Journal of Berry Research 10 (2020) 21–44
DOI:10.3233/JBR-190412
IOS Press

Review

Berries and their components on the prevention of myelodysplastic syndromes (MDS): A review on human clinical trials

Carla Elena Echeveste*

Department of Medicine, Division of Hematology and Oncology, Medical College of Wisconsin, Watertown Plank Rd, Milwaukee, WI, USA

Received 19 March 2019; accepted 22 April 2019

Abstract. Myelodysplastic syndromes ("MDS"), is a group of hematopoietic stem cell disorders that can progress to acute myeloid leukemia. MDS is most commonly found in the aging and elderly population with a 35% 3-year survival rate. With a limited etiological understanding of MDS, and a fast disease progression, patients with MDS may benefit from an increased intake of fresh berries, natural foods, vegetables or products packed with an abundance of vitamins. As of recently, completed and new clinical trials are currently underway to establish an inverse correlation between increased fruit consumption, specifically a berry intake with a generalized decrease in associated symptoms and an overall improved quality of living. In this special review, the author examined current completed and actively recruiting clinical trials focusing on MDS and the use of berries and their components such as vitamins, and any natural product intervention with the treatment of MDS. This review combined the comprehensive results of human clinical studies to arrive at a common trend in this area, supplemented with published studies. Despite the current information available, indicating minimal correlation or strongly suggesting more comprehensive studies, additional clinical trials using berries may prove to be useful and necessary as an intervention or as an alternative therapeutic supplement to remedy the patient's ailment.

Keywords: Myelodysplastic syndromes, berries (*), vitamins, black raspberries, fruits, cancer, review, human clinical trials

1. Introduction

Myelodysplastic syndromes (MDS), is a group of bone marrow and blood disorders [1]. In patients with MDS, their stem cells lack the ability to mature leading to an increased abundance of immature and dysplastic cells. Mature, healthy cells flowing through the blood decrease in count, and cause the bone marrow to halt its function or work ineffectively. The cascade effect is such that there is a decreased red and white blood cell count leading to additional health issues, including but not limited to anemia, thrombocytopenia and neutropenia. As a result, the white blood cells are deemed ineffective at their function and could result in abnormal bone marrow chromosomal cells. The MDS subtypes may undergo additional molecular changes and become acute myeloid leukemia (AML), with about a third of patients developing AML. In this form of cancer (AML), blasts, or immature cells, grow at a rate that is not controlled and lead to further hematological complications.

*Corresponding author: Carla Elena Echeveste, BA, Department of Medicine, Division of Hematology and Oncology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI, 53226, USA. Tel.: +1 414 403 7499; E-mail: cecheveste@mcw.edu.

1878-5093/20/$35.00 © 2020 – IOS Press and the authors. All rights reserved

According to the Surveillance, Epidemiology, and End Results (SEER) Program, about 86% of patients with MDS are diagnosed at or around 60 years or greater with an average, median age at diagnosis of 76 years old [1]. Within the United States, between 2007-2011, the incidence of MDS is estimated to be between 5.3–13.1 for every 100,000 cases [2]. As the population ages, the incidence of MDS for every 100,000 patients increases. For patients aged 65 or greater, MDS incidence is predicted to be between 75 to 162 for every 100,000 cases, whereas MDS prevalence within the United States is projected to be 60,000–170,000 with a steadily increasing estimate [2]. Regarding age as an inclusive factor, MDS is not common in people who are younger than 50 years of age, with MDS becoming more common in people who are 70 years of age or greater. Unfortunately, patients with MDS have a shorter lifespan as a result of infection or bleeding, or after MDS becomes AML.

Further risk factors that compound MDS include radiation exposure, obesity, and viral infections [3]. The 2007 Report by the World Cancer Research Fund/American Institute for Cancer Research found no association between an intake of vegetables and fruit and any type of cancer [3]. However, there was only suggestive or probable evidence rendering a protective effect implying added or benefits yet to be uncovered.

With these parameters established, deficit of conclusive information and studies, it is of utmost value to research the connection between nature products, berries, and vitamins in the prevention of MDS through a comprehensive review of relevant findings. The aim in this review is to find the most current findings on MDS, specifically in human clinical trials. This was achieved through a comprehensive global search, all in order to establish an association between an increased intake of natural products and MDS.

2. Materials and methods

2.1. Search strategy and determining eligibility of human clinical trials

This review was completed first by determining eligible English publications retrieved from the National Institutes of Health (NIH) United States (U.S.) National Library of Medicine Clinical Trials https://www.ClinicalTrials.gov which is a clinical trials registry. This registry is the "largest clinical trials database and currently has over 230,000 trials from 195 countries in the world" [4].

Publications deemed eligible and in the English language were retrieved using the following search filters: under "Condition or disease" the search term was ((MDS)), a term that was auto-populated and affiliated with Myelodysplastic Syndromes AND under the "Other terms" to narrow down the search, the two terms entered, separately, were ((vitamins)) and ((berries)). Only "vitamins" and "berries" were entered to identify any available human clinical trial. The end search date was 07 March 2019 with no start search date in an effort to retrieve any and all studies. The author only analyzed English and Spanish studies. To maximize the amount of information and to identify relevant articles, reference lists and primary studies were cross-referenced to arrive at an aggregated list.

3. Results

3.1. Data extraction

The retrieved articles from ClinicalTrials.gov under the aforementioned search criteria gathered thirty-five clinical trials and only one recruiting human clinical trial when the search terms "MDS" and "berries" was used. For the purpose of this review, the results were further separated into two additional categories based on their status, namely "Recruiting" status and "Completed" status. "Recruiting" status clinical trials rendered seven results under "MDS" and "vitamins" while "Completed" status clinical trials rendered seventeen results. This schematic can be seen on Figure 1 and Figure 2 below. The total worldwide eligible articles based on search

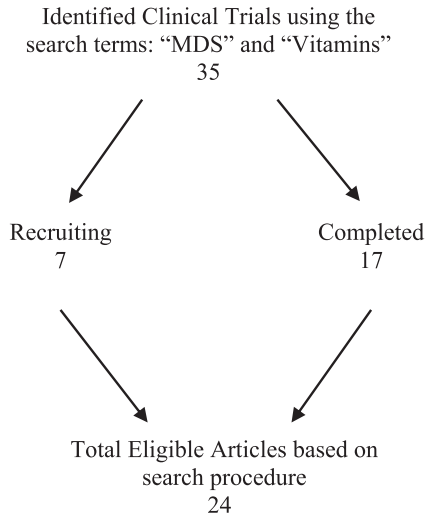


Fig. 1. Flow chart representing the search procedure to identify eligible articles.

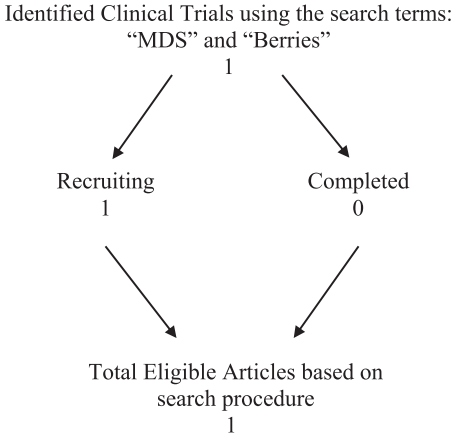


Fig. 2. Flow chart representing the search procedure to identify eligible articles.

criteria had the following information presented in columnar form (Table 1, Table 2, and Table 3): status, study title, conditions, interventions, study type, study design, outcome measures, number enrolled, NCT number, other IDs, and locations. Of the seventeen completed clinical trials (Figure 3), fourteen completed clinical trials were completed in the United States (North America), two in Europe, and one in the Pacific. Of the seven recruiting clinical trials, six are recruiting currently in the United States (North America), and one clinical trial is currently recruiting in Denmark (Europe).

3.2. Selection and description of human clinical trials

Figures 1 and 2 details the sequential steps for the determination and selection of human clinical trials deemed eligible for the review. Comprehensively, thirty-five titles and abstracts were retrieved with the search terms

Table 1

List of 17 interventional and observational completed clinical trials with patients with MDS using vitamins or natural products with an end date on or before 07 March 2019. Items in bold are keywords retrieved from the search procedure

Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome Measures	Number Enrolled	NCT Number	Other IDs	Location(s)
Completed	Epigenetics, **Vitamin** C and Abnormal Hematopoiesis - Pilot Study	**Myelodysplastic Syndrome**	Dietary Supplement: **Vitamin** C	Interventional	Allocation: Randomized	Overall 5-hmC/5-mC ratio	20	NCT02877277 (31)	H-16022249	Rigshopitalet Kobenhavn O, Denmark
		Acute Myeloid Leukemia	Dietary Supplement: Placebo		Intervention Model: Parallel Assignment	Overall lysine methylation levels				
					Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	5-hmC/5-mC ratio at regulatory genomic regions of genes involved in hematopoietic development				
					Primary Purpose: Treatment	(and 6 more...)				
Completed	Cholecalciferol in Treating Patients With **Myelodys-plastic Syndrome**	Leukemia	Dietary Supplement: cholecalciferol	Interventional	Masking: None (Open Label)	–	–	NCT00068276 (14)	CCCWFU-29203	Comprehensive Cancer Center at Wake Forest University
		Myelodysplastic Syndromes			Primary Purpose: Treatment				CDR0000318802	
		Myelodysplastic/ Myeloprolifer-ative Neoplasms							CCCWFU-BG03-117	Winston-Salem, North Carolina, United States

Completed	Decitabine, Arsenic Trioxide and Ascorbic Acid for **Myelodysplastic Syndromes** and Acute Myeloid Leukemia	**Myelodysplastic Syndromes** and Leukemia, Myeloid, Acute	Drug: Arsenic Trioxide	Interventional	Allocation: Non-Randomized	To define the maximum tolerated dose and dose-limiting toxicities during four cycles of combination decitabine, arsenic trioxide and ascorbic acid in patients with myelodysplastic syndromes (MDS) previously untreated with hypomethylating agents.	13	NCT00671697 (15)	07-0916 / 201011797	Washington University
			Drug: Decitabine		Intervention Model: Single Group Assignment	To estimate the rate of complete remission (CR) and partial remission (PR) after four cycles of therapy in patients with MDS.				St. Louis, Missouri, United States
					Masking: None (Open Label)	To determine the rate of hematologic improvement				
					Primary Purpose: Treatment	(and 6 more...)				
Completed	Paricalcitol in Treating Patients With **Myelodysplastic Syndrome**	Leukemia	Drug: paricalcitol	Interventional	Masking: None (Open Label)			NCT00064376 (16)	CDR0000315451	Cedars-Sinai Comprehen-sive Cancer Center at Cedars-Sinai Medical Center

(*Continued*)

Table 1
(*Continued*)

Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome Measures	Number Enrolled	NCT Number	Other IDs	Location(s)
		Myelodysplastic Syndromes			Primary Purpose: Treatment				CSMC-IRB-4107-01	Los Angeles, California, United States
Completed	Zoledronic Acid in Preventing Osteoporosis in Patients Undergoing Donor Stem Cell Transplant	Leukemia	Dietary Supplement: calcium	Interventional	Allocation: Randomized	Mean Change in Bone Mineral Density	61	NCT00321932 (20)	2005NT018	Masonic Cancer Center at University of Minnesota
		Lymphoma			Intervention Model: Parallel Assignment	Mean Change in Serum Osteocalcin			UMN-0506M70866	Minneapolis, Minnesota, United States
		Myelodysplastic Syndromes	Dietary Supplement: cholecalciferol		Masking: None (Open Label)	Mean Change in Serum Bone Specific Alkaline Phosphate			UMN-MT2005-06	University of Wisconsin Paul P. Carbone Comprehensive Cancer Center
		(and 2 more...)	Drug: zoledronic acid		Primary Purpose: Treatment	(and 6 more...)			NOVARTIS-CZOL446EUS29	Madison, Wisconsin, United States
Completed	Leucovorin for the Treatment of 5 q Minus Syndrome	5q Minus Syndrome	Drug: Leucovorin	Interventional	Primary Purpose: Treatment		14	NCT00004997 (21)	980101	Warren G. Magnuson Clinical Center (CC)
		Myelodysplastic Syndrome							98-CC-0101	Bethesda, Maryland, United States
Completed	Combination Chemotherapy Followed By Peripheral Stem Cell Transplantation or Isotretinoin in Treating Patients With Acute Myeloid Leukemia, **Myelodysplastic Syndrome**, or Acute Lymphocytic Leukemia	Chronic Myelo-proliferative Disorders	Biological: filgrastim	Interventional	Primary Purpose: Treatment			NCT00003619 (22)	AUH-MCP-70612-01	Medical College of Pennsylvania Hospital

		Leukemia **Myelodysplastic Syndromes** Thrombocytopenia	Dietary Supplement: **vitamin** E Drug: busulfan (and 7 more...)					CDR0000066698 AUH-MCP-70612-02P NCI-V98-1485	Philadelphia, Pennsylvania, United States Medical College of Pennsylvania Philadelphia, Pennsylvania, United States
Completed	IMG-7289, With and Without ATRA, in Patients With Advanced Myeloid Malignancies	Acute Myeloid Leukemia **Myelodysplastic Syndrome**	Drug: IMG-7289 Drug: All-trans retinoic acid	Interventional	Allocation: Non-Randomized Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Safety and tolerability as measured by monitoring of adverse events, changes in physical examinations, vital signs and laboratory parameters Pharmacokinetic parameters as measured by acute and steady state sampling The adequacy of the treatment regimen in producing a pharmacodynamic effect as measured by the IWG/Cheson response criteria	45	NCT02842827 (23)	IMG-7289-CTP-101	Royal Adelaide Hospital Adelaide, South Australia, Australia
Completed	Arsenic Trioxide, Ascorbic Acid, Dexamethasone, and Thalidomide in Myelofibrosis/ Myeloproliferative Disorder	Chronic Myeloproliferative Disorders	Dietary Supplement: ascorbic acid	Interventional	Intervention Model: Single Group Assignment	Response rate at 6 months	15	NCT00274820 (24)	CASE4Y04	Case Medical Center, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center

(*Continued*)

Table 1
(*Continued*)

Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome Measures	Number Enrolled	NCT Number	Other IDs	Location(s)
		Leukemia	Drug: arsenic trioxide			Bone marrow response at 6 months			P30CA043703	Cleveland, Ohio, United States
		Myelodysplastic Syndromes	Drug: dexamethasone		Masking: None (Open Label)	Spleen size at 12 weeks			CCF-7671	Cleveland Clinic Taussig Cancer Institute, Case Comprehensive Cancer Center
		Myelodysplastic/ Myeloprolifera-tive Diseases	Drug: thalidomide		Primary Purpose: Treatment	Quality of life				Cleveland, Ohio, United States
Completed	Secondary Prevention of Osteoporotic Fractures in Residents of Long-Term Care Facilities	Hip Fractures	Behavioral: Long-term care facilities in the intervention arm will receive education and feedback audit on performance	Interventional	Allocation: Randomized	Number of new prescriptions for FDA-Approved osteoporosis medications.	64	NCT00280943 (25)	4686-05-7R2ER	Duke University Medical Center
		Osteoporosis			Intervention Model: Crossover Assignment					Durham, North Carolina, United States
					Masking: Single	Secondary Outcome Measures: Changes in number of bone mineral density test ordered, change in the number of hip protectors issued, change in the number of prescriptions for calcium and **vitamin** D, changes in the rate of new osteoporotic fractures.				

					Primary Purpose: Prevention					
Completed	PENELOPE Observational Study: Prophylaxis and Treatment of Arterial and Venous Thromboembolism	Hematologic Neoplasm	Other: Observation	Observational	Observational Model: Case-Only	Number of patients with progression of thrombosis.	99	NCT01855698 (26)	EMATO0213	S.O.C. di Ematologia - Azienda Ospedaliera - SS. Antonio e Biagio e Cesare Arrigo Alessandria, Italy
		Acute Leukemia				Type of management strategy (including observation).				Azienda Ospedaliero - Universitaria Ospedali Riuniti Umberto I - G.M. LANCISI - G. SALESI Ancona, Italy
		Myelodysplastic Syndrome			Time Perspective: Prospective	Dosage of the antithrombotic drugs.				Divisione di Immunoema-tologia e Medicina Trasfusionale & Centro Trombosi - A.O. Papa Giovanni XXIII
		(and 2 more...)				(and 3 more...)				Bergamo, Italy (and 20 more...)
Completed	Cephalon Decitabine, Arsenic Trioxide and Ascorbic Acid for **Myelodysplastic Syndrome**	**Myelodysplastic Syndrome**	Drug: Decitabine, Arsenic Trioxide and Ascorbic Acid	Interventional	Intervention Model: Single Group Assignment	Number of Patients With an Overall Response of Complete Response (CR) or Partial Response (PR)	7	NCT00621023 (17)	Pro00011792	Duke University Medical Center

(*Continued*)

Table 1
(*Continued*)

Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome Measures	Number Enrolled	NCT Number	Other IDs	Location(s)
					Masking: None (Open Label)	Duration of a Complete or Partial Response Based on Number of People Who Responded.			7667A	Durham, North Carolina, United States
					Primary Purpose: Treatment	Number of Patients With an Unacceptable Toxicity				
Completed	Donor Peripheral Blood Stem Cell Transplant and Pretargeted Radioimmunotherapy in Treating Patients With High-Risk Advanced Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, or **Myelodysplastic Syndrome**	Chronic Myelomonocytic Leukemia	Biological: Pretargeted Radioimmunotherapy	Interventional	Intervention Model: Single Group Assignment	Incidence of dose-limiting toxicities (DLT) (grade III/IV Bearman) to determine MTD of radiation delivered to normal organ by pretargeted 90Y-DOTA-biotin	17	NCT00988715 (13)	2309.00	Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium
		Myelodysplastic/ Myeloproliferative Neoplasm, Unclassifiable	Drug: Cyclosporine		Masking: None (Open Label)	Rates of engraftment, chimerism, and non-relapse mortality			NCI-2009-01294	Seattle, Washington, United States
		Previously Treated **Myelodysplastic Syndrome** (and 6 more...)	Drug: Mycophenolate Mofetil (and 6 more...)		Primary Purpose: Treatment	Rate of grades III-IV acute GVHD			P01CA044991	
						Achievement and duration of response			P30CA015704	

Completed	Calcitriol and Dexamethasone in Patients With **Myelodysplastic Syndromes**	**Myelodysplastic Syndromes**	Drug: Calcitriol Drug: Dexamethasone	Interventional	Allocation: Non-Randomized Masking: None (Open Label) Primary Purpose: Treatment		32	NCT00030069 (28)	UPCI 01-020 FD-R-002025-01	University of Pittsburgh Pittsburgh, Pennsylvania, United States
Completed	Doxercalciferol in Treating Patients With **Myelodysplastic Syndrome** or Chronic Myelomonocytic Leukemia	Leukemia **Myelodysplastic Syndromes** Myelodysplastic/Myeloproliferative Diseases	Dietary Supplement: doxercalciferol	Interventional	Masking: None (Open Label) Primary Purpose: Treatment			NCT00052832 (18)	CDR0000258754 P30CA014520 WCCC-HO-02403	University of Wisconsin Comprehensive Cancer Center Madison, Wisconsin, United States
Completed	Cytokine Gene Polymorphisms in Bone Marrow Failure	Bone Marrow Diseases		Observational	Observational Model: Cohort Time Perspective: Other	2.1 To define the variability that exists in cytokine genes from bone marrow failure patients by typing their DNA for polymorphisms. Compare cytokine polymorphisms of normal individuals (public domain studies and 03-H-0121) to those of patients with known bone marrow failure.Correlate cytokine gene polymorphisms of aplastic anemia and other bone marrow failure syndrome patien...	79	NCT00085670 (29)	040213 04-H-0213	National Institutes of Health Clinical Center, 9000 Rockville Pike Bethesda, Maryland, United States

(*Continued*)

Table 1
(*Continued*)

Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome Measures	Number Enrolled	NCT Number	Other IDs	Location(s)
Completed	Imetelstat Sodium in Treating Patients With Primary or Secondary Myelofibrosis	Primary Myelofibrosis	Drug: Imetelstat	Interventional	Allocation: Randomized	MF patients: Overall response rate defined as a clinical improvement (CI), partial remission (PR), or complete remission (CR) according to the IWG-MRT consensus criteria	81	NCT01731951 (30)	CR107110	Rochester, Minnesota, United States
		Secondary Myelofibrosis Myeloid Malignancies			Intervention Model: Parallel Assignment	MDS patients: Overall response rate according to the IWG response criteria in myelodysplasia			CP14B019	
					Masking: None (Open Label)	Maximum grade for each type of adverse event for each patient				
					Primary Purpose: Treatment	(and 2 more...)				

Table 2

List of 7 interventional and observational recruiting clinical trials with patients with MDS using vitamins (or natural products) with an end date on or before 07 March 2019. Items in bold are keywords retrieved from the search procedure

Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome Measures	Number Enrolled	NCT Number	Other IDs	Location(s)
Recruiting	A Phase Ib/ IIa Study Evaluating the Safety and Tolerability of Vitamin C in Patients With Intermediate or High Risk Myelodysplas-tic Syndrome With TET2 Mutations	Myelodysplastic Syndromes	Drug: 50 gm CIVI/ 24 hours x 5 days every 4 week	Interventional	Intervention Model: Single Group Assignment	Measure of serum bioavailability of **Vitamin** C in Myelodysplastic syndrome (MDS) patients with TET2 mutations	18	NCT03433781 (8)	17-00978	University of Miami Miller School of Medicine -Sylvester Cancer Center
					Masking: None (Open Label)					Miami, Florida, United States
					Primary Purpose: Treatment					New York University School of Medicine New York, New York, United States
Recruiting	Epigenetics, **Vitamin** C, and Abnormal Blood Cell Formation - **Vitamin** C in Patients With Low-Risk Myeloid Malignancies	**Myelodysplastic Syndromes**	Dietary Supplement: **Vitamin** C (ascorbic acid)	Interventional	Allocation: Randomized	Mean Change from Baseline in 5-hmC/5-mC Level at 12 Months	70	NCT03682029 (9)	H-16022249 low-risk cohort	University of Southern California Los Angeles, California, United States
		Chronic Myelomono-cytic Leukemia-1			Intervention Model: Parallel Assignment	Mean Change from Baseline in 5-hmC/5-mC Level at 3 Months				Rigshospitalet

(*Continued*)

Table 2
(*Continued*)

Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome Measures	Number Enrolled	NCT Number	Other IDs	Location(s)
		Cytopenia	Other: Placebo		Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Prevention	Mean Change from Baseline in 5-mC at Selected Sites at 12 Months (and 7 more...)				Copenhagen, N/A=Not Applicable, Denmark Herlev Hospital Copenhagen, Denmark
Recruiting	Monitoring, Detoxifying, and Rebalancing Metals During Front Line Acute Myeloid Leukemia (AML) and **Myelodysplastic Syndrome** (**MDS**) Therapy	Acute Myeloid Leukemia	Drug: Edetate Calcium Disodium	Interventional	Allocation: Non-Randomized	Cytogenetic response (myelodysplastic syndrome patients)	24	NCT03630991 (10)	2017-0752	M D Anderson Cancer Center
		Acute Myeloid Leukemia Arising From Previous **Myelodysplastic Syndrome**	Dietary Supplement: Multivitamin		Intervention Model: Parallel Assignment				NCI-2018-01610	Houston, Texas, United States
		Chronic Myelogenous Leukemia, BCR-ABL1 Positive (and 4 more...)	Drug: DMSA		Masking: None (Open Label) Primary Purpose: Treatment				P30CA016672	
Recruiting	Ascorbic Acid Levels in **MDS**, AML, and CMML Patients	**Myelodysplastic Syndromes**	Other: Peripheral blood collection	Observational	Observational Model: Case-Only	Peripheral blood ascorbic acid levels	50	NCT03526666 (11)	17022	Cancer and Hematology Centers of Western Michigan

		Acute Myeloid Leukemia		Time Perspective: Prospective	Evaluation of human endogenous retroviral sequences (HERVs) expression			Grand Rapids, Michigan, United States
		Chronic Myelomono-cytic Leukemia			Evaluation of 5-methylcitosine (5-mC) and 5-hydroxymethylcytosine (5-hmC) levels			Metro Health - University of Michigan Health
		(and 3 more...)						Wyoming, Michigan, United States
Recruiting	Therapeutic Use of Intravenous **Vitamin** C in Allogeneic Stem Cell Transplant Recipients	Hodgkin Lymphoma	Drug: Intravenous (IV) and oral **Vitamin** C	Interventional Intervention Model: Single Group Assignment	The proportion of patients that experience non-relapse mortality (NRM)	60	NCT03613727 (6) MCC-17-13299	Virginia Commonwealth University/Massey Cancer Center
		Lymphoid Leukemia		Masking: None (Open Label)	Time from transplant to engraftment		NCI-2018-01502	Richmond, Virginia, United States
		Multiple Myeloma		Primary Purpose: Treatment	To determine the effectiveness of reducing GVHD			
		(and 4 more...)			Characterize the safety and tolerability of the **vitamin** C regimen			

(*Continued*)

Table 2
(*Continued*)

Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome Measures	Number Enrolled	NCT Number	Other IDs	Location(s)
Recruiting	Plasmatic L-AScorbic Acid in MYelodyplastic Syndroms and Controls	**Myelodysplastic Syndrome**	Other: Samples	Interventional	Allocation: Non-Randomized	Plasmatic ascorbic acid concentration at baseline	180	NCT02809222 (12)	PHAO16-EG/PLASMYC	Clinical Research Center, University Hospital, Tours Tours, France
		Secondary Acute Myeloid Leukemia	Other: Quality of life questionnaire		Intervention Model: Parallel Assignment	Plasmatic ascorbic acid concentration during follow-up			2016-A00539-42	Department of Haematology and Cell Therapy, University Hospital, Tours Tours, France
					Masking: None (Open Label)	Plasmatic antioxidants concentrations				
					Primary Purpose: Health Services Research	(and 8 more...)				
Recruiting	TET2 Mutations in **Myelodysplastic Syndromes** and Acute Myeloid Leukemia With Azaciti-dine+Ascorbic Acid	**Myelodysplastic Syndromes**	Drug: Azacitidine	Interventional	Intervention Model: Single Group Assignment	Number of patients with response per MDS International Working Group 2006 Criteria	28	NCT03397173 (7)	CASE1917	Cleveland Clinic, Taussig Cancer Institute, Case Comprehensive Cancer Center
		Myeloproliferative Neoplasm	Drug: Ascorbic acid		Masking: None (Open Label)	Number of AML patients with response				Cleveland, Ohio, United States
		Acute Myeloid Leukemia			Primary Purpose: Treatment	Incidence of adverse events				
						(and 2 more...)				

Table 3

List of 1 interventional recruiting clinical trial with patients with MDS using berries with an end date on or before 27 March 2019. Items in bold are keywords retrieved from the search procedure

Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome Measures	Number Enrolled	NCT Number	Other IDs	Location(s)
Recruiting	Hypomethylating Properties of Freeze-dried Black Raspberries (BRB) in Patients With **Myelodysplastic Syndrome** or **Myelodysplastic Syndrome/**Myeloproliferative Neoplasm (**MDS/**MPN)	**Myelodysplastic Syndromes**	Drug: Freeze-Dried Black Raspberry Powder	Interventional	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Presence of black raspberry metabolites in blood and urine. DNA hypomethylation measured with pyrosequencing. DNA hypomethylation measured with MBDCap-seq. (and 2 more...)	21	NCT03140280 (5)	PRO28985	Froedtert & the Medical College of Wisconsin Milwaukee, Wisconsin, United States

"MDS" and "vitamins", with one study retrieved when the terms "MDS" and "berries" was used. Eleven studies were not included as they were not under the completed status or recruiting status for their respective studies. Within the excluded studies, three studies were terminated (location: two in Italy and one in the United States), two are enrolling by invitation (location: United States), two studies' status is unknown (location: United States and Jerusalem), one study was suspended (location: Korea), and one study was withdrawn (location: Jerusalem).

Collectively, based on their status, seventeen human clinical trials were rendered eligible based on the connection between berries, vitamins, or natural product intervention and MDS. When "berries", as a new search term and new query in combination with "MDS", only one recruiting human clinical trial was retrieved. Table 3 details the status, study title, conditions, interventions, study type, study design, outcome measures, number enrolled, NCT number, other IDs, and the location of this unique human clinical trial. Of the seventeen human clinical trials, fourteen were conducted in the United States of which thirteen were interventional, two studies were completed in Europe, and one study was completed in the Pacific.

3.3. Recruiting trials

Of the entire database within the NIH U.S. National Library of Medicine, only one actively recruiting human clinical trial associated with the established search terms of "MDS" and "berries" was retrieved. This result is of importance in that it is the only currently recruiting human clinical available, further highlighting the urgency to have more human clinical trials in cue using natural products.

A Pilot Study to Investigate the Hypomethylating Properties of Freeze-Dried Black Raspberries in Patients with Myelodysplastic Syndrome

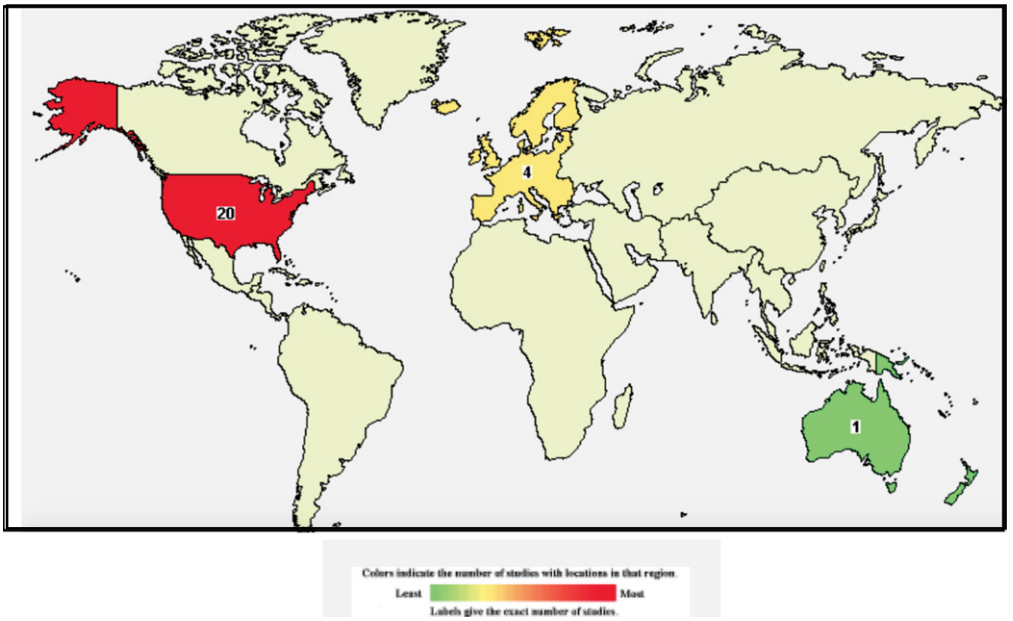
The primary objective is to "evaluate the potential hypomethylating effects of freeze-dried black raspberries (BRBs) in the peripheral blood of patients with MDS or myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) after 3 months of BRB administration" [5]. The secondary objective is to "evaluate the toxicity of BRBs in patients with MDS or MDS/MPN and to evaluate the hematological response according to modified IWG criteria in patients with MDS or MDS/MPN regardless of the initial blood count" [5].

In this first human clinical trial of its kind, "eighteen patients with MDS will be treated with 50 gm/day (25 gm 2×/daily) of BRB powder taken orally in slurry of 240 ml of water" [5]. "Patients will receive oral BRBs for a period of at least 12 weeks and the respective team will plan on evaluating the DNA methylation status in those patients at presentation and then monthly for 3 months from the peripheral blood" [5]. Patients may continue to be on black raspberries if he or she can tolerate it and is benefitting from it for a maximum period of 12 months.

The BRBs may be beneficial and could potentially show promise in the human health treatment and prevention of MDS. The phytochemicals found in BRBs, if timed correctly, and with studies like this one, could be a suitable addition and intervention to positively influence health. As a result, BRBs' biological activities may not only be deemed as a source of endogenous antioxidants, but also as an anti-cancerous fruit in future health regimens.

Of the seven recruiting human trials, only five recruiting human trials were deemed topically relevant to the study based on the method, intervention plan, variables considered, and purpose of the study (Table 2). Two studies, specifically, *Therapeutic Use of Intravenous Vitamin C in Allogeneic Stem Cell Transplant Recipients*, was set to "determine the effect of parenteral vitamin C on non-relapse mortality (NRM) at one year following myeloablative allogeneic HCT" [6] while *TET2 Mutations in Myelodysplastic Syndromes and Acute Myeloid Leukemia With Azacitidine + Ascorbic Acid* is "evaluating the efficacy of treatment with azacitidine (an FDA approved drug for the treatment of MDS) and high dose ascorbic acid in patients with TET2 mutations" [7]. The first study did not focus on MDS patients while the second study had an intervention approach of Azacitidine and ascorbic acid, which does not isolate the latter as a sole variable in improving the health responses of patients with MDS and/or MLS.

The following is a summary of the five remaining, relevant and actively recruiting human clinical trials associated with the established search terms of "vitamins" and "MDS". These studies, based on their categorical



Region Name	Number of Studies
World	24
Europe	4
North America	20
United States	20
Pacifica	1

Fig. 3. Map of 24 studies found by search of vitamins | Recruiting, Completed Studies | MDS | Start date on or before 07 March 2019. Heat legend indicates the number of studies with locations in that region. Table represents the number of studies and breakdown by world region.

nature, unlike the first two studies, focused exclusively on MDS and an intervention of select vitamins, which may help determine and isolate their effectiveness against the progression of MDS.

1. *A Phase Ib/IIa Study Evaluating the Safety and Tolerability of Vitamin C in Patients With Intermediate or High-Risk Myelodysplastic Syndrome With TET2 Mutations [8]*
    a. This is an "open label, Phase Ib/IIa study designed to evaluate the safety, toxicity and biological activity of high dose Vitamin C in bone marrow and peripheral blood when administered as therapy to patients with intermediate or high-risk MDS according to the revised IPSS (international prognostic scoring system) criteria whose disease has a Ten-eleven translocation-2, (TET2) mutation" [8].
2. *Epigenetics, Vitamin C, and Abnormal Blood Cell Formation - Vitamin C in Patients With Low-Risk Myeloid Malignancies (EVITA) [9]*
    a. The primary purpose of this "multi-centre, randomized, placebo-controlled, double-blind phase II study is to investigate if oral vitamin C may change the biology of low-risk myeloid malignancies; i.e., clonal cytopenia of undetermined significance (CCUS), low-risk MDS, and chronic myelomonocytic leukemia (CMML)-0/1 by reversing some of the epigenetic changes characteristic of these disease entities; preclinical studies have shown that active demethylation by the TET enzymes is dependent on vitamin C, and the investigators have shown that plasma vitamin C levels are exceedingly low in hematological cancer patients but are easily corrected by oral vitamin C" [9].

   b. This study is "part of an array of EVITA studies aimed at clarifying whether the standard of care of patients with myeloid malignancies should be changed and oral vitamin C supplement added to the treatment recommendations" [9].
   c. This study is currently being conducted in Denmark.
3. *Monitoring, Detoxifying, and Rebalancing Metals During Front Line Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) Therapy* [10]
   a. The "goal of this clinical research study is to learn if giving calcium disodium edetate (Ca-EDTA) or dimercaptosuccinic acid (DMSA) to patients with acute myeloid leukemia (AML) or MDS while receiving standard chemotherapy can help to lower the level of metals found in the bone marrow and blood" [10].
   b. "Researchers believe lowering the level of metals found in the blood/bone marrow may help to control the disease and/or improve response to chemotherapy" [10].
4. *Ascorbic Acid Levels in MDS, AML, and CMML Patients* [11]
   a. This study is a "non-interventional, specimen collection translational study to evaluate vitamin C levels in the peripheral blood of Acute Myeloid Leukemia (AML), MDS, or Chronic Myelomonocytic Leukemia (CMML) patients [11].
5. *Plasmatic L-AScorbic Acid in Myelodysplastic Syndromes and Controls (PLASMYC)* [12]
   a. MDS is a "group of heterogeneous diseases characterized by the clonal evolution of dysplastic hematopoietic stem cells" [12].
   b. This "evolution is associated with accumulation of cytogenetic mutations which leads to acute myeloid leukaemia (AML); evolution of MDS is also associated with increase of reactive oxygen species (ROS)" [12].
   c. The "increase of ROS is associated with accumulation of cytogenetic mutations" [12].
   d. "Ascorbic acid (AA) is an actor of the regulation of the oxidative metabolism in the human body" [12].
   e. "Studies showed that supplementation with AA can change the proliferation status of MDS cells; adjuvant treatment with AA is associated with a beneficial effect on the evolution of MDS and AML" [12].
   f. The "present study aims at describing the variations of plasmatic ascorbic acid concentrations between healthy volunteers and patients with myelodysplastic syndromes advanced in their treatment or recently diagnosed during a follow-up of 12 months" [12].
   g. This study is currently being conducted in France. The plasma collected will be later analyzed.

3.4. Other nature products

3.4.1. Mushrooms and MDS risk and/or treatment

In a Phase II study, maitake mushroom extract was well received and "enhanced *in vitro* neutrophil and monocyte function following treatment demonstrated that Maitake has beneficial immunomodulatory potential in MDS" [13]. The maitake mushroom treatment suggested "that G-CSF induction in bone marrow leads to HPC maturation and release of more functionally competent cells . . . improving the function in lower-risk MDS patients" [4].

3.5. Completed trials

Below is a summary of five select completed human clinical trials associated with the established search terms (Table 1). Twelve completed human clinical trials were not included in this description as they deviated from

treating MDS or used a combination of a drug and a vitamin potentially proving the effectiveness of natural products cumbersome and difficult to decipher. The results from these trials, however, are pending given their start date.

1. *Cholecalciferol in Treating Patients with Myelodysplastic Syndrome* [14]
    a. This vitamin D study, is a "phase II trial that studied how well vitamin D works to treat MDS patients, as cholecalciferol could increase blood counts, improve MDS symptoms, and lower fatigue" [14].
2. *Decitabine, Arsenic Trioxide and Ascorbic Acid for Myelodysplastic Syndromes and Acute Myeloid Leukemia* [15]
    a. This study is "designed to test the combination of decitabine, arsenic trioxide and ascorbic acid (Vitamin C) in 13 patients with MDS and acute myeloid leukemia" [15].
3. *Paricalcitol in Treating Patients With Myelodysplastic Syndrome* [16]
    a. Paricalcitol is a "form of vitamin D that may help myelodysplastic cells develop into normal bone marrow cells; as a Phase II trial, its purpose was to study the effectiveness of paricalcitol in treating patients who have MDS" [16].
4. *Cephalon Decitabine, Arsenic Trioxide and Ascorbic Acid for Myelodysplastic Syndrome* [17]
    a. This is an "open-label, non-randomized trial pilot Phase II trial open to patients with MDS; the purpose of the study is to determine if the combination of decitabine, arsenic trioxide and ascorbic acid is deemed safe" [17].
5. *Doxercalciferol in Treating Patients With Myelodysplastic Syndrome or Chronic Myelomonocytic Leukemia* [18]
    a. Doxercalciferol, or Vitamin D, "may improve low blood cell counts and decrease the need for blood transfusions and may be an effective treatment for MDS; as a Phase II trial, its purpose was to study the effectiveness of doxercalciferol (Vitamin D) in treating MDS or myelomonocytic leukemia patients" [18].

4. Discussion

The current availability of the clinical trials and the prospective impact the clinical trials could have for patients with MDS has far-reaching implications. Potential benefits that could be included are: (rendering) a positive association between both variables, reducing the symptoms associated with MDS, and in the future identifying therapeutic interventions.

On the other hand, a predicted barrier to executing these clinical trials is the specific targeted population they are seeking. To overcome this, biomarkers may help for an earlier diagnosis and intervention to develop a regimen that is both effective and personalized to meet the genetic and social needs of the patient. Another complexity to this review is the stage at which therapeutic options are offered. As a result, these circumstances will require rigorous preclinical research for tailored decisions. In reviewing the proposed treatment plans, a foreseeable difficulty is that some studies are combining drugs with a natural product, making the pinpointing more difficult (i.e. which natural product is better). Also, another limitation is the fact this review focused solely on completed clinical trials and currently recruiting clinical trials. Supported with Ma X., et. al., "In this analysis ... fruit and vegetable intake did not appear to significantly influence the risk of MDS" ... however, "since these factors were not evaluated in previous studies of MDS, these null findings need to be interpreted with caution" showing a promise for future studies to be warranted [1].

In conducting this review, the inherent total count collected limited the examination of available trials. It must be noted that a small count of human clinical trials strongly suggests an area for further research. Regarding efficacy, larger studies should be conducted to determine power efficacy.

A clear strength of this review is the fact that it is one of few reviews in written existence, bringing awareness, pre- and clinical attention to this type of intervention and an improved therapeutic experience for a better standard of living for patients with MDS. The present study gathers the most reputable resources to find parallels between current findings. Additionally, by conducting repeated searches, it reduced the chance of accidental oversight and reference lists were reviewed to gain full insight into completed clinical trials. Also, other databases were not searched, though it is probable any outstanding studies were not missed.

For the future, a longer study timeframe and period for human clinical trials is recommended to see if the effects will translate into lower infection rates. An interesting point to discuss is that for the future, "it may be important for clinicians to incorporate comorbidities into the risk stratification of patients with MDS when evaluating treatment options" as it could render a preventative and timely protective association [19].

5. Conclusion

At the forefront of advancing groundbreaking research for patients with MDS are human clinical trials that offer alternative options to traditional treatments. As an understudied and minimally explored blood disorder with discrete information, the approval of new natural therapies is welcomed in MDS research development. Despite there being no reported toxicity in natural products and bioactive compounds, additional research is necessary to explore the etiology of MDS, develop preventative and clinically-relevant measures, and improve the quality of life of individuals with MDS. As it was noted, dietary interventions may result as a supplement to the treatment plan. The future findings, too, may benefit and be useful for patients who cannot tolerate aggressive therapy combinations.

In this area of limited research, the author summarized the available completed and currently recruiting human clinical search trials surrounding MDS and berries and their components, particularly vitamins, natural products and vegetables. The returned searches suggested a promising prospect for individuals with MDS, by means of active and currently recruiting studies. It is also noted that improved bioavailability formulation is needed to complement medical interventions. Earlier and better pre-clinical work can help discover mechanisms of potent and timely action. The benefits could, then, be more persuasive for the scientific and medical community to adopt and integrate into regular treatment plans.

Acknowledgments

To my mentor for her constant support, mentorship, and professional guidance. Without her, this special article would not be possible.

Funding

The authors report no funding.

Conflict of interest

No potential conflict of interest was disclosed.

References

[1] Ma X, Lim U, Park Y, Mayne ST, Wang R, Hartge P, et al. Obesity, lifestyle factors, and risk of myelodysplastic syndromes in a large US cohort. American Journal of Epidemiology [Internet]. 2009 Apr 24 [cited 2019 Mar 9];169(12):1492-9. doi: 10.1093/aje/kwp074. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2727203/

[2] Cogle CR. Incidence and burden of the Myelodysplastic Syndromes. Current Hematologic Malignancy Reports [Internet]. 2015 Sep 10 [cited 2019 Mar 9];10(3):272-81. doi: 10.1007/s11899-015-0269-y. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26134527

[3] Sergentanis TN, Psaltopoulou T, Ntanasis-Stathopoulos I, Liaskas A, Tzanninis I-G, Dimopoulos M-A. Consumption of fruits, vegetables, and risk of hematological malignancies: A systematic review and meta-analysis of prospective studies. Leukemia & Lymphoma [Internet]. 2017 Aug 28 [cited 2019 Mar 9]; 59(2):434-47. doi: 10.1080/10428194.2017.1339873. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28847196

[4] United States National Library of Medicine. ClinicalTrials.gov Background [Internet]. ClinicalTrials.gov. 2018 Jan 1 [cited 2019 Mar 9]. Available from: https://clinicaltrials.gov/ct2/about-site/background

[5] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017 June 5 -. Identifier NCT03140280, Hypomethylating properties of freeze-dried black raspberries (BRB) in patients with Myelodysplastic Syndrome or Myelodysplastic Syndrome/Myeloproliferative Neoplasm (MDS/MPN); 2017 Feb 23 [cited 2019 Mar 27]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT03140280

[6] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2018 Oct 1 -. Identifier NCT03613727, Therapeutic use of intravenous vitamin C in allogeneic stem cell transplant recipients; 2018 July 27 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT03613727

[7] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2018 Jan 29 -. Identifier NCT03397173, TET2 mutations in Myelodysplastic Syndromes and Acute Myeloid Leukemia With azacitidine+ascorbic acid; 2018 Dec 5 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT03397173

[8] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2018 May 1 -. Identifier NCT03433781, A phase Ib/IIa study evaluating the safety and tolerability of vitamin C in patients with intermediate or high risk Myelodysplastic Syndrome with TET2 mutations; 2018 Feb 8 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT03433781

[9] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017 Nov 21 -. Identifier NCT03682029, Epigenetics, vitamin C, and abnormal blood cell formation - Vitamin C in patients with low-risk myeloid malignancies; 2018 Sept 20 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT03682029

[10] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2018 Oct 11 -. Identifier NCT03630991, Monitoring, detoxifying, and rebalancing metals during front line Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) Therapy; 2018 Aug 10 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT03630991

[11] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017 Nov 1 -. Identifier NCT03526666, Ascorbic acid levels in MDS, AML, and CMML patients; 2018 May 3 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT03526666

[12] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 Oct 25 -. Identifier NCT02809222; Plasmatic L-AScorbic acid in Myelodyplastic Syndroms and Controls; 2016 June 17 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT02809222

[13] Wesa KM, Cunningham-Rundles S, Klimek VM, Vertosick E, Coleton MI, Yeung KS, et al. Maitake mushroom extract in myelodysplastic syndromes (MDS): A phase II study. Cancer Immunology, Immunotherapy [Internet]. 2014 Oct 29 [cited 2019 Mar 9]; 64(2): 237-47. doi: 10.1007/s00262-014-1628-6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25351719

[14] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2003 July 1 -. Identifier NCT00068276, Cholecalciferol in treating patients with Myelodysplastic Syndrome; 2003 Sept 10 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT00068276

[15] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2008 May 1 -. Identifier NCT00671697, Decitabine, arsenic trioxide and ascorbic acid for Myelodysplastic Syndromes and Acute Myeloid Leukemia; 2008 May 1 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT00671697

[16] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2003 May 1 -. Identifier NCT00064376, Paricalcitol in treating patients with Myelodysplastic Syndrome; 2003 July 8 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT00064376

[17] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2007 Nov 1 -. Identifier NCT00621023, Cephalon decitabine, arsenic trioxide and ascorbic acid for Myelodysplastic Syndrome; 2007 Dec 26 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT00621023

[18] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2002 Sept 1 -. Identifier NCT00052832, Doxercalciferol in treating patients With Myelodysplastic Syndrome or chronic Myelomonocytic Leukemia; 2003 Jan 24 [cited 2019 Mar 9]; [about 2 screens]. Available from: https://ClinicalTrials.gov/show/NCT00052832

[19] Ma X. Epidemiology of myelodysplastic syndromes. The American journal of medicine [Internet]. 2012 Jul 9 [cited 2019 Mar 9];125(7):S2-S5. doi: 10.1016/j.amjmed.2012.04.014. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3394456/

[20] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2005 July 1 -. Identifier NCT00321932, Zoledronic acid in preventing osteoporosis in patients undergoing donor stem cell transplant; 2006 May 2 [cited 2019 Mar 9]; [about 4 screens]. Available from https://ClinicalTrials.gov/show/NCT00321932

[21] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1998 April 1 -. Identifier NCT00004997, Leucovorin for the treatment of 5 q minus syndrome; 2000 Mar 22 [cited 2019 Mar 9]; [about 3 screens]. Available from: https://ClinicalTrials.gov/show/NCT00004997

[22] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1998 Feb 1 -. Identifier NCT00003619, Combination chemotherapy followed by peripheral stem cell transplantation or isotretinoin in treating patients with acute Myeloid Leukemia, Myelodysplastic Syndrome, or Acute Lymphocytic Leukemia; 1999 Nov 1 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT00003619

[23] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 Oct 1 -. Identifier NCT02842827; IMG-7289, with and without ATRA, in patients with advanced myeloid malignancies; 2016 July 12 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT02842827

[24] ClinicalTrials.gov. National Library of Medicine (U.S.). (2005, October 1 -). Arsenic trioxide, ascorbic acid, dexamethasone, and thalidomide in Myelofibrosis/Myeloproliferative disorder. Identifier NCT00274820. Retrieved March 9, 2019 from https://ClinicalTrials.gov/show/NCT00274820

[25] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2005 Jan 1 -. Identifier NCT00280943, Secondary prevention of osteoporotic fractures in residents of long-term care facilities; 2006 Jan 20 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT00280943

[26] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 June 1 -. Identifier NCT01855698, PENELOPE observational study: Prophylaxis and treatment of arterial and venous thromboembolism; 2013 May 14 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT01855698

[27] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2010 April 21 -. Identifier NCT00988715, Donor peripheral blood stem cell transplant and pretargeted radioimmunotherapy in treating patients with high-risk advanced Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, or Myelodysplastic Syndrome; 2006 Feb 3 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT00988715

[28] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2007 Sept 1 -. Identifier NCT00030069, Calcitriol and dexamethasone in patients with Myelodysplastic Syndromes; 2002 Jan 30 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT00030069

[29] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2004 June 10 -. Identifier NCT00085670, Cytokine gene polymorphisms in bone marrow failure; 2004 June 10 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT00085670

[30] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 Oct 31 -. Identifier NCT01731951, Imetelstat sodium in treating patients with primary or secondary myelofibrosis; 2012 Nov 18 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT01731951

[31] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 Aug 8 -. Identifier NCT02877277; Epigenetics, vitamin C and abnormal hematopoiesis - pilot study; 2016 Aug 9 [cited 2019 Mar 9]; [about 4 screens]. Available from: https://ClinicalTrials.gov/show/NCT02877277

[32] Barth BM. Therapeutic effect of blueberry extracts for acute Myeloid Leukemia. International Journal of Biopharmaceutical Science [Internet]. 2018 Jan 2 [cited 2019 Mar 9]; 1(1):1-5. doi: 10.31021/ijb.20181102. Available from: https://www.boffinaccess.com/open-access-journals/international-journal-of-biopharmaceutical-sciences/therapeutic-effect-of-blueberry-extracts-for-acute-myeloid-leukemia.php

[33] Pan P, Skaer C, Yu J, Zhao H, Ren H, Oshima K, Wang LS, et al. Berries and other natural products in pancreatic cancer chemoprevention in human clinical trials. Journal of Berry Research [Internet]. 2017 Aug 18 [cited 2019 Mar 27]; 7(3):147-61. doi: 10.3233/JBR-170159. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5777607/

[34] Hosnijeh FS, Peeters P, Romieu I, Kelly R, Riboli E, Olsen A, et al. Dietary intakes and risk of Lymphoid and Myeloid Leukemia in the European prospective investigation into cancer and nutrition (EPIC). Nutrition and Cancer [Internet]. 2013 Nov 26 [cited 2019 Mar 9]; 66(1):14-28. doi: 10.1080/01635581.2014.847471. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24279598