

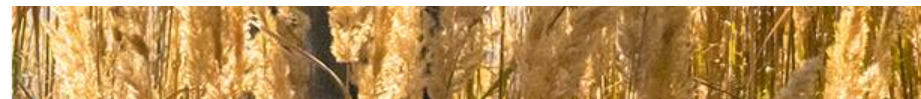
Moderate drinking and the ageing brain; a potential fit for smart ageing? Effects of the consumption of non-alcoholic beer

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Beer and Health

THE 8TH EUROPEAN
BEER AND HEALTH SYMPOSIUM

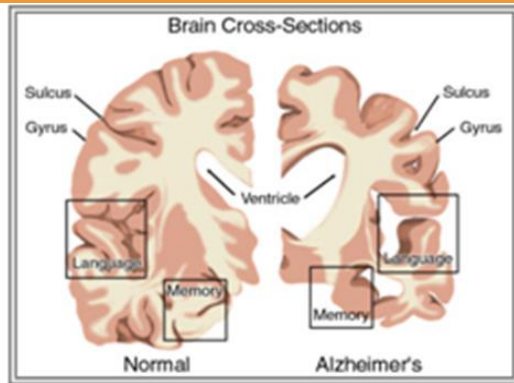


ALZHEIMER'S DISEASE

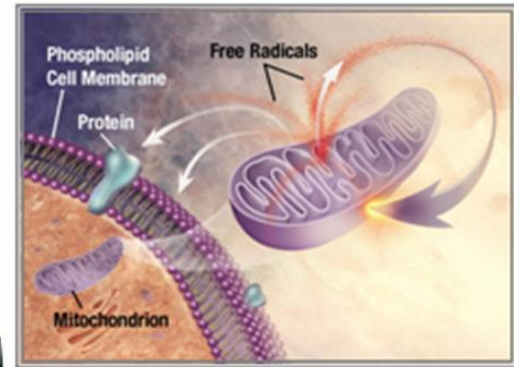
- ❁ The most common form of dementia in the elderly
- ❁ There is no clear consensus on the preventive measures available to prevent the development of this disease



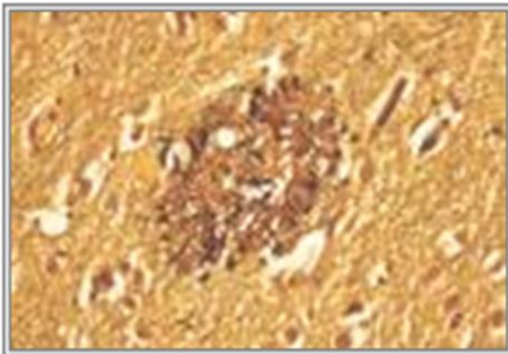
ALZHEIMER'S DISEASE



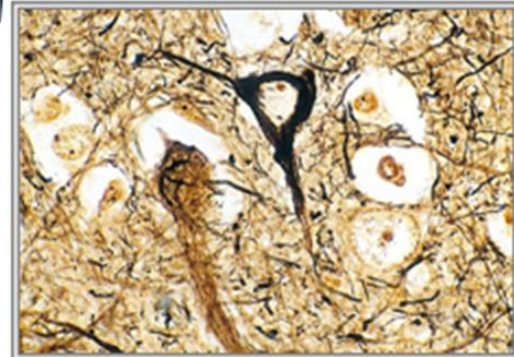
Pérdida de neuronas colinérgicas



Estrés oxidativo



Placas de beta-amiloide



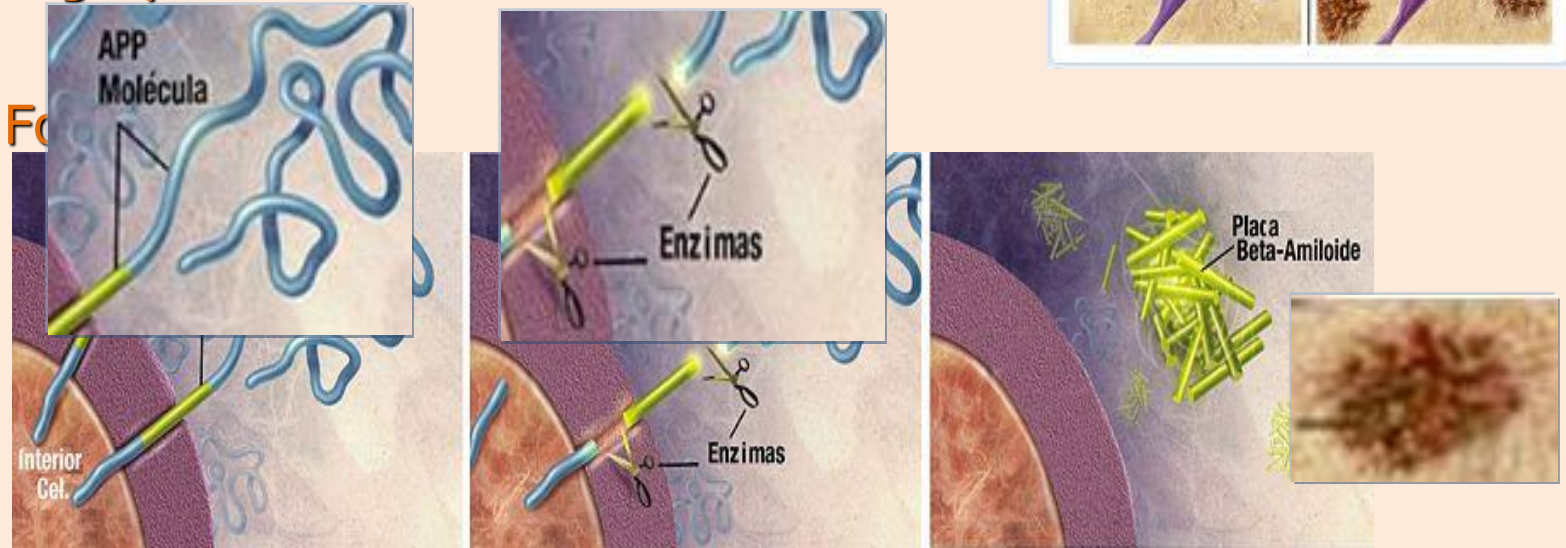
**Ovillos neurofibrilares
(Tau hiperfosforilada)**



ALZHEIMER'S DISEASE

AMYLOID HYPOTHESIS:

Accumulation of amyloid- β peptides
Highly toxic

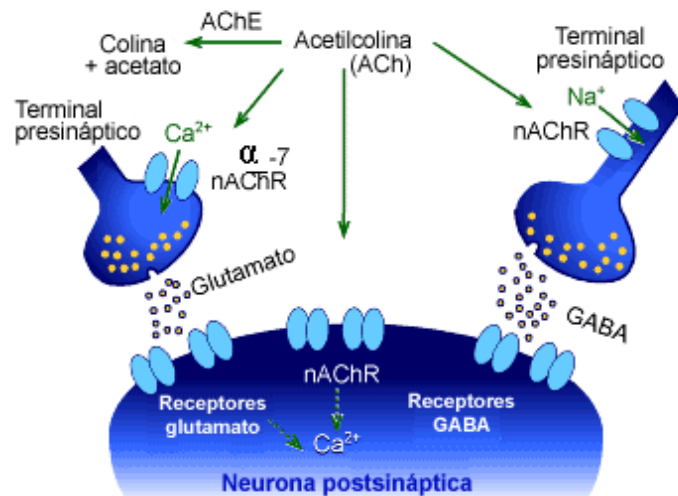


ALZHEIMER'S DISEASE

CHOLINERGIC HYPOTHESIS

Correlation between cholinergic deficiency and loss of patients' cognitive abilities

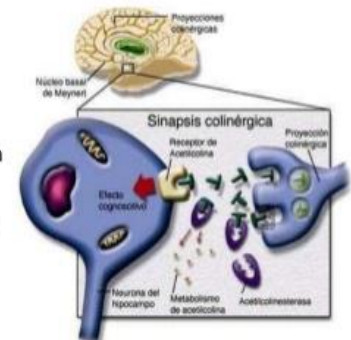
Diagrama de un receptor nicotínico cerebral (nAChR)



INHIBIDORES DE LA COLINESTERASA CEREBRAL

Mejoran el **rendimiento cognitivo**, los **defectos funcionales** y los trastornos de la **conducta**. Indicados en la fase **leve-moderada**.

- **Tacrina**: en desuso por RAM
- **Donezepilo**: inhibidor de la acetilcolinesterasa
- **Rivastigmina**: inhibidor de la acetilcolinesterasa y de la butiril-colinesterasa
- **Galantamina**: inhibidor de la acetilcolinesterasa y modulador de receptores nicotínicos de la Ach



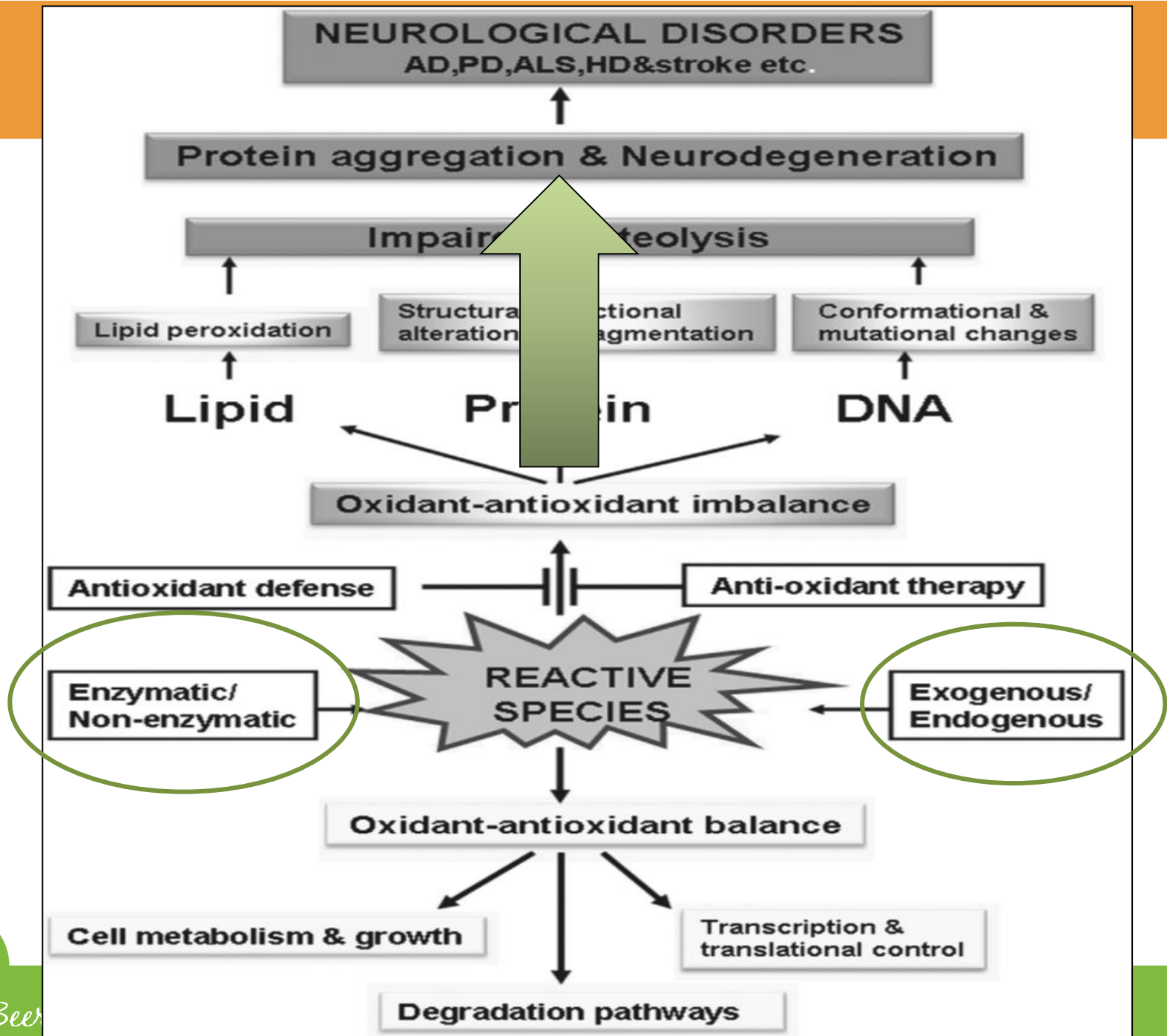
ALZHEIMER'S DISEASE

FREE RADICAL HYPOTHESIS

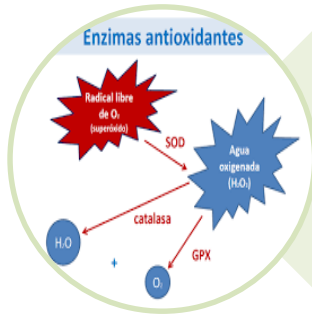


Brain: limited antioxidant capacity



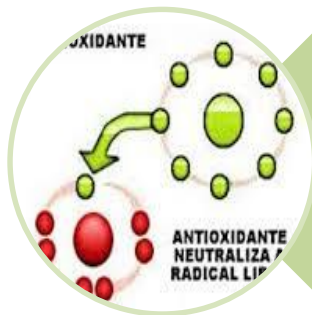


ALZHEIMER'S DISEASE



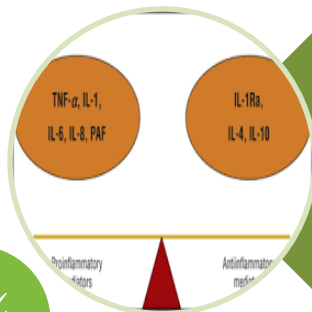
ANTIOXIDANT ENZYMES

Superoxide dismutase
Catalase
Glutathione peroxidase



NON-ENZYMATIC ANTIOXIDANT AGENTS

Albumin, bilirubin
Uric acid, lycopene
Vitamin A, vitamin C, vitamin E



NEUROINFLAMMATORY FACTORS

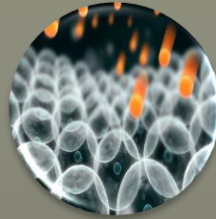
Immunoproteins and cytokines: generated by neurons, astrocytes and microglia

ALZHEIMER'S DISEASE

New development strategies



Antioxidant drugs



Free radical uptake drugs



Neuronal anti-inflammatory drugs



ALUMINIUM

Neurotoxicity mechanisms

Cell damage

Free radicals

Oxidative stress

Biphasic action

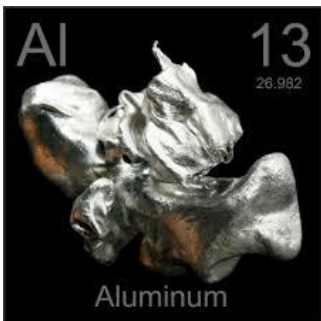
Pro-oxidant (Fe)

Antioxidant enzyme inhibition

ROS: peroxidation

Cholinergic system

Increased AchE activity



ALZHEIMER'S DISEASE

Protective factors

IMPACT ON THE DISEASE BY



BEER

One of the most consumed alcoholic beverages worldwide

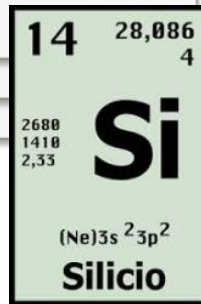


Rich in nutrients

- Carbohydrates, amino acids, minerals, vitamins, polyphenols
- Different in vitro biological activities: antioxidant, anti-carcinogenic, anti-inflammatory, estrogenic and antiviral

Link with AD: intake could provide an alternative for preventing this pathology

- Silicon: one of the main sources of this element in the diet
- Antioxidant substances contained in hop

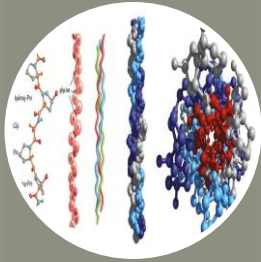


SILICON

Possible therapeutic effects



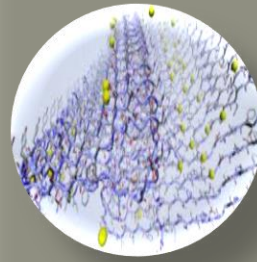
Maintaining the structural integrity of the nails, hair and skin



Global collagen synthesis



Mineralisation and bone health



Reducing the accumulation of metals in Alzheimer's disease



Immune system health



Reducing the risk of atherosclerosis



SILICON

Orthosilicic acid-Aluminium interaction

The simultaneous administration of silicic acid and Al reduces the absorption of Al and increases its clearance from the body

Formation of highly insoluble and inabsorbable hydroxialuminosilicates

Clinical human trials:
administration of mineral water rich in silicic acid

Increased urinary excretion of aluminium

Significant reduction in the aluminium body burden



Possible use of silicic acid as a long-term non-invasive therapy to reduce the body burden of Al, decreasing the possibility of suffering Alzheimer's disease

Exley et al., 2002; Jurkič et al., 2013



Earlier works



SILICON AND BIOAVAILABILITY

Hypothesis

Si could limit the bioavailability of Al by decreasing absorption in the gastrointestinal tract

Objective

To determine the **effect** of **beer** consumption on the **bioavailability** of **Al**, and the possible link in preventing its neurotoxicity



SILICON AND BIOAVAILABILITY

Acute study: 3 days

- **Types:** Alcoholic and non-alcoholic beer
- **Dose:** Moderate-low (0.5 l/day)
Moderate-high (1 l/day)

Chronic study: 3 months

- 🍺 Type and dose of the most effective beer

Work plan

- 🐁 NMRI male mice
- 🐁 Urine, faeces and brain collection
- 🐁 Intracardiac blood extraction
- 🐁 Wet mineralisation of organic matter
 - Determination of Al → ICP-MS
 - Determination of Si → ICP-OES

Role of beer as a possible protective factor in preventing Alzheimer's disease

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Received 13 December 2005; accepted 20 June 2007

Abstract

Aluminium (Al), a neurotoxin, has lately been implicated as one of the possible causal factors contributing to Alzheimer's disease. Because silicon (Si) intake can affect the bioavailability of aluminium, the object of the present study was to assess whether moderate beer consumption might, as a source of dietary Si, affect the toxicokinetics of Al and thereby limit that element's neurotoxicity.



Intake of alcoholic beer, due to its silicic acid content, interferes with Al absorption and excretion kinetics by decreasing its bioavailability

González-Muñoz et al., 2007

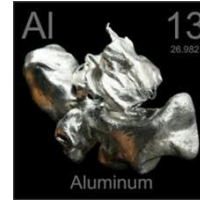
CHRONIC STUDY: EXPERIMENTAL PROTOCOL

Negative control



**Deionised
water**

Positive control



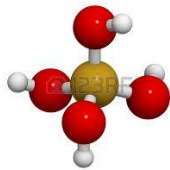
**450 mg/L
 $\text{Al}(\text{NO}_3)_3$**

Positive group with alcoholic beer



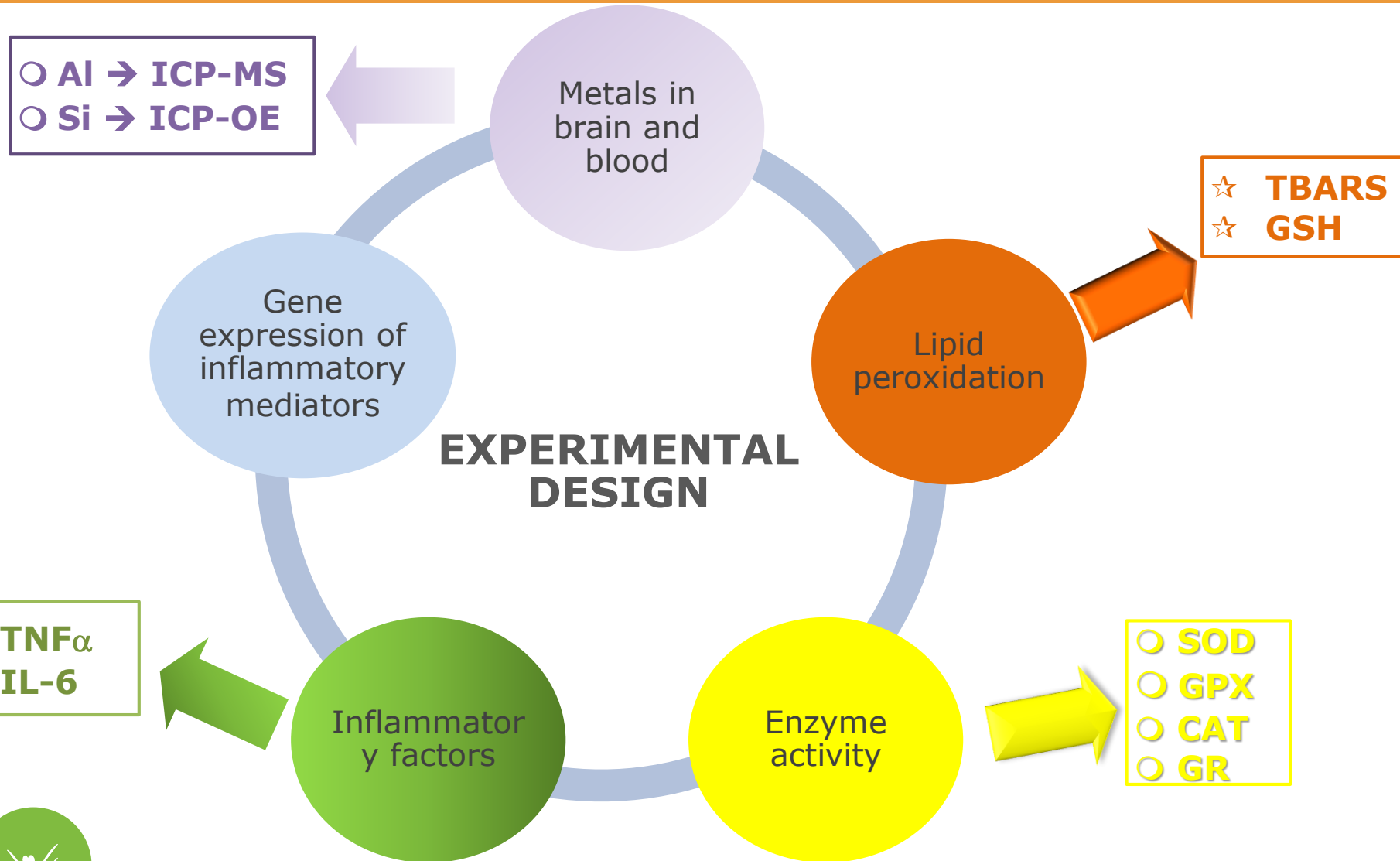
**450 mg/L
 $\text{Al}(\text{NO}_3)_3$ + Beer**

Positive group with silicic acid



**450 mg/L
 $\text{Al}(\text{NO}_3)_3$ + 50 mg/L
of silicic acid**

CHRONIC STUDY: EXPERIMENTAL PROTOCOL



Beer consumption reduces cerebral oxidation caused by aluminum toxicity by normalizing gene expression of tumor necrotic factor alpha and several antioxidant enzymes

M.J. Gonzalez-Muñoz^a, I. Meseguer^a, M.I. Sanchez-Reus^b, A. Schultz^c, R. Olivero^c,
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^a Departamento de Nutrición, Bromatología y Toxicología, Facultad de Farmacia, Universidad de Alcalá, Madrid, Spain

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^c Departamento de Nutrición, Facultad de Farmacia, Universidad Complutense, Madrid, Spain



Si was able to block the proinflammatory and prooxidant actions induced by Al

González-Muñoz et al., 2008



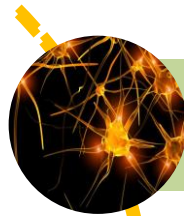
Hypothesis to use beer as an effective prophylactic measure to prevent the development of AD



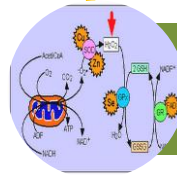
However, its alcohol content, although not very high, would limit its recommendation to the entire population

EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES

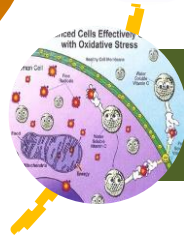
Possible effect of non-alcoholic beer and its ingredients (Si and hop)



Neuronal toxicity



Pro-inflammatory effects



Pro-oxidant effects



EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES

Specific objectives

To evaluate the degree of cerebral oxidative stress produced by AI and determine the effect of non-alcoholic beer and its components

- Glutathione titration
- Levels of lipid peroxidation (TBARS)

To quantitatively evaluate the effect of non-alcoholic beer and its components:

- Enzyme activity, levels and gene expression of antioxidant defence mechanisms (SOD, CAT, GPx and GR) in the brain of rats intoxicated with AI

To determine the possible involvement of inflammatory mediators

- TNF α and IL1 β in the brain tissue of rats intoxicated with AI

To evaluate the neurological progression of animals that have received the different treatments

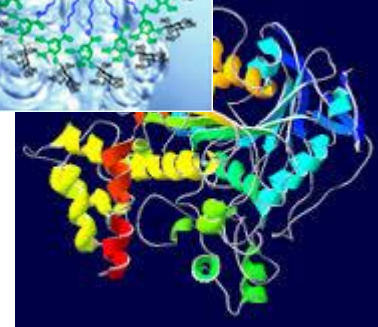
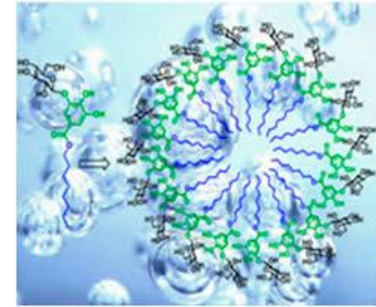
- Specific behavioural tests: study of the neurological damage induced by AI and determination of the preventive capacity of beer and its components to alleviate these problems

EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES

In vitro tests



Antioxidant
capacity
FRAP
DPPH
ORAC

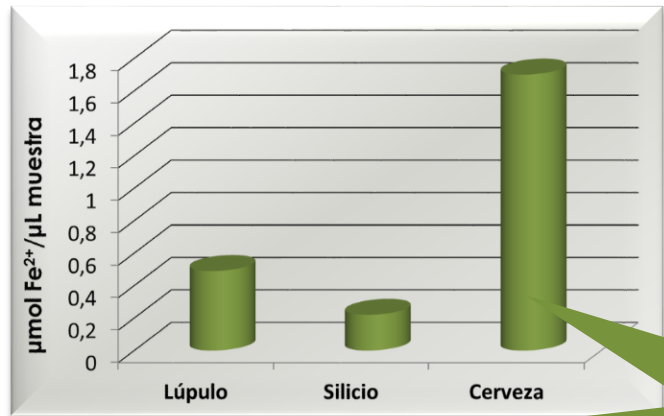


Polyphenol
content in beer
and hop

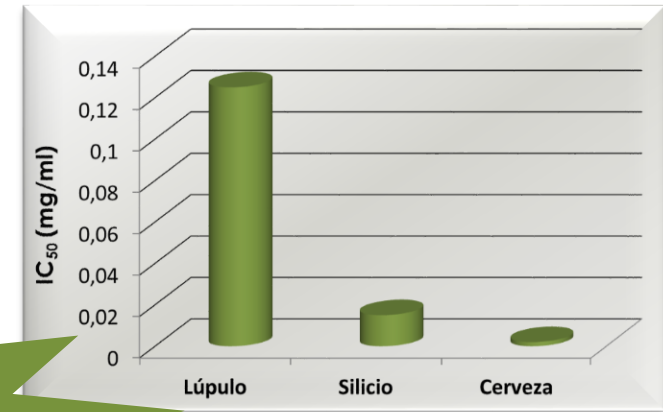
Acetylcholinesterase
activity



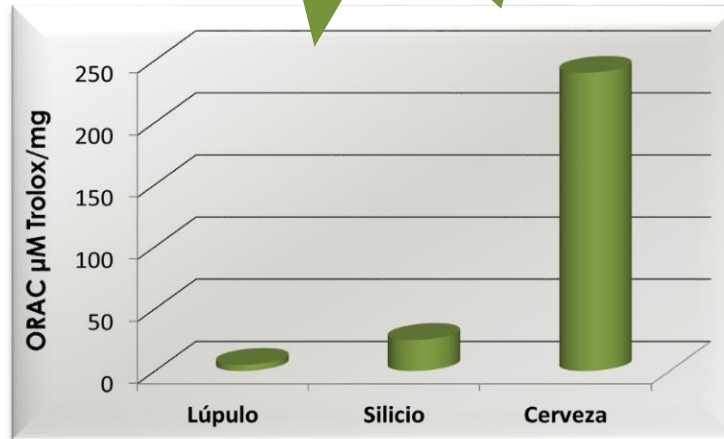
EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES



FRAP: Fe uptake



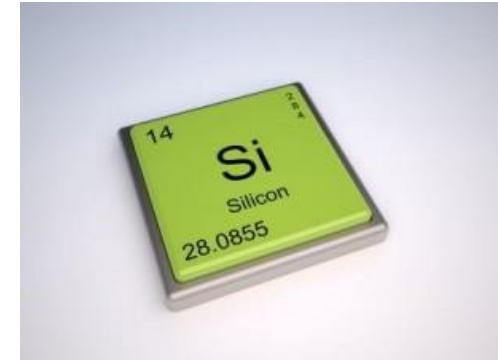
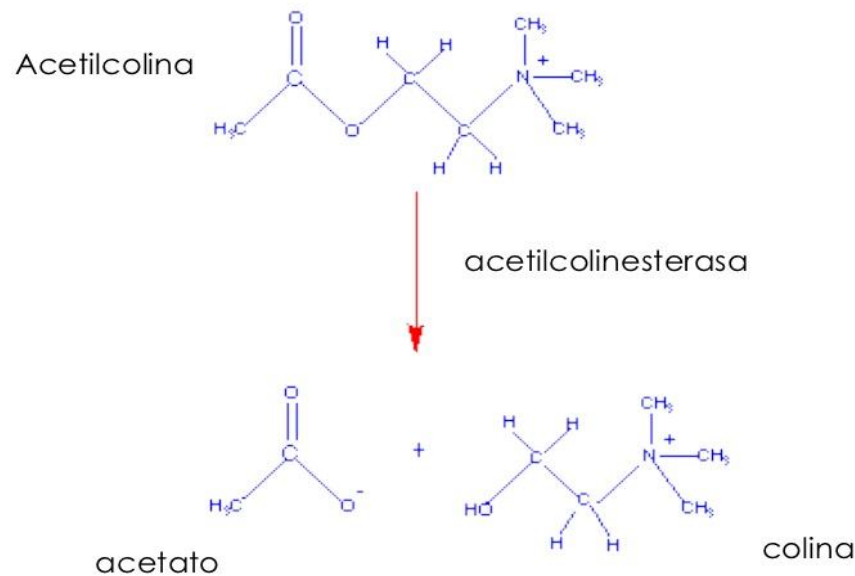
DPPH: DPPH radical uptake



ORAC: free radical uptake



EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES



Si demonstrated a capacity to inhibit AChE activity *in vitro*

Possible new mechanism to reverse Al neurotoxicity

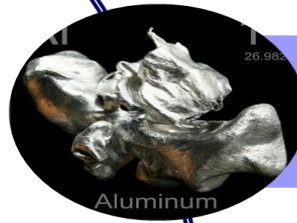
EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES



In vivo tests



Negative control:
Desionized water



Positive control:
450 $\mu\text{g/kg/day}$ $\text{Al}(\text{NO}_3)_3$



Al + non-alcoholic beer:
450 $\mu\text{g/kg/day}$ $\text{Al}(\text{NO}_3)_3$
Beer



Aluminium + hop:
450 $\mu\text{g/kg/day}$ $\text{Al}(\text{NO}_3)_3$
0.4 mg hop extract



Aluminium + silicon:
450 $\mu\text{g/kg/day}$ $\text{Al}(\text{NO}_3)_3$
50 mg/L silicic acid



EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES

In vivo tests: Behavioural tests

Hole
board

Forced
swimming

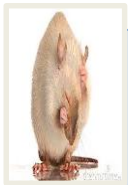


EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES

In vivo tests: Behavioural tests



Variables indicative of motor activity, exploration and emotionality are recorded



Grooming



Defecation index



Immobility



Curiosity



Rearing



Beer and Health

EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES

In vivo tests: Behavioural tests



Forced
swimming



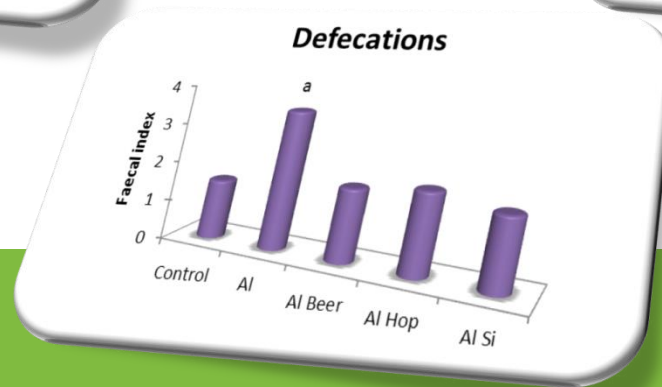
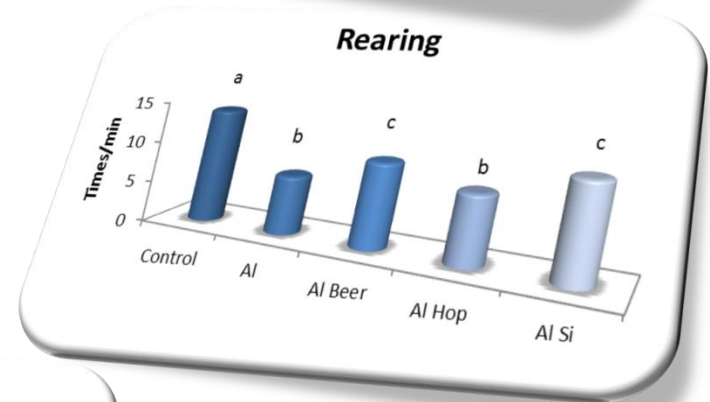
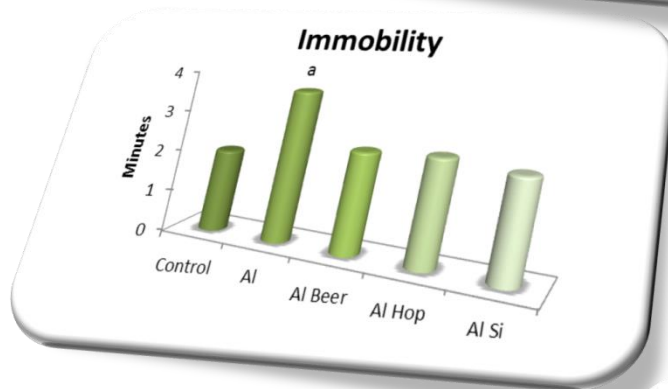
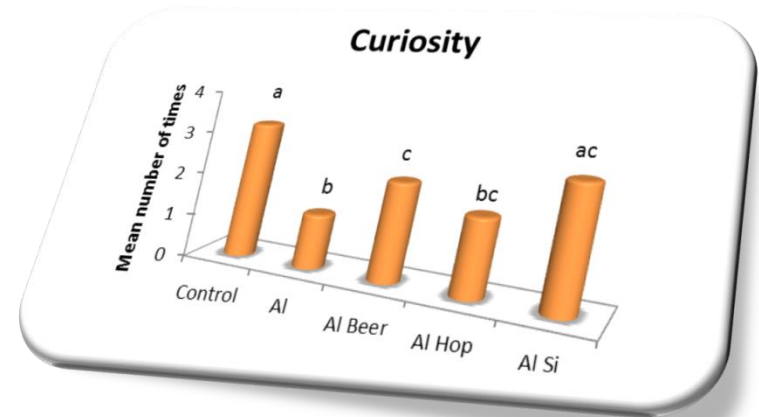
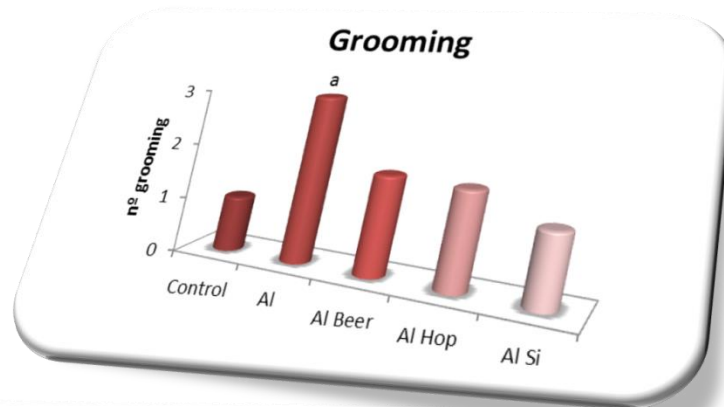
Allows the capacity for
learning and memory to be
evaluated

Swimming time and
immobility time is recorded

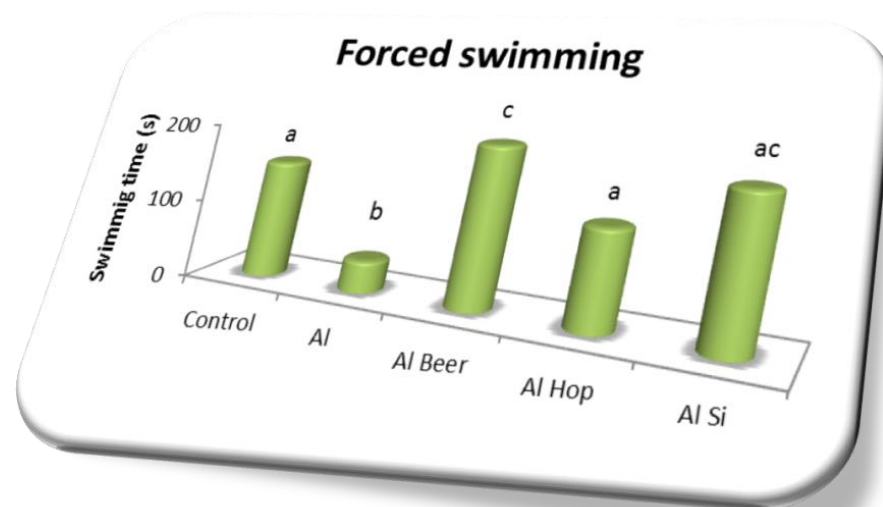
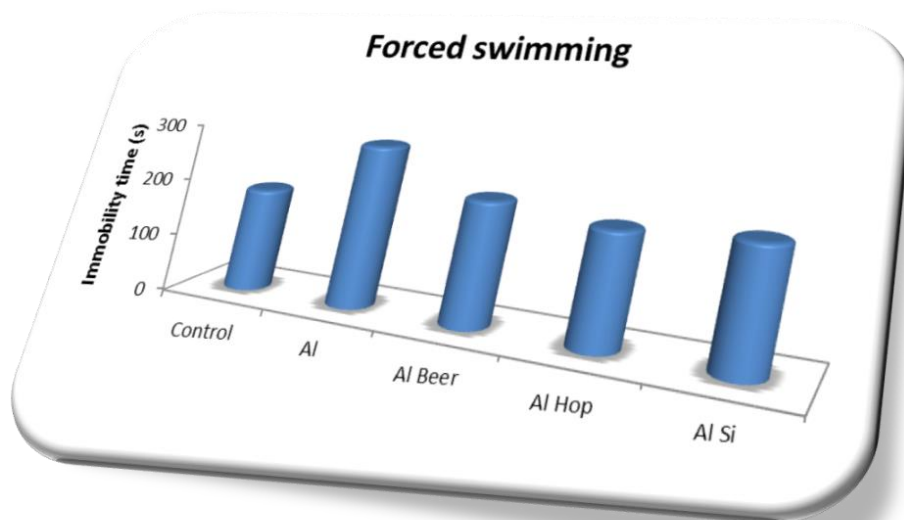


HOLE BOARD TEST

Non-alcoholic beer, Si and hops alleviate the behavioral changes produced by Al



FORCED SWIMMING TEST



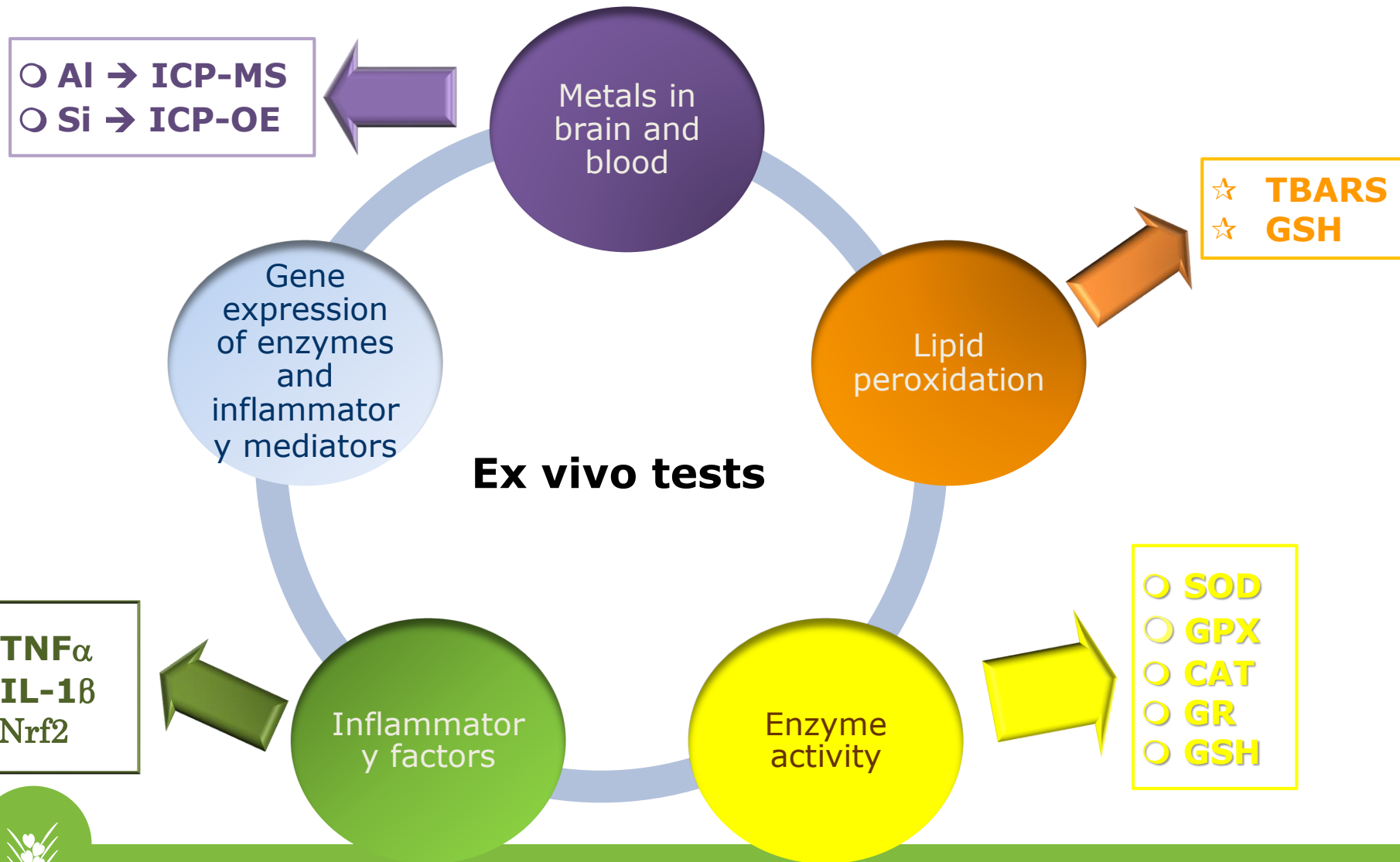
AI increase the learning time of animals →
↑acetylcholinesterase activity

Beer and Si neutralize this effect, obtaining better results than the control animals

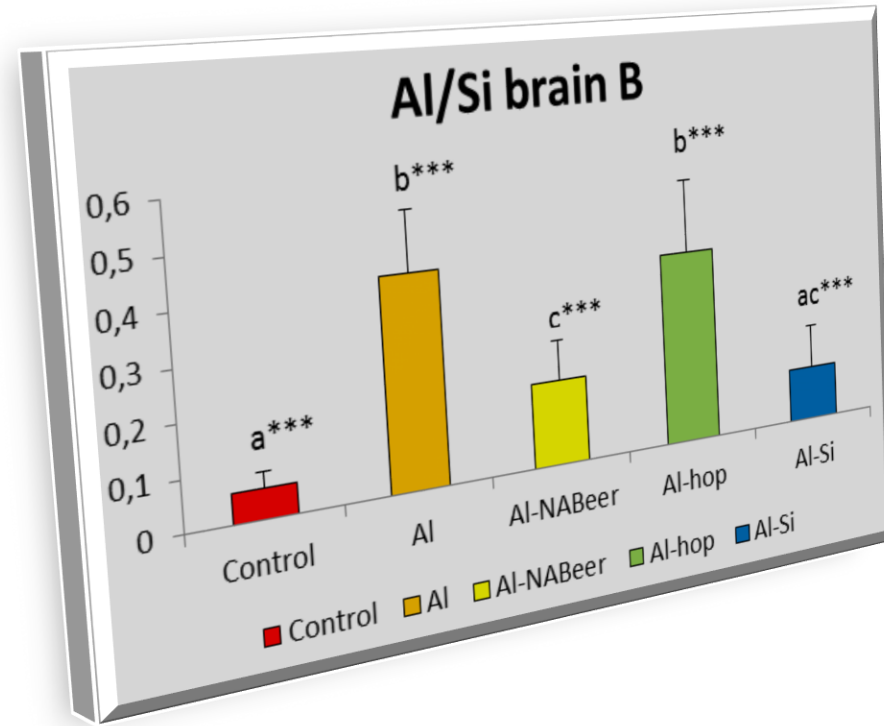
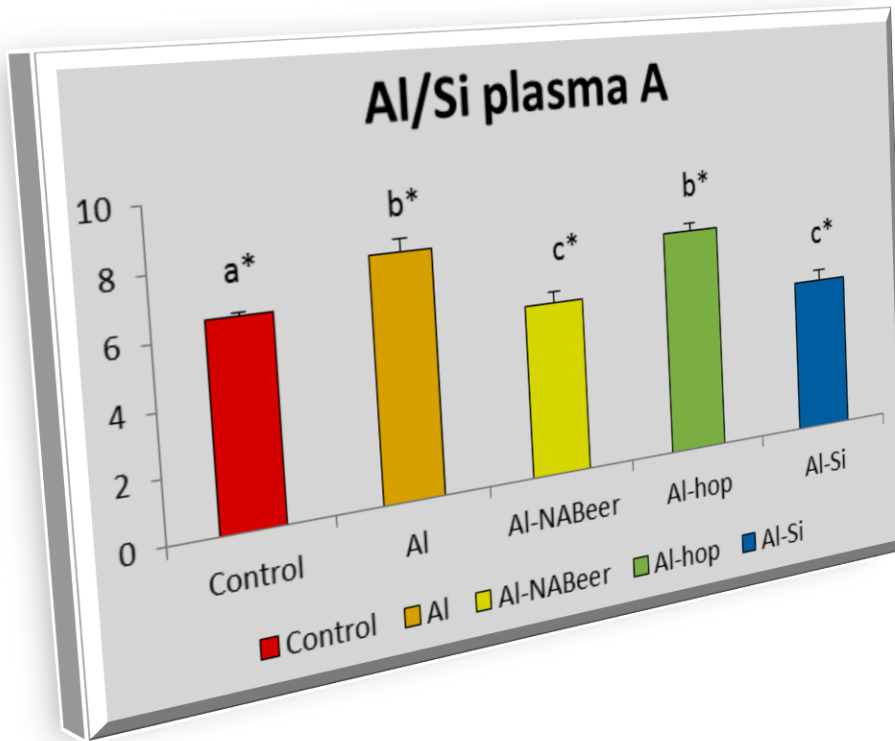
The acetylcholinesterase inhibitory capacity of Si



EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES



Al and Si levels in plasma and brain



**Hop has no effect
at this level:
mechanism of
action different
from chelation**

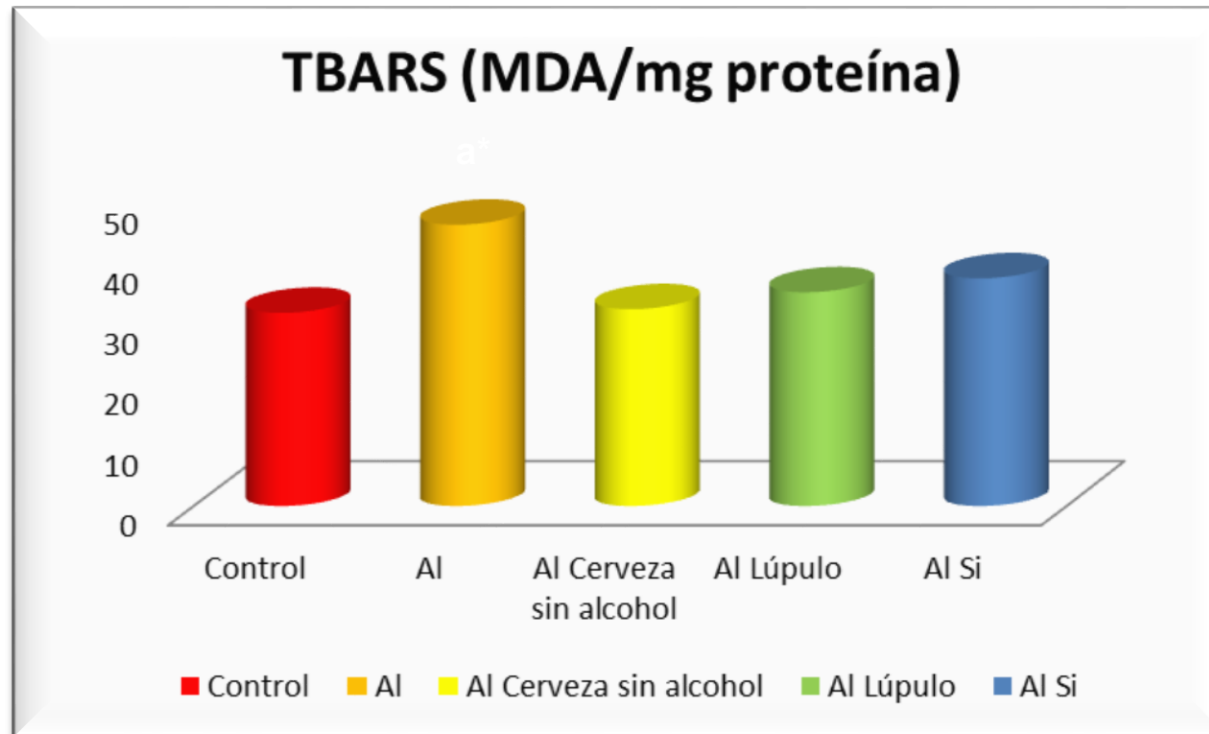


**Non-alcoholic
beer and silicic
acid reduce the
accumulation of
Al in the brain**



**Possible use as a
long-term non-
invasive therapy
to reduce Al in
patients with AD**

Effect of non-alcoholic beer and its components on lipid peroxidation: TBARS, glutathione and redox index



Pattern of oxidative stress induced by Al

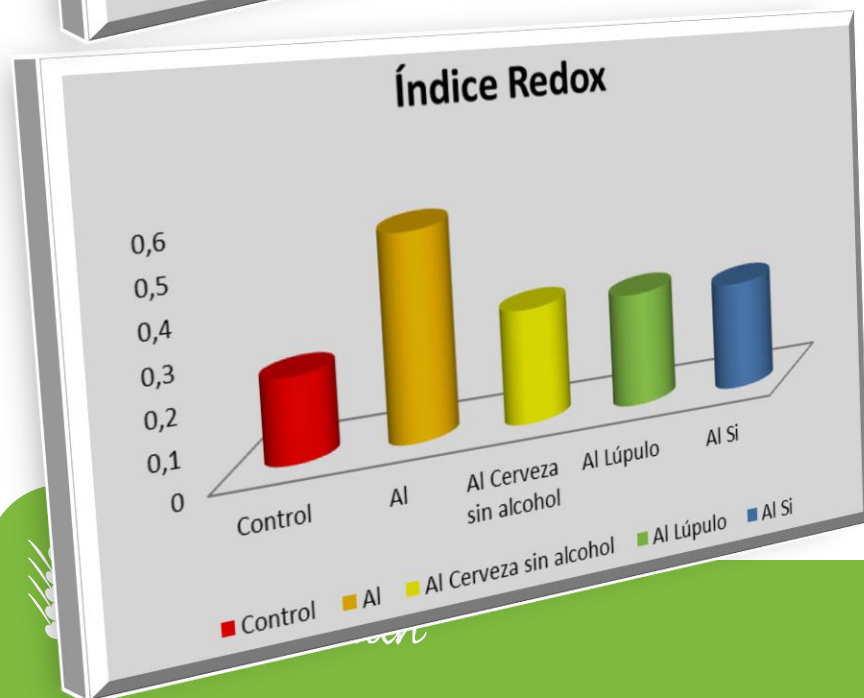
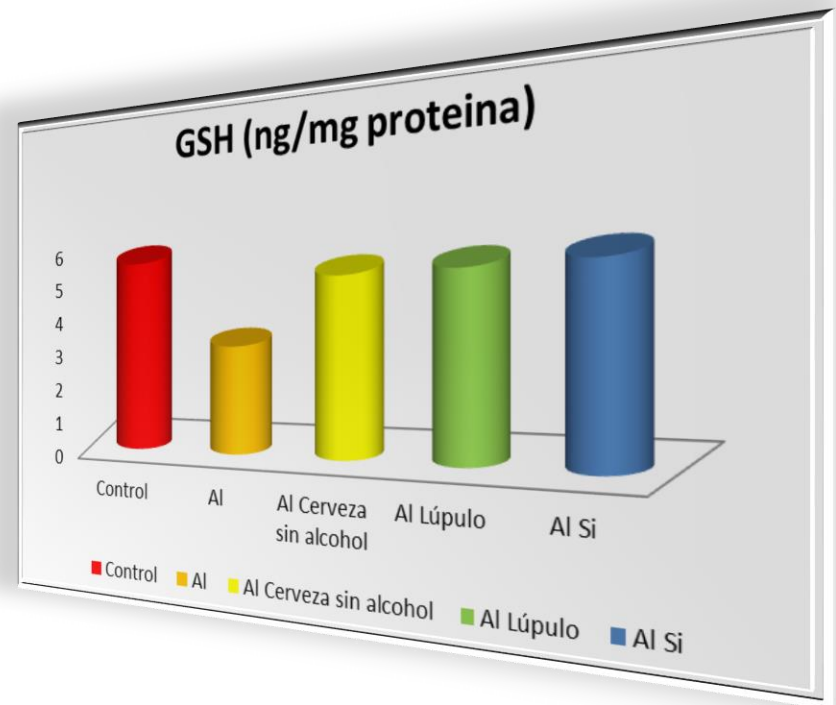
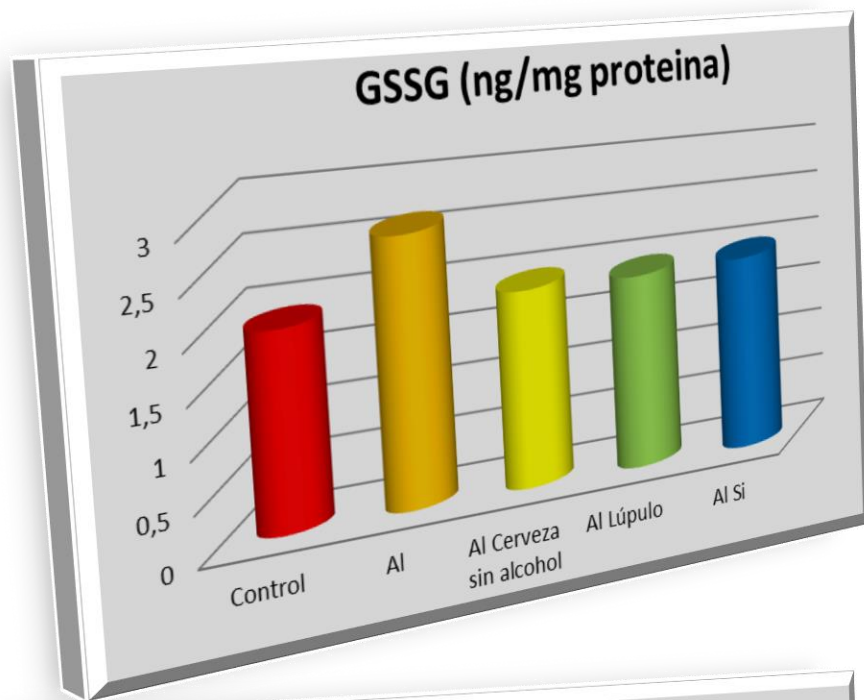


Si significantly decreases lipid peroxidation: neuroprotective



Antioxidant capacity of hop: resveratrol and xanthohumol

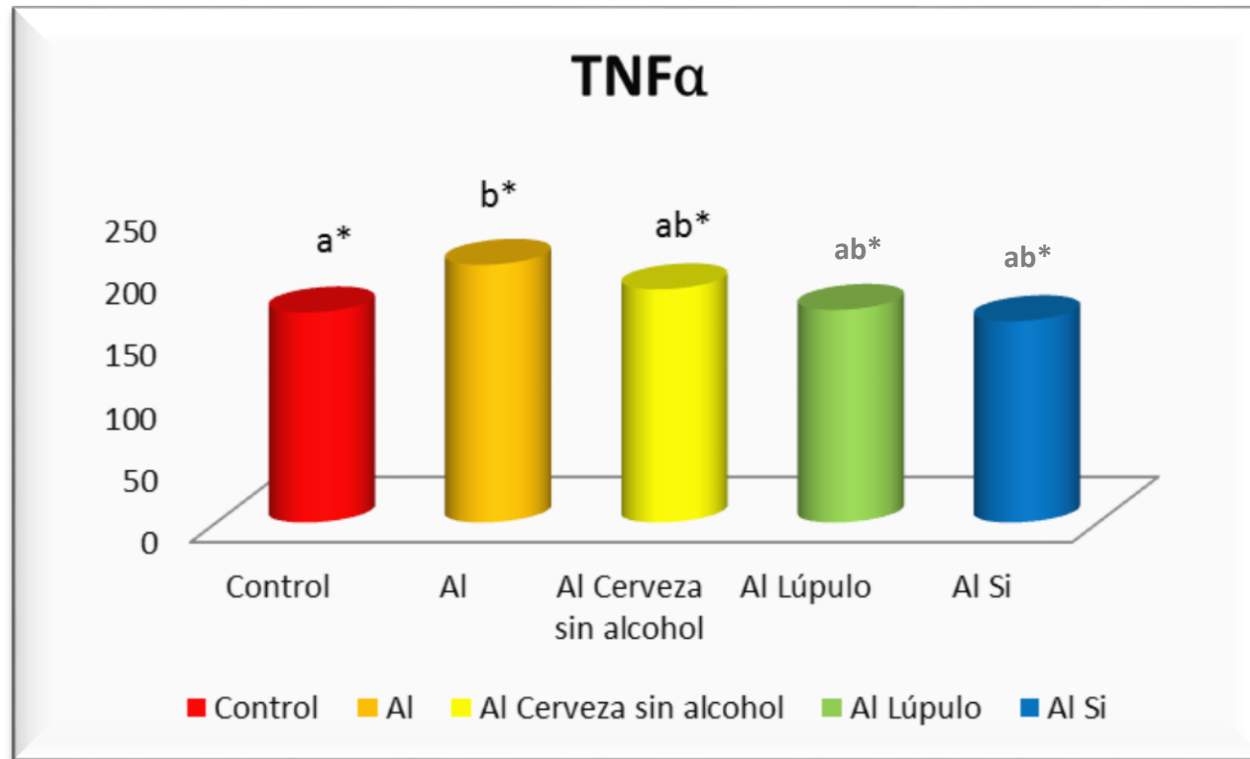




La cerveza sin alcohol resulta más efectiva en la reducción de los niveles de TBARS y GSSG y en el incremento de GSH

Mayor capacidad antioxidante observada *in vitro*

Effect of non-alcoholic beer and its components on TNF α levels



Increased TNF α →
inflammatory response of
the CNS
Interaction with the
cholinergic system



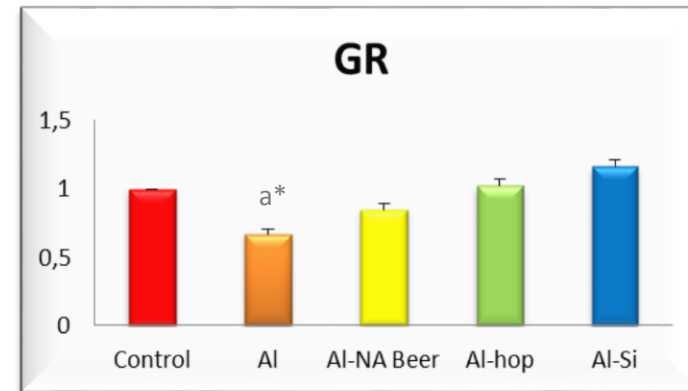
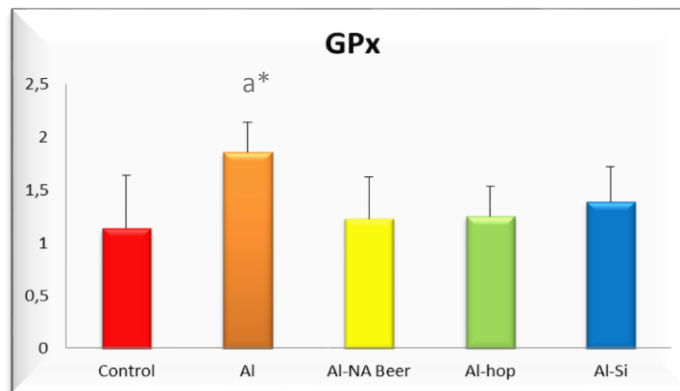
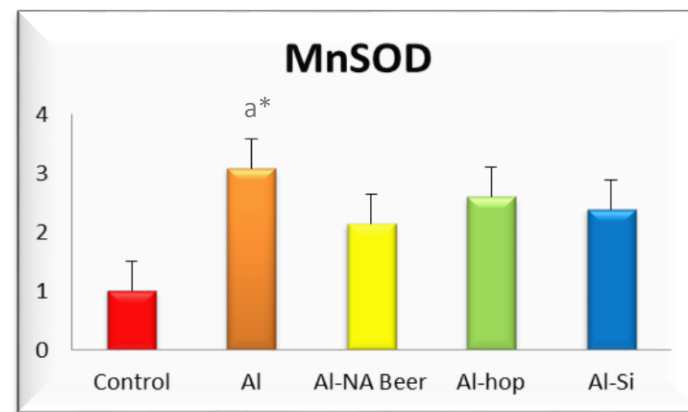
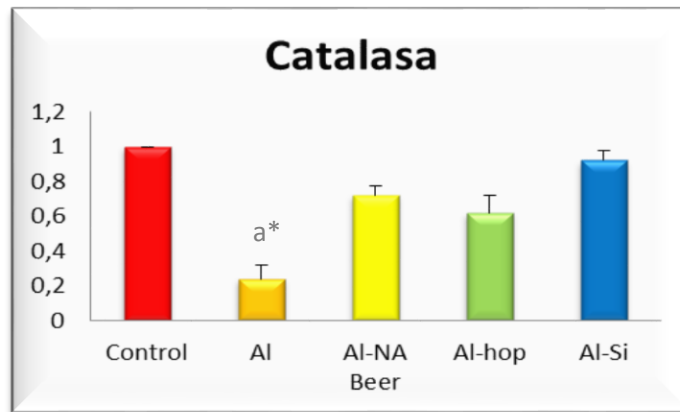
Si → decreased Al body
burden (HAS)



Hop → anti-inflammatory
effect exerted by
polyphenols



Effect of non-alcoholic beer and its components on gene expression and activity of antioxidant enzymes



The expression and activity of antioxidant enzymes altered by the administration of AI is normalised by treatment with non-alcoholic beer and its components → silicon, hop and beer are able to improve antioxidant defence in the brain

EFFECT OF NON-ALCOHOLIC BEER ON GENE EXPRESSION AND ACTIVITY OF CEREBRAL INFLAMMATORY MARKERS AND ANTIOXIDANT ENZYMES

Conclusions



Due to the capacity of its components to alleviate the neurodegenerative effects induced by Al intoxication



Moderate consumption of non-alcoholic beer provides an effective prophylactic measure for preventing the onset and development of AD



Gracias por su atención

