Emerging Innovations

NEW FRONTIERS IN Alzheimer's Support

Alzheimer's Challenges and Potential Support with Anti-Inflammatory Boswellic Acids

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Alzheimer's disease (AD) and related dementia diagnoses are very prevalent in Canada. Approximately 733,040 people in Canada are currently living with dementia, and that number is estimated to grow to nearly 1 million Canadians by 2030. (1) AD is the most common type of dementia, an overall term for conditions that cause problems with memory, thinking and behaviour. In the early stage, dementia symptoms may be minimal, but as the disease causes more damage to the brain, symptoms worsen. The rate at which the disease progresses is different for everyone, but on average, people with AD live for roughly eight years after symptoms begin.

AD is a major unmet need. The main class of drugs approved in Canada to treat Alzheimer's are cholinesterase inhibitors. These drugs prevent the breakdown of acetylcholine, making more of the chemical messenger available to healthy nerve cells, which allows the chemical messenger to continue to fire normally. This messenger is important for memory, language, judgment and other thinking skills. Cholinesterase inhibitors treat the symptoms of AD but do nothing to slow the underlying disease.

Recently, a controversial drug aducanumab, also known by its brand name Aduhelm, was approved in the US. The drug was designed to target amyloid beta plaques for early AD and received conditional approval was based on modifications of biomarkers of the disease, and the effects on functional patient outcomes were minimal and associated with significant adverse events. The conditional approval from the FDA required additional clinical trial data, which unfortunately was equally disappointing. Biogen discontinued the development and commercialization of Aduhelm in Jan 2024. The drug was only available in Canada in a clinical research setting, and in June 2022, Biogen withdrew its submission from Health Canada. Health Canada is currently reviewing two new promising medications, one new drug from Biogen, Leqembi (lecanemab), and Lilly's donanemab, to treat early-stage Alzheimer's disease and mild cognitive impairment due to AD, however Leqembi was rejected by EU's EMA citing the risk outweighs the benefit. The high cost of these immunotherapies will also add to the controversy of future of these drugs for treatment of AD.

AD is characterized by two core pathologies, aberrant tau protein and the presence of β-amyloid (Aβ) plaques. Abnormal chemical changes cause tau to stick to other tau molecules, forming threads that eventually join to form tangles inside neurons. These tangles block synaptic communication between neurons. Amyloid beta is produced due to normal processes but is normally cleared before it can do any damage. It diseased brains, it is not cleared quickly enough, and it clumps together and accumulates into bulky amyloid plaques. Tau and amyloid affect each other in a complicated relationship. Both beta-amyloid plaques and tau damage and destroy neurons and activate the immune system to trigger inflammation.

Acute inflammation in the brain is a well-established defense against infection, toxins, and injury, but when a disruption in the equilibrium of anti-inflammatory and pro-inflammatory signaling occurs, as seen in AD, it results in chronic inflammation (neuroinflammation). The presence of a sustained inflammatory response in the brain of patients with AD was thought to be a result of the neuronal loss occurring in the disorder, however new research has now demonstrated that a persistent immune response in the brain is not only associated with neurodegeneration, but it also facilitates and exacerbates both Aβ and tau pathologies. (3)

Figure 1: Mean MMSE and CDR-SOB scores of patients treated with placebo or Boswellia at baseline and month 6

Mean MMSE and CDR-SOB scores of patients treated with placebo or Boswellia at baseline and month 6

	Boswellia extract ($n=40$), df = 39			Placebo ($n=37$), df = 36			Treatment*time (p)
Clinical Scores	Baseline	Month 6	Change (95% CI)	Baseline	Month 6	Change (95% CI)	
MMSE	16.25 ± 4.06	17.93 ± 4.12	1.7 (1.2 to 2.1)	15.84 ± 3.59	14.41 ± 3.47	−1.4 (−2.0 to −0.9)	$F(1,75) = 73.32$ $p < 0.0001$
CDR-SOB	6.81 ± 2.16	5.99 ± 1.86	−0.8 (−1.1 to −0.6)	7.46 ± 2.46	8.28 ± 2.41	0.8 (0.4 to 1.2)	$F(1,75) = 53.08$ $p < 0.0001$

The table presents the mean scores ± standard deviation, degree of freedom, unit differences with 95% confidence interval (CI). A linear mixed model was run on both CDR-SOB and MMSE outcome. The models included treatment (drug, placebo), time (baseline, 6 months), a treatment by time interaction term, and age and sex. The models also treat patient as a random effect adjusting for the correlation among observations taken on the same patient. For both tests, the interaction term was significant ($p < 0.05$).

Karima et al. Boswellic Acids Improve Clinical Cognitive Scores and Reduce Systemic Inflammation in Patients with Mild to Moderate Alzheimer's Disease, Journal of Alzheimer's Disease 94 (2023) 359–370

A recent clinical study of a strong anti-inflammatory agent, boswellic acid, showed promise to improve memory in Alzheimer's patients. (4) Boswellia serrata is a tree prevalent in India, the Middle East and North Africa. The resin obtained by peeling away the bark is commonly known as frankincense or olibanum. Boswellia is used widely in Ayurveda for treating arthritis, ulcerative colitis, coughs, sores, wound healing, and asthma. The bioactive compound in boswellia is boswellic acids, including β-boswellic acid, 11-keto-β-boswellic acid (KBA), acetyl-11-keto-β-boswellic acid (AKBA). Boswellic acids have been proposed as selective 5-lipoxygenase (5-LO) inhibitors, however there are some questions about this due to the pharmacokinetics of the molecules. One study suggested that inhibition of cathepsin G (catG) and microsomal prostaglandin E synthase (mPGES)-1 by β-boswellic acid might represent the principal mode of action of Boswellia extract. (5)

The double-blind, placebo-controlled study was published in the Journal of Alzheimer's disease Boswellic Acids Improve Clinical Cognitive Scores and Reduce Systemic Inflammation in Patients with Mild to Moderate Alzheimer's Disease (4) and presented at the Alzheimer's Association International Conference (6). The study was performed in collaboration with researchers at the Hurvitz Brain Sciences Program at Sunnybrook Research Institute and demonstrated patients on a Boswellia serrata extract , known as K-Vie™ and used in a product called Memowell™, showed improvement in two standard measures of memory in Alzhemier's patients Mini-Mental State Examination (MMSE) and Clinical Dementia Rating–Sum of Boxes (CDR-SOB scores), when compared to patients on placebo. (4) This prospective trial included both male and female patients 60–85 years old and who met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria for probable Alzheimers and the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for dementia of the Alzheimer's type. Patients were randomly assigned to placebo or boswellia extract (1,200 mg/day, 3*400 mg capsules/day) groups for 6 months. A total of 85 patients were enrolled in the study. The study was sponsored by Kondor Pharma and conducted in collaboration with an international team of scientists, including those from Sunnybrook Research Institute in Toronto, Canada.

Patients in the Boswellia extract group (K-Vie™) showed statistically better scores in both the MMSE (3.1 units $p < 0.0001$) and CDR-SOB scores (1.6 units, $p < 0.0001$). (Figure 1) Interesting in both sets of scores patients showed improvement in the memory tests, while the placebo group showed a decline.

The researchers also followed this up by measuring biomarkers of disease and inflammation in blood samples from the patients. The researchers used plasma Aβ42/40 ratios as surrogate biomarkers of cortical Aβ deposition; there is an inverse relationship between Aβ42/40 ratios and cortical Aβ deposition. (7) The researchers demonstrated a significantly higher Aβ42/40 ratio in the boswellic extract group (0.07, 95% CI 0.05 to 0.1) vs placebo (0.02, 95% CI 0.004–0.03) at 6 months ($F(1,36) = 19.27$, $p < 0.0001$).

Patients in the boswellic acid group also showed reduction of key inflammatory cytokines. The inflammation biomarkers were measured only at patients' second visit at month 1. The biomarker endpoints were changes from baseline to month 1 for plasma levels of IL-1, IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, TNF, interferon-gamma (IFNβ), C-X-C motif chemokine ligand 10 (CXCL10), mitochondrial pyruvate carrier 1 (MPC1), and

prostaglandin E2 (PGE-2). Patients in the boswellic acid group generally displayed a reduction of pro-inflammatory phenotype including decreased levels of cytokines such as IL-1, IL-4, IL-6, IL-1, TNF, and PGE-2 after one month treatment with boswellic extract. (Figure 2)

This study provides interesting data in support of the use of anti-inflammatory medications to slow cognitive decline in Alzheimer's patients, and in particular boswellic acid may warrant further examination. The nutraceutical was well-tolerated, safe, and had no major adverse effects.

More information on boswellic extracts can be found on Kondor Pharma's website.

https://kondorpharma.com/

Figure 2: Plasma levels of inflammation biomarkers in patients treated with placebo or Boswellia at baseline and month 1

Plasma levels of inflammation biomarkers in patients treated with placebo or Boswellia at baseline and month 1

	Boswellia extract ($n=24$), df = 21		Placebo ($n=21$), df = 17		Interaction (treatment*time) p
Marker (pg/mL)	Baseline	Month 1	Baseline	Month 1	
INF-γ	21.92 ± 13.46	21.50 ± 11.23	27.06 ± 16.95	28.79 ± 17.28	F(1,38) = 0.49
Change (95% CI)	–0.4 (–4.7 to 3.8)		1.8 (–3.4 to 7.0)		$p=0.49$
IL-1β	10.39 ± 4.69	5.10 ± 3.25	12.85 ± 7.01	11.32 ± 5.21	F(1,38) = 13.39
Change (95% CI)	–5.3 (–6.4 to –4.1)		–1.5 (–3.4 to 0.4)		$p=0.0008$
IL-2	15.58 ± 8.47	23.07 ± 12.66	16.54 ± 11.45	14.66 ± 8.45	F(1,37) = 20.38
Change (95% CI)	8.0 (5.0 to 10.9)		–1.9 (–5.4 to 1.6)		$p<0.0001$
IL-4	7.15 ± 3.79	3.11 ± 2.16	6.75 ± 4.45	5.37 ± 4.04	F(1,37) = 14.56
Change (95% CI)	–4.0 (–4.9 to –3.1)		–1.1 (–2.5 to 0.3)		$p=0.0005$
IL-6	21.68 ± 11.92	7.59 ± 6.63	16.64 ± 10.98	20.14 ± 12.86	F(1,38) = 71.14
Change (95% CI)	–14.1 (–16.6 to –11.7)		3.8 (–0.2 to 7.8)		$p<0.0001$
IL-8	18.50 ± 9.60	28.01 ± 13.49	18.98 ± 13.95	20.03 ± 14.06	F(1,38) = 11.49
Change (95% CI)	9.5 (6.5 to 12.5)		1.0 (–3.4 to 5.5)		$p=0.0016$
IL-12p70	26.34 ± 14.07	20.81 ± 9.96	24.96 ± 13.04	31.32 ± 17.49	F(1,37) = 16.66
Change (95% CI)	–5.5 (–9.4 to –1.6)		6.6 (1.7 to 11.5)		$p=0.0002$
IL-1α	3.85 ± 2.29	1.51 ± 0.79	4.05 ± 2.29	4.22 ± 2.94	F(1,38) = 33.44
Change (95% CI)	–2.3 (–2.9 to –1.8)		0.2 (–0.6 to 0.9)		$p<0.0001$
TNF	12.08 ± 8.49	5.97 ± 5.25	12.55 ± 7.37	13.05 ± 8.39	F(1,35) = 14.79
Change (95% CI)	–6.1 (–8.4 to –3.8)		0.04 (–2.4 to 2.5)		$p=0.0005$
IL-10	22.97 ± 14.75	23.97 ± 14.01	34.07 ± 20.82	33.90 ± 18.70	F(1,37) = 0.08
Change (95% CI)	1.0 (–3.8 to 5.8)		–0.1 (–7.5 to 7.3)		$p=0.78$
IP-10	701.17 ± 393.40	783.20 ± 281.44	869.58 ± 441.43	674.67 ± 419.50	F(1,35) = 10.00
Change (95% CI)	82.0 (–15.8 to 179.9)		–185.2 (–344.8 to –25.6)		$p=0.0032$
MCP-1/CCL2	1087.51 ± 431.52	1308.36 ± 263.55	1290.06 ± 425.62	1245.72 ± 378.43	F(1,37) = 11.42
Change (95% CI)	218.7 (112.6 to 324.7)		–44.3 (–169.8 to 81.2)		$p=0.0017$
PGE-2	224.72 ± 131.29	187.15 ± 58.66	474.04 ± 149.94	369.41 ± 133.68	F(1,38) = 7.22
Change (95% CI)	–37.6 (–66.2 to –8.9)		–104.6 (–150.8 to –58.5)		$p=0.0106$

The table presents the mean scores ± standard deviation, degree of freedom, unit differences with 95% confidence interval (CI). Blood was collected before treatment (baseline) and after 1 month (month 1) of treatment in patients from the Boswellia and placebo groups. Plasma levels of 13 different cytokines and chemokines were measured and compared between the two groups.

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