imune: resposta, adaptação e sinalização celular. Revista brasileira de medicina do esporte. 2012, v. 18, n. 3, p. 208-14.

Totsch, SK, SORGE, RE. Immune system involvement in specificpainconditions. Molecular Pain. 2017v. 13, p. 1–1.

Wang Y, Romigh T, HE X, Orloff MS, Silverman, RH, et al. Resveratrol regulates the PTEN/AKT pathway through androgen receptor-dependent and independent mechanisms in prostate cancer cell lines. Human Molecular Genetics. 2010, 19 (22):4319-29.

Who - World Health Organization, 2017. World's health ministersre new commitmenttocancerprevention and control. Disponível em: <http://www.who.int/cancer/media/news/cancer-prevention-resolution/en.> Acesso em: jun de 2018.

Woo. Innate immune recognition of cancer. Annual review of immunology, 2015, 33, 445-474.

Wu X, XU Y, Zhu B, Liu Q, Yao Q, Zhao G. Resveratrol in-duces apoptosis in SGC-7901 gastric cancer cells. Oncol Lett. 2018, 16: 2949–2956.

Zhao W, Huang X, Han X, Hu D, Hu X, Li Y, Huang P, Yao W. Resveratrol suppresses gut-derived NLRP3 inflammasome partly through stabilizing mast cells in a rat model. Mediators Inflamm. 2018: 6158671.

Zheng X, Jia B, Tian XT, Song X, WU ML, Kong QY, Li H, LIU J. Correlation of reactive oxygen species levels with resveratrol sensitivities of anaplastic thyroid cancer cells. Oxid Med Cell Longev. 2018: 6235417.

Zhou JH, Cheng HY, Yu Z, Q He, D W, Pan Z, Yang DT. Resveratrol induces apoptosis in pancreatic cells. Clinical Medicine Journal. 2011, 124; 11: 1695

Zhou R, Yi L, YE X, Zeng X, Liu K, Qin Y, Zhang Q, MI M. Resveratrol ameliorates lipid droplet accumulation in liver through a SIRT1/ATF6-dependent mechanism. Cell Physiol Biochem. 2018, 51: 2397–2420.

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