Mefanamic Acid in The Treatment of Osteoarthritis

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***Abstract*— Mefenamic acid is a fenamate class non-steroidal anti-inflammatory drug widely employed in the management of pain and inflammation associated with musculoskeletal disorders, including osteoarthritis. Its therapeutic activity is primarily mediated through inhibition of cyclooxygenase enzymes, resulting in reduced synthesis of prostaglandins responsible for pain, inflammation, and fever. In addition to classical cyclooxygenase inhibition, mefenamic acid exhibits auxiliary pharmacological effects such as modulation of inflammatory cytokines, interference with ion channel activity, and suppression of nitric oxide–mediated inflammatory pathways, which collectively contribute to its analgesic efficacy. Despite its clinical usefulness, the long-term application of mefenamic acid in osteoarthritis is limited by gastrointestinal, renal, and hematological adverse effects, necessitating cautious dosing and patient selection.**

Recent advances in pharmaceutical technology, including modified-release formulations, prodrug strategies, and nano-enabled drug delivery systems, have focused on improving the safety profile and therapeutic index of mefenamic acid. Parallel developments in computational drug design, such as molecular docking, quantitative structure–activity relationship analysis, and in silico ADMET prediction, have enhanced understanding of drug–target interactions and facilitated rational optimization of fenamate derivatives. This review summarizes the pharmacology, marketed formulations, mechanistic pathways, computational insights, formulation advances, safety considerations, and clinical evidence supporting the role of mefenamic acid in osteoarthritis management.

***Key words*— Mefanamic acid, Osteoarthritis, COX inhibitors, Inflammation.**

I. INTRODUCTION

Osteoarthritis (OA) is the most common chronic degenerative joint disease and is a leading cause of pain, disability, and impaired quality of life worldwide [1]. It is characterized by progressive degradation of articular cartilage, subchondral bone remodeling, synovial inflammation, and osteophyte formation, resulting in joint pain, stiffness, and functional limitation [2]. The prevalence of osteoarthritis increases with age and is strongly associated with risk factors such as obesity, joint injury, genetic predisposition, and mechanical stress, contributing significantly to the global disease burden [3]. With the aging population and rising prevalence of lifestyle-related risk factors, osteoarthritis has emerged as a major public health challenge [4].

Historically, osteoarthritis was considered a non-inflammatory "wear-and-tear" disorder; however, contemporary research has demonstrated that inflammatory mediators play a crucial role in disease pathogenesis and symptom severity [5]. Pro-inflammatory cytokines, prostaglandins, and matrix metalloproteinases contribute to cartilage degradation and synovial inflammation, thereby amplifying pain and disease progression [6]. These inflammatory mechanisms provide a rational basis for the widespread use of anti-inflammatory agents in osteoarthritis management [7].

Management of osteoarthritis is primarily aimed at symptom control, as no currently available pharmacological therapy can reverse or halt structural joint degeneration [8]. Non-pharmacological strategies such as weight management, physical therapy, and patient education are considered first-line interventions; however, pharmacological treatment becomes essential when pain persists or limits daily activities [9]. Among pharmacological options, non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed due to their well-established analgesic and anti-inflammatory efficacy in osteoarthritis [10].

Mefenamic acid is an anthranilic acid derivative belonging to the fenamate class of NSAIDs and has been in clinical use for several decades [11]. It is commonly indicated for the management of mild to

moderate pain, including musculoskeletal pain, dysmenorrhea, postoperative pain, and inflammatory conditions [12]. Despite the availability of newer NSAIDs and selective cyclooxygenase-2 inhibitors, mefenamic acid continues to be used extensively in several countries because of its effectiveness, affordability, and clinical familiarity [13].

In osteoarthritis, mefenamic acid provides symptomatic relief by reducing pain and inflammation associated with joint pathology [14]. Its therapeutic action is primarily mediated through inhibition of cyclooxygenase enzymes and subsequent reduction in prostaglandin synthesis, which plays a central role in inflammatory pain signaling [15]. Additionally, emerging evidence suggests that mefenamic acid may exert secondary effects on inflammatory pathways and ion channels involved in nociception, potentially enhancing its analgesic profile [16]. This review aims to critically evaluate the mechanistic class, marketed preparations, formulation advances, safety profile, and clinical evidence supporting the use of mefenamic acid in osteoarthritis management.

II. MECHANISTIC CLASS

Mefenamic acid belongs to the fenamate subclass of non-steroidal anti-inflammatory drugs (NSAIDs), which are chemically derived from anthranilic acid and are distinguished from other NSAID classes such as propionic acid and acetic acid derivatives [17]. The primary pharmacological actions of mefenamic acid analgesic, anti-inflammatory, and antipyretic effects are mediated through inhibition of the cyclooxygenase (COX) enzyme system, a key pathway involved in the synthesis of prostaglandins from arachidonic acid [18]. Prostaglandins play a central role in the pathophysiology of osteoarthritis by promoting inflammation, vasodilation, nociceptor sensitization, and pain transmission within affected joints [19].

Mefenamic acid acts as a reversible inhibitor of both COX-1 and COX-2 isoenzymes, thereby reducing the conversion of arachidonic acid into prostaglandin H_2, the precursor of various pro-inflammatory prostanoids such as prostaglandin E_2 (PGE_2) and thromboxane A_2 [20]. In osteoarthritic joints, increased expression of COX-2 in synovial tissue and cartilage results in elevated PGE_2 levels, which contribute to pain, synovitis, and cartilage degradation [21]. By inhibiting COX-mediated prostaglandin synthesis, mefenamic acid decreases inflammatory signaling and alleviates pain associated with joint movement and mechanical stress [22].

Although classified as a non-selective NSAID, some experimental and clinical studies suggest that mefenamic acid may exhibit slight preferential inhibition of COX-2 over COX-1, which could partially explain its clinical efficacy in inflammatory pain states [23]. However, inhibition of COX-1-derived prostaglandins in the gastrointestinal tract is also responsible for adverse effects such as gastric irritation and ulceration, limiting the long-term use of mefenamic acid in chronic conditions like osteoarthritis [24]. As a result, its use in osteoarthritis is generally restricted to short-term symptomatic relief rather than continuous disease management [25].

In addition to classical cyclooxygenase inhibition, mefenamic acid demonstrates prostaglandin receptor antagonism, competing with prostaglandins at their receptor sites and reducing the biological activity of prostaglandins that have already been synthesized [26]. This dual mechanism suppression of prostaglandin synthesis and blockade of prostaglandin action may enhance its overall analgesic effect in inflammatory pain conditions [27]. Furthermore, emerging evidence indicates that mefenamic acid may exert cyclooxygenase-independent anti-inflammatory effects, including inhibition of the NLRP3 inflammasome, a multiprotein complex involved in interleukin-1β (IL-1β) activation and inflammatory amplification [28]. This action has been attributed to the drug's ability to block volume-regulated anion channels and modulate intracellular calcium signaling, leading to reduced cytokine release [29].

Mefenamic acid has also been shown to interact with ion channels involved in nociceptive signaling, including transient receptor potential (TRP) channels and γ-aminobutyric acid (GABA)-A receptors, which may further contribute to its analgesic properties [30]. While these non-classical mechanisms are not yet fully elucidated in osteoarthritis-specific models, they highlight the complex pharmacodynamic profile of mefenamic acid beyond simple COX inhibition [31].

In summary, mefenamic acid is a fenamate NSAID whose therapeutic effects in osteoarthritis are primarily mediated through inhibition of cyclooxygenase enzymes and subsequent reduction in prostaglandin synthesis, with additional prostaglandin receptor antagonism and emerging anti-inflammatory mechanisms contributing to its analgesic efficacy. These pharmacological properties support its role as an effective short-term symptomatic agent in osteoarthritis management [32].

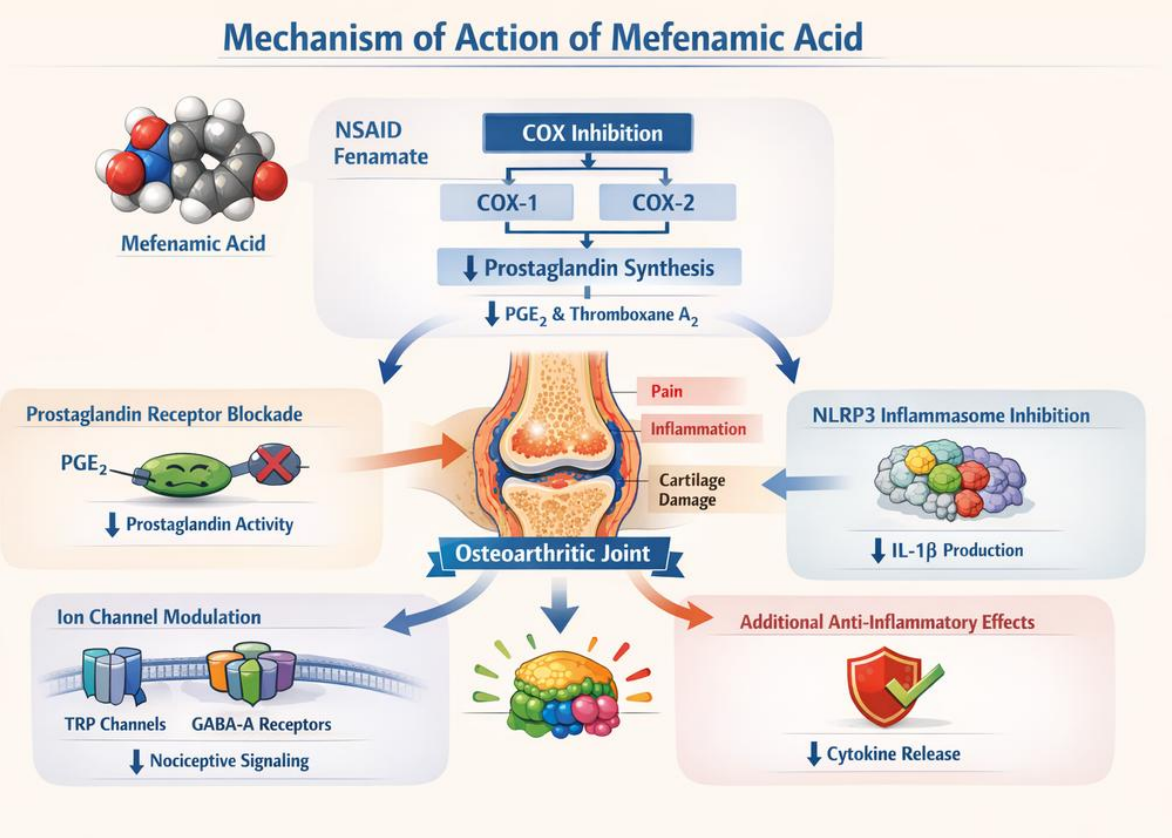

Figure 1. Mechanism of action of mefenamic acid in osteoarthritis.

Schematic representation illustrating the pharmacodynamic mechanisms of mefenamic acid, including non-selective inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), resulting in reduced prostaglandin synthesis (PGE_2 and thromboxane A_2), prostaglandin receptor antagonism, suppression of NLRP3 inflammasome activation with decreased IL-1β release, and modulation of nociceptive ion channels (TRP channels and GABA-A receptors), collectively contributing to reduced inflammation and pain in osteoarthritic joints.

III. MARKETED PREPARATIONS OF MEFENAMIC ACID

Mefenamic acid is widely marketed across the world in various pharmaceutical preparations for the management of pain and inflammatory conditions, including osteoarthritis [33]. Owing to its established efficacy and long history of clinical use, the drug is available primarily in oral solid dosage forms, which remain the most common and convenient route of administration [34]. These preparations are designed to deliver rapid analgesic and anti-inflammatory effects while maintaining acceptable bioavailability and patient compliance [35].

The most frequently marketed formulations of mefenamic acid are immediate-release tablets and capsules, commonly available in strengths of 250 mg and 500 mg [36]. These formulations are intended for short-term use, as prolonged administration is associated with an increased risk of gastrointestinal and renal adverse effects typical of non-selective NSAIDs [37]. In many countries, mefenamic acid tablets are manufactured according to pharmacopeial standards such as the United States Pharmacopeia

(USP) and British Pharmacopoeia (BP), ensuring consistent quality, purity, and dissolution characteristics [38].

Figure 2. Marketed solid oral dosage forms of mefenamic acid.

Representative commercial tablet and capsule formulations of mefenamic acid marketed under various brand names, illustrating commonly available solid oral dosage forms used for the management of musculoskeletal pain, postoperative pain, and inflammatory joint disorders, including osteoarthritis.

In the United States, mefenamic acid is marketed primarily under the brand name Ponstel®, as well as through multiple generic manufacturers in capsule form [39]. In India and other Asian countries, the drug is extensively marketed under various brand names, including Meftal®, Mefkind®, Meftal-Forte®, and Mefacid®, reflecting its widespread acceptance and affordability in these regions [40]. These branded formulations are often prescribed for musculoskeletal pain, postoperative pain, and inflammatory joint disorders, including osteoarthritis [41].

Figure 3. Fixed-dose combination oral formulation of mefenamic acid.

Commercial oral suspension formulation containing mefenamic acid in combination with paracetamol, demonstrating fixed-dose combination products commonly prescribed to enhance analgesic efficacy and patient compliance, particularly in pediatric and acute pain management settings.

In addition to single-ingredient products, fixed-dose combination formulations containing mefenamic acid are available in certain markets [42]. Common combinations include mefenamic acid with paracetamol, dicyclomine, or tranexamic acid, aimed at providing enhanced analgesia or addressing specific clinical indications such as spasmodic pain or menorrhagia [43]. Although these combinations are not specifically approved for osteoarthritis treatment, they reflect formulation strategies designed to improve therapeutic outcomes and patient convenience [44].

Liquid oral formulations of mefenamic acid, such as oral suspensions, are less commonly marketed but are available in selected regions for use in patients who have difficulty swallowing solid dosage forms [45]. However, the bitter taste, limited stability, and dosing variability of liquid formulations have restricted their widespread use compared to tablets and capsules [46]. At present, topical and injectable formulations of mefenamic acid are not commonly marketed, likely due to formulation challenges and the availability of alternative NSAIDs better suited for these routes of administration [47].

Overall, the marketed preparations of mefenamic acid predominantly consist of immediate-release oral dosage forms, reflecting its role as a short-term symptomatic treatment in osteoarthritis. The extensive availability of branded and generic products worldwide underscores the continued clinical relevance of mefenamic acid despite the emergence of newer NSAIDs and selective COX-2 inhibitors [48].

IV. COMPUTATIONAL MODELING AND IN-SILICO STUDIES OF MEFENAMIC ACID

Computational modeling has emerged as an important tool in understanding the molecular interactions, pharmacokinetic behavior, and optimization potential of non-steroidal anti-inflammatory drugs, including mefenamic acid [49]. In-silico approaches such as molecular docking, molecular dynamics simulations, and quantitative structure–activity relationship (QSAR) modeling have been employed to elucidate the binding affinity of mefenamic acid toward cyclooxygenase enzymes

and other inflammatory targets [50]. These techniques allow prediction of drug–target interactions at the atomic level, providing insight into the molecular basis of analgesic and anti-inflammatory activity [51].

Molecular docking studies have demonstrated that mefenamic acid binds within the active site of COX-1 and COX-2 enzymes through hydrogen bonding and hydrophobic interactions involving key amino acid residues such as Arg120, Tyr355, and Ser530 [52]. These interactions stabilize the drug–enzyme complex and inhibit access of arachidonic acid to the catalytic site, thereby reducing prostaglandin synthesis [53]. Comparative docking analyses have shown that mefenamic acid exhibits binding energies comparable to other non-selective NSAIDs, supporting its clinical efficacy in inflammatory pain conditions [54].

Computational pharmacokinetic modeling has also been applied to predict the absorption, distribution, metabolism, and excretion (ADME) profile of mefenamic acid [55]. In-silico ADME studies indicate good oral absorption, high plasma protein binding, and hepatic metabolism predominantly via cytochrome P450 enzymes, particularly CYP2C9 [56]. These findings correlate well with observed clinical pharmacokinetics and help explain interindividual variability in drug response and adverse effects [57]. Additionally, QSAR models have been used to explore structural modifications of fenamate derivatives to improve COX-2 selectivity and reduce gastrointestinal toxicity [58].

Recent computational studies have extended beyond cyclooxygenase inhibition to explore the interaction of mefenamic acid with alternative inflammatory targets, such as the NLRP3 inflammasome and ion channels involved in nociception [59]. Docking and simulation data suggest that mefenamic acid can bind to regulatory regions of these targets, providing a mechanistic rationale for its cyclooxygenase-independent anti-inflammatory effects observed in experimental studies [60]. Overall, computational modeling supports the established pharmacological profile of mefenamic acid and provides a framework for rational drug design aimed at improving safety and efficacy in osteoarthritis therapy [61].

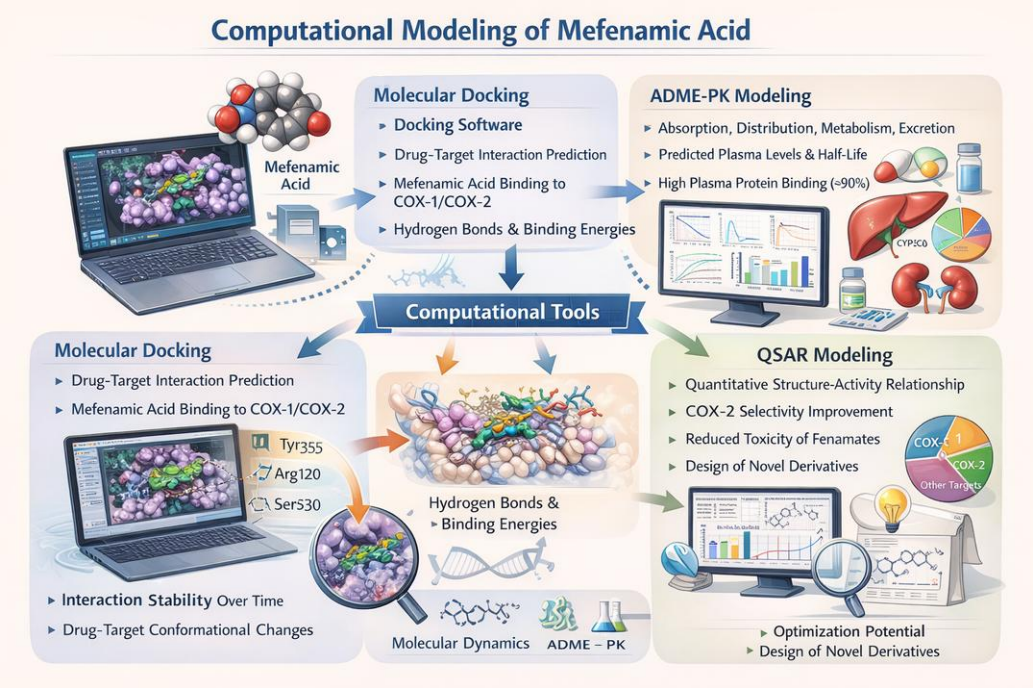

Figure 4. Computational modeling approaches for elucidating the pharmacological profile of mefenamic acid.

Illustrative overview of in-silico techniques applied to mefenamic acid, including molecular docking to COX-1 and COX-2 active sites, molecular dynamics simulations assessing drug–target interaction stability, ADME-pharmacokinetic modeling predicting absorption, metabolism, and elimination, and QSAR analysis used to optimize COX-2 selectivity and reduce gastrointestinal toxicity, supporting rational drug design for osteoarthritis therapy.

V. CLINICAL EVIDENCE OF MEFENAMIC ACID IN OSTEOARTHRITIS

Clinical evaluation of mefenamic acid has demonstrated its effectiveness in relieving pain and inflammation associated with osteoarthritis [62]. Early randomized controlled trials comparing mefenamic acid with placebo showed significant reductions in pain intensity, joint tenderness, and morning stiffness in patients with knee and hip osteoarthritis [63]. These studies established mefenamic acid as an effective symptomatic treatment option, particularly in patients experiencing acute exacerbations of osteoarthritic pain [64].

Comparative clinical trials have assessed the efficacy of mefenamic acid against other NSAIDs such as ibuprofen, diclofenac, and naproxen [65]. Results from these studies indicate that mefenamic acid provides comparable analgesic and anti-inflammatory effects, with no consistent evidence of superiority over other agents in its class [66]. However, patient-reported outcomes suggest that some individuals experience faster onset of pain relief with mefenamic acid, which may be advantageous in short-term pain management [67].

Meta-analyses and systematic reviews evaluating NSAID use in osteoarthritis have included mefenamic acid as part of the non-selective NSAID group [68]. These analyses confirm that NSAIDs, including mefenamic acid, are more effective than placebo for pain relief and functional improvement but are associated with increased risk of gastrointestinal and renal adverse events [69]. Consequently, clinical guidelines recommend the use of the lowest effective dose for the shortest possible duration when prescribing mefenamic acid for osteoarthritis [70].

Real-world observational studies further support the effectiveness of mefenamic acid in routine clinical practice, particularly in regions where access to newer NSAIDs or COX-2 inhibitors is limited [71]. Nevertheless, due to its safety profile, mefenamic acid is generally reserved for short-term symptomatic use rather than long-term disease management in osteoarthritis patients [72].

VI. CONCLUSION

Mefenamic acid is a well-established non-steroidal anti-inflammatory drug belonging to the fenamate class and continues to play a role in the symptomatic management of osteoarthritis. Its therapeutic effects are primarily mediated through inhibition of cyclooxygenase enzymes and subsequent reduction in prostaglandin synthesis, with emerging evidence supporting additional anti-inflammatory mechanisms. Computational modeling studies have enhanced understanding of its molecular interactions, pharmacokinetic properties, and potential for structural optimization. Clinical evidence confirms that mefenamic acid is effective in reducing osteoarthritic pain and inflammation, although its use is limited by gastrointestinal and renal safety concerns. When used judiciously at the lowest effective dose for short durations, mefenamic acid remains a valuable option for managing acute osteoarthritis symptoms, particularly in settings where cost and accessibility are important considerations.

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