

LV101R, LV201R, and LV301R: A New Hope for Cancer Treatment

► What are they?

Promising new compounds derived from the Euphorbia plant, specifically designed to fight cancer. LV201R is a natural substance found in the plant's sap, while LV101R is a modified version created to be more effective and easier for the body to absorb. LV301R is in discovery as a version with enhanced brain penetration qualities. These compounds are part of a group called tetracyclic triterpenes, known for their potential to target cancer cells.

► How do they work?

These compounds attack cancer in multiple ways:

- **Stopping Cancer Growth:** They slow down or stop cancer cells from multiplying in cancers like breast, pancreatic, gastric, and brain (glioblastoma).
- **Triggering Cell Death:** They encourage cancer cells to die naturally, reducing tumour size.
- **Reducing Inflammation and Pain:** They help manage pain and inflammation, which are common in cancer patients.
- **Targeting Key Pathways:** They block specific signals (like MAGL and PKC) that help cancer grow, while boosting the body's natural defences.

► What Makes Them Special?

Unlike some existing treatments, LV101R, LV201R and LV301R come from a plant with a history of medicinal use. They show promise in preclinical studies (lab and animal tests) for being effective against various cancers with fewer side effects. For example, they've shown strong results in reducing tumour growth in gastric cancer and glioblastoma, and they may work even better when combined with existing drugs like temozolomide for brain cancer.

► What's Happening Now?

Researchers are testing LV101R's safety and toxicology in animals, with results expected by late 2025. If these tests go well, a clinical trial with ~100 patients (focused on gastrointestinal cancers and glioblastoma) is planned for 2026 in Brazil. The trial will check if LV101R is safe and effective, especially for pain relief and reducing tumour size. Another compound, LV301R, is being developed to better target brain cancers.

► Why does this matter?

Cancer is a major global health challenge, and current treatments often have harsh side effects or stop working over time. LV101R, LV201R and LV301R could offer a gentler, more effective option, building on the success of other plant-based cancer drugs like Paclitaxel (used for ovarian and breast cancer). If successful, these compounds could help treat a wide range of cancers, including hard-to-treat ones like pancreatic and brain cancer.

► What's Next?

- **Completing safety tests by early 2026.**
- **Starting human trials in 2026 to test LV101R's effects.**
- **Exploring its use for other cancers, like breast and pancreatic.**

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LV101R, LV201R and LV301R: A Promising Tetracyclic Triterpene Series for Cancer Therapy

White Paper

Abstract: Cancer remains a leading cause of morbidity and mortality worldwide, necessitating innovative therapeutic approaches. LV101R is a chemically modified semi-synthetic tetracyclic triterpene derived from Euphorbia species. It has emerged as a promising drug candidate due to its diverse anticancer properties. LV201R is a major bioactive component of Euphorbia tirucalli sap, characterized as a tetracyclic triterpene alcohol and forms the basis of the semi-synthetic variant LV101R. This white paper synthesises current knowledge on LV101R and LV201R's mechanism of action, including inhibition of Monoacylglycerol lipase and inhibition of PKC signalling pathways. Furthermore, there is substantial published evidence of LV201R's impact on cell proliferation, induction of apoptosis, and modulation of cancer-related pathways across various cancer types such as breast, pancreatic, gastric, and glioblastoma. Computational studies, including molecular docking and network pharmacology, further support its potential in cancer therapy. While preclinical data are compelling, gaps remain in safety and toxicology and clinical validation. These gaps are currently being addressed via a 12-month safety and toxicology study in 2 species and a planned 100 patient Phase I/II clinical trial in end stage GI cancer patients with a single Glioblastoma cohort.

This paper highlights LV101R's therapeutic promise and identifies areas for further research to facilitate its development as a novel cancer treatment.

01

Introduction

Cancer is characterized by uncontrolled cell proliferation and invasiveness, disrupting normal organ function and leading to significant global health burdens. Despite advances in pharmacotherapy, challenges such as drug resistance and severe side effects underscore the need for novel treatments. Natural compounds, particularly those derived from plants, have historically significantly contributed to cancer therapy, with examples like:

- Paclitaxel derived from Pacific yew tree approved by the FDA for Ovarian cancer treatment in 1992, Breast cancer in 1994
- Irinotecan (Camptosar) from the Chinese tree Camptotheca acuminata for the treatment of metastatic colorectal cancer approved by the FDA in 1996
- Topotecan also from the Chinese tree Camptotheca acuminata targeting topoisomerase 1 to treat ovarian cancer approved in 1996
- Vincristine (Oncovin) one of the earliest plant derived therapies extracted from the Madagascar periwinkle to treat acute leukaemia and approved by the FDA in 1963)
- Etoposide extracted from the Mayapple (Podophyllum peltatum) which inhibits topoisomerase II for the treatment of testicular cancer and small cell lung cancer

- Combretastatin A4 phosphate extracted from the African willow bush (*Combretum caffer*) which inhibits tubulin polymerisation and achieved orphan drug designation with the FDA to treat Thyroid and ovarian cancer
- Trabectedin (Yondelis) originally isolated from the marine tunicate *Ecteinascidia turbinata* interferes with DNA repair by binding in the minor groove of DNA approved in 2015 to treat soft tissue sarcoma

LV101R, a semisynthetic modified tetracyclic triterpene alcohol extracted from *Euphorbia tirucalli* and other *Euphorbia* species, exhibits strong anti-inflammatory and analgesic properties. More recent studies have highlighted its significant anticancer potential across multiple cancer types, including breast, pancreatic, gastric, and glioblastoma. This white paper aims to consolidate preclinical and computational evidence supporting LV101R as a drug candidate for cancer therapy, while identifying gaps for further investigation.

02

Profile of LV201R

LV201R is a major bioactive component of *Euphorbia tirucalli* sap, characterized as a tetracyclic triterpene alcohol and forms the basis of the semi-synthetic variant LV101R. Its chemical structure enables interactions with various biological targets, contributing to its pharmacological effects. LV201R's physicochemical properties, such as a molecular weight compliant with 4 of the 5 Lipinski's rules and a topological polar surface area (TPSA) of 52.58 Å², suggest favourable oral bioavailability.

2.1__ADME Properties

ADME properties of LV201R comply with 4 of Lipinski's rule of 5. However, it does not meet the solubility criteria, with a LogP of 7, which we believe will be addressed by the semisynthetic modification made to create LV101R. Overall, the profile supports gastrointestinal absorption, a critical factor for oral drug development. Further ADME properties are currently being addressed in a full safety and toxicology research package built in 2 species to enable clinical development in 2026.

2.2__Safety and Toxicology

A complete safety and toxicology package derived in 2 species is currently in process and likely to complete towards the end of 2025 with early read outs in September 2025. However, in the meantime, an acute 90 day repeat dose, oral toxicology study was completed in rodents, accurately determining the NOAEL (No Observed Adverse Effect Level) can be considered to be above the dose of 30 mg/kg. In the subchronic oral toxicity study conducted in mini-pigs over a period of 90 days, the suggested No Observed Adverse Effect Level (NOAEL) in non-rodent species (Minipigs) was found to be 3 mg/kg. The kidneys and liver were identified as the target organs following prolonged treatment (90 consecutive days) with LV201R. This is an encouraging result considering that the potential treatment dose in humans is expected to be between 0.1mg and 0.3mg/kg.

Anticancer Mechanisms of LV201R

LV101R exerts its anticancer effects through multiple mechanisms, including inhibition of cell proliferation, induction of apoptosis, and modulation of signalling pathways. These effects have been studied in vitro across various cancer cell lines and in in vivo models of cancer. The known drug targets are MAG lipase, which, when inhibited, drives up endocannabinoid production, agonising the cannabinoid 1 and 2 receptors, and PKC, a signalling kinase involved in cell growth and known to be involved in many cancers.

3.1_ LV201R inhibits Monoacylglycerol lipase

LV201R has been identified as a potent inhibitor of monoacylglycerol lipase (MAGL), a key enzyme in the endocannabinoid system responsible for hydrolysing 2-arachidonoylglycerol (2-AG) into arachidonic acid and glycerol. By inhibiting MAGL, LV201R elevates 2-AG levels, which in turn enhances cannabinoid receptor signalling, potentially offering therapeutic benefits in conditions such as neuroinflammation, pain, and cancer. Studies suggest that LV201R’s inhibitory effect on MAGL is selective and reversible, with a mechanism involving binding to the enzyme’s active site, thereby reducing its catalytic activity. This inhibition highlights LV201R’s potential as a novel pharmacological agent for modulating endocannabinoid signalling

MAGL Inhibitor Assay (n=3)

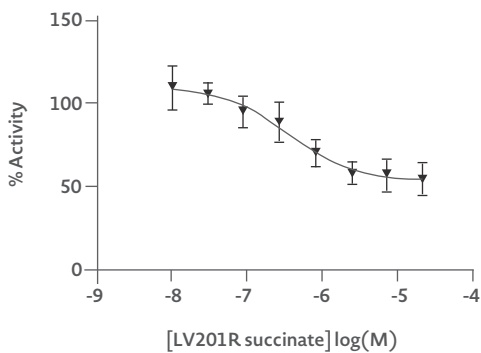


Figure 1: IC50 determination for LV101R using a dose response curve. (LivFul data 2024)

IC50 (nM)

	n=3	t0 corrected n=2	Expected IC50 from Literature
JZL 195	50.67	57.8	65
LV201R (MedChem Express)	Not calculated	Not calculated	315
LV201R (LivFul)	Not calculated	Not calculated	315
LV201R Succinate (LivFul)	360.1	324.3	315

Table 1: Summary of IC50 determinations for the indicated inhibitors (LivFul data 2024)

3.2_ LV201R inhibits PKC

LV201R has been shown to modulate different PKC isozymes in various contexts. For instance, in a study on cutaneous inflammation, LV201Rs ability to reduce leukocyte influx and chemokine levels (e.g., CXCL1/KC and MIP-2) was linked to its inhibition of PKC activation, particularly through the suppression of TPA-induced signalling

pathways. Additionally, LV201R's anti-inflammatory and anticancer properties have been attributed to its ability to inhibit PKC-dependent pathways, such as those involving NF- κ B activation.

Wang et al. studied the cytotoxic effects of LV201R on Leukaemia. This study investigated effects on leukaemia cells, showing that it inhibits cell proliferation and induces apoptosis. The study links LV201R's effects to the inhibition of PI3K/Akt signalling, which intersects with PKC pathways, suggesting a broader role for PKC modulation in its anticancer activity.

3.3_ LV201R inhibits Cell Proliferation

LV201R significantly reduces cell viability in multiple cancer types. In breast cancer T47D cells, MTT assays demonstrated dose-dependent inhibition at concentrations of 0.01–0.3 mM, with a notable arrest in the G0/G1 phase. Similarly, in pancreatic cancer cell lines (MiaPaCa-2 and Panc-1), LV201R at 35.1 μ M inhibited proliferation by 39.4% and 22.4%, respectively.

3.4_ LV201R induces Apoptosis

LV201R promotes apoptosis via mitochondria-dependent pathways. In gastric cancer C512 cells, 20 μ M LV201R increased apoptosis rates, with Annexin V/PI staining confirming controlled cell death. In glioblastoma, LV201R enhanced P53 (S15) activation and reduced anti-apoptotic proteins like BCL-X.

3.5_ LV201R induces Autophagy and Cell Cycle Regulation

LV201R induces autophagy, as evidenced by increased LC3-II expression in GAMG glioma cells. It also modulates cell cycle progression by upregulating p21 and p27 and downregulating cyclins A, B1, and D1 in breast cancer cells.

04

LV201R Series

LV201R is the active component in the drug series with LV101R being the more soluble variant. Additionally, another variant, LV301R, is under investigation as a design for massively enhanced brain penetration by combining LV201R with another technology. The significant body of data is on LV201R but the more soluble LV101R, can easily be bridged to the existing body of data supporting a possible treatment for pain and cancer.

LV101R has been designed to significantly improve solubility and is currently being evaluated in a safety and toxicology study in 2 species. Successful completion of the study with desirable safety profile will allow us to progress to the next phase of manufacture and tableting in Brazil. LV101R has been designed to enhance systemic exposure to initially target GI cancers. The clinical trial is planned for the second half of 2026 and at Hospital ABC in Sao Paulo under the guidance of our acting Chief Medical Officer Dr Auro Del Giglio, and an eminent Brazilian Oncologist. Success in this Phase I/II safety and efficacy study will allow us to evergreen into additional cancer types as there is an expectation that LV101R will have broad anticancer activity.

LV301R is currently being designed in collaboration with a British Biotech company using their platform technology, proven to massively enhance brain penetration. Initiation of the project will likely result in 5 candidates, all modified versions of the active LV201R. The study is likely to complete mid 2026 with safety and toxicology to follow. The target indication for LV301R is the rare disease Glioblastoma.

LV201R Across Cancer Types

LV201R efficacy has been evaluated in several cancer models, demonstrating broad spectrum activity.

5.1_ Gastric Cancer

The 2012 study by Lin et al., published in Evidence-Based Complementary and Alternative Medicine, investigates the anticancer potential of LV201R against human gastric cancer cell lines (CS12, AGS, and MKN45). The researchers found that LV201R selectively inhibits the growth of these cancer cells compared to normal epithelial cells (GES-1), with IC₅₀ values indicating higher sensitivity in malignant cells (e.g., 43.2–48.5 μ M for cancer cells vs. 62.3 μ M for normal cells after 48 hours). The primary mechanism of action is mitochondria-mediated apoptosis, characterized by increased caspase-3 activation, elevated pro-apoptotic Bax expression, reduced anti-apoptotic Bcl-2 levels, and cytochrome c release from mitochondria. Additionally, LV201R enhances phosphorylation of ERK1/2, which contributes to apoptosis induction, while other MAPK pathways (p38 and JNK) remain unaffected, highlighting a specific signalling pathway involvement.

The study employed MTT assays, flow cytometry, and Western blotting to assess cell viability, apoptosis rates, and protein expression, respectively, confirming LV201Rs dose- and time-dependent cytotoxicity. The selective toxicity toward gastric cancer cells is attributed to their higher mitochondrial activity, making them more susceptible to LV201Rs effects. The paper contextualizes these findings within the traditional use of *Euphorbia tirucalli* in herbal medicine and notes euphol's presence alongside other triterpenes, though it focuses on LV201Rs isolated effects. The results suggest LV201Rs potential as a targeted therapeutic agent, but further studies are needed to explore its preclinical safety and clinical relevance to humans.

5.2_ Glioblastoma

In glioblastoma, a study published in Investigational New Drugs (2019) by Silva et al. investigated the effects of LV201R on glioblastoma cells both in vitro and in vivo. In the in vivo component, the researchers utilised the chicken chorioallantoic membrane (CAM) assay, a well-established model for assessing tumour growth and angiogenesis. LV201R demonstrated significant antitumoral and antiangiogenic activity in this model, reducing tumour burden and inhibiting blood vessel formation associated with glioblastoma cells. The study also noted synergistic interactions with temozolomide (TMZ), a standard chemotherapy drug for glioblastoma, suggesting LV201Rs potential as an adjunct therapy. These findings indicate that LV201R exerts cytotoxic effects against glioma cells in vivo through multiple pathways, including the activation of autophagy-associated cell death. In vitro data from the same study and others (e.g.,

Baroni et al (2024) and Bonafé et al., 2022) support LV201Rs cytotoxicity against glioblastoma cell lines (e.g., GAMG and U373), with mechanisms involving apoptosis and inhibition of proliferation and motility. These results, combined with the CAM assay outcomes, provide preclinical support for further exploration of LV201R as a novel therapeutic agent for the treatment of glioblastoma, though additional mammalian in vivo studies are needed to confirm its safety.

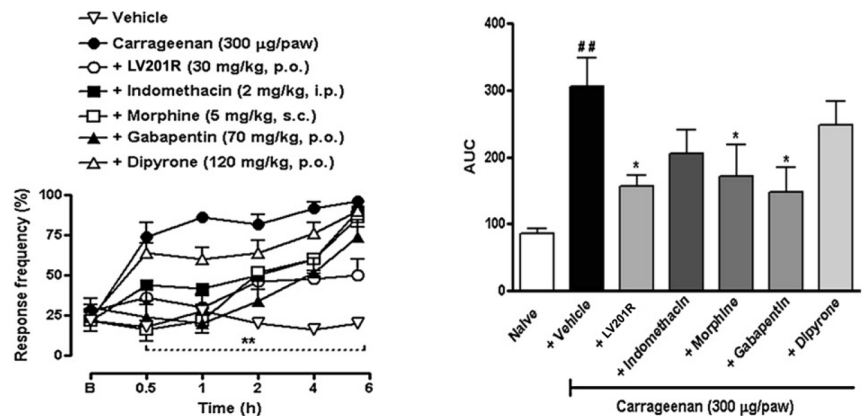
Note: LV201R IC₅₀ values range from 5.98 to 31.05 μ M across 12 cell lines, with paediatric glioma lines showing higher sensitivity. Synergistic effects with temozolomide (TMZ), the current standard of care, suggest potential for combination regimens.

5.3_ Anti-Inflammatory and Antinociceptive Effects

Dutra et al. (2012) tested LV201R's anti-inflammatory and antinociceptive properties in vivo using rodent models of inflammation and pain, such as carrageenan-induced paw oedema and acetic acid-induced writhing in mice. The key findings: Euphol significantly reduced inflammation and pain responses, with effects comparable to standard drugs like dexamethasone and indomethacin. The mechanisms involved inhibition of pro-inflammatory cytokines and modulation of pain pathways. These findings suggest LV201Rs broader therapeutic potential in cancer through pain relief.

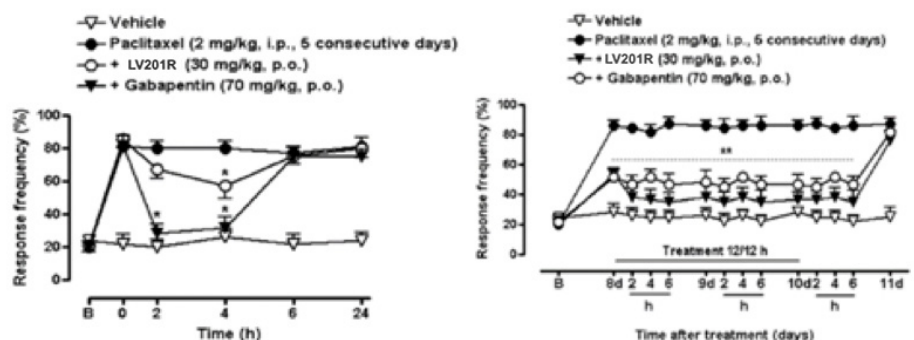
LV201R inhibits mechanical hypersensitivity induced by carrageenan and Complete Freund's Adjuvant(CFA) in mice

Fig. 2 – Comparison of LV201R to potent in-market analgesics such as morphine and gabapentin. The smaller the Area Under Curve (AUC), the better the performance. Considering the error margin, Euphol has the best performance among the competitor drugs.



LV201R reduces chemotherapy induced peripheral neuropathy

Fig. 3 – In comparison to Gabapentin, LV201R reduces CIPN (Chemotherapy-induced peripheral neuropathy), but requires only half the dose.



The results presented in the pharmacological study provide groundbreaking evidence that LV201R exhibits significant analgesic effects when administered orally and evaluated in various pain models in mice and rats. These effects are dependent on its ability to activate both CB1 and CB2 cannabinoid receptors, showing a higher selectivity towards CB2 subtypes. Additionally, the study suggests that inhibition of PKC ϵ and COX-2 expression in primary sensory neurons and the spinal cord plays a crucial role in the mechanisms of LV201R action. Furthermore, LV201R demonstrates inhibitory effects on the release and expression of pro-inflammatory cytokines, reduction of neutrophil influx, activation of PPAR- γ , and inhibition of nuclear factor NF- κ B and CREB activation.

Overall, the findings strongly imply that LV201R represents a novel, attractive, safe, and selective cannabinoid compound, providing new perspectives for clinical research aimed at assessing its potential for developing new analgesic drugs targeting persistent pain often associated with cancer. This includes pain caused by nerve injuries, tumours, and cancer therapy.

5.4__ Breast Cancer

Breast cancer, a leading cause of cancer-related deaths in women, responds to LV201R through cell cycle arrest and reduced proliferation. At 300 μ M, LV201R increased G0/G1 phase cells from 50.63% to 71.41% in T47D cells.

5.5__ Pancreatic Cancer

In pancreatic cancer, LV201R cytotoxic effects are pronounced, with 35.1 μ M reducing cell viability significantly in MiaPaCa-2 cells. Its dose-dependent inhibition highlights its potential as a targeted therapy.

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IP Strategy

We will be utilising a multilayered IP strategy to protect our research and drug assets. This will be a combination of strategic patenting, developing innovative know-how and employing commercial tactics which are designed to provide significant periods of exclusivity.

Future Directions

LV101R and LV201R are being progressed as both pain and cancer therapies. The main current focus is a full safety and toxicology package in 2 species suitable to support clinical development.

6.1__ Safety and toxicology package for LV 101R reads out 4Q2025 with final written report expected 1Q2026

6.2__ Manufacture and CMC is ongoing with recent upscale manufacture from 1g to 55g, 55g to 150g and 150g to 1kg. Manufacture and tableting will take place in Brazil following tech transfer

6.3__On acceptable safety and toxicology outcomes and manufacture tech transfer we will engage with ANVISA, the Brazilian regulatory body, during 4Q25 seeking approval for our up-and-coming clinical trial. We plan to conduct a Phase I/II clinical trial second half of 2026 in Brazil at Sao Paulo ABC Hospital under the guidance of Dr Auro Del Giglio. This is planned to be a 100 patient trial in a mix of end stage GI and Glioblastoma patients. The primary endpoint is pain management with a secondary endpoint of tumour volume

6.4__We also plan to explore the synergistic combinations with the existing standard of care for glioblastoma, the chemotherapeutic TMZ.

6.5__Success in our Phase I/II will also offer evergreening opportunities for the treatment of a range of other cancers including pancreatic, thyroid, breast, prostate, and skin cancers to investigate LV201Rs effects on additional cancer types and resistant cell lines.

07

Summary

LV101R and LV201R represent a promising cancer therapy, with demonstrated efficacy across multiple cancer types through diverse mechanisms. While preclinical evidence is compelling, clinical trials are essential to confirm its therapeutic value. Clinical research to address its utility in humans will be critical to realizing LV101R's potential as a novel anticancer agent.

08

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