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1       **Does flavonoid supplementation alleviate non-alcoholic fatty liver disease? A**  
2               **systematic review and meta-analysis of randomized controlled trials**

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12  
13   **Abbreviations:** non-alcoholic fatty liver disease, NAFLD; randomized clinical trials,  
14   RCTs; low-density lipoprotein cholesterol, LDL-C; aspartate aminotransferase, AST;  
15   alanine aminotransferase, ALT; nuclear factor- $\kappa$ B, NF- $\kappa$ B; high-sensitivity C-reactive  
16   protein, hs-CRP; tumor necrosis factor- $\alpha$ , TNF- $\alpha$ ; body mass index, BMI;  $\gamma$ -glutamyl  
17   transpeptidase, GGT; fasting blood sugar, FBS; homeostatic model assessment of insulin  
18   resistance, HOMA-IR; high-density lipoprotein cholesterol, HDL-C; total cholesterol, TC;  
19   triglycerides, TG; interleukin-6, IL-6.

20  
21   **Keywords:** Flavonoid; non-alcoholic fatty liver disease; liver function; lipid profile;  
22   inflammation

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26 **ABSTRACT**

27 Higher flavonoid intake is associated with reduced risk of non-alcoholic fatty liver  
28 disease (NAFLD). However, there is a large discrepancy in the effects of flavonoid  
29 supplementation on makers of NAFLD. To fill such knowledge gap, we  
30 systematically reviewed randomized clinical trials (RCTs) to critically assess  
31 flavonoid supplementation effect on liver function, lipid profile, inflammation, and  
32 insulin resistance in adults with NAFLD. A systematic search was conducted from  
33 4 databases from inception until May 2023. Twelve RCTs were included in the final  
34 analysis demonstrating beneficial effects of flavonoid supplementation on ALT  
35 (SMD = -3.59, p = 0.034), AST (SMD = -4.47, p = 0.001), GGT (SMD = -8.70, p  
36 = 0.000), CK-18M30 (SMD = -0.35, p = 0.042), TG (SMD = -0.37, p = 0.001),  
37 LDL-C (SMD = -0.38, p = 0.039), TC (MD = -0.25 mmol/l, p = 0.017), steatosis  
38 score (MD = -18.97, p = 0.30), TNF- $\alpha$  (MD = -0.88, p = 0.000), and NF- $\kappa$ B (MD =  
39 -1.62, p = 0.001). This meta-analysis suggests that flavonoid alleviates NAFLD  
40 through exerting favourable effects on liver function, lipid profile, and  
41 inflammation, indicating flavonoid supplementation presents a promising drug  
42 regimen for the management of NAFLD and its associated complications.

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51 **1. Introduction**

52 Non-alcoholic fatty liver disease (NAFLD) represents a broad spectrum of liver disorders  
53 associated with excessive deposition of fatty acids within hepatocytes, ranging from  
54 steatosis to hepatocellular carcinoma. The pathogenesis of NAFLD is complex and  
55 multifactorial, comprising fat accumulation in the liver, inflammation and insulin  
56 resistance <sup>[1]</sup>. Non-alcoholic steatohepatitis (NASH) is an active form of NAFLD,  
57 characterized by liver necrotizing inflammation and faster fibrosis progression <sup>[2]</sup>. The  
58 prevalence of NAFLD is on the rise, affecting one-third of the global population <sup>[3]</sup>.  
59 Specifically, the overall prevalence of NAFLD is 38% in a large middle-aged US cohort  
60 <sup>[4]</sup>. Notably, individuals suffering from NAFLD are at higher risk of developing  
61 coronavirus disease 2019 (COVID-19) <sup>[5,6]</sup>. Meanwhile, the enhanced physical inactivity,  
62 overeating and depression associated with COVID-19 exert adverse effects on NAFLD,  
63 ultimately contributing to elevated liver-related mortality <sup>[7]</sup>.

64 In recent years, increasing efforts have been given towards management of fatty liver  
65 diseases using nutraceuticals, over the last decade with obvious increase in research  
66 papers from 16 records in 2008 to reach 218 in 2022 as retrieved by searching SCOPUS  
67 database for literature using keywords of cereal polyphenols (Appendix A1 Fig. 1). As  
68 shown in Fig. 1, drawn for the co-occurrences on fatty liver and flavonoids as analyzed  
69 by the VOS viewer bibliometric visualization software, circles in different colors  
70 represent the keywords related to different topics, and the links between circles  
71 demonstrate their relations. Four main clusters in literature could be visualized using VOS  
72 viewer as such: with the major cluster 1 of 358 items related to natural products chemistry  
73 and health effects and a second cluster on biochemical markers associated with fatty liver  
74 including term flavonoids appearing (552 times) and fatty liver (312 times) in a total of  
75 997 items all highlighting their close connection. The result indicates huge intersections

76 between flavonoids and NAFLD, presenting great research potential. In contrast, only  
77 one cluster made up of 1 item belonged to anthocyanins revealing that few literature is  
78 made towards assessment of anthocyanins in fatty liver management compared to  
79 flavonoids. Furthermore, papers grouped by subject areas revealed that largest reports of  
80 is in pharmacology, medicine and biochemistry amounting for 60.5% of all fields as  
81 depicted in Appendix A1 Fig. 2.

82 Hence, it is imperative to find remedies to counteract or alleviate NAFLD.  
83 Lifestyle modifications including increased physical activity and healthy diet constitute  
84 the cornerstone of treatment for NAFLD [8, 9]. Importantly, increasing evidence has  
85 revealed a protective role of flavonoids in mitigating NAFLD [10, 11]. Specifically,  
86 flavonoids exert a hepatoprotective effect by regulating the activity of Cytochrome P450  
87 2E1 (CYP2E1) [12]. Flavonoids from *Chimonanthus nitens* Oliv. leaves alleviated  
88 NAFLD in mice by decreasing liver fat deposition, oxidative stress, and inflammatory  
89 response as well as regulating the gut–liver axis [13]. Furthermore, dihydromyricetin  
90 alleviated streptozotocin-induced liver impairment and inflammation in diabetic rats  
91 through the regulation of NF-κB and AMPK signaling pathway [14].

92 Flavonoids comprise secondary metabolites that are found ubiquitous in plants,  
93 categorised into subclasses encompassing flavanones, flavonols, flavanols, flavones,  
94 anthocyanidins and isoflavones [15]. They are well characterized for multiple health effects,  
95 including anti-inflammatory [16], antioxidant [17] and anti-hypercholesterolemic activities  
96 [18], as well as counteracting insulin resistance [19]. Therefore, flavonoids are considered  
97 as promising candidates for the prevention and treatment of NAFLD [20]. Indeed, higher  
98 flavonoid intake is associated with a lower risk of NAFLD progression in the elderly  
99 overweight/obese population [21]. However, results of randomized clinical trials (RCTs)  
100 evaluating the effects of flavonoids on NAFLD appear to be controversial in literature [22,

101 <sup>23]</sup>, obscuring the mechanism by which flavonoids regulate NAFLD and limiting future  
102 clinical application of flavonoids. Hence, given that no comprehensive reviews regarding  
103 the effects of flavonoids on liver function, lipid profile, inflammatory markers and insulin  
104 resistance have been conducted, the aim of the present study was to systematically review  
105 the evidence and quantify the impact of flavonoids on NAFLD risk factors.

## 106 **2. Methods**

### 107 **2.1. Protocol and Registration**

108 The study was conducted following the Preferred Reporting Items for Systematic  
109 Reviews and Meta-Analyses (PRISMA) statement checklist <sup>[24]</sup>. The study was registered  
110 on <https://inplasy.com/> with the registration number of INPLASY202260057, and the  
111 DOI number of 10.37766/inplasy2022.6.0057.

### 112 **2.2. Search Strategy and Selection Criteria**

113 Two reviewers (K.J. and F.D.) carried out literature searching, screening, quality  
114 evaluation, and data extraction, with a third reviewer (L.L.) as arbitrator. Systematic  
115 literature search was conducted in Cochrane Central Register of Controlled Trials  
116 (CENTRAL), PubMed, ScienceDirect and Web of Science from the inception of the  
117 database until May 2023.

118 The following terms were included in the literature search: “flavonoid” as well as  
119 names of individual compounds, liver function (“alanine aminotransferase” or “aspartate  
120 aminotransferase” or “ $\gamma$ -glutamyl transpeptidase” or “cytokeratin 18-M30” or “fibrosis  
121 score”), lipid profile (“triglycerides” or “low-density lipoprotein cholesterol” or “high-  
122 density lipoprotein cholesterol” or “total cholesterol” or “steatosis score”), inflammation  
123 (“tumor necrosis factor- $\alpha$ ” or “high-sensitivity C-reactive protein” or “nuclear factor-  
124  $\kappa$ B”), insulin resistance (“homeostasis model assessment” or “insulin” or “fasting blood  
125 sugar”), “nonalcoholic fatty liver disease”, “randomized controlled trial”, “intervention”

126 (more information is shown in Appendix A2). Bibliographic search was conducted by  
127 reviewing the reference lists of the included studies or key texts. Moreover, manual search  
128 and lists of references from additional studies were included, and other similar systematic  
129 reviews were checked to identify potential studies that might meet the inclusion criteria.

130 Inclusion criteria were as follows: (1) Randomized controlled trials, (2) evaluated  
131 the effect of consuming flavonoids on changes in at least one of these outcomes (liver  
132 function, lipid profile, inflammation, insulin resistance) in adults with NAFLD, (3)  
133 provided sufficient data regarding the baseline and final values within groups or presented  
134 the data regarding the average change from baseline, (4) articles published in English.  
135 The studies meeting any of the following criteria were excluded: (1) having non-  
136 randomized or semi-randomized design, (2) absence of a control group, (3) having a  
137 duration of less than 8 weeks.

### 138 **2.3. Study Selection and Quality Evaluation**

#### 139 **2.3.1. Data Collection Process**

140 For each study included in this systematic review, the following information was  
141 extracted: (1) study (author's last name and year of publication); (2) study design; (3)  
142 country; (4) population (number, age, BMI); (5) intervention group; (6) control group; (7)  
143 duration; (8) main results.

#### 144 **2.3.2. Quality Evaluation**

145 The bias risk of RCTs included in this systematic review and meta-analysis was assessed  
146 using the Risk of Bias2 (RoB2) tool from the Cochrane Collaboration, with a domain-  
147 based evaluation that classifies five domains of each RCT into "low risk of bias", "some  
148 concerns" or "high risk of bias" <sup>[25]</sup>. The five domains include bias arising from the  
149 randomization, deviations from intended intervention, missing data, measurement of the  
150 outcome, and selective outcome reporting. Moreover, Nutri Grade (Grading of

151 Recommendations Assessment, Development, and Evaluation) scoring system was used  
152 to assess the quality according to the following seven aspects: (1) risk of bias, study  
153 quality, and study limitations, (2) precision, (3) heterogeneity, (4) directness, (5)  
154 publication bias, (6) funding bias, (7) study design [26].

### 155 **2.3.3. Statistical Analysis**

156 The statistical analysis was conducted using the Stata version 14.0 (College Station,  
157 TX77845, USA) and the Review Manager 5.4 software (The Cochrane Collaboration,  
158 London, UK, 2020). Mean difference (MD) or the standardized mean difference (SMD)  
159 was used to determine the effect size, using a random-effects model (DerSimonian-Laird  
160 approach (Kelley and Kelley 2012)). Outcomes were presented as mean changes from  
161 baseline. The standard deviation (SD) of the change was calculated if the data were not  
162 stated in the RCTs, using the following equation:  $[SD_{pre}^2 + SD_{post}^2 - 2 \times Corr (pre, post)$   
163  $\times SD_{pre} \times SD_{post}]^{0.5}$ . Specifically,  $SD_{pre}$  was the SD before the intervention,  $SD_{post}$  was the  
164 SD after the intervention, and  $Corr (pre, post)$  was within-participant correlation. If the  
165 correlation was not stated, the within-participant correlation was set as 0.5. If not directly  
166 reported, the SD was calculated from standard error or confidence interval. A subgroup  
167 analysis based on dose ( $\geq 500$  mg/d or  $< 500$  mg/d), and flavonoid type were conducted to  
168 detect potential sources of heterogeneity. Heterogeneity across studies was assessed by  $I^2$   
169 statistics. Heterogeneity was classified as “small”, “moderate”, or “substantial” if  $I^2$  was  
170  $< 25\%$ ,  $25-75\%$ , and  $> 75\%$ , respectively [27].

171 The individual influence of each study on the overall result was evaluated by removing  
172 them individually. Egger’s test and visual inspection of funnel plots were performed to  
173 evaluate publication bias. All statistical results with p value  $< 0.05$  were considered  
174 statistically significant.

## 175 **3. Results**

176 **3.1. Study Selection**

177 The process of study selection is shown as a PRISMA flow diagram (Fig. 2). A total of  
178 1048 publications were identified by searching the databases and other sources.  
179 Following the removal of duplication, 583 publications remained. The titles and abstracts  
180 of the included studies were screened, and 568 were excluded after this preliminary filter.  
181 Subsequently, full text screening was carried out and 12 publications were included in  
182 the final meta-analysis.

183 **3.2. Study Characteristics**

184 The characteristics of the included fourteen studies are shown in Table 1, involving a total  
185 of 831 patients with NAFLD, with 418 participants in intervention group and 413  
186 participants in control group. All studies included men and women. Specifically, one  
187 study did not specify the ratio of men to women. The sample size of the studies ranged  
188 from 36 to 108. The duration of the studies ranged from 8 to 48 weeks, with 12 weeks  
189 being the most common duration (n = 8). The intervention group included hesperidin,  
190 silybum, anthocyanin, genistein, dihydromyricetin at doses ranging from 94 to 2100 mg/d.  
191 The study design of all 12 RCTs was parallel.

192 **3.3. Quality Evaluation**

193 The RoB2 tool summary and risk of bias graphs are shown in Appendix A3. Among all  
194 studies, 12 studies (100%) had no domain as “high risk”, and 10 studies (83.3%) had five  
195 domains as “low risk”. Evaluation of the quality of the present meta-analysis based on  
196 the Nutri Grade scoring system demonstrated a score of 9.4, indicating high meta-  
197 evidence.

198 **3.4. Outcomes**

199 The effects of flavonoid consumption on adults with NAFLD were evaluated in the  
200 present study. The outcome assessed included liver function (alanine aminotransferase

201 (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyl transpeptidase (GGT), cytokeratin  
202 18-M30 (CK-18M30), fibrosis score, steatosis score), lipid profile (triglycerides (TG),  
203 low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-  
204 C), total cholesterol (TC)), inflammation (tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), high-  
205 sensitivity C-reactive protein (hs-CRP), nuclear factor- $\kappa$ B (NF- $\kappa$ B)) and insulin  
206 resistance (homeostatic model assessment of insulin resistance (HOMA-IR), insulin,  
207 fasting blood sugar (FBS)), each described separately in the next subsections.

### 208 **3.4.1. Liver function**

209 The pooled results demonstrated that there was a significant decrease in ALT  
210 concentrations in intervention group, compared with control group (SMD = -3.59, 95%  
211 CI [-6.90, -0.28],  $p = 0.034$ ), with a small heterogeneity ( $I^2 = 16.4\%$ ,  $p = 0.296$ ) (Fig. 3A).  
212 Subgroup analysis showed that dihydromyricetin significantly reduced ALT  
213 concentrations (Appendix A4).

214 Similarly, the pooled results showed that AST significantly decreased in intervention  
215 group, compared with control group (SMD = -4.47, 95% CI [-7.08, -1.86],  $p = 0.001$ )  
216 with a small heterogeneity ( $I^2 = 0.0\%$ ,  $p = 0.507$ ) (Fig. 3B). Subgroup analysis  
217 demonstrated that flavonoid supplementation significantly reduced AST concentrations  
218 with the dose of  $\geq 500$  mg/d. Regarding flavonoid type, subgroup analysis showed that  
219 silymarin significantly reduced AST concentrations (Appendix A4).

220 The pooled results showed that there was a significant decrease in GGT in  
221 intervention group, compared with control group (SMD = -8.70, 95% CI [-12.86, -4.54],  
222  $p = 0.000$ ), with a small heterogeneity ( $I^2 = 0.0\%$ ,  $p = 0.960$ ) (Fig. 3C). Subgroup analysis  
223 showed that flavonoid supplementation significantly reduced GGT concentrations with  
224 the dose of  $\geq 500$  mg/d. Regarding flavonoid type, subgroup analysis showed that  
225 hesperidin significantly reduced GGT concentrations (Appendix A4).

226 Likewise, there was a significant reduction in CK-18M30 in intervention group,  
227 compared with control group (SMD = -0.35, 95% CI [-0.70, -0.01], p = 0.042), with a  
228 small heterogeneity ( $I^2 = 0.0\%$ , p = 0.487) (Fig. 3D).

229 In contrast, fibrosis score did not differ between intervention group and control  
230 group, with a MD of 0.11 (95% CI [-0.44, 0.66], p = 0.696) and a small heterogeneity ( $I^2$   
231 = 0.0%, p = 0.849) (Fig. 3E).

232 Similarly, steatosis score significantly decreased in intervention group, compared  
233 with control group (MD = -18.97, 95% CI [-36.15, -1.80], p = 0.030), with a small  
234 heterogeneity ( $I^2 = 0.0\%$ , p = 0.904) (Fig. 3F).

### 235 **3.4.2. Lipid profile**

236 The pooled analysis demonstrated that flavonoid supplementation significantly decreased  
237 TG levels (MD = -0.37 mg/dl, 95% CI [-0.59, -0.15], p = 0.001) compared to placebo  
238 with a small heterogeneity ( $I^2 = 0.0\%$ , p = 0.649) (Fig. 4A). Subgroup analysis  
239 demonstrated that flavonoid supplementation significantly reduced TG concentrations  
240 with the dose of  $\geq 500$  mg/d and  $< 500$  mg/d. Regarding flavonoid type, subgroup analysis  
241 showed that genistein significantly reduced TG concentrations (Appendix A4).

242 The results showed that there was likewise a significant difference in LDL-C level  
243 between the intervention group and the control group (SMD = -0.38, 95% CI [-0.74, -  
244 0.02], p = 0.039), with a small heterogeneity ( $I^2 = 20.9\%$ , p = 0.270) (Fig. 4B). Regarding  
245 flavonoid type, subgroup analysis showed that hesperidin and dihydromyricetin  
246 significantly reduced LDL-C concentrations (Appendix A4).

247 In contrast, results demonstrated that no significant difference was observed in  
248 HDL-C levels between the intervention group and the control group (SMD = 0.05, 95%  
249 CI [-0.06, 0.16], p = 0.344), with a small heterogeneity ( $I^2 = 0.0\%$ , p = 0.927) (Fig. 4C).

250 The results demonstrated that TC levels in the intervention group decreased  
251 significantly compared with placebo (MD = -0.25 mmol/l, 95% CI [-0.45, -0.04], p =  
252 0.017), and the heterogeneity was small ( $I^2 = 0.0\%$ , p = 0.937) (Fig. 4D). Subgroup  
253 analysis showed that flavonoid supplementation significantly reduced TC concentrations  
254 with the dose of  $\geq 500$  mg/d (Appendix A4).

### 255 **3.4.3. Inflammation**

256 The pooled analysis showed that TNF- $\alpha$  levels in the intervention group decreased  
257 significantly compared with placebo (MD = -0.88 pg/ml, 95% CI [-1.15, -0.62], p =  
258 0.000), and the heterogeneity was small ( $I^2 = 0.0\%$ , p = 0.392) (Fig. 5A). Subgroup  
259 analysis showed that flavonoid supplementation significantly reduced TNF- $\alpha$   
260 concentrations with the dose of  $\geq 500$  mg/d. Regarding flavonoid type, subgroup analysis  
261 showed that hesperidin, genistein and dihydromyricetin significantly reduced TNF- $\alpha$   
262 concentrations (Appendix A4).

263 The results demonstrated that there was no significant difference in hs-CRP  
264 between the intervention group and the control group (MD = -0.26 ng/dl, 95% CI [-0.66,  
265 0.14], p = 0.200), with a small heterogeneity ( $I^2 = 0.0\%$ , p = 0.637) (Fig. 5B).

266 The pooled analysis showed that there was a significant decrease in NF- $\kappa$ B in  
267 intervention group compared to control group (MD = -1.62 ng/mg protein, 95% CI [-2.56,  
268 - 0.69], p = 0.001), with a small heterogeneity ( $I^2 = 0.0\%$ , p = 0.811) (Fig. 5C).

### 269 **3.4.4. Insulin resistance**

270 Comprehensive analysis showed that the HOMA-IR level in the intervention group did  
271 not decrease significantly compared with the placebo group (MD = -0.05, 95% CI [-0.25,  
272 0.15], p = 0.642), with a moderate heterogeneity ( $I^2 = 0.0\%$ , p = 0.842) (Fig. 6A).

273 The results demonstrated that there was no significant difference in insulin  
274 concentrations between the control group and the intervention group (MD = -0.07 mU/L,

275 95% CI [-0.40, 0.25],  $p = 0.659$ ), with a moderate heterogeneity ( $I^2 = 35.9%$ ,  $p = 0.197$ )  
276 (Fig. 6B).

277 No significant difference was observed in FBS levels between the control group  
278 and the intervention group (MD = -0.23 mg/dl, 95% CI [-0.49, 0.02],  $p = 0.075$ ), with a  
279 small heterogeneity ( $I^2 = 0.0%$ ,  $p = 0.866$ ) (Fig. 6C).

280 Sensitivity analysis of markers of liver function, lipid profile, inflammatory  
281 markers and insulin resistance revealed that the overall effect did not change and visual  
282 interpretation of the funnel plots demonstrated no evidence of publication bias (Appendix  
283 A5-A8, respectively). The individual influence of each study on the overall result was  
284 evaluated by removing them individually (Appendix A9). Forest plots of subgroup  
285 analysis are shown in Appendix A10.

#### 286 **4. Discussion**

287 This meta-analysis demonstrated that long-term consumption of flavonoids significantly  
288 reduced ALT, AST, GGT, and CK-18M30, compared with the control group. Given that  
289 ALT, AST, GGT, and CK-18M30 levels represent structural and cellular liver damage,  
290 with elevated levels indicating increased severity of liver injury <sup>[28]</sup>, the present study  
291 showed that flavonoids alleviated the severity of NAFLD. Consistent with a previous  
292 meta-analysis investigating the effect of silymarin on patients with NAFLD <sup>[29]</sup>, ALT and  
293 AST were also significantly reduced following silymarin administration. Similarly,  
294 consumption of silymarin for 24 weeks significantly reduced the levels of AST and ALT  
295 in patients with serum hepatitis C virus <sup>[30]</sup>. In support of these findings, intake of  
296 flavonoid extract of *P. curatellifolia* seeds for 14 days dose dependently prevented  
297 acetaminophen-induced increase in serum activities of ALT, AST, and GGT in rats <sup>[31]</sup>.

298 Dyslipidemia is a common feature of NAFLD <sup>[32]</sup>. The present meta-analysis  
299 showed that flavonoids significantly reduced TG, TC and LDL-C in patients with

300 NAFLD, albeit not HDL-C. Similarly, a previous meta-analysis demonstrated that  
301 flavonoid consumption led to a significant reduction in TG, TC and LDL-C in participants  
302 with type 2 diabetes <sup>[33]</sup>. In support of these findings, flavonoids from mulberry leaves  
303 inhibited lipid accumulation and alleviated hepatic injury in NAFLD rat model <sup>[34]</sup>.  
304 Specifically, quercetin significantly decreased lipid accumulation in HepG2 cells,  
305 through the inhibition of mRNA and protein expression level of SREBP2 and HMGCR,  
306 as well as the upregulation of SR-BI mRNA expression, providing evidence for a  
307 protective role of quercetin in the NAFLD treatment <sup>[34]</sup>. Furthermore, a recent systematic  
308 review and meta-analysis suggested that flavonoid-containing artichoke leaf extract  
309 resulted in a significant reduction in ALT, AST, TC, TG and LDL-C in NAFLD patients  
310 <sup>[35]</sup>.

311 Inflammation is an important hallmark in the development of NAFLD <sup>[36]</sup>. The  
312 present meta-analysis showed that TNF- $\alpha$  and NF- $\kappa$ B in patients with NAFLD  
313 significantly decreased following flavonoid supplementation likely attributed to  
314 flavonoids potential anti-inflammatory actions <sup>[37]</sup>. In support of those findings,  
315 administration of dihydromyricetin (100–400 mg/kg/day) for 6 weeks inhibited TNF- $\alpha$   
316 and IL-1 $\beta$  levels in diabetic rats by the regulation of NF- $\kappa$ B signaling pathway <sup>[38]</sup>.  
317 Consistent with those findings, flavonoids have been reported to inhibit enzymes or  
318 transcription factors important in inflammation, such as TNF- $\alpha$ , IL-6 and NF- $\kappa$ B <sup>[16]</sup>.

319 Given that insulin resistance in both the adipose tissue and the liver contributes to  
320 an accumulation of free fatty acids in hepatocytes, insulin resistance has been suggested  
321 as an independent risk factor for the progression of NAFLD <sup>[39]</sup>. However, this meta-  
322 analysis demonstrated that flavonoid consumption led to no significant changes in insulin,  
323 HOMA-IR and FBS levels in patients with NAFLD. In contrast, a meta-analysis on  
324 patients with diabetes reported that HOMA-IR and FBS were significantly reduced

325 following flavonoid intake, whereas insulin was unaffected <sup>[33]</sup>. Such discrepancy could  
326 be explained by the variances in the baseline levels of those markers in participants with  
327 NAFLD and patients with diabetes, as well as differences in study design.

328 Collectively, regarding the effectiveness of flavonoid supplementation on  
329 NAFLD, the present meta-analysis suggested that dihydromyricetin and hesperidin  
330 demonstrated the most potency among the flavonoids investigated in previous RCTs,  
331 exerting beneficial effects on liver function, lipid profile and inflammation. Regarding  
332 effective doses of flavonoid supplementation on liver function, lipid profile and  
333 inflammation, the dose of  $\geq 500$  mg/d was more effective in reducing AST, GGT, TC, and  
334 TNF- $\alpha$  concentrations, compared with the dose of  $< 500$  mg/d. It is noteworthy that the  
335 RCTs included in this meta-analysis have assessed safety markers and not found any issue,  
336 including side effects. However, discretion is warranted to avoid the possible adverse  
337 effects due to flavonoid overdose <sup>[40]</sup>. Further studies are needed to ascertain the long-  
338 term safety of supplemental flavonoids.

339 The limitations of this meta-analysis need to be acknowledged. Specifically, the  
340 discrepancy in the inclusion criteria of individual RCTs resulted in heterogeneity in the  
341 participant profile with different baseline parameters related to NAFLD. Notably,  
342 differences in study design (flavonoid type, dosage, intervention duration, and ethnicity)  
343 might contribute to heterogeneity among studies.

## 344 **5. Conclusions**

345 This meta-analysis demonstrated that flavonoid supplementation contributes to the  
346 alleviation of NAFLD through regulating liver function (ALT, AST, GGT, CK-18M30,  
347 steatosis score), modulating lipid metabolism (TG, TC, LDL-C), and attenuating  
348 inflammation (TNF- $\alpha$ , NF- $\kappa$ B) (Fig. 7). Although multiple pathways implicated in the  
349 etiology of NAFLD make the treatment challenging, this meta-analysis indicated that

350 flavonoids seem to suit seamlessly in the amelioration of NAFLD, through the regulation  
351 of various pathways. Notably, the present systematic review provides new insights into  
352 how flavonoids alleviate NAFLD, meanwhile facilitating the development of  
353 comprehensive information for future well-designed RCTs. Identification of the best  
354 structural analogues among flavonoid subclasses should now follow by establishing  
355 structure activity relationship (SAR) studies using enzyme-based assays or ideally animal  
356 models.

#### 357 **Authors' contributions**

358 L.L. and K.J. designed the study. K.J., L.L. and F.D. selected the final included studies,  
359 extracted data, and carried out the meta-analysis. L.L. and K.J. interpreted the results  
360 and wrote the article. N.J., C.B., M.A.F., H.L., X.L. and J.X. provided critical revisions  
361 of the final manuscript. All authors have read and approved the final manuscript.

#### 362 **Conflicts of Interest**

363 The authors have declared no conflict of interest.

#### 364 **Data Availability Statement**

365 Data is contained within the article or supplementary material.

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461 **Table**462 **Table 1.** Characteristics of the studies included in the meta-analysis.

Study	Country	Population		Intervention Group	Control Group	Duration (weeks)	Main Results	
		N (IG/CG)	Age					BMI
[41]	Iran	25/24	18-70	IG: 31.70 ± 5.21 CG: 33.00 ± 5.03	hesperidin, 1 g/d + LMP	placebo (starch), 1 g/d + LMP	12	↑: LDL-C, AST ↓: ALT, NF-κB, hs-CRP, TNF-α, fibrosis score, steatosis score ND: BMI, WHR, GGT, FBS, insulin, HOMA-IR, HDL-C
[42]	Spain	18/18	18-67	IG: 36.8 ± 7.9 CG: 35.0 ± 7.4	silybum, 540.3 mg/d; VE, 36 mg/d + LMP	LMP	12	↓: AST, ATG, GGT ND: BMI, TG, HOMA-IR
[43]	Iran	22/21	18-70	IG: 31.07 ± 4.38 CG: 33.06 ± 5.14	hesperidin, 1 g/d + LMP	LMP	12	↑: AST ↓: fibrosis score, steatosis score, ALT, FBS, insulin, HOMA-IR, BMI, hs-CRP, TNF-α ND: GGT, QUICKI, LDL-C, HDL-C, NF-κB
[44]	China	37/37	25-65	IG: 27.10 ± 3.20 CG: 27.3 ± 3.5	anthocyanin, 320 mg/d	placebo, 320 mg/d	12	↓: ALT, AST, MPO, insulin, CK-18M30, HOMA-IR ND: BMI, TC, HDL-C, LDL-C
[45]	Iran	39/39	18-65	IG: 29.90 ± 3.10 CG: 30.8 ± 4.2	quercetin, 500 mg/d	placebo, 500 mg/d	12	↓: TG, TNF-α, TC ND: BMI, ALT, WHR, ALT, AST, GGT
[46]	Malaysia	49/50	>18	IG: 30.0 ± 4.0 CG: 31.0 ± 4.6	silymarin, 2100 mg/d + LMP	placebo, 2100 mg/d + LMP	48	↓: ALT, AST, GGT ND: HOMA-IR, TG, TC, HDL-C, LDL-C
[47]	Iran	39/39	18-65	25-40	quercetin, 500 mg/d	placebo, 500 mg/d	12	↑: RBC ↓: mean corpuscular volume, MCH, ferritin

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Table 1. Continued.

Study	Country	Population		Intervention Group	Control Group	Duration (weeks)	Main Results	
		N (IG/CG)	Age					BMI
[48]	Iran	41/41	18-69	IG: 29.09 ± 4.67 CG: 27.83±4.51	genistein, 250 mg/d + LMP	cornstarch, 250 mg/d + LMP	8	↓: FBS, HOMA-IR, IL-6, TNF- $\alpha$ , MDA ND: BMI, WHR, TG, LDL-C, HDL-C, AST, ALT
[49]	Iran	30/30	18-65	IG: 25.10 ± 3.7 CG: 26.1 ± 3.1	silymarin, 140 mg/d + LMP	placebo, 140 mg/d + LMP	12	↓: BMI ND: TG, HDL-C, LDL-C, FBS, AST, ALT
[50]	China	30/30	20-60	IG: 25.5 ± 2.87 CG: 25.6 ± 2.26	dihydromyricetin, 600 mg/d	placebo, 600 mg/d	12	↓: BMI, TC, TG, HOMA-IR, CK- 18M30, TNF- $\alpha$ , FGF21 ND: TG, HDL-C, LDL-C, FBS, AST, ALT
[51]	Iran	33/31	IG: 43.6 ± 8.3 CG: 39.36 ± 10.5	IG: 27.4 ± 1.70 CG: 27.5 ± 1.90	silymarin, 210 mg/d + LMP	placebo, 210 mg/d + LMP	8	↓: AST, ALT
[52]	Italy	55/53	18-65	IG: 29.9 ± 4.6 CG: 29.3 ± 4.4	silybin, 94 mg/d; PC, 194 mg/d; VE, 89.28 mg/d + LMP	extra white saccharine, 94 mg/d; PC, 194 mg/d; VE, 89.28 mg/d + LMP	48	↓: AST, AST, HOMA-IR ND: TG, TC

465 G = gender; N = number; IG = Intervention Group; CG = Control Group; VE = vitamin E; VD = vitamin D; LMP = lifestyle modification program; PC =  
466 phosphatidylcholine; ND = no significant differences; ↑ = significant increase for intervention group; ↓ = significant decrease for intervention group; LDL-C = low-  
467 density lipoprotein cholesterol; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CK-18M30 = cytokeratin 18-M30; NF- $\kappa$ B = nuclear factor- $\kappa$ B;  
468 hs-CRP = high-sensitivity C-reactive protein; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ ; BMI = body mass index; WHR = waist-to-hip ratio; GGT =  $\gamma$ -glutamyl  
469 transpeptidase; FBS = fasting blood sugar; HOMA-IR = homeostatic model assessment of insulin resistance; HDL-C = high-density lipoprotein cholesterol; QUICKI  
470 = quantitative insulin sensitivity check index; MPO = myeloperoxidase; TC = total cholesterol; TG = triglycerides; RBC = red blood cell; MCH = mean corpuscular  
471 hemoglobin; IL-6 = interleukin- 6; FGF21 = fibroblast growth factor 21.

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474 **Figure Legends**

475 **Figure 1.** The analysis of keywords co-occurrences on fatty liver and flavonoids in  
476 research during 2001–2023 from Scopus (collected on May 14th 2023).

477 **Figure 2.** Flow diagram of the study selection.

478 **Figure 3.** Forest plots from the meta-analyses of randomized controlled trials  
479 investigating the effects of flavonoids compared to control group on liver function: A)  
480 ALT; B) AST; C) GGT; D) CK-18M30; E) fibrosis score; F) steatosis score.

481 **Figure 4.** Forest plots from the ma-analyses of randomized controlled trials  
482 investigating the effects of flavonoids compared to control group on lipid profile: A)  
483 TG; B) LDL-C; C) HDL-C; D) TC.

484 **Figure 5.** Forest plots from the meta-analyses of randomized controlled trials  
485 investigating the effects of flavonoids compared to control group on inflammation: A)  
486 TNF- $\alpha$ ; B) hs-CRP; C) NF- $\kappa$ B.

487 **Figure 6.** Forest plot from the meta-analyses of randomized controlled trials  
488 investigating the effects of flavonoids compared to control group on insulin resistance:  
489 A) HOMA-IR; B) insulin; C) FBS.

490 **Figure 7.** The alleviation of NAFLD by flavonoids through various risk factors.  
491 ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT =  $\gamma$ -glutamyl  
492 transpeptidase; CK-18M30 = cytokeratin 18-m30; TG = triglycerides; TC = total  
493 cholesterol; LDL-C = low-density lipoprotein cholesterol; TNF- $\alpha$  = tumor necrosis  
494 factor- $\alpha$ ; NF- $\kappa$ B = nuclear factor- $\kappa$ B; DMY = dihydromyricetin; SIL = silymarin;  
495 HES = hesperidin; GEN = genistein.

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499 **Supporting Information**

500 **Appendix A1. Fig 1.** Research trend for publications retrieved by searching Scopus  
501 database for the keyword flavonoids and fatty liver as from the year 2000 till 2022.

502 **Appendix A1. Fig 2.** Pie chart showing papers retrieved by subject area by searching  
503 Scopus database for flavonoids and fatty liver from 2000 till now.

504 **Appendix A2.** Search term.

505 **Appendix A3.** A) Risk of bias summary. B) Risk of bias graph.

506 **Appendix A4.** Subgroup analysis of biochemical biomarkers.

507 **Appendix A5.** Forest plot, sensitivity analysis, funnel plot, Egger's regression of liver  
508 function.

509 **Appendix A6.** Forest plot, sensitivity analysis, funnel plot, Egger's regression of lipid  
510 profile.

511 **Appendix A7.** Forest plot, sensitivity analysis, funnel plot, Egger's regression of  
512 inflammation.

513 **Appendix A8.** Forest plot, sensitivity analysis, funnel plot, Egger's regression of insulin  
514 resistance.

515 **Appendix A9.** Sensitivity analysis of one by one deletion method.

516 **Appendix A10.** Forest plot for subgroup analysis.