Cancer Therapy by Nutritional Restrictions: Current Knowledge and Future Guidelines

Fawwaz Shakir Al Joudi[1*]

[1]*TS Diagnostics Ltd., No. 7, Street TPP 5/11, Industrial Park, Puchong 47160, Malaysia.*

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Review Article

ABSTRACT

Cancer therapy has been a major scientific and medical focus for decades, treatment of which has proven to be a challenging task, especially in the light of its escalating incidence all over the globe. The material and moral costs of understanding the nature of the disease and finding successful ways of treatment have been extremely high. One major experimental addition to the methods of dealing with the various types of cancer has been the use of starvation protocols that may halt or delay the progression of malignant cells. In this review, a comprehensive and a pioneering account of the literature on starvation therapy is being demonstrated with an emphasis on the experimental and clinical evidence that exist, in addition to the molecular mechanisms and cellular alterations that accompany the starvation. The major objectives were to open ways for further research into understanding the topic and developing suitable and effective methods based on nutritional manipulations, for combating malignancies. The starvation includes precursors of growth such as energy precursors and others such as amino acids, nucleic acids, in addition to environmental manipulations such as abnormal oxygenation. Additional emphasis has highlighted the synergistic effects of combining conventional chemotherapy and radiotherapy with various modes of the artificial starvation. Methods of manipulating nutritional precursors have also been compiled. Additionally, negative effects of starvation were also briefly explained in an attempt to comprehend future guidelines for antagonizing such negative effects.

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Corresponding author: E-mail: fajoudi@yahoo.com;

1. INTRODUCTION

Cancer is a serious disease that has used exhaustive efforts and exerted heavy financial and scientific burdens to develop an understanding into the nature of its' various types, and to advance therapies and management protocols. The major problem with treating cancer is that its cellular components originate from self, and this raises the particular issue of targeting cancer cells without touching normal cells. For this reason, and although nutrition of cancer patients has been taken as an important determinant for survival, especially in terminally-ill cancer patients [1], the use of starvation is becoming acceptable to reduce or even halt the survival of cancer cells at the time when normal cells would be less dramatically affected. Nevertheless, cancer cells acquire short-cuts in most of their metabolic pathways to compensate for their reduced capabilities to produce energy, through the Warburg effect [2]. General remarks have been made through classical and microscopic observations of various cancer cell lines, explaining and proposing that starvation can be less effective against densely grown cells, epithelial cells can be more dynamic than mesenchymal cells, and that highly aggressive malignant cells are often more resistant to starvation than low aggression cells. However, in the literature, no attempt was found to encompass all the scattered information within a framework that may put the pieces together and possibly transfer the information into potential applications [3]. Nonetheless, and although most of the experiments performed are not related to each other directly, they share the starvation as a basis for their therapeutic approach. Furthermore, some models of starvation-based treatment have been proposed for oncology patients. Many of these models are based on the understanding of the mechanism of the Warburg effect [4] which can be antagonised by starvation [5].

Hence this work was carried out for the purpose of collecting and analysing information that may open avenues for research and promote for applications of starvation-based management of cancer.

2. EARLY REPORTS ON CANCER STARVATION THERAPY

In the mid-twentieth century, a few chemotherapeutic drugs became available for use, and were formerly limited to nitrogen mustard and prednisolone. Starvation therapy was also included as part of the trials with the intention of improving clinical responses, or boosting the effects of the chemotherapies. Variable outcomes were obtained [6-9]. Besides, variable outcomes have been reported with various starvation models and protocols: mice with ascites tumours showed a fasting-dose-related depression of the growth of the tumours [10]. Also, upon serum starvation, cultured fibroblasts entered the G0 phase, then after some delay, re-entered into the G1 phase upon re-feeding, or upon insulin stimulation [11]. When tumour-bearing mice were starved and re-fed intermittently, the DNA synthesis appeared to cease during starvation, and re-start following feeding, clearly implying that starvation can aid in halting tumours from growing [12]. The gluconeogenic pathway was enhanced in rats with tumours compared to normal rats [13], and starvation for glucose as a carbon source showed that normal cells were able to maintain ATP levels for long periods, whereas malignant cell lines had lowered ATP levels in a few hours following incubation [14]. Thus, insulinoma cells were unable to synthesize ATP under glucose starvation, and this was reversed by glucose and mannose, but not galactose [15]. Similarly, soon after starting a starvation episode, EL-4 ascitic tumour cells lost their intra-cellular ATP and allow an influx of calcium that initiated cellular damage and death [16]. Such alterations in the energy production pathways and their tributaries were also outlined in the classical work of Lazo [17], where glucose starvation in ascites cells lead to reductions in energy production and protein synthesis.

Different malignant cells demonstrated a variety of protein expression patterns when exposed to stress, partly following the signalling pathways. Initiation and re-initiation of peptide synthesis was greatly reduced in the absence of at least one amino acid in the growth medium [18,19] and that may have been associated with ADP-ribosylation of glucose regulatory proteins [20]. Also, starvation of Ehrlich ascites tumour cells grown in their own ascites fluid, led to fragmentation of their DNA at what appeared to be specific regulatory sites, unlike the non-specific nicking of DNA induced by alkylating agents [21]. Serum starvation was also found to inhibit the growth of V3T3-transformed fibroblasts, and this inhibition was either

reversible or irreversible [22]. Thus, metabolic effects of starvation, as well as differences among the various cells have been emphasized in early reports.

3. GLUCOSE (ENERGY) STARVATION

From experiments utilizing Ehrlich ascites carcinoma cells, it has been proposed that actively proliferating cells are more sensitive than resting cells to energy starvation and heat shock protein (HSP) deprivation, and that the mode of action may involve destabilization of cytoskeletal proteins [23]. Induction of the HSP itself may later induce a state of resistance to energy starvation [24]. Insulin was found to enhance glucose uptake in growing tumour cells, especially when starved for glucose [25]. Hence, the growth of Ehrlich ascites cells in mice was suppressed by glucose starvation and by inducing diabetes to abolish insulin activity, but the suppression was lifted by administration of insulin, suggesting a role for insulin in the regulation of glucose uptake and sustained metabolism in targeted tumour cells [26]. Under *in vivo* conditions, the glucose and glutamine concentrations are difficult to bring down to very low levels that minimized the survival of HeLa cells [27].

In early experiments, it was found that, in normal mammalian fibroblasts, transport of glucose was enhanced by glutamine and serum factors [28]. It was also reported that the rate of uptake of glucose by cells and tissues in tumour-bearing animals were higher than in normal, non-tumour-bearing animals, and that these differences in the rates became more magnified during starvation, since the measured rate of glucose consumption was highest in tumour cells [29]. However, this high rate of glucose uptake by tumour cells is not insulin-mediated, as these cells appear to be insensitive to insulin [30], and the expression of insulin receptors is reduced following glucose starvation [31]. This information is contradictory to the remark mentioned earlier [26] and must be considered when starvation is a choice for treatment. Also to be considered in starvation is that the glucose supply to vital cells and tissues in the body should not be jeopardised [32]. The low glycolytic rate breast cancer cell line MDA-MB 453 is more liable to ADP inhibition than the higher glycolytic rate MCF-7 cell line [33]. Moreover, virus-transformed cells appeared to increase the expression of their glucose transport sites, in an ATP-regulated fashion [34] and the expression of the Homeodomain-interacting

protein kinase 2 (HIPK2) in colon cancer cells lead to cell death upon glucose deprivation [35]. Growth signals may cause serum starvation-induced apoptosis in wild-type (wt) p53-expressing HCT116 human colon cancer cells [36]. Serum-starved human pancreatic and colon cancer cells undergo cell death through the DPC-4 (deleted pancreatic cancer) antigens through their effects on PUMA and PAK-1 suppressor molecules [37]. Nevertheless, the elevated rate of glucose uptake and survival of human neuroblastoma cells appear to depend on a complicated molecular network, especially under conditions of glucose deprivation [38]. In addition, glucose appears to be the sole usable energy source that head and neck squamous carcinoma cells can utilize, whereas normal cells can utilize glutamine [39].

Inhibition of glycolysis specifically enhances the susceptibility of ovarian and endometrial tumours to anti-GnRH receptor therapy [40]. Serum starvation also causes an arrest of ovarian cancer cells at the G1 phase through suppression of cyclin-dependent kinase 2 (CDK2) [41]. Chinese hamster V79 lung fibroblasts round up, detach and die upon starvation, with induced protein kinase C (PKC) alpha and p53 [42]. Colon cancer cells are also sensitive to glucose deprivation, although they may develop resistance that may be lost through silencing the oncosuppressor protein, the homeodomain-interacting protein kinase 2 (HIPK2) or the starvation may have been mediated through the c-Jun NH2-terminal kinase activation or through the ATM/Chk2/p53 signalling pathway [35,43]. Colorectal cancer cells deprivation off glucose and amino acids leads them to autophagy which itself may allow their extended survival [44]. Cultivation of adenocarcinoma cells under glucose stringency activated glycogen phosphorylase and after a few hours, glycogen synthase started to lose its activity, ultimately leading to huge reductions in cellular ATP [45]. In Hep-2 cells, the suppression due to glucose starvation was found to be compensated by following episodes of hypoxia in the presence of amino acids as alternative energy sources [46]. Furthermore, glucose starvation of rat hepatoma cells appeared to lead to the production of small molecular weight glycoproteins, the significance of which was not clear [47]. Necrosis of malignant glioma cells became evident when hypoxia and serum deprivation existed simultaneously [48], and these cells revived through Tp53-induced glycolysis and accelerated respiration [49].

Similarly, the pancreatic adenocarcinoma cell line MiaPaCa2 recovered from glucose deprivation through the Nupr1 as a defensive mechanism [50].

Hep2 cells cannot survive glucose starvation because of the caspase 8-mediated death, the effects of which are inhibited by ARK5, a member of the AMPK family [51]. However, the death of the same cells due to amino acid starvation is mediated through another mechanism that involves over-expression and stabilization of the mRNA of insulin-like growth factor binding protein (IGFBP-1) [52]. Moreover, immortalised mouse embryonic fibroblasts adopted a different mechanism to survive the starvation, which involved increased expression of cl-1, a member of the bcl-2 family [53].

Controversial findings emphasized that hypoxia and glucose starvation were associated with enhanced invasiveness of a number of cancer cell lines, and studies with HepG2 cells have suggested that this invasiveness may be mediated by hypoxia-induced transforming growth factor-beta1 through AMP-activated protein kinase-alpha activation and the Akt/ARK5 system [54,55].

The above works indicate that various underlying mechanisms function in various cells, to halt the progression of these cells, or otherwise they adopt a number of other mechanisms to evade starvation-induced stagnation.

4. ENERGY RESTRICTION BY THERAPEUTIC MANIPULATIONS

A number of methods of intervention to achieve glucose deprivation or energy restriction have been described. Therapeutic starvation of the prostate cancer cells, PC-3 with 2-deoxy-D-glucose (2DG) ended up with translocation of the autophagy LC3 (light chain 3) membrane protein and autophagy [56]. Also, and in addition to its' anti-cancer activity, the plant extract silybin, exhibited an experimental energy deprivation to cancer cells [57]. Silybin and dehydrosilybin can act upon glucose transporters (GLUT) to reduce glucose uptake in Chinese hamster ovary (CHO) cells and in 3T3-L1 adipocytes, thereby starving cancer cells and preventing their progression [58]. In addition, the HSVtk which is a suicide gene in the murine mammary adenocarcinoma cell line, TSA, and which can be induced by insertion of the promoter of the grp78 gene, and under conditions of glucose starvation, cell death

can be enhanced, implying that this therapeutic approach can halt metastatic breast cancer [59,60]. Metabolomic studies with breast cancer cells have also indicated that stresses may induce a number of pathways, some of which would be unfavourable for the survival of cancer cells, such as the induction of thioredoxin-interacting protein (TXNIP) under lactic acidosis [61].

When tumour cells shift their metabolism into the Warburg effect, lactate becomes one major source of energy in the lack of efficient glycolysis. Lactate diffuses into nearby tumour cells. Lactate sensitivity itself can determine the efficiency of glucose starvation [62]. The lactate in these tumour cells stems from glucose and from glutamine [63] and upon glucose deprivation, cells utilize more glutamine to compensate for energy production [64]. Thus the use of alpha-cyano-4-hydroxycinnamate (CHC) or siRNA to inhibit the uptake of lactate through inhibiting monocarboxylate transporter 1 (MCT1) retarded the growth of the lactate utilizing human cervical squamous carcinoma cell line and eventual death occurred upon glucose deprivation and hypoxia [65]. Hence, glutamine depletion or deprivation can drive tumour cells to apoptosis [66] and avoidance or minimizing glutamine or lactate or both in the circulation may prove to be a useful therapeutic manoeuvre.

Metformin was also used to induce a Pasteur effect associated with inhibition of the growth of leukemic cells, but not normal cells [67]. A further experiment utilized the grape extract resveratrol to induce autophagy in ovarian cancer cells by caspase-independent mechanisms resembling those of glucose deprivation to which the cells are sensitive [68].

An additionally tested method of inducing starvation has been the use of the energy-restricting mimetic agents, OSU-CG5 and OSU-CG12, with promising results obtained with colon cancer and prostate cancer cell lines [69-71].

The apoptosis induced by starving colon cancer cells or by treating them with celecoxib was inhibited by Glycine-extended gastrin (G-Gly) through increasing ERK and p38 MAP kinase phosphorylation and increased nuclear translocation of active NF-kappaB [72]. Osteosarcoma cell lines also underwent apoptosis in serum starvation, and the apoptosis was not prevented by vitamin D3 [73], and D3 analogues potentiated the cytotoxic effects of

starvation of the breast cancer cell lines MCF-7 and Hs578T [74].

Induction of ketosis in dogs with hypoglycemia by (R,S)-1,3-butanediol acetoacetate esters, enhanced the regression of poorly differentiated cancers in a dog model. This maneuver would be especially effective with cells that cannot utilize lipids as fuels [75]. Similarly, controlled ketosis and hypoglycemia may be effective in reducing cancer growth [76]. Another manipulation for autophagy has been from work with starved or rapamycin-treated HeLa cells through the JAk2/STAT3 activation followed by induction of IL-6 production [77]. And as mentioned earlier, the glutamate antagonist MK-801 (Dizocilpine) suppresses hepatocellular cancer cell lines grown under glutamate deprivation through the induction of TXNIP [78]. Benign prostate cells have been reported to have a better ability in utilizing fatty acids than malignant prostate cells, and this may have potential therapeutic uses [79]. Conversely, ovarian cancer cells can survive simultaneous lipid starvation and hypoxia [80].

Resistance to glucose starvation has been reported by a number of cancer cells. Such resistance by the pancreatic cancer cells PANC-1 was alleviated by the use of the extract of Brazilian red propolis or by the soluble extract of Angelica pubescens, angelmarin [81,82]. Glucose starvation acts in synergy with the natural anti-cancer product, arctigenin, which eliminates the resistance of cancer cells to nutrient deprivation, mainly through the activation of some glucose-regulated proteins [83,84]. Similar effects were described by the use of insulin sensitizers, such as troglitazone, with liver cancer cell lines [85]. Furthermore, hydroxyindole-based inhibitors of lactate dehydrogenase A and B (LDH-A and B) have been found to compete with pyruvate uptake and retard the proliferation of various types of cancer cell lines [86]. The resistance of pancreatic cell lines to glucose starvation is diminished by interrupting the AMPK pathway expression through expression of anti-sense, implying that it can be a useful manipulation for successful starvation [87].

Conversely, the survival of serum-deprived PC-3, the human prostate adenocarcinoma cell line, is improved by adding vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide-27 (PACAP) receptors, through inhibiting DNA fragmentation [88].

5. DEFICIENCY OF NUTRITIONAL PRECURSORS OTHER THAN GLUCOSE

The differentiation of promyelocytic leukemia cells into mature granulocytes can take place with single amino acid starvation, indicating their release from their differentiation block [89]. T-cell leukemia cells undergo apoptosis following glucose starvation through apoptosis-inducing factor (AIF)-dependent and caspase-3-dependent mechanisms [90]. Furthermore, methionine starvation in a number of lymphoblastoid and leukemia cell lines has resulted in alterations in cell morphologies and in nuclear proteins expression patterns [91]. Reduction of methionine levels by using recombinant methioninase (rMETase) can also lead to arrest of neuroblastoma cells at the G2 phase [92]. Similarly, Pseudomonas putida methionine-γ-lyase retarded the growth of central nervous system (CNS) tumours, or those metastasizing to the CNS, such as glioblastomas, medulloblastomas, and neuroblastomas [93]. Furthermore, the proliferation of a glioma cell line and a human prostate cancer was arrested in methionine-free media or in media containing methionine analogues [94,95]. Moreover, when rats bearing the Walker-256 carcinosarcoma cells were starved for methionine and valine, the tumours were suppressed following depression in protein and nucleic acid synthesis [96]. Asparagine depletion has also been suggested to be a potentially useful approach in treating pancreatic cancer especially in patients or in cells that lack the ability to synthesize asparagine [97].

Arginine auxotrophic tumour cells, such as melanoma and hepatocellular carcinoma cells rely on external sources of arginine. These cells were shown to have compromised survival by arginine deprivation or by introducing recombinant arginine degrading enzymes [98]. Furthermore, arginine starvation of a variety of cancer cells was found to stimulate apoptosis [99] and the methylation status of the CpG islands may be positive markers for sensitivity of glioblastoma cells to arginine starvation [100]. Arginine starvation can also be achieved by pegylated arginine deiminase (ADI-PEG20) that induced autophagy and cell death of Argininosuccinate synthetase 1 (ASS1)-deficient breast cancer cells [101,102].

Ultimately, the proliferation of methylcholanthrene-induced sarcomas in mice

was attenuated following starvation and polyamine depletion [103] and amino acid starvation appears to act through inhibiting RNA methylation [104]. Another mechanism of inducing autophagy involves the ULK (mammalian homolog of yeast Atg1) activation and the following Beclin-1 phosphorylation [105]. Moreover, morphological alterations have been described in amino-acid-starved cells such as the large nuclear bodies seen following cystine starvation of T24 bladder carcinoma cells, the effects of which remain unclear [106]. Cystine starvation, induced by sulfasalazine was also effective in curbing the growth of the prostate cancer cell lines DU-145 and PC-3 through the reduction of cellular glutathione [107]. Starvation for lysine or histidine induces severe cell stress which may finally trigger the programmed cell death, seen through DNA fragmentation and chromatin condensation [108]. However, contradictory to anticipated results, and under serine stringency, some prostate cancer cells may shift into glutathione production to combat ROS, and this survival saving metabolic shift is mediated by the p53-activated p-21 [109,110].

Nucleic acids starvation was also reported. Starvation for guanine by mycophenolic acid was found to inhibit *de novo* DNA synthesis in mouse T and B lymphoma cell lines and in a human T-cell lymphoblastic leukaemia cell line. The synthesis would be resumed on re-introduction of the missing nucleotides [111,112].

Pyrimidine starvation may be achieved in multiple myeloma cells by the 5-aminoimidazole-4-carboxamide-1-β-riboside (AICAr) pathway which reduces pyrimidine formation though it increases the purine levels [113]. Moreover, in Ehrlich ascites tumour cells and several cancer cell lines lose resistance to starvation through extracellular ATP which generates adenosine and consequent growth inhibition and reduced protein synthesis through adenosine-dependant pyrimidine starvation [114,115]. Nevertheless, thymidine reduction was evident through depletion of calcium in a melanoma cell line, though it did not cause a proliferative block [116] and thymidine deprivation appeared to delay apoptosis in colon carcinoma cells [117].

The NF-kappaB inhibitor BAY11-7082 exerts synergistic apoptotic effects with nutrient starvation to the acute myeloid leukemia (AML) cell line U937 as well as primary CD34(+) bone marrow blasts from AML patients and patients with myelodysplastic syndrome [118].

Copper starvation was found to induce apoptosis of neuroblastoma cells through increasing cellular anti-oxidant activity [119].

Lipids have also been tested as potential starvation aids. It has also been proposed that by feeding low carbohudrate and high fat ketogenic diets would induce metabolic oxidative stress in cancer cells and would also sensitize cancer cells to chemotherapy and radiation A ketogenic diet may also exert anti-inflammatory, anti-angiogenic and pro-apoptotic metabolic therapy that also reduces fermentable fuels in the tumor microenvironment. Such metabolic therapy may have a potential for treatment of malignant brain cancers [120,121]. Ceramide, a component of cellular sphingomyelin, has been shown to induce apoptosis of cancer cells through their increased sensitivity to ceramide creating a bioenergetic crisis [122]. Comberstatin and its derivative Comberstatin A4 appeared to stop tumour growth by minimizing the tumour blood flow [123].

In summary, starvation modes for non-energy nutritional precursors have potential applications in treating cancer, and a number of methods of interventions have been described.

6. STARVATION FOR GROWTH FACTORS

Selective starvation for colony stimulating growth factors has not been recommended for leukemic cells, since they may render the cells resistant to chemotherapeutic drugs and the cells resume their normal growth on re-addition of the growth factor [124]. In a similar way, human neuroblastoma cells were found to be protected from starvation, in culture, by insulin-like growth factor [125]. However, the use of cytokines, including IFNs, IL-4, IL-12 and TNF-alpha that exert anti-angiogenic or vasculotoxic effects, may cause significant local tumour control through a state of tumour starvation [126].

7. COMBINED THERAPY AND STARVATION

In a variety of cellular and animal models, and in a few clinical trials, cycles of fasting halted the progression of tumours and enhanced the efficiencies of chemotherapeutic agents. This was called differential stress syndrome (DSS), a state of enhanced resistance of normal cells to chemotherapy as compared to cancer cells [127,128]. Even the side effects of the drugs

were reduced, and this was termed differential stress resistance (DSR) [129]. Rats bearing tumours and infused with nutrients after being starved for glucose and amino acids had a high DNA synthesis index in the first few hours before the rate went back to normal implying that the best delivery time for DNA alkylating and s-phase-specific agents would be during the high DNA synthetic rates [130]. The protective effect to normal cells was found to be associated with the lack of expression of the oncogene homolog Ras2 (val19) [131]. Furthermore, and although low glucose was found to be ineffective against primary glial cells, it was effective against a number of neuroblastoma and glioma cancer cell lines and short-term starvation provided protection to mice undergoing chemotherapy but not to injected neuroblastoma cells. The survival of glioma-bearing animals was extended when they were made to fast prior to chemotherapy or radiotherapy [132]. In addition, fasting enhanced the efficiency of tyrosine kinase inhibitors against cancer cells [133].

The sensitivies of most solid tumour cells to cisplastin and carboplatin were increased following glucose starvation and increased activity of glucose regulated proteins (GRP) [134]. Conversely, glucose starvation reduced the cisplastin-induced apoptosis of the human epidermoid carcinoma cell line A431 [135].

Glucose starvation activates the ATM/Chk2/p53 signalling pathway which, in turn, potentiates the activity of cisplatin on cancer cells [43]. However, apoptosis of colon cancer cells due to starvation or treatment with celecoxib was inhibited by glycin-extended gastrin (G-Gly) [72] or by upregulation of alpha 5 beta 1 in MCF-7 cells [136].

The anti-helminthic drug, pyrvinium pamoate (PP) possesses an anti-cancer activity and a reported toxicity to PANC-1 cells and to various cancer cell lines grown in glucose-free medium, but not when grown in ordinary medium [137,138]. PP was also reported to have a synergistic anti-cancer autophagy activity with 2-DG [139]. The actinomycete extract Kigamicin D (C(48)H(59)NO(19) also exerted selective cytotoxicity to nutrient-starved pancreatic cancer cells in culture and in nude mice, although testing of kigamicin with other tumour types did not yield favourable results [140,141]. On first introduction of methotrexate, its association with starvation was considered, and it turned out that purine withdrawal in growth media prevented the growth of human choriocarcinoma cells *in vitro*, thereby enhancing the effects of methotrexate [142]. Also, the response of paediatric brain tumours to cisplastin or lomustine can be manipulated by starvation to stimulate autophagy [143].

Deprivation of neuroblastoma cells off methionine boosted the anti-tumour effects of vincristine [92], and the simultaneous methionine deprivation boosted cisplastin therapy of breast cancer cells in nude mice [144]. It was also found that methionine dependence increases the sensitivity of cancer cells to paclitaxel, especially when compared to the non-methionine dependant cells, Hs-27 [145]. Prostate cancer cells have been shown to undergo apoptotic changes upon taxol or Guttiferone F treatment with simultaneous starvation [146,147]. As mentioned earlier, inhibition of glycolysis can specifically enhance the susceptibility of ovarian and endometrial tumours to anti-GnRH receptor therapy [40]. Starvation also enhanced the effects of doxorubicin in killing the HeLa derivative, KB-V1 carcinoma cells [148]. However, negative effects of glucose starvation on the efficiency of 5-fluoro-uracil were noted, and were explained by the reduced incorporation into the RNA of liver carcinoma cells, as compared to normal hepatic and intestinal cells [149], although gastric cancer cells were suppressed by the combination of methionine starvation and fluoruracil therapy [150,151].

Radiosensitivity of tumour cell lines has been reported to be altered following starvation, and p53 appeared to play a role in inducing necrosis rather than apoptosis in starved cells [152]. The radio-iodine therapy of breast cancer was improved with the simultaneous use of 2-DG and metformin [153]. The effects of radiotherapy on human epithelial cancer cell lines are also enhanced by selective arginine starvation [154], and by a simultaneous ketogenic diet during the treatment of malignant glioma [155]. The effects were further enhanced by the combined ketogenic diet with hyperbaric oxygen treatment of VM-M3 glioblastoma multiforme mouse cell model [156].

Nevertheless, when MCF-7 breast cancer cells were grown at low glucose, they developed resistance to photodynamic therapy in what was explained to be adaptation to glucose deprivation [157]. However, in melanoma mice, starvation yielded resistance of normal cells to the toxicity induced by doxorubicin, mostly through reducing the IGF-1 levels. Such a protection was not

achieved with glioma bearing mice treated with cyclophosphamide, although altogether, the animal survival was improved with starvation [158]. Moreover, starved melanoma cells were rendered autophagic upon the simultaneous treatment with the anti-malarial drug amodiaquine [159].

In Summary, a number of therapeutic modes have been researched into, and the major modes of starvation therapies with positive findings and the methods of inducing starvation have been presented and have been summarized in Tables 1 and 2.

Table 1. The experiences with positive findings

Cancer type	Remarks and references
Blood cancers	- T-cell leukemia cells undergo apoptosis following glucose starvation through apoptosis-inducing factor (AIF)-dependent and caspase-3-dependent mechanisms [90].
	- For leukemic cells, use of metformin induces a Pasteur effect associated with inhibition of the growth of leukemic cells, not normal cells [67].
	- Promyelocytic leukemia cells differentiate into mature granulocytes from single amino acid starvation, indicating that the selected starvation enables cells to be released from their differentiation block [89].
	- Methionine starvation in a number of lymphoblastoid and leukemia cell lines results in cellular morphological alterations, in addition to alterations in nuclear proteins expression patterns [91].
	- Starvation for guanine by mycophenolic acid inhibits the *de novo* DNA synthesis in mouse T and B lymphoma cell lines and in a human T-cell lymphoblastic leukemia cell line. The synthesis would be resumed on re-introduction of the missing nucleotides [111, 112].
	- Pyrimidine starvation may be achieved in multiple myeloma cells by the 5-AICAr pathway which reduces the pyrimidine formation though it increases the purine levels [113].
Breast cancer	- Lactic acidosis with induction TXNIP [61].
	- D3 analogues can potentiate the cytotoxic effects of starvation of the breast cancer cell lines MCF-7 and Hs578T [74].
	- Induction of the HSVtk gene by insertion of the promoter of the grp78 gene, and, under conditions of glucose starvation, cell death of the murine mammary adenocarcinoma cell line, TSA can be enhanced. [59, 60].
	- ADI-PEG20 can induce autophagy through arginine starvation SS1-deficient breast cancer cells [102].
	- 2-DG and metformin improve the therapeutic efficiency of radio-iodine (153).
Ovarian and endometrial	- Serum starvation caused a G1 phase arrest of ovarian cancer cells through suppression of cyclin-dependent kinase 2 (CDK2) [41].
	- ovarian and endometrial tumours : 2DG inhibition of glycolysis, especially to enhance the susceptibility to GnRH therapy [40].
	- Resveratrol to induce autophagy in ovarian cancer cells [68].
Cervical	- A lactate utilizing human cervix squamous carcinoma cell line: inhibition of the uptake of lactate through inhibiting monocarboxylate transporter 1 (MCT1 alpha-cyano-4-hydroxycinnamate (CHC) or siRNA, can result in retarded cell growth and eventual death upon glucose deprivation and hypoxia n [65].
Prostate	- Starvation of cancer cells with 2DG leads them to undergo autophagy [44, 56].
	- Human cancer was arrested in methionine-free media or in media

	-	containing methionine analogues [94, 95].
	-	Cystine starvation, induced by sulfasalazine can curb the growth of the prostate cancer cell lines DU-145 and PC-3 through the reduction in glutathione content of cells [107].
	-	Under serine stringency, some prostate cancer cells may shift into glutathione production to combat ROS [109, 110].
	-	Taxol and starvation together induce autophagy of prostate cancer cells [147].
Pancreatic cancers	-	Serum-starved human cancer cells undergo cell death through the DPC-4 antigens [37].
	-	In pancreatic cell lines, resistance to glucose starvation is diminished by interrupting the expression of the AMPK pathway through expression of anti-sense [87].
	-	Asparagine depletion is a potentially useful approach in treating pancreatic cancer especially in patients or in cells that lack the ability to synthesize asparagines [97].
Colon cancers	-	Apoptosis follows serum starvation in wild-type p53-expressing HCT116 human colon cancer cells [36].
	-	Deprivation off glucose and amino acids leads cancer cells to autophagy [44, 56].
	-	Serum-starved human colon cancer cells undergo cell death through the DPC-4 antigens [37] .
Hepatic	-	TXNIP is involved in the suppression of hepatocellular cancer cell lines by glutamate deprivation through the glutamate antagonist MK-801 [78].
	-	Hep2 cells cannot survive glucose starvation because of the caspase 8-mediated death, the effects of which were inhibited by ARK5, a member of the AMPK family [51].
	-	Death of Hep2 cells on amino acid starvation through over-expression of the mRNA of IGFBP-1 [52].
	-	Arginine auxotrophic hepatocellular carcinoma cells have compromised survival by arginine deprivation or by recombinant arginine degrading enzymes [98].
CNS tumours	-	Necrosis of malignant glioma cells takes place in the simultaneous existence of hypoxia and serum deprivation [48].
	-	Rreduction of methionine levels by using rMETase leads to arrest of neuroblastoma cells at the G2 phase [92].
	-	Pseudomonas putida methionine-γ-lyase retards the growth of CNS tumours or those metastasizing to the CNS, such as glioblastomas, medulloblastoma, and neuroblastomas [93].
	-	A glioma cell line is arrested in methionine-free media or in media containing methionine analogues [94, 95].
	-	The methylation status of the CpG islands has been suggested to be a positive marker for sensitivity of glioblastoma cells to arginine starvation [100].
	-	Neuroblastoma: Copper starvation was found to induce apoptosis of neuroblastoma cells through increasing cellular anti-oxidant activity [119].
Others	-	The growth of Ehrlich ascites cells in mice is suppressed by glucose starvation and by abolishing insulin activity [26].
	-	Osteosarcoma cell lines undergo apoptosis in serum starvation, and the apoptosis is not prevented by vitamin D3 [73].
	-	Upon glucose starvation of cultivated adenocarcinoma cells activate their glycogen phosphorylase, and, after a few hours, glycogen synthase starts losing its activity, ultimately leading to huge reductions in the cellular ATP [45].

- When rats bearing the Walker-256 carcinosarcoma cells are starved for methionine and valine, the tumours are suppressed following depression in protein and nucleic acid synthesis [96].
- Arginine auxotrophic melanoma cells were shown to have compromised survival by arginine deprivation or by introducing recombinant arginine degrading enzymes [98].
- The proliferation of methylcholanthrene-induced sarcomas in mice is attenuated by starvation and polyamine depletion [103].

Table 2. The methods that have been used to induce starvation

A basic method is when a specific nutritional component can be deleted from the food or culture media, whenever possible.
Energy-restricting mimetic agents, OSU-CG5 and OSU-CG12 [69-71].
2-deoxy-D-glucose (2DG) to compete for glucose sites [44, 56].
(R,S)-1,3-butanediol acetoacetate esters for induction of ketosis with glucose starvation [75].
The energy deprivation can be manipulated and driven experimentally by the plant extract, silybin which was also found to exhibit an anti-cancer activity [57].
Silybin and dehydrosilybin act upon glucose transporters (GLUT) and reduce glucose uptake [58].
Insertion of the promoter of the grp78 gene, and, under conditions of glucose starvation, [59, 60].
Inhibition of the uptake of lactate through inhibiting monocarboxylate transporter 1 (MCT1) with alpha-cyano-4-hydroxycinnamate (CHC) or siRNA [65].
Metformin induces a Pasteur effect associated with inhibition of the growth of leukemic cells, not normal cells [67].
Resveratrol, a grape extract, induces autophagy in ovarian cancer cells by caspase-independaent mechanisms resembling those of glucose deprivation to which the cells are sensitive [68].
Activation of the JAk2/STAT3 pathway followed by induction of IL-6 production [77].
The use of methionine analogues instead of methionine-free media [94, 95].
CpG islands have been suggested to be positive markers for sensitivity of glioblastoma cells to arginine starvation [100].
Cystine starvation can be induced by sulfasalazine [107].
Ceramide to induce apoptosis of cancer cells through their increased sensitivity to ceramide creating a bioenergetic crisis [120].
Comberstatin derivative appeared to stop tumour growth by minimizing the tumour blood flow [121].
Arginine starvation can be induced by ADI-PEG20 in ASS1-deficient cells [102].

8. RECOMMENDATIONS AND CONCLUSIONS

The experiences outlined throughout this literature review are aimed at understanding the effects of starvation on the growth of cancer cells. They are also meant to shed some light on the possibility of developing suitable and effective methods for combating malignancies based on nutritional manipulations. However, issues like cellular mechanisms of starvation and negative findings with starvation have not been discussed due to space limitations.

This study contains vital information that mark differences among various kinds of tumour cells, and differences within one cell type under various growth stages and conditions. Mostly, it represents a trial to collect together information on starvation work in an attempt to draw lines for further work aimed at developing and standardizing methods for treating cancer. Hence a method selected may be unique to a tumour type and stage, with particular considerations for any negative results expected especially with other cancer types. This has been clearly emphasized with the fact that aggressive or poorly differentiated tumours would be less affected by starvation than differentiated ones. Thus, *in vitro* work and *in vivo* experiments may form proper bases for developing preliminary guidelines for therapeutic manipulations. Certainly, when it comes to clinical settings, further considerations would be taken such as ethical approvals, type and stage of cancer, and the general condition of a patient. In other words, the current experiences point out that there is some reasoning with individualized therapeutic approaches.

However, the trials and experiments reviewed and presented in this work are mostly based on experiments utilizing laboratory animals and cells in culture. Although they do add up to the understanding and future directions, their output as it is now appears to be difficult to implement in a clinical set-up or even close to one. The apparent reason for this is that there are no definitive procedures yet that yield highly reliable results for a certain type of cancer. Bedsides, appropriately designed methods of inducing directed starvation are still required to be standardized, and are expected to minimize the pooling effects of *in vivo* conditions. Examples are the anti-methionine agents that would aid in minimizing the availability of methionine obtained following breakdown of body cells and tissues. Hence, this work serves as orientation for further organized research and clinical trials which are required to optimize modes of therapy and conditions required per cancer type. This work appears to be a first attempt to compile a vast amount of scattered information into a translatable form that may aid in building up and advancing therapeutic strategies for cancer.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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