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NARRATIVE REVIEW

Preclinical Evidence for KPV, the Tripeptide Fragment of Alpha MSH

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ARTICLE TYPE	SOURCES	HUMAN STUDIES	U.S. STATUS
Narrative review	59 · PMID linked	None published	Not FDA approved

ABSTRACT

Background. KPV (lysine proline valine) is the C terminal tripeptide of alpha melanocyte stimulating hormone. It retains much of the anti inflammatory activity of the parent hormone without its pigmentary action, and it is promoted to clinicians and consumers for wound healing and for a wide range of inflammatory conditions. Since 30 October 2026 a temporary federal enforcement discretion policy has allowed licensed pharmacies to compound KPV acetate in topical and oral dosage forms, which has increased the number of questions reaching prescribers.

Methods. This narrative review searched Europe PMC and PubMed through 3 November 2026 for KPV, Lys Pro Val, lysine proline valine and alpha MSH(11 to 13), with ClinicalTrials.gov and regulatory documents from the FDA, the Department of Health and Human Services and the World Anti Doping Agency. One hundred and fifty two unique records were screened and 59 sources are cited. No risk of bias scoring was applied.

Results. Anti inflammatory activity has been reported since 1984 in rabbit fever, murine contact sensitivity and peritonitis, two murine colitis models, rat colitis, rabbit corneal injury, murine traumatic brain injury and murine diabetic wounds. The effect appears independent of melanocortin receptor signalling and is associated with inhibition of nuclear factor kappa B translocation; uptake into intestinal and immune cells occurs through the transporter PepT1, which is induced in inflamed colon. No interventional study in human participants was identified by this search or by the FDA. Human data are confined to cell lines, whole blood stimulated outside the body, donated cadaver skin and observational studies of transporter expression. No pharmacokinetic, toxicological or adverse event data exist.

Conclusions. The preclinical case for KPV is coherent and reproducible, and the clinical case is untested. No dose can be recommended, topical delivery through intact skin is poor, and oral products require formulation specific evidence of absorption. First in human pharmacokinetic and tolerability work is the rate limiting step.

Keywords: KPV; alpha melanocyte stimulating hormone; melanocortin; PepT1; nuclear factor kappa B; pharmacy compounding

1 Introduction

Alpha melanocyte stimulating hormone (alpha MSH) is a tridecapeptide cleaved from pro opiomelanocortin and expressed in the pituitary, the skin, the gut and elsewhere. Its anti inflammatory and cytoprotective actions have been characterised across four decades and in a wide range of experimental models.[12] Interest in the C terminal tripeptide lysine proline valine, written KPV or alpha MSH(11 to 13), arose from the observation that this fragment carries much of the anti inflammatory activity of the parent molecule while lacking its melanotropic effect, a property that removes the principal obstacle to therapeutic use of alpha MSH itself.[13]

Clinicians are now asked about KPV for reasons that have little to do with that literature. The peptide is marketed online for inflammatory bowel disease, psoriasis, eczema, wound healing, mast cell activation syndrome and post viral syndromes, as a single ingredient and in combination products, by topical, oral, injectable and intranasal routes.[4] In July 2026 the Pharmacy Compounding Advisory Committee voted 8 to 6, with one abstention, in favour of adding KPV related bulk drug substances to the 503A bulks list, against the recommendation of FDA staff,[54] and on 30 October 2026 the Department of Health and Human Services issued an enforcement discretion policy covering KPV acetate in topical and oral dosage forms.[67]

This review sets out what the published literature supports, in which species and in which models, and what it does not. It is written for prescribers who need to separate a reproducible preclinical signal from clinical evidence that does not yet exist.

2 Methods

Europe PMC and PubMed were searched on 3 and 4 November 2026 for literature indexed through 3 November 2026. The principal Europe PMC query searched titles and abstracts for "KPV", "Lys Pro Val" or "lysine proline valine" within MEDLINE records and returned 125 records, and a second query covering the forms alpha MSH 11 13, alpha MSH(11 to 13) and MSH 11 13, which returned 32. The corresponding PubMed queries using the tiab field returned 133 and 33 records. Topic specific searches were run for colitis and inflammatory bowel disease (16 records), for wound healing, skin, psoriasis and keratinocytes (27 records), for pharmacokinetics, bioavailability and toxicity (3 records), and for clinical trial publication types and for the terms patients or volunteers (7 records, none of which concerned KPV in human participants). Searches for KdPT (4 records) and for the registrational trials of afamelanotide and bremelanotide were run so that those compounds could be distinguished from KPV.

After duplicates were removed, 152 unique PubMed indexed records were screened by title and abstract. Studies were included when they reported original data on KPV, alpha MSH(11 to 13) or an identified KPV salt, or when they provided mechanistic or regulatory context required for interpretation. Studies of other melanocortin fragments, cyclic analogues such as (CKPV)2, N acetylated derivatives and KdPT were excluded from the evidence synthesis and are cited only where they bear on the interpretation of KPV data. Abstracts were read in full; open access full texts were retrieved from Europe PMC where available and consulted for dose, species and effect size. Where only an abstract was available, no claim was made beyond it. Records were checked for retraction and correction notices through the Europe PMC comment and correction fields; none of the cited studies carries one.

ClinicalTrials.gov was searched on 3 November 2026 for KPV, Lys Pro Val and lysine proline valine; no registered study listed KPV as an intervention.[8] Regulatory material was obtained directly from the issuing agency: the FDA briefing document prepared for the July 2026 Pharmacy Compounding Advisory Committee meeting,[4] the FDA page on bulk drug substances that may present significant safety risks,[9] the advisory committee meeting page,[5] the HHS enforcement discretion policy and its Appendix B,[67] and the 2026 World Anti Doping Agency Prohibited List.[10] Fifty nine sources are cited. This is a narrative review. No protocol was registered, no formal risk of bias instrument was applied and no quantitative synthesis was attempted, so the weighting of individual studies reflects the authors' judgement and should be read as such.

3 Structure, origin and pharmacology

3.1 Identity and physicochemical properties

KPV corresponds to residues 11 to 13 of alpha MSH. The free base has the molecular formula C16H30N4O4 and a molecular weight of 342.43 g/mol; the acetate salt, which is the form named in the federal compounding policy, has a molecular weight of 402.5 g/mol and the same active moiety.[47] There is no United States Pharmacopeia or National Formulary monograph for either form, and neither is a component of an approved drug product.[4] Reported aqueous solubility differs substantially between the two forms, at 0.70 mg/mL for the free base and 5 mg/mL for the acetate, which the FDA considered relevant to the performance of the cream and gel dosage forms proposed in the compounding nomination.[4] Conformational analysis of the acetylated amide Ac Lys Pro Val NH2 has been published and was used to design constrained nonpeptide analogues.[11]

3.2 Melanocortin receptor independence

The anti inflammatory effects of alpha MSH are mediated largely by the melanocortin receptors MC3, MC4 and MC5, with pigmentation driven by MC1 signalling in melanocytes.[1212] Several lines of evidence indicate that KPV does not act this way. The tripeptide failed to displace radiolabelled alpha MSH analogues from binding sites on murine melanoma cells and on MC1 expressing murine macrophages.[1314] In the same macrophages alpha MSH and alpha MSH(1 to 10) stimulated cyclic AMP while alpha MSH(11 to 13) did not, and neither the tripeptide nor its cyclic analogues raised cyclic AMP in RAW 264.7 or B16 F1 cells.[1415] In human keratinocytes neither alpha MSH nor KPV raised cyclic AMP; rapid intracellular calcium transients were instead recorded in HaCaT cells in the presence of an adenosine agonist that inhibits the cyclic AMP pathway, and in normal keratinocytes.[16] In murine peritonitis, the antimigratory effect of KPV was not blocked by the MC3 and MC4 antagonist SHU9119 and persisted in recessive yellow e/e mice, which carry a non functional MC1 receptor.[17] The same persistence was reported in MC1Re/e mice with experimental colitis.[18] Structure activity work pointed in the same direction, since the tripeptide retained activity in inflammation assays while contributing only modestly to melanotropic potency in frog and lizard skin bioassays.[1920] The FDA reached the same conclusion in 2026 and stated that the molecular targets underlying the effects of KPV remain unknown.[4]

3.3 Intracellular actions and PepT1 mediated uptake

Two mechanisms recur in the literature. The first is interference with nuclear factor kappa B (NF kB). In lipopolysaccharide and interferon gamma stimulated RAW 264.7 murine macrophages, alpha MSH(11 to 13) inhibited nitric oxide production and NF kB nuclear translocation at concentrations between 1 nmol/L and 1 micromol/L without raising cyclic AMP.[1415] In the immortalised human bronchial epithelial line 16HBE14o , KPV produced dose dependent inhibition of NF kB reporter activity, matrix metalloproteinase 9 activity and interleukin 8 and eotaxin

secretion, and the authors attributed this to blockade of p65RelA nuclear import at the importin alpha binding site.[21] Immobilised GKPV also inhibited TNF alpha stimulated NF kB activity, which argues for an accessible cell associated site of action.[22] The second is interference with interleukin 1 beta signalling, inferred from the failure of KPV to suppress macrophage release of KC and interleukin 1 beta directly while retaining activity in interleukin 1 beta induced peritonitis.[17]

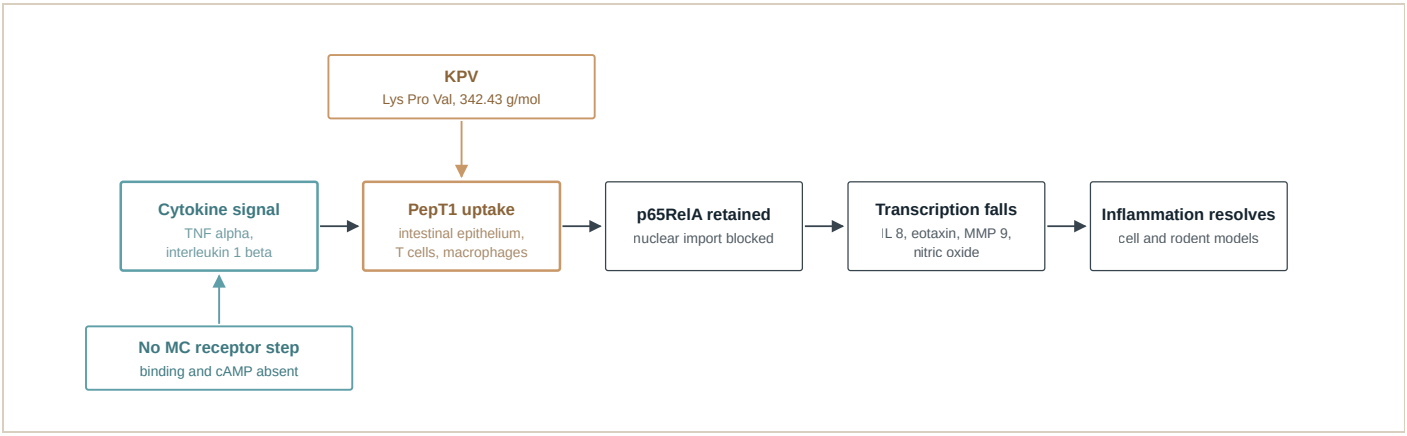


Figure 1. Proposed mechanism of KPV, assembled from cell and rodent data. Uptake through PepT1 was demonstrated with tritiated peptide in human intestinal epithelial and T cell lines, and loss of the in vivo effect in PepT1 knockout mice supports its relevance.[2324] Inhibition of p65RelA nuclear import was shown in a human bronchial epithelial line, and melanocortin receptor binding and cyclic AMP responses were absent in several systems.[2114] No step in this sequence has been measured in a human participant.

Cellular entry is better characterised than the target. PepT1 is a proton coupled di and tripeptide transporter expressed in the small intestine and largely absent from the healthy colon, but aberrantly expressed in colonic epithelium in ulcerative colitis and Crohn disease.[25] Dalmasso and colleagues measured uptake of tritiated KPV into Caco2 BBE and HT29 Cl.19A intestinal epithelial cells and into Jurkat T cells, with unlabelled KPV competing for a radiolabelled PepT1 substrate, and reported anti inflammatory effects at nanomolar concentrations.[23] The dependence was later shown in vivo. KPV reduced tumour number, size and burden in azoxymethane and dextran sodium sulfate treated wild type mice but produced no significant effect in PepT1 knockout animals.[24] This transporter route explains why nanoparticle and hydrogel formulations that concentrate KPV at inflamed mucosa have dominated the recent delivery literature.[262728]

4 Preclinical evidence

4.1 Fever and acute inflammation

The earliest work tested the tripeptide as the antipyretic message sequence of alpha MSH. In rabbits made febrile with leukocytic pyrogen, lysine proline valine reduced fever after central administration of 0.5 to 2.0 mg and after peripheral administration of 2 to 200 mg, at lower potency than the parent peptide.[29] In mice, alpha MSH(11 to 13) produced dose related inhibition of picryl chloride induced ear swelling,[30] and alpha MSH peptides reduced paw oedema and contact sensitivity in the same laboratory.[31] In the acetylated amide Ac alpha MSH(11 to 13) NH2, stereochemical substitution altered potency in a manner consistent with a specific site of action: D Val13 substitution increased anti inflammatory activity about fourfold over that parent analogue, whereas D Pro12 substitution abolished it.[32] Alpha MSH and a D valine substituted analogue of alpha MSH(11 to 13) inhibited murine ear inflammation induced by interleukin 1 beta, interleukin 6 and tumour necrosis factor alpha, while substantial doses of alpha MSH(1 to 13) did not alter inflammation induced by leukotriene B4, platelet activating factor or interleukin 8, which places the action of these peptides upstream of those mediators.[33] Central administration of alpha MSH(1 to 13) reduced peripheral inflammation through a descending, beta 2 adrenergic pathway; that experiment used the parent tridecapeptide rather than the tripeptide.[34] In crystal and interleukin 1 beta induced murine peritonitis, systemic KPV significantly reduced polymorphonuclear leukocyte accumulation.[17]

4.2 Gastrointestinal inflammation

Two groups reported murine colitis data in 2008. Dalmasso and colleagues added KPV to drinking water and reduced the severity of dextran sodium sulfate and trinitrobenzene sulfonic acid colitis, with lower proinflammatory cytokine messenger RNA expression.[23] Kannengiesser and colleagues reported earlier recovery, greater weight regain, reduced histological inflammation and reduced colonic myeloperoxidase activity in dextran sodium sulfate colitis, with comparable findings in CD45RB high transfer colitis; in MC1Re/e animals, KPV treatment prevented death during the colitis protocol.[18] In rats with trinitrobenzene sulfonic acid colitis, rectally administered KPV stabilised in a thiolated polyglutamic acid hydrogel attenuated weight loss and disease activity index, prevented colon shortening, lowered myeloperoxidase and restored epithelial morphology,[35] and a double network hydrogel that bound KPV electrostatically produced similar mucosal recovery and shifted the gut flora.[36] Delivery systems have repeatedly reduced the quantity of peptide required: colon targeted nanoparticles achieved therapeutic efficacy in murine colitis at a

KPV concentration 12,000 fold lower than free peptide in solution,[26] hyaluronic acid functionalised nanoparticles given orally in a hydrogel outperformed untargeted particles,[27] and a reactive oxygen species responsive oral conjugate achieved 3.8 fold greater colonic accumulation than free KPV with retained efficacy at a 20 fold lower dose.[37] Related platforms have combined KPV with teduglutide or with an immunosuppressant.[2838] In a model of colitis associated carcinogenesis, KPV at 100 micromol/L in drinking water reduced tumour number, size and burden in wild type mice; in APC Min/+ mice it did not reduce tumour burden, although lipocalin 2 fell.[24]

4.3 Wound healing, ocular surface and skin

In rabbits whose corneal epithelium had been mechanically denuded, topical KPV at 1, 5 or 10 mg/mL, two drops four times daily for four days, produced a significantly smaller mean residual epithelial defect at each follow up; at 60 hours, eight of eight corneas treated with KPV were completely re epithelialised while none of the placebo treated corneas were. Pretreatment with the nitric oxide synthase inhibitor L NAME abolished the effect.[39] In diabetic mice, a layered film dressing releasing KPV from its lower layer and epidermal growth factor from the upper layers improved the repair rate of full thickness wounds.[40] In rats with chemotherapy induced oral mucositis, a KPV loaded mucoadhesive hydrogel improved food intake and weight recovery and suppressed interleukin 1 beta and tumour necrosis factor alpha.[41] Mechanistic work in human keratinocytes showed calcium signalling without cyclic AMP elevation,[16] and in HaCaT keratinocytes exposed to particulate matter, KPV at 50 micrograms per mL restored viability and reduced interleukin 1 beta.[42] Reviews of melanocortin peptides and of tripeptides in wound repair place KPV among candidates that merit clinical testing and have not yet received it.[4344]

4.4 Central nervous system, antimicrobial and metabolic findings

After controlled cortical impact in mice, a single intraperitoneal injection of 1 mg/kg alpha MSH(11 to 13) acetate 30 minutes after injury reduced secondary lesion volume at 24 hours from 27.7 plus or minus 4.8 mm3 to 21.0 plus or minus 3.4 mm3, a reduction of about 24 percent, with reduced microglial activation and neuronal apoptosis but no difference in neurological testing.[45] Melanocortin peptides including alpha MSH(11 to 13) inhibited cytokine and nitric oxide production in activated murine microglia.[46] Antimicrobial activity has been reported in vitro: alpha MSH and its C terminal tripeptide inhibited colony formation by Staphylococcus aureus and reduced viability and germ tube formation of Candida albicans,[47] and alpha MSH(11 to 13) killed more than 90 percent of methicillin sensitive and methicillin resistant S. aureus at micromolar concentrations.[48] In a later study neither Ac KPV NH2 nor its glycoalkylated analogues showed antimicrobial activity, although the glycoalkylated peptides were stable to proteolytic enzymes, which indicates how narrow the structural tolerance is.[49] Recent cell work has extended the anti inflammatory phenotype to macrophage foam cell formation and to adipocyte differentiation, the latter accompanied by reduced weight gain and dyslipidaemia in mice fed a high fat diet and given KPV orally.[5051]

Table 1. Key in vivo studies of KPV and alpha MSH(11 to 13). All are animal studies; no in vivo human study has been published.

STUDY	SPECIES AND MODEL	INTERVENTION	COMPARATOR	PRINCIPAL FINDING AS REPORTED
Richards 1984[29]	Rabbit, leukocytic pyrogen fever	Lys Pro Val, 0.5 to 2.0 mg central or 2 to 200 mg peripheral	Not stated in abstract	Fever reduced by both routes; potency lower than alpha MSH(1 to 13)
Hiltz 1989[30]	Mouse, picryl chloride ear swelling	Alpha MSH(11 to 13), graded doses	Saline and a large corticosteroid dose	Dose related inhibition of ear swelling
Hiltz 1991[32]	Mouse, picryl chloride ear swelling	Ac alpha MSH(11 to 13) NH2 and D substituted analogues	Parent tripeptide	D Val13 about fourfold more active; D Pro12 inactive
Getting 2003[17]	Mouse, crystal and interleukin 1 beta peritonitis; e/e mice	KPV systemically	Other MSH peptides, SHU9119	Reduced leukocyte accumulation; effect not MC receptor dependent
Bonfiglio 2006[39]	Rabbit, corneal epithelial abrasion	KPV 1, 5 or 10 mg/mL, two drops four times daily, 4 days	Phosphate buffered saline; L NAME pretreatment	8 of 8 corneas re epithelialised at 60 hours versus 0 of 8 with placebo
Dalmasso 2008[23]	Mouse, DSS and TNBS colitis	KPV in drinking water	Colitis without KPV	Reduced colitis incidence and proinflammatory cytokine expression
Kannengiesser 2008[18]	Mouse, DSS colitis and CD45RB high transfer colitis	KPV	Untreated colitic mice	Weight regain, less histological inflammation, lower myeloperoxidase; MC1Re/e mice rescued from death
Laroui 2010[26]	Mouse, DSS colitis	KPV loaded nanoparticles in alginate chitosan hydrogel	Free KPV, empty particles	Equivalent efficacy at a KPV concentration 12,000 fold lower
Schaible 2013[45]	Mouse, controlled cortical impact	Alpha MSH(11 to 13) 1 mg/kg intraperitoneally once at 30 minutes	0.9 percent sodium chloride	Lesion 21.0 plus or minus 3.4 versus 27.7 plus or minus 4.8 mm3 (p = 0.016); neurological score unchanged

STUDY	SPECIES AND MODEL	INTERVENTION	COMPARATOR	PRINCIPAL FINDING AS REPORTED
Viennois 2016[24]	Mouse, AOM and DSS colitis associated cancer; PepT1 knockout	KPV 100 micromol/L in drinking water	AOM and DSS alone	Fewer and smaller tumours in wild type mice; no significant effect in PepT1 knockout mice
Sun 2021[35]	Rat, TNBS colitis	KPV in a self cross linked thiolated polyglutamic acid hydrogel, rectally	Free KPV, blank hydrogel	Lower disease activity index, preserved colon length, lower myeloperoxidase
Zhao 2022[40]	Mouse, full thickness diabetic wound	Layered film releasing KPV and epidermal growth factor	Not stated in abstract	Improved repair rate with less inflammation and more angiogenesis
An 2026[51]	Mouse, high fat diet obesity	Oral KPV	High fat diet alone	Less weight gain, less adipose expansion, lower plasma total cholesterol

AOM, azoxymethane; DSS, dextran sodium sulfate; MC, melanocortin; TNBS, 2,4,6 trinitrobenzene sulfonic acid.

5 Clinical evidence in humans

No interventional study of KPV in human participants has been published. This search identified none, ClinicalTrials.gov lists no registered study with KPV as an intervention,[8] and the FDA review states that the nomination did not include, and the agency did not identify, any clinical studies or human exposure data for KPV by any route of administration.[4] The same document records that no published study described a compounded or non compounded KPV product administered to humans, and that outsourcing facilities reported no KPV products to the agency between January 2017 and June 2025.[4] Any claim of clinical benefit therefore rests on extrapolation from animals.

Three categories of human data do exist and should not be overstated. The first is work in human cell lines, which supplied most of the mechanistic argument summarised in section 3.[23211642] The second is ex vivo work in human blood: in whole blood from patients with HIV infection stimulated with lipopolysaccharide, the melanocortins tested, which included alpha MSH(11 to 13), reduced production of interleukin 1 and tumour necrosis factor alpha in a concentration dependent manner.[52] The third is observational human tissue work on the transporter rather than on the peptide. Colonic hPepT1 expression was demonstrated in biopsies from six patients with ulcerative colitis and four with Crohn disease, and was absent in four normal colons and four with microscopic colitis,[25] and PepT1 staining was increased in human colorectal tumour tissue relative to normal and benign tissue.[24] These observations make the delivery hypothesis plausible in human disease but provide no information on efficacy, dose or safety.

Several related compounds are frequently cited as evidence for KPV. KdPT, which corresponds to residues 193 to 195 of interleukin 1 beta rather than to the alpha MSH C terminus, has its own preclinical dataset in sebocytes and in murine colitis.[5354] Afamelanotide, an alpha MSH analogue, increased pain free sun exposure in randomised trials in erythropoietic protoporphyria,[55] and bremelanotide, a melanocortin receptor agonist, improved sexual desire scores in two phase 3 trials in premenopausal women.[56] Both are different molecules with different receptor pharmacology, and neither result transfers to KPV.

Table 2. Studies involving human material. No study administered KPV to a human participant.

STUDY	HUMAN MATERIAL	DESIGN	PRINCIPAL FINDING AS REPORTED
Merlin 2001[25]	Colonic biopsies, 18 patients	Observational expression study	hPepT1 present in ulcerative colitis (6) and Crohn disease (4), absent in normal colon (4) and microscopic colitis (4)
Catania 1998[52]	Whole blood, patients with HIV	Ex vivo stimulation with lipopolysaccharide	Melanocortins tested, alpha MSH(11 to 13) among them, reduced interleukin 1 and tumour necrosis factor alpha concentration dependently
Elliott 2004[16]	HaCaT and normal keratinocytes	Cell signalling	No cyclic AMP rise; rapid intracellular calcium transients with KPV and KP D V
Dalmasso 2008[23]	Caco2 BBE, HT29 Cl.19A, Jurkat cells	Cell culture, uptake kinetics	PepT1 mediated uptake; nanomolar KPV inhibited NF kB and MAP kinase signalling
Land 2012[21]	16HBE14o bronchial epithelial line	Cell culture, reporter assays	Dose dependent inhibition of NF kB, matrix metalloproteinase 9, interleukin 8 and eotaxin
Pawar 2017[57]	Dermatomed cadaver skin	In vitro permeation	Passive permeation below the 0.01 microgram/mL limit of detection; 4.4 microgram/cm2/h with microneedles
Sung 2025[42]	HaCaT keratinocytes, 3D skin model	Cell culture, particulate matter injury	KPV 50 microgram/mL restored viability and reduced interleukin 1 beta

NF kB, nuclear factor kappa B; 3D, three dimensional.

6 Pharmacokinetics, formulation and doses studied

No pharmacokinetic or toxicokinetic study of KPV free base or KPV acetate has been published in any species, and the FDA identified none during its 2026 evaluation.[4] Nothing is therefore known about absorption, distribution, metabolism, elimination or half life in humans or in animals, and no dose can be recommended. The doses below are those used in the cited experiments and are reported with species and route attached.

6.1 Topical and transdermal

The compounding nomination proposed cream and gel dosage forms at 0.1 percent for topical use.[4] In dermatomed human cadaver skin, passive permeation of KPV was below the limit of detection of 0.01 microgram/mL. Microneedle treatment produced a flux of 4.4 microgram/cm2/h, while anodal iontophoresis and the combination of iontophoresis with microneedles increased the permeation rate 8 fold and 35 fold relative to microneedles alone; confocal imaging confirmed penetration beyond 100 micrometres.[57] The FDA read this as a two edged finding, limiting systemic exposure and therefore systemic toxicity, and equally limiting distribution to the viable epidermis beneath the stratum corneum.[4] A validated stability indicating assay exists for KPV in aqueous solution and in skin homogenate, with a limit of quantitation of 0.25 microgram/mL.[58]

6.2 Oral

Oral administration has been used in mice as peptide in drinking water,[232451] and as nanoparticle or prodrug formulations designed to survive the gastrointestinal tract.[2737] No human absorption data exist, yet the enforcement discretion policy conditions oral dosage forms on documentation held by the compounder that the specific formulation achieves adequate oral bioavailability in humans, a condition that the published literature cannot currently satisfy.[67]

6.3 Parenteral and other routes

Parenteral dosing appears only in animal experiments: single intraperitoneal injection of 1 mg/kg in mice after cortical impact,[45] systemic administration in murine peritonitis,[17] and central and peripheral dosing in febrile rabbits.[29] Rectal and intracolonic hydrogels have been used in rats.[3536] Injectable and intranasal KPV products are promoted commercially, as the FDA documented, but neither route is covered by the federal policy and neither has human data.[47]

6.4 Stability and quality considerations

Under acid, alkaline and oxidative stress, KPV degrades principally to lysine proline diketopiperazine, with additional non polar degradation products under basic conditions and rapid degradation to the diketopiperazine, proline and valine in 0.5 percent hydrogen peroxide.[584] The FDA judged both KPV free base and KPV acetate to be inadequately characterised for compounding purposes, citing inconsistent naming conventions and the absence of impurity, aggregate and microbiological testing data in available certificates of analysis.[4] The enforcement discretion policy addresses part of this through its certificate of analysis and manufacturer registration conditions.[6]

7 Safety and tolerability

There is no human safety dataset. The FDA identified no clinical studies and no human exposure data for KPV by any route, and concluded that the potential safety risks of use in humans are unknown.[4] A search of the FDA Adverse Event Reporting System and of the medical literature through 3 December 2025 retrieved no reports and no cases; a search of the Human Foods Complaint System covering 1 January 2004 to 3 December 2025 retrieved no case in which KPV had been administered.[4] The agency noted that compounders operating under section 503A do not generally report adverse events to it, so an absence of reports carries little information.[4]

Animal toxicology is equally absent. No acute toxicity, repeat dose toxicity, genotoxicity, reproductive and developmental toxicity or carcinogenicity study of KPV free base or KPV acetate was identified.[4] The only information is incidental, since the efficacy studies summarised in Table 1 administered KPV to mice, rats and rabbits without reporting toxicity,[3918] and recent cell work reported no cytotoxicity at the concentrations used.[5042] Unlike alpha MSH, KPV lacks melanotropic activity, which removes the pigmentary effect that limited development of the parent peptide.[120]

Two theoretical concerns were raised in the FDA evaluation and remain open. Peptides can elicit immune responses, including neutralising antibodies capable of cross reacting with the endogenous counterpart, and peptides as short as two residues can aggregate; no immunogenicity or aggregation data exist for KPV.[4] A third consideration comes from the oncology literature. PepT1 is upregulated in human colorectal tumour tissue, and the same transporter that delivers KPV to inflamed mucosa is enriched in neoplastic tissue, although in the murine model KPV reduced rather than promoted tumourigenesis.[24]

CLINICAL CONSIDERATIONS

- No dose can be derived from the literature. Published quantities are animal doses or the 0.1 percent topical strength proposed to the FDA.[457]
- Passive delivery through intact human skin was undetectable in vitro, so a conventional cream may not reach viable epidermis in useful quantity.[574]
- Oral dosage forms require formulation specific documentation of adequate human bioavailability under the federal policy; general peptide data do not satisfy this.[67]
- Effective approved therapies exist for the nominated indications of wound healing and inflammatory skin disease, and the FDA weighed this against inclusion on the bulks list.[4]
- Safety is unknown, and the absence of adverse event reports reflects absence of reporting and of exposure data.[4]

8 Regulatory and anti doping status

KPV is not approved by the FDA for any indication, is not a component of any approved drug product and has no USP or NF monograph.[4] KPV free base and KPV acetate were listed in category 2 of the FDA's bulk drug substances page, meaning substances that may present significant safety risks, from September 2023 until 22 April 2026, when they were withdrawn from that category.[79] The nomination that had placed KPV before the agency, submitted by a compounding pharmacy for cream and gel at 0.1 percent for topical use, was withdrawn; the FDA continued the evaluation on its own initiative and proposed not adding either substance to the 503A bulks list, citing inadequate physicochemical characterisation, unknown extent of historical compounding use, and the absence of effectiveness and safety information in humans.[4] On 23 July 2026 the Pharmacy Compounding Advisory Committee considered KPV related bulk drug substances for wound healing and inflammatory conditions and voted 8 to 6, with one abstention, in favour of inclusion.[54] That vote is advisory; the FDA must still decide and complete rulemaking, and KPV is not on the final list.

The HHS enforcement discretion policy published in the Federal Register on 30 October 2026 covers KPV acetate for topical and oral dosage forms compounded under section 503A.[67] Its conditions include a patient specific prescription from a state licensed pharmacy or physician, a single active ingredient from the covered list with no combination products, active pharmaceutical ingredient from an FDA registered and CGMP compliant original manufacturer accompanied by a valid certificate of analysis, reporting of serious adverse events and quality problems to MedWatch and to the relevant state, the labelling statement that the product is a compounded drug product not for resale, documentation of adequate human oral bioavailability for oral forms, and use of an FDA cleared syringe as the only co packaged device.[67] The policy is temporary, applies until the FDA addresses each substance in a final rule, and states explicitly that compounded drugs are not FDA approved and are not reviewed for safety, effectiveness or quality before marketing.[6] Injectable and intranasal KPV preparations fall outside it.[7]

KPV is not named in the 2026 World Anti Doping Agency Prohibited List, and the terms Lys Pro Val, alpha MSH and melanocortin do not appear in that document. Section S0, non approved substances, prohibits at all times any pharmacological substance not addressed by a subsequent section of the list and with no current approval by any governmental regulatory health authority for human therapeutic use; on that wording KPV would fall within S0, although WADA has not ruled on it by name, and athletes subject to testing should be advised accordingly.[104] A 2026 critical review of peptide use in sport lists KPV among the fragments promoted for recovery and anti inflammatory effect.[59]

9 Discussion

The preclinical record for KPV is unusually consistent for a peptide of this size. The anti inflammatory signal has been reproduced by laboratories in the United States, Germany, the United Kingdom, Italy, Latvia and China, in rabbits, mice and rats, across models that share no common inducing agent, and over four decades.[29301718393521] That consistency is supported by a mechanism that does not depend on a receptor the peptide cannot be shown to bind, and by a transport route whose relevance to inflamed human tissue is documented in biopsy material.[252324]

The clinical implications are narrower. Reproducible activity in animal models of inflammation has historically been a poor predictor of clinical benefit, and for KPV the gap extends beyond efficacy to basic human pharmacology, since the fate of an administered dose has never been measured. The one human tissue experiment relevant to the dominant commercial route, a topical cream, found no measurable passive transport across skin,[57] and the oral route cannot satisfy the absorption condition in the federal policy from published data.[67] It is possible that the topical finding understates performance in inflamed or broken skin, where barrier function is compromised and where the wound healing models were positive, although this remains a hypothesis.

Three further limitations apply. First, much of the recent literature tests the peptide within a delivery system, so efficacy attributable to KPV cannot always be separated from efficacy attributable to a hydrogel, a nanoparticle or a co loaded growth factor.[264028] Second, the older inflammation literature frequently used acetylated and amidated derivatives or D amino acid substituted analogues rather than the free tripeptide, and potency differs between them by several fold.[3211] Third, the FDA's characterisation findings are substantive. The acetate salt and the free base are distinct active ingredients that have been sold under one common name, and impurity, aggregate and microbiological data were missing from the certificates of analysis the agency reviewed.[4]

This review has its own limitations. It is narrative, performed by a single clinical team without a registered protocol, duplicate screening or a formal risk of bias assessment, and it is restricted to English language records indexed in PubMed, which may exclude work published elsewhere. Negative studies of a peptide with no commercial sponsor are unlikely to have been published, so publication bias should be assumed to favour positive findings.

Several studies would address these gaps. A first in human pharmacokinetic and tolerability study of a defined topical formulation, with measurement of skin and plasma concentrations, would resolve more uncertainty than any further rodent model. A small randomised trial in a condition where the animal data are strongest, such as mild to moderate distal ulcerative colitis treated rectally or an ocular surface defect, would be feasible. Independent characterisation of commercially

supplied KPV acetate, including impurity and aggregation profiling, would address the quality questions the FDA raised. Until at least the first of these exists, prescribing rests on mechanism and analogy, without evidence of benefit in people.

10 Conclusions

KPV has been studied extensively in the laboratory and not at all in clinical trials. Four decades of work in cells, rabbits, mice and rats describe a reproducible anti inflammatory and tissue repair signal that operates independently of melanocortin receptors, converges on NF kB, and reaches intestinal and immune cells through PepT1, a transporter that is induced in inflamed human colon.[1232517] No human has been studied, and there are no pharmacokinetic, tolerability, efficacy or toxicology data and no adverse event reports from which absence of harm could be inferred.[4]

The federal enforcement discretion policy makes compounded KPV acetate available for topical and oral use under defined conditions, and it is not a statement about efficacy or safety.[67] Clinicians asked about KPV can describe a credible mechanism, a consistent animal literature, an unquantified risk profile and an unestablished benefit, and should make clear that a credible mechanism does not establish benefit. The evidence base will change only when the first human study is published.

DECLARATIONS

Purpose. This document is an internal evidence review prepared for clinicians at OC Wellness. It has not been externally peer reviewed and is not a clinical guideline or a protocol.

Funding. None.

Competing interests. OC Wellness provides clinical services that may include prescribing compounded preparations of the peptide reviewed.

Data availability. All sources are listed in the references.

Use of sources. Findings are reported as stated in the cited abstracts or full texts. Where only an abstract was available, no claim extends beyond it.

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ABOUT THIS REVIEW

This is an internal evidence review prepared by OC Wellness for licensed clinicians. It summarizes published literature and public regulatory records; it has not been through external peer review and is not a clinical guideline, a protocol, or medical advice for any individual patient. KPV is not approved by the U.S. Food and Drug Administration for any indication; since 30 October 2026 a temporary federal enforcement discretion policy has allowed compounding of KPV acetate in topical and oral dosage forms under section 503A. Treatment decisions rest with the treating physician.

Clinical services at OC Wellness are provided by licensed physicians and clinicians through the supervising professional medical corporation. Family MSO Holdings LLC provides management and administrative services only. It does not practice medicine, employ physicians in the practice of medicine, or influence clinical judgment.

REVIEWING PHYSICIAN	DATE	SIGNATURE

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