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Targeting Cytokines in the 5-LOX Pro-Inflammatory Pathway for Treatment-Resistant Anorexia Nervosa

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Abstract

Cytokines are a class of pro-inflammatory immune responses in the peripheral and central nervous system. Elevated cytokine levels contribute to appetite and weight dysregulation, anxiety, depression and other psychiatric conditions, and may underlie eating disorder (ED). Recently, two meta-analyses of cytokine levels in people with EDs – particularly anorexia nervosa (AN) – confirm elevated levels of cytokines within the 5-LOX inflammatory pathway, namely interleukin 1 (IL-1), interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α). IL-1, IL-6 and TNF-α are leukotrienes that stimulate the prolonged response of nuclear factor kappa beta (NF-κβ) – the major inflammatory gateway molecule – which influences brain development and function within the hypothalamic-pituitary-adrenal (HPA) axis, hippocampus and prefrontal cortex. The structure and function of these brain areas are shown to be aberrant in neuroimaging studies of EDs; thus, neuroinflammatory processes are significant biomarkers for weight and cognitive disturbances in EDs, particularly AN. Against this background, this brief article summarises the current knowledge of IL-1, IL-6 and TNF-α in EDs. Thereafter, the significance of inhibiting the NF-κβ 5-LOX inflammatory pathway with a low-risk, Cochrane-reviewed, anti-inflammatory known as *Boswellia serrata* is considered. Brief discussion of the clinical role for *Boswellia serrata* in weight recovery and reduction of comorbid mental disorder in ED is provided to stimulate further research into natural anti-inflammatory treatment interventions.

Keywords: Anorexia nervosa; Cytokines; Anti-inflammatory; NF-kb; 5-LOX; Treatment resistance

Introduction

Two meta-analyses have recently confirmed elevated cytokine levels – specifically leukotrienes – in eating disorders (ED) with a genome-wide association reported in anorexia nervosa (AN) [1-3]. EDs have dysregulated appetite, weight disturbance and cognitive dysfunction at the core [4]. Common comorbidities in EDs include anxiety, depression and mood disorders that are similarly linked to aberrant cytokine levels [5]. As such, cytokines are significant biomarkers for neuropsychiatric and physical disturbances in ED. Cytokines are a broad class of pro-inflammatory molecules released by various cells in the body and brain, including macrophages, microglia and astrocytes [6]. Cytokines called prostaglandins are synthesized from arachidonic acid (AA) by cyclooxygenases (COX), which are inhibited for acute pain relief by traditional non-steroidal anti-inflammatory drugs (NSAIDs) but are also linked to significant gastro-intestinal complications. Conversely, leukotrienes are synthesised from AA by 5-lipoxygenases (5-LOX) producing cytokines such as interleukins (IL) and tumour necrosis factor alpha (TNF-α). Given the involvement of leukotrienes in various psychiatric disorders – particularly EDs – 5-LOX inhibitors are therefore a viable target for novel psychiatric treatment development [7]. However, despite the link between elevated leukotrienes and EDs – particularly in relation to chronic weight loss and appetite restriction in AN – 5-LOX inhibitors have not yet been explored for their potential to abate clinical symptoms.

Literature Review

ILs are produced by, but also trigger the pro-inflammatory signalling molecule nuclear factor kappa beta (NF-κβ), which interacts with other intra-cellular inflammatory processes between the cellular membrane (e.g. from AA cleaving) to the nuclear membrane (e.g. genetic signalling molecules). ILs trigger – in a feedback loop – the 'canonical' inflammatory pathway leading to activation of protein complexes, which cause NF-κβ to translocate across the nuclear membrane, genetically upregulating the inflammatory response [8]. In turn, triggering of NF-κβ leads to the release of lymphocytes, local tissue destruction, antibody production, and fever, and upregulation of AA for a chronic inflammatory response. Similarly, TNF-α – another cytokine in the 5-LOX pathway – activates vascular endothelium to increase permeability of vessels thought to underlie the 'leaky-gut' syndrome. Within the leaky-gut hypothesis, lipopolysaccharide (LPS) might play a role as a potent inflammogen, found in the bacterial membrane that leaks through the gut to other peripheral and central nervous system regions, potentiating systemic inflammation and increased gut-brain porosity [9].

Symbiosis between IL-6 and NFκβ may drive neuroinflammatory processes when crossing the blood-brain barrier, altering neurogenesis of neurons and glial cells, functioning akin to neurotrophic factors, and playing a major role in many psychiatric disorders [10-12]. Moreover, chronic elevated levels of IL-6 may have a detrimental effect, particularly with a longer duration of illness, on blood-brain barrier integrity and function. Chronic neuroinflammation may lead to a 'leaky-brain' permeability, such that inflammatory molecules may better infiltrate the structure and function of brain regions, in

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particular, hippocampus, hypothalamus and cortex [5]. Similarly, genetic risk for increased expression of TNF-α alters cortical brain volume in psychiatric disorders such as major depression, which is often co-morbid with AN [13].

The expression of 5-LOX cytokines, particularly IL-6 and TNF-α in neuronal cells of the prefrontal cortex, hypothalamus and hippocampus may be associated with physical and mental disorder in EDs [1,2]. As such, the 5-LOX inflammatory pathway may provide a viable target for the development of anti-inflammatory adjuncts to treatment for EDs [7]. And if 5-LOX inhibitors do indeed lead to a significant reduction in ED symptoms, this may increase knowledge as to the neurobiological mechanisms of EDs, providing novel biomarkers for further treatment development. To date, however, no group studies have examined the clinical benefits of cytokine inhibition in AN, and none targeting the 5-LOX inflammatory mechanisms in AN. Only one case study of a single AN patient has reported the beneficial effects of a TNF-α antagonist on depression [14]. A larger study – though not in EDs – following this line of thought has shown that TNF-α suppressing medication increases body weight in chronic inflammatory diseases [15]. And while AN patient's report feeling uncomfortable about weight gain during treatment, weight gain is an essential part of medical improvement, although cytokine inhibitors may also lower anxiety and depression, which would likely be welcomed by AN patient [16].

Against this background, next follows a brief summary of the meta-analyses of cytokine levels in ED to provide a foundation for exploring the hypothesis that cytokine – particularly 5-LOX – inhibitors are a viable target for treatment-resistant AN. In particular, a specific 5-LOX inhibitor, namely the low-risk – according to two recent Cochrane reviews– nutritional supplement anti-inflammatory *Boswellia serrata* will be briefly reviewed [17-22].

Additionally, a brief description of the biological mechanisms of action of the 5-LOX pathway – including NF-κβ in relation to ILs and TNF-α is given, to aid understanding of the link between EDs, 5-LOX inhibitors and novel treatment development.

Summary of meta-analyses of cytokine levels in eating disorders

The first meta-analysis of cytokine levels in EDs was published by Solmi and colleagues in 2014, which included cross-sectional and longitudinal studies of adults with AN. Compared to healthy controls (HC), currently-ill, underweight AN patient in treatment had elevated levels of the leukotrienes: IL-1, IL-6, TNF-α and TNF-receptor-II. Conversely, AN patient had significant decreases in C-reactive protein (normally associated with higher levels of adiposity and overweight) in comparison to HCs [2]. Furthermore, the IL-6 receptor was reported to be downregulated in AN compared to HC, with no differences in TNF-receptor I and transforming growth factor (TGF)-β. In additional longitudinal study analyses – of which there were significantly fewer – Solmi and colleagues showed that acute weight gain (e.g. during treatment) was not associated with significant changes in levels of TNF-α, IL-6 and IL1-β. However, after a sustained period of weight gain after treatment, IL-6 levels in AN patient normalised in line with the levels observed in HC. Meta-regression analyses further revealed that shorter illness duration in those with AN, but not younger age, significantly moderated higher IL-6 levels.

Progressing Solmi et al.'s work five years' later; Dalton and colleagues extended the meta-analyses of cytokine levels in all types of EDs, and additionally included new studies up to May 2018 [1]. On the basis of the previous data, Dalton and colleagues focused on IL-1, IL-6, TNF-α and TGF-β levels only. Dalton and colleagues confirmed that IL-6 and TNF-α were significantly elevated in cross-sectional studies of all EDs compared to HCs, which appeared to be driven by the AN versus HC contrast (there were only four studies of bulimia nervosa [BN]). Taken together, these two meta-analyses highlight that extreme appetite restraint and acute weight loss in AN is linked to elevated levels of cytokines, especially the leukotrienes IL-6 and TNF-α. Moreover, there is some evidence that only sustained – and not acute – weight increases are associated with normalisation of these pro-inflammatory molecules.

Mechanisms of action of NF-κβ in relation to IL-1, IL-6, TNF-α and 5−LOX inflammatory pathways

The NF-κβprotein complex involves Class I and II proteins within a canonical/classic, and a non-canonical pathway. NF-κβ resides within mammalian cell cytoplasm, activates via the metabolism of NF-κβ inhibitors, and is the rapid response of the cell to various pathogens. A feedback loop via increased expression of IL-1, IL-6 and TNF-α, and the receptor activator of NF-κβ RANK) – a type of TNF-α receptor -maintains chronic activation of NF-κβ and a sustained inflammatory response [10]. In an unstimulated state, NF-κβ remains inactive in the cell cytoplasm, inhibited by inhibitors of κB (Iκβs) that mask the nuclear localization signals (NLS), preventing the NF-κβ translocation cascade across the nuclear membrane. However, when degradation of the protein Iκβs via phosphorylation and ubiquitination occurs, the NF-κβ protein complex is free to translocate across the nuclear membrane, docking at a gene promotor region for transcription of inflammatory molecules.

NF-κβ becomes activated when, for example, its receptor-ligand complex (e.g. RANKL) is stimulated by reactive oxygen species (ROS), ionizing radiation, bacterial LPS, stimulant drugs such as cocaine and methamphetamine, and inflammatory molecules such as ILs in a chronic feedback loop [23]. Subunit molecules residing in the mammalian cell cytoplasm, such as p50 and p52 mediate NF-κβ targeted gene transactivation by forming heterodimers with RelA, RelB, or c-Rel [24]. All proteins of the NF-κβ family share a Rel homology in their N-terminus. However, in the non-canonical/alternative pathway, the p50 and p52 proteins in the Class I NF-κβ cascade is not able to activate genetic transcription on their own, but rather function as transcription repressors while binding to the κβ proteins. As such, when the p50 and p52 proteins are phosphorylated, NF-κβ becomes activated. Conversely, the Class II protein subfamily of NF-κβ, including RelA, RelB, and c-Rel, have the transactivation domain at their C-terminus and are able to directly translocate to the nuclear membrane. When the NF-κβ complex is activated by one of these routes, it enters the cell nucleus to influence the expression of various genes. The most common result of NF-κβ activation of these genes are physiological responses such as an immune/inflammatory response, cell proliferation or cell survival. However, NF-κβ also influences central nervous system processes, such as glutamate, and brain-derived neurotrophic factor (BDNF) mediated synaptic plasticity, learning and memory [25].

The classical/non-classical NF-κβ nuclear translocation pathway stimulates gene transcription of various cytoplasmic enzymes such as COX and 5-LOX. The NF-κβ-production of COX enzymes is responsible for the metabolism of AA into pro-inflammatory molecules such as prostaglandins. Conversely, the NF-κβ-production of 5-LOX enzymes is responsible for the metabolism of AA into pro-inflammatory leukotrienes, such as IL-1, IL-6, TNF-α (which are able to activate RANK for chronic NF-κβ activation). Commonly-used non-steroidal anti-inflammatories (NSAIDs) – including ibuprofen

and aspirin – inhibit the enzymatic activity of the COX prostaglandin system for acute pain relief for example. In contrast, other natural anti-inflammatories, such as nutrients in 'Mediterranean diet' foods, (e.g. Olive Oil, resveratrol/red wine) and dietary supplements (e.g. Curcumin and *Boswellia serrata* -specifically the active triterpenoid compound acetyl-11-keto-β –boswellic acid; AKβA) may preferentially inhibit the 5-LOX pathway [19-22,26].

What is the significance of inhibiting 5-LOX and IL-1, IL-6 and TNF-α in EDs?

Improved understanding of the pathophysiology of EDs is urgently needed, given that efficacious psychopharmacological interventions are limited, and that approximately half of ED patients relapse after standard treatment [27-30]. Thus, turning to the mechanisms of cytokine action – particularly within the 5-LOX pro-inflammatory pathway in light of the recent meta-analyses– may prove fruitful for novel treatment development [1,2].

Animal models of disrupted feeding demonstrate that elevated levels of ILs are part of the neuroinflammatory pathway within the hypothalamus, interacting with hypothalamic pro-opiomelanocortin (POMC) and neuropeptide Y (NPY) neurons to influence peptide release such as leptin (the 'satiety' molecule) and ghrelin (the 'appetite' molecule). For example, animal studies have implicated increased levels of IL-1β in reduced meal size and eating duration, but not meal frequency or reduced food-seeking behaviour [31,32]. Similarly, IL-6 interacts with hypothalamic leptin expression to reduce appetite and decrease body fat in animal studies, engaging similar auxiliary signalling molecules to leptin in the hypothalamus and forebrain to suppress appetite, although the exact mechanism of action of ILs on peptide expression is unclear. Moreover, animal models of stress show hyper-release of pro-inflammatory cytokines during acute and chronic stress, implicating the modulation of hypothalamic-pituitary-adrenal (HPA) axis function that plays a major role in EDs [33-39].

Additionally, TNFα and IL-6 together disrupt the function of hypothalamic cells and in mice models, altering serotoninergic metabolism and causing reduced food intake [40].

The role of the hypothalamus in appetite regulation is well-established, with reciprocal pathways to higher cortical brain regions that bi-directionally modulate feeding behaviour. For example, the arcuate nucleus has populations of neurons that when stimulated induce satiety (ventral medial region) or hunger (lateral region) and interact directly with released gut hormones, and inflammatory molecules [41,42]. Moreover, LPS the potent inflammogen that forms part of microbiome bacterial cell walls, when injected directly into the hypothalamus in animal models reduces feeding and stimulates weight loss in line with elevated IL-1β levels [43]. Finally, there is significant evidence that increased levels of these 5-LOX pro-inflammatory cytokines contribute to osteoporosis in females with AN [44]. Taken together, neuroinflammatory processes may contribute to a 'leaky' blood-brain barrier as well as mental and physical disorder in Eds [5].

In terms of the role of TNF-α in EDs, the latest meta-analysis of cytokines found a trend for elevated levels in BN but the small number of studies included (n = 3) prevented definitive conclusions [1]. TNF-α is suggested to be involved in the acute-response to trauma and threat, is secreted into the blood stream following an immunological challenge and activates NFκβ via RANK. TNF-α is released by macrophages, natural killer cells and T-cells to induce fever [45]. Psychological distress is significantly linked to elevated release of cytokines, and in particular, increased concentrations of TNF-α coincide with anxiety, depression and obsessive-compulsive disorder, which are often co-morbid with EDs [46,47]. As such, IL-6 and TNF-α appear to interact with brain processes (e.g. hypothalamic networks) responsible for feeding and weight regulation, psychological distress and anxiety, which has a direct link to chronic activation via the specific receptor-ligand complex RANK. This is particularly pertinent, given that genetic risk for increased TNF-α expression is associated with reduced angular gyrus and visual cortex volume– brain regions that underlie variance in cognitive control of body weight and feeding in EDs [48-50].

Elevated levels of ILs, TNF-α and NF-κβ are also associated with psychiatric comorbidities in AN and appear to have a genetic link, including anxiety, depression, mood and addictive disorders [51-55]. Anxiety is associated with hippocampal synaptogenesis and elevated levels of NF-κβ are demonstrated by animal models of social isolation and stress [56,57]. Human studies of anxiety corroborate the role of increased inflammatory markers, and in relation to the role of NF-κβ in learning, memory and synaptogenesis [25,58]. Similarly, in human studies of depression, an interaction between the glucocorticoid receptor complex and NF-κβ underlies the neuroexcitoxic effects of chronic stress [59]. Moreover, bipolar and other mood disorders often observed in those with EDs are successfully targeted to improve symptoms by suppression of the AA pro-inflammatory pathways [60]. Finally, elevated levels of NF-κβ are typically observed in addictive disorders, and recent advances in the understanding of neural processes underlying AN has led to habitual appetite restraint under risky circumstances (e.g. potentially fatal weight loss and related health consequences) being regarded as an addiction process [61].

Inhibition of the NF-κβ/5−LOX pathway with a low-risk, Cochrane-reviewed, anti-inflammatory: potential novel intervention for EDs?

Against this background, is seems plausible that inhibition of the NF-κβ/5-LOX pro-inflammatory pathway – particularly related to extreme upregulation of IL-6 and TNF-α – may improve disrupted feeding behaviour, weight loss and neuropsychiatric effects in EDs, especially AN. However, caution is needed when considering 5-LOX inhibitors as a clinical adjunct, given that excessive or prolonged NF-κβ/5-LOX inhibition may compromise the immunological response to pathogens. For example, chronic use of NSAIDs, which are COX inhibitors, may be associated with alternate processing of AA into 5-LOX leukotrienes [62]. As such, inhibition of the 5-LOX pathway may similarly lead to alternate processing of AA into COX-mediated prostaglandin expression and increased pain, swelling and fever. As for immunosuppression therapy for various physical illnesses (e.g. cancer, inflammatory conditions), a compromised immunological response may increase susceptibility for infection in those with EDs. That said, two recent Cochrane reviews of a natural anti-inflammatory nutritional supplement described below did not report compromised immunological responses following its use [17,18]. This is probably because certain disorders, including EDs, already have maladaptive and excessive levels of pro-inflammatory molecules that need to be reduced. Furthermore, as described below, certain 5-LOX inhibitors may rather target a specific inflammatory cascade as opposed to the total NF-κβ response, and as such, may not interfere with the general and rapid inflammatory response to pathogens.

The next logical question is whether any candidate NF-κβ/5-LOX inhibition compounds that avoid the gastrointestinal and cardiac adverse effects of NSAIDs are currently being studied in those with Eds [63]. To date, it appears that one case study has examined the effects of

a 5-LOX inhibitor, namely a TNF-α antagonist (infliximab) prescribed for Crohn's Disease appearing at age 24, in a 26-year-old female patient who had experienced AN since age 14 [14]. Crohn's disease can exacerbate AN by altering hunger and energy metabolism via altered levels of TNF-α and IL-6, which moderate leptin and melanocortin signalling in the hypothalamus [14]. In this case study, the TNF-α antagonist improved the patient's eating behaviour, weight status and psychopathy (anxiety, depression and engagement in cognitive behavioural treatments) over approximately 6 months. However, no case versus control studies have yet been conducted to examine the effects of NF-κβ/5-LOX suppressant compounds on ED symptoms.

Discussion

Given that traditional NSAIDs, which have adverse effects, target the COX pro-inflammatory pathway, a non-NSAID 5-LOX inhibitor is rather preferable to test the effects on pro-inflammatory leukotriene levels in Eds [19]. One such nutritional supplement anti-inflammatory exists – *Boswellia serrata* (its active ingredient being AKβA), which may preferentially inhibit the 5-LOX pathway. For example, *Boswellia serrata* appears to specifically inhibit the expression of 5-LOX inflammatory molecules by disrupting upstream inhibitor kinases of kappa beta (IKK), processes that regulate the ability of NF-κβ to translocate through the nuclear membrane to influence leukotriene-related gene transcription [20,64-66]. However, conflicting data exists that instead of inhibiting the 5-LOX pathway, *Boswellia serrata* might rather inhibit cathepsin G (catG) and microsomal prostaglandin E synthase (mPGES)-1 [67]. The mPGES-1 system is an interesting mechanism of action to consider, given that mPGES-1 is implicated as a mediator of inflammatory induced AN in certain mice strains [68]. Furthermore, studies have shown that *Boswellia serrata* intercepts IKK function, preventing the degradation of the NF-κβ inhibitor IrK, and thus preventing phosphorylation of p65, essential for NF-κβ activation and downstream cytokine expression [69,70]. Inhibition of IKK distinguishes *Boswellia serrata* from other nutritional compounds (e.g. Olive Oil, resveratrol) that appear to exert their effects upstream of the IKK, and which are not reported to significantly compromise (in fact might rather enhance, according to statistics on the related benefits of the Mediterranean diet) immunity [71,72]. However, the exact mechanism of action of *Boswellia serrata* is yet to be clarified, although it does appear to broadly alter – or downregulate – the excessive inflammatory response of NF-κβ and its ability to translocate across the nuclear membrane. This in itself is of interest – given that elevated IL-6 levels are related to NF-κβ function– for molecular-based treatment of AN [10].

In support of its use as a safe anti-inflammatory nutritional supplement, *Boswellia serrata* has been clinically examined in two recent Cochrane reviews, albeit in studies of people with physical inflammatory illnesses (e.g. arthritis, colitis, asthma, cancer) and not psychiatric disorders [17,18]. The reviews report that *Boswellia serrata* warrants further exploration, with some evidence of its clinical benefit for reducing excessive inflammation alongside low/rare adverse reactions and significantly reduced leukotriene and NF-κβ levels. Additionally, there is some indication that *Boswellia serrata* might be slower-acting than traditional NSAIDs and so cross-sectional studies over a short duration must consider the potential to commit false negatives, which may prompt future longitudinal analyses [73,74]. Moreover, the concentration of the active ingredient – AKβA – in *Boswellia serrata* is highly variable and not adequately reported in currently marketed brands [74]. However, there is good evidence that one brand available on the market consistently provides the recommended daily dosage of 28-30% AKβA per 100 mg tablet, although it is still traditionally farmed (e.g. gum resin drawn from tree bark), which is unlikely to provide long-term clinical sustainability [75]. In light of this, laboratories are attempting to synthesise compounds that mimic Boswellic acid (AKβA), although this research has a long way to go before providing marketable products fit for human consumption [76]. However, the currently available *Boswellia serrata* products that have been scientifically tested include 5-Loxin® (90 days, 100 mg/250 mg); Aflapin® (100 mg for 30 days); Boswellin® (150 mg daily); Casperome® (dose not known); Curamin® (450 mg for 90 days); Eumastós® (dose not known); H15® (single 800 mg dose); Phytoproflex® (dose not known); Shallaki® (single 125 mg dose).

Boswellia serrata has only been experimentally tested in physical disorders, with significant beneficial effects and reduced 5-LOX cytokine levels reported [17,18]. However, given the comparable link between elevated 5-LOX cytokines, namely IL-1, IL-6 and TNF-α and psychiatric disorders, particularly EDs, there is good reason for further exploration of *Boswellia serrata* in Eds [7]. The justifications for testing *Boswellia serrata* in ED patients to reduce ED symptoms, stimulate weight gain, and improve psychiatric comorbidities are broad.

First, *Boswellia serrata* induces emmenagogue (promotion of menstrual flow, a danger for women seeking to get pregnant), whereas ammenohorea (lack of menstruation) is a major symptom of chronic AN associated with hypothalamic dysfunction that sometimes persists after weight gain [77,78], suggesting that *Boswellia serrata* interacts with hypothalamic inflammatory processes. Second, *Boswellia serrata* appears to preferentially inhibit 5-LOX cytokines over COX cytokines, particularly with regard to preventing phosphorylation of non-canonical NF-κβ subunits at a lower dose within the 100-250 mg range for a daily dose of *Boswellia serrata* enriched with 30% AKβA [19-22,76,77]. However, caution must be taken with higher doses that might be excessively immune-stimulatory or toxic [78-80]. Third, studies (mainly in animals) have demonstrated significant 5-LOX cytokine reduction following *Boswellia serrata* administration. For example, *Boswellia serrata* inhibits LPS-mediated TNF-α induction in monocytes by direct interaction with NF-κβ Iκβ kinases and miRNA [81]. This is pertinent when considering AKβA/*Boswellia serrata* as an adjunct to treatment for AN, given that LPS induction into the hypothalamus can induce the release of leptin and AN symptom [12,11]. And also, that AN is associated with significantly high levels of interleukins – particularly IL-6 – including TNF-α, the latter may specifically activate NF-κβ via the receptor-ligand complex RANKL [1,2].

Concluding Remarks

Relapse rates in EDs are high and account for approximately half of patient's post-treatment, with current psychopharmacological interventions limited by their efficacy and availability. As such, the clinical implications are that novel adjuncts to standard treatment addressing molecular and genetic neuropathology of EDs are urgently needed. Two recent meta-analyses have shifted the focus of neuropathology of EDs towards a molecular and genetic perspective, reporting increased levels of 5-LOX ILs, particularly IL-6 and TNF-α that interact with NF-κβ to form a significant chronic pro-inflammatory response (e.g. a 'leaky gut' and 'leaky brain'). Permeability within the gut may allow LPS within bacteria to infiltrate the peripheral immune system, triggering NF-κβ, IL-6 and related molecules. Permeability within the blood-brain-barrier may allow for the passage of 5-LOX cytokines that may preferentially, or at a higher concentration threshold (e.g. according to genetic susceptibility), target

hypothalamic, hippocampal and prefrontal cortex memory networks, resulting in disrupted feeding behaviour. Disrupted feeding behaviour may in turn exacerbate the chronic inflammatory process in the gut and brain, permeating the structure and function of neurotransmitter and hormone signalling networks. This may lead to ED-comorbid disorders including anxiety, depression, obsessive-compulsivity and addictive disorder.

A 5-LOX inhibitor reduces levels of NF-κβ and therefore ILs – particularly IL-6 and TNF-α The clinical relevance of this is that 5-LOX inhibition might beneficially alter the function of pro-inflammatory cytokines within the neural circuitry (e.g. involving the hypothalamus, hippocampus, prefrontal cortex) underlying the physical and psychological symptoms of EDs (e.g. weight loss, appetite restraint, anxiety, depression, cognitive dysfunction). *Boswellia serrata* (its active ingredient being AKβA) is a nutritional supplement that specifically appears to disrupt the 5-LOX cytokine intracellular pathway, by preventing the phosphorylation of NF-κβ, and is low risk according to two recent Cochrane Reviews. However, no studies have yet examined the inhibiting effect of *Boswellia serrata* on NF-κβ and subsequent benefits in psychiatric disorders, including AN, which is most significantly associated with elevated IL-6 levels. To justify the exploration of *Boswellia serrata* supplementation in AN, animal studies have demonstrated that AkβA inhibits LPS-mediated TNF-α induction in monocytes by direct interaction with NF-κβ Iκβ kinases and miRNA. This is pertinent in that LPS induction into the hypothalamus can induce the release of leptin and AN symptom and AN is associated with significantly high levels of IL-6 TNF-α. Thus, now is the time for careful selection of *Boswellia serrata* products currently available as nutritional supplements, based on existing scientific evidence. This is to probe the clinical relevance of *Boswellia serrata* supplementation during AN treatment for improving feeding and weight status, reducing anxiety, depression and cognitive dysfunction, and ultimately a significant reduction in long-term relapse rates.

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References

1. Dalton B, Bartholdy S, Robinson L, Solmi M, Ibrahim MAA, et al. (2018) A meta-analysis of cytokine concentrations in eating disorders. J Psychiatr Res 103: 252-264.
2. Solmi M, Veronese N, Favaro A, Santonastaso P, Manzato E, et al. (2015) Inflammatory cytokines and anorexia nervosa: A meta-analysis of cross-sectional and longitudinal studies. Psychoneuroendocrinol 51: 237-252.
3. Duncan L, Yilmaz Z, Gaspar H, Walters R, Goldstein J, et al. (2017) Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. Am J Psychiatry 1: 1-2.
4. Brooks SJ, Funk SG, Young SY, Schiöth HB (2017) The role of working memory for cognitive control in anorexia nervosa versus substance use disorder. Front Psychol 8: 1651.
5. Morris G, Fernandes BS, Puri BK, Walker AJ, Carvalho AF, et al. (2018) Leaky brain in neurological and psychiatric disorders: Drivers and consequences. Aust N Z J Psychiatry 52: 924-948.
6. Lichtblau N, Schmidt F, Schumann R, Kirkby K, Himmerich H, et al. (2013) Cytokines as biomarkers in depressive disorder: current standing and prospects. Int Rev Psychiatry 25: 592-603.
7. Cegielska-Perun K, Marczuk E, Bujalska-Zadrozny M (2016) Inhibitors of leukotrienes synthesis: novel agents and their implementation. Acta Pol Pharm 73: 843-849.
8. Karin M, Ben-Neriah Y (2000) Phosphorylation meets ubiquitination: the control of NF-[kappa]-β activity. Annu Rev Immunol 18: 621-663.
9. Herpertz-Dahlmann B, Seitz J, Baines J (2017) Food matters: How the microbiome and gut-brain interaction might impact the development and course of anorexia nervosa. Eur Child Adolescent Psychiatr 26: 1031-1041.
10. Brasier AR (2010) The nuclear factor-kappa-β-interleukin-6 signalling pathway mediating vascular inflammation. Cardiovasc Res 86: 211-218.
11. Taams LS (2018) Inflammation and immune resolution. Clin Exp Immunol 193: 1-2.
12. Erta M, Quintana A, Hidalgo J (2012) Interleukin-6, a major cytokine in the central nervous system. Int J Biol Sci 8: 1254-1266.
13. Zhou R, Wang F, Zhao G, Xia W, Peng D, et al. (2018) Effects of tumor necrosis factor-α polymorphism on the brain structural changes of the patients with major depressive disorder. Transl Psychiatry 8: 217.
14. Solmi M, Santonastaso P, Caccaro R, Favaro A (2013) A case of anorexia nervosa with comorbid Crohn's disease: beneficial effects of anti-TNF-α therapy? Int J Eat Disord 46: 639-641.
15. Ouchi N, Parker JL, Lugus JJ, Walsh K (2011) Adipokines in inflammation and metabolic disease. Nat Rev Immunol 11: 85-97.
16. Himmerich H, Joaquim M, Bentley J, Kan C, Dornik J, et al. (2017) Psychopharmacological options for adult patients with anorexia nervosa: the patients' and carers' perspectives. CNS Spectr 23: 251-252.
17. Cameron M, Chrubasik S (2014) Oral herbal therapies for treating osteoarthritis. Cochrane Database Syst Rev 11: CD002947.
18. Kafil TS, Nguyen TM, Patton PH, MacDonald JK, Chande N, et al. (2017) Interventions for treating collagenous colitis. Cochrane Database Syst Rev 11: CD003575.
19. Safayhi H, Mack T, Sabieraj J, Anazodo MI, Subramanian LR, et al. (1992) Boswellic acids: Novel, specific, nonredox inhibitors of 5-lipoxygenase. J Pharmacol Exp Ther 261: 1143-1146.
20. Ammon HP (2016) Boswellic acids and their role in chronic inflammatory diseases. Adv Exp Med Biol 928: 291-327.
21. Ammon HP (2010) Modulation of the immune system by Boswellia serrata extracts and boswellic acids. Phytomed 17: 862-867.
22. Bishnoi M, Patil CS, Kumar A, Kulkarni SK (2007) Co-administration of acetyl-11-keto beta-boswellic acid, a specific 5-lipoxygenase inhibitor, potentiates the protective effect of COX-2 inhibitors in kainic acid-induced neurotoxicity in mice. Pharmacol 79: 34-41.
23. Liu T, Zhang L, Joo D, Sun SC (2017) NF-kappa-β signaling in inflammation. Signal Transduct Target Ther 2: 1-2.
24. Li Q, Verma IM (2002) NF-kappa-β regulation in the immune system. Nat Rev Immunol 2: 725-734.
25. Albensi BC, Mattson MP (2000) Evidence for the involvement of TNF and NF-kappa-β in hippocampal synaptic plasticity. Synapse 35: 151-159.
26. Yarla NS, Polito A, Peluso I (2018) Effects of olive oil on TNF-alpha and IL-6 in humans: Implication in obesity and frailty. Endocr Metab Immune Disord Drug Targets 18: 63-74.
27. Himmerich H, Treasure J (2018) Psychopharmacological advances in eating disorders. Expert Rev Clin Pharmacol 11: 95-108.
28. Smink F, Hoeken D, Hoek H (2013) Epidemiology, course, and outcome of eating disorders. Curr Opin Psychiatr 26: 543-548.
29. Steinhausen HC (2002) The outcome of anorexia nervosa in the 20th century. Am J Psychiatr 159: 1284-1293.
30. Steinhausen HC, Weber S (2009) The outcome of *Bulimia nervosa*: Findings from one quarter century of research. Am J Psychiatr 166: 1331-1341.
31. Plata-Salaman CR (2001) Cytokines and feeding. Int J Obes Relat Metab Disord 5: S48-52.
32. Wong S, Pinkney J (2004) Role of cytokines in regulating feeding behaviour. Curr Drug Targets 5: 251-263.
33. Iwasa T, Matsuzaki T, Murakami M, Kinouchi R, Gereltset-seg G, et al. (2011) Changes in responsiveness of appetite, leptin and hypothalamic IL-1and TNF-α to lipopolysaccharide in developing rats. J Neuroimmunol 236: 10-16.

34. Wallenius K, Wallenius V, Sunter D, Dickson SL, Jansson JO (2002) Intracerebroventricular interleukin-6 treatment decreases body fat in rats. Biochem Biophys Res Commun 293: 560-565.

35. Senarís RM, Trujillo ML, Navia B, Comes G, Ferrer B, et al. (2001) Interleukin-6 regulates the expression of hypothalamic neuropeptides involved in body weight in a gender-dependent way. J Neuroendocrinol 23: 675-686.

36. Sadagurski M, Norquay L, Farhang J, D'Aquino K, Copps K, et al. (2010) Human IL6 enhances leptin action in mice. Diabetologia 53: 525-535.

37. Timper K, Denson JL, Steculorum SM, Heilinger C, Engström-Ruud L, et al. (2017) IL-6 Improves energy and glucose homeostasis in obesity via enhanced central IL-6 trans-signaling. Cell Rep 19: 267-280.

38. Himmerich H, Fischer J, Bauer K, Kirkby K, Sack U, et al. (2013) Stress-induced cytokine changes in rats. Eur Cytokine Netw 24: 97-103.

39. Monteleone AM, Patriciello G, Ruzzi V, Fico G, Pellegrino F, et al. (2018) Insecure attachment and hypothalamus-pituitary-adrenal axis functioning in people with eating disorders. Psychosom Med 80: 710-716.

40. Dwarkasing JT, Witkamp RF, Boekschoten MV, Ter Laak MC, Heins MS, et al. (2016) Increased hypothalamic serotonin turnover in inflammation-induced anorexia. BMC Neurosci 17: 26.

41. Suzuki K, Simpson KA, Minnion JS, Shillito JC, Bloom SR (2010) The role of gut hormones and the hypothalamus in appetite regulation. Endocr J 57: 359-372.

42. Jang PG, Namkoong C, Kang GM, Hur MW, Kim SW, et al. (2010) NF-kappa-β activation in hypothalamic pro-opiomelanocortin neurons is essential in illness- and leptin-induced anorexia. J Biol Chem 285: 9706-9715.

43. Dantzer R (2006) Cytokine-induced sickness behavior: Mechanisms and implications. Ann NY Acad Sci 933: 222-234.

44. Ostrowska Z, Ziora K, Oświęcimska J, Marek B, Świętochowska E, et al. (2017) Selected pro-inflammatory cytokines, bone metabolism, osteoprotegerin, and receptor activator of nuclear factor-kβ ligand in girls with anorexia nervosa. Endokrynol Pol 66: 313-321.

45. Abbas AK, Lichtman AHH, Pillai S (2014) Functions and disorders of the immune system. In: Basic Immunology E-book, Elsevier Health Sciences, Saint Louis, USA.

46. Kim Y, Won E (2017) The influence of stress on neuroinflammation and alterations in brain structure and function in major depressive disorder. Behav Brain Res 329: 6-11.

47. Furtado M, Katzman M (2015) Neuroinflammatory pathways in anxiety, posttraumatic stress, and obsessive-compulsive disorders. Psychiatry Res 229: 37-48.

48. Zhou R, Wang F, Zhao G, Xia W, Peng D, et al. (2018) Effects of tumor necrosis factor-α polymorphism on the brain structural changes of the patients with major depressive disorder. Transl Psychiatry 8: 217.

49. Nakamura Y, Ikuta T (2017) Caudate-precuneus functional connectivity is associated with obesity preventive eating tendency. Brain Connect 7: 211-217.

50. Burgess CR, Livneh Y, Ramesh RN, Andermann ML (2018) Gating of visual processing by physiological need. Curr Opin Neurobiol 49: 16-23.

51. Tylee DS, Sun J, Hess JL, Tahir MA, Sharma E, et al. (2018) Genetic correlations among psychiatric and immune-related phenotypes based on genome-wide association data. Am J Med Genet B Neuropsychiatr Genet 1: 1-2.

52. Gaspersz R, Lamers F, Wittenberg G, Beekman ATF, Hemert AM, et al. (2017) The role of anxious distress in immune dysregulation in patients with major depressive disorder. Transl Psychiatr 7: 1-2.

53. Valente S, Girolamo DG, Forlani M, Biondini A, Scudellari P, et al. (2017) Sex-specific issues in eating disorders: A clinical and psychopathological investigation. Eat Weight Disord 22: 707-715.

54. Swardfager W, Hennebelle M, Yu D, Hammock BD, Levitt AJ, et al. (2018) Metabolic/inflammatory/vascular comorbidity in psychiatric disorders; soluble epoxide hydrolase (sEH) as a possible new target. Neurosci Biobehav Rev 87: 56-66.

55. Nennig SE, Schank JR (2017) The role of NFkβ in drug addiction: Beyond inflammation. Alcohol Alcohol 52: 172-179.

56. Cao M, Pu T, Wang L, Marshall C, He H, et al. (2017) Early enriched physical environment reverses impairments of the hippocampus, but not medial prefrontal cortex, of socially-isolated mice. Brain Behav Immun 64: 232-243.

57. Fan J, Ding L, Xia D, Chen D, Jiang P, et al. (2017) Amelioration of apelin-13 in chronic normobaric hypoxia-induced anxiety-like behavior is associated with an inhibition of NF-kappa-β in the hippocampus. Brain Res Bull 130: 67-74.

58. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T (2017) Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacol 42: 254-270.

59. Bekhbat M, Rowson SA, Neigh GN (2017) Checks and balances: The glucocorticoid receptor and NFkβ in good times and bad. Front Neuroendocrinol 46: 15-31.

60. Rao JS, Rapoport SI (2009) Mood-stabilizers target the brain arachidonic acid cascade. Curr Mol Pharmacol 2: 207-214.

61. O'Hara CB, Campbell IC, Schmidt U (2015) A reward-centred model of anorexia nervosa: a focussed narrative review of the neurological and psychophysiological literature. Neurosci Biobehav Rev 52: 131-152.

62. Brune K (2004) Safety of anti-inflammatory treatment - new ways of thinking. Rheumatol 43: i16-i20.

63. Tacconelli S, Bruno A, Grande R, Ballerini P, Patrignani P (2017) Nonsteroidal anti-inflammatory drugs and cardiovascular safety - translating pharmacological data into clinical readouts. Expert Opin Drug Saf 16: 1-17.

64. Ammon HP (2010) Modulation of the immune system by *Boswellia serrata* extracts and 825 boswellic acids. Phytomed 17: 862-867.

65. Bishnoi M, Patil CS, Kumar A, Kulkarni SK (2007) Co-administration of acetyl-11-keto848 beta-boswellic acid, a specific 5-lipoxygenase inhibitor, potentiates the protective effect of COX-2 inhibitors in kainic acid-induced neurotoxicity in mice. Pharmacology 79: 34-41.

66. Abdel-Tawab M, Werz O, Schubert-Zsilavecz M (2011) Boswellia serrata: An overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. Clin Pharmacokinet 50: 349-369.

67. Nilsson A, Elander L, Hallbeck M, Kugelberg OU, Engblom D, et al. (2017) The involvement of prostaglandin E2 in interleukin-1beta evoked anorexia is strain dependent. Brain Behav Immun 60: 27-31.

68. Syrovets T, Buchele B, Krauss C, Laumonnier Y, Simmet T (2005) Acetyl-boswellic acids inhibit lipopolysaccharide-mediated TNF-alpha induction in monocytes by direct interaction with Ikappa-β kinases. J Immunol 174: 498-506.

69. Perkins ND (2007) Integrating cell-signalling pathways with NF-kappa-β and IKK function. Nat Rev Mol Cell Biol 8: 49-62.

70. Sontakke ST, Pimpalkhute S, Kabra P, Babhulkar S, Hingorani L (2007) Open, randomized, controlled clinical trial of Boswellia serrata extract as compared to valdecoxib in osteoarthritis of knee. Indian J Pharmacol 39: 27.

71. Shader RI (2018) An anecdote about arthritis and *Boswellia serrata*. Clin Ther 40: 669-671.

72. Meins J, Artaria C, Riva A, Morazzoni P, Schubert-Zsilavecz M, et al. (2016) Survey on the quality of the top-selling european and american botanical dietary supplements containing boswellic acids. Planta Med 82: 573-579.

73. Meka B, Ravada SR, Kumar MMK, Nagasree PK, Golakoti T (2017) Synthesis of new analogs of AKβA and evaluation of their anti-inflammatory activities. Bioorg Med Chem 25: 1374-1388.

74. Paoletti A, Gallo E, Benemei S, Vietri M, Lapi F, et al. (2011) Interactions between natural health products and oral anticoagulants: Spontaneous reports in the Italian Surveillance System of Natural Health Products. Evid Based Complement Alternat Med 11: 1-5.

75. Andrisani A, Sabbadin C, Minardi S, Favaro A, Dona G, et al. (2017) Persistent amenorrhea and decreased DHEAS to cortisol ratio after recovery from anorexia nervosa. Gynecol Endocrinol 33: 311-314.

76. Sengupta K, Alluri KV, Satish AR, Mishra S, Golakoti T, et al. (2008) A double blind, randomized, placebo-controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. Arthritis Res Ther 10: R85.

77. Sengupta K, Krishnaraju AV, Vishal AA, Mishra A, Trimurtulu G, et al. (2010) Comparative efficacy and tolerability of 5-Loxin and Aflapin against osteoarthritis of the knee: A double blind, randomized, placebo controlled clinical study. Int J Med Sci 7: 366-377.

78. Khajuria A, Gupta A, Suden P, Singh S, Malik F, et al. (2008) Immunomodulatory activity of biopolymeric fraction BOS 2000 from Boswellia serrata. Phytother Res 22: 340-348.

79. Kiela PR, Midura AJ, Kuscuoglu N, Jolad SD, Solyom AM, et al. (2005) Effects of *Boswellia serrata* in mouse models of chemically induced colitis. Am J Physiol Gastrointest Liver Physiol 288: G798-808.

80. Syrovets T, Gschwend JE, Buchele B, Laumonnier Y, Zugmaier W, et al. (2005) Inhibition of Ikappa-β kinase activity by acetyl-boswellic acids promotes apoptosis in androgen-independent PC-3 prostate cancer cells *in vitro* and *in vivo*. J Biol Chem 280: 6170-6180.

81. Sayed AS, Gomaa IEO, Bader M, Sayed EN (2017) Role of 3-acetyl-11-keto-beta-boswellic acid in counteracting LPS-induced neuroinflammation via modulation of miRNA-155. Mol Neurobiol 55: 5798-5808.