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Suppression of some IncRNAs and Invasion by Boric Acid Treatment in Human Pancreatic Cancer

İnsan Pankreas Kanserinde Borik Asit Uygulaması ile Bazı IncRNA'ların ve İnvazyonun Baskılanması

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ABSTRACT

Objective: It was aimed to investigate the effects of boric acid on some lncRNAs and invasion in PANC-1 and MIA PaCa-2 pancreatic cancer cells.

Materials and Methods: The effects of boric acid on cell viability and invasion were investigated using XTT test and invasion chambers, respectively. lncRNA H19 and UCA1 expressions were evaluated in pancreatic cancer using TCGA data. Its effects on expressions of these lncRNAs and invasion genes were determined by qRT-PCR analysis.

Results: The IC_{50} doses of boric acid were calculated as 14.25 mM in PANC-1 cells and 15.71 mM in MIA PaCa-2. TCGA data showed that H19 and UCA1 expressions were elevated in pancreatic cancer. H19 and UCA1 lncRNA levels were decreased with boric acid treatment. In addition, boric acid increased CDH1 and TIMP1 in both cell lines. However, it suppressed CDH2 expression. Boric acid increased TIMP2 in PANC-1 cells and TIMP3 expression in MIA PaCa-2 cells. In the invasion test, boric acid significantly suppressed invasion in both cells.

Conclusions: Boric acid suppressed H19 and UCA1 expressions, which were found to be high in pancreatic cancer. In addition, it showed an anti-invasive effect by changing the expressions of genes that are important in invasion.

Keywords: Boric acid, invasion, lncRNA-H19, lncRNA-UCA1, pancreatic cancer

ÖZ

Amaç: Borik asidin bazı lncRNA'lar ve invazyon üzerine etkisinin PANC-1 ve MIA PaCa-2 pankreas kanseri hücrelerinde araştırılması amaçlanmıştır.

Materyal ve Metot: Borik asitin hücre canlılığı ve invazyon üzerine etkileri sırası ile XTT testi ve invazyon kuyucukları kullanılarak araştırılmıştır. TCGA verileri kullanılarak pankreas kanserinde lncRNA H19 ve UCA1 ifadeleri değerlendirilmiştir. Bu lncRNA'ların ve invazyon genlerinin ifadeleri üzerine etkileri qRT-PZR ile belirlenmiştir.

Bulgular: PANC-1 hücrelerinde borik asitin IC50 dozu 14.25 mM, MIA PaCa-2 de ise 15.71 mM olarak hesaplanmıştır. TCGA verileri H19 ve UCA1 ifadelerinin pankreas kanserinde yüksek olduğunu göstermiştir. Borik asit muamelesi ile H19 ve UCA1 lncRNA seviyeleri azalmıştır. Ayrıca borik asit iki hücre hattında CDH1 ve TIMP1 ifadesini arttırmıştır. CDH2 ifadesini baskılamıştır. Borik asit PANC-1 hücrelerinde TIMP2, MIA PaCa-2 hücrelerinde TIMP3 ifadesini arttırmıştır. İnvazyon testinde borik asit her iki hücrede invazyonu anlamlı derecede baskılanmıştır.

Sonuç: Borik asit pankreas kanserinde ifadesinin yüksek olduğu görülen H19 ve UCA1 ifadelerini baskılamıştır. Ayrıca invazyonda önemli olan genlerin ifadelerini değiştirerek anti-invaziv etki göstermiştir.

Anahtar Kelimeler: Borik asit, invazyon, lncRNA-H19, lncRNA-UCA1, pankreas kanseri

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INTRODUCTION

Pancreatic cancer has the seventh-highest death rate.[1] Because of limitations in treating pancreatic cancer, it is important to discover a new target-specific agent. Smear samples were taken from women living in relatively boron-poor (587) and -rich (472) regions. No cytopathological findings were found in boron-rich regions. However, cytopathological findings of cervical cancer were detected in 15 women living in boron-poor regions.[2] Boric acid has antibacterial,[3] anticarcinogenic,[4] and anti-inflammatory[5] properties. High boric acid concentrations (12.5, 25, and 50 mM) exhibited antiproliferative and apoptotic effects in SK-MEL28 human skin melanoma cells.[6] Boric acid also inhibits histone deacetylases.[7] Hung et al.[8] investigated the retention status of boric acid in tumor regions during boron neutron capture therapy for hepatoma. Boric acid was localized in both hepatoma cells and tumor blood vessels. This study demonstrated that boric acid-mediated boron neutron capture therapy would specifically target the hepatoma. Boric acid-induced apoptosis by TNF signaling pathway in SW-480 human colon cancer cells[9] and boron supplementation decreased prostate tumor growth, IGF-1 expression, and serum prostate-specific antigen levels.[10]

Although 90% of the human genome is transcribed, only ~2% of the genomic sequence-includes protein-coding genes. The remaining genome consists of non-coding RNAs. Long non-coding RNAs (lncRNAs) are one of the two main classes of noncoding RNAs. lncRNAs have important functions in gene regulation and controlling many processes including apoptosis, epithelial-mesenchymal transition (EMT), invasion and metastasis.[11] lncRNA -H19 is located on 11p15.5 but is maternally expressed.[12] H19 increased EMT and metastasis through miR-675.[13] H19 is also overexpressed in pancreatic cancer and correlates with TNM stages, poor survival and metastasis.[14] lncRNA-UCA1 has been mapped at 19p13.12 and was first discovered in bladder carcinoma.[15] UCA1 expression was reported to be elevated in pancreatic cancer and correlated with tumor size, invasion and TNM stage.[16]

Cell migration is one of the most important features of solid metastatic tumors. Therefore, suppression of invasion is important in local therapies. During metastasis, cells must lose epithelial properties but acquire mesenchymal properties. In this process, the expressions of decreased CDH1 (E-cadherin) and increased CDH2 (N-cadherin) are important.[17] Decreased matrix metalloprotease inhibitors (TIMPs) are another important factor in acquiring mesenchymal features and the invasion process. Cell motility is present when matrix metalloproteinases are not inhibited.[18] Targeting the invasion cascade seems to be an important therapeutic strategy to prevent invasion. In this study, the effects of boric acid on lncRNA-H19, lncRNA-UCA1 and invasion features were investigated in pancreatic cancer cells.

MATERIALS AND METHODS

Ethical Status: This study was approved by N.E.U. (Date: 09.09.2022, decision no:3950). This study was carried out by international declarations, guidelines, etc.

Cell Culture and Chemicals: PANC-1 and MIA PaCa-2 human pancreatic cancer cells were purchased from ATCC. These cells were cultured with DMEM containing 1% penicillin/streptomycin and 5% FBS in an incubator with humidified 95% air and 5% CO_2. The boric acid obtained from Etimaden and was dissolved in the DMEM. QIAzol was purchased from Qiagen. cDNA synthesis kit was obtained from Bio-Rad. Eva Green Supermix was purchased from Solis BioDyne.

Cell Proliferation Test: The cytotoxic effects of boric acid on human pancreatic cancer PANC-1 and MIA PaCa-2 cells were evaluated using XTT assay as described elsewhere.[19] These cells were treated with eight different boric acid doses between 0.01 and 25 mM, and a previously described protocol was utilised.[20] IC_{50} doses were calculated with CompuSyn Version 1.0 software and used in further analyzes.

lncRNA Expressions: Different expression patterns of H19 and UCA1 lncRNAs were observed between pancreatic cancer tissue (179 cases) and normal tissue (171 cases) using data from the TCGA database (http://gepia.cancer-pku.cn/). The effects of boric acid on the expression of H19 and UCA1 lncRNAs were investigated. Total RNA isolation was performed from both control and boric acid-treated cells. cDNAs were synthesized by the manufacturer's instructions. H19, UCA1 and U6 (as reference gene) primers (Table 1) were designed using an online program (https://eu.idtdna.com/site). qRT-PCR analysis was performed using a previously described protocol.[21]

Invasion-related Gene Expressions: The effects of boric acid on CDH1, CDH2, TIMP1, TIMP2, and TIMP3 genes, which play an important role in invasion, were evaluated. For this purpose, cDNA synthesis was performed after total RNA isolation from control and dose groups. qRT-PCR analyses were conducted using previously designed target and ACTB reference gene primers.[21]

Invasion Assay: Invasion capacities of PANC1 and MIA PaCa-2 pancreatic cancer cells were determined using invasion chambers (Corning, USA). Control and dose group cells were seeded using the basal medium in the upper chamber. The medium

Table 1. Primer sequence of H19, UCA1 and U6 genes used in this study.

Gene	Forward primer sequence (5'-3')	Reverse primer sequence (5'-3')	PCR product size (bp)
H19	CGTGACAAGCAGGACATGA	TCCGTGGAGGAAGTAAAGAAAC	131
UCA1	GAGGATTCCCAGCCATATGAAG	CGGCAGTTGGTGTGCTATAA	127
U6	TTGGAACGATACAGAGAAGATTAGC	CACGAATTTGCGTGTCATCC	60

completed with 10% FBS was placed in the lower well. After 22 h of incubation, invading cells were fixed and stained using crystal violet (0.5%). The experiments were performed in triplicates. The invasive cells were counted and photographed in five random fields.

Statistical Analysis: IC_{50} doses of boric acid were calculated with CompuSyn Version 1.0 software. qRT-PCR analysis was performed with the $2^{(-\Delta Ct)}$ method by normalizing the Ct values of target genes with reference genes. The independent sample *t*-test in the SPSS 26.0 program was–used to compare groups. $p<0.05$ was considered as statistically significant.

RESULTS

The IC_{50} doses of boric acid for PANC-1 and MIA PaCa-2 cells were calculated as 14.25 mM and 15.71 mM for 48 h, respectively as described previously.[19] These doses were treated to these cells in further experiments.

The expression levels of lncRNA H19 and UCA1 in human pancreatic cancer were determined using an online tool in the TCGA database (http://gepia2.cancer-pku.cn). The data showed that expressions of these lncRNAs were upregulated in pancreatic cancer tissues compared with normal tissue (Figure 1; A and B). Furthermore, the GEPIA database showed that H19 and UCA1 expressions were positively associated with poor survival in pancreatic cancer (Figure 1; C and D).

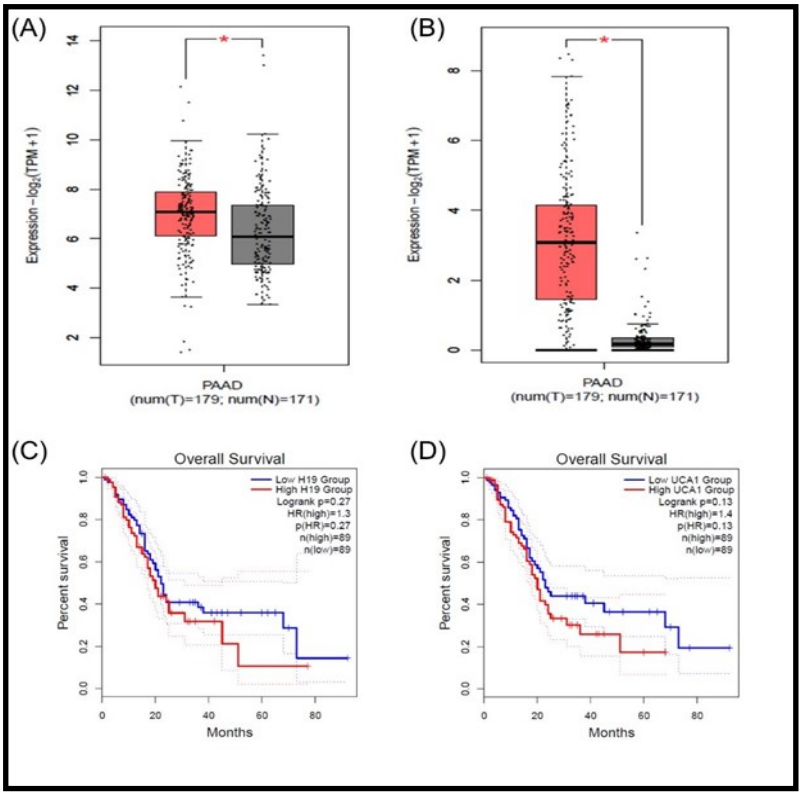

Figure 1. The expression levels of lncRNA-H19 and lncRNA-UCA1 in pancreatic cancer.
A: H19 was upregulated in pancreatic cancer tissue. B: UCA1 was upregulated in pancreatic cancer tissue. C, D: GEPIA database showed that H19 and UCA1 expressions were positively correlated with poor survival in pancreatic cancer. *: $p<0.05$. PAAD: pancreatic adenocarcinoma.

The effect of boric acid on lncRNA H19 and UCA1 expressions in PANC-1 and MIA PaCa-2 cells were determined by qRT-PCR analysis. qRT-PCR analysis results showed that H19 and UCA1 expressions in both cell lines were downregulated by boric acid treatment (Figure 2; A and B).

Results of qRT-PCR analysis indicated that boric acid caused significantly increased CDH1 and TIMP1 expressions and decreased CDH2 expression in both cell lines. In addition, boric acid caused an increase in TIMP2 expression in PANC-1 cells and TIMP3 expression in MIA PaCa-2 cells (Figure 3).

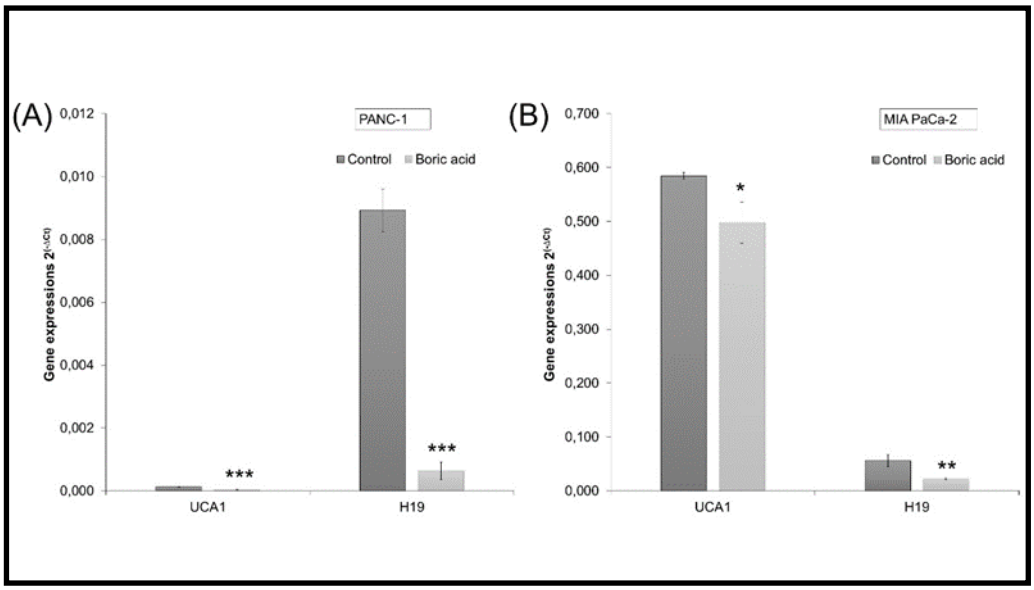

Figure 2. Effects of boric acid on lncRNA UCA1 and H19 in PANC-1(A) and MIA PaCa-2 (B) cells.
*: p<0.05; **: p<0.01; ***: p<0.001.

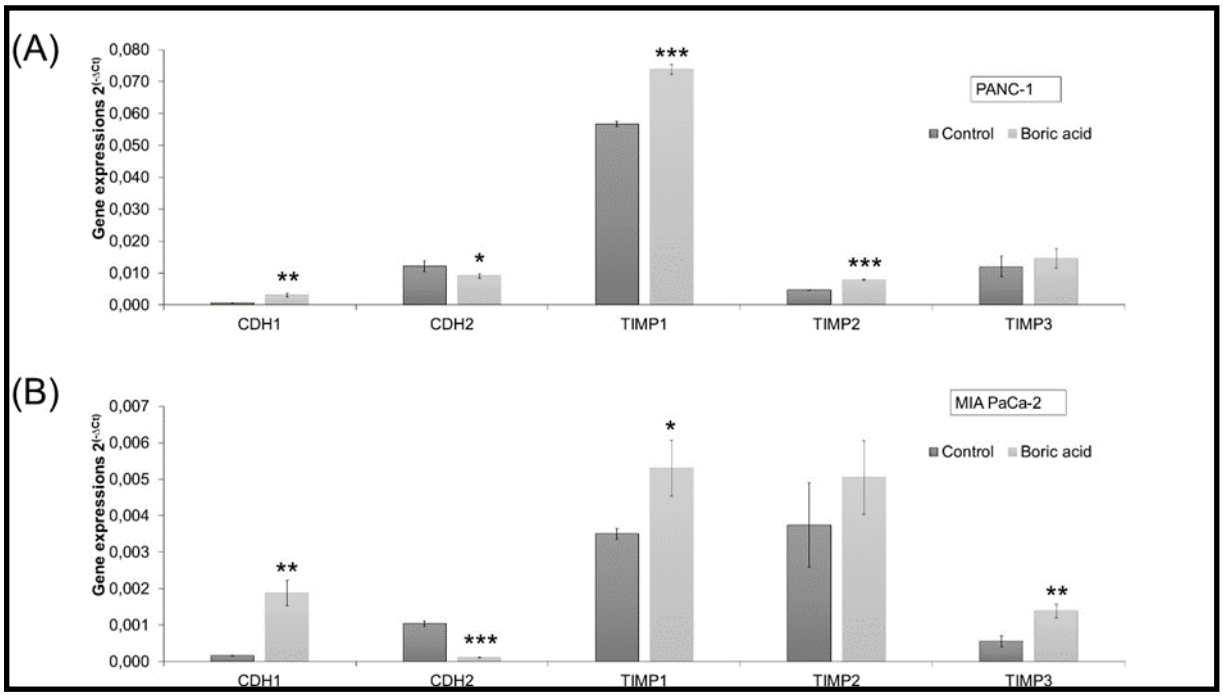

Figure 3. Effects of boric acid on the invasion-related genes in (A) PANC-1 and (B) MIA PaCa-2 cells.
*: p<0.05; **: p<0.01; ***: p<0.001.

The effect of boric acid on cell invasion was determined by the invasion test. The number of invasive cells in PANC-1 cells was counted as 448±44 in control and 334±32 in dose groups. In MIA PaCa-2 cells, control and dose groups were determined as 539±78 and 379±53, respectively (Figure 4).

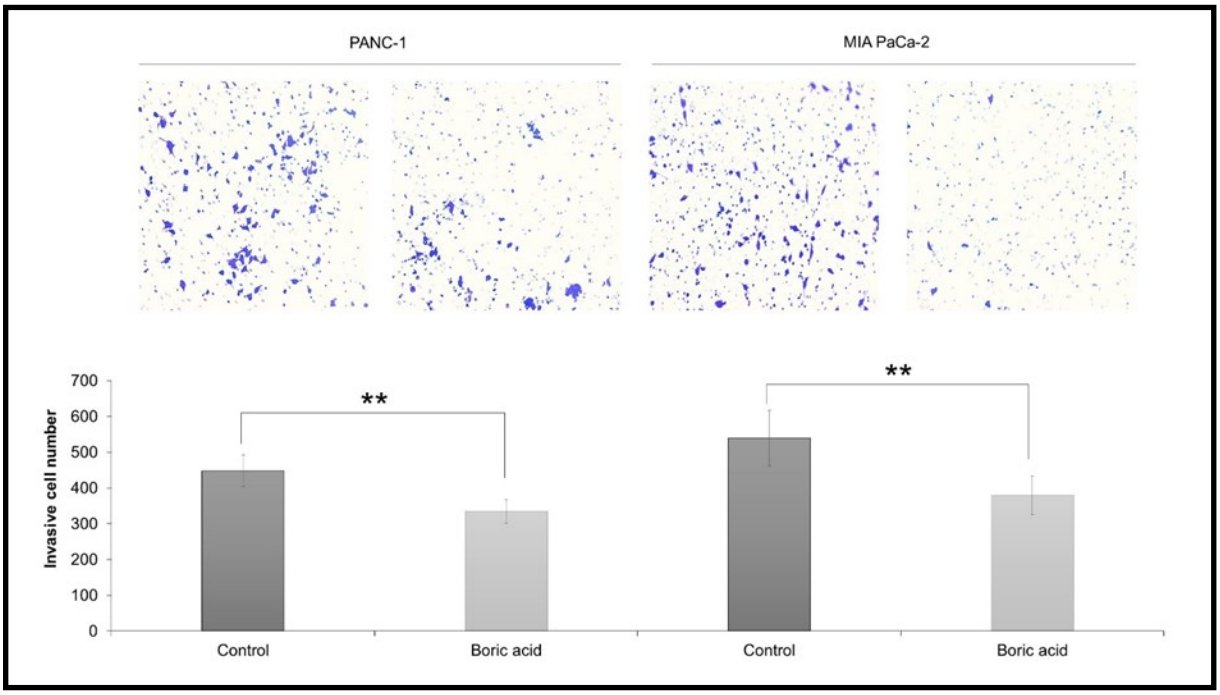

Figure 4. Effects of boric acid on the cell invasion in PANC-1 and MIA PaCa-2 cells. **: p<0.01.

DISCUSSION AND CONCLUSION

Investigating the effects of natural compounds in cancer therapy has gained importance because natural compounds have anticancer properties. Boric acid is a compound of boron. In a previous study, the EC_{50} concentration for boric acid in DMS-114 small-cell lung cancer cells was determined as 1000 µg/mL for 72 h.[22] Boric acid was shown to cause a concentration-dependent decrease in U-87MG human glioma cell viability. The LC_{50} value for boric acid in these cells was reported to be 123.45 µg/ml. Moreover, it has been reported that boric acid has shown an anticancer effect through PI3K/AKT, BRAF/MAPK and PTEN signaling pathways.[23] In a study, the IC_{50} dose of boric acid was shown to be 50 mM for 48 h in CCl-233 human colon adenocarcinoma cells using CCK-8 proliferation assay.[24] El-Hefny et al.[25] reported that the IC_{50} value of boric acid in HepG2 human hepatocellular carcinoma cells using MTT cell viability assay was 64.27 µg/ml. In a previous study conducted in our lab, the anticancer effect of boric acid was investigated in human pancreatic cancer MIA PaCa-2 and PANC-1 cells, and IC50 values of boric acid were calculated as 14.25 mM and 15.71 mM at 48 h for these cell lines, respectively. It was illustrated that boric acid also decreased colony formation and altered expression levels of some genes in apoptosis and endoplasmic reticulum stress pathways in MIA PaCa-2 and PANC-1 cells.[19] The same doses thereby were also used here.

Boric acid (250 and 1000 µM for 8 days) reduced invasion, migration and adhesion of DU-145 human prostate cancer cells with F-actin changes.[26] In the present study, boric acid increased CDH1 and TIMP1 gene expressions and decreased CDH2 expression in PANC-1 and MIA PaCa-2 pancreatic cancer cells. Moreover, boric acid treatment upregulated TIMP2 expression in PANC-1 and TIMP3 expression in MIA PaCa-2 cells (Figure 3). In addition, boric acid caused a decrease in the invasion properties of both cell lines in this study.

As is known, most RNAs are not translated into proteins. One of these classes of non-coding RNAs is called as lncRNAs. Previous literature has shown that expression of lncRNAs is altered in many malignancies including pancreatic cancer.[27] It has been reported that H19 expression is high in pancreatic cancer tissues. It has also been shown that H19 expression is higher in metastasized tumors. Knock-

down of H19 suppressed invasion and metastasis of pancreatic cancer cells. It has been stated that H19 overexpression triggers EMT in pancreatic cancer.[28] Another lncRNA that has been shown to be highly expressed in pancreatic cancer is UCA1.[29] UCA1 suppressed apoptosis and increased cell proliferation, migration and invasion in pancreatic cancer cells.[30] Consistently, the TCGA database (http://gepia2.cancer-pku.cn) suggested that expressions of lncRNA H19 and UCA1 were upregulated in pancreatic cancer tissues compared with normal tissue and correlated with poor survival of pancreatic cancer patients (Figure 1). In the present study, H19 and UCA1 expression were downregulated in both PANC-1 and MIA PaCa-2 cells by boric acid treatment (Figure 2).

In conclusion, boric acid caused a decrease in the expression of H19 and UCA1, which are known to have higher levels in pancreatic cancer. These lncRNAs are associated with poor survival and increased invasion features. In addition, boric acid showed an anti-invasive effect by changing the expression of genes that are important in invasion process. It is thought that boric acid can be a potential anti-invasive compound in pancreatic cancer. Further analyses are required for boric acid's therapeutic use in pancreatic cancer.

Ethics Committee Approval: This study was approved by N.E.U. Non-drug and Non-Medical Device Research Ethics Committee (Date: 09.09.2022, decision no:3950). The study was carried out by international declarations, guidelines, etc.

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Author Contributions: Concept, Analysis and Interpretation, Writing- CEG.

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