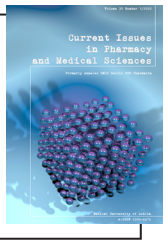
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New uses of ketoprofen – a review of studies from 2015 to 2021

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ABSTRACT

Ketoprofen (K) belongs to the family of nonsteroidal anti-inflammatory drugs (NSAIDs) and demonstrates analgesic, anti-inflammatory and antipyretic properties. K is one of the most commonly used NSAIDs because of the speed and effectiveness of its activity. K is currently used for the treatment of pain and treatment of symptoms in rheumatic diseases, however, many researchers are looking for new uses of K. The aim of the review was to present the possible applications of K as indicated in current literature. We searched research literature and compiled all the reports (2015 onwards) we could find about new possible employments of K in health practices. Many studies have been aimed at obtaining new uses of K. This article describes the use of ketoprofen lysine salt for treating injured gastric mucosa, the anti-allergic potential of K, the employment of K in treating nonalcoholic fatty liver disease, human lymphedema and seizures, as well as the antidepressant and anxiolytic effects of K, prospects for the use of K in oncology and transplantology. The findings of the review confirm that K, its derivatives and complexes have many newly discovered effects. It is likely that in the future, K will have more indications than it has today.

INTRODUCTION

Ketoprofen (K) was synthesized in 1968. K belongs to the family of propionic acid derivatives, which hold analgesic, anti-inflammatory and antipyretic properties [1]. The mechanism of its action inhibits prostaglandin synthesis by non-specific blocking cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX 1 is responsible for the synthesis of prostaglandins with physiological functions, and COX 2 is responsible for the synthesis of pro-inflammatory prostaglandins at the site of inflammation [2]. K is readily distributed into the central nervous system passing the blood brain barrier and inhibiting prostaglandin synthesis in the hypothalamus [3].

K is a chiral molecule and only the S-enantiomer has COX inhibiting activity [4]. It is metabolized in the liver and is mainly excreted in the urine, and to a minor extent, in the feces. It does not accumulate. K is well absorbed after oral and rectal administration; it can be taken in by injection (intravenously, intramuscularly) and transdermally. K is available as an over the counter drug in the form of 50 mg capsules and as a prescription drug in various pharmaceutical forms: capsules (100 mg, 150 mg, 200 mg), tablets (100 mg, 150 mg), suppositories (100 mg), gels (25 mg/g) and injection solution (50 mg/ml) [5].

Side effects of K are associated with its effects on COX [6]. Adverse events of chronic use include: headache and drowsiness, depression, nervousness, nightmares, sleepiness, cardiovascular reactions (peripheral edema), dermatological problems like photosensitization after topical use and skin sensitization. K causes platelet dysfunction, increased liver enzyme activity, gastrointestinal problems such as vomiting, diarrhea, gastric and duodenal irritation, ulcers and bleeding. Side effects of K include renal blood flow reduction, which may lead to renal impairment, electrolyte imbalance and hypertension [7].

However, K is one of the most commonly used nonsteroidal anti-inflammatory drugs (NSAIDs) because of the speed and effectiveness of its activity [8]. It is widely used in the management of inflammatory and musculoskeletal conditions (e.g. rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis), pain and fever [9]. The indications for administration of the drug, according to the characteristics of the medicinal product, are symptomatic treatment of inflammatory and degenerative rheumatic diseases of the skeletal system and alleviation of some pain syndromes. The indications for intramuscular administration are: rheumatoid arthritis, osteoarthritis, and moderate pain.

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The indication for intravenous administration is postoperative pain [10]. Scientists are still looking for new uses for K. In this study, the authors attempt to describe the future prospects of new uses of K based on medical literature from 2015 onwards to 2021.

METHODOLOGY

Standard up-to-date criteria were followed for review of the literature data. A search for English-language articles in the Medline Complete, PubMed, Google Scholar, and database was performed. The Scholar databases were audited in February 2021 using the phrases: "ketoprofen", "ketoprofen and treatment", "ketoprofen and effects". More than 1500 results were found. A total of 441 articles published between 2015 and February 2021 were then scanned. After skimming abstracts, 12 articles were chosen for this review (Fig. 1). The authors chose publications on the off-label use of K.

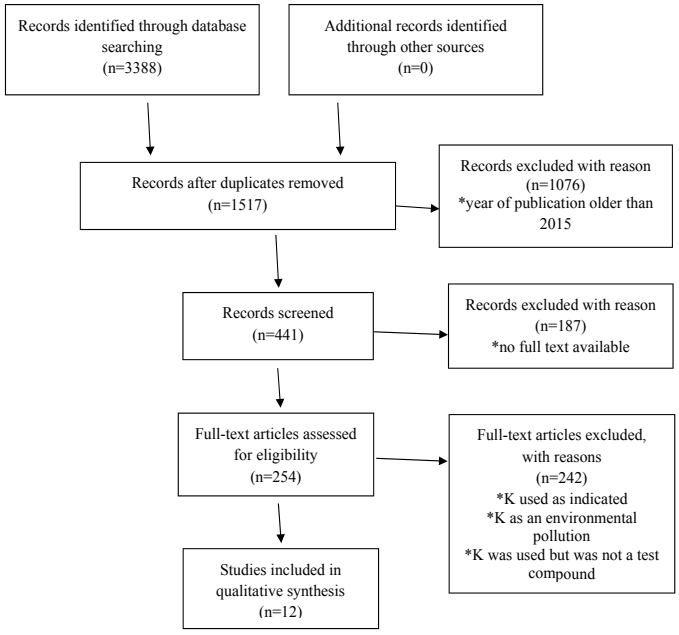


Figure 1. PRISMA flow diagram

Gastrointestinal injury treatment and prevention

Ketoprofen lysine salt (KLS) is widely used due to its analgesic efficacy and tolerability. KLS have a higher solubility and a more rapid pharmacological activity, with an analgesic activity after oral administration compared to K [11]. Unlike the majority of NSAIDs, which are acids, KLS has neutral pH. This feature may explain why manufacturers emphasize its gastroprotective properties.

Camino *et al*. published the results of their study that suggested the gastroprotective effect of KLS on gastric mucosa integrity in 2015. The researchers used monolayers of the human gastric epithelial cell line NCI-N87 and the ethanol-gastric injury model. Cells were treated with ethanol 6%, and incubated cells with K or KLS or lysine for 24, 48 or 72 hours. Accordingly, cells treated with ethanol presented an evident membrane damage resulting in the loss of tight junctions. Moreover, cells treated with ethanol and K appeared severely damaged with evident loss of tissue integrity, while cells treated with ethanol and KLS appeared preserved by ethanol injury [12].

The above study was confirmed by Brandling *et al.* on cell line NCI-N87, in 2018 [10]. They used the same approach as Camino *et al.* – the ethanol-gastric injury model and incubated cells with K or KLS or lysine for 72 hours. As found by Brandling *et al.*, the ethanol induced severe damage to the gastric mucosa layer at morphological level, while the KLS brought about an evident protection of the epithelium that was not observed with K [13]. In the above-mentioned publications, the researchers attempted to understand the mechanism by which KLS improved the condition of damaged human gastric epithelial cells [12,13]. The damage induced by ethanol could be attributed to the increase of reactive oxygen species (ROS). ROS plays a key role in the increase of lipid peroxidation products, including 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA). L-lysine showed a marked antioxidant effect by counteracting ethanol-induced MDA increase in the gastric mucosa layer mode [12,13]. KLS also counteracted the increase in 4-HNE protein adducts generated by ethanol treatment. The cap analysis showed a marked up-regulation of glutathione S-transferase P (GSTP), known to degrade 4-HNE by KLS [2,13].

Further research is needed to be able to use KLS in the presence of gastritis and gastric ulcers in humans. First of all, a test should be performed using laboratory animals with damaged gastric mucosa. During such an examination, not only the gastric mucosa be carefully examined, but other organs should also be assessed to determine the number of side effects of such KLS treatment. Currently, there is one laboratory animal study on the effect of KLS on damaged gastric mucosa in Wistar rats. Its results reduce the current optimism regarding the positive effects of KLS. In this study, K and KLS had a similar effect on the ethanol-damaged gastric mucosa [5].

Gemici *et al.* tested the chemopreventative potential of K and ATB-352. ATB-352 are a hydrogen sulfide (H2S)-releasing derivatives of K [14]. The researchers evaluated the effects of K and ATB-352 in a model of precancerous colon cancer lesions in mice. They used 4 groups of 6-8 animals each. In the experiment, daily treatment for two weeks with K (10 mg/kg) or ATB-352 (in equimolar dose) significantly reduced the number of aberrant crypt foci by 40-50%. They also evaluated the chemopreventive effects of K and ATB-352 in Male Pac Min/+ mice- with a genetic defect that predisposes them to intestinal cancer. Here, daily treatment for 2 weeks with K (10 mg/kg) significantly reduced the polyp score by ~50% ($p<0.05$) and the same treatment with ATB-352 (in equimolar dose) by ~60%. These results suggest that K and ATB-352 may be effective and safe in the chemoprevention of colon cancer [14]. The mechanism of action of these drugs, however, requires further research. The toxicity of K is the major barrier to its use in chemoprevention, and scientists are looking for safer forms of K – such as ATB-352. In a related experiment, Gemini *et al.* showed that ATB-352 did not produce gastric mucous injury and did not provoke significant intestinal damage [14].

Anti-allergic potential

The traditional form of K has no anti-allergic properties. Saunas *et al.* synthesized a novel binuclear μ-oxo diruthenium complex combined with K: $[Ru_2O(K)_2(pie)_6](PF_6)_2$ where py = pyridine [15], and then used rat basophilic leukemia (RBL-2H3) cells to study mast cell degranulation. According to the results of the study, allergens stimulated degranulation of mast cells and the new drug inhibited mast cell activation and degranulation. In this study, pretreatment of IgE-sensitized RBL cells with the new drug at (25 μL, 50 μg/mL), followed by cell stimulation with allergen (DNP-BSA), showed a strong inhibition of degranulation of mast cells. This RBL cells treatment with K alone (in equimolar dose) did not have this effect [15]. The inhibitory potential of the $[Ru_2O(K)_2(pie)_6](PF_6)_2$ against mast cell stimulation suggests its promising application as a therapeutic agent for treating or preventing IgE-mediated allergic diseases. The results also suggest that this molecule shows no allergenic potential and can be safely used for other pharmacological applications besides anti-allergic, but further studies *in vivo* are needed [15].

Treatment of nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is excessive fat build-up in the liver without clear cause such as alcohol use. The main drugs for the treatment of NAFLD include lipid-lowering drugs, antioxidants, hepatic protectors, insulin sensitizers and anti-inflammatory drugs.

Researchers have been investigating multi-targeted treatment NAFLD based on fat reduction, insulin sensitization and inflammation inhibition [16]. For instance, Wang *et al.* developed a co-assembled nano system based on fenofibrate and ketoprofen and performed an NAFLD inhibition assay *in vivo* [16]. In their study, they used mice that had been fed with a high-fat diet for 10 weeks (5 groups without information provided how many animals were in each group, of note, the article lacks data on the dose and duration of treatment by fenofibrate and the new drug). These researchers performed histopathological liver examinations using oil, red O, hematoxylin and eosin staining for evaluation of hepatic lipid accumulation. They also determined the inflammatory factors (IL-1b, IL-6 and TNF-α) in the liver tissue fluid by applying a quantitative real-time polymerase chain reaction. The outcome of this work was that, compared to fenofibrate, the new drug had a better therapeutic effect on NAFLD by reducing hepatic lipid accumulation and inflammatory responses in the liver [16]. Wang *et al.* concluded that this could be an effective strategy for fenofibrate delivery and dual-targeted therapy of NAFLD, but clinical studies are needed.

Treatment of human lymphedema

Lymphedema is a consequence of relative lymphatic vascular insufficiency. In this disease, an imbalance of growth factors occurs due to the presence of persistent tissue inflammation [17]. All forms of lymphedema are characterized by structural changes that include fibrosis of the lymphatic vasculature and surrounding tissues, increased interstitial tissue fluid content, adipose hypertrophy and inflammation. Preclinical investigations *in vitro* and *in vivo* strongly suggest that the therapeutic benefit of K in experimental lymphedema is specifically attributable to its inhibition of the 5-lipoxygenase (5-LO) pathway [17].

In 2018, Rockson *et al.* published the results of a study of K efficacy in humans with lymphedema [18]. This was an open-label pilot study followed by a prospective, randomized, double blind, placebo-controlled exploratory study. Together, 21 patients were enrolled in the open-label trial, and 34 in the placebo-controlled study. Patients aged 18-90 years, with a history of lymphedema of >6 months duration met inclusion criteria. In both trials, the patients in research groups received 75 mg K per os 3 times a day for 4 months. Ketoprofen therapy was found to induce therapeutic architectural remodeling of the diseased skin. Participants in the K groups demonstrated reduced skin thickness, as well as improved composite measures of histopathology and decreased plasma granulocyte CSF (G-CSF) expression [18]. The conclusion was that ketoprofen confers benefit in patients through its upstream inhibition of the 5-LO metabolite, LTB4. The improvement in skin thickness and histology in lymphedema following K treatment is a finding that paves the way for drug therapies of lymphedema, but further and larger clinical trials are needed.

Treatment of seizures

Many aspects of pathophysiology of epilepsy still remain unknown, but there is a relationship between epilepsy and inflammation. An increase in COX levels has been reported in neurodegenerative diseases such as epilepsy, Parkinson's disease and Alzheimer's disease. Neuronal loss is observed in these diseases and inflammation may be considered to have a significant role in its pathogenesis [19].

Eras *et al.* investigated the effects of dexketoprofen in rat models of pentylenetetrazol (PTZ)-induced epilepsy accompanied by EEG records [19]. They used 24 male Sprague-Dawley rats for EEG recording (4 groups with 6 animals each) and 24 for behavioral studies (4 groups with 6 animals each). The Racine convulsion scale (RCS), first myoclonic jerk (FMJ) onset time, and spike percentages were evaluated. As an outcome of the work, the experimenters found that FMJ onset time values were significantly longer, while RCS and Spike percentage values were significantly lower in dexketoprofen given groups (once 20 mg/kg or 40 mg/kg intraperitoneally) [19]. This study showed that dexketoprofen has an antiepileptic feature by increasing epileptic threshold and this effect increases as the dosage increases. Dexketoprofen can be preferred as an administered NSAID to epileptic patients, but clinical trials are needed. Dexketoprofen is the (S)-enantiomer of ketoprofen.

Antidepressant and anxiolytic effects

Epidemiological studies suggest links between pain, inflammatory response, and depression, and researchers have described a strong correlation between treatment resistant depression and increase in inflammatory cytokines in plasma and cerebrospinal fluid [20].

From the first quarter of 2004 to the first quarter of 2017, Makunts *et al.* ran a retrospective data analysis of 430,783 individual Food and Drug Administration Adverse Event

Reporting System (FAERS) and Adverse Event Reporting System (AERS) reports of patients treated for pain to identify potential antidepressant and anxiolytic effects of various anti-inflammatory. Patients treated for depression and patients taking any known antidepressants were excluded. The NSAID group contained 139 072 records and the non-NSAID group contained 291,711 records. Among the NSAID group were 1,534 records of patients who received K. Their work revealed that patients who received K had a decreased number of depression and suicidal behavior reports and a decreased number of anxiety reports [20]. More future prospective clinical trials, however, are needed to evaluate K in treatment of depression and anxiety caused by chronic or acute pain and inflammation. Research is also required to establish treatment and dosing guidelines for K to ensure proper management of pain and inflammation-related depression and anxiety.

Prospects for the use in oncology

In recent years, several studies have been published suggesting the chemopreventive potential of K [14,21-24]. In several diverse types of tumors, researchers found enhanced COX-2 expression. This suggests that COX-2 plays a role in carcinogenesis. For this reason, COX inhibitors, including K are suggested for cancer prevention [14,21,22].

Ravera *et al.*, in 2019, synthesized a dual-action cisplatin-based Pt (IV) conjugate containing K, and tested this drug for its biological features on a panel of human cancer cell lines [21]. In the work they investigated cells of ovarian endometrioid adenocarcinoma A2780, lung adenocarcinoma A-549, biphasic malignant pleural mesothelioma MSTO-211H, colon carcinoma HCT 116, HT-29 and SW480. According to the outcome of the work, the Pt. (IV)-K complex (concentration 1-5 mM) showed higher antiproliferative activity on the cancer cell lines treated for 72h as compared to cisplatin (concentration 1 mM) and K (concentration 5 mM). In this study, K and the Pt (IV) conjugate containing K inhibited cell growth through a COX-independent mechanism. Most of the biological effects were related to the cisplatin metabolite. The Pt. (IV)-K complex increased the overall lipophilicity and the cellular accumulation of this drug, offered a little additive contribution in terms of gene NAG-1 activation (a member of the transforming growth factor beta (TGF-β) superfamily). The induced expression of NAG-1 correlates with the growth inhibition of cancer cells [21].

In 2019, Çoban *et al.* developed a PEGylated nanocochleate formulation containing imatinib and dexketoprofen (IMA-DEX PEG COH) against fibrosarcoma. They also synthesized three similar drugs that were not as effective [23]. In this study, a mouse fibrosarcoma model was used and tumor size, histopathology and tyrosine kinase receptor inhibition were assessed after 14 days of treatment with the new drug. Herein, *in vivo* studies were performed on fibrosarcoma-bearing Blab-C male mice (5 groups of 5 animals each). The drug was designed for oral administration, and the doses were adjusted so that each animal received 4.8 mg imatinib and 0.09 mg dexketoprofen daily. In the IMA-DEX PEG COH group the researchers observed reduction of tumor volume and no neural cell division in the tumor stroma. Moreover, the percentage of healing at the cellular level was the highest compared to the other groups. No lymphocytic infiltration and no necrotic area were found in the tissues. The IMA-DEX PEG COH group also demonstrated the greatest tyrosine kinase receptor inhibition [23]. More future studies are, however, needed to investigate chemotherapy resistance and survival rates.

Ferreira *et al.* synthesized a K-loaded pomegranate seed oil nanoemulsion stabilized by pullulan which is a selective antiglioma formulation for intravenous administration [24]. The research was conducted *in vitro* on the rat malignant glioma (C6) and fibroblasts cell line (3T3). The new drug presented 40% inhibition of cell growth C6 after 72 h of incubation at two different concentrations (50 and 100 μM) and did not exhibit cytotoxicity action against fibroblast 3T3 in a non-transformed cells model. The study demonstrated that the nanostructures increased cell membrane permeability and caused cell death by necrosis [24]. This is a promising alternative for the treatment of glioma, but further studies *in vivo* are needed.

Use in transplantation

The microencapsulation of cells and tissue appears as a promising strategy for the development of allotransplantation or xenotransplantation therapies [25]. The main function of the encapsulation materials is to effect isolation from the host immune response and bidirectional diffusion of molecules essential for cell survival and metabolism. A semipermeable immobilization matrix has been found to offer protection cells against mechanical stress and deteriorating environmental effects. These combined properties have the potential to enable transplantation of encapsulated nonhuman cells [25].

In 2018, Noverraz *et al.* described the antifibrotic effect of K-grafted alginate microcapsules in the transplantation of insulin producing cells [25]. The study was carried out on mice and had a follow-up period of 30 days. In the work, the researchers transplanted insulin producing cells in K-grafted alginate microcapsules to evaluated the ability of K to reduce inflammation at the implantation site and prevent pericapsular fibrotic overgrowth [25]. *In vitro* quantification of K release indicated regular and sustained drug delivery over 14 days. The transplanted material demonstrated a clear reduction in the severity of pericapsular fibrotic overgrowth for microspheres functionalized with K and revealed the significant effect of K release to decrease fibrotic tissue formation. The present study provides a new approach to mitigate fibrotic response to microencapsulated cells transplantation [25].

CONCLUSIONS

K is a well-known and widely used substance and this indicates its safety and tolerance. The findings of the review confirm that K, its derivatives and complexes have many newly discovered effects. This article has described K in the treatment and prevention of gastrointestinal injuries, its antiallergic potential, its possible use in the treatment of nonalcoholic fatty liver disease, human lymphedema and seizures, as well as its antidepressant and anxiolytic effects, and prospects for the use of K in oncology and transplantology. It is

likely that in the future K will have more indications than it is today, but further studies are needed.

The studies described in the review are mainly preliminary observations. Each potential new use of K requires additional detailed research. We hope to see this come about in the near future. K is a substance with great potential in medicine.

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