ISSN 1029-8940 (Print)
ISSN 2524-230X (Online)
UDC 582.89:615.322
https://doi.org/10.29235/1029-8940-2026-71-2-116-124 Received 04.03.2026

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ANTI-INFLAMMATORY PROPERTIES OF EXTRACTS FROM PLANTS OF THE *RUBIACEAE* FAMILY

Abstract. *Rubiaceae* species are widely distributed, mainly concentrated in tropical regions. They contain various alkaloids, flavonoids, and other active compounds that have significant therapeutic effects on many diseases. In this study a meta-analysis of the existing experimental data on the therapeutic effects of *Rubiaceae* was conducted using Cochrane, PubMed, Google Scholar, and Web of Science databases for report retrieval. The search contained "*Gardenia*", "*Hedyotis*", "*Morinda*", "*Nauclea*", and "*Paederia*" species of *Rubiaceae*, which were used in animal inflammation models. A total of 348 papers were analyzed, duplicate studies were removed, data reliability and adequate sample sizes were filtered. Proinflammatory cytokines (PCs), and the expression of inflammatory gene *NF-κB* were used to evaluate the inflammatory levels in two animal models, the *Rubiaceae*-treated (RT) and Inflammation Model (IM). Subgroup analysis was used to explore: 1) the anti-inflammatory effects of different genera; 2) the anti-inflammatory effects of different extracts. The results from meta-analysis show that *Rubiaceae* extracts exert significant anti-inflammatory effects in animal models, with the RT group exhibiting lower levels of PCs (IL-1β, IL-6, TNF-α) and *NF-κB* expression than the IM group ($p < 0.05$). Subgroup analysis found that *Gardenia*, *Hedyotis*, and *Morinda* all significantly reduced IL-1β and TNF-α levels, while only *Morinda* had a notable inhibitory effect on IL-6; aqueous, ethanol, and terpenoid extracts all showed significant anti-inflammatory activity. Substantial heterogeneity was observed, which subgroup and meta-regression analyses identified as being primarily due to intergeneric differences. Begg's and Egger's tests indicated the presence of publication bias across the included studies. Further *in vivo* and *in vitro* experiments are therefore required to verify the anti-inflammatory effects of various medicinal plants of the *Rubiaceae* family.

Keywords: *Rubiaceae*, anti-inflammatory, *Gardenia*, *Hedyotis*, *Morinda*, *Nauclea*, *Paederia*

For citation: Yuxuan Peng, Bakhmetava A. F., Mysleika M. A., Demidchik V. V. Anti-inflammatory properties of extracts from plants of the *Rubiaceae* family. *Vestsi Natsyyanal'nai akademii navuk Belarusi. Seryya biyalagichnykh navuk = Proceedings of the National Academy of Sciences of Belarus. Biological series*, 2026, vol. 71, no. 2, pp. 116–124 (in Russian). https://doi.org/10.29235/1029-8940-2026-71-2-116-124

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ПРОТИВОВОСПАЛИТЕЛЬНЫЕ СВОЙСТВА ЭКСТРАКТОВ РАСТЕНИЙ СЕМЕЙСТВА *RUBIACEAE*

Аннотация. Виды семейства Мареновые (*Rubiaceae*) широко распространены преимущественно в тропических регионах. Они содержат различные алкалоиды, флавоноиды и другие активные соединения, обладающие выраженным терапевтическим действием в отношении широкого спектра заболеваний. В данном исследовании был проведен мета-анализ экспериментальных данных о терапевтических эффектах представителей *Rubiaceae* на основе информации из баз данных Cochrane, PubMed, Google Scholar и Web of Science. Поиск включал виды родов *Gardenia*, *Hedyotis*, *Morinda*, *Nauclea* и *Paederia*. Всего было проанализировано 348 работ, удалены дублирующие исследования, проведена фильтрация достоверности данных и наличия адекватных размеров выборок. Показано, что оценка уровня воспаления в большинстве работ проводилась на двух группах животных (группе, обработанной препаратами *Rubiaceae*, и модельной группе) с использованием тестов на присутствие провоспалительных цитокинов и экспрессию воспалительного гена *NF-κB*. Внутригрупповой анализ был направлен на изучение: 1) противовоспалительного действия растений различных родов семейства Мареновые; 2) противовоспалительного действия различных экстрактов. Результаты метаанализа показали, что экстракты растений семейства *Rubiaceae* оказывают выраженное противовоспалительное действие на животных моделях: в группе, обработанной ими, наблюдались более низкие уровни провоспалительных цитокинов (IL-1β, IL-6, TNF-α) и экспрессии *NF-κB* по сравнению с модельной группой воспаления ($p < 0,05$). Внутригрупповой анализ выявил, что экстракты растений родов *Gardenia*, *Hedyotis* и *Morinda* достоверно снижали уровни IL-1β и TNF-α, тогда как только растения рода *Morinda* оказывали выраженное ингибирующее действие по отношению к IL-6; водные, этанольные и терпеноидные экстракты демонстрировали значительную противовоспалительную активность. Установлено, что гетерогенность, обнаруженная в результате внутригруппового анализа и метарегрессии, в основном обусловлена межвидовыми различиями. Тесты Бегга и Эггера указали на наличие публикационной смещенности в отобранных исследованиях. Проведенное исследование показало, что необходимы дальнейшие эксперименты *in vivo* и *in vitro* для подтверждения противовоспалительного действия различных лекарственных растений семейства *Rubiaceae*.

Ключевые слова: *Rubiaceae*, противовоспалительное действие, *Gardenia*, *Hedyotis*, *Morinda*, *Nauclea*, *Paederia*

Для цитирования: Противовоспалительные свойства экстрактов растений семейства *Rubiaceae* / Юйсюань Пэн, А. Ф. Бахметова, М. А. Мыслейка, В. В. Демидчик // Весці Нацыянальнай акадэміі навук Беларусі. Серыя біялагічных навук. – 2026. – Т. 71, № 2. – С. 116–124. https://doi.org/10.29235/1029-8940-2026-71-2-116-124

Introduction. The *Rubiaceae* family belongs to *Angiospermae*, *Magnoliopsida*, and *Gentianales*. The *Rubiaceae* is widely distributed, mainly concentrated in tropical regions. The *Rubiaceae* is a large plant family, ranking fourth in species diversity among angiosperms. It includes approximately 637 genera and 13,500 species [1]. The plants from *Rubiaceae* family were often used as herbs because they include iridoids, indole alkaloids, anthraquinones, terpenoids, flavonoids, and other phenolic derivatives, as well as secondary metabolite alkaloids with rich biological activity. These organic compounds have important pharmacological effects and are used in research on the treatment of various diseases [1–3]. Among them, iridoids have been proven to have strong anti-inflammatory activity. Iridoids belong to the monoterpenoid components of terpenoids, with typical binary rings, ene bonds, and ether bonds, often connected to sugars to form cycloene ether terpenoid glycoside structures [4]. Iridoids are commonly found in *Rubiaceae* family, including *Hedyotis*, *Gardenia*, *Morinda*, *Paederia*, *Lasianthus*, and other genera [1, 4, 5]. There are various types of iridoid compounds with complex structures, including ordinary, cracked ring, dimer, and other types [1, 2]. It was found that the iridoids compound geniposide extracted from *Gardenia* can alleviate LPS induced cellular inflammatory damage by inhibiting the expression of the *NF-κB* pathway [6]. It was used to treat skin inflammation, cardiovascular inflammation, enteritis, and improve non-alcoholic fatty liver disease by enhancing animal antioxidant ability [7–10]. Moreover, glycosides from *Paederia* have been found to inhibit the production of nitric oxide (NO) by inhibiting the *NF-κB* pathway, reducing the expression of Proinflammatory Cytokines (PCs), and alleviating the cyto-inflammation caused by lipopolysaccharide (LPS) [11].

In this study, extracts from five very important genera of *Rubiaceae*, *Gardenia*, *Hedyotis*, *Morinda*, *Nauclea*, and *Paederia*, were included in the meta-analysis to explore the mechanisms of action of *Rubiaceae* compounds in treating different animal inflammatory diseases.

Materials and research methods. *Inclusion criteria.* The following inclusion criteria were applied: 1) research on evaluating inflammation in experimental animals; 2) research results published in English; 3) research results with clear animal numbers, mean values, and standard deviations. Previously, this approach has been used in studies investigating the effects of plant-derived medicines on hypoglycemia [12], silver nanoparticles on inflammatory diseases [13], and flavonoids as antidiabetic and anti-inflammatory agents [14].

Exclusion criteria. Typical criteria that were previously designed elsewhere [12–14] were used, including the following: 1) conference abstracts, comments, editorials, and letters; 2) treatment of human patients, *in vitro*, or other unrelated research; 3) researches without English full text; 4) studies that cannot obtain/extract data; 5) studies with sample size less than 5; 6) research without clear drug extraction methods; 7) studies that have been withdrawn.

Reports search. The following steps were carried out: 1) retrieving keywords in various databases, classifying and organizing qualified reports, and deleting duplicate reports; 2) analyzing the topic and abstract of the reports, and excluding reports that do not meet the research criteria according to the standards; 3) studying independently screened, extracted, and collected reports according to the inclusion and exclusion criteria mentioned above, while recording the number and reasons for the excluded reports.

Quality assessment. Review Manager 5.4 (Cochrane Collaboration, UK) was used to evaluate the quality of selected reports. The evaluation process includes: 1) random sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias);

4) blinding of outcome assessment (detection bias); 5) incomplete outcome data (attrition bias); 6) selective reporting (reporting bias); 7) other bias.

Statistical analysis. Origin 2019b (OriginLab Corporation, USA) was used to extract data from bar charts in various reports (Mean and SD). Review Manager 5.4 and Stata SE 17 (StataCorp LLC, USA) were used for meta-analysis. A random-effects model was used during meta-analysis when $I^2 > 50$ % (indicating high heterogeneity). Otherwise, a fixed-effects model was used. For subgroup analysis, each subgroup included at least 2 reports. Meta-regression with 95 % CIs was performed for all subgroup analyses. Begg's and Egger's tests were applied to assess publication bias when the number of included reports was ≥10.

Results. *Reports screening and study characteristics.* By searching for keywords *Gardenia* or *Hedyotis* or *Morinda* or *Nauclea* or *Paederia*, and "Inflammation" or "Inflammatory" in the title and abstract. By reading the title and abstract, 32 references were remained (Fig. 1). After full-text screening, 13 reports were excluded due to unclear extract (*n* = 1), insufficient evaluation indicators (*n* = 7), unclear number of animal samples (*n* = 3), lack of inflammation evaluation (*n* = 1), and incomplete animal individual samples (*n* = 1). (Fig. 1). Finally, 19 studies were selected that were suitable for this study and were organized according to the characteristics of the reports (Table 1).

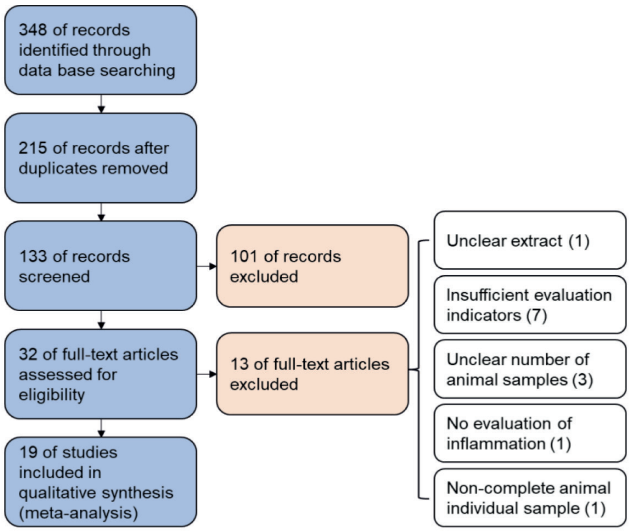

Fig. 1. Scheme of literature screening procedures for preliminary data analysis

Table 1. **Basic characteristics of the included studies**

Genera, Author, Year	Animal, *n* (RT/IM)	Inflammation model	Extracts	Outcomes	
				Proinflammatory cytokines	Genes/Proteins
Gardenia, Chen X.-Y. [et al.], 2022 [15]	R, 19/19	Dermatitis	Terpenoids	TNF-a, IL-1β, IL-6	–
Gardenia, Cheng S. [et al.], 2019 [16]	M, 10/10	Cardiovascular inflammation	Terpenoids	TNF-a	MAPK
Gardenia, Cui Y. [et al.], 2019 [17]	R, 10/10	Enteritis	Aqueous extracts	TNF-a, IL-2	*NF-κB*
Gardenia, Deng R. [et al.], 2018 [6]	R, 12/12	Arthritis	Terpenoids	IL-1β, IL-17	*NF-κB*, MAPK
Gardenia, Li H. [et al.], 2022 [18]	M, 5/5	Cardiovascular inflammation	Terpenoids	IL-1β, IL-18	AMPK, ACC, NLRP3
Gardenia, Sun Q. [et al.], 2023 [19]	R, 30/30	Cardiovascular inflammation	Terpenoids	TNF-a, IL-6, IL-1β	*NF-κB*, iNOS
*Hedyoti*s, Dai M. [et al.], 2017 [20]	M, 26/26	Hepatitis	Aqueous extracts	TNF-a, IL-1β, IL-6	–
Hedyotis, Li Y. [et al.], 2022 [21]	M, 6/6	Nephritis	Aqueous extracts	TNF-a, IL-6, IL-17, MCP-1	STAT
Hedyotis, Liu R. [et al.], 2018 [22]	M, 15/15	Pneumonia	Ethanol extracts	TNF-a, IL-1β	*NF-κB*

End of the Table 1

Genera, Author, Year	Animal, *n* (RT/IM)	Inflammation model	Extracts	Outcomes	
				Proinflammatory cytokines	Genes/Proteins
Hedyotis, Wang L.-F. [et al.], 2021 [23]	R, 10/10	Arthritis	Aqueous extracts	TNF-a, IL-1β, IL-18	Caspase-1, NLRP3
Hedyotis, Ye J.-H. [et al.], 2015 [24]	M, 8/8	Nephritis	Aqueous extracts	TNF-a, IL-1β, IL-6, MCP-1	–
Morinda, Krishnakumar N. M. [et al.], 2022 [25]	M, 6/6	Systemic inflammation	Ethanol extracts	TNF-a, IL-1β, IL-6	*NF-κB*, iNOS, COX-2
Morinda, Liang J. [et al.], 2020 [26]	M, 6/6	Enteritis	Ethanol extracts	TNF-a, IL-6, IL-17	–
Morinda, Wan Osman W. N. [et al.], 2017 [27]	R, 6/6	Arthritis	Ethanol extracts	TNF-a, IL-1β	–
Morinda, Zhang Q. [et al.], 2020 [28]	R, 10/10	Arthritis	Terpenoids	IL-1β, IL-6, IL-17	–
Nauclea, Xu H. [et al.], 2022 [29]	M,18/18	Pneumonia	Aqueous extracts	TNF-a, IL-1β, IL-6	–
Paederia, Borgohain M. P. [et al.], 2017 [30]	R, 6/6	Nephritis	Ethanol extracts	TNF-a, IL-1β, IL-6	*NF-κB*
Paederia, Hou Sh.-X. [et al.], 2014 [31]	R, 10/10	Nephritis	Terpenoids	TNF-a	–
Paederia, Zhu W. [et al.], 2012 [32]	R, 10/10	Nephritis	Terpenoids	MCP-1	*NF-κB*

N o t e. RT/IM – *Rubiaceae*-treated group/Inflammation model group; R – rats; M – mice; TNF – tumor necrosis factor; IL – interleukin; MCP – monocyte chemoattractant protein; MAPK – mitogen-activated protein kinase; AMPK – adenosine 5′-monophosphate (AMP)-activated protein kinase; *NF-κB* – nuclear factor kappa-B; NLRP – nucleotide binding domain and oligomerization domain (NOD)-like receptor thermal protein; STAT – Signal transducer and activator of transcription; Caspase– cysteinyl aspartate specific proteinase; COX – cyclooxygenase.

Risk of bias. After bias risk assessment of the 19 included studies, the main sources of bias were detection bias (100 % unclear risk of bias; Fig. 2), as none of the studies mentioned whether double-blind design was adopted. In addition, there was unclear risk of performance bias (10.53 %) and reporting bias (68.42 %; Fig. 2).

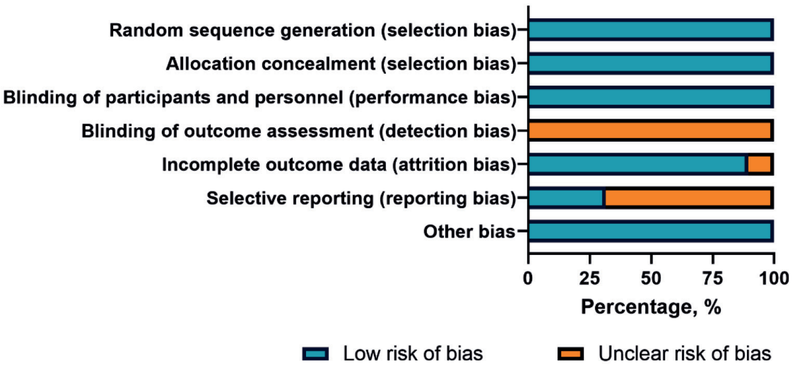

Fig. 2. Risk of bias (random sequence generation – selection bias due to inadequate generation of a randomized sequence; allocation concealment – selection bias due to inadequate concealment of allocations prior to assignment; blinding of participants and personnel – performance bias due to knowledge of the allocated interventions by participants and personnel during the study; blinding of outcome assessment – detection bias due to knowledge of the allocated interventions by outcome assessors; incomplete outcome data – attrition bias due to amount, nature or handling of incomplete outcome data; selective reporting – reporting bias due to selective outcome reporting; other bias – bias due to problems not covered)

Meta-analysis for outcomes. After screening the common detection indicators across included studies, only the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α were evaluated for anti-inflammatory activity in 5 or more studies, with 13 studies for IL-1β, 10 for IL-6, and 15 for TNF-α. Therefore, meta-analysis was performed only for these indicators, and forest plots were constructed (Fig. 3). The vertical

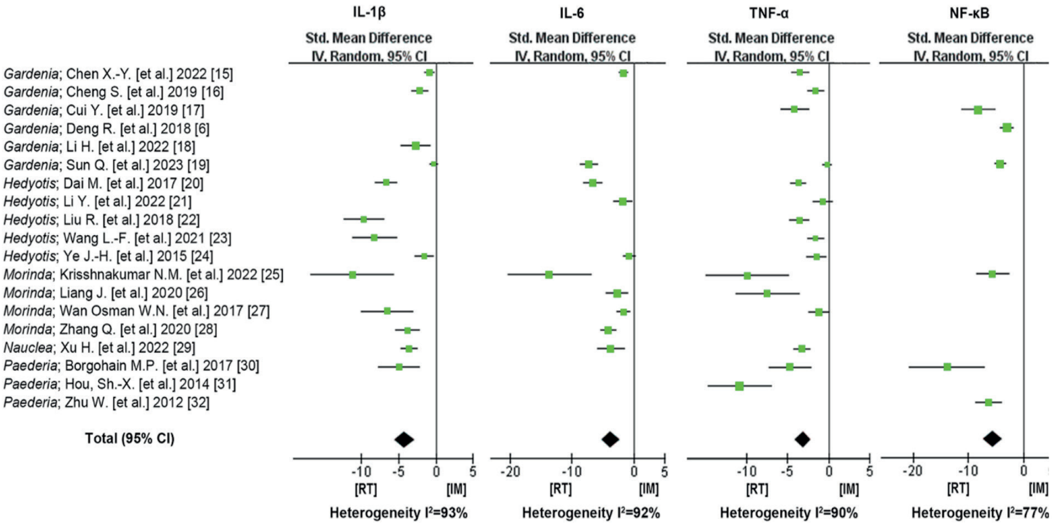

Fig. 3. Forest plot used for meta-analysis (effect of size estimates are depicted by filled squares, with horizontal whiskers corresponding to 95 % CIs. The filled diamond indicates the overall mean effect size)

line at 0 indicates no difference between the RT group and the IM group. Each green square represents the standardized mean difference (SMD) of an individual study, the horizontal line represents its 95 % confidence interval (CI), and the diamond at the bottom indicates the pooled effect size and 95 % CI. When the 95 % CI of an individual study lies entirely to the left of 0 (negative region) and does not cross the vertical line, the level of the indicator in the RT group is significantly lower than that in the IM group ($p < 0.05$). If the 95 % CI lies entirely to the right (positive region) without crossing the line, the level in the RT group is significantly higher than that in the IM group ($p < 0.05$). If the 95 % CI crosses the vertical line, the difference between the two groups is not statistically significant. As shown in Fig. 3, no significant differences in pro-inflammatory cytokine levels between the RT and IM groups were observed in some studies, including Sun Q. et al. (2023) [19] for IL-1β and TNF-α, Ye J.-H. et al. (2015) [24] for IL-6, and Li Y. et al. (2022) [21] and Wan Osman W. N. et al. (2017) [27] for TNF-α. However, the overall pooled effects (diamonds) were all located to the left of the vertical line, indicating that pro-inflammatory cytokine levels were significantly lower in the RT group than in the IM group ($p < 0.05$). While a total of 6 studies detected the expression of nuclear transcription factor *NF-κB*, the results showed that the expression of *NF-κB* in the RT group was significantly lower than IM group ($p < 0.05$). As the meta-analysis results for all four indicators showed substantial between-study heterogeneity ($I^2 > 50$ %), a random-effects model was employed for the pooled analysis. To explore the potential sources of this heterogeneity, subgroup analyses were subsequently performed.

Subgroup analysis and meta-regression test. Subgroup analyses were performed to evaluate the anti-inflammatory activity of different genera within the *Rubiaceae* family and to investigate the effects of different extraction methods on anti-inflammatory efficacy, with the aim of exploring potential sources of between-study heterogeneity. Due to the availability of sufficient data, only IL-1β, IL-6, and TNF-α were included in the subgroup analysis.

Analysis of anti-inflammatory effects of different plants was carried out. Subgroup analysis was performed to explore the anti-inflammatory effects of different *Rubiaceae* genera. The results showed that *Gardenia*, *Hedyotis*, and *Morinda* all significantly reduced IL-1β levels ($p < 0.05$; Fig. 4). Similarly, *Gardenia*, *Hedyotis*, and *Morinda* all significantly decreased TNF-α levels ($p < 0.05$; Fig. 4). For IL-6, subgroup analysis revealed that only the *Morinda* subgroup showed a significant reduction ($p < 0.05$), whereas *Gardenia* and *Hedyotis* did not exhibit a significant effect ($p > 0.05$; Fig. 4). This finding differs from the overall pooled analysis results. After subgroup analysis, the between-study heterogeneity for IL-6 and TNF-α was reduced to $I^2 < 50$ % (IL-6: $I^2 = 0$ %; TNF-α: $I^2 = 30.9$ %; Fig. 4). Meta-regression analysis showed that the p-values for both IL-1β and TNF-α were <0.05 (IL-1β: $p = 0.037$; TNF-α: $p = 0.033$; Fig. 4), suggesting that intergeneric differences may be one of the key sources of the observed heterogeneity.

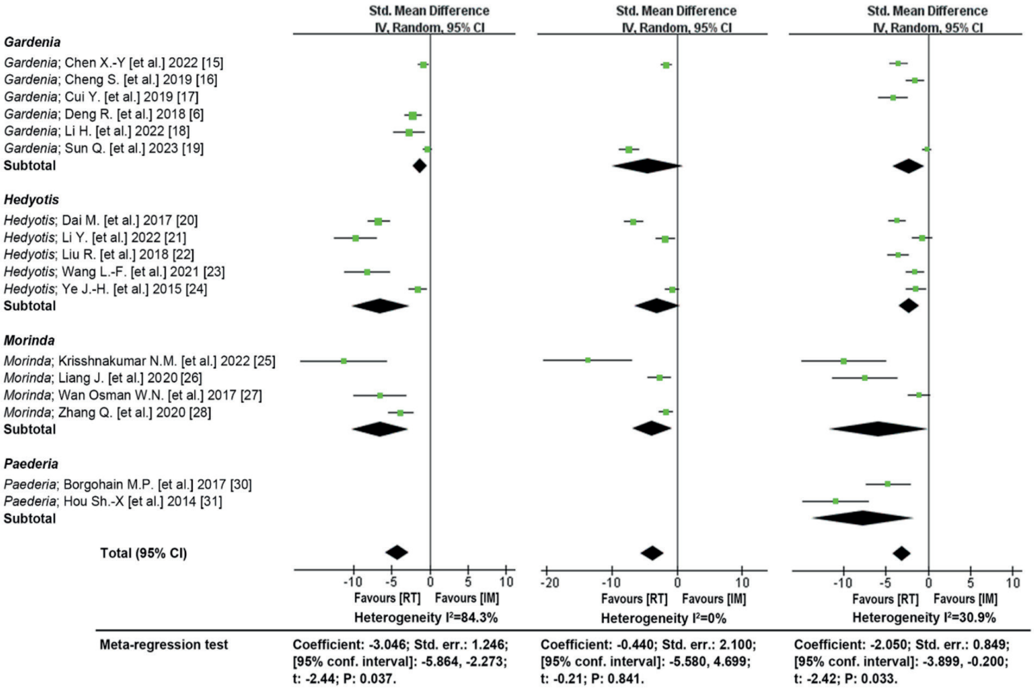

Fig. 4. Subgroup analysis of effects of different genera

An analysis of the anti-inflammatory effects of different extracts was carried out. Subgroup analysis was performed according to different extract types, including aqueous extracts, ethanol extracts, and terpenoid compound extracts. The results showed that all three types of extracts in the RT group significantly reduced the levels of IL-1β, IL-6, and TNF-α in animals ($p < 0.05$; Fig. 5). Within the subgroups, the between-study heterogeneity for IL-6 and TNF-α was reduced (IL-6: $I^2 = 0$ %; TNF-α: $I^2 = 27.8$ %; Fig. 5). However, meta-regression analysis revealed no statistically significant association between extract type and effect size for any of the three indicators ($p > 0.05$; Fig. 5). These findings suggest that extract type may contribute to the observed heterogeneity, although this could also be attributable to random variation.

Publication bias. The Begg's test and Egger's test were used to analyze IL-1β, IL-6, and TNF-α data to determine publication bias. The analysis results of IL-1β showed significant publication bias (Begg's

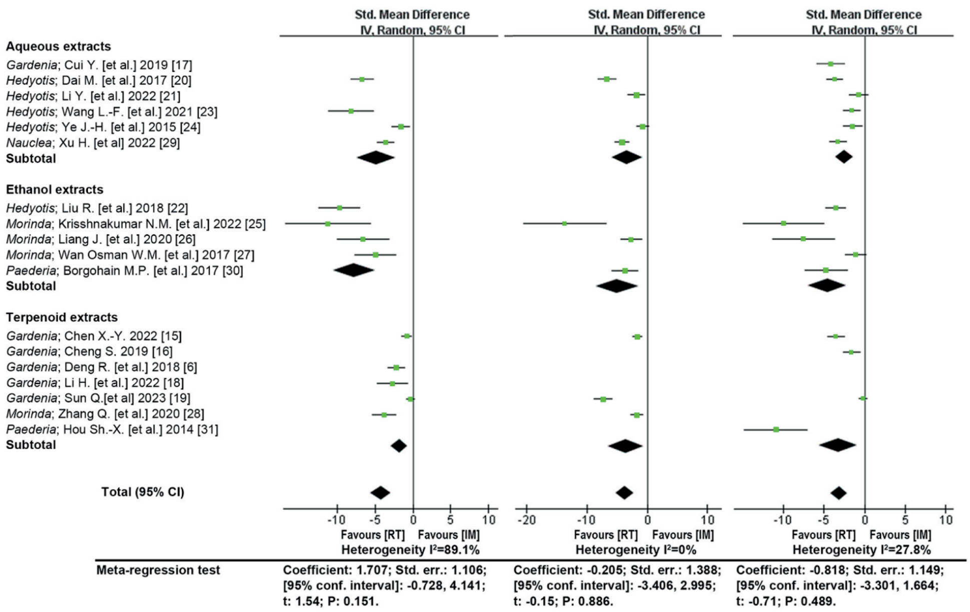

Fig. 5. Subgroup analysis of effects of different extracts

Table 2. **Publication bias test results**

Outcome indicators	p-value of Begg's test	p-value of Egger's test
IL-1β	<0.001	0.033
IL-6	0.069	0.032
TNF-α	0.001	0.138

Note. When the p-value is no more than 0.05, it suggests that the analyzed data has a pronounced publication bias within the 95 % CI.

$p \leq 0.05$; Egger's $p \leq 0.05$; Table 2). The Begg's test showed that there was no publication bias in IL-6 ($p > 0.05$; Table 2), while there was publication bias in TNF-α ($p \leq 0.05$; Table 2). The Egger's test showed that IL-6 ($p \leq 0.05$; Table 2) had publication bias, while TNF-α ($p > 0.05$; Table 2) did not have publication bias. Overall, there was a publication bias in the study of animal inflammation models treated with *Rubiaceae*.

Discussion. *Rubiaceae* plays an important role in regulating inflammatory factors and cellular immune signaling pathways. PCs and intracellular inflammatory pathways were analyzed in this study. PCs are a type of cytokine that promotes immune responses in the body during the inflammatory process [33]. Under normal immune function, their levels can directly reflect the level of animal inflammation [33]. PCs are involved in regulating vascular endothelial permeability, promoting endothelial surface adhesion, and recruiting white blood cells, lymphocytes, and monocytes [33]. While they also promote the development of inflammation and tissue damage, leading to pathological changes [34, 35]. Three types of PCs, IL-1β, IL-6, and TNF-α, were included in the meta-analysis in this study. IL-1β, IL-6, and TNF-α are involved in the development of various inflammatory diseases. Among them, IL-1 not only directly promotes cellular inflammatory response, but also induces the secretion of IL-6, and TNF-α to enhance inflammatory response [33–35]. The excessive development of inflammation undoubtedly brings damage and dysfunction to organisms, especially in inflammation caused by excessive immunity, such as rheumatoid arthritis, lupus erythematosus and delayed allergic reactions [35].

Among the 19 studies included, 6 were included in the meta-analysis. The results showed that *Rubiaceae* can inhibit the expression of *NF-κB* (Fig. 3). *NF-κB* is a key signaling pathway that regulates cellular inflammation. PCs can activate the Toll-like receptors on cells and activate the *NF-κB* signaling pathway through phosphorylation of *IκB* [36]. The activation of *NF-κB* can induce cellular inflammation and apoptosis [36]. In chronic inflammation, overexpression of *NF-κB* is an important cause of sustained cellular inflammation [36]. The anti-inflammatory mechanism of *Rubiaceae* compounds is complex, and more experiments on molecular mechanisms underlying this mechanism are needed to explore its therapeutic potential for treatment of specific inflammatory disorders.

This study mainly includes research on animal experiments, and most of the included reports do not mention laboratory double-blind settings, so it has a high risk of detection bias. In the process of conducting meta-analysis on various data, heterogeneity remained at a high level. Therefore, the study conducted subgroup analysis by genera, extracts, and treated diseases, and conducted meta-regression analysis. However, only in genera subgroups, meta-regression analysis shows that genera differences may be one of the sources of heterogeneity. Moreover, after grouping by extracts, the heterogeneity did not change. The subgroups contain aqueous extracts, ethanol extracts, and terpenoids. Terpenoids are easily soluble in water, ethanol, and methanol, so they are also abundant in both aqueous and ethanol extracts [5], which indirectly indicates that iridoids are important substances for *Rubiaceae* to exert anti-inflammatory effects. Due to the lack of quantitative analysis of all organic compounds in each report, the reference of drug dosage cannot be accurately included in the meta-analysis, which may be one of the sources of heterogeneity.

Conclusion. Nineteen studies were finally included in this meta-analysis from an initial 348 relevant reports, indicate that most published research lacks standardized experimental design and complete quantitative data eligible for meta-analysis. *Rubiaceae* plants exert significant anti-inflammatory efficacy in animal models of cardiovascular, digestive, urinary and respiratory inflammatory diseases, primarily by regulating the expression of key PCs (IL-1β, IL-6, TNF-α) and inhibiting the *NF-κB* signaling pathway. Subgroup analyses and meta-regression indicated that high heterogeneity mainly stems from intergeneric differences. Eligible reports on *Nauclea* and *Paederia* available for this study are limited, and combined with the presence of publication bias revealed by Begg's and Egger's tests, these all demonstrate that the anti-inflammatory activity of *Rubiaceae* plants requires further verification through more rigorous animal experiments.

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

Acknowledgments. This research is supported by the following funds: Natural Science Foundation of Hainan, China (No. 324QN284); Grants of BFFR B24-060-1 (State Registration Number 20242032) and B25KI-086 (State Registration Number 20250436).

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