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Effects of olives and their constituents on the expression of ulcerative colitis: a systematic review of randomised controlled trials

Kenneth Daniel[1]*, Luis Vitetta[2] and Maria A. Fiatarone Singh[1,2,3]

[1]*Sydney School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, NSW 2006, Australia*
[2]*Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, NSW 2006, Australia*
[3]*The Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA 02131, USA*

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Abstract

Extra virgin olive oil is often associated with anti-inflammatory and antioxidant properties. Its effects on inflammatory conditions such as ulcerative colitis (UC), however, have yet to be defined. As such, we aimed to conduct a systematic review and meta-analysis of studies investigating olive-based interventions in UC. A comprehensive database search for randomised controlled trials was performed between 9 July 2018 and 16 August 2018. Studies identified from search alerts were included up to 22 June 2020. Both individuals living with UC at any disease stage and murine models of UC were included in this review. No human trials meeting the eligibility criteria were identified, while nineteen animal studies comprised 849 murine models of UC were included in this review. Pooling of the data could not be performed due to heterogeneous outcomes; however, general trends favouring olive-based interventions were identified. Milder disease expression including weight maintenance, reduced rectal bleeding and well-formed stools favouring olive-based interventions was statistically significant in 16/19 studies, with moderate-to-large effect sizes (−0·66 (95 % CI −1·56, 0·24) to −12·70 (95 % CI −16·8, −8·7)). Olive-based interventions did not prevent the development of colitis-like pathologies in any study. In conclusion, effects of olive-based interventions on murine models of UC appear promising, with milder disease outcomes favouring the intervention in most trials and effect sizes suggesting potential clinical relevance. However, the lack of published randomised controlled human trials warrants further investigation to determine if these effects would translate to individuals living with UC.

Key words: **Ulcerative colitis: Olive oil: Inflammatory bowel disease: Systematic review**

Ulcerative colitis (UC) is a chronic condition characterised by inflammation and ulcerations along the colonic mucosa. The disease predominantly affects the large bowel and develops from the rectum to other parts of the colon in a progressive fashion. Symptoms occur intermittently, cycling between active disease and periods of remission. These range from gastrointestinal issues, such as loose stools, urgency, frequency and bleeding, to systemic issues such as fatigue, joint pain, malnutrition and the development of colon cancer. As such, those living with this condition often report a significant impact on quality of life, although overall lifespan is not reduced[1]. Along with other inflammatory bowel diseases (IBD), the prevalence of UC is increasing globally[2]. The reason for this trend is not well understood; however, a combination of environmental[3], lifestyle[4] and genetic risk factors[3,5] has been proposed.

Diet has been a key lifestyle focus for both clinicians and patients. Its role in modifying disease risk factors, disease severity and symptoms has previously been reported in prospective studies and small trials[5,6]. In contrast to medical therapy, dietary approaches are often viewed as an attractive option due to the side effects of conventional treatment such as immunosuppressive therapy and monoclonal antibodies[7]. As such, patients often report a range of self-prescribed dietary behaviours and restrictions with potentially negative implications for health outcomes and quality of life[8]. Unfortunately, the efficacy of such practices remains unclear due to the lack of robust evidence[9].

Amongst the various dietary strategies proposed, the Mediterranean diet is one approach that has gained interest in recent years. Early findings suggest that dietary patterns which emulate the Mediterranean diet were associated with reduced faecal calprotectin[10,11], reduced inflammatory markers and improvements to anthropometric measures and quality of life measures[12]. Definitions of the diet tend to vary and may extend to include social aspects of food consumption and lifestyle; thus, it can be challenging to identify how specific elements of the diet impact health outcomes.

Abbreviations: DAI, Disease Activity Index; DSS, dextran sulphate sodium; ES, effect size; IBD, inflammatory bowel diseases; RCT, randomised controlled trial; UC, ulcerative colitis.

* **Corresponding author:** Kenneth Daniel, email Kenneth.daniel@sydney.edu.au

Amongst the various elements of the diet, extra virgin olive oil consumption is one aspect of the diet which is often credited with positive health outcomes[13]. Epidemiological studies have shown associations between higher olive oil consumption with lower UC prevalence[14–16]. However, it is unknown whether such observational associations indicate any causal relationships between olive oil and disease risk[15,16]. By contrast, one uncontrolled trial in eight adults with UC using 1 g olive oil capsules demonstrated no effects on UC disease activity scores after a 12-month period[17]. However, higher doses have yet to be investigated; no randomised controlled trials or systematic review of human or animal trials has been published to our knowledge.

Aim

We aimed to systematically review and, if appropriate, perform a meta-analysis of interventions using extra virgin olive oil from table olives (*Olea europaea*) or their constituents on disease outcomes of individuals living with UC and murine models of UC at any stage of the disease.

Methods

Searches for eligible articles for the systematic literature review commenced on 9 July 2018 and concluded on 16 August 2018. Inclusion of hand-searched literature and new trials identified through alerts and the Cochrane central registry of clinical trials concluded on 22 June 2020. This systematic literature review adhered to PRISMA guidelines[18] and was prospectively registered with the international prospective register of systematic reviews (PROSPERO) under CRD42018103754 on 9 August 2018.

Search strategy

A systematic literature search was conducted using the following databases: MEDLINE (1946 to August 2018), AMED (1985 to August 2018), CINAHL (1981 to August 2018), Embase (1947 to August 2018), Web of Science (1900 to August 2018), Google Scholar (first 100 results from 2008 to August 2018) and Cochrane central registry of clinical trials (1955 to 22 June 2020). Alerts were established for MEDLINE, AMED, CINAHL, Embase, Web of Science and Google Scholar, and additional references found were included up until 22 June 2020. Search strategy included a combination of 'Population' (UC) AND 'Intervention'(olives/constituents) terms. 'Comparison intervention' or 'Outcome' terms were not used, to optimise sensitivity. Searches using the following terms: ('ulcerative colitis' or 'colitis' or 'colitis, ischemic' or 'colitis, microscopic' or 'colitis, ulcerative' or 'proctocolitis' or 'inflammatory bowel diseases' or 'inflammatory bowel disease' or 'IBD' or 'Crohn disease' or 'proctitis' or 'enterocolitis') AND ('dietary fats' or 'dietary fat' or 'olive oil' or 'olive' or 'virgin olive oil' or 'fatty acid' or 'monounsaturated' or 'diet' or 'monounsaturated fat' or 'phenols' or 'polyphenols' or 'flavonoids' or 'phenyl ethyl alcohol' or 'antioxidant' or 'olea' or 'Tyrosol' or 'Hydroxytyrosol' or 'Oleocanthal' or 'plant oils' or 'plant extracts' or 'fatty acids' or 'fatty acids, unsaturated' or 'fatty acids, monounsaturated' or 'dietary fats, unsaturated'). Due to the range of phenols present in olives, we explicitly searched for phenols specific to olives which have been examined in previous clinical trials[19] in addition to broad search terms such as 'phenols' and 'plant extracts' (see online, Supplementary Material). Reference list of articles meeting the inclusion criteria was also examined to identify studies which may be eligible. No limitations were set for publication year, language or study location. Both human and animal studies were included. Potentially eligible abstracts not in English were translated to determine eligibility.

Selection of eligible studies

Inclusion criteria for both human and animal studies were as follows:

1) randomised experimental trials including a control arm,
2) peer-reviewed publication, either full-length articles or chapters,
3) clinical validation of UC in humans at any stage of disease or comparative pathology in animals,
4) ability to assess UC as an independent study arm,
5) *in vivo* intervention,
6) interventions using the olive fruit (*O. europaea*) and its products including olive oil, paste, freeze-dried powdered products and capsules, or phenolic compounds (Hydroxytyrosol, Tyrosol, Oleuropein and Oleocanthal). Studies using olives or its constituents as part of a broader dietary intervention were also included,
7) administration of the intervention either orally or rectally,
8) ability to isolate the effects of the olive fruit or its components as an intervention,
9) disease activity outcomes via disease activity score, weight loss, mortality, histology or inflammatory markers.

No limitations were set on disease severity or duration. Other conditions not meeting the definition of UC[20] such as Crohn's disease, Inflammatory Bowel Disease Unclassified and indeterminate colitis were excluded. Animal studies fulfilling the selection criteria were further screened for (1) mammalian models of the disease and (2) equivalent condition matching UC pathologies comprising both experimental and sporadic disease[21–23]. Mammalian models were selected due to the relative similarity of intestinal function and morphology to humans[21]. Other transient forms of colitis such as acute or episodic colitis, allergic colitis and stress colitis were excluded from this review. Studies which include olive-based interventions as part of a broader dietary intervention were considered.

The reference management software Endnote X9.3.3 was used for this review. The primary author (K.D.) was responsible for database searches, collation of studies and removal of duplicates and screening of eligible studies. Full text of remaining articles was assessed by K. D. and M. A. F. S. When agreement could not be reached, L.V. was consulted. All eligible articles were included in this systematic review.

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Data extraction and analysis

Data extraction of eligible studies was completed by the first author (K. D.). A second reviewer (M. A. F. S.) verified extracted data and discrepancies for review. Summary of data extracted at each study level (aggregate) was reported. A meta-analysis for each outcome was considered if appropriate. Human and animal studies were analysed separately.

Data extraction included the following: (1) Publication metrics (first author surname, publication year, volume and number of publication), (2) population characteristics (sex, age, number recruited/studied, covariates), (3) disease & co-morbidities, (4) description of intervention, (5) duration and dose and (6) study outcomes and statistical analysis.

Outcome assessment

Due to the breadth of outcomes, assessment tools identified were in accordance with what was described in the literature, with some general trends identified. For both Disease Activity Index (DAI) scores and histology scores, an increase in the scores correspond to greater damage to colon tissue. Specific outcomes and assigned sub-scores varied between tools and are outlined accordingly in the results.

Similarly, colon shortening and increased colon weight are hallmarks of inflammation and indicators for disease progression in experimental colitis in animal models[23]. As such, increased colon weight:length ratios compared with non-colitis animals are typically considered a hallmark of disease severity. Negative effect sizes for DAI, histology score and colon weight:length ratio are indicative of milder disease expression favouring the intervention, with the reverse true for controls. Colon lengths and weight outcomes independent from colon weight:length ratios reported were included in the analysis.

Quantification of inflammatory cytokines and gut microbiome outcomes may vary between studies dependent on the techniques used and the measures selected. Outcomes extracted in the results were dependent on what was described in text, with no assumptions made in the event that no measurement value was described.

WebPlotDigitizer version 4.1 was used to extract graphical data in the absence of raw values. All results are expressed as mean and standard deviation unless stated otherwise. Post-study outcomes were analysed in all studies due to incomplete baseline data. Standard deviations between groups were assumed to be the same if data were not available, and when such assumptions were made, this was identified within tables. Mean values were used for studies expressing population numbers as ranges. An effect size calculator published by the Centre of Evaluation & Monitoring was used to calculate Hedge's bias-corrected effect sizes (ES) and 95 % CI using values extracted from the literature[24]. Interpretation of ES was determined based on the benchmark proposed by Cohen[25] with effects categorised as small ($d = 0{\cdot}2$), medium ($d = 0{\cdot}5$) and large ($d = 0{\cdot}8$).

Quality assessment

Two review authors K. D. and M. A. F. S. performed the risk of bias assessment independently. Human studies were evaluated using the Cochrane Collaboration Risk of Bias tool[26] which examines six types of bias comprising selection, performance, detection, attrition, reporting and other bias. The tool assigns each aspects of the trial with high, low or unclear risk of bias. Animal trials were evaluated using the SYRCLE's Risk of Bias Tool which was developed based on the Cochrane Collaboration Risk of Bias tool. The tool is composed of ten questions which are assigned high, low or unclear risk of bias on aspects of the study pertinent to animal interventions[27]. No final score is assigned for the studies assessed, and outcomes are summarised in the form of tables. Inter-observer variability was evaluated using Kappa statistics based on evaluations by authors K. D. and M. A. F. S.

Results

Thirty-two potentially eligible studies were identified through electronic searches and search alerts (Fig. 1). All human trials identified were excluded due to uncontrolled study design (n 1) and dietary interventions in which the effects of olives could not be isolated (n 2). Ten murine studies were excluded due to non-olive interventions (n 6), interventions bypassing the gastrointestinal tract (n 2) and combined interventions in which the effects of olive components could not be isolated (n 2). This resulted in a total of nineteen eligible animal studies, with no eligible human trials. Studies were heterogeneous which precluded a meta-analysis; however, effect sizes were calculated to demonstrate the magnitude of effect of olive-based intervention in each study.

Risk of bias

The overall study quality for eligible studies was deemed to be low. An average of 6/10 items in the risk of bias tool was not reported across all studies. Two of nineteen studies described allocation sequences through simple randomisation[28] or by weight[29] with no additional description. Eight of nineteen studies reported assessing representative histology specimens within each study arm; however, the sampling process was not described in any text (Table 1).

Study characteristics

Characteristics of animals. Twelve mouse studies and seven rat studies, representing more than 849 animals, were identified. The most common strains used were 6-to-8-week-old C57BL/6 mice and Wistar rats, and 10/19 studies used female animals. In all studies reporting age at baseline, all animals had reached sexual maturity but none could be considered old[30]. Study populations could not be assessed in three studies[31–33] (Table 2).

Environmental and control conditions. Husbandry conditions were poorly reported, with only 3/19 studies adequately describing number of animals per cage[34–36]. The American Institute of Nutrition-purified rodent diet[37,38] with modified fat content was the most common food used (7/19 studies), while remaining studies reported various commercial or non-specific diets. Energy content of the diet was described in 4/19 studies and ranged between 2900 and 3970 kcal/kg[28,31,32,34], while fat

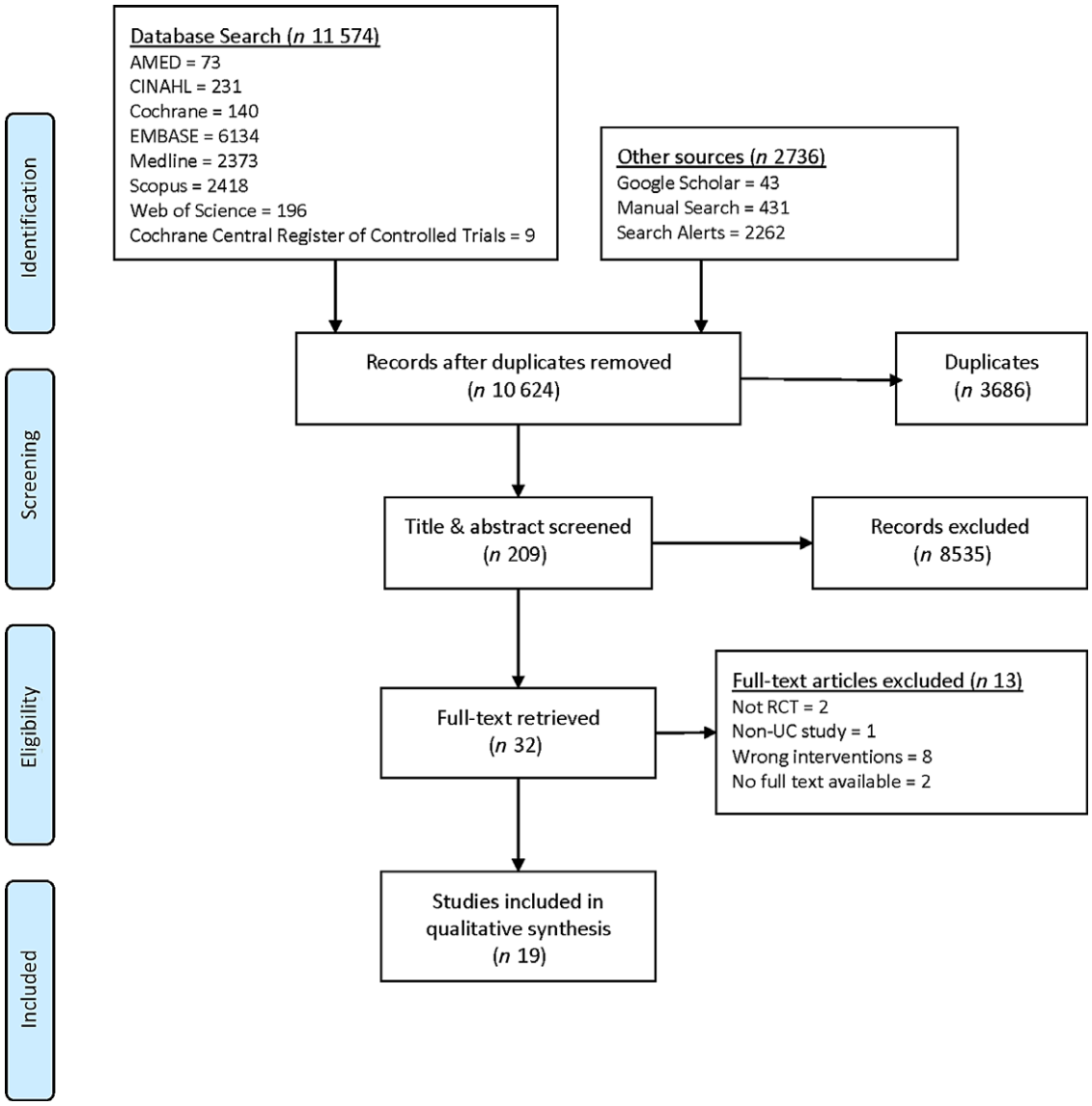

Fig. 1. Flow diagram of the literature search and selection of eligible studies.

content ranged from 4 to 10 % by weight (Table 2). Energy-matched diets between study groups were reported in only 1/19 study[34], while 5/19 studies[35,39–42] described matched fat, protein and carbohydrate content between diets. Sunflower oil was the most commonly used fat source in control diets[35,36,39–41], while maize oil[42] or soyabean oil[34] were used in the remaining studies.

Induction of colitis. Chemically induced colitis models were the most common method of simulating UC (17/19 studies), which was achieved predominantly using dextran sulphate sodium (DSS) (14/19 studies). Despite variances between study protocols, the overall procedures were similar. Briefly, DSS solution was prepared daily to the desired concentration (wt./vol.) using distilled water. This solution was provided in place of drinking water which could be consumed *ad libitum*. Duration of DSS exposure and concentration used varied between studies; acute models were induced between 3 and 15 d with a DSS concentration of 2–5 %, while chronic colitis models were induced between 28 and 259 d using 0·7–2 %. The remaining studies used either 2,4,6-trinitrobenzenesulfonic acid[28] or rectal administrations of acetic acid[43,44]. Two studies reported using transgenic HLA-B27 rats[42] or IL-10 knockout mice[45] predisposed to inflammation (Table 3).

Intervention. Interventions comprised olive oil (virgin and refined oils), Oleuropein, Hydroxytyrosol acetate and Tyrosol administered between 5 and 273 d, with a median of 30 d. Most studies combined olive-based intervention into dietary preparations, with 9/19 having enough information to estimate doses. These included 0·2–2·25 ml/d olive oil[28,42,46], 10–40 mg/d Oleuropein[31,32,47], 1·2–4·0 mg/d Hydroxytyrosol acetate[33,39]

Table 1. SYRCLE's risk of bias assessment

Study	Allocation sequence	Baseline similarity	Concealed allocation	Random housing	Caregiver blinding	Random assessment	Blinded assessment	Incomplete outcomes addressed	Reporting bias addressed	Other bias
Camuesco *et al.*[34]	NR	✓	✓	NR	✓	NR	✓	✓	X	✓
Hegazi *et al.*[45]	NR	NR	NR	NR	NR	NR	✓	✓	NR	✓
Sánchez-Fidalgo *et al.*[35]	NR	✓	NR	NR	NR	NR	NR	X	NR	✓
Giner *et al.*[31]	NR	✓	NR	NR	NR	NR	NR	X	✓	✓
Sánchez-Fidalgo *et al.*[39]	NR	✓	NR	NR	NR	NR	NR	X	NR	NR
Sánchez-Fidalgo *et al.*[40]	NR	✓	✓	NR	✓	NR	✓	X	X	✓
Sánchez-Fidalgo *et al.*[41]	NR	✓	✓	NR	✓	NR	✓	X	X	✓
Giner *et al.*[32]	NR	✓	NR	NR	NR	NR	NR	X	X	NR
Takashima *et al.*[49]	NR	✓	NR	NR	NR	NR	NR	X	X	X
Hamam *et al.*[43]	NR	✓	NR	NR	NR	NR	NR	X	X	X
Sánchez-Fidalgo *et al.*[33]	NR	✓	✓	NR	✓	NR	✓	✓	✓	X
Voltes *et al.*[28]	NR	✓	NR	NR	NR	NR	✓	✓	X	✓
Bigagli *et al.*[42]	NR	✓	NR	NR	NR	NR	✓	✓	✓	✓
Park *et al.*[46]	NR	✓	NR	NR	NR	NR	✓	✓	NR	✓
Güvenç *et al.*[48]	NR	NR	NR	NR	NR	NR	NR	✓	NR	✓
Wu *et al.*[44]	NR	NR	NR	NR	X	NR	NR	✓	✓	✓
Cariello *et al.*[29]	NR	✓	NR	NR	NR	NR	NR	✓	✓	✓
de Paula do Nascimento *et al.*[36]	NR	✓	NR	NR	✓	NR	✓	X	X	✓
Huguet-Casquero *et al.*[47]	NR	NR	NR	NR	NR	NR	NR	X	X	✓

NR, not reported in text, variables could not be assessed; ✓, Satisfied; X, Not satisfied.

and 3·6–5·0 mg/d Tyorosol[48]. Doses in eight studies could not be calculated due to unreported food consumption, one study due to unreported animal weights[44] and one study in which the olive oil was combined with a reagent prior to administration[28]. Voltes *et al.*[28] was the only study to intervene post-colitis, while all remaining studies administered the intervention either prior to, or concurrent with, colitis induction (Table 4).

Five studies reported food consumption, with mice consuming 3–4 g/d[31,34,35,49], and HLA-B27 rats 15 g/d[42]. One study[42] described the method of evaluating food consumption. Lower food intake in untreated animals was reported in one study[49], while four studies reported no difference between groups[31,34,35,42]. None of the studies intervening via oral gavage[29,43,44,46–48] or rectal administration[28] of an olive-based therapy described matching for potential energy contributions of the intervention.

Study outcomes

Mortality. Mortality was reported in 7/19 studies[31,32,39,42,43,45,49] and ranged from 0 to 40 %. Animals in the olive-based interventions had lower mortality rates (2·9 ± 6·6 %) compared with controls (13·9 ± 16·9 %), with three studies reporting no mortality in either group (Table 5). Deceased animals were included in the DAI analysis in one study[39], while two studies did not report if deceased animals were included in any outcome analyses[43,49]. None of the studies documented cause of death.

Disease activity. All experimental models of colitis in this review demonstrated intestinal inflammation and mucosal damage and symptoms consistent with UC, including rectal bleeding, loose stools, weight changes, altered colon morphology, altered histology and up-regulation of inflammatory markers[23,50]. Disease severity was reported in 11/19 studies[31–36,39–41,47,49] as DAI, comprised sub-scores for rectal bleeding, weight loss and stool consistency. One study reported rectal bleeding scores and weight loss to characterise disease activity without using a scoring index[29].

Colitis induction increased the DAI in all studies, while cessation of reagents used improved DAI outcomes, although they did not return to non-colitis levels in any study. Inclusion of an olive-based intervention reduced disease activity scores (between –0·07 and –2·1 points) compared with control–colitis animals, indicating milder symptoms, in ten of twelve studies[29,31–35,40,41,47,49] reporting this outcome. The differences between groups were statistically significant in nine studies[29,31–35,40,41,49], with all but one of these[35] reporting moderate-to-large effects (ES –0·66 (95 % CI –1·56, 0·24) to –12·70 (95 % CI –16·8, –8·7)). Disease activity improvements were not seen in transgenic HLA-B-27 rats, however[42] (Table 6). Improvements to stool consistency[31] and reduced rectal bleeding[32] were the greatest contributors to the differences in DAI; however, only three studies reported these sub-scores[31,32,35]. Comparing studies using the same intervention, higher intervention doses for Hydroxytyrosol[33,39,51] and Oleuropein[31,32,47] were associated with greater DAI differences between groups.

Weight changes post-study. Ten of nineteen studies[28,29,33,36,40–42,45,46,49] reported weight changes as an outcome independent of the DAI score. Seven of ten studies showed benefit in the intervention group indicated by reduced weight loss (–19 ± 21·3 % from baseline measures in the intervention group, –28 ± 25·3 % from baseline measures in controls)[29,33,40,41,45,46] or greater weight gain at study completion (246 ± 18·4 g in the intervention group, 184 ± 18·4 g in animals receiving control diets)[49].

Among the studies reporting outcomes favouring the intervention, four were statistically significant ($P < 0{\cdot}05$ - 0·001)[29,33,40,41] and six studies reported large ES between 0·97 (95 % CI 0·12, 1·82) and 8·73 (95 % CI 6·14, 11·33)[29,33,40,45,46,49]. Within the

Table 2. Design characteristics of eligible animal studies

Study	Location	Animal	Strain	Sex	Age	Baseline Wt (g)	*n*	Housing	Cages	Temperature (°C)	Humidity (%)	Day–night cycle	Base diet	% Fat (by wt)
Camuesco *et al.*[34]	Spain	Rats	Wistar	F	NR	180–200	40	Individual	Makrolon® cages	'AC atmos-phere'	'AC atmos-phere'	12D–12N	Semi-synthetic diet	4
Hegazi *et al.*[45]	USA	Mice	IL-10 knockout	NR	8 week	NR	92	NR	NR	NR	NR	NR	Defatted regular mouse chow (Bio-Serv)	7
Sánchez-Fidalgo *et al.*[35]	Spain	Mice	C57BL/6	F	6 weeks	NR	84	5–6 per cage	NR	24–25	'constant'	12D–12N	Modified AIN-76A Diet	10
Giner *et al.*[31]	Spain	Mice	BALB/c	F	6–8 weeks	18–20	40*	NR	NR	22	60	12D–12N	'Standard Laboratory Rodent Diet'	NR
Sánchez-Fidalgo *et al.*[39]	Spain	Mice	C57BL/6	F	6 weeks	NR	75	NR	NR	24–25	70–75	12D–12N	AIN standard reference diet	10
Sánchez-Fidalgo, *et al.*[40]	Spain	Mice	C57BL/6	F	6 weeks	NR	80	NR	NR	24–25	70–75	12D–12N	AIN standard reference diet	10
Sánchez-Fidalgo *et al.*[41]	Spain	Mice	C57BL/6	F	6 weeks	NR	60	NR	NR	24–25	70–75	12D–12N	AIN standard reference diet	10
Giner *et al.*[32]	Spain	Mice	C57BL/6	F	6–8 weeks	18–20	40*	NR	NR	22	60	12D–12N	'Standard Laboratory Rodent Diet'	NR
Takashima *et al.*[49]	Japan	Rats	Sprague–Dawley	M	6 weeks	NR	41	NR	NR	24–25	'constant'	12D–12N	Modified AIN-76A Diet	5
Hamam *et al.*[43]	Egypt	Rats	Albino	M	3–5 months	200–225	35	NR	'standard cages'	NR	NR	NR	'Standard diet'	NR
Sánchez-Fidalgo *et al.*[33]	Spain	Mice	C57BL/6	F	6 weeks	NR	36*	NR	NR	24–25	70–75	12D–12N	'Standard diet'	NR
Voltes *et al.*[28]	Spain	Rats	Wistar	F	NR	205–294	40	NR	NR	NR	NR	NR	'Standard labora-tory feed'	NR
Bigagli *et al.*[42]	Italy	Rats	HLA-B27	M	6–8 weeks	200–230	26	NR	NR	NR	NR	NR	Modified AIN76 diet	10
Park *et al.*[46]	Korea	Mice	C57BL/6	M	8 weeks	22–25	27	NR	NR	21–22	NR	12D–12N	'Standard mouse chow'	NR
Güvenç *et al.*[48]	Turkey	Rats	Wistar-Albino	M	NR	180–250	35	NR	NR	20–22	NR	12D–12N	'Standard com-mercial feed'	NR
Wu *et al.*[44]	Taiwan	Rats	Sprague–Dawley	M	6 weeks	NR	36	NR	NR	NR	NR	NR	NR	NR
Cariello *et al.*[29]	Italy	Mice	C57BL/6	M	8 weeks	NR	50	NR	NR	23	NR	12D–12N	NR	NR
de Paula do Nascimento *et al.*[36]	Brazil	Mice	C57BL/6	F	8–9 weeks	NR	80	2 per cage	NR	23–27	60–70	12D–12N	AIN-93M diet	10
Huguet-Casquero *et al.*[47]	Belgium	Mice	C57BL/6	M	8 weeks	21–26	48	NR	NR	NR	NR	NR	'Standard labora-tory feed'	NR

F, Female; NR, not reported in text; AIN, American Institute of Nutrition; M, male; 12D–12N, 12-h daylight and 12-h night cycles.
* Total number of animals quantified from study results with the assumption of no mortality.

Table 3. Method of inducing colitis

Study	Reagent	Dose (wt/v)	Route	Colitis model	Duration of induction
Camuesco *et al.*[34]	DSS	5 % and 2 % cycles	Drinking water	Acute	15 d (5/10 d cycles)
Hegazi *et al.*[45]	N/A	N/A	N/A	NR	N/A
Sánchez-Fidalgo *et al.*[35]	DSS	0·7 %	Drinking water	Chronic	259 d
Giner *et al.*[31]	DSS	5 %	Drinking water	Acute	7 d
Sánchez-Fidalgo *et al.*[39]	DSS	3 %	Drinking water	Acute	5 d
Sánchez-Fidalgo *et al.*[40]	DSS	3 %	Drinking water	Chronic	5 d
Sánchez-Fidalgo *et al.*[41]	DSS	3 %	Drinking water	Acute	5 d
Giner *et al.*[32]	DSS	1 % and 2 % cycles	Drinking water	Chronic	28 d (14/14 d cycles)
Takashima *et al.*[49]	DSS	4 %	Drinking water	Chronic	35 d
Hamam *et al.*[43]	Acetic acid	2 %	Intra-rectal	Acute	3 d
Sánchez-Fidalgo *et al.*[33]	DSS	3 %	Drinking water	Acute	5 d
Voltes *et al.*[28]	TNBS	0·5 ml	Intra-rectal	Acute	3 d
Bigagli *et al.*[42]	N/A	N/A	N/A	Chronic	N/A
Park *et al.*[46]	DSS	3 %	Drinking water	Acute	4 d
Güvenç *et al.*[48]	DSS	4 %	Drinking water	Acute	7 d
Wu *et al.*[44]	Acetic acid	4 %	Intra-rectal	Acute	21 d
Cariello *et al.*[29]	DSS	5 %	Drinking water	NR	10 d
de Paula do Nascimento *et al.*[36]	DSS	3 %	Drinking water	Acute	5 d
Huguet-Casquero *et al.*[47]	DSS	3 %	Drinking water	Acute	5 d

wt/v, weight/volume; DSS, dextran sulphate sodium; N/A, not applicable; NR, not reported in text; TNBS, 2,4,6-trinitrobenzene sulfonic acid.

remaining studies, one study using DSS mouse models[36] and HLA-B27 rats[42] reported greater weight gain in controls, while a study using 2,4,6-trinitrobenzenesulfonic acid colitis models reported non-significant outcomes with no examinable data[28]. No differences were observed between studies using acute[28,33,36,41,42,46] *v.* chronic[40,49] models of colitis (Table 7). None of the studies investigated the source of weight loss; thus, it is unknown if weight changes were attributed to anorexia, secondary effects of inflammation, altered fluid balance or other physiological changes.

Colon morphology

Histology score. Sixteen of nineteen studies[28,29,31,33–36,39–42,44–46,48,49] reported histology outcomes using parameters of colonic damage[52,53]. Grading methods varied between studies, with scores ranging between 4 and 120. Fourteen studies reported blinded assessments[28,31,33–36,39–42,45,46,48,49].

Improved histology outcomes favouring the intervention group were demonstrated in fourteen of sixteen studies[28,29,31,33–35,39–41,44–46,48,49], with nine studies[29,31,33,39,40,44,46,48,49] showing large ES between –0·81 (95 % CI –1·64, 0·02) and –4·51 (95 % CI –6·16, –2·86). Microscopic outcomes were reported in one study[48], with statistically significant improvements in mucosal architecture, cell infiltration, crypt abscess formation and preservation of goblet cells (ES –0·5 (95 % CI –0·78, 1·98) to –1·15 (95 % CI –0·01, 2·89), $P < 0·001$). Five studies using DSS-colitis models reported sub-scores for proximal, middle and distal colon sections with the greatest difference noted in middle[40] and distal[33,39,41,49] colon sections. (Table 8).

Colon weight:length ratio. Nine of nineteen studies[31,32,34–36,39–41,47] reported colon weight:length ratios which were expressed as either mg/cm in five studies[31,32,34,36,39], g/cm[35] or percentages compared with non-colitis animals in two studies[40,41]. Favourable weight:length ratios in intervention animals were reported in six studies, with a mean difference of –11·9 ± 3·1 mg/cm[31,32,34,39] and –67·5 ± 10·6 %[40,41] compared with controls. Four studies showed large effects with an ES between –1·31 (95 % CI –2·27, –0·34) and –2·41 (95 % CI –3·56, –1·26)[31,32,40,41]. Results were omitted in one paper reporting no statistically significant differences between groups[47] (Table 9).

Colon length. Colon length was reported by 6/19 studies, comprised four mouse studies[31,33,36,46] and two rat studies[44,49]. Average colon length of non-colitis animals was 7·9 ± 0·7 cm for mice and 17·3 ± 2·8 cm for rats, which was shortened in all animals induced with colitis, a sign of inflammation and colonic injury. Olive-based interventions attenuated this change, with longer colon lengths reported in intervention animals (mean 6·3 ± 0·6 cm in mice, 13·1 ± 1·4 cm in rats) compared with controls (mean 5·9 ± 0·6 cm in mice, 11·2 ± 1·3 cm in rats). One of six studies reported statistical significance favouring the intervention[44], while 4/6 studies[31,33,44,49] reported large ES between +0·88 (95 % CI 0·04, 1·72) and +2·36 (95 % CI 1·22, 3·50) (Table 10).

Inflammatory cytokines

TNF-α. Fourteen studies reported TNF-α outcomes post-kill[31,34–36,39–44,46–49]; nine studies reported concentrations in colon tissue[31,34–36,43,44,47–49], three studies quantified TNF-α mRNA in tissue samples[40–42], one study expressed TNF-α in percentages compared with non-colitis animals[39] and one study reported number of cells expressing antibodies[46]. Twelve of fourteen studies[31,34,35,39–44,46–48] reported lower TNF-α expression in the intervention group compared with controls, with nine studies statistically significant ($P < 0·001$ to 0·05)[31,39,41–44,46–48]. ES ranged from –0·34 (95 % CI –1·15, 0·48) to –4·63 (95 % CI –6·31, –2·95), with nine of fourteen moderate-to-large favouring the intervention[31,34,41–44,46–48]. One study reported outcomes favouring controls[36] which was not statistically significant but had a large ES (+0·95, 95 % CI 0·00, 1·89). (Table 11).

Table 4. Characteristics of the intervention and comparator study arms

Study	Control	*n*	Intervention	*n*	Time point intervention	Route	Consumption	Estimated dose	Treatment duration
Camuesco *et al.*[34]	SD + SBO	10	SD + EVOO (4 %)	10	Pre UC & Concurrent	Diet	NR	Unable to calculate	29 d
Hegazi *et al.*[45]	SD + CO	28	SD + OO (7 %)	29	Concurrent	Diet	NR	Unable to calculate	84 d
Sánchez-Fidalgo *et al.*[35]	SD + SFO	20	SD + EVOO (10 %)	20	Pre UC & Concurrent	Diet	NR	Unable to calculate	273 d
Giner *et al.*[31]	SD	NR	SD + Oleuropein (1 %)	NR	Concurrent	Diet	4 g food/d	40 mg Oleuropein/d	7 d
Sánchez-Fidalgo *et al.*[39]	SD + SFO	17	SD + EVOO (0·04 % Hty-Ac)	17	Pre UC & Concurrent	Diet	3 g food/d	1·2 mg Hty-Ac/d	51 d
Sánchez-Fidalgo *et al.*[40]	SD + SFO	12	SD + EVOO (10 %)	12	Pre UC & Concurrent	Diet	NR	Unable to calculate	30 d
Sánchez-Fidalgo *et al.*[41]	SD + SFO	12	SD + EVOO (10 %)	12	Pre UC & Concurrent	Diet	NR	Unable to calculate	39 d
Giner *et al.*[32]	SD	Between 7 and 10	SD + Oleuropein (0·25 %)	Between 7 and 10	Concurrent	Diet	4 g food/d	10 mg Oleuropein/d	56 d
Takashima *et al.*[49]	SD	17	SD + EVOO (5 %)	12	Pre UC & Concurrent	Diet	NR	Unable to calculate	35 d
Hamam *et al.*[43]	None	10	EVOO	10	Pre UC & Concurrent	Oral Gavage	1 ml/100 g body weight	2·00–2·25 ml EVOO/d	10 d
Sánchez-Fidalgo *et al.*[33]	SD	NR	SD + Hty-Ac (0·10 %)	12	Pre UC & Concurrent	Diet	4 g food/d	4 mg Hty-Ac/d	28 d + 10 d*
Voltes *et al.*[28]	Pectin/ alginate	10	Pectin/alginate + EVOO	10	Post UC	Rectal	2 ml solution/d	Unable to calculate	5 d
Bigagli *et al.*[42]	SD + CO	6	SD + EVOO (10 %)	7	Concurrent	Diet	15 g food/d	1·5 g EVOO/d (4·3 mg/kg polyphenols/d)	84 d
Park *et al.*[46]	None	5	OO	5	Concurrent	Oral gavage	0·2 ml/d	0·2 ml/d	10 d
Güvenç *et al.*[48]	None	7	Saline solution + Tyrosol	7	Pre UC & Concurrent	Oral gavage	20 mg/kg body weight	3·6–5·0 mg /d	21 d
Wu *et al.*[44]	SBO	6	OO	6	Pre UC	Oral gavage	2 ml/kg body weight	Unable to calculate	21 d
Cariello *et al.*[29]	0·9 % NaCl solution	10	OO (Monocultivar Coratina)	10	Pre UC & Concurrent	Oral gavage	NR	Unable to calculate	11 d
de Paula do Nascimento *et al.*[36]	SD + SFO	Between 10 and 12	SD + EVOO	Between 10 and 12	Pre UC	Diet	NR	Unable to calculate	30 d
Huguet-Casquero *et al.*[47]	Deionized water	8	Oleuropein + deionised water	8	Concurrent	Oral gavage	0·5 g/kg body weight	10·5–13 mg/d	5 d

SD, standard diet; SBO, soyabean oil; EVOO, extra virgin olive oil; Pre UC, prior to induction of experimental colitis; NR, not reported in text; CO, Maize Oil; OO, olive oil; SFO, sunflower oil; Hty-Ac, hydroxytyrosol acetate; NaCl, sodium chloride. Concurrent, intervention and induction of colitis occurring at the same time points.

Table 5. Animal mortality at study completion (Percentages)

Study	Control colitis	%	Intervention colitis	%
Camuesco *et al.*[34]	NR		NR	
Hegazi *et al.*[45]	1/27	4	1/29	3
Sánchez-Fidalgo *et al.*[35]	NR		NR	
Giner *et al.*[31]	0/10	0	0/10	0
Sánchez-Fidalgo *et al.*[39]	7/17	40	3/17	17·6
Sánchez-Fidalgo *et al.*[40]	NR		NR	
Sánchez-Fidalgo *et al.*[41]	NR		NR	
Giner *et al.*[32]	0/10	0	0/10	0
Takashima *et al.*[49]	4/17	23·5	0/12	0
Hamam *et al.*[43]	3/10	30	0/10	0
Sánchez-Fidalgo *et al.*[33]	NR		NR	
Voltes *et al.*[28]	NR		NR	
Bigagli *et al.*[42]	0/6	0	0/7	0
Park *et al.*[46]	NR		NR	
Güvenç *et al.*[48]	NR		NR	
Wu *et al.*[44]	NR		NR	
Cariello *et al.*[29]	NR		NR	
de Paula do Nascimento *et al.*[36]	NR		NR	
Huguet-Casquero *et al.*[47]	NR		NR	

NR, not reported in text.

IL. Four families were identified in this systematic review: IL-1*β*, IL-6, IL-10 and IL-17.

IL-1β. Nine studies assessed pro-inflammatory IL-1*β* expressed as quantities in tissue[31,32,36,44], relative gene expression[29,42], percentages compared with non-colitis animals[39] and number of stained cells in sampled colon tissue[46]. Induction of experimental colitis resulted in higher IL-1*β* expression compared with non-colitis animals in all studies. Animals receiving an olive-based intervention showed a lower expression of IL-1*β* in 6/9 studies (ES −0·54 (95 % CI − 1·61, 0·52) to −3·57 (95 % CI − 5·40, −1·75)[29,31,32,42,44,46]. Statistical significance ($P < 0·05$) was reported in 3/9 studies[29,31,44], all favouring the intervention. Results were omitted in one paper reporting no statistically significant differences between groups[49]. (Table 12).

IL-6. Ten studies examined pro-inflammatory IL-6 expressed as tissue concentration[31,32,35,36,44,47,48], number of stained cells in colon samples[46] or relative gene expression[29]. Nine of ten studies[29,31,32,35,36,44,46–48] reported lower IL-6 favouring the intervention group, with 6/10 statistically significant ($P < 0·01$ to $P < 0·001$)[29,31,32,44,47,48]. Seven of ten studies had large ES between −0·84 (95 %CI −1·76, 0·07) and −2·81 (95 % CI −4·29, −1·33)[29,31,32,44,46–48]. Results were omitted in one paper reporting no statistically significant differences between groups[49] (Table 13).

IL-10. Three studies reported anti-inflammatory IL-10 outcomes which were expressed using varying units of measure[32,36,39]. Colitis induction reduced IL-10 expression in all the animals, which was attenuated by olive-based interventions in 2/3 studies[32,39]. Measures of IL-10 were 34–43 % greater in intervention animals compared with controls at kill. Outcomes from two studies were statistically significant, with large ES of +0·99 (95 % CI 0·13, 1·85)[39] and +10·33 (95 % CI 6·30, 14·17)[32]. Results were

Table 6. Post-Study disease activity index (DAI) score
(Numbers; mean values and standard deviations; 95 % confidence intervals)

Study	Scoring method	Max score	Control			Intervention			Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
			Mean	SD	*n*	Mean	SD	*n*				
Camuesco *et al.*[34]	Cooper *et al.*[94]	4	3·1	1·58	10	1·9	1·9	10	−1·2	−0·66	−1·56, −0·24	$P < 0·05$
Sánchez-Fidalgo *et al.*[35]	Gommeaux *et al.*[95]	3	0·29	0·13	20	0·22	0·18	20	−0·07	−0·43	−1·06, 0·19	$P < 0·05$
Giner *et al.*[31]	Unknown	4	2·6	0·32	10	1·5	0·63	10	−1·1	−2·11	−3·20, −1·02	$P < 0·01$
Sánchez-Fidalgo *et al.*[39]	Melgar *et al.*[96]	3	0·53	1·07	17	0·63	0·7	25	0·1	0·18	−0·44, 0·79	NS
Sánchez-Fidalgo *et al.*[40]	Melgar *et al.*[97] modified	3	0·77	0·35	12	0	0·35*	12	−0·77	−2·12	−3·12, −1·12	$P < 0·001$
Sánchez-Fidalgo *et al.*[41]	Melgar *et al.*[97] modified	3	1·8	0·69	12	1·1	0·69	12	−0·7	−0·98	−1·83, 0·13	$P < 0·001$
Giner *et al.*[32]	Unknown	4	1	0·41	10	0·47	0·25	10	−0·53	−1·49	−2·49, −0·50	$P < 0·01$
Takashima *et al.*[49]	Gommeaux *et al.*[95]	3	1·8	0·36	13	0·8	0·69	12	−1	−1·78	−2·71, −0·85	$P < 0·01$
Sánchez-Fidalgo *et al.*[33]	Melgar *et al.*[97] modified	3	2	0·69	12	0·9	0·35	12	−1·1	−5·30	−6·99, −3·60	$P < 0·001$
Cariello *et al.*[29]	Unknown	4	3·8	0·1	10	1·7	0·2	10	−2·1	−12·7	−16·8, −8·7	$P < 0·05$
de Paula do Nascimento *et al.*[36]	Gommeaux *et al.*[95]	3	1·16	0·33	11	1·38	0·46	11	0·22	0·49	−0·36, 1·34	NS
Huguet-Casquero *et al.*[47]	Melgar *et al.*[97]	3	1·46	0·62	8	1·36	0·76	8	−0·1	0·14	−1·12, 0·85	NS

* SD values unavailable in the intervention group, assumed to be same with controls.
† Negative effect size indicates lower disease activity scores and reduced severity.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

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Table 7. Post-study weight changes
(Numbers, mean values and standard deviations; 95 % confidence intervals)

		Control colitis			Intervention colitis			Mean difference‡				
Author	Measure	Mean	SD	*n*	Mean	SD	*n*	Raw weight (g)	Weight change (%)	Effect size†‡	95 % CI‡	Reported *P*-value
Hegazi *et al.*[45]	Weight loss (g)	−0·46	0·36	26	0	0·16	27	0·46	Unable to calculate	1·76	1·13, 2·40	NS
Sánchez-Fidalgo *et al.*[40]	% Weight Change*	−7·6	2·1	12	11·2	2·1	12	Unable to calculate	18·8	8·73	6·14, 11·33	$P < 0·001$
Sánchez-Fidalgo *et al.*[41]	% Weight Change*	−23·7	NR	12	−17·6	NR	12	Unable to calculate	6·1	Unable to calculate		$P < 0·001$
Takashima *et al.*[49]	Post Weight (g)	329	39	17	376	25	12	47	62	3·28	2·16, 4·40	NS
Sánchez-Fidalgo *et al.*[33]	% Weight Change*	−26	11·4	12	−18	8·7	12	Unable to calculate	8	0·97	0·12, 1·82	$P < 0·001$
Voltes *et al.*[28]	Weight loss (g)	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate	Unable to calculate		0·91
Bigagli *et al.*[42]	Post Weight (g)	319	NR	6	306	NR	7	−13	Unable to calculate	NR		NS
	Net Weight Gain (g)	99	93	6	95	116	7	−4	Unable to calculate	−0·03	−1·13, 1·06	NS
Park *et al.*[46]	Post Weight (g)	17·0	0·6	5	17·9	1·4	5	0·9	Unable to calculate	1·79	0·32, 3·25	NS
	% From Baseline Weight*	74	1·5	5	80	4·0	5	Unable to calculate	6	5·42	2·74, 8·09	NS
Cariello *et al.*[29]	% From Baseline Weight*	18·9	6·6	10	40	6·9	10	Unable to calculate	20·7	2·94	1·67, 4·20	$P < 0·05$
de Paula do Nascimento *et al.*[36]	Post Weight (g)	20·3	1·3	11	19·5	2·3	11	−0·8	Unable to calculate	−0·79	−1·66, 0·07	NS

NR, not reported in text.
* Studies reporting '% From Baseline Weight' and '% Weight Change' assumes animals are 100 % at baseline.
† Positive effect sizes indicate higher weights in the study intervention.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

omitted in one paper reporting no statistically significant differences between groups[36].

IL-17. Park *et al.* was the only study reporting pro-inflammatory IL-17 outcome, expressed as number of positive cells[46]. Mean cell count expressing IL-17 in non-colitis animals was 10·5 ± 5·4 cells, while induction of colitis resulted in a marked increase in IL-17 expression. This increase was milder in intervention animals (55·9 ± 12·0 cells) compared with controls (71·2 ± 5·0 cells). This outcome was not statistically significant; however, calculated ES was −1·49 (95 % CI −2·89, −0·09).

Other outcomes

Microbiome outcomes were reported in only 1/19 studies[44], expressed as colony forming units of three bacteria families. Experimental colitis reduced *Lactobacillus* spp. and *Bifidobacterium* spp. counts in all study arms, while *Clostridium perfringens* counts remained stable. Animals supplemented with olive oil maintained greater *Lactobacillus* spp. counts compared with controls post induction of colitis, while *Bifidobacterium* spp. counts were not impacted by the intervention.

Outcomes not discussed due to word limits include myeloperoxidase activity, cyclo-oxygenase-2, monocyte chemoattractant protein-1, PPAR-γ, inducible nitric oxide synthase, p38 mitogen-activated protein kinases, interferon gamma, alkaline phosphatase activity, glutathione concentration, leukotriene B4, proliferating cell nuclear antigen, erythropoietin activity, N-acetyl-B-D-glucosaminidase activity, IκB kinase activity, pJNK, proteins p53, p65, STAT3, prostaglandin E synthase, pERK1/2 activation, caspase 3, NF-κB, b-catenin staining pattern, matrix metalloproteinase-9, Foxp3 expression and A1 mRNA expression.

Discussion

To our knowledge, this is the first systematic review investigating the effects of olive-based interventions on the expression of UC in both humans and animal models. A significant body of work has been done in murine models of colitis, while no randomised controlled trials in humans have been published at the time of writing. Studies were heterogeneous, which precluded a meta-analysis; however, general trends were identified, as discussed below.

Overall effects of olive-based interventions

Animals receiving olive-based interventions had milder UC severity in most studies, as shown by lower disease activity scores and favourable inflammatory markers compared with controls at kill. Interestingly, such findings were not replicated in HLA-B27 rats[42] and one study using C57BL/6 mice[36]. All remaining studies using C57BL/6 mice models demonstrated outcomes favouring the intervention[29,32,33,35,36,39–41,46,47], while no other study used HLA-B27 models. Other rat models however demonstrated outcomes favouring olive-based interventions[28,34,43,44,48,49]; thus, it is unclear if the use of HLA-B27 rat models or other experimental variables influenced these outcomes.

Table 8. Histology score from colon samples
(Numbers; mean values and standard deviations; 95 % confidence intervals)

Study	Colon site	Score method*	Max score	Control			Intervention			Mean Difference‡	Effect Size†‡	95 % CI‡	Reported *P*-value
				Mean	SD	*n*	Mean	SD	*n*				
Camuesco *et al.*[34]	Full length	Modified Histology Score[98]	27	15·1	3·5	10	10·3	24	10	–4·8	–0·27	–1·15, 0·61	NS
Hegazi *et al.*[45]	Full length	Colitis Score[99]	4	2·0	1·0	26	2·3	1·6	27	0·3	0·22	–0·32, 0·76	NS
		% Animals with dysplasia	100	15	NR	26	4	NR	27	–11	Unable to calculate		$P < 0·05$
		ACF	4	1·4	1·0	26	1·3	1·0	27	–0·1	–0·10	–0·63, 0·44	NS
		Crypt Index	Unknown	127·7	76·5	26	121·6	50·4	27	–6·1	–0·09	–0·63, 0·45	NS
Giner *et al.*[31]	Full length	Histology Score	10	8·5	4·7	10	2·5	4·7	10	–6	–1·21	–2·16, –0·26	$P < 0·01$
Sánchez-Fidalgo *et al.*[39]	Proximal	Modified Histology Score[96]	4	1	1·73	3	0·33	0·57	3	–0·7	–0·41	–2·03, 1·20	NS
	Distal		4	1·67	1·16	3	0·67	0·57	3	–1	–0·87	–2·55, 0·80	NS
	Rectum		4	3·67	0·57	3	1·33	0·57	3	–2·3	–3·27	–5·71, –0·82	NS
Sánchez-Fidalgo *et al.*[40]	Proximal	Colitis Score[100]	40	9·5	12·5	12	2·1	0·07	12	–7·4	–0·81	–1·64, 0·02	$P < 0·001$
	Distal		40	36·5	2·08	12	18·4	23·6	12	–18·1	–1·05	–1·90, –0·19	$P < 0·001$
	Rectum		40	16	6·24	12	15·5	17·7	12	–0·5	–0·04	–0·84, 0·76	NS
Sánchez-Fidalgo *et al.*[41]	Proximal	Histology Score[100]	40	2·6	0·69	12	1·9	2·08	12	–0·7	–0·44	–1·25, 0·37	NS
	Distal		40	35·7	1·73	12	23·6	26·7	12	–12·1	–0·62	–1·44, 0·20	$P < 0·05$
	Rectum		40	34·2	6·24	12	20·1	35·3	12	–14·1	–0·54	–1·35, 0·28	$P < 0·001$
Takashima *et al.*[49]	Proximal	Histology Score[96]	6	3·2	0·45	5	3	0·11	5	–0·2	–0·55	–1·82, 0·71	$P < 0·05$
	Distal		6	3·3	0·45	5	3	0·11	5	–0·3	–0·83	–2·12, 0,46	NS
	Rectum		6	5·3	0·67	5	3·9	0·67	5	–1·4	–1·88	–3·37, –0·39	$P < 0·05$
Sánchez-Fidalgo *et al.*[33]	Distal colon	Histology Score[100]	40	27·5	19·9	12	8·6	5·2	12	–18·9	–1·25	–2·13, –0·38	$P < 0·01$
Voltes *et al.*[28]	Full length	Modified Hunter Score[101]	8	3·4	2·63	10	2·6	1·36	10	–0·8	–0·37	–1·25, 0·52	NS
Bigagli *et al.*[42]	Full length	Colitis Score[102]	7	1·83	0·91	6	2	0·9	7	0·2	0·18	–0·92, 1·27	NS
Park *et al.*[46]	Full length	Modified Histology Score[103]	12	11·7	0·3	5	11	1	5	–0·7	–0·86	–2·15, 0·44	NS
Güvenç *et al.*[48]	Full length	Macroscopic damage[104]	5	4·26	0·85	7	1·97	1·22	7	–2·29	–2·03	–3·32, –0·74	$P < 0·001$
Wu *et al.*[44]	NR	Focal Haemorrhage	Unknown	3·67	1·37	6	2·17	1·18	6	–1·5	–1·08	–2·30, 0·13	$P < 0·05$
	NR	Injury Score[105]	Unknown	25	5·44	6	20·17	6·25	6	–4·83	–0·76	–1·93, 0·41	NS
Cariello *et al.*[29]	Distal colon	Histology Score[96]	6	4·6	0·3	10	3·4	0·2	10	–1·2	–4·51	–6·16, –2·86	$P < 0·05$
de Paula do Nascimento *et al.*[36]	Distal colon	Histology Score[100]	Unknown	1·01	0·79	10	1·94	0·85	10	0·93	1·08	0·14, 2·02	NS
	Distal colon	Histology Score[98]	Unknown	10·7	6·83	10	16·55	7·65	10	5·85	0·77	–0·14, 1·68	NS
Sánchez-Fidalgo *et al.*[35]	Low Grade Dysplasia	Dysplasia[106]	100	100	NR	20	100	NR	20	0	Unable to calculate		NS
	High Grade Dysplasia		100	85	NR	20	55·55	NR	20	–29	Unable to calculate		NS
	Adeno-carcinoma		100	55	NR	20	22·2	NR	20	–33	Unable to calculate		NS
	Tumour		100	30	NR	20	0	NR	20	–30	Unable to calculate		NS

ACF, Aberrant Crypt Foci.
*For all scoring methods, lower scores indicate less damage on the colon samples.
† Negative effect size indicates lower histology scores and less tissue damage.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

Table 9. Colon weight/length ratio
(Numbers; mean values and standard deviations; 95 % confidence intervals)

		Control colitis			Intervention colitis						
Study	Unit	Mean	SD	*n*	Mean	SD	*n*	Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
Camuesco *et al.*[34]	mg/cm	100·6	19	10	84·2	18	10	–16·4	–0·85	–1·76, 0·07	$P < 0·05$
Hegazi *et al.*[45]	NR	NR	NR	26	NR	NR	27	Unable to calculate	Unable to calculate		NS
Sánchez-Fidalgo *et al.*[35]	g/cm	105·9	37·1	20	107·1	18·3	20	1·2	0·04	–0·72, 0·80	NS
Giner *et al.*[31]	mg/cm	40·5	6·01	10	29·1	2·21	10	–11·4	–2·41	–3·56, –1·26	NS
Sánchez-Fidalgo *et al.*[39]	mg/cm	118·3	47·4	10	108	33·7	14	–10·32	–0·25	–1·06, 0·56	NS
Sánchez-Fidalgo *et al.*[40]	%*	215	52	12	140	34·6	12	–75	–1·64	–2·56, –0·71	$P < 0·001$
Sánchez-Fidalgo *et al.*[41]	%*	147	52	12	87	24·3	12	–60	–1·43	–2·33, –0·53	$P < 0·001$
Giner *et al.*[32]	mg/cm	53·7	0·95	10	44·2	9·8	10	–9·5	–1·31	–2·27, –0·34	$P < 0·05$
de Paula do Nascimento *et al.*[36]	mg/cm	26·1	4·3	11	26·8	4	11	0·7	0·16	–0·67, 1·00	NS

NR, not reported in text.
* Percentage of colon weight:length ratios compared with non-colitis control animals at kill; control animals were assumed to be 100 %.
† Negative effect size indicates lower weight/length ratio in the intervention.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

Table 10. Colon length between study arms
(Numbers; mean values and standard deviations; 95 % confidence intervals)

			Control			Intervention						
Author	Animal	Group	Mean (cm)	SD	*n*	Mean (cm)	SD	*n*	Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
Giner *et al.*[31]	Mice	Non-colitis	8·86	0·95	10	NR*	NR*	NR*	Unable to calculate	2·36	1·22, 3·50	NS
		Colitis	5·35	0·16	10	6·65	0·73	10	1·3			
Takashima *et al.*[49]	Rat	Non-colitis	18·0	3·12	12	NR*	NR*	NR*	Unable to calculate	1·28	0·41, 2·14	NS
		Colitis	11·2	0·61	13	12·65	1·46	12	1·45			
Sánchez-Fidalgo *et al.*[33]	Mice	Non-colitis	7·5	0·7	12	7·3	0·7	12	–0·2	0·88	0·04, 1·72	NS
		Colitis	6·5	0·7	12	7	0·4	12	0·5			
Park et al.[46]	Mice	Non-colitis	6·20	0·10	2	NR*	NR*	NR*	Unable to calculate	–0·55	–1·81, 0·72	NS
		Colitis	4·24	0·38	5	4·01	0·38	5	–0·23			
Wu *et al.*[44]	Rats	Non-colitis	159·1	22·1	6	NR*	NR*	NR*	Unable to calculate	1·20	–0·03, 2·42	$P < 0·05$
		Colitis	112·1	22·5	6	141·3	11·8	6	29·2			
de Paula do Nascimento *et al.*[36]	Mice	Non-colitis	7·6	0·3	10	NR*	NR*	NR*	Unable to calculate	–0·29	–1·13, 0·55	NS
		Colitis	6·5	0·7	10–12	6·3	0·7	10 – 12	–0·2			

NR, not reported in text.
*In studies not reporting colon lengths of non-colitis intervention animals (NR), Mean and Standard Deviation values assumed to be the same as non-colitis controls.
† Positive effect sizes indicate greater colon lengths favouring the intervention arm.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

Table 11. TNF-α in colon tissue post kill
(Numbers; mean values and standard deviations; 95 % confidence intervals)

		Control colitis			Intervention colitis						
Author	Units of measurement	Mean	SD	*n*	Mean	SD	*n*	Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
Camuesco *et al.*[34]	pmol/g tissue	846·1	295·7	10	596·9	235·0	10	–249·2	–0·89	–1·81, 0·03	NS
Sánchez-Fidalgo *et al.*[35]	pg/mg tissue	4	2·2	20	3·2	1·8	20	–0·8	–0·39	–1·02, 0·23	NS
Giner *et al.*[31]	pg/ml	37·1	4·8	7	22	9·5	7	–15·1	–1·86	–3·12, –0·61	$P<0·01$
Sánchez-Fidalgo *et al.*[39]	% compared to non-UC controls	170·4	34·5	10	149·6	71·8	14	–20·8	–0·34	–1·15, 0·48	$P<0·05$
Sánchez-Fidalgo *et al.*[40]	NR	8·1	5·0	4	6·3	3·4	4	–1·8	–0·37	–1·76, 1·03	NS
Sánchez-Fidalgo *et al.*[41]	NR	13·95	9·84	4	4·78	0·74	4	–9·17	–1·14	–2·64, 0·35	$P<0·001$
Takashima *et al.*[49]	NR	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate		NS
Hamam *et al.*[43]	% area expressing TNF-α	31·45	6·18	10	7·65	3·22	10	–23·8	–4·63	–6·31, –2·95	$P<0·05$
Bigagli *et al.*[42]	NR	1·33	0·15	6	1·19	0·08	7	–0·14	–1·11	–2·28, 0·06	$P<0·05$
Park *et al.*[46]	*n* cells	227·71	28·29	5	139·16	65·99	5	–88·55	–1·57	–2·99, –0·16	$P<0·05$
Güvenç *et al.*[48]	pg/ml	2·77	0·95	7	1·32	0·053	7	–1·446	–1·99	–3·28, –0·71	$P<0·05$
Wu *et al.*[44]	pg/mg tissue	55·1	35·5	6	11·2	8·1	6	–43·9	–1·57	–2·87, –0·28	$P<0·05$
de Paula do Nascimento *et al.*[36]	pg/mg tissue	0·5	0·3	7–12	1·1	0·7	7–12	0·57	0·95	0·00, 1·89	NS
Huguet-Casquero *et al.*[47]	pg/g protein	2650	876	7–8	1340	356	7–8	–1310	–1·84	–3·05, –0·63	$P<0·05$

NR, not reported in text.
† Negative effect size indicates lower colon TNF-α expression in the intervention group.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

Table 12. IL-1β in colon tissue post kill
(Numbers; mean values and standard deviations; 95 % confidence intervals)

		Control colitis			Intervention colitis						
Author	Units of measurement	Mean	SD	*n*	Mean	SD	*n*	Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
Giner *et al.*[31]	pg/ml	175·1	15·9	7	133·9	23·6	7	–41·2	–1·91	–3·17, –0·64	$P<0·05$
Sánchez-Fidalgo *et al.*[39]	%*	162·4	35·1	10	180·8	55·0	14	18·90	0·37	–0·45, 1·19	NS
Giner *et al.*[32]	pg/ml	34·5	27·5	7	23·1	2·4	7	–13·70	–0·54	–1·61, 0·52	NS
Takashima *et al.*[49]	NR	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate		NS
Bigagli *et al.*[42]	NR	3·53	0·3	6	2·95	0·5	7	–0·58	–1·34	–2·54, –0·13	NS
Park *et al.*[46]	*n* cells	125	6·7	5	94·4	17·9	5	–30·5	–2·06	–3·59, –0·52	NS
Wu *et al.*[44]	pg/mg tissue	175·9	24·5	6	60	34·5	6	–115·9	–3·57	–5·40, –1·75	$P<0·05$
Cariello *et al.*[29]	Relative gene expression	1·62	1·96	10	0·31	0·51	10	–1·31	–0·88	–1·79, 0·04	$P<0·05$
de Paula do Nascimento *et al.*[36]	pg/mg tissue	12·7	11·4	7–12	37	35·1	7–12	24·3	0·89	–0·05, 1·83	NS

NR, not reported in text.
* Expressions in % refer to proportions compared with non-colitis control animals at time of kill.
† Negative effect size indicates lower expression of IL-1β in the intervention group.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

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Table 13. Interleukin-6 post kill
(Numbers; mean values and standard deviations; 95 % confidence intervals)

Author	Units of measurement	Control colitis			Intervention colitis			Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
		Mean	SD	*n*	Mean	SD	*n*				
Sánchez-Fidalgo *et al.*[35]	pg/mg tissue	2·2	2·24	20	2	1·79	20	−0·20	−0·10	−0·72, 0·52	NS
Giner *et al.*[31]	pg/ml	101·0	16·67	7	57·4	17·46	7	−43·60	−2·38	−3·74, −1·01	$P < 0·01$
Giner *et al.*[32]	pg/ml	121·4	30·43	7	76·5	16·40	7	−44·90	−1·71	−2·93, −0·48	$P < 0·05$
Takashima *et al.*[49]	NR	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate		NS
Park *et al.*[46]	*n* cells	51·04	4·63	5	33·13	9·85	5	−17·91	−2·10	−3·64, −0·56	NS
Güvenç *et al.*[48]	pg/ml	1·841	0·317	7	1·142	0·079	7	−0·70	−2·81	−4·29, −1·33	$P < 0·001$
Wu *et al.*[44]	pg/mg tissue	69·7	37·2	6	37·1	20·8	6	−32·60	−1·00	−2·20, 0·20	$P < 0·05$
Cariello *et al.*[29]	gene expression	1·65	2·53	10	0·07	0·22	10	−1·58	−0·84	−1·76, 0·07	$P < 0·05$
de Paula do Nascimento *et al.*[36]	pg/mg tissue	34·8	31·1	7–12	23·9	24·7	7–12	−10·90	−0·37	−1·28, 0·54	NS
Huguet-Casquero *et al.*[47]	pg/g protein	1840	301	7–8	920	411	7–8	−920	−2·41	−3·74, −1·08	$P < 0·01$

NR, not reported in text.
† Negative effect size indicates lower expression of IL-6 in the intervention group.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

Insufficient intervention doses may have contributed to this discrepancy. Polyphenol content was not described in one study[36], while Bigagli *et al.* reported hydroxytyrosol concentration of 15 mg/kg olive oil, equivalent to a daily dose of 90 µg/kg body weight in HLA-B27 rats[42]. By contrast, findings from other studies in this review suggest clinically significant outcomes were associated with polyphenol concentrations above 0·4 mg/kg body weight[39,40]. Similarly, in this review, we identified greater attenuation of disease scores at higher concentration of Hydroxytyrosol[33,39,51] and Oleuropein[31,32]. It should be noted that adverse effects may occur at higher doses[54]; however, this was not evident in any study in this review. Furthermore, a dose–response relationship cannot yet be established due to the small sample sizes, heterogeneity of studies and variable reporting of experimental methods.

Effects on body weight

Weight loss and malnutrition are known complications associated with colitis in both animal models[55,56] and human cohorts[9,57]. Anorexia, malabsorption, dietary restrictions and gut microbiome disturbances are some of the contributors to this phenomenon[58–60]. In this systematic review, olive-based interventions improved weight outcomes concordant with milder disease activity, as indicated by weight maintenance or increased weight gain. Energy density of control and intervention diets was matched in most studies; however, such precautions were not evident in studies intervening through oral gavage or rectal administration. As such, it is unknown if these interventions influenced daily energy intake and subsequent weight outcomes. Similarly, housing conditions and husbandry were poorly described in most studies and potential confounders for feeding behaviour and subsequent weight outcomes[61,62].

Interestingly, olive oil supplementation increased oral intake in one study[49]. Although exact mechanisms are unclear, associations between gastrointestinal dysfunction and feeding behaviours are plausible[60], as milder symptoms may promote feeding behaviour. In conjunction with these changes, mucosal healing as indicated by stool consistency and histology outcomes may offer greater opportunity for fluid and nutrient absorption along the gastrointestinal tract. In combination, these changes may ultimately contribute towards favourable weight outcomes in intervention animals. This relationship remains speculative as few studies quantified oral intake, further complicated by multiple animals per cage and *ad libitum* feeding.

Finally, gut microbiome favourable shifts mediated by olive interventions may have contributed to the outcomes observed. Reduced gut bacterial diversity and abundance of commensal species have been associated with disease severity in both UC and experimental colitis[63]. Such changes are significant considering the microbiome's role in supporting gut barrier integrity, gut inflammatory tone and intestinal immunity through the production of SCFA (e.g., butyrate) and other host interactions. By contrast, previous studies have shown that olive oil supplementation promotes α-diversity of commensal bacterial species and accumulation of lean muscle mass in healthy C57BL/6J mice[64], a finding which was replicated in this review[44]. No other study assessed microbiome outcomes; thus, any conclusions are premature.

Colon morphology

Chemically induced colitis results in several features which differ depending on the reagent and dosage used. DSS-colitis models exhibit loss of surface epithelium which subsequently increases mucosal permeability, predominantly impacting the distal colon. Administration of 2,4,6-trinitrobenzenesulfonic acid results in thickening of the proximal colon accompanied by loss of haustration, while intra-rectal administration of acetic acid solution results in necrosis of intestinal mucosa and submucosa[23]. Despite the variability of these changes, several shared features such as oedema, ulcerations, granulocyte infiltration and dysplasia can be used to ascertain severity of experimental colitis.

Findings from this review suggest that olive-based interventions may have a role in preserving colonic architecture and metabolic-immunological function in experimental UC. This was evident through milder microscopic and macroscopic outcomes, histology scores and normalised weight:length ratios favouring intervention animals. It should be noted that olive-based interventions did not *prevent* intestinal injury in any study; however, the degree of damage was considerably lower compared with animals in the control arm.

Comparing sub-sections of the colon, middle and distal sections are known to be most affected by colitis[65,66]. Importantly, these sub-sections showed the greatest improvements in response to olive-based interventions, suggesting specific protection on these sites. Promotion of wound healing and protection against oxidative damage of intestinal cells mediated by olive polyphenols have previously been demonstrated[32] which may explain how olive-based interventions protect against chemically induced colitis.

Beneficial alterations to the microbiome mediated by olive polyphenols may have conferred additional protective effects against experimental colitis. Consumption of olive oil and olive polyphenols has been demonstrated to facilitate growth of butyrate producing bacteria such as *Lactobacillus and Bifidobacterium*[67], increase mucosal concentrations of SCFA[67] and inhibit growth of pathogenic species associated with inflammation[68]. SCFA such as butyrate play a vital role in preserving intestinal epithelial barrier and serve as fuel for colonocytes[69,70]. Furthermore, SCFA have been demonstrated to exert anti-inflammatory effects in the intestinal mucosa[69]. Metabolism of SCFA is impaired in UC and has been correlated with poorer histology and endoscopy outcomes[71]. As such, strategies targeting both the microbiome and SCFA production may assist in maintaining colon homoeostasis; however, current evidence remains inconsistent, and further investigations are warranted.

Inflammatory markers

Many health outcomes of olive-based interventions have been ascribed to component effects on inflammatory responses. Olive oil is predominantly composed of the MUFA oleic acid, which has been shown to protect against oxidative stress, regulate immune function in intestinal smooth muscle cells and disrupt arachidonic acid and NF-κB signalling pathways associated with chronic inflammation[29,72]. Prospective studies in healthy cohorts suggest an inverse association between oleic acid consumption and risk of developing UC[16], although such findings have yet to be replicated in larger studies[73]. Similarly, associations between dietary oleic acid and disease severity in individuals living with UC remain inconclusive despite promising findings in pre-clinical and clinical data[74].

Consumption of olive oil may confer additional benefits through displacing less desirable fatty acids in the diet. Specific fatty acids such as *n*-6 PUFA, saturated fats, trans fats and high fat diets have been associated with increased markers of pro-inflammatory cytokines[75], increased risk of developing UC[16] and worsening symptoms in individuals living with UC and animal models[75,76]. Similarly, inclusion of *n*-3 fatty acids have been demonstrated to exert protective effects against experimental colitis[77,78]; however, its role in prevention and treatment of UC remains controversial[79–81]. Finally, although dietary fat manipulation through olive oil consumption may confer some benefits on inflammatory markers and disease outcomes, it is unlikely that the effects observed in this review could be attributed to the fatty acid profile alone.

Previous experiments have highlighted the bioavailability and anti-inflammatory properties of olive oil polyphenols such as Oleuropein, Hydroxytyrosol and Oleocanthal in the gut[82]. In this review, we identified dose-dependent associations between Hydroxytyrosol and Oleuropein interventions with lower cytokine expression in concert with improved disease outcomes in murine models of UC. These findings further support previous *in vitro* studies on colonic biopsies of UC cohorts[83] and healthy cohorts[84,85], in which cytokine expression was reduced by olive polyphenols such as Hydroxytyrosol and Oleuropein.

Regulation of inflammatory markers has been identified as a potential therapeutic target in IBD, as increased secretion of pro-inflammatory (TNF-α, IL-1β, IL-6) and reduction of anti-inflammatory cytokines (IL-10) are associated with chronic inflammation and symptoms[86–88]. However, limited evidence is available on the specific markers associated with UC outcomes and their response to olive-based interventions, with several inconsistencies identified in the literature. Moraes *et al.* found minimal differences in cytokine expression between a cross-sectional study of UC cohorts with and without gastrointestinal symptoms[89]. Similarly, an uncontrolled study comparing 50 ml/d extra virgin olive oil and rapeseed oil interventions in UC cohorts reported alleviation of gastrointestinal symptoms and reduction of hs-CRP without alterations to serum TNF-α favouring extra virgin olive oil, although no other markers were quantified[90]. Finally, a meta-analysis in non-IBD populations similarly reported no changes to TNF-α despite favourable CRP and IL-6 outcomes with olive oil interventions[91]. The discrepancies between animal data in this review and human studies highlight the limitations of translating our findings to human cohorts and current gaps in the evidence. As such, although olive-based interventions appear to influence disease activity and symptoms as well as attenuation of pro-inflammatory cytokine expression in experimental UC models, it is unknown if findings would be replicated in human trials. Therefore, further investigations are warranted.

Limitations of this review methodology

The search strategy for this review was comprehensive, although no unpublished studies were sought, and no non-English language databases were searched, which could have limited the number of trials available for review. In addition, only one author (K. D.) performed the search and initial selection of eligible articles. However, the final selection was agreed upon by all authors.

Limitations of the literature to date

The studies identified were heterogeneous, with variations between experimental models, outcome measures and methods of evaluating disease severity. Chemically induced colitis models formed the majority of the evidence, which may limit the translation of our findings to other models of UC and human cohorts. Scaling up of olive oil doses described in this review for individuals living with UC should consider the feasibility and safety of implementing these interventions. Furthermore, quality of the evidence through the SYRCLE's Risk of Bias tool was sub-optimal due to limited reporting of key domains such as animal characteristics and husbandry; factors known to influence disease severity and experimental outcomes (such as individual animal stool volumes), as well as determine actual individual animal consumption of both food and olive-based product[92,93]. Moreover, strength to murine models of IBD would be further enhanced if researchers conducting the histology studies were unsighted to the collected colon samples.

Most of the studies intervened prior to, or during induction of, experimental colitis, limiting our ability to determine the efficacy of such strategies post-colitis. It does lend support to epidemiological data on consumption patterns and risk of developing disease[14–16]. However, translation to therapeutic interventions in cohorts who have established UC or similar conditions require explicit human studies with robust experimental designs.

Conclusion

Olive-based interventions exerted protective effects against chemically induced colitis in murine models. Despite these promising outcomes, conclusions are limited by the overall low quality of existing animal trials due to sub-optimal reporting of key parameters. Future investigations should include well-defined baseline characteristics, greater transparency regarding randomisation, blinding and husbandry as well as mortality. Most importantly, translation of these basic studies to human trials is warranted given the absence of robustly designed trials investigating the relationship between olive-based interventions and outcomes in UC cohorts.

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Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114521001999

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