

Adrenoleukodystrophy

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This paper reviews evidence relating to the nutritional management of the condition adrenoleukodystrophy. In doing so, the efficacy of proposed nutritional supplementation and dietary interventions will be evaluated. An exploration of the biochemical properties of selected nutrients and foods relevant to ALD sufferers will also be presented. Nutritional research included in this paper explores the effect of Zinc, N-Acetyl-Cysteine, Glutathione, Vitamin E and Vitamin C. Additionally, critical evaluation regarding foods have also been assessed which includes, turmeric, ginger, rapeseed oil and olive oil. This paper also includes a brief outline of a potential research project related to adrenoleukodystrophy.

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ABBREVIATIONS

ALD: Adrenoleukodystrophy; ABC: ATP binding cassette; LCFA: Long chain fatty acid; VLCFA: Very long chain fatty acids; CoA: Coenzyme A, ABCD1: ATP-binding cassette, sub-family D (ALD), member 1; AMN: Adrenomyeloneuropathy; ACTH: Adrenocorticotrophic releasing hormone; IL: Interleukin, IL-2: Interleukin 2; IL-6: Interleukin 6; TNF- α : Tumour necrosis factor-alpha; IL-1 β : Interlukin beta; LP: Lipopolysaccharide; AA: Arachidonic acid; DPI: diphenylene iodonium; NADPH: Nicotinamide adenine dinucleotide phosphate; ROS: Reactive Oxygen Species; SOD: Superoxide dismutase; CRP: C-reactive protein; NF- κ B: Nuclear transcription factor kappaB; PPAR- α : Peroxisome proliferator-activated receptor-alpha; AP1: Activator protein 1; COX-2: Cyclooxygenase-2; iNOS: Inducible nitric oxide synthase; CuZnSOD: Copper zinc superoxide dismutase; NAC: N-Acetyl-Cysteine; HSCT: Hematopoietic stem cell transplantation; RNS: Reactive nitrogen species; BSO: Buthionine sulphoximine; 5-LOX: 5-lipoxygenase; CSF: Cerebro-spinal fluid; Cys LT: Cysteinyl leukotrienes; A-tocopherol: Alpha-tocopherol; PA2: Phospholipase A2; AD: Alzheimer's disease; EPCK1: A water and lipid soluble ester of vitamin C and E; NO: Nitric Oxide; ADP: Adenosine diphosphate; TEAC: Trolox equivalent activity concentration; PGE2: Prostaglandin 2; LO: Lorenzo's oil, CCER: Childhood cerebral.

BACKGROUND

Pathophysiology and Disease Mechanism

X-linked adrenoleukodystrophy (ALD) is a complex peroxisomal disease which affects the nervous system, adrenal cortex, and testes. According to Singh and Pujol (2010) it occurs 1 in 17,000 males.

Peroxisomes are single membraned sub-cellular organelles present in most organisms, carrying out essential functions related to lipid homeostasis (Schluter 2010). The process which they are involved in are both catabolic (oxidation of fats) and anabolic. Additionally, they play a role in free radical detoxification. All peroxisomes have at least one ATP binding cassette (ABC) transporter on their membrane. According to Schluter (2010), in mammals, four peroxisome transporters are present: ABCD1, 2, 3 and 4.

Adrenoleukodystrophy is a metabolic disorder, caused by a genetic mutation of the ABCD1 transporter. The X-linked Adrenoleukodystrophy Database, an international database, cited in Lan F et al (2010, pg.1992) shows that there have been more than 500 mutations reported in relation to this gene. Singh I and Pujol (2010) add that ABCD1 plays a crucial role in transporting very long chain fatty acids (VLCFA), or their Coenzyme A (CoA) derivatives, into peroxisomes to undergo metabolism. Mutation of this gene will lead to a loss of its function and render beta oxidation ineffective, ultimately leading to excessive accumulation of VLCFAs in body tissues (mainly brain and adrenal cortex), and plasma. Most of the fat accumulated is saturated. However according to Singh and Pujol (2010), there is, to a lesser extent, an accumulation of monounsaturated fats as well.

The inactivation of the ABCD1 gene results in clinically diverse phenotypes; patients may present with cerebral ALD in childhood, adolescence or adulthood. They may also present with Addison's disease, adrenomyeloneuropathy (AMN) and gonadal insufficiency.

Ferrer et al (2010) states that there is a lack of genotype-phenotype correlations in this disease and suggests that this is due to the fact that a mutation of the ABCD1 gene may be associated with a variety of phenotypes within one family. Based on this suggestion, it would be sound to conclude that genetic and environmental factors contribute to the development and progression of this disease.

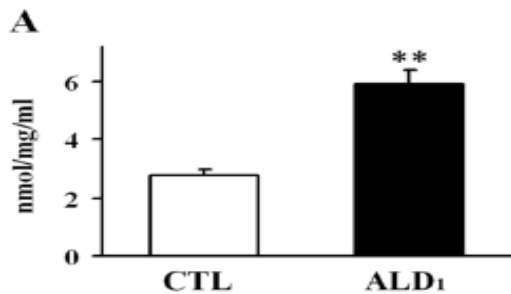
Oxidative damage and ALD

Axonopathy of the spinal cord, demyelination of the cerebral hemispheres and adrenal insufficiency are degenerative changes occurring in ALD. Ferrer et al (2010) suggests that this is possibly related to the impaired metabolism of VLCFAs and "the associated alterations (i.e. oxidative damage)". Additionally, Ferrer et al (2010) note that a more aggressive phenotype is witnessed secondary to cerebral demyelination of nerve fibres. This manifestation is seen alongside inflammatory processes within the white matter of the brain and involves hyper-activity of T lymphocytes, CD1 presentation, increased cytokines, interferons, interleukin (IL) 1-alpha, IL-2, IL-6, macrophage colony stimulating factors, tumour necrosis factor-alpha (TNF-a), chemokines, and chemokine receptors. Such neuro-degeneration often leads to death in patients before they reach adolescence.

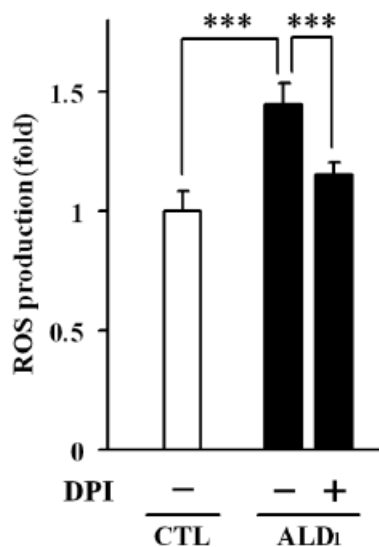
Uto et al (2008) compared levels of TNF-a and interleukin beta (IL-1 β) in control and ALD lymphoblasts and concluded that there was 2.1 times increased synthesis of TNF-a in ALD cells and 2.3 times more IL-1 β . Uto T et al (2008) gathered that blood cells of an ALD patient, when triggered by a bacterial lipopolysaccharide (LP), a gram negative endotoxin, produced increased IL-2, and TNF-a, which is characteristic of a Th1 immune response. In addition, lymphoblasts were investigated to observe whether they would express cytokines without inflammatory stimulation. Results

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showed that even without any stimulation, these cells produced 2.1 times more nitric oxide (NO) than the control cells (Uto et al 2008, pg. 18):



Furthermore, fibroblasts of ALD patients have higher baseline and arachidonic acid (AA) induced IL-1 β levels. Quite a high level of oxidative stress was demonstrated in these cells based on measuring nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity. When these cells were treated with diphenylene iodonium (DPI), an NADPH oxidase inhibitor, a significant reduction of reactive oxygen species (ROS) production was demonstrated (Uto et al 2008, pg. 13):



Singh and Pujol (2010) state “molecular events that trigger the transition from the metabolic phase to neuroinflammation and demyelination in the brain in cerebral ALD are largely unknown.” They also add “the exact mechanism that links the VLCFA excess...to inflammation and demyelination in cALD remains elusive.”

However, Uto et al (2008 pg. 7) mentions that due to increased NADPH-oxidase induced free radical formation, development and progression of neuroinflammation in ALD takes place. This pinpoints that oxidative stress is the chief driving force behind ALD development.

It is evident that there is vast inflammation in this condition. Singh and Pujol (2010) imply the importance of antioxidants as they state “production of free radicals might lead to oxidative stress when antioxidant defences are overwhelmed.” Furthermore, antioxidants would be so beneficial in managing ALD as a lack of antioxidants whilst oxidative stress in increasing will cause damage to macromolecules such as DNA and RNA of a cell.

NUTRIENTS

Zinc

Superoxide dismutase (SOD) is a metallo-protein and is the first enzyme, which acts as a scavenger of superoxide radicals, catalyzing them to form oxygen and hydrogen peroxide. This potent antioxidant relies on cofactors to carry out its free radical scavenging function; zinc is one of the essential components required for it to act.

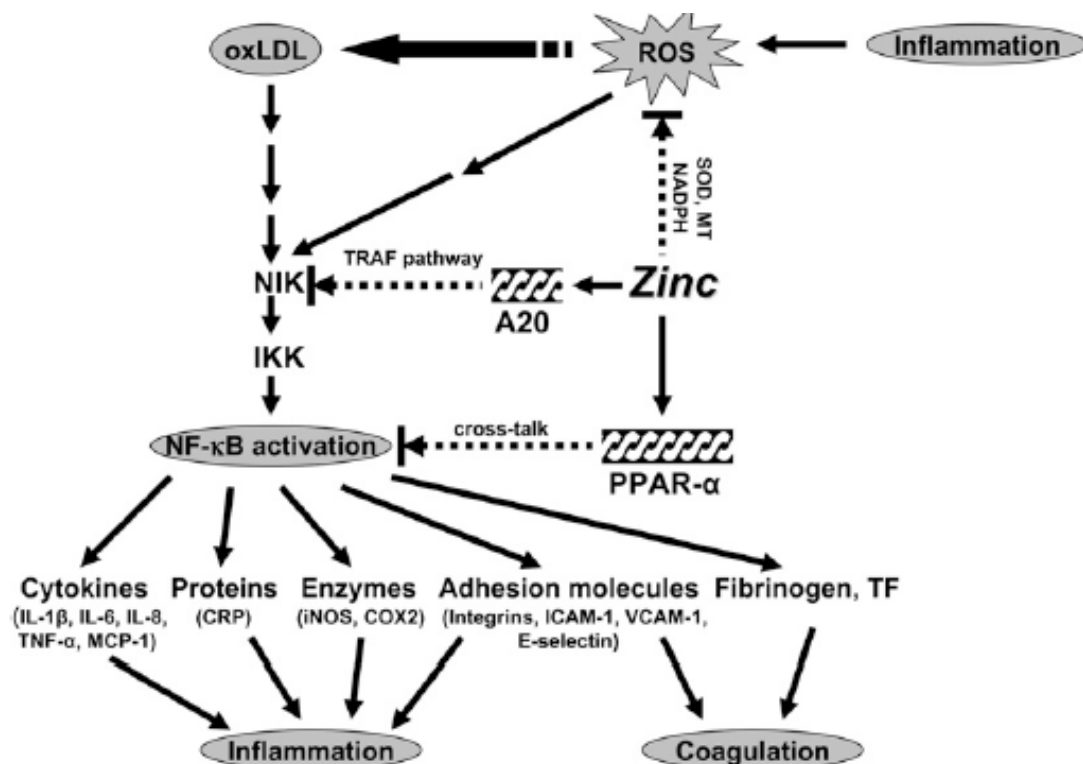
Fischer and Glass (2010) demonstrated that a loss of SOD predisposed dorsal root ganglia axons to degeneration due to a lack of protection from oxidative stress. Their study demonstrated that SOD is “required for dorsal root ganglia axon survival” (Fischer and Glass, 2010 pg. 255).

Bao et al (2010) explored the anti-inflammatory effects of zinc by administering 45mg/day (as zinc gluconate) to subjects aged 56-83 years for six months. This was compared to a placebo group receiving nothing. Although this study aimed to demonstrate the atheroprotective action of zinc, the mechanisms by which zinc brings about this effect is also relevant to the underlying pathologies of neuro-degeneration occurring in ALD. The beneficial effects of zinc were seen to significantly decrease C-reactive protein (CRP), IL-6, IL-1 β and reduce TNF- α production, in addition to other inflammatory markers which typically abound in ALD. Bao et al (2010) confirmed that a deficiency of zinc would increase oxidative stress.

Additionally, ROS production arising from a zinc deficiency has the ability to initiate nuclear transcription factor κ B (NF- κ B)-activation of pro-inflammatory genes. Therefore the data presented demonstrates the potential benefits of zinc in a neuro-inflammatory condition like ALD, as the inflammatory mediators indicated in this study are also seen excessively in ALD.

Peroxisome proliferator activated receptor-alpha (PPAR- α) activation relies on zinc. Peroxisome proliferator activated receptor-alpha regulates lipid metabolism and fatty

acid beta-oxidation (Bouwens et al, 2008), the characteristic mechanism which is rendered ineffective in ALD patients. Reiterer et al (2004) adds that PPARs regulate glucose homeostasis, cell proliferation, cell differentiation and also modulates the inflammatory response. Bouwens et al (2008) concluded that genes which up-regulate beta-oxidation are dependant upon PPAR-a activation, and are therefore crucial in ALD. Bao et al (2010) have demonstrated that PPAR-a activation plays a role in inflammation by showing that its activation causes a down-regulation of pro-inflammatory cytokines. Reiterer G et al (2004) also explored PPAR-a in relation to inflammatory mediators. They reported an increased TNF-a induced inflammatory response in zinc deficient cells. Further, that when zinc was added back into these cells, PPAR-a activation caused a down-regulation of NF-kB and activation protein-1 (AP-1). Their study demonstrated that adequate amounts of zinc are required for the anti-inflammatory effect of PPAR-a to take place. The significant factor at this point is that activation of PPAR-a, is a zinc dependant reaction, and this is illustrated below (Bao et al, 2010 pg. 1639):



It is evident that the deficiency of zinc will lead to increased ROS, subsequently activating NF- κ B and up-regulating the production of inflammatory cytokines, CRP, and inflammatory enzymes (Cyclooxygenase-2 [COX-2], and inducible nitric oxide synthase [iNOS]).

The production of superoxide radicals occurs naturally as a part of the complexes of the electron transport chain. If SOD enzymes do not quench these free radicals, they have the ability to undergo chemical reactions and produce other highly toxic free radicals such as hydroxyl radicals (Fischer and Glass 2010).

In mice lacking SOD, neuro-degeneration and motor neuropathies were evident. The neurons also exhibited increased apoptosis under ischemic, excitotoxic and trauma scenarios (Fischer and Glass, 2010 pg. 256). Additionally, the effect of a potent herbicide, diquat, on axonal health was exacerbated by a SOD deficiency. Therefore, The deficiency of SOD demonstrated increased axonal toxicity.

Song et al (2009) observed that zinc status was a major contributor towards DNA damage, and that some DNA damage may be reversible after zinc repletion. Due to the role of zinc in maintaining DNA integrity, in their study, Song et al (2009, pg. 327) reported that a low zinc intake will increase the breakage of DNA strands either due to oxidative stress and/or disruptions to DNA repair pathways. A key finding in their study was that physical manifestations of a zinc deficiency became apparent before a decline of plasma zinc levels. This clearly indicates the importance of zinc in maintaining DNA stability and therefore its role in genetic homeostasis.

Copper zinc superoxide dismutase (CuZnSOD) activity was seen to reduce when zinc levels in subjects were deplete (Song et al 2009, Mariana et al 2006), however CuZnSOD levels were seen to rise as soon as zinc was replete. Furthermore a key damaging mechanism in ALD, lipid peroxidation, has been shown to increase in rats that were zinc deficient (Song et al 2009).

Zinc will increase antioxidant capacity; decrease CRP, inflammatory cytokines and overall oxidative stress markers after six months supplementation, as demonstrated by

Bao et al (2010). Zinc will also decrease the generation of TNF-a, IL-1 β , NF-kB and up-regulate PPAR-a. All these mechanisms of zinc are implicated in ALD and would pose a beneficial effect in treatment.

N-Acetyl-cysteine (NAC)

Tolar et al (2008) used NAC as an antioxidant to prove it protects from neurodegeneration in ALD patients. N-acetyl-cysteine was administered to boys with cerebral ALD who had undergone hematopoietic stem cell transplantation (HSCT). Tolar et al (2008) demonstrated that the boys were alive and radiographically stable 100 days later. N-Acetyl-cysteine was shown to be safe for usage in childhood ALD as its role in reducing oxidative stress was implicated in this study.

In an earlier study, Tolar et al (2007) administered NAC as adjunct therapy to patients who underwent HSCT to aid protection against neurological decline. The study showed that NAC administration alongside HSCT protected from demyelination, with Tolar et al (2007) recognising that this was due to NAC's "antioxidant and radical scavenging properties" (Tolar et al 2007, pg. 213). The neuronal protective effect of NAC was exhibited as patients were stable clinically and by MRI. This demonstrates the potential in administering NAC alongside orthodox medical therapy in ALD. Another benefit reported by Tolar et al (2007) is that NAC administration is safe and no significant adverse reactions have been observed.

Charnas et al (2007) explored the effects of NAC and found that there is increased risk of death after HSCT. They administered NAC in an attempt to halt disease progression and demyelination of nerve fibres. A subject who was considered at high risk from dying after a transplant, was given NAC during and after his transplantation. Hypothesised from the antioxidant actions of NAC, stable neurological exams and radiography was witnessed shortly after.

Charnas et al (2007) go as far as stating that "NAC, a drug already in clinical use, merits investigation as a therapeutic strategy for patients with advanced ALD and has a potential to change this lethal disease to a condition amendable to treatment with hematopoietic stem cell transplantation."

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Tolar et al (2008) reasoned that NAC would be beneficial in their subjects as NAC is considered a beneficial broncho-pulmonary mucolytic agent, and as a nutrient to aid the liver with detoxification of acetaminophen/paracetamol toxicity.

As seen in the table below, the amount of the ABCD transporters within human tissue is outlined. The transporter with a genetic defect in ALD, ABCD1, is shown to be highly expressed in pulmonary tissue. With the strong correlation existing between NAC being a beneficial nutrient to the pulmonary system, and as mentioned by Tolar et al (2008), it is a mucolytic agent. This may further reiterate why NAC has been shown to be helpful in trials concerning ALD.

Table 1. Expression profiles of the four peroxisomal ABC half-transporters in 20 different human tissues using real-time RT-PCR analysis

	placenta	trachea	lung	small intestine	colon	liver	kidney	salivary gland	thyroid gland	adrenal gland	prostate	testis	spleen	thymus	bone marrow	brain, whole	brain, cerebellum	uterus	heart	skeletal muscle
ABCD1	●●●	●	●●●●●	●	●	●	●	●	●	●●	●●	●●●	●●	●	●	●	●	●●●	●●	●
ABCD2	●	●●●●	●	●	●	●	●	●	●	●●	●●	●	●●	●	●	●●●	●●●●●	●●●●	●	●
ABCD3	●	●●●●●	●●	●	●	●	●●	●	●	●●●●●	●●●	●●●	●	●	●	●	●	●●	●	●
ABCD4	●●●●	●●●●●	●●●●●	●●	●	●●	●●●	●●	●●●	●●●●	●●●●	●●●●	●●●●	●●●	●	●	●●	●●●●	●	●

Additionally, because NAC is a precursor for the manufacture of glutathione in enterocytes, and glutathione is a potent antioxidant which is seen in low levels in conditions of excess oxidative stress, namely ALD, this further validates that NAC is an appropriate nutrient for the management of ALD.

Rats administered antioxidant supplementation, including NAC, demonstrated a near complete prevention of peroxidative damage (Bagh et al 2008). Bagh et al (2008) administered NAC as part of their antioxidant treatment in order to scavenge a variety of ROS, reactive nitrogen species (RNS), and peroxy radicals.

More recently, Bagh et al (2010) discussed how NAC can help restore mitochondrial health and transmembrane potential, an issue which arises in ALD. They state that this is possible by long term antioxidant therapy which includes NAC. This implies that damage to mitochondrial function, is attributed to oxidative damage, especially

due to ROS. Bagh et al (2010) witnessed rat brain deterioration due to lipid peroxidation, and also observed that the effects of antioxidants, including NAC, markedly improve oxidative stress in that scenario.

N-Acetyl-Cysteine, due to its antioxidant action has a prospective position in ALD management. In addition to its role in overall nervous system health, due to demonstrated efficacy on mitochondrial insufficiency, NAC could possibly be considered further as part of ALD treatment. That is, with mitochondrial damage seen as a prominent factor in ALD. Based on results discussed in the studies involving NAC, the data suggests that further investigation surrounding the therapeutic benefits of NAC would be advantageous for patients with ALD. Particularly if this disease has the potential to be ameliorated with aggressive treatment such as HSCT. Adjunct therapy with NAC may aid in patient prognosis.

Glutathione

Synthesised from the amino acid glutamate, glutathione has the ability to quench ROS. Furthermore, the mutation and inactivation of the ABCD1 gene sensitises fibroblasts to cell death due to glutathione depletion, indicating the protective effect of glutathione against ROS and that ABCD1 dysfunction alters oxidative stress homeostasis.

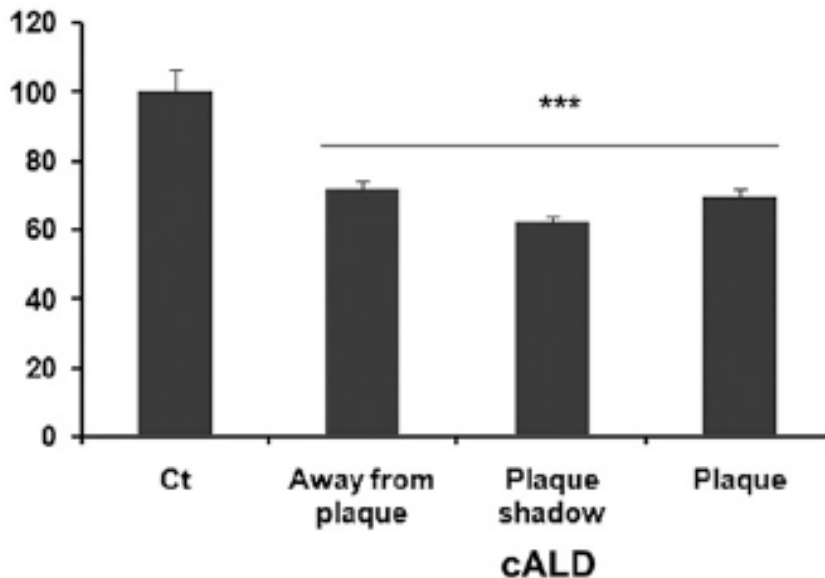
Ahmed RD et al (2008) reports findings of significantly decreased glutathione levels in rats undergoing exposure to a herbicide (Lindane) which is known to cause enhanced lipid peroxidation. Rats exposed to Lindane also exhibited increased activity of glutathione dependant enzymes: glutathione reductase, and glutathione peroxidase; indicating increased oxidation and the need for neutralisation during lipid peroxidation. The decrease of serum glutathione levels in rats after Lindane exposure may have been due to the increased activity of glutathione peroxidase, which requires glutathione to take effect.

Fourcade et al (2008) show that ALD fibroblasts are more sensitive to oxidative stress when compared to control fibroblasts. Fourcade et al (2008) treated ALD fibroblasts with a gamma-glutamylcysteine synthetase (the enzyme which synthesises glutathione) inhibitor, buthionine sulfoximine (BSO). Twenty-four hours post treatment, ALD cells were observed to lose viability and cell death was much higher in these cells compared to fibroblasts of healthy individuals (13%-59% vs. 0%-11%). This pinpoints that ALD cells are more reactive in the state of a glutathione insufficiency and are therefore more likely to undergo oxidative stress-induced apoptosis.

Khan et al (2010) observed that increased 5-lipoxygenase (5-LOX) derived leukotrienes were present within the white matter in childhood ALD. This correlated with “reduced levels of glutathione and enhanced expression of ...superoxide dismutase” (Khan et al 2010, pg. 1685). Song et al (2009) reported that there was reduced glutathione in the ALD brain as they took measurements in three different

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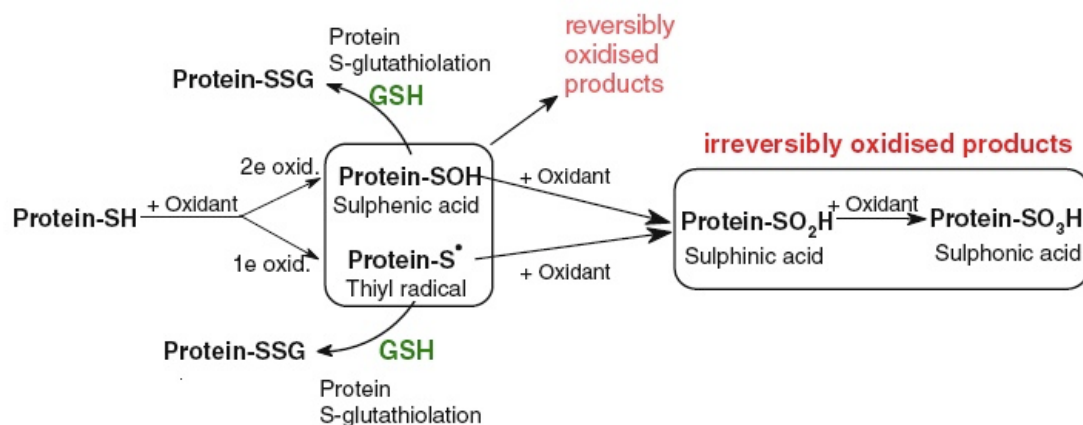
areas of white matter. Compared to the control brain, glutathione in all three areas of the white matter were significantly lower:



In support, Fourcade et al (2008) implies that C26:0 in high amounts correlates with increasing ROS and decreasing glutathione in human fibroblasts. In ALD, high C26:0 levels up-regulates inflammation by way of the 5-LOX pathway producing leukotrienes which Khan et al (2010, pg. 1693) reports to reduce glutathione. Brock TG (2005) states leukotrienes have the ability to form toxic compounds which may elicit an immune response. Khan et al (2010) noted that leukotrienes, particularly cysteinyl leukotrienes (Cys LT) were increased in all areas of the ALD brain; furthermore, Cys LT have the ability to deplete glutathione.

Visovsky et al (2007) demonstrated the neuro-protective effects of glutathione in patients undergoing chemotherapeutic cancer treatment. By administering 1500mg/m² intravenous glutathione to subjects in a randomised, double-blind, placebo-controlled trial, Visovsky et al (2007) noted that those in the experimental group performed better during neurological examinations following multiple chemotherapy cycles. Those in the placebo group, however, experienced increased neuropathy and neurotoxicity whilst those who received glutathione did not experience any neurotoxicity.

Fischer and Glass (2010) demonstrated that axonal degeneration and neurotoxicity induced by potent herbicides was attenuated when glutathione supplementation was implemented. Glutathione plays a role in maintaining the redox state of protein suphydryls, which are required for adequate DNA functioning and repair (Jomova et al 2010). The illustration below summarises the protective role of glutathione in oxidation of protein suphydryl groups (Jomova et al 2010, pg. 97):



According to Fourcade et al (2008, pg. 1768), glutathione, abundant in mammalian cells, plays a role in protecting cells of all organs, particularly the brain, against oxidative damage. Because accumulated C26:0 has the ability to produce ROS, oxidative stress is a major contributor to ALD. And thus based on the above findings, glutathione potentially has a beneficial role in the management of this illness.

Vitamin E

There are a variety of different forms of vitamin E, i.e. the α -, β -, γ -, δ -tocopherols and the α -, β -, γ -, δ -tocotrienols. However, Leonarduzzi et al (2010, pg. 342) states that alpha-tocopherol (a-tocopherol) is the most potent. A-tocopherol is an antioxidant that acts upon cell membranes and has the ability to neutralize compounds which may potentially disrupt membrane stability.

Fourcade et al (2008) explored whether a-tocopherol had the ability to quench the excess peroxy radicals, which is produced by excess VLCFAs in ALD. Trolox, an analogue of a-tocopherol, was administered to cultured human fibroblasts with high levels of C26:0, mimicking ALD. Fourcade et al (2008, pg. 1768) noted that there was a reduction of SOD, indicating there was neutralisation of superoxide radicals by Trolox. Additionally, Fourcade et al (2008) found that Trolox was able to reduce oxidative lesion markers in ALD fibroblasts, by way of detecting and measuring modification of protein structures due to oxidative stress. Similarly, Berger et al (2010), explored Vitamin E as a successful therapeutic measure in order to reverse the oxidative lesions caused by excessive VLCFAs.

The anti inflammatory effect of a-tocopherol was further explored by Leonarduzzi et al (2010) as they state that it has the ability to down regulate eicosanoid synthesis. Phospholipase A2 (PA2), the substrate for AA release, is efficiently downgraded by vitamin E. This is a noteworthy point as AA is the main precursor for eicosanoid synthesis, inflammation and eventually, neuro-degeneration. The biochemical pathway which vitamin E does this, is discussed by Leonarduzzi et al (2010). Vitamin E binds directly to PA2 forming a three-dimensional structure comprising of one molecule tocopherol and two molecules PA2. This compound then creates a change in the structure of phospholipase, which inhibits its expression. Farooqui et al (2006) discusses how a-tocopherol-induced PA2 inhibition is evident in the brain, and as this enzyme is involved in neurodegenerative diseases, vitamin E would therefore be highly implicated in ALD management.

In addition to suppressing PA2, vitamin E also blocks inflammation through inhibition of COX enzymes, which converts AA to prostaglandin H2. According to Leonarduzzi et al (2010) LP induced COX-2 synthesis is counteracted by a-tocopherol. Inflammatory enzyme 5-LOX, has also been shown to bind with a-tocopherol and therefore reducing IL-1 β production. Leonarduzzi et al (2010) states that the pathway by which a-tocopherol reduces IL-1 β is through blockage of leukotriene B4 synthesis, which is a bi-product of 5-LOX activity.

Song et al (2009) demonstrated that as lipid peroxidation increased with a zinc deficiency, hepatic vitamin E stores were depleted. However, serum vitamin E levels were constant and did not change. Song et al (2009 pg. 327) reports that vitamin E status of the liver may be “sacrificed to maintain circulating vitamin E concentrations.” They hypothesised that lipid peroxidation caused by zinc deficiency may be partially controlled by maintaining serum vitamin E levels. This emphasises the requirement of vitamin E in times of oxidative stress, ie: lipid peroxidation in ALD.

Jomova et al (2010) mentions the role of vitamin E in neurodegeneration, and that patients with Alzheimer’s disease (AD) who were given vitamin E and C daily exhibited increased vitamin E and C plasma and cerebro-spinal fluid (CSF) levels, making CSF and plasma lipoproteins more durable against oxidative damage. Jomova et al (2010, pg. 96) discusses that as vitamin E is the major lipophilic antioxidant in the brain, low levels are seen in patients with neurodegenerative conditions, and that vitamin E supplementation is correlated with reduced prevalence and incidence of AD. Hypothetically, this may be due to the fact that the core of AD, corresponding with ALD, is oxidative stress too, as Jomova et al (2010, pg. 97) describes AD, “oxidative stress underlies the molecular pathogenesis of this dementing disorder”. This indicates the efficacy of vitamin E as an antioxidant, in the brain, it signifies its importance in a neuro-inflammatory condition like ALD.

Gamma-tocopheryl quinone, a vitamin E homologue, was seen to elevate glutathione levels and elicit a cyto-protective effect as demonstrated by Ogawa et al (2008). It reportedly does this via up-regulating the availability of cysteine for glutathione

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synthesis (Ogawa et al 2008, pg. 685). Bagh et al (2008) supports this finding. They used a-tocopherol to up-regulate cellular antioxidant defences as it increased intracellular glutathione. Additionally Bagh et al (2008) reports a-tocopherol to successfully inhibit lipid peroxidation, and eliminate ROS. All the mechanisms linked to the antioxidant and non-antioxidant action of a-tocopherol would potentially be beneficial in the treatment of ALD.

Vitamin C

Vitamin C (ascorbic acid) is considered “the major aqueous phase antioxidant” (Jomova et al 2010, pg. 96) and would potentially be very beneficial in ALD, firstly due to its vitamin E recycling role. Vitamin C and E work synergistically. During the process of quenching free radicals, a-tocopherol donates a hydrogen ion to a lipid or a lipid peroxy radical, causing the a-tocopherol to convert to the a-tocopheroxy free radical. The role of ascorbic acid is crucial at this stage as it has the ability to reduce the a-tocopheroxy radical back to its a-tocopherol form (Harrison and May 2009, pg. 723). Because the brain is a lipid rich environment, the recycling of a-tocopherol is a very important function of ascorbate, especially in ALD. The role of vitamin C is further emphasised by Leonarduzzi et al (2010) as recycling of a-tocopherol by ascorbic acid makes this compound “the key player in preventing the generation and propagation of oxidative stress in biomembranes” (Leonarduzzi et al 2010, pg. 342).

Jomova et al (2010) noted that patients suffering neuro-degeneration in AD presented with reduced levels of CSF vitamin C when compared to control patients. Low levels of vitamin C may hinder the reduction of a-tocopherol radicals back to its a-tocopherol form and could potentiate inflammation.

Further evidence of vitamin C’s benefit is set out in the table below:

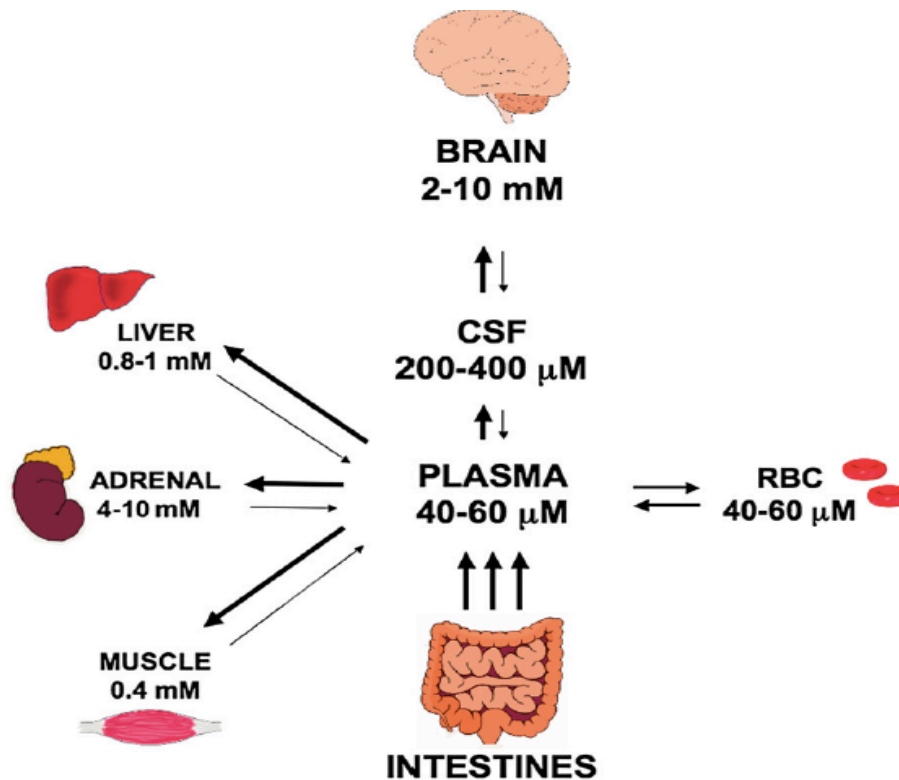
Author and year	Research
Harrison and May (2009)	<p>Ascorbate effects explored in guinea pigs with a vitamin E deficiency and an intentionally induced vitamin C deficiency. In the vitamin E deficient state the animals appeared normal however when vitamin C intake was completely prohibited, neurological symptoms appeared followed by death 24 hours later.</p> <p>Additionally, the importance of vitamin C in mice was demonstrated as when the neuronal ascorbate transporter was deleted, the mice died shortly after birth.</p> <p>Vitamin C acts in the brain to directly scavenge ROS or</p>

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	RNS, both produced during oxidative stress and C26:0 accumulation in ALD
Herrera E et al (2009)	The importance of vitamin C in controlling oxidative stress by eliciting an antioxidant action and decreasing overall inflammation.
Shingu et al (2010)	<p>A water and lipid soluble ester of vitamin C and E (EPCK1), was shown to prevent systemic inflammation. Lipopolysaccharide induced mice were compared to mice who were also exposed to LP but were treated with EPCK1 beforehand. The mice given the antioxidant treatment prior to being exposed to LP exhibited lower mortality rates, with more mice surviving. There was also a better outcome for mice who were administered with EPCK1 after lipopolysaccharide exposure in comparison to those who were not given any at all. Lower iNOS and in turn lower NO levels were evident in those pre-treated with EPCK1, in comparison to those who did not receive antioxidant treatment.</p> <p>that antioxidant treatment was shown to inactivate hydroxyl radicals. Because increased iNOS is associated with high levels of ROS, and there were low levels of iNOS in those being administered EPCK1, this indicates that vitamin C and E poses a free radical scavenging action and decreases systemic inflammation.</p>

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Vitamin C concentrations are highest in the brain and the adrenals, as illustrated in the image below (Harrison and May 2009, pg. 722):



These are the principal areas, which are severely affected by oxidative stress seen in ALD, indicating the importance of and the necessity of antioxidant measures. Additionally, neurons are particularly sensitive to low vitamin C (Harrison and May 2009, pg. 719) and especially whilst there is increased oxidative stress, such as in ALD (Harrison and May 2009, pg. 727). Harrison and May (2009, pg. 723) add that in vivo, ascorbate will “effectively scavenge superoxide.”

The contributory role of ROS in neuro-degeneration pinpoints the importance of antioxidant therapy in conditions such as ALD. In sum, ascorbate plays a role in protecting the nervous system in pathologies with oxidative stress-induced damage and increased ROS production, such as ALD. This highlights that ascorbate is essential in ALD for protection against oxidative stress, preventing loss and oxidation of a-tocopherol, and to decrease lipid peroxidation

Very long chain saturated fatty acids

(C22:0 docosanoic acid, C24:0 tetracosanoic acid, C26:0 hexacosanoic acid)

Ofman et al (2010 pg. 90) emphasises that VLCFA accumulation in ALD is partially absorbed from the diet. This indicates the importance of dietary and nutritional factors of an ALD patient and maintaining the correct intake of fats. The information below details the effect of three VLCFAs, considered anti-nutrients, implicated in ALD.

Very long chain fatty acids are found as constituents of lipids such as phosphatidilcholine, ganglioside, and cholesterol ester fractions of brain myelin and in the proteolipid protein (the most abundant protein found in myelin). According to Singh and Pujol (2010), gangliosides of an ALD brain contain 28% to 50% fatty acids, those which chains exceed 22 carbons. The build-up of VLCFA causes toxicity, eliciting an immune response. Additionally, by VLCFA incorporating to complex lipids, cell membranes may lose their stability.

Singh and Pujol (2010) state that C26:0 alters the physiological properties of membranes. Turnover of hexacosanoic acid from phospholipid membranes is “10,000 times slower than long or medium chain fatty acids” (Singh and Pujol, 2010). Uto et al (2008) is supportive of this in demonstrating that accumulation of VLCFAs alters the plasma membrane and will eventually disrupt cell signalling. An example of this is seen as the viscosity of adrenocortical cell membranes in ALD patients is abnormally increased. In turn, this reaction decreases ACTH-stimulated cortisol secretions. In addition, Uto et al (2008 pg. 7) states that the high levels of TNF- α and IL-1 β cytokines will alter other membrane proteins required for cell-to-cell communication including lipid rafts, which may be damaged through VLCFA accumulation and superoxide radicals (Zhang et al, 2006).

Singh and Pujol (2010) noted that fibroblasts with a C26:0 excess, damaged membrane proteins due to oxidative stress. Damage was occurring in ALD fibroblasts and not on control fibroblasts in the presence of excess C26:0.

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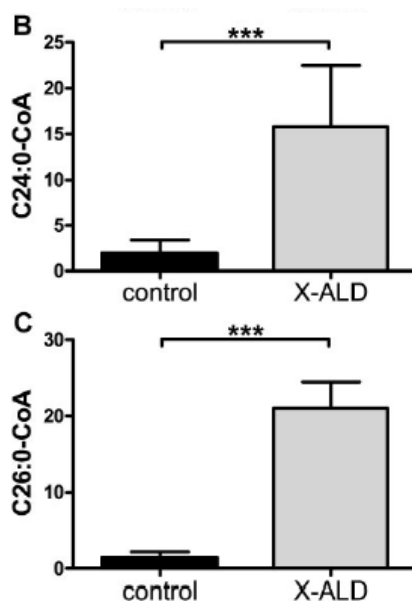
Hein et al (2008) explored the toxicity mechanisms of excess VLCFA in rats' neural cells and discovered changes in mitochondrial function, cellular calcium levels, and finally cell death. At levels of 20mmol/L and higher, VLCFAs (C22:0, C24:0, and C26:0) were seen to induce death of oligodendrocytes and astrocytes. Oligodendrocytes are more sensitive than astrocytes and neurons, and intracellular calcium levels were seen to increase in these cells. Mitochondrial function was altered due to increased levels of C22:0, as the membrane potential was significantly decreased. Cellular respiration was inhibited too, regardless of whether adenosine diphosphate (ADP) was present or absent. Hein et al (2008) concluded that eventually cell death was induced by excessive VLCFA accumulation through disrupting calcium homeostasis and mitochondrial function.

Fourcade et al (2008) explored the effects of excessive VLCFA accumulation on human fibroblasts. Doses up to 100uM generated ROS, depleted glutathione, and decreased mitochondrial membrane potential. Studies by Fourcade et al (2008) and Hein et al (2008) further demonstrated that mitochondrial damage and disturbance of membrane potential was apparent in neural cells and fibroblasts.

VLCFAs are synthesised through elongation pathways of long chain fatty acids (LCFAs) and it is the balance between fatty acid beta-oxidation and synthesis through elongation of LCFAs, which determines VLCFA levels. Ofman et al (2010 pg. 91) and Kemp et al (2005) states the different fatty acid breakdown capacities of ALD fibroblasts:

C22:0	25%
C24:0	25%
C26:0	15%
This demonstrates how C26:0 could accumulate with ease as this suggests the elongation of C22:0 and C24:0 to C26:0.	

Over-expression of ABCD1 (the defective gene in ALD) in yeast *Saccharomyces cerevisiae* allows the transport of fatty acyl-CoA esters of LCFAs and VLCFAs (C18:1w9, C16:0, C22:0, and C24:6w3) across the peroxisomal membrane. In turn, the peroxisomes acts upon them and prompts beta-oxidation. Based on this, Ofman et al (2010) explored whether CoA esters were elevated in ALD fibroblasts, as theoretically, a dysfunction of ABCD1 would cause raised cytosolic VLCFA acyl-CoA levels. After culturing ALD fibroblasts with C24:0 for 24 hours, C24:0 CoA and C:26 CoA levels were eight and fourteen times higher than when compared to the control:



This experiment showed that a defective ABCD1 gene caused increased cytosolic C24:0 CoA, which acted as a substrate and became further elongated to C26:0 CoA.

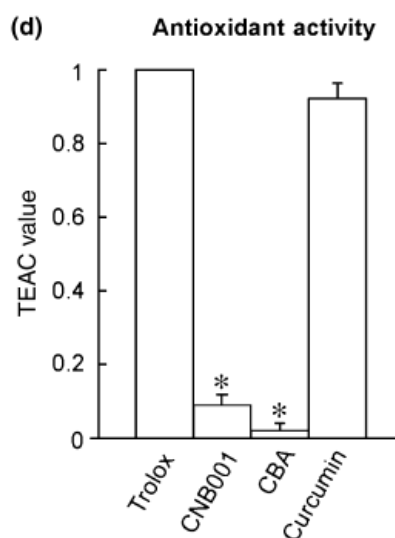
It is clear that increased consumption of very long chain fatty acids would likely lead to increased damage in ALD. It would therefore be advised to monitor and reduce the dietary intake of these fats.

FOODS

Food recommendations, which will benefit a patient with ALD, are outlined below. Broadly, it is important to note from the outset that foods should be fresh and organic; not been grown with chemicals. Fisher and Glass (2010) demonstrated the effect of paraquat and diquat, (two very common herbicides) on axonal health. Results showed that these chemicals increased cellular superoxide and caused “robust, dose-dependant axon degeneration” (Fisher and Glass, 2010 pg. 250). Fischer and Glass (2010) further emphasised this initial critical observation by stating that “axon degeneration precedes death of cell bodies”.

Turmeric (Curcuma Longa)

Curcumin, a polyphenolic compound, is the active component present in turmeric. Liu et al (2008) found that curcumin is neuro-protective and specifically protects against oxidative stress. Liu et al (2008, pg. 1342) suggest that this is because it acts as an antioxidant and scavenges peroxy-radicals and ROS. They compared the antioxidant activity of curcumin to Trolox (a water soluble derivative of Vitamin E), using the Trolox equivalent activity concentration (TEAC) assay. Results demonstrated that they elicited similar antioxidant effects (Liu et al 2008, pg. 1341):



Additionally, curcumin also has the ability to reduce inflammation, Ahmed S et al (2005) states that curcumin is an inhibitor of NF-kB as well as the AA cascade by blocking COX-2 and LOX, which are elevated in ALD. Therefore, less AA is incorporated into the lipid membranes, and there is less prostaglandin 2 (PGE2) and leukotriene B4 formation.

According to Jomova et al (2010), curcumin elicits a neuro-protective effect by reversing lipid peroxidation as demonstrated in rats with brain damage. Additionally, curcumin poses the ability to increase gamma-glutamylcysteine synthetase, which up-regulates glutathione production. Its neuroprotective role was also seen as curcumin protects a model of cells responsible for neuronal differentiation from oxidative damage. Jomova et al (2010, pg. 99) discusses the effect of curcumin on mice brains and noted that curcumin effectively suppresses inflammation and oxidative damage as a significant decrease of IL-1 β and oxidized protein was observed in the mice.

Mythri et al (2010) reported that curcumin has the ability to detoxify peroxynitrite, eliciting this protective mechanism in vitro and in vivo. They have successfully demonstrated this neuro-protective role of curcumin derivatives against oxidative stress and conclude that curcumin "...could serve as a potential neuroprotective ... in neurological disorders... involving oxidative stress" (Mythri et al 2010, pg. 8).

Matson and Cheng (2006) mention that the neuro-protective effect of curcumin derives from its ability to induce phase two enzymes. Matson and Cheng (2006) discussed the neuro-protective effects of curcumin in gerbils through dietary intake. Two months dietary supplementation of curcumin before induced brain ischemia demonstrated reduced neuronal damage and prevented motor deficits by suppressing apoptosis. Moreover, rats given dietary curcumin expressed reduced brain damage and "improved functional outcome" after brain injury (Matson and Cheng 2006, pg. 636). Takano et al (2007) states that curcumin can elicit a neuro-protective action as curcumin was seen to promote survival of dopaminergic neurons (Takano et al 2007, pg. C1893).

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Additionally, curcumin has the ability to block TNF- α , LP and interferon-gamma-induced NO production by inhibiting NF- κ B (Rahman I 2008, pg. 2 and Ippoushi et al 2003) and AP1 activation. It is through the suppression of AP1 activation, that inhibition of iNOS by curcumin takes place.

Rahman I (2008) states that curcumin elicits antioxidant properties against ROS, RNS, and nitric oxide in vitro and in vivo and that their findings demonstrates curcumin's ability to quench ROS within 1-4 hours, faster acting than other polyphenols they tested. This study further reiterates the points mentioned above regarding glutathione levels as Rahman I (2008) also found that curcumin induced antioxidant mechanisms by increasing glutathione production. Rahman I (2008) further observed that curcumin, through its anti-inflammatory action, has the ability to restore glucocorticoid efficacy, which would be particularly beneficial in ALD. Curcumin does this through restoring pro-inflammatory gene expression. The antioxidant mechanism of curcumin is evident through its ability to decrease lipid peroxidation and uphold activity of different antioxidant enzymes. As ROS is associated with ALD pathogenesis due to excess VLCFA accumulation, curcumin has the ability to contribute to the control of ALD through its antioxidant mechanism.

Olive Oil (Oleic acid) and Rapeseed Oil (Euricic acid)

A combination of these two oils make up the well-known concoction, Lorenzo's Oil (LO). Moser (2006) reports that dietary intake of these oils significantly lowers VLCFA levels in ALD patients within four weeks. This food oil, a 4:1 concoction of glyceryl-trioleate and glyceryl-trierucate, is used as a part of dietary therapy in ALD. In addition to lowering VLCFAs, it is reported to prevent the onset in two-thirds of susceptible boys (Lan et al, 2010).

Rapeseed oil derived from *Brassica napus*, contains a large amount of euricic acid (docos-13-enoic acid; C22:1), as seen in the table below:

Table 2. Fatty acid composition of rapeseed and low erucic acid (canola) oil compared to olive oil, soybean and sunflower

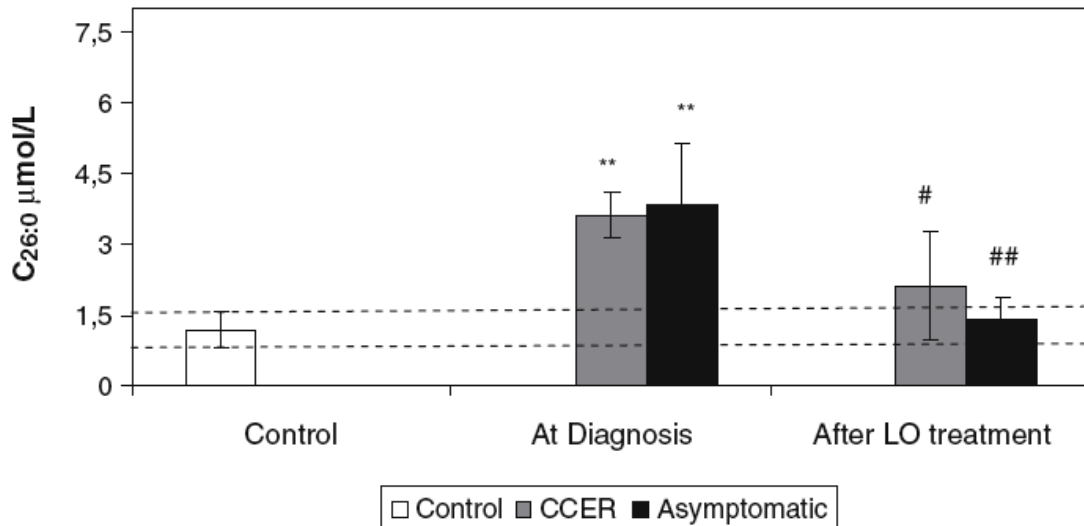
Oil type	Fatty acid composition in %						
	16:0	18:0	18:1	18:2	18:3	20:1	22:1
Rapeseed	4.0	1.5	17.0	13.0	9.0	14.5	41.0
Canola	4.1	1.8	63.0	20.0	8.6	1.9	0.0
Olive		15	75.0	9.0	1.0	0.0	0.0
Soy		14	28.0	50.0	7.0	0.0	0.0
Sunflower		12.5	20.0	66.0	0.1	0.0	0.0

The use of the two oils in ALD is aimed to diminish the synthesis of VLCFAs. Moser et al (2007) states that oleic acid (C18:1) reduced VLCFA synthesis in fibroblasts of ALD patients up to 50% in three months. Optimistically, Moser et al (2007) states that normalisation of VLCFA levels can be achieved by most patients. In order to lower VLCFA levels, plasma euricic acid levels must be maintained, however a total fat intake in excess of 30-35% may diminish the beneficial effects of this oil.

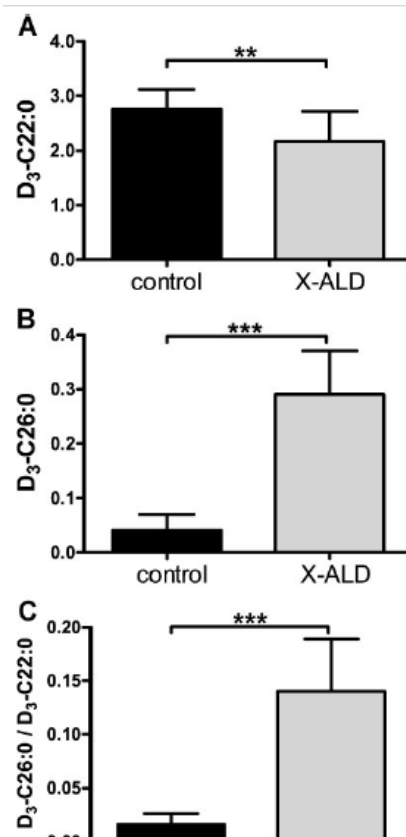
A study by Deon M et al (2008) successfully demonstrated the beneficial effects LO has on lowering C26:0. From the graph below (Deon M et al 2008, pg. 46), it is evident that concentrations of C26:0 decreased significantly in patients with childhood cerebral (CCER) ALD, and in asymptomatic patients. The dotted lines

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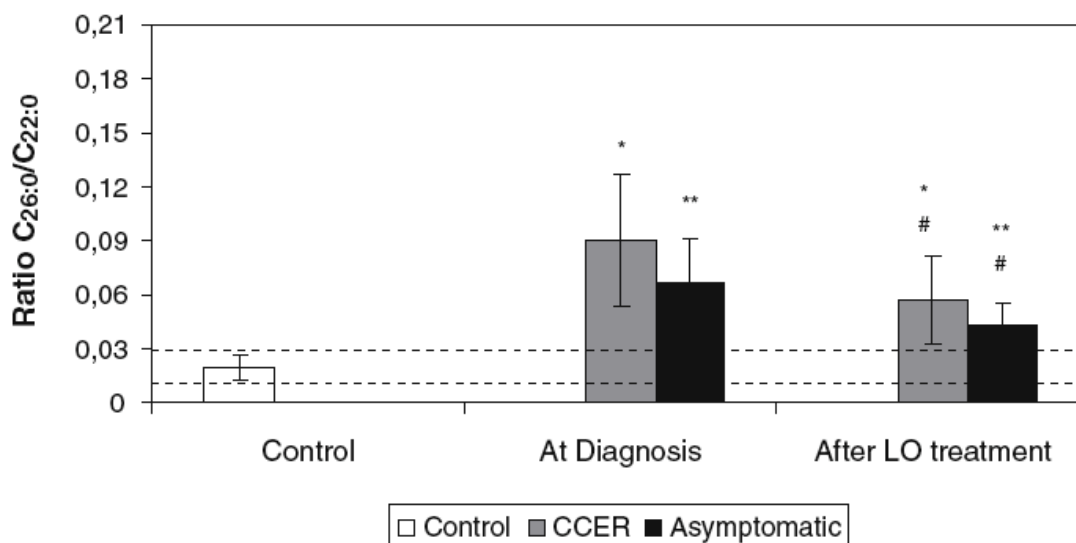
indicate normal ranges of C26:0. It is evident that in asymptomatic patients being treated with dietary LO, C26:0 plummeted from excessive amounts, more than the levels of CCER patients, to within the normal range:



Ofman et al (2010) endeavoured to confirm that in ALD, LCFAs were metabolised to VLCFAs and concluded that C24:0 was elongated to C26:0 in ALD cells. This was demonstrated by treating fibroblasts with C16:0. After three days, these fibroblasts had 20% lower levels of C22:0, seven times higher C26:0 and a nine fold increase of the ratio of C:26:0 : C22:0. This data is illustrated the tables below (Ofman et al 2010, pg. 91):



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Uto et al (2008) and Deon M et al (2008) further support this analysis. They report a significant accumulation in ALD lymphoblasts of a high C26:0 to C22:0 ratio. The graph above (Deon M et al 2008, pg. 46) illustrates the ratio of C26:0 to C22:0 in CCER and asymptomatic patients. It is clear that after dietary treatment of the LO, the ratio was brought down significantly.

The biochemical mechanism by which LO reduces VLCFA synthesis is due to competitive inhibition of elongation enzymes by fatty acids. If there is no competitive inhibition of enzymes, there will be continual and excessive production of VLCFAs, contributing to the neuro-inflammation and damage seen in ALD.

Golovko and Murphy (2006) compared brain uptake of AA and euristic acid, and found that euristic acid enters the brain at one-fifth the rate of AA. Furthermore, euristic acid was metabolised rapidly and sixty percent underwent beta-oxidation. This may suggest the importance of continually supplying a fat source that will compete with AA. AA is pro-inflammatory and “is well known to cross the blood brain barrier and be incorporated into brain compartments” (Moser et al 2007, pg. 108). Furthermore, as AA is incorporated to brain compartments, it would then pose its inflammatory role and up-regulate synthesis of inflammatory mediators, driving oxidative damage, which is highly undesirable in ALD as Moser et al (2007) states

that damage induced by inflammatory cytokines and chemokines, immunological reactions, and oxidative stress cannot be reversed.

In support of Golovko and Murphy (2006), Khan et al (2010) observed that the increase of PA2, 5-LOX, COX-2 and AA was correlated with VLCFAs in the ALD brain. As in mice, treating neural cells with exogenous VLCFAs (C26:0) resulted in an increased of 5-LOX, which further drives inflammation. When Khan et al (2010) purposely silenced the ABCD1 gene to mimic ALD, they noted that the combination of oleic and euristic acids significantly reduced VLCFAs, in turn reducing the expression of 5-LOX, and ultimately, a reduction of inflammatory mediators.

Ofman et al (2010) and Kemp and Wanders (2010) state that although a combination of the two oils has the ability to reduce plasma C26:0 levels, it cannot stop the progression of the disease. Moser et al (2007) states that although it cannot stop the progression of ALD, the oil may pose a preventative effect in neurologically asymptomatic patients with ALD and may slow the degeneration in AMN. From the information provided, it indicates that there is benefit in early detection of ALD, and that early treatment with LO may be helpful.

Ginger (Zingiber Officinale)

6-Gingerol, a phenolic compound contained in ginger, plays a major role in acting to block the COX-2 pathway. COX-2 enzymes will drive inflammation and oxidative stress, and in ALD will further potentiate neurodegeneration. Nitric oxide, has the ability to react with oxygen and superoxide to form reactive nitrogen species and directly or indirectly cause DNA damage and mutation. Ahmed et al (2005) attributes the beneficial anti-inflammatory effects of ginger to its ability to block COX and LOX pathways which in turn inhibits the production of inflammatory PGE2 and leukotriene B4.

The following protective mechanisms of 6-gingerol have been demonstrated by Ippoushi et al (2003):	
Inhibits NO production	Ippoushi et al 2003 (pg. 3432), treated macrophages which exhibited LP-induced NO expression with 6-gingerol; and observed an inhibition of NO. The reduction of nitric oxide was not due to cell death, indicating the anti-inflammatory action of ginger.
Inhibits iNOS	Ippoushi et al 2003 (pg. 3432) treated LP stimulated macrophages with 6-gingerol and observed a reduction of iNOS levels altogether when compared to LP induced control cells. As such, upregulation of iNOS will lead to increased production of NO and 6-gingerol acts to inhibit iNOS induction.
Protects against oxidation	Ippoushi et al 2003, pg. 3433
Protects against DNA damage	Peroxynitrite induced oxidation was seen to be inhibited by 6-gingerol as demonstrated by Ippoushi et al (2003).

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	<p>Peroxynitrite is a ROS derivative which can cause oxidative damage to “mitochondria and damage macromolecules, such as DNA, proteins and lipids” (Ippoushi et al 2003, pg. 3428). DNA is vulnerable and susceptible to peroxynitrite oxidative damage, which may lead to breakage of strands as well as modify base subunits. Modification of bases may potentially cause genetic mutation, which in ALD is the underlying cause of the disease.</p>
Protects against protein damage	Ippoushi et al 2003, pg. 3435

Ansari et al (2008) demonstrated that ginger acts to decrease inflammation by direct attack of free radicals and will also reduce lipid peroxidation. Ansari et al (2008, pg. 148) also discusses how ginger significantly decreases protein oxidation in diabetic rats. Rats were seen with high markers of oxidative stress, and those which were treated with ginger saw significantly lower levels. Glycosylated haemoglobin, another marker of inflammation was measured in rats by Ansari et al (2008) and much higher levels were seen in the control group as opposed to rats administered with ginger. Their study also showed an increase of SOD in rats not treated with ginger, indicating that ginger may be a scavenger of the free oxygen radicals, and that it potentially prevents the increase of SOD in the experimental group.

Ahmed et al (2008) demonstrated that oxidative damage in male rats exposed to synthetic pesticide Lindane, were protected by ginger. Rats exposed to Lindane saw an increase in SOD activity, indicating a higher need for antioxidant action and levels of SOD were reduced when ginger was given. Similarly catalase, another enzyme quenching ROS and controlling hydrogen peroxide levels, was seen to decrease significantly in diabetic rats (control). Ansari et al (2008) demonstrated that the consumption of ginger was able to restore the levels of catalase to normal. In addition, serum glutathione levels were decreased in rats exposed to Lindane whilst increasing

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activity of glutathione dependant enzymes. However, the feeding of ginger altered enzyme function and “restored activity to near normal” (Ahmed et al 2008, pg. 903). Ahmed et al (2008) gathers that ginger is protective against oxidative stress and improves host antioxidant systems. Additionally, ginger may be beneficial in neutralising the effects of toxic free radicals by reducing lipid peroxidation. In sum, the mechanisms of actions mentioned above concerning ginger would be incredibly beneficial in the case of ALD.

Research Proposal

<p>The proposal is to conduct research surrounding LO (4:1 ratio of glyceryl-trioleate and glyceryl-trierucate) therapy alongside antioxidant therapy in ALD for 2-3 years. The purpose is to explore what degree of benefit antioxidant therapy will give in early/developing ALD and to examine the effect of the combination of both LO and antioxidants. The aim for this to be carried out is to give antioxidants and LO a definite place/relevance in ALD therapy.</p>	
Design methods	Placebo-controlled double blind study of the efficacy of LO and LO with antioxidants.
Sample population and size	At least 100 participants, boys with early ALD, they may be asymptomatic and may not have cognitive manifestations yet. The ages of the boys may vary, depending on the age of their diagnosis, however it would be more beneficial if they were younger and ALD was therefore less aggressive in order to thoroughly explore the benefit of LO and antioxidants in preventing further neurodegeneration.
Data collections methods	<p>Because ALD is X-linked, it would be possible to screen boys who have known X-ALD relatives, or family members. It would also be beneficial to screen boys with idiopathic Addison's disease.</p> <p>Continue to take data of individuals monthly, and do an overall monthly data analysis. At baseline and at every month during the study, participants will be required to get MRIs and undergo cognitive/sensory/motor testing, measure plasma VLCFAs and VLCFA ratio, markers of oxidative stress, and assess adrenal function monthly.</p> <p>It is essential to ensure excellent communication between the participant, the participant's family, specialist/neurologist, nutritionist, and laboratories. Finally, Participants have the option to terminate or opt</p>

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	out at any time.
Main variables being measured	Very long chain fatty acid levels, and ratio of C26:0 to C22:0, ACTH, markers of oxidative stress, cognitive function, radiological (MRI) examination.
Intervention to be studied	Group 1: LO Group 2: LO + ascorbic acid (500mg TDS) + a-tocopherol (200IU/Day) Group 3: No treatment.

CONCLUSION

Based on the studies explored in this paper, nutritional and dietary intervention holds a promising position in the maintenance of ALD. Antioxidant therapy particularly has shown to markedly decrease oxidative stress and may therefore be used as a tool to prevent further progression of the disease in ALD sufferers. Dietary treatment with close monitoring of fat intake has progressively shown to be beneficial in ALD as VLCFA accumulation is a key contributor to the advancement of ALD. In sum, nutritional treatment should be considered more thoroughly as adjunct treatment in order to maintain a patient's quality of life whilst being subjected to such a debilitating condition.

REFERENCES

Ahmed RS, Suke SG, Seth V, Chakraborti A, Tripathi AK, Banerjee BD, 2008, 'Protective effects of dietary ginger (*Zingiber officinale* Rosc.) on Lindane-induced oxidative stress in rats', *Phytother. Res*, 22:902, viewed 1 November 2010,

<<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/doi/10.1002/ptr.2412/pdf>>

Ahmed S, Anuntiyo J, Malemud CJ, Haqqi TM, 2005, 'Biological Basis for the Use of Botanicals in Osteoarthritis and Rheumatoid Arthritis: A Review', *Evidence-Based Complementary and Alternative Medicine*, 2:301-308, viewed 1 November 2010,

<<http://www.hindawi.com/journals/ecam/2005/409178.abs.html>>

Al-Omar MA, 2006, 'The X-Linked Adrenoleukodystrophy (X-ALD) and Oxidative Stress', *Journal of Herbal Pharmacotherapy*, 6:125-134, viewed 1 November 2010,

<http://informahealthcare.com.ezproxy.lib.monash.edu.au/doi/abs/10.1080/J157v06n03_07?prevSearch=allfield%253A%2528The%2BX-Linked%2BAdrenoleukodystrophy%2B%2528X-ALD%2529%2Band%2BOxidative%2BStress%2529&searchHistoryKey=>>

Ansari K, Karimipour M, Salami S, Shirpoor A, 2008, 'The Effect of Ginger (*Zingiber officinale*) on Oxidative Stress Status in the Small Intestine of Diabetic Rats', *Int J Endocrinol Metab*, 3:144-140, viewed 1 November 2010,

<http://www.sid.ir/En/VEWSSID/J_pdf/101120080307.pdf>

Aranda A, Olmo M, 2003, 'Response to acetaldehyde stress in the yeast *Saccharomyces cerevisiae* involves a strain-dependent regulation of several *ALD* genes and is mediated by the general stress response pathway', *Yeast*, 20:747-759, viewed 1 November 2010,

<<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/doi/10.1002/yea.991/full>>

Assies J, Haverkort EB, Lieverse R, Vreken P, 2003, 'Effect of dehydroepiandrosterone supplementation on fatty acid and hormone levels in patients

with with X-linked adrenoleucodystrophy', *Clinical Endocrinology*, 59:459-466, viewed 1 November 2010,

<<http://ehis.ebscohost.com.ezp.lib.unimelb.edu.au/eds/detail?vid=1&hid=101&sid=c607d948-7ab0-4d03-8820-e16b6ec56903%40sessionmgr113&bdata=JnNpdGU9ZWRzLWxpdmU%3d#db=mnh&AN=14510908>>

Bagh MB, Thakurta I, Biswas M, Behera P, Chakrabarti S, 2010, 'Age-related oxidative decline of mitochondrial functions in rat brain is prevented by long term antioxidant supplementation', *Biogerontology*, 11, viewed 1 November 2010,

<<http://www.springerlink.com.ezp.lib.unimelb.edu.au/content/70m2555727g61p39/>>

Bagh MB, Maiti AK, Roy A, Chakrabarti S, 2008, 'Dietary supplementation with *N*-acetylcysteine, a-tocopherol and a-lipoic acid prevents age related decline in Na⁺, K⁺-ATPase activity and associated peroxidative damage in rat brain synaptosomes', *Biogerontology*, 9:421-428, viewed 1 November 2010,

<<http://www.springerlink.com.ezp.lib.unimelb.edu.au/content/m22184t42812822r/>>

Bao B, Prasad AS, Beck FWJ, Fitzgerald JT, Snell D, Bao GW, Singh T, Cardozo LJ, 2010, 'Zinc decreases c-reactive protein, lipid peroxidation, and inflammatory cytokines in elderly subjects: a potential implication of zinc as an atheroprotective agent', *Am J Clin Nutr*, 91: 1634-41, viewed 1 November 2010,

<<http://www.ajcn.org.ezp.lib.unimelb.edu.au/cgi/content/full/91/6/1634>>

Bao B, Prasad AS, Beck FWJ, Snell D, Suneja A, Sarkar FH, Doshi N, Fitzgerald JT, Swerdlow J, 2008, 'Zinc supplementation decreases oxidative stress, incidence of infection, and generation of inflammatory cytokines in sickle cell disease patients', *Transl Res*, 152:67-80, viewed 1 November 2010,

<http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B83WW-4SYKWK1-1&_user=559483&_coverDate=08/31/2008&_rdoc=1&_fmt=high&_orig=search&_origin=search&_sort=d&_docanchor=&view=c&_acct=C000028178&_version=1&_u>

[rlVersion=0&_userid=559483&md5=b1da5b1fd83e60acdf34ca06c1536a4b&searchtype=a>](#)

Batra N, 2005, Optimisation of Trierucin Content in Oilseed Rape, Master of Science Thesis, Rheinisch-Westfaelischen Technischen Hochschule Aachen.

Berger J, Pujol A, Aubourg P, Forss-Petter S, 2010, 'Current and future pharmacological treatment strategies in X-linked adrenoleukodystrophy', *Brain Pathol* 20:845–856, viewed 1 November 2010,
<<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/doi/10.1111/j.1750-3639.2010.00393.x/full>>

Bonkowsky JL, Nelson C, Kingston JL, Filloux FM, Mundorff MB, Srivastava R, 2010, 'The burden of inherited leukodystrophies in children', *Neurology*, 75:718-725, viewed 1 November 2010,
<<http://www.mdconsult.com.ezp.lib.unimelb.edu.au/das/article/body/225397643-3/jorg=journal&source=MI&sp=23562120&sid=1078895556/N/761738/1.html?issn=0028-3878>>

Bouwens M, Afman LA, Muller M, 2008, 'Activation of peroxisome proliferator-activated receptor alpha in human peripheral blood mononuclear cells reveals an individual gene expression profile response', *BMC Genomics*, 9:262, viewed 1 November 2010,
<<http://www.biomedcentral.com/1471-2164/9/1/262>>

Brand A, Schonfield E, Isharel I, Yavin E, 2008, 'Docosahexanoic acid-dependent iron accumulation in oligodendroglia cells protects from hydrogen peroxide-induced damage', *J Neurochem*, 105:1325-1335, viewed 1 November 2010,
<<http://ehis.ebscohost.com.ezp.lib.unimelb.edu.au/eds/detail?vid=1&hid=101&sid=5520193b-9965-479d-bcff-7c59c0949baf%40sessionmgr112&bdata=JnNpdGU9ZWRzLWxpdmU%3d#db=mnh&AN=18208540>>

Brock TG, 2005, 'Regulating leukotriene synthesis: the role of nuclear 5-lipoxygenase', *J Cell Biochem*, 96:1203-1211, viewed 1 November 2010, <<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/doi/10.1002/jcb.20662/full> >

Cartier N, Aubourg P, 2010, 'Hematopoietic Stem Cell Transplantation and Hematopoietic Stem Cell Gene Therapy in X-Linked Adrenoleukodystrophy', *Brain Pathology*, 20:857-862, viewed 1 November 2010, <<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/doi/10.1111/j.1750-3639.2010.00394.x/full> >

Charnas L, Tolar J, Orchard PJ, 2007, 'N-Acetyl-L-cysteine improves outcome of advanced cerebral adrenoleukodystrophy', *Molecular Genetics and Metabolism*, 92:23-24, viewed 1 November 2010, <http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B6WNG-4PXNHVJ-1X&_user=559483&_coverDate=12/31/2007&_alid=1528056113&_rdoc=4&_fmt=high&_orig=search&_origin=search&_zone=rslt_list_item&_qd=1&_cdi=6962&_docanchor=&view=c&_ct=4&_acct=C000028178&_version=1&_urlVersion=0&_userid=559483&md5=c03583b47bfec1edfdee90dbc1a80cea&searchtype=a >

Deon M, Garcia MP, Sitta A, Barschak AG, Coelho DM, Schimit GO, Pigatto M, Jardim LM, Wajner M, Giugliani R, Vargas CR, 2008, 'Hexacosanoic and docosanoic acids plasma levels in patients with cerebral childhood and asymptomatic X-linked adrenoleukodystrophy: Lorenzo's oil effect', *Metab Brain Dis*, 23:43-49, viewed 1 November 2010, <<http://www.springerlink.com.ezp.lib.unimelb.edu.au/content/m502721201q03515/> >

Devore EE, Khang JH, Stampfer MJ, Grodstein F, 2010, 'Total antioxidant capacity of diet in relation to cognitive function and decline', *Am J Clin Nutr*, 92:1157-64, viewed 1 November 2010, <<http://www.ajcn.org.ezp.lib.unimelb.edu.au/cgi/content/abstract/92/5/1157> >

Eichler FS, Ren JQ, Cossoy M, Rietsch AM, Nagpal S, Moser AB, 2008 'Is

microglial apoptosis an early pathogenic change in cerebral X-linked adrenoleukodystrophy?’ *Ann Neurol* 63:729–742, viewed 1 November 2010, <<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/doi/10.1002/ana.21391/abstract>>

Engelen M, Ofman R, Dijkgraaf MGW, Hizen M, van der Wardt LA, van Geel BM, de Visser M, Wanders RJA, Poll-The BW, Kemp S, 2010, ‘Lovastatin in X-Linked Adrenoleukodystrophy’, *N Engl J Med*, 362:276-277, viewed 1 November 2010, <<http://www.nejm.org.ezp.lib.unimelb.edu.au/doi/full/10.1056/NEJMc0907735>>

Farooqui AA, Ong WY, Horrocks LA, 2006, ‘Inhibitors of brain phospholipase A2 activity: their neuropharmacological effects and therapeutic importance for the treatment of neurologic disorders’, *Pharmacol Rev*, 58:591–6, viewed 1 November 2010, <<http://pharmrev.aspetjournals.org.ezp.lib.unimelb.edu.au/content/58/3/591.full>>

Ferrer I, Aubourg P, Pujol A, 2010, ‘General aspects and neuropathology of X-linked adrenoleukodystrophy’, *Brain Pathol*, 20:4, viewed 1 November 2010, <<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/doi/10.1111/j.1750-3639.2010.00390.x/full>>

Ferrer I, Kapfhammer JP, Hindelang C, Kemp S, Troffer-Charlier N, Broccoli V, Callyzot N, Mooyer P, Selhorst J, Vreken P, Wanders RJA, Mandel JL, Pujol A, 2005, ‘Inactivation of the peroxisomal ABCD2 transporter in the mouse leads to late-onset ataxia involving mitochondria, Golgi and endoplasmic reticulum damage’, *Human Molecular Genetics*, 14:3565-3577, viewed 1 November 2010, <<http://hmg.oxfordjournals.org.ezp.lib.unimelb.edu.au/content/14/23/3565.full?sid=e0e40b60-cd56-4973-b50d-2e94616f7153>>

Fischer LR, Glass JD, 2010, ‘Oxidative stress induced by loss of Cu,Zn-superoxide dismutase (SOD) or superoxide-generating herbicides causes axonal degeneration in mouse DRG cultures’, *Acta Neuropathol*, 119:249-259, viewed 1 November 2010, <<http://www.springerlink.com.ezp.lib.unimelb.edu.au/content/32q6wh2v40642647/>>

Fourcade S, Lopez-Erauskin J, Galino J, Duval C, Naudi A, Jove M, Kemp S, Villaroya F, Ferrer I, Pamplona R, Portero-Otin M, Pujol A, 2008, 'Early oxidative damage underlying neurodegeneration in X-adrenoleukodystrophy', *Hum Mol Genet* 17:1762–1773, viewed 1 November 2010,

<<http://hmg.oxfordjournals.org.ezp.lib.unimelb.edu.au/content/17/12/1762.full> >

Fourcade S, Ruiz M, Camps C, Schutler A, Houten SM, Mooyer PAW, Pampols T, Dacremont G, Wanders RJA, Giros M, Pujol A, 2009, 'A key role for the peroxisomal *ABCD2* transporter in fatty acid homeostasis', *Am J Physiol Endocrinol Metab*, 296:211-221, viewed 1 November 2010,

<<http://ajpendo.physiology.org.ezp.lib.unimelb.edu.au/cgi/content/full/296/1/E211> >

Golovko MY, Murphy EJ, 2006, 'Uptake and metabolism of plasma-derived euristic acid by rat brain', *J Lipid Res*, 47:1289-1297, viewed 1 November 2010,

<<http://www.jlr.org.ezp.lib.unimelb.edu.au/content/47/6/1289.full> >

Gosalakkal J, Balky AP, 2010, 'Intra familial phenotypical variations in adrenoleukodystrophy', *Neurology India*, 58:109-112, viewed 1 November 2010,

<<http://ehis.ebscohost.com.ezp.lib.unimelb.edu.au/eds/detail?vid=1&hid=101&sid=c43ad342-4d7c-4f55-a31a-ae3be005b23%40sessionmgr115&bdata=JnNpdGU9ZWRzLWxpdmU%3d#db=a9h&AN=49019138> >

Harrison FE, May JM, 2009, 'Vitamin C function in the brain: vital role of the ascorbate transporter SVCT2', *Free Radical Biology & Medicine*, 46:719-730, viewed 1 November 2010,

<http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B6T38-4V9S3G0-1&_user=559483&_coverDate=03%2F15%2F2009&_rdoc=4&_fmt=high&_orig=browse&_origin=browse&_zone=rslt_list_item&_srch=doc-info%28%23toc%234940%232009%23999539993%23941139%23FLA%23display%23Volume%29&_cdi=4940&_sort=d&_docanchor=&_ct=19&_acct=C000028178 >

[&_version=1&_urlVersion=0&_userid=559483&md5=256c1d9330fec0e4452acf6e7aab7aa9&searchtype=a](#) >

Hein S, Schonfeld P, Kahlert S, Reiser G, 2008, 'Toxic effects of X-linked adrenoleukodystrophy-associated, very long chain fatty acids on glial cells and neurons from rat hippocampus in culture', *Hum Mol Genet* 17:1750–1761, viewed 1 November 2010,

<<http://hmg.oxfordjournals.org.ezp.lib.unimelb.edu.au/content/17/12/1750.full> >

Herrera E, Jimenez R, Aruoma O, Hercberg S, Sanchez-Garcia I, Fraga C, 2009, 'Aspects of antioxidant foods and nutrients in health and disease', *Nutrition Reviews*, 67:S140-144, viewed 1 November 2010,

<<http://onlinelibrary.wiley.com/doi/10.1111/j.1753-4887.2009.00177.x/full> >

Ippoushi K, Azuma K, Ito H, Horie H, Higashio H, 2003, '[6]-Gingerol inhibits nitric oxide synthesis in activated J774.1 mouse macrophages and prevents peroxynitrate-induced oxidation and nitration reactions', *Life Sciences*, 73:3427-3437, viewed 1 November 2010,

<http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B6T99-49SKSWW-7&_user=559483&_coverDate=11%2F14%2F2003&_rdoc=1&_fmt=high&_orig=search&_origin=search&_sort=d&_docanchor=&view=c&_acct=C000028178&_version=1&_urlVersion=0&_userid=559483&md5=6a8000167997d8f4c7a80d356fa4ccbd&searchtype=a >

Jenkins DD, Chang E, Singh I, 2009, 'Neuroprotective Interventions: Is It Too Late?', *J Child Neurol*, 24:1212, viewed 1 November 2010,

<<http://jcn.sagepub.com/content/24/9/1212> >

Jomova K, Vondrakova D, Lawson M, Valko M, 2010, 'Metals, oxidative stress and neurodegenerative disorders', *Mol Cell Biochem*, 345:91-104, viewed 1 November 2010, <<http://www.springerlink.com/content/r3258750lr62n308/> >

Kagitani-Shimono K, Mohri I, Fujitani Y, Suzuki K, Ozono K, Urade Y, Taniike M, 2005, 'Anti-inflammatory therapy by ibudilast, a phosphodiesterase inhibitor, in demyelination of twitcher, a genetic demyelination model', *Journal of Neuroinflammation*, 2:10, viewed 1 November 2010, <<http://www.jneuroinflammation.com/content/2/1/10> >

Kemp S, Wanders RJA, 2007, 'X-linked adrenoleukodystrophy: Very long chain fatty acid metabolism, ABC half-transporters and the complicated route to treatment', *Molecular Genetics and Metabolism*, 90:268-276, viewed 1 November 2010, <http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B6WNG-4M9414N-2&_user=559483&_coverDate=03/31/2007&_rdoc=1&_fmt=high&_orig=search&_origin=search&_sort=d&_docanchor=&view=c&_acct=C000028178&_version=1&_urlVersion=0&_userid=559483&md5=4d529535cda6ac9fd1e2c2a20bceb569&searchtype=a >

Kemp S, Valianpour F, Denis S, Ofman R, Sanders R-J, Mooyer P, Barth PG, Wanders RJA, 2005, 'Elongation of very long-chain fatty acids is enhanced in X-linked adrenoleukodystrophy', *Molecular Genetics and Metabolism*, 84:144-151, viewed 1 November 2010, <http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B6WNG-4DTKMPJ-1&_user=559483&_coverDate=02/28/2005&_rdoc=1&_fmt=high&_orig=search&_origin=search&_sort=d&_docanchor=&view=c&_acct=C000028178&_version=1&_urlVersion=0&_userid=559483&md5=c0e433406b15e0ab918a52c5e8acd768&searchtype=a >

Kemp S, Wanders R, 2010, 'Biochemical Aspects of X-Linked Adrenoleukodystrophy', *Brain Pathology*, 20:831-837, viewed 1 November 2010, <<http://onlinelibrary.wiley.com/doi/10.1111/j.1750-3639.2010.00391.x/full> >

Khan M, Singh J, Gilg AG, Uto T, Singh I, 2010, 'Very long-chain fatty acid

accumulation causes lipotoxic response via 5-lipoxygenase in cerebral adrenoleukodystrophy', *J Lipid Res*, 51:1685-1695, viewed 1 November 2010, <<http://www.jlr.org.ezp.lib.unimelb.edu.au/content/51/7/1685.full> >

Khan M, Singh J, Singh I, 2008, 'Plasmalogen deficiency in cerebral adrenoleukodystrophy and its modulation by lovastatin', *J Neurochem*, 106:1766-1779, viewed 1 November 2010, <<http://ehis.ebscohost.com.ezp.lib.unimelb.edu.au/eds/detail?vid=9&hid=101&sid=5520193b-9965-479d-bcff-7c59c0949baf%40sessionmgr112&bdata=JnNpdGU9ZWRzLWxpdmU%3d#db=mnh&AN=18540993> >

Kim WJ, Weickert S, Garner B, 2008, 'Role of ATP binding cassette transporters in brain lipid transport and neurological disease', *J Neurochem*, 104:1145-1166, viewed 1 November 2010, <<http://ehis.ebscohost.com.ezp.lib.unimelb.edu.au/eds/detail?vid=1&hid=101&sid=0d70a206-8462-46e6-8a6d-d112fb829694%40sessionmgr115&bdata=JnNpdGU9ZWRzLWxpdmU%3d#db=mnh&AN=17973979> >

Klockgether T, Wullner U, 2006, 'Methionine metabolism and phenotypic variability in X-linked adrenoleukodystrophy', *Neurology*, 66:442-443, viewed 1 November 2010, <http://ovidsp.tx.ovid.com.ezp.lib.unimelb.edu.au/sp-3.2.4b/ovidweb.cgi?&S=HLCBFPFHOODDMCIHNCDLHBOBNEGAAA00&Link+Set=S.sh.15.17.22.27|36|sl_10>

Kumar N, 2010, 'Neurologic Presentations of Nutritional Deficiencies', *Neurol Clin*, 28:107-170, viewed 1 November 2010, <<http://www.mdconsult.com.ezp.lib.unimelb.edu.au/das/article/body/225397643-7/jorg=journal&source=MI&sp=22722588&sid=1078920590/N/725445/1.html?issn=0733-8619> >

Lan F, Wang Z, Ke L, Xie H, Huang L, Huang H, Tu X, Zheng D, Zeng J, Li H, Yang B, 2010, 'A rapid and sensitive protocol for prenatal molecular diagnosis of X-linked adrenoleukodystrophy', *Clinica Chimica Acta*, 411:1992-1997, viewed 1 November 2010,

<http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B6T57-50W1TJM-2&_user=559483&_coverDate=12/14/2010&_rdoc=1&_fmt=high&_orig=search&_origin=search&_sort=d&_docanchor=&view=c&_acct=C000028178&_version=1&_urlVersion=0&_userid=559483&md5=3ef0f7bfecb25da52616d9da7150feae&searchtype=a>

Leonarduzzi G, Sottero B, Poli G, 2010, 'Targeting tissue oxidative damage by means of cell signaling modulators: The antioxidant concept revisited', *Pharmacology & Therapeutics*, 128:336-374, viewed 1 November 2010,

<http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TBG-50V2072-3&_user=10&_coverDate=11%2F30%2F2010&_rdoc=6&_fmt=high&_orig=browse&_origin=browse&_zone=rslt_list_item&_srch=doc-info%28%23toc%235142%232010%23998719997%232433739%23FLA%23display%23Volume%29&_cdi=5142&_sort=d&_docanchor=&_ct=8&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=cfc50c8214822e23794c0b8fdef8bf7&searchtype=a>

Linnebank M, Kemp S, Wanders RJA, Kleijer WJ, van der Sterre MLT, Gartner J, Fliesbach K, Semmler A, Sokolowski P, Kohler W, Schlegel U, Schmidt S, Kassmann CM, Lappe-Siefke C, Baes M, Brugger B, Mildner A, Werner HB, Natt O, Michaelis T, Prinz M, Frahm J, Klaus-Armin N, 2007, 'Axonal loss and neuroinflammation caused by peroxisome –deficient oligodendrocytes', *Nature Genetics*, 39:969-976, viewed 1 November 2010,

<<http://proquest.umi.com.ezproxy.lib.monash.edu.au/pqdweb?index=0&did=1311402341&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1288920439&clientId=16397>>

Linnebank M, Semmler A, Kleijer WJ, van der Sterre MLT, Gartner J, Fliesbach K, Sokolowski P, Kohler W, Schlegel U, Klockgether T, Wanders RJA, Schmidt S, Wullner U, Kemp S, 2006, 'The Cystathionine Beta-Synthase Variant c.844_845ins68 Protects Against CNS Demyelination in X-linked Adrenoleukodystrophy', *Human Mutation*, 930, viewed 1 November 2010, <<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/doi/10.1002/humu.9459/abstract>>

Liu Y, Dargusch R, Maher P, Schubert D, 2008, 'A broadly neuroprotective derivative of curcumin', *J Neurochem*, 105:1336-1345, viewed 1 November 2010, <<http://ehis.ebscohost.com.ezp.lib.unimelb.edu.au/eds/detail?vid=1&hid=101&sid=7c299c26-b731-4a39-9e91-4b66e17ab073%40sessionmgr115&bdata=JnNpdGU9ZWRzLWxpdmU%3d#db=a9h&AN=31777607>>

Mattson MP, Cheng A, 2006, 'Neurohormetic phytochemicals: low-dose toxins that induce adaptive neuronal stress responses', *Trends Neurosci*, 29:632-639, viewed 1 November 2010, <http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B6T0V-4M04DV1-2&_user=559483&_coverDate=11/30/2006&_rdoc=1&_fmt=high&_orig=search&_origin=search&_sort=d&_docanchor=&view=c&_acct=C000028178&_version=1&_urlVersion=0&_userid=559483&md5=0d76f5dab9826dc794153e2553894618&searchtype=a>

Mariani E, Cornacchiola V, Polidori MC, Mangialasche F, Malavolta M, Cecchetti R, P Bastiani, Baglioni M, E Mocchegiani, P Mecocci, 2006, 'Antioxidant enzyme activities in healthy old subjects: influence of age, gender and zinc status', *Biogerontology*, 7:391-398, viewed 1 November 2010, <<http://www.springerlink.com.ezproxy.lib.monash.edu.au/content/k373332757820805/>>

Moser HW, Moser AB, Hollandsworth K, Brereton NH, Raymond GV, 2007, '“Lorenzo’s Oil” Therapy for X-linked Adrenoleukodystrophy: Rationale and Current Assessment of Efficacy', *J Mol Neurosci*, 33:105-113. , viewed 1 November 2010,

<<http://www.springerlink.com.ezp.lib.unimelb.edu.au/content/9664r05136022034/>>

Moser HW, 2006, 'Therapy of X-Linked Adrenoleukodystrophy', *NeuroRx*, 3:246-253, viewed 1 November 2010,

<http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B82Y2-4JJ69XJ-D&_user=559483&_coverDate=04%2F30%2F2006&_rdoc=1&_fmt=high&_orig=search&_origin=search&_sort=d&_docanchor=&view=c&_acct=C000028178&_version=1&_urlVersion=0&_userid=559483&md5=1f2f162013f8e1067de1a4bf5f8bc6c6&searchtype=a>

Moser HW, Raymond GV, Dubey P, 2005, 'Adrenoleukodystrophy: New approaches to neurodegenerative disease', *JAMA*, 294:3131-31314, viewed 1 November 2010,

<<http://jama.ama-assn.org.ezp.lib.unimelb.edu.au/cgi/content/abstract/294/24/3131>>

Mythri RB, Harish G, Dubey SK, Misra K, Bharath MMS, 2010, 'Glutamoyl diester of the dietary polyphenol curcumin offers improved protection against peroxynitrite-mediated nitrosative stress and damage of brain mitochondria in vitro: implications for Parkinson’s disease', *Mol Cell Biochem*, 345, viewed 1 November 2010,

<<http://www.springerlink.com/content/ew56891pk3062n87/>>

Nasser M, Javaheri H, Fedorowicz Z, Noorani Z, 2009, 'Carnitine supplementation for inborn errors of metabolism', *Cochrane Database of Systematic Reviews*, 2, viewed 1 November 2010,

<<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/o/cochrane/clsysrev/articles/C006659/frame.html>>

Ofman R, Dijkstra IME, van Roermund CWT, Burger N, Turkenburg M, van Cruchten A, van Engen CE, Wanders RJA, Kemp S, 2010, 'The role of ELOVL1 in

very long-chain fatty acid homeostasis and X-linked adrenoleukodystrophy', *EMBO Mol Med*, 2:90-97, viewed 1 November 2010, <<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/doi/10.1002/emmm.201000061/full> >

Ogawa Y, Saito Y, Nishio K, Yoshida Y, Ashida H, Niki E, 2008, 'g-Tocopheryl quinone, not a-tocopheryl quinone, induces adaptive response through up-regulation of cellular glutathione and cysteine availability via activation of ATF4', *Free Radical Research*, 42:674-678, viewed 1 November 2010, <<http://ehis.ebscohost.com.ezp.lib.unimelb.edu.au/eds/pdfviewer/pdfviewer?vid=3&hid=102&sid=6fc431b1-be10-4adc-9d38-da3185dbb812%40sessionmgr114> >

Palaniappan AR, Dai A, 2010, 'Mitochondrial Ageing and the Beneficial role of a-Lipoic Acid', *Neurochemical Research*, 32:1552-1558, viewed 1 November 2010, <<http://www.springerlink.com.ezp.lib.unimelb.edu.au/content/t888v018476u3563/> >

Powers JM, Pei Z, Heinzer AK, Deering R, Moser AB, Moser HW, Watkins PA, Smith KD, 2005, 'Adreno-leukodystrophy: Oxidative Stress of Mice and Men', *Journal of Neuropathology and Experimental Neurology*, 64:1067, viewed 1 November 2010, <<http://proquest.umi.com.ezproxy.lib.monash.edu.au/pqdweb?index=0&did=947391451&SrchMode=1&sid=2&Fmt=4&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1288921094&clientId=16397> >

Press C, Milbrandt J, 2008, 'Nmnat Delays Axonal Degeneration Caused by Mitochondrial and Oxidative Stress', *J Neurosci*, 28:4861-4871, viewed 1 November 2010, <<http://www.jneurosci.org.ezp.lib.unimelb.edu.au/cgi/content/full/28/19/4861> >

Rahman I, 2008, 'Dietary polyphenols mediated regulation of oxidative stress and chromatin remodeling in inflammation', *Nutr Rev*, 66:S42-S45, viewed 1 November 2010, <<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2556856/> >

Reiterer G, Toborek M, Hennig B, 2004, 'Peroxisome Proliferator Activated Receptors alpha and gamma Require Zinc for their Anti-Inflammatory Properties in Porcine Vascular Endothelial Cells', *J Nutr*, 134:1711-1715, viewed 1 November 2010, <<http://jn.nutrition.org.ezp.lib.unimelb.edu.au/cgi/content/full/134/7/1711> >

Ricciarelli R, Argellati F, Pronzato MA, Domenicotti C, 2007, 'Vitamin E and neurodegenerative diseases', *Molecular Aspects of Medicine*, 28:591-606, viewed 1 November 2010, <http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B6T9P-4MSXT78-B&_user=559483&_coverDate=12%2F31%2F2007&_rdoc=1&_fmt=high&_orig=search&_origin=search&_sort=d&_docanchor=&view=c&_acct=C000028178&_version=1&_urlVersion=0&_userid=559483&md5=81b024093c6b39f30a050366115e17f1&searchtype=a >

Semmler A, Bao X, Cao G, Kohler W, Weller M, Aubourg P, Linnebank M, 2009, 'Genetic variants of methionine metabolism and X-ALD phenotype generation: results of a new study sample', *J Neurol*, 256:1277-1280, viewed 1 November 2010, <<http://www.springerlink.com.ezproxy.lib.monash.edu.au/content/4r69t85272051846/> >

Shingu C, Hagiwara S, Iwasaka H, Matsumoto P, Koga H, Yokoi I, Noguchi T, 2010, 'EPCK1, a Vitamin C and E Analogue, Reduces Endotoxin-Induced Systemic Inflammation in Mice', *Journal of Surgical Research*, 1-7, viewed 1 November 2010, <http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_udi=B6WM6-4YWC44C-1&_user=559483&_coverDate=04%2F18%2F2010&_rdoc=1&_fmt=high&_orig=search&_origin=search&_sort=d&_docanchor=&view=c&_acct=C000028178&_version=1&_urlVersion=0&_userid=559483&md5=14cf25e0d6d3db4166ab8e37fab9dd35&searchtype=a >

Singh I, Pujol A, 2010, 'Pathomechanisms Underlying X-Adrenoleukodystrophy: A Three-Hit Hypothesis', *Brain Pathol*, 20:4, viewed 1 November 2010,

<<http://onlinelibrary.wiley.com.ezp.lib.unimelb.edu.au/doi/10.1111/j.1750-3639.2010.00392.x/full> >

Schluter A, Real-Chicharro A, Gabaldon T, Sanchez-Jimenez F, Pujol A, 2010, 'PeroxisomeDB 2.0: an integrative view of the global peroxisomal metabolome', *Nucleic Acids Res*, 38:1, viewed 1 November 2010,

<http://nar.oxfordjournals.org.ezp.lib.unimelb.edu.au/content/38/suppl_1/D800.full >

Song Y, Chung CS, Bruno RS, Traber MG, Brown KH, King JC, Ho E, 2009,

'Dietary zinc restriction and repletion affects DNA integrity in healthy men', *Am J Clin Nutr*, 90: 321-8, viewed 1 November 2010,

<<http://www.ajcn.org.ezp.lib.unimelb.edu.au/cgi/content/full/90/2/321> >

Table 2: Fatty acid composition of rapeseed and low erucic acid (canola) oil compared to olive oil, soybean and sunflower, viewed 1 November 2010,

<<ftp://ftp.fao.org/es/esn/food/bio-10t.pdf> >

Takano K, Kitao Y, Tabata Y, Miura H, Sato K, Takuma K, Yamada K, Hibino S, Choshi T, Iinuma M, Suzuki H, Murakami R, Yamada M, Ogawa S, Hori O, 2007, 'A dibenzoylmethane derivative protects dopaminergic neurons against both oxidative stress and endoplasmic reticulum stress', *Am J Physiol Cell*

Physiol, 293:1884-1894, viewed 1 November 2010,

<<http://ajpcell.physiology.org/cgi/reprint/293/6/C1884> >

Tolar J, Charnas L, Orchard P, 2008, 'Antioxidant neuroprotection with hematopoietic cell transplantation in cerebral adrenoleukodystrophy', *Molecular Genetics and Metabolism*, 93:S14-S46, viewed 1 November 2010,

<http://www.sciencedirect.com.ezp.lib.unimelb.edu.au/science?_ob=ArticleURL&_u di=B6WNG-4RKJTN0-

[3R&_user=559483&_coverDate=02/29/2008&_alid=1534509630&_rdoc=71&_fmt=high&_orig=search&_origin=search&_zone=rslt_list_item&_cdi=6962&_sort=r&_st=13&_docanchor=&view=c&_ct=193&_acct=C000028178&_version=1&_urlVersion=0&_userid=559483&md5=de03dd1d78e1ad967e9e57003b1dda43&searchtype=a](#) >

Tolar J, Orchard P, Bjoraker KJ, Zeigler RS, Shapiro EG, Charnas L, 2007, 'N-acetylcysteine improves outcome of advanced cerebral adrenoleukodystrophy', *Bone Marrow Transplantation*, 39:211-215, viewed 1 November 2010,

<<http://ehis.ebscohost.com.ezp.lib.unimelb.edu.au/eds/detail?vid=1&hid=102&sid=d4781dd6-a2bb-406a-adc1-852cbff5126a%40sessionmgr113&bdata=JnNpdGU9ZWRzLWxpdmU%3d#db=mnh&AN=17290278> >

Uto T, Contreras MA, Gilg AG, Singh I, 2008, 'Oxidative imbalance in non-stimulated X-Adrenoleukodystrophy derived lymphoblasts', *Dev Neurosci*, 30:410-418, viewed 1 November 2010,

<<http://content.karger.com/produktedb/produkte.asp?typ=fulltext&file=000191212> >

Visovsky C, Collins M, Abbott L, Aschenbrenner J, Hart C, 2007, 'Putting Evidence Into Practice: Evidence-Based Interventions for Chemotherapy-Induced Peripheral Neuropathy', *Clin J Oncol Nurs*, 11:901-913, viewed 1 November 2010,

<<http://ons.metapress.com/content/38054849w7731327/> >

Zhang AY, Yi F, Zhang G, Gulbins E, Li PL, 2006, 'Lipid raft clustering and redox signaling platform formation in coronary arterial endothelial cells', *Hypertension*, 47:74-80, viewed 1 November 2010,

<<http://hyper.ahajournals.org/cgi/content/full/47/1/74> >