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Dietary factors in nonalcoholic fatty liver disease: impacts on human and animal health - a review

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Non-alcoholic fatty liver disease (NAFLD) is defined as a clinical syndrome characterized by excessive fat accumulation in liver, predominantly influenced by dietary choices. This study provides an extensive quantitative literature analysis on dietary influences on NAFLD. Bibliometric data were collected through the search string TOPIC = ("NAFLD*" OR "nonalcoholic fatty liver*" OR "non-alcoholic fatty liver*") AND TOPIC = ("diet*" OR "nutrition*" OR "food*" OR "feed*"), which yielded 12,445 publications indexed within the Web of Science Core Collection. Utilizing VOSviewer software, term maps were generated to visually illustrate recurring phrases alongside citation data. The literature, which has seen exponential growth since the 2010s, predominantly

consists of original articles, with a ratio of 4.7:1 compared to reviews. Notably, the significant contributors to this field were China and the United States. The majority of publications were found journals specialized in Gastroenterology & Hepatology, Nutrition & Dietetics, Biochemistry & Molecular Biology, Endocrinology & Metabolism, and Pharmacology & Pharmacy. Key dietary compounds/compounds classes such as resveratrol, polyphenols, curcumin, berberine, quercetin, flavonoids, omega-3 fatty acids, docosahexaenoic acid (DHA), genistein, and palmitic acid were frequently mentioned and cited. Many of them were demonstrated to have some potential benefits on NAFLD, both in human and animal studies.

KEY WORDS: NAFLD / obesity / liver / resveratrol / curcumin / bibliometrics / Web of Science / VOSviewer

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinical syndrome characterized by excessive fat accumulation in liver [Loomba and Sanyal 2013, Rizzo *et al*. 2023]. It is now the leading cause of liver diseases globally, with its prevalence on the rise [García-Compeán and Jiménez-Rodríguez 2022, Loomba and Sanyal 2013]. NAFLD is diagnosed when steatosis affects more than 5% of hepatocytes, in individuals consuming less than 20 g of ethanol daily [Eslam *et al*. 2020, Loomba and Sanyal 2013, Rizzo *et al*. 2023].

The disease progresses in two main stages [Loomba and Sanyal 2013]. The initial stage, non-alcoholic fatty liver (NAFL), is considered reversible. However, the advanced stage of NAFLD, non-alcoholic steatohepatitis (NASH), involves irreversible liver changes, such as fibrosis, which can lead to cirrhosis and hepatocellular carcinoma (HCC) [García-Compeán and Jiménez-Rodríguez 2022, Loomba and Sanyal 2013, Rizzo *et al*. 2023]. Approximately 25% of the adult population is affected by NAFLD, with one-fifth of these cases progressing to NASH [García-Compeán and Jiménez-Rodríguez 2022, Lazarus *et al*. 2022].

End-stage liver disease is associated with high patient mortality [Jahn *et al.* 2019, Lazarus *et al*. 2022]. Numerous studies have explored NAFLD using animal models and human subjects, but no pharmacotherapy has been confirmed to halt disease progression [Jahn *et al*. 2019]. Currently lifestyle changes including dietary modification and increased physical activity, are the most established interventions against NAFLD [Rizzo *et al*. 2023]. Thus, more research is essential to develop effective therapies [Jahn *et al*. 2019].

In animal research, the development of fatty liver is significant not only for modelling human NAFLD but also in the context of farming and animal welfare. For instance, a study by Remignon and Burgues [Remignon and Burgues 2023] on ducks force-fed for 10 days and used to produce the delicacy “foie gras”, found rapid oxidative stress in the liver cells, similar to NAFLD in humans, and reflected by elevated liver biomarkers [Remignon and Burgues 2023].

One of the primary drivers triggering the development of NAFLD is improper diet, which can lead to obesity, insulin resistance, and type 2 diabetes [Moore *et al.* 2020, Vancells Lujan, Vinas Esmel, and Sacanella Meseguer 2021]. Diets high in calories, simple sugars, saturated fatty acids, and low in polyunsaturated fatty acids and fiber increase the risk of NAFLD [Vancells Lujan, Vinas Esmel, and Sacanella Meseguer 2021]. The only confirmed treatment of NAFLD is dietary modification and increased physical activity to reduce body weight [Haigh *et al*. 2022, Moore *et al*. 2020, Vancells Lujan, Vinas Esmel, and Sacanella Meseguer 2021]. Such view has been also endorsed by authoritative international communities – the American Association for the Study of Liver Diseases and the European Association for the Study of Liver Diseases (EASL), which have dedicated two practical guidelines to non-alcoholic fatty liver disease [Chalasani *et al*. 2018, European Association for the Study of The Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity 2016]. Along this line, European experts believe that patients with NAFLD do not need pharmacotherapy. Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression (i.e., with diabetes, metabolic syndrome, persistently increased ALT, high necroinflammation) could also be candidates to prevent disease progression. While no firm recommendations can be made, pioglitazone (most efficacy data, but off-label outside T2DM) or vitamin E (better safety and tolerability in the short-term) or their combination could be used for NASH. Statins may be confidently used to reduce LDL-cholesterol and prevent cardiovascular risk, with no benefits or harm on liver disease. Similarly, n-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH. European experts also emphasize: "Cardiovascular disease is a more common cause of death than liver disease in NAFLD", thus indicating the need for timely diagnosis and adequate treatment of comorbidity. Despite the formulated recommendations outlined above, EASL experts encourage further clinical trials. No drug has currently been tested in phase III trials and is approved for NASH by regulatory agencies. However, a large number of pharmacological agents are now in the clinical stage. Pharmaceutical agents considered to be potentially effective are: weight-loss drugs, hypoglycemic agents, hypolipidemic drugs, antioxidants (e.g., vitamin E), hepatoprotectors (e.g., ursodeoxycholic acid), etc. [Borisov *et al.* 2023, Bril *et al.* 2019, Chalasani *et al.* 2018, Musso *et al*. 2017, Newsome *et al*. 2021, Sanyal *et al.* 2010, Simental-Mendía *et al*. 2020]. Raising awareness, early intervention, and combining effective lifestyle modification with pharmacological approaches is expected to radically change the course of NAFLD in the future. On this background, lifestyle modification remains the cornerstone of the prevention and treatment of NAFLD and all patients with NAFLD are advised to modify their diet and increase aerobic exercise.

The most promising nutritional scheme in NAFLD appears to be the Mediterranean diet, which is rich in fresh vegetables, fruits, legumes, nuts, whole grains products, fish and olive oil, and moderate in poultry, eggs, dairy products, and red wine [Moore *et al*. 2020, Suárez *et al.* 2017, Vancells Lujan *et al*. 2021]. This diet is ranked as the top choice for counteracting NAFLD because it has lots of antioxidants, fiber, the right balance of omega 3 to omega 6 fatty acids, and the low amount of saturated fatty acids and simple sugars [Suárez *et al*. 2017]. In addition, the simultaneous adherence to the principles of the Mediterranean diet along with the reduction of calorie intake may be an effective measure in managing NAFLD [Haigh *et al*. 2022].

Unfortunately, there is still a lack of reliable evidence regarding specific dietary ingredients that could be supplemented and be an effective non-pharmacological treatment of NAFLD [Vancells Lujan *et al*. 2021]. For this reason, in the perspective of natural products applications and integrated therapy approach [Atanasov *et al.* 2021, Singla *et al.* 2023] the impact of individual nutraceuticals has been intensively studied for years in order to find the optimal strategy in the fight against NAFLD [Rizzo *et al.* 2023, Suárez *et al.* 2017]. Research continues in potential dietary solutions, including omega-3, silymarin, berberine, curcumin, coenzyme Q10, and vitamin E – especially in combination with ursodeoxycholic acid [Tewari *et al*. 2017, Humminiecki, Horbańczuk 2018, Wang *et al.* 2018, 2020, Yeung *et al.* 2018, 2019, 2020ab, 2021ab, 2022, Chao *et al*. 2021, Mozos *et al*. 2021, Chopra *et al*. 2022, Rizzo *et al*. 2023].

Given the importance of this condition, a bibliometric study was undertaken to obtain a broad-range of qualitative and quantitative data from the existing literature [Yeung *et al*. 2021] and to further understand potential dietary interventions for NAFLD.

Material and methods

The Web of Science (WoS) Core Collection online literature database was queried on 15 August 2023 with the following search string: TS = (“NAFLD*” OR “nonalcoholic fatty liver*” OR “non-alcoholic fatty liver*”) AND TS = (“diet*” OR “nutrition*” OR “food*” OR “feed*”). This strategy could identify papers listing these words and their derivatives in their titles, abstracts, and/or keywords. The query returned 12,445 papers. No additional filter was applied to limit the search (Tab. 1). After obtaining the basic publication and citation data from the WoS database, the full records of the 12,445 papers were exported to VOSviewer [van Eck and Waltman 2009], a software for further bibliometric analyses. A term map visualizing phrases recurring in >1% (n = 125) of the titles and abstracts of the 12,445 papers was produced to reveal which phrases had higher citations per paper (CPP) than others. A similar term map was generated to visualize author keywords that appeared in >0.1% (n = 13) of the papers. Apart from these threshold settings, default settings were used in VOSviewer to generate the term maps.

Table 1. The search strategy in Web of Science literature database.

Filter	Details
Databases searched	Science Citation Index Expanded (1970–present) Social Sciences Citation Index (1956–present) Arts & Humanities Citation Index (1975–present) Conference Proceedings Citation Index – Science (2009–present) Conference Proceedings Citation Index – Social Science & Humanities (2009–present) Emerging Sources Citation Index (2005–present)
Search string	("NAFLD*" OR "nonalcoholic fatty liver*" OR "non-alcoholic fatty liver*") AND ("diet*" OR "nutrition*" OR "food*" OR "feed*")
Fields searched	Topic field (i.e., title, abstract, and keywords)
Timespan	All years (1956–present)

Results and discussion

The 12,445 papers were cited a total of 408,531 times. Both the publication and citation counts have experienced exponential growth since the 2010s (Fig. 1). Three-quarters of the papers were classified as original articles by WoS (n = 9660, 77.6%, CPP = 30.4) and the rest were mainly reviews (n = 2068, 16.6%, CPP = 53.8). The original article-to-review ratio was 4.7:1. The top 5 most productive affiliations, countries, journals, and journal categories are listed in Table 2. China (n = 3357, CPP = 21.6) and the United States (n = 3190, CPP = 52.0) each contributed to around 25% of the papers, with their leading affiliations being Shanghai Jiao Tong University (n = 208, CPP = 31.0) and University of California system (n = 317, CPP = 72.9), respectively. The leading roles of China and the United States were similarly observed

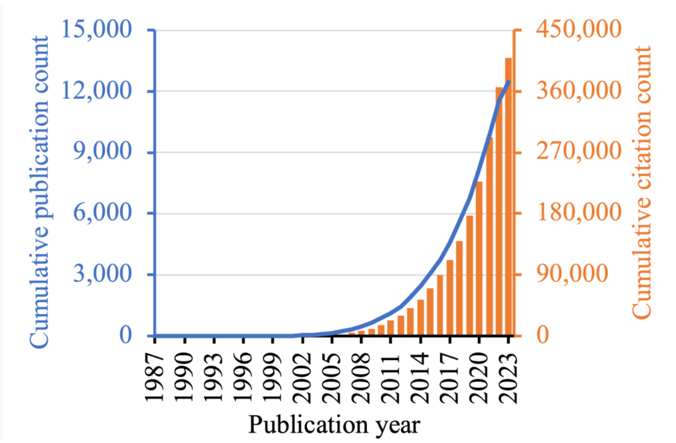

Fig. 1. Cumulative publication and citation counts.

Table 2. The top-five most productive affiliations, countries, journals, and journal categories

Item	Number of papers (% of 12,445)	Citations per paper (CPP)
Affiliation		
University of California system	317 (2.5)	72.9
Centro de Investigación Biomédica en Red (CIBER, Spain)	245 (2.0)	46.4
US Department of Veterans Affairs	224 (1.8)	69.1
Harvard University	211 (1.7)	61.5
Shanghai Jiao Tong University	208 (1.7)	31.0
Country		
China	3357 (27.0)	21.6
United States	3190 (25.6)	52.0
Italy	921 (7.4)	49.7
South Korea	769 (6.2)	24.2
Japan	724 (5.8)	31.9
Journal		
Nutrients	488 (3.9)	20.3
Hepatology	381 (3.1)	82.9
Journal of Hepatology	270 (2.2)	80.5
International Journal of Molecular Sciences	263 (2.1)	23.2
Scientific Reports	201 (1.6)	28.4
Journal category		
Gastroenterology & Hepatology	2590 (20.8)	56.0
Nutrition & Dietetics	2040 (16.4)	25.6
Biochemistry & Molecular Biology	1906 (15.3)	28.2
Endocrinology & Metabolism	1299 (10.4)	36.3
Pharmacology & Pharmacy	1299 (10.4)	20.6

for the overall NAFLD literature [Putri *et al.* 2015] as well as a subset focusing on the gut-liver axis [Yang *et al*. 2023]. Before the mid-2010s, Japan and Italy were more productive than China in publishing NAFLD papers in general [Zhang *et al*. 2015]. In the 2010s, China was the most productive country surpassing even the United States in terms of the overall NAFLD literature [Li *et al*. 2023]. Nutrients was the most productive journal (n = 488, CPP = 20.3), but Hepatology received the highest CPP among the top 5 journals (n = 381, CPP = 82.9). Overall, papers published in Gastroenterology & Hepatology journals (n = 2590, CPP = 56.0) had higher CPP than other most productive journal categories such as Nutrition and Dietetics (n = 2040, CPP = 25.6).

Figure 2 shows a term map that visualized the recurring terms in the titles and abstracts of the papers. Some of the most recurring terms located around the center of the map included obesity (n = 3711, CPP = 42.2), and high-fat diet (n = 3684, CPP = 25.0). Upon closer examination (Tab. 3), the terms with the highest CPP were hyperinsulinemia (n = 144, CPP = 73.6) and hepatic insulin resistance (n = 155, CPP = 69.5). In fact, the most cited paper among the analyzed dataset was a study that traced 9 patients for several days to identify the sources of fatty acids stored in their liver, with results showing that 15% of the liver triacylglycerol came from dietary fatty acids [Donnelly et al. 2005] (2358 citations). The 7th most cited paper surveyed 328 patients and found that NAFLD was associated with hypertension, diabetes, higher body-mass index, more frequent consumption of fast food, and less physical exercise [Williams *et al.* 2011] (1517 citations).

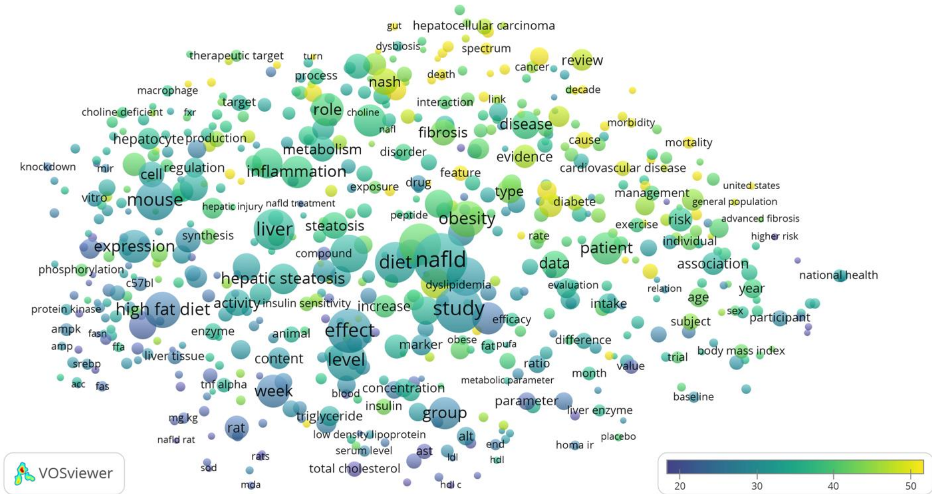

Fig. 2. Term map of recurring terms in the titles and abstracts of the papers. The node color represents the citations per paper (CPP) of the terms, whereas the node size represents the number of papers, and the inter-node distance represents how frequently the terms co-occurred with each other in the same papers.

Table 3. Top 20 medical terms with highest citation per paper (CPP) identified from the titles and abstracts of the papers

Medical term	Number of papers (% of 12,445)	Citations per paper (CPP)
Hyperinsulinemia	144 (1.2)	73.6
Hepatic insulin resistance	155 (1.2)	69.5
Liver biopsy	361 (2.9)	69.3
Liver transplantation	156 (1.3)	67.4
Kupffer cell	159 (1.3)	62.4
Simple steatosis	369 (3.0)	60.3
Cytokine	352 (2.8)	60.1
Gut	217 (1.7)	59.8
Lipotoxicity	249 (2.0)	59.6
Lifestyle modification	291 (2.3)	57.7
Mortality	469 (3.8)	57.4
Choline	144 (1.2)	56.5
Disease progression	308 (2.5)	56.1
Cirrhosis	999 (8.0)	54.9
Nonalcoholic steatohepatitis	1264 (10.2)	54.8
Liver fat	239 (1.9)	53.7
Etiology	220 (1.8)	53.6
Comorbidity	265 (2.1)	52.6
Hepatic manifestation	209 (1.7)	52.5
Adiposity	311 (2.5)	51.7

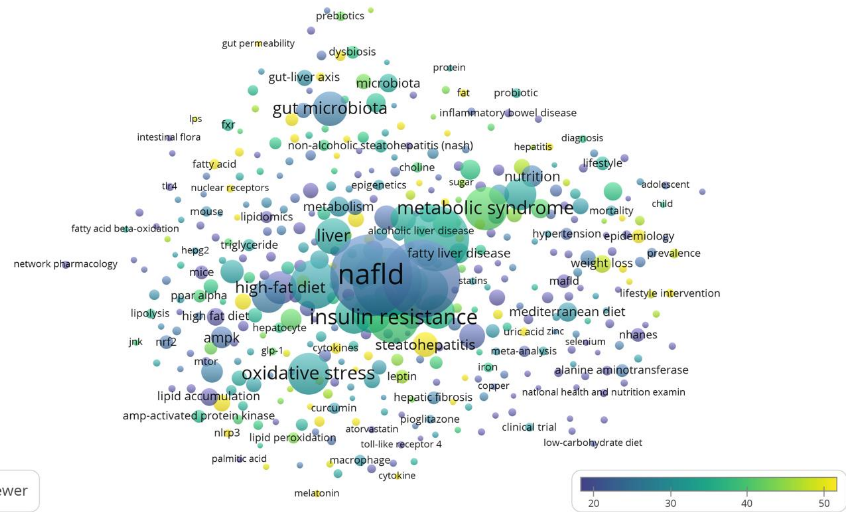

Fig. 3. Term map of recurring author keywords of the papers. The node color represents the citations per paper (CPP) of the terms, whereas the node size represents the number of papers, and the inter-node distance represents how frequently the terms co-occurred with each other in the same papers.

Figure 3 visualizes the recurring author keywords. Ten most recurring keywords (excluding NAFLD and its variations) included obesity (n = 1324, CPP = 32.7), insulin resistance (n = 854, CPP = 39.1), inflammation (n = 772, CPP = 30.4), NASH (n = 606, CPP = 33.5), metabolic syndrome (n = 595, CPP = 40.5), fatty liver (n = 572, CPP = 31.4), oxidative stress (n = 562, CPP = 30.7), steatosis (n = 478, CPP = 35.5), gut microbiota (n = 383, CPP = 25.5), and lipid metabolism (n = 376, CPP = 25.5).

As seen, oxidative stress was a key concept, suggesting that dietary anti-oxidants could be beneficial to the management of NAFLD. As determined from the author keywords, recurring food substances with anti-oxidative or anti-inflammatory properties are listed in Table 4, and their chemical structures are illustrated in Figure

Table 4. Recurring food substances with anti-oxidative or anti-inflammatory properties as identified from author keywords

Food substance	Number of papers (% of 12,445)	Citations per paper (CPP)
Resveratrol	56 (0.4)	48.7
Polyphenols	56 (0.4)	35.8
Curcumin	42 (0.3)	28.6
Berberine	36 (0.3)	25.0
Quercetin	25 (0.2)	33.4
Flavonoids	19 (0.2)	23.9
Omega-3 fatty acids	16 (0.1)	40.2
Docosahexaenoic acid (DHA)	16 (0.1)	34.0
Genistein	16 (0.1)	31.4
Palmitic acid	16 (0.1)	18.0

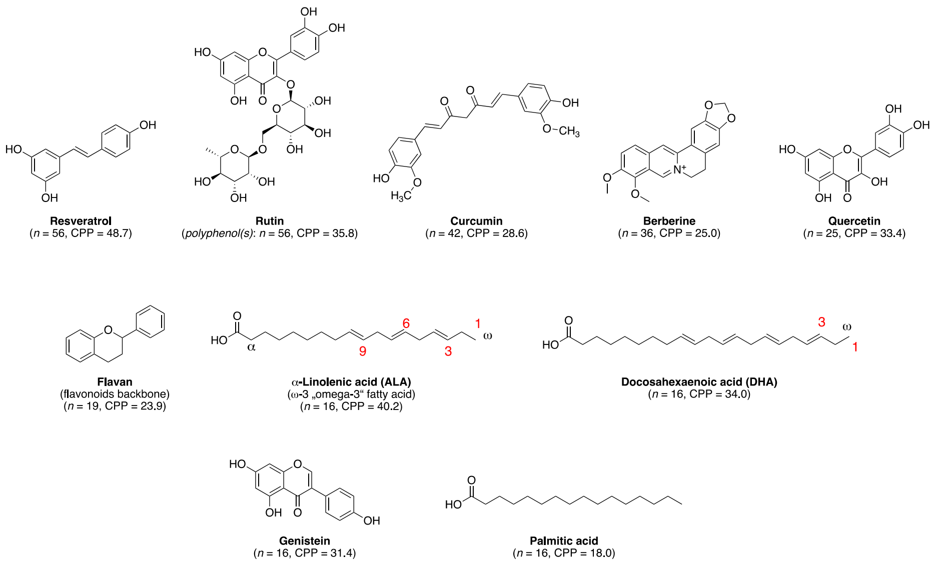

Fig. 4. Chemical structures of frequently mentioned food chemicals/chemical classes.

4. Resveratrol (n = 56, CPP = 48.7) and polyphenols (n = 56, CPP = 35.8) were most frequently mentioned, followed by curcumin (n = 42, CPP = 28.6).

Indeed, a mouse study has shown that resveratrol-treated mice showed preponderant polarization of M2 Kupffer cells (which produce anti-inflammatory mediators), apoptosis of M1 Kupffer cells (which produce pro-inflammatory cytokines), and resistance to hepatocyte steatosis and apoptosis after feeding alcohol or high-fat diet [Wan *et al.* 2014]. Further, it was found that interleukin-10 secreted by M2 cells promoted apoptosis of M1 cells [Wan *et al*. 2014]. The beneficial clinical effect of resveratrol was demonstrated in a randomized clinical trial with 60 patients with NAFLD [Chen *et al*. 2015]. Compared to a placebo, two 150 mg resveratrol capsules twice (600 mg in total) daily for 3 months exhibited beneficial effects on liver enzymes, insulin resistance, as well as glucose and lipid metabolism [Chen *et al*. 2015]. Meanwhile, another randomized clinical trial with 20 patients with NAFLD showed that 3000 mg resveratrol daily for 2 months did not reduce insulin resistance, steatosis, or abdominal fat distribution relative to the baseline [Chachay *et al*. 2014].

Meanwhile, a randomized clinical trial of 102 patients with NAFLD found that taking curcumin of 1000 mg daily for 8 weeks led to a reduction in serum levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, non-high-density lipoprotein cholesterol, and uric acid, compared to placebo [Panahi *et al.* 2016]. Another randomized clinical trial of 52 patients with NAFLD found that, however, daily intake of 1500 mg curcumin for 12 weeks could reduce hepatic fibrosis, serum cholesterol, glucose, and alanine aminotransferase compared to placebo, but not anthropometric indices, blood lipid profile, insulin resistance, and hepatic steatosis [Saadati *et al.* 2019]. A rat study showed that curcumin attenuated hepatic steatosis in rats with NAFLD by altering the gut microbial composition to resemble that of healthy rats [Feng *et al*. 2017].

The above results of the bibliometric analysis give hope that the evidence base for these dietary substances will soon expand and that they may be included in the guidelines for the treatment of NAFLD.

Conclusions

The publications on dietary influences on NAFLD received substantial contributions from China and the United States as well as European and other Asian states such as Italy, South Korea, and Japan. Many publications focused on the areas of Gastroenterology & Hepatology, Nutrition & Dietetics, Biochemistry & Molecular Biology, Endocrinology & Metabolism, and Pharmacology & Pharmacy. Frequently mentioned food substances included resveratrol, polyphenols, curcumin, berberine, quercetin, flavonoids, omega-3 fatty acids, docosahexaenoic acid (DHA), genistein, and palmitic acid. The literature has shown that these dietary substances were beneficial to both animals and humans with NAFLD. This bibliometric analysis gives readers an overview of the existing literature and could facilitate further studies examining the relationship between diet and NAFLD.

Conflict of interest. The authors declare no conflict of interest.

Author contributions. AWKY, NK, and AGA conceived the work, performed data collection, analyses, and drafted the manuscript. All authors critically reviewed and revised the manuscript , and approved its submission for publication in the journal Animal Science Papers and Reports.

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