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Pyrazole Derivatives as Anti-Inflammatory Agents: A Comprehensive Review of Synthesis, In-Silico Studies and Therapeutic Prospects

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ABSTRACT

Inflammation plays a crucial role in the body's immune response against infections; however, in certain diseases, it can become dysregulated, leading to tissue damage. Chronic inflammation has been linked to various health conditions, necessitating the development of effective anti-inflammatory agents. This review paper summarizes recent advancements in the synthesis and in-silico evaluation of pyrazole derivatives as potential anti-inflammatory agents. Various studies have focused on the synthesis of chalcone, pyrazole, and pyrazoline derivatives and their evaluation for inhibitory activity against inflammation-related enzymes, including cyclooxygenase (COX), lipoxygenase, and nitric oxide production. Some compounds exhibited promising anti-inflammatory effects, with higher potency than standard drugs. Docking studies provided valuable insights into the binding modes and interactions of these derivatives with target enzymes. The review highlights the structure-activity relationships and optimization strategies for developing novel pyrazole derivatives as potential anti-inflammatory agents. Further research into the development of novel compounds with improved efficacy and reduced side effects is crucial to effectively manage inflammation-associated diseases and improve patient outcomes. The findings contribute to the expanding knowledge and potential therapeutic applications of pyrazole-based compounds in the field of inflammation research.

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INTRODUCTION

Inflammation is a process through which the body's white blood cells and their products defend against infections caused by external invaders like bacteria and viruses. However, in certain diseases such as arthritis, the immune system triggers inflammation even in the absence of any invaders, leading to damage (1)

There are two main types of inflammation: acute and chronic. Acute inflammation is short-lived and typically resolves within hours or days, while chronic inflammation can persist for months or years, even after the initial trigger is gone. Chronic inflammation has been linked to various conditions, including cancer, heart disease, diabetes, asthma, and Alzheimer's disease (1). Certain types of arthritis, such as rheumatoid arthritis, psoriatic arthritis, and gouty arthritis, are characterized by inflammation. However, there are other painful joint and musculoskeletal conditions, such as osteoarthritis, fibromyalgia, muscular low back pain, and muscular neck pain, that may not involve inflammation (1).

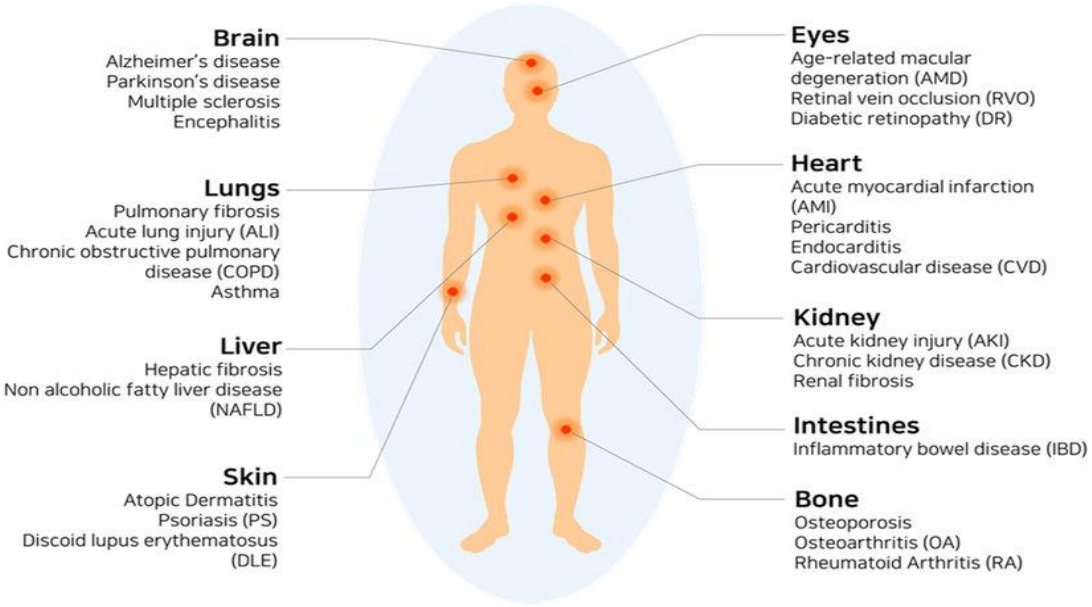

Fig. 1. Types of inflammatory diseases on different parts of the human body.

Inflammatory diseases with genetic susceptibility and autoimmune diseases, such as rheumatoid arthritis, atherosclerosis, colitis, and dermatitis, are relatively common. These diseases are often complex and multifactorial, involving both genetic susceptibility and individual behavior. Constructing genetically modified animal models to study these diseases is challenging due to the complexity of their causes and mechanisms (2).

Inflammation manifests through five cardinal signs: heat, pain, redness, swelling, and loss of function. Inflammation is considered a mechanism of innate immunity, which is a general response compared to the specific response of adaptive immunity. Insufficient inflammation can result in tissue destruction, while excessive inflammation, known as chronic inflammation, is associated with various diseases such as hay fever, periodontal disease, atherosclerosis, and osteoarthritis (2).

Several factors can contribute to inflammation overload, including lifestyle choices (e.g., smoking and diet), genetics, environmental pollutants, and autoimmune diseases, where the immune system targets the body's own tissues, leading to chronic inflammation (2).

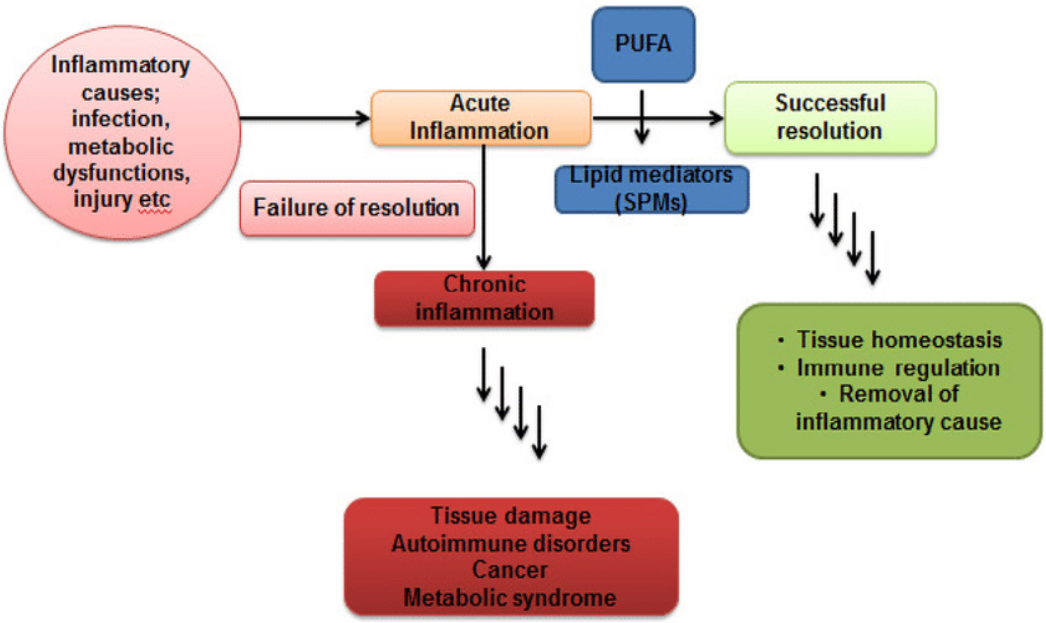

Fig.2. Resolution of inflammation: causes, acute and chronic inflammation**.**

Anti-inflammatory drugs

To alleviate pain, swelling, and inflammation, various drugs are used, including nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin, ibuprofen, and naproxen, corticosteroids such as prednisone, antimalarial medications like hydroxychloroquine, and disease-modifying antirheumatic drugs (DMARDs) such as azathioprine, cyclophosphamide, leflunomide, methotrexate, and sulfasalazine. Biologic drugs such as abatacept, adalimumab, certolizumab, etanercept, infliximab, golimumab, rituximab, and tocilizumab are also used. Some of these medications are also employed for treating cancer, inflammatory bowel disease, and preventing organ rejection after transplantation. However, when used for inflammatory

diseases, chemotherapy-type medications like methotrexate or cyclophosphamide are typically prescribed at lower doses with reduced risks of side effects compared to cancer treatment (3).

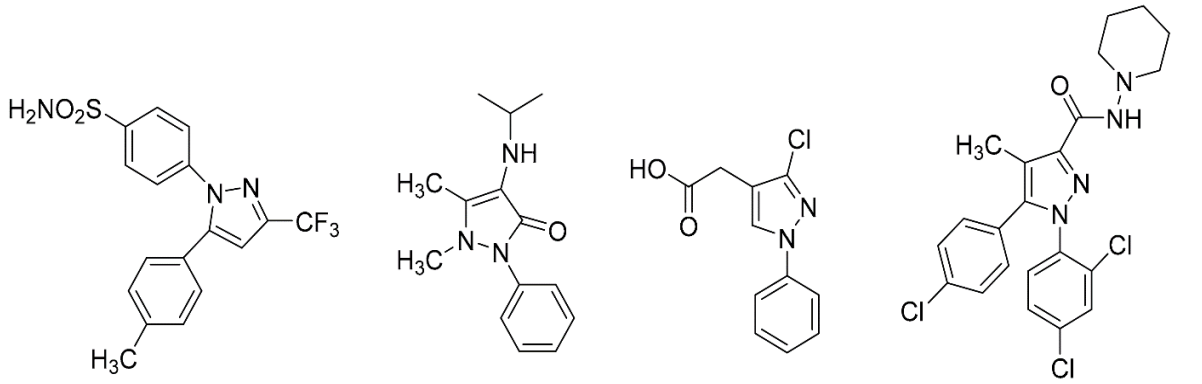

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fig. 3. Previously available anti-inflammatory drugs.

Mechanism of action of NSAIDs

The primary mechanism of action of NSAIDs involves the inhibition of the enzyme cyclooxygenase (COX). Cyclooxygenase is responsible for the conversion of arachidonic acid into thromboxanes, prostaglandins, and prostacyclins. The therapeutic effects of NSAIDs arise from the reduction in the production of these eicosanoids. Thromboxanes are involved in platelet adhesion, prostaglandins cause vasodilation, increase the temperature set-point in the hypothalamus, and play a role in anti-nociception (4).

There are two main isoforms of cyclooxygenase, namely COX-1 and COX-2. COX-1 is constitutively expressed in the body and plays a role in maintaining gastrointestinal mucosal lining, kidney function, and platelet aggregation. On the other hand, COX-2 is inducibly expressed during an inflammatory response. Most NSAIDs are nonselective and inhibit both COX-1 and COX-2. However, COX-2 selective NSAIDs (e.g., celecoxib) specifically target COX-2 and therefore exhibit a different side effect profile. Notably, since COX-1 is primarily responsible for maintaining gastric mucosal integrity and COX-2 is mainly involved in inflammation, COX-2 selective NSAIDs are expected to provide anti-inflammatory relief without compromising the gastric mucosa (5).

Adverse Effects of NSAIDs

NSAIDs are associated with well-known adverse effects that affect the gastric mucosa, renal system, cardiovascular system, hepatic system, and hematologic system.

Gastric adverse effects are primarily attributed to the inhibition of COX-1, which prevents the production of prostaglandins responsible for protecting the gastric mucosa. These adverse effects are more likely to occur in patients with a history of peptic ulcers. The use of COX-2 selective NSAIDs presents a lower-risk alternative as they are more specific to COX-2 and spare COX-1 (6).

Renal adverse effects result from the role of COX-1 and COX-2 in renal hemodynamics, where prostaglandins play a significant role. In patients with normal renal function, the inhibition of prostaglandin synthesis does not pose a significant problem. However, in patients with renal dysfunction, the reduction of these prostaglandins through NSAID use can lead to complications such as acute renal dysfunction, fluid and electrolyte disorders, renal papillary necrosis, and nephrotic syndrome/interstitial nephritis (7).

Cardiovascular adverse effects are also associated with NSAID use, including myocardial infarction (MI), thromboembolic events, and atrial fibrillation. Diclofenac is reported to have the highest increase in adverse cardiovascular events among NSAIDs (5) (8).

Hepatic adverse effects are relatively uncommon, and NSAID-associated hepatotoxicity (elevated aminotransferase levels) is rare. Diclofenac has a higher incidence of hepatotoxic effects compared to other NSAIDs (9).

Hematologic adverse effects are possible, especially with nonselective NSAIDs due to their antiplatelet activity. This antiplatelet effect may pose a problem in patients with a history of gastrointestinal ulcers, platelet impairments (e.g., hemophilia, thrombocytopenia, von Willebrand disease), and certain perioperative cases (10).

Other minor adverse effects include anaphylactoid reactions involving the skin and respiratory system, such as urticaria and aspirin-exacerbated respiratory disease.

The provided information consists of summaries of various research studies related to the synthesis and biological activity of chalcone, pyrazole, and pyrazoline derivatives. Here is a summary of the key findings from each study:

- *Septianingtyas et al.* (2021): The authors synthesized chalcone derivatives using a simple stirring process. The presence of hydroxyl substitution on the chalcone resulted in higher yields compared to non-substituted derivatives (11).

- *Mantzanidou et al.* (2021): The researchers synthesized pyrazolines and pyrazole derivatives and evaluated their inhibitory activity. Compound 1-(3-(4-chlorophenyl)-5-(naphthalen-1-yl)-1H-pyrazol-1-yl)-ethan-1-one showed potent lipoxygenase inhibition. Compounds 5-(4-((4-bromobenzyl)oxy)-phenyl)-3-phenyl-4,5-dihydro-1H-pyrazole and 5-(4-((4-bromobanzyl)-oxy)-phenyl)-3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole exhibited high potency in inhibiting carrageenin-induced paw edema and nociception (12).

- *Mishra et al.* (2019): The authors synthesized pyrazole ethanone-linked compounds through a cyclization reaction. The synthesized derivatives were characterized using various identification tests and spectroscopic techniques (13).

- *Abdellatif et al.* (2019): The researchers synthesized Schiff and chalcone substituted pyrazoles and evaluated their anti-inflammatory activities. The synthesized compounds showed considerable edema inhibition and some exhibited superior screening results compared to the reference drug celecoxib (14).

- *Hassan et al*. (2019): New pyrazole derivatives were synthesized and evaluated for COX-1 and COX-2 inhibitory activity. Some compounds showed a selective inhibitory effect on COX-2 and potent inhibition of PGE2 production (15).

- *Noisier et al.* (2017): The authors synthesized pyrazole-substituted nitrogenous heterocyclic compounds and evaluated their anti-inflammatory activity. Compound 6-(4-Methoxyphenyl)-4-(1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)-1,2-dihydro-2-oxo-pyridine-3-carbonitrile showed increased potency in inhibiting edema compared to the standard reference drugs (16).

- *Abdelgawad et al.* (2017): The researchers designed and synthesized pyrazole-hydrazone derivatives and evaluated their inhibitory activity on COX-1, COX-2, and 5-LOX enzymes. Some compounds exhibited better COX-2 inhibitory activity than celecoxib, along with good anti-inflammatory activity (17).

- *He et al.* (2015): Twenty-eight pyrazoline derivatives derived from pyranochalcones were synthesized and evaluated for their inhibitory potency on NO production in RAW 264.7 cells. Some compounds showed potent inhibitory effects on NO production and iNOS activity (18).

- *Doma et al*. (2014): The authors synthesized JNK-1 inhibitors containing a pyrazole heterocyclic group and evaluated their JNK-1 inhibitory activity and anti-inflammatory activity. Several synthesized analogues exhibited potent JNK-1 inhibitory activity, with some compounds being particularly potent (19).

- *Tewari et al.* (2014) synthesized a novel series of pyrazole derivatives and evaluated their anti-inflammatory activity in a rat paw edema model. One compound, {4-[2-(5-Methyl-2-phenyl-2Hpyrazol-3-yloxy)]-benzylidine}-aryl-amine, showed comparable anti-inflammatory activity to Nimesulide. In silico docking studies were performed to investigate the binding mode of the compounds to target cyclooxygenase-2 (COX-2) (20).

- *El-Din et al*. (2010) screened newly synthesized compounds for their anti-inflammatory activity using carrageenan-induced paw edema and cotton pellet granuloma tests. Compound AD 532, (4-(3-(4-Methylphenyl)-4-cyano-1H-pyrazol-1-yl)-benzenesulfonamide) showed promising results. It exhibited no ulcerogenic effect and minimal effects on renal function. While it was a less potent inhibitor of COX-2 in vitro compared to celecoxib, it may have lower potential cardiovascular toxicity. Compound AD 532 appears to be a promising and safe option for managing chronic inflammatory conditions (21).

- *Sauzem et al.* (2009) evaluated the antinociceptive and antiedematogenic effects of 5-trifluoromethyl-4,5-dihydro-1H-pyrazole derivatives EPFCA3 and MPFCA4 in a rat model of adjuvant-induced arthritis. Acute and chronic administration of EPFCA3 and MPFCA4 produced antinociceptive effects but not antiedematogenic effects. No signs of toxicity were observed in animals treated with EPFCA3 or MPFCA4. Chronic administration of EPFCA3, MPFCA4, or dipyrone did not alter the relationship between parameters and inflammation (22).

- *El Sayed et al*. (2011) designed and synthesized arylhydrazone derivatives and a series of 1,5-diphenyl pyrazoles. The synthesized compounds were investigated for their anti-inflammatory activities using a carrageenan-induced rat paw edema model and tested for inhibitory activity against ovine COX-1 and COX-2 in vitro. Docking studies revealed a similar binding mode to SC-558, a selective COX-2 inhibitor, indicating their potential as COX-2 inhibitors (23).

- *Gokhan-Kelki et al.* (2007) synthesized 1-thiocarbamoyl-3-substituted phenyl-5-(2-pyrrolyl)-4,5-dihydro-(1H)-pyrazole derivatives as potential MAO-B inhibitors. The

synthesized compounds were tested for their ability to selectively inhibit the activity of the A and B isoforms of monoamine oxidase (MAO) and their in vivo anti-inflammatory activity. Compound 1-N-Allylthiocarbamoyl-3-(4-methoxyphenyl)-5-(2-pyrrolyl)-4,5-dihydro-(1H)-pyrazole exhibited anti-inflammatory activity comparable to that of indomethacin without causing ulcerogenic effects (24).

These studies demonstrate the synthesis of various pyrazole and pyrazoline derivatives and their potential biological activities, including anti-inflammatory, COX inhibition, lipoxygenase inhibition, and inhibitory effects on NO production.

Rationale of the study

The most of the anti-inflammatory drugs have very less specificity, effectiveness and have more side effects. The major problem is the treatment of different types of inflammatory diseases for which huge effort is employed to implement novel anti-inflammatory agents. The current anti-inflammatory agents have restrictive usage for the management of human microbial diseases due to numerous side effects, adverse effect, toxicity and narrow spectrum. drug, it is a major reason for the failure of many forms of anti-inflammatory drugs. So, there is a requirement of some new anti-inflammatory agents having better selectivity, more efficiency, and safety.

CONCLUSION

Numerous studies have focused on the synthesis and evaluation of chalcone, pyrazole, and pyrazoline derivatives for their potential anti-inflammatory activity. These derivatives have shown promise in inhibiting inflammation-related enzymes and pathways, including COX-1, COX-2, lipoxygenase, and nitric oxide production. Some compounds exhibited potent anti-inflammatory effects, while others demonstrated selectivity in targeting specific enzymes.

Pyrazole derivatives have attracted significant attention in medicinal chemistry due to their diverse biological activities, particularly as anti-inflammatory agents. This review paper provides an overview of recent advancements in the synthesis and evaluation of pyrazole derivatives for their anti-inflammatory properties. The reviewed studies encompass various spyrazoline syntheses. The anti-inflammatory activities of the synthesized compounds were evaluated through in vitro and in vivo assays, such as carrageenan-induced paw edema, nociception inhibition, and COX-1/COX-2 enzyme inhibition. Several compounds exhibited promising anti-inflammatory effects, with higher potency than standard drugs. Docking

studies provided valuable insights into the binding modes and interactions of these derivatives with target enzymes. Furthermore, the reviewed studies shed light on the structure-activity relationships and optimization strategies for developing novel pyrazole derivatives as potential anti-inflammatory agents. These findings contribute to the expanding knowledge and potential therapeutic applications of pyrazole-based compounds in the field of inflammation research. Overall, further research into the development of novel anti-inflammatory compounds with improved efficacy and reduced side effects is necessary to effectively manage inflammation-associated diseases and improve patient outcomes.

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