Review

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

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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.

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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

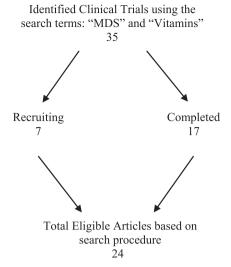


Fig. 1. Flow chart representing the search procedure to identify eligible articles.

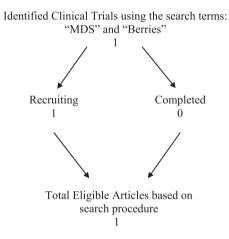


Fig. 2. Flow chart representing the search procedure to identify eligible articles.

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

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 Table 1

				,		•				
Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome	Number	NCT Number	Other IDs	Location(s)
						Measures	Enrolled			
Completed	Epigenetics,	Myelodysplastic	Dietary	Interventional	Allocation:	Overall	20	NCT02877277	H-16022249	Rigshopitalet
	Vitamin C and	Syndrome	Supplement:		Randomized	5-hmC/5-mC		(31)		Kobenhavn O,
	Abnormal		Vitamin C			ratio				Denmark
	Hematopoiesis - Pilot Study									
		Acute Myeloid	Dietary		Intervention	Overall lysine				
		Leukemia	Supplement:		Model:	methylation				
			Placebo		Parallel	levels				
					Assignment					
					Masking:	5-hmC/5-mC				
					Quadruple	ratio at				
					(Participant,	regulatory				
					Care Provider,	genomic				
					Investigator,	regions of				
					Outcomes	genes involved				
					Assessor)	ii				
						hematopoietic				
						development				
					Primary Purpose:	(and 6 more)				
					Treatment					
Completed	Cholecalciferol	Leukemia	Dietary	Interventional	Masking: None	1	ı	NCT00068276	CCCWFU-29203	Comprehensive
	in Treating		Supplement:		(Open Label)			(14)		Cancer Center
	Patients With		cholecalciferol							at Wake Forest
	Myelodys-									University
	plastic									
	Syndrome									
		Myelodysplastic			Primary Purpose:				CDR0000318802	
		Syndromes			Treatment					
		Myelodysplastic/							CCCWFU-	Winston-Salem,
		Myeloprolifer-							BG03-117	North
		ative								Carolina,
		Neoplasms								United States

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

Table 1 (Continued)

				(20)	(Continued)					
Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome	Number	Number NCT Number	Other IDs	Location(s)
						Measures	Enrolled			
		Myelodysplastic			Primary Purpose:				CSMC-IRB-4107- Los Angeles,	Los Angeles,
		Syndromes			Treatment				01	Califomia,
										United States
Completed	Zoledronic Acid in	Leukemia	Dietary	Interventional	Allocation:	Mean Change in	19	NCT00321932	2005NT018	Masonic Cancer
	Preventing Osteoporosis		Supplement:		Randomized	Bone Mineral		(20)		Center at
	in Patients Undergoing		calcium			Density				University of
	Donor Stem Cell Transplant									Minnesota
		Lymphoma			Intervention	Mean Change in			UMN-	Minneapolis,
					Model: Parallel	Serum			0506M70866	Minnesota,
					Assignment	Osteocalcin				United States
		Myelodysplastic	Dietary		Masking: None	Mean Change in			UMN-MT2005-06	University of
		Syndromes	Supplement:		(Open Label)	Serum Bone				Wisconsin Paul
			cholecalciferol			Specific				P. Carbone
						Alkaline				Comprehensive
						Phosphate				Cancer Center
		(and 2 more)	Drug: zoledronic		Primary Purpose:	(and 6 more)			NOVARTIS-	Madison,
			acid		Treatment				CZOL446EUS29 Wisconsin,	Wisconsin,
										United States
Completed	Leucovorin for the	5q Minus	Drug: Leucovorin Interventional	Interventional	Primary Purpose:		14	NCT00004997	980101	Warren G.
	Treatment of 5 q Minus	Syndrome			Treatment			(21)		Magnuson
	Syndrome									Clinical Center
										(CC)
		Myelodysplastic							98-CC-0101	Bethesda,
		Syndrome								Maryland,
										United States
Completed	Combination	Chronic Myelo-	Biological:	Interventional	Primary Purpose:			NCT00003619	AUH-MCP-	Medical College
	Chemotherapy Followed	proliferative	filgrastim		Treatment			(22)	70612-01	of Pennsylvania
	By Peripheral Stem Cell	Disorders								Hospital
	Transplantation or									
	Isotretinoin in Treating									
	Patients With Acute									
	Myeloid Leukemia,									
	Myelodysplastic									
	Syndrome, or Acute									
	Lymphocytic Leukemia									

Machine Spintones Primario	2		Supplement:						
Vitumin E Syndromes Acute Myeloid Drug: IMG-7289 Interventional Allocation: Non- Sifely and tolerability as 45 NCT00342827 Leukemia Acute Myeloid Drug: IMG-7289 Interventional Allocation: Non- Sifely and tolerability as 45 NCT00342827 Leukemia Acute Myeloid measured by monitoring of adverse events, changes in physical examinations, vital signs (23) Myeloidysplaste Drug: All-trans Intervention Pharmacolpinameters Syndrome retinoic acid Model: Single as measured by acute and Group Assignment Assignment Assignment Assignment Interventional Interventional Abunacy Purpose: Treatment regimen in producing as measured by the pharmacolyamic effect as measured by the pharmacoly	×		The state of the s						Pennsylvania,
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Principle Prin		Iyelodysplastic	Drug: busulfan					AUH-MCP-70612	- Medical College of
No. No. No. No. No. No. Safety and tolerability as No.		Syndromes						02P	Pennsylvania
Acute Myeloid Drug: IMG-7289 Interventional Allocation: Non- Safety and tolerability as 45 NCT02842827 IMG-7289-CTP. Re Leukernia Randomized measured by monitoring (23) 101 Changes in physical as measured by acute and Group Steady state sampling Assignment The adequacy of the producing a pharmacodynamic effect as measured by the producing a pharmacodynamic effect as measured by the Primary Purpose: Chronic Myelopro- Dictary Interventional Interventional Response rate at 6 months 15 NCT00274820 CASE4Y04 CAIlliferative Supplement: Model: Single Chronic Response rate at 6 months 15 CA) Disorders ascorbic acid Chron physical Case Assignment Assignment	F	hrombocytopenia	(and 7 more)					NCI-V98-1485	Philadelphia,
Acute Myeloid Drug: IMG-7289 Interventional Allocation: Non- Safety and tolerability as 45 NCT02842827 IMG-7289-CTP- Resolutions of adverse events. Application of adverse events. Myelodysphastic Drug: All-trums Intervention Model: Single as measured by acute and albocatory parameters Syndrome retinoic acid Model: Single as measured by acute and Assignment regiment retinoic acid Treatment regiment in producing a parametery as measured by acute and Masking: None The adequacy of the Chopen Label Interventional Interventional Interventional Response rate at 6 months 15 NCT00274820 CASE4Y04 Collificative Supplement: Model: Single Response rate at 6 months 15 NCT00274820 GASE4Y04 Collificative Supplement: Model: Single Assignment Disorders ascorbic acid Assignment									Pennsylvania,
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Myelodysplastic Drug: All-trans Intervention Pharmacokinetic parameters Advantage of the parameters						examinations, vital signs			
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Disorders ascorbic acid Group Assignment		liferative	Supplement:		Model: Single		(24)		Center,
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biliterative	fibrosis/				Assignment				Hospitals
	proliferative								Seidman Cancer
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Productosplacity Programment Copper Links Copper Link			Leukemia	Drug: arsenic			Bone marrow response at 6			P30CA043703	Cleveland, Ohio,
Syndroms				trioxide			months				United States
Syndrones Assumethanone Copen Label				Drug:		Masking: None	Spleen size at 12 weeks			CCF-7671	Cleveland Clinic
Myelodyoptatic/ by Application Drag thatistomide by Primary Purpose: Quality of life Primary Purpose: Quality of life Complete by Primary Purpose: Treatment in the Practices of the Principle of the Practices of the Practi			Syndromes	dexamethasone		(Open Label)					Taussig Cancer
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Myelotycyleiseix Myelotycyleiseix Princate Princate Treatment Trea											Cancer Center
Myeloprolifen- Diseases Secondary Prevention It bits Diseases Secondary Prevention of Okeoporotic Fractires Facilities I Oseoporosis Oseop			Myelodysplastic/	Drug: thalidomide		Primary Purpose:	Quality of life				Cleveland, Ohio,
Diseases Secondary Prevention Hip Finetures Behavioral: Interventional Allocation: Number of new 64 NCT00280943 4686-65-7R2BR Diseases Allocation: Randomized PDA-Approved Pacilities in the arm will receive medications. PDA-Approved Pacilities Arabida and technology Pacilities Arabida and technology Pacilities Posteroprovsis Allocations Posteroprovsis Allocations Posteroprovsis Allocations Posteroprovsis Posteroprovsis Allocations Posteroprovsis Posteroprovsis Allocations Posteroprovsis Posteropr			Myeloprolifera-			Treatment					United States
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Facilities in the intervention State Order FDA-Approved Intervention Osteoporosis medications. Medications Medications Medications Medications Model: Crossover Assignment Assignment Masking: Single Secondary Outcome Measures: Changes in number of Pone mineral Change in the number of persecriptions for calcium and vitamin D. changes in the rate of new oosteoprotic fractures. Changes in the rate of new oosteoprotic fractures. Changes in the rate of new oosteoprotic fractures. Changes in the rate of new oosteoporotic fractures. Changes i		of Osteoporotic		Long-term care		Randomized	prescriptions for	(2;	5)		Medical Center
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education and feedback audit on performance Dosteoporosis Model: Crossover Assignment Masking: Single Secondary Outcome Masking: Single Secondary Outcome Assignment Assignment Assignment Assignment Assignment Assignment Assignment Assignment Assignment Assignment Assignment Assignment Assignment Assignment Masking: Single Secondary Outcome Phase Assignment Assignment Assignment of hip protectors is saued, change in the number of hip protectors is saued, change in the number of prescriptions for calcium and vitamin D, changes in the rate of new osteoporotic fractures.		Long-Term Care		arm will receive			medications.				
feedback audit on performance Model: Crossover Assignment 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.		Facilities		education and							
On performance Model: Crossover Assignment 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.				feedback audit							
Model: Crossover Assignment 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.				on performance							
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.			Osteoporosis			Intervention					Durham, North
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.						Model:					Carolina,
S						Crossover					United States
S						Assignment					
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.						Masking: Single	Secondary Outcome				
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.							Measures: Changes in				
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.							number of bone mineral				
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osteoporotic fractures.							in the rate of new				
							osteoporotic fractures.				

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	EMATO0213																																Pro00011792					
	NCT01855698	(26)																															NCT00621023	(17)				
	66																																7					
	Number of patients with	progression of	thrombosis.							Type of management	strategy (including	observation).								Dosage of the	antithrombotic drugs.									(and 3 more)			Number of Patients With	an Overall Response of	Complete Response	(CR) or Partial	Response (PR)	
Prevention	Observational	Model:	Case-Only																	Time Perspective: Dosage of the	Prospective												Intervention	Model: Single	Group	Assignment		
	Observational																																Myelodysplastic Drug: Decitabine, Interventional			pi		
	Other:	Observation																															: Drug: Decitabin	Arsenic	Trioxide and	Ascorbic Acid		
	Hematologic	Neoplasm								Acute Leukemia										Myelodysplastic	Syndrome									(and 2 more)			Myelodysplastic	Syndrome				
	PENELOPE	Observational Study:	Prophylaxis and	Treatment of Arterial	and Venous	Thromboembolism																											Cephalon Decitabine,	Arsenic Trioxide and	Ascorbic Acid for	Myelodysplastic	Syndrome	
	Completed																																Completed					

Primary Purpose:

(Continued)

Table 1 (Continued)

				2)	(Continued)					
Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome	Number	Number NCT Number	Other IDs	Location(s)
						Measures	Enrolled			
					Masking: None	Duration of a			7667A	Durham, North
					(Open Label)	Complete or Partial				Carolina,
						Response Based on				United States
						Number of People				
						Who Responded.				
					Primary Purpose:	Number of Patients				
					Treatment	With an				
						Unacceptable				
						Toxicity				
Completed	Donor Peripheral Blood	Chronic	Biological:	Interventional	Intervention	Incidence of	17	NCT00988715	2309.00	Fred Hutchinson
	Stem Cell Transplant and	d Myelomono-	Pretargeted		Model: Single	dose-limiting		(13)		Cancer
	Pretargeted	cytic	Radioim-		Group	toxicities (DLT)				Research Cen-
	Radioimmunotherapy in	Leukemia	munotherapy		Assignment	(grade III/IV				ter/University
	Treating Patients With					Bearman) to				of Washington
	High-Risk Advanced					determine MTD of				Cancer
	Acute Myeloid					radiation delivered				Consortium
	Leukemia, Acute					to normal organ by				
	Lymphoblastic					pretargeted				
	Leukemia, or					90Y-DOTA-biotin				
	Myelodysplastic									
	Syndrome									
		Myelodysplastic/ Drug:	Drug:		Masking: None	Rates of engraftment,			NCI-2009-01294	Seattle,
		Myeloproliferative Cyclosporine	ve Cyclosporine		(Open Label)	chimerism, and				Washington,
		Neoplasm,				non-relapse				United States
		Unclassifiable				mortality				
		Previously Treated Drug:	Drug:		Primary Purpose:	Rate of grades III-IV			P01CA044991	
		Myelodysplas-	Mycophenolate		Treatment	acute GVHD				
		tic	Mofetil							
		Syndrome								
		(and 6 more)	(and 6 more)			Achievement and			P30CA015704	
						duration of response	1)			

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	Calcitriol and Dexamethasone in Patients With Myelodysplastic Syndromes	Myelodysplastic Syndromes	Drug: Calcitriol	Interventional	Allocation: Non-Randomized	32	NCT00030069 (28)	UPCI 01-020	University of Pittsburgh
			Drug: Dexamethasone		Masking: None (Open Label) Primary Purpose:			FD-R-002025-01	Pittsburgh, Pennsylvania, United States
Completed	ol in Treating ith plastic ocytic	Leukemia	Dietary Supplement: doxercalciferol	Interventional	Treatment Masking: None (Open Label)		NCT00052832 (18)	CDR0000258754 University of Wisconsin Comprehen Cancer Cer	University of Wisconsin Comprehensive Cancer Center
	Гейкенна	Myelodysplastic Syndromes Myelodysplastic/Myeloproliferative	lyeloproliferative		Primary Purpose: Treatment			P30CA014520	Madison, Wisconsin, United States
Completed	Cyokine Gene Polymorphisms in Bone Marrow Failure	Bone Marrow Diseases		Observational	Observational Model: Cohort Time Perspective: Other	2.1 To define the variability 79 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.	NCT00085670 (29)	040213 04-H-0213	National Institutes of Health Clinical Center, 9000 Rockville Pike Pike Maryland, United States

Table 1 (Continued)

Standy Title Conditions Interventions Study Title Number NCT Number Other IDs Location(s) Completed Inneclosar Sodium in Prinary Prinary Prinary Randomized Optical (30) NCT017319S1 CR10710 Rocksteer, Randomized Prinary or Scondary A prinary						(Communea)					
Treating Patients With	Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome	Number	NCT Number	Other IDs	Location(s)
Treating Patients With Mychithrosis Randomized Solution: MF patients: 81 NCT01731951 CR107110 Randomized Solution: Randomiz							Measures	Enrolled			
Myelofibrosis Randomiized Overall (30) response rate defined as a chinical as a chinical as a chinical as a chinical as a complete (CL), partial complete (CL), partial complete remission (PR). or complete remission (PR). CP (4B019) Recondary Intervention MDS patients: CP (4B019) Myelofibrosis Model: Parallel Overall CP (4B019) Myelofibrosis Model: Parallel Overall CP (4B019) Myelofibrosis Model: Parallel Overall CP (4B019) Malignancies Assignment response rate CP (4B019) Making: None Maximum grade CP (1B019) Assignment (Open Label) for each type of adverse event Adverse event Primary Purpose: for each patient Treatment	Completed	Imetelstat Sodium in	Primary	Drug: Imetelstat	Interventional	Allocation:	MF patients:	81	NCT01731951	CR107110	Rochester,
Actinical defined as a		Treating Patients With	Myelofibrosis			Randomized	Overall		(30)		Minnesota,
defined as a clinical improvement (CI), partial remission (PR), or complete remission (PR), according to the IWG-MRT consensus Criteria Secondary Myeloid Myeloid Assignment response rate Malignancies Madel: Parallel Overall Myseloid Assignment response rate Assignment (Open Labe) Assignment response rate Masking: None Maximus grade (Open Labe) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment		Primary or Secondary					response rate				United States
clinical improvement (CI), partial remission (PR), or complete remission (CR) according to the IWG-MRT consensus criteria Intervention MDS patients: Model: Parallel Overall Assignment response rate raccording to the IWG response criteria in myclodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event Freatment Treatment		Myelofibrosis					defined as a				
improvement (CD), partial remission (PR), or complete remission (CR) according to the IWG-MRT consensus criteria Intervention MDS patients: Model: Parallel Overall Assignment response rate according to the IWG response criteria in myelodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment							clinical				
(CD, partial remission (PR), or complete remission (CR) according to the IWG-MRT consensus criteria Intervention MDS patients: Model: Parallel Overall Assignment response rate response criteria in myelodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment							improvement				
remission (PR), or complete remission (CR) according to the IWG-MRT consensus criteria Intervention MDS patients: Model: Parallel Overall Assignment response rate response rate TWG response criteria in myelodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment							(CI), partial				
or complete remission (CR) according to the IWG-MRT consensus criteria Intervention MDS patients: Model: Parallel Overall Assignment response rate IWG response criteria in myelodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment							remission (PR)				
remission (CR) according to the IWG-MRT consensus criteria Intervention MDS patients: Model: Parallel Overall Assignment response rate according to the IWG response criteria in myelodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment							or complete				
according to the IWG-MRT CONSENSUS Criteria Intervention MDS patients: Model: Paralle Overall Assignment response rate according to the IWG response Criteria in myelodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment							remission (CR)				
IWG-MRT consensus criteria Intervention MDS patients: Model: Paralle Overall Assignment response rate according to the IWG response criteria in myelodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event for each patient Treatment Treatment							according to the	6			
consensus criteria Intervention MDS patients: Model: Parallel Overall Assignment response rate according to the IWG response Criteria in myelodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment							IWG-MRT				
criteria Intervention MDS patients: Model: Parallel Overall Assignment response rate according to the IWG response criteria in myelodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment							consensus				
Intervention MDS patients: Model: Parallel Overall Assignment response rate according to the IWG response criteria in myelodysplasia Masking: None Maximum grade (Open Label) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment							criteria				
osis Model: Parallel Assignment Cies Masking: None M (Open Label) Primary Purpose: (a			Secondary				MDS patients:			CP14B019	
Assignment cies Masking: None M (Open Label) Primary Purpose: (a			Myelofibrosis			Model: Parallel	Overall				
Masking: None M (Open Label) Primary Purpose: (a			Myeloid			Assignment	response rate				
;; (a			Malignancies				according to the	6			
.: (a							IWG response				
.: (a							criteria in				
.: (a							myelodysplasia				
(Open Label) for each type of adverse event for each patient Primary Purpose: (and 2 more) Treatment						Masking: None	Maximum grade				
adverse event for each patient Primary Purpose: (and 2 more) Treatment						(Open Label)	for each type of	£			
for each patient Primary Purpose: (and 2 more) Treatment							adverse event				
Primary Purpose: (and 2 more) Treatment							for each patient				
Treatment						Primary Purpose:	(and 2 more)				
						Treatment					

(Continued)

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

Table 2 (Continued)

				(2000)				
Status Study Title	Conditions	Interventions	Study Type	Study Design	Outcome Measures Number	er NCT Number	Other IDs	Location(s)
					Enrolled	led		
	Cytopenia	Other: Placebo		Masking: Quadruple	Mean Change from			Copenhagen,
				(Participant, Care Provider,	Baseline in 5-mC at			N/A=Not
				Investigator, Outcomes	Selected Sites at 12			Applicable,
				Assessor)	Months			Denmark
				Primary Purpose: Prevention	(and 7 more)			Herlev Hospital
								Copenhagen,
								Denmark
Recruiting Monitoring,	Acute Myeloid	Drug: Edetate	Interventional	Allocation: Non-Randomized	Cytogenetic response 24	NCT03630991	2017-0752	M D Anderson
Detoxifying,	Leukemia	Calcium			(myelodysplastic	(10)		Cancer Center
and		Disodium			syndrome patients)			
Rebalancing								
Metals During								
Front Line								
Acute Myeloid								
Leukemia								
(AML) and								
Myelodysplas-								
tic Syndrome								
(MDS) Therapy	y							
	Acute Myeloid	Dietary		Intervention Model: Parallel			NCI-2018-0161	NCI-2018-01610 Houston, Texas,
	Leukemia	Supplement:		Assignment				United States
	Arising From	Multivitamin						
	Previous							
	Myelodysplas-	1						
	tic							
	Syndrome							
	Chronic	Drug: DMSA		Masking: None (Open Label)			P30CA016672	
	Myelogenous							
	Leukemia,							
	BCR-ABL1							
	Positive							
	(and 4 more)			Primary Purpose: Treatment				
Recruiting Ascorbic Acid	Myelodysplastic	c Other: Peripheral Observational	Observational	Observational Model:	Peripheral blood 50	NCT03526666	17022	Cancer and
Levels in MDS,	s, Syndromes	blood collection	и	Case-Only	ascorbic acid levels	(11)		Hematology
AML, and								Centers of
CMML Patients	š							Western Michigan

	Leukemia endogenous Michigan, United	retroviral sequences States	(HERVs) expression	Chronic Evaluation of Metro Health -	Myelomono-	cytic (5-mC) and 5- Michigan Health	Leukenia	(5-hmC) levels	(and 3 more)	Michigan, United	States	utic Use Hodgkin Drug: Intravenous Interventional Intervention Model: Single The proportion of 60 NCT03613727 (6) MCC-17-13299 Virginia	ravenous Lymphoma (IV) and oral Group Assignment patients that Commonwealth	ıin Cin Vitamin C experience University/Massey	eneic non-relapse Cancer Center	Cell mortality (NRM)	plant	ients	Lymphoid Masking: None (Open Label) Time from transplant NCI-2018-01502 Richmond, Virginia,	Leukemia to engrafiment United States	Multiple Myeloma Primary Purpose: Treatment To determine the	effectiveness of	reducing GVHD	(and 4 more)	and tolerability of	the vitamin C	regimen	(Continued)
Acute Myelold	Leukemi			Chronic	Myelom	cytic	Leukemi		(and 3 mor			Recruiting Therapeutic Use Hodgkin	of Intravenous Lympho	Vitamin C in	Allogeneic	Stem Cell	Transplant	Recipients	Lymphoid	Leukemi	Multiple M			(and 4 mor				

Table 2 (Continued)

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

					Table 3					
List of	1 interventional recrui	ting clinical trial	with patients wi	ith MDS using b	perries with an end da	ate on or before 27 Mar	ch 2019. It	ems in bold a	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	e
					search procedure					
Status	Study Title	Conditions	Interventions	Study Type	Study Design	Outcome	Number]	NCT Number	Number NCT Number Other IDs Location(s)	l
						Measures	Enrolled			- 1
Recruitin	Recruiting Hypomethylating	Myelodysplastic Drug:	Drug:	Interventional	Intervention Model:	Presence of black raspberry	21	T03140280 (5)	NCT03140280 (5) PRO28985 Froedtert & the Medical	
	Properties of	Syndromes	Freeze-Dried		Single Group	metabolites in blood and			College of Wisconsin	
	Freeze-dried Black		Black		Assignment	urine.				
	Raspberries (BRB) in		Raspberry							
	Patients With		Powder							
	Myelodysplastic									
	Syndrome or									
	Myelodysplastic Syn-									
	drome/Myeloproliferative	ive								
	Neoplasm (MDS/MPN)									
					Masking: None (Open	Masking: None (Open DNA hypomethylation			Milwaukee, Wisconsin,	
					Label)	measured with			United States	
						pyrosequencing.				
					Primary Purpose:	DNA hypomethylation				
					Treatment	measured with				
						MBDCap-seq.				
						(and 2 more)				

"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

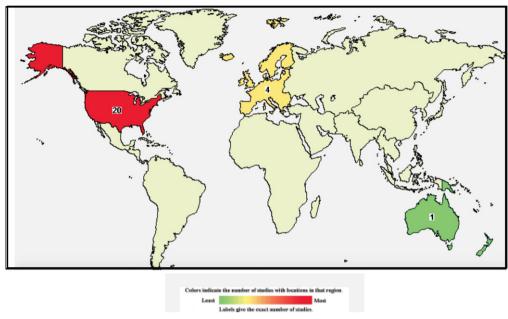
The primary objective is to "evaluate the potential hypomethylating effects of freeze-dried black raspberries (BRBs) in the peripheral blood of patients with MDS or myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) after 3 months of BRB administration" [5]. The secondary objective is to "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 $2 \times /\text{daily}$) 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.

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Conflict of interest

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