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Nicotine and Inflammatory Disease in Humans: A Systematic Review *

by

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SUMMARY

Introduction: Previous studies have shown that nicotine interacts in inflammatory pathways and may have both pro- and anti-inflammatory actions. The aim of this study was to carry out a systematic review of publications investigating the inflammatory effects of nicotine in models of human disease.
Methods: The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklists were followed during the design and implementation of this study. Searches were carried out across PubMed, Science Direct, and the Cochrane Library. Articles were included if they were published in English, in peer-reviewed journals, reported an effect of nicotine in the treatment of a clinical condition, experimental studies or clinical trials which investigated an effect of nicotine administration in patients with a clinical condition or epidemiological studies which investigated an effect of nicotine administration in patients with a clinical condition.
Results: Thirty-eight studies were identified and categorized into disease areas before systematic review. Nineteen studies were related to digestive diseases (primarily Crohn's disease and ulcerative colitis), six to atherosclerosis, five to skin and healing, four to pain and infection, three to pulmonary sarcoidosis, and three to multiple sclerosis (one study reported data on three disease areas). Risk of bias assessment was not carried out, but the general quality of the studies was low, mostly offering preliminary data in small numbers of participants. No consistent effects of nicotine treatment (primarily through use of transdermal nicotine patches or nicotine chewing gums) were reported across any of the disease models.
Conclusion: No reliable evidence of a pro- or anti-inflammatory effect of nicotine was observed in patients with any of the diseases included in this study. [Contrib. Tob. Nicotine Res. 31 (2022) 10–24]

ZUSAMMENFASSUNG

Einleitung: Frühere Studien haben gezeigt, dass Nikotin mit inflammatorischen Signalwegen interagiert und hierbei sowohl entzündungsfördernd als auch entzündungshemmend wirken kann. Ziel dieser Studie war die Erstellung einer systematischen Übersicht von Veröffentlichungen, die sich mit der entzündlichen Wirkung von Nikotin in Modellen für Humankrankheiten befassen.
Methoden: Design und Umsetzung dieser Studie erfolgten unter Verwendung der Checklisten zum Bericht einer systematischen Übersicht oder einer Meta-Analyse (PRISMA). Folgende Datenbanken wurden für die Recherche verwendet: PubMed, Science Direct und Cochrane Library. Artikel wurden eingeschlossen, sofern sie auf Englisch veröffentlicht wurden, in Fachzeitschriften mit Peer-Review-Verfahren erschienen waren, über die Wirkung von Nikotin bei

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der Therapie einer klinischen Erkrankung berichteten, sich mit experimentellen oder klinischen Studien befassten, in denen die Wirkung der Gabe von Nikotin bei Patienten mit einer klinischen Erkrankung untersucht wurde, oder epidemiologische Studien betrafen, in denen die Wirkung der Verabreichung von Nikotin bei Patienten mit einer klinischen Erkrankung untersucht wurde.
Ergebnisse: Vor der Erstellung der systematischen Übersicht wurden 38 Studien identifiziert und jeweils Indikationsgebieten zugeordnet. Neunzehn Studien befassten sich mit gastroenterologischen Erkrankungen (hauptsächlich Morbus Crohn und Colitis ulcerosa), sechs mit Arteriosklerose, fünf mit Hauterkrankungen und Heilungsprozessen, vier mit Schmerzen und Infektionen, drei mit Lungensarkoidose und drei mit Multipler Sklerose (in einer Studie wurden Daten zu drei verschiedenen Indikationsgebieten berichtet). Das Risiko einer Verzerrung wurde nicht beurteilt, jedoch war die allgemeine Qualität der Studien gering. Meist wurden nur vorläufige Daten für eine kleine Zahl an Studienteilnehmern veröffentlicht. Für keines der Krankheitsmodelle wurde eine konsistente Wirkung der Nikotintherapie (im Wesentlichen mit transdermalen Nikotinpflastern oder Nikotinkaugummis) berichtet.
Schlussfolgerung: Für keine der in dieser Studie eingeschlossenen Indikationen wurde bei Patienten eine zuverlässige Evidenz für eine entzündungsfördernde oder entzündungshemmende Wirkung von Nikotin beobachtet. [Contrib. Tob. Nicotine Res. 30 (2021) 10–24]

RESUME

Introduction: De précédentes études ont démontré que la nicotine interagissait avec les voies inflammatoires et était susceptible de produire une action à la fois pro- et anti-inflammatoire. La finalité de la présente étude est un passage en revue systématique des publications examinant les effets inflammatoires de la nicotine sur des modèles de maladies humaines.
Méthodes: Les lignes directrices pour l'écriture et la lecture des revues systématiques et des méta-analyses (PRISMA) furent suivies durant la conception et la mise en œuvre de cette étude. Les recherches furent menées sur PubMed, Science Direct et la Cochrane Library. Les articles furent inclus à la condition d'être parus en anglais, dans des revues à comité de lecture, de faire état d'un effet de la nicotine sur le traitement d'un état clinique, de concerner des études expérimentales ou des essais cliniques examinant un effet de l'administration de la nicotine à des patients présentant un état clinique ou de relater des études épidémiologiques analysant un effet de l'administration de la nicotine à des patients présentant un état clinique.
Résultats: Trente-huit études furent identifiées et classées selon les pathologies avant d'entamer la revue systématique. Dix-neuf études portaient sur les maladies du système digestif (surtout la maladie de Crohn et la rectocolite hémorragique), six sur l'athérosclérose, cinq sur le derme et la cicatrisation, quatre sur la douleur et les infections, trois sur la sarcoïdose pulmonaire et trois sur la sclérose en plaques (une étude livrait des données sur trois domaines pathologiques). Aucune évaluation du risque de biais ne fut accomplie mais la qualité générale des études était faible et la plupart d'entre elles ne divulguait que des données préliminaires sur un nombre limité de sujets participants. Aucun effet systématique d'un traitement à base de nicotine (principalement administré par des timbres transdermiques à la nicotine ou des chewing-gums à la nicotine) ne fut signalé pour aucun des modèles de maladies.
Conclusion: Aucune preuve fiable d'un effet pro- ou anti-inflammatoire de la nicotine ne fut observée chez les patients souffrant des pathologies incluses dans la présente étude. [Contrib. Tob. Nicotine Res. 30 (2021) 10–24]

INTRODUCTION

The inflammatory response is a highly regulated and critically balanced process involving a wide variety of cell types, cytokines and biochemical mediators with pleiotropic and redundant functions. Too much inflammation may be damaging to tissues, and even fatal in cases such as sepsis; however, an insufficient inflammatory response can lead to delayed healing or failure to resist infection. For this reason, any compound that is active within inflammatory pathways should be comprehensively understood in terms of its intervention potential and unintended consequences of exposure.
Smoking has long been linked to a heightened inflammatory state and has been shown to exacerbate inflammatory conditions such as rheumatoid arthritis and atherosclerosis (1). However, smoking is also negatively associated with some specific inflammatory-based disorders such as ulcerative colitis and primary sclerosing cholangitis (2). Previous studies have shown that nicotine interacts in inflammatory pathways and may have both pro- and anti-inflammatory actions. This finding is more relevant today than ever before as new nicotine-containing products are entering the marketplace, leaving the additional confounding constituents from cigarette smoke behind. Both the pro- and anti-inflammatory pathways of nicotine, which have been proposed through *in vitro* and *in vivo* models (3–5) and thoroughly reviewed (6–8), are briefly outlined below.

Pro-inflammatory pathway linked to nicotine

The mechanisms behind the pro-inflammatory response to nicotine are thought to arise from stimulation of the sympathetic nervous system. Simplistically, nicotine binds to nicotinic acetylcholinergic receptors (nAChRs) on sympathetic nerve cells, leading to increased noradrenaline (9), stimulation of β3 adrenergic receptors, and release of hematopoietic stem and progenitor cells from bone marrow niches (10). These in turn differentiate into monocytes, which infiltrate sites of existing inflammation and recruit further immune cells, perpetuating chronic inflammation.

Anti-inflammatory pathway linked to nicotine

Anti-inflammatory mechanisms in response to nicotine are thought to arise through the direct interaction of nicotine with nAChRs on the surface of immune regulatory cells. The α7 sub-type of nAChRs is expressed on a variety of immune cells such as B cells, eosinophils, dendritic cells, monocytes,

Table 1. Search strategies employed to identify published articles relevant to nicotine and inflammation in humans.

Search engine	Search strategy	Number of papers returned
PubMed	nicotine [title] AND inflam* [title/abstract]	490
	nicotine [title] AND pro*inflam* [title/abstract]	135
	nicotine [title] AND anti*inflam* [title/abstract]	55
Science Direct	nicotine [title] AND inflammation [title/abstract/keywords]	164
Cochrane Library	Searched 'nicotine' and manually screened reported hits for relevant inflammation-related systematic reviews and meta-analyses	1
References from review articles	Relevant review articles were identified from excluded papers (n = 28). The reference lists of these reviews were screened for any further studies of interest	10
References from JTI database	Internal JTI databases were searched for additional articles of relevance	10
Additional articles identified from PubMed alerts	Daily email alerts created for nicotine [title/abstract] and searched for articles which meet the inclusion criteria and which were published between 5th April 2021 and 19th November 2021	1

macrophages, T cells and neutrophils, with the inflammatory response specific to each cell type (8). Nicotine binding to the receptor brings about a conformational change to the receptor structure, opening of ion gated channels and the subsequent flux of calcium, potassium and sodium. This leads to reduced inflammatory cytokine release through the JAK/STAT pathway (the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway plays critical roles in orchestrating the immune system), as well as decreased NF-κB signaling and a reduction in TNF-α production (7).

Although the proposed pro- and anti-inflammatory mechanisms have been demonstrated in animal and cell models, the effects of nicotine in humans are less clear. The aim of this study was to carry out a systematic review of publications investigating the inflammatory effects of nicotine in models of human disease.

METHODS

Search strategy

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklists were followed during the design and implementation of this study (Supplementary File 1) (11). Meta-analyses were not conducted. The prevalence of studies with small sample size, the heterogeneity of the reported study designs and the range of inflammatory disorders covered precluded the use of meta-analyses. PubMed, Science Direct and the Cochrane Library databases were searched using the strategies outlined in Table 1. Initial searches were carried out on 5th April 2021. No time restrictions were applied with respect to article inclusion. No restrictions were applied with respect to the quality of the articles included in this review. Reference lists of relevant review articles were screened for additional original articles that did not appear in the searches. JTI internal databases were also searched. A subsequent database screen from 5th April 2021 – 19th November 2021 was carried out to make sure the most up-to-date publications were included before submission.

Inclusion criteria

Articles were considered for inclusion in this review if they were:
- Published in English;
- Published in peer-reviewed journals;
- Published as a medical case series detailing the clinical treatment of more than one patient using the same nicotine treatment approach;
- Studies which reported an effect of nicotine in the treatment of a clinical condition;
- Experimental studies or clinical trials which investigated an effect of nicotine administration in patients with a clinical condition; or
- Epidemiological studies which investigated an effect of nicotine administration in patients with a clinical condition.

Exclusion criteria

Articles were excluded from this review if they were:
- Published in any language other than English;
- Including data in the form of journal abstracts, conference posters, conference proceedings, book chapters or patents;
- Medical case reports;
- *In vivo* studies which utilized laboratory animals in their experimental methodology;
- *In vitro* studies which utilized human and/or animal cell lines in their experimental methodology;
- Experimental studies or clinical trials which investigated an effect of nicotine in patients with a clinical condition where nicotine administration was achieved exclusively through smoking of conventional cigarettes, whether or not the experimental study or clinical trial included one or more treatment arm(s) utilizing denicotinized ("nicotine-free") conventional cigarettes;
- Review articles containing no original data; or
- Studies testing drugs acting as nicotinic receptor agonists.

RESULTS

As outlined in Table 1, searches across PubMed and Science Direct returned a total of 844 publications. Duplicates were removed (n = 252), leaving 592 papers to screen for relevance. Studies containing "mouse"/ "mice"/ "rat" or "*in vitro*" in the title (n = 130) were excluded automatically. Details of exclusion/inclusion may be reviewed in Supplementary File 2. Figure 1 shows a flow diagram of the study screening process.

A total of 16 original studies carried out in humans and relating to nicotine and inflammation were identified. After a search of the Cochrane Library, one additional systematic review containing a meta-analysis was added (12), bringing the total to 17 studies to analyze. Twenty-eight relevant review articles were identified from the excluded papers, the references of which were screened for any further studies of interest, returning 10 additional papers. Screening of JTI internal databases added 10 studies. An additional article relating to pulmonary sarcoidosis was identified between 5th April 2021 and 19th November 2021. The final list of 38 studies were categorized into disease areas (digestive diseases, atherosclerosis, skin and healing, pain and infection, pulmonary sarcoidosis, and multiple sclerosis) and detailed below.

Digestive diseases

The 19 studies reviewed in this section are listed in Supplementary File 3.

- *Crohn's disease*

Crohn's disease is one of the two major non-specific inflammatory bowel diseases with the other being ulcerative colitis. Unlike ulcerative colitis, Crohn's disease can affect any segment of the gastrointestinal tract. Symptoms typically include abdominal pain, diarrhea, fever and weight loss. It is believed to result from a combination of environmental, immune, and bacterial factors in genetically susceptible individuals.

A single open non-randomized clinical study is available on the potential effects of nicotine administration on Crohn's disease (13). Ten patients with active Crohn's disease were recruited to participate in the study. The patients comprised seven men and three women and had a mean age of 52 years. Seven were former smokers and three were non-smokers. The patients were given nicotine enemas (containing 6 mg of nicotine) each day for four weeks in an open study in addition to their conventional treatment(s) which continued unchanged throughout the study. At the beginning and end of the trial, a Crohn's disease activity index (CDAI) score was calculated, sigmoidoscopy was performed, and hematological inflammatory markers were measured. The mean CDAI score decreased from 202 to 153 for the ten patients; the score was reduced in six patients, unchanged in three, and increased in one. Frequency of bowel movements decreased in eight patients and the sigmoidoscopy grade was reduced in seven. The authors concluded that "*in ten patients with active Crohn's disease, 6 mg nicotine enemas were associated with clinical improvement in the majority of patients, they were safe and well tolerated, and did not appear to worsen the condition"* (13). However, the authors also highlighted a caveat in that *"a relatively small open pilot study of this nature can only provide preliminary data on efficacy and safety. Hence, although our observations suggest improvement in most of the patients, and certainly no overall deterioration, the findings will need to be corroborated by larger randomised controlled studies"*.

In a study investigating chronic inflammatory disease in Swedish construction workers, exclusive use of Swedish moist snuff (snus) was not associated with either an increase or decrease in risk of Crohn's disease compared to never users of tobacco (relative risk (RR): 1.0; 95 % CI: 0.8–1.4) (14). This suggests that nicotine is not protective against this particular inflammatory disease; however, it is not likely to be responsible for the increased risk observed in smokers either (13). It should be noted that risk of developing disease is not equivalent to treatment of incident disease. Therefore, nicotine may still have pro- or anti-inflammatory properties in a treatment context without protecting against inflammatory disease onset. There were also some important limitations to the study. For example, although the participants were followed-up for a long period (1978–1993) tobacco use was only recorded at one time-point. Therefore, it is impossible to analyze any effect of change in tobacco usage such as quitting after the data was collected.

- *Ulcerative colitis*

Ulcerative colitis (UC) has been defined as "*a recurrent inflammatory and ulcerative disease of the colon and rectum, characterised by rectal bleeding, diarrhoea, cramping and abdominal pain, anorexia and weight loss*" (15). UC is the second of the two major non-specific inflammatory bowel diseases, the other being Crohn's disease (15, 16). The onset of UC is characterized by lesions that develop in the base of the mucosal layer, originating in the rectum and extending proximally into the colon, which eventually ulcerate due to immunological inflammatory processes, producing the symptoms described previously (15). The etiology of UC is unknown and likely reflects a heterogeneous disorder.

In their study of Swedish construction workers (also included in other sections of this review), CARLENS *et al.* investigated the relationship between exclusive snus use and risk of developing UC. Similar to their results for CD, the authors showed no effect of snus use on risk of developing UC (RR: 1.0; 95 % CI: 0.8–1.2) (14).

After positive results from a pilot study using nicotine patches in 10 UC patients in conjunction with mesalazine (17), another trial comparing the efficacy of nicotine with prednisone treatment was carried out (18). Fifteen participants were randomly assigned to receive nicotine or prednisone whilst continuing with mesalazine therapy. Results demonstrated that even though short-term use of corticosteroids seemed to be more effective than nicotine therapy, a lower incidence of relapse was observed in those patients who received transdermal nicotine patches compared to those patients who received corticosteroid treatment. The authors suggested that nicotine therapy may be a suitable alternative in patients who cannot tolerate corticosteroids (18).

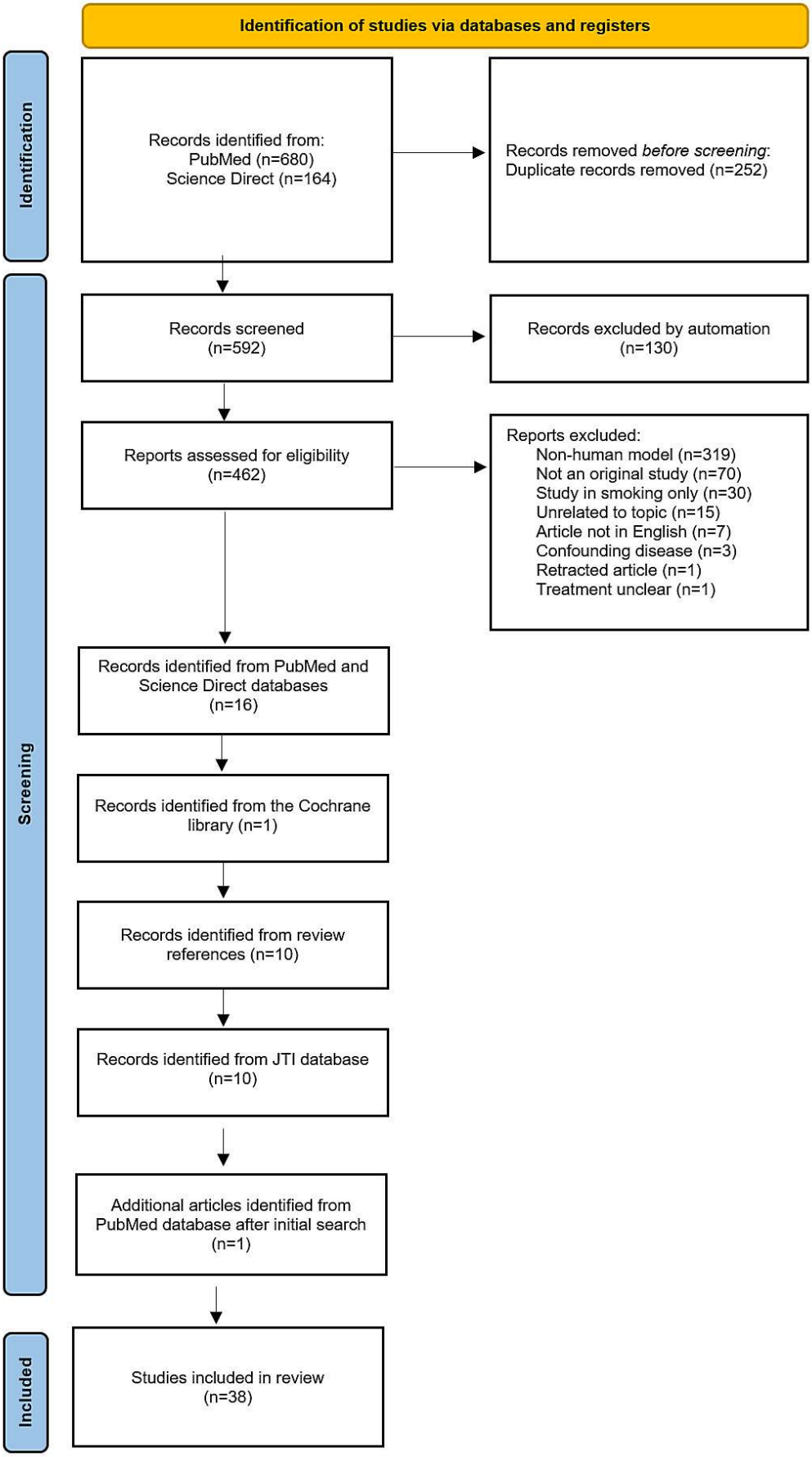


Figure 1. Flow diagram of study inclusion/exclusion. Modified from Page, M.J. *et al.*: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews; BMJ 372 (2021) n71. DOI: 10.1136/bmj.n71

LOUVET *et al.* used different sized nicotine patches to achieve a highest tolerable dose in participants with UC. After 4 weeks of use, a positive clinical effect was observed in nicotine-treated participants compared to placebo controls. In addition, a significant decrease in mucosal gene expression of interleukin (IL)-8 was found in those who showed the greatest nicotine response (19). Interleukin expression was also altered in blood mononuclear cells of healthy volunteers after 4 weeks of nicotine exposure *via* patch (20). Cells were cultured after isolation so the effect must be interpreted cautiously; however, a significant decrease in IL-2 was observed in participants who received nicotine *vs*. placebo control. IL-8 was not measured in this study and the isolation of a different cell type may preclude any comparison with results from LOUVET *et al.*

An oral formulation known as 'Nicolon' was designed to deliver sustained levels of nicotine directly to the ileum and colon over a six-hour period as an alternative to nicotine enemas, nicotine chewing gum or transdermal nicotine patches (21). An initial investigation into its safety and tolerance in patients with inflammatory bowel diseases reported it to be a safe potential treatment but also noted that there was considerable variation in tolerance between patients (22). Although more participants were asymptomatic at the end of the study, compared to baseline, no conclusions regarding the efficacy of nicotine for the treatment of inflammatory bowel disease can be drawn from this preliminary study as no placebo control participants were included. The researchers stated that "*there may be a role for oral nicotine therapy in inflammatory bowel disease, particularly as an adjunct to standard therapy; controlled trials in defined patient groups are needed to evaluate this, possibly using the maximum tolerated dose for individual patterns*" (22). To date, no such controlled clinical trials have been published.

COULIE *et al.* carried out a small study in 13 patients with the hypothesis that the beneficial effects of nicotine observed in UC patients are not due to its anti-inflammatory action, but instead due to the stimulation of colonic motor function (23). Low-dose intravenous nicotine (equivalent to a 22 mg-nicotine patch) was administered, as well as a higher dose. The authors found that intravenous nicotine had a dose-dependent effect on colonic motor activity in healthy subjects. The lower dose was not associated with any changes in phasic colon contractility of colonic tone; however, the high dose induced a burst of high amplitude contractions and accelerated colonic transport followed by colonic relaxation. The authors suggest that the lack of changes in response to the lower dose of nicotine "*do not support the hypothesis that the beneficial therapeutic effects of nicotine in UC are consequent to its motor effects*" and suggest that the mode of nicotine delivery (transdermal *vs*. intravenous) may have an effect on which pathways are activated. They concluded "*we cannot completely exclude an effect of transdermal nicotine on colonic motor functions. Future studies are necessary to assess the effects of long-term transdermal nicotine on colonic transit and motility in healthy participants and in patients with UC, to dissect the effects of nicotine on inflammation and motility*" (23).

There are two meta-analyses currently available which have attempted to assess the efficacy of nicotine for achieving remission in UC patients.

The first meta-analysis, published as a Cochrane Review, investigated the efficacy of transdermal nicotine administration for induction of remission in UC (24). The authors only included randomized, controlled clinical studies in which patients with active mild to moderate UC were randomly allocated to receive transdermal nicotine patches (between 15 and 25 mg per day total dose), placebo or another pharmaceutical treatment (corticosteroids or mesalamine). The authors of the Cochrane Review identified nine studies, five of which met their inclusion criteria (18, 25–28) and four of which were excluded due to use of nicotine chewing gum (29), nicotine enemas (30, 31) or as a result of the fact that they investigated maintenance of remission rather than induction of remission (32). Four of these nine studies were excluded from this current systematic review as they did not meet the inclusion criteria (26, 28, 30, 31). A meta-analysis of two trials (25, 27) in which 71 patients were randomized to receive nicotine and 70 to receive placebo showed a statistically significant benefit for nicotine treatment. After four to six weeks of treatment, 19 of 71 patients treated with transdermal nicotine were in clinical remission compared to 9 of 70 treated with placebo (odds ratio of 2.56; 95% CI of 1.02 to 6.45). A further 29 of the 71 patients assigned to receive nicotine showed signs of improvement or remission compared to 14 of the 70 patients assigned to receive placebo (odds ratio of 2.72; 95% CI of 1.28 to 5.81). For patients with left sided colitis the odds ratio for improvement or remission was 2.31 (95% CI of 1.05 to 5.10). A meta-analysis of the three other trials where transdermal nicotine was compared to standard medical therapy (18, 26, 28) found no significant benefit for nicotine. After four to six weeks of standard therapy (oral prednisone or mesalamine), 34 of 63 patients were in clinical or sigmoidoscopic remission compared to 33 of 66 patients treated with transdermal nicotine (odds ratio of 0.77; 95% CI of 0.37 to 1.60). A meta-analysis of all five studies which included 137 patients treated with transdermal nicotine and 133 patients treated with a placebo or standard therapy demonstrated no statistically significant benefit of nicotine therapy (odds ratio of 1.23; 95% CI of 0.71 to 2.14). Patients treated with transdermal nicotine were significantly more likely to withdraw due to adverse events (odds ratio of 5.82; 95% CI of 1.66 to 20.47) and were significantly more likely to suffer from an adverse event (odds ratio of 3.54; 95% CI of 2.07 to 6.08), than patients treated with placebo or standard medical therapy. The authors of the Cochrane Review concluded that overall "*the results of this review provide evidence that transdermal nicotine is superior to placebo for the induction of remission in patients with UC. The review did not identify any significant advantage for transdermal nicotine therapy compared to standard medical therapy. Adverse events associated with transdermal nicotine are significant and limit its use in some patients*" (24).

The excluded study by THOMAS *et al.* investigated whether nicotine patches could be used to maintain remission in UC patients (32). Eighty participants were randomized to receive nicotine patches (n = 40) or a placebo patch (n = 40), although the drop-out rate was high with only 18 participants completing the trial from the nicotine treatment group and 20 in the placebo group. No difference was found in

the number of remissions between the groups, leading the authors to conclude that nicotine is ineffective as maintenance therapy for UC. This is in contrast to another study from the same group (included in the McGrath *et al.* meta-analysis (24), which showed a positive effect of nicotine as a treatment for active UC (26). Later, the authors used biopsy samples from their 1995 study to show that, although α3 nAChR are expressed on the mucosal epithelium in the colon of UC patients, nicotine patch application makes no difference to the levels of expression observed (33).

In the excluded study by Lashner *et al.*, seven UC patients were randomized to receive either nicotine gum or placebo gum for a two-week period followed by a crossover. The three participants who showed the largest improvement were all former smokers. Due to the mixture of responses shown by the participants, the authors recommend that nicotine therapy should be considered on a case-by-case basis (29).

The excluded study by Sandborn *et al.* investigated the effect of nicotine tartrate enemas in ten patients with active UC over a period of four weeks (34). Seven participants completed the study, of which five showed significant clinical improvement. As in the studies by Guslandi and Tittobello (17, 18), the participants continued receiving mesalazine, corticosteroids or both throughout the trial period. There were no placebo control participants.

The second meta-analysis investigated the efficacy and tolerability of nicotine preparations in inducing remission of UC (35). The authors included three placebo-controlled trials representing 233 patients with UC and two randomized controlled trials that compared nicotine to corticosteroids (prednisolone/prednisone) in 81 patients with UC (18, 25, 26, 27, 31). Two of these studies were excluded from this current systematic review as they did not meet the inclusion criteria (26, 31). The RR for clinical remission after nicotine administration compared to placebo was 1.40 (95% CI of 0.63 to 3.12; $p > 0.05$). The RR for experiencing an adverse event after nicotine administration compared to placebo was 1.95 (95% CI of 1.38 to 2.78; $p < 0.001$) and the RR for withdrawal from a study after nicotine administration compared to placebo was 3.44 (95% CI of 0.71 to 16.71; $p > 0.05$). The RR for clinical remission after nicotine administration compared to corticosteroid administration was 0.74 (95% CI of 0.50 to 1.09; $p > 0.05$) and the RR for withdrawal from a study after nicotine administration compared to corticosteroid administration was 2.28 (95% CI of 0.76 to 6.83; $p > 0.05$). The authors of the meta-analysis concluded that "*the findings from this meta-analysis do not support the efficacy or tolerability of nicotine preparations for induction of remission in UC*" (35).

- *Primary sclerosing cholangitis*

Twelve patients with Primary Sclerosing Cholangitis (PSC) were recruited into a randomized, double-blind, placebo-controlled study (36). Of the 12 patients, 11 were male and had a median age of 37 years. Six suffered from UC which was reported to have been in remission in all cases. All patients had been treated with ursodeoxycholic acid (UDCA; one of the key treatments currently prescribed for PSC) for at least six months without normalization of alkaline phosphatase, aspartate aminotransferase or alanine aminotransferase levels. The patients were randomized to receive either a transdermal nicotine patch (Nicorette®) or an identical placebo patch for eight weeks. After a washout period of four weeks, the patients were switched to the opposite treatment for a further eight weeks. The initial nicotine dose was 5 mg per day which was increased by 5 mg every three days until a maintenance dose of 15 mg was achieved. The patches were applied each day from 7am until 11pm. One patient developed *de novo* UC (but completed the study) and two patients did not complete the entire protocol due to intercurrent bacterial cholangitis. No statistically significant changes in pruritus (a common symptom observed in patients with PSC) or fatigue were observed during either treatment period although an increase in bodyweight was observed during the placebo treatment period only. Mean changes in serum liver hematological tests (bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase and bile salts) during nicotine patch treatment did not differ significantly from those during placebo treatment. Subgroup analysis for those patients with and without UC gave the same findings. The authors concluded that they "*found no evidence of a beneficial effect of short-term transdermal nicotine administration on symptoms and serum liver tests for PSC patients on UDCA maintenance therapy*" (36). Very similar results were found in another trial of eight patients with clinically defined PSC who were administered up to 24 mg oral nicotine per day. No change was observed in any of the liver parameters measured and the authors concluded "*The results of this pilot study suggest that nicotine is not effective in the treatment of primary sclerosing cholangitis*" (37).

- *Post-operative ileus*

Post-operative ileus is an inflammatory response triggered by the manipulation of the intestines during abdominal surgery. A double-blind randomized control trial was carried out to assess the safety and efficacy of nicotine chewing gum in patients undergoing colorectal surgery, compared to chewing gum without nicotine. Forty patients were recruited, with 20 receiving the nicotine-containing gum and 20 receiving the non-nicotine-containing gum two hours preoperatively and three times per day postoperatively. The primary outcome was the post-operative time to first passage of feces and tolerance of solid food for at least 24 hours. Serum IL-6, C-reactive protein (CRP) and white blood cells count were also measured. No significant differences were observed in the recovery of the two groups. The authors suggest that this may be due to the low concentration of nicotine gum used in the study (2-mg Nicorette®), or that the patients were non-compliant, as they self-administered the gum during their hospital stay. No biochemical measurements were assessed to check patient participation (38).

Atherosclerosis

The six studies reviewed in this section are listed in Supplementary File 3.

The acute effects of nicotine on vascular function have been extensively investigated, whereby the mechanisms predominantly manifest through stimulation of the sympa-

thetic nervous system and activation of the hypophysis adrenal axis leading to increased plasma levels of adrenocorticotropic hormone (ACH), cortisol and adrenaline (39). The development of atherosclerosis, however, is a chronic process. Although definitive pathways relating nicotine to atherosclerosis have not been established, one proposed mechanism is through the recruitment of inflammatory cells via release of adhesion molecules (6). Evidence for this mechanism has been extensively provided though *in vitro* and *in vivo* animal models, however, human studies are rare. In all of the published studies, current smokers were recruited to take part, making it necessary to interpret all results with caution. One example is a placebo-controlled trial which investigated circulating adhesion molecules in healthy smokers after quitting with high dose transdermal nicotine patch or a placebo patch. After cigarette cessation, a dramatic decline in circulating soluble intracellular adhesion molecule-1 (sICAM-1), soluble CD44 splice variants sCD44v5 and sCD44v6 levels were observed, with no difference between those receiving nicotine patches and those receiving sham patches. The authors concluded "*as NRT did not influence the rapid decline in soluble adhesion molecule concentrations, this study provides strong in vivo evidence that it is a constituent(s) of tobacco smoke other than nicotine, or its metabolites, that is responsible for the elevated sICAM-1, sCD44v5 and sCD44v6 concentrations noted in habitual smoker*s" (40).

MOBARREZ *et al.* investigated the effect of acute exposure to nicotine-containing and nicotine-free e-cigarette vapor in 15 young healthy occasional smokers. Participants were required to abstain from any nicotine intake for two weeks prior to the trial, which was confirmed by biochemical testing. Four hours after 30 puffs of 3 s duration, an increase in extracellular vesicles derived from endothelial cells were observed. No increase was found when nicotine-free e-liquid was inhaled. Extracellular vesicles are known to have a variety of functions, including regulation of the inflammatory response; however, other than knowing the cell type of origin, this study did not allow any indication of the function(s) of the extracellular vesicles produced. The authors also acknowledged that the cigarette consumption of the participants may have influenced the results and the small number of participants means that the outcomes should be interpreted cautiously (41).

In another study in 23 young, healthy smokers, 24 h smoking abstinence with nicotine replacement therapy (NRT) did not result in a change to markers of inflammation such as C-reactive protein, monocyte chemo-attractant protein-1 (MCP-1), soluble intracellular adhesion molecule-1 (sICAM-1) or myeloperoxidase (MPO), or changes in flow mediated dilation (FMD). Co-administration of nicotine replacement therapy and γ-tocopherol-rich mixture of tocopherols (antioxidants) resulted in a significant decrease in FMD, suggesting that the mechanism was driven by oxidative stress, rather than inflammation in this study. The authors suggest that smokers who quit using NRT may limit any improvement of vascular endothelial function (42).

Contrary to this finding, serum levels of the inflammatory markers sICAM-1 and interleukin (IL)-1β decreased after three months when healthy male smokers transitioned to nicotine patches. Improvements were found in arterial stiffness; however, no change was observed in endothelial function. The authors concluded "*these findings indicated that NRT-assisted smoking cessation might have important beneficial effects in vascular function by the way of reducing the inflammatory process*"; however, it is not clear whether the improvement observed was due to nicotine or whether the reduction in the inflammatory effect of smoking led these changes (43).

A randomized, double-blinded, crossover trial in 17 healthy occasional users of tobacco products was carried out to investigate acute vascular and pulmonary effects of nicotine-containing e-liquids. After 30 puffs of an e-cigarette containing either nicotine or no nicotine, no difference was found in the exhaled marker of pulmonary inflammation, fractional exhaled nitric oxide. Although acute vascular response was measured, markers of vascular inflammation were not (44). These results repeated a finding from a previous study from the same group, where there was no difference in fractional exhaled nitric oxide or serum inflammatory-associated micro-vesicles found after 10 puffs of an e-cigarette containing nicotine. In this previous clinical trial, the authors did find a significant increase in endothelial progenitor cells (EPC) circulating after e-cigarette exposure; however, it is unclear if this increase related to an inflammatory response (45). In fact, the premise that increased circulating EPC levels indicated a pathological response was challenged by a letter to the editor pointing out that a reduction in circulating EPCs is usually associated with chronic diseases such as hyperlipidemia, hypertension, obesity and diabetes. Longer term interventions such as exercise and green tea consumption have also been shown to increase circulating EPCs (46). Overall, the relationship between EPC release into the bloodstream and inflammation or atherosclerosis is far from clear, especially considering the differences in acute and chronic responses (47).

Skin and healing

The five studies reviewed in this section are summarized in Supplementary File 3.

In a small study of ten participants, nicotine patches were applied before the skin was exposed to different irritants. The authors found that nicotine suppressed the inflammatory response to topical sodium lauryl sulphate and UV-B irradiation. No difference in cutaneous blood flow was observed (48). The authors point out that despite the therapeutic potential of transdermal nicotine in the context of inflammatory skin conditions, application in non-smokers could be limited due to the adverse events typically experienced in those not desensitized to nicotine.

A Japanese medical team demonstrated that transdermal nicotine patches were effective in the treatment of eosinophilic pustular folliculitis. Of the eight patients recruited, six showed significant clinical improvement; two were unchanged (49).

A systematic review highlighted six studies where smokers were randomized either to receive transdermal nicotine patches or complete nicotine abstinence post wound infliction (either surgical or as a controlled procedure). Different wound healing mechanisms seemed to be affected

both positively and negatively in the studies, making overall interpretation difficult. The authors concluded that "*nicotine appears to attenuate inflammatory wound healing mechanisms, compared to proliferative wound healing mechanisms including angiogenesis and collagen synthesis. Clinically, there is no evidence to suggest that nicotine administered as nicotine replacement drugs to abstinent smokers has a detrimental or beneficial effect on postoperative outcome of wound or tissue healing*". Smoking status was a significant confounder in these studies and could have led to the inconclusive result (50).

• *Behçet's disease*

Behçet's disease is a rare and poorly understood systemic vasculitis that results in inflammation of the blood vessels and tissues. The disease is characterized by periods of remission and exacerbation with symptoms including genital and oral aphthae.

Two non-smoking patients with Behçet's disease (among a larger group of ten patients) were given either a transdermal nicotine patch (14 mg per 24 h) or nicotine chewing gum (2 mg) (51). Use of a nicotine transdermal nicotine patch or the nicotine chewing gum resulted in complete resolution of oral lesions within a three-week period. It is not reported which patients were administered which product. In the first patient, who initially exhibited three oral lesions, a further three oral lesions developed once nicotine administration was stopped. No information is provided for the second patient. In a second study, five former smokers with active mucocutaneous lesions which were not responsive to standard pharmacological treatments, were treated with transdermal nicotine patches (52). The patients were administered 14 mg transdermal nicotine patches on a daily basis for six months. Four out of the five patients experienced complete resolution of mucocutaneous lesions within the six-month treatment period. Symptoms returned once nicotine administration was stopped in these individuals. One patient experienced no benefit from nicotine administration; she re-started smoking through her own choice after the six-month treatment period had ended and experienced complete resolution of oral aphthae and partial resolution of genital ulcers. The authors concluded that "*nicotine in its pure form is well tolerated and its use could be justified in selected cases of ex-smoker Behçet's disease patients with predominant and recurrent refractory mucocutaneous manifestations*". However, "*a randomized controlled trial including non-smokers would be required to establish the effective therapeutic role of nicotine in Behçet's disease*" (52).

Pain and infection

The four studies reviewed in this section are listed in Supplementary File 3.

Twenty healthy non-smokers were randomized and blinded to receive either a nicotine patch or a placebo patch during their recovery from third molar tooth removal. During the post-operative period, the participants who had received the nicotine patches were administered significantly fewer analgesic tablets compared to the placebo control group (mean 2.35 *vs*. 4.35, respectively; $p = 0.026$) and rated their recovery as more satisfactory than those who received the placebo. Swelling was also reduced during the first 72 h post-surgery, indicating an anti-inflammatory effect in the patients who received the nicotine patch (53). The authors suggest that the nicotine patch is the most effective mode of administration as peak plasma concentration occurs at around the same time as peak post-operative pain and initiation of the inflammatory response.

Infection with gram negative bacteria, such as *E. coli* and *Salmonella* induces a strong immune response via interaction of lipopolysaccharides (LPS) on the bacterial outer membranes with various immune cells such as monocytes and macrophages, leading to release of pro-inflammatory cytokines. In a small study, 11 healthy, young male volunteers were exposed to intravenous LPS whilst wearing a nicotine patch or a placebo dressing. After LPS administration, the authors showed that all participants had similar increased concentrations of plasma inflammatory cytokines TNF-α, IL-6 and IL-8; however, those participants who were pre-treated with nicotine patches returned to baseline levels of inflammatory cytokines TNF-α and IL-6 at a faster rate. The authors propose that nicotine administration could aid in a faster resolution of inflammation in patients with systemic endotoxemia (54). In a similar study, 17 healthy, non-smoking males aged 18 to 35 were included in an LPS administration model of systemic inflammation with a nicotine patch intervention. Unlike the WITTEBOLE study (54), the participants were not blinded to their treatments nor was there a placebo control group, and the authors found no effect of nicotine on cytokine release or pain perception after LPS administration (55).

A Cochrane Review investigated the effect of transdermal or intranasal nicotine administration on post-operative pain, opioid analgesic use and opioid-related adverse events (12). The meta-analysis identified nine randomized, placebo-controlled studies including a total of 666 patients. Nicotine was estimated to reduce post-operative pain scores at 24 h post-surgery by a small, but statistically significant, amount compared with placebo (mean difference of −0.88 on a 0 to 10 scale; 95% CI of −1.58 to −0.18; eight studies). Statistical heterogeneity was substantial and not adequately explained by stratification of studies according to type of surgical procedure, smoking status of the patient, method of nicotine administration or timing of nicotine administration. Nicotine increased the risk of post-operative nausea to a statistically significant extent (relative risk of 1.24; 95% CI of 1.03 to 1.50; seven studies). However, it did not increase the risk of vomiting (risk difference of 0.03; 95% CI of −0.04 to 0.09; seven studies). The authors of the meta-analysis concluded that "*nicotine may reduce post-operative pain at twenty-four hours [post-surgery] compared to placebo but the effects were relatively small (less than one point on a ten-point pain scale)*" and "*nicotine does not appear to reduce post-operative use of opioids or opioid-related adverse events but probably increases the risk of nausea*" (12).

Pulmonary sarcoidosis

The three studies reviewed in this section are listed in Supplementary File 3.

Pulmonary sarcoidosis is a systemic granulomatous disease of unknown cause which affects young to middle-aged

adults. It is characterized by the development of non-necrotizing granulomatous inflammation in the absence of identifiable infectious, autoimmune or environmental causes (56). The disease typically involves the lungs, frequently leading to impaired exercise tolerance and associated shortness of breath. The majority of patients with active pulmonary sarcoidosis complain of overwhelming fatigue which often persists despite immune-modulating drugs typically used to treat sarcoidosis (56).

A pilot study noted that treatment of symptomatic pulmonary sarcoidosis patients (n = 7) with transdermal nicotine patches over a twelve-week period, in addition to their existing medications, resulted in an immunological phenotype which was highly comparable to that of asymptomatic patients (57). The daily nicotine dose was increased from 7 mg to 14 mg to 21 mg at one-week intervals from the start of the study. The authors concluded that their results "*supported the notion that nicotine treatment may be beneficial in this patient population*".

CARLENS *et al.* carried out a large study investigating chronic inflammatory disease in a cohort of Swedish construction workers, the results of which have been included in several sections of this review. Within that study, there was no effect of exclusive use of Swedish snus on the risk of developing sarcoidosis compared to never use of any tobacco product (14).

A study protocol for a randomized, double-blind, placebo-controlled clinical trial investigating the effect of transdermal nicotine patch administration as a treatment approach for pulmonary sarcoidosis has been published (56). The primary objective outcome of the study was reported as being an improvement in forced vital capacity at study week 26 from baseline measurements. Results from this clinical trial have recently been published and indicated that treatment with transdermal nicotine patches (21 mg daily) over a 26-week period was associated with a clinically significant, approximate 2.1% (70 mL) improvement in forced vital capacity (FVC) from baseline to 26 weeks (58). FVC decreased by a similar amount (2.2%) in the placebo group with a net increase of 140 mL (95% confidence intervals of 10 mL to 260 mL) when comparing nicotine and placebo treatment groups at 26 weeks. No improvements were observed in lung texture scores, fatigue assessment scores, St George's Respiratory Questionnaire Score or the Sarcoidosis Assessment Tool. The study was, however, underpowered to show the expected treatment effect for nicotine treatment, and despite randomization there were large baseline differences in FVC.

Multiple sclerosis

The three studies reviewed in this section are listed in Supplementary File 3.

In their 2009 study, HEDSTRÖM *et al.* showed that there was an increased risk of developing multiple sclerosis (MS) in smokers, which did not reflect the risk seen in snus users, even when adjusted for smoking. In fact, the results suggested snus use may have an inverse association with development of the disease compared to never users of snus (59). Data from their follow-up study from two Swedish population-based case-control studies was used to estimate the association between snus use and risk of developing MS. The combined studies had a total of 7,883 cases and 9,437 controls respectively and were matched for age, gender and residential area. Of these participants, 223 cases and 392 controls used snus but had never smoked. Results indicated that these exclusive snus users had a statistically significant decreased risk of developing MS compared to those who had never used snus (odds ratio of 0.75; 95% CI of 0.63 to 0.90). An inverse dose-response correlation between cumulative dose of snus use and the risk of developing MS was also observed. The authors concluded that they had "*found clear evidence of an inverse dose-response correlation between cumulative dose of snuff [snus] use and the risk of developing multiple sclerosis. Nicotine, by targeting alpha 7 nicotinic receptors, exerts anti-inflammatory and immune-modulation effects in a way that might decrease the risk of developing multiple sclerosis*" (60).

In contrast to this finding, a study investigating chronic inflammatory disease in Swedish construction workers, reported that exclusive use of Swedish snus was associated with a marginally increased risk of MS compared to never tobacco users (relative risk of 1.8; 95 % CI of 1.1 to 2.9) (14). The authors could not offer an explanation for their findings, although they did point out that they had limited information about other risk factors for disease in their participants and the result was of "*borderline statistical significance*", and therefore, may be due to unknown confounding.

DISCUSSION

Digestive diseases

UC dominated the literature related to digestive diseases, contributing 14 studies out of the 19 studies analyzed in this section. Each of the studies varied greatly in terms of participant number, study design and study endpoints. Two meta-analyses were carried out. MCGRATH *et al.* focused on whether nicotine had an effect on achieving remission in UC patients (24) whereas NIKFAR *et al.* aimed to assess the efficacy and tolerability of nicotine whilst also achieving remission in UC patients (35). Both studies included five clinical trials in their analysis and had four in common. Despite these similarities, the authors drew different conclusions, with MCGRATH *et al.* finding that nicotine was significantly better than placebo for achieving remission although there was little clinical advantage for its use, whereas NIKFAR *et al.* concluded that their data did not support a role for nicotine in achieving remission in UC patients. The high number of adverse events and withdrawals in relation to nicotine application may explain these differences in conclusion.

Studies investigating nicotine in relation to clinical improvements in patients with UC seem to more consistently suggest a beneficial role of nicotine, especially when used in conjunction with traditional therapies such as mesalazine and corticosteroids (17, 18, 34). As LASHNER *et al.* pointed out in their study, it seems that nicotine can elicit an anti-inflammatory response in some UC patients, however, its use is probably most appropriately assessed on a case-by-case basis (29). Mode of delivery and dose are also key to

the effects and adverse effects observed, although a change in interleukin 2 and 8 expression in response to nicotine does support an anti-inflammatory role within the context of UC as a disease (19, 20).

In contrast to the relatively large body of evidence surrounding the use of nicotine as a treatment in patients with UC, very few studies have been published in relation to other digestive diseases. INGRAM *et al.* (13) reported clinical improvement in ten patients with Crohn's disease who were treated with nicotine enemas and CARLENS *et al.* (14) reported no increased risk of developing Crohn's disease in exclusive users of Swedish snus. These two studies are insufficient to support an inflammatory role of nicotine, pro- or anti-.

Two studies investigated the use of nicotine as a treatment for primary sclerosing cholangitis, one using transdermal treatment (36) and the other oral treatment (37). VLEGGAAR *et al.* (36) showed no significant effect of nicotine in their participants. ANGULO *et al.* (37) saw almost all of their participants drop-out of their already small study, suffering adverse effects. Although both negative, only 20 participants were included across both studies combined, therefore leaving the question of whether nicotine could be an effective treatment for PSC unanswered.

Finally, in this section a single study assessed whether nicotine could reduce the inflammatory response in the gut post-surgery. Nicotine gum was used as the mode of delivery; however, no overall benefit was seen in the 40 participants who took part.

Atherosclerosis

Six papers were analyzed in relation to the potential effects of nicotine on atherosclerosis via inflammatory pathways. All the studies recruited current smokers and therefore the results are heavily confounded. Three of the studies investigated acute cardiovascular responses after use of electronic cigarettes as their mode of nicotine delivery, measuring markers of endothelial function such as endothelial progenitor cells and extracellular vesicles (41, 44, 45). Unfortunately, the full characteristics of the measured biomarkers are not known, so it is impossible to conclude whether the effects observed are pro- or anti-inflammatory in nature.

Two studies found no effect of nicotine replacement therapies on inflammatory markers associated with atherosclerotic formation (40, 42). One study found a beneficial effect of nicotine replacement therapies on markers of vascular inflammation compared to continued smoking. This is not necessarily surprising, given the relationship between smoking and cardiovascular disease (61); however, as there was no comparator group of never smokers, it is impossible to state that the decrease in inflammatory markers observed was as a result of nicotine administration or as a result of the removal of other pro-inflammatory agents found in cigarette smoke (43).

Overall, the data surrounding the relationship between nicotine and atherosclerosis is inconclusive. Mechanisms have been proposed via *in vitro* and *in vivo* animal studies involving particularly the activation of α7 nicotinic receptors. However, there is also conflicting evidence arising from these models (39). Longitudinal studies in human participants that consider smoking history will be necessary to assess the risk of atherosclerosis in relation to nicotine use and inflammation.

Skin and healing

Five studies addressed the effect of nicotine on inflammatory conditions of the skin, although these were spread across a range of conditions. Two very small studies in participants with Behçet's disease both described positive clinical outcomes when nicotine was administered via transdermal patch or gum (51, 52). In two other studies that used transdermal patch administration, an anti-inflammatory effect of nicotine was shown in response to dermal irritation and to symptoms of eosinophilic pustular folliculitis (48, 49). A systematic review of the effect of nicotine on wound healing, however, showed mixed results. Analysis of six studies suggested that nicotine may have an anti-inflammatory effect on the wound healing process, whilst maintaining other proliferative and angiogenic mechanisms. Overall, no beneficial or detrimental effect was recognized (50).

Although there was an anti-inflammatory effect of nicotine observed in all five of the studies included in this section, the small study sizes and confounding smoking histories of the participants mean that the evidence is insufficient to support an anti-inflammatory effect of nicotine on human skin conditions or healing.

Pain and infection

Three small studies (maximum participant number = 20) were reviewed in relation to pain and infection. One study related to post-operative pain management and reported positive outcomes of nicotine administration on both pain and oedema. Two studies used a LPS administration as a model of systemic inflammation; the first showed no effect of nicotine patch application on relieving any of the associated symptoms; the other showed a faster resolution of inflammation in the participants who received nicotine patch treatment. A fourth study reviewed in this section was a Cochrane systematic review and meta-analysis, which analyzed nine studies with a total of 666 participants and concluded that there was a small but positive effect of nicotine on post-operative pain. Although these results support an anti-inflammatory role for nicotine in the resolution of pain and infection, it should be noted that adverse effects of nicotine were repeatedly cited. Nicotine administration in never smokers can lead to symptoms of mild nicotine adverse effects, such as nausea, vomiting and increased heart rate, which unless managed with careful dosing, is likely to nullify the positive effects of nicotine over the use of other established analgesics.

Pulmonary sarcoidosis

Three studies regarding pulmonary sarcoidosis were identified. Two addressed treatment of active symptoms with transdermal nicotine patches (57, 58) and the other investigated the risk of developing pulmonary sarcoidosis in users of nicotine-containing products (14). As in the studies that suggested improvement of inflammatory skin

conditions with nicotine application, significant clinical improvement was observed in the small group of patients treated with nicotine for their pulmonary sarcoidosis. No effect on the risk of developing pulmonary sarcoidosis was seen in the 37,459 cohort participants who exclusively used snus. The results of these three separate studies cannot be compared as the risk of developing disease is a distinct process from treatment of symptoms when disease has already manifested.

Multiple sclerosis

Three studies were analyzed in relation to nicotine use and risk of developing MS, all of which were carried out in Swedish cohorts and all investigated snus as the mode of nicotine delivery (14, 59, 60). Despite the similarities in the studies, conflicting results were found. HEDSTRÖM *et al.* (59) reported an inverse relationship between snus use and onset of MS, compared to CARLENS *et al.* (14) who showed a marginally increased risk of developing MS in exclusive snus users compared to never users of any tobacco product. The authors point out that their findings may be as a result of residual confounding. It should also be noted that although snus offers a method of nicotine delivery that is devoid of smoke, other tobacco constituents are also present within the product, meaning that the role of nicotine in complete isolation cannot be elucidated. In addition, correlations between product use and inflammatory disease risk investigated in these studies were not supported by any investigation into the levels of inflammatory markers in any of the participants, leaving a large piece of the puzzle missing.
The role of nicotine in the development of MS remains unclear. No studies exist in humans where nicotine is administered as a potential treatment of MS symptoms, and therefore its role in the inflammatory pathways of this disease remains unknown.

STUDY LIMITATIONS

Although multiple databases were searched, there is the possibility that some studies, especially those only included on clinical trial databases, may have been missed from the analysis. This review was not pre-registered and a protocol was not prepared. Many of the studies included in this systematic review were small, pilot trials carried out in a convenience sample of participants with no placebo controls. For this reason, most are considered of low quality and are open to a high chance of recruitment bias. Therefore, significant caution should be used in their interpretation. Studies such as these can only be regarded as preliminary evidence as the improvement in the reported clinical condition may be due to a pharmaceutical or environmental variable not reported by the patient(s) to the authors rather than being a direct result of nicotine administration. In addition, there is a possibility that publication bias may be present in the reported studies. Furthermore, since inflammation is an orchestrated dynamic process with various phases involving a wide variety of cell types, cytokines, and biochemical mediators with pleiotropic and redundant functions it is possible that nicotine may differentially modulate these mechanisms leading to variable apical effects on different types of inflammatory processes. For instance, one potential effect is that nicotine increased corticosteroids release which decreased the severity of the inflammatory conditions. In addition, the action of the α7 nicotinic acetylcholine receptor involved in the "cholinergic anti-inflammatory pathway" may also contribute. On the other hand, proinflammatory effects mediated through other nicotinic receptors in cells involved in inflammation may counteract those anti-inflammatory mechanisms.
Randomized, double-blind, placebo-controlled clinical studies are required for each of these disease states to determine whether or not nicotine administration does have a pro- or anti-inflammatory effect allowing statistically significant differences between treatment arms to be determined.
The role of nicotine and inflammation in the progression of COVID-19 in humans was eventually considered. Unfortunately, we found the publications list returned from our search essentially not complying with our manuscript inclusion and exclusion criteria, and thus have not addressed any additional content regarding issues related to animal models of COVID-19 human disease, as this subject falls beyond the scope of the paper.

CONCLUSIONS

This literature review analyzes detailed clinical scientific articles which have investigated whether controlled administration of nicotine can result in a pro- or anti-inflammatory effect in individuals with inflammatory-based diseases or conditions. There was weak evidence for an anti-inflammatory effect of nicotine when used to treat some dermatological conditions. However, the studies included were not able to offer strong enough data to draw a definitive conclusion. For other diseases, no consistent evidence of a pro- or anti-inflammatory effect of nicotine was observed in patients with atherosclerosis, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis, postoperative ileus, pain, infection, Behçet's disease or other dermatological conditions, pulmonary sarcoidosis or multiple sclerosis.

AUTHOR CONTRIBUTIONS

LP: Planning, literature searching, analysis, draft preparation, editing
KT: Analysis, draft preparation, editing
JM: Conceptualization, draft preparation, supervision, editing

CONFLICTS OF INTEREST

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SUPPLEMENTAL INFORMATION

Supplementary File 1 - Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 Checklist

Supplementary File 2 - Details for inclusion/exclusion after searches across PudMed and ScienceDirect

Supplementary File 3 - List of publications reviewed in relation to the various diseases