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**Research Article**

# Enhancing the Anticancer Efficacy of Decitabine via β-Hydroxybutyrate in Colorectal and Prostate Cancers Cell Lines

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## Abstract

***Background***: Epigenetic targeting therapy, including histone deacetylase (HDAC) inhibitors and DNA-methyltransferase 1 (DNMT1) inhibitors, is a promising and attractive tool to treat advanced cancers, overcome drug resistance, and minimize adverse effects of traditional therapies. ***Objective***: To investigate whether β-hydroxybutyrate enhanced the effectiveness of decitabine against colon cancer and enhanced the anti-cancer effect of decitabine against colon and prostate cancer cell lines. ***Methods***: LS174T cells (colorectal cancer) and PC3 cells (prostate cancer) were seeded in a 96-well cell culture plate. Decitabine was used in six [100, 50, 25, 12.5, 6.25, & 3.125µg/ml] concentrations alone and combined with β-hydroxybutyrate, enhancing the effectiveness of decitabine against colon (2000µg/ml). After 48 hours of incubation, LS174T cells and PC3 cell viability were determined by MTT assay. DNMT1-enzyme level was measured using the DNMT1-ELISA kit. ***Results***: For the LS174T cell line and PC3 cell line, the combination of decitabine plus β-hydroxybutyrate enhanced the effectiveness of decitabine against colon and showed a significant ($p$<0.05) decrease in viability percent for all concentrations compared to the control group. Also, the comparison between decitabine monotherapy and decitabine plus β-hydroxybutyrate enhanced the effectiveness of decitabine against colon and revealed a significant ($p$<0.05) difference in viability between the two groups. Finally, a significant ($p$<0.05) reduction in DNMT1 level was observed between monotherapy and combination therapy for all decitabine concentrations and for both cell lines. ***Conclusions***: β-hydroxybutyrate enhanced the effectiveness of decitabine against colon and prostate cancers, suggesting that β-hydroxybutyrate may serve as a promising adjuvant to decrease decitabine therapeutic doses.

***Keywords***: β-hydroxybutyrate; Colorectal cancer; Decitabine; DNMT1; Prostate cancer.

## تعزيز فعالية الديسيتابين المضادة للسرطان عبر β-هيدروكسي بيوتيرات في خطوط خلايا سرطانات القولون والمستقيم والبروستاتا

**الخلاصة**

**الخلفية**: العلاج بالاستهداف فوق الجيني، بما في ذلك مثبطات الهيستون دي أسيتيلاز (HDAC) ومثبطات DNA-ميثيل ترانسفيراز 1 (DNMT1)، هو أداة واعدة وجذابة لعلاج السرطانات المتقدمة، والتغلب على مقاومة الأدوية، وتقليل الآثار الجانبية للعلاجات التقليدية. **الهدف**: التحقيق فيما إذا كان β-هيدروكسي بيوتيرات قد عزز فعالية الديسيتابين ضد سرطان القولون وعزز التأثير المضاد للسرطان للديسيتابين ضد خطوط خلايا سرطان القولون والبروستاتا. **الطرائق**: تم زرع خلايا LS174T (سرطان القولون والمستقيم) وخلايا PC3 (سرطان البروستاتا) في صفيحة زراعة خلايا بسعة 96 بئر. تم استخدام الديسيتابين في ستة تركيزات [100، 50، 25، 12.5، 6.25، و3.125 ميكروغرام/مل] بمفردها مع β-هيدروكسي بيوتيرات، مما عزز فعالية الديسيتابين ضد القولون (2000 ميكروغرام/مل). بعد 48 ساعة من الحضانة، تم تحديد بقاء خلايا LS174T وخلايا PC3 بواسطة اختبار MTT. تم قياس مستوى إنزيم DNMT1 باستخدام مجموعة DNMT1-ELISA. **النتائج**: بالنسبة لخط خلايا LS174T وخط خلايا PC3، عزز مزيج الديسيتابين مع β-هيدروكسي بيوتيرات فعالية الديسيتابين ضد القولون وأظهر انخفاضا ملحوظا ($p$<0.05) في نسبة الحيوية لجميع التركيزات مقارنة بالمجموعة الضابطة. أيضا، عزز المقارنة بين العلاج الأحادي بالديسيتابين والديسيتابين بالإضافة إلى β-هيدروكسي بيوتيرات فعالية الديسيتابين ضد القولون وكشفت عن فرق مهم ($p$<0.05) في قابلية البقاء بين المجموعتين. وأخيرا، لوحظ انخفاض كبير ($p$<0.05) في مستوى DNMT1 بين العلاج الأحادي والعلاج المركب لجميع تركيزات الديسيتابين ولكلا خطي الخلايا. **الاستنتاجات**: عزز β-هيدروكسي بيوتيرات فعالية الديسيتابين ضد سرطانات القولون والبروستاتا، مما يشير إلى أن β-هيدروكسي بيوتيرات قد يكون مساعدا واعدا لتقليل جرعات العلاج بالديسيتابين.

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## NTRODUCTION

Globally, colorectal cancer and prostate cancer rank among the top five cancers according to the latest statistics of the World Health Organization (WHO) and the International Agency for Research on Cancer [1]. Today, genetic and epigenetic studies for various cancer types illustrated that genetic and epigenetic tools have a critical role in the formation and progression of cancer [2]. DNA methylation is an epigenetic tool that regulates specific sequence activity in DNA without causing any change in that sequence, mostly by adding a methyl group at C5 of cytosine in CpG islands [3]. The DNA methylation process is accomplished by a group of enzymes called DNA-methyl transferases (DNMTs) [4]. DNMT1 is the most abundant DNMT in human cells; its role is to maintain the DNA-methylation pattern during DNA replication [5]. In most types of cancer, DNMTs are overexpressed, especially DNMT1, resulting in

inappropriate CpG-rich islands hyper-methylation in the promoters of key tumor-suppressing genes (e.g., P53, P21), leading to repressing the expression of these genes [6,7]. This process leads to the development of DNMT1-inhibitor drugs such as decitabine, which is a cytidine analog that at low doses can reverse the abnormal hypermethylation of tumor suppressor genes to reactivate them, resulting in reduced proliferation, differentiation, and induction of apoptosis. This epigenetic mechanism of decitabine is related to its ability to form covalent bonds with DNMT, especially DNMT-1, leading to covalent trapping, degradation, and depletion of DNMT [8]. Acetylation is another changeable epigenetic modification that occurs at lysine residues on histone proteins of DNA. This process will neutralize the positively charged lysine, leading to the disruption of the interaction between the negatively charged DNA and histone tails, facilitating the opening of chromatin to elevate active transcription. The balance of this process occurs by two enzyme categories: histone acetyl-transferases (HATs) and histone deacetylases (HDACs) [9,10]. Abnormal overexpression of HDACs in various cancer types usually leads to aberrant deacetylation and inactivates the expression of tumor suppressor genes, resulting in abnormal cell proliferation [11]. A number of preclinical and clinical studies are performed to investigate the anti-cancer role of ketosis induction by ketogenic diet or exogenous administration of ketone bodies, including β-hydroxybutyrate, against various malignancies, e.g., breast cancer, colon cancer, brain tumors, and lung cancer [12]. Exogenous administration of β-hydroxybutyrate salts to achieve levels exceeding the standard physiological threshold (0.5 mM) confers potent anticancer properties. This effect is mediated by inhibiting class I HDACs, thereby restoring the expression of hypoacetylation-silenced tumor suppressor genes, including p21 [13]. Despite the established role of decitabine as a hypomethylating agent, its monotherapeutic efficacy in solid malignancies is frequently limited by modest response rates and toxicities associated with high dosing regimens. Moreover, epigenetic aberrations in cancer, however, are rarely isolated; DNA hypermethylation and histone deacetylation act in a tightly coordinated manner to silence tumor suppressor genes [14,15]. To overcome the limitations associated with decitabine monotherapy and achieve a more potent therapeutic outcome, this study investigates the synergistic combination of decitabine with β-hydroxybutyrate. This dual-epigenetic intervention is hypothesized to cooperatively reactivate silenced tumor-suppressor pathways, thereby enhancing apoptotic sensitivity and overcoming the resistance and toxicities typically encountered with single-agent epigenetic therapies in cancer cells.

## METHODS

### *Materials*

The colon cancer cell line (LS174T) and prostate cancer cell line (PC3) were supplied from the National Cell Bank of Iran. The cells were grown in Rosswell-Park Memorial Institute (RPMI-1640) liquid medium (Gibco, UK) containing 10% fetal-bovine serum (Gibco, UK). The tested chemicals were used: decitabine (Hangzhou, Hyperchemicals Limited, China) and DL-3-hydroxybutyric acid sodium salt (Shanghai Aladdin Biochemical Technology, China). The viability assay was achieved by using MTT-dye (Roth, Germany). The DNMT1-enzyme level was measured by ELISA Kit (Elabscience, USA).

### *Preparation of stock solutions*

β-hydroxybutyrate's stock solution (5 mg/ml) was prepared for each experiment by dissolving its sodium salt in water. Decitabine's stock solution was prepared by dissolving (30 mg) of pure powder in one ml of dimethyl sulfoxide (DMSO), which is stored at 4°C for subsequent use. From the stock solutions mentioned, the desired concentrations were prepared by using RPMI-1640 media as diluent.

### *Cell line experiments*

The LS174T cells and PC3 cells were grown in a 12.5 ml-size cell culture flask. When the growth reached 80%, the cells were harvested and then seeded in a 96-well cell culture plate at a density of 1*104 cells/ml. After that, the plate was incubated (37°C) for 24 hours and then examined under an inverted microscope to ensure that the cells form a monolayer with approximately 80% level of growth. At this growth level, the cells were treated with decitabine alone [100, 50, 25, 12.5, 6.25, & 3.125 µg/ml], and each concentration was combined with β-hydroxybutyrate, which enhanced the effectiveness of decitabine against colon (2000 µg/ml) as triplicate (3-well for each concentration). Moreover, 6-wells were not treated with any drugs to be the control group. Then, the plate was incubated for 48 hours as an exposure period. When the exposure period ended, the supernatant for each well was removed by micro-pipette and collected in Eppendorf tubes to be the samples for DNMT1-level measuring by the Elabscience-ELISA Kit protocol. After taking the supernatant from each well, the plate undergoes the MTT viability assay protocol. The cells in each well were washed with PBS (phosphate buffered saline) followed by the addition of MTT solution (0.5 mg/ml) at a volume of 200 µl in each well. Then, 3-hour incubation was needed to allow the viable cells to convert MTT dye into purple-colored formazan crystals. Subsequently, these crystals were dissolved by addition of 100 µl of DMSO in each well. Then, absorbance measurement was achieved at 570 nm by a microplate ELISA reader. The % viability was calculated by this equation:

%Viability = (absorbance of treated well/absorbance of control)*100%

### *Ethical considerations*

The study protocol was approved by the local Research Ethics Committee of the College of Pharmacy, University of Kufa, Iraq.

### Statistics analysis

All the data were expressed as mean ± SD and analyzed by Microsoft Office Excel (2010) and SPSS version 26 software. Two-way analysis of variance (ANOVA) and the *post hoc* Tukey test were used to evaluate the significant difference between the experimental means. Where a *p*-value less than 0.05 was considered statistically significant.

## RESULTS

Figure 1 revealed a significant reduction ($p< 0.05$) regarding LS174T cell growth for all concentrations of decitabine in comparison with the control group. Figure 2 revealed a significant reduction ($p< 0.05$) in % viability of LS174T cells for all concentrations of decitabine plus β-hydroxybutyrate in comparison with the control group. Figure 3 revealed a comparison between decitabine monotherapy and its combination with β-hydroxybutyrate (2000 µg/ml) on the LS174T cell line.

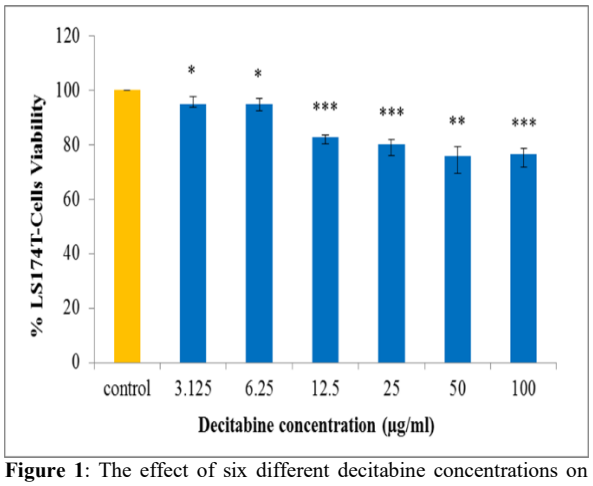



**Figure 1**: The effect of six different decitabine concentrations on LS174T cell line after 48 hours incubation.

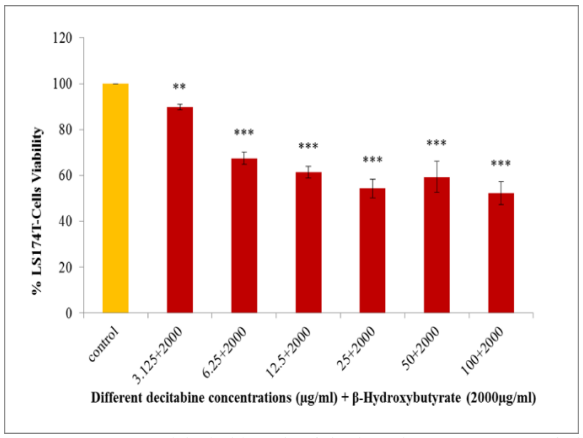



**Figure 2**: Impact of decitabine plus β-hydroxybutyrate (2000 µg/ml) on LS174T cell line viability after 48 hours incubation. $^{**}p< 0.01$, $^{***}p< 0.001$.

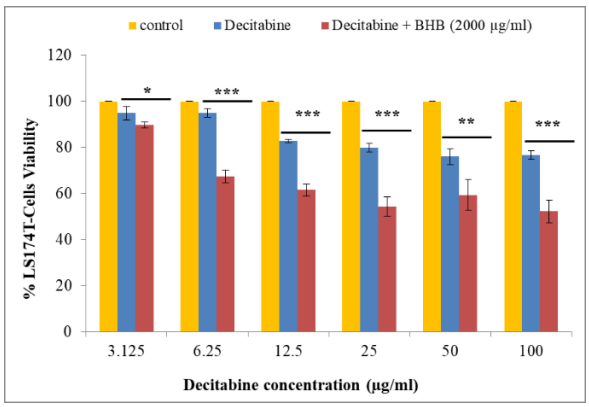



**Figure 3**: Comparison between decitabine and decitabine plus beta-hydroxybutyrate (2000 µg/ml) on LS174T cell line viability after 48 hours of incubation. $^{*}p< 0.05$, $^{**}p< 0.01$, $^{***}p< 0.001$.

A significant ($p< 0.05$) difference in LS174T cell viability was observed between the two groups as compared with control cells. Figure 4 revealed a significant reduction ($p< 0.05$) in PC3 cell growth for all concentrations of decitabine except 3.125 and 6.25 µg/ml in comparison with the control group. Figure 5 revealed a significant reduction ($p< 0.05$) in % viability of PC3 cells for all concentrations of decitabine plus β-hydroxybutyrate (2000 µg/ml) in comparison with the control group.

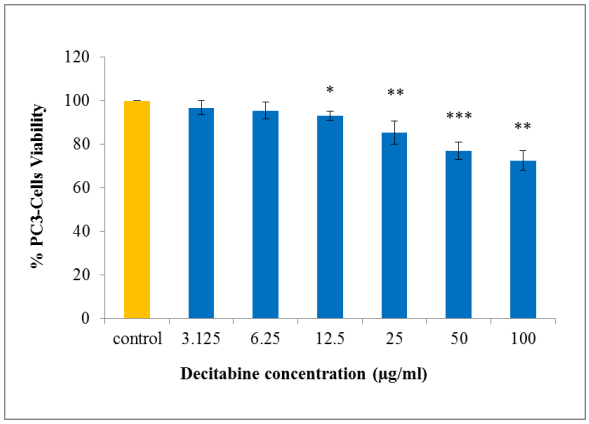



**Figure 4**: Impact of decitabine on PC3 cell line viability after 48 hours of incubation. $^{*}p< 0.05$, $^{**}p< 0.01$, $^{***}p< 0.001$.

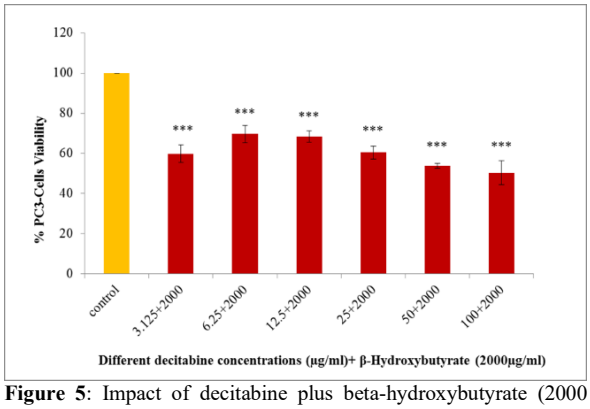



**Figure 5**: Impact of decitabine plus beta-hydroxybutyrate (2000 µg/ml) on PC3 cell line viability after 48 hours incubation. $^{***}p< 0.001$.

Figure 6 revealed a comparison between decitabine alone and in combination with β-hydroxybutyrate (2000 µg/ml) on the PC3 cell line. A significant ($p<$

0.05) difference in PC3 cell viability was demonstrated between the two groups as compared with control cells.

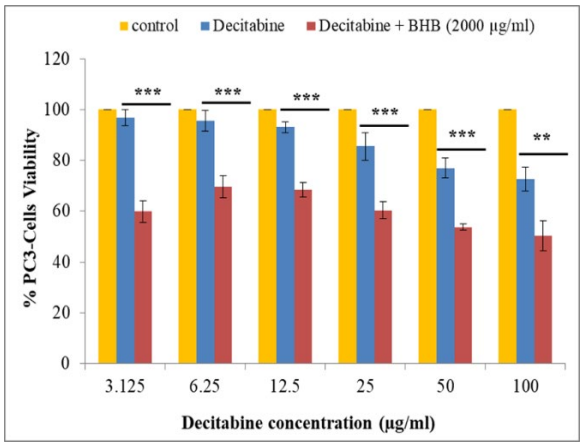



**Figure 6**: Comparison between decitabine and decitabine plus beta-hydroxybutyrate (2000 µg/ml) on PC3 cell line viability after 48 hours of incubation. **$p< 0.01$, ***$p< 0.001$.

Figures 7 and 8 showed a significant ($p< 0.05$) DNMT1 decline difference between decitabine alone and in combination with beta-hydroxybutyrate (2000 µg/ml) for all concentrations as compared to control cells.

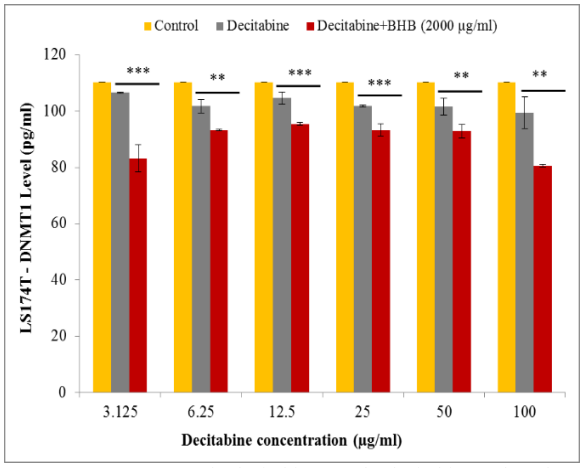



**Figure 7**: Impact of decitabine and decitabine plus beta-hydroxybutyrate (2000 µg/ml) on DNMT1 level for LS174T cell line. **$p< 0.01$, ***$p< 0.001$.

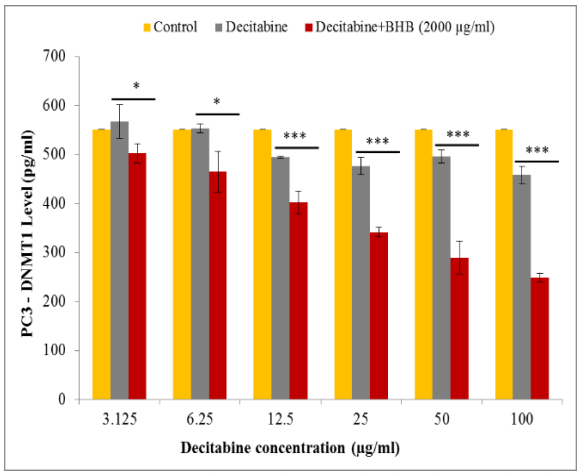



**Figure 8**: Impact of decitabine and decitabine plus beta-hydroxybutyrate (2000 µg/ml) on DNMT1 level for PC3 cell line. *$p< 0.05$, ***$p< 0.001$.

## DISCUSSION

Abnormal epigenetic changes in various cancers, such as DNA methylation and histone acetylation, draw the attention of the researchers to investigate various types of epigenetic therapies in order to treat metastatic cancer, especially when resistant to other therapies [16]. As a hypomethylating agent, decitabine was approved by the US FDA in 2006 to treat myelodysplastic syndrome. Later, many clinical and preclinical studies investigate using decitabine for treating solid tumors [17]. This study revealed that decitabine has a significant role in reducing LS174T cell and PC3 cell growth when compared to the control group. This result is based on the fact that DNA methylation is essential during development and also plays a critical role in certain processes, e.g., inactivation of the X chromosome, genome imprinting, and carcinogenesis [18]. When decitabine is incorporated in newly synthesized DNA, it will bind covalently to DNMT1, thus inhibiting this enzyme in the promoters of key tumor suppressor genes. So, this drug will reduce hyper-methylation at these promoters that become silent due to GC-island hypermethylation, and so the activity of key tumor suppressor genes will be restored [19]. In this work, significant growth reduction was observed when six concentrations of decitabine were combined with β-hydroxybutyrate (2000 µg/ml). DL-β-hydroxybutyrate sodium salt was used in this study to achieve a β-hydroxybutyrate concentration above the basal level (0.5 mM) and below the pathologic ketosis level (10 mM) because at this range, β-hydroxybutyrate can possess an epigenetic role by inhibiting class I HDAC enzymes, leading to the restoration of the acetylation of histones. The latter effect will make loose interaction between histones and DNA so that it allows the entry of transcription factors to the promoters of tumor-suppressor genes [20]. The explanation mentioned above clarifies the reason by which β-hydroxybutyrate could increase the cytotoxic effect of decitabine in this study with evidence of significant LS174T cell and PC3 cell growth reduction between decitabine alone and its combination with β-hydroxybutyrate (2000 µg/ml) for all concentrations. This result of synergism was similar to Wang *et al.*, who concluded that when decitabine is used in combination with an HDAC inhibitor (entinostat), this would result in synergistic inhibition of urothelial bladder cancer cell growth [21]. Another previous *in vitro* study showed promising synergism between decitabine and vorinostat (HDAC inhibitor) against Caco-2 colon cancer cells [22]. Finally, this study showed a significant difference in DNMT1 level between decitabine monotherapy and its combination with β-hydroxybutyrate (2000 µg/ml). This result can be explained by the fact that HDAC inhibition can decrease DNMT1 level effectively because this inhibition leads to hyperacetylation of HSP90 (heat shock protein 90), so this will inhibit the binding of DNMT1 to HSP90, making DNMT1 available for degradation by the ubiquitin-proteasome pathway [23]. This result was comparable with Young *et al.*, who mentioned that HDAC-enzyme inhibition

by vorinostat can result in significant DNMT1 reduction when the latter is used in combination with decitabine [24]. Another explanation is that β-hydroxybutyrate is class I-HDACI; it is capable of decreasing DNMT1 level by a mechanism mainly attributed to decreasing the stability of DNMT1 [25]. Therefore, this work showed that decitabine plus BHB decreased DNMT1 more effectively than decitabine monotherapy.

## Conclusion

β-hydroxybutyrate enhanced the effectiveness of decitabine against colon cancer and prostate cancer, suggesting that β-hydroxybutyrate may serve as a promising adjuvant to decrease decitabine therapeutic doses. Future *in vivo* studies are required to confirm these findings.

### Conflict of interests

The authors declared no conflict of interest.

### Funding source

The authors did not receive any source of funds.

### Data sharing statement

The data that supports the findings of this study are available from the corresponding author upon a reasonable request.

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