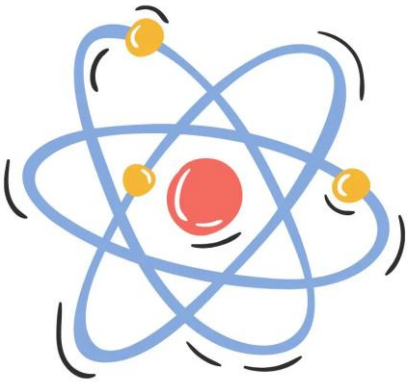

ISSN: 1672 - 6553

JOURNAL OF DYNAMICS AND CONTROL

VOLUME 10 ISSUE 07: P187-213

TARGETING ALZHEIMER'S DISEASE WITH CARNOSIC ACID: THERAPEUTIC MODULATION OF THE P2X7 RECEPTOR–NLRP3 INFLAMMASOME PATHWAY IN RAT MODELS

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JOURNAL OF DYNAMICS AND CONTROL
https://doi.org/10.71058/jodac.v10i0709

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Abstract: *Alzheimer disease is a progressive neurodegenerative disorder which illustrates cognitive loss, synaptic dysfunction and neuronal loss. There are emerging accumulating evidences that chronic neuroinflammation is at the center of the pathogenesis of the disease as well as traditional amyloid beta and tau pathology. The purinergic P2X7 receptor and NLRP3 inflammasome signalling are two of the main types of inflammatory mechanism induction to be found to be controlling the activation of microglia and long-term maintenance of inflammatory signals in the brain with Alzheimer disease. Carnosic acid is a natural phenolic diterpene compound which is mainly produced by rosemary and has received interest due to its strong antioxidant behavior as well as anti-inflammatory effects. In preclinical studies of rat models of Alzheimer disease, carnosic acid positively affects cognitive behavior, neuroinflammatory reactions, oxidative stress, and P2X7 receptor-mediated NLRP3 inflammasome activation. Carnosic acid is a multi-target therapeutic agent by blocking upstream stress and downstream inflammatory pathways. The article is a review that summarizes what is known today as to the role of P2X7 receptor and NLRP3 inflammasome in the pathogenesis of Alzheimer disease and critically assesses whether carnosic acid can act as neuroprotective in preclinical rat models. Mechanistic understandings, comparative study to other treatment therapies, difficulties in clinical translation and future research perspectives are also presented. Altogether, carnosic acid is a potentially valid candidate to include in inflammation-based therapeutic approaches in the case of Alzheimer disease.*

Keywords: *Alzheimer disease; Neuroinflammation; Carnosic acid; P2X7 receptor; NLRP3 inflammasome; Oxidative stress.*

1. Introduction

https://doi.org/10.71058/jodac.v10i0709

Alzheimer's disease (AD) is an age-related neurodegenerative disorder that happens to be the leading cause of dementia in the world. It is defined by a slow deterioration of memory, thinking and functional functions to a point where they are severely affected in the day-to-day life **[1]**. As global population is growing older, AD is becoming a rapidly spreading disease that poses a serious medical, social and economic liability. Effective disease-modifying therapies are still difficult to achieve despite decades of effective research, and new therapeutic targets and strategies are required.

1.1 Background on Alzheimer's Disease

Alzheimer is a disease that targets mostly the elderly members and it is a condition that is clinically presented by loss of memory, poor judgment, language problems and behavioral disorders [2]. Pathologically AD is characterized by the presence of extracellular amyloid beta plaques and intracellular neurofibrillary tangles that are made out of hyperphosphorylated tau protein. The result of these pathological changes is the functioning of the synaptic system, loss of nerve cells and atrophy of the brain and especially the areas of the brain that are attached to learning and memory like the hippocampus and cerebral cortex. There is growing evidence indicating that AD can be regarded as a multifactorial disorder, which includes oxidative stress, mitochondrial dysfunction/oxidative stress, neuroinflammation and/or impaired neuronal signaling.

1.2 Pathophysiology of Alzheimer's Disease

The pathophysiology of AD is incomprehensible and contains interrelated molecular and cellular processes. The process of aggregation of amyloid beta triggers a cascade of neurotoxic mechanisms, such as damage of the synapses and glial cell activation [3**]**. Tau hyperphosphorylation causes disruption on the stability of microtubules, which degenerate into neurons. In addition to these characteristic signs, chronic neuroinflammation causes the central role in the course of the disease. The release of pro-inflammatory cytokines, reactive oxygen species and inflammasome-related mediators by activated microglia and astrocytes further promotes the damage of neurons. Recent research shows that purinergic signaling and inflammasome mechanisms play a major role in long-lasting inflammatory mechanisms of AD.

Table 1: Key Pathological Features of Alzheimer's Disease

https://doi.org/10.71058/jodac.v10i0709

Sr. No.	Parameter	Description	Impact on Disease
1	Amyloid Beta	Extracellular plaque formation	Synaptic dysfunction
2	Tau Protein	Neurofibrillary tangles	Neuronal degeneration
3	Oxidative Stress	Excess ROS production	Cellular damage
4	Neuroinflammation	Microglial activation	Chronic inflammation
5	Mitochondrial Dysfunction	Energy imbalance	Neuron death

1.3 Current Therapeutic Challenges

The existing treatments of the Alzheimer disease are mainly symptomatic and do not have much or much clinical advantage [4]. Neurotransmitter systems: Approved drugs principally address the neurotransmitter systems and briefly enhance the cognitive process without halting or reversing the aspects of the disease. Numerous disease-modifying interventions of amyloid or tau have been minimally effective in clinical trials in part because of late treatment intervention, and incomplete knowledge of disease mechanisms. Also, the heterogeneity of AD pathology and translation deficiency with regard to the preclinical results and findings in humans are a significant challenge. These shortcomings highlight the necessity to investigate other mechanisms, especially those that are engaged in the early pathogenesis.

1.4 Rationale for Targeting Neuroinflammation

Neuroinflammation has become a major factor in the pathogenesis and progression of Alzheimer's disease as opposed to a secondary reaction to it. Repeated stimulation of inflammatory processes causes cell impairment, neural deterioration, and impairment of cognition. Therapeutic opportunities with the aim of halting disease progression depend on a promising treatment method that aims at major regulators of neuroinflammation [5]. Recent studies have shown that the process of inflammatory signaling can be regulated to minimize microglial overactivation, cytokine release, and neuronal inflammatory damage in the long term. Thus, one logical and possibly successful approach toward managing the Alzheimer disease is therapeutic agents that are capable of controlling neuroinflammatory processes.

2. Molecular Targets in Alzheimer's Disease

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Research in the field of Alzheimer disease has identified a number of the molecular targets that have key roles in the processes of neurodegeneration and neuroinflammation **[6]**. Of these, purinergic P2X7 receptor and NLRP3 inflammasome pathway are increasingly gaining interest because of their role in chronic inflammatory pathways in the central nervous system. Intervention of these pathways can be a prospective plan in changing the progression of a disease but not just alleviation of symptoms.

2.1 P2X7 Receptor (P2X7R)

P2X7 receptor is a receptor of the purinergic P2X receptor family and is found mostly in microglia, astrocytes and other immune related cells in the brain [7]. It is triggered by a large amount of extracellular adenosine triphosphate (ATP) that are normally released as a result of cell stress or damage. With respect to the Alzheimer disease, prolonged P2X7R activation has been associated with an exaggerated inflammatory reaction and cell damage.

2.1.1 Structure and Function

P2X7R is a ligand-gated ion channel, which consists of three identical subunits comprising of two transmembrane domains, a large extracellular loop and intracellular N- and C-terminal parts [8] . P2X7R, in contrast to other P2X receptors, contains a long C-terminal tail that helps the receptor to create the large membrane pores with the long-term use. P2X7R P2X7R is functionally capable of permitting calcium and sodium ions and potassium ion efflux into the cell to initiate downstream signaling. These ionic variations serve as the major indicators of inflammatory mediator emission and inflammasome.

2.1.2 Role in Neuroinflammation

Extracellular ATP which is released during the damage of neurons and amyloid beta plaques in the case of Alzheimer disease is an effective activator of P2X7R [9]**.** Activation of P2X7R facilitates the activation of the microglia and release of pro-inflammatory cytokines including interleukin-1 beta and tumor necrosis factor-alpha. Clinical overstimulation of this receptor also plays a role in long-lasting neuroinflammation, synaptic impairment as well as in neuronal damage. Its importance in therapy P2X7R has been demonstrated to be a therapeutic target because evidence of inhibition or genetic deletion to reduce inflammatory reactions and enhance cognitive functions has been demonstrated in animal studies.

2.2 NLRP3 Inflammasome Pathway

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One of the complexes is the NLRP3 clearing, which is a multiprotein complex that acts as a central controller of brain inner defenses. It is greatly incorporated in microglia and is important in detecting cellular stress and danger-associated molecular patterns. Inappropriate activation of NLRP3 inflammasome has been greatly implicated in the pathology of Alzheimer disease [10] .

2.2.1 Activation and Signaling

NLRP3 inflammasome is activated in a two-step process. The priming phase entails the upgrading of NLRP3 and pro-inflammatory cytokines through the transcriptional signaling pathways. Signs of cellular stress, including potassium efflux, mitochondrial dysfunction, the formation of reactive oxygen species, lysosome destruction, and others are the triggers of the activation step. The NLRP3 inflammasome once activated helps cut off pro-caspase-1 into its active form and thus produces the maturation and release of interleukin-18 and interleukin-1-beta [11]. The effect of these cytokines is the enhancement of the inflammatory responses and neuronal damage.

2.2.2 Cross-talk with P2X7R

P2X7R activation is strongly functionally interacting with NRLP3 inflammasome signaling. P2X7R activation leads to potassium release, which is a major stimulant of NLRP3 inflammasome assemblies. ATP release through amyloid beta activation of P2X7R in Alzheimer disease results in the activation of microglial NLRP3 inflammasomes [12]. This cross-talk leads to a feed-forward inflammatory loop which maintains neuroinflammation and increases the rate of disease progression. This interconnected pathway will be an important target in inhibiting excessive inflammation and loss of neuronal integrity.

Table 2: Different components of Alzheimer's Disease

Sr. No.	Component	Function	Outcome
1	P2X7 Receptor	ATP-activated ion channel	Triggers inflammation
2	Potassium Efflux	Ionic imbalance	Activates inflammasome
3	NLRP3 Inflammasome	Protein complex	Caspase-1 activation
4	IL-1β / IL-18	Cytokine release	Neuroinflammation

https://doi.org/10.71058/jodac.v10i0709

5	Microglial Activation	Immune response	Neuronal damage

3. Carnosic Acid: Biological Properties

Carnosic acid is a naturally occurring diterpene phenolic nutritionally active substance which has a great potential due to its strong antioxidant and anti-inflammatory effects. It has been used to study neurodegenerative diseases because it can penetrate the blood-brain barrier and regulate additional essential chips in oxidative stress and neuroinflammation. These are the properties that have led to the way carnosic acid can be used as a therapeutic intervention in Alzheimer disease.

3.1 Chemical Structure and Sources

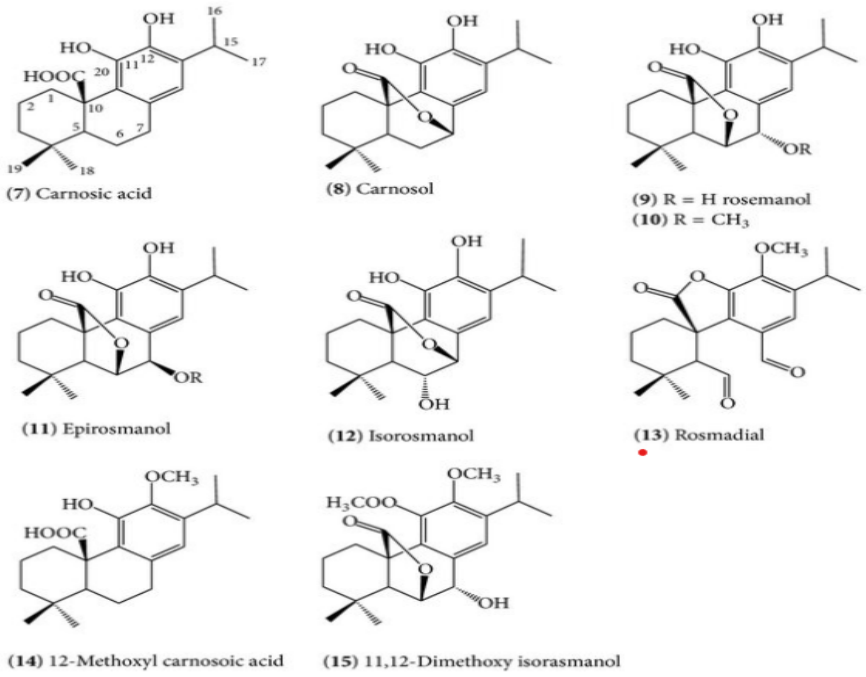

Figure 1. Chemical structure of carnosic acid, a phenolic diterpene found primarily in rosemary (Rosmarinus officinalis) with strong antioxidant activity.

Carnosic acid is a phenolic ring diterpene that is a lipophilic abietane-type diterpene which gives it a strong redox property. The carnosic acid is able to exhibit a high level of free radical scavenging attributes as a result of this chemical structure, which stabilizes reactive oxygen species [13]**.** It is also mostly present in aromatic herbs like rosemary and sage, among which

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it plays part in the natural defense system of the plants. Carnosic acid has received a lot of research attention both as a dietary supplement and a pharmacological agent because of its stability and bioactivity.

3.2 Pharmacokinetics and Bioavailability

Carnosic acid has good pharmacokinetic characteristics of central nervous system action. It is lipophilic, which makes it easy to be absorbed by the gastrointestinal tract and increases its capacity to pass the blood-brain barrier. After the absorption, carnosic acid is converted metabolically into active derivatives that still have neuroprotective potential. Preclinical evidence indicates that carnosic acid has adequate bioavailability, tissue localization, especially in the brain parts susceptible to neurodegeneration [14]. Nevertheless, dose, formulation, and metabolic stability are some of the factors that can affect its therapeutic effect.

3.3 Neuroprotective Mechanisms

Neuroprotective action of carnosic acid is achieved by a series of complementary actions on oxidative stress and inflammatory pathways. Instead of having just one molecular target it changes a network of signalling processes that all contribute to neuronal survival and functioning.

3.3.1 Antioxidant Effects

A major neuroprotective effect of carnosic acid is good antioxidant property [15]. It will act as a pro-electrophilic molecule that will only be activated in conditions of oxidative stress enabling it to selectively protect the damaged neurons. Carnosic acid augments the endogenous antioxidant defense mechanisms by elevating cytoprotective enzymes as well as decreasing lipid peroxidation. It also prevents the synaptic damage and neuronal survival during Alzheimer disease by decreasing oxidative damage to proteins, lipids and DNA.

3.3.2 Anti-inflammatory Effects

Besides having antioxidant effects, carnosic acid has potent anti-inflammatory effects. It prevents the hyperactivation of microglia and decreases secretion of non-neurostimulatory cytokines that accompany neurodegeneration. Carnosic acid was found to regulate inflammasome activation signal formation and inflammatory mediator [16]**.** By doing so, it is

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helping in reducing persistent neuroinflammatory conditions, which is a key cause of neuronal injury and mental impairment in Alzheimer disease. This means that carnosic acid can be used as a promising neuroinflammation modulator of inflammatory processes that enable it to manage neuroinflammation.

Table 3: Pharmacological Actions of Carnosic Acid

Sr. No.	Property	Mechanism	Effect
1	Antioxidant	ROS scavenging	Reduces oxidative stress
2	Anti-inflammatory	Cytokine inhibition	Decreases inflammation
3	Neuroprotective	Synaptic preservation	Improves cognition
4	Mitochondrial Support	Energy stabilization	Prevents neuron loss
5	P2X7 Modulation	Receptor regulation	Reduces inflammasome activation

4. Therapeutic Modulation by Carnosic Acid

Carnosic acid has been discussed to be a possible neuroprotective compound in that it has the capability to stimulate key inflammatory signal transduction pathways that contribute to the formation of Alzheimer lesion. Accomplishing preclinical evidence, its therapeutic ability is highly linked to the mechanism of the regulation of the purinergic signaling process and stimulation of the inflammatory reactions [17]**.** In particular, carnosic acid is involved in the activation of the P2X7 receptor and NLRP3 inflammasome, and these two are the pathways of preserving the neuroinflammation and neuronal damage.

4.1 Effects on P2X7 Receptor (P2X7R)

P2X7 receptor has a major role in mediating ATP provocation of inflammation in microglia. Chronic inflammation and neurodegeneration of Alzheimer disease are some of the contributors of unregulated stimulation of this receptor [18]. Carnosic acid was proven to have regulatory effects on P2X7R-related signaling and consequently reduces the size of inflammatory burden in experimentation models.

Towards the part of the title 7.1.1, it is possible to find the mechanisms of inhibition and regulation.

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The key effect of Carnosic acid in the control of the P2X7R activity is in the inhibition of the ATP-induced receptor activity. It prevents the high level of stimulation of P2X7R indirectly, forcefully convincing oxidative stress and eventually stabilizing cell code membranes. Furthermore, the action of the carnosic acid may be an increase or decrease in the degree of expression of the receptors in the activated microglia, and this has the effect of desensitizing the microglia to stimuli of inflammation. This regulating measure contributes to the prevention of the formation of permanent pores and the unnecessary ionic imbalance in the causes of inflammatory signaling and cell damage.

Perfusion influences downstream signalling in ACS domains with the greatest BMIs.

The P2X7R is a calcium influx and potassium efflux downstream inflammatory pathway that is inhibited by Carnosic acid by regulating the activity. This suppresses the transcription factor pro-inflammatory translation and cytokine secretion of interleukin-1B. Carnosic acid suppresses such signaling events and preserves the synapses and prevents neuronal damage associated to chronic microglial activation.

4.2 Effects on NLRP3 Inflammasome

The NLRP3 inflammasome is one of the key mediators of neuroinflammatory events in the Alzheimer disease and in the micro glial cells that are subject to exposure to amyloid beta and oxidative stress. Carnosic acid has been shown to disrupt various steps of NLRP3 inflammasome activation, and is thus a good target anti-inflammatory agent.

4.2.1 Modulation of Activation and Expression

Carnosic acid also inhibits NLRP3 inflammasome activation by lowering the upstream triggers that include oxidative stress, mitochondrial dysfunction, and ionic imbalance. It also suppresses the expression of inflammasome components and inhibits the activation of pro-caspase-1 to the active state. Consequently, release and maturation of pro-inflammatory cytokines is strongly diminished resulting into the suppression of chronic inflammatory signaling in the brain [19].

4.2.2 Interaction with Other Pathways

In addition to direct inhibiting the NLRP3 inflammasome, carnosic acid is unrelated to different signaling pathways that regulate the survival of neurons and the occurrence of inflammation.

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Its antioxidant effect suppresses reactive oxygen species otherwise likely to be the activators of inflammasomes . Also, the carnosic acid can control signaling pathways surrounding microglial polarization, and favour a switch towards a more neuroprotective phenotype. All of these effects together cause it to break the feed-forward inflammatory loop between P2X7R activation and NLRP3 inflammasome signaling and decelerate neurodegenerative processes.

5. Rat Models of Alzheimer's Disease

The animal models are important in the investigation of the pathophysiology of the Alzheimer disease and also in assessing possible therapeutic interventions. The value of rat models is especially high because it has familiar neuroanatomy and cognitive behaviour as well as it can be used in pharmacological research. Those models are useful to recreate the major characteristics of Alzheimer disease such as cognitive dysfunction, neuroinflammation, oxidative stress, and neuronal death.

5.1 Commonly Used Rodent Models

Several rat models have been developed to mimic different aspects of Alzheimer's disease pathology. These models can be broadly classified into transgenic and induced models, each offering specific advantages and limitations depending on the research objective.

5.1.1 Transgenic Models

Transgenic rat models are the genetically engineered animals that express human genes related to the disease Alzheimer including those relating to processing of amyloid precursor protein or tau pathology [20]**.** These models have the progressive cognitive impairments, amyloid deposition, and synaptic dysfunction, which is very similar to the irreversibility of the Alzheimer disease. The transgenic models are especially beneficial in research of the disease progression and the long-term treatment effects. Nevertheless, they are expensive and not always easily available to be use widely.

5.1.2 Induced AD Models

The induced rat models are made using chemical, surgical or pharmacological manipulations which are imitating the Alzheimer-like characteristics. Widely used methods are intracerebral

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injection of amyloid beta peptides, neurotoxins or chronic oxidative stress. These models are highly applicable, because they are reproducible, cost effective, and suitable in the assessment of neuroprotective compounds. Induced models are, however, useful in investigating the genetic factors in the pathological processes of Alzheimer disease, even though they do not cover the complexity of the disease.

5.2 Behavioural and Cognitive Assessment Techniques

The assessment of the learning, memory, and executive functioning through behavioural and cognitive tests is very important in Alzheimer rat models. The tests that are usually carried out are spatial memory, object recognition paradigm, and maze-based test [23]. These methods enable researchers to be able to measure cognitive impairments and test the therapeutic effectiveness of the interventions. The positive outcomes of the tasks after the treatment are frequently formulated as a gauge of neuroprotection and cognitive recovery.

5.3 Biochemical and Histopathological Endpoints

Through the biochemical and histopathological analyses, there is an important insight of the molecular and cellular alterations that are involved in the Alzheimer disease. Some typical endpoints are detection of oxidative stress signal, inflammatory cytokines and neurotransmitter concentration. The pathology of the brain can be examined by histopathology where neuron loss, gliosis, and protein aggregation in major areas of the brain like hippocampus and cortex are observed. These endpoints combined can determine correlates of behavioural outcomes and underlying biological processes, as well as be effective in proving the efficacy of therapeutic agents in preclinical trials.

6. Preclinical Evidence: Carnosic Acid in AD Rat Models

The neuroprotective benefits of carnosic acid are supported by very significant results of preclinical studies on the model of rat-based Alzheimer disease. Taken as a whole, these studies prove that it has mental activity enhancing properties, neuroinflammation suppressing properties, the regulation of important inflammatory signaling pathways, and anti-oxidative stress effects **[24]**. The results also show that it has a promising safety profile and it is suitable to conduct additional translational study.

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| **Table 4: Preclinical Evidence in Rat Models**

Sr. No.	Model Type	Intervention	Outcome
1	Amyloid-induced rats	Carnosic acid	Improved memory
2	Oxidative stress model	Treatment	Reduced ROS
3	Neuroinflammation model	Anti-inflammatory effect	Decreased cytokines
4	Behavioral tests	Maze tests	Better cognition
5	Histological analysis	Brain tissue study	Reduced neuronal loss

6.1 Cognitive Outcomes

Learning and memory performance in Alzheimer disease rat models has always been linked with carnosic acid treatment [26]. Behavioural analysis has shown accelerated spatial memory, better recognition skill and immediate decrease in latency of learning after carnosic acid intake. Such cognitive advantages are found especially in those tasks that rely on hippocampal function indicating maintenance of synaptic integrities and neuron-neuron communication. The improvements that have been observed suggest that carnosic acid does not solely cause mitigation of pathological damage, but can also promote functional recovery in cognitively impaired rats.

6.2 Neuroinflammatory Markers

Treatment with carnosic acid induces a massive decrease in neuroinflammatory markers in animal models. Research indicates that there is reduced microglia and astrocyte activation, with resultant low amounts of pro-inflammatory cytokines [25]. This prevention of inflammatory reactions indicates the capacity of the compound to inhibit the occurrence of chronic neuroinflammation that is a big cause of neuronal destruction in Alzheimer disease. Lowering of the inflammatory burden is also linked to well-being of the neuronal survival and cognition.

6.3 P2X7R/NLRP3 Expression and Activity

Molecular evidence has shown that carnosic acid mediates P2X7 receptor and NLRP3 inflammasome activity in the Alzheimer disease rat models. Down regulation in the expression of P2X7R and inhibition of inflammasome in microglial cells is connected to treatment. This

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leads to a reduction in caspase activation and a reduction in the release of inflammatory cytokines. Carnosic acid inhibits the romantic relationship between P2X7R signaling and NLRP3 inflammasome stimulation, thus preventing the self-perpetuating cycle of inflammation, which promotes disease pathogenesis.

6.4 Oxidative Stress Parameters

The oxidative stress is a major pathological characteristic of the Alzheimer disease and carnosic acid has proven to be highly effective in alleviating oxidative damage in rats. Treatment reduces the level of lipid peroxidation and reactive oxygen species and increases the level of endogenous antioxidant defense. These fallouts assist in the defense of neuronal membranes, mitochondria and DNA against oxidative damages. Indirect impact on the inflammatory signaling also supports the dual protective effect of the compound, as the oxidative stress was also decreased.

6.5 Safety and Tolerability

The preclinical trials on carnosic acid suggest that the compound is well tolerated in rat models at therapeutic levels of dosage. It has not been reported to have any major side effects on the body weight, the functioning of the organs, and overall behaviour. The safety of its use is also substantiated by histological studies that do not reveal any signs of toxicity of the main organs or the brain tissue. This positive phase safety and evidence-based neuroprotective effect suggest that carnosic acid can be utilized as an effective candidate to proceed with further application in the treatment of Alzheimer disease.

7. Mechanistic Insights

It is important to examine how carnosic acid is able to implement its neuroprotective action mechanisms so as to determine its therapeutic value in the Alzheimer disease [27]. Based on results of preclinical trials, there is an indication that carnosic acid functions by engaging several interrelated pathways, including oxidation stressfulness, neuroinflammation, and protein aggregation. Its capacity to change the way the P2X7 receptor and NLRP3 inflammasome work puts it at a focal point between the inflammatory and degenerative mechanisms of damages during diseases progression [28].

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7.1 Proposed Pathways of Action

It is biologically active in the circumstances of cellular stress and improves endogenous protective signaling pathways [29]. Carnosic acid decreases low-level reactive oxygen species and normalizes the non-sustainability of the mitochondrion, thereby restricting the occurrence of stress signals at an early stage and causing inflammatory reactions [30]. This regulates P2X7 receptor activation via ATP in an indirect fashion which inhibits excessive ionic imbalance and inflammasome assembly [31]. All these activities will help lower the microglial activation, maintain the functions of the synapses and enhance the survival of the neurons.

7.2 Interaction with Amyloid and Tau Pathology

Accumulation of amyloid betas and hyperphosphorylation of tau is the main pathological process in the pathogenesis of Alzheimer disease, which is strongly associated with neuroinflammatory processes [32] .It has already been demonstrated that Carnosic acid can alleviate amyloid beta-impaired toxicity through alleviation of oxidative stress and release of inflammatory mediators [33]. It has reduced the inflammatory environment of promoting amyloid aggregation and tau pathology by inhibiting microglial overactivation. Moreover, less oxidative damage contributes to the preservation of cytoskeleton which has an indirect effect on tau stability [34]. The possible effect of these findings is that the amyloid, and tau-related pathology could be slowed down by the carnosic acid, using inflammation-depending effects [35].

7.3 Integration of P2X7R/NLRP3 Modulation with AD Pathogenesis

P2X7 receptor activation and NLRP3 inflammasome signalling interaction are one of the main perpetrators of chronic neuroinflammation in the Alzheimer disease [36]. Continuous stimulation of this axis causes long-term cytokine release, malfunction of their synapses, and the death of neurons. The effect of Carnosic acid on this pathological cycle is the inhibition of inflammasome activation downstream through ATP-mediated stimulation of P2X7R and the inhibition of P2X7R stimulation of inflammasomes. This combined modulation is in line with the existing knowledge regarding the Alzheimer disease as an inflammatory driven neurodegenerative disease. Carnosic acid provides a mechanistically adequate response to alter

https://doi.org/10.71058/jodac.v10i0709

disease progression as opposed to just symptom control by inhibiting this central inflammatory pathway.

8. Comparative Analysis with Other Therapeutics

Increasing literature has delved into natural compounds as well as synthetic compounds as the possible therapeutic approaches in Alzheimer disease. Most agents focus on the specific pathological characteristics, whereas carnosic acid can be unique as it acts as a multi-target, especially by regulating oxidative stress and neuroinflammation by the P2X7R-NLRP3 axis. The comparison of carnosic acid against other treatment methods will serve to aid in understanding its advantages and constraints compared to the latter.

8.1 Natural Compounds

A number of naturally occurring compounds have shown neuroprotective efficacies in preclinical models of the Alzheimer disease, mainly via antioxidant and anti-inflammatory reactions. Compounds such as Polyphenols, the flavonoids and terpenoids have been demonstrated to decrease oxidative stress, reduce the production of inflammatory cytokines and enhance cognitive functionality in animals. Nevertheless, the poor bioavailability and low penetration to the brain and/or narrow mechanistic action are common among many natural compounds.

Carnosic acid, when compared to these agents, has desirable pharmacokinetic qualities and has a wider mechanism of action. Selective targeting of damaged neuronal environment is possible because of its capacity to be induced in response to oxidative stress. Notably, carnosic acid does not only suppress overall inflammation but also regulates certain inflammatory signaling, on the one hand, purinergic signaling and, on the other hand, inflammasome activation. This is a specific but multi-level action which offers an opportunity compared to compounds that mostly behave as nonspecific antioxidants.

8.2 Synthetic P2X7R/NLRP3 Modulators

P2X7 receptor or NLRP3 inflammasome synthetic inhibitors have demonstrated encouragingly promising results in the reduction of neuroinflammation in investigative models. These agents

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can be typically highly specific and with high levels of inhibition on their targets. Their clinical translation has however been curtailed by issues to do with toxicity, immune suppression and off target effects. Moreover [37], it is possible that selective inhibition will not be effective enough to deal with the multifactorial and complicated case of Alzheimer disease.

On the contrary, carnosic acid is a better-balanced therapeutic profile. Instead of full antagonism of P2X7R or NLRP3 pathways, it suppresses these pathways though indirect means disintegrating the levels of upstream stressors such as oxidative damage and ATP release. Such form of regulation could avoid overactivation of important immune processes at the same time maintaining pathological immune functions [38]. Carnosic acid is therefore an alternative/complementary approach to synthetic modulators especially in chronic conditions of neurodegeneration over the long-term [39].

Table 5: Comparison of Natural vs Synthetic Modulators

Sr. No.	Type	Example	Advantages	Limitations
1	Synthetic	P2X7 antagonists	Target-specific	Toxicity
2	Natural	Carnosic acid	Multi-target	Variable bioavailability
3	Natural	Curcumin	Anti-inflammatory	Low absorption
4	Synthetic	NLRP3 inhibitors	Strong effect	Side effects
5	Natural	Polyphenols	Safe	Requires high dose

9. Challenges and Limitations

Although preclinical results were encouraging, there are a number of issues that should be overcome before carnosic acid can be regarded as a promising treatment of Alzheimer disease [40]. Such constraints point to the fact that the translation of the results of experiments into clinical interventions may be complicated, and it is essential to take the existing evidence into consideration.

9.1 Translational Barriers from Rodents to Humans

Lack of rodent model translational value is one of the major problems with the Alzheimer disease research [41]. Although rat models recapitulate some of the most important pathological and behavioural characteristics of the disease in humans, the rat models lack any

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sufficient description of the complexity and heterogeneity of the human form of Alzheimer disease. It is possible that differences in brain architecture, lifespan, immune reaction and disease progression can result in discrepancies between preclinical results and clinical efficacy. Consequently, effects of treatment on rats may not directly be applicable on human patients [42]. The safety will take time under long-term conditions, the pharmacodynamics, and the site of the disease are also yet to be established through human trials.

9.2 Dosing, Delivery, and Bioavailability Issues

Even though carnosic acid has shown good pharmacokinetic conditions in preclinical trials, there are still certain challenges in the optimization of dosing and delivery. Oral bioavailability may change according to formulation, stability in metabolism and inter-individual variability. More investigation is needed to have therapeutically effective levels of the drug in the human brain that are not systemic and can cause adverse side effects. Also, chronic regimen might cause the problem of accumulation or interaction with metabolism. Further drug delivery methods and drug formulations could be required to improve targeting of the brain and make them more clinical.

9.3 Model-Specific Limitations

Every rat model of Alzheimer disease has its inherent limitations which apply in the interpretation of data [43]. Transgenic models usually concentrate on certain genetic mutations and they may not be sporadic Alzheimer which is prevalent in humans [44]. Although induced models are good in the study of isolated pathological phenotypes, including neuroinflammation or oxidative stress, disease mechanisms are potentially simplified. Such model-specific restrictions are able to influence the study of the effectiveness of carnosic acid and restrict the applicability of the results. Thus, they should be confirmed in a number of models to reinforce the belief in therapeutic potential.

10. Future Directions

The proposed therapeutic candidate of carnosic acid to treat Alzheimer disease needs a balanced approach to transition the preclinical evidence to the clinical practice [45]. The

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next step in the research effort is to validate its mechanisms and optimize delivery in future studies and find quantifiable signs of therapy response[46]. Such initiatives will be critical in revealing their contribution to disease replacement, as well as its clinical management.

10.1 Clinical Translation Prospects

The positive preclinical data of carnosic acid is the reason, why the paper warrants further exploration in the clinical areas. Clinical trials at an early stage are required to assess the safety, tolerability, pharmacokinetic and optimality of dosing in humans. Patients stratified according to the disease stage and inflammatory condition can enhance the results of the trials because it seems that neuroinflammation is more apparent in the early or middle stages of the Alzheimer disease [47]. Moreover, longitudinal studies shall be of importance to evaluate long-term outcomes and disease-modifying benefits, and not short-term symptomatic enhancement.

10.2 Novel Combination Therapies

Since the Alzheimer disease is multifactorial, combination therapy is a natural continuation [48]. Carnosic acid can be especially useful as a combination with an agent against amyloid or tau pathology, or synaptic dysfunction or metabolic impairment [49]. Its anti-inflammatory and antioxidant effects may be used in addition to current or new treatment to provide a neuroprotective milieu to boost the overall effectiveness of [50]. Future research ought to consider both synergies, optimal dose regimens, and possible adverse effect lowering when carnosic acid is implemented as a multi-target pharmacotherapy.

10.3 Biomarker Development

Stable biomarkers are important because they should be used to determine the response to therapy and direct clinical translation [51]. Neuroinflammatory, oxidative stress, purinergic biomarkers are of possibly special value in order to track the impact of carnosic acid [52]. It

https://doi.org/10.71058/jodac.v10i0709

may be useful to develop changes in inflammatory mediators, imaging evidence of microglial activation, or molecular evidence of P2X7R and NLRP3 activity to select patients and measure their outcomes [53]. The inclusion of biomarker-based models in future research will increase the accuracy and understanding of clinical trials.

11. Conclusions

The Alzheimer disease is still a big challenge that has not been adequately addressed because it is complex and multifactorial. Increasing evidence demonstrates the importance of chronic neuroinflammation in the progression of the disease, which makes inflammatory signalling pathways the key therapy. P2X7 receptor and NLRP3 inflammasome modulation is a logical, desirable intervention in this case.

Carnosic acid has become an interesting neuroprotective agent with the potential to mediate the oxidative stresses as well as inflammatory mechanisms in preclinical models of Alzheimer disease. The rat literature supports these claims showing carnosic acid enhances cognitive functions, lowers neuroinflammatory biomarkers, abates oxidative damage and like all the major biomarkers of the P2X7R-NLRP3 signaling axis. It has a multi-target mode of action, which covers multiple pathological processes related, as opposed to a single disease mechanism-based therapy.

These positive results notwithstanding, there are still numerous issues associated with conversion of preclinical success into clinical practice. The variability between the animal models and human disease and those associated with dosing and delivery must be attended to. However, the positive safety and mechanistic applicability of carnosic acid justify further research.

Altogether, carnosic acid is a prospective solution to the creation of inflammatory-targeted therapeutic approaches to Alzheimer disease. Bringing together of clinical trials, combination therapies, biomarker-driven study will be the key towards the totally defining its potential application in altering course of the disease and enhancing patient outcomes.

Abbreviations

AD – Alzheimer’s Disease

https://doi.org/10.71058/jodac.v10i0709

Aβ – Amyloid Beta

ATP – Adenosine Triphosphate

BBB – Blood–Brain Barrier

CA – Carnosic Acid

CNS – Central Nervous System

IL-1β – Interleukin-1 Beta

IL-18 – Interleukin-18

NLRP3 - NOD-Like Receptor Family Pyrin Domain Containing 3

P2X7R – P2X7 Receptor

ROS – Reactive Oxygen Species

TNF- alpha- Tumor Necrosis Factor Alpha.

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