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Buffered vs. Non-Buffered Aliphatic Fatty Acids and their Anti-Proliferative Effects in Human Tumor Cell Lines

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Abstract

Background: Tumor cells generate a micro-acidic environment due to increased fermentative metabolism and poor perfusion. It is believed that this action is responsible for creating a lower pH environment which promotes invasive tumor growth in primary and metastatic cancers, through a form of acid-induced micro-environmental remodeling. Dietary fats, both saturated and unsaturated, have profound impacts on the viability and growth of neoplastic cells. This study examines the impact that saturated and unsaturated fatty acids, both alkalized and non-alkalized, have on the viability and growth of various neoplastic cell lines.

Methods: In this study, the potential anti-viability and antiproliferative effects of both saturated, and an unsaturated, fatty acids, when introduced as buffered (NaHCO₃), and non buffered formulations, were investigated in a comparative fashion in a panel of tumor cell lines.

Results: We show that both buffered and non-buffered fatty acids, exerted inhibition of their proliferative activity and had a negative impact on cell viability in a concentration-dependent manner. Buffered fatty acids had a greater negative impact on all tumor cell lines.

Conclusions: Findings indicate that the environment, as well as the type of fatty acid to which the neoplastic cell line was exposed, were both important predictors of antiproliferative effects.

Keywords: Saturated vs. unsaturated fatty acids, Omega-5, Alkaline buffered fatty acids

Abbreviations: SA: Stearic Acid; MA: Myristic Acid; PA: Palmitic Acid; CM: Cetyl-Myristoleate

Introduction

It is believed that tumor cells, due to their altered metabolism, generate their own 'vehicle for metastasis' in the form of an acid pH micro-environment [1,2]. This study examines the impact that saturated and unsaturated fatty acids, both alkalized and non-alkalized, have on the viability and behavior of various neoplastic cell lines.

Background

Dietary fats, saturated and unsaturated, have profound and varied influences on the cell membrane. Studies have shown that in both whole organisms, as well as in cell cultures, saturated and unsaturated fats have the ability to impact a number of tissue and cellular metabolic functions [2-6]. The suggested mechanisms, by which these processes may be occurring, are thought to involve changes in cell membrane fluidity, and cell membrane receptor availability [7-10], as well as suppression, or up-regulation of cell-to-cell growth factor signaling [1,11,12], and inflammatory factor generation [13,14]. Saturated vs. unsaturated lipid mediated cellular behavioral changes have been shown to impact the overall behavior [15] and the fluidity of peripheral muscle tissue. A direct relationship exists between an increase in polyunsaturated fatty acids and membrane fluidity, and the opposite (rigidity) in the presence of some monosaturated and predominantly saturated fatty acids, and cholesterol [10]. Membrane fluidity is believed to influence the capability of some cancer cells to metastasize [16].

Certain long chain, saturated and unsaturated, fatty acids alike have a demonstrated ability to inhibit abnormal cell proliferation. Stearic acid (its esters - stearates) a saturated 18 carbon chain fatty acid (octadecanoic acid), and palmitic acid (its esters - palmitates)

are two fats in the saturated fatty acid family known to inhibit breast cancer cell proliferation to varying degrees. Studies suggest that the mechanism of inhibition in this case involves suppression of a cell-to-cell membrane receptor epidermal growth factor signal [17] or an, as yet unidentified, cell membrane receptor signaling mechanism [18]. Certain monosaturated (MA) and polyunsaturated fatty acids (PUFAs) have also demonstrated an *in vitro* selective cytotoxic, or anti-proliferative, effect on tumor cells, and minimal or no effect on normal cell lines [19,20]. Several of these novel fatty acids, possessing anti-proliferative activity, have been identified belonging to the omega-5 and omega-9 oxygenation class. Fatty acids from these groups can act on leukocytes, platelets and endothelial cells, as well as participate in cell-cell interactions that impact micro-inflammation [20,21]. Long-chain fatty acids have anti-inflammatory and anti-proliferative activity [22,23]. Individuals with colorectal or breast cancer have been observed having lower levels of these fatty acids [24], where as elevated levels appear to be protective [24-27].

Cetylated fatty acids are a group of naturally occurring fats which include cetyl myristoleate, cetyl myristate, cetyl palmitoleate, cetyl laureate, cetyl palmitate, and cetyl oleate. The monounsaturated, 14 carbon cis-mono form of this acid of the omega-5 series, myristoleic

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acid has demonstrated its ability to inhibit the growth of certain oral bacteria [28], reduce cell susceptibility to infection from herpes simplex virus [29], and also possess anticancer activity, inducing apoptosis (cell death) in prostatic tumors, in vitro [30].

Another factor which is thought to influence the neoplastic cell's invasiveness is pH. Extracellular pH around neoplastic cells is typically lower than that found in normal tissue, not atypically observed to be below pH 6.5 as a consequence of lactate accumulation [31]. The pH of solid tumors is acidic due to increased fermentative metabolism and poor perfusion [32]. It is believed that this lower pH environment promotes invasive tumor growth in primary and metastatic cancers through a form of acid-induced micro-environmental remodeling [32-34]. A low pH, for instance, was shown to increase the release of active cathepsin B, an important matrix remodeling protease in a mouse tumor model [34,35]. When the pH environment is increased through the use of sodium bicarbonate (NaHCO_3), a significant reduction in tumor growth and invasiveness has been observed in some tumor models [33], justifying the potential use of this benign alkalizing agent (NaHCO_3) in cancer therapy.

In this study, the potential antiproliferative effects of both saturated and unsaturated fatty acids, when introduced as buffered (NaHCO_3), and non buffered formulations, was investigated in a comparative fashion in a panel of tumor cell lines.

Methods

Aliphatic fatty acids (stearic, myristic, palmitic, and cetyl myristoleate) were tested for antiproliferative effects against human tumor cell lines. The panel included: the MGH-U1 human bladder carcinoma line, acute promyelocyte leukemia HL-60, the chronic myeloid leukemia LAMA-84, the Hodgkin-lymphoma HD-MY-Z and the multiple myeloma-derived cell lines OPM-2, U-266 and RPMI-23366. All cells were obtained from the German Collection of Microorganisms and Cell Cultures (Bruns, Germany) and were routinely maintained under standard conditions - RPMI-1640 medium, supplemented with 10% fetal calf serum and L-glutamine, in a 5% CO_2 humidified atmosphere (at 37 °C).

For the cytotoxicity assessment phase, exponentially growing cells were plated in 96-well flat-bottomed microplates and allowed to grow undisturbed for 24 hours after which time they were treated with the test fats.

Test Materials and Controls

All tested compounds were dissolved in Dimethyl sulfoxide (DMSO) and deionized water (the solvent). The pH of the buffered fatty acids, before they were utilized, was pH 10. This was achieved using sodium carbonate (Na_2CO_3). A pH of 10 was selected for this experiment because, in our lab, it was observed to function the best in all our stabilized cell line studies. In addition, previous studies in our lab have indicated that in a proprietary product intended for human use, this buffering material has been shown to be ingested by humans without causing gastro intestinal problems.

After dissolution, the pH was adjusted back to neutrality with an organic acid before the mixture was serially diluted in RPMI-1640 to the desired level. For each concentration, 8 wells were used. A solvent only series was included as one of the controls; a cultural media only was included as the other. Cells were exposed to the test compounds, or controls, for 72 hours. After 72 hours exposure the cellular viability was monitored by the standard MTT-dye reduction assay. The relative potencies of the non-buffered and buffered fatty acids were analyzed on

the basis of the IC_{50} values obtained. IC_{50} calculations were performed as follows:

Linear Regression

The simplest estimate of an IC_{50} is to plot x-y and fit the data with a straight line (linear regression). An IC_{50} value is then estimated using the fitted line.

Linear Regression Calculation In addition, an Excel add-in was used (Figure 1).

$$Y = a \cdot X + b$$

$$\text{IC}_{50} = (0.5 - b) / a$$

Excel add-in

ED50V10 (Read me) is an Excel add-in for calculating $\text{IC}_{50}/\text{EC}_{50}$ values. Input your data in the left columns, and your results will be shown in the right half of the Excel table.

To calculate IC_{50} input 50 in the "INTERPOLATE..." table (highlighted in blue), the result will be shown on the right (highlighted in green). For log-transformation, go to Data Transformation on the upper-right, input 3 in the DOSE (X-axis)/1st cell.

Four-Parameter Logistic Function

Four-parameter (A, B, C, D) logistic function (or Sigmoidal) is frequently used to fit dose-response curves. The drug data x is in logarithmic form. This is a standard function in most statistics software. The parameter C is the estimate of IC_{50} or EC_{50} .

Sigmoidal Calculation (Figure 2).

$$Y = D + \frac{A - D}{1 + 10^{(x - \log C)B}}$$

Results

The 72 hours exposure period to both buffered and non-buffered fats was sufficient to exert a measureable inhibitory effect on their proliferative activity. A negative impact on cell viability, in a concentration-dependent manner, was also observed across the spectrum of malignant cell lines. This allowed the calculation of the corresponding IC_{50} values, i.e., concentration causing half-maximal inhibition of cell viability, indicating the merit of the antiproliferative potency of the tested compounds. In Tables 1 and 2, and Figures 1-12 (data presented using standard deviation [SD]), dose-response plots show the observed shift in the IC_{50} values when cells were exposed to the test fats. Exposure to buffered fatty acids produced an increasingly negative growth/viability effect on each tumor cell line as the concentration of the test substance increased.

Antiproliferative Effects Observed In Tumor Cell Lines: Assessed by the MTT-dye reduction assay. Assessment performed after 72 hours continuous exposure to test substance. Each data point represents the arithmetic mean \pm SD of 8 separate experiments (Figures 1-12).

Discussion

Intracellular pH homeostasis is important for normal cell function. Shifts in pH, away from neutrality, or slight alkalinity, have a profound impact on cell and organ function. Tumor cell growth and differentiation appears to favor an acetic environment. A number of studies have demonstrated that pH homeostasis is often shifted radically away from near neutrality toward an acidified environment

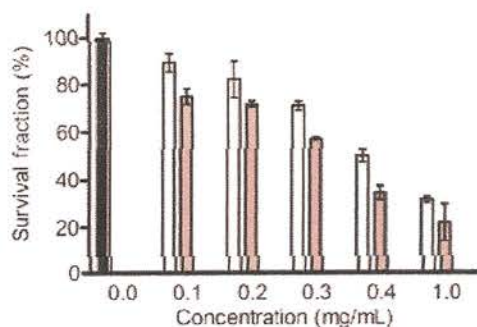


Figure 1: Non-buffered cetyl-myristoleate (white columns) Vs. buffered (grey columns) against the human acute promyelocyte leukemia HL-60

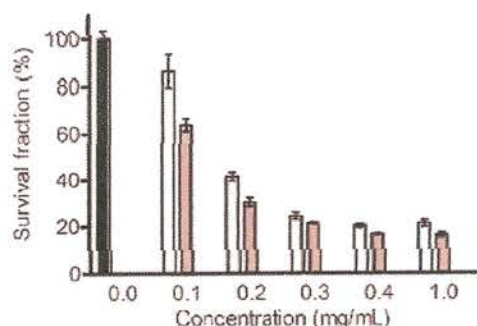


Figure 2: Non-buffered cetyl-myristoleate (white columns) Vs. buffered (grey columns) against the human chronic myeloid leukemia LAMA-84.

Cell line	IC ₅₀ (mol/L)					
	SA	SA (buffered)	MA	MA (buffered)	PA	PA (buffered)
LAMA-84	266.7 ± 21.1	173.3 ± 15	135.0 ± 11.2	88.3 ± 10.4	188.3 ± 9.7	168.3 ± 5.2
MGH-U1	378.3 ± 14.4	141.7 ± 10.2	338.3 ± 17.2	245.0 ± 7.9	180.0 ± 3.9	173.3 ± 6.4

(SA) stearic acid, (MA) myristic acid, (PA) palmitic acid

Table 1: Antiproliferative effects of non-buffered vs. buffered, saturated fatty acids against LAMA-84 and MGH-U1 human tumor cell lines, as assessed by the MTT-dye reduction assay after 72 hours continuous exposure.

Cell line	Origin	IC ₅₀ (mg/ml)	
		Non-buffered CM	Buffered CM
HL-60	Acute promyelocyte leukemia	0.41 ± 0.07	0.32 ± 0.03
LAMA-84	Chronic myeloid leukemia	0.18 ± 0.04	0.12 ± 0.02
HD-MY-Z	Hodgkin lymphoma	0.27 ± 0.04	0.22 ± 0.03
OPM-2	Multiple myeloma	0.12 ± 0.02	0.08 ± 0.01
U-266	Multiple myeloma	0.32 ± 0.05	0.24 ± 0.06
RPMI	Multiple myeloma	0.20 ± 0.03	0.17 ± 0.01

Table 2: Antiproliferative effect of buffered vs. non-buffered, cetyl-myristoleate (CM) in human tumor cell lines

in cancer [36]. This desire to generate and remain in a lower pH environment is likely due to certain critical transcriptional regulatory factors and signal transduction pathways, each requiring a pH below 6.5 to function efficiently [37,38]. Conversely, raising the pH of the immediate surroundings is expected to have a negative impact by down regulating specific tumor-related critical proteins and regulatory factors. Manipulating the pH of a tumor's environment *in vitro*, through

the use of proton inhibitors or alkalinizing agents has been demonstrated to be anti-neoplastic in nature, in certain cancer cell lines. In a rodent model, the oral administration of sodium bicarbonate was shown to negatively impact neoplastic metastasis by inhibiting or partially blocking angiogenesis. This rendered the cancer more susceptible to certain cytotoxic compounds [33].

Fats, especially those of the omega family, have demonstrated the ability to exert negative influences on tumor cell growth. Because these neoplastic cells exhibit significantly altered metabolic functions (and reduced pH generated environments), reactive oxygen species production also increases. To compensate, it has been suggested

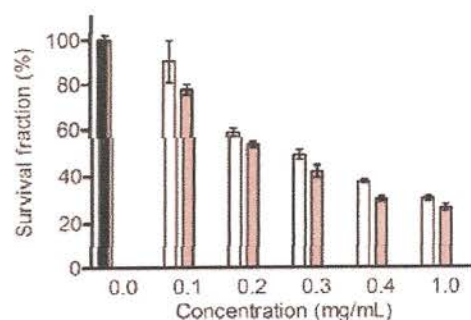


Figure 3: Non-buffered cetyl-myristoleate (white columns) Vs. buffered (grey columns) against the human Hodgkin-lymphoma HD-MY-Z.

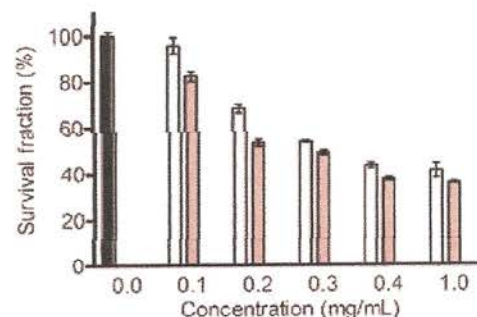


Figure 4: Non-buffered cetyl-myristoleate (white columns) vs. buffered (grey columns) against the human multiple myeloma OPM-2.

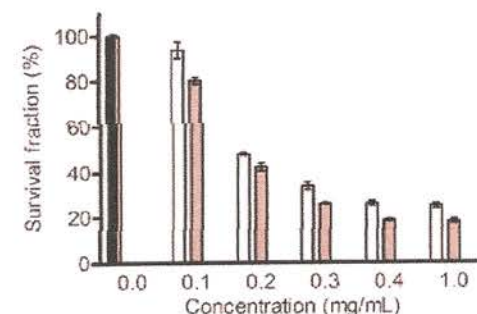


Figure 5: Non-buffered cetyl-myristoleate (white columns) vs. buffered (grey columns) against the human multiple myeloma U-266.

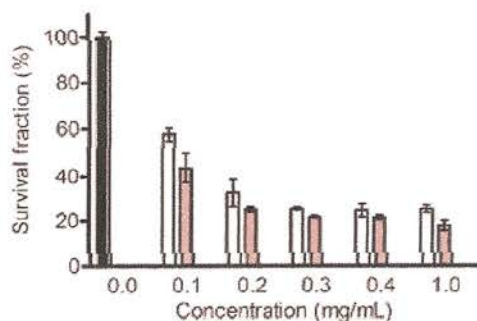


Figure 6: Non-buffered cetyl-myristoleate (white columns) vs. buffered (grey columns) against the human multiple myeloma RPMI.

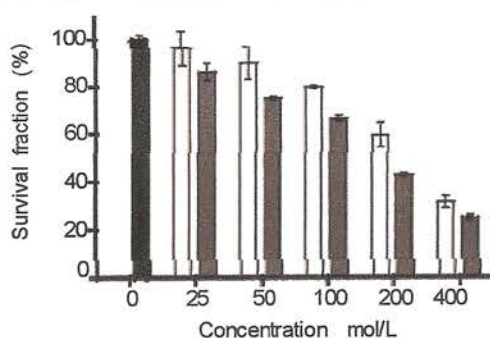


Figure 7: Non-buffered stearic acid (white columns) vs. buffered (grey columns) against the human chronic myeloid leukemia LAMA-84.

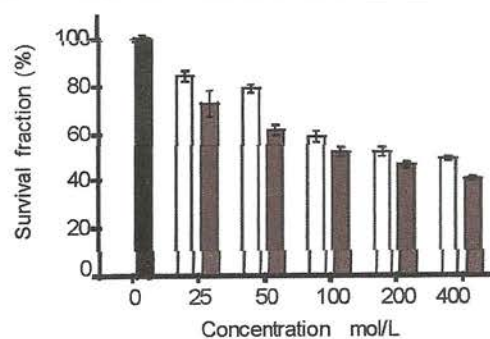


Figure 8: Non-buffered stearic acid (white columns) vs. buffered (grey columns) against the human bladder carcinoma MGH-U1.

that the cells are up regulating glucose and peroxide metabolism to compensate. Forcing these cells to metabolize fats as their most available energy source has been observed to have a very negative impact on their growth and viability. In a direct human application, a high ketogenic diet would theoretically force these cells to use the very oxidative metabolism they are trying to offset. Hence fat exposure in and of itself (as an energy source) is expected to be anti-neoplastic in nature for several reasons [39].

In these experiments, the acute promyelocyte leukemia HL-60 demonstrated sensitivity to both non-buffered and buffered fats, although the latter proved to be more active as evidenced by the

comparison of survival fractions for each concentration. At the highest level evaluated the non-buffered fats lowered the fraction of living cells to approximately 31.7%, while the buffered fats decreased the percentage of viable cells to 21.9%. The IC_{50} values were 0.41 mg/ml for the non-buffered fats vs. 0.32 mg/ml for the buffered ones respectively.

Antiproliferative effects were also established in LAMA-84 cells. As in the preceding cell line, the buffered fats proved to be superior antiproliferative agents as evidenced by the MTT-data. At the highest concentration tested, the non-buffered fats reduced the cellular viability by a calculated 79%, while the buffered fats lowered it by approximately

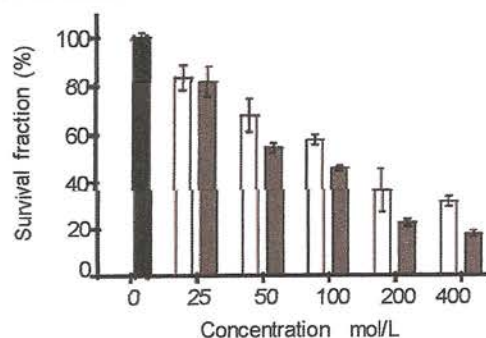


Figure 9: Antiproliferative effects of non-buffered myristic acid (white columns) vs. buffered (grey columns) against the human chronic myeloid leukemia LAMA-84.

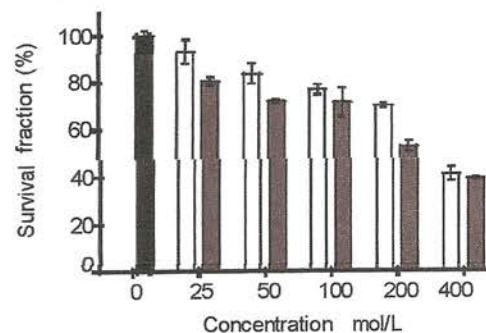


Figure 10: Non-buffered myristic acid (white columns) vs. buffered (grey columns) against the human bladder carcinoma MGH-U1.

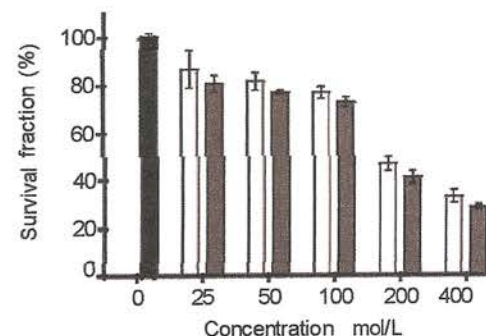


Figure 11: Antiproliferative effects of non-buffered palmitic acid (white columns) vs. buffered (grey columns) against the human chronic myeloid leukemia LAMA-84.

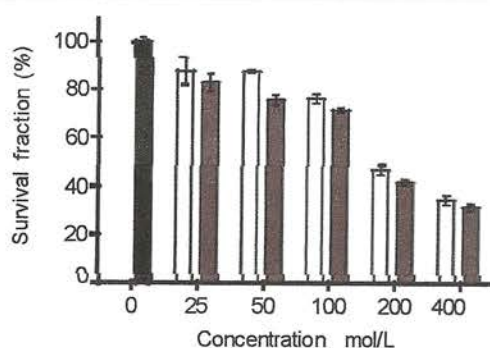


Figure 12: Non-buffered palmitic acid (white columns) vs. buffered (grey columns) against the human bladder carcinoma MGH-U1.

84%. The IC_{50} values obtained were 0.18 mg/ml for the non-buffered and 0.12 mg/ml for the buffered.

The evaluation of the antiproliferative effects of tested compounds against the Hodgkin lymphoma derived cell line HD-MY-Z revealed that buffered fats exerted a stronger inhibitory activity. At a concentration of 1 mg/ml the viable cells were 30.7 after exposure to non-buffered fats and 26.8 after treatment with buffered fats. The calculated IC_{50} values – 0.27 mg/ml for non-buffered fats vs. 0.22 mg/ml for the buffered ones.

Conclusion

The presented data indicates that throughout the panel of malignant cells the buffered fats exerted a more pronounced antiproliferative effects vs. the non-buffered fats, as evidenced by comparison of survival fractions after treatment with equivalent concentrations. This data also supports the concept that introducing a treatment substance, in an alkaline buffered environment, contributed toward inhibition of neoplastic cell growth and survival. A pH modified strategy warrants further investigation and should be considered when designing an anti-neoplastic therapy modality.

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