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REVIEW

Potential of natural products in inflammation: biological activities, structure–activity relationships, and mechanistic targets

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Abstract

A balance between the development and suppression of inflammation can always be found in the body. When this balance is disturbed, a strong inflammatory response can damage the body. It sometimes is necessary to use drugs with a significant anti-inflammatory effect, such as nonsteroidal anti-inflammatory drugs and steroid hormones, to control inflammation in the body. However, the existing anti-inflammatory drugs have many adverse effects, which can be deadly in severe cases, making research into new safer and more effective anti-inflammatory drugs necessary. Currently, numerous types of natural products with anti-inflammatory activity and distinct structural features are available, and these natural products have great potential for the development of novel anti-inflammatory drugs. This review summarizes 260 natural products and their derivatives with anti-inflammatory activities in the last two decades, classified by their active ingredients, and focuses on their structure–activity relationships in anti-inflammation to lay the foundation for subsequent new drug development. We also elucidate the mechanisms and pathways of natural products that exert anti-inflammatory effects via network pharmacology predictions, providing direction for identifying subsequent targets of anti-inflammatory natural products.

Keywords Natural products · Anti-inflammatory · Derivatization · Structure–activity relationship · Network pharmacology

Introduction

Inflammation is the first response of the body's immune system to external stress and injury and serves as a protective mechanism for the body (Hou et al. 2020a; Camba-Gomez et al. 2021). Inflammation is usually accompanied by localized redness, swelling, heat, and pain, even becoming fatal in extreme cases. The external factors triggering inflammation usually include blood clots, disorders of the immune system, cancer, infection, chemical agents, physical damage, or neurological disorders such as Alzheimer's disease or depression (Roe 2021). Inflammation generally occurs through the activation of the body's pro-inflammatory mechanisms as a result of damage caused by external stimuli. Inflammation involves the accumulation and activation of immunosuppressive cells, proinflammatory factors, chemokines, and growth and angiogenic factors (Kanterman et al. 2012). A general hallmark of inflammation is the production and secretion of proinflammatory factors such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interferon-gamma (IFN-γ), nitric oxide (NO), and prostaglandin E2 (PGE2) (Fu et al. 2020). Most of the currently developed anti-inflammatory drugs have been designed for the production and secretion process of these pro-inflammatory factors (Dinarello 2010).

Currently, anti-inflammatory drugs mainly consist of glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) (Bacchi et al. 2012; Song and Feng 2023). With their extensive clinical use, it was discovered that adverse

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reactions could cause damage to the body. These impairments decreased the quality of patients' lives and detracted value from the original purpose of using the drugs to treat inflammation. Glucocorticoids can inhibit the expression of proinflammatory genes but risk triggering and exacerbating infections (Fan and Morand 2012). In addition, long-term high doses of glucocorticoids might lead to Cushing's syndrome in clinical practice, as well as cause sodium and water retention and an increased risk of hypertension (Decani et al. 2014; Üstyol et al. 2017). On this basis, NSAIDs were selected for anti-inflammatory treatment. NSAIDs can inhibit the body's production of prostaglandins by suppressing the activity of cyclooxygenase (COX), thereby achieving antipyretic and analgesic effects. Due to the protective effect of prostaglandins on the gastric mucosa, the use of NSAIDs caused several gastrointestinal reactions, including anorexia, abdominal pain, and possibly severe myocardial infarction, stroke, etc. In a survey of 61,971 patients with first myocardial infarction, Olsen et al. (2015) found an increased incidence of combined cardiovascular events (cardiovascular death, nonfatal recurrent myocardial infarction, ischemic stroke, transient ischemic attack, and systemic arterial embolism) in patients treated with NSAIDs.

Natural products originate from a wide variety of sources and show great potential in the field of new drug development. It was discovered that natural products isolated from some plants, animals, or microorganisms, such as phenylpropanoids, quinones, alkaloids, terpenoids, and flavonoids, possess good anti-inflammatory activity (Liu and Yu 2019). Then, some studies demonstrated the mechanism by which these isolated natural products exert anti-inflammatory activity (Aswad et al. 2018). In recent years, the emerging approach of network pharmacology has become an essential tool for identifying drug targets and exploring mechanisms of action. The application of network pharmacology could help to identify new targets and approaches for existing diseases and provide new avenues for drug discovery in complex diseases. Currently, several studies have predicted and validated the relevant targets of natural products with anti-inflammatory effects, such as TNF-α, IL-6 and interleukin-1β (IL-1β), as well as the mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK)/signal transducer and activator of transcription (STAT) and phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathways, through network pharmacology, which lays the foundation for further development of lead compounds with anti-inflammatory activity (Song et al. 2020a, b; Aihaiti et al. 2021; Gan et al. 2021; Guo et al. 2022; To et al. 2022; Wang et al. 2022). Hence, this review attempts to summarize the research progress on the anti-inflammatory activity of natural products from structure–activity relationships and the application of network pharmacology, for over two decades, which is used to determine the anti-inflammatory mechanism. Network pharmacology focuses on the relationship between the structure of different active natural components and their anti-inflammatory activity, which is important in the search for new, efficient, and safe anti-inflammatory drugs as well as the redevelopment of existing anti-inflammatory drugs.

Phenylpropanoids

Phenylpropanoids refer to natural organic compounds containing one or several C6–C3 units, including simple phenylpropanoids, coumarins, lignans, and several other major categories, which contain most of the natural aromatic organic compounds. A large number of in vitro experiments have shown that certain phenylpropanoids have a well-defined anti-inflammatory potency, which indicates great potential for the development of anti-inflammatory agents. However, there is a lack of large-scale experimental data and structure-effect relationship studies based on validated evidence in human studies, which limits research on the anti-inflammatory agents of phenylpropanoid natural product molecules (Korkina et al. 2011).

Network pharmacological studies on the anti-inflammatory activity of phenylpropanoids

Zhu et al. (2022) explored the therapeutic mechanism of wuyao-danshen on endometrial inflammation and found that coumarin could bind to inflammation-associated proteins such as signal transducer and activator of transcription 3 (STAT3), phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1), and mitogen-activated protein kinase 1 (MAPK1) through network pharmacological prediction, which was demonstrated to be related to these proteins through subsequent experiments. Wei et al. (2019) revealed that the anti-inflammatory targets of lignans from *S. chinensis* were related to MAPK, tumor necrosis factor (TNF), and arachidonic acid metabolism through network pharmacological prediction, which was found to be the same as the prediction in the subsequent experimental validation. By constructing a protein–protein interaction (PPI) network, Yang et al. (2020a) reported that inositol-trisphosphate 3-kinase C and tyrosyl—deoxyriboNucleic acid (DNA) phosphodiesterase 1 might be the key targets of heptaphyllum lactone in pudilan xiaoyan oral liquid for the treatment of tonsillitis. Duan et al. (2022) performed a network pharmacological prediction study on the dichloromethane extract of chamomile containing coumarin and concluded that their anti-inflammatory targets were IL-6, the nuclear factor kappa-B (NF-κB) pathway,

extracellular regulated protein kinases 1 (ERK1) and extracellular regulated protein kinases 2 (ERK2) cascade reactions, and TNF. These targets were confirmed to be important for the anti-inflammatory activity of coumarins in the following studies. Ma et al. (2022b) identified STAT3, MAPK1, and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) as the targets of ferulic acid, caffeic acid, and other coumarin-like extracts based on network pharmacology in a biomarker study of shaoyao gancao decoction, which was validated by in vitro cellular experiments. Yuan et al. (2021) determined that the PI3K/AKT pathway associated with anti-inflammation in the network pharmacological prediction of the target of scopolamine's action on small-cell lung cancer and verified this association by molecular docking. Signaling pathways such as NF-κB, STAT3, PI3K/AKT and MAPK might be associated with the exertion of anti-inflammatory activity by phenylpropanoid analogs, as predicted by network pharmacology and verified experimentally.

Anti-inflammatory activity of phenylpropanoids

We have included a summary of the structures of phenylpropanoids and their derivatives with anti-inflammatory activity in Figs. 1 and 2. The two stronger anti-inflammatory phenylpropanoid derivatives P1 and P2 were identified in the study of *Croton velutinus* extract by Abreu and coworkers. The concentration for 50% of maximal effect (EC_{50}) values of P1 for NO and IL-1β were 4.3 ± 0.6 and 3.68 ± 0.2 μM, respectively, and those of P2 were 1.7 ± 0.4 and 1.6 ± 0.1 μM, respectively, similar to the anti-inflammatory effect of dexamethasone on NO and IL-1β (Abreu et al. 2020). Cheng et al. (2017) demonstrated the anti-inflammatory activity of Compounds P3, P4, and P5 from the root extract of *Ficus hirta Vahl*. Compounds P3 and P4 showed weak inhibitory effects on NO release, while Compound P5 (half maximal inhibitory concentration = 19.33 ± 2.41 μM) showed a stronger inhibitory effect on NO than indomethacin (IC_{50} = 48.26 ± 2.83 μM). Zhao and associates examined the fruits of *Xanthium sibiricum* and reported that the phenylpropanoid P6 had a significant inhibitory effect on NO release in lipopolysaccharide (LPS)-activated RAW264.7 cells, with a half maximal inhibitory concentration (IC_{50}) value of 9.54 ± 0.57 μM (Xia et al. 2022). Yang et al. (2021) obtained Compounds P7 and P8 from the roots of *Dendropanax dentiger* with IC_{50} values of 6.25 ± 0.42 and 7.87 ± 0.67 μM, respectively, which probably achieved their anti-inflammatory effects through inhibition of the NF-κB, Akt, and JNK signaling pathways. Zhang et al. (2019b) derived seven phenylpropanoids (P9-P15) from *Canarium album Raeusch.* that significantly dampened the expression of the pro-inflammatory mediators inducible nitric oxide synthase (iNOS) and COX-2 in BV-2 cells induced by LPS in a dose-dependent manner, which was comparable to the anti-inflammatory effect of the positive control drug minocycline. Grover and Jachak (2015) identified the coumarin derivatives P16 and P17 as the most potent inhibitors of carrageenan gum-induced rat paw edema inhibition assay, with the potential to be exploited in acute inflammation studies. Son et al. (2022) developed the phenylpropanoid P18 from the roots of *Polygala tenuifolia Willd*, which possessed considerable inhibitory effects on NO and PGE2 synthesis, with IC_{50} values of 32.92 and 4.57 μM, respectively. Qiu et al. (2021) obtained phenylpropanoid derivatives P19-P24 from the roots of *Oxybaphus himalaicus*, which displayed some inhibitory effects on NO release and IL-6 secretion, with IC_{50} values of less than 50 μM, with P24 being the most potent and comparable to dexamethasone. Jackson's team synthesized several derivatives based on coumarin matrices and examined their inhibitory effects on iNOS expression. Among them, compounds P25 (IC_{50} = 0.061 μM), P26 (IC_{50} = 0.143 μM), and P27 (IC_{50} = 0.441 μM) showed excellent inhibitory activities relative to other similar compounds (Jackson et al. 2005). Tuohongerbieke et al. (2021) investigated the lignan amines P28-P32 in a study of *Limonium gmelinii (Willd.) Kuntze*, with inhibitory effects on COX-2 and IC_{50} values in the range of 15–23 μM. In a study of active coumarins in *pomelo peel*, Zhao et al. (2019) and equivalents yielded five coumarin analogs, P33-P37, with strong inhibitory effects on the secretion of the inflammatory factors IL-1β, PGE2, and TNF-α, comparable to the effects of dexamethasone (10 μg/ml) at a concentration of 5 μg/ml. Buran et al. (2021) introduced piperazine and piperidine groups on 7-hydroxycoumarin and obtained Compounds P38 and P39, which produced the best inflammatory inhibitory effects. The nitrite inhibition percentages of these compounds were 55.18 and 50.29% and were better than that of the control indomethacin (33.50% inhibition). Kontogiorgis and Hadjipavlou-Litina (2005) synthesized a series of mannich base derivatives of coumarin in their study of the anti-inflammatory activity of coumarin, in which compounds P40 and P41 had a significant inhibitory effect on carrageenan gum-induced edema in rats with inhibition rates of more than 75%, stronger than that of the positive drug indomethacin with an inhibitory rate of 45%. Nayeli et al. (2020) extracted Compound P42 from *Tagetes lucida Cav*, which yielded the best edema inhibition with 81.1%, and the anti-inflammatory effect was related to the 7-position substitution of the parent nucleus. Al-Wabli et al. (2018) synthesized five new coumarin analogs, P43-P47, which exhibited notable anti-inflammatory activity compared to that of the positive drug celecoxib, with 30 min edema inhibition ranging from 72.59 to 91.75% in a formalin-induced edema assay in rats. Hamid and Salih (2022) synthesized four derivatives

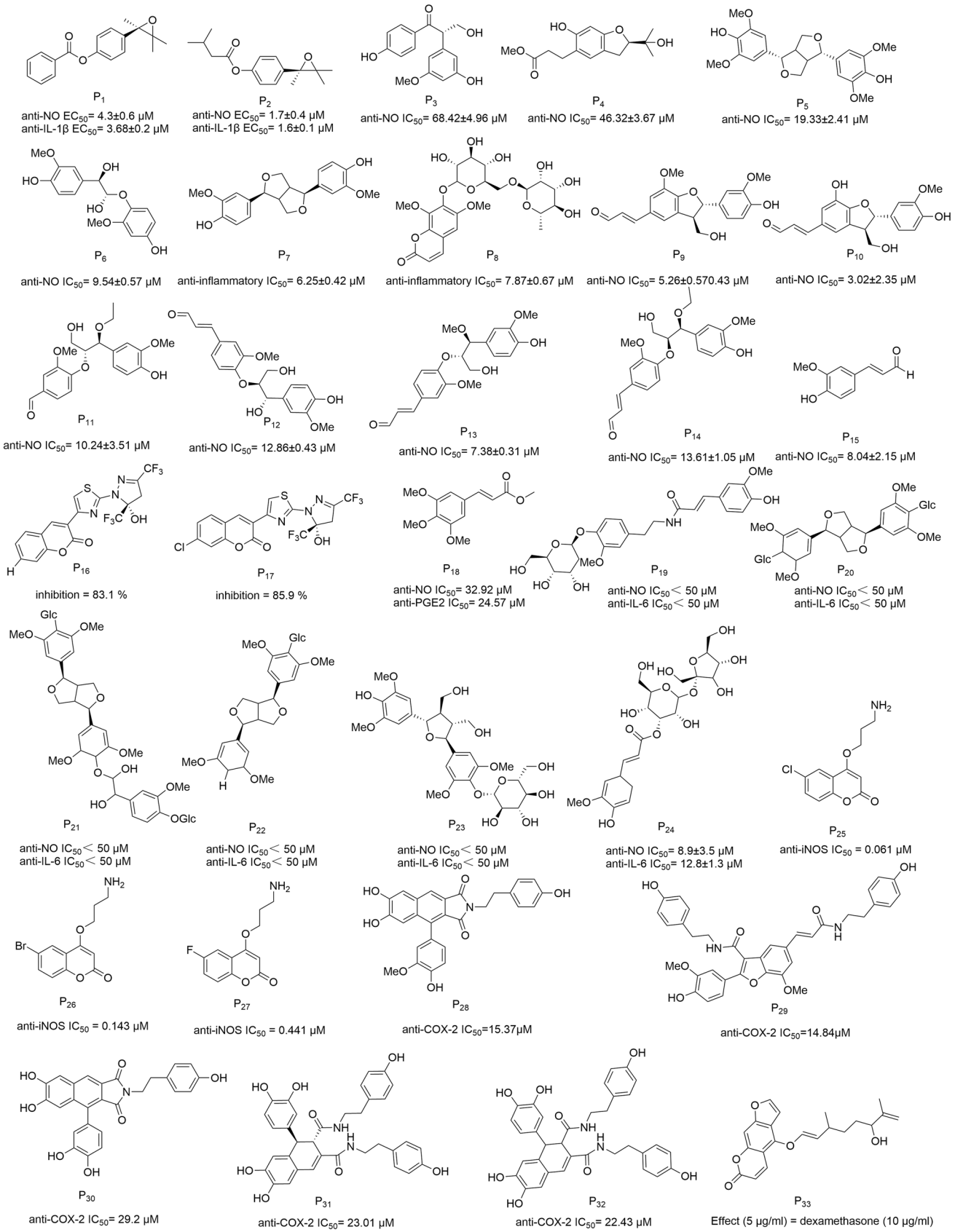

Fig. 1 Structures of Phenylpropanoids (and their derivatives) P1–P33 with anti-inflammatory activity

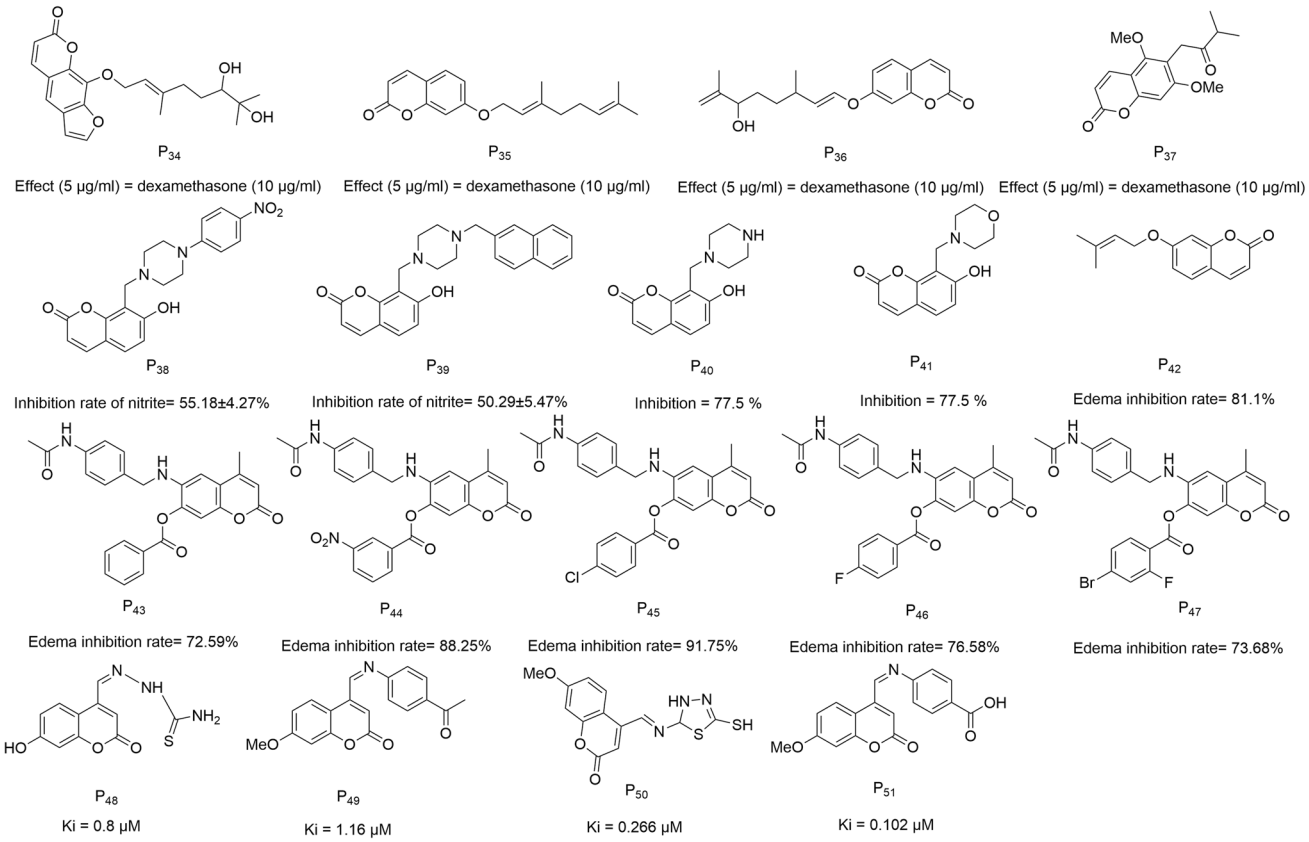

Fig. 2 Structures of Phenylpropanoids (and their derivatives) P34–P51 with anti-inflammatory activity

of the coumarin Schiff base, P48- P51, which showed anti-inflammatory activity comparable to that of ibuprofen and had Ki values between 1.16 and 0.1 µM.

Structure–activity relationships for the anti-inflammatory activity of phenylpropanoids

The anti-inflammatory effects of phenylpropanoids were reported mostly for coumarin derivatives, so the following section was devoted to coumarin parent nucleus substitutions, and the structure-effect relationships are presented in Fig. 3. The modifications of coumarins were concentrated at the 3, 4, and 7 positions. In the study of the parent nuclei of coumarin molecules, it was determined that most of the synthetic products had C-3 and C-4 substituents, C-5 substituents were rare in plant-derived products, and the C-7 and C-8 substituents generally had similar characteristics (Bansal et al. 2013). The introduction of a thiazole ring at the C-3 position of the parent nucleus potentiated anti-inflammatory activity and had possible therapeutic potential in acute inflammation, moreover, the compound P16, which was unsubstituted at the C-7 position, had a better anti-inflammatory effect than the chlorine atom-containing compound P17 (Grover and Jachak 2015). Small aliphatic groups could be added at the C-4 position, and the introduction of Schiff bases altered the anti-inflammatory activity of the products (Cheng et al. 2004), e.g., compounds P46-P49 increased their anti-inflammatory effect compared to the original aldehyde activity after the introduction of Schiff bases (Hamid and Salih 2022). The reaction of 4-bromomethylcoumarin with 2,4-dihydroxyacetophenone synthesized 4-(4′-acetyl-3′-hydroxyphenoxymethyl)-coumarin, which was less active, and it was found that the cyclization, of the portion with an o-hydroxyl structure to a chromone or a benzofuran, increased the analgesic and anti-inflammatory activity (Ghate et al. 2005). The substituent group at the C-5 position was often a hydroxyl group, and when halogen substitution was made at the C-6 position, the Cl substitution was associated with greater anti-inflammatory activity than the fluorine and bromine atoms in comparison to compounds P45-P47 (Grover and Jachak 2015). The presence of N,N-dimethylcarbamate at the C-7 position resulted in stronger anti-inflammatory activity when replaced by N,N-dimethylthiocarbamate, N,N-diethylcarbamate, or isopentadienyl substituents.

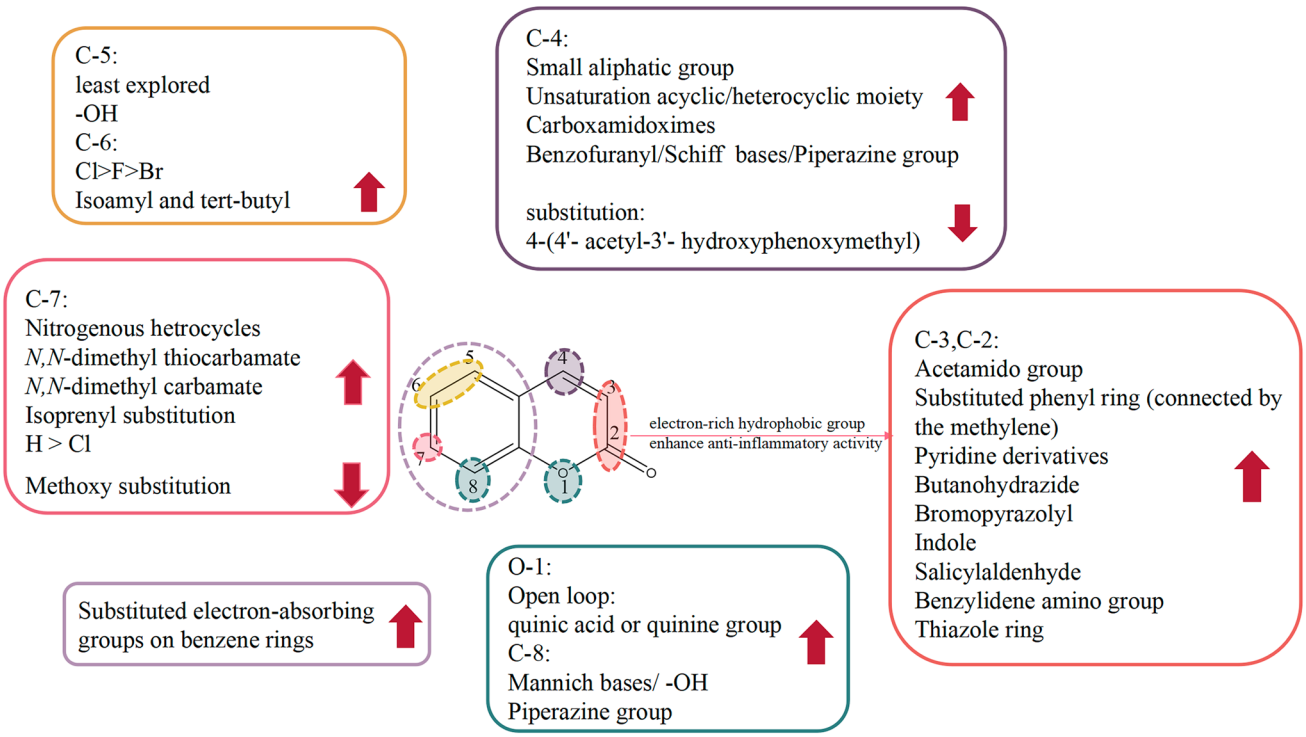

Fig. 3 Structure–activity relationship for the anti-inflammatory activity of phenylpropanoids

However, the anti-inflammatory activity was observed to be significantly reduced when the position was replaced by methoxy substituents (Nayeli et al. 2020). Displacement of some Mannich bases at the C-8 position increased their inhibitory effect on inflammation, even exceeding that of indomethacin under the same conditions (Kontogiorgis and Hadjipavlou-Litina 2005), and the introduction of specific piperazine groups also boosted the anti-inflammatory activity. For example, compounds P40 and P41 C-8 introduced piperazine and piperidine groups, which increased the anti-inflammatory activity and inhibited inflammation optimally (Buran et al. 2021). With further structural modifications on the introduced piperazine moiety, the anti-inflammatory activity of P39 containing a strongly conjugated naphthalene ring was superior to that of P38 containing a nitroacyl group (Kontogiorgis and Hadjipavlou-Litina 2005). The more electron-withdrawing groups on the substituted benzene ring, the stronger the COX-2 inhibition; for example, an electron-withdrawing group intensified the anti-inflammatory activity, and an electron-donating group decreased the anti-inflammatory activity in the coumarin-benzimidazole system (Singh et al. 2019). Ma et al. (2022a) compared the anti-inflammatory activity of different coumarin parent compounds and showed that the introduction of quinuclidic acid or quinuclidinic acid groups at the 1-position of coumarin augmented the anti-inflammatory activity of the molecules.

Quinones

Quinones are natural organic compounds that widely exist in nature and have various chemical structures. The common backbone structures were mainly categorized into four types: benzoquinone, naphthoquinone, anthraquinone, and phenanthrenequinone. Quinones and their derivatives with anti-inflammatory activity are summarized in Figs. 4 and 5.

Network pharmacological studies on the anti-inflammatory activity of quinones

Wen et al. (2020) conducted a network pharmacological study on chaiqin chengqi decoction and discovered that its anthraquinone components could inhibit inflammation by affecting the regulation of toll-like receptor 4 (TLR4)/NOD-like receptor thermal protein domain associated protein 3 (NLRP3)—related proteins and the inhibition of NO production. Sun et al. (2022) predicted that dihydrotanshinone I, the active ingredient in the cyberpharmacological study of Huo Luo Xiao Ling Dan,

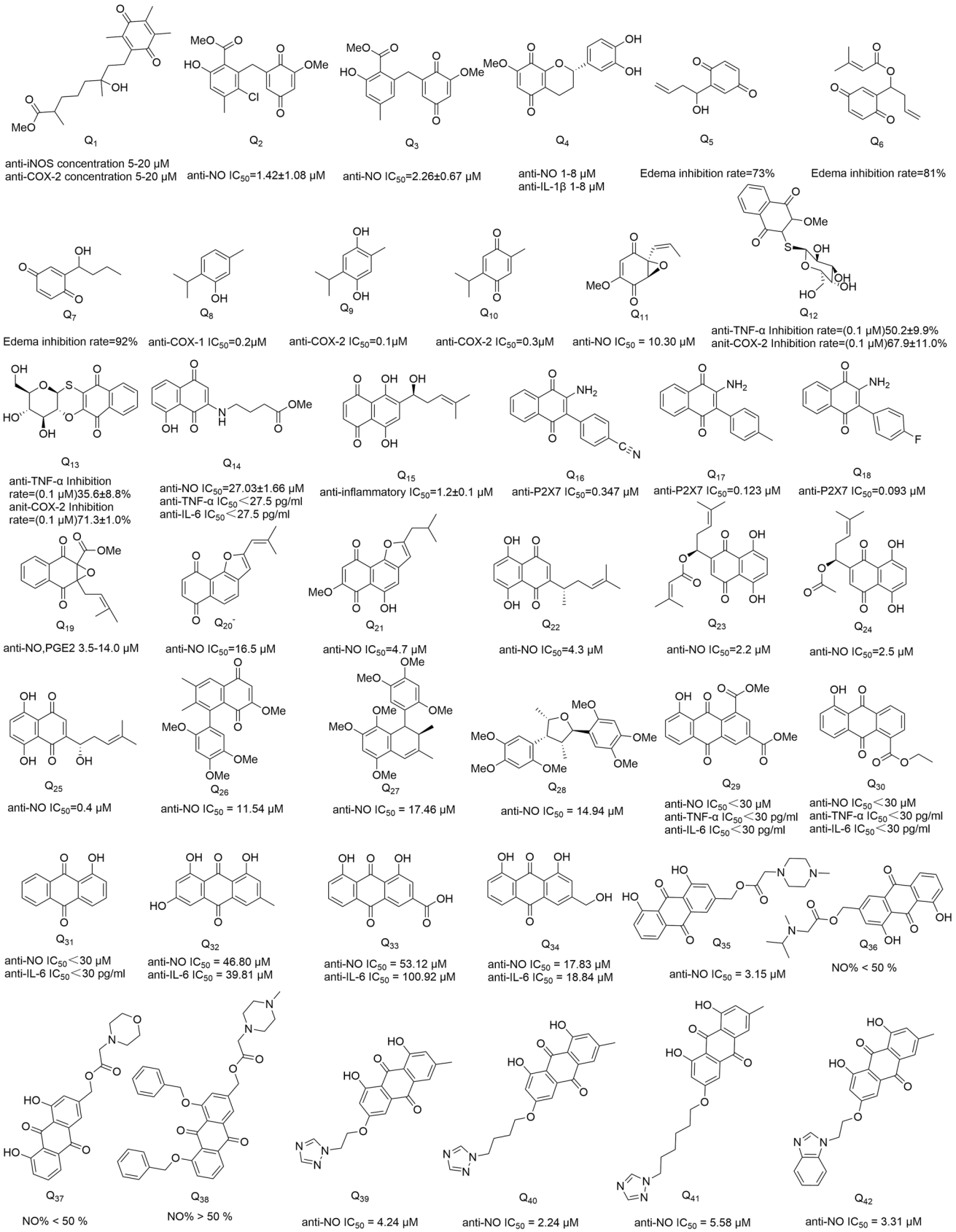

Fig. 4 Structures of quinones (and their derivatives) Q1–Q42 with anti-inflammatory activity

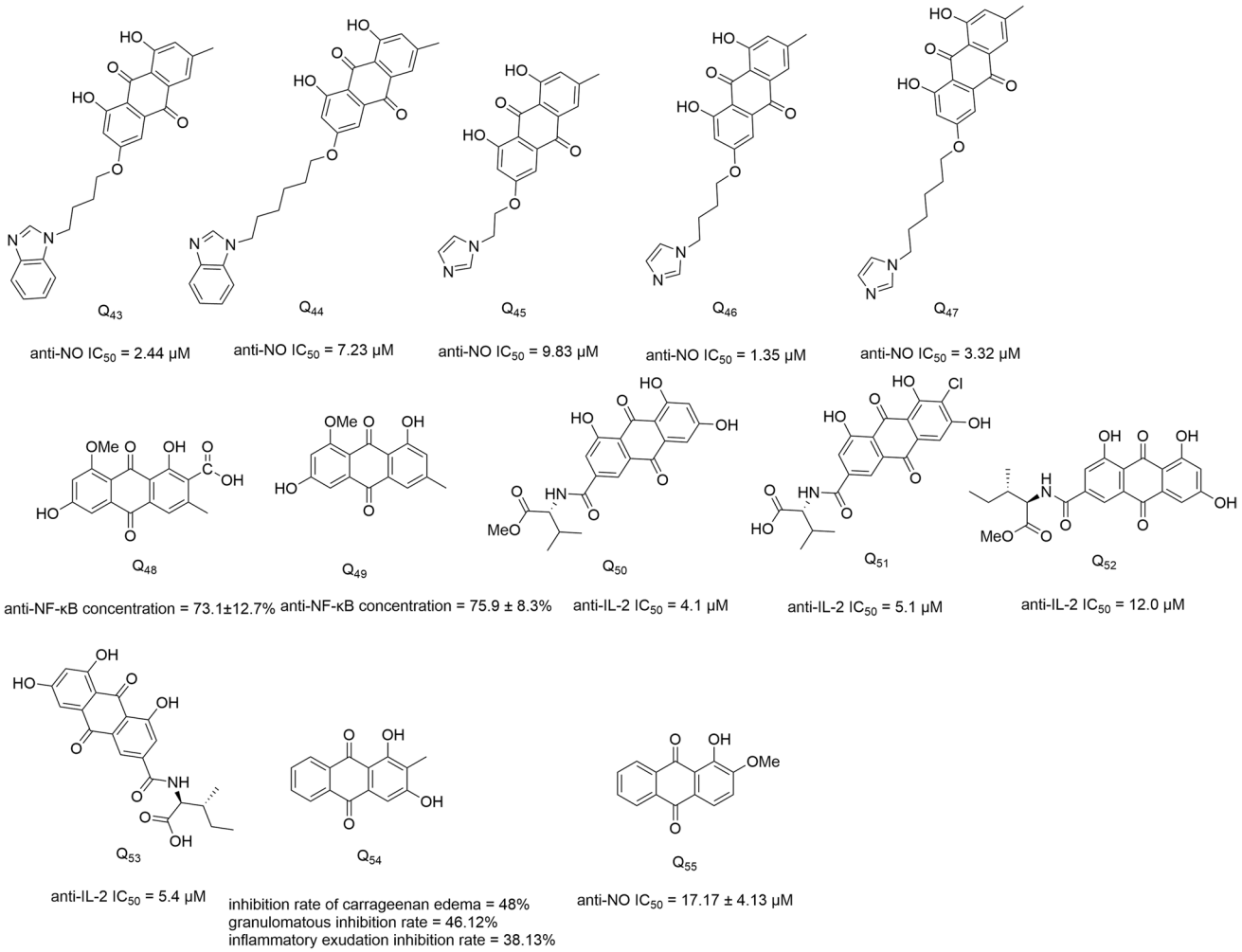

Fig. 5 Structures of quinones (and their derivatives) Q43–Q55 with anti-inflammatory activity

could target the STAT3, AKT1, and MAPK signaling pathways, and the predicted targets were confirmed to be accurate and effective in the further experiments. Zhou et al. (2021) predicted the anti-inflammatory-related targets PI3K-Akt, adenosine 5′-monophosphate-activated protein kinase (AMPK), and Janus tyrosine kinase (Jak)—STAT3 of the active ingredient aloe-emodin in their network pharmacology-based anti-hepatic fibrosis study, as well as confirming that the targets mentioned above were indeed the targets of anti-inflammatory effects of aloe-emodin through in vitro cellular experiments. Rhodopsin, as a homolog compound of aloe-emodin, was revealed to bind to anti-inflammatory-related targets such as TNF as well as the MAPK pathway in the network pharmacological study prediction (Liang et al. 2021). Yin et al. (2022) discovered that the main targets of anthraquinones might be the MAPK pathway, IL-6, and vascular endothelial growth factor (VEGF) in their network pharmacological prediction of the active ingredients of dachengqi decoction, which were confirmed to be truly related to the anti-inflammatory effects exerted by their anthraquinone constituents within a later study. Network pharmacological and experimental demonstration studies showed that the potential targets for quinones when exerting anti-inflammatory activity are IL-6, VEGF, TLR4/NLRP3, STAT3, PI3K-Akt, MAPK, etc.

Anti-inflammatory activity of benzoquinones

Lin et al. (2013) obtained a quinone compound (Q1) from the cultured soft coral *Sinularia flexibilis*, which dramatically injured the accumulation of pro-inflammatory iNOS and COX-2 proteins in an in vitro anti-inflammatory action assay, and the inhibition was more prominent within the concentration of 5–20 μM. Zhang et al. (2019a) isolated two compounds, Q2 and Q3, with anti-inflammatory activity from *Eurotium cristatum*, with quinone matrices and

IC_{50} values of 1.48 ± 1.08 and 2.26 ± 0.67 μM, respectively. Long et al. (2019) obtained a new para-quinone flavane (Q4) from the leaves of *Ilex chinensis Sims*, and the compound dose-dependently inhibited NO and IL-1β production in the range of 1–8 μM, which indicated a beneficial in vitro anti-inflammatory activity. Sagnou et al. (2009) synthesized three novel benzoquinone compounds, Q5, Q6 and Q7, which showed significant inhibition of horny goat gum-induced rat paw edema by 73%, 81%, and 92%, respectively. The in vitro anti-inflammatory activity of Compounds Q8–Q10 from *Nigella sativa seeds* was investigated by Marsik et al. (2005) Q8 demonstrated a marked inhibitory effect on COX-1 (IC_{50} = 0.2 μM). Q9 and Q10 presented potent COX-2 inhibition (IC_{50} = 0.1 and 0.3 μM), which was stronger than the inhibitory effect of indomethacin. Lee et al. (2013) performed anti-inflammatory and cytotoxicity assays on Q11, a benzoquinone derivative obtained from *Acorus gramineus*, which showed a weak cell-killing effect and a stronger inhibitory effect on NO production than the positive control (IC_{50} = 10.30 μM).

Anti-inflammatory activity of naphthoquinones

Kozlovskiy et al. (2023) secured two 1,4-naphthoquinone derivatives of thioglucosides, Q12 and Q13, both of which exerted an inhibitory effect on TNF-α and COX-2, with Q12 having a stronger inhibitory effect on TNF-α than Q13. Compound Q14 was isolated from the roots of *Juglans mandshurica* by Park and colleagues as a naphthoquinone product with good anti-inflammatory activity, inhibiting NO production (IC_{50} = 27.03 ± 1.66 μM) and inhibiting the expression of TNF-α and IL-6 (Piao et al. 2022). Lohberger et al. (2022) found that purslane (Q15) blocked the expression of phorbol 12-myristate 13-acetate (PMA)-induced COX-2 mRNA and protein (IC_{50} = 1.2 ± 0.1 μM), thereby blocking PGE2 biosynthesis in human mammary epithelial cells transfected with luciferase and achieving COX-2 inhibition. The structural modification of 2-amino-3-aryl-1,4-naphthoquinone by de Luna Martins et al. (2020) successfully yielded three derivatives, Q16, Q17, and Q18, with inhibitory activity against the P2X7 receptor, IC_{50} values of 0.347, 0.123, and 0.093 μM, and low cytotoxicity. Ju Woo et al. (2017) discovered that Q19, a naphthoquinone constituent of *R. cordifolia* L., had a prominent anti-inflammatory effect, inhibiting NO and PGE2 synthesis in the range of 3.5–14.0 μM. Compounds Q20–Q25 that Dong et al. (2017) developed from *Onosma paniculatum* possessed naphthoquinone matrices and had potent inhibitory effects on NO, with IC_{50} values below 17 μM. Lee et al. (2013) reported that the naphthoquinone derivatives Q26–Q28 not only possessed low cytotoxicity but also showed an inhibitory effect equivalent to that of the positive control in inhibiting NO release, with IC_{50} values all below 17.5 μM.

Anti-inflammatory activity of anthraquinones

Piao et al. (2022) derived Compounds Q29–Q31 from the roots of *Juglans mandshurica*, which contained anthraquinones and possessed good anti-inflammatory activity, suppressing the release of inflammatory mediators, such as NO, TNF-α, and IL-6, with an IC_{50} value of less than 30 μM. Vanisree et al. (2020) extracted rhodopsin (Q32) from *Aloe barbadensis*, which exerted an inhibitory effect on NO, TNF-α, and IL-12 (interleukin-12) and did not affect cell viability at a concentration of 400 μM (IC_{50} = 120 μM). Xin et al. (2022) studied the effect of anthraquinone on the immune response and found that rhubarbic acid (Q33) produced inhibitory effects on iNOS, TNF-α accumulation, and NF-κB activation in LPS-induced RAW264.7 mouse macrophages at concentrations of 60–140 μM and inhibited the release of NO and IL-6 when the concentration was in 35 μM. Whereas Hu et al. (2021) demonstrated some differences in the anti-inflammatory effects of rhodopsin (Q32), rhubarbic acid (Q33), and aloe rhodopsin (Q34) obtained from Rhei Radix et Rhizoma, with Q34 having a stronger inhibitory effect on IL-6 as well as NO than both Q32 and Q33. Shang and his collaborators carried out a derivatization synthesis using rhodopsin (Q32) as the parent to obtain compounds Q35–Q38 and revealed that Q35 had the most prominent inhibitory activity for NO (IC_{50} = 3.15 μM), which held the potential for further development (Shang et al. 2022). Zhu et al. (2020) synthesized a series of imidazole derivatives Q39–Q47 based on Q32, of which Q46 displayed the strongest inhibitory activity against NO (IC_{50} = 1.35 μM), which was stronger than the positive drug dexamethasone (IC_{50} = 12.61 μM). The anthraquinone products Q48 and Q49, secured by Du et al. (2018) in the study of polyketide derivatives of the sponge-associated *fungus Aspergillus europaeus*, both inhibited NF-κB activation by 73.1 ± 12.7 and 75.9 ± 8.3%, respectively. Luo et al. (2017) yielded four anthraquinone products, Q50–Q53, in an amino acid-conjugated anthraquinone study of the marine fungus *Penicillium* sp. SCSIO sof101, which were inhibitory to interleukin-2 (IL-2) secretion ($IC_{50} \leq$ 12.0 μM). Chitsaz et al. (2021) revealed that methylisocynarin (Q54) exhibited a significant anti-inflammatory effect and suppressed granuloma and inflammatory exudation in cotton ball-induced inflammation assays in rats with inhibition rates of 46.12% and 38.13%, respectively, which

were superior to those of indomethacin, a positive control drug. Luo et al. (2021) derived Compound Q55 from the rhizome of *Morinda officinalis*, which strongly inhibited NO with an IC_{50} value of 17.17 ± 4.13 μM.

Structure–activity relationships for the anti-inflammatory activity of quinones

Most of the quinones with anti-inflammatory activity were reported to have 1,4-naphthoquinone and anthraquinone matrices, and their anti-inflammatory conformational

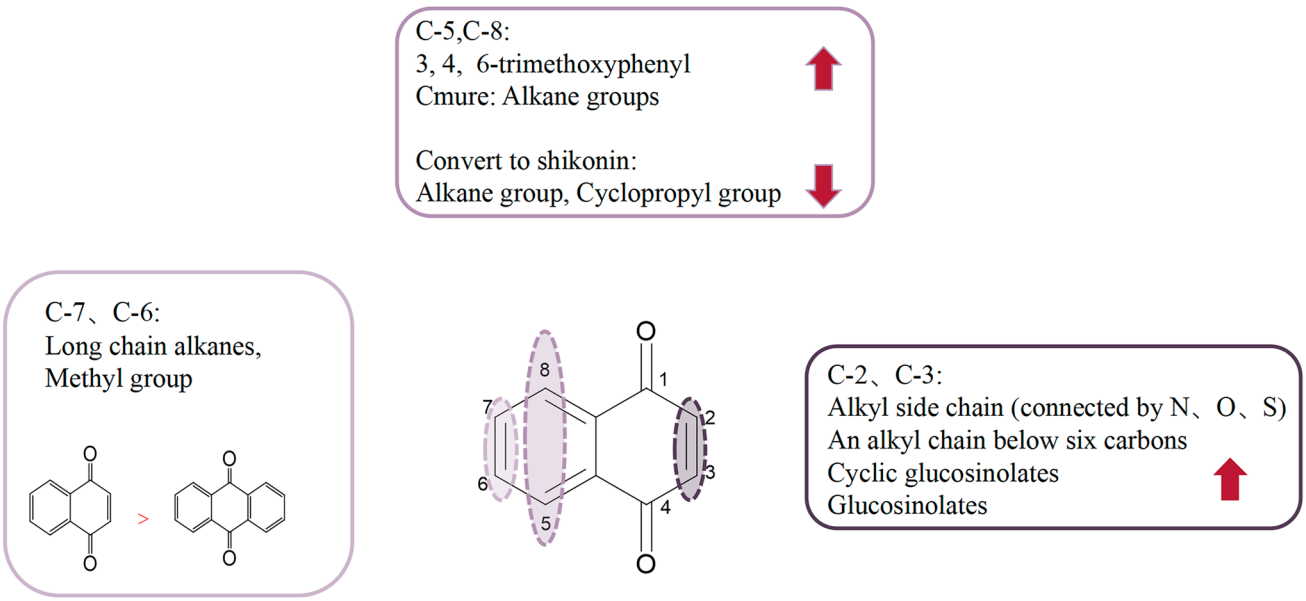

Fig. 6 Structure–activity relationship for the anti-inflammatory activity of naphthoquinones

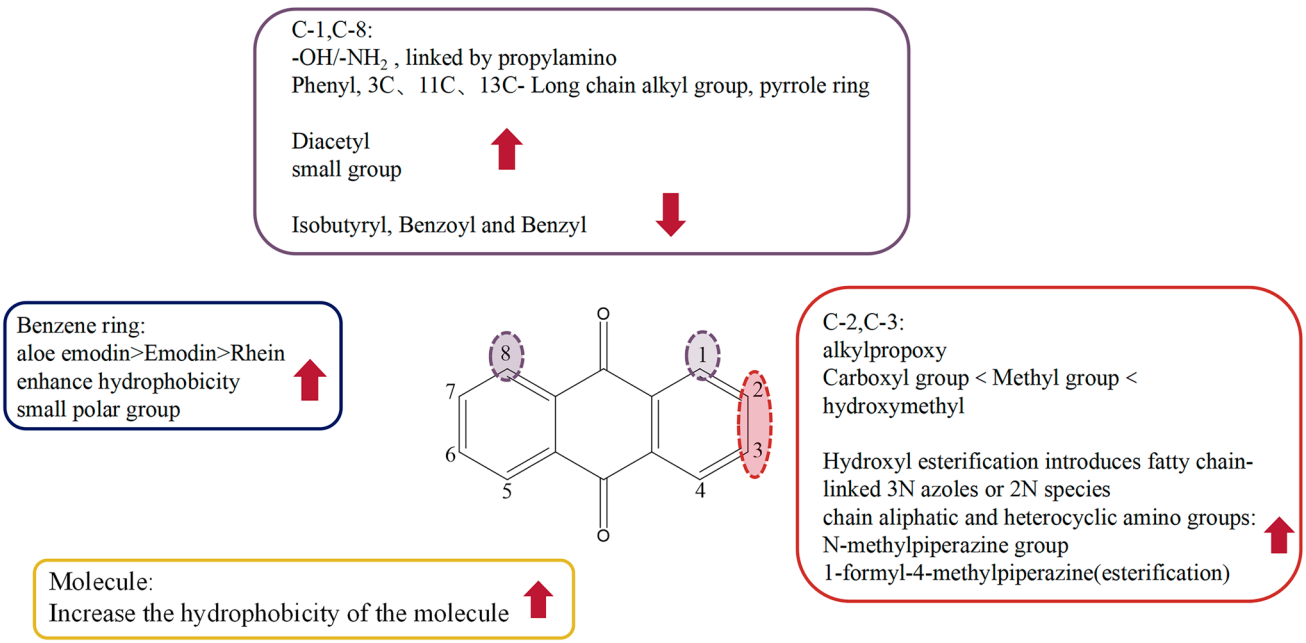

Fig. 7 Structure–activity relationship for anti-inflammatory activity of anthraquinones

relationships are outlined in Figs. 6 and 7. The comparative study of four quinone matrices, 1,4-benzoquinone, 1,4-naphthoquinone, 9,10-anthraquinone, and 5,12-naphthoquinone, suggested that the anti-inflammatory activity of 1,4-naphthoquinone was stronger than that of the other three matrices (Kobayashi et al. 2011). In the study of 1,4-naphthoquinone thiosylation products, cyclic thiosides were more inhibitory for COX-2, and acyclic thiosides were more inhibitory for TNF-α. For instance, compound Q13 showed stronger inhibition of COX-2 than compound Q12, however the effect on TNF-α was the opposite (Kozlovskiy et al. 2023). The introduction of hydroxyl groups at the C-5 and 8 positions of 1,4-naphthoquinone and a 4-methylpent-3-en-1-ol group at the C-7 position resulted in shikonin (Q25), which inhibited inflammation less effectively than 1,4-naphthoquinone, but the difference was not significant (Mahmoud et al. 2021). Hydroxyl esterification of shikonin to introduce an alkyl group at the 5- or 8-position side chain yielded compounds Q23 and Q24, both of which were greatly weakened in anti-inflammatory tests compared to shikonin (Lohberger et al. 2022); thus, hydroxyl esterification at the C-5 or C-8 position introduced alkyl groups that were not suitable. Comparing the anti-inflammatory effects of compound Q26 as well as Q27, the introduction of 3,4,6-trimethoxyphenyl in 1,4-naphthoquinone at the C-5 or C-8 position might be a desirable derivatization direction (Lee et al. 2013).

The receptors of rhodopsin analogs had a hydrophobic pocket, and among rhodopsin (Q32), rhodopsinic acid (Q33), and aloe rhodopsin (Q34), aloe rhodopsin (Q34) was the most hydrophobic and notably more anti-inflammatory than the other two, so modification could be carried out to increase the hydrophobicity of the anthraquinone molecule by introducing a small polar group. With the introduction of a small polar group such as methoxy on the benzene ring, compound Q49 demonstrated a stronger inhibitory activity against NF-κB than Q48 (Hu et al. 2021). After the addition of chain aliphatic amino groups and heterocyclic amino groups by hydroxymethyl esterification at the C-3 position of aloe rhodopsin, the anti-inflammatory activity of the compound 35–37 was greatly increased, with the highest activity being seen in the compound 35 with the introduction of the N-methylpiperazine moiety (Shang et al. 2022). Moreover, the anti-inflammatory activity of Q34 was increased by introducing diacetyl groups at C-1 and 8 positions. Compound Q38, which was based on compound Q35 and introduced a benzyl group on its hydroxyl group, showed decreased or even no anti-inflammatory activity, hence it was desirable to enhance the anti-inflammatory activity with the introduction of small groups at the 1-position and the 8-position (Shang et al. 2022). By comparing the anti-inflammatory activities of compounds Q39–Q47, it could be noticed that the introduction of aliphatic chain-linked triazole or imidazole moiety by hydroxyl esterification at the C-3 position helped to improve the anti-inflammatory activity, and the four-carbon linked imidazole moiety had the highest anti-inflammatory activity. The introduction of benzazole moiety also contributed to the anti-inflammatory activity, and the anti-inflammatory activity of Q43 containing benzazole structure was significantly better than that of the parent compound (Zhu et al. 2020).

Anthraquinone was used as the parent nucleus for C-1,4-N-alkylation and O-alkylation modifications bridged by propylamino groups. Among the products, N-alkylation side chain carbons of 11 and 13 carbons in length and linking pyrrole ring and phenyl were less cytotoxic, and O-alkylation cytotoxicity was lower for the 13-carbon linkage and pyrrole ring and phenyl modifications. The cytotoxicity after N-alkylation was smaller than that after O-alkylation, so the C-1,4-position might be unsuitable for alkylation modifications with intermediate elastic chain lengths, and phenyl substitution was relatively less cytotoxic in alkylation modifications (Oliveira et al. 2020).

Alkaloids

Alkaloids are a class of nitrogenous alkaline organic compounds found in nature that originate from secondary plant metabolites and have significant pharmacological activity (Talib and Mahasneh 2010). Studies have demonstrated that alkaloids have great potential for anti-inflammatory activity, similar to sophocarpine (A1) and 5α-hydroxymatrine (A2), which proved to have favorable anti-inflammatory activity (He et al. 2019). This review covers alkaloids that have been tested for anti-inflammatory activity and are structurally classified as indole alkaloids, quinoline alkaloids, isoquinoline alkaloids, etc. The structures and their anti-inflammatory activities are depicted in Fig. 8.

Network pharmacological studies on the anti-inflammatory activity of alkaloids

In recent years, network pharmacology has rapidly become a new method for mining and predicting natural product-target interrelationships (Liu and Du 2010; Wang et al. 2011). Through network pharmacology, Jin et al. (2022) predicted that the anti-inflammatory effects of Pingbeijian alkaloids might be related to targets such as caspase 3 (CASP3), IL-6, TNF-α, nuclear receptor subfamily 3, Group C, member 1 (NR3C1), IL-1β and peroxisome proliferator-activated receptor gamma (PPARG) and might exert anti-inflammatory effects through signaling pathways such as C-type

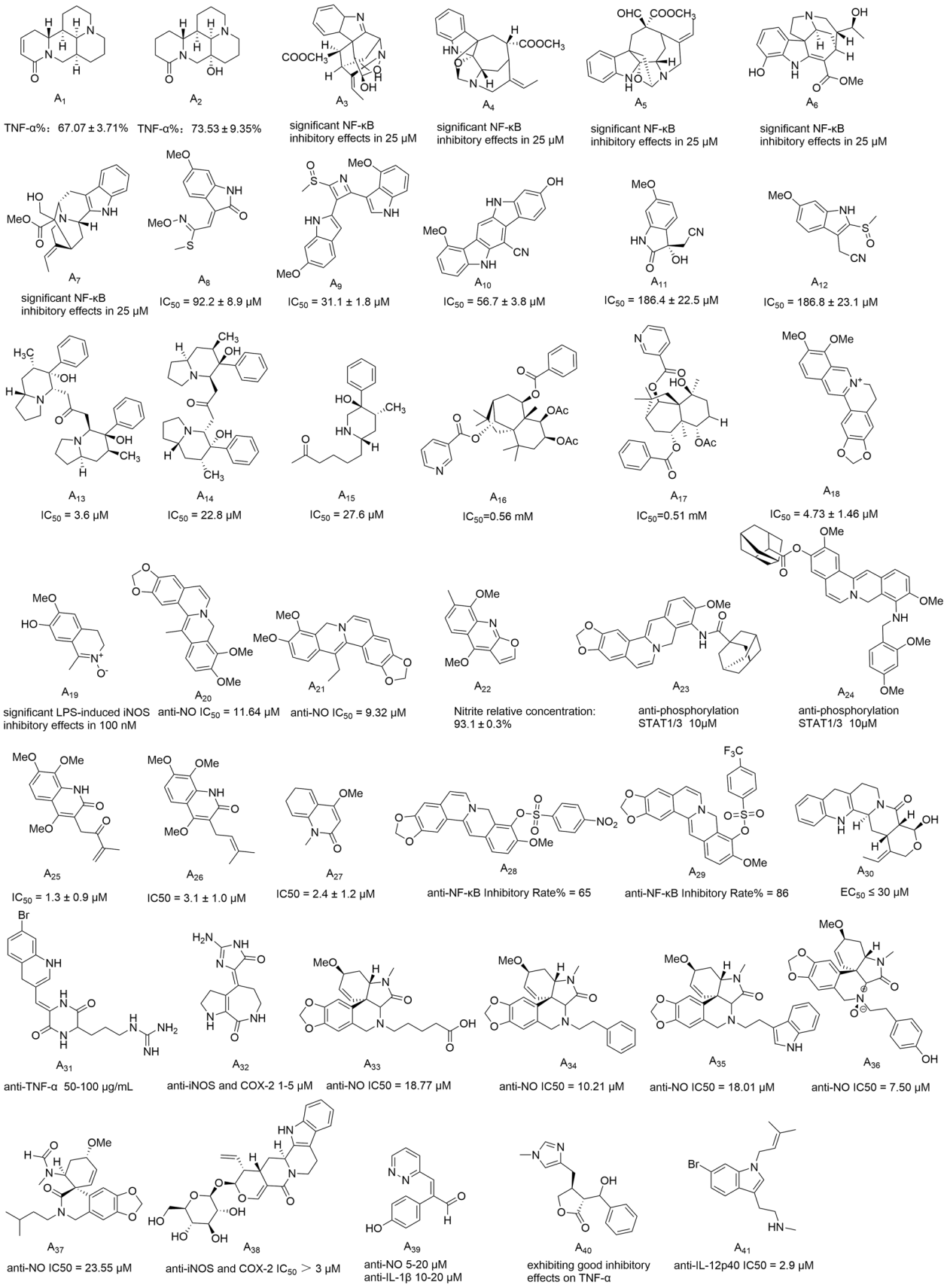

Fig. 8 Structures of alkaloids (and their derivatives) with anti-inflammatory activity

hemagglutinin receptors, interleukin-17 (IL-17), NF-κB and MAPK, as well as tested by in vitro cellular experiments, western blot, and molecular docking. Du et al. (2020) found that berboside could regulate the expression of inflammatory mediators such as TNF-α, IL-1β, and IL-6 and cause the NF-κB signaling pathway to exert anti-inflammatory effects. Xiao et al. (2021) determined that total alkaloids of Flos Daturae have nephroprotective effects, possibly related to the activation of advanced glycosylation end products (AGEs)—receptor of AGEs (RAGE)—transforming growth factor-beta (TGF-β) / SMAD family member 2 (Smad2) and PI3K-Akt signaling pathways, via network pharmacology. Picrasidine is a potent anti-inflammatory agent, but the underlying mechanisms of its anti-inflammatory properties are not clear. Wu et al. (2022) conducted network pharmacology analysis and cellular validation of bitter ginseng alkaloids, such as IL-6 and TNF-α, to identify their critical anti-inflammatory targets. *Picrasma quassioides* (D. Don) Benn was found to contain a variety of alkaloidal components, and Xu's team determined that its anti-inflammatory effects were related to the MAPK signaling pathway, chemotaxis signaling pathway, and NF-κB signaling pathway through network pharmacological prediction, which was consistent with the results of anti-inflammatory experiments performed by his team previously (Jiao et al. 2011; Xu et al. 2023). Wang et al. (2022) discovered that Sipeimine, an alkaloid from *Fritillaria roylei*, could exert its anti-inflammatory effect through the PI3K/Akt pathway through a network pharmacological study, and subsequently confirmed it through cellular experiments and Western blot. After network pharmacological prediction and experimental verifications, it was revealed that the pivotal anti-inflammatory targets of the alkaloids included IL-6, TNF-α, IL-1β, and IL-17, which mainly functioned in signaling pathways with NF-κB and MAPK.

Anti-inflammatory activity of indole and terpenoid alkaloids

Indole alkaloids are a group of pentameric pyrrole ring alkaloids with a benzene ring structure that express remarkable anti-inflammatory activity (Marinho et al. 2016). Yang et al. (2018a) isolated five monoterpenoid indole alkaloids, scholarisine S (A3), picrinine (A4) picralinal (A5), epischolaricine (A6), and aluammidine (A7), from the leaves of *Alstonia scholaris*, which inhibited TNF-α-induced NF-κB activation at a concentration of 25 μM. Nukulkit et al. (2022) elucidated five indole alkaloids from the roots of *Maerua siamensis* with anti-inflammatory activity to induce the production of NO. Among them, maeroxime C (A8), maeruabis indoles B (A9) and maeruabis indoles C (A10) showed better anti-inflammatory effects than indomethacin ($IC_{50} = 150.0 \pm 16.0$ μM). The effect of maeruanitriles A (A11) and B (A12) on NO inhibition was comparable to that of indomethacin, with IC_{50} values of 186.4 ± 22.5 and 186.8 ± 23.1 μM, respectively. Hu et al. (2016) extracted the indolizidine alkaloids (±)-homocrepidine A (A13, A14) and homocrepidine B (A15) from the stems of *Dendrobium*. (+)-homocrepidine A (A13) was able to restrain the production of NO ($IC_{50} = 3.6$ μM) and markedly reduced the expression of i-NOS. (−)-homocrepidine A (A14) and Compound A15 also showed medium anti-inflammatory activity with IC_{50} values below 30 μM. Ochienga et al. (2017) derived two terpene alkaloids, A16 ($IC_{50} = 0.56$ mM) and A17 ($IC_{50} = 0.56$ mM), which showed good inhibitory effects on COX-2, from the above-ground parts of the African plant *Gymnosporia heterophylla*.

Anti-inflammatory activity of isoquinoline and quinoline alkaloids

Isoquinoline alkaloids are alkaloids with isoquinoline or tetrahydroisoquinoline as the parent nucleus. Berberine (A18, BBR) is an isoquinoline alkaloid originally isolated from the herb *Coptidis rhizome* (Mohammadian Haftcheshmeh and Momtazi-Borojeni 2021). Jia et al. (2019) discovered that oral administration of BBR at a concentration of 120 mg/kg for 7 weeks could improve the resorption of alveolar bone in a rat model of periodontitis, which led to successful periodontitis suppression in rats. Gu et al. (2021) also found that BBR may exert its anti-inflammatory influence by blocking the G protein-coupled estrogen receptor-mediated p38MAPK/NF-κB pathway. Oshima et al. (2018) analyzed the anti-inflammatory effects of raw herbal extracts from the Chinese herbal medicine orengedokuto, revealing that BBR was the main component of these raw herbs and exhibited inhibition of NO production ($IC_{50} = 4.73 \pm 1.46$ μM). Litcubanine A (A19, LA), a novel isoquinoline alkaloid with anti-inflammatory activity, was derived from *Litsea cubeba*. Xia et al. (2021) revealed that LA potently inactivated LPS-induced RAW264.7 macrophages to produce NO and notably reduced the expression of iNOS, and attenuated the expression of TNF-α and IL-1β, resulting in anti-inflammatory effects. Lee et al. (2003) synthesized two alkyl derivatives, A20 and A21, using berberine as the parent, and found them to have good inhibitory effects on pro-inflammatory factors ($IC_{50} = 11.64$ and 9.32 μM). Yang et al. (2019b) studied the quinoline alkaloid haplopine (A22) from *Cortex Dictamni*, which exhibited a potential inhibitory effect on NO production with a nitrite relative concentration (NRC) of $93.1 \pm 0.3\%$. Zeng et al. (2017) chemically modified berberine and discovered that compounds A23 and A24 showed good inhibitory effects on IL-6 expression and STAT signaling pathway.

Gao et al. (2020) conducted a study on quinoline alkaloids derived from the root bark of *Dictamnus dasycarpus* and reported that Compounds A25, A26, and A27 had strong inhibitory effects on LPS-stimulated NO production in BV-2 microglia with IC_{50} values below 5.0 μM. Wang et al. (2017) derivatized and modified berberine to obtain compounds A28 and A29, both of which had inhibitory effects on the inflammatory factor NF-κB, and the inhibitory activity of A28 was significantly stronger than that of A29.

Anti-inflammatory activity of other alkaloids

Naucleoffieine H (A30) was an alkaloid dissociated from *Nauclea officinalis*, which Song et al. (2020a) detected to significantly inhibit the LPS-induced release of NO and tumor necrosis factor-α (TNF-α) from RAW 264.7 cells, and to decreased the expression of iNOS. In addition, Lind et al. (2013) isolated the brominated alkaloid Barettin (A31) from *Geodia barretti* and discovered that Barettin was able to reduce the levels of TNF-α and IL-1β in LPS-stimulated THP-1 cells to combat inflammation. Lee et al. (2019) extracted pyrole alkaloid (10Z)-debromohymenialdisine (A32) from sponges of the genus *Stylissa*, showing its ability to reduce the expression of IL-1β, IL-6, TNF-α, iNOS, and COX-2 thereby exerting an anti-inflammatory effect. Jin and Yao (2019) summed up five organic amine alkaloids (A33-A37) from *Amaryllidaceae and Sceletium* with good inhibitory effects on LPS-induced NO release in RAW264.7 cells, which presented IC_{50} values between 7 and 24 μM and potential for deep exploitation. Liu et al. (2009b) revealed that the action of the pyrrolizidine alkaloid Wuzhuine (A38) from *Evodia rutaecarpa* on hypoxia-induced inflammation was capable of being therapeutic by multiple mechanisms and held great potency in counteracting hypoxic inflammation. Compound A39, an alkaloid containing a pyridazine structure, was recovered from *Portulaca oleracea* L., which dose-dependently inhibited NO release and suppressed IL-1β production (Liu et al. 2022a). Silva et al. (2013) established that an alkaloid with an imidazole structure, A40, obtained from *Pilocarpus microphyllus*, exhibited good inhibitory effects when treated with it in carrageenan gum-induced edema in mice, as well as stronger inhibitory effects on TNF-α and IL-1β than the positive drug indomethacin. Di et al. (2020) identified an alkaloid A41 from *Flustra foliacea* with strong inhibitory effects on IL-12 ($IC_{50} = 2.9$ μM), which could offer potential as a lead compound in the development of novel anti-inflammatory drugs.

Structure–activity relationships for the anti-inflammatory activity of alkaloids

Currently, alkaloids derived from anti-inflammatory aspects have focused on isoquinoline alkaloids, with nitrogen-containing heterocycles exhibiting good anti-inflammatory activity. The study of the structure–activity relationship of alkaloids, regarding anti-inflammation, was mainly abandoned for berberine parent alkaloids (Fig. 9). The current

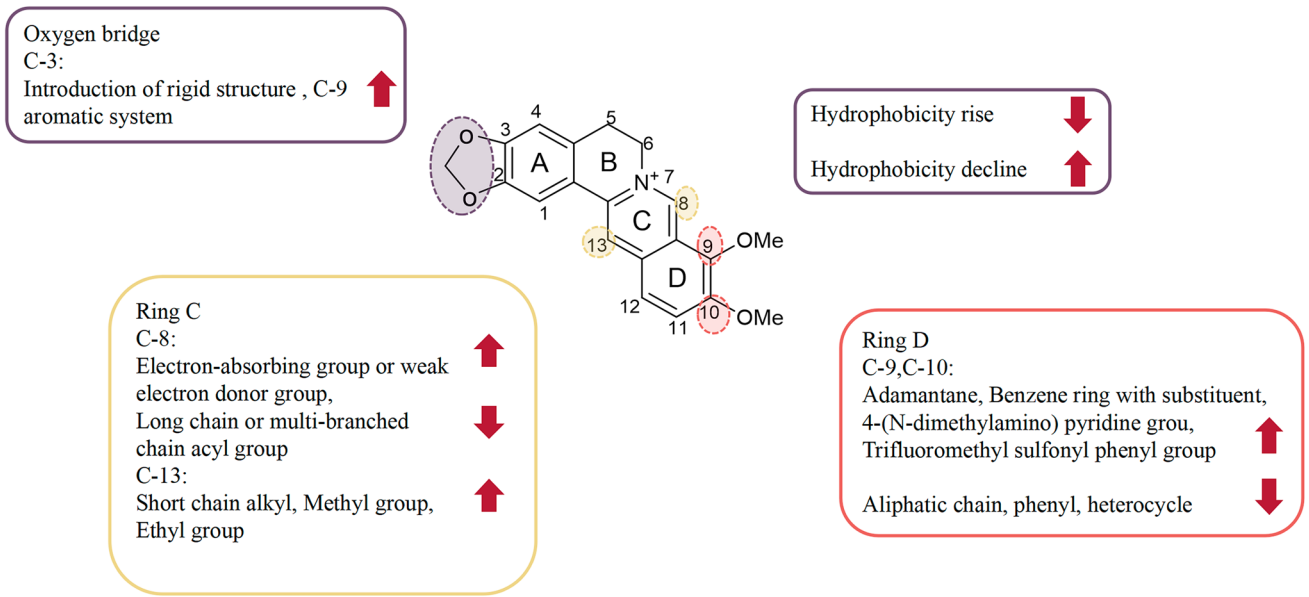

Fig. 9 Structure–activity relationship for the anti-inflammatory activity of alkaloids

anti-inflammatory modifications of berberine parent alkaloids mainly focus on positions 8 and 13 of the C ring and positions 9 and 10 of the D ring. The introduction of electron-withdrawing or weakly electron-donating groups at the 8-position of the C-ring resulted in positive anti-inflammatory activity; however, when an acyl carbon chain was attached to the 8-position, an increase in the length of the acyl carbon chain or the number of branched chains led to a decrease in the anti-inflammatory activity. The introduction of only alkyl chains also caused increased cytotoxicity. Short-chain alkyl substitution at position 13 of the C ring resulted in compounds A20 and A21, which inhibited NO production and introduced ethyl better than methyl, but did not perform as well in inhibiting other inflammatory targets (Lee et al. 2003). Substitutions such as A23, which introduced adamantane via an amino group at the 9-position of the D-ring, or A24, which inserted phenyl groups with substituents, as well as derivatives with 4-(N,N-dimethylamino) pyridine, were found to have enhanced anti-inflammatory activity, so that rigid structural substituents at the C-9 position favored anti-inflammatory activity, while substitutions such as those of aliphatic chains, phenyl groups, heterocycles, etc., led to the reduction of the anti-inflammatory activity (Zeng et al. 2017). With the introduction of a sulfonyl phenyl group at C-9 of the D-ring, A28 and A29 inhibited NF-κB by more than 65%, which was stronger than that of the berberine prototype, and among the substituents on the phenyl group, the anti-inflammatory activity of trifluoromethyl group was stronger than that of the nitro group (Wang et al. 2017). Breaking the dioxygen bridge at the 2,3 position of the berberine nucleus, attaching a rigid structure at the 3 position of the A-ring, and introducing an aromatic system at the 9 position of the D-ring, compound A24 exhibited an improved anti-inflammatory activity relative to the berberine nucleus (Zeng et al. 2017). Liu et al. (2023) enhanced bioavailability and anti-inflammatory activity by disrupting the methylenedioxy or methoxy groups of the A and D rings of the proto-berberine skeleton and then attaching different groups. Compounds A21 and A22, by way of example, were those whose anti-inflammatory activity was enhanced by methylenedioxygenation of the A-ring of the proto-berberine skeleton, followed by the attachment of other moieties. The type of substituent at position 10 was similar to that at position 9, and the rigid structure favored anti-inflammatory activity.

Terpenoids

Terpenoids are a class of compounds whose molecular skeleton is based on the isoprene unit with the formula $(C_5H_8)_n$, and their derivatives are derived from methylenedihydroxy acids. In terms of structure, terpenoids are mainly classified into monoterpenes, sesquiterpenes, diterpenes, triterpenes, and tetraterpenes (Ge et al. 2022). As one of the most abundant and diverse natural products in recent years, terpenoids have attracted much attention due to their anticancer, antioxidant, antiviral, and anti-inflammatory biological activities (Pichersky and Raguso 2018; Harmange Magnani et al. 2020; Zielińska-Błajet and Feder-Kubis 2020). Terpenoids with anti-inflammatory activity mentioned in the text are displayed in Figs. 10 and 11.

Network pharmacological studies of terpenoids exerting anti-inflammatory activity

Terpenoids share a unique anti-inflammatory mechanism of action (Souza et al. 2014), and network pharmacology revealed that terpenoids mainly suppressed inflammation-related diseases by inhibiting the NF-κB, MAPK1, IL-6, and STAT3 pathways (Salminen et al. 2008; Zhang et al. 2019d; Dai et al. 2021; Niu et al. 2021; Zhao et al. 2022). Shan's colleagues conducted a network pharmacological analysis of cyclic enol ether terpenoids, which is called geniposide in *Gardenia jasminoides* J. Ellis, and verified that the key anti-inflammatory target genes were vascular endothelial growth factor A (VEGFA), Rho-associated protein kinase 2 (ROCK2), nitric oxide synthase 3 (NOS3), and C–C motif chemokine ligand 2 (CCL2), with validation experiments suggesting that geniposide modulated the NF-κB pathway, increased the level of cellular tight junctions, and alleviated inflammation (Shan et al. 2023). Karthikkeyan et al. (2020) demonstrated that liquorice could mediate anti-inflammatory effects by modulating the cell cycle, MAPK1/3, and PI3K/AKT pathways through network pharmacological analyses and in vitro experiments.

Anti-inflammatory activity of sesquiterpenes, monoterpenes and diterpenoid

Sesquiterpenes are natural terpenoids with 15 carbon atoms in the molecule, containing three isoprenoid units and having a variety of backbone structures, such as chains and rings, which are widely found in plants, insects, and marine organisms in nature (Guo et al. 2018). Queiroz's group isolated eight sesquiterpene lactones (T1–T8) from leaves and flowers of the plant *Chresta martii*, which manifested excellent NF-κB pathway inhibitory activity, all with IC_{50} values below 14 μM

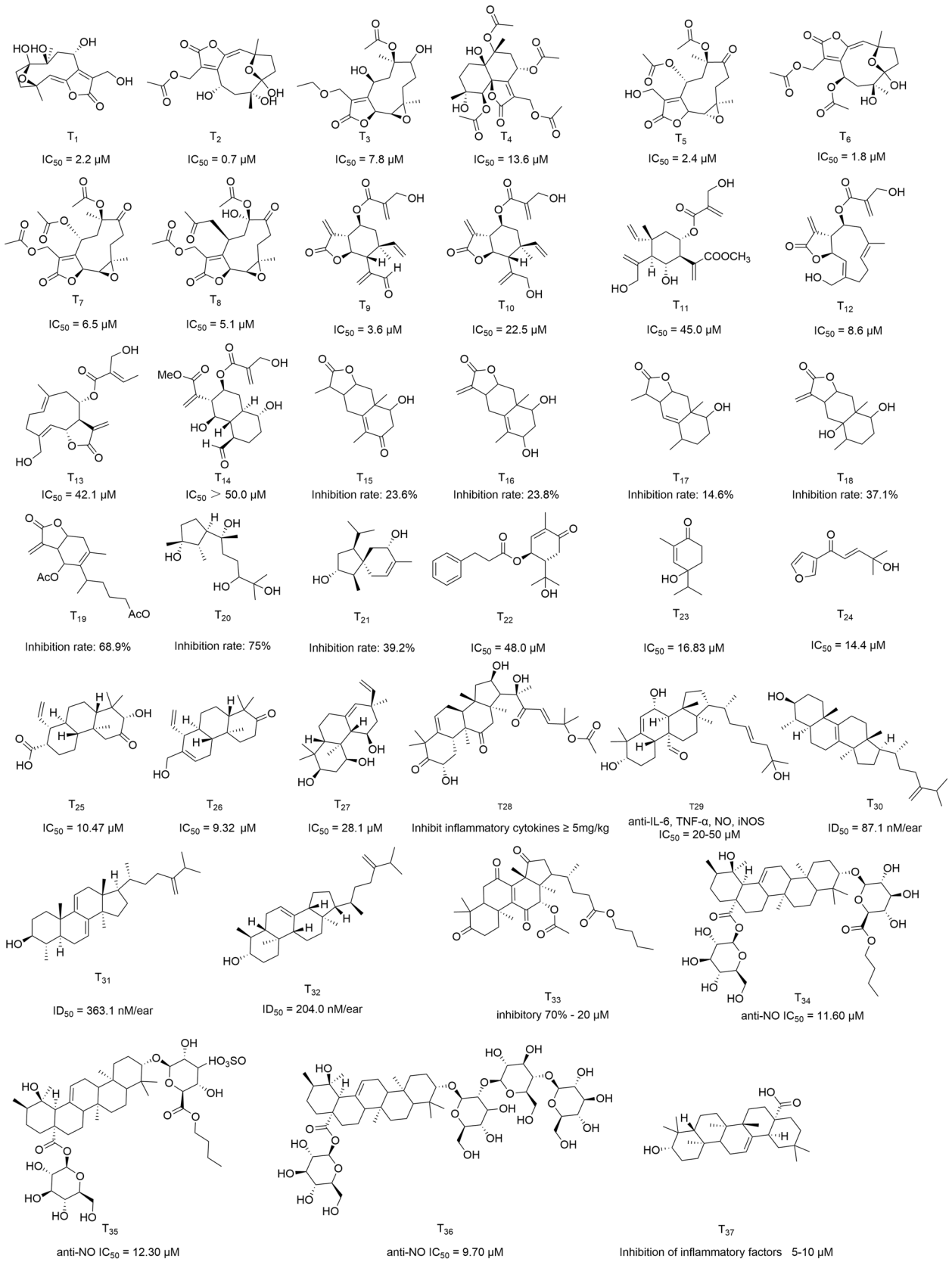

Fig. 10 Structures of terpenoids (and their derivatives) T1–T37 with anti-inflammatory activity

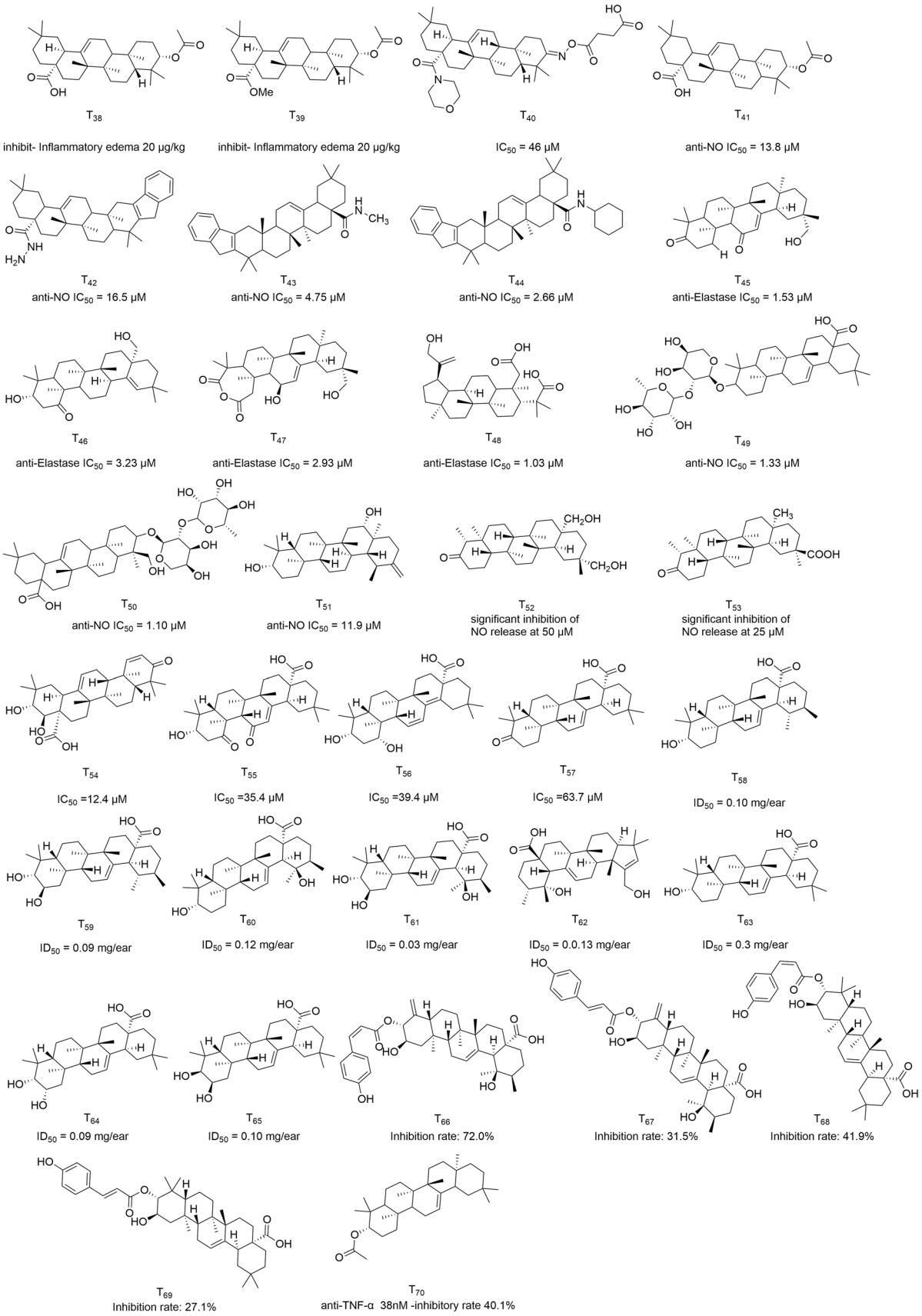

Fig. 11 Structures of terpenoids (and their derivatives) T38–T70 with anti-inflammatory activity

(Queiroz et al. 2018). Formisano et al. (2017) assigned six sesquiterpene lactones (T9–T14) from the ground of the plant *Onopordum illyricum* L. They also showed significant anti-inflammatory effects and exhibited significant activity against NF-κB, with IC_{50} values ranging from 3.6 to 50.0 μM. Tang et al. (2014) isolated five terpenoids (T15–T19) from *Inula japonica*, of which T19 showed the strongest inhibition of NO production at 25 μM, and the inhibition rate was 68.9%. Zhang et al. (2017) derived cyclonerodiol B (T20) and Compound T21 from endophytic fungi, which showed positive inhibitory effects on LPS-induced NO production in BV2 cells, with inhibitory rates of 75.0 and 39.2%, respectively. Monoterpenes are terpenoids consisting of two isoprene units with 10 carbon atoms. They are widely distributed in the secretory tissues of higher plants, such as glands, oil chambers, and resin tracts, and constitute the main components of plant volatile oils (de Cássia da Silveira e Sá et al. 2013). Hou et al. (2017) isolated Illigerate A (T22) from the stems of *Illigera aromatica*, which displayed a favorable suppression of LPS-induced NO production, with an IC_{50} value of 48.0 μM. They also obtained the novel polyol monoterpene T23, which showed moderate inhibition of LPS-induced NO production with an IC_{50} value of 16.83 μM. Wang et al. (2018a) identified a perillaketone monoterpene, T24, from the medicinal herb *Perilla frutescens var. crispa*, which was capable of inhibiting NO production, with an IC_{50} value of 14.4 μM.

Diterpenoids are compounds consisting of 4 molecules of isoprene polymerized with 20 carbon atoms in the molecule, which are widely found in plants, insects, fungi, and marine organisms, with anti-inflammatory, antitumor, antibacterial, and antiviral effects (Liu et al. 2009a; Wang et al. 2021). Zhang et al. (2019c) found that Compounds T25 and T26 from the traditional plant *M. conspurcatus* had strong anti-inflammatory activity and were able to inhibit NO production with IC_{50} values of 10.47 and 9.32 μM, respectively. Marginaol B (T27), an isopimarane diterpene derived from the rhizomes of *Kaempferia marginata*, exhibited modest inhibitory effects on LPS-induced NO production in RAW 264.7 cells (IC_{50} = 28.1 μM), suggesting moderate anti-inflammatory activity (Chokchaisiri et al. 2020).

Anti-inflammatory activity of tetracyclic triterpenoids

Tetracyclic triterpenoids were a class of natural products with a wide range of biological activities, consisting of six isoprene units and containing four cyclic structures. Cucurbitacin B (T28) produced a class of tetracyclic triterpenoids isolated from Cucurbitaceae (Dai et al. 2023), it was studied that T28 could effectively inhibit the production of reactive oxygen species (ROS) in macrophage cells and release of inflammatory factors in animals at a concentration of 5 mg/kg to achieve anti-inflammatory effects (Kim et al. 2015; Aljohani 2020). Chou et al. (2022) obtained compound T29 from *Momordica charantia L.* and achieved a dose-dependent inhibition of LPS-induced IL-6, TNF-α, and NO release and iNOS expression at concentrations of 20–50 μM. Sun et al. (2018) and his collaborators derived three compounds T30–T42 from Euphorbia maculata L. and determined their inhibitory effects on tissue plasminogen activator (TPA)-induced inflammatory ear edema using indomethacin as a positive control (ID_{50} = 838.0 nM/ear), which exhibited ID50 values of 87.1, 363.1 and 204.0 nM/ear, all of which showed superior inflammatory inhibition to the positive drug. Choi et al. (2014) got the compound T33 from *Ganoderma lucidum (Curtis) P. Karst* and achieved 70% inhibition of LPS-induced NO release in RAW264.7 cells, which possessed a promising anti-inflammatory potential.

Anti-inflammatory activity of pentacyclic triterpenoids

Pentacyclic triterpenoids are common triterpenoids consisting of six isoprene units linked into five closed rings, with the closed ring as the parent body. Shi et al. (2017) obtained three pentacyclic triterpenoids T34-36 from *Ilex dunniana H. Lév.* that showed moderate inhibitory effects on LPS-induced NO production in BV2 microglial cells, with IC_{50} values all below 13 μM. In exploring the inhibitory effect of oleanolic acid on IL-1β-induced inflammation in SW982 cells, Lian and colleagues discovered that oleanolic acid (T37) could inhibit the production of a variety of inflammatory factors between concentrations of 5–20 μM (Lian et al. 2016). Nkeh-Chungag et al. (2015) synthesized two esterified derivatives of oleanolic acid, T38 as well as T39, and revealed that the anti-inflammatory inflammatory activity of T38 and T39 was stronger than that of oleanolic acid and comparable to that of the positive control indomethacin. Krajka-Kuźniak et al. (2019) prepared four oleanane-type compounds with an oxime structure and identified compound T40 having a low cytotoxicity relative action concentration (IC_{50} = 46 μM) and a good inhibitory effect on the STAT inflammatory pathway by cellular experiments. Bhandari's team analyzed four derivatives T41–T44 with good anti-inflammatory activity using oleanolic acid as a parent, which inhibited LPS-induced NO production in RAW264.7 cells, with IC_{50} values of less than 17 μM for all of them, which was stronger than the positive drug (IC_{50} = 69.21 μM) (Bhandari et al. 2014). Chen et al. (2014) isolated three oleanane-type triterpenes

T45–T48 from *Microtropis fokienensis*, which displayed remarkable inhibitory activities in the inhibition assay of elastase release from human neutrophils, and the IC_{50} values of all three were lower than 3.5 μM. Ba Vinh and equivalents derived the compound eleutheroside E (T49) and compound kalopanaxsaponin A (T50) from the fruits of *Stauntonia hexaphylla(Thunb.)Decne.* By determining the changes in NO release in LPS-induced RAW264.7 cells after administration of the compounds, it was noticed that both of them had good anti-inflammatory effects, with IC_{50} values of 1.33 and 1.10 μM (Ba Vinh et al. 2019). Xue et al. (2020) yielded a triterpenoid compound, T51, of the lupine alkane type from Centipeda minima, which was detected to have good anti-inflammatory activity with an IC_{50} value of 11.9 μM. Villar-Lorenzo et al. (2016) revealed that the corkypane-type pentacyclic triterpenoids T52 and T53 significantly inhibited the release of intracellular NO and reduced the mRNA expression of proinflammatory cytokines at concentrations of 50 and 25 μM, respectively. Zhang et al. (2022a) found that four terpenoids, T54–T57, from *Pterocephalus hookeri* (Dipsacaceae) could restrain NO production (IC_{50} = 12.4–63.7 μM). Banno et al. (2004) identified eight triterpenoids isolated from *Perilla frutescens* (T58-65) and found significant anti-inflammatory properties in TPA-induced ear edema in mice, with ID_{50} values in the range of 0.09–0.3 mg/ear. Zhang et al. (2023) identified that the presence of Compounds T66-69 in the ethanolic extract of *Lyonia doyonensis* significantly decreased NO production to 72.0%, 31.5%, 41.9%, and 27.1%, respectively, compared with that in the LPS group. Ding et al. (2010) separated a pentacyclic triterpene, T70, from the plant *Acer mandshuricum*, which displayed a good anti-inflammatory effect by inhibiting LPS-induced TNF-α secretion in RAW264.7 cells at nanomolar concentrations.

Structure–activity relationships for the anti-inflammatory activity of pentacyclic triterpenoids

Currently, the derivatization of terpenoids for anti-inflammatory purposes has focused on pentacyclic triterpenoids, with the parent types broadly classified as oleanocarpane-type, ursane-type, and lupulane-type. Studies indicated that the modification sites of pentacyclic triterpenoids affecting anti-inflammatory activity were mainly concentrated at the C-1, C-3, C-5, C-7, C-15, C-21, C-24, C-28, and C-30 positions (Fig. 12) (Zhao et al. 2021). Acetylation of C-1 or hydroxylation of C-7, C-15, C-21, and C-24 as well as the introduction of glycosidic bonds at C3, C28, and C30 could increase the anti-inflammatory activity of pentacyclic triterpenoids (Villar-Lorenzo et al. 2016; Zhang et al. 2019a, b, c, d; Chokchaisiri et al. 2020; Zhang et al. 2022a, b). The free hydroxyl group at the C-3 position and the free carboxyl group at the end of the side chain at the C-28 position were essential groups for the anti-inflammatory activity of triterpenoids (Liu et al. 2022b). Pentacyclic triterpenoids such as oleanolic acid (T37), corosolic acid, and cumaric acid displayed good anti-inflammatory activity (He et al. 2023). Oleanolanes were reported to be more commonly modified than ursanes and lupinanes due to their rich backbone and diverse biological activities. Currently, the structural modification sites of oleanolic acid (T37) are mainly concentrated at the C-3 position and the C-28 position (Liu

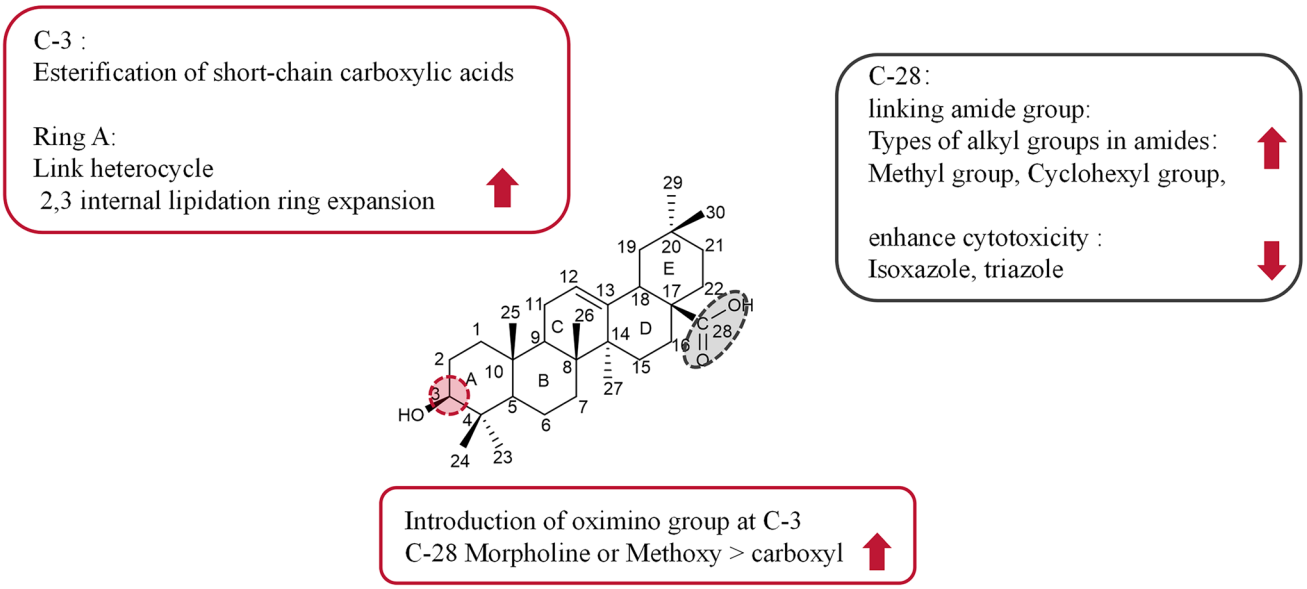

Fig. 12 Structure–activity relationship of the anti-inflammatory activity of pentacyclic triterpenoids

et al. 2022a, b). Compounds A42 and A43, which acetylated the hydroxyl group at the C-3 position of oleanolic acid, presented stronger anti-inflammatory activity compared to oleanolic acid (T37) (Nkeh-Chungag et al. 2015), and the oxidation of the hydroxyl group to a carbonyl group had less impact on the anti-inflammatory activity of the molecule (Bhandari et al. 2014). The oximide group at C-3 and morpholine group at C-28 of compound T40 appeared to be a good inhibitor of the inflammatory pathway in cellular experiments (Krajka-Kuźniak et al. 2019), but the introduction of isoxazole or triazole at the C-28 position increased the cytotoxicity of the molecule (Chouaïb et al. 2016). In addition, compounds T43 and T44, which combined the introduction of a heterocyclic ring in the A ring with an amide group at the C-28 position, both exerted an inhibitory activity on NO production equivalent to ten times that of oleanolic acid, which greatly enhanced the anti-inflammatory activity (Bhandari et al. 2014). The ring expansion of the oleanolane A ring at 2,3 position led to compound T47, which possessed more significant anti-inflammatory activity as compared with the oleanolane parent nucleus as well as compounds of the same type, T45, and T46, indicating that the ring expansion of the A ring at the 2,3 position was a good strategy to improve the anti-inflammatory activity (Chen et al. 2014).

Flavonoids

Flavonoid is a general term for a type of compound derived from the skeleton of 2-phenylchromone. According to their chemical structure, these compounds can be classified as flavonoids, flavonols, isoflavones, etc. (Panche et al. 2016). They have a variety of pharmacological activities, such as anticancer, antioxidant, anti-infective, anti-inflammatory, and antiviral activities (Middleton et al. 2000; Rathee et al. 2009; Pan et al. 2010; Vinayagam and Xu 2015; Al-Ishaq et al. 2019; Maleki et al. 2019; Ferraz et al. 2020; Šudomová et al. 2022). The structures of flavonoids with anti-inflammatory activity, that were mentioned in the text, are sketched in Fig. 13.

Network pharmacological studies of flavonoids exerting anti-inflammatory activity

In recent years, network pharmacological studies indicated that flavonoids could inhibit the TNF pathway, activator protein-1 (AP-1), MAPK, PI3K/AKT, and NF-κB signaling pathways, thereby suppressing the inflammatory response (Al-Khayri et al. 2022; Chen et al. 2022; Long et al. 2022; Motallebi et al. 2022).

Zhang et al. (2022b) found that IL-6, IL-1β, and TNF-α were potential targets of quercetin in the treatment of ulcerative colitis through network pharmacological prediction, and the results of protein blotting experiments were consistent with the network pharmacological prediction. Chen et al. (2022) conducted a network pharmacological analysis to predict the mechanism of action of total flavonoids of crushed tonic (TFRD) in the treatment of rheumatoid arthritis (RA) and later verified that its anti-inflammatory effects involved the T-cell receptor, helper T cell 17 (Th17) cell differentiation, IL-17, TNF, MAPK, and PI3K/AKT signaling pathways through cellular experiments. Wu et al. (2023) predicted that seven proteins, including TNF-α, IL-6, and AKT1, were the main anti-inflammatory targets of baicalein by performing network pharmacological analyses and cellular experiments on baicalein. Alamri and associates used network pharmacology predictive screening to find that flavonoids from *Dodonea angustifolia* played a role in inflammation by affecting AKT1, VEGFA, and epidermal growth factor receptor (EGFR), and molecular docking and integrated molecular dynamics simulations were in agreement with the network pharmacology predictions (Alamri and Qamar 2023). Liu's research team discovered that quercetin was the key component in the anti-inflammatory effect, and the main target might be the PI3K/AKT signaling pathway, using network pharmacology to study the active ingredients and core targets in Sophora Huai Hua San. Therefore, they carried out molecular docking on quercetin and the results were consistent with the predicted results, and subsequent cellular experiments showed that quercetin could indeed inhibit the release of inflammatory factors and the PI3K/AKT signaling pathway in LPS-induced RAW264.7 cells (Liu et al. 2021). Zou and other researchers investigated the therapeutic targets and molecular mechanisms of Si-Miao-Yong-An decoction in thromboembolic vasculitis using a network pharmacology approach and revealed that quercetin, the active ingredient, was mainly targeted at IL-6, Matrix metalloproteinase-9 (MMP9), and VEGFA. The molecular docking results demonstrated that the target molecules were well bound to the target and the expression of IL-6 and MMP9 was reduced in vivo as well as in vitro (Zou et al. 2023). Sun et al (2023) used network pharmacology to predict naringenin's targets on chronic skin wounds and identified AKT1, MAPK1, and MAPK3 as potential targets. Molecular docking and in vitro cellular assays were consistent with the network pharmacology prediction that naringenin promoted wound healing by inhibiting inflammation. To date, the main anti-inflammatory targets of flavonoids, identified by network pharmacological studies, include TNF-α, IL-6, AKT1, VEGFA, EGFR, IL-1β, and so on, and the main anti-inflammatory pathways are the TNF, AP-1, MAPK, PI3K/AKT, and NF-κB signaling pathways.

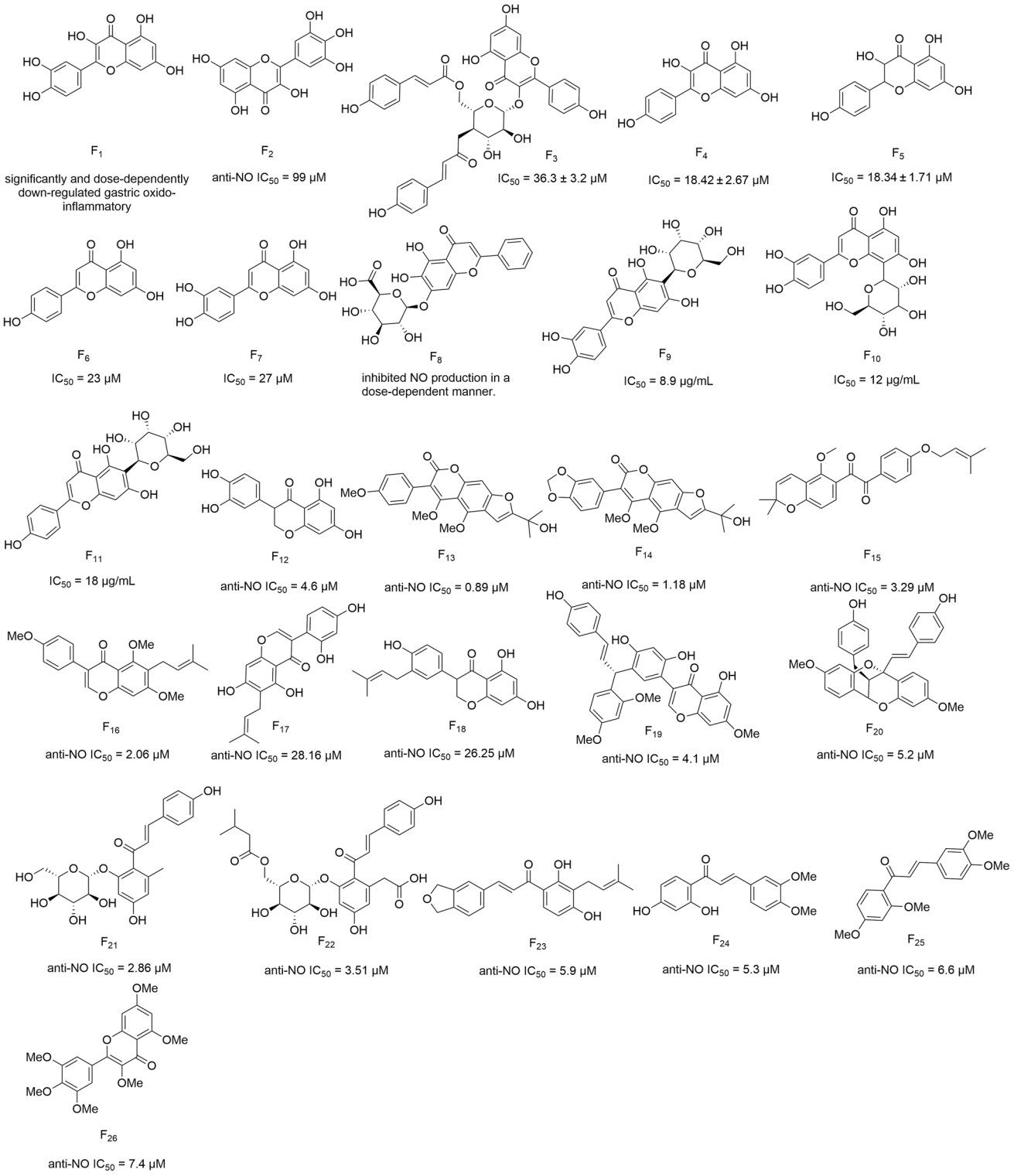

Fig. 13 Structures of flavonoids (and their derivatives) with anti-inflammatory activity

Anti-inflammatory activity of flavonoids

Quercetin (F1) is a common flavonol compound in nature with potent anti-inflammatory effects (Li et al. 2016; Salehi et al. 2020; Yang et al. 2020b). In an experimental model of acetic acid-induced gastric ulcers in rats, quercetin isolated from *Madhuca indica* J. F. Gmel achieved anti-inflammatory effects by repressing IL-1β, TNF-α, NO, and

prostaglandin production by decreasing COX-2 expression (Mohod et al. 2016). Shamsudin et al (2022) identified an analog of quercetin, myricetin (F2), which differed from quercetin's significant inhibitory activity against COX-2 and had little or no inhibitory activity against COX-2. Matsuda et al. (2003) methylated and modified myricetin to obtain compound F26, which enhanced the inhibitory effect on NO by more than tenfold with an IC_{50} value of 7.4 μM. Yang et al. (2019a) isolated a new flavonol acyl glycoside (F3) from *Lindera akoensis* Hayata that inhibited NO production with an IC_{50} value of 36.3 ± 3.2 μM. Yang's team found that two flavonoids derived from *H. plantaginea*, kaempferol (F4) and dihydrokaempferol (F5), were able to potently control the overproduction of NO at a concentration of 40 μM, with IC_{50} values of 18 μM. In addition, these two flavonoids effectively inhibited the secretion of TNF-α, PGE2, IL-1β, and IL-6, indicating that they could be used to treat inflammatory diseases by blocking the NF-κB signaling pathway and repressing the overproduction of inflammatory mediators (Yang and He 2022). Gong et al. (2012) also found that 10 and 20 μmol/L kaempferol (F4) were able to prohibit the adhesion of eosinophilic granulocytes to TNF-α-exposed epithelial cells. Kim et al. (1999) demonstrated that apigenin (F6) and luteolin (F7) had strong inhibitory effects on NO production with IC_{50} values of 23 and 27 μM, respectively. Baicalin (F8), one of the main bioactive components of *Scutellaria baicalensis*, is a glycoside flavonoid. Baicalin was shown to reduce the production of IL-6, IL-8, and TNF-α, while it could inactivate the NF-κB pathway and inhibit chondrocyte apoptosis, resulting in an anti-inflammatory effect (Chen et al. 2017; Yang et al. 2018b). Bello et al. (2019) isolated three flavonoids from *Vitex grandifolia*, isoorientin (F9), orientin (F10), and isovitexin (F11), all of which had good inhibitory effects on NF-κB, with IC_{50} values of 8.9, 12, and 18 μg/mL, respectively. In addition, F11 showed moderate activity for iNOS inhibition, whereas F9 and F10 showed poor iNOS inhibition.

Tewtrakul's team identified an isoflavone F12 from *Eclipta prostrata* and exhibited good performance (IC_{50} = 4.6 μM) in the LPS-induced NO release assay of RAW264.7 cells, which had good potential for development (Tewtrakul et al. 2011). Liu et al. (2019) extracted four isoflavone derivatives (F13–16) from the fruits of *Ficus carica*, and these four compounds exerted a good inhibitory effect on LPS-induced NO production in RAW264.7 cells, and the IC_{50} values ranged from 0.89 to 2.06 μM, with significant anti-inflammatory activity. Yao et al. (2021) discovered in the presence of two isoflavone derivatives F17 and F18 derived from *Ficus altissima* extracts with strong anti-inflammatory activity, showed stronger than positive drug indomethacin inhibitory activity, with IC_{50} values of 28.16 and 26.25 μM, in the assay of the amount of NO produced by LPS-induced RAW264.7 cells. Wang and associates developed two chalcone-isoflavone dimers, F19 and F20, from *Caragana jubata* and achieved effective anti-inflammatory effects (IC_{50} = 4.1 and 5.2 μM), with potential for anti-inflammatory development (Wang et al. 2019a). Two chalcone derivatives, F21 and F22, were extracted from *Lysimachia baviensis* by Hung's team and expressed strong anti-inflammatory activity in an assay to determine LPS-induced NO production by RAW264.7 cells, with IC_{50} of both below 4 μM (Hung et al. 2023). Wen et al. (2018) obtained three chalcone compounds (F23–F25) with good inhibitory effects on LPS-induced NO production in BV-2

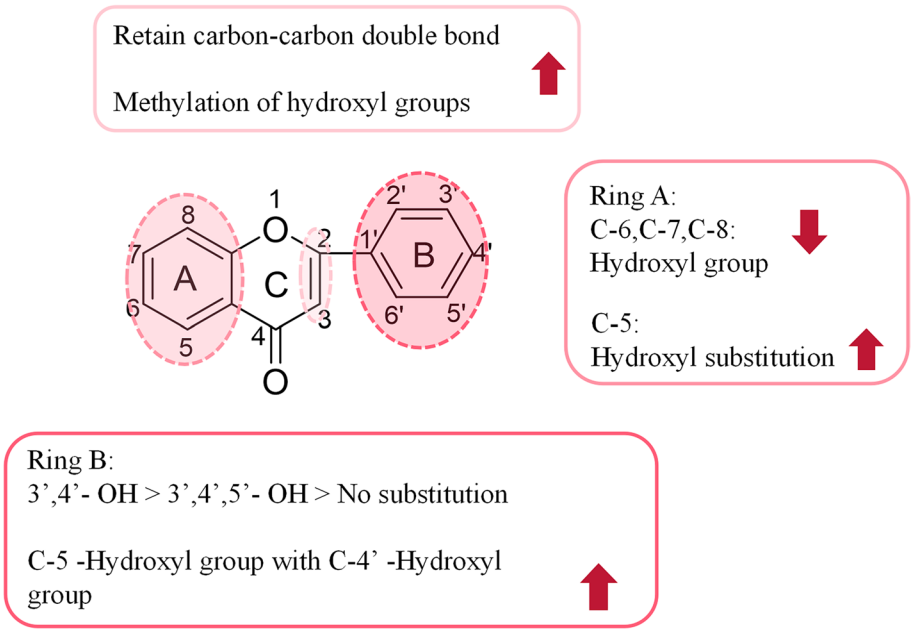

Fig. 14 Structure–activity relationship of the anti-inflammatory activity of flavonoids

cells in their study of extracts of *Pongamia pinnata* (L.) Pierre, and all of them showed stronger inhibitory activities than the positive drug for NO release.

Structure–activity relationships for the anti-inflammatory activity of flavonoids

To date, the modification of flavonoids for anti-inflammatory purposes has been centered around the parent nucleus. Most flavonoids have a C6–C3–C6 backbone structure and the types and positions of substituent groups influence their anti-inflammatory activities. The specific conformational relationships were already simplified in Fig. 14. The position and number of substituents of hydroxyl groups on the B-ring were one of the important factors affecting the anti-inflammatory activity of flavonoids. In the case of myricetin (F2), which carried three hydroxyl groups on the B ring, the position and number of substituents showed little inhibitory effect on inflammatory mediators (Shamsudin et al. 2022), whereas quercetin (F1) had two hydroxyl groups present at the C3′ and C4′ positions on the B ring and significantly inhibited the expression of COX-2. However, the loss of hydroxyl groups results in the loss of the anti-inflammatory activity of the compound (Choy et al. 2019). Hydroxyl groups at the C-5 and C-4′ positions of the A ring and the B ring potentiated their anti-inflammatory activity, whereas hydroxyl groups at the C-6, C-7, C-8, and C-3′ positions inhibited their anti-inflammatory activity. For example, compounds F4, F6, and F7 were linked with –OH at the A-ring C-5 and B-ring C-4′ positions, increasing their anti-inflammatory activity. In comparison with compounds F2 and F26, methylation of hydroxymethylated F26 resulted in enhanced inhibition of NO production, thus methylation was a possible direction for structural modifications (Matsuda et al. 2003). In a review article on flavonoids, it was mentioned that quercetin (F1) and lignans (F7) could exert anti-inflammatory effects by inhibiting LOX and that the unsaturated double bond at C2–C3 of the C-ring was an important factor influencing the activity (Shamsudin et al. 2022). Therefore, the disruption of the double bond at C2–C3 and the presence of hydroxyl groups at the C-3 position in the B-ring weaken the anti-inflammatory activity of flavonoid glycosides.

Others

In addition to the mentioned natural products and their derivatives, there were some other natural products with anti-inflammatory activity with different parent structures, which could be equally valuable for the development of anti-inflammatory agents, and their structures are summarized in Fig. 15. Tan et al. (2020) yielded Compounds O1 and O2 from the endophytic fungus *Edenia gomezpompae* with strong anti-inflammatory activity, and the IC_{50} values for NO were 2.61 and 1.32 mmol/L, respectively. Raju and his colleagues received two phytosterols from the Australian rainforest plant *Alphitonia petriei* and examined their anti-inflammatory factor inhibitory effects. Compounds O3 and O4 showed the strongest anti-inflammatory activity with IC_{50} values of 1.7 ± 0.3 and 3.5 ± 0.5 μM, respectively (Raju et al. 2016). Luo et al. (2021) separated Compound O5 from the rhizome of *Morinda officinalis*, which possessed a pronounced inhibitory effect on NO ($IC_{50} = 34.32 \pm 4.87$ μM). Susana and her colleagues purified the marine sponge *Neopetrosia compacta* extract to form two compounds, O6 and O7, which displayed better anti-inflammatory activity and were able to significantly inhibit NO production ($IC_{50} = 2.5 \pm 0.39$, 4.0 ± 2.4 μM) (Susana and Salvador-Reyes 2022). Tuan Anh et al. (2021) achieved Compounds O8 and O9 from *Physalis angulata* with IC_{50} values ranging from 0.30 to 1.06 μM for NO inhibition, similar to the positive control. Wang et al. (2018b) obtained Compound O10 from Forsythia, which had strong anti-inflammatory activity ($IC_{50} = 1.30$ μM), comparable to the effect of dexamethasone ($IC_{50} = 2.09$ μM). Xu and his associates separated an anti-inflammatory natural product, O11, from *Reineckia carnea herbs*, which was a newly discovered natural product with an IC_{50} value of 56.1 μM for NO inhibition and belonged to the steroidal parent nucleus group, with some modification value (Xu et al. 2020). Compound O12 and Compound O13, derived from the fungus *Aspergillus rugulosa* by Xu's team, displayed outstanding anti-inflammatory activity with IC_{50} values of 1.49 ± 0.31 and 3.41 ± 0.85 μM for NO inhibition (Xu et al. 2021). Tseng and others obtained Compounds O14–O16 in a study of the anti-inflammatory activity of derivatives of β-lapachone, which exerted potent inhibitory effects on NO with IC_{50} values in the range of 0.7–1.3 μM and low cytotoxicity (Tseng et al. 2013). Gui et al. (2020) found Compound O17, which had good anti-inflammatory activity in the sponge *Dysidea septosa* and significantly inhibited TNF-α ($IC_{50} = 9.15$ μM) and IL-6 ($IC_{50} = 17.62$ μM).

Conclusion and outlook

Inflammation is one of the most important bodily responses initiated by the immune system, as it protects the tissues from damage or infection, and elicits symptoms such as pain to remind the organism of the damage (Kazemi et al. 2018). However, inflammation serves as a trigger for certain diseases, such as inflammation-induced hyperthermia, atherosclerosis (van der Valk et al. 2012), depression (Caneo et al. 2016), and chronic obstructive pulmonary

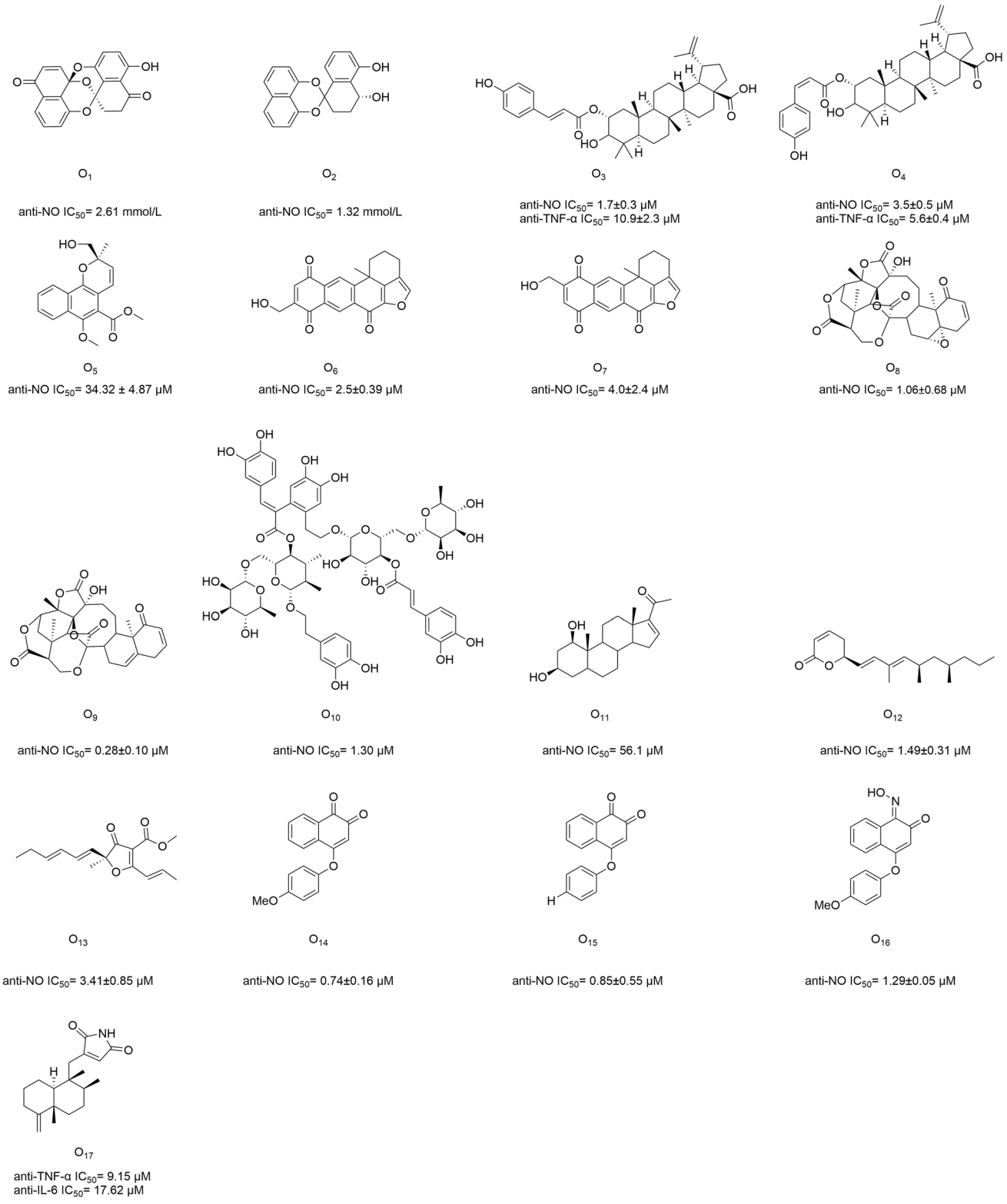

Fig. 15 Structures of other natural products (and their derivatives) with anti-inflammatory activity

disease (COPD) (Oudijk et al. 2003). Hence, the search for an effective and safe anti-inflammatory drug is important for the protection of human health. The current clinical use of NSAIDs and steroidal hormonal anti-inflammatory drugs carries many side effects, leading to the search for new anti-inflammatory drugs. Plant-derived drugs are considered to have fewer side effects than their synthetic counterparts (El-Saber Batiha et al. 2020). Natural products from plants and animals, in terms of their rich variety of molecular types and biological activities, conveniently facilitate this search for new anti-inflammatory drugs (Azab et al. 2016).

According to the classification of the active ingredients of natural products, we reviewed the anti-inflammatory activities of phenylpropanoids, quinones, alkaloids, terpenoids, flavonoids, and other compounds, and determined that the existing studies on the anti-inflammatory activities of natural products mostly concentrated on the anti-inflammatory activities of the natural products themselves, with fewer studies focusing on the structural modifications and derivatizations of the natural products. Meanwhile, with the development of modern chemistry and other subdisciplines, the synthesis methods are becoming more and more diversified, and the structural modification of compounds from natural sources is becoming cheaper and more efficient. Therefore, we explored the structure–activity relationships of various types of natural products and identified some specific structures of natural products, such as pentacyclic triterpenes, isoquinoline alkaloids, coumarins, naphthoquinones, and anthraquinones, which exhibited good anti-inflammatory activities. The presence of specific groups or changes in the position of groups resulted in the variation of the anti-inflammatory activity of the compounds, e.g., the introduction of a hydrophobic group at the C-3 position of the coumarin parent nucleus enhanced the anti-inflammatory activity and the introduction of a hydrophilic group decreased the anti-inflammatory activity. The introduction of small polar groups such as methoxy groups on the benzene ring of anthraquinone could strengthen the hydrophobicity of the structure and thus increase the anti-inflammatory activity, but the introduction of alkane groups at the 5 and 8 positions of naphthoquinone was not favorable for increasing its anti-inflammatory activity. The introduction of rigid structures in isoquinoline alkaloids favored anti-inflammatory activity, whereas the number and position of hydroxyl groups contained in flavonoids affected their anti-inflammatory activity. This finding provided some direction and ideas for the subsequent anti-inflammatory derivatization and structural modification of natural products.

Moreover, many natural product molecules with anti-inflammatory activity simultaneously exhibited a certain degree of cytotoxicity, and many studies emphasized the improvement of anti-inflammatory activity while neglecting cytotoxicity. Wang et al. (2019b) investigated the anti-neuroinflammatory effect of Erinacine C but only highlighted its inhibitory effect on inflammatory factors and lacked a discussion of cytotoxicity. Similarly, Kuang and colleagues analyzed the transcriptional fractions of Nigrospora sphaerica and discovered anti-inflammatory active ingredients, but only experimented on their inhibitory effects on inflammatory factors and did not involve cytotoxicity studies (Kuang et al. 2022). Therefore, strengthening the cytotoxicity study of natural product anti-inflammatory molecules to reduce toxicity and increase efficiency is very important. For instance, Hou and his coworkers determined that structural modification of the A- and B-ring parts could reduce cytotoxicity in the study of the structural modification of Leiogangtengrongxin and that connecting the carboxyl group at the C-20 position could enhance the affinity for Nurr77 and thus enhance the anti-inflammatory activity (Hou et al. 2020b).

Despite the large number of studies on the anti-inflammatory activity of natural products, there is currently no complete range of anti-inflammatory drugs, derived from natural products, available on the market. Although some natural product molecules were discovered to have anti-inflammatory activity, they could not be enriched in large quantities due to their low effective concentrations, making these natural products difficult to use as drugs, and many of the studies were not in-depth, only investigating the inhibition of a few inflammatory factors or simply conducting preliminary screening for anti-inflammatory activity. Due to the small yield of natural products, experiments are usually carried out at the cellular level, resulting in little clinical data, which greatly reduces the possibility of natural products being marketed as novel anti-inflammatory agents. To a certain extent, research on the anti-inflammatory activity of natural products has been limited to a superficial level thus far. However, in recent years, the rapid development of biosynthesis technology has brought new hope for the mass production of active compounds with low yields from natural sources. The parent nuclear structures of these natural compounds often existed as active centers, so there were few changes to the parent nuclear structure in the literature that we had searched. Therefore, the study of these natural products with anti-inflammatory activity was still of great significance, and their semi-synthetic modification to make up for the structural defects of the target molecules had become an alternative direction. Through the classification and summary of the structure of natural anti-inflammatory molecules in this review, some rules of structure–activity relationship were obtained, which could provide some guidance for the follow-up structural modification. With the rapid development of science and technology, research could be enhanced by a large number of new technologies, such as high-throughput screening, computer-aided drug design

(CADD), and biosynthesis technology, which would hasten the research process and would facilitate the development of better anti-inflammatory drugs that can protect human health.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

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