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Phytocannabis for the treatment of cancer-related or cancer treatment related symptoms: Evidence Based Review

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Abstract

Cancer is defined as a generic term for a large group of diseases that was observed to affect any part of the body, often characterized by abnormal rapid growth of abnormal cells. According to WHO report, Cancer was the leading cause of morbidity and mortality worldwide. The primary goal of the treatment is to cure cancer or to considerably prolong life, along with improved patient's quality of life by palliative care, psychological support and alternative treatments. The present report focused on the use of Phytocannabis and its derivatives to alleviate the symptoms occurred due to cancer that included reduced appetite, chemotherapy-induced nausea and vomiting, radiotherapy-induced pain, nausea and vomiting in order to attenuate the disease process. Cancer, Chemotherapy and Radiotherapy-induced emesis and pain, all these mentioned factors led to the interrogation and investigation of the anti-emesis, pain relief, and mood stabilizing properties of Phytocannabis. This study presented the update on health and social consequences of Phytocannabis use, with a focus on the long-term and frequent use of medicinal Cannabis and its derivatives in alleviating the cancer related symptoms. It aimed to present the current knowledge on the impact of Phytocannabis use on health, from its impact on treating cancer related symptoms to its role in chemotherapy and Radiotherapy induced symptoms. This report evaluated the evidence on whether long-term Phytocannabis use is a contributory cause of the following health outcomes: relief from pain, nausea, vomiting, appetite, food taste, night sweats, and adverse physical and mental health effects such as mood swings, fatigue, hallucinations, postural hypotension, dizziness, mind alertness. Thus, the present paper reported of the use of Phytocannabis and its derivatives such as, Nabilone, Delta-9-THC, and Cannabis available in different forms (Oral, Inhaled, Sublingual) on the Quality of life of cancer patients who underwent Chemotherapy treatment and Radiotherapy treatment.

***Keywords*:** *'cannabis', 'marijuana', 'cannabinoids', 'tetrahydrocannabinol', 'THC', 'dronabinol', 'cannabidiol', 'CBD', 'cannabidivarin', 'nabilone', 'CBDV', 'cancer', 'chemotherapy', 'radiotherapy' ,'nausea' 'vomiting', 'pain', 'open-label studies', Randomized controlled trials'.*

Abbreviations

THC = Tetrahydrocannabinol
WHO = World Health Organization
CBD = Cannabinoid
CBM = Cannabis based medicine
CBN = Cannabinol

Introduction

Cancer today has become the leading cause of death worldwide, which accounted for approximately 8.2 million deaths in the year 2012[1]. According to WHO survey report, the most common cause of cancer deaths were observed for lung cancer (1.59 million deaths), liver cancer (745 000 deaths), stomach cancer (723 000 deaths), colorectal cancer (694 000 deaths), breast cancer (521 000 deaths), esophageal cancer (400 000 deaths) [1]. Epidemiologically, it was observed that approximately more than 60% of the world's total

new annual cases along with 70% of the world's cancer deaths occured in Africa, Asia and Central and South America [1]. This disease burden had led to the invention of various effective conventional treatments [1]. However, there were very few of the treatments found to be effective in improving the quality of life of cancer patients undergoing different regimen of treatments[1]. Therefore, the present paper highlighted the use of Phytocannabis as an alternative treatment to alleviate the side effects produced in the treatment of cancer[1]. Phytocannabinoids weredefined as the cannabinoid compounds that were obtained from the female*Cannabis sativa* or *Cannabis indica*plant which wasfound to act on cannabinoid receptors in cells that modulated neurotransmitter release in the brain[1, 2]. The principal cannabinoids in the cannabis plant included delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN)[1, 2]. The known chemical composition of *Cannabis sativa* kept constantly changing[2]. From 2005 to 2015, the number of cannabinoids identified in the whole plant increased from 70 to 104 and other known compounds in the plant increased from some 400 to around 650[2]. Nevertheless, there were some relatively good data on the prevalence of Phytocannabis in some parts of the world[2]. Levels of lifetime use differ considerably between countries, ranging from around one third of adults in Denmark, France and the United Kingdom, to 8% or less than 1 in 10 in Bulgaria, Romania and Turkey [2].

Aim

The main objective of this review was:

a. To understand the role of Phytocannabis and its derivatives in the treatment of cancer associated symptoms, like pain, nausea and vomiting,
b. To assess clinical safety and efficacy of Phytocannabis in reducing accompanied symptoms due to result of cancer, Chemotherapy or Radiotherapy treatment,
c. To evaluate the potential therapeutic value of Phytocannabis in preventing cancerous tumor growth, as well as, alleviating and reduction in pain, nausea and vomiting.
d. To collect more data on the increasing use of PHYTOCANNABIS in CANCER.

Search methodology

The primary and foremost point that was focused throughout the article review was 'Cannabis and Cancer'. All types of studies were included in this regard. Moreover, children, Adolescents and Adults suffering from Cancer were included in this review. The methodology being adopted for the relevant literature review, searching the databases like, PUBMED, Cochrane Library, MEDLINE, EMBASE, Clinical trials.gov by using keywords such as, 'cannabis', 'marijuana', 'cannabinoids', 'tetrahydrocannabinol', 'THC', 'cannabidiol', 'CBD', 'cannabidivarin', 'CBDV', 'cancer', 'nausea' and 'vomiting' was utilized. Moreover, a greater number of google searches were done to gather reliable and valid information from websites primarily focusing on safety and efficacy of medicinal cannabis used in cancer patients. The search was confined to studies being published in English language. Moreover, PRISMA methodology was adopted for inclusion of relevant studies.

Prisma flowchart methodology

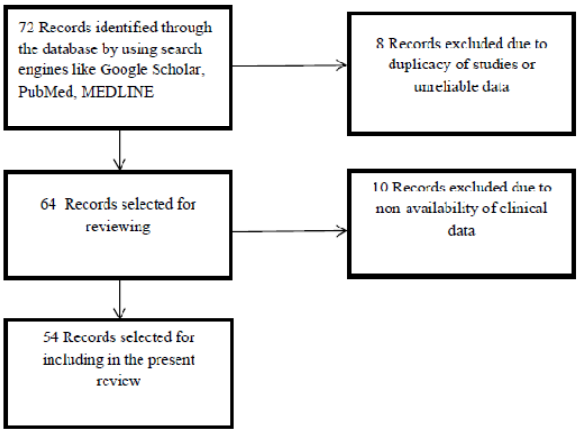

Fig 1*:* PRISMA FLOWCHART For Selection of Clinical Studies.

Description of Randomized Controlled Clinical Studies

S.No.	Study	Indication	Population	Study Design	Intervention + Route of Administration	Intervention	Control	Results	Adverse Events	Significance
1.	Côté, M. *et al*. 2015 [3].	Cancer	56 patients with cancer undergoing Radiotherapy	Controlled study	Nabilone Orally	Nabilone	Placebo	Pain, nausea and loss of appetite persisted	Weight reduction and abrupted sleep	Efficacy not obtained, no significant results
2.	Lynch, M.E. *et al*. 2014 [4].	Cancer	16 patients with chemotherapy-induced neuropathic pain	Controlled study, cross-over study	Cannabis Sublingually	cannabinoid agent, nabiximols (oral mucosal spray containing cannabinoids)+ Chemotherapy	Placebo	Greater reduction in pain	Nausea and loss of appetite	Reduction in pain intensity
3.	Portenoy, R.K. *et al*. 2012 [5].	Cancer	263 patients with advanced cancer	Controlled study	Cannabis Sublingually	nabiximols at a low dose (1-4 sprays/day), medium dose (6-10 sprays/day), or high dose (11-16 sprays/day)	Placebo	Reduction in pain	Dose related side effects	Could be considered as an add-on Therapy for additional pain reduction
4.	Brisbois,	Cancer	46	Controlled	Delta-9-THC	THC (2.5 mg, n	placebo	THC	None	useful in the

	T.D. *et al.* 2011 [6].		patients with advanced cancer	study	Orally	= 24)	oral capsules (n = 22) twice daily for 18 days	improved taste and appetite		palliation of chemosensory alterations and improved food taste
5.	Duran, M. *et al.* 2010 [7].	Cancer	16 patients of chemotherapy-induced nausea	Controlled study	Cannabis Sublingually	cannabis-based medicine (CBM) containing delta-9-tetrahydrocannabinol and cannabidiol	Placebo (standard anti-emetic treatment)	Reduction in nausea and vomiting	no relevant side-effects	Well tolerated drug
6.	Johnson, J.R. *et al.* 2010 [8].	Cancer	177 cancer patients with pain	Controlled study	Cannabis + Delta-9-THC extract Sublingually	THC:CBD extract (n = 60), THC extract (n = 58)	Placebo (n = 59)	Improved sleep quality, reduced pain and nausea	drug-related adverse events	A cannabis extract containing THC:CBD was superior in reducing pain
7.	Meiri, E. *et al.* 2007 [9].	Cancer	64 patients undergoing chemotherapy	Controlled study	Delta-9-THC Orally	dronabinol, ondansetron, or combination therapy	Placebo	Reduction in nausea and vomiting	no relevant side-effects	Well tolerated
8.	Strasser, F. *et al.* 2006 [10].	Cancer	243 cancer patients with weight	Controlled study	Cannabis + Delta-9-THC extract orally	Cannabis Extract n= 95 (standardized for 2.5 mg THC and 1 mg	Placebo (n= 48)	Increased appetite	no relevant side-effects	Well tolerated

			loss			cannabidiol) or THC (2.5 mg) n= 100				
9.	Jatoi, A. *et al.* 2002 [11].	Cancer	469 cancer patients	Controlled study	Delta-9-THC Orally	1. oral megestrol acetate 800 mg/d liquid suspension + placebo, 2. oral dronabinol 2.5 mg twice a day + placebo, or 3. both agents	placebo	Improved appetite	no relevant side-effects	Combination therapy not effective
10.	Lane, M. *et al.* 1991 [12].	Cancer	67 patients on various cancer chemotherapy treatments	Controlled study	Delta-9-THC Orally	1. dronabinol 10 mg every 6 hr plus placebo; 2. placebo plus prochlorperazine 10 mg every 6 hr; or 3. dronabinol and prochlorperazine, each 10 mg every 6 hr	placebo	Prevented vomiting	no relevant side-effects	Effective treatment
11.	McCabe, M. *et al.* 1988	Cancer	36 patients with	Controlled study	Delta-9-THC Orally	Oral Delta-9-THC	Placebo (Prochlorperazine)	Reduction in nausea and vomiting	Dysphoria	Excellent antiemetic control

	[13].		cancer							
12.	Chan, H.S. *et al.* 1987 [14].	Cancer	30 children with cancer	Controlled study	Nabilone orally	Oral Nabilone	Placebo (prochlorperazine)	Reduction in vomiting	dizziness, drowsiness, and mood alteration	safe, effective, and well-tolerated
13.	Dalzell, A.M. *et al*. 1986 [15].	Cancer	18 children with cancer	Controlled study	Nabilone orally	cannabinoid nabilone	Placebo (oral domperidone)	Reduction in nausea and vomiting	Dizziness and hallucinations	Better alternative to conventional antiemetic treatment
14.	Niederle, N. *et al*. 1986 [16].	Cancer	20 cancer patients	Controlled study	Nabilone orally	Oral Nabilone	Placebo (alizapride)	Reduction in nausea and vomiting	Dose-related toxicity	Better tolerated
15.	Pomeroy, M. *et al*. 1986 [17].	Cancer	38 cancer patients	Controlled study	Nabilone orally	cannabinoid nabilone	Placebo (butyrophenone analogue domperidone)	Reduction in nausea and increased appetite	drowsiness, dizziness, dry mouth, and postural hypotension	Better tolerated
16.	Ungerleider, J.T. *et al.* 1985 [18].	Cancer	139 patients who received both medications	Controlled study	Delta-9-THC Orally	Oral Delta-9-THC	Placebo Compazine (prochlorperazine)	Mood effects, nausea reduction	Dose-related toxicity	Well tolerated
17.	Niiranen, A., & Mattson, K.	Cancer	24 cancer patients	Controlled study	Nabilone orally	Nabilone	Placebo (prochlorperazine)	Reduction in vomiting	Vertigo, mild drowsiness	Well tolerated

	1985 [19].									
18.	Citron, M.L. *et al.* 1985 [20].	Cancer	26 cancer patients	Controlled study	Delta-9-THC Orally	Delta-9-THC	levonantradol	Reduction in vomiting	drowsiness and dizziness	Effective treatment
19.	Levitt, M. *et al.* 1984 [21].	Cancer	20 chemotherapy patients	Controlled study	Inhalation of Cannabis+ Delta-9-THC Orally	Oral Delta-9-Tetrahydrocannabinaol (THC)	Inhaled cannabis	Reduction in vomiting	mild psychological side effects	Greater potency of THC achieved
20.	Ahmedzai S, *et al*. 1983 [22].	Cancer	34 patients with lung cancer	Controlled study	Nabilone orally	Nabilone	Placebo (Cyclophosphamide, Adriamycin and Etoposide)	Reduction in nausea, retching and vomiting	Drowsiness, Euphoria, postural dizziness, lightheadedness, reduced systolic blood pressure	Well tolerated, effective oral anti-emetic drug
21.	George, M. *et al*. 1983 [23].	Cancer	20 patients with advanced gynaecological cancer who received Chemotherapy	Controlled study	Nabilone orally	Nabilone	Placebo (chlorpromazine)	No significant change	somnolence, dry mouth and orthostatic hypotension	No significant effect still patients preferred Nabilone
22.	Hutcheon	Cancer	108	Controlled	Levonantradol	Levonantradol	Placebo	Reduction in	Minimal side	Well

	, A.W. *et al.* 1983 [24].		patients undergoing cancer chemotherapy	study	orally	cannabinoid	(chlorpromazine)	vomiting	effects	tolerated
23.	Ungerleider, J.T. *et al.* 1982 [25].	Cancer	214 cancer patients receiving chemotherapy	Controlled study	Delta-9-THC Orally	Delta-9-THC	Placebo (prochlorperazine)	Reduction in nausea and vomiting	less ability to concentrate , less social interaction, and less activity	Well tolerated
24.	Johansson, R. *et al.* 1982 [26].	Cancer	27 patients on chemotherapy	Controlled study	Nabilone orally	Nabilone	Placebo (prochlorperazine)	Reduction in nausea, vomiting and dry retching episodes	Postural hypotension, Vertigo, headache, depression, general weakness, mood alterations with dysphoria	Well tolerated
25.	Jones, S.E. *et al.* 1982 [27].	Cancer	54 patients who experienced nausea and vomiting due to chemotherapy	Controlled study	Nabilone orally	Nabilone	Placebo	Reduction in nausea and vomiting	dizziness, drowsiness, dry mouth, sleep disturbance, ataxia	Well tolerated

26.	Chang, A.E. *et al.* 1981 [28].	Cancer	8 patients on chemotherapy	Controlled study	oral and inhaled delta-9-tetrahydrocannabinol (THC)	oral and smoked delta-9-tetrahydrocannabinol (THC)	Placebo (Adriamycin and Cytoxan chemotherapy)	No significant effect on nausea and vomiting produced	Minimal	No significant change
27.	Neidhart, J.A. *et al.* 1981 [29].	Cancer	52 patients with cancer chemotherapy	Controlled study	Delta-9-THC orally	Delta-9-THC	Placebo (haloperidol)	Reduction in nausea and vomiting	no serious side effects	Well tolerated
28.	Einhorn, L.H. *et al.* 1981 [30].	Cancer	85 patients receiving chemotherapy	Controlled study	Nabilone orally	Oral Nabilone	Placebo (prochlorperazine)	Reduction in nausea and vomiting	hypotension and lethargy	Well tolerated
29.	Sallan, S.E. *et al.* 1980 [31].	Cancer	20 cancer patients	Controlled study	Delta-9-THC orally	Oral Delta-9-THC	Placebo (prochlorperazine)	Reduction in nausea and vomiting and improved appetite	minimal	Well tolerated
30.	Orr, L.E. *et al.* 1980 [32].	Cancer	55 cancer patients	Controlled study	Delta-9-THC orally	Oral Delta-9-THC	Placebo (prochlorperazine)	Reduction in nausea and vomiting and improved appetite	no serious side effects	Well tolerated
31.	Steele, N. *et al.* 1980 [33].	Cancer	37 patients on chemother	Controlled study	Nabilone orally	Oral Nabilone	Placebo (prochlorperazine)	Reduction in vomiting	Mild drowsiness and dizziness	Well tolerated

			apy							
32.	Frytak, S. *et al.* 1979 [34].	Cancer	116 cancer patients	Controlled study	Delta-9-THC orally	Oral Delta-9-THC	Placebo ,prochlorperazine	Reduction in vomiting	psychic effects	Well tolerated
33.	Chang AE et al. 1979 [35].	Cancer	15 patients receiving chemotherapy	Controlled study	oral and inhaled delta-9-tetrahydrocannabinol (THC)	oral and smoked delta-9-tetrahydrocannabinol (THC)	Placebo (methotrexate)	Reduction in nausea and vomiting	no serious side effects	Well tolerated
34.	Herman, T.S. *et al.* 1979 [36].	Cancer	113 cancer patients receiving chemotherapy	Controlled study	Nabilone orally	Oral Nabilone	Placebo (prochlorperazine)	Reduction in nausea and vomiting	somnolence, dry mouth and dizziness	Well tolerated
35.	Sallan, S.E. *et al.* 1975 [37].	Cancer	84 cancer patients	Controlled study	Delta-9-THC orally	Oral Delta-9-THC	Placebo	Reduction in vomiting	Sedation and mental clouding	Well tolerated
36.	Noyes, R. Jr *et al.* 1975 [38].	Cancer	10 cancer patients	Controlled study	Delta-9-THC orally	Oral Delta-9-THC	Placebo	Reduction in pain	substantial sedation and mental clouding	Well tolerated
37.	Noyes, R. Jr *et al.* 1975 [39].	Cancer	36 cancer patients	Controlled study	Delta-9-THC orally	Oral Delta-9-THC	Placebo	Reduction in pain	somnolence, dizziness, ataxia, and blurred vision	Small dose well tolerated

Description of open label clinical studies

S.No.	Study	Indication	Population	Study Design	Intervention + Route of Administration	Intervention	Control	Results	Adverse Events	Significance
1.	Waissengrin, B. *et al.* 2015 [40].	Advanced Cancer	113 patients with cancer	Open-label study	Cannabis orally and by inhalation	Detailed Questionnaire	Nil	Pain reduction, Improvement in appetite, Reduced nausea	fatigue and dizziness	Highly effective
2.	Johnson, J.R. *et al.* 2013 [41].	Cancer	43 patients with chronic cancer pain	Open-label study	Cannabis Sublingually	THC/CBD spray (n=39) + THC spray (n=4)	Placebo	Improvement in insomnia, pain, and fatigue	None serious side effect	Long-term use Well tolerated
3.	Maida, V. *et al.* 2008 [42].	Cancer	112 patients with advanced cancer	Open-label study	Nabilone orally	Nabilone (n = 47)	Placebo (n = 65)	Improvement in appetite and reduction in pain, nausea, anxiety and overall distress	no relevant side-effects	Significant improvement of pain
4.	Maida, V. 2008	Cancer	4 advanced	Open-label	Nabilone orally	synthetic orally administered	Nil	Significant improvement	None	Well tolerated

	[43].		cancer patients with severe night sweats	study		cannabinoid Nabilone (n = 4)		of night sweats within 2 days		
5.	Engels, F.K. *et al.* 2007 [44].	Cancer	24 cancer patients treated with irinotecan or docetaxel	Open-label study	Cannabis orally as herbal tea	irinotecan (600 mg, n = 12) + medicinal cannabis; docetaxel (180 mg, n = 12) + medicinal cannabis	Placebo	Reduction in pain	no relevant side-effects	Well tolerated
6.	Maida V. 2006 [45].	Cancer	139 cancer patients	Open-label study	Nabilone orally	Nabilone (n = 82)	Placebo (n = 57)	improved pain, nausea, insomnia, night sweats, distress	Anxiety and Depression	Well tolerated
7.	Zutt, M. *et al.* 2006 [46].	Cancer	7 patients with hematogenous metastatic melanoma	Open-label study	Delta-9-THC Orally	Dronabinol n= 7	After 4 weeks evaluation from baseline	increase in appetite and decrease in nausea	dizziness	Well tolerated
8.	Guzman, M. *et al.* 2006 [47].	Cancer	9 patients with glioblastoma multiforme (brain	Open-label study	Delta-9-THC intratumoraly	Delta-9-THC n = 9	After 24 weeks (dose escalation regimen)	antiproliferative action on tumor cells	no relevant side-effects	Well tolerated+ safety profile

			tumor)							
9.	Musty, R.E.& Rossi, R. *et al.* 2001 [48].	Cancer	1093 patients	Open-label study	Inhalation of Cannabis+ Delta-9-THC Orally	Inhalation of Cannabis (n= 748); oral THC capsule (n = 345)	placebo	relief from nausea and vomiting	no relevant side-effects	Canbe used as an add-on therapy for relief from nausea and vomiting
10.	Abrahamov, A. *et al.* 1995 [49].	Cancer	8 children with cancer	Open-label study	Delta-9-THC Orally	Delta-9-THC 2 hours before chemotherapy	From baseline	complete prevention of vomiting	no relevant side-effects	Well tolerated
11.	Nelson, K. *et al.* 1994 [50].	Cancer	18 patients with cancer	Open-label study	Delta-9-THC Orally	Delta-9-THC	one hour after meals for four weeks	Increased appetite	no relevant side-effects	effective appetite stimulant
12.	Wadleigh, R. *et al.* 1990 [51].	Cancer	30 cancer patients.	Open-label study	Delta-9-THC Orally	dronabinol	placebo	stimulated mood and appetite	Weight loss	Well tolerated
13.	Cunningham, D. *et al.* 1988 [52].	Cancer	80 chemotherapy patients	Open-label study	Nabilone orally	Nabilone + prochlorperazine	Placebo (metoclopramide and dexamethasone)	Complete control of nausea and vomiting	no relevant side-effects	Better tolerated
14.	Vinciguerra, V. *et al.* 1988 [53].	Cancer	56 patients with cancer	Open-label study	Inhalation of Cannabis	Inhaled Cannabis	Placebo	Reduction in nausea and vomiting	Sedation and xerostomia	Well tolerated
15.	Priestman, T.J., &	Cancer	30 patients	Open-label	Nabilone orally	Nabilone	Placebo (metoclopr	Reduction in resistant	Minimal side effects	Efficacy of Nabilone

	Priestman, S.G. 1984 [54].		undergoing radiotherapy	study			amide)	radiation-induced sickness.		

Description of uncontrolled case reports:

S.No.	Study	Indication	Population	Study Design	Intervention + Route of Administration	Intervention	Control	Results	Adverse Events	Significance
1.	Gottschling, S. 2011 [55].	Cancer	50 children with cancer	Uncontrolled case report	Delta-9-THC Orally	Dronabinol dose was 0.2 mg/kg bodyweight in children	Placebo	Reduced pain, spasticity and improved appetite and nausea	no relevant side-effects	No relevant side effects on long-term treatment
2.	Gonzalez-Rosales, F., & Walsh, D. 1997 [56].	Cancer	1 patient (whole brain radiation)	Uncontrolled case report	Delta-9-THC Orally	Dronabinol	Placebo	Relief from nausea and vomiting	no relevant side-effects	Well tolerated

7. Data interpretation

On the basis of the data collected and retrieved, following observations were made in the form of plots and graphs.

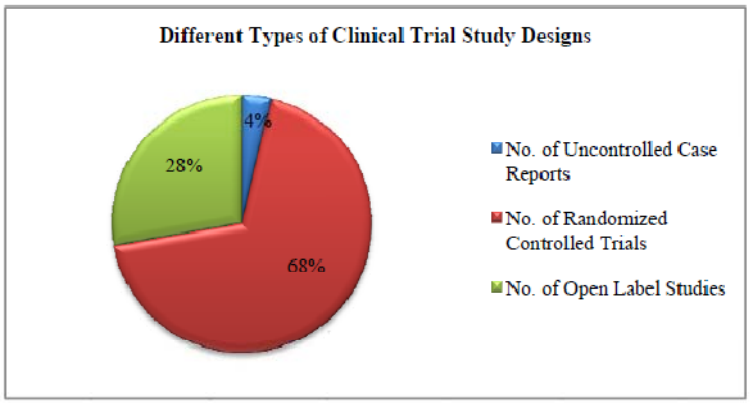

Fig. 2. Different Clinical Study Designs[3-56].

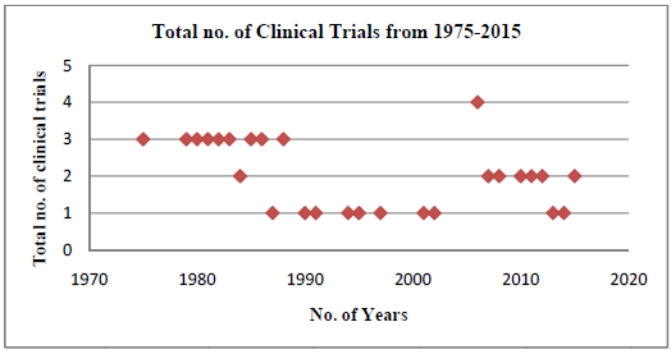

Fig. 3. Clinical Trials from 1975-2015[3-56].

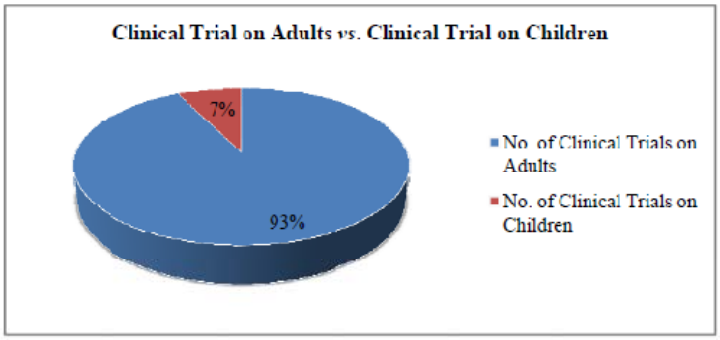

Fig. 4. Adults Clinical Trials vs. Chidren Clinical Trials[3-56].

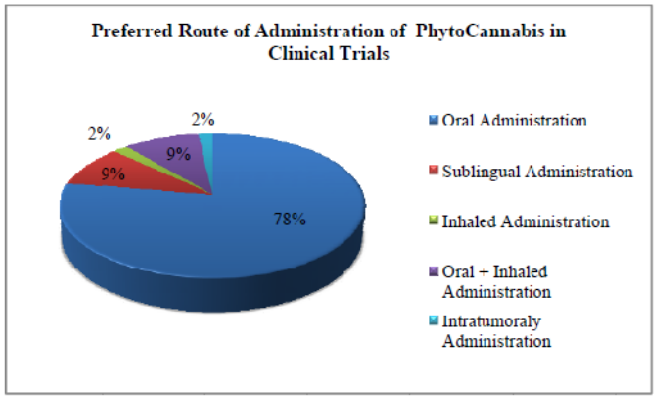

Fig. 5 Preferred Route of Administration of PhytoCannabis[3-56].

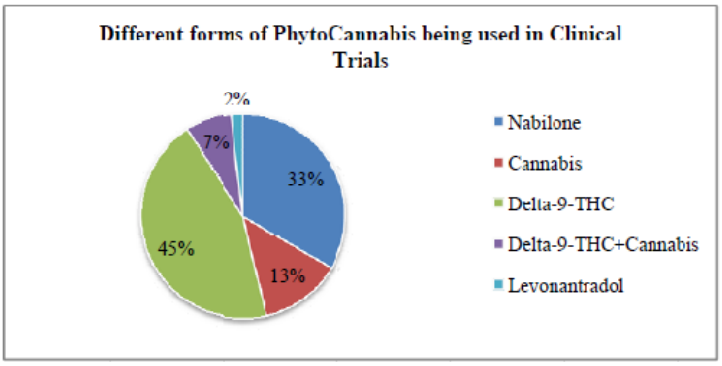

Fig. 6. Different forms of PhytoCannabis Used[3-56].

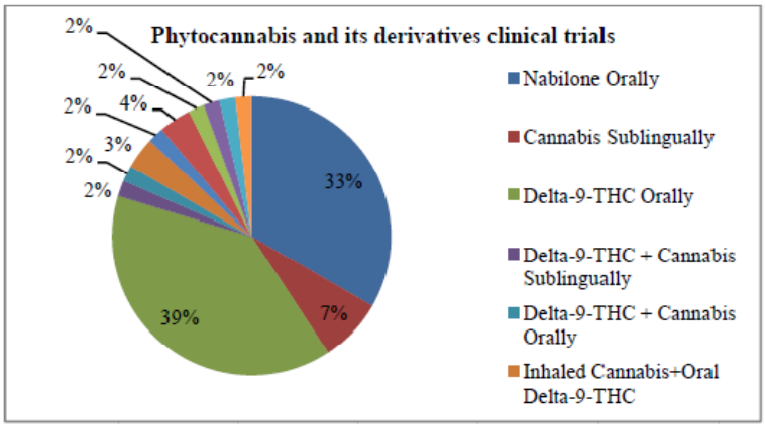

Fig. 7. Phytocannabis and its derivatives clinical trials[3-56].

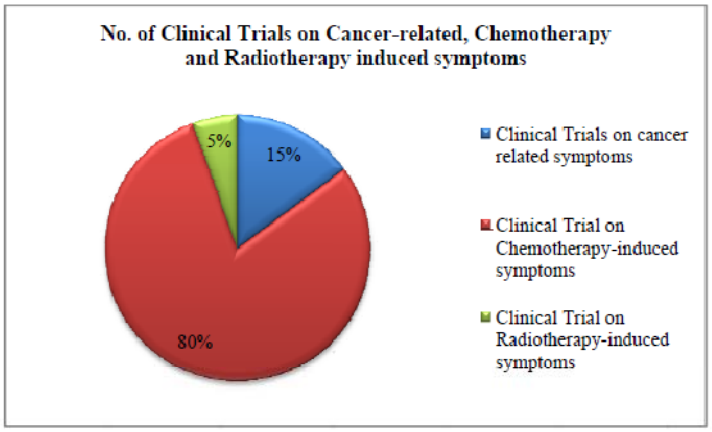

Fig. 8 No. of Clinical Trials on Cancer-related, Chemotherapy and Radiotherapy induced symptoms[3-56].

Discussion

From the literature and data reviewed, it was observed that 37 studies were identified with Phytocannabis use in cancer treatment, amongst which only 2 trials reported for its efficacy in children as compared to that on adults in 35 trials [3-39]. Nabilone (Phytocannabis) when administered orally was well tolerated with marked improvement in pain intensity, improved appetite, reduced nausea and vomiting along with minimal side effects such as, dizziness, drowsiness, hallucinations, dry mouth, vertigo, postural hypotension, sleep disturbances and fatigue[3-39]. In some studies, where no significant improvement was observed, still the patient's choice of preference was Oral Nabilone in either capsule form or as herbal tea [3-39]. When Phytocannabis (Cannabis) was administered sublingually in the form of Sprays, there was marked great reduction in pain intensity accompanied by reduced nausea and vomiting along with minimal side effects of loss in appetite [3-39]. When Phytocannabis (Delta-9-THC) was administered orally was found to be useful in palliation of chemosensory alterations and improved food taste and appetite, reduced nausea and vomiting along with less concentration ability, less social interaction, sedation, mental clouding and blurred vision [3-39]. In a study conducted by Johnson, J.R. *et al*. (2010), THC: CBD was found to be more effective in reduction of pain in cancer patients [8]. On the other hand, mild psychological effects were found to be associated with inhaled form of Phytocannabis [8].

On the other hand, it was observed that 2 uncontrolled case reports presented with intervention of Phytocannabis (Delta-9-THC) led to reduction in nausea and vomiting that was induced by chemotherapy and radiotherapy treatments [40-54]. It was also found that due to this intervention there was marked improvement in appetite and pain [40-54]. From the open-labeled studies conducted, it was observed that 15 studies were identified from the year 1984to 2015 for the use of Phytocannabis in the treatment of cancer and treatment related side effects [40-54]. Moreover, it was observed that Nabilone when administered orally was well tolerated with significant improvement in pain intensity, reduced nausea and vomiting, improved insomnia and night sweats, reduced distress and reduced radiotherapy-induced sickness[40-54]. The intervention of the Phytocannabis Nabilone orally produced mild side effects of anxiety and depression [40-54]. Secondly, when Phytocannabis was administered orally, inhaled/smoked or sublingually, it was highly effective in reduction of pain intensity along with improved appetite, reduced nausea and vomiting, with minimal side effects such as sedation, dizziness and Xerostomia [40-54]. Another form of Phytocannabis, namely, Delta-9-THC when administered orally was also well tolerated by increased appetite and reduced nausea and vomiting with minor side effects of weight loss and dizziness [40-54]. According to Guzman, M. *et al*. (2006)study, Phytocannabis in the form of Delta-9-THC when administered intracranially to the brain tumor patients after undergoing Whole Brain

Radiotherapy showed anti-proliferative action on tumor cells thereby reduced the associated symptoms of Radiotherapy [18]. However, much insight into its effectiveness is required for its standardization [18].

Moreover, it was seen that only two out of 15 clinical trials were conducted on children suffering from cancer [55, 56]. This in part reflected difficulties in collecting comparable data onillicit drug usage [55, 56, 57]. Some countries did not conduct surveys of drug use, some conducted surveys annually and others conducted them less frequently [55, 56, 57]. Of those surveys that were conducted, there was variation between countries in assessing frequency of use, and age groups were divided differently or differed in the settings in which the adolescents and young adults were surveyed [55, 56, 57].

On the whole, it could be concluded from this presented report that there had been more number of Randomized controlled trials in comparison to open-labelled and uncontrolled case studies as retrieved from 1975-2015. During those subsequent 40 years, there were comparatively less number of clinical trials for the use of Phytocannabis and its derivatives for the cancer-related and cancer treatment related studies as compared to the increased burden of the disease globally. Moreover, only few studies focused on the subjects that consisted children which was a major pitfall in finding the compassionate treatment for children group as well who were at the same risk level of developing the disease. Phytocannabis (Nabilone) oral route of administration either alone or as add-on therapy was found to be more preferred, safe and effective to be used in patients who underwent either chemotherapy or radiotherapy treatment.

Conclusion

The presented report contributed to the development of evidence based use of Phytocannabis for cancer treatment which ultimately contributed to the improvement of the quality of life of people suffering from cancer who underwent either chemotherapy or radiotherapy treatments. Therefore, it was concluded that the treatment decisions should be based on standard principles of medical-care ethics – that provided equitable access to treatment and psychosocial support that best meet the needs of the individual cancer patient [58]. Treatment should respect and validate the autonomy of the individual, with patients being fully informed about the risks and benefits of treatment choices [58]. The development and maintenance of Phytocannabis treatment services evidently needs to take place within the broader system of health-care financing and provision in a given country [58]. The presented report thus, highlighted the benefic use of Phytocannabis and its derivatives in the treatment of cancer patients thereby by enhanced quality of life of those patients with minimal side effects being associated with the prolonged disease. In a nutshell, Phytocannabis (Nabilone, Delta-9-THC, Cannabis) in the form of capsules or inhaled form was found to be safe and effective to be used in Metastatic cancer, Advanced cancer, Neuropathic pain, nausea and vomiting induced by Chemotherapy and radiotherapy, Head and Neck cancer, Malignant Melanoma, Hematologic cancer, Brain tumor, Gastrointestinal carcinoma, Osteogenic sarcoma, Liver cancer, Bone cancer, Lungs cancer, Non-seminatous Testicular cancer, Abdominal cancer and Soft tissue sarcoma.

Future directions

There were certain areas that required more research as mentioned below:

1. There were none to minimal standard measures of the Phytocannabis and its content used in most of the countries and regions worldwide.
2. Global data were required on the frequency of Phytocannabis use (more than once daily, daily, near daily, weekly, etc.) and the prevalence of health and social consequences.
3. Data was required on the typical doses of Phytocannabis (smoked, vaporized, ingested) with the potency of Phytocannabis for long term usage and its impact on

health and quality of life of the cancer patients. Larger cohort and better designed case-control studies were needed to better understand the control for benefic effects.

4. Global assessments were needed to establish the relationship between the use of Phytocannabis and other conventional drugs.
5. Most of the studies on risk and protective factors for Phytocannabis use had been conducted in a limited number of high-income countries. There was some uncertainty as to whether the same risk factors prevailed in low- and middle-income countries. More research was required on Phytocannabis use in low- and middle-income countries for the treatment of cancer and related symptoms.

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