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RESEARCH

Repurposing of modafinil as an anti-inflammatory drug: a systematic review of experimental studies

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Abstract

Previous studies suggested the anti-inflammatory properties of modafinil. This study aimed to review the current literature to provide a comprehensive insight into the anti-inflammatory uses of modafinil in experimental studies. We conducted a systematic search using Medline (via PubMed), Web of Science, Scopus, and Embase databases from their commencement until 10 October 2022. All original articles focusing on modafinil anti-inflammatory effects were included. Our initial search yielded 1398 articles. Fourteen publications were included in our systematic review. Recent studies attempted to provide evidence for repurposing modafinil for several diseases, including autoimmune encephalomyelitis, nonalcoholic liver disease, gastric mucosal injury, neuropathic pain, atherosclerosis, intestinal ischemia, pulmonary hypertension, pancreatitis, ischemic stroke, testicular torsion, and lithium-pilocarpine–induced status epilepticus. Current evidence supports that modafinil can modulate inflammation, suppress the immune response, and improve disease severity partly by inhibiting NF-κB, NOS, Kca3.1, Kca2.3, and COX-2. By reviewing recent findings from experimental studies, we discussed the beneficial effects of modafinil on several inflammatory diseases, with a particular focus on the underlying mechanisms.

Keywords Modafinil · Anti-inflammatory · Systematic review

Introduction

Modafinil is a weak but selective dopamine reuptake inhibitor, which is deemed to indirectly promote orexin and histamine release to induce wakefulness (Russell and Spiller 2019; Yu et al. 2019; Ishizuka et al. 2012). Modafinil has been previously granted FDA approval for narcolepsy, sleep work shift disorder, and obstructive sleep apnea (Greenblatt and Adams 2022). Furthermore, modafinil currently has off-label use in attention-deficit hyperactivity disorder; acute unipolar and bipolar depressive episodes; cocaine dependence; and cancer-related, Parkinson's disease-related, and multiple sclerosis–related fatigue (Greenblatt and Adams 2022; Ketter et al. 2016; Sheng et al. 2013). Previous studies have also shown that sleep disorders are accompanied by neuroinflammation, and behavioral improvement following treatment with modafinil is associated with attenuation of neuroinflammation and immune dysregulation, suggesting a possible mechanism by which modafinil relieves the symptoms of sleep disorder (Wadhwa et al. 2015; Wadhwa et al. 2018; Xiong et al. 2022).

Accumulating evidence supports the anti-inflammatory properties of modafinil (Ghorbanzadeh et al. 2022; Yousefi-Manesh et al. 2019; Yousefi-Manesh et al. 2019). Primarily, it was found that modafinil modulates the immune response, alleviates inflammation, and protects against cell death in neuroinflammation (Raineri et al. 2012; Ozturk et al. 2021). Based on these observations, a greater number of studies soon set out to investigate the anti-inflammatory and cytoprotective effects of modafinil on other organs (Raineri et al. 2012; Dejban et al. 2020a; Dejban et al. 2020b; Aryannejad et al. 2021). Modafinil not only downregulates proinflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis

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factor α (TNF-α), and interferon γ (IFN-γ) but also upregulates anti-inflammatory cytokines such as IL-4 and IL-10 (Han et al. 2018). Furthermore, modafinil was shown to significantly inhibit reactive oxygen species (ROS) production (Ornell et al. 2014). Inhibition of nuclear factor kappa B (NF-kB) was found to be a major mechanism behind the anti-inflammatory properties of modafinil (Bagcioglu 2023).

Repurposing "old" medications to treat diseases other than what they were approved for is appealing due to their known safety profile. Repurposing can also substantially lower overall development costs and expedite the development process. Thus, due to the high attrition rates, high costs, and slow pace of drug discovery, repurposing is always a preferable option (Pushpakom et al. 2019). Globally, repurposing of pharmaceuticals in experimental studies has recently received much attention (Ala et al. 2021; Khalilzadeh et al. 2022). Owing to its anti-inflammatory effects, recent studies attempted to provide evidence for repurposing modafinil for several diseases, including but not limited to peripheral neuropathy, skin flap ischemia, autoimmune encephalomyelitis, and inflammatory bowel disease. A concise systematic review of these studies is missing; therefore, in this study, we systematically reviewed the current literature to provide a comprehensive insight into the anti-inflammatory uses of modafinil in experimental studies.

Methods

Search strategy

We conducted a systematic search using Medline (via PubMed), Web of Science, Scopus, and Embase databases from their commencement until 10 October 2022. The following search strategy is provided as an example of how we retrieved articles via PubMed: (" Modafinil"[mh] OR "Modafinil"[tiab] OR "Vigil"[tiab] OR "Sparlon"[tiab] OR "Nuvigil"[tiab] OR "Alertec"[tiab] OR "Benzhydrylsulfinylacetamide"[tiab] OR "Armodafinil"[tiab] OR "2-((Diphenylmethyl)sulfinyl)acetamide"[tiab] OR "R-Modafinil"[tiab] OR "Provigil"[tiab] OR "Modiodal"[tiab] OR "Alertec"[tiab] OR "Modasomil"[tiab] OR "Sparlon"[tiab]) AND ("Inflammation"[mh] OR "Cytokines"[mh] OR "Inflammation"[tiab] OR "Inflammatory"[tiab] OR "Anti-Inflammation"[tiab] OR "Anti-inflammatory"[tiab] OR "Cytokines"[tiab] OR "Cytokine"[tiab] OR "Experimental"[tiab] OR "Animal"[tiab]).

Eligibility criteria

We used the following criteria throughout our screening process: First, the study used modafinil in an animal model. Second, the anti-inflammatory effects of modafinil have been examined in the study. Articles that did not assess the effect of modafinil on inflammatory diseases were excluded. Moreover, we excluded human studies reporting the anti-inflammatory effects of modafinil. Systematic reviews, meta-analyses, and letters to editors were also excluded.

Screening and data extraction

The full texts of the articles were checked after the title and abstract were initially evaluated by two independent researchers. Disagreements were resolved through discussions with a third researcher. A spreadsheet in Excel was used to extract the data. The following data were extracted: author name, year of publication, country of study, the type of animal model, dose and route of administration, and anti-inflammatory mechanisms.

Results

Characteristics of included studies

Our initial search yielded 1398 articles. Figure 1 shows the entire screening procedure in detail. Eventually, 14 publications were included in our systematic review. Table 1 displays the features of the included studies. Current evidence supports that modafinil can modulate inflammation, suppress the immune response, and improve disease severity partly by inhibiting NF-κB, NOS, Kca3.1, Kca2.3, and COX-2.

Modafinil protected against testicular torsion/detorsion

Testicular torsion is a surgical emergency because of the devastating effect of acute ischemia and subsequent inflammatory response, oxidative stress, and apoptosis on the testis. Overproduction of ROS after surgical detorsion leads to germ cell apoptosis in testicular torsion (Shimizu et al. 2016). To measure the anti-inflammatory effects of modafinil on testicular ischemia/reperfusion, Yousefi-Manesh et al. 2019 used a rat model of torsion/detorsion. In this study, the testis of rats was twisted 720° clockwise and left in this position for 1 h. They found that intraperitoneal administration of modafinil (10 mg/kg/day for 7 days) markedly ameliorated the inflammatory response and oxidative stress after torsion/detorsion. In particular, higher levels of MDA, IL-1β, and TNF-α were detected in the testicular tissue of the torsion/detorsion group compared to healthy rats. In contrast, treatment with modafinil decreased these inflammatory mediators. In addition, histopathological assessments indicated that pretreatment with modafinil mitigated germinal cell degeneration, hemorrhage, and edema compared to the torsion/detorsion group (Yousefi-Manesh et al. 2019).

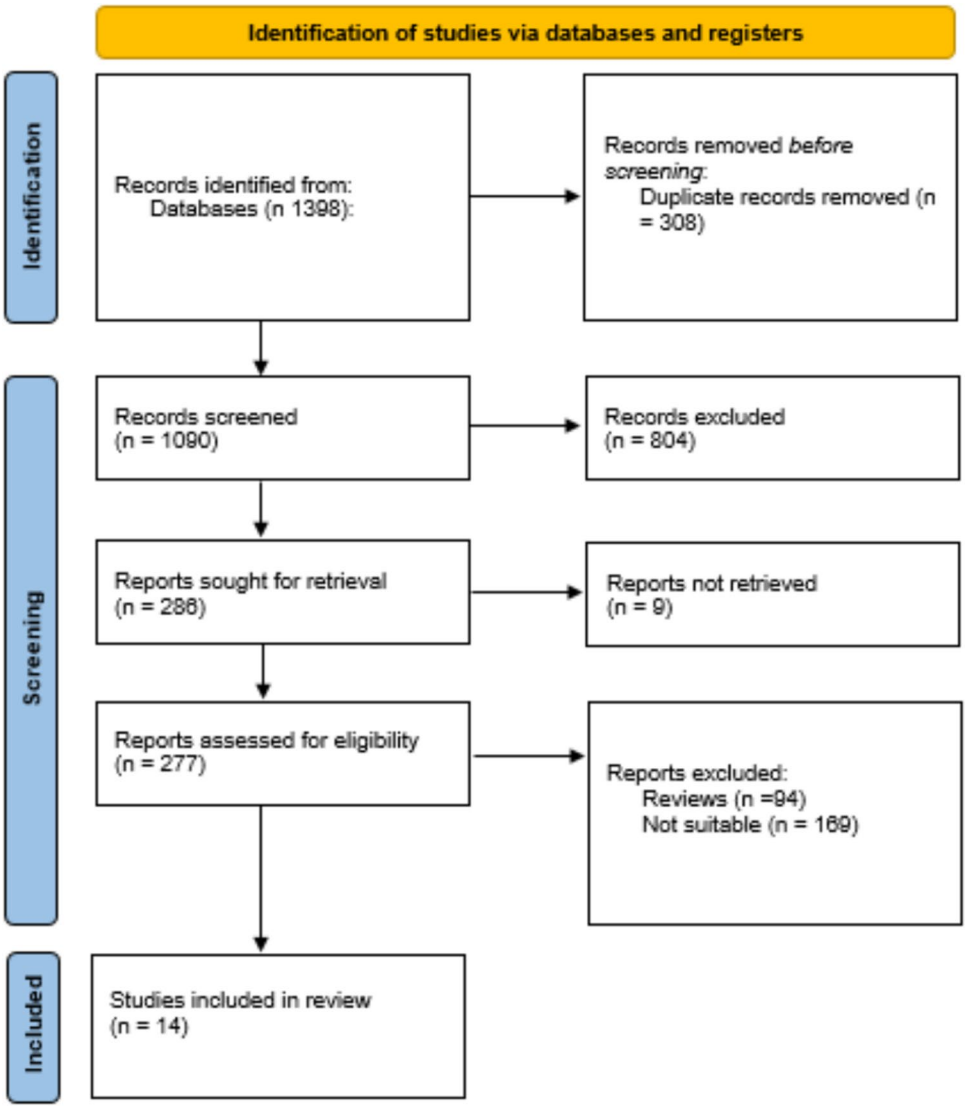

Fig. 1 PRISMA flow diagram

Modafinil improved brain damage after ischemic stroke

Ischemic stroke is a leading cause of serious disabilities and death worldwide (GBD 2019 Stroke Collaborators 2021). Diffuse activation of microglia, uncontrolled release of inflammatory mediators, and oxidative burst have been implicated in neuronal loss after ischemic stroke (Granger and Kvietys 2015; Shi et al. 2019). Yousefi-Manesh et al. 2019 investigated the effect of modafinil in a rat model of ischemic stroke. The rats intraperitoneally received 80 mg/kg of modafinil 30 min before occluding bilateral common carotid arteries. Treated animals had significantly reduced tissue expression of IL-1β, MDA, and NF-κB. Behavioral tests 24 h after ischemic stroke exhibited that modafinil considerably improved post-stroke behavioral impairments. However, no significant alteration was detected in the tissue levels of TNF-α levels and PET scan results (Yousefi-Manesh et al. 2019). Another study by Abbasi et al. 2020 assessed the effect of combination therapy with ethanol and modafinil in a rat model of focal cerebral ischemia. Locomotor activity, neurological deficit score, and unexpected thigmotaxis (anxiety) were dose-dependently increased in the modafinil (10, 30, and 100 mg/kg/day for 7), ethanol (1.5 g/kg at the time of reperfusion), and ethanol + modafinil. Thus, both single and combination therapy with modafinil and ethanol improved neurological function and locomotor activity but increased anxiety (Abbasi et al. 2020).

Modafinil maintained bowel viability in a rat model of intestinal ischemia/reperfusion

The small intestine is extremely sensitive to ischemia/reperfusion (IR) injury (Granger and Korthuis 1995). Reperfusion after ischemia can further deteriorate intestinal injury

Table 1 The characteristics of included studies

Author	Year of publication	Animal model	Dose and route of administration	Anti-inflammatory mechanisms
Amirkhanloo et al. 2020	2020	Vincristine-induced peripheral neuropathy in adult male Wistar rats	5, 25, and 50 mg/kg, intraperitoneally	Decreased TNF-α and IL-1β levels
Aryannejad et al. 2021	2021	Skin flap model in Wistar male rats	10, 25, 50, and 100 mg/kg, intraperitoneally	Histopathological examination showed decreased inflammation
Brandão et al. 2019	2019	Autoimmune encephalomyelitis in female C57BL/6 J mice	90 mg/kg, intraperitoneally	Decreased IFN-γ, IL-10, TGF-β, TBX21, and FoxP3 expression and increased IL-23 expression
Choi et al. 2021	2021	Nonalcoholic liver disease in C57BL/6 mice	10, 50, or 100 mg/kg, orally	Decreased TNF-α and IL-6 levels
Dejban et al. 2020b	2020	Gastric mucosal injury in adult male Wistar rats	20, 50, and 100 mg/kg, intraperitoneally	Decreased TNF-α, IL-1β, and MPO levels
Dejban et al. 2020a	2020	Gastric mucosal injury in adult male Wistar rats	50, 100, and 150 mg/kg, intraperitoneally	Decreased TNF-α and IL-1β levels
Ghorbanzadeh et al. 2022	2022	Neuropathic pain in male NMRI mice	50, 100, and 200 mg/kg, intraperitoneally	Decreased TNF-α and IL-6 levels
Han et al. 2018	2018	Atherosclerosis in C57BL/6 mice	5 mg/kg, intraperitoneally	Decreased IFN-γ, TNF-α and IL-6 levels and increased IL-4 and IL-10 expression
Kamel et al. 2020	2020	Intestinal ischemia/reperfusion in adult male Wistar rats	10 mg/kg, intraperitoneally	Decreased TNF-α, IL-1β, and P-gp expression and reduced intestinal MDA levels
Lee et al. 2016	2016	Pulmonary hypertension in male Sprague–Dawley rats	4, 10, and 50 mg/kg, orally	Downregulated TNF-α, Bcl2-associated X (Bax), VEGF, and IL-6
Wu et al. 2020	2020	Pancreatitis in adult Sprague–Dawley rats	10 mg/kg, intraperitoneally	Decreased CRP, TNF-α, MDA, and IL-6 levels and increased SOD
Yousefi-Manesh et al. 2019	2019	Ischemic stroke in adult male Wistar rats	80 mg/kg, intraperitoneally	Decreased levels of NF-kB, IL-1β, and MDA
Yousefi-Manesh et al. 2019	2019	Testicular torsion/detorsion in adult male Wistar rats	10 mg/kg, intraperitoneally	Downregulated TNF-α, IL-1β, and MDA
Moradi et al. 2022	2022	Lithium-pilocarpine–induced status epilepticus in adult male Wistar rats	50, 75, 100, and 150 mg/kg, intraperitoneally	Decreased TNF-α expression

TNF-α tumor necrosis factor α, *IFN-γ* interferon γ, *IL* interleukin, *TGF-β* transforming growth factor β, *TBX21* t-box transcription factor 21, *FoxP3* forkhead box P3, *MPO* myeloperoxidase, *MDA* malondialdehyde, *VEGF* vascular endothelial growth factor, *CRP* C-reactive protein, *SOD* superoxide dismutase, *NF-kB* nuclear factor kappa B

due to the accelerated production of ROS and inflammatory cytokines (Li et al. 2021; Mallick et al. 2004; Tahir et al. 2018). Pretreatment and treatment with modafinil (10 mg/kg once daily for 7 days) both protected against intestinal ischemia/reperfusion, although treatment with modafinil was more effective than pretreatment in this study (Kamel et al. 2020). Treatment with modafinil significantly ameliorated intestinal injuries, such as distorted intestinal mucosa and epithelial separation in histopathological assessments. Modafinil significantly reduced MDA levels; suppressed the expression of inflammatory mediators such as nitric oxide (NO), TNF-α, and IL-1β; and downregulated caspase-3 activity, a hallmark of apoptosis. Modafinil also enhanced total antioxidant capacity (TAC) activity and promoted P-glycoprotein expression. The decreased expression of P-glycoprotein predicts more severe intestinal inflammation and has been implicated in the pathogenesis of inflammatory bowel disease (Cario 2017). In addition, treatment with modafinil decreased the increased expression of cyclooxygenase 2 (COX-2) overexpression after intestinal ischemia (Kamel et al. 2020). Consistently, previous studies have shown that inhibition of COX-2 can alleviate the inflammatory response and ameliorate structural damage after intestinal ischemia/reperfusion (Gugliandolo et al. 2020). Structurally, modafinil increased the mean number of goblet cells in comparison with the IR group, demonstrating its protective effect on histopathology. Thanks to its anti-inflammatory, antiapoptotic, and antioxidant properties, modafinil can be

a potential candidate for treating acute intestinal ischemia/reperfusion (Kamel et al. 2020).

Modafinil effectively reduced the severity of acute pancreatitis

Acute pancreatitis is an inflammatory condition in which pancreatic enzymes are activated in the lumen of the pancreas and lead to autodigestion of the pancreas and local and systemic inflammatory response (Steinberg et al. 2017; Goodchild et al. 2019). Despite extensive research, the management of acute pancreatitis is still based on supportive care, and specific treatments are still lacking (Goodchild et al. 2019). In a rat model of acute pancreatitis reproduced by retrograde injection of 5% sodium taurocholate into the main pancreatic duct, treatment with modafinil (10 mg/kg ip once daily for 3 days after induction of acute pancreatitis) ameliorated histological damage, including tissue necrosis, inflammatory cell infiltration, bleeding, and interstitial edema; decreased the severity of ascites; and lowered the serum levels of amylase and lipase (Wu et al. 2020). Modafinil significantly decreased the serum levels of IL-6, TNF-α, and C-reactive protein (CRP) and the tissue levels of MDA, while increasing the tissue expression of superoxide dismutase (SOD), a major endogenous antioxidant. Furthermore, modafinil prevented apoptotic cell death in the rat model of pancreatitis and cultured pancreatic cells exposed to lipopolysaccharide, evidenced by the increased expression of the antiapoptotic protein Bcl-2, decreased expression of the proapoptotic protein Bax, and inhibition of caspase-3. It was uncovered that the therapeutic effects of modafinil on acute pancreatitis were associated with the upregulation of Smad nuclear-interacting protein 1 (SNIP1) expression (Wu et al. 2020). Consistently, previous studies found that SNIP1 overexpression can inhibit NF-κB activation and downregulate inflammatory cytokines (Shi et al. 2018).

Modafinil ameliorated inflammatory bowel disease

Inflammatory bowel disease is a chronic and debilitating inflammatory disease of the gastrointestinal tract that is currently managed by several groups of anti-inflammatory drugs, such as corticosteroids, anti-TNF agents, and 5-aminosalicylic acids (Lamb et al. 2019). In a rat model of acetic acid-induced colitis (Dejban et al. 2020a), modafinil (50, 100, and 150 mg/kg/day for 2 days) dose-dependently improved tissue inflammation in both macroscopic and microscopic views. In addition, modafinil (100 and 150 mg/kg) significantly potentiated the anti-inflammatory effects of dexamethasone on experimental colitis. Treatment with modafinil significantly decreased the increased expression of IL-1β and TNF-α in the damaged tissue. Interestingly, administration of nitric oxide synthase (NOS) inhibitors such as L-NG-nitro-arginine methyl ester, 7-nitroindazole, and aminoguanidine before or with modafinil injection attenuated the protective effects of modafinil on acetic acid–induced colitis (Dejban et al. 2020a).

Modafinil alleviated gastric ulcer

Gastric ulcers are a common gastrointestinal disease caused by NSAIDs, stress conditions, and alcohol (Zheng et al. 2014; Everhart et al. 1998). Dejban et al. 2020b investigated the effect of modafinil on indomethacin-induced, water immersion–induced, and alcohol-induced rat models of gastric ulcers. Modafinil pretreatment (50 and 100 mg/kg IP) significantly improved gastric ulcer on macroscopic view and decreased the increased expression of TNF-α, IL-1β, and myeloperoxidase (MPO) in a rat model of indomethacin-induced and stress-induced gastric ulcer. However, modafinil was not effective in the rat model of ethanol-induced gastric. In line with their previous study in a colitis rat model (Dejban et al. 2020), co-administration of L-NAME (10 mg/kg I.P.) and aminoguanidine (50 mg/kg I.P.) with modafinil abolished the protective effects of modafinil on gastric ulcer. However, 7-nitroindazole (40 mg/kg I.P.) did not alter the protective effect of modafinil (Dejban et al. 2020b; Miyoshi et al. 2003; Wallace and Miller 2000).

Modafinil improved liver inflammation and fibrosis in NAFLD

Choi et al. 2021 assessed the potential anti-inflammatory and anti-fibrotic effects of modafinil on non-alcoholic fatty liver disease (NAFLD). C57BL/6 mice were given a high-fat diet (HFD) to induce hepatic steatosis and fibrosis. Another group of C57BL/6 mice received thioacetamide (100 mg/kg I.P. 3 times/week), a hepatotoxic agent, which induces hepatitis and liver fibrosis. However, modafinil could not prevent hepatic steatosis; it significantly suppressed inflammatory cell infiltration into the damaged liver and downregulated the expression of inflammatory cytokines and chemokines such as TNFα, IL-6, chemokine ligand 2 (CCL2), and C–C chemokine receptor type 2 (CCR2) in both animal models. In addition, histopathological measurements revealed that treatment with modafinil markedly decreased the severity of liver fibrosis in both animal models, which was associated with decreased tissue expression of pro-fibrotic factors such as matrix metalloproteinase 9 (MMP9), tissue inhibitor of metalloproteinase 2 (TIMP2), collagen 1, collagen 3, α-smooth muscle actin (α-SMA), and hydroxyproline, a metabolite of collagen. Likewise, mice treated with modafinil had lower serum levels of procollagen type I N-terminal propeptide (P1NP) (Choi et al. 2021). Previously, it was shown that inhibition of TIMP2 in NAFLD can protect against tissue fibrosis and hinder the progression

of NAFLD to non-alcoholic steatohepatitis (NASH) (Deng et al. 2017). Besides, patients with NASH have increased levels of MMP9, and MMP9 expression in these patients positively correlates with NAFLD activity score, suggesting the importance of extracellular matrix remodeling in the progression of NAFLD to NASH (Wagner et al. 2023).

Moreover, in HFD-fed mice, treatment with modafinil decreased the increased expression of high mobility group box 1 (HMGB1), a damage-associated molecular pattern molecule (Choi et al. 2021). The hepatic deletion of HMGB1 is correlated with liver steatosis. Moreover, HMGB1 is upregulated in NAFLD, activates hepatic stellate cells, and promotes liver fibrosis (Choi et al. 2021; Tang et al. 2021). This study showed that the antifibrotic, anti-inflammatory, and antioxidant effects of modafinil on NAFLD were mainly mediated through the downregulation of Ca^{2+}-activated K^+ channels (Kca2.3 and Kca3.1) (Choi et al. 2021). Consistently, previous studies have shown that $K_{Ca}3.1$ plays a major role in the development of fibrosis in different organs, which makes it a potential therapeutic target (Roach and Bradding 2020).

Modafinil alleviated pain, a main feature of inflammation

Pain is a cardinal sign of both acute and chronic inflammation, which can offer protection as an alarm sign (Ji et al. 2016). Based on the analgesic properties of some psychostimulant drugs (Shyu et al. 1992; Tocco and Maickel 1984) and the psychostimulant effect of modafinil (Rasetti et al. 2010), Gupta et al. 2014 investigated whether single-dose modafinil (50, 100, or 200 mg/kg i.p.) affects acute and persistent pain of Swiss albino male mice in tail-flick, hot plate, and formalin tests. Single-dose modafinil exhibited a dose-dependent antinociceptive effect, while chronic administration of modafinil (100 mg/kg for 10 days) led to thermal hyperalgesia. They found that pretreatment with nitric oxide synthase inhibitors (7-nitroindazole (on day 7) and L-NAME (on day 10)) reversed modafinil-induced hyperalgesia but had no effect on the antinociceptive property of modafinil, suggesting the possible role of the NO pathway in modafinil-induced hyperalgesia. In contrast, naloxone (on day 10) could not reverse the hyperalgesic effect of modafinil (Gupta et al. 2014). Ghorbanzadeh et al. reported the analgesic and neuroprotective effects of single-dose modafinil. They induced neuropathic pain by inserting a polyethylene tubing cuff around the common branch of the sciatic nerve in male NMRI mice. After 7 days, they administered modafinil (50, 100, and 200 mg/kg; intraperitoneal) or morphine (10 mg/kg, i.p.), a standard treatment of pain for control. Modafinil (100 mg/kg) and morphine both increased the decreased threshold of paw withdrawal after modeling. Furthermore, modafinil downregulated the inflammatory mediators, including NO, IL-6, and TNF-α, which were markedly upregulated after cuff surgery. Pretreatment with nonselective NOS inhibitors (L-NAME, 7-nitroindazole, and aminoguanidine) and citalopram, a selective serotonin reuptake inhibitor, reversed the analgesic effects of modafinil, suggesting the involvement of NO and serotonin in antinociceptive effects of modafinil (Ghorbanzadeh et al. 2022).

Modafinil protects against atherosclerotic cardiovascular disease

Atherosclerosis is a major driver of ischemic heart disease and stroke, which are currently the leading cause of mortality and morbidity worldwide (Roth et al. 2020). Accumulation of lipid-laden cells, tissue infiltration of macrophages and other inflammatory cells, deregulated release of inflammatory cytokines subsequent to NF-κB and inflammasome activation, local death of endothelial cells and vascular smooth muscle cells, and tissue matrix remodeling have been implicated in the pathogenesis of atherosclerosis (Soehnlein and Libby 2021). Han et al. 2018 found that modafinil can decelerate the development of atherosclerosis in $apoE^{-/-}$ mice and reduce the extent and severity of aortic atherosclerotic lesions. Modafinil (5 mg/kg ip) downregulated CRP and proinflammatory cytokines, including IL-6, TNF-α, and IFN-γ. Modafinil also prevented the accumulation of lipid-laden macrophages and local degeneration of affected blood vessels, evidenced by reduced tissue levels of scavenger receptor class A (SR-A), CD36, and MMP1. At the same time, modafinil upregulated the expression of anti-inflammatory cytokines such as IL-4 and IL-10 and reduced the expression of COX-2 and inducible nitric oxide synthase (iNOS), which are responsible for producing noxious metabolites such as NO, prostaglandins, and thromboxanes (Han et al. 2018; Piper and Garelnabi 2020; Hayashi et al. 2006). These metabolites can exacerbate inflammation, promote inflammatory cell infiltration, and induce vasospasm and platelet aggregation (Piper and Garelnabi 2020; Hayashi et al. 2006). They found that modafinil (100 μM) suppressed macrophage proliferation and viability by blocking the protein kinase B (Akt)/NF-κB pathway. NF-κB singling pathway modulates the thrombotic potential of atherosclerotic plaques by regulating the expression of tissue factors, inflammatory cytokines, and matrix metalloproteinases (Monaco et al. 2004). Modafinil attenuated inflammation and reduced atherosclerotic lesions by inhibiting NF-κB in macrophages of $apoE^{-/-}$ mice (Han et al. 2018).

Modafinil improved pulmonary arterial hypertension (PAH)

PAH is the main cause of right ventricular failure (Voelkel et al. 2012). Thickening of precapillary pulmonary arteries,

intimal lesions, and medial hypertrophy are pathological characteristics of PAH (Rabinovitch 2008). Lee et al. 2016 assessed the effect of modafinil in a rat model of monocrotaline (MCT)-induced PAH. Modafinil (4, 10, and 50 mg/kg) successfully reduced right ventricular pressure, improved right ventricular hypertrophy, and decreased the number of intra-acinar arteries. Modafinil also decreased the expression of endothelin-1 (ET-1), endothelin receptor A (ERA), Bax, TNF-α, and IL-6 (Lee et al. 2016). Consistently, previous studies have found that endothelin levels are correlated with the severity of PAH, and endothelin receptor agonists can decrease mortality and increase functional capacity in patients with PAH (Rubens et al. 2001; Liu et al. 2021). Thus, modafinil might be able to attenuate the vasoconstriction caused by the endothelin/ERA pathway in PAH (Lee et al. 2016). Modafinil also downregulated the expression of vascular endothelial growth factor (VEGF), which is a main promoter of angiogenesis (Lee et al. 2016). Recent studies observed that patients with PAH have higher levels of inflammatory cytokines and proangiogenic factors, whose expression levels were significantly associated with mortality among these patients (Hirsch et al. 2023). Moreover, modafinil reduced the increased expression of KCa3.1 and subsequently upregulated cyclic adenosine monophosphate (cAMP) (Lee et al. 2016; Choi et al. 2012; Wort et al. 2000; Pal China et al. 2018). They revealed that modafinil prevented pulmonary vascular remodeling and decreased medial wall thickening of pulmonary arterioles by suppressing Kca3.1-dependent proliferation of pulmonary artery smooth muscle cells (PASMCs) (Lee et al. 2016). Previous studies also indicated that inhibition of Kca3.1 can downregulate several proliferative pathways, such as the extracellular signal–regulated kinase (ERK) pathway in PASMCs (Guo et al. 2017). In addition, dual activation of cAMP and cyclic guanosine monophosphate (cGMP) by phosphodiesterase 4 and 5 inhibition was shown to maintain the normal structure of the right ventricle and pulmonary artery and decrease their remodeling (Muraki et al. 2019). Therefore, the protective effect of modafinil on PAH seems to be multifaceted and mediated through Kca3.1 inhibition.

Modafinil protects against vincristine-induced peripheral neuropathy

Vincristine is a chemotherapeutic agent that is widely used for treating leukemia and lymphoma; however, it can induce peripheral neuropathy and lead to hyperesthesia and neuropathic pain (Mora et al. 2016). Vincristine-induced peripheral neuropathy can significantly limit its clinical application and undermine its therapeutic efficacy (Velde et al. 2017). Amirkhanloo et al. (Amirkhanloo et al. 2020) measured the effect of pretreatment with modafinil (5, 25, and 50 mg/kg), gabapentin (20 mg/kg), and their combination (modafinil 5 mg/kg or 50 mg/kg, and gabapentin 20 mg/kg) on vincristine-induced peripheral neuropathy. The study indicated that vincristine increased the expression of TNF-α and IL-1β in dorsal root ganglia. In contrast, modafinil pretreatment reduced TNF-α and IL-1β expression. They also indicated that modafinil ameliorated vincristine-induced peripheral neuropathy by rehabilitating the mechanical and thermal disturbances. Modafinil increased the latencies of tail-flick (thermal) and von Frey filament (mechanical) tests, motor nerve conduction velocity (MNCV), and excitation of nerve conduction which all were decreased after exposure to vincristine (Amirkhanloo et al. 2020). Moreover, modafinil improved the effect of gabapentin on vincristine-induced peripheral neuropathy.

Modafinil mitigated experimental autoimmune encephalomyelitis

Previous studies reported the beneficial effects of modafinil on fatigue and motor function in multiple sclerosis (MS) (MacAllister and Krupp 2005; Shangyan et al. 2018). Recently, it was found that modafinil can alleviate *Bordetella pertussis* toxin-induced experimental autoimmune encephalomyelitis (EAE), an experimental model of MS (Brandão et al. 2019). Treatment with modafinil (90 mg/kg/day for 5 days, from day 12 to day 15 after modeling) improved the symptoms and motor function in EAE, which was associated with reduced inflammatory cell infiltration and decreased Th1 cell percentage in the central nervous system (CNS) (Brandão et al. 2019). Modafinil downregulated the expression of Th1-related genes, such as IFN-γ and T-box transcription factor 21 (TBX21). However, modafinil did not affect the expression pattern of Th17-related genes, such as IL-17 and RAR-related orphan receptor gamma t (ROR-γt). Lower abundances of splenic T CD4 + cells were identified in modafinil-treated mice, but no changes were detected in T CD8 + and CD11b + abundance. Additionally, modafinil increased the splenic abundance of $CD11b^{+}CD86^{+}$ and $CD11b^{+}MHC\ II^{+}$ cells in the mice model of EAE (Brandão et al. 2019).

Modafinil preserved flap survival in a rat model of skin flap

Skin flaps are widely used to cover skin defects, and flap necrosis is still the most severe complication of skin flap surgeries (Gurtner and Neligan 2017; Tschoi et al. 2005). The nitric oxide pathway has been previously implicated in skin flap survival due to its role in VEGF-mediated angiogenesis and vasodilation (Pipili-Synetos et al. 1993; Kimura and Esumi 2003; Wang et al. 2011). Aryannejad et al. 2021 measured the effect of pretreatment with modafinil (10, 25, 50, and 100 mg/kg) on skin flap survival. They found that

25 mg/kg was the most effective dose of modafinil for flap survival, while modafinil 100 mg/kg was not effective. NOS inhibitors or glibenclamide, a K_{ATP} channel blocker, significantly reversed the protective effects of modafinil 25 mg/kg. In contrast, a non-effective dose of cromakalim, a K_{ATP} channel opener, improved the protective effects of modafinil (10 mg/kg) on flap survival. Moreover, VEGF expression was higher in modafinil 25 mg/kg or cromakalim 40 µg/kg + modafinil 10 mg/kg group compared to the control group. These findings suggest that modafinil enhanced skin flap survival partly through K_{ATP} channels and NO pathway (Aryannejad et al. 2021).

The anti-inflammatory properties of modafinil can improve epilepsy

Ozsoy et al. 2015 evaluated the effects of modafinil on pentylenetetrazole-induced convulsion. They observed that modafinil delayed the onset of myoclonic jerks and decreased the duration of generalized seizures. Furthermore, Zolkowska et al. 2015 uncovered that modafinil significantly elevates the threshold of convulsion in mice. In addition, Moradi et al. 2022 observed that modafinil (100 mg/kg) can reduce pilocarpine- and lithium chloride–induced status epilepticus scores in rats. Modafinil diminished NO metabolite and TNF-α levels in the hippocampus of rats. Anticonvulsive effects of modafinil were reversed by non-selective NOS inhibitors including L-NAME, 7-nitroindazole, and aminoguanidine. Although NOS inhibitors considerably reduced NO levels, they increased TNF-α levels in modafinil-treated rats (Moradi et al. 2022).

Discussion

In this study, we reviewed the newly discovered applications of modafinil in several experimental studies. Taken together, the results of these studies support the potential of modafinil for treating inflammatory diseases. Current evidence supports that modafinil can modulate inflammation, suppress the immune response, and improve disease severity partly by inhibiting NF-κB, NOS, Kca3.1, Kca2.3, and COX-2. Previous studies found that modafinil elevates cAMP levels in osteoblasts (Pal China et al. 2018) and fibroblasts (Choi et al. 2012). As cAMP is a well-known inhibitor of inflammation, which downregulates KCa2.3 and KCa3 (Choi et al. 2012; Abiraman et al. 2018), previous studies investigated the involvement of KCa2.3 and KCa3.1 in the anti-inflammatory effects of modafinil (Choi et al. 2021; Lee et al. 2016). Besides, many studies reported that the anti-inflammatory properties of modafinil are mediated through the NO pathway (Dejban et al. 2020b; Dejban et al. 2020; Aryannejad et al. 2021; Brandão et al. 2019; Kamel et al. 2020; Gupta et al. 2014). Furthermore, it was unveiled that modafinil can maintain BBB integrity and suppress microglial activation and leukocyte infiltration in lipopolysaccharide (LPS)-induced inflammation through dopaminergic D1 receptor signaling (Zager et al. 2018). The protective effects of modafinil on neuroinflammation were accompanied by the decreased expression of inflammatory cytokines (Raineri et al. 2012; Wadhwa et al. 2018) such as IL-1β (Yousefi-Manesh et al. 2019). Similarly, Wu et al. 2020 observed that modafinil lowered the serum levels of CRP, IL-6, and TNF-α in acute pancreatitis. Likewise, modafinil downregulated proinflammatory cytokines, such as IL-6 and TNF-α, in animal models of atherosclerosis by inhibiting the NF-κB pathway (Yousefi-Manesh et al. 2019), suggesting the anti-inflammatory properties of modafinil. However, future research is needed to uncover the exact mechanisms underlying its anti-inflammatory effects.

The FDA approved modafinil in 1998 for narcolepsy treatment and for shift work sleep disorder and obstructive sleep apnea in 2003. (Golicki et al. 2010; Kumar 2008). This drug can also improve the health problems of patients with obstructive sleep apnea (Kuan et al. 2016). However, with the discovery of its immunomodulatory effects in various studies, including animal models, further studies have been conducted to unravel its effects and the underlying mechanisms in the inflammatory diseases of the nervous and other systems. Modafinil was shown to exert anti-inflammatory effects on Parkinson's disease, multiple sclerosis, brain ischemia, and systemic inflammation, supporting its effects on both peripheral and central inflammation (Zager 2020). In 2019, a study unveiled that modafinil can mitigate experimental autoimmune encephalomyelitis in a mouse model by inhibiting the brain T-helper 1 response, suggesting its efficacy for the treatment of this disease (Brandão et al. 2019). Treatment with modafinil was found to downregulate proinflammatory cytokines (e.g., IL-1β, TNF-α) and upregulate anti-inflammatory factors (e.g., IL-10) in animal models (Xiong et al. 2022).

The half-maximal inhibitory concentration of drugs, including modafinil, should be considered for their clinical application. The IC50 for modafinil ranges from 3.2 to 4.0 µM based on the literature (Minzenberg and Carter 2008; Wisor 2013; Volkow et al. 2009), suggesting that although modafinil affects dopamine levels, its potency is lower than other stimulants. Research on the long-term effects of modafinil remains limited, primarily due to various influencing factors, such as dosage (low-dose versus high-dose), frequency of administration (daily versus intermittent), and the route of administration (central versus peripheral). These factors make it hard to understand the long-term effects of modafinil on health and cognitive function (Murillo-Rodríguez et al. 2018).

A 2014 study found that modafinil can reduce the negative symptoms of schizophrenia in the short term. The results showed that side effects, fatigue, and drowsiness were not significantly different between the modafinil group and the placebo group, and modafinil was generally safe and well tolerated. However, this effect was not observed in patients with chronic schizophrenia or those with a high burden of negative symptoms, and it did not modulate other dimensions of schizophrenia symptoms (Andrade et al. 2015).

Exploring the structure–activity relationships of modafinil derivatives can provide a deeper insight into their anti-inflammatory properties. Studies have indicated that specific modifications, such as the introduction of aliphatic or cyclic groups, can significantly affect the inhibition of proinflammatory enzymes, like iNOS and COX-2, in microglial cells (Jung et al. 2012). Besides, modafinil has been shown to upregulate adenosine A2A and A2B receptors, which suppress inflammation through cyclic adenosine monophosphate (cAMP) signaling pathways (Li et al. 2024).

An important advantage of repurposing drugs compared to new drug discovery is that previously approved drugs mostly have known adverse effects. Despite its promising effects on several conditions, modafinil has some unpleasant side effects. Pal China et al. 2018 reported that modafinil may have a negative impact on peak bone accrual in rats, mainly by inducing high turnover bone loss and promoting osteoclastogenesis. Similarly, Wagener et al. 2022 indicated that modafinil may decrease bone matrix mineralization by inhibiting osteoblastogenesis. On the other hand, Canyurt et al. reported that supratherapeutic doses of modafinil may cause adverse cardiovascular events, including atrioventricular block and ischemic heart disease in the long term; however, these findings all were driven from animal studies and are not definite (Canyurt et al. 2022).

By reviewing recent findings from experimental studies, we discussed the beneficial effects of modafinil on several inflammatory diseases. Studies with larger sample sizes and more diverse populations should be conducted to determine the effects of this drug on various diseases, providing more robust evidence for clinical translation of the experimental findings. In addition, the clinical translation of experimental findings demands robust clinical trials with rational design and appropriate dosing of the drug for its new purpose.

Authors contributions A.D, R.B: conceptualization, project Administration, data curation, writing (original draft), writing (review and editing), visualization

M.J.A, R.M.J, N.S, M.A: validation, resources, methodology, software, formal analysis, writing (original draft). The authors declare that all data were generated in-house and that no paper mill was used.

Data availability All source data for this work (or generated in this study) are available upon reasonable request.

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Declarations

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