Research & Reviews in Pharmacy and Pharmaceutical Sciences e-ISSN: 2320-1215
p-ISSN: 2322-0112

Chemistry and Pharmaceutical Perspectives of Licofelone Drug

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Research Article

Received: 04-Jun-2023, Manuscript No. JPPS-23-101260; **Editor assigned:** 06-Jun-2023, Pre QC No. JPPS-23-101260 (PQ); **Reviewed:** 20-Jun-2023, QC No. JPPS-23-101260; **Revised:** 25-Aug-2023, Manuscript No. JPPS-23-101260 (R); **Published:** 01-Sep-2023, DOI: 10.4172/2320-1215.12.4.008

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Citation: Rahat I, et al. Chemistry and Pharmaceutical Perspectives of Licofelone Drug. RRJ Pharm Pharm Sci. 2023;12:008.

ABSTRACT

Inflammation has long been a symptom of many infectious diseases and is suggested to be closely associated to a wide range of non-infectious diseases. Inflammation's crucial role allows the development of new drugs to treat cancers, autoimmune disorders, and infectious diseases. Licofelone is a drug for osteoarthritis that is approved by the FDA. It blocks both the COX and 5-LOX pathways. Licofelone can relieve pain and reduce inflammation. It also protects nerve cells in the central nervous system, which may be related to how it controls the COX/5-LOX pathway, inflammatory cytokines, and immune responses. Better understanding of the chemistry and pharmacology of licofelone will be essential for demonstrating the potential efficacy of Licofelone in inflammatory conditions. The previously explored experimental findings for licofelone that were reviewed here lend support to the development of dual inhibitors of 5-LOX/COX as an alternative therapy to currently available NSAIDs. The findings strongly suggest that licofelone reduces LT and PG production *via* its inhibitory impact on 5-LOX, COX-1, and COX-2. So, it might be better than NSAIDs or selective COX-2 inhibitors in terms of clinically important benefits and effectiveness. However, further research needs to be done on a significant number of patients before we can be sure that this compound has an anti-inflammatory and analgesic impact in humans.

Keywords: Licofelone; NSAIDs; COX/5-LOX inhibitor; Inflammation; Pharmacology

e-ISSN: 2320-1215
p-ISSN: 2322-0112

INTRODUCTION

Developing novel compounds to target a biomolecule in order to achieve a therapeutic effect is the primary focus of drug discovery. The rational design of new drugs mostly focuses on proteins as biological targets [1]. DNA and RNA based gene therapy and membrane lipid therapy have brought attention to other biomolecules in recent decades. Lipids were the latest biomolecules to be explored as biological targets because

There is such a wide variety of lipids in the human body, and recently, powerful lipid profiling techniques, including high resolution mass spectrometry were developed. Inflammation has long been acknowledged as a symptom of numerous infectious diseases, but molecular and empirical research indicates that it is also intimately associated with a vast array of non-infectious diseases, if not all of them. Although these insights may not result in a unified theory of disease, the crucial role of inflammatory processes enables the development of a new generation of drugs to treat cancers, autoimmune disorders, and infectious diseases. Hence, anti-inflammatory drugs have been developed to treat such disorders [2]. Several studies have shown that the Cyclooxygenases (COX)/Lipoxygenases (LOX) pathway is markedly activated in neurological disorders. It has been demonstrated that inflammation increases the expression and activity of enzymes such as Phospholipase A2 (PLA2), COX-2, and LOX. Subsequently, arachidonic acid is produced and converted to the pro-inflammatory substances Prostaglandin-2 (PGE2) and leukotriene B4, hence exacerbating the inflammatory response. Simultaneously, the levels of inducible Nitric Oxide Synthase (iNOS) and Nitric Oxide (NO) are increased, hence amplifying the inflammatory response. Nonsteroidal Anti-Inflammatory Medicines (NSAIDs) are medications that have anti-inflammatory, antipyretic, and analgesic properties. Many experimental, pharmacologic, and clinical research in recent years have suggested that NSAIDs are viable anticancer medicines. NSAIDs help to restore apoptosis in human adenomatous colorectal polyps and cancer cell lines that have lost the activity of the adenomatous polyposis coli gene. In cell lines and rodent models of angiogenesis, NSAIDs also suppress angiogenesis. Several epidemiologic studies have discovered that long term NSAID use is related with a decreased risk of cancer [3].

Likewise, various anti-inflammatory and anti-neurodegenerative drugs have been researched, mostly based on each neurodegenerative illness. Anti-inflammatory drugs that affect CYP450 enzymes' COX/LOX or epoxygenase activity are utilized in SCI. Some medications minimize oxidative damage, which causes motor and cognitive issues [4]. NSAIDs mitigate neuronal damage and improve CNS blood flow through vasodilation and vasoconstriction, helping motor and cognitive functions recover. In most cases, there is no treatment that can be absolutely guaranteed to alleviate the symptoms of neurological illnesses. Several companies were developing dual COX/LOX inhibitors as NSAIDs with enhanced gastrointestinal safety. Many anti-inflammatory dual COX/LOX inhibitors are in clinical trials. Among these compounds, (2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl) acetic acid (licofelone), was shown in clinical trials to have similar anti-inflammatory and pain-relieving effects on osteoarthritis as traditional NSAIDs, but with a safer gastrointestinal profile. It acts as a strong competitive inhibitor of 5-LOX, COX-1, and COX-2.

LITERATURE REVIEW

Licofelone has been studied as an inhibitor of cyclooxygenase-1 (COX-1), 5-lipoxygenase (5-LOX), and microsomal prostaglandin E2 synthase-1 (mPGES-1) [5]. Licofelone appears to limit inflammatory prostaglandin E2 (PGE2) synthesis preferentially by inhibiting mPGES-1 at dosages that do not influence COX-2. Moreover, it improved apoptosis in HCA-7 colon

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p-ISSN: 2322-0112

cancer cells and prostate cancer cells *via* the mitochondrial pathway. Licofelone is an NSAID that inhibits COX/LOX. Licofelone, recently licenced for osteoarthritis treatment, inhibits enzymes that produce PGEs and leukotrienes. Licofelone's analgesic, anti-inflammatory, and neuroprotective (particularly CNS) properties are well documented. When compared to other drugs, Licofelone has less Gastrointestinal (GI) side effects. Recent research showed that Licofelone's anti-inflammatory activities benefit SCI, epilepsy, HD, etc. Licofelone may reduce neurological diseases, as discussed in this review [6].

Category

Licofelone is a substrate analogue of arachidonic acid that has anti-inflammatory, anti-asthmatic, antiplatelet, and analgesic properties. Its chemical name is (2,2–dimethyl–6-(4-chloropheny-7-phenyl-2,3-dihydro-1H-pyrrazoline-5-yl) acetic acid [7]. Licofelone (ML3000), a dual COX/LOX inhibitor developed by Merckle GmbH and EuroAlliance partners Alfa Wassermann and Lacer, is the first medicine in this new family of analgesic and anti-inflammatory treatments. It is currently being studied as a therapy for Osteoarthritis (OA), the most frequent kind of arthritis. Even though phase III trials with OA patients have been completed successfully, no dates have been set for regulatory submission [8].

Chemistry of licofelone

Chemical Formula: $C_{23}H_{22}ClNO_2$

IUPAC name: 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H pyrrolizin-5 yl) acetic acid

Chemical taxonomy:

Kingdom: Organic compound

Super class: Organoheterocyclic compounds

Class: Pyrroles

Sub class: Substituted pyrrols

Direct parent: Diphenylpyrroles

Molecular framework: Aromatic heteropolycyclic compounds

Alternative parents: Pyrrolizines, chlorobenzenes, aryl chlorides, heteroaromatic compounds, monocarboxylic acids and derivatives, carboxylic acids, azacyclic compounds, organopnictogen compounds, organonitrogen compounds, organochlorides, organic oxides, hydrocarbon derivatives, carbonyl compounds [9].

Substituents: 3,4-diphenylpyrrole, aromatic heteropolycyclic compound, aryl chloride, aryl halide, azacycle, benzenoid, carbonyl group, carboxylic acid and its derivative, chlorobenzene, halobenzene, heteroaromatic compound, hydrocarbon derivative, monocarboxylic acid or derivatives, monocyclic benzene moiety, organic nitrogen compound, organic oxide, organic oxygen compound, organochloride, organohalogen compound, organonitrogen compound, organooxygen compound, organopnictogen compound, pyrrolizine [10].

Structure

The arrangement of atoms and the chemical bonds that hold them together make up a molecule's chemical structure. There are 52 bonds in the Licofelone molecule as a whole, thirty non-H bonds, 18 multiple bonds, 4 rotatable bonds, single double bond, 17 aromatic bonds, 2 five membered rings, 2 six-membered rings, 1 eight-membered rings, 1 aliphatic carboxylic acid, 1 hydroxyl group, and 1 pyrrole are present [11]. Figure 1 displays the 2D and 3D model for the chemical structure of licofelone. The 2D figure of Licofelone chemical structure is called a "skeletal formula," In the chemical structure of

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Licofelone, the carbon atoms are assumed to be at the corner(s), and the hydrogen atoms attached to the carbon atoms are not shown. Each carbon atom is thought to be linked to enough hydrogen atoms to form four bonds with the carbon atom. The figure of Licofelone's 3D chemical structure is based on the ball-and-stick model, which shows both where the atoms are in space and the bonds between them [12]. So, the diameters of the spheres are smaller than the lengths of the rods. This makes it easier to see the atoms and bonds in the Licofelone chemical structure model (Table 1) [13].

Figure 1. 2D and 3D models for chemical structure of licofelone.

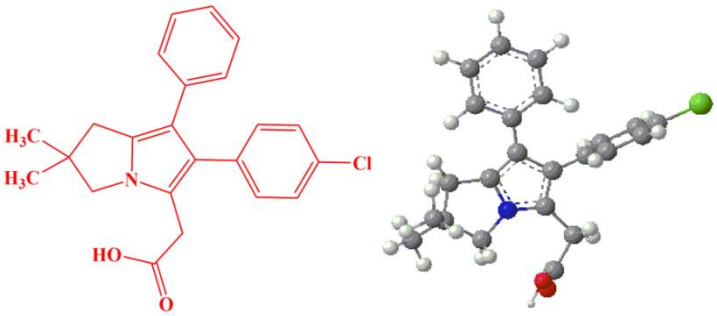

Table 1. Chemical and physical properties.

S. No.	Property	Value
1	Molecular weight	379.9
2	Exact mass	379.1339
3	Monoisotopic mass	379.1339
4	Topological polar surface area	42.2 Å²
5	Heavy atom count	27
6	Complexity	537
7	Appearance	Slightly yellowish solid
8	Melting point	162-163°C
9	Solubility	Methanol, chloroform
10	Loss on drying	≤ 1%

Synthesis: The parent moiety of the drug can be constructed in a number of different ways; however, it is most commonly produced through the condensation of the relatively unstable 2-benzyl-4,4-dimethyl-1-pyrroline (A) and 4-chlorophenacyl bromide (B), which results in the production of 2,3-dihydro-1H-pyrrolizine (C). Nevertheless, an alternative synthesis of (C) based on the Suzuki cross-coupling reaction has been reported. The strategy that was originally used, which involved the intermediacy of (A), appears to be more effective [14]. When Compound (C) is treated with ethyl diazoacetate, ester (D1) is obtained, and the hydrolysis of ester (D1) yields licofelone. Alternately, acid can be obtained from Compound (C) by treating it with oxalyl chloride and then subjecting it to hydrolysis. Licofelone is then produced as a result of the Wolff-Kishner reduction as shown in Figure 2. The only known ways to turn 3 into licofelone without using diazoacetate are to reduce the oxo group of 5 using the classical Wolff–Kishner reduction or to change it by using NaBH3CN to reduce the corresponding p-toluenesulfonyl hydrazide. The same method can also be used to get (D1) by reducing the corresponding ethyl ester [15].

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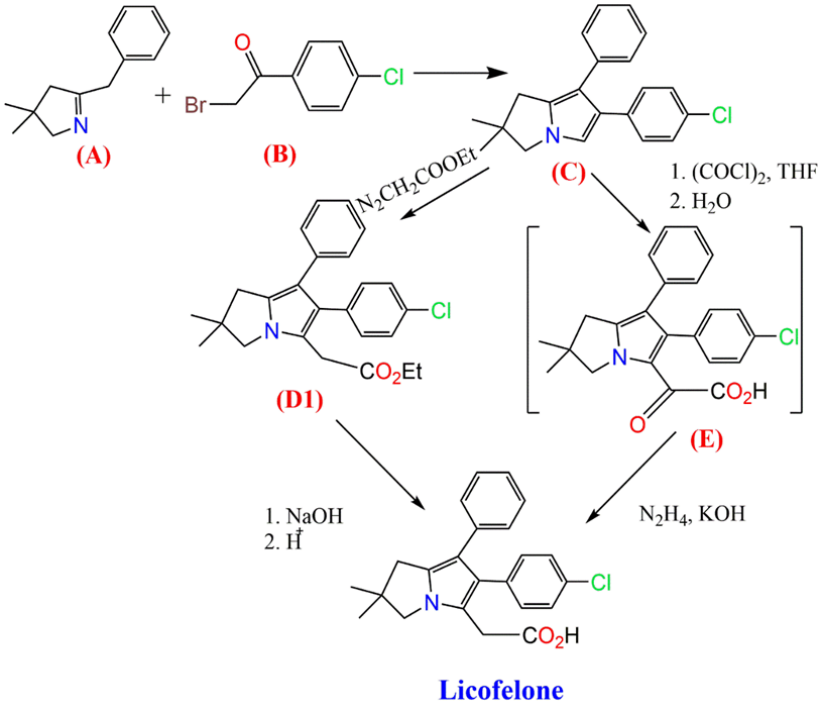
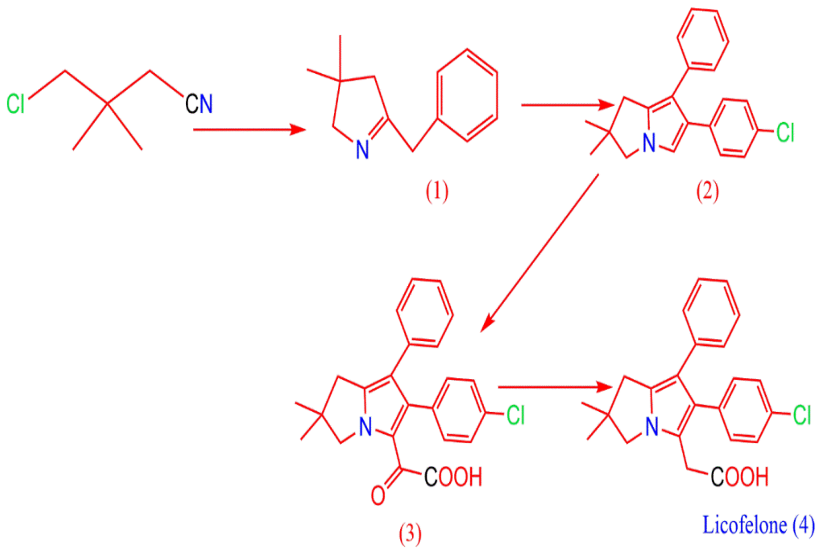
Figure 2. Procedure for licofelone synthesis.



Moreover, licofelone was also synthesized using previously described procedures. With the help of the easily available benzyl Grignard, 4-chloro-3,3-dimethyl-butyronitrile was condensed, and then the more unstable 5-benzyl-3,3-dimethyl-3,4-dihydro-2H-pyrrole was formed (1). By cyclizing 2-bromo-1-(4-chlorophenyl) thenone and 1 in ethanol/aqueous NaHCO3 solution at room temperature, 6,7-Diaryl-2,3- dihydro-1H-pyrrolizine (2) was produced in moderate yields. Licofelone was produced by Friedel-Craft acylation of (2) with oxalyl chloride and Wolff-Kishner reduction with hydrazine hydrate (Figure 3) [16].

Figure 3. Method to synthesize licofelone.



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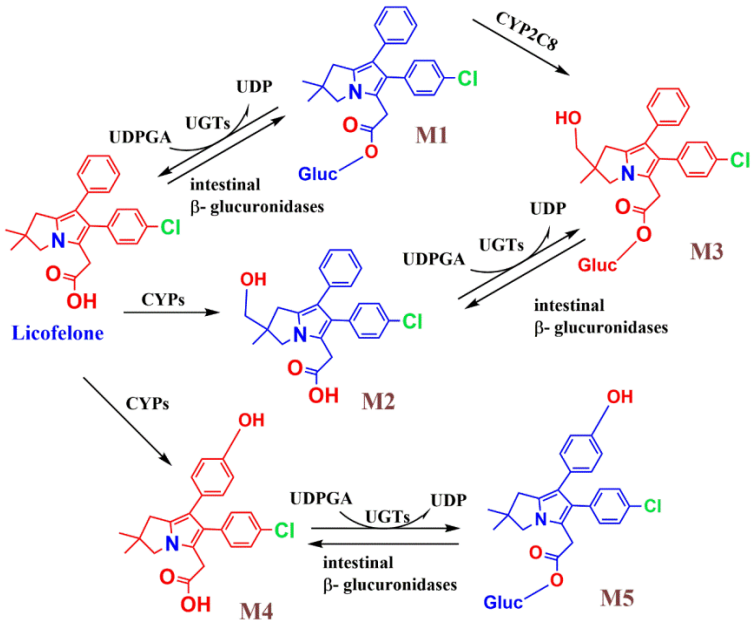
RESULTS

Biotransformation pathway of licofelone

Licofelone is quickly absorbed from the gastrointestinal tract in humans following oral administration of immediate release tablets, and highest plasma concentrations are reached 2–3 hours after treatment. Systemic elimination is biphasic, with a rapid initial drop in plasma concentration ($T^{1/2}$ (α)=1 h) and a slow final elimination ($T^{1/2}$ (β)=7-9 h). After a single administration of the drug, the metabolites ML3000-1-O-acyl glucuronide (M1) and Hydroxy-ML3000 (M2) were found in the plasma. The systemic exposure was below 2% of the parent drug. With repeated administration, the steady-state exposure of M2 was roughly 20% greater than that of the parent medication, but the systemic clearance rate was slower (monophasic, T12=10-12 h) than that of the parent drug. Nevertheless, M1 remained a trace metabolite [17]. In this regard, the disposition of licofelone in humans differs from the conventional animal species (mouse, rat, dog, and monkey) in which systemic concentrations of M2 were minimal even after prolonged administration. M4 is an additional licofelone hydroxymetabolite. This chemical was initially identified in microsomal tests but not in plasma samples from patients following single and repeated therapeutic dosages of 200 mg or 400 mg b.i.d. relevant concentrations were obtained in plasma samples from subjects treated with various dosages to establish the maximum tolerated dose. Figure 1 depicts the molecular structures of licofelone and its metabolites from a chemical standpoint. *In vitro* metabolism studies show that in humans, hydroxylation of the glucuronide M1 is the key step in M2 production [18]. Although the Cytochrome P-450 (CYP)-dependent hydroxylation of glucuronides has been described in the literature, the production of M2 represents 6 of 40 distinct cases because human systemic exposure to this primary metabolite is predicated on glucuronidation of the parent drug followed by glucuronidation of the glucuronide (Figure 4) [19].

Figure 4. Probable biotransformation pathway of licofelone.



Mode of action

Arachidonic acid is important in biology because it can be metabolized by three enzyme systems Cyclooxygenases (COXs, also known as PGG/H synthases), Lipoxygenases (LOXs), and Cytochrome P450 (CYP) enzymes (ω-hydroxylases and

e-ISSN: 2320-1215
p-ISSN: 2322-0112

epoxygenases) to produce a wide range of biologically active fatty acid mediators displayed in Figure 5. The first enzymes to process AA were COXs, which produce prostanoids such PGs and TXA2. Phospholipases release the plasma membrane lipid, and COX enzymes convert it to PGG2 and PGH2. PG synthases convert them to PGs. COX-1, which is constitutively expressed in most cells, produces most prostanoids for housekeeping. Inflammatory stimuli, hormones, and growth factors stimulate COX-2 (PTGS2), which is thought to be the main prostanoid source in inflammation and proliferative disorders like cancer. Nonetheless, both enzymes generate autoregulatory and homeostatic prostanoids and can release prostanoids during inflammation. Actually, aspirin and NSAIDs, especially COX-2 inhibitors, relieve pain and inflammation. COX2 inhibitors may cause cardiovascular adverse effects due to endothelium-inhibited PGI2 generation. Aspirin reduces the incidence of ischemic events like heart attacks and stroke, and prostacyclin analogues alleviate pulmonary hypertension [20].

The second pathway of eicosanoids and inflammation to receive therapeutic attention is the LOX pathway. Leukotrienes (LTs) are produced by enzymes and were initially reported in 1979 by Bengt I. Samuelsson, who won the Nobel Prize in Physiology or Medicine in 1982. Arachidonate 5-LOX (ALOX5) and LT receptor antagonists treat asthma and seasonal allergies. As new receptors and metabolites are discovered and their involvement in various diseases are clarified, COX and LOX are becoming more relevant therapeutic targets.

The Cytochrome P450 (CYP) pathway, which was first discovered in 1980, is the third AA metabolizing mechanism. The most relevant subclasses of the CYP family of enzymes for AA metabolism are ω-hydroxylase and epoxygenase. Yet, many CYP enzymes can produce a variety of compounds due to their dual hyprolase and epoxygenase activities. AA is transformed into Hydroxyeicosatetraenoic acids (HETEs) by the activity of CYP enzymes' ω-hydroxylase. The most researched metabolite in this context is 20-HETEs, which has been demonstrated to have pro-inflammatory effects as well as contributing to vascular function. AA epoxides or epoxyeicosatrienoic acids (EETs; 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET) are formed by the epoxygenase activity of CYP enzymes, such as the CYP2J and 2C families. Bioactive EETs are formed in liver, also detected in the vasculature and cardiomyocytes. Soluble Epoxide Hydrolase (sEH) converts EETs to diols or Dihydroxyeicosatrienoic acids (DHET). AA diols were formerly assumed to be less active than epoxides, although they may even function antagonistically in specific conditions. Hypertension, Heart Failure (HF), and stroke are being treated with this route and its metabolites because EETs cause vasodilatation. CYP-derived EETs also affect endothelial cell death, capillary formation, progenitor cell differentiation, proliferation, and migration. CYP-derived AA metabolites can promote tumour development, progression, and metastasis. The structure of the active site of 5-LOX on the molecule of arachidonic acid was compared with the structure of licofelone to further assess the mechanism of action of the drug. Although the crystal structure of the 5-LOX protein has not been determined, Summers et al., hypothesized that the arachidonic acid 5-LOX active site has a horseshoe like configuration based on the structure of other 5-LOX inhibitors. It possesses all the characteristics of a COX inhibitor, according to considerable research on the pharmacodynamics of licofelone. The licofelone possesses characteristics that render it analgesic, anti-inflammatory, antipyretic, and antiplatelet. Moreover, its potent antibronchoconstrictory effect supports the 5-LOX inhibition. According to the findings of these preliminary investigations, NSAIDs and licofelone share many characteristics, but there are also some important changes that allow for equal efficacy in treating inflammation and pain with fewer gastrointestinal side effects. Similar to diclofenac and indomethacin, licofelone COX inhibitory effect on PGE2 production in the stomach was reduced. In contrast to NSAIDs, licofelone does not cause arachidonic acid shunting to the 5-LOX pathway or elevated LTB4 levels in the stomach, as found with diclofenac and indomethacin. Because of this significant difference, the mechanism of action of licofelone may be distinguished from that of conventional NSAIDs (Figure 5).

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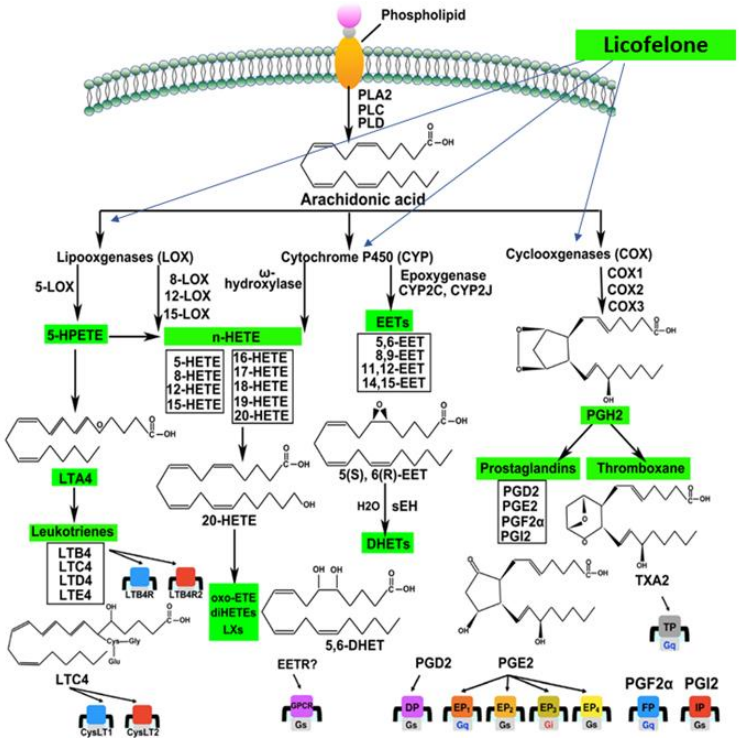
Figure 5. Effects of licofelone on the metabolism of arachidonic acid.



Effect of licofelone on different organ systems

When administered to animals for testing, licofelone was well tolerated and did not appear to have any discernible effects on their overall behaviour. Licofelone in doses ranging from 30 to 300 mg/kg had no effect on any of the parameters measured in the Irwin test, nor did it produce hexobarbital induced sleep or change locomotor activity. Intraduodenal injection of licofelone (100 mg/kg) had no noteworthy effects on the cardiovascular system or respiration in anesthetic rats or dogs or on neuromuscular function in anesthetized cats. Oral administration of licofelone did not result in any signs of gastric damage or disturbances in peristalsis that could be observed. *In vivo*, licofelone suppressed spasmogenic reactions in the guinea pig ileum in a dose dependent manner, whether they were triggered by acetylcholine, barium chloride, or histamine. After administering the highest dose of licofelone (300 mg/kg), researchers discovered that rats' urine volume and electrolyte excretion experienced a slight but momentary decrease. In general, animal toxicological investigations have shown that licofelone has no negative effects on the autonomic nervous system, CNS, or cardiovascular system, and is safe at dosages considerably above pharmacologically active concentrations. Moreover, licofelone lacks genotoxic potential. Animal studies have shown that licofelone has a lesser ulcerogenic potential than aspirin, indometacin, and diclofenac. In contrast to COX-2 inhibitors, licofelone does not make gastric mucosal damage worse, even in rats that have been given aspirin. This means that osteoarthritis patients with cardiovascular risk who need long term aspirin therapy could be treated with both aspirin and licofelone. A clinical investigation verified that there was no clinically significant increase in the incidence of gastrointestinal ulcers when low dose, enteric coated aspirin and licofelone were taken together. However, the long term impact of this connection on cardiovascular outcomes is still being demonstrated.

Adverse effects

Initial human investigations show very good stomach safety, a favourable impact on osteoarthritis and bone cell remodelling,

e-ISSN: 2320-1215
p-ISSN: 2322-0112

as well. Another clinical investigation included 148 patients with knee osteoarthritis who were given licofelone 200 mg bid or naproxen 500 mg bid for 12 weeks. Using the WOMAC (Western Ontario and McMaster universities) osteoarthritis index, the efficacy of the treatment was determined. The mean WOMAC index improved by 23.3 mm with licofelone and 21.5 mm with naproxen. Regarding the WOMAC index, 69.4% of patients receiving licofelone responded (compared to 68.4% of individuals receiving naproxen). Gastrointestinal side effects were noted by 13.9% (licofelone) and 26.3% (naproxen) of individuals. In a clinical investigation that lasted for 12 weeks, participants who had symptomatic osteoarthritis of the knee were given either celecoxib 200 mg once daily or licofelone 200 mg twice daily for the duration of the study. Licofelone was just as effective as celecoxib, but it was easier to take and had fewer side effects.

Contraindications

In comparison to traditional NSAIDs, licofelone is associated with fewer instances of general and Gastrointestinal (GI) side effects. Diarrhoea and abdominal pain were the side effects that occurred the most frequently. When aspirin and licofelone were given at the same time, there was no evidence of an increase in ulceration.

DISCUSSION

Interactions

Combining Licofelone with Abatacept has the potential to speed up the metabolism of both drugs. When Licofelone is coupled with Abciximab, the risk or severity of bleeding and hemorrhage can be enhanced. When coupled with Abiraterone, the metabolism of Licofelone can be slowed. When Abrocitinib is taken with Licofelone, its metabolism can be slowed. Acebutolol's antihypertensive activity may be reduced by Licofelone. When Licofelone is coupled with Aceclofenac, the chance or severity of undesirable effects can be enhanced. When Licofelone is taken with Acemetacin, the risk or severity of undesirable effects can be enhanced. When Licofelone is coupled with Acenocoumarol, the risk or severity of bleeding and hemorrhage is enhanced. When Acetaminophen is taken with Licofelone, the chance or severity of undesirable effects can be enhanced. Acetohexamide's protein binding can be reduced when coupled with Licofelone. Azilsartan medoxomil and Licofelone may cause renal failure, hyperkalemia, and hypertension. Balsalazide and Licofelone may enhance undesirable effects. Beclomethasone dipropionate and Licofelone may aggravate gastrointestinal discomfort. Licofelone and Bemiparin may increase bleeding risk. Licofelone with Benazepril may worsen renal failure, hyperkalemia, and hypertension. Licofelone with Bendazac may enhance undesirable effects. Licofelone decreases Bendroflumethiazide's therapeutic effectiveness. Licofelone and Benorilate may enhance undesirable effects. Celecoxib with Licofelone may enhance undesirable effects. Licofelone slows chloroquine metabolism. Licofelone with Cilazapril may worsen renal failure, hyperkalemia, and hypertension. Ciprofloxacin may be neuroexcitatory with Licofelone. Delafloxacin may be neuroexcitatory with Licofelone. Licofelone and Deflazacort may aggravate gastric discomfort. Dexamethasone and Licofelone may exacerbate gastric discomfort. Diclofenac and Licofelone may enhance undesirable effects. Eprosartan with Licofelone may exacerbate renal failure, hyperkalemia, and hypertension. Licofelone slows Estradiol metabolism. Favipiravir decreases Licofelone metabolism. Licofelone with Fenbufen may enhance undesirable effects. Ginkgo biloba slows Licofelone metabolism. Ibuprofen with Licofelone may enhance side effects. Indomethacin with Licofelone may enhance undesirable effects. Meloxicam with Licofelone may enhance side effects. Licofelone slows Montelukast metabolism. Neomycin and Licofelone may induce nephrotoxicity. Ofloxacin may be neuroexcitatory with Licofelone. Quinine slows Licofelone metabolism. Rofecoxib with Licofelone may enhance undesirable effects.

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Licofelone's potential applications in drug therapy

Effects of licofelone from preclinical data:

- Anti-inflammatory
- Analgesic
- Antipyretic
- Antiplatelet

Effects *in vitro*

- Suppression of the PMN leukocyteplatelet transcellular.
- Metabolism of arachidonic acid.
- Prevention of PMN aggregation and activation.
- Reduction of PMN and platelet adhesion.
- Effects in animal models.
- Reduction of erythema and oedema in osteoarthritis.
- Reduction of synovial cell proliferation.
- Reduction of bone/cartilage erosion.

In a study, Carrageenan induced paw edema and an adjuvant arthritis model revealed that licofelone is a potent anti-inflammatory agent. In that work, carrageenan-induced paw edema model, licofelone demonstrated an ED50 of 17 mg/kg p.o. and a plasma concentration of approximately 20 µg/ml. Despite the fact that indomethacin was four times as active as licofelone with an ED50 of 3 mg/kg, its UD50 was 7 mg/kg. In contrast, the UD50 could not be estimated in rats treated with licofelone due to the strong stomach tolerance at the tested doses. This study demonstrated that licofelone possesses strong anti-inflammatory effect without causing the typical gastrointestinal damage associated with conventional NSAIDs. The analgesic effects of licofelone were seen in two animal models. The writhing of phenylquinone is used as a screening tool to assess the analgesic effectiveness of peripherally and centrally acting drugs. Licofelone 10 mg/kg p.o. was shown to be more efficient than aspirin 50 mg/kg p.o. in reducing phenylquinone writhing in mice. Oral treatment of peripherally active analgesics, such as NSAIDs, increases the pain threshold of inflamed paws in rats in the Randall and Selitto assay. After 0.5, 1, 2, and 3 hours after injection, the effects of licofelone 30 mg/kg were as effective as indomethacin 10 mg/kg in improving the pain threshold of inflamed paws in rats. Moreover, Antipyretic efficacy was seen with licofefone in a rat model of hyperthermia induced by brewer's yeast. The antipyretic impact of licofelone 10 mg/kg p.o. was observed to be considerable, and it lasted for more than three hours. This effect was equivalent to the effect of indomethacin 10 mg/kg p.o in another report, licofelone completely prevented arachidonic acid-induced platelet aggregation in rabbit platelet rich plasma at a dosage of 0.1 µg/ml and was about 25 times as powerful as aspirin at a dose of 2.5 µg/ml in the *in vitro* arachidonic acid-induced platelet aggregation assay. Two investigations confirmed platelet anti-aggregative efficacy *in vivo*. Licofelone 30 mg/kg p.o. enhanced bleeding time in mice just as effectively as aspirin 100 mg/kg p.o. Licofelone 10, 30, and 100 mg/kg p.o. demonstrated a strong antithrombic effect in rat mesenteric arteries, comparable to aspirin.

Licofelone has great gastrointestinal tolerance, according to two single-dose studies. Licofelone 30, 100, and 300 mg/kg delivered orally to groups of 10 rats indicated no notable or statistically significant alterations as compared to control rats. Single doses of indomethacin 20 mg caused severe gastrointestinal harm in groups of five rats, but single doses of

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licofelone 3, 10, 30, 100 mg/kg did not cause damage that varied significantly from control. Multiple dosing trials on rats and cynomologus monkeys revealed a good level of gastrointestinal safety. There were no significant macroscopic or microscopic abnormalities in the gastrointestinal tract after 26 weeks of licofelone dosage at up to 120 mg/kg orally per day. The investigations mentioned in this publication show that licofelone and conventional NSAIDs have different gastrointestinal tolerance. Since both COX and 5-LOX metabolites are significant contributors to the endpoints of this paradigm, the anti-asthmatic efficacy of licofelone and its COX and 5-LOX inhibitory activities are further proven in the sheep asthma model. When given as an aerosol, Licofelone 100 mg/sheep significantly decreased the early airway response in 7 sheep and significantly stopped the late airway response. Based on the results of this study, it seems that giving an aerosol of a balanced inhibitor of COX and 5-LOX may help treat allergic airway disease.

CONCLUSION

The need for safer drugs is the primary driver behind the search for a new class of anti-inflammatory agents. This is because traditional and more recent anti-inflammatory medications have been unable to demonstrate a high safety profile, particularly in "frail" patients such as the elderly. Licofelone has been shown to have anti-inflammatory, analgesic, antipyretic, anti-asthmatic, and antiplatelet aggregation activity in animal models, as shown by the studies that are discussed in this review. Licofelone is a novel, potent, balanced, and competitive inhibitor of both COX and 5-LOX. It is also a novel, balanced, and competitive inhibitor of 5-LOX. In addition, the results of our research indicate that this structural alteration of licofelone may have the potential to improve the qualities of the compound that limit the growth of cancer. More research is being conducted to gain a more in depth understanding of the method of action as well as the structure activity relationship, both of which are currently being investigated.

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e-ISSN: 2320-1215
p-ISSN: 2322-0112

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