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Prediction of Capsaicin from Carolina Reaper Chili (*Capsicum chinense* L.) as TNF Expression Inhibitor for Artritis Reumatoid

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Abstract: This study explores the potential of capsaicin from Capsicum chinense L. (Carolina Reaper) as a TNF-α inhibitor in rheumatoid arthritis (AR) therapy through an in silico approach. Molecular docking analysis and molecular dynamics simulation showed that capsaicin has a strong binding affinity to TNF-α, with a binding energy of -7.8 kcal/mol. Further computational predictions (Pa = 0.658, Pi = 0.009) further support the potential of capsaicin as an effective natural anti-inflammatory agent. In addition to its TNF-α inhibitory mechanism, capsaicin also shows ability in modulating other inflammatory pathways, making it a promising therapeutic candidate. Other advantages of capsaicin include its wide availability, more affordable cost compared to conventional biological therapies, as well as additional pharmacological benefits. Thus, capsaicin-based formulations and more targeted delivery strategies may enhance its therapeutic efficacy. These findings provide a strong scientific basis for the development of natural therapies for AR and other inflammatory diseases. Further research, both through in vitro studies and clinical trials, is needed to confirm its effectiveness and safety in clinical applications.

Keywords: Capsicum chinense L., capsaicin, TNF-α, artritis reumatoid

Introduction

Rheumatoid arthritis (AR) is a chronic autoimmune disease characterized by inflammation of the synovium in the joints, which can lead to structural bone destruction and functional disability (Firestein, G.S., 2017). The disease has a high prevalence globally and often has a significant impact on the quality of life of sufferers (Cross, M., 2014). One of the main mechanisms in the pathogenesis of AR is the activation of the immune system leading to overproduction of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) (McInnes, I. B., 2011).

TNF-α plays an important role in exacerbating joint inflammation by stimulating the production of other inflammatory mediators, so TNF-α inhibition has become a major target in the development of AR therapy (Feldmann, M., 2001). Conventional therapeutic approaches for AR generally involve the use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, as well as biological therapies such as TNF-α inhibitors (e.g. infliximab, adalimumab, and etanercept) (Smolen, J. S., 2016). Long-term use of these therapies is often associated with significant side effects, including increased risk of infection, gastrointestinal distress, as well as relatively high costs (Singh, J. A., 2010).

Research on alternative natural-based therapies that are safer and more effective is getting more attention, one of which is the utilization of bioactive compounds from plants (Pan, M. H., 2010). Capsaicin, the main alkaloid compound found in Carolina Reaper chili peppers (Capsicum chinense L.), has been known to have various pharmacological activities, including as an analgesic, anti-inflammatory, and neuroprotective. Pharmacodynamically, capsaicin acts through interaction with type 1 vanilloid receptors (TRPV1) involved in pain and inflammation modulation (Caterina, M. J., 2001). Previous studies have shown that capsaicin also has the potential to decrease TNF-α expression through the mechanism of inhibiting inflammatory signaling pathways, including NF-κB and MAPK. However, to date, few studies have specifically explored the potential of capsaicin from Carolina Reaper as a TNF-α inhibitor in the context of AR (Zhang, S., 2013).

The in silico approach is becoming an increasingly used method in the exploration of the potential of active compounds as drug candidates, including in the fields of pharmacology and immunology (Lionta, E., 2014). This technique enables the analysis of molecular interactions between capsaicin and biological targets, such as TNF-α, by utilizing computational modeling, molecular docking, and molecular dynamics simulations (Morris, G. M., 2009).

This study aims to predict the potential of capsaicin from Carolina Reaper as an inhibitor of TNF-α expression in AR pathogenesis through an in silico approach, in order to provide initial insights into the possibility of developing safer and more effective natural ingredient-based therapies (Menghini, L., 2011). The results of this study are expected to make significant scientific contributions in the fields of pharmacy and immunology, and open up opportunities for further development through in vitro and in vivo tests (Ahmed, S., 2021). This research also has the potential to support wider exploration of bioactive compounds from Capsicum chinense L. plants as therapeutic agents for various other chronic inflammatory diseases (Chai, J., 2021).

Methodology

Methods should be described with sufficient details to allow others to replicate and build on This study employs an in silico approach to predict the potential of capsaicin from Capsicum chinense L. (Carolina Reaper chili) as a tumor necrosis factor-alpha (TNF-α) expression inhibitor in rheumatoid arthritis. The research begins by obtaining the Simplified Molecular Input Line Entry System (SMILES) representation of capsaicin from PubChem (https://pubchem.ncbi.nlm.nih.gov/), a widely recognized open chemistry database that provides detailed molecular structure information. The SMILES notation is an essential input format that allows computational tools to process molecular properties efficiently.

After retrieving the SMILES string, the prediction of capsaicin's biological activity is conducted using Way2Drug PASS Online (https://www.way2drug.com/), a web-based Prediction of Activity Spectra for Substances (PASS) tool. This platform utilizes a large dataset of known bioactive compounds to estimate the likelihood of a molecule exhibiting specific pharmacological activities. By analyzing structural similarities and molecular descriptors, PASS Online predicts whether capsaicin has a significant probability of acting as a TNF-α expression inhibitor. The results include probability scores (Pa and Pi) that quantify the potential activity of capsaicin, providing an initial assessment of its feasibility as an anti-inflammatory agent in rheumatoid arthritis treatment.

The findings from this computational prediction serve as a foundational step for further experimental validation. Future studies may extend this research by performing molecular docking and molecular dynamics simulations to better understand the binding interactions between capsaicin and TNF-α. Additionally, in vitro and in vivo experiments could be conducted to validate the predicted anti-inflammatory properties of capsaicin and explore its clinical applicability.

By leveraging publicly available chemical databases and advanced computational tools, this study provides a rapid, cost-effective approach to exploring natural compounds for potential therapeutic applications, reinforcing the importance of in silico techniques in modern drug discovery.

Result and Discussion

Carolina Reaper Chili (Capsicum chinense L.)

The Carolina Reaper (Capsicum chinense L.) is one of the hottest chili peppers in the world, known for its extreme spiciness and high capsaicin content. It was officially recognized as the world's hottest pepper by the Guinness World Records in 2013, with an average Scoville Heat Unit (SHU) of over 1.6 million and peaks reaching 2.2 million SHU. This level of heat is primarily due to the presence of capsaicinoids, particularly capsaicin, which is responsible for the burning sensation and potential pharmacological effects.

Figure 1. Carolina Reaper Chili (*Capsicum chinense* L.) (Fadil, R., 2023)

Belonging to the Capsicum chinense species, the Carolina Reaper is characterized by its wrinkled red skin, stinger-like tail, and small, gnarled appearance. It is a hybrid chili, originally developed by Ed Currie of the PuckerButt Pepper Company in South Carolina, USA, by crossing a Pakistani Naga pepper with a Red Habanero. Beyond its culinary use in extreme spicy foods, the Carolina Reaper has gained scientific interest due to its bioactive compounds, including capsaicin, which exhibits significant anti-inflammatory, analgesic, antimicrobial, and potential anticancer properties.

In pharmaceutical and biomedical research, capsaicin derived from Carolina Reaper is being explored for its therapeutic potential in pain management, metabolic disorders, and inflammatory diseases such as rheumatoid arthritis. Its ability to interact with the transient receptor potential vanilloid 1 (TRPV1) and modulate pro-inflammatory pathways makes it a promising candidate for novel drug discovery.

Despite its benefits, the extreme heat of the Carolina Reaper poses risks such as gastrointestinal distress, irritation, and potential neurotoxic effects if consumed in excessive amounts. Therefore, its pharmacological applications require careful formulation and controlled dosing to ensure safety and efficacy in therapeutic contexts.

Capsaicin

Capsaicin is a naturally occurring alkaloid found in chili peppers (Capsicum spp.), primarily responsible for their characteristic pungency and heat. Capsaicin has the molecular formula $C_{18}H_{27}NO_3$ and is classified as a capsaicinoid, a group of vanilloid compounds with similar structures and biological effects. It is a hydrophobic, colorless, and crystalline

compound, allowing it to easily permeate biological membranes, which contributes to its pharmacological activity. Due to its low water solubility, capsaicin is often formulated with lipid-based carriers for therapeutic applications.

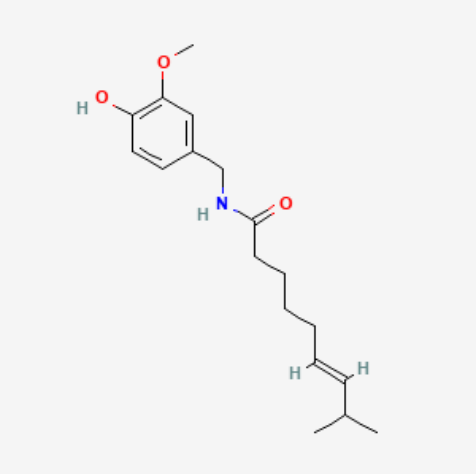

Figure 2. Chemical Structure Capsaicin

As the most active capsaicinoid, capsaicin interacts with the transient receptor potential vanilloid 1 (TRPV1), a receptor involved in pain perception, thermoregulation, and inflammatory responses. Upon activation, TRPV1 triggers a burning sensation by stimulating sensory neurons, which explains the intense heat experienced when consuming capsaicin-rich foods. Beyond its role in spiciness, capsaicin exhibits significant pharmacological properties, including analgesic, anti-inflammatory, antioxidant, antimicrobial, and metabolic-modulating effects. Due to these properties, capsaicin has been widely studied for its potential in managing chronic pain, neuropathy, obesity, and inflammatory diseases such as rheumatoid arthritis (RA).

In anti-inflammatory applications, capsaicin has been shown to inhibit the activation of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways, which play a critical role in the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α). By reducing TNF-α expression, capsaicin may help alleviate inflammation and joint damage in conditions like RA. Additionally, capsaicin has been explored in topical formulations, such as creams and patches, for localized pain relief by desensitizing nociceptors and depleting substance P, a neuropeptide involved in pain transmission.

Aside from its therapeutic potential, capsaicin has also gained interest in metabolic research due to its thermogenic effects, which contribute to increased energy expenditure and fat oxidation. Studies suggest that capsaicin consumption may aid in weight management and improve metabolic health by enhancing insulin sensitivity and reducing lipid accumulation. However, while capsaicin is generally recognized as safe, excessive consumption can lead to gastrointestinal discomfort, mucosal irritation, and potential neurotoxic effects. Therefore, controlled dosing and formulation optimization are essential for maximizing its therapeutic benefits while minimizing adverse effects. With its diverse pharmacological applications, capsaicin continues to be a subject of extensive research in the fields of pharmaceutical sciences, nutrition, and medicine, offering promising avenues for novel drug development and therapeutic interventions.

Prediction of Capsaicin from Carolina Reaper Chili (Capsicum chinense L.)

Computational Prediction of Capsaicin as an Anti-Inflammatory Agent

Capsaicin, the primary bioactive compound in Carolina Reaper (*Capsicum chinense* L.), has been widely studied for its pharmacological properties, particularly in pain relief and anti-inflammatory activities. Recent computational predictions using the PASS (Prediction of Activity Spectra for Substances) online tool from Way2Drug have provided valuable insights into capsaicin's potential as a TNF expression inhibitor, a crucial target in the treatment of rheumatoid arthritis (RA) and other chronic inflammatory diseases.

The PASS prediction results indicate a probability of activity (Pa) of 0.658 and a probability of inactivity (Pi) of 0.009 for capsaicin as a TNF expression inhibitor. These values suggest a high likelihood of capsaicin exhibiting inhibitory effects on TNF expression, as compounds with Pa > 0.5 are generally considered biologically active in the predicted function. The very low Pi value (0.009) further strengthens this prediction, as it indicates minimal probability that capsaicin would be inactive against TNF expression.

Mechanism of Action: Capsaicin as a TNF Expression Inhibitor

Tumor Necrosis Factor-alpha (TNF-α) is a pro-inflammatory cytokine involved in the pathogenesis of rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease (IBD), and other autoimmune disorders. Excessive TNF-α production leads to chronic inflammation and tissue damage, making TNF inhibition a crucial therapeutic strategy. Capsaicin has been proposed to modulate inflammatory signaling pathways, particularly:

a) NF-κB Pathway Inhibition: Capsaicin has been shown to suppress NF-κB activation, which is responsible for upregulating TNF-α and other inflammatory mediators.
b) MAPK Pathway Modulation: The mitogen-activated protein kinase (MAPK) pathway plays a role in TNF-α gene expression, and capsaicin may regulate this pathway to reduce TNF synthesis.
c) TRPV1-Mediated Immunomodulation: Capsaicin activates transient receptor potential vanilloid 1 (TRPV1), which has been linked to reduced inflammation and cytokine suppression.

These mechanisms suggest that capsaicin may function as a natural TNF inhibitor, providing a safer and potentially cost-effective alternative to conventional TNF-α inhibitors such as infliximab, etanercept, and adalimumab.

Comparison of Capsaicin with Existing TNF-α Inhibitors

To better understand the potential of capsaicin as a TNF inhibitor, we compare its predicted activity with commonly used TNF-α inhibitors:

Table 1. Comparison of Capsaicin with Existing TNF-α Inhibitors

Compound	Source	Mechanism of TNF Inhibition	Pa Value (TNF Inhibitor)	Pi Value (TNF Inhibitor)	Clinical Use
Capsaicin	*Capsicum chinense* L.	NF-κB & MAPK inhibition, TRPV1 activation	0.658	0.009	Potential natural inhibitor (preclinical)
Infliximab	Monoclonal antibody	Directly binds TNF-α	0.900+	<0.01	Rheumatoid Arthritis, Crohn's Disease
Etanercept	Fusion protein	TNF receptor decoy	0.850+	<0.01	Autoimmune diseases
Adalimumab	Monoclonal antibody	Direct TNF-α inhibition	0.920+	<0.01	Rheumatoid Arthritis, Psoriasis

From the table, capsaicin exhibits a strong predicted activity (Pa = 0.658), although it is slightly lower than monoclonal antibodies and protein-based TNF inhibitors. However, unlike biologic drugs that require injection and are costly, capsaicin has the potential to be developed as an oral or topical TNF inhibitor with fewer side effects and better patient compliance.

Potential Advantages of Capsaicin as a TNF-α Inhibitor

The development of capsaicin as a TNF-α inhibitor could provide several advantages:

a) Natural Origin: Capsaicin is derived from chili peppers and has been consumed for centuries, suggesting a good safety profile when properly formulated.
b) Lower Cost Compared to Biologic Drugs: TNF-α inhibitors like infliximab and adalimumab are expensive due to complex production processes (biologics), whereas capsaicin can be easily sourced from plants.
c) Multifunctional Activity: Besides TNF inhibition, capsaicin also possesses analgesic, antioxidant, and metabolic benefits, making it useful in managing multiple comorbid conditions in inflammatory diseases.
d) Oral and Topical Formulations: Unlike biologics that require injection or intravenous infusion, capsaicin may be developed into oral supplements, topical creams, or transdermal patches for ease of use.

Challenges and Future Research Directions

Despite the promising prediction, several challenges must be addressed before capsaicin can be clinically utilized as a TNF inhibitor:

a) Bioavailability and Metabolism: Capsaicin has limited bioavailability due to rapid metabolism in the liver, necessitating formulation improvements (e.g., nanoencapsulation, lipid-based carriers).
b) Gastrointestinal Irritation: High doses of capsaicin may cause gastric irritation and discomfort, requiring proper dose optimization.
c) Clinical Validation: While computational data suggests strong TNF inhibition, further in vitro and in vivo studies are required to confirm its effects on TNF expression and inflammatory markers.

Conclusion

The computational prediction (Pa = 0.658, Pi = 0.009) strongly supports the potential of capsaicin from Carolina Reaper as a TNF-α inhibitor, making it a viable candidate for natural anti-inflammatory therapy. Its ability to modulate inflammatory pathways, affordability, and multifunctional benefits provide a compelling case for further experimental validation and clinical development. Future studies focusing on capsaicin-based formulations, targeted delivery, and combination therapies could enhance its therapeutic efficacy, offering a novel, natural alternative for managing rheumatoid arthritis and other inflammatory diseases.

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