# Histopathological Effects of Cytarabine on Rabbit Tongue Tissue and the Possibility of Treatment with Vitamin E

**Original Article**

*Ammar L. Alshibib*

*Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Al-Farahidi University, Baghdad, Iraq*

## ABSTRACT

**Introduction:** This study aimed to investigate the possibility of treating the side effects of cytarabine on the tongue using vitamin E in rabbits.

**Material and Methods:** Three-month-old rabbits weighing 1.5 to 2.0 kg were utilized in this investigation. A total of 18 rabbits were separated into 3 equal groups at random, with each group containing 6 rabbits. Vitamin E was administered orally, and cytarabine was administered intraperitoneally. Each treatment was administered daily for one week, following groups distilled water was administered parenterally to a control group, and A 50 mg/kg dosage of cytarabine was administered to the second group. The third group was given cytarabine 50 mg/kg, and then 5 hours later, it was given vitamin E at a dose of 800 IU.

**Results:** The result revealed The tongue Cytarabine treated group showed hyperkeratosis with hyalinization, ballooning degeneration, necrosis of the epithelial cells degeneration, (Zenker's) of skeletal muscle cells with atrophy, oedema between it, inflammation, and congestion of blood vessels, while the Cytarabine with vitamin E treated group showing intact mucosa with filiform and epithelial cells, and longitudinal and transverse skeletal muscles, also showing mild hyperkeratosis, and degeneration of the epithelial cells and intact fungiform papillae.

**Conclusions:** The conclusion from this study is that vitamin E is a promising treatment for cytarabine's side effects and that combining them has positive effects on treating rabbits' tongue lesions.

**Key Words:** Cytarabine, rabbits, tongue, vitamin E.

**Received:** 25 September 2022, **Accepted:** 13 December 2022

**Corresponding Author:** Ammar L. Alshibib, PhD, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Al-Farahidi University, Baghdad, Iraq, **Tel.:** 009647831316137, **E-mail**: ammarloay83@gmail.com

**ISSN:** 2090-0740, 2022

## INTRODUCTION

A variety of types of leukaemia, including acute myelogenous and meningeal leukaemia, are treated with the anti-metabolic medication cytarabine. The DNA building blocks purines and pyrimidines, which are anti-metabolites, influence the DNA of cancer cells and prevent them from merging during the cell cycle's "S" phase, halting the normal growth and division of these cells[1]. The regimen for hematopoietic stem cell transplantation (HSCT) includes high doses of cytarabine, which frequently result in acute oral mucositis[2].

Recent research has demonstrated that cytarabine is excreted in saliva by individuals taking large doses of the drug and that this directly and locally promotes the onset of oral mucositis. This finding therefore strongly implies a role for salivary cytarabine secretion in the emergence of cytarabine-associated oral mucositis[3]. Cytarabine is toxic to a variety of mammalian cells in *vitro*, showing specificity especially in the death of cells in the S phase, slowing the transition of cells from G1 to the S phase, and killing cells that are undergoing DNA synthesis[4].

A significant side effect of cytotoxic therapy is oral mucosal and tongue inflammation, which causes severe morbidity and elevated mortality. In addition to excruciating pain, cancer treatment may need to be interrupted due to mucosal issues, which reduce its efficacy and reduce the quality of life due to the inability to eat, which also affects recovery times and expenditures associated with health services[5].

Due to the high concentration of opportunistic bacteria in the oral cavity, the oral mucosa and tongue are vulnerable to cytotoxic substances, localized radiation, and focal or diffuse desquamation[6]. Recent findings in the literature imply that vitamin E might make a good option for cancer adjuvant therapy. Although a-tocopherol has been the subject of most studies. Recent research indicates that different vitamin E isomers have different proapoptotic capacities, indicating that mitochondria are the primary target of apoptosis induction by vitamin E isomers and analogues. Additionally, various signalling pathways regulated by vitamin E help determine the intrinsic apoptotic pathway that was initially triggered by mitochondria[7].

 *DOI: 10.21608/ejentas.2022.165013.1563*

According to additional research, vitamin E may prevent cancer in males with prostate cancer[8]. While another study revealed that higher circulating a-TOC levels within the normal range were linked to fewer deaths in male smokers[9], a third study revealed that dietary vitamins E and C were statistically protective for both colorectal cancers and that there was a dose-response effect for protection against colon cancer for both vitamins[10].

## MATERIALS AND METHODS

### *Animals*

Three-month-old rabbits weighing 1.5 to 2.0 kg were utilized in this investigation. They were housed in a laboratory at a temperature of 23+ 4 °C with a 12-hour light/dark cycle. Before the trial, the rabbits were kept in the lab for six days. The animals were fed rabbit chow pellets with a 22% protein content. The University of Mosul's guidelines were followed in regard to the treatment of the bunnies, which was humane. This study was carried out at the College of Dentistry, the University of Mosul, Iraq with the ethical approval number UM.DENT/ A.L.72/21 at 15/10/2021.

### *Experience Design*

A total of 18 rabbits were separated into 3 equal groups at random, with each group containing 6 rabbits. Vitamin E was administered orally, and cytarabine was administered intraperitoneally (Figure 1). Each treatment was administered daily for one week, with the following groups:

- **G1:** Distilled water was administered parenterally to a control group.
- **G2:** A 50 mg/kg dosage of cytarabine was administered to the group.
- **G3:** This group was given cytarabine 50 mg/kg, and then 5 hours later, it was given vitamin E at a dose of 800 IU.

Following a week of therapy, the rabbits received ether anaesthesia for sacrifice and dissection. The tongue was then removed, thoroughly washed, and fixed for three days in a 10% formalin solution. slides were stained with hematoxylin-eosin and examined Under a light microscope.

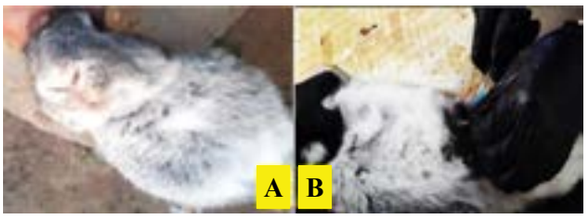


**Fig. 1:** A representative image for the administration of vitamin E oral (A) and cytarabine intraperitoneal (B).

## RESULTS

Histopathology of the experimental groups revealed that the rabbit's tongue of the control group showed normal architecture, represented by mucosa, taste buds, submucosa, and longitudinal and transversal skeletal muscles (Figure 2,Table 1). The tongues of the Cytarabine treated group showed necrosis and hyaline degeneration (Zenker's) of skeletal muscle cells with atrophy and oedema between it, hyperkeratosis with hyalinization, ballooning degeneration, necrosis of the epithelial cells, inflammation and congestion of blood vessels (Figure 2, Table 1).

The rabbit's tongue of the Cytarabine with vitamin E treated group revealed intact mucosa with filiform and epithelial cells, and longitudinal and transverse skeletal muscles (Figure 2 and Table 1), also the other rabbit's tongue of the Cytarabine with vitamin E treated group showed mild hyperkeratosis, and degeneration of the epithelial cells and intact fungiform papillae (Figure 2, Table 1).

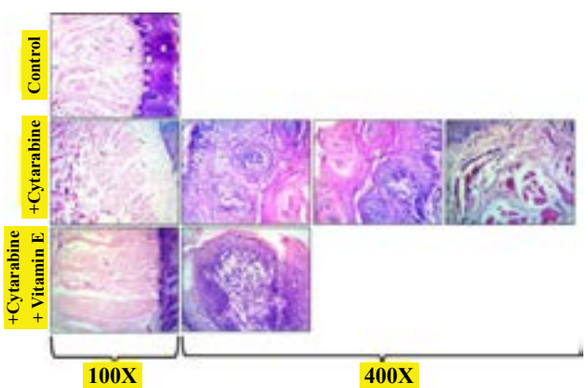


**Fig. 2:** Representative image for the studied section of rabbits tongue for cytarabine-induced oral lesions with potential suppression by vitamin E.

**Table 1:** Histopathological findings of rabbit tongue after exposure to cytarabine and potential suppression by vitamin E.

| Groups | Control | +Cytarabine | +Cytarabine +Vitamin E |
|---|---|---|---|
| Histological Findings | • Normal architecture is represented by mucosa, taste buds, submucosa and longitudinal and transverse skeletal muscles. | • Necrosis and hyaline degeneration (Zenker's) of skeletal muscle cells with atrophy and oedema between it.<br>• Hyperkeratosis with hyalinization, ballooning degeneration and necrosis of the epithelial cells.<br>• Hyperkeratosis with hyalinization, ballooning degeneration and necrosis of the inflammation of the epithelial cells.<br>• Necrosis and hyaline degeneration (Zenker's) of skeletal muscle cells with atrophy, oedema between it and congestion of blood vessels. | • Intact mucosa with filiform and epithelial cells, and longitudinal and transverse skeletal muscles.<br>• Mild hyperkeratosis, and degeneration of the epithelial cells and intact fungiform papillae. |

## DISCUSSION

The findings of our study demonstrated that cytarabine, a cancer medication, can have hazardous effects in non-target or non-cancerous tissues, including the tissues of the tongue and oral cavity, The tongue Cytarabine treated group showed hyperkeratosis with hyalinization, ballooning degeneration, necrosis of the epithelial cells degeneration, (Zenker's) of skeletal muscle cells with atrophy, oedema between it, inflammation and congestion of blood vessels. Acute side effects are common during or after therapy and chronic side effects can linger for a very long period after the end of cancer treatment. These treatment-related adverse effects are common in the mouth, pharynx, and oesophagus because these are organs having mucous membranes made up of epithelial cells that regenerate rapidly[11-13].

The use of anticancer medications causes lesions to appear on both keratinized and non-keratinized mucosa, whereas other studies claim that ulcers only appear in non-keratinized areas, The buccal surfaces, labia, soft palate, ventral side of the tongue, and mouth floor are among the mucosal regions of the mouth[14-16]. The dorsal surface of the tongue, gums, and hard palate is less frequently impacted structures[17]. Clinically, mucositis and tongue may exhibit a variety of complicated symptoms, Redness and scaly spots that become mildly uncomfortable upon pressing are the first signs of the condition, Following early radiation, vascular atrophy, ulcers, increased salivary viscosity, dry mouth, and oral pain are the most noticeable oral alterations[15].

Antineoplastic agents administered into the spinal cord: increase the neurotoxicity of cytarabine. Digoxin: may reduce the absorption of digoxin from the gastrointestinal tract. Flucytosine: cytarabine reduces the anti-inflammatory effect of flucytosine. Gentamicin: cytarabine reduces the effect of gentamicin and the liposome (liposomal) cytarabine affects the result of the white cell assay. In the cerebrospinal fluid, the result is greater than reality[18]. Our study's treatment time was set at 7 days, according to prior research, the detrimental consequences start to manifest after 7 to 10 days, and oral mucositis progressively gets worse, peaking in 7 to 17 days[17,15]. Numerous anticancer medications prevent mucosal regeneration and directly block DNA replication from cellular proliferation[19].

Pathological tongue lesions may result from indirect toxicity to the mouth, which is the second mechanism, during the period of treatment-induced neutropenia, as a result of the emergence of subclinical gum infection. Additionally, chemotherapy-induced dry mouth reduces salivary mucous secretions in the mouth. As a result, the mucous membranes' protective barrier is partially compromised, making it simple for germs and fungi to infiltrate the body[20-22].

Lysozymes, lactoperoxidases, immunoglobulins, lactoferrins, and histastatins are only a few of the compounds in saliva that have antibacterial action and are important for maintaining the health of the oral mucosa[23,24]. Another hypothesis for the pathogenesis of oral and tongue mucositis is the influence of cytokines that play an important role in pro-inflammatory transcription factors in the development of mucositis[25,26].

Following exposure to cytotoxic agents, the production of reactive oxygen species causes immediate damage to tissues and mucous membrane components. This is followed by the stage of regulation and message generation, one of which is the activation of transcription factors, in particular nuclear factor jB (NFjB). This transcription factor, which is activated in response to chemotherapy and radiation therapy, controls up to 200 genes that affect the integrity of the mucosa by inducing clonal cell death, apoptosis,

and tissue injury across the mucosa. jB mucositis-related production of pro-inflammatory cytokines such as tumour necrosis factor (TNF), interleukin-1b (IL-1b), and interleukin-6 (IL-6)[27], The third stage involves signal amplification and arises from proinflammatory cytokines acting through positive feedback mechanisms that further activate NF-kB cause an increase in the production of other bioactive cytokines or pro-inflammatory mediators, like cyclooxygenase-2 COX-2[28,29]. These mediators also start an inflammatory stimulation that results in matrix activation of proteins producing more tissue that develops the ulcerative stage[30].

One of the ways that many chemotherapy drugs kill cancer cells is by oxidative stress. Chemotherapy-induced ROS types and concurrent oxidative damage to proteins (including antioxidants and energy-generating enzymes), lipids, nucleic acids, and cellular components (such as membranes and mitochondria are responsible for the acute or chronic toxic side effects of chemotherapy. Laterally affecting non-target tissues (i.e., non-cancerous) under conditions of oxidative stress[31].

To prevent ROS formation and maintain a stable cellular redox state, cellular antioxidants and antioxidant enzymes are essential. Cellular antioxidants are consumed by the ROS -induced chemotherapeutic drug, which results in an oxidative action[32]. Reactive chemical production can severely affect cell integrity by changing the permeability and fluidity of the lipid bilayer membrane[33].

Given that vitamin E is a potent antioxidant and that tocotrienols are proapoptotic agents, investigations have shown that vitamin E administration improved the histopathological lesions of the tongue[34]. When vitamin E analogues were used, the synergistic effects of vitamin E with anticarcinogens were investigated. The researchers looked at daily supplementation with 50 mg of tocopherol acetate and/or 20 mg of b-carotene decreased the number of fatalities from laryngeal, oesophagal, and oral cancers[35,36].

Isomers of vitamin E have been demonstrated to have cytotoxic and anticancer properties in research studies involving cancer cell lines, animal models, and clinical trials[37]. The literature's data support vitamin E and its equivalents' ability to induce caspase-independent apoptosis.

Initially, it was believed that vitamin E's chemopreventive effects resulted from its capacity to scavenge free radicals produced by faecal bacteria in the colon and so prevent DNA damage. However, research shows that signal transduction activities are unrelated to vitamin E's antioxidant properties[7]. Despite these protective effects of vitamin E, the endogenous milieu of the extracellular compartment is highly sensitive to local factors of inflammatory/proinflammatory markers[38,39], cellular integrity[40], and oxygen supply[41,42].

We think that all of the mentioned factors discussed in this study explain why the histopathological changes of the tongue were improved in the animals treated with cytarabine and given vitamin E doses. The difference is also apparent when comparing the pathological effects and looking at the outcomes.

## CONCLUSION

We found in this study that vitamin E is a promising treatment for Cytarabine's side effects and that combining them has positive effects on treating rabbits' tongue lesions.

## ACKNOWLEDGEMENT

We thank the College of Dentistry at the University of Baghdad for supporting this research.

## CONFLICT OF INTEREST

There are no conflicts of interest.

## REFERENCES

1. Ma J, Li X, Su Y, Zhao J, Luedtke DA, Epshteyn V, Edwards H, Wang G, Wang Z, Chu R, Taub JW. Mechanisms responsible for the synergistic antileukemic interactions between ATR inhibition and cytarabine in acute myeloid leukemia cells. Scientific reports. 2017; 7(1): 1-4. https://doi.org/10.1038/srep41950

2. Chhikara BS, Parang K. Development of cytarabine prodrugs and delivery systems for leukemia treatment. Expert opinion on drug delivery. 2010; 7(12): 1399-414. https://doi.org/10.1517/17425247.2010.527330

3. Liu R, Jiang Y, Hu X, Wu J, Jiang W, Jin G, Luan Y. A preclinical evaluation of cytarabine prodrug nanofibers assembled from cytarabine-lauric acid conjugate toward solid tumors. International Journal of Pharmaceutics. 2018; 552(1-2): 111–118. https://doi.org/10.1016/j.ijpharm.2018.09.043

4. Momparler RL. Optimization of cytarabine (ARA-C) therapy for acute myeloid leukemia. Experimental hematology & oncology. 2013; 2(1): 1-5. https://doi.org/10.1186/2162-3619-2-20

5. Qin T, Youssef EM, Jelinek J, Chen R, Yang AS, Garcia-Manero G, Issa JP. Effect of cytarabine and decitabine in combination in human leukemic cell lines. Clinical Cancer Research. 2007; 13(14): 4225-32. https://doi.org/10.1158/1078-0432.CCR-06-2762

6. Cros E, Jordheim L, Dumontet C, Galmarini CM. Problems related to resistance to cytarabine in acute myeloid leukemia. Leukemia & lymphoma. 2004; 45(6): 1123-32. https://doi.org/10.1080/1042819032000159861

7. Constantinou C, Papas A, Constantinou AI. Vitamin E and cancer: An insight into the anticancer activities of vitamin E isomers and analogs. International journal of cancer. 2008; 123(4): 739-52. https://doi.org/10.1002/ijc.23689

8. Parnes HL, House MG, Kagan J, Kausal DJ, Lieberman R. Prostate cancer chemoprevention agent development: the National Cancer Institute, Division of Cancer Prevention portfolio. The Journal of urology. 2004 Feb 1;171(2):S68-75. https://doi.org/10.1097/01.ju.0000107220.64675.74

9. Weinstein SJ, Wright ME, Pietinen P, King I, Tan C, Taylor PR, Virtamo J, Albanes D. Serum alpha-tocopherol and gamma-tocopherol in relation to prostate cancer risk in a prospective study. J Natl Cancer Inst. 2005; 97: 396–9. https://doi.org/10.1093/jnci/dji045

10. Kune G, Watson L. Colorectal cancer protective effects and the dietary micronutrients folate, methionine, vitamins B6, B12, C, E, selenium, and lycopene. Nutr Cancer. 2006; 56:11–21. https://doi.org/10.1207/s15327914nc5601_3

11. Jungsuwadee P, Vore M, Clair DK. Chemotherapy-induced oxidative stress in nontargeted normal tissues. InOxidative Stress in Cancer Biology and Therapy 2012 (pp. 97-129). Humana Press, Totowa, NJ. https://doi.org/10.1007/978-1-61779-397-4_6

12. Abraham P, Rabi S, Selvakumar D. Protective effect of aminoguanidine against oxidative stress and bladder injury in cyclophosphamide-induced hemorrhagic cystitis in rat. Cell Biochemistry and Function: Cellular biochemistry and its modulation by active agents or disease. 2009 Jan;27(1):56-62. https://doi.org/10.1002/cbf.1534

13. Ahles TA, Saykin AJ, Furstenberg CT, Cole B, Mott LA, Skalla K, Whedon MB, Bivens S, Mitchell T, Greenberg ER, Silberfarb PM. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. Journal of Clinical Oncology. 2002 Jan 15;20(2):485-93.

14. Almquist KC, Loe DW, Hipfner DR, Mackie JE, Cole SP, Deeley RG. Characterization of the M r 190,000 multidrug resistance protein (MRP) in drug-selected and transfected human tumor cells. Cancer Research. 1995 Jan 1;55(1):102-10.

15. Anderson AB, Arriaga EA . Subcellular metabolite profi les of the parent CCRF-CEM and the derived CEM/C2 cell lines after treatment with doxorubicin. J Chromatogr B Analyt Technol Biomed Life Sci. 2004, 808(2): 295–302 https://doi.org/10.1016/j.jchromb.2004.05.017

16. Ballatori N, Hammond CL, Cunningham JB, Krance SM, Marchan R. Molecular mechanisms of reduced glutathione transport: role of the MRP/CFTR/ABCC and OATP/SLC21A families of membrane proteins. Toxicology and applied pharmacology. 2005 May 1;204(3):238-55. https://doi.org/10.1016/j.taap.2004.09.008

17. Araki, S., Omori, Y., Lyn, D., Singh, R.K., Meinbach, D.M., Sandman, Y., Lokeshwar, V.B. and Lokeshwar, B.L., 2007. Interleukin-8 is a molecular determinant of androgen independence and progression in prostate cancer. Cancer research, 67(14), pp.6854-6862. https://doi.org/10.1158/0008-5472.CAN-07-1162.

18. Adema AD, Laan AC, Myhren F, Fichtner I, Verheul HM, Sandvold ML, Peters GJ. Cell cycle effects of fatty acid derivatives of cytarabine, CP-4055, and of gemcitabine, CP-4126, as basis for the interaction with oxaliplatin and docetaxel. International journal of oncology. 2010 Jan 1;36(1):285-94. https://doi.org/10.3892/ijo_00000499.

19. Al-Abdaly YZ, Saeed MG, Al-Hashemi HM. Effect of methotrexate and aspirin interaction and its relationship to oxidative stress in rats. Iraqi J Vet Sci. 2021; 35(1): 151-6. DOI: 10.33899/ijvs.2020.126490.1335

20. Gilson E, Higgins CF, Hofnung M, Ames GF, Nikaido H. Extensive homology between membrane-associated components of histidine and maltose transport systems of Salmonella typhimurium and Escherichia coli. Journal of Biological Chemistry. 1982 Sep 10;257(17):9915-8. https://doi.org/10.1016/S0021-9258(18)33962-0

21. Lorico A, Nesland J, Emilsen E, Fodstad O, Rappa G. Role of the multidrug resistance protein 1 gene in the carcinogenicity of aflatoxin B1: investigations using mrp1-null mice. Toxicology. 2002 Feb 28;171(2-3):201-5. https://doi.org/10.1016/S0300-483X(01)00584-4

22. Maiorino M, Wissing JB, Brigelius-Flohé R, Calabrese F, Roveri A, Steinert P, Ursini F, Flohé L. Testosterone mediates expression of the selenoprotein PHGPx by induction of spermatogenesis and not by direct transcriptional gene activation. The FASEB journal. 1998 Oct;12(13):1359-70. https://doi.org/10.1096/fasebj.12.13.1359

23. Leslie EM, Haimeur A, Waalkes MP. Arsenic transport by the human multidrug resistance protein 1 (MRP1/ABCC1): evidence that a tri-glutathione conjugate is required. Journal of Biological Chemistry. 2004 Jul 30;279(31):32700-8. https://doi.org/10.1074/jbc.M404912200

24. Leslie EM, Ito KI, Upadhyaya P, Hecht SS, Deeley RG, Cole SP. Transport of the β-O-glucuronide conjugate of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) by the multidrug resistance protein 1 (MRP1): requirement for glutathione or a non-sulfur-containing analog. Journal of Biological Chemistry. 2001 Jul 27;276(30):27846-54. https://doi.org/10.1074/jbc.M102453200

25. Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. Oral Oncol. 1998; 34(1):39-43. doi: 10.1016/s1368-8375(97)00053-5.

26. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: part 1, pathogenesis and prophylaxis of mucositis. Head Neck 2003; 25(12): 1057–70. 13. https://doi.org/10.1002/hed.10318

27. Sonis ST. The biologic role for nuclear factor-jB in disease and its potential involvement in mucosal injury associated with antineoplastic therapy. Crit Rev Oral Biol Med 2002; 13(5): 380–90. https://doi.org/10.1177/154411130201300502

28. Hall PD, Benko H, Hogan KR, Stuart RK. The influence of serum tumor necrosis factor-a and interleukin-6 concentrations on nonhematologic toxicity and hematologic recovery in patients with acute myelogenous leukemia. Exp Hematol. 1995; 23(12): 1256–60.

29. Ferrà C, de Sanjosé S, Gallardo D, Berlanga JJ, Rueda F, Marìn D, de la Banda E, Ancìn I, Peris J, Garcìa J, Grañena A. IL-6 and IL-8 levels in plasma during hematopoietic progenitor transplantation. Haematologica. 1998 Jan 1;83(12):1082-7. https://doi.org/10.3324/%25x

30. Yasuda T. Cartilage destruction by matrix degradation products. Mod Rheumatol. 2006; 16(4):197-205. doi: 10.1007/s10165-006-0490-6.

31. Merkhan MM, Faisal IM, Alsaleem DZ, Shindala OM, Almukhtar HM, Thanoon IA. Immunodepressant and oxidant potential of standard leukaemia drug regimen. International Journal of Research in Pharmaceutical Sciences. 2020;11(4):1-4. DOI:10.26452/ijrps.v11i4.3199

32. Chen Y, Jungsuwadee P, Vore M, Butterfield DA, St Clair DK. Collateral damage in cancer chemotherapy: oxidative stress in nontargeted tissues. Molecular interventions. 2007; 7(3):147. doi: 10.1124/mi.7.3.6

33. T. A. Dix and J. Aikens, "Mechanisms and biological relevance of lipid peroxidation initiation," Chemical Research in Toxicology. 1993; 6(1): 2–18.

34. Burton GW, Traber MG. Vitamin E: antioxidant activity, biokinetics, and bioavailability. Annu Rev Nutr. 1990; 10:357–82.

35. Heinonen OP, Koss L, Albanes D, Taylor PR, Hartman AM, Edwards BK, Virtamo J, Huttunen JK, Haapakoski J, Malila N, Rautalahti M. Prostate cancer and supplementation with α-tocopherol and β-carotene: incidence and mortality in a controlled trial. JNCI: Journal of the National Cancer Institute. 1998 Mar 18;90(6):440-6.https://doi.org/10.1093/jnci/90.6.440

36. Wright ME, Weinstein SJ, Lawson KA, Albanes D, Subar AF, Dixon LB, Mouw T, Schatzkin A, Leitzmann MF. Supplemental and dietary vitamin E intakes and risk of prostate cancer in a large prospective study. Cancer Epidemiol Biomarkers Prev. 2007; 16:1128–35. https://doi.org/10.1158/1055-9965.EPI-06-1071

37. Shun MC, Yu W, Gapor A, Parsons R, Atkinson J, Sanders BG, Kline K. Pro-apoptotic mechanisms of action of a novel vitamin E analog (a-TEA) and a naturally occurring form of vitamin E (d-tocotrienol) in MDA-MB-435 human breast cancer cells. Nutr Cancer. 2004; 48: 95–105. https://doi.org/10.1207/s15327914nc4801_13.

38. Chen L, Merkhan MM, Forsyth NR, Wu P. Chorionic and amniotic membrane-derived stem cells have distinct, and gestational diabetes mellitus independent, proliferative, differentiation, and immunomodulatory capacities. Stem Cell Research. 2019 Oct 1;40:101537. https://doi.org/10.1016/j.scr.2019.101537

39. Shephard MT, Merkhan MM, Forsyth NR. Human Mesenchymal Stem Cell Secretome Driven T Cell Immunomodulation Is IL-10 Dependent. International Journal of Molecular Sciences. 2022 Nov 6;23(21):13596. https://doi.org/10.3390/ijms232113596.

40. Narayanasamy KK, Price JC, Merkhan M, Elttayef A, Dobson J, Telling ND. Cytotoxic effect of PEI-coated magnetic nanoparticles on the regulation of cellular focal adhesions and actin stress fibres. Materialia. 2020 Sep 1;13:100848. https://doi.org/10.1016/j.mtla.2020.100848.

41. Merkhan MM, Shephard MT, Forsyth NR. Physoxia alters human mesenchymal stem cell secretome. Journal of Tissue Engineering. 2021 Oct;12:20417314211056132. https://doi.org/10.1177/2041731421105613

42. Forsyth NR, Steeg R, Ahmad M, Al Zubaidi M, Al-Jumaily R, Merkhan M, Dale T. Mimicking Physiological Oxygen in Cell Cultures. InCell Culture Technology 2018 (pp. 129-137). Springer, Cham. DOI: 10.1007/978-3-319-74854-2_8.