Original Article

Effect of fasting therapy in chemotherapy-protection and tumor-suppression: a systematic review

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Background: The role of fasting therapy in cancer treatment has been evaluated in a number of studies with controversial results reported. Relevant studies are systematically reviewed to comprehensively evaluate the effects of fasting therapy in chemotherapy-protection and tumor-suppression, and to provide assistance for the further clinical trials.

Methods: Electronic literature searches were conducted in PubMed, Web of Science, Embase and Cochrane Library. Studies were examined by two independent reviewers, and all eligible studies were included according to inclusion criteria.

Results: A total of 22 studies including 18 studies on mice and dogs, and 4 preliminary experiments on humans published from 2002 to 2016 were identified on chemotherapy-protection effects (n=10), tumor-suppression effects (n=15) and the relevant regulation in pathways (n=14). The methodologies and results of the studies were summarized and concluded in tables. Overall, fasting was found to have considerable effects in reducing chemotherapy side-effects (organ damage, toxic features, immunosuppression, reduced body weight and chemotherapy-induced death), suppressing tumor progression (tumor growth, metastasis, metabolic activity), and improving survival. Besides, fasting duration of longer than 48 hours was found to be crucial for exerting the effects of fasting therapy.

Conclusions: Overall, fasting may be a potentially feasible and effective option in cancer treatment to reduce chemotherapy side-effects, suppress tumor progression and further improve prognosis. Further prospective clinical trials with more patients included are still needed before fasting could be used in standard practice.

Keywords: Fasting therapy; nature therapy; cancer treatment

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Introduction

Cancer is the second leading cause of mortality worldwide and suspected to be the foremost killer in the coming decades by the World Health Organization (1). Cancer treatments including surgery, chemotherapy and radiotherapy has achieved considerable therapeutic efficacy, but damage to the normal tissue and the subsequent side-effects is inevitable, and the further improvement of prognosis is still challenging. Accordingly, besides the conventional therapy modalities, it is important to identify other assistant treatment methods to further enhance the therapeutic efficacy, reduce side-effects and improve prognosis. A growing number of recent studies in cancer

treatments have suggested that factors in the categories of naturopathic medicine such as physical activity (2-4), psychological emotion (5), and healthy diet (6,7) have a profound effect on the initiation and treatment outcomes of cancer.

Fasting therapy is a naturopathic treatment method that has been used as a valid therapeutic modality for acute and chronic diseases in traditional medicine worldwide. In a most recent study, Wang *et al.* confirmed that fasting was protective while nutritional supplementation was detrimental in mice with bacterial sepsis (8). As in cancer-bearing models, fasting therapy was reported to be a reproducible and efficient intervention strategy in protecting mammals against tumor and prolonging overall survival (9,10). Besides, the chemotherapy-protection effects of fasting therapy in reducing chemotherapy side-effects and related death were also suggested in experiments (11,12).

However, controversy still existed in this field with inconsistent results reported. Besides, studies focusing on this issue have not been systematically reviewed and summarized. Therefore, we performed the current systematic review to combine published studies and to comprehensively evaluate the potential effects of fasting therapy in chemotherapy-protection and tumor-suppression.

Methods

Comprehensive literature searches were conducted in PubMed, Embase, Web of Science and Cochrane Library with no restriction to language and date of publication. The last search was conducted on Jul 3, 2016. The search terms were as follows: ("fasting"(mesh) or "starvation"(mesh)) and ("tumor" or "neoplasm" or "cancer" or "sarcoma" or "malignancy" or "carcinoma") and ("prognosis" or "prognostic" or "predictive" or "survival" or "outcome" or "mortality" or "growth" or "progression" or " proliferation" or "size" or "weight" or "volume" or "metastasis" or "chemotherapy" or "side effects" or "vomiting" or "diarrhea" or "immunosuppression"). In addition, reference lists of identified studies were traced by Google Scholar for potential studies.

Assessment of eligibility was undertaken independently by two authors. Studies were eligible for inclusion if the following criteria were met: (I) peer-reviewed research articles based on animals or humans; (II) presented the correlations of fasting therapy with chemotherapy side-effects (e.g., weight loss, vomiting, nausea, diarrhea, fatigue, cardiac function, bone marrow suppression, and chemotherapy-induced death) or tumor progression results (e.g., tumor weight, growth rate, metastasis, metabolic activity, and survival time with tumor); (III) the fasting therapy should be launched with complete deprivation of food (articles investigating partial calorie restriction (CR) were excluded); (IV) the duration of time for one fasting should be at least 24 hours (articles investigating nightly fasting were excluded); (V) were in language of English.

The quality of included animal studies was assessed according to the ARRIVE guidelines (animal research: reporting in vivo experiments) (https://www.nc3rs.org.uk/arrive-guidelines), which are recommended for quality assessment of animal experiments. The items are based on the presence and description of several important study characteristics, including title, abstract, background, objectives, study design, ethical statement, experimental procedures, experimental animals, sample sizes, allocating animals to experimental groups, housing and husbandry, experimental outcomes, adverse events, statistical method, adverse events, interpretation/scientific implications, conflict of interest, and funding. For human studies, NOS (Newcastle-Ottawa Scale) scoring system (www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was used to assess the quality. Based on the quality of each publication in selection, comparability and exposure, a score with a maximum of nine points was appointed. Articles with six or more of the NOS scores were deemed as high quality and were included in the systematic review.

Data of interest were extracted independently by three authors. A Microsoft Excel sheet was designed to collect the following records: (I) basic information including first author, year of publication, experimental subject, tumor type and tumor inoculation method; (II) intervention strategies including chemotherapy regimens (when the chemotherapy is applied), fasting duration and fasting cycles; (III) outcome measures including chemotherapy side-effects and tumor progression data; and (IV) relevant regulations in pathways including changes in expression of effectors and the following alternations in pathways. Study results that were reported to be "statistically significant" reached P value <0.05 according to the original data.

Results

In the initial searches, a total of 1,218 articles were identified after duplicated removed. Then, 1,153 articles were

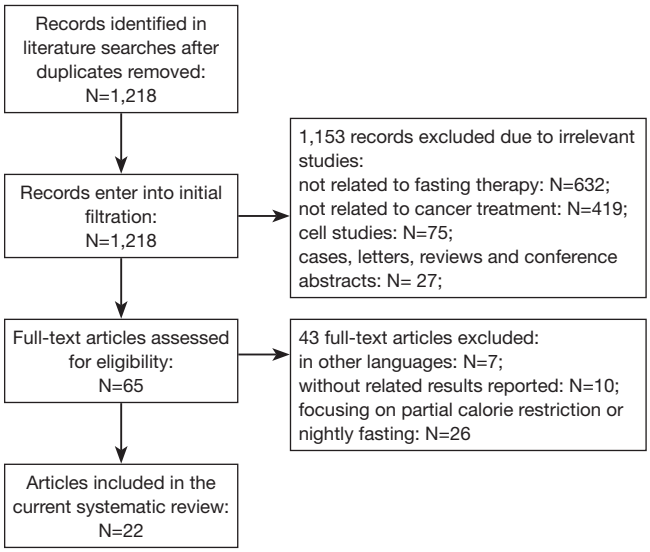

Figure 1 Flow diagram of study selection.

excluded due to irrelevant contents, including 632 studies not related to fasting therapy, 419 studies not related to cancer treatment, 75 studies on cells, and 27 cases, letters and conference abstracts. Among the remaining 65 studies, 43 were excluded after secondary full-text screening, including 7 studies in other languages, 10 studies without related results reported, and 26 studies focusing on partial CR or nightly fasting. Eventually, a total of 22 articles published from 2002 to 2016 were considered as eligible and included in the current systematic review (9-30) (*Figure 1*).

The basic characteristics of the 22 eligible studies are summarized in *Table 1*. The experimental subject was mice in 18 studies, dogs in one study; as one study with mice experiments also included a preliminary trial on human, a total of four studies evaluated the effects of fasting therapy on cancer patients. For the 19 animal studies, fasting duration of 24 to 72 hours was adopted in most of the studies. Besides experiments using non-cancer bearing models, animal models with heterogeneous tumor types were adopted, including colon cancer, pancreatic cancer, breast cancer, lung cancer, breast cancer, lymphoma, glioblastoma, astrocytoma and sarcoma. All the animal studies were randomized controlled trials, and reported the title, abstract, background, objectives, study design, ethical statement, experimental procedures, experimental animals, sample sizes, allocating animals to experimental groups, experimental outcomes, adverse events, statistical methods, and interpretation/scientific implications. As for the housing environment, 16 of the 19 (84.2%) animal studies mentioned it. The animal studies were in accordance with the ARRIVE guidelines. For the four human studies, as patients with different cancers were included, chemotherapy regimens were heterogeneous. Fasting cycles were also different according to each patient's clinical circumstances. All the human studies have more than six of the NOS scores.

The chemotherapy-protection effects of fasting therapy were summarized in *Table 2*. Overall, majority of the studies suggested satisfactory chemotherapy-protection effects of fasting therapy, which included reducing toxic features, relieving bone marrow suppression, restoring cardiac function and reducing chemotherapy-induced death. In addition, Dorff (13) and Cheng (20) suggested that, compared with 24-hour fasting group, 72-hour fasting group had more normal hematological examination results, less toxic features, and less DNA damaging. Besides, the only study that reported negative effects of fasting therapy in chemotherapy-protection adopted a fasting duration of 24 hours (19), which was consistent with the aforementioned studies (13,20) and indicated the significance of fasting duration in exerting its protection effects.

The tumor-suppression effects of fasting therapy were summarized in *Table 3*. Six studies did not combine fating therapy with chemotherapy, and almost all the studies reported less tumor growth rate, less metastasis and better survival in mice treated with fasting therapy than mice in the *ad libitum* feeding group. Nine studies combined fasting therapy with chemotherapy/radiotherapy, and seven studies reported significantly more favorable results including smaller tumor size, less metastasis, lower tumor metabolic activity and better survival in the combined treated group than mice only treated with chemotherapy/radiotherapy. The rest two studies found a trend of smaller tumor size in the combined treated group but did not reach significance.

For the relevant regulations in pathways during fasting therapy, effectors including IGF-1, p-Akt, IRS, BAD, mTOR, p-S6K and Ras that were involved in pI3K-Akt, mTOR and MAPK pathways were found to be down-regulated in mice with fasting therapy (9,16,17,20-22,28). Besides, the proliferation marker Ki-67 (16) and hypoxia-inducible factor (HIF) (28) which promote angiogenesis were down-expressed, while eIF2α (22) which attenuate protein synthesis and apoptosis marker casp-3 and casp-9 (22,28) were up-expressed in tumors of fasting mice. Under microscope inspection, tumor section of fasting mice showed less invasive and destructive features than that in *ad libitum* feeding mice (9).

Table 1 Characteristics of eligible studies included in the systematic review

Studies	Reference number	Experimental subject	Tumor type	Inoculation method	Fasting duration (hours)	Fasting cycle	Chemotherapy regimen
Animal studies							
Huisman 2016	(11)	6–8 wk male BALB/c mice	Colon cancer	5×10^5 C26 cells s.c. on the right flank	72	One fasting cycle	Irinotecan
Huisman 2015	(14)	27 wk Apc15lox mutant mice	Intestinal tumors	Spontaneously developed	72	One fasting cycle	Irinotecan
D'Aronzo 2015	(16)	5–6 wk female Nu/Nu mice	Pancreatic cancer	5×10^6 B×PC-3-luc s.c. in the right flank	24	One fasting cycle	Gemcitabine
Bianchi 2015	(18)	6 wk female BALB/c mice	Colon cancer	2×10^5 CT26 cells s.c in the lower back	48	Two fasting cycles with 4-day interval	Oxaliplatin
Caffa 2015	(17)	6–8 wk male BALB/c mice	Breast cancer	5×10^6 H3122 cells	48	Three fasting cycles with 1-week intervals	Crizotinib
		6–8 wk male BALB/c mice	Colorectal cancer	2×10^6 HCT116 cells	48	Three fasting cycles with 1-week intervals	Regorafenib
Withers 2014	(19)	Dogs	Lymphoma	Spontaneously developed	24	One fasting cycle	Doxorubicin
Cheng 2014	(20)	C57BL/6J mice	Non-cancer bearing	Non-cancer bearing	48	Six fasting cycles with 13-day intervals	Cyclophosphamide
Saleh 2013	(21)	6–8 wk female BALB/c mice	Breast cancer	5×10^4 67NR or 4T1 tumor cell into the mammary fat pad anterior to the rear leg	24	Alternative day fasting	Radiation therapy
Kawaguchi 2012	(23)	Adult GFP–LC3 transgenic mice	Non-cancer bearing	Non-cancer bearing	48	One fasting cycle	Doxorubicin
Chen 2012	(9)	6–8 wk female BALB/c mice	Lung, liver and ovary carcinoma	2×10^6 A549, HepG-2 or SKOV-3 cells s.c in the right hind foot paws	24 or 48	One fasting per week	None
Lee 2012	(22)	BALB/c, C57BL/6 mice	Neuroblastoma, breast cancer and ovarian cancer	CAN, MDA-MB-231 or OVCAR3 cells	48–60	One fasting cycle	Doxorubicin
Safdie 2012	(10)	12 wk male C57BL/6N mice	Glioblastoma	2×10^5 GL26 cells s.c in the lower back region	48	Two fasting cycles with 1-week interval	Temozolomide
		12 wk male C57BL/6N mice	Glioblastoma	1×10^4 GL26luc cells intracranial in the right frontal lobe of the skull	48	Two fasting cycles with 1-week interval	Temozolomide
		12 wk male C57BL/6N mice	Glioblastoma	2×10^5 GL26 cells s.c in the lower back region	48	Two fasting cycles with 1-week interval	Radiation therapy

Table 1 *(continued)*

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Studies	Reference number	Experimental subject	Tumor type	Inoculation method	Fasting duration (hours)	Fasting cycle	Chemotherapy regimen
Lee 2010	(25)	CD1 mice	Non-cancer bearing	Non-cancer bearing	48	One fasting cycle	Doxorubicin
Thomas 2010	(24)	7–8 wk male CB-17 mice	Prostate cancer	1×10^5 LAPC-4 tumor cells s.c in the right flank	24	Mon. and Thurs. fasting per week	None
Buschemeyer 2010	(26)	6 wk male SCID mice	Prostate cancer	1×10^5 LAPC-4 cells s.c in the flank	24 or 48	One fasting per week	None
Marsh 2008	(28)	14 wk male C57BL/6J mice	Astrocytoma	1 mm^3 CT-2A tumor implanted intracranial into the right cerebral hemisphere	24	Alternative day fasting	None
Raffaghello 2008	(12)	A/J mice	Non-cancer bearing	Non-cancer bearing	48	One fasting cycle	Etoposide
		A/J mice	Neuroblastoma	2×10^5 NXS2 tumor cells s.c	48	One fasting cycle	Etoposide
Descamps 2005	(29)	8 mo female OF1 mice	Lymphoma	Spontaneously developed	24	Alternative day fasting	None
Berrigan 2002	(30)	9 mo p53-deficient mice	Sarcoma and lymphoma	Spontaneously developed	24	One fasting cycle per week	None
Human studies							
Dorff 2016	(13)	Human	Heterogeneous cancer types	–	24, 48 or 72	Most 1–2 fasting cycles	Heterogeneous chemotherapy
de Groot 2015	(15)	Human	Breast cancer	–	48	Six fasting cycles with 21-day intervals	Docetaxel, Adriamycin and Cyclophosphamide with G-CSF
Cheng 2014	(20)	Human	Heterogeneous cancer types	–	24 or 72	–	Platinum-based drug
Safdie 2009	(27)	Human	Heterogeneous cancer types	–	36 to 180	1–8 fasting cycles	Heterogeneous chemotherapy

F group, fasting group; AL group, *ad libitum* feeding group; wk, week; mo, month; s.c, subcutaneously.

Table 2 Chemotherapy-protection effects of fasting therapy

Studies	Reference number	Chemotherapy-protection results
Animal studies		
Huisman 2016	(11)	Toxic features: AL group—oxic diarrhea (P<0.001), less active (P=0.003), hunchback posture (P<0.001) and ruffled coat (P<0.001); F group—none of these visible side effects; WBCs: significantly higher blood leukocyte count in F group than AL group. Weight: AL group—substantial weight loss initially after irinotecan injection; F group—transient weight loss during fasting, but gradually recovered to the initial level after irinotecan injection (refeeding began at the same time)
Huisman 2015	(14)	Toxic features: AL group—oxic features: AL grouping fasting, but gradually recovered to the initial le, ruffled coat (P<0.001); F group—group features visible side effects; WBCs: significant reduction in leukocyte numbers in AL group compared with F group (3.4±0.6×10^6/mL *vs.* 6.6±0.7×10^6/mL). Weight: AL group—mL; Weigh ±1.9% during fasting period, showed weight loss following the first irinotecan injection, and lost 22.1±3.7% at the end of the experiment; weight loss was 22.5±3.0% during fasting, but gained weight following the first irinotecan injection (refeeding started at the same time) and at the end of the experiment the weight had returned to the baseline level (94.8±3.5% of the initial level)
Withers 2014	(19)	Vomiting: 6 of 9 (67%) in AL group compared to 1 of 10 (10%) in F group (P=0.02); toxic features: no difference in the score of nausea (P=0.81), appetite (P=0.70), diarrhea (P=0.10), activity (P=0.64) between the two groups; blood examinations: no difference in the incidence of neutropenia (P=0.14) and thrombocytopenia (P=0.30) between the two groups
Raffaghello 2008	(12)	Chemotherapy induced death: 43% death rate in AL group, compared to 5.8% in F group (P<0.005); toxic features: AL group—chemotherapy induced death: 43% death rate in AL group, coF group—no visible signs of stress or pain; weight: AL group—lost 20% of their weight after etoposide treatment; F group—lost 20% of weight during fasting, regained most the weight in the 4 days after chemotherapy (refeeding started at the same time)
Cheng 2014	(20)	Bone marrow suppression: AL group—WBC suppression, especially the number of lymphocytes, persisted for more than 70 days; F group—return of lymphocytes to normal levels after day 56, and have normal ratios of lymphoid and myeloid cells (L/M); DNA damage: decreased DNA damage caused by cyclophosphamide in F group than AL group; chemotherapy induced death: 60% in AL group; 0% in F group (P<0.05); HSPCs self-renewal: 6-fold increase of newly generated HSPCs in F group than AL group (P<0.05)
Kawaguchi 2012	(23)	Left ventricular cavity: significant enlargement of the left ventricular cavity in AL group (LVDd: 3.9±0.25 mm) than F group (LVDd: 3.4±0.31 mm); cardiac function: significant signs of reduced cardiac function, i.e., increased left ventricular end-diastolic pressure and decreased left ventricular ejection fraction, in AL group compared with F group
Lee 2010	(25)	Chemotherapy induced death: 62% in AL group; 0% in F group (P<0.05)
Human studies		
Safdie 2009	(27)	Toxic features: a reduction in fatigue, weakness and gastrointestinal side-effects in F group compared to AL group
de Groot 2015	(15)	Bone marrow suppression: significantly higher mean erythrocyte-counts (P=0.007) and thrombocyte-counts (P<0.001) 1 week post-chemotherapy) in the F group compared to the A group
Cheng 2014	(20)	Bone marrow suppression: 72 hour fasting group but not 24 hour fasting group showed normal lymphocyte counts and maintenance of a normal lineage balance in WBCs
Dorff 2016	(13)	Toxic features: less fatigue, nausea, vomiting, constipation and peripheral neuropathy in 48 and 72 h fasting group compared to 24 h fasting group; DNA damage: 24 h fasting group continued to have evidence of increased DNA damage; decreased chemotherapy-induced DNA damage in 48h and 72h fasting group

F group, fasting group; AL group, *ad libitum* feeding group.

Table 3 Tumor-suppression effects of fasting therapy

Studies	Reference number	Tumor-suppression results
Studies not combining fating therapy with chemotherapy/radiotherapy		
Berrigan 2002	(30)	Metastasis: AL group—13/32 (40%); F group—8/31 (26%) (P<0.05); survival: 313 (SD =17) days in AL group; 357 (SD =23) days in F group (P<0.05)
Descamps 2005	(29)	Survival: significantly better in F group (100% till end of experiments) than AL group (66.7%) (P<0.001)
Marsh 2008	(28)	Tumor weight: 70% less in F group (57.3 mg) than in the AL group (188.2 mg) (P<0.05); tumor growth rate: 63% lower in the F group than in the AL group (7.2±1.0% day-1 for the F group versus 19.2±3.6% day-1 for the AL group, P<0.05); survival: higher survival rate in the F group (50%) than the AL group (12.5%) (P<0.05)
Buschemeyer 2010	(26)	Survival: a trend to better survival in 24 h- and 48 h- F group than AL group
Thomas 2010	(24)	Tumor volume: no significant difference in tumor volume between the two groups (P=0.58); survival: no significant difference in survival between the two groups (P=0.37)
Chen 2012	(9)	Survival: 100% in 48 h F group, 62.5–68.75% in 24 h F group, and 31.25–37.5% in AL group (P<0.05); tumor regression rate: 48 h F group: 50% *vs.* 24 h F group: 12.5% *vs.* AL: 0% (P<0.05); tumor volume: 48 h F group: 243.5 mm^3 *vs.* 24 h F group: 1,072.7 mm^3 *vs.* AL group: 1,602.3 mm^3 (P<0.05); lung metastasis rate: 48 h F group: 6.25% *vs.* 24 h F group: 37.45% *vs.* AL group: 100% (P<0.05); multi lung metastasis rate: 48 h F group: 0% *vs.* 24 h F group: 25% *vs.* AL group: 100% (P<0.05); lymph node metastasis rate: 48 h F group: 12.5% *vs.* 24 h F group: 50% *vs.* AL group: 87.5% (P<0.05)
Studies combining fating therapy with chemotherapy/radiotherapy		
Raffaghello 2008	(12)	Survival: significant better in F/Eto group than AL/Eto group
Lee 2012	(22)	Tumor size: significant smaller tumor size in F/DOX group than AL/DOX group; tumor metabolic activity: significant reduction in bioluminescence in F/DOX group than AL/DOX group; metastasis: significant less metastases in F/DOX group than AL/DOX group
Safdie 2012	(10)	Tumor size: AL/TMZ group—1,882 mm^3; F/TMZ group—340 mm^3 (P<0.05); survival: AL/TMZ group—40.3%; F/TMZ group—83.3% (P<0.05); tumor metabolic activity: significantly lower metabolic activity in F/TMZ group (1×104 photons/sec) than AL/TMZ group (4×105 photons/sec) detected by bioluminescence imaging; tumor size: AL/RT group—2,074 mm^3; F/RT group—1,204 mm^3 (P<0.05); survival: AL/RT group—33.3%; F/RT group—85.0% (P<0.05)
Saleh 2013	(21)	Tumor growth: 16% and 30% average growth delay in F group compared with AL group (P<0.05); pulmonary metastasis: delayed breathing difficulties caused by pulmonary metastatic tumors in F group than AL group (P<0.05)
Caffa 2015	(17)	Tumor volume: AL/Criz group—472 mm^3; F/Criz group—269 mm^3 (P<0.05)
Bianchi 2015	(18)	Tumor volume: AL/OXP group—206.7 mm^3; F/OXP group—126.3 mm^3; tumor metabolic activity: significantly lower average glucose consumption in F/OXP group (48.5 $nMol \times min^{-1} \times gr^{-1}$) than AL/OXP group (70.2 $nMol \times min^{-1} \times gr^{-1}$) detected by micro-PET
D'Aronzo 2015	(16)	Tumor weight: AL/Gem group—1.2 g; F/Gem group—0.9 g (P<0.05); tumor metabolic activity: significant lower metabolic activity in F/Gem group than AL/Gem group detected by bioluminescence signaling
Huisman 2015	(14)	Trends to be smaller tumor size in F/Irino group than AL/Irino group
Huisman 2016	(11)	Trends to be smaller tumor size in F/Irino group than AL/Irino group

F group, fasting group; AL group, *ad libitum* feeding group; Eto, etoposide; Dox, doxorubicin; TMZ, temozolomide; RT, radiation therapy; Criz, crizotinib; Reg, regorafenib; OXP, oxaliplatin; Gem, gemcitabine; Irino, irinotecan.

Discussion

Nutrient deprivation encompasses several forms of dietary restriction including CR and fasting. CR commonly described a reduction in calorie intake by 20–40%, and it can also refer to more or less strict calorie limitation, or reduced or lack of some particular components of the diet (31,32). Fasting is another form of dietary restriction, which refers to the complete lack of food or calorie intake for a period. The fasting duration usually lasts for 24 to 120 hours, followed by the refeeding period, during which the *ad libitum* to food was permitted, thus forming a cycle. When fasting protocols contain cycles of fasting, it is called as intermittent fasting (IF). Generally, CR is more studied than fasting in treating tumors, partly due to that a common therapeutic goal in cancer treatment is trying to avoid excess weight loss to counteract wasting syndromes, and that CR which avoided massive fluctuations in dietary intake was initially believed to be more tolerated and causing less side-effects in cancer patients. However, a growing number of recent studies have demonstrated that fasting may be a more advisable choice for nutrient deprivation in these patients, for which the reasons are listed as the followings.

Firstly, gradual and continuous loss of body weight is commonly seen in CR, which could cause the weakening of the immune system (33-35). On the contrary, although the weight loss during fasting was substantial, it was temporary and the weight would regain to the initial level during *ad libitum* refeeding in the post-fasting period. In fact, no remarkable difference in total food consumption was observed between fasting mice and *ad libitum* feeding mice in the control group (9,29,30,36), indicating that the efficacy of fasting did not really depend on the calorie deprivation. Secondly, fasting may be more efficient than CR in forming a protection effect. After undergoing CR or fasting for the same time, metabolic parameters such as blood glucose level and IGF-1 level in fasting mice were significantly lower (25,37-39), indicating that fasting is less time-consuming and more efficient than CR. Thirdly, compliance remained an issue in CR because it required the reduction of caloric intake for extended periods of time, whereas fasting therapy could be well implemented and tolerated in cancer patients, although it may be psychologically uncomfortable in some cases (27,40). Therefore, fasting therapy cold avoided the common weight loss in CR, meanwhile having a more efficient effect and a better compliance. Accordingly, we conducted the current systematic review to combine published studies in this field and to comprehensively evaluate the effects of fasting therapy in cancer treatment.

Chemotherapy treatment often relies on the combination of several DNA-damaging drugs such as etoposide, doxorubicin and cyclophosphamide. Although these agents are generally much more toxic to cancer cells than normal cells, the damage to normal tissues is inevitable, possibly leading to intestinal, hematological and systemic toxicities including diarrhea, vomiting, fatigue, myelosuppression, and in some cases chemotherapy interruption and even death (41,42).

In recent studies, pre-chemotherapy fasting was found to have a promising effect on protecting mammalian cells from chemotherapeutic toxicities. Raffaghell reported that mice that have been starved for 48–60 hours showed no visible signs of toxicity under 80 to 110 mg/kg doses of etoposide, which was nearly three times of the maximum allowable concentration of etoposide in humans (30–45 mg/kg). In contrast, the mortality rate of *ad libitum* feeding mice was over 40%. More interestingly, while the etoposide application caused a 20–40% weight loss in *ad libitum* feeding mice, the fasting mice gained back most of the weight loss that was lost during fasting in only 4 days after the chemotherapy initiation (12). Similarly, Kawaguchi found that, after doxorubicin treatment, *ad libitum* feeding mice suffered a more significant cardiac deterioration characterized by enlargement of ventricular cavity and reduced cardiac function compared with mice that was pre-starved for 48 hours, while the fasting itself had no effect on cardiac function in the saline group (23). In addition, consistent results were also reported in other studies that chemotherapy toxic features including lower activity, hunched-back posture, ruffled coat, diarrhea and leukopenia were much more significant in *ad libitum* feeding mice than fasting mice with a 48- to 72-hour starvation (11,14,20,25).

Apart of the aforementioned mice experiments, the chemotherapy-protection effects were also evaluated in dogs and humans, and moreover, these studies may have indicated the importance of the duration of fasting. As reported by Withers (19), the rates of nausea, diarrhea, lower activity, neutropenia, thrombocytopenia and IGF-1 levels showed no difference between fasting dogs and *ad libitum* feeding dogs, which were inconsistent with the aforementioned studies. One of the major differences was the fasting duration, which was 24 hours in the study and at least 48 hours in other studies (*Table 1*), indicating a potential impact of fasting duration on its efficacy. Interestingly, Dorff conducted a study on cancer patients which included three cohorts fasted for 24, 48 and 72 hours

before chemotherapy. The study suggested that patients in the 48- or 72-hour fasting group had significantly lower rate of chemotherapy toxicities with decreased DNA damaging compared with the 24-hour fasting group (13). Similar results were also reported by Cheng that normal lymphocyte counts and normal lineage balance of WBCs were observed in cancer patients with 72-hour fasting but not found in those with 24-hour fasting (20). Although species differences between mice and dogs or human beings could influence the outcomes of fasting therapy, these studies still highlight that the 24-hour fasting period may be insufficient to exert the chemotherapy-protection effects.

In addition to chemotherapy-protection effects, it was found that fasting therapy had remarkable effects in inhibiting tumor progression. The tumor size in mice treated with IF alone could be comparable to that in mice underwent two or three cycles of chemotherapy (10,22), which indicated that IF may be as effective as chemotherapeutic agents in delaying tumor growth. When compared to al libitum feeding mice, the tumor size or weight in mice under IF were significantly smaller (*Table 3*).

The effects of fasting therapy in inhibiting tumor metastasis were also remarkable. Berrigan reported a multiple tumor rate of 26% in mice that underwent IF compared to 40% in *ad libitum* feeding mice 4 weeks after tumor cell inoculation (30). Similarly, Chen found that the lung metastasis rate was 100% in *ad libitum* feeding mice and all were multiple lung metastases, whereas the rate was only 6.25% in mice that underwent IF and none had a multiple metastasis (9). As fasting mice trend to have favorable results in tumor growth and metastasis, almost all the included studies reported significantly better survival in mice with fasting therapy alone than *ad libitum* feeding mice (*Table 3*).

When fasting therapy was coupled with chemotherapy, the anti-tumor effect of chemotherapeutic drugs was observed to be increased. Among the nine studies combining chemotherapy with fasting therapy on mice, seven studies reported significantly more favorable outcomes including smaller tumor size, less metastases and better survival than those with chemotherapy alone (*Table 3*). Besides, four studies detected tumor metabolic activity by bioluminescence imaging and micro-PET imaging, all found that the tumor metabolism was significantly lower in combined treatment group (10,16,18,22). In addition to the conventional chemotherapy regimens, the combination of IF with tyrosine kinase inhibitors (TKIs) such as Crizotinib or Regorafenib also could achieve significantly better therapeutic effects (17), suggesting IF as a potential means to enhance the activity of TKIs in clinical practice. Thus, a synergistic effect could be formed by combining chemotherapy with fasting therapy, which would achieve a more satisfactory therapeutic outcome than utilizing either of the individual treatment method alone.

One point that needs to be mentioned is the refeeding protocol during the post-fasting period. All the included studies did not limit the food intake during refeeding. The overfeeding is common in the period and the weight of mice generally would regain to their initial levels. In fact, after completing a whole fasting cycle, the total food consumption between fasting mice and *ad libitum* feeding mice was similar. Thus, it seems that the effects of fasting therapy were not really dependent on the calorie deprivation. There still lack of study that limits the calorie intake of refeeding to the same as age-matched *ad libitum* feeding mice, thus preventing the overfeeding. Whether the sufficient calorie supply in the whole fasting therapy cycle is necessary in exerting its effects still remains a question, and it needs to be clarified in future studies, which would help us to further understand the action processes of fasting therapy.

The chemotherapy-protection mechanisms of fasting therapy were partly correlated with the viewpoint that normal cells would rearrange the energy intake into maintenance pathways instead of growth and reproduction during fasting, enhancing resistance to the environment. Fasting was correlated with reduced levels of IGF-1, p-Akt, IRS, BAD, mTOR, p-S6K and Ras, which are effectors involved in several important pathways including PI3K-Akt, mTOR and MAPK pathways (9,16,17,20-22,28). Through this, growth factors and proliferation signals drop during fasting, and normal cells which require these factors and signals for proper growth and reproduction would redistribute the limited resource to maintain survival and turnoff unnecessary energy expenditures including synthesis, growth and proliferation. However, cancer cells are self-sufficient of growth factors due to mutations in proto-oncogenes, which could enable cancer cells to proliferation independently and show no response to the stressed conditions (43).

As effects of chemotherapy drugs were correlated with metabolic activity of cells, fasting mice with lower metabolic levels would suffer less impact of chemotherapy regimens to the normal cells, thus reducing side-effects. Besides, fasting was found to play a crucial role in protecting hematopoietic stem cell from chemotoxicity, promoting

its self-renewal and regeneration, and thus reversing the immunosuppression (20). As a result, mice under fasting therapy which had less chemotherapy-induced side effects showed a higher tolerance to chemotherapy regimens, and it seems that higher doses of chemotherapy regimens could be applied if fasting therapy was combined with the chemotherapy. Thus, whether the combination with fasting therapy could raise the upper limits of tolerable chemotherapy doses, and whether the methods could achieve a higher tumor control rate may be promising directions for future researches.

As the normal cells and cancer cells exhibit differential stress resistance to fasting, it is likely that cancer cells are more sensitive to the extreme environments for their inability to timely adjust metabolism pathways. The intratumoral HIF was down-expressed in fasting mice (28), which indicated decreased tumoral angiogenesis processes under fasting condition. Besides, cancer cells in mice with fasting therapy showed significant decreased activity, which was suggested by down-expression of proliferation marker Ki-67 (16), up-expression of eIF-2α that impairs protein synthesis (22), and up-expression of apoptosis marker casp-3 and casp-9 (22,28). In addition, microscopical findings by Chen showed that local tumor nests in *ad libitum* feeding mice were faster growing with invasive and destructive features, whereas tumor nests in fasting mice underwent pyknosis and shrinking (9), which could further provide morphological evidence of tumor-suppression effects of fasting therapy.

Currently, studies investigating fasting therapy on cancer patients are limited, with only 10 to 20 patients included in each study, and all were in the stage of evaluating safety and chemotherapy-protection effects of fasting therapy (13,15,20,27). The tumor-suppression effects of fasting, e.g., its influence on tumor growth, metastasis and prognosis of patients, have not been evaluated until now.

On the other hand, the appliance of fasting therapy on cancer patients should be with caution and needs to be more firmly established. The patients with diabetics and the very old may should avoid fasting therapy, and whether fasting therapy would reinforce cachexia should also be assessed. Another point that needs to be paid attention is the fasting duration. In the systematic review, we inferred that fasting duration of 24 hours may be insufficient for exerting the chemotherapy protection effects of fasting therapy. However, overlong fasting duration should also be avoided for the possible severe calorie insufficiency and weakening of the body. The length of fasting duration is like a cost-benefit ratio, and exploring an optimal fasting duration may be a promising way for future studies. Moreover, the effects of fasting therapy could be influenced by the tumor types and the applied chemotherapy drugs. Combined with what chemotherapy drugs and treating what tumor types could maximize the effects of fasting therapy are still largely unknown, and it needs to be clarified by future studies.

It needs to be mentioned that studies about the Ramadan fasting is not included in the current systematic review, for it usually lasts for about 12 hours per cycle and the water is also forbidden during fasting, which is not in accordance with our inclusion criteria. However, the influence of Ramadan fasting in cancer patients should be paid attention, for that very few studies have been carried out focusing on this issue (44). Investigating the correlation between Ramadan fasting and cancer treatment not only could provide a new way to further understand the mechanisms of fasting therapy, but also could help physicians to properly advise cancer patients fasting in Ramadan (44).

Overall, fasting therapy may have effective chemotherapy-protection and tumor-suppression effects in mammals, and may be a feasible option in cancer treatment to further improve prognosis. Future well-designed clinical trials are still needed before fasting therapy could be used in standard practice.

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Footnote

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