pH and Cancer (Example Alkalization Therapy)

Alkaline (having a ph >7)

"There's no way the foods you eat can alter the pH level of your blood." "The body's pH is a very tightly regulated system. If you change your diet, you may see changes in the pH of your saliva or urine because these are waste products, but there's no way you could ever eat enough that it really impacts your blood." (https://www.mdanderson.org/cancerwise/alkaline-diet--what-cancer-patients-should-know.h00-159223356.html)

Notes:

1 Blood pH deos not have to change to affect the extracellular pH of cancer cells! After all pH changes in different areas of the body.
https://pmc.ncbi.nlm.nih.gov/articles/PMC3195546/

2. is Boron a factor due to the high vegatable and fruit intake (which has boron)?

3. "Interfering with pH regulation in tumours as a therapeutic strategy" https://www.nature.com/articles/nrd3554
" regulation of pH in tumours involves the interplay of several proteins..... compounds as well as antibodies that interfere with these proteins may represent valuable new antitumour drugs"

4. Could Quercetin be a factor which is also abundant in fruits and vegetables?

https://www.nature.com/articles/s41430-020-0684-6

The Ph paradigm in cancer 2020

Malignant tissues show a peculiar feature regarding pH: while normal tissues have a higher extracellular pH than intracellular pH, in cancer is exactly the opposite. This phenomenon is called the inversion of the pH gradient and is now considered a hallmark of malignancy. For some time, this inverted pH gradient was believed to be a secondary effect of cancer. Now, it is becoming clear that pH inversion is not an innocent consequence, but a key player in the etiopathogenesis of cancer.

https://www.nature.com/articles/nrc3110

Dysregulated pH: a perfect storm for cancer progression 2011

Dysregulated pH is emerging as a hallmark of cancer because cancers show a 'reversed' pH gradient with a constitutively increased intracellular pH that is higher than the extracellular pH. This gradient enables cancer progression by promoting proliferation, the evasion of apoptosis, metabolic adaptation, migration and invasion.

https://pubmed.ncbi.nlm.nih.gov/32992762/

Cancer and pH Dynamics: Transcriptional Regulation, Proteostasis, and the Need for New Molecular Tools 2020

An emerging hallmark of cancer cells is dysregulated pH dynamics. Recent work has suggested that dysregulated intracellular pH (pHi) dynamics enable diverse cancer cellular behaviors at the population level, including cell proliferation, cell migration and metastasis, evasion of apoptosis, and metabolic adaptation.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7226178/

The Interplay of Dysregulated pH and Electrolyte Imbalance in Cancer 2020

This leads to extracellular acidosis and intracellular alkalinization. Dysregulated pH dynamics influence cancer cell biology, from cell transformation and tumorigenesis to proliferation, local growth, invasion, and metastasis. Moreover, this dysregulated intracellular pH (pHi) drives a metabolic shift to increased aerobic glycolysis and reduced mitochondrial oxidative phosphorylation, referred to as the Warburg effect, or Warburg metabolism, which is a selective feature of cancer.

https://pubmed.ncbi.nlm.nih.gov/28202602/

Cancer cell behaviors mediated by dysregulated pH dynamics at a glance 2017

Dysregulated pH is a common characteristic of cancer cells, as they have an increased intracellular pH (pH_i) and a decreased extracellular pH (pH_e) compared with normal cells. Recent work has expanded our knowledge of how dysregulated pH dynamics influences cancer cell behaviors, including proliferation, metastasis, metabolic adaptation and tumorigenesis. Emerging data suggest that the dysregulated pH of cancers enables these specific cell behaviors by altering the structure and function of selective pH-sensitive proteins, termed pH sensors. Recent findings also show that, by blocking pH_i increases, cancer cell behaviors can be attenuated. This suggests ion transporter inhibition as an effective therapeutic approach, either singly or in combination with targeted therapies. In this Cell Science at a Glance article and accompanying poster, we highlight the interconnected roles of dysregulated pH dynamics in cancer initiation, progression and adaptation.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3917353/

The chemistry, physiology and pathology of pH in cancer 2014

Cell survival is conditional on the maintenance of a favourable acid–base balance (pH). Owing to intensive respiratory CO_2 and lactic acid production, cancer cells are exposed continuously to large acid–base fluxes, which would disturb pH if uncorrected. The large cellular reservoir of H^+-binding sites can buffer pH changes but, on its own, is inadequate to regulate intracellular pH.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7730959/

Targeting the pH Paradigm at the Bedside: A Practical Approach 2020

The inversion of the pH gradient in malignant tumors, known as the pH paradigm, is increasingly becoming accepted by the scientific community as a hallmark of cancer. Accumulated evidence shows that this is not simply a metabolic consequence of a dysregulated behavior, but rather an essential process in the physiopathology of accelerated proliferation and invasion.

https://pmc.ncbi.nlm.nih.gov/articles/PMC9467452/

Tumor acidity: From hallmark of cancer to target of treatment 2022

Tumor acidity is one of the cancer hallmarks and is associated with metabolic reprogramming and the use of glycolysis, which results in a high intracellular lactic acid concentration.

Cancer cells have an inverted pH gradient: extracellular and intracellular pHs (pHe, pHi) are acid and alkaline, respectively (1). The acid shift in the tumor microenvironment (TME) is closely associated with hypoxia (2) but, more specifically, with highly activated glycolysis in tumor cells.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7479815/

Intracellular pH Regulates Cancer and Stem Cell Behaviors: A Protein Dynamics Perspective 2020

Moreover, it is now well-established that dysregulated pHi is seen with many diseases, most notably cancers, which often have a constitutively increased pHi (13–18), and neurodegenerative disorders, which are associated with a constitutively decreased pHi (19, 20). Our review focuses on dysregulated pHi dynamics in cancer; however, another feature of cancers is a dysregulated extracellular pH that is lower (~7.0) compared with normal tissues (~7.4).
The higher pHi of cancer cells enables many behaviors, including directional migration and tumorigenesis as well as the tumorigenic functions of proteins with charge-changing arginine to histidine mutations.

https://pubmed.ncbi.nlm.nih.gov/35780182/
Alkalization of cellular pH leads to cancer cell death by disrupting autophagy and mitochondrial function 2022
Alkalizing cellular pH by bicarbonate decreased pH gradient (ΔpH), membrane potential ($\Delta\Psi_m$), and proton motive force (Δp) across the inner membrane of mitochondria; disruption of oxidative phosphorylation (OXPHOS) due to collapsed Δp led to a significant increase in adenosine monophosphate (AMP), which activated the classical AMPK-mediated autophagy. Meanwhile, the autophagic flux was ultimately blocked by increased cellular pH, reduced OXPHOS, and inhibition of lysosomal proton pump in alkalized lysosome. Bicarbonate also induced persistent mitochondrial permeability (MPT) and damaged mitochondria. Collectively, this study reveals that interfering cellular pH may provide a valuable approach to treat cancer.

https://waterjournal.org/archives/persinger-2/
Serial pH Increments (~20 to 40 Milliseconds) in Water During Exposures to Weak, Physiologically Patterned Magnetic Fields: Implications for Consciousness 2014
The pH values for volumes (50 ml) of spring water were measured for 12 hours while being exposed to a weak (8±4 μT) decelerating frequency-modulated magnetic field that has been shown to diminish the growth of cancer cells and inhibit the movement of planarian. Compared to sham field-exposed water, the magnetic field-exposed water displayed a greater increase in pH (towards alkalinity) that involved an increase between 0.5 and 1 pH units after about 7 to 8 hr. This shift occurred slowly as successive 0.02 pH transient peaks (about 7 per s) that were between 20 to 40 ms in duration. This pattern was not observed in water exposed to background conditions (0.11 μT).

https://liebertpub.com/doi/10.1089/ees.2020.0182
Magnetic Field Effects on pH and Electrical Conductivity: Implications for Water and Wastewater Treatment 2020
Magnetic fields have been shown to affect the properties of water and its constituents. In this study, theoretical assessments of changes in electrical conductivity and proton concentration, as a function of flow velocity through a magnetic field, were developed and experimentally verified. Experiments were done using a flow-through system consisting of permanent neodymium magnets arranged in a helical pattern in a pipe to generate a constant multidirectional magnetic field (1.350 T). In accordance with increasing flow velocity (8–6 cm/s), the proton concentration decreased from 10−7 to 6×10−8 mol/L (pH 7–7.22). The model developed in this study indicated that pH would increase from 7 to 14 at a velocity of 100 cm/s.

https://www.sciencedirect.com/science/article/abs/pii/S0022286009005559?via%3Dihub
The effects of magnetic fields on water molecular hydrogen bonds 2009
Many claims have been made that magnetic fields (MFs) change the physicochemical properties of water, or prepared laboratory solutions [2], [3], by influencing pH value, nucleation and growth, surface tension and chemical equilibria. Tombácz et al. have tested both flowing and static systems, and concluded that only in a flowing system is the magnetic effect observed [4]. The magnetic flux density ranges from 0.1 to 0.8 T among those magnetic treatment experiments. Kobe et al. took 0.5 T as the magnetic flux density in their experiments to obtain successful treatment results [5].

https://www.researchgate.net/publication/322962235_Does_Magnetic_Field_Change_Water_pH
Does Magnetic Field Change Water pH? 2018
The application of all magnetic field treatment showed slightly an increase in the pH of treated water compared to untreated water

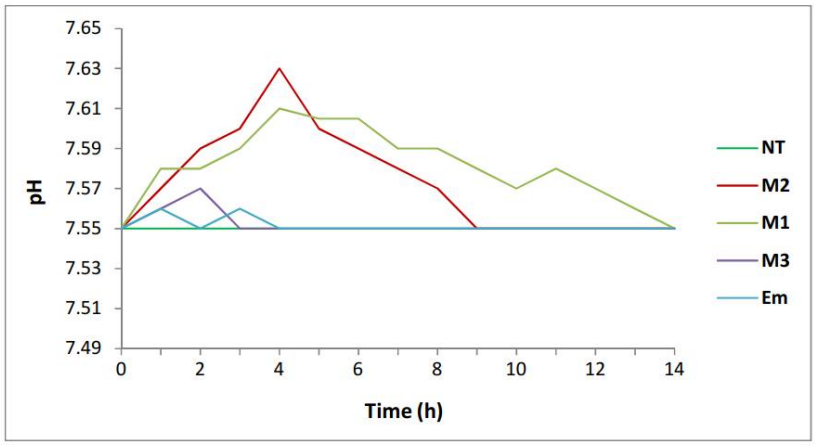


Fig. 3. pH monitoring of water treated with magnetic devices M1, M2, M3 and Em at T = 18 ° C, flow rate = 0.06 l / s (NT: untreated)

https://pubmed.ncbi.nlm.nih.gov/19276390/
Bicarbonate increases tumor pH and inhibits spontaneous metastases 2009
The external pH of solid tumors is acidic as a consequence of increased metabolism of glucose and poor perfusion. Acid pH has been shown to stimulate tumor cell invasion and metastasis in vitro and in cells before tail vein injection in vivo. The present study investigates whether inhibition of this tumor acidity will reduce the incidence of in vivo metastases. Here, we show that oral NaHCO(3) selectively increased the pH of tumors and reduced the formation of spontaneous metastases in mouse models of metastatic breast cancer. This treatment regimen was shown to significantly increase the extracellular pH, but not the intracellular pH, of tumors by (31)P magnetic resonance spectroscopy and the export of acid from growing tumors by fluorescence microscopy of tumors grown in window chambers. NaHCO(3) therapy also reduced the rate of lymph node involvement, yet did not affect the levels of circulating tumor cells, suggesting that reduced

organ metastases were not due to increased intravasation. In contrast, NaHCO(3) therapy significantly reduced the formation of hepatic metastases following intrasplenic injection, suggesting that it did inhibit extravasation and colonization. In tail vein injections of alternative cancer models, bicarbonate had mixed results, inhibiting the formation of metastases from PC3M prostate cancer cells, but not those of B16 melanoma. Although the mechanism of this therapy is not known with certainty, low pH was shown to increase the release of active cathepsin B, an important matrix remodeling protease.

https://pubmed.ncbi.nlm.nih.gov/39457509/

How Does Cancer Occur? How Should It Be Treated? Treatment from the Perspective of Alkalization Therapy Based on Science-Based Medicine 2024

The article also explores the acidic tumor microenvironment (TME), a consequence of intensive glycolytic activity and proton production by cancer cells. This acidic milieu enhances the invasiveness and metastatic potential of cancer cells and contributes to increased resistance to chemotherapy. Alkalization therapy, which involves neutralizing this acidity through dietary modifications and the administration of alkalizing agents such as sodium bicarbonate, is highlighted as an effective strategy to counteract these adverse conditions and impede cancer progression.

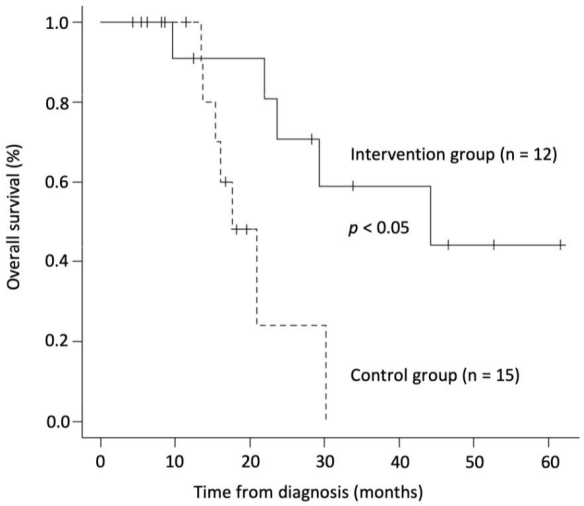


Figure 3. Overall survival comparison in small cell lung cancer patients [Cited from [78]]. Kaplan–Meier curves show the OS from diagnosis for small cell lung cancer patients. The intervention group, treated with chemotherapy, alkalization therapy, and vitamin C (n = 12), shows a median OS of 44.2 months, compared to 17.7 months for the control group, which received chemotherapy only (n = 15).

long-term sodium bicarbonate administration at 0.17 g/kg/day for 90 days was safe and effectively increased urine pH, indicating its safety and efficacy [84]. In summary, alkalization therapy shows promise for several cancers and is safe based on initial trials, but further randomized controlled trials are needed to confirm its efficacy.

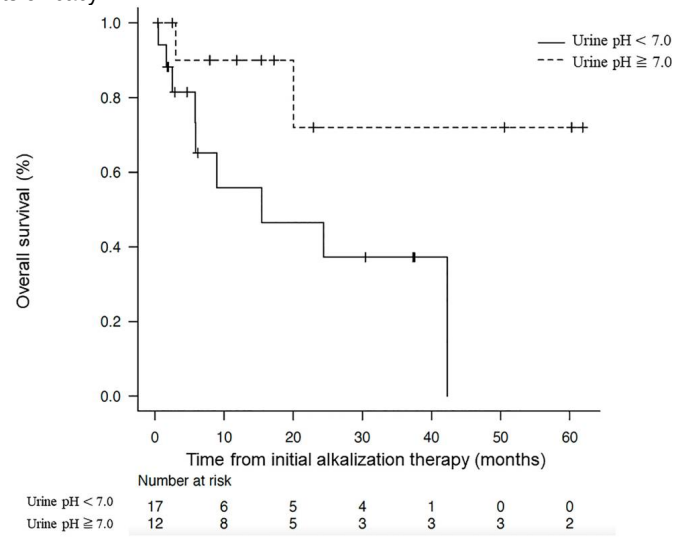


Figure 4. Association between overall survival and urine pH in hepatocellular carcinoma patients [Cited from [79]]. Kaplan–Meier curves compare the OS from the start of alkalization therapy in hepatocellular carcinoma patients categorized by mean urine pH levels. Patients with a mean urine pH ≥ 7.0 (n = 12) showed a median OS that was not reached, significantly longer than the 15.4 months median OS for those with a mean urine pH < 7.0 (n = 17).

https://pubmed.ncbi.nlm.nih.gov/39433427/

Microenvironmental alkalization promotes the therapeutic effects of MSLN-CAR-T cells 2024

Triple-negative breast cancer (TNBC) is characterized by high invasion, prone metastasis, frequent recurrence and poor prognosis. Unfortunately, the curative effects of current clinical therapies, including surgery, radiotherapy, chemotherapy and immunotherapy, are still limited in patients with TNBC. In this study, we showed that the heterogeneous expression at the protein level and subcellular location of mesothelin (MSLN), a potential target for chimeric antigen receptor-T (CAR-T) cell therapy in TNBC, which is caused by acidification of the tumor microenvironment, may be the main obstacle to therapeutic efficacy. Alkalization culture or sodium bicarbonate administration significantly promoted the membrane expression of MSLN and enhanced the killing efficiency of MSLN-CAR-T cells both *in vitro* and *in vivo*, and the same results were also obtained in other cancers with high MSLN expression, such as pancreatic and ovarian cancers.

Moreover, mechanistic exploration revealed that the attenuation of autophagy-lysosome function caused by microenvironmental alkalization inhibited the degradation of MSLN. Hence, alkalization of the microenvironment improves the consistency and high expression of the target antigen MSLN and constitutes a routine method for treating diverse solid cancers *via* MSLN-CAR-T cells.

https://pmc.ncbi.nlm.nih.gov/articles/PMC10881708/

Tumor alkalization therapy: misconception or good therapeutics perspective? – the case of malignant ascites 2024

Tumor acidity has been identified as a key factor in promoting cancer progression, metastasis, and resistance. Tumor alkalization therapy has emerged as a potential strategy for cancer treatment. This article provides preclinical and clinical evidence for tumor alkalization therapy as a promising cancer treatment strategy. The potential of tumor alkalization therapy using sodium bicarbonate in the treatment of malignant ascites was studied. The concept of intraperitoneal perfusion with an alkalizing solution to increase the extracellular pH and its antitumor effect were explored. The significant extension in the overall survival of the Ehrlich ascites carcinoma mice treated with sodium bicarbonate solution compared to those treated with a sodium chloride solution was observed. In the sodium bicarbonate group, mice had a median survival of 30 days after tumor cell injection, which was significantly ($p<0.05$) different from the median survival of 18 days in the sodium chloride group and 14 days in the intact group. We also performed a case study of a patient with ovarian cancer malignant ascites resistant to previous lines of chemotherapy who underwent intraperitoneal perfusions with a sodium bicarbonate solution, resulting in a significant drop of CA-125 levels from 5600 U/mL to 2200 U/mL in and disappearance of ascites, indicating the potential effectiveness of the treatment. The preclinical and clinical results obtained using sodium bicarbonate perfusion in the treatment of malignant ascites represent a small yet significant contribution to the evolving field of tumor alkalization as a cancer therapy. They unequivocally affirm the good prospects of this concept.

https://www.researchgate.net/publication/277304766_Safety_and_Tolerability_of_Long-Term_Sodium_Bicarbonate_Consumption_in_Cancer_Care

Safety and Tolerability of Long-Term Sodium Bicarbonate Consumption in Cancer Care 2015

Healthy volunteers were recruited to consume 2-3 times per day a total maximum dose of 0.5 g/kg/ day sodium bicarbonate. Volunteers were permitted to downward dose to find a tolerable dose they were willing to consume daily for 90 days. Volunteers returned to the clinic on day 10, 30, 60, and 90 to monitor vital signs, BMP, and urine pH. In between visits, the volunteers recorded their urine pH before and after sodium bicarbonate consumption. Volunteer journals and routine communication between clinical personnel and volunteers was maintained to monitor adherence and adverse events (AEs). Results: The trial accrued 15 volunteers, 11 women and 4 men. The average age of volunteer was 55 years. The average daily dose was 0.17 ± 0.03 g/kg. Most adverse events were Grade 1. Two AEs were Grade 2. Most symptoms were gastrointestinal in nature. Two subjects withdrew from the study before the 90 day time point. One incidence of metabolic alkalosis occurred and was resolved by downward dose adjustment. Conclusions: The study demonstrates that voluntary long-term consumption of sodium bicarbonate is feasible and safe, but the predicted upward tolerable dose was too high for healthy volunteers.

https://ar.iiarjournals.org/content/40/2/873

Effects of Alkalization Therapy on Chemotherapy Outcomes in Metastatic or Recurrent Pancreatic Cancer 2020

Background/Aim: The acidic tumor microenvironment is associated both with the progression and drug resistance of cancer. We aimed to investigate the effects of alkalization therapy performed concurrently with chemotherapy on the survival of advanced pancreatic cancer patients (study registration: UMIN 000035659). Patients and Methods: Twenty-eight patients with metastatic or recurrent pancreatic cancer were assessed in this study. Alkalization therapy consisted of an alkaline diet with supplementary oral sodium bicarbonate (3.0-5.0 g/day). Results: The mean urine pH was significantly higher after the alkalization therapy (6.85±0.74 vs. 6.39±0.92; $p<0.05$). The median overall survival from the start of alkalization therapy of the patients with high urine pH (>7.0) was significantly longer than those with low urine pH (≤ 7.0) (16.1 vs. 4.7 months; $p<0.05$). Conclusion: An alkalization therapy may be associated with better outcomes in advanced pancreatic cancer patients treated with chemotherapy.

All patients received supplementary intravenous (*i.v.*) vitamin C (25-50 g/day once every 1 or 2 weeks).

Oral bicarbonate (3.0-5.0 g/day) was given when urine pH did not increase above 7.0 or when patients wished to take it.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3125283/

Bicarbonate and dichloroacetate: Evaluating pH altering therapies in a mouse model for metastatic breast cancer 2011

In a previous study, it was reported that the saturating dose of oral bicarbonate in mice (which roughly translates to about 0.18 g/kg/day in humans) was only sufficient to counteract the acid load of a 15 mg tumor consisting of about 100,000 cells or 1.0 mm^3 [16]. Moreover, chronic application of oral bicarbonate at doses higher than 0.5 g/kg/day is predicted to induce systemic alkalosis

Conclusions

This study confirms earlier reports about the role of systemic bicarbonate in the inhibition of metastatic spread from primary tumors, but highlights the limitations of this approach. While DCA has been shown both safe and effective against tumor cells in other studies, the findings reported here concur with the most recent investigations warning of potential pitfalls with DCA use [23,24]. First, it is not universally effective against all cancer cells. Secondly, tumor hypoxia serves as a confounding micro-environmental factor against DCA efficacy. The unpredictable effect of DCA against tumors therefore signals caution against using this agent as a therapeutic approach until new studies can determine the molecular role of DCA in different tumor microenvironments.

https://pmc.ncbi.nlm.nih.gov/articles/PMC10264763/

Editorial: The impact of alkalizing the acidic tumor microenvironment to improve efficacy of cancer treatment 2023

In recent years, the acidic tumor microenvironment (TME) that is created by cancer-specific metabolism has attracted much attention in cancer therapy.

In addition, the influence of the daily diet should also be considered. Diets with alkalizing effects are rich in vegetables and fruits, which at the same time have anti-inflammatory and gut-regulating properties (12). Alkalization therapy is a treatment that acts on cancer metabolism, and can be used in combination with anticancer drugs, radiation therapy, and other therapies, and is also a safe treatment method. In the future, the combination of alkalization therapy and conventional therapy for the treatment of cancer needs to be further investigated in prospective clinical trials.

https://pmc.ncbi.nlm.nih.gov/articles/PMC9364696/

Meaning and Significance of "Alkalization Therapy for Cancer" 2022

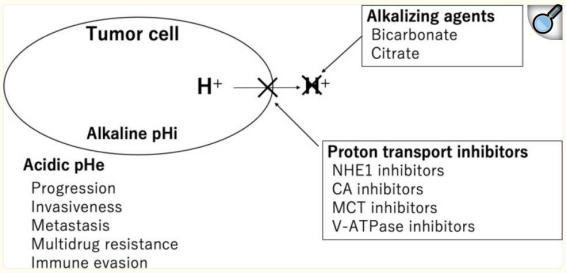
The "alkalization therapy" that we advocate does not compete with any of the current standard treatments, but improves the effectiveness of standard treatments, reduces side effects, and lowers medical costs.

Furthermore, extracellular acidic pH and intracellular alkaline pH of cancer cells is known to induce malignant behaviors, such as increased invasion and metastasis, multi drug resistance, and suppression of immune surveillance (13). One interesting example of this was reported in human lung cancer cell culture experiments, where 0.4 increase in intracellular pH was associated with a 2000-fold increase in the level of doxorubicin resistance in the tumor (14), proliferation and metastasis, expression of genetic abnormalities, growth factor activation, MDR and multidrug resistance, and vascular proliferation are activated.

It is well known that current cancer treatments often leave the TME acidic, resulting in poor therapeutic efficacy and severe side effects (4, 15). Therefore, our alkalization therapy aims to change the acidic TME to an alkaline.

The actual methods are dietary interventions and the oral or intravenous administration of drugs that alkalize the body. As our bodies are made from the food that we eat, we believe that the act of alkalizing the body via food is a logical approach. A method to measure the pH of the TME has not yet been established to date, and hence we use urine pH as a surrogate indicator. The reason for this is that through our clinical practice, we have experienced that the urine of most patients who have achieved radical remission has an alkaline pH of 7.5 to 8.
The biggest problem is that current medicine treats stage 4 cancer based on the assumption that it cannot be cured. To solve this problem, it is important to study people who have been cured of stage 4 cancer.
As a proposition to deny this, it is important to construct a hypothesis because 'there are people who have been cured of stage 4 cancer', and to perform inductively what those who have been cured have done in the treatment of stage 4 cancer.
The patient should first be advised to change his/her diet. It is important to measure the patient's urine daily with a litmus test paper. Under normal conditions, the urine pH is almost 5-5.5 acidic, but as the diet is changed to an alkalinizing diet (fruits and vegetables, no meat, no dairy products), the patient's urine pH will increase. The aim is to achieve a urine pH of 7.5-8 or higher, and if this is not achieved, alkalinizing agents may be given intravenously or orally.
The **next thing to do is to reduce inflammation**. C-reactive protein (CRP) is used as an indicator. The patient should be taught to keep the CRP below 0.05. It is reasonable to assume that the elevated CRP in carcinoma carriers is due to acidification of the TME, where protons present in the TME attract primary immune cells such as neutrophils and macrophages (22, 23). A rapid reduction in CRP can be achieved by 'donating' electrons to the patient. A large intravenous dose of ascorbic acid (at least 4 grams) is very effective. Warming the patient's body and making him sweat are also helpful.
It has also been reported that the microbiome can worsen the prognosis of cancer, by producing carcinogenic toxins and metabolites. Therefore, to improve the gut microbiome, foods rich in 'water-soluble pectin' should be consumed.
In our clinical experience, we found that patients who show improvement have a neutrophil/lymphocyte ratio of less than 2, or even less than 1.5, and a lymphocyte count of more than 1,500, or even more than 2,000, which we use to determine the clinical status of the patient. CRP is also useful in determining neutrophil activity, and a CRP of 0.05 or less is considered as low neutrophil activity. The goal is to achieve a urine pH of 7.5 to 8.0 or more. Once this is achieved, it is often our experience that anticancer drugs can be given at less than half the standard dose and still show satisfactory effects.
In conclusion, tumors acquire resistance to anticancer drugs and the ability to metastasize because of the acidification of the microenvironment surrounding the tumor (TME), and therefore, alkalization of the TME is expected to substantially reduce cancer activity.
In our clinic we often use intravenous ascorbic acid in the treatment of cancer. There has been much debate as to whether ascorbic acid (vitamin C) is effective in the treatment of cancer, but it has recently been shown that the pharmacological effects of taking this substance orally and administering it intravenously are quite different. Although the function of vitamin C in vivo is not clearly and fully understood, it is understood that this substance acts in vivo as an electron donor (38).
The antitumor effect of ascorbic acid can only be achieved by intravenous or intrathoracic or intraperitoneal administration. Oral administration does not have such an antitumor effect, which the authors intend to report in detail elsewhere (39–41).
Conclusion
The treatments we advocate do not in conflict with conventional standard therapies but can be used in combination to increase their efficacy and reduce side effects. The human body is a dissipative structure, which means that it is an open system that is not in thermodynamic equilibrium. This means that it is possible to reduce the entropy of the body. It is our experience that alkalization of the TME enables various treatments to become more effective, and with the future collaboration of many researchers, we hope that it will soon become possible to treat intractable cancers using standard treatments combined with alkalization therapy (19, 21, 21, 68, 69, 77, 78).
***** many example clients were given ****

https://pmc.ncbi.nlm.nih.gov/articles/PMC9516301/
Clinical review of alkalization therapy in cancer treatment 2022
One of the most unique characteristics of cancer metabolism is activated aerobic glycolysis, which is called the "Warburg effect", and is a hallmark of cancer. An acidic tumor microenvironment (TME) resulting from activated anaerobic glycolysis is associated with cancer progression, multi-drug resistance, and immune escape. Several *in vitro* and *in vivo* studies reported that neutralization of the acidic TME by alkalizing agents, such as bicarbonate, resulted in the suppression of cancer progression and a potential benefit for anti-cancer drug responses. In clinical settings, alkalizing effects were achieved not only by alkalizing agents, but also by a following a particular diet. An epidemiological study demonstrated that more fruits and vegetables and less meat and dairy products are associated with an increase in urine pH, which may reflect the alkalizing effect on the body.
An *in vitro* study of human lung tumor cells demonstrated that a close to 2,000-fold increase in doxorubicin resistance was observed when the pHi increases from 7.0 to 7.4 (13).
Current cancer treatment strategies do not consider pH changes in cancer and its association with sensitivity to drug therapies, and treatment approaches aiming at pH regulation of the TME may hence be a future therapeutic strategy.



Open in a new tab

Therapeutic approaches targeting the acidic pH of the TME. Alkalizing agents and proton transporter inhibitors are shown.

A prospective clinical trial in healthy volunteers was conducted for investigation of the safety of the long-term consumption of sodium bicarbonate for cancer care, and demonstrated that 90 days of sodium bicarbonate consumption (median 0.17 g/kg/day) was feasible and safe, and an increase in urine pH as a surrogate marker for buffering effect was observed following bicarbonate intake (29). It has also been reported that the oral administration of sodium potassium citrate as an alkalizing agent increases HCO−3 concentrations in the blood and urine, leading to an increase in urine pH and neutralization of the acidic TME in a pancreatic cancer xenograft model, thereby enhancing the therapeutic effects of anticancer drugs (tegafur/gimeracil/oteracil) (30).
Proton transport inhibitors
NHE1 inhibitors
In cancer cells, NHE1 is activated even at resting pH, and the activation of NHE1 directly results in an increase in intracellular pH and a decrease in extracellular

pH of cancer cells (7). NHE1 is a major plasma membrane pump that extrudes intracellular protons from cells, and is associated with tumor growth and progression (7). There are several NHE1 inhibitors, including derivatives of amiloride, such as 5-(N-ethyl-N-isopropyl) amiloride, 5-(N,N-dimethyl) amiloride, 5-(N,N-hexamethylene) amiloride (HMA), and cariporide (9).
A total of 28 patients with advanced pancreatic cancer who agreed to receive alkalization therapy, were treated with alkalization therapy, consisting of an alkaline diet with oral sodium bicarbonate (3.0−5.0 g/day). We found that alkalization therapy significantly increased the mean urine pH. A significantly prolonged median OS was observed in patients with a urine pH of higher than 7.0, compared with patients with a urine pH of 7.0 or lower (n = 28, 16.1 vs. 4.7 months; $p < 0.05$).
Third, we conducted a retrospective study investigating the effects of alkalization therapy combined with intravenous vitamin C treatment on small cell lung cancer patients treated with chemotherapy (55). Twelve patients who agreed to be assigned to the intervention group (alkalization therapy plus vitamin C treatment together with chemotherapy) were compared with 15 patients in the control group (chemotherapy only) who did not agree to receive interventional treatment. Similar to our previous studies, urine pH of the intervention group was significantly increased compared with that of the control group (**Figure 3A**). A prolonged median OS was observed in the intervention group compared with the control group (44.2 vs. 17.7 months; $p < 0.05$) (**Figure 3B**). Although this study was a retrospective study with a small number of patients, alkalization therapy may be associated with favorable outcomes in patients with small cell lung cancer receiving chemotherapy, and it is speculated that supplementary intravenous vitamin C may have also affected their treatment outcomes. However, the effect of intravenous vitamin C treatment in combination with alkalization therapy remains unclear, and further investigation is needed.

https://pmc.ncbi.nlm.nih.gov/articles/PMC10777900/
Potential of Alkalization Therapy for the Management of Metastatic Pancreatic Cancer: A Retrospective Study 2023
In this study, we noted a trend in which longer patient survival was associated with a higher average urine pH, suggesting a correlation between the effectiveness of alkalization therapy and increased urine pH levels.
All patients received alkalization therapy (a combination of an alkaline diet, bicarbonate, and citric acid administration), alongside standard chemotherapy.
In the 98 patients analyzed, the median overall survival (OS) from the time of diagnosis was 13.2 months.
Patients with a mean urine pH of 7.5 or greater had a median OS of 29.9 months,
compared with 15.2 months for those with a mean urine pH of 6.5 to 7.5,
and 8.0 months for those with a mean urine pH of less than 6.5,
which suggests a trend of a longer OS in patients with a higher urine pH ($p = 0.0639$). Alkalization therapy may offer a viable approach to extending the survival of stage 4 pancreatic cancer patients, who typically have an unfavorable prognosis.
The use of proton pump inhibitors (PPIs) to alkalize the TME has been attracting attention. It has been observed that PPIs prevent tumor cells from acquiring resistance to cytotoxic anticancer drugs and induce the apoptosis of tumors in animal models and cultured cells of malignant melanoma, adenocarcinoma, and malignant lymphoma [30,31,32].
Furthermore, the TME can also act as a sufficient therapeutic target itself, and hence alkalization therapy is a promising treatment method that is gentle on the patient's body, does not cost much, and is expected to lead to a paradigm shift.

https://pubmed.ncbi.nlm.nih.gov/30615983/
Sodium bicarbonate nanoparticles modulate the tumor pH and enhance the cellular uptake of doxorubicin 2019
Acidic pH in the tumor microenvironment is associated with cancer metabolism and creates a physiological barrier that prevents from drugs to penetrate cells. Specifically, ionizable weak-base drugs, such as doxorubicin, freely permeate membranes in their uncharged form, however, in the acidic tumor microenvironment these drugs become charged and their cellular permeability is retarded. In this study, 100-nm liposomes loaded with sodium bicarbonate were used as adjuvants to elevate the tumor pH. Combined treatment of triple-negative breast cancer cells (4T1) with doxorubicin and sodium-bicarbonate enhanced drug uptake and increased its anti-cancer activity.

https://pubmed.ncbi.nlm.nih.gov/21936635/
Dimethyl sulfoxide-sodium bicarbonate infusion for palliative care and pain relief in patients with metastatic prostate cancer 2011
Prostate cancer (adenocarcinoma of the prostate) is the most widespread cancer in men. It causes significant suffering and mortality due to metastatic disease. The main therapy for metastatic prostate cancer (MPC) includes androgen manipulation, chemotherapy, and radiotherapy and/or radioisotopes. However, these therapeutic approaches are considered palliative at this stage, and their significant side effects can cause further decline in patients' quality of life and increase non-cancer-related morbidity/mortality. In this study, the authors have used the infusion of dimethyl sulfoxide-sodium bicarbonate (DMSO-SB) to treat 18 patients with MPC. The 90-day follow-up of the patients having undergone the proposed therapeutic regimen showed significant improvement in clinical symptoms, blood and biochemistry tests, and quality of life. There were no major side effects from the treatment. In searching for new and better methods for palliative treatment and pain relief, this study strongly suggested therapy with DMSO-SB infusions could provide a rational alternative to conventional treatment for patients with MPC.

https://pubmed.ncbi.nlm.nih.gov/38931908/
Exploring the Potential Use of Natural Products Together with Alkalization in Cancer Therapy 2024
Alkalization therapy has been demonstrated to be effective for various cancers. In addition, natural products, such as triterpenoids, parthenolides, fulvic acid, *Taxus yunnanensis*, and apple pectin have the potential to alleviate symptoms, maintain physical fitness, and improve treatment outcomes of cancer patients through their anti-inflammatory, antioxidant, and anticancer properties. In this review, we focus on the effects of alkalization therapy and natural products on cancer. Furthermore, we present a case series of advanced cancer patients who received alkalization therapy and natural products alongside standard treatments, resulting in long-term survival.
Definition of Alkalization Therapy
An "alkalizing diet" is defined as a diet containing a large number of fruits and vegetables, with blue-back fish as the main source of protein, and as little meat and dairy as possible [43,44]. Specifically, patients are instructed to consume at least 400 g of fruits and vegetables daily, and to keep a dietary record for the first 4 weeks.
Furthermore, parthenolide inhibits the mitochondrial respiratory chain and increases the production of ROS [61]. ROS cause DNA damage and apoptosis in cancer cells, and hence parthenolide can also be expected to have anticancer effects by reducing the expression of antioxidant enzymes and increasing the sensitivity of cancer cells to oxidative stress.

https://jnm.snmjournals.org/content/51/8/1167
Tumor pH and Its Measurement 2010
Studies over the last few decades have demonstrated that the intracellular pH of solid tumors is maintained within a range of 7.0–7.2, whereas the extracellular pH is acidic. A low extracellular pH may be an important factor inducing more aggressive cancer phenotypes.

https://pubmed.ncbi.nlm.nih.gov/8640796/

Cellular pH gradient in tumor versus normal tissue: potential exploitation for the treatment of cancer 1996
Although limited data exist, electrode-measured pH values of human tumors and adjacent normal tissues, which are concurrently obtained by the same investigator in the same patient, consistently show that the electrode pH (believed to primarily represent tissue extracellular pH) is substantially and consistently lower in the tumor than in normal tissue. In contrast, the 31P-magnetic resonance spectroscopy estimated that intracellular pH is essentially identical or slightly more basic in tumor compared to normal tissue. As a consequence, the cellular pH gradient is substantially reduced or reversed in tumor compared to normal tissue: in normal tissue the extracellular pH is relatively basic, and in tumor tissue the magnitude of the pH gradient is reduced or reversed.

https://www.mdpi.com/1422-0067/22/18/9910
Effect of Exogenous pH on Cell Growth of Breast Cancer Cells 2021
One key feature of cancer cells, including breast cancer cells, is a reversed pH gradient which causes the extracellular pH of cancer cells to be more acidic than that of normal cells. Growing literature suggests that alkaline therapy could reverse the pH gradient back to normal and treat the cancer; however, evidence remains inconclusive. In this study, we investigated how different exogenous pH levels affected the growth, survival, intracellular reactive oxygen species (ROS) levels and cell cycle of triple-negative breast cancer cells from MDA-MB-231 cancer cell lines. Our results demonstrated that extreme acidic conditions (pH 6.0) and moderate to extreme basic conditions (pH 8.4 and pH 9.2) retarded cellular growth, induced cell death via necrosis and apoptosis, increased ROS levels, and shifted the cell cycle away from the G0/G1 phase. However, slightly acidic conditions (pH 6.7) increased cellular growth, decreased ROS levels, did not cause significant cell death and shifted the cell cycle from the G0/G1 phase to the G2/M phase, thereby explaining why cancer cells favored acidic conditions over neutral ones. Interestingly, our results also showed that cellular pH history did not significantly affect the subsequent growth of cells when the pH of the medium was changed. Based on these results, we suggest that controlling or maintaining an unfavorable pH (such as a slightly alkaline pH) for cancer cells in vivo could retard the growth of cancer cells or potentially treat the cancer.

https://aacrjournals.org/cancerres/article/72/16/3938/576339/Chronic-Autophagy-Is-a-Cellular-Adaptation-to
Chronic Autophagy Is a Cellular Adaptation to Tumor Acidic pH Microenvironments 2012
Tumor cell survival relies upon adaptation to the acidic conditions of the tumor microenvironment. To investigate potential acidosis survival mechanisms, we examined the effect of low pH (6.7) on human breast carcinoma cells.
Taken together, these results argue that acidic conditions in the tumor microenvironment promote autophagy, and that chronic autophagy occurs as a survival adaptation in this setting.

https://pubmed.ncbi.nlm.nih.gov/31730395/
The Acidic Tumor Microenvironment as a Driver of Cancer 2020
Acidic metabolic waste products accumulate in the tumor microenvironment because of high metabolic activity and insufficient perfusion. In tumors, the acidity of the interstitial space and the relatively well-maintained intracellular pH influence cancer and stromal cell function, their mutual interplay, and their interactions with the extracellular matrix. Tumor pH is spatially and temporally heterogeneous, and the fitness advantage of cancer cells adapted to extracellular acidity is likely particularly evident when they encounter less acidic tumor regions, for instance, during invasion. Through complex effects on genetic stability, epigenetics, cellular metabolism, proliferation, and survival, the compartmentalized pH microenvironment favors cancer development.

https://pmc.ncbi.nlm.nih.gov/articles/PMC10258336/
Effects of alkalization therapy on hepatocellular carcinoma: a retrospective study 2023
we hypothesized that the combination of alkalization therapy with standard treatments will improve the prognosis of HCC. We here report the clinical results of HCC patients treated with alkalization therapy at our clinic.
Patients with HCC treated at Karasuma Wada Clinic (in Kyoto, Japan), from January 1, 2013, to December 31, 2020 were analyzed. Overall survival (OS) from both the time of diagnosis and the start of alkalization therapy for each patient was compared. The mean urine pH was also calculated as a surrogate marker of tumor microenvironment pH, and OS from the start of alkalization therapy was compared between patients with a mean urine pH of ≥ 7.0 and those with a mean urine pH of < 7.0.
Alkalization therapy was defined as a combination of an alkalizing diet and oral bicarbonate (3.0−5.0 g/day) and/or citric acid (3.0−6.0 g/day) therapy. The alkalizing diet was a diet high in vegetables and fruits, and as low in meat and dairy products as possible. All patients who received alkalization therapy were instructed to take at least 400 g of fruit and vegetables a day, and not to take any meat and dairy products, and they recorded their daily meals for at least the first 4 weeks from the start of the alkalizing diet.
Conclusions
The addition of alkalization therapy to standard therapies may be associated with more favorable outcomes in HCC patients with increased urine pH after alkalization therapy.

https://www.emedihealth.com/nutrition/alkaline-foods-improve-health
While the human body has a tight regulation mechanism that strictly maintains its pH at around 7.4, (1) recent schools of thought believe that eating foods that will produce alkaline ash is beneficial for general health.
fruits, vegetables, and lentils are alkaline ash-producing foods.
Foods are classified as being acidic or alkaline based on their potential renal acid load (PRAL) scores. This is a measure of the amount of acid or alkali in the urine that your diet produces in the body. The lower the score of a food, the more alkaline promoting it is. (3)
1. Cruciferous vegetables
Vegetables such as cabbage, cauliflower, broccoli, and Brussels sprouts are commonly categorized as cruciferous. (4) They are common alkaline-contributing foods containing anti-inflammatory properties. (4) Due to their benefits, they are highly studied for their role in cancer therapies.
Cruciferous vegetables are also rich in carotenoids; antioxidants; vitamins C, E, and K; folate; and minerals such as potassium and calcium; arginine; and fiber. (5)
2. Citrus fruits
Although most fruits are classified as alkaline due to their potassium or bicarbonate content, citrus fruits in particular produce alkaline ash upon metabolism due to their high citric acid content. (6)
Active metabolites present in citrus fruits, such as oranges, lemons, and grapefruits, have anti-inflammatory, antioxidant, and antimicrobial properties. These properties make the fruits beneficial in reducing the risks of diabetes, cardiovascular diseases, and even cancer. (7)
3. Root vegetables
Root vegetables are those that grow underground, such as potatoes, sweet potatoes, turnips, radishes, beetroot, and carrots. In addition to being energy-giving foods, they also have a low PRAL score. (8)
These vegetables function as antioxidants, help in regulating blood glucose, reduce cholesterol, and also exhibit antimicrobial properties. (9) As they are high-

energy-giving foods and relatively inexpensive, they are often preferred across all age groups.

4. Lentils

An excellent source of plant protein, lentils have a low PRAL score. (10) They are cost-effective legumes and have high potassium content.
Their increased intake is associated with reduced risks of obesity and cardiovascular diseases. Due to their abundant polyphenol content, they also possess antioxidant properties. (11)

5. Nuts

Nuts often form a part of a low-PRAL, alkalizing diet. (8) Rich sources of healthy fats, high-quality vegetable protein, fiber, and minerals, they provide many beneficial health effects. (12)
Studies have shown their cholesterol-lowering effect and benefits in reducing oxidative stress and inflammation in the body. (12)

https://pmc.ncbi.nlm.nih.gov/articles/PMC3195546/

The Alkaline Diet: Is There Evidence That an Alkaline pH Diet Benefits Health? 2011 (University of Alberta)

Even the pH of the soil in which plants are grown can have considerable influence on the mineral content of the food we eat (as minerals are used as buffers to maintain pH). The ideal pH of soil for the best overall availability of essential nutrients is between 6 and 7. Acidic soils below pH of 6 may have reduced calcium and magnesium, and soil above pH 7 may result in chemically unavailable iron, manganese, copper and zinc.
With the agricultural revolution (last 10,000 years) and even more recently with industrialization (last 200 years), there has been an decrease in potassium (K) compared to sodium (Na) and an increase in chloride compared to bicarbonate found in the diet [6]
The ratio of potassium to sodium has reversed, K/Na previously was 10 to 1 whereas the modern diet has a ratio of 1 to 3 [7]. It is generally accepted that agricultural humans today have a diet poor in magnesium and potassium as well as fiber and rich in saturated fat, simple sugars, sodium, and chloride as compared to the preagricultural period [6]. This results in a diet that may induce metabolic acidosis which is mismatched to the genetically determined nutritional requirements [8]. With aging, there is a gradual loss of renal acid-base regulatory function and a resultant increase in diet-induced metabolic acidosis while on the modern diet [9]. A low-carbohydrate high-protein diet with its increased acid load results in very little change in blood chemistry, and pH, but results in many changes in urinary chemistry. Urinary magnesium levels, urinary citrate and pH are decreased, urinary calcium, undissociated uric acid, and phosphate are increased. All of these result in an increased risk for kidney stones [10].
Foods can be categorized by the potential renal acid loads (PRALs) see Table 2.
There is some evidence that chronic low back pain improves with the supplementation of alkaline minerals [47]. With supplementation there was a slight but significant increase in blood pH and intracellular magnesium. Ensuring that there is enough intracellular magnesium allows for the proper function of enzyme systems and also allows for activation of vitamin D [48].
The human body has an amazing ability to maintain a steady pH in the blood with the main compensatory mechanisms being renal and respiratory.
9. Conclusion
Alkaline diets result in a more alkaline urine pH and may result in reduced calcium in the urine, however, as seen in some recent reports, this may not reflect total calcium balance because of other buffers such as phosphate. There is no substantial evidence that this improves bone health or protects from osteoporosis. However, alkaline diets may result in a number of health benefits as outlined below

Increased fruits and vegetables in an alkaline diet would improve the K/Na ratio and may benefit bone health, reduce muscle wasting, as well as mitigate other chronic diseases such as hypertension and strokes.

The resultant increase in growth hormone with an alkaline diet may improve many outcomes from cardiovascular health to memory and cognition.

An increase in intracellular magnesium, which is required for the function of many enzyme systems, is another added benefit of the alkaline diet. Available magnesium, which is required to activate vitamin D, would result in numerous added benefits in the vitamin D apocrine/exocrine systems.

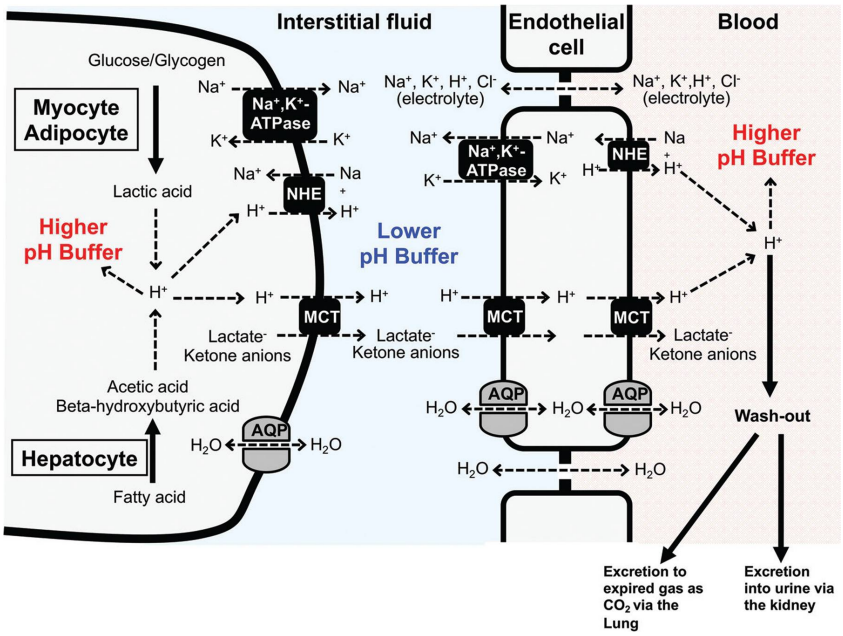
Alkalinity may result in added benefit for some chemotherapeutic agents that require a higher pH.

One of the first considerations in an alkaline diet, which includes more fruits and vegetables, is to know what type of soil they were grown in since this may significantly influence the mineral content. At this time, there are limited scientific studies in this area, and many more studies are indicated in regards to muscle effects, growth hormone, and interaction with vitamin D.

https://onlinelibrary.wiley.com/doi/full/10.2991/efood.k.190924.001

Body Fluid pH Balance in Metabolic Health and Possible Benefits of Dietary Alkaline Foods 2019

Thus, the intracellular fluid pH is decreased under conditions of poor oxygen supply and excess glycolysis [9,10].
The intracellular fluid pH of living cells is mostly maintained at alkaline levels by various systems (Figure 1). As typical examples, the bicarbonate–carbonate ($HCO_3^- - CO_2$) system, protein–proton binding, and phosphoric acids (H_3PO_4) act as proton-buffering systems. In addition, several membrane transporters have important roles in proton excretion from the cytosol to the extracellular space and contribute to the maintenance of alkaline pH. For example, Monocarboxylate Transporters (MCTs) cotransport protons and monocarboxylate anions, such as lactate, pyruvate, beta-hydroxybutyrate, and acetoacetate, across the plasma (cellular) membrane [9,10,13-17]. In addition to these systems, the Na^+/H^+ Exchanger (NHE), HCO_3^--coupled transporters, and proton-coupled transporters also play key roles in the release of protons into the extracellular space [9,10,18,19].



To maintain the intracellular pH in most living cells at alkaline levels as mentioned above, the acid produced in the intracellular space is extruded into the interstitial fluid (the extracellular fluid) [1,9]. Growing concepts suggest that the acidity of the interstitial fluid is one of the most serious pathogenesis causing various diseases including diabetes mellitus, tumor metastasis, and so on [1,9] (see the detail in Section 4).
This review focuses on the significance of regulation of intracellular and extracellular fluid pH and the possible benefits of dietary foods associated with the prevention of disease development and improving physical fitness level.
Several buffering systems primarily contribute to the prevention of abnormal pH arising from excess proton production. A major buffering system is the bicarbonate–carbonate reaction in intracellular and extracellular fluids. The bicarbonate (HCO_3^-) reacts with proton and is protonated to H_2CO_3, and then establishes equilibrium with the dissolved CO_2 and H_2O. The acid–base metabolism in the body is thus regulated by the following equilibrium equation: $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- (pKa = 6.10)$. Finally, the CO_2 is exhaled or removed mainly via breathing gas from the lungs, which accounts for the removal of proton.
Na^+/H^+ exchanger also acts as a major proton transporter that maintains the intracellular fluid pH homeostasis. It extrudes the intracellular proton by taking in the extracellular Na^+ using the Na^+ chemical gradient between intra- and extra-cellular fluids [18,35].
The pH of blood (arterial blood pH) is strictly regulated within the range of 7.35–7.45 as blood has strong pH buffers such as albumin and Hb (Figure 2). On the other hand, interstitial fluids have only relatively weak pH buffers, bicarbonate and phosphate. Therefore, the pH of interstitial fluids has relatively variable pH values compared with the blood pH (Figure 2).
Several intervention studies in humans have shown that fruit and vegetable-rich foods improve the acid–base balance and raise the urinary pH; these foods are collectively referred to as the alkaline diet [81].
Furthermore, this study [57] clearly reports that the pH of ascites and interstitial fluids around metabolic tissues is improved (elevated) by the intake of **propolis** compared with normal diet (without propolis intake), suggesting a possibility that dietary propolis suppresses the production of organic acids and/or elevates the pH-buffering capacity in those tissues.
In addition, we have shown in a double-blind randomized placebo-controlled study in type 2 diabetic patients that the supplementation of propolis for 8 weeks has prevented the worsening of blood uric acid and improved the estimated glomerular filtration rate [104]. Therefore, propolis may be a useful compound to improve glucose metabolism associated with the prevention of acidic state.
On the other hand, Japanese traditional herbal medicine is also known to improve various types of metabolic disorder symptoms including diabetes mellitus. Ninjin'yoeito (NYT), a Japanese traditional herbal medicine, consists of 12 species of crude drugs: rehmannia root, Japanese angelica root, atractylodes rhizome, poria sclerotium, ginseng, cinnamon bark, polygala root, peony root, citrus unshiu peel, astragalus root, glycyrrhiza, and schisandra fruit. NYT has also been shown to improve insulin resistance by elevating the interstitial fluid pH possibly via an increase in sodium-coupled monocarboxylate transporter 1 expressed in the colon, which transports only the part of carboxyl group without H^+, leading to an increase in pH-buffering capacity [1,105,106] (Figure 6).

https://pubmed.ncbi.nlm.nih.gov/23416075/
Improvement of insulin resistance, blood pressure and interstitial pH in early developmental stage of insulin resistance in OLETF rats by intake of propolis extracts 2013
Propolis, a resinous mixture collected from plants by the Apis mellifera bee, contains high level nutrient factors including vitamins, polyphenols, and amino acids that would be expected to improve insulin sensitivity. Insulin resistance would secondarily cause elevation of blood pressure and increase the risk of cardiovascular diseases. The purpose of this study is to investigate the effect of propolis extracts on blood glucose levels and blood pressures in an early developmental stage of insulin resistance in Otsuka Long-Evans Tokushima Fatty (OLETF) rats.
Propolis decreased systolic blood pressure with no significant changes in plasma aldosterone levels. We also found that **interstitial fluid pH in ascites, liver, and skeletal muscle was higher in rats fed propolis diet than rats fed normal diet.**

https://www.tandfonline.com/doi/full/10.2147/CMAR.S65444
Interstitial fluid flow in cancer: implications for disease progression and treatment 2014
As cancer progresses, a dynamic microenvironment develops that creates and responds to cellular and biophysical cues. Increased intratumoral pressure and corresponding increases in interstitial flow from the tumor bulk to the healthy stroma is an observational hallmark of progressing cancers. Until recently, the role of interstitial flow was thought to be mostly passive in the transport and dissemination of cancer cells to metastatic sites. With research spanning the past decade, we have seen that interstitial flow has a promigratory effect on cancer cell invasion in multiple cancer types. This invasion is one mechanism by which cancers can resist therapeutics and recur, but the role of interstitial flow in cancer therapy is limited to the understanding of transport of therapeutics. Here we outline the current understanding of the role of interstitial flow in cancer and the tumor microenvironment through cancer progression and therapy. We also discuss the current role of fluid flow in the treatment of cancer, including drug transport and therapeutic strategies. By stating the current understanding of interstitial flow in

cancer progression, we can begin exploring its role in therapeutic failure and treatment resistance.

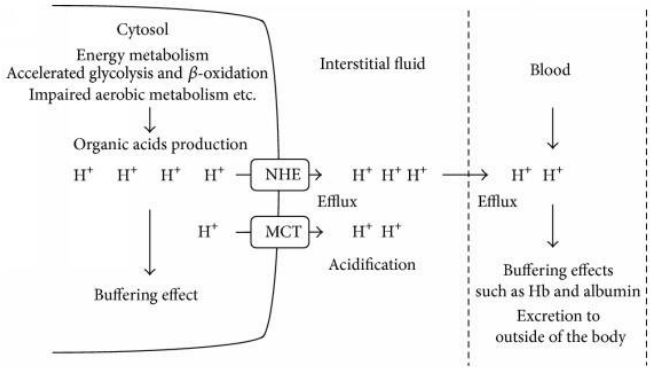
https://onlinelibrary.wiley.com/doi/10.1155/2014/598986

Importance of pH Homeostasis in Metabolic Health and Diseases: Crucial Role of Membrane Proton Transport 2014

Body fluid pH is determined by the content of protons (H+) generated from organic acids produced in living cells. Lactic acid (lactate−/H+) is a typical proton source and is involved in the regulation of physiological pH. In metabolic tissues such as skeletal muscle and adipose tissue, the glycolytic anaerobic metabolism mediates the conversion of glucose and glycogen into lactic acid. Because the pKa of lactic acid is 3.80, it is immediately dissociated into lactate (lactate−) and protons under physiological conditions, resulting in reduced intracellular pH. Pyruvic acid (pyruvate−/H+), an intermediate metabolite in the glycolytic system, is also a source of protons, although it generates much less protons compared to lactic acid. In addition, metabolites such as ketone bodies also act as proton sources. Beta-hydroxybutyric acid (beta-hydroxybutyrate−/H+), a typical ketone body, is generated as a result of fatty acid metabolism in the liver and is also dissociated into beta-hydroxybutyrate anions and protons, leading to the reduction of intracellular pH.

The intracellular pH in most living cells is alkaline compared to the pH generated by protons that are transported passively through the plasma membrane by electrochemical forces. In addition to buffering systems such as the bicarbonate-carbonate system, protein-proton binding, and phosphoric acid, several membrane transporters are responsible for proton removal from the cytosol and play important roles in maintaining the alkaline pH in cells (Figure 1). In most mammalian cells, H+-monocarboxylate cotransporters (MCTs) participate in the transport of monocarboxylic acids such as lactate, pyruvate, beta-hydroxybutyrate, and acetoacetate across the cellular membrane by cotransporting protons and monocarboxylate anions [1–3]. Other transporters such as the Na+/H+ exchanger (NHE) and bicarbonate-dependent exchanger also contribute to proton extrusion from the cytosol to the extracellular space [4, 5]. This review focuses on the critical role of the membrane transport system of protons in regulation of intracellular and extracellular fluid pH and its importance in maintaining physiological homeostasis and preventing diseases development.

The normal physiological pH of mammalian arterial blood is strictly maintained at 7.40; blood has pH buffers such as Hb (hemoglobin) and albumin. A decrease of more than 0.05 units from the normal pH results in acidosis.



The buffering capacity is relatively high in the cytosol and blood but low in the interstitial fluid due to limited buffering factors such as proteins [45, 46]. Therefore, interstitial fluid pH in metabolic tissues easily changes (Figure 1) and may contribute to the onset of insulin resistance.

5. pH Regulation by Diet and Exercise Intervention

The maintenance of pH in metabolic organs is achieved through various regulatory systems. Physical exercise and appropriate diet contribute to pH homeostasis. Habitual exercise adaptively accelerates the entry of fatty acids both from the plasma into the muscle cell and from the cytosol into the mitochondria, while also enhancing Krebs cycle function in the resting state.

Based on the results of our *in vitro* study, the skeletal muscle may be entirely dependent on MCT1-mediated lactate uptake by erythrocytes to maintain pH homeostasis [71]. In addition, there is a high correlation between the athletic performance of horses and their erythrocyte lactate concentrations after racing [73]. Therefore, efficient proton transport via MCTs induced by habitual exercise may contribute to the improvement of insulin sensitivity and muscle fatigue caused by lowered pH.

The effects of these nutrients are only beneficial when administered in combination. In contrast to the successful application of dietary approaches or combined nutrients [85–87], various types of intervention studies using single nutrients have failed to clarify their beneficial action on cardiovascular risk and insulin resistance [88, 89]. Therefore, administration of multiple nutrients is considered more effective when compared to administration of a single bioactive factor. **Propolis, a natural product derived from the plant resins collected by honeybees, contains various types of compounds including polyphenols, phenolic aldehydes, sesquiterpene quinones, coumarins, amino acids, steroids, and inorganic compound**s [90] and has been reported to reduce the metabolic defects caused by abnormal blood glucose and insulin in young (18 weeks of age) OLETF rats [42] characterized by hyperphagia, obesity, decreased glucose infusion rate in a euglycemic clamp at 16–18 weeks of age, hyperinsulinemia around 25 weeks of age responding to an intravenous glucose infusion, and developing type 2 diabetes [91, 92]. Thus, our study indicates that propolis has a beneficial and preventive action on type 2 diabetes mellitus at early stages developing insulin resistance. Further, we have **obtained evidence that intake of propolis elevates the pH of ascites and metabolic tissues compared with normal diet,** indicating that dietary propolis diminishes production of organic acids or increases buffering capacity in those tissues. Therefore, propolis may be a useful compound to improve insulin sensitivity via prevention of metabolic acidosis. The **molecular mechanism of how propolis improves interstitial pH is unclear**, and we should strive to better understand the mechanism of this bioactive supplement.

https://pmc.ncbi.nlm.nih.gov/articles/PMC6068141/

Systems analysis of intracellular pH vulnerabilities for cancer therapy 2018

Acidification of the extracellular milieu (low pHe) and concomitant intracellular alkalization of the cytoplasm (high pHi) are other hallmarks of cancer, leading to a reverse pH gradient in cancer cells (pHi > 7.2, pHe ~ 6.7–7.1) vs. normal cells (pHi ~ 7.2, pHe ~ 7.4)[6].

Collectively, our findings suggest that cancer cells have superior fitness at an alkaline pHi, and that their reliance on an alkaline intracellular environment confers vulnerabilities that can be exploited for therapeutics. In accord with previous studies[9,26], our findings clearly demonstrate that lowering pHi is a selective vulnerability for cancer cells.

https://www.nature.com/articles/nrd3554

Interfering with pH regulation in tumours as a therapeutic strategy 2011

Key Points

The regulation of pH in tumours involves the interplay of several proteins, including: the carbonic anhydrases (EC 4.2.1.1) CA2, CA9 and CA12; the vacuolar ATPase (V-ATPase); anion exchangers AE1, AE2 and AE3; Na+/HCO3− co-transporters (NBCs); electroneutral Na+-driven Cl−/HCO3− exchanger (NDCBE); the monocarboxylate transporters MCT1, MCT2, MCT3 and MCT4; and Na+/H+ exchanger 1, among others.

The concerted action of these proteins maintains a slightly alkaline intracellular pH (pHi) and an acidic extracellular pH (pHe) within the tumours, which favours the growth and spread of the primary tumour, leading to the formation of metastases.

The inhibition of one or more of these pH regulators with specific inhibitors causes both pHi and pHe values to return to normal, with the consequent impairment of tumour growth. This property represents an antitumour mechanism that is not exploited by the classical anticancer drugs.

The inhibition of CA9 and/or CA12 with sulphonamide- or coumarin-based small-molecule inhibitors reverses the effects of tumour acidification, leading to inhibition of cancer cell growth in both primary tumours and metastases. Some of these compounds are in preclinical development. This effect can also be exploited for the imaging and treatment of tumours that overexpress CA9 or CA12. The same effect has been observed with antibodies targeting CA9 (and, more recently, also CA12). Some of these antibodies (for example, cG250) are in Phase III clinical development as antitumour and diagnostic agents.

Some sulphonamides also inhibit anion exchangers, whereas proton pump inhibitors of the omeprazole type show antitumour effects by inhibiting V-ATPase, thus interfering with other tumour pH regulators.

Potent, specific and non-toxic compounds as well as antibodies that interfere with these proteins may represent valuable new antitumour drugs.

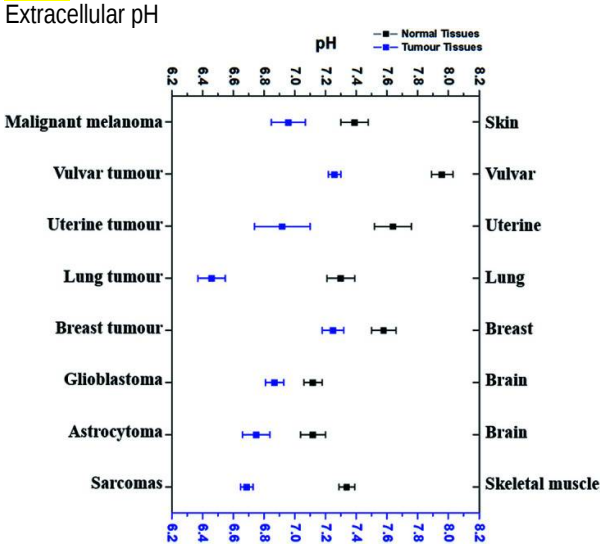
Changes in pHi towards basic values lead to the production of splice isoforms of extracellular matrix components at the tumour site, which are ideal targets for antibody-based pharmacodelivery strategies.

https://pubmed.ncbi.nlm.nih.gov/35541713/

Manipulating extracellular tumour pH: an effective target for cancer therapy 2018

The pH in tumour cells and the tumour microenvironment has played important roles in cancer development and treatment. It was thought that both the extracellular and intracellular pH values in tumours are acidic and lower than in normal cells. However, recent progress in the measurement of pH in tumour tissue has disclosed that the intracellular pH (pH_i) of cancer cells is neutral or even mildly alkaline compared to normal tissue cells. This review article has summarized the recent advancement in the measurement pH_i and extracellular pH (pH_e) in cancer cells, and the effect of pH_i and pH_e on proliferation, migration and biological functions of cancer cells. This paper has also elaborated recent treatment strategies to manipulate pH_i and pH_e for cancer treatment. Based on the recent progress in pH_i and pH_e manipulation in cancer treatment, we have proposed potential nanoparticle-based strategies to manipulate pH_i and pH_e to effectively treat cancer.

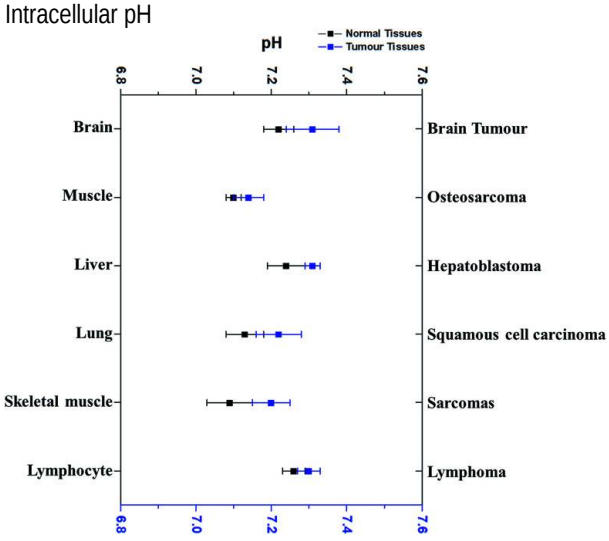
Extracellular pH



It is widely accepted that the pH_e of cancer cells is more acidic than normal cells.[4–6]

During the process, the tumour growth requires a large amount of energy compared to the normal tissue, which produces more CO_2 and lactic ions in tumour. The produced CO_2 was excreted extracellularly, resulting in the acidic condition in the tumour microenvironment, *i.e.* 0.3–0.7 pH units lower than the average pH_e of normal tissues.

Intracellular pH



For most cells, the maintenance of neutral (or mild alkaline) pH_i is achieved by transporting respiratory end-products (such as CO_2 and lactate) across the cell

membrane. When the extracellular concentration of acidic respiratory end-products is lower than intracellular, the excess CO_2 can passively across the cell membrane by diffusion.[47] However, in most cases, the CO_2 and lactate generated from glucose metabolise is accumulated in extracellular tumour site due to low blood flow rate, resulting in development of acidic microenvironments in tumour.[48,49] In this situation, the release of CO_2 and lactate in microenvironments mainly relies on numerous special membrane proteins, such as carbonic anhydrase enzymes (CA2, CA9 and CA12).

The summary of some major pH regulators in cancer cells and their main functions in manipulating the ratio of extracellular pH and intracellular pH in tumour cells.

Name	Description	Function	Reference
SLC4A1 SLC4A2 SLC4A3	Anion exchangers	Transport HCO_3^- out of cancer cells	53 and 54
SLC4A7	Sodium bicarbonate cotransporters	Mediate the coupled movement of sodium and bicarbonate ions across the plasma membrane	55
SLC4A8	Sodium ion-based chloride/bicarbonate	Transport Cl^- out of tumour cells and simultaneously import HCO_3^- into cancer cells powdered by Na^+	56
SLC9A1	Na^+/H^+ exchanger 1	Transport intracellular produced H^+ to the extracellular environment, and import Na^+ at the same time	56
MCT1 MCT2 MCT3 MCT4	Monocarboxylate transporters	Transport (both inside to outside and outside to inside) the products of glycolysis (such lactic acid and other monocarboxylates)	57 and 58
V-ATPase	Proton transporter vacuolar ATPase	A proton pump on the membrane of tumour cells, responsible for the stransportation of H^+ between intracellular and extracellular plasma	

For instance, the balance of HCO_3^-/CO_3^{2-} buffer system in tumour is administrated by carbonic anhydrase enzymes CA2, CA9 and CA12.[12,70,71] Besides, the Na^+/H^+ buffer system is manipulated by Na^+/H^+ exchangers, such as SLC9A1.[72] The regulation of pH_e and pH_i depends on the synergic effect of all of these pumps and buffer systems.
It is well known that acidic condition and hypoxia are important characteristics in the tumour microenvironment.

4. Strategies to manipulate the pHe/pHi ratio

4.1. Direct manipulation using small molecule drugs

The drugs for direct manipulation are mainly small molecular substances (such as bicarbonates). This approach is to directly increase pHe of tumour tissues to the normal level (0.3–0.7 pH unit). It can be achieved by oral administration of alkaline agents or even by simple adjustment of diet habit.
The alkaline agents include sodium bicarbonate and trisodium citrate.[77] In practice, it seems difficult to maintain the mildly alkaline microenvironment near tumour tissues *via* oral administration, as a high dose and continuous intake of the alkaline substrate is required. Based on the breast cancer study, White *et al.* investigated the exact daily dose of sodium bicarbonate needed for breast cancer treatment.[78] The calculated daily dose for a normal human (with 70 kg weight) would be 31.75 g sodium carbonate or 32.5 g trisodium citrate.[79]
Although it is possible for a cancer patient to intake more than 30 g alkaline agents (such as sodium carbonate or trisodium citrate) with daily drinking water, it would be more efficient to deliver alkaline agent to the tumour tissues rather than to the whole body.
The adjusted diet could be low in protein but high in potassium and/or magnesium.[82–84] It has been proved that potassium can effectively neutralize mineral acidity and even mildly alkaline pH of urine *via* $KHCO_3$ generation or glutamine sparing.[85] The pH_i may be altered by a large change of the intake of potassium due to its fundamental physiologic and metabolic importance.[85] Based on another big data analysis (based on more than 300 000 cases), the risk of suffering from pancreatic cancer decreased by 18% for each 100 mg increase of magnesium intake per day by men on the continuous scale.[86] These results may provide a diet-based way to manipulate the pH environment *in vivo* and assist cancer treatment.

4.2. Indirect manipulation: proton pump inhibitors

The second alternative strategy to administrate the pH_e/pH_i ratio is to inhibit the functional proton pumps. It is well known that the maintenance of high pH_e/pH_i ratio in tumour tissues relies on many proton regulators (pumps) on the cell membrane.
Table 4 lists some inhibitors and their target proton pumps.[90,94–102] As seen in Table 4, the current inhibitor drugs mainly focus on two major pH regulators (V-ATPase and SLC9A1) and only one of these drugs, cariporide, has been successfully developed to phase III clinical trial.

4.3. Alternative methods to manipulate the pHe/pHi ratio

Several research reports have showed that the apoptosis of tumour cells can be boosted by the adequately large decrease of their pH_i.[87–92] One way to achieve the reduction of pH_i in tumour cells is to promote cancer glycolysis to the utmost extent by maximizing the glucose supplement
The tumour glycolysis can be promoted by inhibiting the production of mitochondrial ATP, which requires some specific inhibitors. *meta*-Iodobenzylguanidine is one of the inhibitors of mitochondrial complex 1, acting as proton extrusion inhibitors (or hyperglycemia) and then decreasing pH_i in cancer cells.[100,109–111] However, this drug is normally used as a radioiodine therapy agent, and the dose used for radioiodine therapy is not high enough to perform a strong inhibition on proton transportation.

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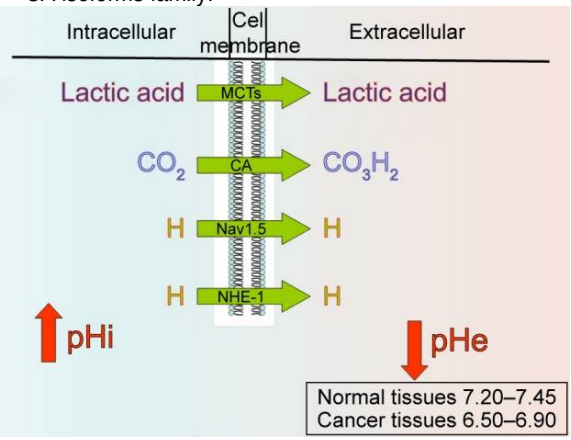
Cancer: fundamentals behind pH targeting and the double-edged approach 2016

Targeting tumor pH may go in two directions:
1) increasing extracellular pH which should result in less migration, invasion, and metastasis; and
2) decreasing intracellular pH which may result in acidic stress and apoptosis.
Both objectives seem achievable at the present state of the art with repurposed drugs.
Six important pH regulators have been identified at the cellular level (there are probably more, but these six account for most of the activity; Figure 1):
Vacuolar ATPase proton pump.
NHE family.

Bicarbonate transporter family.
Monocarboxylate transporter (MCT) family.
VGSCs.
CA isoforms family.



Precisely, we propose using the association of eight pharmaceuticals (and a possible ninth) to achieve this goal:

Lansoprazole or pantoprazole
Amiloride or an analog of amiloride and cariporide could be another option
Phenytoin
Quercetin
Lipophilic statins like simvastatin, atorvastatin, cerivastatin and lovastatin
Metformin or phenformin
Doxycycline
Atovaquone
If the tumor overexpresses CA, acetazolamide should be added to the combination.

Each of these drugs has low toxicity at therapeutic doses. Except for cariporide, there is adequate experience with all of them, and they are FDA-approved.