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Preclinical Evaluation of Kardin: Pharmacological Properties and Anti-Inflammatory Potential of Peptides Derived from the Hearts of Neonatal Lambs

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Method Article

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Abstract

Bioactive peptides derived from animal tissues have gained increasing attention for their anti-inflammatory and immunomodulatory properties. Kardin is a novel peptide preparation obtained by enzymatic hydrolysis of cardiac proteins from neonatal lambs. This study aimed to evaluate the anti-inflammatory, antiexudative, and immunomodulatory effects of Kardin in preclinical models and to explore its potential molecular mechanisms. The anti-inflammatory activity was assessed in Wistar rats using carrageenan- and formalin-induced paw edema models as well as cotton pellet-induced granuloma. Kardin was administered orally at ultra-low doses (10^{-6} and 10^{-4} mg/kg) and compared with acetylsalicylic acid and prednisolone. Serum biochemical parameters (CRP, ASO, ALT, AST) were analyzed. In silico molecular docking and dynamics simulations were performed to investigate peptide interaction with the CysLT1 receptor. Kardin significantly reduced acute and chronic inflammation, exhibiting superior antiexudative activity compared to reference drugs even at ultra-low doses. Treatment markedly decreased ASO levels without altering liver or kidney function markers. *In silico* analyses revealed stable binding of Kardin peptides to CysLT1, suggesting allosteric modulation of inflammatory signaling. These findings indicate that Kardin possesses potent anti-inflammatory and immunomodulatory effects with a favorable safety profile, supporting its potential as a promising therapeutic candidate for inflammatory disorders.

Introduction

Bioactive peptides obtained through enzymatic hydrolysis of animal proteins have attracted considerable attention in recent years due to their wide range of pharmacological activities, including anti-inflammatory, antioxidant, immunomodulatory, analgesic, and tissue-regenerative effects [1, 2]. Among various sources, protein hydrolysates derived from neonatal animal tissues, particularly cardiac tissue, have shown promising therapeutic potential in preclinical models by accelerating wound healing, reducing oxidative stress, suppressing pro-inflammatory cytokine production, and modulating key components of the immune system such as T and B lymphocytes [3, 5].

Kardin is a novel peptide preparation produced by controlled enzymatic hydrolysis (using trypsin) of cardiac proteins from neonatal lambs. The resulting mixture contains highly bioactive low-molecular-weight peptides exhibiting pronounced anti-exudative and anti-inflammatory properties [6]. The preparation is rich in amino acids such as L-arginine and L-tyrosine, which play important roles in regulating nitric oxide (NO) production, decreasing vascular permeability, reducing edema formation, and attenuating inflammatory responses [7, 8].

Preliminary preclinical findings suggest that Kardin may demonstrate superior efficacy compared to conventional anti-inflammatory agents, including acetylsalicylic acid and prednisolone, even when administered at substantially lower doses [6, 9]. Despite these encouraging results, the precise molecular mechanisms underlying the interaction of Kardin peptides with receptors relevant to

respiratory and cardiovascular inflammatory pathways — particularly the cysteinyl leukotriene receptor 1 (CysLT1) remain poorly characterized.

Computational approaches such as molecular docking and molecular dynamics (MD) simulations provide powerful tools to predict peptide–receptor interactions at the atomic level, estimate binding affinities, identify key interacting residues, and reveal the dynamic behavior of peptide–receptor complexes under physiological conditions [10, 11]. Such *in silico* analyses can help elucidate whether Kardin peptides act as allosteric modulators, influencing receptor conformational states, inhibiting agonist-induced signaling, reducing intracellular Ca^{2+} influx, and preventing smooth muscle contraction and tissue fibrosis [12, 13].

However, systematic preclinical pharmacological profiling particularly regarding anti-inflammatory, antiexudative, and biochemical safety parameters is essential to validate the predicted therapeutic potential and to establish a solid mechanistic foundation. The present study was therefore designed to comprehensively characterize the general pharmacological properties of Kardin in preclinical models. Specifically, the objectives were:

- to evaluate the antiexudative and anti-inflammatory effects of Kardin in carrageenan- and formalin-induced paw edema models in rats;
- to compare its efficacy with standard anti-inflammatory agents (acetylsalicylic acid and prednisolone);
- to assess the impact of Kardin on key biochemical parameters, including liver enzymes (ALT, AST), C-reactive protein (CRP), and antistreptolysin O (ASO), in order to determine its systemic safety profile;
- to investigate the molecular interactions and potential allosteric modulation of the CysLT1 receptor by Kardin peptides using molecular docking and MD simulation approaches.

Through the integration of in vivo experimental models and computational analyses, this study provides a detailed preclinical evaluation of Kardin, aiming to clarify its mechanisms of action and therapeutic potential as a novel anti-inflammatory and tissue-protective agent.

Materials and Methods

Animals and ethical considerations

The study was conducted on 6-month-old male and female albino Wistar rats weighing 160–180 g, obtained from the certified animal facility “YTT ALSU” (Tashkent, Uzbekistan). Animals were housed under standard laboratory conditions (temperature 22 ± 2°C, relative humidity 50–55%, 14:10 h light/dark cycle) with free access to standard pellet diet and water. All experimental procedures were approved by the Institutional Animal Ethics Committee (approval number: 1-2-1451-2-524) and performed in

accordance with international guidelines for the care and use of laboratory animals and the ARRIVE 2.0 recommendations.

Experimental design and grouping

Animals were randomly allocated to experimental groups using a simple randomization method. Each group consisted of six animals (n = 6). The following groups were used: Control (normal saline, oral), Kardin 10^{-6} mg/kg (oral), Kardin 10^{-4} mg/kg (oral), Acetylsalicylic acid 100 mg/kg (oral), Prednisolone 7 mg/kg (oral). Investigators measuring inflammatory parameters were blinded to the treatment allocation.

Preparation of Kardin

Kardin was prepared by enzymatic hydrolysis of neonatal lamb cardiac proteins using trypsin. Peptides were isolated and purified by gel filtration chromatography (Sephadex G-25) followed by ion-exchange chromatography (CM-Sephadex C-25). The purified fraction was desalted, lyophilized, and quantified. Peptide composition was confirmed by high-performance liquid chromatography (HPLC) and liquid chromatography–mass spectrometry (LC-MS).

Carrageenan-induced paw edema

Acute inflammation was induced by subplantar injection of 0.1 mL of 1% carrageenan into the right hind paw. Paw volume was measured at 1, 2, 3, 4, 5, and 24 h using a plethysmometer. Formalin-induced paw edema Subplantar injection of 0.1 mL of 2% formalin was administered. Edema was evaluated at 1, 2, 3, 4, 24, 72, and 168 h post-injection.

Cotton pellet-induced granuloma

Sterile cotton pellets (10 mg) were implanted subcutaneously under aseptic conditions. On day 8, pellets were excised, weighed in both wet and dry states to assess chronic inflammation.

Biochemical analysis

Blood samples were collected on days 1 and 7. Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), antistreptolysin O (ASO), creatinine, and urea were determined using standard automated methods.

Molecular modeling and in silico analysis

Molecular docking of representative Kardin peptides with the CysLT1 receptor was performed using CABS-dock. Binding stability was further evaluated through 100 ns molecular dynamics (MD) simulations. Root mean square deviation (RMSD) values and cluster analysis were used to assess conformational stability and dominant binding modes.

Statistical analysis

Data are expressed as mean ± standard deviation. Intergroup comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Differences were considered statistically significant at $p \leq 0.05$.

Results

Characterization of Kardin peptides

Enzymatic hydrolysis and subsequent chromatographic purification yielded a heterogeneous peptide mixture. HPLC analysis revealed multiple peptide fractions, while LC-MS identified peptide fragments with molecular masses ranging from 932 to 2915 Da, confirming successful preparation of the bioactive peptide pool.

Antiexudative activity in carrageenan-induced paw edema

Oral administration of Kardin produced a significant reduction in paw edema in carrageenan-injected rats. At the dose of 10^{-4} mg/kg, Kardin reduced edema by 73% at 3 hours post-induction, which was markedly greater than the effect of acetylsalicylic acid (50%) and prednisolone (45%) at their standard doses ($p < 0.01$). The anti-inflammatory effect was evident within the first few hours and persisted throughout the 24-hour observation period, with paw volume returning to near-baseline values in Kardin-treated animals.

Antiexudative activity in formalin-induced paw edema

In the formalin model, Kardin at 10^{-4} mg/kg significantly suppressed paw swelling compared to reference drugs. At 4 hours, edema was reduced to 28% in the Kardin group versus 79% in the acetylsalicylic acid group and 47% in the prednisolone group ($p < 0.01$). By day 3, inflammation in Kardin-treated animals was almost completely resolved, demonstrating a sustained anti-inflammatory action.

Effect on cotton pellet-induced granuloma

In the chronic inflammation model, Kardin treatment led to a significant inhibition of granuloma formation. Both wet and dry weights of the implanted cotton pellets were substantially lower in Kardin-treated groups compared to the control group, indicating strong suppression of chronic inflammatory response.

Serum biochemical parameters

Administration of Kardin did not cause any adverse changes in markers of liver or kidney function. Serum levels of ALT, AST, creatinine, and urea remained within physiological ranges across all groups. Notably, antistreptolysin O (ASO) levels were significantly reduced in both Kardin dose groups compared to control ($p < 0.05$). C-reactive protein (CRP) showed a mild, non-significant decrease (Table 1).

Table 1
Effects of Kardin and prednisolone on selected serum biochemical parameters in the cotton pellet granuloma model

Parameter	Control	Prednisolone mg/kg	Kardin 10^{-6} mg/kg	Kardin 10^{-4} mg/kg
Glucose (mmol/L)	6.15 ± 0.13	5.97 ± 0.15	4.93 ± 0.59	4.83 ± 0.13
ALT (U/L)	72.3 ± 3.93	56.7 ± 4.18*	47.0 ± 6.57**	61.3 ± 2.97*
AST (U/L)	140.7 ± 3.18	154.7 ± 11.1	147.7 ± 11.7	150.3 ± 16.2
Total protein (g/L)	70.2 ± 1.59	64.8 ± 1.91	76.0 ± 1.16	72.3 ± 0.33
Creatinine (µmol/L)	42.9 ± 1.91	38.7 ± 1.35	45.0 ± 2.0	48.0 ± 3.8
Urea (mmol/L)	6.8 ± 0.89	6.33 ± 0.93	6.23 ± 0.45	7.87 ± 1.43
CRP (mg/L)	30.0 ± 0.4	29.0 ± 1.5	28.0 ± 0.7	26.0 ± 0.9
ASO (mmol/ml)	23.77 ± 7.2	10.9 ± 1.64*	10.0 ± 0.06*	9.47 ± 0.47*
• $p \leq 0.05$, ** $p \leq 0.001$ compared to control				

In silico molecular docking and dynamics

Molecular docking studies showed that representative Kardin peptides (e.g., YIFGTGRR, RMIEKIAE) interacted strongly with the extracellular domain of the CysLT1 receptor, forming multiple hydrogen bonds and electrostatic interactions (CABS-dock score < − 120, 4–6 hydrogen bonds). Molecular dynamics simulations (100 ns) confirmed the stability of the peptide–receptor complexes, with low RMSD fluctuations (~ 1.5 Å). Cluster analysis identified dominant conformational states associated with reduced Gi-mediated signaling, decreased Ca^{2+} influx, and suppression of smooth muscle contraction.

Molecular docking analyses revealed that representative Kardin peptides (e.g., YFTGRR and RMIKKAE) bind strongly to the extracellular domain of the CysLT1 receptor via multiple hydrogen bonds and hydrophobic interactions. Molecular dynamics (MD) simulations over 100 ns demonstrated the stability of the peptide–receptor complexes, evidenced by stabilized and low RMSD values over time. These results indicate favorable conformational fitting and sustained binding of Kardin peptides within the receptor interface, supporting high binding affinity and stable complex formation.

Cluster analysis of MD trajectories identified multiple dominant conformational states of the Kardin–CysLT1 complexes. The table summarizes the average RMSD, maximum RMSD, and the number of structural elements in each cluster. The presence of large clusters with low average RMSD values indicates high structural stability of the complexes, whereas the coexistence of several clusters suggests conformational flexibility and a potential allosteric binding behavior of Kardin peptides within the receptor binding pocket.

Table 2.

Cluster analysis and RMSD distribution of Kardin–CysLT1 complexes during MD simulation.

Persistent contact points observed throughout the simulation highlight critical binding regions responsible for peptide anchoring and receptor modulation. The distribution of stable contacts supports a mechanism in which Kardin peptides act as allosteric modulators, influencing receptor conformation rather than directly competing with endogenous ligands.

Cluster density	Average RMSD (Å)	Maximum RMSD (Å)	Number of elements
23.8575	5.910	29.688	141
21.9166	5.384	28.739	118
21.158	6.853	27.317	145
17.346	8.532	29.606	148
14.656	5.800	15.651	85
13.666	9.293	30.963	127
7.999	10.002	33.865	80
5.784	7.953	26.088	46
5.652	9.377	19.685	53
5.280	10.795	28.551	57

Discussion

The present study provides robust preclinical evidence that Kardin, a peptide mixture derived from enzymatic hydrolysis of neonatal lamb cardiac proteins, exerts pronounced anti-inflammatory and antiexudative effects in both acute and chronic models of inflammation. In the carrageenan-induced paw edema model, Kardin at an ultra-low dose of 10^{-4} mg/kg reduced edema by 73% at the peak time point (3 h), significantly outperforming acetylsalicylic acid (50%) and prednisolone (45%). A similar pattern was observed in the formalin-induced edema model, where Kardin not only suppressed early-phase swelling but also almost completely resolved inflammation by day 3, demonstrating a sustained therapeutic effect.

These findings are consistent with previous reports showing that bioactive peptides from animal tissue hydrolysates can effectively modulate inflammatory pathways at very low concentrations [1, 3, 6]. The exceptionally high potency of Kardin at doses several orders of magnitude lower than conventional anti-inflammatory drugs suggests the presence of highly active peptide sequences and/or synergistic interactions within the mixture.

In the cotton pellet granuloma model, which mimics chronic inflammation, Kardin markedly inhibited granuloma formation, as evidenced by significant reductions in both wet and dry pellet weights. This result indicates systemic anti-inflammatory activity and potential suppression of fibroblast proliferation and collagen deposition, which are key features of chronic inflammatory processes [14, 15].

Importantly, biochemical analysis revealed that Kardin treatment did not induce any detectable hepatotoxicity or nephrotoxicity, as serum ALT, AST, creatinine, and urea levels remained within normal physiological ranges. The significant reduction in antistreptolysin O (ASO) levels observed in both Kardin dose groups suggests immunomodulatory activity, possibly through regulation of antibody production or modulation of T- and B-cell responses, in line with earlier observations on cardiac hydrolysates [5, 25].

In silico analyses provided mechanistic insight into these effects. Molecular docking and 100 ns molecular dynamics simulations demonstrated that representative Kardin peptides interact stably with the extracellular domain of the CysLT1 receptor, forming multiple hydrogen bonds and exhibiting low RMSD fluctuations. The conformational states identified through cluster analysis were associated with reduced Gi-protein signaling, decreased intracellular Ca^{2+} influx, and inhibition of smooth muscle contraction all of which are consistent with the observed antiexudative and anti-inflammatory activity in vivo [12, 13, 30].

The presence of L-arginine- and L-tyrosine-containing peptides in the Kardin mixture may further contribute to its effects by modulating nitric oxide production and vascular permeability [7, 8, 22]. The sustained activity observed in the formalin model likely reflects the synergistic action of multiple bioactive peptides, enabling suppression of pro-inflammatory cytokines, mitigation of oxidative stress, and promotion of tissue repair [2, 18, 33]. Despite these promising results, the study has certain limitations. The experiments were conducted only in Wistar rats, so extrapolation to other species or humans should be made cautiously. The sample size per group (n = 6) was relatively small, although statistically powered for the primary endpoints. In addition, while the in silico analyses provide valuable mechanistic hypotheses, they require validation through functional receptor assays and/or binding studies.

Conclusion

In conclusion, the data demonstrate that Kardin possesses potent anti-inflammatory, antiexudative, and immunomodulatory properties with an excellent safety profile at ultra-low doses. These findings position Kardin as a promising candidate for the development of novel anti-inflammatory agents, particularly for conditions involving leukotriene-mediated pathways. Future studies should focus on identifying the most

active individual peptides, characterizing their pharmacokinetics, and evaluating efficacy in advanced preclinical models and eventually clinical settings.

Declarations

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Figures

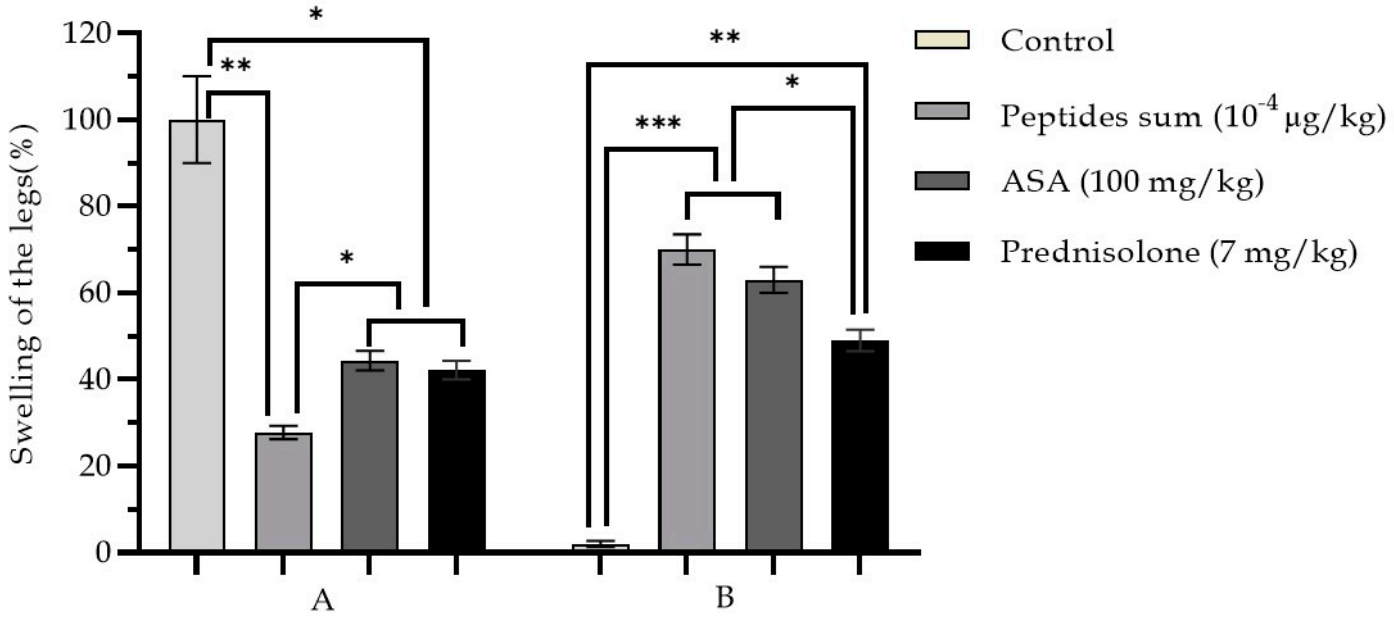


Figure 1

Effect of the peptide mixture, acetylsalicylic acid (ASA), and prednisolone on the dynamics of inflammation in rats in the carrageenan-induced exudative inflammation model (increase in paw volume, % relative to baseline, *n* = 6).

A: Increase in paw volume 3 hours after induction, %.

B: Antiexudative activity, %.

P ≤ 0.05; **P** ≤ 0.01; **P** ≤ 0.005.

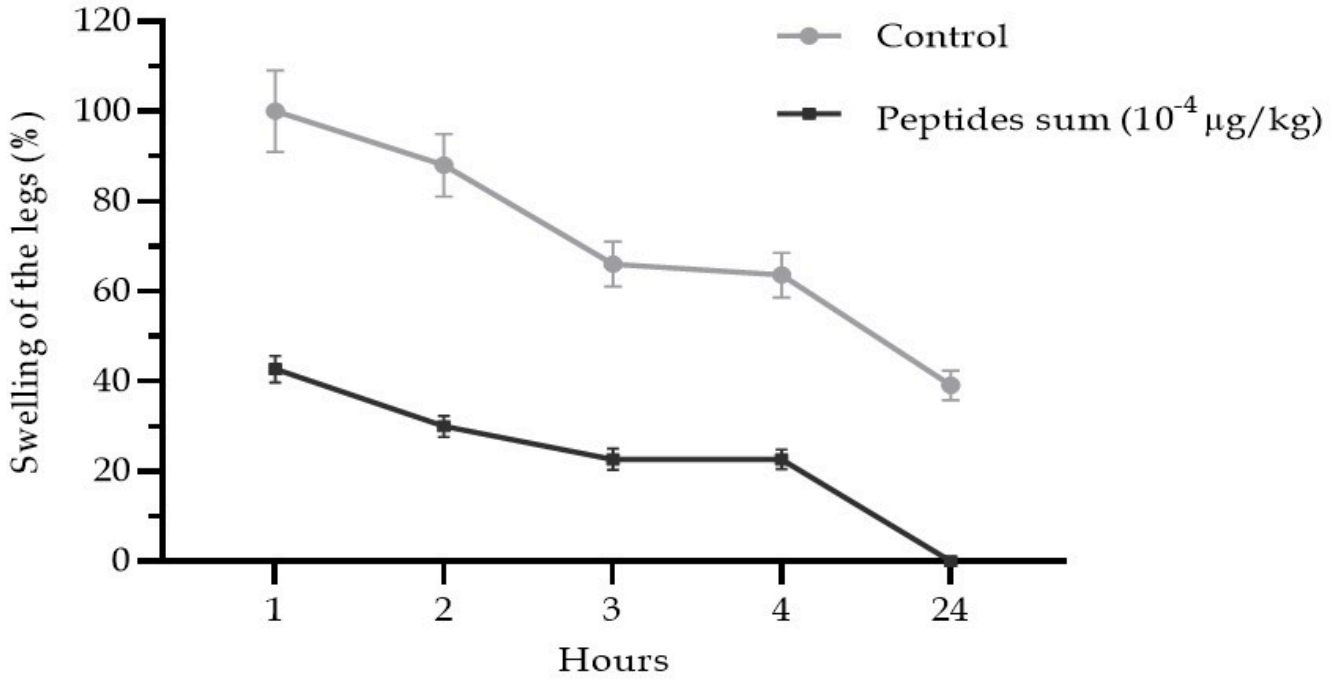


Figure 2

Therapeutic effect of the peptide mixture on the dynamics of inflammation in rats with carrageenan-induced exudative inflammation (increase in paw volume, % relative to baseline, *n* = 6).

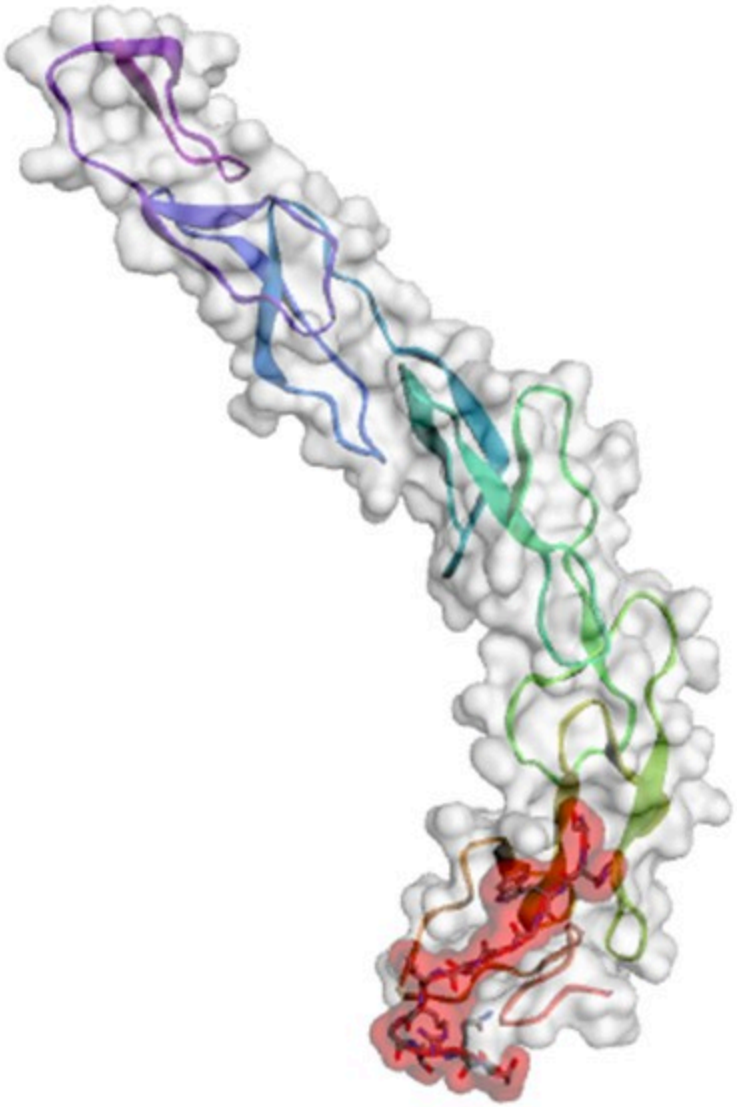


Figure 3

Molecular docking and dynamics of Kardin peptides with the CysLT1 receptor (*in silico* analysis).