Available online at www.SciMedJournal.org

SciMedicine Journal

(ISSN: 2704-9833)

Vol. 4, No. 1, March, 2022

Simple Physical Process Can Slow Down the Progression of Cancer

Jozsef Garai [1*], Pal Kertai [2]

[1] *Formerly: University of Debrecen, Debrecen, Hungary.*

[2] *Institute of Preventive Medicine, University of Debrecen, Debrecen, Hungary.*

Received 09 January 2022; Revised 21 February 2022; Accepted 26 February 2022; Published 01 March 2022

Abstract

If a liquid contains suspended solids and flows out of a perforated pipe, the suspended particles of the right size can accumulate and eventually clog the openings. It is suggested that this physical process could be employed to effectively block the openings of the intercellular gaps in angiogenic capillaries supplying cancer tissues. Clogging the big openings supplying cancer tissues would reduce the nutrition supply, resulting in deprivation. This process predictively could slow down the tumor progression. If the proposed physical process is effective, then societies that drink water containing colloidal-size particles should have fewer occurrences of cancer. Epidemiological data is consistent with this prediction and shows an inverse correlation between the total dissolved solid concentrations in drinking water and the incidence of cancer. The effectiveness of the proposed physical process was tested in a pilot project on six rats. Four of them had suspended kaolinite minerals in the drinking water, and two of them got regular tap water. All the treated rats developed smaller tumors than the untreated control group of two. The average weight of the developed tumors was 42 percent less in the treated group.

Keywords: Angiogenesis; Cancer Treatment; Nanoparticle Treatment; Enhanced Permeability and Retention Effect; Anticancer; Nano Medicine.

1. Introduction

Cancer occurs when cell replication fails to be regulated by the usual mechanisms and the growth of the cells becomes uncontrolled. It is generally assumed that chemical processes control the regulation of cell replication. Thus, the traditional cancer treatments are chemical, like chemotherapeutics. The problem with this traditional treatment is two folded. The employed drug deprecates rapidly in the body, and is unable to differentiate between hostile, and non-hostile cells.

One of the characteristics of the tumor tissues is that the very fast growth of the tumor prevents the complete development of capillary blood vessels supplying nutrition to cancer cells. The gaps between the endothelial cells are 200 to 1200 nm in comparison to the normal size of 10-50 nm. Consequently, the tumor vasculature has an altered, leaky structure with much higher permeability than the normal one. The much larger openings allow enhanced accumulation of nanoparticles at the tumor site [1]. This enhanced permeability and retention effect allows targeting tumors directly by nanoparticles [2, 3]. This newly developed nanotechnology plays an important role in

* Corresponding author: jozsef.garai@fiu.edu

http://dx.doi.org/10.28991/SciMedJ-2022-0401-4

the diagnosis, early detection, and treatment of malignancies [4, 5]. An overview of the currently approved nano-medicines for cancer treatment can be found in Rodriguez et al. [6]. Here, based on the different gaps between the endothelial cells in the tumor-supplying and healthy blood vessels, a simple physical process is proposed to slow down the progression of cancer.

2. Method

It is well established that angiogenesis is one of the essential parts, critical to the growth of cancer [7]. Occlusion of these tumor-feeding vessels has been proposed for cancer treatment [8]. The growth of new capillaries supplying the tumors with nutrients is very rapid [9]. Resulting from this rapid growth, the capillaries are irregular and leaky [10]. The gaps or openings in their walls are much larger than in healthy capillaries. The gap sizes in normal capillaries are 2–6 nm. The gap sizes of angiogenic capillaries, which supply tumor cells, generally range from a few hundred nanometers to a few micrometers [11]. The exact size of the gaps varies as the function of location and type of malignancy. This purely physical phenomenon, many orders of bigger openings in the capillaries, allows the drug to selectively accumulate in tumor tissue without damaging healthy cells [10, 12]. The size of the nano-particles used for targeted drug delivery to cancer is between 10 and 300 nm in diameter. This size range is just right to pass through the gaps but not penetrate healthy tissue.

If liquid flows through the perforations of a tube and contains suspended solids with similar sizes as the size of the perforations, then the suspended particles would accumulate and eventually clog the openings [13]. The experimental validation data of such blockage for fine particles (diameter < 0.01 mm) are lacking. The microscopic hydrodynamic phenomena, such as aggregation, cementation, and transport in the capillaries, are not known. Despite these uncertainties, it can be predicted that the intercellular gaps of the angiogenesis capillaries would be clogged by the right size of suspended substance. The clogging should significantly reduce the nutrition supply to cancer tissues, resulting in a slower development of the tumor (Figure 1).

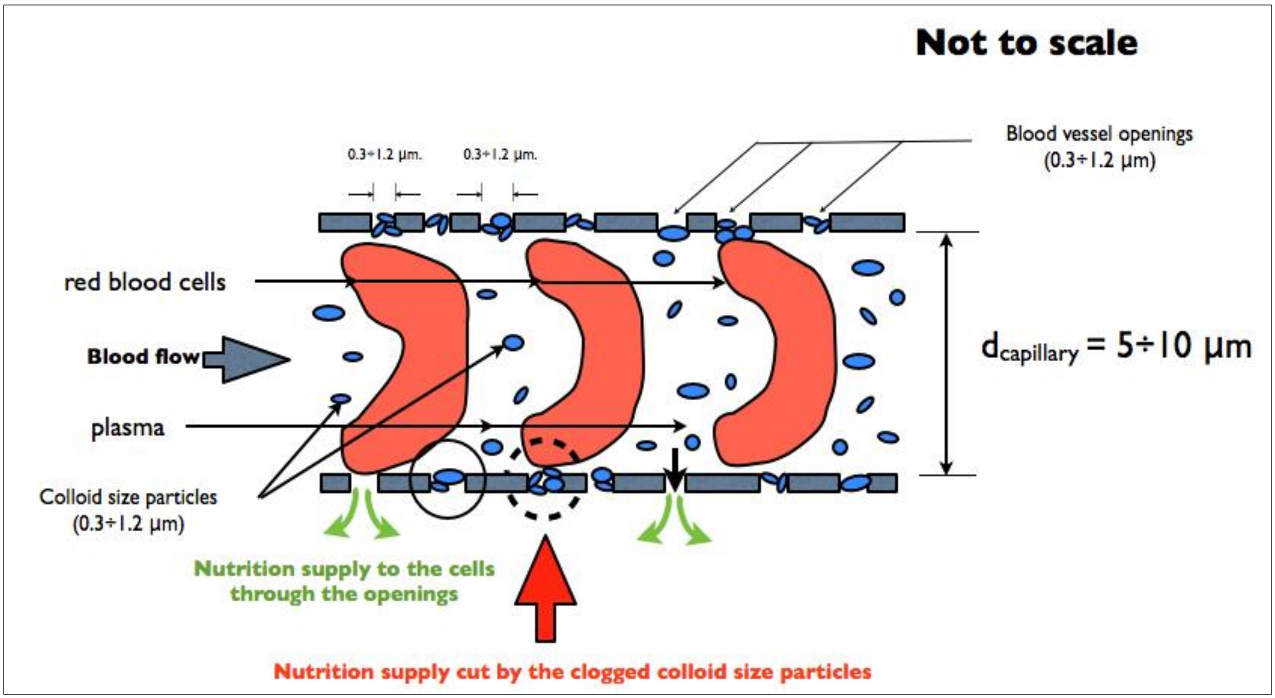


Figure 1. Schematic figure of a capillary blood flow supplying cancer cells is shown. The many orders of bigger gaps on the capillaries (0.3-1.2 µm), supplying cancer cells, can be clogged by colloid size particles present in the plasma of the blood. This physical process can significantly reduce the nutrition supply to cancer tissues, and slow down tumor progression

The colloid-size particles could enter from drinking water through the intestines and pass into the bloodstream. Clinically, it is also possible to deliver these particles by intravenous injection. Theoretically, with an appropriately chosen particle size, this physical process should effectively slow down the progression of any kind of cancer. The flow chart of the methodology and the process is shown in Figure 2.

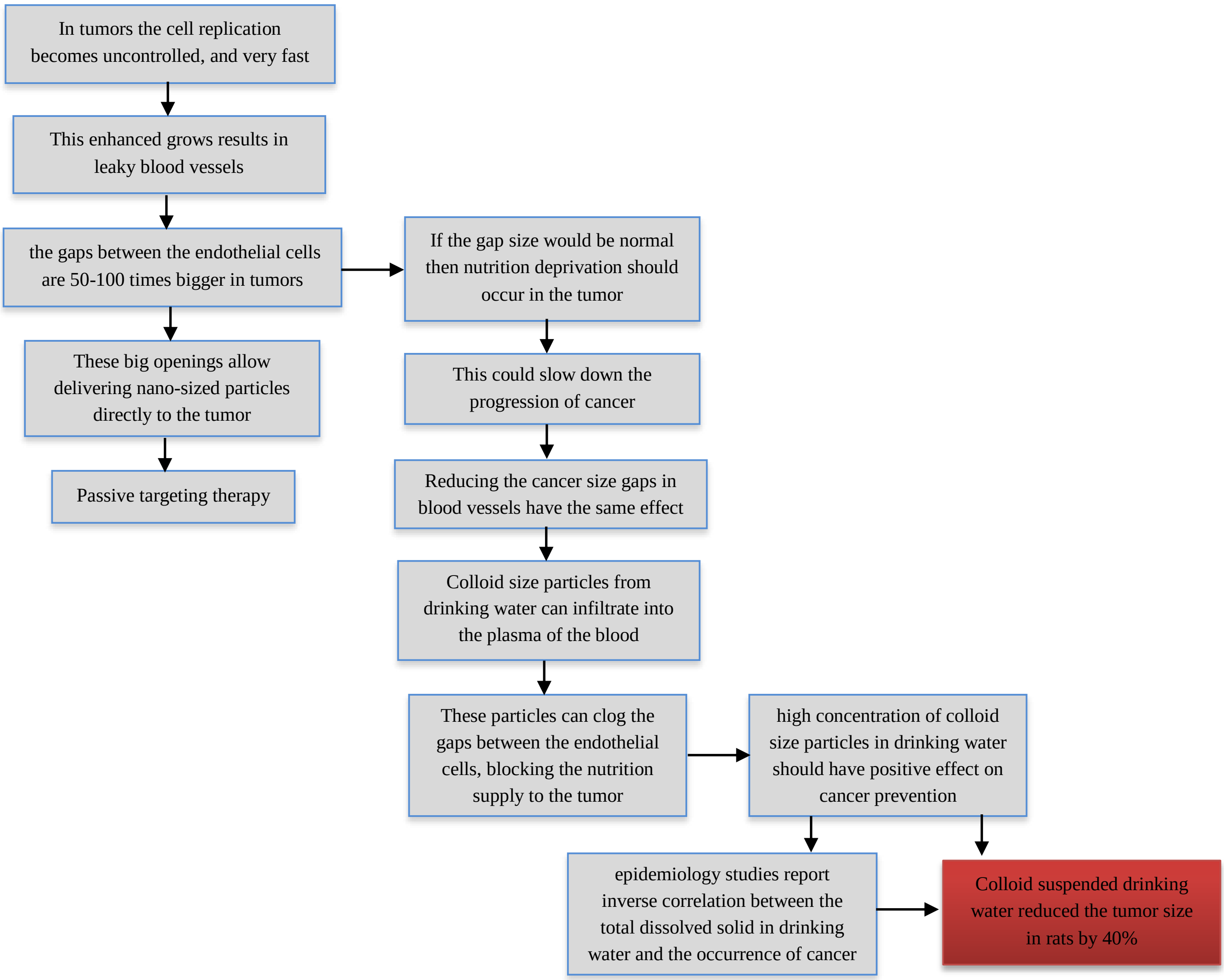
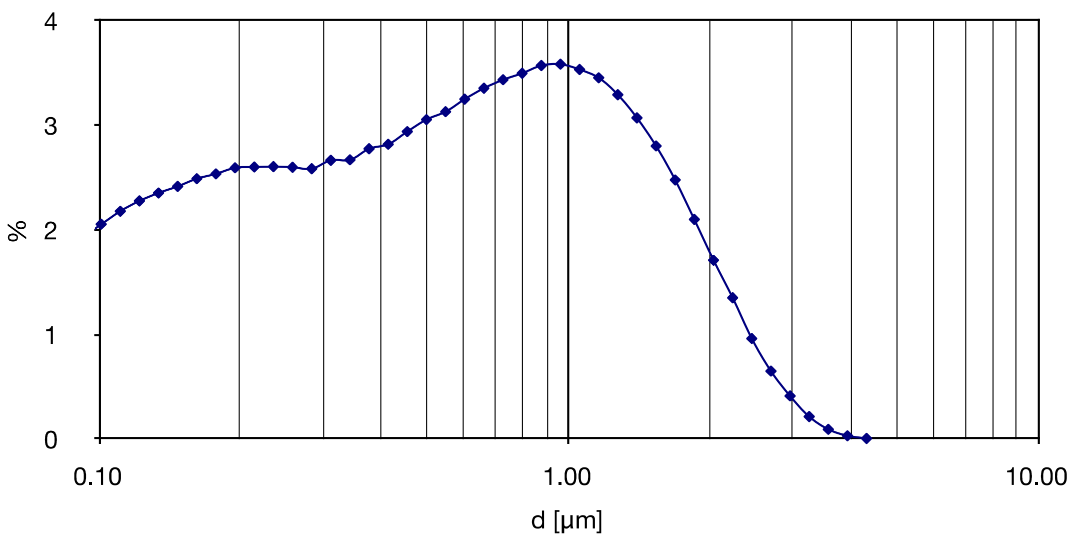


Figure 2. The flow chart of the methodology and the research is shown

3. Material

The intercellular gaps in the angiogenesis capillaries supplying cancer tissues are between 0.1-1.2 µm. Clogging these gaps requires similar particle size. Among the clay minerals, kaolinite [$Al_2Si_2O_5(OH)_4$] has the smallest surface to volume ratio. Consequently, this clay mineral is the least active. For these reasons, kaolinite has been chosen for this study. In order to cover the entire gap size region of the angiogenic capillaries from 50 nm to 2 µm, kaolinite with the particle size distribution shown in Figure 3 was chosen.



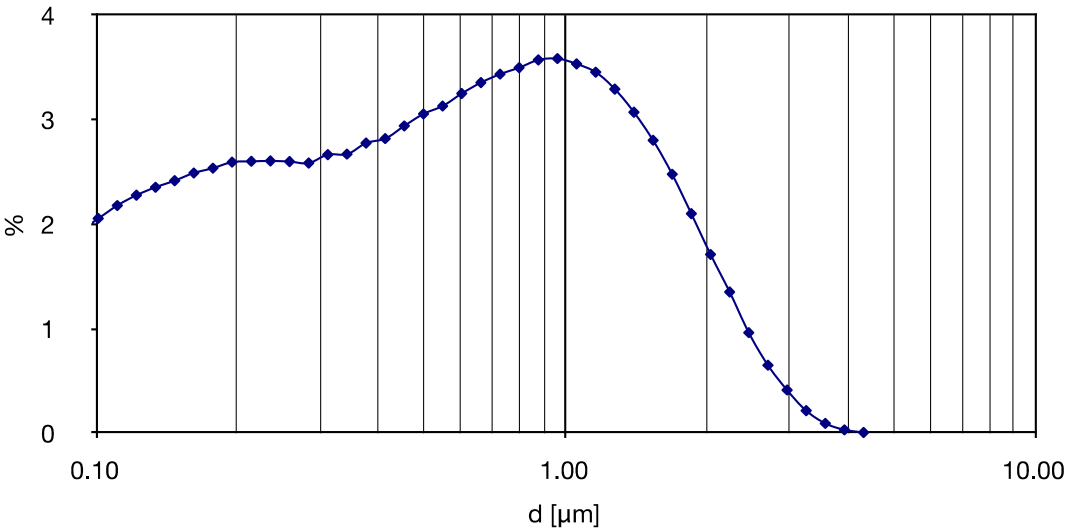


Figure 3. The particle size distribution curve of the used kaolinite, measured by laser diffraction is plotted

4. Results and Discussion

Solid particles, like minerals, can be found in drinking water. These fine particles can be taken up by the intestines from the water and passed into the bloodstream. If the proposed hypothesis is correct, then societies drinking water with substantial amounts of colloid-size particles should have less cancer occurrence in comparison to those drinking regular water with fewer colloid-size particles.

In drinking water, the colloid-size mineral particles are not measured separately but rather together with all solids whose size is smaller than 2 micrometers. This is expressed as the total dissolved solid (TDS), given in mg/L. TDS includes anything present in water other than pure H_2O molecules. The solids in the water are primarily minerals, salts, and organic matter. Thus, the value of TDS does not directly express the quantity of the micro-granular, suspended colloid minerals in water. However, it can be assumed that a high value of TDS is a good indicator for a high content of colloid-size minerals. Concentrations of TDS from natural sources have been found to vary from less than 30 mg/l to as much as 6000 mg/l [14], depending on the solubility of minerals in different geological regions. The presence of dissolved solids in water may affect its taste, and TDS greater than 1200 mg/l is unacceptable for drinking water [15]. Water with extremely low concentrations of TDS may also be unacceptable because of a flat, insipid taste. There is no health-based guideline value for mineral intake [16]. Thus, mineral-enriched drinking water has no known toxicity or side effects.

Epidemiological studies suggest that even low concentrations of TDS in drinking water may have beneficial effects on cancer prevention. Investigating the quality of the water supply of the 100 largest cities in the United States (population over 60 million), an inverse relationship was reported between TDS concentrations in drinking water and the incidence of cancer [17]. The inverse correlation between total mortality rates and TDS levels in drinking water has also been reported [18–20]. Mortality highly correlates with the occurrence of cancer, indicating that higher TDS levels in drinking water have a positive effect on cancer prevention.

Glacial water contains a significant amount of levitated colloid-size mineral particles [21], which gives the water a milky appearance. Societies drinking exclusively "glacial milk" with high mineral content, like the Georgians in Abkhazia, in the Caucasus, the Vilcabamba, in the Andean, and the Hunza, in the Himalayan Mountain region [22], have the highest reported longevity and an almost cancer-free population [23, 24]. Some researchers doubted the accuracy of these age claims [25] because only the age of Georgians was verifiable since neither the Hunzas nor the Vilcabambans have written birth records. The reported cancer-free population, drinking a high concentration of colloid-size mineral particles, is consistent with the proposed clogging hypotheses.

Based on the available worldwide epidemiological data, the inverse correlation between cancer and mineral intake in drinking water seems well established. This correlation indicates that the proposed physical process, drinking water with enhanced colloid size solids, could be effective in cancer prevention and treatment.

The effect of the suspended nanoparticles in the drinking water was tested on rats. The experiments were carried out using male inbred Fischer 344 rats. First, it was tested to see if the animals were willing to drink the water with kaolinite suspension. This test had a positive result. In order to test the effectiveness of the proposed treatment, a Gelaspon disc with 10^6 Ne/De cells has been implanted under the capsule of the left kidney in six rats. The method is described in detail in Trencsenyi et al. [26]. Four of the rats were drinking the kaolinite suspension, and two rats were drinking regular tap water.

After twelve days, the animals were euthanized, and their kidneys and the developed tumor had been weighted. All four of the treated rats had smaller tumors compared to the two untreated rats. The average of the total body weight losses, 3.6 and 3.9 percent, were similar for the untreated and treated rats, respectively. The average weight of the left kidneys, where the cancer cells had been implanted, was 32.4 percent lower for the treated rats. The average weights of the developed tumors were 6.83 g and 3.94 g for the untreated and treated rats, respectively. Thus, the average weight of the tumors was 42.3% lower in the treated rats compared to the untreated ones. All the treated rats had smaller tumors than the untreated ones. The dissection revealed that in all the treated and untreated rats, the lumen of the vessels was wide with many collaterals, and metastases were seen in the lungs, kidneys, and lymph nodes. The individually measured weights are reported in Table 1.

Table 1. The measured total weight of the six rats at the beginning and the end of the test period, the weights of the kidneys, and the weights of the tumors are listed

Treatment	Animal ID #	Weight (g)				
		Total		Kidneys		Tumor
		Beginning	End	Left	Right	
Tap water	1	304	298	6.60	0.90	5.70
	2	287	272	7.86	0.90	6.96
	Average	295.5	285.0	7.23	0.90	6.83
Kaolinite suspension	3	285	291	4.73	0.79	3.94
	4	362	333	4.47	0.94	3.53
	5	387	359	5.25	1.06	4.19
	6	387	383	5.10	1.00	4.10
	Average	355.25	341.5	4.89	0.95	3.94

It can be concluded that the proposed physical process of clogging the gaps between endothelial cells in the tumor-supplying capillaries can significantly slow down the progression of tumor development. Assuming linear correlation between the size of the tumor and the expected overall survival time it can be predicted that the proposed treatment has the potential to expand by an additional 70 percent the average survival time.

5. Conclusion

The characteristic of the tumor tissue is that the intercellular gaps in the angiogenic capillaries are about two orders of magnitude bigger than the normal ones. These big openings are sufficient to supply nutrition to the extremely fast-growing cancer cells. It has been hypothesized that if the size of the openings would be reduced then the smaller permeability of the capillary vessels would lead to nutrition deprivation. This physical process should slow down the progression of cancer. The reduction of the intercellular gaps of the angiogenic capillaries, which supply cancer cells, can be achieved by clogging them with the right colloid size particles. These particles can infiltrate from the drinking water into the blood plasma. This hypothesis is supported by previous epidemiology studies, which reported inverse correlations, between cancer and mineral intake in drinking water.

The hypothesis was also tested on rats. Kaolinite, with particle sizes between 50 nm - 2 μm, has been suspended in the drinking water to test the clogging effect. Cancer cells were transplanted into the kidneys of the rats. The developed tumors were removed and weighted. All of the treated rats had smaller tumors compared to the untreated control group. On average, the weights of the developed tumors were 42.3% lower. If there is a linear correlation between the tumor size and the expected overall survival time, then the proposed treatment has the potential to expand the average survival time by an additional 70 percent.

The size of the gaps of endothelial cells is characteristic of the given cancer. Adjusting the particle size distribution of the suspended colloid particles to the gap sizes allows using the proposed treatment effectively on all kinds of cancers. Mineral-enriched drinking water has no known toxicity or side effects. Thus, the treatment, supposedly, should have no harm to humans.

6. Declarations

6.1. Author Contributions

Conceptualization, J.G. and P.K.; methodology, J.G.; formal analysis, J.G. and P.K.; data curation, P.K.; writing—original draft preparation, J.G. and P.K.; writing—review and editing, J.G. All authors have read and agreed to the published version of the manuscript.

6.2. Data Availability Statement

The data presented in this study are available in the article.

6.3. Funding

The present research is funded by the University of Debrecen.

6.4. Acknowledgement

The authors would like to thank Andras Telekes, and Gyorgy Trencsenyi for reading the manuscript and making comments. The authors also thank to ELTE, Department of Petrology and Geochemistry, and to the Institute for Geological and Geochemical Research at the Hungarian Academy of Science for conducting the particle size distribution tests with laser diffraction analyzers.

6.5. Ethical Approval

Animals were kept in a conventional laboratory environment and fed on a semi-synthetic diet (Charles River Mo, Kft, Godollo, Hungary). Animals received humane care according to the Declaration of Helsinki and the criteria outlined in the United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR) Guidelines for the Welfare of Animals in Experimental Neoplasia (Second Edition), authorized by the Ethical Committee for Animal Research, University of Debrecen (permit number: 22/2007).

6.6. Informed Consent Statement

Not applicable.

6.7. Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

7. References

[1] Matsumura, Y., & Maeda, H. (1986). A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer research, 46(12_Part_1), 6387-6392.

[2] Aslan, B., Ozpolat, B., Sood, A. K., & Lopez-Berestein, G. (2013). Nanotechnology in cancer therapy. Journal of Drug Targeting, 21(10), 904–913. doi:10.3109/1061186X.2013.837469.

[3] Gmeiner, W. H., & Ghosh, S. (2014). Nanotechnology for cancer treatment. Nanotechnology Reviews, 3(2), 111–122. doi:10.1515/ntrev-2013-0013.

[4] Wu, J. (2021). The enhanced permeability and retention (EPR) effect: The significance of the concept and methods to enhance its application. Journal of Personalized Medicine, 11(8), 771. doi:10.3390/jpm11080771.

[5] Leporatti, S. (2022). Thinking about Enhanced Permeability and Retention Effect (EPR). Journal of Personalized Medicine, 12(8), 1259. doi:10.3390/jpm12081259.

[6] Rodríguez, F., Caruana, P., De la Fuente, N., Español, P., Gámez, M., Balart, J., Llurba, E., Rovira, R., Ruiz, R., Martín-Lorente, C., Corchero, J. L., & Céspedes, M. V. (2022). Nano-Based Approved Pharmaceuticals for Cancer Treatment: Present and Future Challenges. Biomolecules, 12(6), 784. doi:10.3390/biom12060784.

[7] Folkman, J., & Kalluri, R. (2003). Chapter 11: Tumor angiogenesis Cancer Medicine, 6th Ed. BC Decker Inc., Hamilton, Canada.

[8] Das, U. N. (2003). Erratum: Abrupt and complete occlusion of tumor-feeding vessels by γ-linolenic acid (Nutrition 18:7-8). Nutrition, 19(1), 90. doi:10.1016/S0899-9007(02)00944-9.

[9] Hanahan, D., & Weinberg, R. A. (2000). The Hallmarks of Cancer. Cell, 100(1), 57–70. doi:10.1016/s0092-8674(00)81683-9.

[10] Cho, K., Wang, X., Nie, S., Chen, Z., & Shin, D. M. (2008). Therapeutic nanoparticles for drug delivery in cancer. Clinical Cancer Research, 14(5), 1310–1316. doi:10.1158/1078-0432.CCR-07-1441.

[11] Hobbs, S. K., Monsky, W. L., Yuan, F., Roberts, W. G., Griffith, L., Torchilin, V. P., & Jain, R. K. (1998). Regulation of transport pathways in tumor vessels: Role of tumor type and microenvironment. Proceedings of the National Academy of Sciences of the United States of America, 95(8), 4607–4612. doi:10.1073/pnas.95.8.4607.

[12] Maeda, H. (2010). Tumor-selective delivery of macromolecular drugs via the EPR effect: Background and future prospects. Bioconjugate Chemistry, 21(5), 797–802. doi:10.1021/bc100070g.

[13] Pérez Paricio, A. (2001). Integrated modelling of clogging processes in artificial groundwater recharge. Ph.D. Thesis, Universitat Politècnica de Catalunya headquarter, Barcelona, Spain.

[14] WHO/UNEP, GEMS. (1989). Global freshwater quality. Alden Press, Oxford, United Kingdom.

[15] Bruvold, W. H., & Ongerth, H. J. (1969). Taste Quality of Mineralized Water. Journal - American Water Works Association, 61(4), 170–174.doi:10.1002/j.1551-8833.1969.tb03732.x.

[16] World Health Organization (2003). Total dissolved solids in Drinking water, Background document for development of WHO Guidelines for Drinking-water Quality. WHO, Geneva, Switzerland.

[17] Burton, A. C., & Comhill, J. F. (1977). Correlation of cancer death rates with altitude and with the quality of water supply of the 100 largest cities in the United States. Journal of Toxicology and Environmental Health, 3(3), 465–478. doi:10.1080/15287397709529579.

[18] Craun, G. F., & McCabe, L. J. (1975). Problems Associated With Metals in Drinking Water. Journal - American Water Works Association, 67(11), 593–599. doi:10.1002/j.1551-8833.1975.tb02307.x.

[19] Crawford, M. D., Gardner, M. J., & Morris, J. N. (1968). Mortality and hardness of local water-supplies. Lancet, 1(7547), 827–831. doi:10.1016/s0140-6736(68)90297-3.

[20] Gardner, M. J., Crawford, M. D., & Morris, J. N. (1969). Patterns of mortality in middle and early old age in the county boroughs of England and Wales. British Journal of Preventive & Social Medicine, 23(3), 133–140. doi:10.1136/jech.23.3.133.

[21] Keller, W. D., & Reesman, A. L. (1963). Glacial milks and their laboratory-simulated counterparts. Bulletin of the Geological Society of America, 74(1), 61–76. doi:10.1130/0016-7606(1963)74[61:GMATLC]2.0.CO;2.

[22] Leaf, A. (1973). Every day is a gift when you are over 100. National Geographic, 143(1), 93-118.

[23] Leaf, A. (1973). Getting old. Scientific American. Available online: https://www.scientificamerican.com/article/getting-old/ (accessed on January 2022).

[24] McCarrison, R. (1922). Faulty food in relation to gastro-intestinal disorder. Journal of the American Medical Association, 78(1), 1–8. doi:10.1001/jama.1922.02640540007001.

[25] Kart, C. S., Metress, E. K. & Metress, S. P. (1988). Biological theories of aging. Aging, Health and Society, Jones and Bardet, Boston, United States.

[26] Trencsenyi, G., Kertai, P., Bako, F., Hunyadi, J., Marian, T., Hargitai, Z., ... & Banfalvi, G. (2009). Renal capsule-parathymic lymph node complex: a new in vivo metastatic model in rats. Anticancer Research, 29(6), 2121-2126.