



Research Article

Resveratrol and Copper Nutraceutical Combination: Protection against Chemotherapy-Induced Toxicity

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Received: 11 June 2024

Published: 01 July 2024

Abstract

Background: Cancer is still classed as the major leading cause of death with the uncontrollable growth of cells resulting in many complications. One of the effective ways to reduce the progression of cancer is chemotherapy, but most of the patients are scared of this treatment because of the imposed side effects such as nausea, alopecia, immunosuppression etc. However the unwanted effects of chemotherapeutic drugs are not due to drugs themselves as they were believed to be, but rather due to vicious cycle of DNA damage, apoptosis and hyperinflammation caused by the cell free chromatin particles (cfChps) which are released in cancer patients during chemotherapy due to drug induced cell death. The Resveratrol and copper nutraceutical combination is found to be harnessing the toxicity produced by cfChps because it has capacity to generate unstable free radicals which can degrade cfChps preventing the chemotherapy toxicity. The main objective of this review is to understand the basic mechanism behind chemotherapy toxicity and the protective role of resveratrol and copper against this toxicity.

Methods: The publications were identified by thorough comprehensive searching of PubMed, Frontier and Science Direct data base. Search terms included combinations of “Cancer,” “Resveratrol,” “Copper,” “Chemotherapy,” “Toxicity.” The literature selection is mainly focused on resveratrol and copper combination in reducing the chemotherapy toxicity.

Results: Several articles were referred in this review to outline the protective mechanism of resveratrol and copper nutraceutical combination against chemotherapy toxicity. Among which, the results from clinical trials of RESCU001(2) and RESCU003(15) provides a significant evidence and proves that the combination of Resveratrol and Copper along with chemotherapy helps in reducing the unwanted effects and thereby enhances the viability of treatment.

Conclusion: This study provides a systematic research briefing of resveratrol and copper nutraceutical combination in fighting against the chemotherapy toxicity and enhancing the therapeutic outcomes of treatment. Since the area is still exploratory and results are promising in the previous clinical trials, I propose further studies using randomized controlled trials.

Keyword: Cancer, resveratrol, copper, chemotherapy, toxicity, treatment, cell-free chromatin.

Introduction

The traditional and effective treatment for reducing the progression of cancer is chemotherapy, but the cytotoxicity produced by these drugs affect both normal and neoplastic cells(13). Some of the common side effects of chemotherapy include immunosuppression, nausea, alopecia, etc. In some cases, the range of unwanted effects are seriously debilitating or sometimes life threatening. So the chemotherapy toxicity became a major therapeutic challenge. This review will showcase the underlying mechanism of Resveratrol and Copper combination in treating chemotherapy toxicity. By understanding these mechanisms effectively, we can further optimize the design and efficacy of Resveratrol and Copper dosage approaches for advancements in reducing toxic effects of chemotherapy.

Resveratrol – The French Paradox

Resveratrol is a polyphenolic compound, derived from plants such as grapevine, nuts, pines(11) etc.

The compound is known to be of great benefits for its prooxidant properties in cancer and cardiovascular diseases. In cancerous cells, it increases oxidative stress within the mitochondria resulting in apoptosis. In myocardium, it can upregulate autophagy and reverses the cardiac remodeling, which are the major targets for the prevention of cardiovascular diseases. These initial findings were primarily because of phenomena of ‘French paradox’; which is a paradoxical finding that the incidence of coronary heart diseases is relatively low in southern France population despite having higher intake of saturated fats in their diet; it is correlated with their high consumption of red wine in which resveratrol is found to be major constituent responsible for this effect. As discussed, resveratrol is popular for its prooxidant properties but Fukuhara and Miyata were the first to report the antioxidant activity of Resveratrol in the presence of Copper(12) which is the impetus for this study

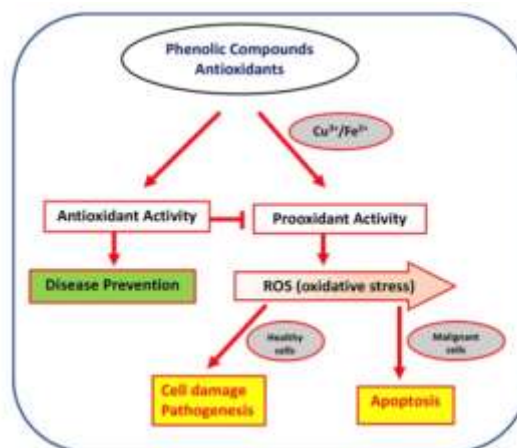


Figure 1. *Dual nature of phenolic compounds. Collected from Scientific research an academic publisher*
<https://www.scirp.org/journal/journalarticles.aspx?journalid=207>

Methodology

To evaluate the association between the nutraceutical combination of R + Cu and chemotherapy toxicity, thorough secondary analysis of previous clinical trials, research studies and comprehensive reviews of relevant literature were conducted in PubMed, Frontier and Science Direct data base using key words such as Cancer, Resveratrol, Copper, Chemotherapy, Toxicity. Selection of material was limited to papers that are published in English Language. All the publications were thoroughly checked. Patents, dissertations and books were excluded. Also the therapeutic benefits of Resveratrol on virus, fungi, inflammation etc. were excluded. The inclusion criteria for the methods I have used is mainly focused on therapeutic outcomes of resveratrol and copper with regard to chemotherapy toxicity. Literature was limited to articles published no later than 20 years old to ensure the validity of this study.

Results

Using the search strategies I have mentioned above, I collected the relevant and appropriate literature for my study. Upon studying and analyzing the data, I understood the basic mechanism behind chemotherapy toxicity which helped me construct the idea behind how resveratrol and copper nutraceutical combination could help in achieving the therapeutic outcomes of chemotherapy by reducing its toxic effects.

Understanding The Mechanism underlying Chemotherapy Toxicity

Cell-free chromatin particles are released from dying cells in our body and are eliminated by Reactive Oxygen Species (ROS) production under normal cases. But in cancer patients, the chemotherapy induced cell death results in release of imbalanced/enormous amounts of cfChPs impairing the clearance mechanism performed by ROS inflicting the mitochondrial damage, especially breaking the dsDNA & thereby activating inflammatory cytokines(2). The cfChPs or fragments of chromosomes have the ability to enter surrounding healthy cells; Genomic integration of these cfChp particles in healthy cells occurs, which results in global deregulation of transcription and upregulation of phagocytosis pathways, DNA damage and inflammation.

Hence they turn normal healthy cells into cancerous ones causing new tumors. The combination of Resveratrol and copper is believed to be effective in fighting against these cfChps because the Resveratrol has a property to reduce Cu^{2+} to Cu^+ in Fenton like Reaction(14) resulting in the generation of unstable free radicals which can degrade cell free chromatin and thereby preventing the chemotherapy toxicity. This principle is the basis for series of clinical trials like RESCU001, RESCU003 etc. which were conducted in patients who were receiving chemotherapy with multiple myeloma, advanced gastric cancer respectively. These clinical trials provided me with significant evidence to form an idea that resveratrol and copper may help chemotherapy toxicity for other types of cancers as well.

To summarize, RESCU001 was designed as an exploratory study, conducted in patients suffering from Multiple myeloma(2) who were receiving high dose melphalan (chemotherapy) along with resveratrol and copper nutraceutical combination . The research objective was to investigate the efficacy of resveratrol and copper in reducing chemotherapy toxicity. The patients were divided into three groups; Group 1 receiving only vehicle, serving as a control group; Group-2 receiving R-Cu at dose level 1 (R-5.6mg, Cu-560ng) and Group-3 receiving R-Cu at dose level 2 (R-50mg, Cu-5 μ g). Common Terminology Criteria for adverse events was used to assess toxic effects and inflammatory cytokines were detected in blood and saliva by ELISA. In the results section of this study, I observed that the patients who received chemotherapy along with R-Cu are protected from toxic effects such as oral mucositis and also there was significant reduction of proinflammatory cytokines in their saliva. The maximum efficacy was detected in the group-2 who received R-Cu at low doses establishing the dose-response effect in the study.

Toxicity		Control	DI-I	p value	DL-II	p value
		(n = 5)	(n = 15)		(n = 5)	
Oral mucositis	Incidence of grade 3-4 mucositis	5 (100%)	6 (40%)	0.038	2(40%)	0.167
	Median duration of grade 3-4 mucositis (range)	5 (2-8)	4.5 (2-6)	0.848	4.5 (3-6)	0.693
Diarrhoea	Incidence of grade 3-4 diarrhoea	3 (60%)	6 (40%)	0.617	3 (60%)	1.000
	Median duration of grade 3-4 diarrhoea (range)	3 (2-11)	2.5 (2-9)	0.492	1(1-3)	0.178
Vomiting	Incidence of grade 3-4 vomiting	0 (0%)	2 (13%)	1.000	0(0%)	1.000
	Median duration of grade 3-4 vomiting (range)	-	1 (1-1)	-	-	-
Nausea	Incidence of grade 3-4 nausea	1 (20%)	4 (27%)	1.000	0 (0%)	1.000
	Median duration of grade 3-4 nausea (range)	4	4.5 (2-9)	0.480	-	-
Use of analgesics	Incidence of use of opioid analgesics	5 (100%)	8 (53%)	0.114	3 (60%)	0.444
	Median duration of use of opioid (range)	7(5-11)	6.5(1-10)	0.374	8(4-10)	0.763
TPN use	Incidence of use of TPN	4 (80%)	5 (33%)	0.127	2 (40%)	0.524
	Median duration of use of TPN (range)	7(5-9)	8(7-15)	0.201	8(8-8)	0.340
Engraftment fever	Incidence of engraftment fever	3 (60%)	9(60%)	1.000	3(60%)	1.000

P<0.05 is statistically significant

Table. 1 Comparison of toxicity in control and resveratrol-copper group. *Collected from RESCU001 study in PLOS ONE* <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0262212>

RESCU003(15) is a similar clinical trial where patients with advanced gastric cancer were enrolled in the study. The research objective is to investigate if R-Cu would reduce the toxicity from docetaxel-based multi-agent chemotherapy in advanced gastric cancer patients. Common Terminology Criteria For Adverse Events was used to assess toxic effects; and the results found were there is significant reduction in the incidence of non-hematological toxicity consisting of hand-foot syndrome, diarrhea, vomiting etc.

Conclusion

To sum up, the resveratrol and nutraceutical combination represents a promising frontier in reducing chemotherapy toxicity. In general, Resveratrol is used as a nutraceutical with its known benefits in initiating cell induced death in neoplastic cells as it interferes with the metabolism of those cells. The Resveratrol alone is used as prooxidant because it enhances the oxidative stress(8) within the mitochondria of cancer cells, resulting in damage and death. But interestingly in the presence of copper it acts as an antioxidant, helping in combat against the toxicity generated by cfChPs. Also one more key finding in previous studies is that they

investigated not only the efficacy of Resveratrol and copper in reducing toxicity, but also established the dose-response effect with molar ratio of Resveratrol to Copper at 1:0.0001 as effective(2). However there are limited number of participants in those studies, it may have intervened with the outcomes. Since the area is still exploratory and the results are promising, there is a need for further research using randomized controlled trials. The significance of this study is that there are agents such as palifermin, curcumin etc. which are currently used for the prevention of chemotherapy toxicity. However among these, only Palifermin got approved by FDA for commercial use. But it is prohibitively expensive (approximately 5500 USD per day) to be used in low-middle income countries(5). Hence there is a serious need for an alternative which is affordable for everyone and is feasible to be used in a wide population. The resveratrol and copper nutraceutical combination offers hope for improved and affordable treatment.

References

- 1)Aishwarya Pilankar et al(2022, September 16). A pro-oxidant combination of resveratrol and copper down-regulates hallmarks of cancer and immune checkpoints in patients with advanced oral cancer: Results of an exploratory study. National Library of Medicine. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9525028/>
- 2)Anshul Agarwal et al. (n. d). A novel pro-oxidant combination of resveratrol and copper reduces transplant related toxicities in patients receiving melphalan for multiple myeloma (RESCU001). PLOS ONE. <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0262212>
- 3)C Alarcon de la Lastra et al. (2007, Nov). Resveratrol as an antioxidant and pro-oxidant agent: mechanisms and clinical implications. PubMed. <https://pubmed.ncbi.nlm.nih.gov/17956300/>
- 4)Indraneel M et al. (n.d). Cell-free chromatin particles released from dying host cells are global instigators of endotoxin sepsis in mice. PLOS ONE. <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0229017>
- 5)Ajay Nooka et al. (2014, March). Pharmacoeconomic Analysis of Palifermin to Prevent Mucositis among Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation. Research Gate. https://www.researchgate.net/publication/260644809_Pharmacoeconomic_Analysis_of_Palifermin_to_Prevent_Mucositis_among_Patients_Undergoing_Autologous_Hematopoietic_Stem_Cell_Transplantation
- 6)Naig Gueguen et al. (n.d). Resveratrol Directly Binds to Mitochondrial Complex I and Increases Oxidative Stress in Brain Mitochondria of Aged Mice. PLOS ONE.

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0144290>

7)Int J Mol Sci. (2017, December). The Role of Resveratrol in Cancer Therapy. National library of medicine. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5751192/>

8)Lolita Kursvietiene et al. (2023). Anti-Cancer Properties of Resveratrol: A Focus on Its Impact on Mitochondrial Functions. National library of Medicine. <https://pubmed.ncbi.nlm.nih.gov/38136176/>

9)Snehal Shabrish. (n.d). Cell-free chromatin particles released from dying cancer cells activate immune checkpoints in human lymphocytes: implications for cancer therapy. *Frontiers*. <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1331491/full>

10)Channa B Rajashekar. (2023). Dual Role of Plant Phenolic Compounds as Antioxidants and Prooxidants. Scientific Research an academic publisher.

<https://www.scirp.org/journal/paperinformation?paperid=122414#:~:text=Thus%2C%20the%20dual%20nature%20of,malignant%20cells%20and%20foodborne%20pathogens.>

11)Qicai Xiao et al. (2019, Jan 9). A Review of Resveratrol as a Potent Chemoprotective and Synergistic Agent in Cancer Chemotherapy. Pubmed Central. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6333683/>

12)Kavita pal et al. (2022, October 14). A pro-oxidant combination of resveratrol and copper down-regulates multiple biological hallmarks of ageing and neurodegeneration in mice. *Scientific Reports*. <https://www.nature.com/articles/s41598-022-21388-w>

13)Lowenthal, R. M et al. (1996, August 10). Toxicity of chemotherapy. *PubMed*. <https://pubmed.ncbi.nlm.nih.gov/8811311/>

14)Mittra, I. (2024, Feb). Exploiting the damaging effects of ROS for therapeutic use by deactivating cell-free chromatin: the alchemy of resveratrol and copper. *Frontiers*. <https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2024.1345786/full>

15) Ostwal, V. et al. (2022, Nov). A pro-oxidant combination of resveratrol and copper reduces chemotherapy-related non-haematological toxicities in advanced gastric cancer: results of a prospective open label phase II single-arm A study (RESCU III study). National library of Medicine. <https://pubmed.ncbi.nlm.nih.gov/36372825/>



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