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Review

Quality Evaluation of the Clinical Trials for Natural Products Used in Cancer: An Evidence-Based Literature Review

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Abstract: The amount of data regarding the use of herbs/herbal products in cancer clinical trials at times creates a great challenge for oncologists to prescribe or counsel patients. It urges critical evaluation of the quality of clinical trials. Herein, for the first time, the clinical trials for herbs used in cancer were critically evaluated on the basis of three widely used scales, i.e., Jadad, Delphi, and Cochrane scales. The literature was collected with the help of online databases, journals, libraries, and books using a number of specific keywords as mentioned in detail in forthcoming sections. A total of 73 clinical trials were extracted, evaluated, and scored for 14 herbs, according to the predefined criteria mentioned below. A major deficiency of "non-blinding of clinical trials" was observed. The principal component analysis revealed four components (PC1–PC4) with a total variability of 68.21%, wherein the highest percentage variability was observed for PC1 loaded with "non-blinding of the clinical trials, no concealment of the treatment allocation, non-blindness of the patient and care provider", which accounted for 30.81% of the total variability. The next major variability of 14.70% was observed for PC2 loaded with "non-randomization of the studies, non-blinding of the outcome assessors, no proper drop-out procedures, and lack of information regarding baseline characteristics for the groups". Pearson's correlation further confirmed a similar correlation pattern for the mentioned deficiencies ($p = 0.05$). An in-house grading scale was developed, showing a very small portion (16.44%), i.e., 12/73 studies with a good quality, whereas the majority (57.54%) of the studies, i.e., 42/73, were found to be of poor quality. The rules and regulations governing the quality of clinical trials needs to be more stringent and updated for the natural products/herbs used in cancer clinical trials.

Keywords: cancer; Jadad; Delphi; Cochrane; quality evaluation

1. Introduction

Cancer is a term implicated for an uncontrolled cell division that may invade nearby tissues and spread to other body parts via blood and lymph systems [1]. The major risk factors for this disease include age, family history, hormones, tobacco use, irradiations, chronic inflammation, diet, and sedentary lifestyle [2,3]. A study reported 1,735,350 cancer cases in the United Stated for the year 2018, with total deaths of 609,640 [4]. The new estimates for 2040 revealed a global burden of up to

27.5 million new cases with 16.3 million deaths [5]. Breast cancer is reported more prevalent among the type of cancers, however, cervix (Southern Asia, Africa), prostate (North America, Western Europe), and oral cancers (India) are also widely observed [6]. A range of treatment strategies such as surgery, systemic therapy, and radiation therapy are available for cancer treatment, but the disadvantages associated with these treatment exceeds their desired therapeutic outcomes. For instance, an increased wound complication with damage to surrounding tissues during radiation therapy, site-specific complications with more risks of infections after surgery, and systemic toxicities following systemic therapy are few of the uncontrolled circumstances reported after treatment [7,8]. On the contrary, the use herbs has shown a decreased incidence for cancer. *Solanum nigrum* and *Cassia auriculata* flowers [9], *Aloe vera* (radiation-induced mucositis) [10], *Matricaria aurea* (skin, prostate, breast, and ovarian cancer), *Zingiber officinal*, and *Punica granatum* are a few examples with promising growth inhibitory effects. [11–13] Even a number of potent active chemicals have been isolated from various genera such as *Catharanthus*, *Taxus*, *Camptotheca*, *Curcuma*, *Betula*, *Podophyllum*, and *Cephalotaxus* [14] and applied for anticancer activity, including the chemicals irinotecan (colorectal cancer), colchicine (leukemia and solid tumors), and cucurbitacin (various cancers) [15]. Clinical trials for herbs and herbal products are also increasing where studies are performed to evaluate the effectiveness and therapeutic safety. For instance, a study by Getz (1995–2005) reported an annual increase of new procedures (6.5%), inclusion criteria (nearly thrice), and investigator site burden (10.5%) in clinical trials. Ultimately, this huge burden on behalf of the investigator will adversely affect the performance [16]. An additional factor, underlined with a significant effect upon the clinical trial quality and compliance, is "globalization of clinical trials". An annual increase of 15% for the number of active investigators along with a twofold increase in the number of countries have been reported from 1995 to 2005 [17]. Interestingly, a major portion of these clinical trials is conducted in developing countries that have huge disparities in comparison with developed countries in terms of socioeconomic standards, education, and healthcare systems as well as differences in health infrastructure, medical training, and clinical practices and ethical values, which exerts a huge impact upon the quality of clinical trials. During the last few decades, a confronting challenge of increased cost along with a delay in new drug development has been faced in the global market, especially the pharmaceutical industry. To properly address the issue, with the best of solutions available for saving cost and time, the trend of clinical trial has been opted as one of the most promising tools. Although defining the quality of a clinical trial may be challenging at times, and the fact that no clinical trial can be perfect, it is nevertheless important to account for customer satisfaction with regards to needs and their expectations. Most of the time the outcomes of a clinical study may reach the general public, who may use these results as evidence for treating various diseases. Hence, it is important to assess the quality of clinical trials so to report a valid and authentic "quality clinical trial". Several systems are available to assess and evaluate the quality of a clinical trial. For instance, the Jadad score, final Delphi score, and Cochrane back review group score. The current study critically evaluates the clinical trials reported for natural products in cancer on an individual basis by using the three scales, wherein a score for each scale along with a final score in the three scales is calculated and reported in forthcoming sections. The scales are applied to each trial and the deficiencies observed per each scale are reported in a table below.

2. Materials and Methods

Databases and relevant literature search strategy: Journals: *Cancer Research*, *Clinical Cancer Research*, *Journal of Clinical Oncology*, *Natural Product Research*, *Phytotherapy Research*, *Journal of Ethnopharmacology*, *BMC Complementary and Alternative Medicines*. Databases: Science Direct, PubMed, SciFinder, Scopus, Google Scholar, e-resources, e-portal of Imam Abdulrahman Bin Faisal University library. Books: indigenous drugs of India, phytochemistry and ethnopharmacology, herbalism, etc.

The literature was thoroughly checked for duplication, as well as incomplete and ineligible study, as per inclusion criteria. The data were finalized, evaluated, and an individual as well as cumulative score was assigned to each clinical trial as per the points mentioned in the Jadad, Delphi, and Cochrane

scale. Furthermore, an aggregate score was calculated and the quality of clinical trials was agreed on the basis of an in-house developed rating scale.

Keywords searched: The keywords searched for in literature included: randomized clinical trial, clinical trials, cancer, tumor, malignancy, aloe, *Aloe vera*, black seed, *Nigella sativa*, *Boswellia*, *Boswellia serrata*, chamomile, *Matricaria suaveolens koch*, colocynth, *Citrullus lanatus*, garlic, *Allium sativum*, ginger, *Zingiber officinale*, onion, *Allium cepa*, pomegranate, *Punica granatum*, senna, *Cassia senna*, *Pistacia terebinthus*, thyme, *Thymus vulgaris*, wheat, *Triticum aestivum*, *Artemisia abaensis*, *Artemisia abbreviata*, wormwood.

2.1. Inclusion Criteria

Inclusion criteria included clinical trials published in the English language; clinical trials using natural products and studies/reported in human subjects; any clinical trials using natural products with established folklore uses in cancer or with a reported use in a community worldwide (ethnopharmacological relevance); any clinical trial (phase I-V) reported for natural products in cancer, irrespective of blinding, randomization, statistical models, outcomes, and results presented; and all clinical trials using natural products along with conventional medication.

For ethnopharmacological relevance, a list of herbs/natural products was sorted and evaluated individually for its reported use in cancer in any community worldwide. The information regarding ethnopharmacological or folklore uses was searched in reputable journals and any data presented in the form of interviews, community surveys, or data collected from local inhabitants/herbal practitioners was extracted and analyzed.

2.2. Exclusion Criteria

Exclusion criteria included clinical trials reported for cancer using sources other than natural products; any clinical trial for cancer using natural products without proper ethnopharmacological relevance or community use in cancer; all natural products with a sound ethnopharmacological relevance in cancer but are yet to be evaluated in a clinical study; all preclinical studies (in vivo animal models or cell culture reports); any incomplete or duplicate study; clinical trials using vitamins, minerals, and conventional drugs only; and phase-0 clinical trials.

Review period: An extensive search strategy was applied where retrospective data were collected without any restriction from September 2019 to April 2020. The literature was collected according to eligibility criteria, studied, and reported in the review herein. Until preparation and finalization of the manuscript, we updated the literature data on a regular basis, and any new information, if obtained, was added to the literature search.

Search result: The literature search consisted of 1342 articles, which was confined to 73 following a proper scrutiny of the eligible articles according to the pre-defined criteria. The flow diagram for selection and scrutiny of the literature is given in Figure 1.

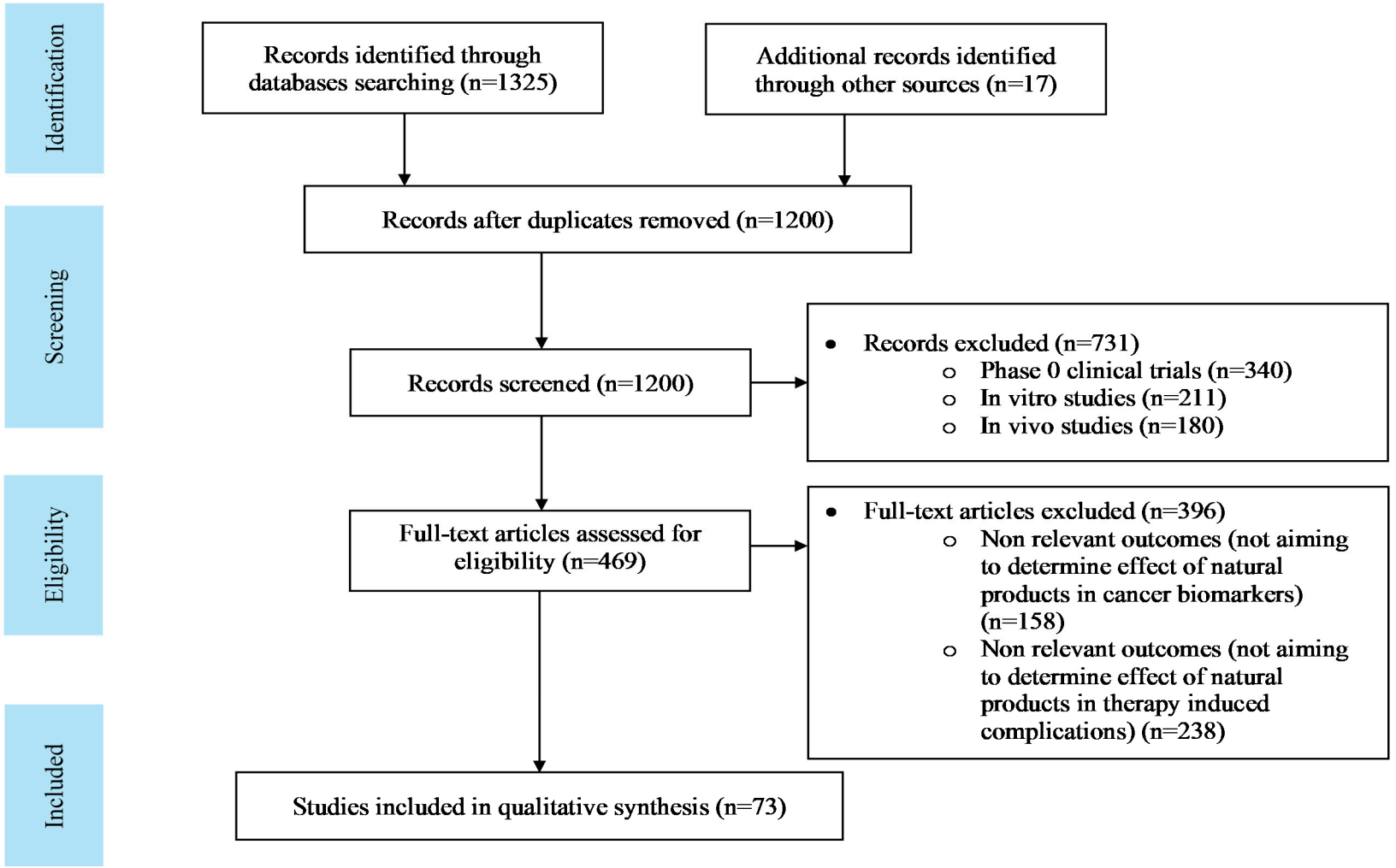


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow sheet for literature search.

3. Literature Search

The relevant literature data were studied and the extracted information is presented in a step-wise pattern below.

3.1. Folklore Uses/Ethnopharmacological Relevance of the Selected Herbs in Cancer

The ethnopharmacological relevance for the included herbs is given in detail in Table 1. The herbs were reported to have folklore uses in cancer in various communities including those of Pakistan, Palestine, Morocco, India, Turkey, Bangladesh, Ghana, Jordan, and Yemen. Various parts of these herbs such as leaves, fruit, dried sap, bulb, flowers, barks, rhizomes, seeds, rind, resin, and oleogum have been used for the intended purposes. Various types of cancers such as breast, head, skin, stomach, colorectal, liver, lungs, esophageal, and prostate cancers have been cured or treated using these herbs. These applications were used as a source of evidence for folklore or ethnopharmacological relevance of the selected herbs in order to evaluate the application and quality of clinical trials performed.

3.2. Cancer Clinical Trials

We searched the literature for clinical trials involving the selected herbs, finding a total of 73 clinical trials: aloe (15), black seeds (2), *Boswellia* (5), chamomile (3), colocynth (1), garlic (4), ginger (20), onion (1), pomegranate (8), senna (4), terebinth (1), thyme (3), wheat (5), and wormwood (1).

The current section highlights the key features of each clinical trial conducted for herbs in cancer. The part of an herbal product used as such or in a dosage form, the type of cancer studied, and the observed outcomes in a clinical trial were concluded as shown in Table 2.

3.3. Evaluation of Clinical Trials (Jadad, Delphi, and Cochrane Scale)

Three different scales, i.e., Jadad, Delphi, and Cochrane, were used in this study to evaluate clinical trials individually as per the items mentioned in the scales (Table 3). Each scale evaluated the quality of a clinical trial on certain specific key features mentioned in the table, where most of the items were overlapping/common for the three scales. Every scale possessed positive as well as negative aspects in terms of evaluation criteria and it is worth mentioning that no "best-fit scale" exists to critically analyze a clinical trial; hence, the three scales were applied together for assessing the quality of each clinical trial. This step may help cover the deficiencies present in a scale. In addition, as Jadad is the only scale that uses a scale (0–5) to assign score to a study, whereas Delphi and Cochrane lack a scoring system. For the sake of simplicity and ease of calculation/comparative scoring, we assigned an internal score to each item of the Delphi (0–9) and Cochrane scale (0–10). This summed up the total score for the three scales as being between 0 and 24 [18]. All the clinical trials included in this study were assessed and scored using the three scales and an individual as well as final score were assigned for classification of the clinical trials. Table 4 shows in detail all the items present in the three scales and the deficiencies observed for individual clinical trials according to the items in each scale.

Table 1. Literature regarding ethnopharmacological relevance of the plants used in cancer.

Herb	Botanical Name	Part/s Used	Ethnopharmacological Relevance
Aloe	*Aloe vera*	leaves, dried sap (fluid), extracted gel	breast cancer in Palestine [19] and lung cancer in a Pakistani community [20]
Black seeds	*Nigella sativa*	seeds	general/colorectal cancer in Morocco [21] and Bangladesh [22]
Boswellia	*Boswellia serrata*	bark	general cancers in Near East region [23] and India [24]
Chamomile	*Matricaria suaveolens koch*	flowers	lung, liver, and prostate cancer in Palestine [19,25]
Colocynth	*Citrullus lanatus*	fruit	general cancer treatments in Pakistan [25] and India [24]
Garlic	*Allium sativum*	bulb, leaves	general cancers in Morocco [21] and treatment of lung, esophageal, and breast cancers in Palestine [19]
Ginger	*Zingiber officinale*	rhizome	general cancers in Morocco [21] and stomach cancer in Palestine [19]
Onion	*Allium cepa*	leaves, bulb, oil and seeds	skin cancers in Ghana [26] and general cancers in Jordan [27]
Pomegranate	*Punica granatum*	fruit, rind	general cancers in Yemen [28] and skin cancers in Morocco [21]
Senna	*Cassia senna*	leaves	general cancer treatments in India [29,30]
Terebinth	*Pistacia terebinthus*	resin, branches, fruit	Islamic traditional medicine [31] and general cancer in Turkey [32]
Thyme	*Thymus vulgaris*	leaves	head, lung, colorectal cancer in Turkey [33] and breast cancer in Palestine [34]
Wheat	*Triticum aestivum*	shoot	general cancer [35] and breast/colorectal cancers in Trinidad [36]
Wormwood	*Artemisia abaensis*, *Artemisia abbreviata*	leaves	general/digestive cancers in Turkey and Morocco [21,37]

Table 2. Clinical trials in cancer for the selected herbs with details about type of cancer and its outcome observed.

Plant	Trial	Part/Dosage Form Used	Type of Cancer	Results
Aloe	A1	gel	breast cancer	↓ radiation-induced skin side effects [38]
	A2	lotion	head/neck, breast cancers	↓ intensity of radiation-induced dermatitis [39]
	A3	aloe and myrrh mixture	various cancers	induced a control of the neoplastic disease [40]
	A4	pure gel syrup	head and neck cancer	↓ severity of radiation-induced mucositis [41]
	A5	gel + natural agents	head and neck cancer	no effect on mucositis [42]
	A6	gel	breast cancer	↓ prevalence of radiation-induced dermatitis [43]
	A7	juice	head and neck cancer	lack of effects as adjunct to head and neck radiotherapy [10]
	A8	gel	breast cancer	no effect against radiation-induced dermatitis [44]
	A9	gel	breast cancer	↓ acute skin reactions [45]
	A10	cream	breast cancer	protective role with ↓ radiation-induced dermatitis [46]
	A11	ointment	pelvic malignancies	improved proctitis and enhanced QOL [47]
	A12	gel	head/neck, abdomen tumors	protective effect to prevent skin reactions [48]

Table 2. *Cont.*

Plant	Trial	Part/Dosage Form Used	Type of Cancer	Results
Aloe	A13	mouthwash solution	acute myeloid and lymphocytic leukemia	↓ intensity of stomatitis pain [49]
	A14	juice	head and neck cancer	↓ severity of radiation-induced mucositis [50]
	A15	leaf extract cream	breast cancer	no effect on acute skin toxicity or symptom severity [51]
Black seeds	B1	seeds	brain tumor	↓ incidence of febrile neutropenia [52]
	B2	oil in soft gelatin capsule	lymphoblastic leukemia	↓ methotrexate hepatotoxicity [53]
Boswellia	C1	extract as tablet	glioblastoma multiform	↓ radio-chemotherapy-induced cerebral edema [54]
	C2	extract as capsule	brain tumors	↓ cerebral edema measured by MRI [55]
	C3	*Boswellia* as cream	breast cancer	↓ erythema and skin superficial symptoms [56]
	C4	spirulina–curcumin–*Boswellia* mixture	benign thyroid nodules	↓ size of benign thyroid nodules [57]
	C5	*Boswellia serrata* as OPERA	breast, lung, prostate, endometrial cancer	improved chemotherapy-induced peripheral neuropathy symptoms [58]
Chamomile	D1	flower infusion	gastric or colorectal cancer	↓ oral mucositis [59]
	D2	gel	head and neck cancer	↓ radiation-related dermatitis [60]
	D3	mouthwash	mucositis	no effect on 5-fluorouracil-induced mucositis [61]
Colocynth	E1	dry fruit extract oil	neuropathy	no improvement in peripheral neuropathy [62]
Garlic	F1	extracts as capsule	hematological malignancy	no effect in febrile neutropenia [63]
	F2	extract as capsule	colorectal adenoma	↓ adenomas and suppressed growth/proliferation [64]
	F3	extract as capsule	colon and liver cancer	improved NK cell activity [65]
	F4	extract + steam-distilled garlic oil in a supplement	gastric cancer	↓ mortality due to gastric cancer [66]
Ginger	G1	extract as capsules	solid tumors	↓ chemotherapy-induced nausea and vomiting [67]
	G2	ginger as capsules	chemotherapy	no effect on chemotherapy-induced nausea/vomiting [68]
	G3	extract + essential oil	thyroid cancer	effective to prevent salivary gland/thyroid cancer [69]
	G4	extract as capsule	lung, head/neck cancers	no effect on nausea due to cisplatin therapy [70]
	G5	ginger powder capsule	ovary and cervix cancers	no effect on nausea due to cisplatin therapy [71]
	G6	ginger powder capsule	bone sarcomas	effective in chemotherapy-induced nausea/vomiting [72]
	G7	extract as capsules	chemotherapy	no clear results mentioned [73]
	G8	powder capsules	breast cancer	↓ frequency of nausea and vomiting [74]
	G9	powder capsules	breast cancer	↓ frequency of nausea and vomiting [75]
	G10	essential oils	breast cancer	no effect in chemotherapy-induced nausea/vomiting [76]
	G11	powder capsules	breast cancer	no effect in chemotherapy-induced nausea/vomiting [77]

Table 2. *Cont.*

Plant	Trial	Part/Dosage Form Used	Type of Cancer	Results
Ginger	G12	powder capsules	lung cancer	no effect in chemotherapy-induced nausea/vomiting [78]
	G13	powder capsules	breast cancer	no well-defined effect in nausea and vomiting [79]
	G14	purified liquid extract in capsule	alimentary, breast, genitourinary, lung tumors	↓ severity of acute chemotherapy-induced nausea [80]
	G15	powder + yogurt	breast cancer	↓ nausea severity and vomiting episodes [81]
	G16	extract as capsule	chemotherapy	no benefit in chemotherapy-induced nausea/vomiting [82]
	G17	powder capsules	breast, bladder, lung, gastric, and prostate cancers	↓ nausea during chemotherapy [83]
	G18	extract as capsule	breast, lymphoma, and colon tumors	enhances chemotherapy-induced nausea-related quality of life and less cancer-related fatigue [84]
	G19	essential oil	acute leukemia and lymphomas, tumors	no significant decrease in nausea [85]
	G20	ginger moxibustion	ovarian, cervical, endometrial cancer	↓ gastrointestinal tract reactions to chemotherapy [86]
Onion	H1	fresh raw onion	breast cancer	↓ tumor markers in breast cancer [87]
Pomegranate	I1	whole fruit powder	prostate cancer	↓ prostate-specific antigen [88]
	I2	extract pills	prostate cancer	no effect on 8-hydroxy-20-deoxyguanosine levels [89]
	I3	extract pills	prostate cancer	↑ PSA (prostate-specific antigen) doubling time [90]
	I4	liquid extract	prostate cancer	no effect on PSA doubling time (PSADT) [91]
	I5	liquid extract	colorectal cancer	colon tissue gene expression changed [92]
	I6	liquid extract	colorectal cancer	effect on specific colon tissue miRs [93]
	I7	juice	prostate cancer	↓ proliferation marker (c-Myc) [94]
	I8	juice	prostate cancer	↑ PSA doubling time, cell proliferation, and apoptosis [95]
Senna	J1	sennosides as tablets	colon cancer	effective in bowel preparation for colon surgery [96]
	J2	syrup	lung, breast, stomach, liver, colon, prostate tumors	no efficacy of senna over lactulose in terminal cancer patients [97]
	J3	extract as tablet	lung, breast, gastric, liver, prostate tumors	no statistically significant difference in laxative action [98]
	J4	senna solution	colonic and rectal carcinoma	colonic or rectal resection with senna is better than polyethylene glycol, especially patients with stenosis [99]

Table 2. *Cont.*

Plant	Trial	Part/Dosage Form Used	Type of Cancer	Results
Terebinth	K1	extracted fruit oil as soap	colorectal cancer	safe use in the treatment of skin toxicity [100]
Thyme	L1	sage tea–thyme–peppermint hydrosol	colon, rectal, esophageal, gastric, breast cancers	↓ oral mucositis [101]
	L2	thyme honey	head and neck cancer	effective in radiation-induced oral mucositis [102]
	L3	thyme honey	head and neck cancer	effective in radiation-induced xerostomia [103]
Wheat	M1	fermented wheat germ extract	colorectal cancer	beneficial in colorectal cancer in terms of overall and progression-free survival [104]
	M2	fermented wheat germ extract	skin melanoma	effective with significant differences in progression-free (PFS) and overall survival (OS) [105]
	M3	wheat bran fibersupplement	colorectal cancer	inhibits DNA synthesis and epithelial cell proliferation in rectal mucosa crypts of colorectal cancer [106]
	M4	fermented wheat germ extract	solid cancers	↓ incidence of treatment-related febrile neutropenia in children with solid cancers [107]
	M5	wheat grass juice	breast cancer	↓ myelotoxicity, dose reductions, and need for granulocyte colony-stimulating factor support [108]
Wormwood	N1	oral artesunate	breast cancer	no major safety concerns were observed [109]

Table 3. Scales for clinical trial evaluation and the items in each scale.

Jadad Score Calculation	Final Delphi List	Cochrane Back Review Group List
Was the study described as randomized (this includes words such as randomly, random, and randomization)? Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer generated, etc.)?	1. Treatment allocation (a) Was a method of randomization performed? (b) Was the treatment allocation concealed?	Was the method of randomization adequate?
		Was the treatment allocation concealed?
Was the study described as double blind?	2. Were the groups similar at baseline regarding the most important prognostic indicators?	Were the groups similar at baseline regarding the most important prognostic indicators?
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?	3. Were the eligibility criteria specified?	Was the patient blinded to the intervention?

Table 3. *Cont.*

Jadad Score Calculation	Final Delphi List	Cochrane Back Review Group List
Was there a description of withdrawals and dropouts?	4. Was the outcome assessor blinded?	Was the care provider blinded to the intervention?
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.).	5. Was the care provider blinded?	Was the outcome assessor blinded to the intervention?
Deduct one point if the study was described as double blind but the method of blindingwas inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	6. Was the patient blinded?	Were co-interventions avoided or similar?
	7. Were point estimates and measures of variability presented for the primary outcome measures?	Was the compliance acceptable in all groups?
	8. Did the analysis include an intention-to-treat analysis?	Was the drop-out rate described and acceptable? Was the timing of the outcome assessment in all groups similar?

Table 4. Evaluation of clinical trials on the basis of various scales, where (X) represents the deficiency.

Plant	Study Number	* Jadad Deficiencies					Jadad Score (5)	** Delphi Deficiencies									Delphi Score (9)	*** Cochrane Deficiencies										Cochrane Score (10)	Total Score (24)
		a	b	c	d	e		a	b	c	d	E	f	g	h	i		a	b	c	d	e	f	g	h	i	j		
Aloe	A1	-	-	-	X	-	3	-	-	X	-	X	-	-	-	X	4	-	-	X	-	-	X	X	X	-	-	3	10
	A2	X	X	X	X	X	0	X	X	X	-	X	X	X	X	X	−1	X	X	X	X	X	X	X	X	X	-	−3	−4
	A3	X	X	X	X	X	0	X	X	X	-	X	X	X	-	-	1	X	X	X	X	X	X	X	X	X	-	−3	−2
	A4	-	-	-	-	-	5	-	-	X	-	-	-	-	-	-	7	-	-	X	-	-	-	X	X	-	-	4	16
	A5	-	X	-	-	-	3	-	-	X	-	-	-	-	-	X	7	X		X	-	-	-	X	-	-	-	7	17
	A6		X	X	X	-	2	-	X	X	X	X	X	X	X	X	0	X	X	X	X	X	X	X	X	-	-	0	2
	A7	-	-	-	-	-	5	-	-	-	-	X	-	-	-	X	6	-	-	-	-	-	X	X	X	-	-	6	17
	A8	-	-	-	X	-	3	-	-	-	-	X	-	-	-	X	6	-	-	-	-	-	X	-	X	-	-	6	15
	A9	X	X	X	X	-	1	X	X	X	-	X	X	X	-	X	0	X	X	X	X	X	X	-	X	-	-	0	1
	A10	-	X	X	X	X	0	-	X	X	-	X	X	X	-	X	1	X	X	X	X	X	X	-	X	X	-	−1	0
	A11	-	-	-	-	-	5	-	-	-	-	-	-	-	-	-	9	-	-	-	-	-	-	X	-	-	-	8	22

Table 4. *Cont.*

Plant	Study Number	* Jadad Deficiencies					Jadad Score (5)	** Delphi Deficiencies									Delphi Score (9)	*** Cochrane Deficiencies										Cochrane Score (10)	Total Score (24)
		a	b	c	d	e		a	b	c	d	E	f	g	h	i		a	b	c	d	e	f	g	h	i	j		
Aloe	A12	-	-	X	X	-	3	-	-	X	-	X		X	-	X	4	-	-	X	X		X		X	-	X	2	9
	A13	-	-	X	X	-	3	-	X	-	-	-	X	X	-	-	6	-	X		X	X	-	X	X	-	-	3	12
	A14	-	-	-	-	-	5	-	-	X	-	-	-	-	-	-	8	-	-	X	-	-	-	-	X	-	-	8	21
	A15	-	-	-	X	-	3	-	-	-	-	-	-	-	-	-	9	-	-	-	-	-	-	-	-	-	-	10	22
Black Seeds	B1	-	-	X	X	X	2	-	X	-	-	X	X	X	-	X	3	-	X	-	X	X	X	-	X	X	-	1	6
	B2	-	X	X	X	X	0	-	X	-	-	X	X	X	-	X	3	X	X	-	X	X	X	X	X	X	-	1	4
Boswellia	C1	X	X	X	X	-	1	X	X	X	-	X	X	X	-	X	−1	X	X	X	X	X	X	-	X	-	-	1	1
	C2	-	-	-	-	-	5	-	-	X	-	-	-	-	-	-	7	-	-	X	-	-	-	X	X	-	-	5	17
	C3	-	X	X	X	X	0	-	X	X	-	X	X	X	-	-	2	X	X	X	X	X	X	X	X	X	-	−5	−3
	C4	-	X	-	-	-	3	-	-	X	-	-	-	-	-	X	6	X	-	X	-	-	-	X	X	-	-	3	12
	C5	X	X	X	X	-	1	X	X	X	-	X	X	X	-	-	1	X	X	X	X	X	X	X	X	-	-	−1	1
Chamomile	D1	-	-	X	X	-	3	-	-	-	-	X	-	X	-	-	7	-	-	-	X	-	X	-	X	-	-	6	16
	D2	-	-	X	X	-	3	-	X	X	-		X	X		X	2	-	X	X	X	X		X	X	-	X	0	5
	D3	-	X	-	-	-	3	-	-	-	X	X	-	-	-	X	5	X	-	-	-	-	X	X	X	-	-	4	12
Colocynth	E1	-	-	-	-	-	5	-	-	-	-	-	-	-	-	-	9	-	-	-	-	-		X	-	-	-	9	23
Garlic	F1	-	-	-	-	-	5	-	-	-	-	X	-	-	-	X	6	-	-	-	-	-	X	X	X	-	X	4	15
	F2	-	X	-	X	-	1	-	-	-	-	X	-	-	-	X	7	X	-	-	-	-	X	X	X	-	-	4	12
	F3	-	-	-	-	-	5	-	-	X	-	X	-	-	-	-	5	-	-	X	-	-	X	X	-	-	-	5	15
	F4	-	-	-	-	-	5	-	-	X	-	X	-	-	-	-	5	-	-	X	-	-	X	X	-	-	-	4	14
Ginger	G1	-	-	-	X		3	-	-	X	-	X	-	-	-	-	6	-	-	X	-	-	X	X	-	-	-	6	15
	G2	-	X	-	-	X	2	-	X	-	-	X	-	-	-	X	3	X	-	X	-	-	X	X	X	X	X	−1	4
	G3	-	-	X	X		3	-	X	-	-	X	X	-	-	X	2	-	X	-	-	X	X	X	X	-	-	0	5
	G4	-	-	-	-	-	5	-	-	-	-	X	-	-	-	X	6	-	-		-	-	X	X	X	-	X	4	15
	G5	-	-	-	-	-	5	-	-	X		X	-	-	-	X	4	-	-	X	-	-	X	X	X	-	X	2	11
	G6	-	-	-	X	-	3	-	-	-	-	X	-	-	-	X	6	-	-	-	-	-	X		X	-	X	5	14
	G7	-	-	-	-	X	4	-	-	X	-	X	-	-	-	-	5	-	-	X	-	-	X	X	-	X	-	4	13
	G8	-	-	-	X	-	3	-	-	-	-	-	-	-	-	X	8	-	-	-	-	-	-	-	X	-	-	8	19
	G9	-	X	X	X	-	1	-	X	-	-	X	X	X	-	X	4	X	X	-	X	X	X	-	X	-	-	3	8
	G10	-	-	X	X	-	3	-	X	-	-	X	X	-	-	X	4	-	X	-	-	X	X	X	X	-	-	3	10
	G11	-	-	-	-	-	5	-	-	X	-	X	-	-	-	-	5	-	-	X	-	-	X	-	X	-	-	4	14
	G12	-	-	-	-	-	5	-	-	X	-	X	-	-	-	-	6	-	-	X	-	-	-	X	-	-	-	7	18
	G13	-	X	-	-	-	3	-	-	X	-	X	-	-	-	X	4	X	-	X	-	-	X	X	X	-	-	2	9
	G14	-	-	-	-	-	5	-	-	-	-	X	-	-	-	-	7	-	-	-	-	-	X	X	X	-	-	6	18

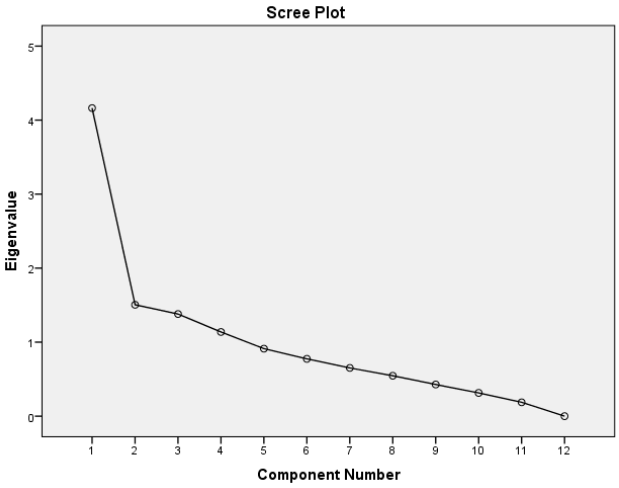
Table 4. *Cont.*

Plant	Study Number	* Jadad Deficiencies					Jadad Score (5)	** Delphi Deficiencies									Delphi Score (9)	*** Cochrane Deficiencies										Cochrane Score (10)	Total Score (24)
		a	b	c	d	e		a	b	c	d	E	f	g	h	i		a	b	c	d	e	f	g	h	i	j		
Ginger	G15	-	X	X	X	X	0	-	X	-	-	X	X	X	-	-	4	X	X	-	X	X	X	X	X	X	-	0	4
	G16	-	-	-	X	-	3	-	-	-	-	-	-	-	-	-	9	-	-	-	-	-	-	X	X	-	-	8	20
	G17	-	X	X	X	-	1	-	X	-	-	X	X	X	-	X	3	X	X	-	X	X	X	X	X	-	-	1	5
	G18	-	-	-	-	-	5	-	-	-	-	-	-	-	-	-	9	-	-	-	-	-	-	X	X	-	-	8	22
	G19	-	-	-	X	X	2	-	-	-	-	X	-	-	-	-	7	-	-	-	-	-	X	X	X	X	X	2	11
	G20	-	-	X	X	-	3	-	X	-	-	-	X	X	-	-	6	-	X	-	X	X	-	-	-	-	-	7	16
Onion	H1	-	-	-	-	-	5	-	-	-	-	-	-	-	-	X	8	-	-	-	-	-	-	-	-	-	-	10	23
Pomegranate	I1	-	-	-	-	-	5	-	-	-	-	-	-	-	-	X	8	-	-	-	-	-	-	X	-	-	-	8	21
	I2	-	-	-	-	-	5	-	-	-	-	-	-	-	-	X	8	-	-	-	-	-	-	X	X	-	-	7	20
	I3	-	-	-	X	-	3	-	-	-	-	X	-	-	-	-	7	-	-	-	-	-	X	X	X	-	-	6	16
	I4	-	-	-	-	-	5	-	-	-	X		-	-	-	-	8	-	-	-	-	-	-	-	-	-	X	8	21
	I5	-	X	X	X	-	1	-	X	-	-	X	X	X	-	X	3	X	X		X	X	X	X	X	-	X	0	4
	I6	-	-	-	X	-	3	-	-	-	-	X	-	-	-	X	6	-	-	-	-	-	X	X	X	-	X	3	12
	I7	-	X	X	X	X	0	-	X	X	-	X	X	X	-	X	1	X	X	X	X	X	X	X	X	X	-	−2	−1
	I8	X	X	X	X	-	1	X	X	X	-	-	X	X	-	X	2	X	X	X	X	X	-	-	X	-	-	2	5
Senna	J1	-	-	X	X	-	3	-	X	-	X	X	X	X	-	-	3	-	X	-	X	X	X	-	X	-	-	3	9
	J2	-	X	X	X	-	1	-	X	-	-	X	X	X	-	X	3	X	X	-	X	X	X	X	X	-	-	1	5
	J3	-	X	X	X	-	1	-	X	X	-	X	X	X	X	X	0	X	X	X	X	X	X	X	X	-	-	−1	0
	J4	-	-	X	X	-	3	-	-	-	-	X	-	X	-	X	5	-	-	-	X	-	X	X	X	-	X	2	10
Terebinth	K1	X	X	X	X	X	0	X	X	X	-	X	X	X	X	-	0	X	X	X	X	X	X	-	-	X	-	1	1
Thyme	L1	-	-	X	X	-	3	-	X	-	-	X	X	X	-	-	4	-	X	-	X	X	X	X	-	-	-	4	11
	L2	-	-	X	X	-	3	-	X	-	-	-	X	X	-	X	5	-	X	-	X	X	-	X	X	-	-	3	11
	L3	-	-	X	X	-	3	-	X	-	-	-	X	X	-	X	5	-	X	-	X	X	-	X	X	-	-	3	11
Wheat	M1	X	X	X	X	X	0	X	X	X	-	X	X	X	-	X	1	X	X	X	X	X	X	X	X	X	-	−1	0
	M2	-	X	X	X	-	1	-	X	-	-	X	X	X	-	X	3	X	X	-	X	X	X	-	X	-	-	2	6
	M3	X	X	X	X	X	0	X	X	X	-	X	X	-	-	-	2	X	X	X	-	X	X	-	-	X	-	2	4
	M4	X	X	X	X	X	0	X	X	-	-	X	X	X	-	-	3	X	X	-	X	X	X	X	X	X	-	0	3
	M5	-	X	X	X	X	0	-	X	-	-	X	X	X	-	-	4	X	X	-	X	X	X	-	X	X	-	2	6
Wormwood	N1	X	X	X	X	-	1	X	X	X	X	X	X	X	-	X	−1	X	X	X	X	X	X	X	X	-	-	−1	−1

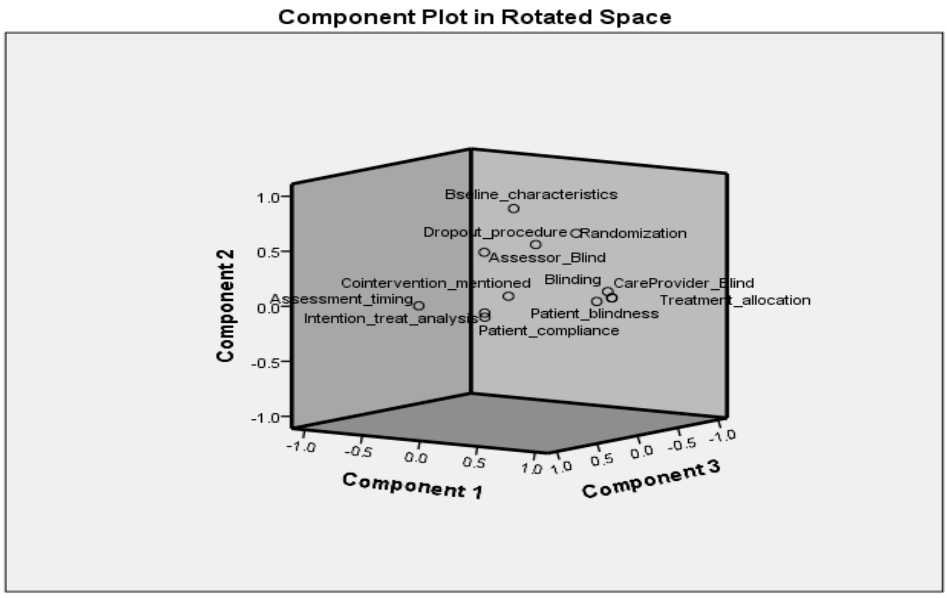
* Jaded deficiencies: a: randomization mentioned, b: randomization method, c: double-blind words, d: double-blind method, e: description of withdrawals and dropouts. ** Delphi scale deficiencies: a: randomization performed, b: treatment allocation concealed, c: similarity at baseline, d: eligibility criteria specified, e: outcome assessor blinded, f: care provider blinded, g: patient blinded, h: point estimates and of variability presented for the primary outcome measured, i: intention-to-treat analysis. *** Cochrane scale deficiencies: a: randomization adequate, b: treatment allocation concealed, c: similarity at baseline, d: patient blinded, e: care provider blinded, f: outcome assessor blinded, g: co-interventions avoided or similar, h: compliance acceptable, i: description of withdrawals and dropouts, j: similarity in timing of the outcome assessment.

3.4. Statistical Analysis

Statistical tools of PCA (principal component analysis) and Pearson's correlation were used to categorize the data. The factors analyzed showed a total variability of 68.21% for four components (PC1-PC4), as shown in Table 5. The scree plot for the components is presented in Figure 2. An individual variability (%) was observed as PC1 (30.81), PC2 (14.70), PC3 (12.69), and PC4 (9.99). The factors loaded in PC1, i.e., the highest variability, were the deficiencies of non-blinding of the clinical trials, no concealment of the treatment allocation, and non-blindness of the patient and care provider. The next high percentage variability, i.e., PC2, showed loading for deficiencies, non-randomization of the studies, non-blinding of the outcome assessors, no proper drop-out procedures, and lack of information regarding baseline characteristics for the groups. The individual percentage variability with cumulative percentage is shown in Table 5. In addition, a three-dimensional representation of the deficiencies in the components is shown in Figure 2.



(**a**)



(**b**)

Figure 2. Scree plot (**a**) and loading (**b**) of components.

Table 5. Principal components analysis (PCA) with component loading.

Factors	PC1	PC2	PC3	PC4
(A) Clinical trial randomized or non-randomized	0.542	0.662	−0.053	0.013
(B) Clinical trial blinded or non-blinded	0.792	0.153	−0.088	0.121
(C) Treatment allocation concealed or not	0.930	0.131	0.058	0.010
(D) The outcome assessor was blinded or non-blinded	0.090	0.515	0.441	−0.416
(E) Patient was blinded in the study or non-blinded	0.871	0.107	0.162	−0.067
(F) The care provider was blinded or non-blinded	0.930	0.131	0.058	0.010
(G) The intention to treat analysis was mentioned in clinical trial or not	0.168	−0.013	0.547	0.478
(H) Proper drop-out procedure mentioned or not	0.304	0.559	0.108	−0.162
(I) Patient compliance for the clinical trial reported or not	0.269	−0.020	0.689	0.061
(J) Timing of outcome assessment mentioned or not	−0.29	0.028	0.700	−0.092
(K) Baseline characteristics for the group were mentioned or not	−0.03	0.822	−0.100	0.215
(L) Co-interventions were mentioned or not	0.005	0.047	0.019	0.833
Variability %	30.81	14.70	12.69	9.99
Cumulative %	30.81	45.52	58.22	68.21

Pearson's correlation was constructed to cross-verify the PCA analysis. For Pearson's correlation, all the pairs showed a positive correlation, i.e., none of the pairs were found to have a negative correlation. A similar phenomenon to PCA was observed in Pearson's correlation. Even for the deficiency "co-interventions were not mentioned" that was loaded separately in PC4 of the PCA was observed with no correlation/pair to any other factors in Pearson's analysis. The correlation matrix for Pearson's analysis is shown in detail in Table 6.

The statistical analysis below confirms a descending order (Figure 3) of occurrence for the deficiencies.

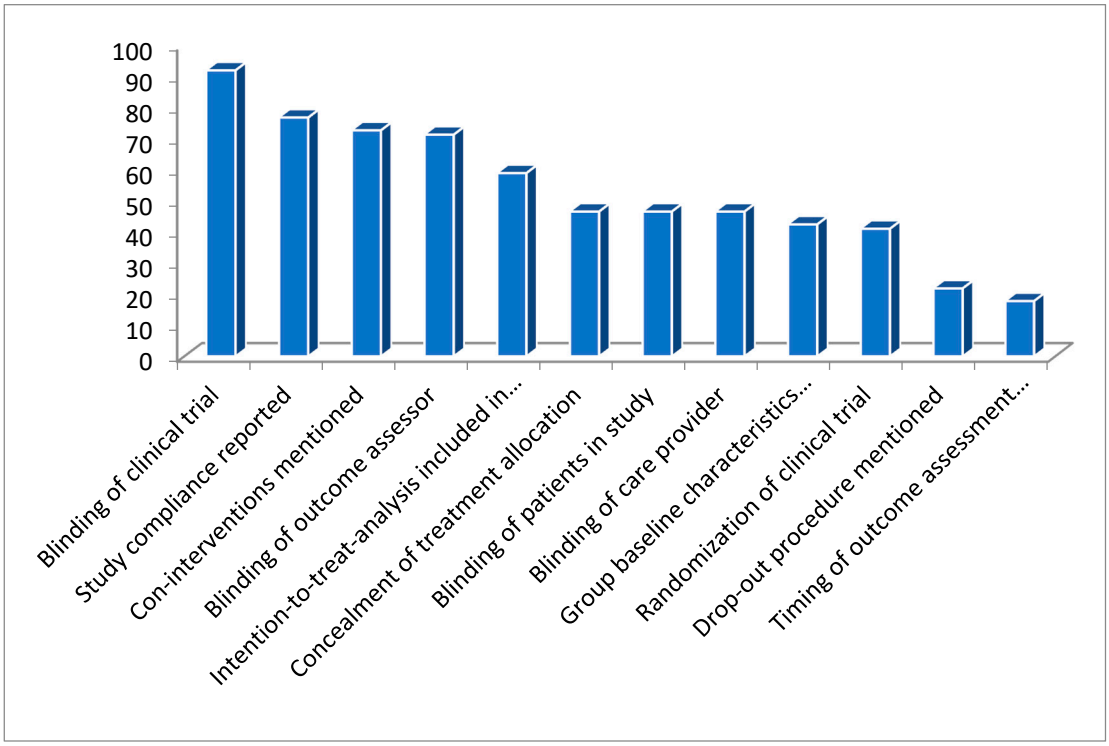


Figure 3. Figure representing the percentage of deficiencies in these clinical trials.

Table 6. Pearson correlation analysis; A-L denotes factors mentioned in Table 5.

	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**
A	1											
B	0.503	1										
C	0.54	0.626	1									
D	0.31	0.035	0.204	1								
E	0.516	0.72	0.767	0.164	1							
F	0.54	0.626	1	0.204	0.767	1						
G	0.155	0.13	0.172	0.065	0.166	0.172	1					
H	0.426	0.299	0.335	0.31	0.307	0.335	−0.059	1				
I	0.101	0.143	0.237	0.256	0.293	0.237	0.238	0.127	1			
J	−0.193	−0.209	−0.203	0.137	−0.033	−0.203	0.181	0.051	0.172	1		
K	0.453	0.151	0.102	0.187	0.101	0.102	0.037	0.184	−0.018	−0.009	1	
L	−0.036	0.07	0.053	−0.16	−0.058	0.053	0.145	0.051	0.093	−0.049	0.055	1

"non-blinding of clinical trials > no compliance reported for the study > co-interventions not mentioned > outcome assessor non blinded > intention-to-treat analysis was not included in a study > treatment allocation was not concealed > patients were non-blinded > care provider was non-blinded > group baseline characteristics were not mentioned > studies were non-randomized > drop-out procedure were not mentioned > timing for outcome assessment were not mentioned".

3.5. Score for Clinical Trials

An in-house grading scale was developed in order to simplify the classification of quality of the bulk of clinical trials. The clinical trials were graded out of 24 points, with distribution as "very poor quality" (≤6 including negative values), "poor quality" (7 to 12), "acceptable quality" (13 to 18), "good quality" (19 to 24). Detailed information regarding study score is given in Table 7. A small portion, i.e., 16.44% (12 out of 73) of the studies were found to be of good quality, whereas more than half the proportion (57.54%; 27 very poor + 15 poor quality) of the studies were found to be of poor quality.

Table 7. Final in-house scoring for the clinical trials.

Quality of Trial Based on Assigned Scale	Frequency (N)	Percent (%)	Cumulative Percent (%)
Very poor quality clinical trials (6 and below, i.e., negative value)	27	36.99	36.99
Poor quality clinical trials (7–12)	15	20.55	57.53
Acceptable quality clinical trials (13–18)	19	26.03	83.56
Good quality clinical trials (19–24)	12	16.44	100.00
Total	73	100.00	

4. Discussion

The evaluation and assessment of the clinical trials developed a few basic questions necessary for any study such as "what is the source/background of the herb?", "what is its phytochemical profile?", "what are the parts, dosage forms, and extraction solvents used?", "what is the asking information, dose used, and its clinical phase studied?" All these questions are summarized briefly below.

Source and background data regarding the herb: Basic information relevant to the herb in terms of family, genus, species, folkloric use in cancer, geographical origin, and identification from authentic resources are very important. The plant may vary with regard to phytochemistry, which is subjected to differences in terms of place of origin, wherein altitude, temperature, stress, salinity, irrigation, etc. may affect the nature and quantity of active chemical present [110,111]. The majority of the trials were unable to explain the authentication process for the source of plant used and its background information. This may affect the quality of a clinical trial.

Phytochemical profile for the part used: The part of a plant may differ in the nature and amount of active chemicals when compared to other parts of the same plant; hence, there is a need for proper phytochemical profiling. These clinical trials used various parts of the plants such as leaves, roots, fruits, infusion, juice, and essential oils; however, the phytochemistry for the part of the plant used was missing in most of the studies [100].

Final dosage form used and its preparation/extraction: A number of clinical trials used dosage forms (extract or dried powder in capsule/tablet, creams, gels, mouthwashes, liquid extract, pills, syrup, etc.), however, the method of extraction or dosage form preparation was observed often. For a herbal product to be effective, appropriate extraction/processing is the basic step for success. The factors

involved in extraction/drying/preparation of final dosage form (sunlight, temperature, solvent polarity and non-polarity, extraction time, pressure etc.) may either degrade or enhance the amount of an active ingredient or its activity thereof [112–114]. It is very crucial to investigate the effect of these factors upon the potential of an herbal dosage, but none of the clinical trial undertook such an investigation.

Choice of green solvent and extraction: Most of the extraction at present is performed using green solvents (water, ethanol, acetonitrile, etc.) due to dual properties of being eco- and human-friendly with less adverse effects. The infusion, juice, and fermentation products prepared in the reported clinical trials used alcohol-based solvents that are unhealthy, costly, and carry more adverse effects. Most of these solvents release toxic chemicals upon heating [115]. A need to shift to green extraction may be promoted.

Phase (0-V) selection: Although phase-0 is mandatory for sub-therapeutic dose and toxicity, often the phase-I studies are skipped for the herbs with proper ethnopharmacological/folklore data available at community level [116]. In such cases, phase-II studies are started without a prior phase-I study, and hence proper evidence is necessary for an herb to start with a clinical trial.

Masking of clinical study: Equally important, a clinical trial should be properly blinded with respect to the patient, care provider/administrator, and data assessor in order to avoid the risk of bias in the data [117,118]. A number of clinical trials we reported do present the issue of improper blinding.

Treatment strategy (interactions, complications, and duration): The duration of treatment needs to be shorter in order to avoid complications, particularly in subjects using conventional medication for treatment. These clinical trials continued the studies from weeks until years, which is difficult at times because the subjects enrolled may either have stopped conventional medication or are already using natural products. Herbs are best known for their cytochrome P450 inhibitory or induction properties, of which both are dangerous. A long-term treatment strategy may expose the subjects to various herb–drug/drug–food interactions and nutritional deficiencies, which may produce emergency conditions. All these factors are the major sources of non-compliance in a study, being was observed in most of these clinical trials [111,119,120].

Dose used: A dose up to 10 g in most of the cases was observed in these clinical trials. It is quite difficult to administer such a high dose in the form of a tablet or capsule as it outweighs the capacity for available size. In addition, it becomes impossible to administer a huge dose in divided doses, especially in subjects using conventional drugs where a serious risk of herb–drug interaction exists. More importantly for herbs with a lack of phase-0 data, it is a serious risk to use such a high dose that can predispose potential health risks. This urges researchers to explore the herb for proper phase-0 data, half-life, PKs (Pharmacokinetics), PDs (Pharmacodynamics), etc. and to ensure the quality variation for active principle in herbs, prior any clinical study [121,122]. The reported clinical trials did not mention any such information, which is utmost required for a study.

5. Recommendations to Enhance Quality of a Clinical Trial

Ethno-botanical/pharmacological and folklore evidence with quality evaluation: A detailed literature search needs to be ensured in order to collect appropriate information regarding the folklore use of a herb in various communities, followed by uniformity of geographical origin, part, family, genus, and species of the herb to study. In addition, a proper phytochemical profile must be established to evaluate and declare the quality and quantity of active chemicals present in a herb that are responsible for anticancer effects [117,118].

Herbal pharmacovigilance: Herbal pharmacovigilance is necessary to ensure the mainstream data necessary for a herbal clinical trial. Phase-0, i.e., toxicity studies, sub-therapeutic dose selection, adverse effects of the herb/herbal product, long-term effects, and herb–drug/food interaction studied, as well as PKs and PDs for half-life, metabolizing enzymes, and the excretion process need to be established. Pharmacovigilance assures a small dose with shorter treatment strategy/duration so as to avoid the untoward effects of the herb, especially when combined with conventional drugs. In addition, the pharmacovigilance ensures the quality variation and standardization of herbs [121,122].

Need for extraction or isolation and shape of final dosage form: The researcher needs to be clear regarding the pros and cons related to extracts/extraction and isolation. It is tiresome to isolate an active chemical; however, extracts due to presence of multi component nature pose restriction and complications when it is needed to study the molecular or genetic level effects for a treatment. Pursuit of isolation of the main active ingredient responsible for the cancerous effects in a herbal product/extract is mainly favored. In addition, dosage form compatibility is more important. Powder drugs and injectables are more easily absorbed and show enhanced bioavailability and therapeutic effects; still, the idea of nanoformulations, i.e., nano-particles, emulsions, micelles, and gels are more preferred due to low dose, enhanced and targeted treatment, and less side effects or adverse effects.

Clinical trials with tailored treatment approach: The paradigm shift from empirical to tailored approach, i.e., treatment strategy based on biologically relevant question, is the upcoming future for cancer clinical trials. Although the idea demands a profound change in infrastructure and methodology of clinical research and is challenging, it will bring about new opportunities in cancer treatment with a better understanding of the disease and mechanism of action of the treating agent [123]. The clinical trials may focus on acquiring such concept.

Immune-oncology: Clinical trials with a specific focus on immune boosting properties are also a unique source of accelerating cancer treatment [124]. A number of herbs such as leaves of muicle, aguacate, and muerdago; bark of cuachalalate and una de gato; and roots of matarique and guizazo de caballo have immune-enhancement/stimulant properties that may serve as a novel source of cancer treatment [125].

Nano-oncology: Nano-dosage form in the shape of liposomes, dendrimers, gold nanoparticles, micelles, nanoemulsions, nanogels, etc. are widely used in cancer treatment as they are inert, noncorrosive, targeted, safe, and free of the adverse effects associated with conventional treatments. A number of nano-dosage forms such as Myocet and Doxil for doxorubicin are available in the market [126]. It is worthwhile to convert the herbal products or extracts into various nano-dosage forms, which may add the benefits of more therapeutic efficiency and less adverse effects.

Precision medicine: Avoiding the idea of "one-size-fits-all" and matching the most appropriate and relevant individualized treatment approaches for a patient on the basis of the genetic profile of the patient and cancer type is known as precision medicine [127] In spite of tumor heterogeneity, which may affect precision medicine, promising outcomes may be observed if precision medicine is applied in herbal clinical trials.

6. Conclusions

The clinical trials in the systemic review revealed a poor quality according to the evaluation scales used. The majority of the studies were non-blinded and non-randomized. With respect to herbs used, a proper pharmacovigilance background was not reported in the studies. It is highly recommended that researchers enhance/uplift the studies of these clinical trials via addition of appropriate ethnopharmacological relevance, quality variation and standardization, phytochemical profile, focus on the hot area of cancer, and precision medicine when planning to conduct a clinical trial using a herb (powder/extract, etc.) or herbal product.

Author Contributions: R.A. and L.H.A. conceived the idea, study design, methodology, statistical analysis, discussion, and conclusion; L.H.A., A.K.A. and S.M.A. was responsible for the literature review, data extraction, introduction write up, evaluation, and scoring of individual clinical trial with tables for ethnopharmacological relevance and deficiencies/scoring of the clinical trials, as well as arrangement of the references. R.A. conducted analyses. All authors have read and agreed to the published version of the manuscript.

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