

Exploring Melissa Officinalis Properties for Glioblastoma Multiforme Treatment

Cerli Rocha Gattass*

Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro Rio de Janeiro, RJ, Brazil

*Corresponding author: Cerli Rocha Gattass, Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil, Tel: 55 21 3938-6564; Fax: 55 21 2280-9120; Email: cerli@biof.ufrj.br

Received date: 13 July, 2015; Accepted date: 24 August, 2015; Published date: 31 August, 2015

Copyright: © 2015 Gattass CR. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

Despite advances in molecular biology and biology of tumors, in techniques for cancer detection or in the development of target directed compounds, the treatment of cancer is still a challenge. Thus, although some leukemias are now often curable and breast cancer became a chronic illness after treatment, the prognostic for other neoplasias remain poor. These tumors initially respond to chemotherapy, but eventually became resistant to a broad spectrum of structurally and functionally unrelated anticancer agents characterizing the so-called multidrug resistance (MDR) phenotype. Development of MDR is one of the major obstacles to the success of cancer chemotherapy. In clinical settings, patients that exhibit the MDR phenotype usually do not respond to chemotherapy, present tumor recurrence, develop metastasis and evolve to death. Therefore, the search of drugs able to bypass MDR mechanisms and increase the patient's life expectancy is of great clinical relevance for cancer therapy. In the last years, several extracts and substances isolated from plants had shown to modulate drug resistance in cancer cells. In 2014, a paper published by Queiroz and collaborators [1] showed that Melissa officinalis essential oil (EO) and its major component citral, are cytotoxic for glioblastoma multiforme cells, killing cells by a mechanism dependent of the production of reactive oxygen species (ROS). Data demonstrating that they also inhibit the transporter protein MRP1 suggest that these components would be of interest for GBM treatment. Here, we discuss the main mechanisms of drug resistance, with emphasis in GBM, and we describe the properties of M. officinalis EO, which could be effective against MDR tumors.

Cancer Drug Resistance

Multidrug resistance (MDR) is a multifactorial process with several underlying mechanisms such as expression of transporter proteins of the ABC super-family, alterations of pathways that control apoptosis, alterations of DNA repair mechanisms and alterations of mitochondrial functions, among others [2]. Super-expression of transporter proteins of the ABC super-family ("ATP-binding cassette") is one of the most investigated MDR mechanisms. Among the 48 known human ABC genes, p-glycoprotein (Pgp/ABCB1), multidrug resistance associated protein 1 (MRP1/ABCC1) and breast cancer resistance protein (BCRP/ABCG2) are the main targets for drug resistance studies due to their association with MDR phenotype in cancer. These proteins work as efflux pumps actively removing drugs from the cells, decreasing their intracellular concentration and therefore preventing cell death [3]. Also, defects in apoptosis pathways contribute to chemoresistance or radioresistance. As most chemotherapeutic drugs exert their cytotoxic effects by inducing apoptosis, defects in apoptosis pathways emerged as another important drug resistance mechanism. Apoptosis signaling may be disrupted by the aberrant expression of antiapoptotic and/or apoptotic inhibitor

proteins. Moreover, alterations in mitochondria function has also been pointed as an important target to cancer chemotherapy resistance, inasmuch as alterations of the mitochondria membrane potential may activate the intrinsic pathway of apoptosis or induce the production of ROS, another important pathway in drug induced cell death [4].

Glioblastoma Multiforme

Glioblastoma multiforme (GBM), a grade IV astrocytoma, is the most common and aggressive CSN primary tumor, with an average life expectancy of less than 15 months [5]. Representing 50% of all gliomas, GBMs are renowned for their radio- and chemo resistance and is considered an incurable malignancy. Frequently, initial treatment leaves a residual disease from which the tumor relapses, generally with more aggressive and resistant cells. Indeed, even after neurosurgical resection, followed by aggressive chemotherapy and radiotherapy, GBM prognosis is dismal [6]. Intrinsic and acquired drug resistances remain a major problem for GBM treatment. GBMs are composed of a heterogeneous population of invasive and rapidly proliferating neoplastic astrocytes with a high degree of cellularity, vascular proliferation and tumor cell chemoresistance. The genome of the GBM is highly mutated. Aberrations in the signaling elements controlling apoptosis (such as mutations/deletions of EGFR, IDH1, PT53, PTEN, P16), in the expression of anti-apoptotic proteins of the Bcl2 and XIAP families and in the expression of transporter proteins of the ABC superfamily may explain the intrinsic resistance of GBM cells to chemotherapy. The expression of ABC transporter proteins in GBM has been correlated with poor prognostic [7]. Also, pharmacological inhibition of MRP1 activity or expression resulted in increased drug cytotoxicity [8,9].

The current GBM treatment, which comprises surgical resection, radiation and/or chemotherapy, have low efficacy. The location of GBM in the central nervous system and the lack of clear margins between healthy and neoplastic tissues prevent complete resection of the tumor and presumes additional radio- and/or chemotherapy. However, use of these approaches alone or in combination are unable to improve significantly the median survival time of GBM patients that remain low [5,6]. Restricted drug delivery across the blood brain barrier (BBB) and tumor cell resistance to chemotherapy and irradiation contribute to the poor prognosis of the disease, despite treatment. Thus, although the BBB may be disrupted at the tumor core, it is intact at other tumor areas where the presence of tight junctions and transporter proteins of the ABC family prevents access of chemotherapeutic drugs to tumor cells. The alkylating agent temozolomide (TMZ), the front-line drug used for GBM treatment induces mitochondria uncoupling, ROS production, DNA strand breaks in GBM cells [10,11] and show a modest increase in patients survival rate [6]. However, a great number of patients with recurrent GBM develop resistance to the second cycle of TMZ and the treatment

efficacy is further decreased. Expression of ATP-dependent drug efflux pumps, increase in mitochondria function and decrease of ROS production are just some of the mechanisms responsible for TMZ resistance [11,12].

Essential Oils

Essential oils (EO) are volatile compounds produced by plants that present different biological activities including antitumor effect [13, 14]. Although essential oils also seem to have anti-MDR activity and induce death of resistant cells [14] their anti-MDR activity still needs to be better understood/explored. The antitumor activity of *Melissa officinalis* EO is a potential alternative for tumors treatment. *Melissa officinalis* is an aromatic plant of the Lamiaceae family. Its EO presents different biological activities including an antitumor activity that was described by de Souza and colleagues [15]. In this work, it was shown that the essential oil of the plant could inhibit the viability of cell lines from various types of cancer such as breast, lung, colon, melanoma and leukemia. However, although these cells include a number chemo resistant lines like lung (A540) and melanoma (B16F10) the mechanism of their death was not investigated. The study of the composition of this EO, by gas chromatography, showed that it has as major components nerol (39.28%) and geranial (47.32%), which together represent almost 90% of the oil composition [15]. These two compounds are isomers of the same molecule, citral. Citral (3,7-dimethyl-2,6-octadienal) is a reactive and volatile aldehyde, belonging to the class of the terpenes, specifically a monoterpene. This compound induces apoptosis of leukemia and breast cancer-cell lines through Caspase-3 activation and cell cycle arrest [16,17]. Queiroz and colleagues [1] showed that *M. officinalis* essential oil presents antitumor activity in GMB cell lines and that its major component, citral, has the same effect on these tumor cells, possibly being the bioactive component of *M. officinalis* oil. In this paper, they also showed that citral-induced apoptosis was mediated by ROS and that this compound negatively modulated the expression and activity of the MDR protein MRP1, an active transporter present in glioma cells and in the BBB.

Conclusion

Treatment of GBM continues to be a challenge. Cure is not attained with the protocols currently used that translate mainly in a modest increase in survival rate, emphasizing the need to improve GBM therapy. Several studies have aimed improvement of clinical efficacy of GBM chemotherapy by targeting resistance mechanisms. The low efficacy of target directed drugs may be explained by the high number of genomic mutations and mechanisms of drug resistance present in GBM and by different routes to escape from death. Thus, compounds that interfere simultaneously with more than one of these pathways may help to improve GBM treatment. *Melissa officinalis* EO was shown to be cytotoxic for cell lines of chemoresistant tumors such as melanoma and lung. The ability of *Melissa officinalis* EO (and citral) to induce ROS production in GBM suggests its use as a co-adjuvant in the treatment of patients resistant to TMZ. In addition, Citral, the main component of *M. officinalis* EO, inhibits the expression and activity of transporter protein MRP1, an important mechanism of drug resistance in GBM. The effect of this inhibition on drug transport through the BBB remains to be investigated. Thus, *M. officinalis* EO is emerging as a promising tool to treat GBM and other MDR tumors. Nonetheless, studies directed to other mechanisms of tumor resistance

such as pathways involved in apoptosis control, stem cells and miRNA could bring additional clues to *M. officinalis* EO anti-MDR properties.

Acknowledgement

This work was supported by grants from Conselho Nacional de Ciência e Tecnologia (CNPq grant #309056/2014-4) and from Fundação Carlos Chagas Filho de Amparo a Pesquisa do Rio de Janeiro (FAPERJ grant #E-26/ 010.002894/2014).

References

1. Queiroz RM, Takiya CM, Guimarães LPTP, Rocha GdA, Alviano DS, et al. (2014) Apoptosis-Inducing Effects of *Melissa officinalis* L. Essential Oil in Glioblastoma Multiforme Cells. *Cancer Inv* 32: 226-235.
2. Longley DB, Johnston PG (2005) Molecular mechanisms of drug resistance. *J Pathol* 205: 275-292.
3. Fletcher JL, Haber M, Henderson MJ, Norris MD (2010) ABC transporters in cancer: more than just drug efflux pumps. *Nature Rev Cancer* 10: 147-156.
4. Indran IR, Tufo G, Pervaiz S, Brenner C (2011) Recent advances in apoptosis, mitochondria and drug resistance in cancer cells. *Biochim Biophys Acta* 1807: 735-745.
5. Stupp R, Mason WP, Van Den Bent MJ, Weller M, Fisher B, et al. (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352: 987-996.
6. Daresky AS, King JRJT, Dubrow R (2012) Adult Glioblastoma Multiforme Survival in the Temozolomide Era: A Population-Based Analysis of Surveillance, Epidemiology, and End Results Registries. *Cancer* 118: 2163-2172.
7. Nakagawa T, Ido K, Sakuma T, Takeuchi H, Sato K, et al. (2009) Prognostic significance of the immunohistochemical expression of O6-methylguanine-DNA methyltransferase, P-glycoprotein, and multidrug resistance protein-1 in glioblastomas. *Neuropathol* 29: 379-388.
8. Benyahia B, Huguet S, Declèves X, Mokhtari K, Crinière E, et al. (2004) Multidrug resistance-associated protein MRP1 expression in human gliomas: chemosensitization to vincristine and etoposide by indomethacin in human glioma cell lines overexpressing MRP1. *J Neurooncol* 65: 65-70.
9. Garrido W, Muñoz M, San Martín R, Quezada C (2011) FK506 confers chemosensitivity to anticancer drugs in glioblastoma multiforme cells by decreasing the expression of the multiple resistance-associated protein-1. *Biochem Biophys Res Commun* 411: 62-68.
10. Zhang WB, Wang Z, Shu F, Jin YH, Liu HY, et al. (2010) Activation of AMP-activated protein kinase by temozolomide contributes to apoptosis in glioblastoma cells via p53 activation and mTORC1 inhibition. *J Biol Chem* 285: 40461-40471.
11. Oliva R, Moellering DR, Gillespie GY, Griguer CE (2011) Acquisition of chemoresistance in gliomas is associated with increased mitochondrial coupling and decreased ROS production. *PLoS One* 6: 1-10.
12. Happold C, Roth P, Wick W, Schmidt N, Florea AM, et al. (2012) Distinct molecular mechanisms of acquired resistance to temozolomide in glioblastoma cells. *J Neurochem* 122: 444-455.
13. Bayala B, Bassole IRN, Gnoula C, Nebie R, Albert Yonli A, et al. (2013) Chemical Composition, Antioxidant, Anti-Inflammatory and Anti-Proliferative Activities of Essential Oils of Plants from Burkina Faso *Plos One* 9: e92122.
14. Russo R, Corasaniti MT, Bagetta G, Morrone LA (2015) Exploitation of Cytotoxicity of Some Essential Oils for Translation in Cancer Therapy. *Evid Based Complement Alternat Med Article ID: 397821*, 9.
15. de Sousa AC, Alviano DS, Blank AF, Alves PB, Alviano CS, et al. (2004) *Melissa officinalis* L. essential oil: antitumoral and antioxidant activities *J Pharm Pharmacol* 56: 677-681.
16. Dudai N, Weinstein Y, Krup M, Rabinski T, Ofir R (2005) Citral is a new inducer of caspase-3 in tumor cell lines. *Planta Med* 71: 484-488.

17. Chaouki W, Leger DY, Liagre B, Beneytout JL, Hmamouchi M (2009) Citral inhibits cell proliferation and induces apoptosis and cell cycle arrest in MCF-7 cells. *Fundam Clin Pharmacol* 23: 549-556.