REVIEW ARTICLE

The Positive Impact of Vitamin C (Ascorbic Acid) Utilisation in Cancer Treatment: A Scoping Review of Published Articles From the Perspective of the in Vitro Studies

Nurul Ain Mohammad Hamdi[1], Muhammad Salahuddin Haris[2], Ahmad Fahmi Harun Ismail[3]

[1] Advanced Drug Delivery Laboratory, Kulliyyah of Pharmacy, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.
[2] Department of Pharmaceutical Technology, Kulliyyah of Pharmacy, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.
[3] Department of Physical Rehabilitation Sciences, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia

ABSTRACT

Survival benefit of patients with advanced cancer was reported with intravenous vitamin C administration. Nevertheless, a recent systematic review failed to support the clinically use of vitamin C in cancer patients due to the diversity of interventions and cancer type. This study aimed to provide a scoping review of vitamin C utilisation and its impact on cancer treatment from the perspective of in vitro studies. The review was conducted using predefined search terms in three scientific databases. 44 articles were retrieved with a total of 15 cancer types being studied from 2015 to 2020. The findings were classified into primary and secondary outcome. The primary outcome refers to chief consequences of vitamin C treatment, while the secondary outcome denotes the additional advantages generated as a result of the primary outcome, which occurs both in monotherapy and combination therapy. This review discussed the major mechanism of vitamin C as anti-cancer and its relation with the outcomes.

Keywords: Ascorbic acid, Vitamin C, Treat cancer, Anti-cancer, in vitro study

Corresponding Author:
Ahmad Fahmi Harun Ismail, PhD
Email: ahmadfahmi@iium.edu.my
Tel: +609 571 6400 ext 5388

INTRODUCTION

In 2018, cancer was listed as the second leading cause of death worldwide (1). While several treatment options are available, chemotherapy remains the most common approach chosen for cancer cure. Nevertheless, chemotherapy-resistant results in more than 90% mortality among cancer patients (2). The prevalence of drug-resistant in cancer treatment warrants the discovery of a new potential drug that possess anti-neoplastic properties such as vitamin C. Vitamin C is one of the nutrients that offer essential physiological roles as well as metabolic activities in humans. It serves as a co-factor for fifteen mammalian enzymes (3). However, human are unable to synthesize vitamin C endogenously, thus they rely exclusively on the dietary component (4–6). Survival benefit and symptomatic relief of patients with advanced cancer were first reported in the 1970s with intravenous vitamin C administration (7). Afterwards, two rigorous double-blind placebo-controlled prospective trials conducted at the Mayo Clinic using the same dose administered orally failed to benefit the patients with advanced cancer (8). Hence, the role of vitamin C in cancer treatment is controversial due to the lack of reproducibility in regards to therapeutic benefit in cancer patients (9). However, the interest of utilising ascorbic acid in cancer treatment was reignited, seeing that pharmacokinetics data of intravenous ascorbic acid and oral ascorbic acid behave differently (10,11). The difference could be due to low physiological concentration offered by oral administration (plasma concentration in micromolar, μM range) compared to the parenteral administration (plasma concentration in millimolar, mM range) which is subjected to saturable intestinal active transport of vitamin C (10,12). The positive impact of vitamin C utilisation in various cancer treatment has been manifested in the majority of in vitro studies, animal studies and human studies (13). Nevertheless, a recent systematic study failed to support the clinically relevant vitamin C supplementation in cancer patients due to the diversity of interventions and groups of the cancer patient. The systematic review study also acknowledged the chances of overlooking

the effect on some patients due to this diversity (14). Thus, this study was conducted to map the outcomes of vitamin C utilisation against various cancer cells from the perspective of in vitro studies.

METHODS

Design

The general methodological framework for conducting scoping studies outlined by H. Arksey & L. O'Malley and enhanced further by Levac et al. was followed as the basis for conducting this scoping review (15). The framework comprises five stages: 1) identifying the research question, 2) identifying relevant literature, 3) selecting literature, 4) Charting data, 5) Collating, summarizing and reporting results.

Identifying the research question

This review focus on studying the application and outcomes of vitamin C utilisation against various cancer cell lines. The following research questions guided the procedure of included studies, extract, and summarise the data type and reporting the result:

1. What are the types of cancer being studied from the retrieved literature?
2. What are the outcomes of vitamin C utilisation against cancer cell as monotherapy or combination therapy?
3. What is the major mechanism of action of the anti-cancer effect of vitamin C on cancer cells?

Identifying relevant literature

We included scientific literature consisted of the original research articles using vitamin C as the intervention to treat cancer. The search was limited to 6 years of articles published between 2015 and 2020 that reported the utilisation of vitamin C in cancer treatment. Review article, meta-analysis studies, book chapters and conference proceedings were excluded from the study. Scopus, PubMed and Google Scholar databases were searched to retrieve studies of interest using relevant predefined terms. The search term used is ("ascorbic acid" AND cancer) OR ("vitamin C" AND cancer).

Selecting literature

PRISMA method was used in the process of selecting the articles. Two reviewers independently identified the included studies according to the predefined inclusion criteria presented in Table I.

Charting data

Data charting was done in an iterative process. Two authors categorized the summaries of each article into the cancer type, cell line, application, vitamin C dose and outcomes into a scoping table. Table II provides an overview of the included studies.

Collating, summarizing, and reporting the result

A descriptive analysis of the extracted data was conducted. A summary of the study characteristics, namely types of cancer, types of application, types of outcome towards cancer cells and summary of the outcomes, were provided.

Table I: Inclusion criteria

Category	Inclusion criteria
Language of publication	English
Year of publication	2015-2020
Publication type	Original research article
Application	Monotherapy and/or combination therapy in vitro studies
Outcomes	Impact of the utilisation of vitamin C in cancer cells

RESULTS

Study selection

A total of 420 articles was retrieved by the Scopus, PubMed and Google Scholar databases search. About 70 articles were included for further investigation. By scanning the title and abstract of the articles of these records, 15 articles were excluded because they did not match the inclusion criteria. 55 articles were evaluated in their full text. 11 articles were excluded as they focus on human study, animal study and combination of vitamin C with other herbs. Finally, 44 articles were included for scoping review.

Study characteristics

The study characteristics of 44 articles selected for this scoping review are described in Table II.

Vitamin C dose

In this review, micromolar concentration of vitamin C is classified as low dose and millimolar concentration of vitamin C is classified as high dose.

Type of cancer

44 research articles were retrieved from the literature with 15 types of cancer. The utilisation of vitamin C has been studied in various cancer that is breast cancer, skin cancer, colorectal cancer, oral cancer, gastric cancer, cervical cancer, blood cancer, bone cancer, liver cancer, lung cancer, prostate cancer, pancreatic cancer, brain cancer, bile cancer, and epithelial cancer (Table III).

Type of application

The vitamin C was used either as monotherapy or as a combination with chemotherapeutic agents or radiation therapy. 18 articles studied vitamin C as monotherapy, 22 articles studied vitamin C as combination therapy and four articles studies vitamin C utilisation both as monotherapy and combination therapy.

Outcomes

The outcomes of the vitamin C utilisation were divided into primary outcome and secondary outcome.

Table II: Characteristics and outcomes of the included studies

Reference	Cancer type	Cell line	Application	vitamin C dose	Outcomes
Bober et al (16)	Breast	MCF-7	Combination with doxorubicin	200 µM	Combination therapy showed the highest cytotoxic effect
Wu et al (17)	Breast	MDA-MB-231, MDA-MB-468	Combination with methotrexate	5 µM	The combination therapy showed the lowest cancer cell viability against triple-negative breast cancer
Lee at al (18)	Breast	MCF7, SK-BR3 and MDA-MB-231 cell line	combination with conventional anti-cancer agents	1.25 to 20 mM	The combination therapy further facilitated anti-cancer activity in relative to the single agent
Sinha et al (19)	Breast	MCF-7	Combination with topotecan	1mM	Combination therapy enhanced cytotoxicity towards MCF-7 cell lines
Zeng et al (20)	Breast	Bcap37, MDA-MB-453	Monotherapy	2 mM	High dose Vitamin C inhibited invasion of breast cancer cell line by suppressing epithelial-mesenchymal transition (EMT)
Gan et al (21)	Breast	MDA-MB-231 and BT-549	Monotherapy	100 µM	Vitamin C inhibited triple-negative breast cancer progression by downregulating the key protein responsible for cancer metastasis
Sant et al (22)	Breast	MDA-MB-231, BT549, HCC1937	Monotherapy	100 µM	Low dose of vitamin C induced cancer cell death via apoptosis
Miles et al (23)	Skin	WM1366, WM9	Monotherapy	10-50 µM	The level of HIF-1α proteins responsible for cancer progression significantly reduced
Shin et al (24)	Skin	UCDK9M1, UCDK9M3, UCDK9M4, UCDK9M5	Monotherapy	20 mM	Vitamin C inhibited tumour growth and induced cell death due to the production of reactive oxygen species (ROS)
Mustafi et al (25)	skin	A2058	Monotherapy	100 µM	Vitamin C induced apoptosis on A2058 cancer cell by downregulation of clusterin expression
Yang et al (26)	skin	SK-MEL-28, A2058	Combination therapy with vemurafenib	1 – 5mM	Increased toxicity and efficacy of vemurafenib towards cancer cell
Mustafi et al (27)	Skin	A2058, SK-MEL28, SK-MEL2, C8161, 1205Lu	Combination with BET inhibitor drug	100 µM	Vitamin C synergized the anti-cancer effect of BET inhibitor drug
Gustafson et al (28)	Skin	RGP, SBcl2, WM35, VGP, WM278, WM3248, C8161, A2058	Monotherapy	0.1 mM	Low dose of vitamin C restore 5-hydroxymethylcytosine (5hmC) and reduce cancer invasiveness
Chen et al (29)	Skin	A 375	Monotherapy	0.6 Mm-1.4 mM	High dose of vitamin C induced cancer cell death via apoptosis
Pires et al (30)	Colorectal	C2BBe1, WiDr	Combination therapy with irinotecan, 5-fluorouracil and oxaliplatin	0.6 mM -17.71 mM	Combination therapy reduced the half-maximal inhibitory concentration all anti-cancer agents
Cho et al (31)	Colorectal	Sw620, Sw480, HCT15, HCT116, DLD-1, LoVo, CoLo-205, SNU-C4, SNUC5	Monotherapy	1 mM	high dose of vitamin C exerted the anti-cancer effect on cell lines with the high expression level of SVCT-2
Jung et al (32)	Colorectal	DLD1, SW480, SW620, HCT8, HCT116	Combination therapy with cetuximab	0.3 – 0.7 mM	Combination therapy selectively induced cell death towards cetuximab resistance cancer cells in SVCT-2 dependant manner
Pires et al (33)	Colorectal	C2BBe1, WiDr, LS- 1034	Monotherapy	2mM-20 mM	Vitamin C inhibited cancer proliferation in a dose-dependent manner and induced cancer cell death
Gong et al (34)	colorectal	HCT116	Combination therapy with sulindac	0.5 mM	Vitamin C and sulindac synergistically induced cell death of the cancer cell
Tian et al (35)	Colorectal	SW620, LoVo	Combination therapy with arsenic trioxide	1mM	Vitamin C and arsenic trioxide synergistically induce cancer cells death
Gerecke et al (36)	colorectal	HCT116	Combination therapy with decitabine and azacytidine	50 µM	Vitamin C synergized anti-cancer effect of decitabine and azacytidine by increasing tumour suppressor gene
Ohwada et al (37)	Oral cancer	HSC-4	Monotherapy	1 – 20 mM	Cell viability significantly suppressed
Baek et al (38)	Oral cancer	Hep2	Monotherapy	1-3 mM	Vitamin C induced significant cancer cell death
Zhou et al (39)	Oral cancer	CAL27, SCC9,SCC25	Monotherapy	0.3 – 0.6 mg/ml	Vitamin C promotes apoptosis and cell cycle arrest
O'Leary et al (40)	Gastric	AGS, MKN-45	Combination therapy with conventional cancer treatments and radiation	1-20 mM	Vitamin C enhanced the efficacy of several types of chemotherapeutics and radiation therapy
Lim et al (41)	Gastric	AGS	Monotherapy	1mM	Vitamin C induced significant cell death in AGS cell line
Gha et al (42)	Gastric	IBRC C 10071	Combination with Cisplatin	0.1 mg/mL	Vitamin C and cisplatin synergistically induced cancer cell death
Roberts et al (43)	Cervix	HeLa	Monotherapy	7-10 mM	7 mM and 10 mM of vitamin C induced cell death via an extrinsic and intrinsic apoptotic pathway
Leekha et al (44)	Cervix	SiHa	Combination therapy with cisplatin	5 mM	Vitamin C synergized the anti-cancer effect of cisplatin
Tsai et al (45)	Cervix	HeLa, SiHa	Combination with cisplatin and doxorubicin	1-10 mM	Vitamin C increase susceptibility of HeLa cells towards cisplatin and doxorubicin

Continue.....

Table II: Characteristics and outcomes of the included studies (continued)

Reference	Cancer type	Cell line	Application	vitamin C dose	Outcomes
Yiang et al (46)	Blood cancer	HL-60	Monotherapy	5 mM	Vitamin C inhibited cells growth and prevented cancer cells proliferation
Shenoy et al (47)	Blood cancer	DLBCL LY-1	Monotherapy and combination with doxorubicin and cisplatin	1 mM, 10 mM	High dose ascorbic acid chemosensitize cisplatin and doxorubicin via epigenetic mechanism. Monotherapy also exhibit cytotoxic effect through pro-oxidant pathway
Hosokawa et al (48)	Blood cancer	HL-60	Combination with radiation therapy	1mM, 5 mM	Combination therapy exerted enhanced cytotoxic effect
Fernandes et al (49)	Bone	G292	Monotherapy	1mM	High dose ascorbic acid exerted significant cytotoxic effect
Naohiro et al(50)	Bone	U20S, 143B	Combination with cisplatin	1 – 30 umol/L	Vitamin C reverse cisplatin resistant
Sajadian et al (51)	Liver	HLE, Huh7	Combination therapy with 5-azacytidine	1 mM	Enhanced cytotoxic effect of the anti-cancer agent
Rouleau et al (52)	Liver	Hep G2	Combination with sorafenib	5 mM	Vitamin C enhanced the anti-cancer effect of sorafenib
Lee et al (53)	lung	A549, Calu-3 and HCC827	Combination therapy with gefitinib	0.5 mM – 5mM	Vitamin C enhanced the cytotoxicity effect of gefitinib
Wei et al (54)	Prostate	LNCaP, PC3	Combination with radiotherapy	1 mM	Vitamin C reduced radiotherapy resistant and protect the normal cells from toxicity induced by radiotherapy
Alexander et al (55)	Pancreas	MIA PaCa-2, PANC-1	Combination with radiation therapy	5 mM	Vitamin C radio sensitized cancer cell line but protect the normal cell line
Gokturk et al (56)	Brain	U87MG (HTB-14)	Triple combination of vitamin C, etoposide and temozolomide	1 mM	Maximum effectiveness for cancer inhibition achieved with triple therapy
Somparn et al (57)	Bile duct	K 100	Monotherapy	0.5 mM-100 mM	High dose vitamin C induced significant cell death via apoptosis
Wang et al (58)	Breast and colon	Murine 4T1, CT26	Monotherapy and combination with cisplatin	200, 500 and 1,000 µg/ml	High dose monotherapy of vitamin C induced significant cell death via apoptosis. Combination therapy exerted enhanced cancer cell death
Hosokawa et al (59)	Epithelial	HT1080, SAS and A549 cells	Combination with radiation therapy	5 mM	Combination therapy exerted enhanced cytotoxic effect

Remarkable cancer cells death and reduction of malignant properties were regarded as the primary outcome, whereas, alteration of response in the drug/radiation-resistant cell line and synergistic effect were denoted as the secondary outcome. The main outcomes of vitamin C utilisation are summarized in Figure I.

Result of the studies

Results of the individual studies are summarized in Table II.

Primary outcome: significant cancer cell death

40 studies reported significant cancer cells death with 18 articles used vitamin C as monotherapy and 26 articles used vitamin C as a combination therapy. Two studies reported significant cancer cells death with low dose monotherapy of vitamin C in breast cancer cell lines and skin cancer cell lines (22,25). Meanwhile, 16 studies exhibited significant cancer cells death with high dose monotherapy of vitamin C. For combination therapy, 8 articles reported remarkable anti-proliferative effect with the combination of low dose vitamin C and 18 articles exhibited significant cancer cell deaths with the combination of high dose vitamin C (Table III).

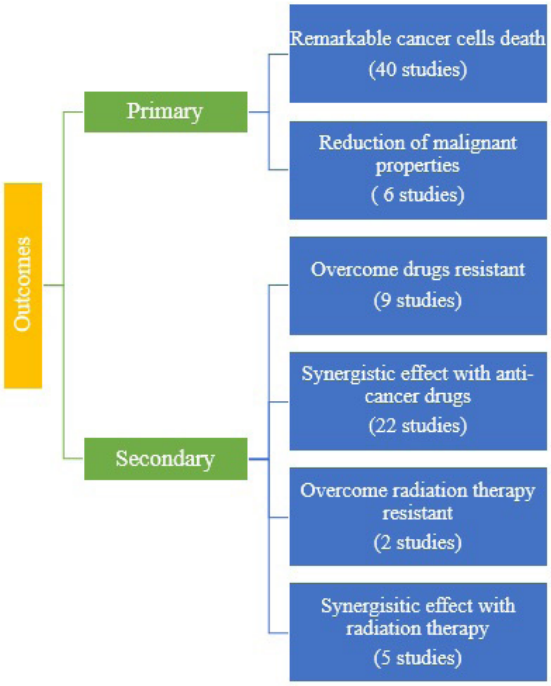

Figure 1: The main outcomes of vitamin C utilisation

Primary outcome: reduction of malignant properties

Six studies reported reduction of malignant properties (20,21,23,26,28,40). Three of the included studies showed a reduction of malignant properties with monotherapy of low dose vitamin C (21,23,28). Two studies involved skin cancer cell lines and one study involved breast cancer cell lines. Micromolar dose of vitamin C suppressed the level of HIF-1α proteins that responsible for cancer progression in metastatic skin cancer cell lines (23) and restore 5-hydroxymethylcytosine (5hmC) in various skin cancer cell lines that further reduce cancer invasiveness (28). The

micromolar dose of ascorbic acid also downregulated the key protein that responsible for metastasis of triple-negative breast cancer cell lines (21). Meanwhile, one studies utilized high dose vitamin C as monotherapy reported the downregulation of malignant properties in breast cancer cell line by suppressing epithelial-mesenchymal transition (20). Two studies reported significant inhibition of cancer cell invasion through in vitro invasion assay with combination therapy of high dose vitamin C and anti-cancer drugs namely in skin cancer cell lines and gastric cancer cell lines (26,40).

Secondary outcome: alter response in drug-resistant cell lines

Nine articles reported remarkable anti-proliferative effect against various chemotherapy-resistant-cancer cell lines with vitamin C treatment namely in breast cancer, skin cancer, colorectal cancer, blood cancer and bone cancer (17–19,26,30,32,33,47,50). Monotherapy of high dose vitamin C exerted significant cytotoxic effect against tamoxifen-resistant breast cancer cell line, docetaxel-resistant breast cancer cell line, doxorubicin-resistant breast cancer cell line, chemoresistant colorectal cancer cell line, and vemurafenib-resistant skin cancer cell line (18,26,33). Besides, a combination treatment of vitamin C with chemotherapeutic agents have been reported to overcome drug resistance in topotecan-resistant breast cancer cell line, methotrexate-resistant triple-negative breast cancer cell line, chemoresistant-colorectal cancer cell line and cetuximab-resistant in mutant KRAS colon cancer cell line (19,26,30,32). Two studies reported that a high dose of vitamin C increases the sensitivity of cisplatin-resistant cancer cells in bone cancer cell line and blood cancer cell line (47,50).

Secondary outcome: Alter response to radiation therapy

Two of the included studies utilized a combination of radiation with high dose ascorbic exhibited changes of response to radiation therapy in prostate cancer cell line and pancreatic cancer cell line (54,55). Both studies reported vitamin C sensitized radiotherapy and protect the normal cell from radiation injury.

Secondary outcome: Synergistic effect

The synergistic effect of vitamin C with anti-cancer agents have been reported in both low dose and high dose vitamin C. Vitamin C enhanced the efficacy of various chemotherapeutic agents towards cancer cells in the in vitro studies. The additive anti-cancer effect in combination of high dose vitamin C reported with eribulin mesylate, tamoxifen, fulvestrant, and topotecan in breast cancer cell line, combination with vemurafenib in skin cancer cell lines, combination with irinotecan, 5-fluorouracil, oxaliplatin, and arsenic trioxide in colorectal cancer cell lines, cisplatin, carboplatin, irinotecan, and paclitaxel in gastric cancer cell lines, combination with cisplatin in cervical cancer cell lines, combination with cisplatin and doxorubicin in blood cancer cell lines, combination with cisplatin in bone cancer cell lines and combination with azacytidine and sorafenib in the hepatocellular carcinoma cell line (18,19,26,30,35,40,42,44,45,47,48,51,52,54,56,58–60). Signifcant cancer cells death was observed with triple-therapy of high dose vitamin C with etoposide and temozolamide in brain cancer cell line (56). Eight studies reported the synergistic effect of anti-cancer agents with low dose vitamin C namely combination with doxorubicin and methotrexate in breast cancer cell lines, combination with epigenetic modulator drug that is BET inhibitor in skin cancer cell lines, combination with cetuximab, sulindac, azacitidine and decitabine in colorectal cancer, combination with cisplatin in bone cancer cell lines, and cell lines combination with gefitinib in non-small cell lung cancer cell (16,17,27,34,36,50,53,61). Synergistic effect of high dose vitamin C also has been documented with radiation therapy namely in gastric cancer, blood cancer, prostate cancer and epithelial cancer cell line (40,48,54,59). The application and outcomes of vitamin C utilisation in cancer treatment were summarized in Table III.

DISCUSSION

The overall aim of the scoping review was to investigate the effect of vitamin C utilisation in cancer treatment from the perspective of the in vitro studies. All in all, 44 studies were included and the results of the studies were classified into two outcome measures namely primary outcome and secondary outcome. primary outcome refers to chief consequences of vitamin C treatment meanwhile secondary outcome denotes the additional advantages generated as a result of the primary outcome. Remarkable cancer cells death and reduction of cancer cells invasiveness were regarded as the primary outcome, meanwhile, alteration of cancer cell resistance towards cancer treatments (chemotherapy and radiation therapy) and the synergistic effect were considered as the secondary outcome.

Remarkable cancer cells death has been reported in 40 studies out of 44 studies included. This outcome was observed in both monotherapy and combination with various cancer treatments. The major initiator of cancer cell death discovered from this review was the formation of a high level of reactive oxygen species particularly hydrogen peroxide in the cancerous cells. This effect is known as prooxidant activity and was studied specifically towards breast cancer, skin cancer, colorectal cancer, oral cancer, gastric cancer, cervix cancer, blood cancer, bone cancer, liver cancer, prostate cancer, pancreas cancer, blood cancer, bile duct cancer and epithelial cancer (Table III). Millimolar vitamin C (1 mM to 100 mM) behaves as a peroxide delivery system for the generation of sustainable free radicals with consequent oxidative damage to cancer cells (62). It is suggested that the cytotoxic effect of a high dose of vitamin C is cancer-selective due to differences in catalase activity in cancerous cell and normal cells. Catalase is known as

Table III: The application and specific outcomes of the included studies

Ref	Monotherapy or combination therapy	Application (low/high dose)	Cancer type	Primary outcome		Secondary outcome	
				Significant cancer cells death	Reduction of malignancy	Overcome cancer cells resistant	Synergistic effect
(16)	Combination	Low	Breast	✓ (epigenetic mechanism)			✓ (anti-cancer drug)
(17)	Combination	Low	Breast	✓ (ROS)		✓	✓ (anti-cancer drug)
(18)	Both	High	Breast	✓ (ROS)		✓	✓ (anti-cancer drugs)
(19)	Combination	High	Breast	✓ (ROS)		✓	✓ (anti-cancer drug)
(20)	Monotherapy	High	Breast		✓ (inhibit EMT)		
(21)	Monotherapy	Low	Breast		✓ (inhibit YAP1)		
(22)	Monotherapy	Low	Breast	✓			
(23)	Monotherapy	Low	Skin		✓ (inhibit HIFα)		
(24)	Monotherapy	High	Skin	✓ (ROS)			
(25)	Monotherapy	Low	Skin	✓			
(26)	Combination	High	Skin	✓ (ROS)	✓ (invasion assay)	✓	✓ (anti-cancer drug)
(27)	Combination	High	Skin	✓			✓ (anti-cancer drug)
(28)	Monotherapy	Low	Skin		✓ (restore 5HMC)		
(29	Monotherapy	High	Skin	✓ (ROS)			
(30)	Combination	High	Colorectal	✓ (ROS)		✓	✓ (anti-cancer drug)
(31)	Monotherapy	High	Colorectal	✓ (ROS)			
(32)	Combination	Low	Colorectal	✓ (ROS)		✓	✓ (anti-cancer drug)
(33)	Monotherapy	High	Colorectal	✓ (ROS)		✓	
(34)	Combination	Low	Colorectal	✓ (ROS)			✓ (anti-cancer drug)
(35)	Combination	High	Colorectal	✓ (ROS)			✓ (anti-cancer drug)
(36)	Combination	Low	Colorectal	✓ (epigenetic mechanism)			✓ (anti-cancer drug)
(37)	Monotherapy	High	Oral	✓ (ROS)			
(38)	Monotherapy	High	Oral	✓ (ROS)			
(39)	Monotherapy	High	Oral	✓ (ROS)			
(40)	Combination	High	Gastric	✓ (ROS)	✓ (invasion assay)		✓ (drug and radiation therapy)
(41)	Monotherapy	High	Gastric	✓ (ROS)			
(42)	Combination	High	Gastric	✓ (ROS)			✓ (anti-cancer drug)
(43)	Monotherapy	High	Cervix	✓ (ROS)			
(44)	Combination	High	Cervix	✓ (ROS)			✓ (anti-cancer drug)
(45)	Combination	High	Cervix	✓ (ROS)			✓ (anti-cancer drug)
(46)	Monotherapy	High	Blood	✓ (ROS)			
(47)	Both	High	Blood	✓ (ROS and epigenetic mechanism)		✓	✓ (anti-cancer drug)
(48)	Both	High	Blood	✓ (ROS)			✓ (radiation therapy)
(49)	Monotherapy	High	Bone	✓			
(50)	Combination	Low	Bone	✓ (ROS)		✓	✓ (anti-cancer drug)
(51)	Combination	High	Liver	✓ (epigenetic mechanism)			✓ (anti-cancer drug)
(52)	Combination	High	Liver	✓ (ROS)			✓ (anti-cancer drug)
(53)	Combination	Low	Lung	✓ (epigenetic mechanism)			✓ (anti-cancer drug)
(54)	Combination	High	Prostate	✓(ROS)		✓	✓ (radiation therapy)
(55)	Combination	High	Pancreas	✓ (ROS)			✓ (radiation therapy)
(56)	Combination	High	Brain	✓ (epigenetic mechanism)			✓ (anti-cancer drug)
(57)	Monotherapy	High	Bile duct	✓ (ROS)			
(58)	Both	High	Breast and colon	✓			✓ (anti-cancer drug)
(59)	Combination	High	Epithelial	✓ (ROS)		✓	✓ (radiation therapy)

ROS (reactive oxygen species), EMT (epithelial – mesenchymal transition), YAP1 (Yes-associated protein 1), HIFα (hypoxia-inducible factor α), 5HMC (5-hydroxymethylcytosine)

the enzyme responsible to protect the cell from damage by metabolizing the reactive oxygen species to safer compounds namely water and oxygen. Interestingly, catalase depletion has been documented in all cancer cells except human renal adenocarcinoma and normal healthy cells (18,37,63). Thus, the exposure of cancer cells to a millimolar dose of vitamin C would lead to cancer cells death as a result of the decreased metabolizing capacity of the reactive oxygen species.

Another primary advantage of vitamin C utilisation was the reduction of cancer cell invasiveness. This outcome has been reported in 6 studies notably in breast cancer, skin cancer and gastric cancer (20,21,23,26,28,40). Vitamin C served as an epigenetic modulator in several cancer cell lines. This effect was shown in both micromolar and millimolar dose of vitamin C in which independent of pro-oxidant activity. It was found that the cancer cells invasion and migration were determined based on the analysis of genes/proteins responsible for cancer progression or cell invasion assay. The dose of vitamin C responsible to inhibit cancer cells invasiveness is not similar to all cell lines even within the same cancer type. For example, high dose vitamin C (2 mM) have been reported to suppress the invasion of breast cancer cell by inhibiting epithelial-mesenchymal transition (EMT) (20). EMT is well associated with cancer invasion and metastasis (64). The cell invasion assay of this study verified that treatment of a high dose of vitamin C significantly reduced the cell migration meanwhile low dose vitamin C (10 μM) did not exert the effect (20). In contrast, downregulation of Yes-associated protein 1 (YAP1) oncogene was observed with a low dose of vitamin C (100 μM) in triple-negative breast cancer cell lines (21). Similarly, two studies reported the reduction of skin cancer invasiveness with a low dose of vitamin C (10-100 μM) via two different mechanisms namely downregulation of Hypoxia-Inducible Factors (HIF-1α) protein in metastatic melanoma cell lines (23) and restoration of 5- hydroxymethylcytosine (5-hmC) content in melanoma cells (28). High HIF-1α activity has been reported to be associated with poor prognosis in various cancers (13). Correspondingly depletion of 5- hydroxymethylcytosine (5-hmC) has been reported as the novel epigenetic hallmark of cancer cells. Meanwhile, another study using high dose vitamin C (1-5 mM) exhibited significant inhibition of melanoma cell invasion but not with a low dose of vitamin C (100 μM) (26).

Interestingly, vitamin C treatment either as monotherapy or combination therapy had a significant anti-proliferation effect on anti-cancer-drug-resistant cells. This effect was further regarded as a secondary outcome called alteration of cancer cell resistance towards cancer treatments. This effect was reported in 9 articles namely in breast cancer, skin cancer, colorectal cancer, bone cancer and blood cancer (17–19,26,30,32,50). The increment of cancer cell sensitivity towards the commonly used anti-cancer agents was observed with co-treatment of vitamin C and anti-cancer drugs. Three studies reported that the combination of micromolar vitamin C with methotrexate in triple-negative breast cancer, cetuximab in colorectal cancer and cisplatin in bone cancer restore the anti-cancer sensitivity in the chemoresistant-cancer cells respectively (17,32,50). Whereas, a high dose of vitamin C (1mM) enhanced the sensitivity of lymphoma cells towards commonly used anti-cancer agents in salvage lymphoma namely doxorubicin and cisplatin (47). The other five articles exhibited that reduction of chemotherapy-resistant cancer cell lines was achieved with a millimolar dose of vitamin C. Monotherapy with a millimolar dose of vitamin C exerted remarkable anti-proliferative effect in various chemoresistant cancer cell lines notably tamoxifen-resistant breast cancer cell line, docetaxel-resistant breast cancer cell line, doxorubicin-resistant breast cancer cell line, topotecan-resistant breast cancer cell line, vemurafenib-resistant skin cancer cell line, and chemoresistant colorectal cancer cell line (18,19,26,30,33). These studies reported that the cytotoxicity effect of high dose vitamin C towards various chemoresistant cancer cell lines was driven by the production of reactive oxygen species primarily hydrogen peroxide that subsequently generate cancer cells oxidative damage and death (18,19,26,30,33).

Besides, four studies reported similar outcome utilising a millimolar dose of vitamin C combined with radiation therapy namely in prostate, pancreas, blood and epithelial cancer cell line (48,54,55,59). High dose ascorbic acid sensitized radiotherapy towards cancer cell and protected the normal cell from radiation injury (54,55). It was found that the generation of a high concentration of reactive oxygen species suppress the expression of RelB protein in prostate cancer and upregulate the RelB expression in healthy normal cells. Downregulation of RelB resulting in suppression of oxidative defence capacity in the cancer cell and consequently enhance cancer cell sensitivity towards radiation therapy. In contrast, The high expression of RelB protein in normal cells increased the antioxidant capacity of the normal cell, thus protect the normal cells from radiotherapy (54).

Synergistic effect is an effect seen when the combination of vitamin C with chemotherapeutics or radiation therapy created an effect that is greater than either one of them could have exhibited by itself. Thus, in this review enhanced cytotoxic effect reported with combinations therapy against cancer cells was regarded as a synergistic effect. 26 articles reported the synergistic effect of vitamin C with various anti-cancer agents and radiation therapy (Table III). This effect observed in both micromolar and millimolar dose of vitamin C based on cancer cell lines. For illustration, the co-treatment of high dose ascorbic acid (1 mM) with an anti-cancer agent, topotecan in breast cancer cell lines. Ascorbic acid in which served as a hydrogen peroxide generator

enhanced the conversion of topotecan to topotecan free radical that augment the DNA damage and cell death resulting in a stronger anti-cancer effect (19). Meanwhile, low dose vitamin C (50 μM) synergized epigenetic drugs such as azacytidine and decitabine in colorectal cancer through an epigenetic mechanism by upregulating tumour suppressor genes in colorectal cell lines (36).

several studies manifested that each cancer cell lines presented a different effective cytotoxic dose of ascorbic acid (Table II). A study proposed that the effective cytotoxic dose of ascorbic acid depends on the expression of ascorbic acid tissue transporter that is sodium-dependent vitamin C transporter 2 (SVCT-2) in cancer cells as a result of 7 colorectal cell lines exhibiting differential responses to ascorbic acid. The cytotoxic effect of ascorbic acid is proposed to be proportional to the expression of SVCT-2 in cancer cells. High expression of SVCT-2 cancer cell lines require a low dose of ascorbic acid to induce cancer cell death compared to low expression SVCT-2 cancer cell line (31). Correspondingly, a study conducted on colon cancer cell lines reported the same results notably the most sensitive cancer cell line exhibited the highest expression of ascorbic acid transporter (33). Moreover, the theory of different in vitro cancer cell line having different effective cytotoxic ascorbic acid dose was supported by several other studies (31,33,43). Hence, the potential source of the inconsistent outcome pointed out in a recent systematic study (14) regarding the clinical use of ascorbic acid in cancer treatment was suggested to arise due to variability of cellular expression of ascorbic acid transporter on cancer cell which further leads to individual effective cytotoxic dose.

The multi outcomes generated by this study suggested that the outcomes of vitamin C utilisation may vary according to the dose of the ascorbic acid employed, the type of the cancer cell lines and the co-treatment with other agents either with anti-cancer agents or radiation therapy. Nevertheless, the promising outcomes reported from this study should be explored more specifically in the in vivo study to validate the potential role of vitamin C in treating cancer. The limitation of this study is, different articles have dissimilarity of study focus and may overlook other possible outcomes.

CONCLUSION

From the data gathered throughout this study, vitamin C has widely employed as an alternative as well as a complementary approach for the treatment of various cancer cell lines. This study manifested that the formation of high amount of hydrogen peroxide was regarded as the major initiator of cancer cell death and may lead to other secondary advantages. However, the effective dose of vitamin C against cancer cells differ according to cancer type yet even varies in different cancer cell lines. Nevertheless, vitamin C has shown a synergistic effect with different conventional anti-cancers and radiation therapy. The majority of the data support the favourable role of vitamin C in cancer treatment. Thus, it has the potential to become complementary cancer therapy in the future.

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