UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

Consumption of Aloe to improve health outcomes in adults with irritable bowel syndrome: A systematic review and meta-analysis.

Francisco J. Fong

Student No. FNGFRA001

DISSERTATION IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE MASTER'S OF PUBLIC HEALTH

FACULTY OF HEALTH SCIENCES

UNIVERSITY OF CAPE TOWN

Supervisors:

Associate Professor Mark E. Engel

Professor Mashiko Setshedi

University of Cape Town

February 2019

DECLARATION

I, Francisco Fong, Student No. FNGFRA001, declare that the work that I have submitted is my original work and where the work of others has been used (whether paraphrased, quoted verbatim, or referred to) it has been acknowledged and attributed.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed: Francisco Fong

Signed by candidate

Date: 8 February 2019

Acknowledgements

First and foremost, I would like to express my sincere gratitude to my supervisors whose guidance has been invaluable for this research. Associate Professor Mark Engel, thank you for your patience, continuous support and motivation. Professor Mashiko Setshedi, thank you for helping me define the focus of my research and for answering my questions throughout the process. My sincere thanks also go to my co-reviewer, Inge Smit. Thank you for your continuous support with the data extraction and attention to detail.

To my best friend Jacinda, thank you for being there for me. Your love and good nature always got me through the difficult times.

Last but not the least, I would like to thank my family, my parents and sisters. To my parents Pancho and Titilla, thank you for unconditional love and for helping your children become who we are today.

ABSTRACT

PART A is a research protocol which describes the background and proposed methodology of this systematic review and meta-analysis. This section details the quantitative and qualitative methods to be used when analysing the effect of Aloe in the treatment of patients with irritable bowel syndrome (IBS).

PART B is an extended literature review which expands on some of the topics raised in the background section of the protocol. A more in-depth explanation of the epidemiology of IBS, is presented, as well as the strengths and limitations of current treatment options in order to understand the context around the proposed research.

PART C presents this research in the form of a journal manuscript in a format suitable for submission to Plos ONE. This manuscript includes a background to the research followed by the results section which is then discussed. Lastly, implications for clinical practice are posited and suggestions for further research are offered.

TABLES AND FIGURES

PART A: PROTOCOL

Tables

PART B: LITERATURE REVIEW

Tables

Figures

PART C: MANUSCRIPT

Tables

Figures

TABLE OF CONTENTS

PART A: PROTOCOL

ABBREVIATIONS AND DEFINITIONS

Abbreviations

FGIDs	Functional Gastrointestinal Diseases
GSRS	Global Symptoms Rating Scale
HRQoL	Health-related Quality of Life
IBS	Irritable Bowel Syndrome
IBS-C	IBS with Predominant Constipation
IBS-D	IBS with Predominant Diarrhoea
IBS-M	IBS with Mixed Bowel Habits
IBS-U	Unclassified IBS Subtype
RCT	Randomized Control Trial

Definitions

Aetiology	The cause or set of causes of causation of a disease or condition [1].
Antispasmodic	A pharmaceutical drug or agent that suppresses muscle spasms [1].
Bulking agent	Non-nutritive substances that reduce the amount of strain produced during defecation by promoting peristalsis and maintaining fecal softness [1].
Laxative	Pharmaceutical drug or agent that promotes bowel loosening and movement [1].
Pathogenesis	The manner of development of a disease [2].
Rome Criteria	A set of guidelines that have been used to indicate the criteria needed to be met before IBS can be diagnosed [3].

REGISTRATION

This systematic review and meta-analysis protocol has been published in the PROSPERO International Prospective Register of systematic reviews [4], registration number CRD42018082663.

1. BACKGROUND

Functional gastrointestinal disorder (FGID) is a term used for defining several variable combinations of recurrent or chronic gastrointestinal (GI) symptoms that lack an identified underlying pathophysiology. In the absence of an objective biomarker, the identification and classification of FGIDs has been based on symptoms [5].

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain and changes in bowel habit in the form of constipation, diarrhoea or both [6–8]. IBS is categorized depending on the predominant stool pattern: Constipation-predominant (IBS-C), Diarrhoea-predominant (IBS-D), Mixed pattern (IBS-M), or unclassified phenotype (IBS-U) [8].

It is estimated that IBS affects between 5-15% of the world's population; making it one of the more common gastrointestinal (GI) disorders [8,9]. In addition, it is reported that as much as 30% of visits to gastroenterologists belong to patients showing IBS-related symptoms[6]. IBS patients have shown similar or worse health-related quality of life (HRQoL), compared to chronic diseases like diabetes mellitus [8]. As a functional gastrointestinal disease (FGID), IBS is said to represent a major part of the work load of primary care physicians and gastroenterologists, and is one of the leading causes for referral to emergency care units, thus draining substantial amounts of healthcare resources [10].

IBS largely remains an unexplained disorder of the gut function, as multiple disease pathways can lead to identical clinical phenotypes [11]. These include changes in the gut microbiome, impaired sensitivity and motility, increased permeability, psychological distress and alterations in the brain-gut

axis [9,11]. Food also seems to play a key role, as exacerbation of symptoms after meals is reported by most IBS patients. Also, self-reported food intolerance is associated with reduced quality of life and higher symptom severity scores [11].

Conventional medical treatment is purely based on the predominant symptoms, and includes treatment with antispasmodics and laxatives to treat constipation-related symptoms, as well as bulking agents in the case of diarrhoea. More severe cases of the disorder may require psychological therapies, anxiolytics or even antidepressants [7,9,11]. However, these treatment options have shown limited efficacy, and many patients resort to complementary and alternative medicine (CAM) therapies, despite lack of evidence to support their use. These include dietary interventions and herbal preparations including peppermint oil and Aloe [7,12,13].

Aloe is a plant genus that produces latex and gel [7]. The gel is extracted from the leaf, and it is this substance that is most used as a treatment. Previous research in rats suggests its laxative and anti-inflammatory actions may have a beneficial effect in the treatment of constipation-predominant IBS [14,15], and research conducted on humans suggests it may be effective in treatment of inflammatory bowel disease symptoms [16,17]. Clinical trials have also been carried out to assess the effectiveness of Aloe in treating IBS symptoms among humans subjects, however the evidence of its effects is limited and contradictory [13]. To date, the effectiveness of Aloe in treating IBS symptoms in clinical trials has not been systematically studied. Therefore, the aim of this study is to evaluate the effect of Aloe on symptoms associated with Irritable Bowel Syndrome in adults.

2. AIMS AND OBJECTIVES

2.1. AIMS

To evaluate the effect of Aloe on symptoms associated with Irritable Bowel Syndrome (IBS) in adults.

2.2. OBJECTIVES

To summarize the existing evidence on the contribution of Aloe to improved health outcomes among adult patients diagnosed with IBS and where possible, identify potential factors that may influence this response.

3. REVIEW QUESTION

Among adults diagnosed with irritable bowel syndrome, is the consumption of Aloe, compared with placebo, associated with improved health outcomes?

4. METHODS

The reference for methods employed in this study is the Cochrane Handbook of Systematic Reviews of Interventions [18].

4.1. Criteria for considering studies in this review

4.1.1. Type of studies

The systematic review is to include randomised controlled trials (RCTs), non-randomised controlled trials, retrospective and prospective cohort studies, and controlled before-and-after (CBA) studies.

4.1.2. Types of participants

Participants include adults ≥18 years of age who have been diagnosed with irritable bowel syndrome (IBS) based on relevant diagnostic criteria, including Manning criteria or Rome iterations [3,19].

4.1.3. Types of interventions/ exposures

For this systematic review, the term 'Aloe' will be used to denote *Aloe Vera*, *Aloe Ferox* or any species in the Aloe genus in their natural form or in any commercially-available form. This study authors

include Aloe in its different forms as a therapeutic intervention to address symptoms related to IBS. This includes patients who received conventional medications in addition to Aloe, as well as those not taking any conventional medication but seeking treatment in the form of complementary and alternative medicine (CAM) therapies.

4.1.4. Types of outcome measures

The primary outcome measure is patients' self-reported quality of life or improvement of symptoms. The outcome measures for IBS will be based on the Gastrointestinal Symptoms Rating Scale (GSRS) or similar rating scales, as well as Quality of Life validated tools such as EuroQol (EQ5D), Short Form 12 (SF12) and Short Form 36 (SF36) quality of life questionnaires. This choice of primary outcome is in keeping with most studies reported to date.

4.2. Search strategy

A comprehensive search strategy will be developed to search both published and unpublished literature. This will include peer-reviewed journal articles, conference proceedings and grey literature. The strategy will include free-text as well as Medical Subject Headings (MeSH) terms relating to IBS and Aloe literature. Table 1 shows the main search terms to be used, which will be adapted to suit individual databases using applicable syntax and vocabulary.

4.2.1. Electronic searches

This study will use the following databases for its electronic searches: Medline/PubMed, EMBSAE/Scopus, EBM reviews, Global Health and International Pharmaceutical Abstracts, CINAHL, Web of Science, Mednar, Cochrane Central Register of Control Trials, Pan African Clinical Trials Register, clinicaltrials.gov, World Health Organization Library Information System (WHOLIS) and Ebscohost. Grey literature will be searched as well.

Table 1: Terms used for searching databases (Comprehensive search strategy available in Appendix

Subject	Key search terms
#1: Irritable Bowel Syndrome	Intestinal diseases, colonic diseases, irritable bowel syndrome, gastrointestinal motility, irritable colon, peristalsis, constipation, diarrhea, feces, stool, abdominal pain, bloating, defecation, laxatives, bulking agent, dysmotility, visceral hypersensitivity, spastic colon, Rome criteria
#2: Aloe	Xanthorrhoeaceae, Aloe, Asphodelaceae, Aloeaceae, Aloeandongensis, Aloedent, Aloe emodin, aloe*, emodin, barbaloin

4.2.2. Selection of studies for inclusion

A screening form will guide the evaluation of articles identified by the search strategy against the inclusion criteria. Two review authors (FF and IS), working independently, will screen the titles and abstracts of all studies identified through the literature searches for eligibility. Thereafter, the two authors will independently assess the full-text of each article for eligibility. Any discrepancies will be resolved through discussion and consensus, and in case of persistent disagreements, a third author (MS), will be consulted. All the reasons for studies being excluded from the systematic review will be documented by the reviewers.

5. DATA EXTRACTION AND MANAGEMENT

Two authors (FF and IS) will extract descriptive and outcome data for each included article using a standardised data extraction form. Any discrepancies will be resolved by discussion and consensus. In case no consensus is reached, a third author (MS) will arbitrate. The final data will be analysed with Review Manager V.5.3 statistical software [20], and will be cross-checked by a second author (ME) to ensure that there are no data entry errors. References will be managed using the Mendeley citation manager [21].

The data extraction will include the following key eligibility criteria:

1. Study design
2. Type of participants
3. Form of treatment
4. Details of outcome

6. RISK OF BIAS AND QUALITY APPRAISAL

Two reviewers (FF and IS) will apply the Cochrane tool for Risk of Bias assessment tool for randomized controlled trials and similar tool for other applicable study designs. The criteria used to assess the risk of bias in RCTs includes allocation concealment, blinding of participants and study personnel, random sequence generation, incomplete outcome data, selective reporting of outcomes and overall risk of bias, in accordance with the methods used by the Cochrane Collaboration. The same tool will be used to assess the quality of evidence for the contribution of Aloe and its derived products towards improving quality of life or overall symptoms. Two reviewers (FF and IS) will independently assign the grade scores and compare results as per the process for the recording of previous aspects of the study. Discrepancies will be resolved by consensus discussion between the two primary reviewers, with arbitration by a third reviewer as necessary.

6.1. Dealing with missing data

Where necessary, the authors of the selected studies will be contacted for missing data. If the authors are not able to respond, missing data will be indicated in the review.

7. DATA ANALYSIS AND SYNTHESIS

7.1. Subgroup analyses

Subgroup analyses will be performed by IBS diagnosis subtypes: Constipation variety (IBS-C) and diarrheal variety (IBS-D), as well as by method used to measure self-reported quality of life or improvement of symptoms.

7.2. Sensitivity analyses

Where possible, sensitivity analyses will be conducted. It will first be determined whether the study design (randomized vs. nonrandomised study) could influence the meta-analysis results. Secondly, the model of the statistical method will be evaluated to determine if it could change the results (i.e. fixed-effects vs. random effects model). The impact of excluding studies with a high-risk bias on the results will be determined, with emphasis on loss to follow-up, allocation concealment and blinded outcome assessment (with a cut-off of 25% loss to follow-up).

7.3. Assessment of heterogeneity

Outcomes of interest will be expressed as risk ratios and their respective 95% confidence intervals (CI) and p-values will be calculated for dichotomous outcomes, while for continuous data, mean differences and standard deviations (SDs) will be calculated. If outcomes are measured using different scales, these will be recoded into dichotomous measures based on study authors' definition of patients' response to treatment.

Heterogeneity will be assessed by examining types of interventions, types of participants, and types of outcomes in each study with the intention to pool data and estimate effect sizes using a fixed-effects model only from studies in which outcomes are judged to be homogeneous. Alternatively, the random-effects model will be used if outcomes or interventions are not judged to be

homogeneous. Statistical heterogeneity in each meta-analysis will be assessed using the χ^2 test and quantified using the I^2 statistic. The findings will be discussed as a narrative summary if the heterogeneity remains significant. Included studies will be summarised in tables to highlight the main existing evidence.

7.4. Assessment of reporting biases

In order to assess risk of publication bias, funnel plots will be used to examine asymmetry, provided there are 10 or more studies included. If evidence is found of small study effects, publication bias will be considered as a possible explanation. A sensitivity analysis will be undertaken if plots suggest treatment effects may not be from a symmetric distribution.

8. REPORTING OF THIS SYSTEMATIC REVIEW

The findings of this review will be reported in several ways. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram will be used to summarise the process of study selection. A κ statistic will be used to assess agreements between the full-text screening, data extraction and risk of bias assessment by the authors. Where necessary, the authors will adapt the reporting to ensure that all items relevant to this review are included.

9. ETHICS

Ethics will not be required for this study as it utilises existing public health data. The authors will obtain a waiver letter from the university health research ethics committee.

REFERENCES

1. Warner's pocket medical dictionary of to-day : comprising pronunciation and definition of 10,000 essential words and. Natl Libr Med [Internet].
2. The prescriber : a dictionary of the new therapeutics. Natl Libr Med [Internet].
3. Drossman Douglas. The Functional Gastrointestinal Disorders and the Rome III Process. Gastroenterology [Internet]. 2006;130:1377–90. Available from: http://www.romecriteria.org/pdfs/p1377_FGIDs and the Rome III Process.pdf
4. PROSPERO International Prospective Register of systematic reviews [Internet]. Available from: http://www.crd.york.ac.uk/PROSPERO
5. Corazziari E. Definition and epidemiology of functional gastrointestinal disorders. Best Pract Res Clin Gastroenterol. 2004;18(4):613–31.
6. Canavan C. CLEP-40245-the-epidemiology-of-irritable-bowel-syndrome. 2014;71–80.
7. Davis K, Philpott S, Kumar D, Mendall M. Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. Int J Clin Pract [Internet]. 2006 Sep 2 [cited 2017 Nov 14];60(9):1080–6. Available from: http://doi.wiley.com/10.1111/j.1742-1241.2006.00980.x
8. Vanuytsel T, Tack JF, Boeckxstaens GE. Treatment of abdominal pain in irritable bowel syndrome. J Gastroenterol. 2014;49(8):1193–205.
9. Cuomo R, Andreozzi P, Zito FP, Passananti V, Carlo G De, Cuomo R, et al. Irritable bowel syndrome and food interaction. 2014;20(27):8837–45.
10. Stanghellini V. Functional Dyspepsia and Irritable Bowel Syndrome : Beyond Rome IV. 2018;14–7.
11. Talley NJ, Holtmann G. Irritable bowel syndrome and functional dyspepsia : what can epidemiology tell us about etiology ? Irritable bowel syndrome and functional dyspepsia : what can epidemiology tell us. Expert Rev Gastroenterol Hepatol [Internet]. 2018;12(7):633–5. Available from: https://doi.org/10.1080/17474124.2018.1476136
12. Hutchings HAH, Wareham K, Baxter JNJ, Atherton P, Kingham JGC, Duane P, et al. A Randomised, Cross-Over, Placebo-Controlled Study of *Aloe vera* in Patients with Irritable Bowel Syndrome: Effects on Patient Quality of Life. ISRN Gastroenterol [Internet]. 2011 [cited 2017 Nov 14];2011:206103. Available from: http://www.hindawi.com/journals/isrn/2011/206103/
13. Størsrud S, Pontén I, Simrén M (2015), Storsrud S, Ponten I, Simren M, et al. A Pilot Study of the Effect of Aloe barbadensis Mill. Extract (AVH200®) in Patients with Irritable Bowel Syndrome: a Randomized, Double-Blind, Placebo-Controlled Study. J Gastrointest Liver Dis [Internet]. 2015 Sep 1 [cited 2017 Nov 14];24(3):275–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26405698

14. Zihong L, Jingxun W, Journal XZ-GM, 2005 undefined. The curative effect of aloe on constipation and its primary mechanism. en.cnki.com.cn [Internet]. [cited 2019 Feb 7]; Available from: http://en.cnki.com.cn/Article_en/CJFDTOTAL-GAYX200510016.htm

15. Shamirzadi. Benefit of Aloe vera and Matricaria recutita Mixture in Rat Irritable Bowel Syndrome : Combination of Antioxidant and. 2012;1–9.

16. Langmead L, Makins RJ, Rampton DS. Anti-inflammatory effects of aloe vera gel in human colorectal mucosa in vitro. Aliment Pharmacol Ther. 2004 Mar;19(5):521–7.

17. Langmead L, Rampton DS. Review article: herbal treatment in gastrointestinal and liver disease-benefits and dangers. Aliment Pharmacol Ther [Internet]. 2001 Sep 27 [cited 2018 Jul 8];15(9):1239–52. Available from: http://doi.wiley.com/10.1046/j.1365-2036.2001.01053.x

18. Green S, Higgins J. Cochrane handbook for systematic reviews of interventions. 2005 [cited 2019 Feb 7]; Available from: http://www.rismes.it/pdf/Cochrane_handbook 2009.rtf

19. Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. 1978;(September):653–4.

20. Cochrane Collaboration. RevMan 5 Statistical Management Software [Internet]. [cited 2019 Oct 13]. Available from: https://community.cochrane.org/help/tools-and-software/revman-5

21. Mendeley Citation Management Software [Internet]. Available from: www.mendeley.com

PART B: LITERATURE REVIEW

1. INTRODUCTION

Functional gastrointestinal disorder (FGID) is a term used for defining several variable combinations of recurrent or chronic gastrointestinal (GI) symptoms that lack an identified underlying pathophysiology. In the absence of an objective biomarker, the identification and classification of FGIDs has been based on symptoms [1].

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain, and changes in bowel habit including diarrhoea, constipation or both [2–4]. IBS is categorized according to the predominant stool pattern: Constipation-predominant (IBS-C), Diarrhoea-predominant (IBS-D), Mixed pattern (IBS-M), or unclassified phenotype (IBS-U) [3]. The severity, frequency and duration of symptoms can range from negligible to incapacitating, and often affect the usual activities of affected individuals. According to its latest definition based on the Rome IV criteria, symptom onset should occur at least 6 months before diagnosis, and symptoms should be present for at least the last three months [5].

Although IBS has no impact on mortality, IBS subjects tend to show similar or worse health-related quality of life (HRQoL) when compared to chronic diseases like diabetes mellitus [3]. IBS is reported to account for 12% of all visits to primary care physicians, and as much as 30% of visits to gastroenterologists [6]. Like other FGIDs, IBS can also cause indirect costs in the form of absenteeism [3]. In Europe, costs to industry through absenteeism related to IBS are estimated between USD 500 – 1,200 per patient annually [6].

2. EPIDEMIOLOGICAL ASPECTS OF IBS

2.1. Aetiology and pathophysiology of IBS

The causes of IBS are not fully elucidated, largely due to the lack of specific biomarkers. IBS largely remains an unexplained disorder of the gut function, since multiple disease pathways can lead to identical clinical phenotypes [7]. These include impaired motility and sensitivity, increased permeability, changes in the gut micro-biome, psychological distress and alterations in the brain-gut axis [7,8]. Food also seems to play a key role, as most IBS patients report onset or exacerbation of symptoms after meals. Also, self-reported food intolerance is associated with reduced quality of life and higher symptom severity scores [7].

IBS is a lifelong condition where incidence seems to increase with age [9]. A bidirectional relationship is thought to exist between the psyche and the gut as studies on the natural history of FGIDs have shown that IBS patients are particularly prone to develop psychological problems [10]. Psychological distress is considered to be a risk factor for IBS, although causality has not yet been established. Depression, anxiety, neuroticism as well as emotional and physical abuse, as well as difficulties coping with life events are reported to be frequent among IBS patients [10]. Two population-based cohort studies have shown that those with psychological distress at baseline were at greater risk of developing IBS, suggesting a brain-gut pathway through the stress response. Likewise, these same studies have shown that those with IBS are at greater risk of new onset psychological distress [7].

Post-infectious gastroenteritis has also been identified as a risk factor for IBS: Among 45 studies in a meta-analysis, the rate of post-infectious IBS following enteritis turned out to be higher with parasitic or protozoan infestation (42%) than with bacterial infection (14%). Overall, the risk of IBS was 4 times higher in those with infectious enteritis compared to the controls [11].

Dietary factors are also thought to play a role in the determination of the syndrome, as most IBS patients report the onset or exacerbation of their symptoms after having a meal [8]. Gluten and lactose sensitivities, as well as ingestion of excessive amounts of fermentable carbohydrates are thought to play a role in the pathogenesis of IBS [10].

Genetic factors are also thought to play a role. Family cohort and case-control studies indicate that those with a family member with IBS have 2 to 3 times greater risk of developing IBS compared to those people without an affected family member. Genetic case-control studies have identified single nucleotide polymorphisms (SNP) that may be linked to IBS and functional dyspepsia (FD), however evidence of causality is missing in most cases as replication of these studies has been inconsistent [7]. The different likely pathophysiological mechanisms make IBS a heterogeneous disorder that poses a challenging task in the development of effective treatments [3]. In summary, the causes of IBS appear multifactorial and have not been completely understood.

2.2. Prevalence of IBS

Worldwide, IBS prevalence varies significantly between countries. A meta-analysis shows a pooled estimate of international IBS prevalence of 11.2%, with variation by geographic region. The lowest prevalence occurs in South Asia (7.0%), and the highest in South America (21%), with considerable heterogeneity between the studies [6]. Women are at greater risk of IBS compared to men, as well as individuals older than 50 years. IBS prevalence rates are 1.5 to 3 times higher among women compared to men [2]. The effect of socioeconomic status has not yet been clearly described [12].

Because of different diagnostic criteria being used, high frequency of symptoms, lack of specific biomarkers and point of onset, epidemiological studies of IBS can be very challenging, with measures of occurrence such as prevalence being largely dependent on diagnostic criteria used [4].

2.3. IBS Sub-types

Depending on the predominant stool pattern, IBS is categorized as a diarrhoea-predominant (IBS-D), constipation-predominant (IBS-C), mixed-pattern (IBS-M), or unclassified sub-type (IBS-U) [5,10]. Stool form and consistency is defined based on the Bristol stool scale, and used as a proxy measure for intestinal transit time [13,14]. The IBS sub-types can be defined as follows:

IBS with predominant constipation (IBS-C): This is defined as >25% of bowel movements with Bristol stool form types 6 or 7 and <25% of bowel movements with Bristol stool form types 1 or 2 [5]. IBS-C is usually distinguished from chronic idiopathic constipation (CIC) by the presence of abdominal pain in the former. However in reality, the two disorders can often overlap in the same individual [10].

IBS with predominant diarrhoea (IBS-D): This is defined as <25% of bowel movements with Bristol stool form types 6 or 7 and >25% of bowel movements with Bristol stool form types 1 or 2.

IBS with mixed bowel habits (IBS-M): Defined as >25% of bowel movements with Bristol stool form types 1 or 2 and >25% of bowel movements with Bristol stool form types 6 or 7.

Unclassified subtype (IBS-U): Describes those patients who meet diagnostic criteria for IBS but whose bowel habits cannot be categorized into any of the three previous groups [10].

2.4. Diagnosis of IBS

Despite IBS being a common problem, there is no “gold standard” or objective diagnosis method in the absence of biological markers. Therefore, IBS diagnosis has traditionally been one of exclusion [15]. Recently however, it has been recommended that a positive diagnosis of IBS should be made based on symptoms (using the Rome IV criteria), exclusion of alarm features and judicious biochemical testing [16].

The first widely-used diagnostic criterion was the result of a study aimed at enabling the identification of symptoms that could help doctors distinguish IBS from other functional gastrointestinal disorders.

The results of this study were published in 1978, and became known as the "Manning criteria". Later efforts at fine-tuning diagnosis methods took place in the 1980s through the work of Dr Aldo Torsoli, professor of gastroenterology at Rome University. Dr Torsoli used a Delphi approach to select experts from around the world to develop a consensus criterion for the diagnosis of IBS and other FGIDs. This work would later result in the publication of a book titled "The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment", which would later be regarded as the Rome I criteria. Rome I would be refined in various iterations over the years, resulting in Rome II in the year 2000, Rome III in 2006 and Rome IV in 2016 [17]. In the absence of biological markers, these various iterations of the Rome guidelines have been used to indicate the criteria needed to be met before IBS can be diagnosed. Table 1 presents a summary table that summarizes these diagnostic tools.

Table 1 – Summary table of Manning and Rome criteria used frequently in epidemiological studies for identification of cases. Adapted from [5,9].

Manning (1978)	Rome I (1989)	Rome II (1999)	Rome III (2006)	Rome IV (2016)
2 or more of the following symptoms: Abdominal distension Pain relief with defecation. Frequent stools with pain. Looser stools with pain Passage of mucus Sensation of incomplete evacuation.	At least 3 months of continuous or recurrent abdominal pain, relieved with defecation or, Associated with change in stool consistency with at least 2 of the following on at least 25% of days: Altered stool frequency Altered stool form Altered stool passage Passage of mucus Bloating or abdominal	At least 12 weeks in the past 12 months of continuous or recurrent abdominal pain or discomfort, with at least 2 of the following: Relief with defecation Altered stool frequency Altered stool form Onset of symptoms more than 12 months before diagnosis.	At least 3 days per month in the past 12 weeks of continuous or recurrent abdominal pain or discomfort With at least 2 of the following: Relief with defecation Altered stool frequency Altered stool form Onset of symptoms more than 6 months before diagnosis.	Recurrent abdominal pain, at least 1 day /week in last 3 months, associated with 2 or more of the following: Related to defecation Associated with change in frequency of stool Associated with change in appearance of stool. Criteria fulfilled for the last 3 months, with symptom onset at least 6 months before

Although the validity of the Rome criteria in its various iterations has been studied, conventional measurements of sensitivity and specificity have not been used in the absence of biomarkers. Instead, sensitivity has been assessed through cases that have presented and have already been diagnosed, and specificity has been assessed through those with organic gastrointestinal disease. It has been shown that these criteria have modest specificity to diagnose IBS for those with gastrointestinal disease (about 70% specificity) although it is believed that this can be increased to 90% if patients with symptoms such as weight loss, rectal bleeding and anaemia can be investigated more extensively and IBS can be ruled out by exclusion. It is reported that sensitivity across the criteria used can vary from 40% to 90%, depending on the skill and level of experience of the clinician [2]. Given the inconsistent application of diagnostic criteria over the years, the definition of cases in epidemiological studies has been problematic. This lack of uniformity in diagnostic criteria is said to partially account for the variability in prevalence studies [2].

3. TREATMENT OF IBS

Traditionally, treatment of IBS has started with the identification of predominant symptoms and their severity. Patients should be counselled on lifestyle recommendations that include exercise, managing stress and increasing the intake of fluids, and reassured that IBS follows a benign course [18].

3.1. Conventional treatment

3.1.1. Non-pharmacological treatment

Non-pharmacological treatment is first offered, especially among patients that don't show severe enough symptoms that can affect their quality of life [19].

Diet modifications

IBS patients are often advised to avoid foods that produce gas such as onions, beans, celery, carrots and prunes. Also, a lactose-free diet should be prescribed if patients are lactose-intolerant. Fermentable Oligo-, Di-, Mono-saccharides And Polyols (FODMAPs) are short chain carbohydrates that are poorly absorbed in the small intestine. A FODMAP-low diet is commonly recommended and includes the avoidance of high-fructose corn syrup, wheat, honey, cherries, mangoes and pears. IBS patients are initially asked to eliminate FODMAPs in their diets for a period between 6-8 weeks and then to restart intake of foods that are high in fermentable carbohydrates so as to determine the tolerance to particular fermentable carbohydrates [19].

Physical exercise

In addition to improving muscle and bone conditioning and reducing the risk of cardiovascular disease, physical activity has also shown to be beneficial for IBS in reducing anxiety and depression. A clinical trial with 75 patients showed that increased physical activity over a 12 week period reduced the symptoms related to IBS [20].

3.1.2. Pharmacological treatment

Irritable bowel syndrome, as it is currently labelled, is believed to consist of a group of conditions with different pathophysiological mechanisms. This heterogeneity complicates drug development and when interpreting study results. Thus it is important to link outcomes to specific pathophysiological mechanisms, such as anxiety-related dysfunctions, visceral hypersensitivity, constipation, etc. [3]. Conventional pharmacological treatment of IBS is purely symptomatic, and includes treatment with laxatives, bulking agents and antidiarrheal medication, depending on the sub-type. More severe cases of the disorder may require anxiolytics or antidepressants [7,8,21]. Regardless of IBS sub-type, antispasmodics such as hyosciamine and dyclomine can be also be dosed

as needed and have been shown to be beneficial in relief of symptoms in the short term. Antispasmodics relieve abdominal pain brought on by IBS by relaxing the smooth muscle of the gut [5].

Laxatives

Patients with constipation-predominant IBS (IBS-C) may benefit from specific treatment of constipation through the use of laxatives. Commonly used laxatives have an osmotic mechanism of action, being poorly absorbed in the gut, they increase the water content in stools, making them easier to pass as well as increasing peristalsis in the colon [22]. Common osmotic laxatives include milk of magnesia, lactulose and polyethylene glycol (PEG). PEG is more commonly considered a safe initial treatment of constipation symptoms, as it has shown few side effects. PEG is used to increase the osmotic pressure of fluids in the intestinal lumen, which helps cleanse the GI tract [5,19]. Although it has shown its efficacy in improving bowel movements in clinical trials, PEG has not been more effective than placebo in reducing bloating or abdominal pain, bloating or other symptoms related to IBS [22]. Both PEG and lactulose work by increasing water in the intestinal lumen to decrease intestinal transit time, although lactulose may cause abdominal pain from fermentation in the intestinal lumen [22]. Among laxative-resistant IBS-C patients, chloride-secretion stimulating drugs such as linaclotide and lubiprostone are thought to have analgesic effects, reducing abdominal pain while at the same time improving stool patterns [3]. A systematic review and meta-analysis found linaclotide to be moderately effective in improving IBS-C symptoms, with diarrhoea being a major side effect, and recommended further studies to evaluate linaclotide's long-term safety and efficacy for patients with for IBS-C [23].

Bulking agents

It is not uncommon for physicians to advise the intake of bulking agents in the form of fibre supplements to address altered bowel habits and abdominal pain. Ispaghula husk, also known as psyllium, as well as bran, are common fibre supplements. Fibre increases luminal osmotic load, influences the micro-biome and attracts water which results in an increased biomass, which in turn helps decrease colonic transit time. Although commonly used, its benefit in addressing common IBS symptoms has not yet been established. A Cochrane systematic review and meta-analysis did not find a significant effect on abdominal pain or global improvement of symptoms [3,24].

Antidiarrheals

The most common anti-diarrheal medication used for treatment of IBS-D patients is Loperamide. Loperamide is a synthetic opioid that acts on the intestinal muscles to prolong intestinal transit time and inhibit peristalsis [3], and has proven to be effective in improving IBS-D symptoms: A meta-analysis of four RCTs found Loperamide to be effective in decreasing stool frequency while at the same time improving stool consistency [25]. A dose of 2mg taken 45 minutes prior to a meal on a regular schedule is recommended [5,19,22]. Although it has been known to improve diarrhoea-like symptoms, it has not been shown to improve other symptoms like bloating and abdominal pain [25].

Antispasmodics

These are medications that can relax smooth muscle in the colon through anticholinergic mechanisms or calcium channel antagonists. Common antispasmodics include dicyclomine, alverine, hyoscyamine, otilonium, scopolamine and pinaverium to mention a few. Generally, antispasmodics have been used for their effects on improving gastrointestinal motility as a way to reduce abdominal pain associated with IBS [22]. Antispasmodics have been generally utilized for their effects on gastrointestinal motility to reduce abdominal pain. A Cochrane systematic review and meta-analysis

of 29 trials suggests that some but not all antispasmodics may decrease abdominal pain. Sub-group analyses in this study showed that pinaverium, trimebutine and a combination of dicyclomine and cimetripium were effective in improving symptoms. Adverse effects of these agents include dizziness and dry mouth, as well as constipation. Thus they should be prescribed to IBS-C patients with caution [22].

Antidepressants

These have commonly been used as analgesics to treat chronic pain disorders, including FGIDs. Current guidelines endorse the use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). It is believed that these agents act via centrally-mediated pathways that inhibit the sensation abdominal pain associated with IBS. In addition to their positive effect on the mood of patients with psychiatric comorbidities like anxiety and depression, antidepressants are also thought to be useful in patients without depression, but who suffer from refractory and severe functional abdominal pain, albeit at a lower dosage. The proposed mechanisms of action include antidepressants' central pain-modulatory action, peripheral analgesic effects, improving sleep and influence on motility. A Cochrane systematic review and meta-analysis reported antidepressants' superiority over placebo in improving global IBS symptom scores, including those for abdominal pain. However, subgroup analysis showed a modest superiority of TCAs but not SSRIs in relieving abdominal pain [26].

Despite extensive studies conducted, there remains a proven lack of efficacious pharmacological treatments for IBS. In many instances, conventional treatment options for IBS have shown limited efficacy in improving patients' quality of life, and it is not uncommon for individuals with IBS to seek complementary and alternative medicine treatments [27].

3.2. Psychological therapies

Cognitive behavioural therapy (CBT)

It has been shown that when compared to healthy individuals, patients with IBS are more prone to suffer from anxiety and depression [28]. In addition, central processing mechanisms have been linked to the pathophysiology of IBS including visceral hypersensitivity and anxiety. Thus, cognitive behavioural therapy is thought to help improve symptoms by targeting these processes. CBT patients are taught to recognize and correct thoughts and behaviours that can undermine well-being or amplify their symptoms [29]. CBT has been demonstrated to reduce IBS symptoms in a meta-analysis of seven studies with 491 patients, with 57% of patients in the CBT group reporting improved symptoms compared with 39% in the placebo group ($p<0.01$), and a relative risk (RR) of 0.60 (95% CI 0.42-0.87) [30]. Although CBT has demonstrated positive results in IBS patients, its labour-intensive nature and limited availability have limited their routine use among patients [3].

Hypnotherapy

Hypnosis has been defined as a state of consciousness that involves focused attention and a reduced peripheral awareness that is characterized by an enhanced capacity to respond to suggestions [31]. Hypnotherapy then is the use of hypnosis for the treatment of medical or psychological disorders or concerns [31]. It is thought that by affecting certain parts of the brain that influence bowel movements or experience abdominal pain, hypnotherapy can provide benefits for IBS. Hypnotherapy has been previously studied for treating IBS symptoms in various randomized controlled trials [32]. A Cochrane collaboration systematic review and meta-analysis provided some evidence suggesting that hypnotherapy may be effective in treating IBS symptoms including abdominal pain in the short

term. However the study authors advise caution with the results given the poor quality of studies and small sample size [32].

3.3. Complementary and Alternative Medicine (CAM) treatment

Complementary and Alternative Medicine (CAM) refers to a group of diagnostic and therapeutic disciplines that currently exist outside the institutions where conventional medical practices are taught and provided [33]. The terms complementary refers to when theories and practices of medicine that deviate from the conventional, are used in addition to standard medical practices, and alternative refers to when these treatments are used instead of conventional medicine [34].

CAM practices differ significantly from conventional medicine in terms of heterogeneity of treatments, perspectives on disease mechanisms and therapeutic measures. These practices are influenced by ethnic, cultural, social, regional, educational and economic factors [4]. Clinically speaking, it is estimated that more than 80% of the population in developing countries rely on herbal medicine for their primary care. Aside from its well-known acceptance in India and China, the use of CAM therapies has also become common in European countries [35].

The efficacy of herbs and other forms of CAM to treat IBS has been a controversial topic. Physicians have often regarded CAM, particularly in the treatment of FGID, as having an "enhanced placebo effect" [4]. This has been thought to be the result of a heightened expectation of treatment efficacy due to the higher frequency of contacts with the therapist, which in turn results in a more positive relationship between the patient and the practitioner [4]. A study based on a single-blind RCT seems to support this notion, as it found that when conducting sub-group analyses within patients in the control group, the quality of the interaction between the patient and the practitioner did account for a significant difference in the way patients responded to treatment within this sub-group [36]. However, two meta-analyses have found that the placebo response rate for both CAM and

conventional medicine is quite similar. One meta-analysis of 73 RCTs using conventional medical treatments to treat IBS found that the pooled placebo response rate was 37.5% (95% CI 34.4–40.6%) [30]. Another meta-analysis of 19 RCTs using CAM treatments for IBS patients found a pooled effect of 42.6% (95% CI 38.0–46.5%) [37]. The considerable overlap in the response rate between the two studies suggests that the placebo effect may be independent of the type of therapy used, and that it may not be "enhanced" as initially thought by the use of CAM [37].

3.3.1. Acceptance of CAM as treatment for FGIDs in western countries

A study published in 1998 reported an increase use of CAM from 34% in 1991 to 42% in 1997 in the United States, 10% of which was for the treatment of digestive complaints. Among this group, relaxation and herbal therapy was reported as the most sought-after therapy [38]. The use of CAM is particularly prevalent among patients with gastrointestinal issues, in particular women and individuals with symptoms of diarrhoea, constipation and bloating [39]. Complementary and alternative medicine (CAM) is reported to be even higher among patients that suffer from FGIDs. Dissatisfaction with conventional treatment and female gender continue to be valid predictors for the use of CAM. In one study, as much as 70% of FGID patients have reported to discuss CAM use with their physicians with either neutral or encouraging responses, which may reflect a shift in attitudes among FGID patients to try CAM treatments, and among gastroenterologists who may even be open to consider probiotics as conventional treatment for some GI disorders [39,40].

CAM treatments for all digestive issues seem to be more popular in North America than in Europe, although it seems that in Europe the CAM industry is growing at a faster pace, with herbal remedies being the most widely-used form of CAM [41]. The use of herbal remedies appears to be particularly common in patients with IBS and IBD, which may be related to the refractory nature of these disorders as well as psychological factors. In the case of symptoms such as constipation, plant extracts

are commonly used as a symptomatic approach to its management. The anthraquinones found in Aloe and Senna are known to have laxative properties [42]. Dietary fibre can also have a bulk-forming laxative effect as in the case of ispaghula husk, and it is not uncommon for people with constipation to self-prescribe with herbal remedies to treat constipation symptoms [41].

3.3.2. CAM treatments for IBS commonly used

In many instances, conventional treatment options for IBS have shown limited efficacy in improving patients' quality of life [27], and many individuals with IBS have resorted to CAM treatments. It has been reported that use of CAM treatments has been greater among patients with IBS than among patients with other FGIDs, and that as much as 50% of IBS patients would resort to CAM if conventional remedies failed [40,43].

Broadly speaking, CAM treatments for IBS include fibre, probiotics, cognitive behavioural therapy (CBT), hypnotherapy and herbal preparations including peppermint oil and aloes, with varying degrees of success [4,29,44,45].

Fibre

It is not uncommon for IBS patients to be first advised to increase their fibre intake through diet. Psyllium, otherwise known as Ispaghula husk, is the ground seed coat of members that belong to the plant genus *Plantago,* and can also be found in whole grains, vegetables and fruits. Psyllium has been employed as a bulking agent, by increasing the bulk of stools, which in turn encourages the bowels to move the stools through the colon, which ultimately helps relieve constipation [29]. Psyllium has been used as a dietary fibre to relief symptoms of both constipation and diarrhoea. Another soluble fibre that has been used in the treatment of IBS is miller's bran. Also known simply as bran, it is the hard outer layer of cereal grain. Bran is an integral part of whole grains and is commonly produced as a by-product when producing refined grains [45]. A systematic review and meta-analysis looking

to evaluate the effect of fibre in the treatment of IBS included both psyllium and bran. When evaluating the effect of psyllium, 6 RCTs were included in one of the meta-analyses which showed a statistically significant effect on improvement of symptoms. The pooled relative risk was 0.78 (95% CI 0.63 to 0.96) [45]. The meta-analysis evaluating the effect of bran in the same study found no significant effect on improvement of symptoms with a relative risk of 1.02 (95% CI 0.82 to 1.27) [45].

Probiotics

Probiotics are diet supplements that contain live bacteria or bacterial products. When ingested, they have a beneficial effect by improving the gastrointestinal microbial balance. Although probiotics' precise mechanism of action is not yet known, it is thought that a disproportion of the gastrointestinal flora may play a role in the pathogenesis of IBS. Thus it is thought that supplementing the gastrointestinal flora with the right types of microorganisms can improve the gut flora and promote health [22]. Probiotics may include formulations that include a single or mixed culture of microorganisms and are available in various preparations that include fermented milk drinks, capsules, pills, liquid supplements and powders. Existing evidence suggests that certain strains of probiotics may improve visceral hypersensitivity and stimulate an anti-inflammatory response, which could in turn lead to improvement of IBS symptoms [46].

Herbal extracts commonly used to treat IBS

The provenance of herbal medicine is extraordinarily diverse. Indeed, its trans-cultural origin and centuries of continuing use suggest that at least some of its constituents are likely to be of therapeutic value. This has become clear with the derivation from plants of a number of conventional drugs, including digoxin from foxgloves, aspirin from willow-bark, quinine from cinchona-bark and morphine

from the opium poppy [34]. Furthermore, pharmaceutical companies are now engaged in extensive screening programmes to identify and isolate therapeutically active agents from plants [34].

Every culture has explored and used plants for medicinal purposes. The presence of several plants with medicinal properties in a Neanderthal tomb in Iraq suggests that herbs may have been used therapeutically for more than 60,000 years. The first records come from China, where the Emperor Shen Nung compiled the Pen Tsao (The Great Herbal, or Chinese Materia Medica), around the year 3,000 BC. This book had many subsequent editions, and many of the thousand or more drugs described are still used in China today [47].

Peppermint oil

As the name suggests, peppermint oil is essentially the oil extracted from the peppermint plant *Mentha piperita*, and has been traditionally used as an antispasmodic to treat upset stomach for centuries [29]. Peppermint oil appears to work by interfering with calcium channels which result in intestinal smooth muscle relaxation [22], and may provide short-term relief of abdominal pain. A meta-analysis of 4 RCTs found that when compared to placebo, peppermint oil did contribute to overall symptom improvement, with a relative risk of 0.43 (95% CI 0.32 to 0.59), although with statistical heterogeneity between studies [45].

Senna

Senna is a genus of flowering plants in the legume family Fabaceae. This genus is native to the tropics and some temperate regions. Senna has been historically used as a laxative by either ingesting the plant pods or as herbal tea made from the leaves. It is considered a stimulant laxative as it induces peristaltic contractions, while at the same time acting on the intestinal mucosa by increasing water and electrolyte secretion [48,49]. At least three RCTs have compared the effect of senna with other

laxatives in the treatment of chronic constipation. The three studies showed senna to be a better choice, especially when administered in combination with other agents. Despite these findings, recommendations on the use of senna remain moderate based on the observation that excessive use can lead to *Melanosis coli,* which is considered a risk factor for developing cancer of the colon. In addition to senna, another herbal laxative commonly used in treating IBS symptoms is the genus Aloe, which for the purposes of this study, a separate section is dedicated.

4. THE ALOE GENUS – HISTORY AND BACKGROUND

Aloe is a plant genus that belongs to the *Asphodelaceae* family. The origins of the genus have been traced back to Southern Africa, about 16 million years ago. Aloes went through two major evolutionary radiations that have given rise to the extraordinary diversity of the species known today [50]. There are about 500 known species, with the majority found in southern Africa, Madagascar, the Arabian Peninsula and some western Indian Ocean islands. Of these, an estimated 160 are considered indigenous to South Africa [51].

The name "Aloe" given to the genus is the result of one if its species, *Aloe Vera*, being so commonly used throughout history. It is derived from the Arabic word *alloeh*, which means "shining bitter substance" while *vera* in Latin means ´truth´ [47]. Native to the Arabian Peninsula, the historical preference for the *Aloe Vera* species in Western culture seems to be due to its early introduction to cultivation and trade, as well as its proximity to important historical trade routes. The resilience and ease of transport of this genus helps explain why Aloes can now be found in tropical and sub-tropical areas worldwide [47,50].

Aloes have a well-documented history of use as medicine and have been used since ancient times. The earliest credible testimony concerning the human use of aloe has been found in Egypt dating

back to about 3,000 BC and consists of pictorial representations adorning funerary monuments and tombs [47]. The earliest evidence of the medicinal use of Aloe is found in the form of Mesopotamian clay tablets dated between 2,100 and 1,800 BC which describe in cuneiform the plant's laxative properties [47]. Hippocrates of Kos, a physician from ancient Greece and often regarded as the "father of modern medicine", described some medicinal properties of aloe, including the ability to promote hair growth, as a cure for tumours and for the relief of dysentery and stomach-ache [47]. Later on, the widespread use of Aloe as a laxative appeared in the work of Greek physician Galen of Pergamon, dated between 129-216 AD [41]. Aloes are also one of only a few plants that appear in San rock paintings in South Africa, dating between 2,500 and 150 years [52,53]. An ethno-botanical study has documented its usage by the Khoi-San in the Karoo region of South Africa as a purgative and laxative agent [54].

4.1. Aloe species used for therapeutic purposes

Two review studies focusing on the utility and bio-cultural value of the Aloe genus found that *Aloe Vera, Aloe Ferox* and *Aloe Arborescens* are the three species that make up the majority of documented medicinal and commercial applications [54,55]. *Aloe Vera*, also known as *Aloe Barbadensis,* has been cultivated worldwide for more than two centuries. *Aloe Ferox* and *Aloe Arborescens* are originally from Southern Africa and are currently cultivated there, supplying processed and unprocessed natural products to export markets, especially in Europe and Asia [54].

4.2. Chemical composition of Aloes

Aloes produce anthraquinone glycosides like aloin A and B (10-30%), sugars (25%), a resinous material (16-63%), mucilage (30%), fatty acids (cholesterol, b-sitosterol, campesterol), mucopolysaccharides acemannan and betamannan, glycoproteins including aloctins A and B, enzymes including cyclooxygenase and bradykininase, and other compounds including salicylic acid, lupeol, cinnamic

acid, urea nitrogen, sulphur, phenol, prostanoids, magnesium lactate, fibre etc. [42]. Of these compounds, some possess antiseptic properties (salicylic acid, lupeol, phenol and sulphur), immunostimulant properties (acemannan), anti-inflammatory properties (aloctins, b-sitosterol, cholesterol, campesterol, acemannan), and laxative properties (aloin A and B) [42].

Aloes are perennial succulents, and characterized by long and thick fleshy leaves that are lance-shaped, with spiny margins and a sharp apex [51]. The outer rind of the leaf consists mainly of structural components, and where anthraquinones and their glycosides are found. The region in the outer pulp below the rind is where the bitter sap or latex is derived. This latex consists mainly of anthraquinones, anthrones, flavonoids, chromones and pyrones. The inner leaf pulp contains parenchyma cells which forms the gel. This pulp is high in water content (approximately 99% for *Aloe Vera* species) and is high in the polysaccharide known as acemannan, as well as various phenolic phytochemicals such as alkaloids, anthrones, anthraquinones and flavonoids. Enzymes, vitamins and minerals are also found in the pulp [55]. Figure 1 shows a schematic representation of the Aloe leaf morphology, and shows a leaf cross-section.

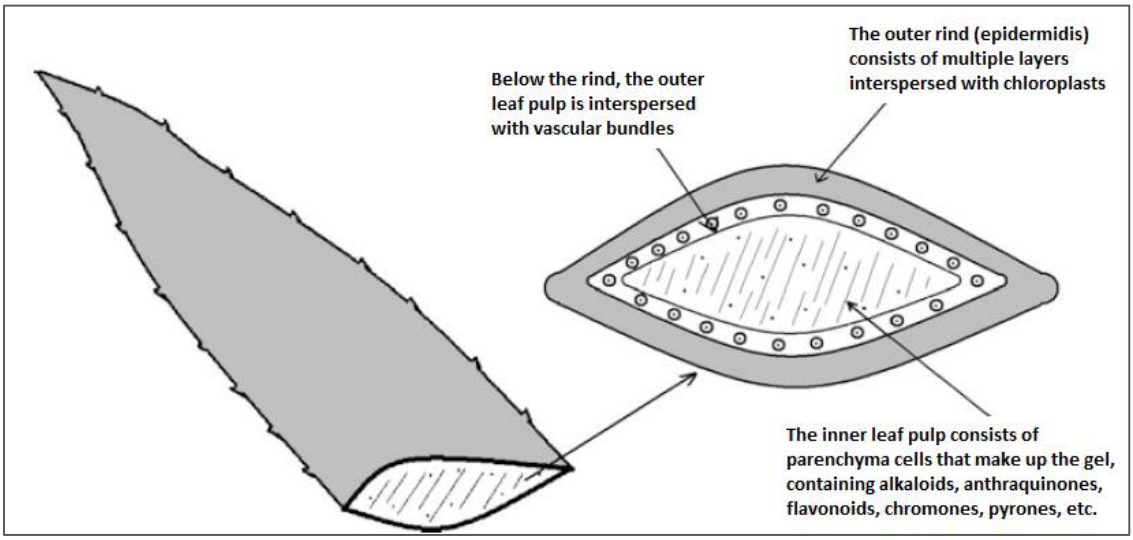

Figure 1: Schematic representation of the Aloe leaf morphology and cross-section. Adapted from [55].

4.3. Aloe – In vitro and in vivo properties

4.3.1. Burn wound healing properties

Aloe has shown to be effective in burn would healing in a four-arm comparative study conducted with guinea pigs. In this study, group 1 was given silver sulfadiazine (Silvadine), group 2 was given Aloe gel extract, group 3 received salicylic acid cream, and group 4 was given plain gauze occlusive resin only. The study reported that after 50 days of treatment, of the four groups, the only statistically significant difference was found in the group of animals that received Aloe, in which wound healing time was significantly shorter ($p<0.02$) [56]. It is argued that these effects may be due to the increased rate of epithelialization brought about by the acemannan polysaccharide in its ability to stimulate fibroblasts and collagen synthesis, in addition to its anti-inflammatory, antimicrobial and moisturizing effects [57].

A study with human subjects conducted in Pakistan compared the effectiveness of Aloe gel with silver sulphadiazine (SSD) cream at 1% concentration, as burn wound dressing for second degree burns. Using systematic random sampling, 25 patients were assigned to each of the groups. The study reported that the time needed for healing of burn wounds was remarkably shorter among those in the Aloe gel group compared to those receiving silver SSD. In addition to being more cost-effective, the patients in the Aloe group also reported pain relief much earlier than those treated with SSD [58]. In Thailand, Aloe gel has been formally included in the Thai Herbal Fundamental Public Health Drug List as a therapy for burn wounds [57].

4.3.2. Immunostimulant properties

A carbohydrate found in Aloe gel known as Acemannan, has been evaluated for its antiviral activities and activation of immune responses. One study set out to define the properties of Acemannan on dendritic cells in vitro. After phenotypic analysis, the study confirmed that Acemannan could induce

maturation of immature dendritic cells and provided support to this claim [59]. Another study has shown that Acemannan can inhibit the replication of HIV-1 virus when the latter is introduced in vitro to blood cells of human subjects who have taken oral doses of Acemannan. This suggests that it may have a prophylactic effect. No adverse events were observed in the study [60].

Between 2008 and 2009, a preliminary study was conducted in Nigeria to evaluate the use of Aloe to treat HIV infection. This controlled before-and-after (CBA) study included 10 young women with HIV infection and another 20 age-matched controls who were taking antiretroviral drugs. During the 1-year study period, their CD4 counts, general improvement and physical well-being were monitored. The results showed an average CD4 cell increase in the intervention group of 153.7 cells/µl, compared to 238.85 cells/µl for the controls ($p=0.087$), with no significant side effects in both groups. Although the mean difference in CD4 count between the two groups was not statistically significant, the authors suggest that consumption of Aloe may help HIV-infected individuals in the tropics with significant cost-effectiveness potential [61].

4.3.3. Anti-inflammatory properties

Aloes have been used topically by ancient and modern cultures for their wound healing and anti-inflammatory properties. In the West, Aloes have been used as an oral preparation for their anti-inflammatory effects [62]. Aloes contain 3 malic acylated carbohydrates, which are Veracylglucans A, B and C. These three compounds have demonstrated anti-inflammatory properties [51].

A study reports that the anti-inflammatory action of Aloe gel in human colorectal mucosa in vitro may have a therapeutic effect in treating inflammatory bowel disease [62]. In a later study, the same author conducted a randomized control trial to evaluate the efficacy and safety of Aloe gel for treating ulcerative colitis. This study found that after 4 weeks of treatment, when compared to the placebo group, the patients in the Aloe group showed decreased clinical colitis activity index and

histological scores (p=0.01 and p=0.03 respectively), pointing to therapeutic potential of Aloe in treating patients with inflammatory bowel disease [62].

4.3.4. Laxative properties

The laxative properties of Aloe have been mainly attributed to the anthraquinones (mainly aloin) that are found in the yellow exudates of the leaves [63]. The laxative effect is believed to take place through water accumulation in the intestine via active Na+ transport or by water secretion due to aprostaglandin-dependent mechanism [47].

Previous research in rats suggests Aloe's laxative actions may have a beneficial effect in the treatment of constipation-predominant IBS [64–66]. Aloe's laxative properties have also been studied in patients with *schizophrenia* [67]. Antipsychotic treatment for schizophrenia is most often in the form of dopamine D2 receptor antagonists. However, these medications often cause peripheral adverse effects including dry mouth and constipation. In three different studies, Aloe gel was evaluated in the treatment of antipsychotic-induced constipation. All three studies reported that Aloe was effective in relieving constipation symptoms [67].

4.3.5. Aloe and its mechanism of action in the colon

The laxative properties of Aloe have been mainly attributed to the anthraquinones (mainly in the form of aloin) that are found in the gel and yellow exudates of the leaves [63]. Once ingested, aloin is stable in the stomach, and the sugar moiety prevents its absorption in the gut and detoxification in the liver. This protects the aloins from breakdown before they reach the colon and rectum [68]. Once the Aloins reach the large intestine, they behave like pro-drugs in that they are metabolized by gut bacteria into aloe-emodin, which is more readily absorbed and is ultimately responsible for Aloe's purgative activity [47,69]. The laxative effect is thought to take place through accumulation of water in the intestine through active Na+ transport, or by water secretion caused by a prostaglandin-

dependent mechanism [47,51]. A study that explored Aloe's activities in the gastrointestinal tract in rats also suggests a relationship between an increase in intestinal water content caused by Aloe-emodin, and stimulation of peristalsis [70–72].

4.3.6. Traditional and conventional uses of aloe to treat digestive issues

Although there is mention of Aloe gel being formally recognized in the Thai health system for topical use, no evidence has been found of Aloe being formally recognized as treatment for digestive issues. However, there is ample evidence of its use as a traditional and CAM treatment for these issues. In addition to Aloe's documented use as laxative dating back to at least 1,000 BC in Egypt and Mesopotamia, more recent evidence of its use is found in Africa, Europe and Asia [47].

In southern Africa, Aloes remain one of the most popular components of the rich and diverse floral landscape. The genus is of great importance from the taxonomic and ethno-medicinal perspectives [73]. Aloe bitters, also known as Cape Aloes, is the end product of extracting the bitter *Aloe Ferox* leaf exudate (also known as sap), which is heated until it crystallizes. The Aloin, which is the main ingredient found in the crystals, has been known in South Africa and Europe as a potent laxative [51,66,68]. These crystals are orally consumed as laxative medicine in humans, and are also used for the same indication to treat cattle in Lesotho. The literature shows numerous other ethno-medicinal applications of the *Aloe Ferox* sap in southern Africa, such as its use to relieve conjunctivitis, ophtalmia and other eye ailments by topical application of the leaf sap as eye drops [68].

Cape aloes is a component of *Lewensessens,* a bitter digestive tonic with a long history in South Africa, and also known as "Swedish bitters", an early modern herbal preparation that has been widely used in Europe since the 1730s [74].

Despite Aloe's apparent popularity in treating constipation, not many studies have been conducted to evaluate the effectiveness of Aloe as a stand-alone herbal treatment for IBS-related symptoms.

The first known randomized controlled trial was published in 1991, where Aloe was used as part of an herbal preparation in combination with ispaghula husk and celandine in the ratio of 3:1:6 respectively, for 28 days. The study found that the mix was effective in treating functional constipation and constipation-predominant IBS symptoms [75]. Similarly in 2002, another study looked at a Tibetan herbal formula that contained Aloe for the treatment of constipation-predominant IBS [76]. Like in a previous study, this study also found that the herbal concoction was effective in the treatment of IBS-C [76]. However, given that these are poly-herbal preparations where Aloe is used in addition to other compounds, it is difficult to attribute the effect solely to one single plant or ingredient.

In addition to its use as laxative, Aloe is also thought to be useful in treating other IBS-associated symptoms, such as diarrhoea, bloating and abdominal pain. Its anti-inflammatory properties are also thought to reduce gastrointestinal inflammation [62].

The first known randomized control trial that examined a purer form of Aloe was published in 2006 and looked at evaluating the effectiveness of an Aloe supplement in treating all IBS sub-types. Although the study failed to detect a significant effect when compared to placebo overall, a slight benefit was seen among the diarrhoea-predominant IBS patients while the treatment was being taken [21]. A later study in 2013 found that Aloe did have a positive effect in reducing abdominal pain and flatulence among patients with IBS, however this study did not have a control group, which did not make it possible to determine if the relief of symptoms could be solely attributable to Aloe [77].

Although clinical trials have been carried out to assess the effectiveness of Aloe in treating IBS symptoms, the evidence of its effects is limited and contradictory [78]. To date, the effectiveness of Aloe in treating IBS symptoms in clinical trials has not been systematically studied. This presents an

opportunity to conduct a systematic review and meta-analysis to summarize the existing evidence on its contribution to improve IBS symptoms, and if possible, identify potential factors that may influence this response.

5. SUMMARY AND CONCLUSION OF THE LITERATURE REVIEW

In conclusion, the reviewed literature highlights the complex and heterogeneous nature of IBS, where multiple pathways point to a brain-gut axis that influences and mediates commonly associated symptoms such as abdominal pain, bloating, constipation and diarrhoea. Despite extensive research, evidence on the effectiveness of conventional pharmacological treatments for IBS patients is not yet conclusive.

The refractory nature of the disorder, and in many cases, patients' lack of satisfaction with conventional treatments prompts many to seek CAM therapies. These include psychological interventions such as cognitive behavioural therapy and hypnosis. Symptomatic treatments include the use of soluble fibre, probiotics and herbal extracts such as Peppermint oil, Senna and Aloe gel.

The literature highlights the Aloe genus' many chemical constituents and therapeutic potential. Various studies suggest its laxative and anti-inflammatory properties may be effective in treating IBS. However, to date, the effectiveness of Aloe in addressing IBS symptoms has not yet been systematically studied.

REFERENCES

1. Corazziari E. Definition and epidemiology of functional gastrointestinal disorders. Best Pract Res Clin Gastroenterol. 2004;18(4):613–31.
2. Canavan C. CLEP-40245-the-epidemiology-of-irritable-bowel-syndrome. 2014;71–80.
3. Vanuytsel T, Tack JF, Boeckxstaens GE. Treatment of abdominal pain in irritable bowel syndrome. J Gastroenterol. 2014;49(8):1193–205.
4. Chang FY, Lu C-LL. Treatment of Irritable Bowel Syndrome Using Complementary and Alternative Medicine. J Chinese Med Assoc [Internet]. 2009 Jun [cited 2017 Nov 14];72(6):294–300. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1726490109703752
5. Defrees DN, Bailey J. Irritable Bowel Syndrome: Epidemiology, Pathophysiology, Diagnosis, and Treatment. Prim Care - Clin Off Pract. 2017;44(4):655–71.
6. Canavan C, West J, Card T. Review article: The economic impact of the irritable bowel syndrome. Aliment Pharmacol Ther. 2014;40(9):1023–34.
7. Talley NJ, Holtmann G. Irritable bowel syndrome and functional dyspepsia : what can epidemiology tell us about etiology ? Irritable bowel syndrome and functional dyspepsia : what can epidemiology tell us. Expert Rev Gastroenterol Hepatol [Internet]. 2018;12(7):633–5. Available from: https://doi.org/10.1080/17474124.2018.1476136
8. Cuomo R, Andreozzi P, Zito FP, Passananti V, Carlo G De, Cuomo R, et al. Irritable bowel syndrome and food interaction. 2014;20(27):8837–45.
9. Marshall JK. The origins of irritable bowel syndrome: Experience of a lifetime. Gastroenterology [Internet]. 2014;147(1):18–20. Available from: http://dx.doi.org/10.1053/j.gastro.2014.05.024
10. Stanghellini V. Functional Dyspepsia and Irritable Bowel Syndrome : Beyond Rome IV. 2018;14–7.
11. Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, Camilleri M, et al. Prevalence, Risk Factors, and Outcomes of Irritable Bowel Syndrome After Infectious Enteritis: A Systematic Review and Meta-analysis. Gastroenterology. 2017;152(5):1042-1054.e1.
12. Lovell RM, Ford AC. Global Prevalence of and Risk Factors for Irritable Bowel Syndrome: A Meta-analysis. Clin Gastroenterol Hepatol [Internet]. 2012;10(7):712–21. Available from: http://dx.doi.org/10.1016/j.cgh.2012.02.029
13. Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disease and functional abdominal pain. Gastroenterol Int. 1992;5(2):75–91.
14. Lewis SJ, Heaton KW. Stool Form Scale as a Useful Guide to Intestinal Transit Time. Scand J Gastroenterol [Internet]. 1997 Jan 1;32(9):920–4. Available from:

https://doi.org/10.3109/00365529709011203

15. Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. 1978;(September):653–4.

16. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. Longo DL, editor. N Engl J Med [Internet]. 2017 Jun 29 [cited 2019 Feb 7];376(26):2566–78. Available from: http://www.nejm.org/doi/10.1056/NEJMra1607547

17. Drossman DA. Functional gastrointestinal disorders: History, pathophysiology, clinical features, and Rome IV. Gastroenterology [Internet]. 2016;150(6):1262-1279e2. Available from: http://dx.doi.org/10.1053/j.gastro.2016.02.032

18. Lunsford TN, Harris LA. Lubiprostone: Evaluation of the newest medication for the treatment of adult women with constipation-predominant irritable bowel syndrome. Int J Womens Health. 2010;2(1):361–74.

19. Rawla P, Sunkara T, Raj JP. Updated review of current pharmacological and non-pharmacological management of irritable bowel syndrome. Life Sci [Internet]. 2018;212(September):176–81. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0024320518306180%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/30290187

20. Johannesson E, Simrén M, Strid H, Bajor A, Sadik R. Physical activity improves symptoms in irritable bowel syndrome: A randomized controlled trial. Am J Gastroenterol. 2011;106(5):915–22.

21. Davis K, Philpott S, Kumar D, Mendall M. Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. Int J Clin Pract [Internet]. 2006 Sep 2 [cited 2017 Nov 14];60(9):1080–6. Available from: http://doi.wiley.com/10.1111/j.1742-1241.2006.00980.x

22. Wall GC, Bryant GA, Bottenberg MM, Maki ED, Miesner AR, Wall GC, et al. Irritable bowel syndrome: A concise review of current treatment concepts. World J Gastroenterol. 2014;20(27):8796–806.

23. Atluri DK, Chandar AK, Bharucha AE, Falck-Ytter Y. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): a systematic review and meta-analysis. Neurogastroenterol Motil [Internet]. 2014 Apr 1 [cited 2018 Nov 19];26(4):499–509. Available from: http://doi.wiley.com/10.1111/nmo.12292

24. Wall G, Bryant G, … MB-WJ of, 2014 undefined. Irritable bowel syndrome: a concise review of current treatment concepts. ncbi.nlm.nih.gov [Internet]. [cited 2019 Feb 7]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4112883/

25. Review AS, Trials C, Jailwala J, Imperiale TF, Kroenke K. Review Pharmacologic Treatment of the Irritable Bowel Syndrome : Ann Intern Med. 1999;

26. Ruepert L, Ao Q, Nj DW, Gj VDH, Rubin G, Jwm M. Bulking agents , antispasmodics and

antidepressants for the treatment of irritable bowel syndrome (Review). 2013;(8).

27. Whitehead WE, Levy RL, Von Korff M, Feld AD, Palsson OS, Turner M, et al. The usual medical care for irritable bowel syndrome. Aliment Pharmacol Ther. 2004;20(11–12):1305–15.

28. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: What are the causes and implications? Gastroenterology. 2002;122(4):1140–56.

29. Shen H. Discussion on certain issues of the diagnosis and treatment of functional constipation. Chin J Integr Med. 2009;15(2):89–92.

30. Ford AC, Moayyedi P. Meta-analysis: Factors affecting placebo response rate in the irritable bowel syndrome. Aliment Pharmacol Ther. 2010;32(2):144–58.

31. Elkins G, Barabasz A, … JC-IJ of, 2015 undefined. Advancing Research and Practice: The Revised APA Division 30 Definition of Hypnosis. Taylor Fr [Internet]. [cited 2018 Nov 19]; Available from: https://www.tandfonline.com/doi/abs/10.1080/00207144.2014.961870

32. Webb AN, Kukuruzovic R, Catto-Smith AG, Sawyer SM. Hypnotherapy for treatment of irritable bowel syndrome. Cochrane Database Syst Rev [Internet]. 2007;(1). Available from: http://doi.wiley.com/10.1002/14651858.CD005110.pub2

33. Zollman C, Vickers A. What is complementary medicine ? Clinical review. 1999;319(September):693–6.

34. Langmead L, Makins RJ, Rampton DS. Anti-inflammatory effects of aloe vera gel in human colorectal mucosa in vitro. Aliment Pharmacol Ther. 2004 Mar;19(5):521–7.

35. Frass M, Strassl RP, Friehs H, Mullner M, Kundi M, Kaye AD. Use and acceptance of complementary and alternative medicine among the general population and medical personnel: A systematic review. Ochsner J [Internet]. 2012;12(1):45–56. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L364480632%5Cnhttp://www.ochsnerjournal.org/doi/pdf/10.1043/1524-5012-12.1.45%5Cnhttp://cf5pm8sz2l.search.serialssolutions.com?sid=EMBASE&issn=15245012&id=doi:&atitle=Use+and+accepta

36. Kelley JM, Lembo AJ, Ablon JS, Villanueva JJ, Conboy LA, Levy R, et al. Patient and practitioner influences on the placebo effect in irritable bowel syndrome. Psychosom Med. 2009;71(7):789–97.

37. Dorn SD d., Kaptchuk TJ j., park JB b., Nguyen LT t., canenguez K, Nam BH h., et al. A meta-analysis of the placebo response in complementary and alternative medicine trials of irritable bowel syndrome. 2007 Aug [cited 2018 Jul 8];19(October 2006):630–7. Available from: http://doi.wiley.com/10.1111/j.1365-2982.2007.00937.x

38. Eisenberg D, Davis R, Ettner S, Appel S, Jama SW-, 1998 undefined. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey.

jamanetwork.com [Internet]. [cited 2019 Feb 7]; Available from: https://jamanetwork.com/journals/jama/fullarticle/188148

39. Hung A, Kang N, Bollom A, Wolf JL, Lembo A. Complementary and Alternative Medicine Use Is Prevalent Among Patients with Gastrointestinal Diseases. Dig Dis Sci [Internet]. 2015;60(7):1883–8. Available from: http://dx.doi.org/10.1007/s10620-014-3498-3

40. Shi J, Tong Y, Shen JG, Li HX. Effectiveness and safety of herbal medicines in the treatment of irritable bowel syndrome: A systematic review. World J Gastroenterol. 2008;14(3):454–62.

41. Langmead L, Rampton DS. Review article: herbal treatment in gastrointestinal and liver disease-benefits and dangers. Aliment Pharmacol Ther [Internet]. 2001 Sep 27 [cited 2018 Jul 8];15(9):1239–52. Available from: http://doi.wiley.com/10.1046/j.1365-2036.2001.01053.x

42. Capasso F, Borrelli F, Capasso R, Di Carlo G, Izzo AA, Pinto L, et al. Aloe and its therapeutic use. Phyther Res. 1998;12(SUPPL. 1).

43. Hussain Z, Quigley EMM. Systematic review: Complementary and alternative medicine in the irritable bowel syndrome. Aliment Pharmacol Ther. 2006;23(4):465–71.

44. Chan TYK, Tam HP, Lai CK, Chan AYW. A multidisciplinary approach to the toxicologic problems associated with the use of herbal medicines. Ther Drug Monit. 2005;27(1):53–7.

45. Ford AC, Talley NJ, Spiegel BMR, Foxx-Orenstein AE, Schiller L, Quigley EMM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: Systematic review and meta-analysis. Bmj. 2008;337(7683):1388–92.

46. Reid G, Younes JA, Van Der Mei HC, Gloor GB, Knight R, Busscher HJ. Microbiota restoration: Natural and supplemented recovery of human microbial communities. Nat Rev Microbiol. 2011;9(1):27–38.

47. Chinchilla N, Carrera C, Durán AG, Macías M, Torres A, Macías FA. Aloe barbadensis: How a miraculous plant becomes reality. Phytochem Rev. 2013;12(4):581–602.

48. Leung L, Riutta T, Kotecha J, Rosser W. Chronic Constipation: An Evidence-Based Review. J Am Board Fam Med [Internet]. 2011;24(4):436–51. Available from: http://www.jabfm.org/cgi/doi/10.3122/jabfm.2011.04.100272

49. Gordon M, MacDonald JK, Parker CE, Akobeng AK, Thomas AG, Morris G, et al. Osmotic and stimulant laxatives for the management of childhood constipation. Cochrane Database Syst Rev [Internet]. 2016 Aug 17 [cited 2018 Jul 24]; Available from: https://mednar.com/mednar/desktop/en/service/link/track?redirectUrl=http%3A%2F%2Fcochranelibrary-wiley.com%2Fdoi%2F10.1002%2F14651858.CD009118.pub3%2Ffull&collectionCode=MEDNAR-COCLIB&searchId=2e3cdad4-43a8-4b70-9aab-905bf3215df7&type=RESULT&signature=2ea

50. Grace OM, Buerki S, Symonds MRE, Forest F, van Wyk AE, Smith GF, et al. Evolutionary history and leaf succulence as explanations for medicinal use in aloes and the global popularity of Aloe vera [Internet]. Vol. 15, BMC evolutionary biology. 2015. p. 29. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=awn&AN=25879886&site=ehost-live

51. Steenkamp V, Stewart MJJ. Medicinal applications and toxicological activities of Aloe products. Pharm Biol. 2007;45(5):411–20.

52. Reynolds G. The Aloes of South Africa. AA Balkema; 1982.

53. Daley J. New Technique Shows San Rock Art Is 5,000 Years Old | Smart News | Smithsonian [Internet]. Smithsonian.com. 2017 [cited 2019 Feb 7]. Available from: https://www.smithsonianmag.com/smart-news/new-technique-shows-san-rock-art-5000-years-old-180962948/

54. Grace OM, Simmonds MSJ, Smith GF, van Wyk AE. Therapeutic uses of Aloe L. (Asphodelaceae) in southern Africa. J Ethnopharmacol. 2008;119(3):604–14.

55. Cock IE. The genus aloe: Phytochemistry and therapeutic uses including treatments for gastrointestinal conditions and chronic inflammation. Vol. 70, Progress in Drug Research. 2015. 179–235 p.

56. Rodríguez-Bigas M, Cruz NI, Suárez A. Comparative evaluation of aloe vera in the management of burn wounds in guinea pigs. Plast Reconstr Surg [Internet]. 1988 Mar [cited 2018 Nov 19];81(3):386–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3340673

57. Maenthaisong R, Chaiyakunapruk N, Niruntraporn S, Kongkaew C. The efficacy of aloe vera used for burn wound healing: A systematic review. Burns. 2007;33(6):713–8.

58. Shahzad MN, Ahmed N. Effectiveness of Aloe Vera gel compared with 1% silver sulphadiazine cream as burn wound dressing in second degree burns. J Pak Med Assoc. 2013;63(2):225–30.

59. Lee JKJK, Lee MKMK, Yun Y-PYP, Kim YSYYS, Kim JSJS, Kim YSYYS, et al. Acemannan purified from Aloe vera induces phenotypic and functional maturation of immature dendritic cells. Int Immunopharmacol. 2001;1(7):1275–84.

60. Cooper M. Acemannan inhibits HIV-1. CDC AIDS Wkly [Internet]. 1989 Oct 23 [cited 2019 Feb 7];7–9. Available from: http://go.galegroup.com.ezproxy.uct.ac.za/ps/i.do?id=GALE%7CA8072309&v=2.1&u=unict&it=r&p=AONE&sw=w

61. Olatunya OS, Olatunya AM, Anyabolu HC, Adejuyigbe EA, Oyelami OA. Preliminary trial of aloe vera gruel on HIV infection. J Altern Complement Med. 2012;18(9):850–3.

62. Langmead L, Feakins RM, Goldthorpe S, Holt H, Tsironi E, De Silva A, et al. Randomized,

double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. Aliment Pharmacol Ther. 2004 Apr;19(7):739–47.

63. Maan AAAA, Nazir A, Khan MKIMKI, Ahmad T, Zia R, Murid M, et al. The therapeutic properties and applications of Aloe vera: A review. J Herb Med. 2018;12(September 2016):1–10.

64. Zihong L, Jingxun W, Journal XZ-GM, 2005 undefined. The curative effect of aloe on constipation and its primary mechanism. en.cnki.com.cn [Internet]. [cited 2019 Feb 7]; Available from: http://en.cnki.com.cn/Article_en/CJFDTOTAL-GAYX200510016.htm

65. Shamirzadi. Benefit of Aloe vera and Matricaria recutita Mixture in Rat Irritable Bowel Syndrome : Combination of Antioxidant and. 2012;1–9.

66. Wintola OA, Afolayan AJ. Ethnobotanical survey of plants used for the treatment of constipation within nkonkobe municipality of south africa. African J Biotechnol. 2010;9(45):7767–70.

67. Kwon M, Ju SO. The effect of aloevera for constipation in schizophrenia patients. Indian J Sci Technol. 2016;9(41).

68. Chen W, Van Wyk BEB-E, Vermaak I, Viljoen AMAMAM. Cape aloes - A review of the phytochemistry, pharmacology and commercialisation of Aloe ferox. Phytochem Lett [Internet]. 2012;5(1):1–12. Available from: http://dx.doi.org/10.1016/j.phytol.2011.09.001

69. Radha MH, Laxmipriya NPNP. Evaluation of biological properties and clinical effectiveness of Aloe vera: A systematic review. J Tradit Complement Med. 2015 Jan;5(1):21–6.

70. Ishii Y, Takino Y, Toyo'oka T, Tanizawa H. Studies of aloe. VI. Cathartic effect of isobarbaloin. Biol Pharm Bull. 1998 Nov;21(11):1226–7.

71. Ishii Y, Tanizawa H, Takino Y. Studies of Aloe. V.[1)] Mechanism of Cathartic Effect. (4). Biol Pharm Bull. 1994;17(5):651–3.

72. Ishii Y, Tanizawa H, Takino Y. Fluorophotometry of Barbaloin in Aloe. Chem Pharm Bull. 1984;32(12):4946–50.

73. Amoo SO, Aremu AO, Van Staden J. Unraveling the medicinal potential of South African Aloe species. J Ethnopharmacol. 2014;153(1):19–41.

74. Ahnfelt NO, Fors H. Making Early Modern Medicine: Reproducing Swedish Bitters. Ambix. 2016;63(2):162–83.

75. ODES HSSHS, Madar Z. A double-blind trial of a celandin, aloevera and psyllium laxative preparation in adult patients with constipation. Digestion [Internet]. 1991 Jun [cited 2018 Jul 8];49(2):65–71. Available from: https://www.karger.com/Article/FullText/200705

76. Sallon S, Ben-arye E, Davidson R, Shapiro H, Ginsberg G, Ligumsky M. Original Paper :

Functional Disorders A Novel Treatment for Constipation-Predominant Irritable Bowel Syndrome Using Padma ® Lax , a. 2002;161–71.

77. Khedmat H, Karbasi A, Amini M, Aghaei A, Taheri S. Aloe vera in treatment of refractory irritable bowel syndrome: Trial on Iranian patients. J Res Med Sci [Internet]. 2013 Aug [cited 2017 Nov 14];18(8):732. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24379854

78. Størsrud S, Pontén I, Simrén M (2015), Storsrud S, Ponten I, Simren M, et al. A Pilot Study of the Effect of Aloe barbadensis Mill. Extract (AVH200®) in Patients with Irritable Bowel Syndrome: a Randomized, Double-Blind, Placebo-Controlled Study. J Gastrointest Liver Dis [Internet]. 2015 Sep 1 [cited 2017 Nov 14];24(3):275–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26405698

PART C: MANUSCRIPT

Consumption of Aloe to improve health outcomes in adults with irritable bowel syndrome: A systematic review and meta-analysis.

ABSTRACT

Study aim: To evaluate the effect of Aloe on symptoms associated with Irritable Bowel Syndrome (IBS) in adults.

Study objective: To summarize the existing evidence on the contribution of Aloe to improved health outcomes among adult patients diagnosed with IBS and where possible, identify potential factors that may influence this response.

Design: Systematic review and meta-analysis of randomized controlled trials, non-randomised controlled trials, retrospective and prospective cohort studies, and controlled before-and-after (CBA) studies.

Data sources: Medline, Scopus, EBM reviews, Africa-wide, CINAHL, Web of Science, Mednar, Cochrane Library, clinicaltrials.gov, World Health Organization Library Information System (WHOLIS), Ebscohost and Google Scholar up to August 2018.

Review methods: Randomized controlled trials, non-randomised controlled trials, retrospective and prospective cohort studies, and controlled before-and-after (CBA) studies comparing Aloe in different preparations to placebo in adults with irritable bowel syndrome were eligible for inclusion. Minimum duration of therapy considered was two weeks, and studies had to evaluate either a global assessment of cure or improvement in symptoms, or cure, or improvement in abdominal pain, after treatment. A random effects model was used to pool the effect of therapy compared with placebo or no treatment. This was reported as the risk ratio (95% confidence interval) of those who responded to treatment versus those who responded to placebo.

Results: Compared with placebo, this systematic review found evidence for improvement in symptoms for Aloe-containing preparations in patients with IBS (relative risk (RR), 2.75; 95% confidence Interval (CI), 1.88 to 4.03, 5 studies, n=325; I^2=0%). In sub-group analyses, this finding was consistent amongst patients with constipation-predominant IBS (IBS-C) (RR, 3.41; 95% CI, 2.11 to 5.51; 3 studies, n=199. This finding was not replicated in the single study comparing Aloe with placebo in patients with diarrhoea-predominant IBS (IBS-D) and mixed-pattern IBS (IBS-M).

Conclusion: Aloe-containing preparations were more effective than placebo in improving symptoms among all IBS sub-types combined. In sub-group analyses, Aloe was more effective than placebo in the treatment of constipation-predominant IBS, however this was not the case with IBS-D and IBS-M sub-types. Given the variation in the formulae of Aloe preparations in the included studies, generalizability of this finding may be a challenge. Thus, further research with adequately-powered studies using a standardised formulation for Aloe-containing preparations for IBS is advised.

Keywords: Irritable bowel syndrome, Aloe, constipation, laxatives.

1. BACKGROUND

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain and changes in bowel habit in the form of constipation, diarrhoea or both [1–3]. IBS is categorized depending on the predominant stool pattern: Constipation-predominant (IBS-C), Diarrhoea-predominant (IBS-D), Mixed pattern (IBS-M), or unclassified phenotype (IBS-U) [3].

IBS is estimated to affect between 5-15% of the world's population; making it one of the more common GI disorders [3,4]. In addition it is reported that as much as 30% of visits to gastroenterologists belong to patients showing IBS-related symptoms [5]. IBS patients have shown similar or worse health-related quality of life (HRQoL), compared to chronic diseases like diabetes mellitus[3]. As a functional gastrointestinal disease (FGID), IBS is said to represent a major part of the work load of primary care physicians and gastroenterologists, and is also one of the leading causes for referral to emergency care units, thus draining substantial amounts of healthcare resources [6].

IBS largely remains an unexplained disorder of the gut function, as multiple disease pathways can lead to identical clinical phenotypes [7]. These include impaired motility and sensitivity, increased permeability, changes in the gut microbiome, psychological distress and alterations in the brain-gut axis [4,7]. Food also seems to play a key role, as most IBS patients report onset or exacerbation of symptoms after meals. Food intolerance is in turn associated with reduced quality of life and higher symptom severity scores [7].

Conventional medical treatment is purely symptomatic, and includes treatment with antispasmodics and laxatives to treat constipation-related symptoms, as well as bulking agents in the case of diarrhoea. Severe cases of the disorder may require muscle relaxants, antidepressants and anxiolytics [4,7]. Cognitive behavioural therapy (CBT) as well as hypnotherapy have also been used

as psychological interventions. However, these treatment options have shown limited efficacy, and many patients resort to complementary and alternative medicine (CAM), despite lack of evidence to support its use. These include dietary interventions and herbal preparations including peppermint oil and Aloe [8].

Aloe is a plant genus that belongs to the Asphodelaceae family. They are perennial succulents, and characterized by long and thick fleshy leaves that are lance-shaped, with spiny margins and a sharp apex. Although the genus originated in the dry and warm climates of Africa, Aloes are very adaptable and can be found worldwide. Aloe leaves produce a yellow latex, referred to as Aloe sap. The leaf pulp is composed of parenchyma cells that make up a gel [9].

The gel and sap are extracted from the leaf, and it is these substances that are often used as treatment. Previous research in rats suggests Aloe's laxative and anti-inflammatory actions may have a beneficial effect in the treatment of constipation-predominant IBS [10,11,41], and research conducted on humans suggests it may be effective in treatment of inflammatory bowel disease symptoms[10,11]. Clinical trials have also been carried out to assess the effectiveness of Aloe in treating IBS symptoms among humans, however the evidence of its effects is limited and contradictory [12]. To date, the effectiveness of Aloe in treating IBS symptoms in clinical trials has not been systematically studied. Therefore, the objective of this study is to summarize the existing evidence on the contribution of Aloe to improved health outcomes among patients diagnosed with IBS, and where possible, identify potential factors that may influence this response.

2. AIM AND OBJECTIVES

2.1. AIM

To evaluate the effect of Aloe on symptoms associated with Irritable Bowel Syndrome (IBS) in adults.

2.2. OBJECTIVES

To summarize the existing evidence on the contribution of Aloe to improved health outcomes among adult patients diagnosed with IBS and where possible, identify potential factors that may influence this response.

Review Question

Among adults diagnosed with irritable bowel syndrome, is the consumption of Aloe, compared with placebo, associated with improved health outcomes?

2. METHODS

2.1. Protocol and Registration

This systematic review and meta-analysis protocol has been published in the PROSPERO International Prospective Register of systematic reviews [20], registration number CRD42018082663.

2.2. Search strategy

The authors searched the medical literature using Medline, Scopus, EBM reviews, Africa-wide, CINAHL, Web of Science, Mednar, Cochrane Library, clinicaltrials.gov, World Health Organization Library Information System (WHOLIS), Ebscohost and grey literature (Google Scholar) up to August 2018. Randomized controlled trials of adults (>18 years) diagnosed with IBS based on diagnostic criteria (Manning or Rome iterations) were considered. If studies induced constipation or other IBS-related symptoms using drugs, such as opioids, these were excluded from the analysis. In addition to randomized controlled trials (RCTs), the authors considered as eligible for inclusion non-randomised controlled trials, retrospective and prospective cohort studies, and controlled before-and-after (CBA) studies.

A comprehensive search strategy was developed to search both published and unpublished articles. These included peer-reviewed journal articles, conference proceedings and grey literature (including unpublished, internal or non-reviewed papers and technical reports). The strategy included MeSH and free-text terms relating to IBS and Aloe literature. No language restrictions were applied. The lead reviewer evaluated the titles and abstracts of papers identified by the initial search for appropriateness to the study question. Potentially relevant papers were downloaded and reviewed in detail. Two reviewers independently assessed pre-selected articles using predesigned data extraction forms according to pre-defined eligibility criteria. Any disagreement between investigators was resolved by consensus.

Table 1 details the search strategy used for PubMed. This strategy was adapted to suit individual databases using applicable vocabulary and syntax.

2.3. Types of interventions

For this review, the term 'Aloe' was used to denote any species of Aloe either in its natural form or in any commercially-available forms, including those used in conjunction with other compounds. Aloe was included in its different forms as a therapeutic intervention to address symptoms related to IBS. These included patients who had received conventional medications in addition to Aloe, as well as those who were no longer taking any conventional medication and were seeking further treatment.

Table 1: PubMed search strategy, modified as needed for use in other databases		
	Subject/ Related term	**Search Terms**
PubMed search strategy		
#1	Intestinal diseases, colonic diseases, irritable bowel syndrome, gastrointestinal motility, irritable colon, peristalsis, constipation, diarrhea, feces, stool, abdominal pain, bloating, defecation, laxatives, bulking agent, dysmotility, visceral hypersensitivity, spastic colon, Rome criteria	intestinal diseases"[MeSH Terms] OR "colonic diseases"[MeSH Terms]) OR "irritable bowel syndrome"[MeSH Terms]) OR irritable bowel syndrome[Title/Abstract]) OR "gastrointestinal motility"[MeSH Terms]) OR "irritable bowel syndrome"[MeSH Terms]) OR irritable colon[Text Word]) OR "peristalsis"[MeSH Terms]) OR peristalsis[Title/Abstract]) OR "constipation"[MeSH Terms]) OR constipation[Text Word]) OR "diarrhea"[MeSH Terms]) OR diarrhea[Text Word]) OR "feces"[MeSH Terms]) OR stool[Text Word]) OR "feces"[MeSH Terms]) OR feces[Text Word]) OR abdominal pain[Title/Abstract]) OR abdominal pain[Text Word]) OR "defecation"[MeSH Terms]) OR defecation[Text Word]) OR "laxatives"[MeSH Terms]) OR laxative[Title/Abstract]) OR bulking agent[Title/Abstract]) OR dysmotility[Text Word]) OR visceral hypersensitivity[Text Word]) OR spastic colon[Title/Abstract]) OR spastic colon[Text Word]) OR Rome criteria[Text Word]) OR bloating[Title/Abstract]) OR "abdominal pain"[MeSH Terms]) OR abdominal pain[Title/Abstract]
#2	Xanthorrhoeaceae, Aloe, Asphodelaceae, Aloeaceae, Aloeandongensis, Aloedent, Aloe emodin, aloe*, emodin, barbaloin	"xanthorrhoeaceae"[MeSH Terms] OR Xanthorrhoeaceae[Text Word]) OR "aloe"[MeSH Terms]) OR (aloe[Title/Abstract] OR aloe'[Title/Abstract] OR aloe's[Title/Abstract] OR "Asphodelaceae"[MeSH Terms] OR Asphodelaceae[Text Word] OR aloeaceae[Title/Abstract] OR aloeandongensis[Title/Abstract] OR aloedent[Title/Abstract] OR "aloe emodin"[Title/Abstract] OR aloei[Title/Abstract] OR aloeicola[Title/Abstract] OR aloemannan[Title/Abstract] OR aloemodin[Title/Abstract] OR aloenin[Title/Abstract] OR aloepecia[Title/Abstract] OR aloeresin[Title/Abstract] OR aloeride[Title/Abstract] OR aloes[Title/Abstract] OR aloes'[Title/Abstract] OR aloesin[Title/Abstract] OR aloesinol[Title/Abstract] OR aloesol[Title/Abstract] OR aloesone[Title/Abstract] OR aloesorb[Title/Abstract] OR aloespanoarin[Title/Abstract] OR aloestron[Title/Abstract] OR aloeswood[Title/Abstract] OR aloethanes[Title/Abstract] OR aloetic[Title/Abstract] OR aloetica[Title/Abstract] OR aloeticola[Title/Abstract] OR aloetron[Title/Abstract] OR aloeus[Title/Abstract] OR aloev[Title/Abstract] OR aloeVera[Title/Abstract] OR aloeVerae[Title/Abstract] OR aloeverose[Title/Abstract] OR aloexylon[Title/Abstract])) OR Aloctin[Text Word]) OR aloin[Title/Abstract]) OR aloin[Text Word]) OR "emodin"[MeSH Terms]) OR emodin[Text Word]) OR barbaloin[Text Word]
Search		**#1 AND #2**
Filters: Publication date from 1970 to 31 August 2018		

2.4. Outcome assessment

The primary outcomes assessed were the efficacy of Aloe compared with placebo on global IBS symptoms after treatment, including patients' improvement of symptoms or self-reported quality of life. These included various self-reported measurement scales such as the Gastrointestinal Symptoms Rating Scale (GSRS), visual analogue scale (VAS), EuroQol (EQ5D), Short Form 12 (SF12) and Short Form 36 (SF36) quality of life questionnaires. This choice of primary outcome is in keeping

with most studies reported to date. Any adverse events in the selected studies were also reported on and summarized.

Two reviewers (FF and IS) independently extracted data onto a Microsoft Word data extraction form. The following data was extracted for each trial: Study design, setting, type and form of intervention (including dose), duration of treatment, IBS diagnosis criterion used, and primary and secondary outcome measures.

2.5. Study quality

Two reviewers (FF and IS) assessed study quality independently according to the Cochrane tool for Risk of Bias assessment. This assessed aspects of study included selection bias (dealing with confounding, adjustment and comparability of groups), performance bias (in terms of the fidelity of the interventions); detection bias (regarding unbiased and correct assessment of outcomes, including blinding of assessors); attrition bias (with regard to completeness of sample, follow-up and data); and reporting bias (with regard to publication biases and selective reporting of results). Studies were scored as having low, moderate or high risk of bias.

2.7. Data synthesis and statistical analysis

The individual study authors' assessments were used as to what constituted a response to treatment in order to recode trial data into a dichotomous outcome of response versus non-response to treatment. Where necessary, the authors of the selected studies were contacted for missing data. If the authors are not able to respond, or if they could not provide the data requested, missing data was indicated in the review.

Data was pooled using a random effects model to give a more conservative estimate of the effect of individual treatments, allowing for heterogeneity between studies. The effects of different

interventions were expressed as a Risk Ratio with 95% confidence interval (CI) of global symptoms of irritable bowel syndrome persisting with Aloe compared with placebo. Statistical heterogeneity in each meta-analysis was assessed using the χ2 test and quantified using the I^2 statistic with a cut-off point of 25% to assess heterogeneity between studies. It was planned to do sub-group analysis according to IBS sub-type. The final data was analysed with Review Manager V.5.3 statistical software [43], and references were managed using the Mendeley citation manager [44].

3. RESULTS

The search strategy generated 2,386 citations, and an additional 13 articles were identified separately through snowballing and random searches in Google scholar. Out of this total, 139 were duplicates and the remaining 1974 were potentially relevant and retrieved for assessment. Of these, 1,948 were excluded and the remaining 26 studies were assessed for full-text eligibility. The full-text assessment resulted in six eligible RCTs, which compared Aloe or Aloe in combination with other compounds with placebo. The PRISMA diagram in Figure 1 shows the flow of information through the various phases of the systematic review. It maps the number of records identified, included and excluded, as well as those that were finally included in the meta-analysis.

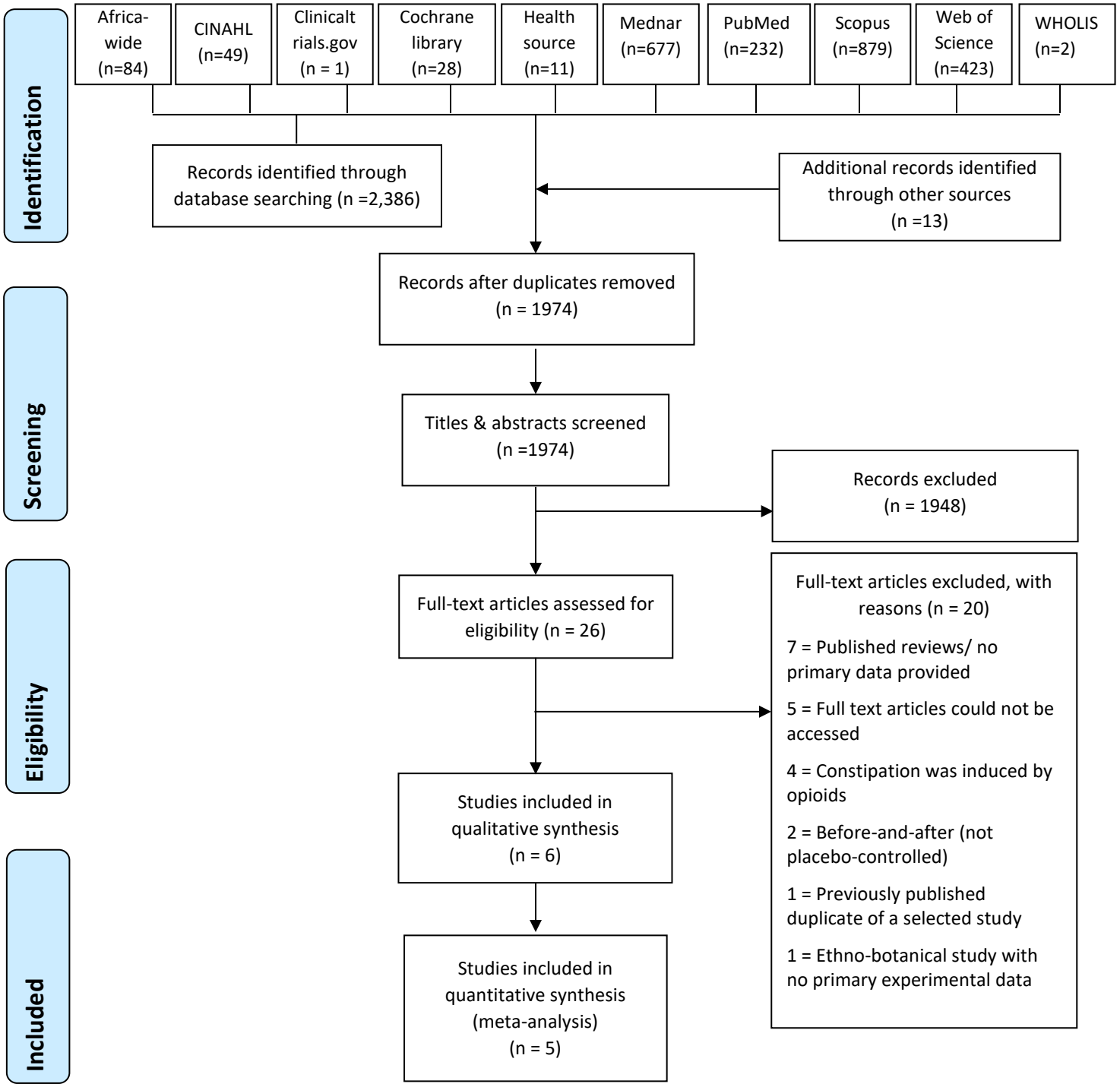

Figure 1: PRISMA diagram showing flow of information through the various phases of the systematic review

3.1. Characteristics of included studies

Table 1 provides a summary of the studies included in this review. Six studies, comprising 435 participants were included in this systematic review. Studies were conducted in China (1 study, 84 participants), Israel (2 studies, 115 participants), Sweden (1 study, 68 participants) and the United Kingdom (2 studies, 168 participants). Participants' age ranged from 18 to 81 years of age, diagnosed with IBS or functional constipation through the Manning and Rome criteria (Rome iterations include Rome I, Rome II and Rome III). Interventions included: 50ml Aloe drink, prescribed four times daily for one month; 60ml Aloe drink prescribed two times daily for five months (followed by a two-week washout period after which placebo and experimental groups would be crossed-over); 105mg Traditional Chinese Medicine capsule, containing Aloe extract; 500mg of celandin, Aloe Vera and psyllium in the ratio of 6:3:1 (i.e. 150mg Aloe Vera), where initial dose was 1 capsule per day and increasing to 3 capsules per day depending on response; and 250mg Aloe Extract + 60mg ascorbic acid effervescent tablets dissolved in water two times daily for one month. Comparison interventions were placebo, matched in appearance and other characteristics. One study [17] incorporated multiple arms, of which those relevant to this study's inclusion criteria were included. Another study [16] was a crossover RCT, but unfortunately no data was available to include in the meta-analysis. Information on the characteristics of studies included in this systematic review is shown in Table 2.

Table 2: Characteristics of included studies

Study ID	Study design	Country	Population	Intervention	Control group	Outcome
Davis, Philpott, Kumar & Mendall 2006 [15]	RCT	UK	Patients aged 18-65; diagnosed with IBS by Rome II	Aloe Vera (NLP formulation); 50ml 4 times daily; 1-month duration	Matching placebo	Improvement of symptoms through global summated score of 500 points with a ≥50 point improvement considered as response to treatment. Patients assessed at end of treatment, and 3 months post treatment.
Hutchings et al., 2011 [16]	RCT (cross-over)	UK.	Patients aged 18 and older, diagnosed with IBS by Rome II for at least one year.	Aloe Vera drink 60ml 2 times daily; 5 months duration for 5 months followed by 2 weeks wash out and then crossed over	Matching placebo	Improvement of patient quality of life. Four self-reported quality of life scales were used in the study including EQ5D, GSRS, SF12 and IBSQOL. Response to treatment was not defined by authors. Patients assessed at end of each study cross-over period, each lasting 5 months.
Jia et al., 2010 [17]	RCT (3-arm study)	China	Patients aged 18-65. Diagnosed with functional constipation by Rome III	70mg of Yun-chang capsule plus 35mg placebo (group A), 105mg of Yun-chang capsule (group B), 3 times daily for 2 weeks.	Matching placebo for Group C (105mg of placebo).	Improvement of symptoms using two rating scales to rate symptoms: main symptoms included stool frequency, consistency and dyschezia, and were rated using 7-point scale. Distension, dry mouth and throat, weakness and hectic fever were scored through 4-point scale. Response to treatment was defined as change in main symptom scores and cumulative symptom scores 2 weeks following treatment.
Odes & Madar, 1991 [18]	RCT	Israel	Patients aged 18 and older with constipation for over two years or diagnosed with IBS-C by unspecified criteria.	500mg capsule of Celandine, Aloe Vera and Psyllium in the ratio of 6:3:1 (i.e. 150mg Aloe Vera). Initial dose was 1 capsule per day and increasing to 3 times daily depending on response	Matching placebo	Improvement of symptoms (incl. stool rate, and consistency, abdominal pain, distension). Response to treatment was defined by patients as to whether they regarded themselves as improved following treatment.
Sallon et al., 2002 [19]	RCT	Israel	Patients aged 20-81. Diagnosed with IBS-C by Rome I and international consensus criteria for constipation.	482mg of Padma Lax formula (containing 12.5mg of Aloe extracts taken 2 times daily for 3 months.	Matching placebo	Improvement of symptoms. The patients compared their overall response to the trial therapy with previous treatments tried for IBS-C using ordinal scale: 0 (worse), 1 (same), 2 (better) and 3 (much better). Patients were also asked at each monthly visit to state their overall impression of any positive effect of treatment. Response to treatment was not defined by authors.
Størsrud et al., 2015 [14]	RCT	Sweden	Patients aged 18-65. Diagnosed with IBS by Rome III	Aloe Vera Extract effervescent tablets (250mg AVH200® + 60mg ascorbic acid and excipients) dissolved in water 2 times daily; 1 month duration	Matching placebo	Improvement of symptoms through the use of the IBS symptom severity scoring system (IBS-SSS), with range 0-500, with a ≥50 point improvement considered as response to treatment.

3.2. Excluded Studies

Twenty studies [19-38] were excluded during the full-text screening phase. The reasons for exclusion are summarized in Table 3. One study [35] was excluded by the main author on account of having been published later in a different journal [14], and which was considered for inclusion as shown in Table 1.

Table 3: Table of excluded studies

Study ID	Reason for exclusion
Bhaludra et al., 2013 [17]	Review study – no primary data provided
Chang and Lu, 2009 [18]	Review study – no primary data provided
Cirillo and Capasso 2015 [19]	Review study – no primary data provided
Franz, 1992 [20]	Full text article could not be accessed
Flück 1970 [21]	Full text article could not be accessed
Gordon et al., 2016 [22]	Review study – no primary data provided
Hu, 2009 [23]	Constipation was induced by opioids
Hutcheon, 2014 [24]	Review study – no primary data provided
Khedmat et al., 2013 [25]	Before-and-after study (not placebo-controlled)
Koch, 1993 [26]	Before-and-after study (not placebo-controlled)
Jekat, 1990 [27]	Review study – no primary data provided
Koch, 1995 [28]	Full text article could not be accessed
Kwon and Sun, 2016 [29]	Constipation was induced by opioids
Liu et al., 2006 [30]	Review study – no primary data provided
Ma, 2015 [31]	Constipation was induced by opioids
Melzig, 2008 [32]	Full text article could not be accessed
Størsrud et al., 2009 [33]	Previously published duplicate of a selected study [14]
Wintola, 2017 [34]	Ethno-botanical study with no primary experimental data
Wiessner, 2008 [35]	Full text article could not be accessed
Zhao et al., 2004 [36]	Constipation was induced by opioids

3.3. Quantitative data synthesis

3.3.1. Effect of Aloe on improving IBS symptoms among all IBS sub-types

Compared with placebo, all Aloe (Aloe only and/or Aloe combined) improved symptoms in IBS patients (all subtypes) (RR, 2.75 (95% CI 1.88 to 4.03), 5 studies, n=325, I^2=0%) (Figure 2).

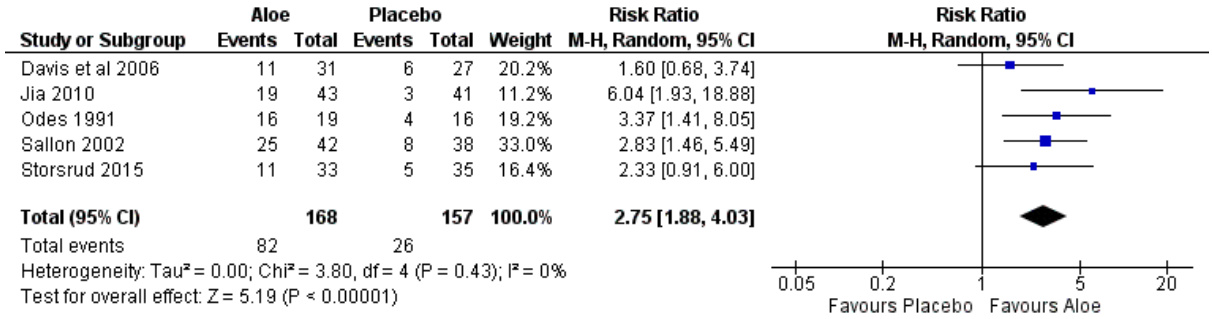

Figure 2: Aloe (all types) for improving IBS symptoms (All IBS subtypes)

3.3.2. Effect of Aloe (Aloe only) on improving IBS symptoms among all IBS sub-types.

Compared with placebo, Aloe (Aloe only) improved symptoms with all subtypes of IBS (RR, 1.89 (95% CI, 1.01 to 3.56); 2 studies, n= 126; I^2=0%) (Figure 3).

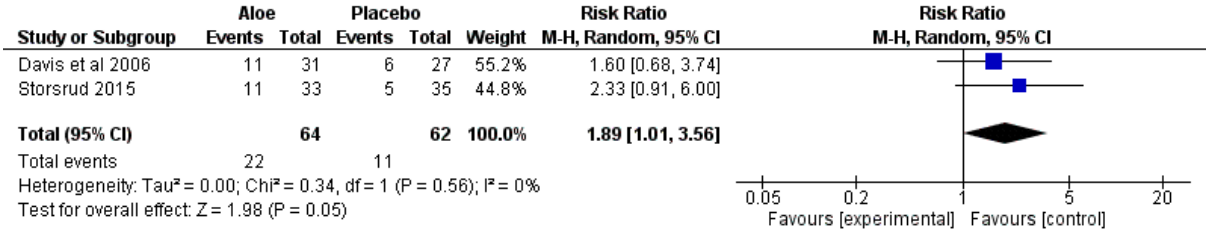

Figure 3: Aloe (only) for improving IBS symptoms (All IBS subtypes)

3.3.3. Effect of Aloe (Aloe combined) on improving IBS symptoms among constipation-predominant IBS (IBS-C) patients only

Compared with placebo, Aloe (Aloe combined) improved symptoms in IBS-C patients (RR, 3.41 (95% CI 2.11 to 4.03), 3 studies, n=199, I^2=0%) (Figure 4)

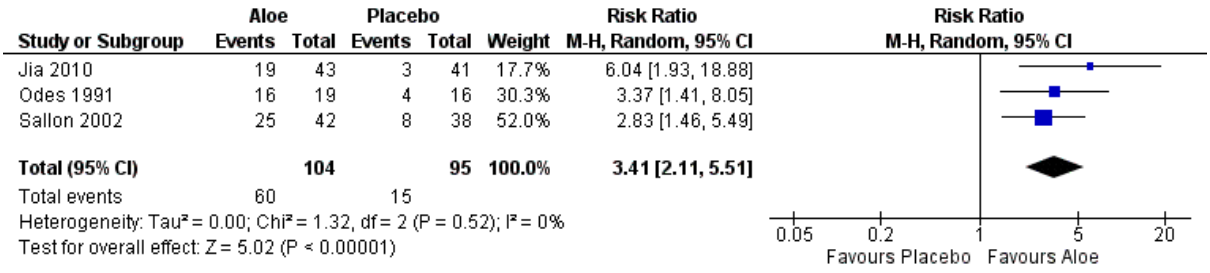

Figure 4: Aloe (Aloe combined) for improving symptoms among constipation-predominant IBS patients

3.3.4. Effect of Aloe on improving Diarrhoea-predominant IBS symptoms (IBS-D and IBS-M)

The single study [13] amongst IBS-D and IBS-M patients, failed to demonstrate effectiveness of Aloe (Aloe only) in relieving symptoms.

3.4. Assessment of risk of bias in included studies

Assessment of risk of bias was done using the Cochrane Risk of Bias tool. Of the studies assessed, two were deemed as having high risk of bias due to attrition. Two studies indicated random sequence generation, while the remaining studies did not provide this information. Four studies made clear mention of allocation concealment, while two did not provide details. Two studies reported a high number of dropouts and their risk of attrition bias was ranked as high. Two studies provided details on blinding of outcome assessment and the remaining four did not. Table 3 shows the summary of risk of bias assessment. Number studies were deemed as being of high risk of bias (reference of study).

Table 4: Summary of risk of bias assessment using the Cochrane tool

Study ID	Risk of bias 1	Risk of bias 2	Risk of bias 3	Risk of bias 4	Risk of bias 5	Risk of bias 6	Risk of bias 7	Risk of bias
Davis et al., 2006 [15]	+	+	+	?	-	?	?	High risk of bias
Hutchings 2011 [16]	?	?	?	?	-	?	?	High risk of bias
Jia et al., 2010 [17]	+	+	+	?	+	?	?	Moderate risk of bias
Odes & Madar 1991 [18]	?	?	?	?	+	+	?	Moderate risk of bias
Sallon et al., 2002 [19]	?	+	+	+	+	+	?	Moderate risk of bias
Størsrud et al., 2015 [14]	?	+	?	+	+	+	?	Moderate risk of bias

Bias 1: Random sequence generation (selection bias)
Bias 2: Allocation concealment (selection bias)
Bias 3: Blinding of participants and personnel (performance bias)
Bias 4: Blinding of outcome assessment (detection bias)
Bias 5: Incomplete outcome data (attrition bias)
Bias 6: Selective reporting (reporting bias)
Bias 7: Other bias

3.5. Adverse events

Cases of adverse events were reported by three trials [12,15,37]. Given that these were few in number, the data were not pooled. One was the three-arm study [15] and the only adverse events were reported in Group A, which was not considered for the meta-analysis. This was the case of one patient developing diarrhoea, accompanied by abdominal pain after which the patient was advised to reduce dosage and the symptoms receded.

Another study that dealt specifically with IBS-C patients [37], reported that 10 out of the 34 patients in the experimental group had complained of mild side effects. These included 1 patient with nausea, 1 with a slight headache and 1 with hoarseness. In addition, 7 patients developed loose stools or diarrhoea, including 1 patient who also complained of a mild episode of shortness of breath, dizziness and chest pain, which was resolved within 24 hours. According to the protocol, patients who

developed diarrhoea were to lower their dose by half. In the placebo group, 5 out of 27 patients reported side effects including 2 with abdominal pain, 1 with nausea and 2 with heartburn.

In the third study that reported cases of adverse events, only 1 out of the 33 patients in the experimental group reported minor haemorrhoidal rectal bleeding, after which he withdrew from the study. After the study, this patient reported that he had occasional rectal bleeding five years before the study and that the current bleeding had stopped three days after he had stopped taking the Aloe and was not different from previous bleeding episodes. No adverse events were reported in the placebo group. All in all, when taking into consideration those studies included in the meta-analysis, 11 out of 168 (6%) in the experimental groups, and 5 out of 157 patients (3%) were reported to have developed mild side effects.

4. DISCUSSION

4.1. Principal Findings

This systematic review found statistically significant evidence for Aloe-containing preparations being more effective than placebo in improving IBS symptoms overall. This finding was especially pronounced amongst IBS-C patients, regardless of the nature of the Aloe preparation. Among patients with diarrhea-predominant IBS (IBS-D), however, there is no evidence of Aloe's effectiveness in improving symptoms. This work provides the first attempt at a systematic approach to summarizing the evidence of the effectiveness of Aloe in alleviating IBS symptoms.

Laxatives are considered a primary measure for the treatment of IBS-C and functional constipation. The finding of Aloe's effectiveness in improving constipation symptoms may be explained by Aloe's laxative properties, which in turn, supports the biological plausibility of this finding. However, although laxatives such as Aloe have been shown to improve stool frequency, they have no proven

effect on other symptoms such as bloating and abdominal pain [15]. Thus, it is possible that the effect of Aloe in relieving abdominal pain is indirect, in that improving stool frequency can lead to reduced pain. It is also worth noting that in some of the studies, participants were advised to alter their dosage depending on the symptoms experienced. This suggests that the optimal aloe dosage may differ in IBS sub-types, although it may require further investigation.

It was initially thought that, because people considered CAM to be more effective than conventional medicine in treating IBS symptoms, the placebo effect would be larger in CAM clinical trials. A meta-analysis comparing CAM treatments for IBS to placebo have found a rather high pooled placebo response rate greater than 40%. However, when compared with the placebo response rate in conventional medicine trials for IBS, the response rate is similar. This suggests that the placebo response rate is not dependent on the type of therapy used, and that it may not be "enhanced" as initially thought by the use of CAM [38].

4.2. Study limitations

This systematic review employed a detailed search strategy in sourcing relevant articles; however, considering the widespread use of Aloe, one surprising finding was the paucity of controlled clinical trials. In addition, high attrition rates were evident in two the selected studies [13,14], one of which was included in the meta-analysis [13]. However, the effect of attrition in this study appears to be negligible, given that the direction of effect was congruent with the other studies in the meta-analysis, as reflected by the low heterogeneity.

Another limitation was the lack of access to non-English journals, especially in Chinese as these could only be accessed through Chinese academic institutions. There was also the challenge of dealing with the different ways in which study authors defined response to treatment. Some studies employed

continuous scales to rate improvement of symptoms, while others use ordinal scales, all with differences in value ranges. In some studies, only a ≥10% improvement in symptoms was considered a response to treatment, while in others a ≥50% improvement in symptoms was considered adequate. Thus, the methods used to assess effect estimates were not standardized. More methodological consistency ought to be considered when designing and carrying out clinical trials involving IBS patients. Furthermore, given the variations in formulae of Aloe preparations in the included studies, standardized formulations would be desirable. Nevertheless, the meta-analysis found low heterogeneity amongst the studies.

5. CONCLUSION

5.1. Implications for further research

Aloe-containing preparations were more effective than placebo in improving symptoms among all IBS sub-types combined. In sub-group analyses, Aloe was more effective than placebo in the treatment of constipation-predominant IBS, however this was not the case with IBS-D and IBS-M sub-types. Given the variation in the formulae of Aloe preparations in the included studies, generalizability of this finding may be a challenge. Thus, further research with adequately-powered studies using a standardised formulation for Aloe-containing preparations for IBS is advised.

While this review has demonstrated sufficient evidence for the use of Aloe in IBS-C, there remains nevertheless, a dearth of knowledge on further IBS-subtypes. This work highlights the need for applying methodological consistency in further studies, including (1) Standardized methods of assessing response to treatment and (2) Standardized symptom rating scales. In addition, adequately-powered studies are warranted especially when considering the high patient attrition rates in some of the reviewed studies.

5.2. Implications for clinical practice

The complex and heterogeneous nature of IBS suggests that instead of using one single agent, it may be more effective to use a combination of agents directed at treating each individual symptom [14]. When comparing effect size between those studies that used Aloe by itself with those that used Aloe in combination with other agents, a much stronger effect was visible in the latter. This could be due to the multi-symptom nature of IBS and how the other agents were able to address each symptom more effectively.

In conclusion, the results suggest that Aloe may be a safe and effective treatment for patients with IBS-C. However, for patients with IBS-D and remaining IBS sub-types, further large trials are warranted.

ACKNOWLEDGEMENTS

Contributions of Authors

Conception of the review: Francisco Fong, Mashiko Setshedi

Writing of first drafts of the protocol, literature review and manuscript: Francisco Fong

Methodological advice: Mark Engel, Mary Shelton (Expert Librarian)

Content advice: Mashiko Setshedi, Mark Engel, Inge Smit

Data collection: Francisco Fong, Inge Smit

Data analysis: Francisco Fong

Contributions to editing subsequent versions of the protocol and manuscript: All authors

Competing interests

The authors report no conflicts of interest

Sources of Funding

None

REFERENCES

1. Canavan C. CLEP-40245-the-epidemiology-of-irritable-bowel-syndrome. 2014;71–80.
2. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterology. 2002;123(6):2108–31.
3. Vanuytsel T, Tack JF, Boeckxstaens GE. Treatment of abdominal pain in irritable bowel syndrome. J Gastroenterol. 2014;49(8):1193–205.
4. Cuomo R, Andreozzi P, Zito FP, Passananti V, Carlo G De, Cuomo R, et al. Irritable bowel syndrome and food interaction. 2014;20(27):8837–45.
5. Canavan C, West J, Card T. Review article: The economic impact of the irritable bowel syndrome. Aliment Pharmacol Ther. 2014;40(9):1023–34.
6. Stanghellini V. Functional Dyspepsia and Irritable Bowel Syndrome : Beyond Rome IV. 2018;14–7.
7. Talley NJ, Holtmann G. Irritable bowel syndrome and functional dyspepsia : what can epidemiology tell us about etiology ? Irritable bowel syndrome and functional dyspepsia : what can epidemiology tell us. Expert Rev Gastroenterol Hepatol [Internet]. 2018;12(7):633–5. Available from: https://doi.org/10.1080/17474124.2018.1476136
8. Ford AC, Talley NJ, Spiegel BMR, Foxx-Orenstein AE, Schiller L, Quigley EMM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: Systematic review and meta-analysis. Bmj. 2008;337(7683):1388–92.
9. Steenkamp V, Stewart MJJ. Medicinal applications and toxicological activities of Aloe products. Pharm Biol. 2007;45(5):411–20.
10. Langmead L, Makins RJ, Rampton DS. Anti-inflammatory effects of aloe vera gel in human colorectal mucosa in vitro. Aliment Pharmacol Ther. 2004 Mar;19(5):521–7.
11. Langmead L, Feakins RM, Goldthorpe S, Holt H, Tsironi E, De Silva A, et al. Randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. Aliment Pharmacol Ther. 2004 Apr;19(7):739–47.
12. Størsrud S, Pontén I, Simrén M (2015), Storsrud S, Ponten I, Simren M, et al. A Pilot Study of the Effect of Aloe barbadensis Mill. Extract (AVH200®) in Patients with Irritable Bowel Syndrome: a Randomized, Double-Blind, Placebo-Controlled Study. J Gastrointest Liver Dis [Internet]. 2015 Sep 1 [cited 2017 Nov 14];24(3):275–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26405698
13. Davis K, Philpott S, Kumar D, Mendall M. Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. Int J Clin Pract [Internet]. 2006 Sep 2 [cited 2017 Nov 14];60(9):1080–6. Available from: http://doi.wiley.com/10.1111/j.1742-1241.2006.00980.x

14. Hutchings HAH, Wareham K, Baxter JNJ, Atherton P, Kingham JGC, Duane P, et al. A Randomised, Cross-Over, Placebo-Controlled Study of *Aloe vera* in Patients with Irritable Bowel Syndrome: Effects on Patient Quality of Life. ISRN Gastroenterol [Internet]. 2011 [cited 2017 Nov 14];2011:206103. Available from: http://www.hindawi.com/journals/isrn/2011/206103/

15. Jia G, Meng M Bin, Huang ZW, Qing X, Lei W, Yang XN, et al. Treatment of functional constipation with the Yun-chang capsule: A double-blind, randomized, placebo-controlled, dose-escalation trial. J Gastroenterol Hepatol. 2010;25(3):487–93.

16. ODES HSSHS, Madar Z. A double-blind trial of a celandin, aloevera and psyllium laxative preparation in adult patients with constipation. Digestion [Internet]. 1991 Jun [cited 2018 Jul 8];49(2):65–71. Available from: https://www.karger.com/Article/FullText/200705

17. Chandra Sekhar Singh Bhaludra, Rama Rao Bethapudi, Adharvana Chari Murugulla, Chakrapani Pullagummi, Thota Latha, Kandula Venkatesh, Arun Jyothi Bheemagani AP and ARR. Cultivation, Phytochemical Studies, Biological Activities and Medicinal Uses of Aloe ferox, Grandfather of Aloes an Important Amazing Medicinal Plant [Internet]. International Journal Of Pharmacology, 2013 Oct 1, Vol.9(7), pp.405-415; 2013. Available from: https://scialert.net/archivedetails.php?issn=1811-7775&issueno=58

18. Chang FY, Lu C-LL. Treatment of Irritable Bowel Syndrome Using Complementary and Alternative Medicine. J Chinese Med Assoc [Internet]. 2009 Jun [cited 2017 Nov 14];72(6):294–300. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1726490109703752

19. Cirillo C, Capasso R. Constipation and Botanical Medicines: An Overview. Phytother Res [Internet]. 2015 Oct [cited 2018 Jul 8];29(10):1488–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26171992

20. Franz G. Plant laxatives. Indications for general practice . Dtsch Apotheker Zeitung [Internet]. 1992;132(33):1697–704. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-0026671688&partnerID=40&md5=9f03a67b569e5c708f8adfca5f848e5e

21. Flück H, Bubb WP. [A lamaistic prescription-formula for the treatment of chronic constipation]. Schweiz Rundsch Med Prax [Internet]. 1970 Aug 18 [cited 2019 Feb 7];59(33):1190–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/5528157

22. Gordon M, Jk M, Ce P, Ak A, Ag T. Osmotic and stimulant laxatives for the management of childhood constipation. Cochrane database Syst Rev [Internet]. 2012;7(8):CD009118. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22786523

23. HU Chun-sheng. Study on Facilitating Feces Excretion Function of Aloe Soft Capsule. Pract Prev Med [Internet]. 2009;3:114. Available from: http://en.cnki.com.cn/Article_en/CJFDTotal-SYYY200903114.htm

24. Hutcheon DA. The Efficacy and Safety of 4 Natural Products for the Management of IBS.

Top Clin Nutr [Internet]. 2014 [cited 2018 Jul 8];29(2):113–22. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00008486-201404000-00003

25. Khedmat H, Karbasi A, Amini M, Aghaei A, Taheri S. Aloe vera in treatment of refractory irritable bowel syndrome: Trial on Iranian patients. J Res Med Sci [Internet]. 2013 Aug [cited 2017 Nov 14];18(8):732. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24379854

26. Koch A. Investigations on the laxative action of aloin in the human colon. Planta Med. 1993;59(7 SUPPL.).

27. Jekat FW, Winterhoff H, Kemper FH. Anthraquinone drugs. Zeitschrift fur Phyther. 1990;11(6):177–84.

28. Koch A. Metabolizing of aloin. Correlation between in vitro and in vivo experiments . Dtsch Apotheker Zeitung [Internet]. 1995;135(13):34–6. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-0028943523&partnerID=40&md5=7a1f428edf4f07e2bae0689a279e56f3

29. Kwon M, Ju SO. The effect of aloevera for constipation in schizophrenia patients. Indian J Sci Technol. 2016;9(41).

30. Liu JP, Yang M, Liu Y, Wei ML, Grimsgaard S. Herbal medicines for treatment of irritable bowel syndrome. Cochrane Database Syst Rev [Internet]. 2006 Jan 25 [cited 2018 Jul 24]; Available from: http://doi.wiley.com/10.1002/14651858.CD004116.pub2

31. Ma L, Zhang E. Constipation caused by antipsychotics treated by acupuncture and Compound Aloe Capsule for 30 cases [Internet]. Vol. 13, Chinese medicine modern distance education of china [zhong guo zhong yi yao xian dai yuan cheng jiao yu]. 2015. p. 76–7. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/227/CN-01435227/frame.html

32. Melzig MF. Plant-based laxatives: Phytopharmaceuticals as laxatives . Pharm Unserer Zeit [Internet]. 2008;37(2):136–41. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-43349101449&doi=10.1002%2Fpauz.200700256&partnerID=40&md5=f0312a4db108c75671cb789fcbd673f7

33. Störsrud S, Midenfjord I, Lindh A, Ringstrom G, Agerforz P, Jerlstad P, et al. T1256 Aloe Vera-aPromising Treatment Option for Patients with Irritable Bowel Syndrome (IBS). Gastroenterology [Internet]. 2009;136(5):A-533. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0016508509624513

34. Wintola OA, Otang WM, Afolayan AJ. The prevalence and perceived efficacy of medicinal plants used for stomach ailments in the Amathole District Municipality, Eastern Cape, South Africa. SOUTH AFRICAN J Bot. 2017 Jan;108:144–8.

35. Wiessner R. Irritable bowel syndrome: Regulatory treatment with a Tibetan medicine .

Schweizerische Zeitschrift fur GanzheitsMedizin [Internet]. 2008;20(7–8):384. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-57449092715&partnerID=40&md5=92d99155fd5164f2ba73fe185b5e9c8b

36. Zhang Zhao-Cui; Gao Hui-Zhi. Therapeutic effects of aloe-paste in the treatment of antipsychotic agents induced constipation. J Qilu Nurs [Internet]. 2004;06:1–4. Available from: http://en.cnki.com.cn/Article_en/CJFDTotal-QLHL200406015.htm

37. Sallon S, Ben-arye E, Davidson R, Shapiro H, Ginsberg G, Ligumsky M. Original Paper : Functional Disorders A Novel Treatment for Constipation-Predominant Irritable Bowel Syndrome Using Padma ® Lax , a. 2002;161–71.

38. Dorn SD d., Kaptchuk TJ j., park JB b., Nguyen LT t., canenguez K, Nam BH h., et al. A meta-analysis of the placebo response in complementary and alternative medicine trials of irritable bowel syndrome. 2007 Aug [cited 2018 Jul 8];19(October 2006):630–7. Available from: http://doi.wiley.com/10.1111/j.1365-2982.2007.00937.x

PART D: APPENDICES

APPENDIX 1: PRISMA 2009 CHECKLIST (For Manuscript)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	17
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	15-16
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	17
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	15-16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-19

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

APPENDIX 2: Comprehensive Search Strategy

	Subject/ Related term	Search Terms
PubMed search strategy		
#1	Intestinal diseases, colonic diseases, irritable bowel syndrome, gastrointestinal motility, irritable colon, peristalsis, constipation, diarrhea, feces, stool, abdominal pain, bloating, defecation, laxatives, bulking agent, dysmotility, visceral hypersensitivity, spastic colon, Rome criteria	intestinal diseases"[MeSH Terms] OR "colonic diseases"[MeSH Terms]) OR "irritable bowel syndrome"[MeSH Terms]) OR irritable bowel syndrome[Title/Abstract]) OR "gastrointestinal motility"[MeSH Terms]) OR "irritable bowel syndrome"[MeSH Terms]) OR irritable colon[Text Word]) OR "peristalsis"[MeSH Terms]) OR peristalsis[Title/Abstract]) OR "constipation"[MeSH Terms]) OR constipation[Text Word]) OR "diarrhea"[MeSH Terms]) OR diarrhea[Text Word]) OR "feces"[MeSH Terms]) OR stool[Text Word]) OR "feces"[MeSH Terms]) OR feces[Text Word]) OR abdominal pain[Title/Abstract]) OR abdominal pain[Text Word]) OR "defecation"[MeSH Terms]) OR defecation[Text Word]) OR "laxatives"[MeSH Terms]) OR laxative[Title/Abstract]) OR bulking agent[Title/Abstract]) OR dysmotility[Text Word]) OR visceral hypersensitivity[Text Word]) OR spastic colon[Title/Abstract]) OR spastic colon[Text Word]) OR Rome criteria[Text Word]) OR bloating[Title/Abstract]) OR "abdominal pain"[MeSH Terms]) OR abdominal pain[Title/Abstract]
#2	Xanthorrhoeaceae, Aloe, Asphodelaceae, Aloeaceae, Aloeandongensis, Aloedent, Aloe emodin, aloe*, emodin, barbaloin	"xanthorrhoeaceae"[MeSH Terms] OR Xanthorrhoeaceae[Text Word]) OR "aloe"[MeSH Terms]) OR (aloe[Title/Abstract] OR aloe'[Title/Abstract] OR aloe's[Title/Abstract] OR "Asphodelaceae"[MeSH Terms] OR Asphodelaceae[Text Word] OR aloeaceae[Title/Abstract] OR aloeandongensis[Title/Abstract] OR aloedent[Title/Abstract] OR "aloe emodin"[Title/Abstract] OR aloei[Title/Abstract] OR aloeicola[Title/Abstract] OR aloemannan[Title/Abstract] OR aloemodin[Title/Abstract] OR aloenin[Title/Abstract] OR aloepecia[Title/Abstract] OR aloeresin[Title/Abstract] OR aloeride[Title/Abstract] OR aloes[Title/Abstract] OR aloes'[Title/Abstract] OR aloesin[Title/Abstract] OR aloesinol[Title/Abstract] OR aloesol[Title/Abstract] OR aloesone[Title/Abstract] OR aloesorb[Title/Abstract] OR aloespanoarin[Title/Abstract] OR aloestron[Title/Abstract] OR aloeswood[Title/Abstract] OR aloethanes[Title/Abstract] OR aloetic[Title/Abstract] OR aloetica[Title/Abstract] OR aloeticola[Title/Abstract] OR aloetron[Title/Abstract] OR aloeus[Title/Abstract] OR aloev[Title/Abstract] OR aloeVera[Title/Abstract] OR aloeVerae[Title/Abstract] OR aloeverose[Title/Abstract] OR aloexylon[Title/Abstract])) OR Aloctin[Text Word]) OR aloin[Title/Abstract]) OR aloin[Text Word]) OR "emodin"[MeSH Terms]) OR emodin[Text Word]) OR barbaloin[Text Word]
Search		**#1 AND #2**
Filters: Publication date from 1970 to 31 August 2018		

	Subject/ Related term	Search terms
Scopus search strategy		
#1	Intestinal diseases, colonic diseases, irritable bowel syndrome, gastrointestinal motility, irritable colon, peristalsis, constipation, diarrhea, feces, stool, abdominal pain, bloating, defecation, laxatives, bulking agent, dysmotility, visceral hypersensitivity, spastic colon, Rome criteria	(TITLE-ABS-KEY ("Intestinal diseases" OR "colonic diseases" OR "irritable bowel syndrome" OR "gastrointestinal motility" OR "irritable colon" OR "peristalsis" OR "constipation" OR "diarrhea" OR "diarrhoea" OR feces" OR "stool") OR TITLE-ABS-KEY ("defecation" OR "laxative" OR "bulking agent" OR "dysmotility" OR "visceral hypersensitivity" OR "spastic colon" OR "Rome criteria" OR "Bloating" OR "Abdominal pain" OR "Functional"))
#2	Xanthorrhoeaceae, Aloe, Asphodelaceae, Aloctin, Aloeaceae, Aloin, Aloedent, emodin, barbaloin	(TITLE-ABS-KEY ("Xanthorrhoeaceae" OR "Aloe" OR "asphodelaceae" OR "aloctin" "aloeaceae" OR "aloin" OR "aloedent" OR "emodin" OR "barbaloin"))
Search		**#1 AND #2**
Filters: Publication date from 1970 to 31 August 2018		

Note: Search terms were also adapted to suit other individual databases using applicable syntax and vocabulary. These included EBM reviews, Global Health and International Pharmaceutical Abstracts, CINAHL, Web of Science, Mednar, Cochrane Central Register of Control Trials, Pan African Clinical Trials Register, clinicaltrials.gov, World Health Organization Library Information System (WHOLIS) and Ebscohost.

APPENDIX 3: Data Extraction Form

Review Title:	**Consumption of Aloe to improve health outcomes in adults with irritable bowel syndrome: A systematic review and meta-analysis.**
Study ID **(e.g. Lopez, 2017)**	
Full article title	

I. General information

Date form completed (dd/mm/yyyy)	
Name of person extracting data	
Full reference citation (i.e. full reference citation, Harvard style()	
Study author contact details (e.g. E-mail, phone)	
Publication type (e.g. full report, abstract)	
Bibliography hand search, (i.e. References for possible eligible studies)	
Notes:	

II. Study Eligibility

Study Characteristics	Eligibility criteria	Eligibility criteria met?
Types of study	**RCT, CCT, CBA, Before-and-after, Quasi-randomised trial, cross-over study, cohort study, Observational study, letter to editor of journal**	Yes ☐ No ☐ Unclear ☐ (Specify below)
Participants	**Including adults >= 18 years of ages**	Yes ☐ No ☐ Unclear ☐ (specify below)
Types of Outcome measure	**Primary outcome** (please specify below)**:**	Yes ☐ No ☐ Unclear ☐ (specify below)
INCLUDE ☐ **EXCLUDE** ☐ **PENDING** ☐		
Reason for exclusion/pending?		
Notes:		

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

III. Characteristics of the Study

	Descriptions as stated in report/paper
Aim of study	
Start date	
End date	
Total duration of study	
Type of intervention/exposure	
Was **sequence generation** conducted? If yes, how?	
Was **allocation concealment** conducted? If yes, how?	
Was **Blinding** conducted? If yes, how?	
Describe in general terms the reported measure/s used for primary outcome (e.g. Health-related quality of life (HRQoL) self-assessment questionnaire, visual analogue scale, etc.)	
Country, language	
Ethical approval needed/ obtained for study	**Yes** ☐ **No** ☐ **Unclear** ☐
Notes:	

IV. Participants

	Descriptions as stated in report/paper	
Country		
Population description		
Condition being addressed through the intervention (e.g. IBS, constipation, diarrhoea)		
Inclusion criteria / Diagnostic criteria (e.g. Rome criteria)		
Exclusion criteria		
Method of recruitment of participants (e.g. mail, phone, existing records, in-hospital)		
Site of recruitment of participants (e.g. hospital/ health facility)		
Selection methods (e.g. randomized)		
Initial recruited sample size	**Intervention group**	**Control/Placebo group**
Loss to follow up	**Intervention group**	**Control/Placebo group**
Final participant count	**Intervention group**	**Control/Placebo group**
Age(s)		
Gender		
Ethnicity		
Data source (e.g. medical, interviews, surveys)		
Notes:		

V. INTERVENTION CHARACTERISTICS

Intervention: Aloe to treat IBS-related symptoms

Details of intervention (e.g. aloe pills, gel or aloe in combination with other compounds) **and dose**	
Details of co intervention (if any) in all groups	
Delivery of intervention (e.g. stages, timing, frequency, duration)	
Fidelity/integrity (Was the intervention delivered as intended? Record any assessment of this)	
Other remarks	

VI. Control or placebo group:

Details of control/ placebo group	
Placebo substance provided	
Frequency	
Other remarks	

VII. Outcomes

Primary Outcome: Self-reported quality of life/ improvement of symptoms

Description of primary outcome and scale used to measure it						
Primary outcome:	**Intervention**	**%**	**Control**	**%**	**Difference**	**P-value**
Age-group Breakdown						

Secondary Outcomes in the study (if any)

Description of secondary outcome and scale used to measure it						
Secondary outcome:	**Intervention**	**%**	**Control**	**%**	**Difference**	**P-value**
Age-group Breakdown						

VIII. Discussion

	Descriptions as stated in report/paper
Key conclusions of study authors	
Study Limits as reported by authors	
Recommendations	
Notes:	

IX. Other Information

Study funding sources	
Possible conflicts of interest **(For study authors)**	
Missing data	
Statistical methods and their appropriateness (if relevant)	
Correspondence required for further study information	
Notes:	

APPENDIX 4: Ethics Waiver

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338
Email: amees.emjedi@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

06 July 2018

Prof M Engel
Pharmacology
K Floor
Old Main Building

Dear Prof Engel

PROJECT TITLE: Among adults diagnosed with irritable bowel syndrome, is the consumption of Aloe Vera, compared to placebo associated with improved health outcomes? Rationale and protocol for a systematic review
(MPH Candidate Francisco Fong)

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC note that the proposed study is a systematic review.

As the systematic review involves published literature available through publicly accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: *"Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research."*

The HREC recommend that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to http://www.prisma-statement.org/.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015).

The HREC acknowledge that the MPH Candidate Francisco Fong, was also involved in this project.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

APPENDIX 5: Plos ONE Submission Guidelines for Authors

PLOS ONE Submission Guidelines

STYLE AND FORMAT	
File Format	Manuscript files can be in the following formats: DOC, DOCX, or RTF. Microsoft Word documents should not be locked or protected.
Length	Manuscripts can be any length and there are no restrictions on word count, number of figures, or amount of supporting information. We encourage you to present and discuss your findings concisely.
Font	Use a standard font size and any standard font, except for the font named "Symbol". To add symbols to the manuscript, use the Insert → Symbol function in your word processor or paste in the appropriate Unicode character.
Headings	Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
Layout & Spacing	Manuscript text should be double-spaced. Do not format text in multiple columns.
Page & Line Numbers	Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).
Footnotes	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.
Language	Manuscripts must be submitted in English.
Abbreviations	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. Keep abbreviations to a minimum.
Reference Style	PLOS uses "Vancouver" style
Nomenclature	Use correct and established nomenclature wherever possible.
MANUSCRIPT ORGANISATION	
Beginning Section	*The following elements are required, in order:* • Title page: List title, authors, and affiliations as first page of manuscript • Abstract • Introduction
Middle Section	*The following elements can be renamed as needed and presented in any order:* • Materials and Methods • Results • Discussion • Conclusions (optional)
Ending Section	*The following elements are required, in order:* • Acknowledgments • References • Supporting information captions (if applicable)
Other Elements	• Figure captions are inserted immediately after the first paragraph in which the figure is cited. Figure files are uploaded separately. • Tables are inserted immediately after the first paragraph in which they are cited. • Supporting information files are uploaded separately.

If your article is a systematic review or a meta-analysis you should:

- State this in your cover letter
- Select "Research Article" as your article type when submitting
- Include the PRISMA flow diagram as Fig 1 (required where applicable)
- Include the PRISMA checklist as supporting information