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Unveiling the Impact of Sodium Bicarbonate on Metabolic Acidosis in Cancer-A Systematic Review

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Abstract

Background: Tumor microenvironment has elevated levels of extracellular acidity as a result of its glycolytic nature.

Aim: The aim of the study is to analyse whether oral administration of sodium bicarbonate can prevent cancer by increasing the tumor pH and controlling tumor invasion and metastases through various experimental research.

Materials and Methods: In this study, the electronic databases were searched from the time of their conception until 2023, in compliance with PRISMA guidelines. Original studies conducted among experimental mice, were given sodium bicarbonate orally, which was found to be a significant global cancer prevention strategy.

Result and Conclusion: The result shows that oral administration of sodium bicarbonate prevents cancer progression in mice by increasing the tumor pH. However, more clinical trials are required to show its efficacy in patients as an adjuvant therapy or a stand-alone treatment. Furthermore, it is necessary to look at patients' sodium bicarbonate tolerance and safety.

Keywords: Cancer prevention, metabolic acidosis, oral administration, pH buffer, Sodium bicarbonate, tumor

Introduction

GLOBOCAN in the year 2020, the estimated lifetime risk of cancer among 185 countries from the time of birth to death was 25.10%; for men, the risk was 26.27%, and for women, 23.96%. The lifetime cancer risk was found to be 38.48% in very high, 25.38%, 11.36%, and 10.34% in high, medium, and low Human Development Index countries and regions, respectively. Worldwide, the highest lifetime risks for men and women were linked to prostate and breast cancer (4.65% and 5.90%, respectively). With a residual risk of 12.61% after the age of 70, the lifetime risk of cancer declined with age. Men and women have similar lifetime risks for developing cancer, which amounts to about one in four people getting the disease [1].

The need for effective treatments is growing along with the global incidence of cancer. Patients with cancer have much longer survival times due to the accessibility of recent advancements in

surgery, chemotherapy, and radiation therapy, as well as newer forms of treatment such as immunotherapies and targeted therapies. For individuals with oral cancer, low-level helium-neon laser therapy may be a useful therapeutic option for treating radiation-induced oral mucositis [2]. However, cancer is still a fatal illness, especially when it reaches an advanced stage. From this angle, alternative medicine is often used by cancer patients, either to treat symptoms or in the hopes of a cure.

Tumor pH acidity is one of the main factors in tumor proliferation. Because of their low perfusion and elevated fermentative metabolism, solid tumors have an acidic pH. Various theories suggest acid pH encourages metastatic and local invasive development. Alkalinizing substances can help reduce this acidic pH. It's a fallacy that ingesting sodium bicarbonate aids in the activity that fights cancer. Despite these regular reports and clinical evidence regarding the role, there is still no evidence of sodium bicarbonate treatment for cancer. New experimental findings indicate that sodium has a positive impact. The effect of bicarbonate on tumor growth suggests that salt may play a part in bicarbonate treatments for cancer. In this study, an attempt is made to analyze whether consumption of oral sodium bicarbonate is associated with the prevention of cancer progression.

Materials and methods

Information sources

The following electronic databases were searched from the time of their conception until 2023, in compliance with PRISMA guidelines: PubMed, Wiley online library, Elsevier Science Direct, and SpringerLink.

Search strategy

Boolean operators were used in the search strategies for the following keyword combinations: "sodium bicarbonate," "baking soda," "cancer prevention," "metabolic acidosis," "pH buffer," "increases tumour pH," "randomised controlled trial," "oral administration," and "experimental research."

Inclusion criteria

We have included research conducted on experimental mice given sodium bicarbonate orally, which is a significant global cancer prevention strategy and is accessible through several sources. Included were original research studies that had full texts available and were published in English. The study contained research that had been conducted using proper statistical analysis. The study includes studies that made use of validation tools and standardised measurement techniques. Animal studies and human studies were included.

Exclusion criteria

Research that was determined to be duplicate or irrelevant was not included. Articles with a simple abstract and those published in other languages were excluded.

Methodology

In this study, original studies that were done on mice from 2001 to the present were collected. 1602 full-text articles out of the 5,803 total articles were evaluated separately. Eight articles that met the inclusion criteria were included in the study after eligibility was determined using the

inclusion and exclusion criteria, duplicates were eliminated, and additional procedures were carried out.

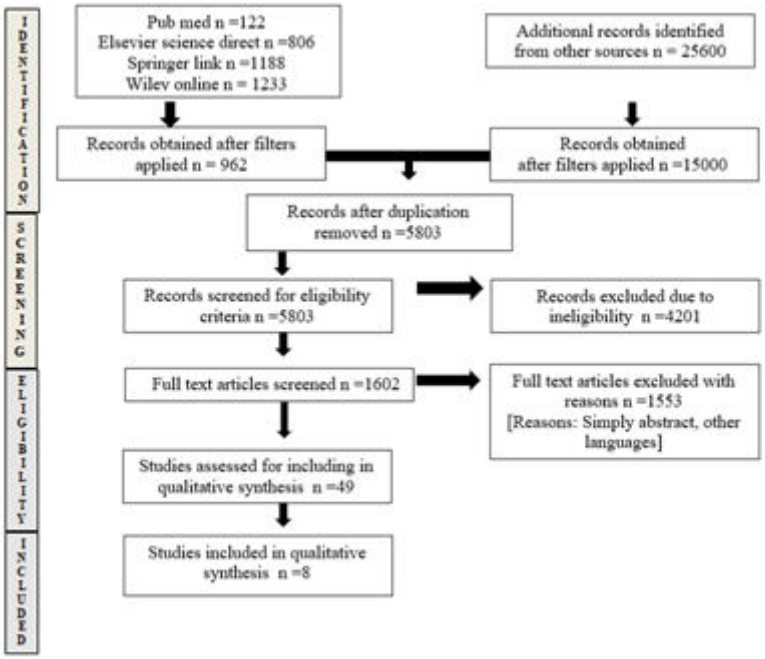

Figure 1 shows flow diagram illustrating the number of papers found, screened, evaluated for eligibility, omitted, and included in the systematic review.

Results

Table 1: Characteristics of the Study Included in the Systematic Review

Author	Year	Place of study	Sample	Intervention	Technique
Natarajan Raghunand et al[3]	2001	University of Arizona health sciences center	5-6 week-old female C3H /Hen mice	Oral 0.7 ml 1M $NaHCO_3$ and Intraepithelial administration of $NaHCO_3$	MRS was performed after the tumors had grown to >300mm3
Aristo S .Silva et al[4]	2009	Sao Paulo Brazil	Computer simulation	$NaHCO_3$	Two steps: 1. Diffusion of the species 2. Cellular activities
Ian F Robey Et Al[5]	2009	Arizona Cancer Center	6-8 Week-Old Female SCID mice of MDA-MB-231 tumor 6 week old female SCID beige mice of PC3M tumor Nu/nu mice of B16 tumor	Oral 200 mmol/L of $NaHCO_3$ ad libitum	Experiment observed on 30 days and 60 days of tumor growth
Ian F.Robey et al[6]	2011	University of Arizona	6-8 week old female SCID mice having MDA-MB-231/Egfptumor	$NaHCO_3$ 200 mM	120 days of treatment
Arig Ibrahim Hashim et al[7]	2012	H.Lee Moffitt cancer center	Transgenic mouse model having prostate cancer n=37	Oral 200 mM of $NaHCO_3$	Application of $NaHCO_3$ therapy before 6 weeks and after 6 weeks
Veronica Estrella et al[8]	2013	H.Lee Moffitt Cancer Center	8-10 Week Old SCID Mice Control =4 Experimental=8	Oral 200 mmol/L of $NaHCO_3$ ad libitum	Taken from 6 days before the inoculation of tumor constructs into the dorsal window chamber
Hidenori Ando et al[9]	2021	Tokushima University, Japan	5weeks old female B16 tumor-bearing mouse 5 weeks old female colon-26 tumor-bearing mouse	Oral $NaHCO_3$ 500 mg/kg BALB/C mice Oral $NaHCO_3$ 200 mM colon-26 tumor bearing mice	7 days of daily dose given to B16 tumor bearing mice 14 days of ingestion given to colon -26 tumor-bearing mice
Hidenori Ando et al[10]	2022	Japan	Colon 26 tumor bearing mouse	Oral $NaHCO_3$	$NaHCO_3$ was purchased from KENEI Pharmaceutical [Osaka,

					Japan]

Table 1 shows the characteristics of the intervention in the studies that are included. In all the above studies oral administration of sodium bicarbonate on mice associated with cancer prevention that are given by many authors were taken and in which technique it was performed was also mentioned.

Table 2: Results as given in the included studies

Author	Year	Place of study	Intervention	Inference
Natarajan Raghunand et al[3]	2001	University of Arizona Health Sciences Center	Oral 0.7 ml 1M NaHCO3 and Intraepithelial administration of NaHCO3	Increases tumorpH. Increases the efficacy of weak base chemotherapy.
Aristo S .Silva et al[4]	2009	Sao Paulo Brazil	NaHCO3	Increases tumor pH
Ian F Robey Et Al[5]	2009	Arizona Cancer Center	Oral 200 mmol/L of NaHCO3 ad libitum	Increases tumorpH. Decreases metastasis.
Ian F.Robey et al[6]	2011	University of Arizona	NaHCO3 200 mM	Inhibition of metastatic spread from primary tumors
Arig Ibrahim Hashim et al[7]	2012	H.Lee Moffitt Cancer Center	Oral 200 mM of NaHCO3	Reduces tumor growth
Veronica Estrella et al[8]	2013	H.Lee Moffitt Cancer Center	Oral 200 mmol/L of NaHCO3 ad libitum	Increase peritumoralpH. Reduce local invasion.
Hidenori Ando et al[9]	2021	Tokushima university, Japan	Oral NaHCO3 500 mg/kg BALB/C mice Oral NaHCO3 200 mM colon-26 tumor-bearing mice	Increases tumor interstitial pH
Hidenori Ando et al[10]	2022	Japan	Oral NaHCO3	Increases tumor pH

Table 2 shows the outcome and result of oral administration of sodium bicarbonate in mice associated with cancer prevention in the studies that are mentioned above positive outcomes and findings were seen in the above studies showing increase in tumor pH and inhibits the metastatic spread from primary tumors.

TABLE 3: OHAT RISK OF BIAS ASSESSMENT AS INCLUDED IN THE STUDIES

Author name	1	2	3	4	5	6	7	8	9	10	11
Natarajan Raghunand et al[3]	−	−	−	++	++	−	++	++	+	++	++
Ian F Robey Et Al[5]	++	+	++	+	++	−	−−	++	+	++	++
Ian F.Robey et al[6]	++	+	++	++	+	++	++	++	++	++	++
Arig Ibrahim Hashim et al[7]	++	−	++	++	++	−	++	+	+	++	++
Veronica Estrella et al[8]	++	−	++	−	++	−	−−	++	+	++	−
Hidenori Ando et al[9]	−	−	++	++	++	−	−	++	++	++	++

Hidenori Ando et al[10]	−	−	+	−	+	−	+	+	+	−	−

1-Random sequence generation
2- Allocation concealment
3- Appropriate comparison groups
4- Confounding and modifying variables
5- Experimental conditions identical across study groups
6-Blinding of research personnel
7-Incomplete outcome data
8-Exposure characterization
9-Outcome assessment
10- Outcomes reported
11- Potential threats to internal validity

Table 3 shows the bias analysis of all the included studies. It is categorized as Definitely low risk of bias "++", Probably low risk of bias "+", Probably high-risk bias "-", Definitely high-risk bias "--". Categorization was done according to the OHAT [Office of Health Assessment and Translation] risk of bias tools for randomized controlled trials(2019).

Discussion

Apart from the cancer cells themselves, the microenvironment surrounding the tumor is a complex structure made up of various cell types [11]. An increased amount of acidity produced by tumor cells combined with inadequate blood flow and vascular circulation results in an acidic pH [12]. There is evidence that acidity encourages the growth of metastases. When injected into the tail vein of mice, melanoma cells that had previously been exposed to an acidic medium metastasized to the lungs more frequently [13,14,15]. The proteolytic enzymes MMP-2, MMP-9, cathepsin B, and cathepsin L were found to be up-regulated, indicating that acidity promotes the breakdown of the extracellular matrix and basement membrane by cancer cells [13,16]. It has been reported that cancer cells become more motile and invasive at low pH levels, which is similar to the observation that cancer cells exhibit an aggressive phenotype after being exposed to acidity [15,17]. Additionally, the low pH causes necrosis and apoptosis in normal cells, but developed resistance mechanisms allow cancer cells to survive [18,19]. Significant niche engineering is brought about by regional acidosis through the promotion of the formation of new blood vessels, extracellular matrix degradation, normal cell death, and immune response suppression [20,21,22].

Because of increasing extracellular tumor pH promoted cellular uptake of weak-base chemotherapies, sodium bicarbonate was found to augment their anti-cancer efficacy. Tumor growth was tracked after injecting MCF-7 human breast cancer cells into the mammary fat pads of immunodeficient mice. When combined with doxorubicin, sodium bicarbonate dramatically enhanced the anti-cancer efficaciousness of the drug; however, the tumour growth of mice treated with sodium bicarbonate alone was comparable to that of normal animals [23]. Mitoxantrone had similar outcomes in a mouse model of breast cancer [3].

It was demonstrated that sodium bicarbonate raised the tumor pH in mice with breast tumour xenografts, which enhanced the anti-tumor efficacy of doxorubicin [23]. Mathematical models were used to reinforce the possibility of using sodium bicarbonate. Through computer simulations, it was shown that ingesting sodium bicarbonate reduces tumor acidity without

changing the pH of blood or tissue. Moreover, the alteration in tumor pH that follows reduces the growth and invasion of the tumor [4].

These findings were validated by more research using tumor mouse models. Mice with impaired immune systems were used to create breast tumor xenografts. After that, mice were randomly assigned to treatment and control groups, and their drinking water either contained sodium bicarbonate or not. Mice given sodium bicarbonate had noticeably longer lifespans and showed a decrease in the quantity and size of lung, colon, and diaphragm metastases. Notably, sodium bicarbonate did not significantly increase toxicity or affect the growth of primary tumors. The intratumoral pH is raised by sodium bicarbonate, as demonstrated by magnetic resonance spectroscopy. Following treatment, no abnormalities in blood electrolytes were observed. Specifically, metabolic alkalosis was not the result. In the same study, sodium bicarbonate reduced liver metastasis of spleen-injected human breast cancer cells. Furthermore, it lessened the development of metastases after injecting PC3M human prostate cancer cells into the tail vein. In contrast, sodium bicarbonate had no significant effect on metastatic spread when injected into B16 mouse melanoma cells. Although the exact cause of this discrepancy remained unknown, the authors hypothesised that as B16 cells multiplied more quickly, their rates of acid production may have simply surpassed sodium bicarbonate's buffering abilities. [5].

Based on an interventional survival study using the MDA-MB-231 mouse model for metastatic breast cancer, in which tumor-bearing mice were given DCA, bicarbonate, or DCA-bicarbonate (DB) treatments on a long-term basis. Whether used alone or in conjunction with bicarbonate, dichloroacetate did not cause mice's systemic alkalosis to rise. The mice those received treatments based on bicarbonate had the longest survival. After surgery, the recurrence of primary tumours is related to survival rates. Even though oral bicarbonate did not significantly increase with DB treatment, they report reduced pulmonary lesions sizes and show in vitro evidence that hypoxia may have caused this outcome. Chronic oral bicarbonate treatment did not seem to be improved by DB combo therapy. This suggests that the effectiveness of DCA as a cancer treatment is unexpected and that more research is required to understand this agent's function in the tumour microenvironment [6]

A transgenic mouse model of prostate cancer was also used to test the effects of sodium bicarbonate [7]. According to this model, the probasin promoter controls the oncoprotein SV40 T antigen, which causes prostate intraepithelial neoplasia before the age of five weeks and progresses to invasive cancer between the ages of five and eight weeks [24]. After six weeks, starting sodium bicarbonate did not stop the progression of prostate cancer; in fact, the primary tumour growth characteristics of the mice in question were identical to those of the mice who were not given any treatment. On the other hand, when administered beginning at 4 weeks of age, sodium bicarbonate notably inhibited the growth of prostate cancer. Most of these mice had prostate hyperplasia at necropsy, and thirty percent had small cancer foci. Interestingly, compared to untreated or late-treated mice, the pH of early-treated mice was substantially higher. This implies that sodium bicarbonate may stop the growth of invasive prostate cancer by addressing acidity in intraepithelial neoplasia.

Systemic buffers, like sodium bicarbonate, were effectively employed in between these methods in order to raise intratumoral pH. The impact of sodium bicarbonate on tumor growth in a mouse dorsal skin window chamber was also investigated. Human colon cancer cells HCT116 cells were found to grow less rapidly when sodium bicarbonate was taken. Moreover, it was shown that sodium bicarbonate could raise the pH of the tumour. More importantly, it was demonstrated that pH values at the invasive front of the tumour were significantly higher than those at the tumour's

centre, where there was no significant difference between mice treated with bicarbonate and those under control. This further implies that sodium bicarbonate, by focusing on acidity, may have a role in decreasing tumour invasion [8].

By raising serum HCO3 concentrations, which are correlated with urinary HCO3 concentrations and urinary pH values, alkalinizing agents raise the acidic tumour interstitial pH. The findings suggest that urinary pH values and serum HCO3 concentrations, which correlate to tumour pH, may be significant predictors of the clinical results of several anticancer treatments when paired with an alkalinizing drug [9]. In a mouse model of Colon26 tumours, the anticancer effectiveness of Doxil® when combined with oral NaHCO3 treatment was examined. NaHCO3 unquestionably improved Doxil®'s tumour-growth inhibitory action without aggravating any systemic side effects. High concentrations of DXR were internalised into cells at a neutral pH, according to in vitro research. These investigations show that neutralising the acidic tumor microenvironment with oral NaHCO3 delivery may be a viable strategy to improve Doxil® treatment results. In a tumor-bearing mouse model, oral administration of NaHCO3 appears to somewhat augment the anticancer impact of greater concentrations of Doxil®[10]

A study among patients with non-muscle-invasive bladder cancer (NMIBC) found that sodium bicarbonate maximised the effectiveness of intravesical instillation of mitomycin-C (IVI-MMC) therapy by alkalinizing the urine. The purpose of this study was to assess the effectiveness of sodium bicarbonate in preserving the concentration of the active form of MMC during IVI-MMC and to examine variations in MMC concentration in relation to urine pH. The high concentration of active urine MMC in NMIBC was not maintained by sodium bicarbonate delivery for urine alkalinization for IVI-MMC [25].

Patients with advanced pancreatic cancer and those who have recurring pancreatic cancer and whose urine pH increased during alkalization therapy are said to have better results when chemotherapy and alkalization therapy are combined. To find out if alkalization therapy leads to better results and the alkalization of the tumor microenvironment, more research is needed [26]. If sodium bicarbonate is taken systemically by patients, there are significant risks involved. These include hypernatremia and the development of metabolic alkalosis and associated consequences. Furthermore, stopping sodium bicarbonate suddenly could have negative effects. It is noteworthy that a number of scholarly studies have been published detailing the harmful effects of prolonged consumption of sodium bicarbonate [27,28,29,30]. Heartburn can often be relieved by using baking soda, a common home product that contains sodium bicarbonate, as an antacid. As predicted, consuming too much baking soda causes a severe electrolyte imbalance that needs to be treated by a doctor. Along with other symptoms, tiredness, lethargy, patients usually experience digestive issues like vomiting, diarrhoea, stomach discomfort and metabolic syndromes like blood hypercapnia, respiratory compensation was also observed. Patients ingesting fewer than two teaspoons of baking soda, each of which contains 4.8 g of sodium bicarbonate, have already been shown to experience adverse effects [29].

Notably, a case study of a 79-year-old man with advanced renal cell carcinoma who started self-medication with vitamins, supplements, and 60 g of sodium bicarbonate every day for ten months showed that the high dose of sodium bicarbonate was well tolerated without causing any negative side effects [4]. On the other hand, patients with sickle cell disease or chronic metabolic acidosis have received long-term sodium bicarbonate therapy without experiencing significant adverse effects, indicating that dietary sodium bicarbonate use is safe when monitored by a physician [31,32,33]. Moreover, alternative medicine uses sodium bicarbonate to treat cancer, and at a dose of 12 g daily, it appears to be well tolerated [34]. Although sodium bicarbonate can be hazardous

when consumed over a long period of time, it may be more tolerable when administered quickly. Patients with advanced cancer stages who did not respond well to traditional treatment are given preference when testing new therapies. It is important to know the country's misery index to perform more clinical trials on patients. An individual's country's HDI and health indicators will undoubtedly reflect its high or low misery index scores. As a result, a nation's health indicators, HDI, and misery index have an indirect or direct impact on one another.[35] Therefore, the likelihood of proving a novel treatment's anticancer efficacy may be reduced, requiring a sizable cohort to demonstrate an impact.

Conclusion:

Numerous online testimonials describe sodium bicarbonate self-medication by cancer sufferers. Physicians are still doubtful about the use of bicarbonate as a cancer treatment, despite rising pre-clinical evidence supporting its anti-cancer efficacy and a scientific justification for its usage. Regarding its safety and effectiveness, questions are raised. It is noteworthy that there may not be much willingness to test sodium bicarbonate in expensive clinical studies because its sale does not yield any financial gain. Proven effective among mice but it will take further experimental research to fully understand the mechanism behind sodium bicarbonate's anti-cancer effects on humans. Moreover, clinical trials are required to show its efficacy in patients as an adjuvant therapy or a stand-alone treatment. Furthermore, it is necessary to look at patients' sodium bicarbonate tolerance and safety.

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Authors Contribution:

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Sujitha S:Data collection and Methodology

Sindhu R:Data quality assessment and corrections in manuscript

Rajmohan M: Review and corrections in manuscript

Dinesh Dhamodhar: Proof reading and Plagiarism check

Data Availability:The article includes references to the data that supported the findings of the study. Full text articles can be provided upon request.

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