Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Ivermectin

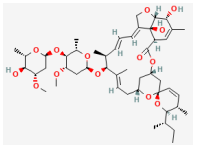
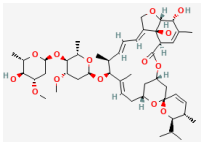
Evidence Summary

Ivermectin is a broad-spectrum anti-parasitic agent with excellent safety and efficacy at standard doses. It shows immune and neuro-modulatory activity *in vitro* at doses that exceed the level of acceptable safety.

Neuroprotective Benefit: Ivermectin can modulate neurotransmitter receptors, but this can only be achieved by the use of very high doses, which can also cause neurotoxic side effects.

Aging and related health concerns: Ivermectin does not show broad immunomodulatory activity at clinically safe doses. It may have utility as an adjunct in cancer therapy.

Safety: Ivermectin is safely used by millions of people annually in single doses or short-term administration for its anti-parasitic activity. Administration at higher doses could result in visual disturbances, sedation, and other neurological side effects.

Availability: Rx (and OTC for 0.5% topical lotion for head lice).	**Dose**: Oral tablets (3 mg) at a dose of 150 to 200 µg/kg are used for parasitic infections. Typically, as single dose administration. Topical (1% cream) formulation is applied to the face once daily for rosacea.	**Ivermectin 80:20 mixture of avermectin B1a and B1b** Avermectin B1a **Chemical formula:** $C_{48}H_{72}O_{14}$ **MW**: 873.1 g/mol  Source: PubChem Avermectin B1b **Chemical formula**: $C_{47}H_{70}O_{14}$ **MW**: 859.0 g/mol  Source: PubChem
Half-life: 12-36 hours (metabolites may persist up to 3 days)	**BBB**: Very low penetrance at standard doses (PgP substrate)	
Clinical trials: Ivermectin has been tested in numerous trials for parasitic diseases, as well as in several large trials (<1,000 participants) for covid-19. Topical ivermectin has been tested for rosacea.	**Observational studies**: There are no studies to indicate that ivermectin can prevent/protect against non-parasite-related diseases.	

What is it?

Ivermectin is a member of the avermectin family. It is the world's first endectocide, or broad anti-parasitic agent [1]. It is an 80: 20 mixture of two macrocyclic lactone derivatives, avermectin B1a and avermectin B1b. Avermectin, produced by the bacterium *Streptomyces avermectinium*, was isolated from a soil sample in Japan in the 1970s, and was found to have robust anti-parasitic properties by a team at Merck [2]. Via chemical modification, the avermectin derivatives that make up ivermectin were synthesized, and found to be effective against a variety of parasites in livestock, with little to no toxicity to the farm animals. Ivermectin became a commercial veterinary product in 1981 and was marketed to the public under the name Heartgard® starting in 1987. Merck worked with the World Health Organization (WHO) to conduct clinical trials in populations where river blindness, a chronic parasitic infection of *Onchocerca volvulus* worms, is endemic, and ivermectin was approved for human use for this indication in 1987 under the tradename Mectizan®. The Mectizan Donation Program allowed for the widespread use of ivermectin in developing countries. Ivermectin is used in mass administration programs to around 250 million people annually for the prevention and treatment of parasitic diseases. Ivermectin is listed as one of the WHO's essential medicines [1]. It was subsequently found to be

effective against a variety of parasites and is now considered to be a broad spectrum anti-parasitic agent, particularly against helminths, or worm-like parasites. According to the WHO, ivermectin shows efficacy against onchocerciasis (river blindness), strongyloidiasis, lymphatic filariasis, trichuriasis, ascariasis, ancylostomiasis, hookworm diseases, and scabies (WHO). Ivermectin, in the form of a 1% topical cream, was also approved for the treatment of rosacea in 2014 [3].
Ivermectin's anti-parasitic activity stems from its potent activation of invertebrate specific glutamate-gated chloride channels [1]. Ivermectin can also affect related mammalian ion channels, but due to the difference in affinity, mammalian channels are unaffected at standard anti-parasitic doses [4]. Due to its impacts on Cys-loop receptors and other related targets, ivermectin has been found to exert a wide variety of effects in *in vitro* studies. The vast majority of these findings have no pathway toward clinical translation because the high doses required for these effects would lead to a variety of off-target effects and toxicities. Ivermectin was found to have anti-viral activity against SARS-CoV2 in *in vitro* assays, and was subsequently tested in a variety of clinical trials for covid-19 [5]. However, the dose required to achieve robust antiviral efficacy was substantially higher than standard dosing, and the trials failed to find clinical benefit in symptomatic patients.

Neuroprotective Benefit: Ivermectin can modulate neurotransmitter receptors, but this can only be achieved by the use of very high doses, which can also cause neurotoxic side effects.

Types of evidence:

- 1 review of pre-clinical and clinical studies of ivermectin for Epilepsy
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

There is currently no evidence to suggest that ivermectin can prevent or slow cognitive decline.

Human research to suggest benefits to patients with dementia:

There is currently no evidence to suggest that ivermectin impacts disease course in dementia patients.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Epilepsy: NO CLEAR BENEFIT AT SAFE DOSES

Ivermectin has the capacity to modulate several Cys-loop receptors in the mammalian nervous system, including $GABA_A$, glycine, and nicotinic acetylcholine receptors [4]. As a result, ivermectin has been proposed as a potential therapeutic for several neurological disorders. However, the effects seen in preclinical studies may not be achievable in humans due to the potential for toxicity at the doses required to exert the neurological effects in the mammalian CNS.

Despite its lipophilic nature, ivermectin is typically prevented from accumulating in the CNS at standard doses used for parasites because it is a substrate for the P-glycoprotein (P-gp) multidrug transporter at the BBB [6]. However, high doses of ivermectin can inhibit the transporter and allow it to exert effects in the CNS [4].

The initial testing done by the scientists at Merck concluded that ivermectin was not a suitable drug for epilepsy because, at doses in the low mg/kg range, adverse CNS effects such as sedation and tremor were apparent, while robust antiseizure effects were not observed in their animal models [4].

Ivermectin was also tested as part of the Epilepsy Therapy Screening Program by the US National Institute of Neurological Disorders and Stroke (NINDS), which found that the median effective doses (ED_{50}s) for anticonvulsant activity in rodent models led to adverse effects or were close to median lethal dose (LD_{50}) [4]. Both the anti-seizure and neurotoxic effects involve the modulation of $GABA_A$Rs, thus it may not be possible to safely use ivermectin for this therapeutic indication.

Due to its role as an anti-parasitic, ivermectin has been used in epileptic patients infected with *Onchocerca volvulus* worms [4]. Infection with *O. volvulus* has been associated with multiple seizure and epilepsy subtypes. Therefore, the primary anti-seizure activity of ivermectin in these patients likely stems from a direct effect on the filarial worms. Clinical trials in this population have found that ivermectin did not offer additional anticonvulsant benefit relative to phenobarbital alone, and that seizure frequency decreased in conjunction with reductions in microfilarial density, suggesting that ivermectin's mitigation of parasite-induced seizures relates to its anti-parasitic activity [4]. Antiseizure activity was observed with ivermectin (10 mg/day) as an adjunct in a small observational study in patients with refractory epilepsy (n=32), however, the outcomes of the study were not in line with what is typically seen in this population, raising questions as to the reliability of this finding [4].

Ivermectin was patented by Equilibre Neuroscience in 2021 as a once-daily oral adjunctive therapy for focal seizures in adults with refractory epilepsy. They tested ivermectin (EQU-001) up to 60 mg/day in a Phase 2 trial assessing clinical safety, tolerability, and preliminary efficacy in adults with epilepsy (n=43) (NCT05063877). Topline results indicated a general dose response trend with increasing median percent reductions in focal seizures per 28 days of 41.6% (95% Confidence Interval [CI] -5.6 to 83.5), 7.4% (95%

CI -51.3 to 29.1), 19.9% (95% CI -33.6 to 50.2), 12.3% (95% CI -32.1 to 83.1), and 5.8% (95% CI -110 to 36.9) in 60 mg, 40 mg, 20 mg, 10 mg, and placebo treatment arms, respectively (Press release). An anti-inflammatory effect was also observed *ex vivo* based on the reduction in IL-17, IL-21, IFN-γ and TNF-α secretion from stimulated peripheral blood mononuclear cells (PBMCs). Plasma levels of IL-17 and IL-1β were also reduced in the highest dose group. A planned Phase 2 RCT testing 20 mg and 60 mg EQU-001 in patients with uncontrolled focal onset seizures (NCT05473442) was terminated by the sponsor due to lack of funding, as the company ceased operations in mid-2023.

Preclinical studies have shown protective effects in other neurological disease-related models, but these are generally not thought to have clinical applicability because of the concern that these effects are likely not achievable at safe dose ranges.
A phenotypic small molecule screen found that ivermectin and other related compounds in the avermectin family could influence the ratio of Aβ38/Aβ42 by increasing levels of Aβ38 [7]. Ivermectin exerted a neuroprotective role in a rat model of transient cerebral ischemia-reperfusion by increasing AMPK activity and mitigating oxidative stress [8]. Higher brain levels were likely achievable in this model due to leakiness of the BBB stemming from cerebrovascular damage. Ivermectin in combination with multi-walled carbon nanotubes mitigated damage in rat spinal cord injury model by attenuating oxidative stress and modulating macrophage polarization [9].

APOE4 interactions: Not established.

Aging and related health concerns: Ivermectin does not show broad immunomodulatory activity at clinically safe doses. It may have utility as an adjunct in cancer therapy.

Types of evidence:

- 4 meta-analyses/systematic reviews on RCTs testing ivermectin for covid-19
- 3 meta-analyses/systematic review on RCTs testing topical ivermectin for rosacea
- 1 systematic review of RCTs testing ivermectin for scabies
- 1 review on ivermectin for parasitic diseases
- 7 well conducted large RCTs of ivermectin for covid-19
- 1 clinical study of the immune effects of standard dose ivermectin
- Numerous laboratory studies

Parasitic diseases: BENEFIT

Ivermectin has been characterized as a 'wonder drug' based on its broad-spectrum activity against a variety of parasites [1]. It is primarily used for helminths, or worm-like parasites. Although resistance has been observed in livestock following widespread use, evidence of confirmed drug resistance has not been observed in human parasites despite being used regularly by millions of people, primarily in developing countries [10].

The strong efficacy and safety of ivermectin stems from its mechanism of action. Ivermectin activates glutamate-gated chloride channels, which are only found in invertebrates [11]. The sustained activation of these inhibitory channels can lead to muscle paralysis and death in the worms. In filarial diseases, ivermectin works by reducing the density of the microfilariae (immature worms), and reduces the fecundity of the adult worms, but does not directly kill the adult worms. It was thought that ivermectin may also impact the host immune system's response to the pathogens, but was subsequently found that ivermectin instead acts on the ability of the parasites to evade detection by the host immune system. Ivermectin suppresses the ability of the parasites to secrete the proteins/molecules that enable the parasites to evade detection [1].

Onchocerciasis, also known as river blindness, is the second leading cause of infection-induced blindness [1]. It is a human filarial disease caused by infection with *Onchocerca volvulus* worms transmitted through the bites of infected blackflies. Population-based mass drug administration of ivermectin is the primary strategy used to combat onchocerciasis in endemic regions. Ivermectin has become the leading choice for the treatment of onchocerciasis because of its rapid anti-microfilarial effects and strong safety. Ivermectin kills only the larvae (microfilarie), and not the adult worms. It generally does not directly trigger the death of the *Onchocerca* worms within the eye, which could exacerbate ocular damage via the induction of an inflammatory reaction, as has been observed with other treatments for onchocerciasis. Rapid microfilarial clearance is observed such that dermal microfilarial loads are generally reduced by 78% within two days, and by around 98% within two weeks.

Lymphatic Filariasis, also known as Elephantiasis, is a human filarial disease caused by the filarial worms, *Wuchereria bancrofti*, *Brugia malayi* or *Brugia timori*, which are transmitted via the bite of an infected mosquito [1]. Ivermectin kills the microfilarie, but not the adult worms.

Strongyloidiasis is a chronic parasitic infection caused by the roundworm helminth (nematode) *Strongyloides stercoralis,* transmitted through contaminated soil. Primary symptoms include abdominal pain and diarrhea, cough and bronchitis, as well as rash and itching, due to infection of the intestine,

lung, and skin, respectively [12]. It is most concerning in those with immunosuppression, as this can lead to hyperinfection and disseminated disease. The cure rate with ivermectin has been found to be around 95-98%, making it a treatment of choice in various countries where this parasite is endemic [13].
Scabies is an itchy rash caused by the skin mite *Sarcoptes scabiei var. hominis* which burrows in the skin and lays eggs there [14]. It can be transmitted by contact with an infected person. A Cochrane systematic review of 15 RCTs including 1,896 participants found that oral ivermectin and topical ivermectin were associated with similar rates of complete clearance compared with permethrin 5% cream following the standard four weeks of treatment [14].
Malaria is caused by the *Plasmodium* family of parasites which are transmitted to humans via infected mosquitos [15]. Ivermectin is being considered for widespread use in malarial control. Ivermectin has mosquitocidal activity and has been shown to kill mosquitos that have fed from ivermectin-treated humans and livestock. As a result, mass administration of ivermectin has been proposed as a potential mechanism to reduce malaria transmission by reducing the population of mosquitos [16]. Ivermectin could also act on the Plasmodium parasite itself which may make them more vulnerable to other antimalarial agents, though further studies are needed.
Ivermectin is also routinely used for other roundworm, whipworm, and hookworm infections [10].

Covid-19: NO CLINICAL BENEFIT IN SYMPTOMATIC PATIENTS
Ivermectin has been tested in several large (>1,000 participants) RCTs in diverse populations in countries around the world for covid-19 [17]. All of these large trials demonstrated a lack of benefit for ivermectin on clinically meaningful outcomes. Some studies did find benefits in terms of self-reported symptom duration, but they were not supported by significant effects on objective measures of disease severity or recovery.
The rationale for testing ivermectin stems from an *in vitro* study finding that ivermectin was able to reduce SARS-CoV2 replication with an IC_{50} of 2 to 2.5 µM (1,750 to 2,190 ng/mL) [18]. The plasma Cmax of the standard dose (150 to 200 µg/kg) is around 30 to 50 ng/mL, and the lung exposure level is substantially lower [19]. A dosing scheme of 300 to 400 µg/kg ivermectin for three days resulted in a plasma Cmax of approximately 135 ng/mL [20]. Even at a dose of 600 µg/kg, modeling suggests that the identified IC_{50} for antiviral activity is at least three times greater than the plasma Cmax and at least 21 times greater than the lung Cmax [21]. The pharmacokinetic modeling suggests that ivermectin is unlikely to have appreciable antiviral activity towards SARS-CoV2 in the tested dose range of 200 to 600 µg/kg, which is consistent with the outcomes of the clinical trials.

Prevention: A systematic review and meta-analysis of 65 studies assessing interventions of repurposed drugs for the prevention of covid-19, including eight studies for ivermectin, found that ivermectin was associated with reduced risk of SARS-CoV2 infection when observational studies were included, but not when the analysis was restricted to only clinical trials (RR: 0.35, 95% CI 0.10 to 1.26) [22]. There were no significant associations between ivermectin prophylaxis and prognostic clinical outcomes. An earlier Cochrane systematic review concluded that there was insufficient evidence to determine whether ivermectin showed efficacy for primary prevention of covid-19 [17].

Treatment: A meta-analysis of 28 RCTs testing interventions for severe covid-19, including two trials with ivermectin, found that ivermectin had no significant impacts on rates of hospitalization (RR: 0.80, 95% CI 0.62 to 1.04) or the need for mechanical ventilation (RR: 0.82, 95% CI 0.48 to 1.42) [23]. A systematic review and meta-analysis of 25 RCTs conducted in 16 different countries (n=6,310 participants) testing ivermectin for covid-19 found that most of these studies had concerns regarding a high risk of bias [24]. Ivermectin did not show evidence for reducing mortality (RR: 0.76, 95% CI 0.52 to 1.11) or mechanical ventilation (RR: 0.74, 95% CI 0.48 to 1.16) in this analysis.

CORVETTE-01: This double-blind, randomized, placebo-controlled trial tested the impact of a single standard dose of ivermectin (200 µg/kg) in 248 patients with mild-to-moderate COVID-19 in Japan (NCT04703205) [25]. There was no significant difference on the primary outcome of time to a negative COVID-19 RT-PCR test (HR: 0.96; 95% CI 0.70 to 1.32), as the median time to a negative RT-PCR test was 14.0 (13.0–16.0) days for ivermectin treated patients and 14.0 (12.0–16.0) days for placebo treated patients.

Due to concerns that the standard dose (0.15 to 0.2 mg/kg) for anti-parasitic activity was too low to exert antiviral activity, other clinical trials used higher doses. Several used a dose range of 0.3 to 0.4 mg/kg, which is two times higher than the standard dose, while other trials used a dose that was about three times higher (0.6 mg/kg), though still lower than the level needed to exert antiviral activity *in vitro*. No clear benefits were observed on viral clearance or clinical outcomes at the tested dose ranges.

TOGETHER: This double-blind, randomized, placebo-controlled, adaptive platform trial (NCT04727424) tested the impact of ivermectin (400 µg/kg daily for 3 days) and other interventions in symptomatic SARS-CoV2-positive adults with symptoms for up to 7 days and at least one risk factor for disease progression [26]. The study included 3,515 participants, 679 of whom received ivermectin. Ivermectin had no significant effect on the primary composite outcome of hospitalization due to covid-19 within 28

days after randomization or an emergency department visit due to clinical worsening (RR: 0.90, 95% Bayesian credible interval, 0.70 to 1.16).

PRINCIPLE: This open label, randomized, controlled, adaptive platform trial assessed short and long-term outcomes in response to ivermectin at a target dose of 300 to 400 µg/kg daily for three days plus standard of care relative to other interventions or standard of care alone in adults with covid-19 in the UK [5]. The study included 11,768 participants, 2,439 of whom were randomized to ivermectin. The primary analysis included 8,811 participants, with 2,157 in the ivermectin arm. Evidence of a benefit in the time to self-reported recovery was observed in the ivermectin group relative to standard of care (HR: 1.145, 95% Bayesian credible interval 1.066 to 1.231) based on the Bayesian primary analysis model, but the effect size was below the pre-specified probability of meaningful effect (HR ≥1.2). Ivermectin did not significantly impact rates of covid-19 related hospitalization/deaths. There was no difference in the long-term outcome of the proportion feeling fully recovered at six months (74.3% vs. 71.2%; RR: 1.05, 95% CI 1.02 to 1.08).

COVID-OUT: This Phase 3, double-blind, randomized, placebo-controlled trial (NCT04510194) assessed the impact of repurposed drug interventions, including metformin, ivermectin (390 to 470 µg/kg for 3 days), and fluvoxamine, on preventing serious SARS-CoV2 infection in non-hospitalized overweight/obese adults (30-85 years of age) enrolled within three days of a confirmed covid-19 diagnosis and less than seven days from symptom onset [27]. None of the interventions showed a benefit on the primary composite endpoint of hypoxemia, emergency department visit, hospitalization, or death (RR: 1.05, 95% CI 0.76 to 1.45 for ivermectin). The ability of these interventions to reduce the risk for long-covid was also assessed in this study with a follow-up of 300 days (n=1,126) [28]. There was no effect on the cumulative incidence of long-covid with ivermectin (HR: 0.99, 95% CI 0.59 to 1.64), or for fluvoxamine, but a reduction was observed with metformin (HR: 0.37, 95% CI 0.15 to 0.95).

IVERMILCO: This study was designed to address the concern that ivermectin administration had been too late to show efficacy in prior trials. Based on the proposed antiviral mechanism of action, it is thought that ivermectin needs to be administered as early as possible after infectionThis multicenter, placebo-controlled, randomized, double-blind, parallel-group, Phase 3 trial assessed the efficacy of ivermectin (300 to 400 µg/kg daily for 3 days) in 1,030 patients with mild covid-19 in Japan and Thailand [20]. Participants received the drug within three days of the onset of covid-19. Ivermectin was not associated with benefit on the primary endpoint of time to an improving trend in clinical symptoms by 168 hours after drug administration. The time to an improvement trend occurred at approximately 96 hours in both the ivermectin and placebo groups (HR: 1.04, 95% CI 0.90 to 1.21).

PLATCOV: This open label, randomized, controlled adaptive platform trial (NCT05041907) tested the impact of high-dose oral ivermectin (600 µg/kg daily for 7 days with food) compared with the monoclonal antibodies casirivimab (600 mg) and imdevimab (600 mg) directed against the spike protein of SARS-CoV-2, or no study drug, on viral clearance rates in participants with early symptomatic covid-19 [29]. Randomization to the ivermectin arm was stopped after enrolling 205 patients into all arms because the prespecified futility threshold (<12.5% acceleration of viral clearance) was reached. The analysis dataset included 101 participants, 46 of whom received ivermectin. Compared to those who had not received any study drug, those receiving ivermectin tended to have slower viral clearance by 9.1% (95% CI –27.2% to +11.8%), such that the viral clearance took 1.9 hours longer (95% CI –2.1 to +6.6) relative to controls, for which the mean viral clearance half-life was 19.2 hours (95% CI 14.8 to 23.9). In contrast, viral clearance was significantly accelerated (by 52.3%, 95% CI +7.0% to +115.1%) with the monoclonal antibody treatment, which is in line with what was observed in other studies.

ACTIV-6: This double-blind, randomized, placebo-controlled platform trial included 1,206 adults (≥30 years old) in the United States with symptomatic mild to moderate covid-19 with at least two symptoms of acute infection for ≤ 7 days in an outpatient setting [30]. Participants were treated with high dose ivermectin (600 µg/kg) or placebo daily for six days. There was no improvement in time to recovery with ivermectin (HR: 1.02, 95% credible interval 0.92 to 1.13). There was also no benefit on the composite of hospitalization, death, or urgent/emergent care utilization by day 28 (HR: 1.0, 95% credible interval 0.6 to 1.5).

Non-specific immune modulation: NO CLEAR IMMUNE EFFECTS AT STANDARD DOSES
It has been suggested that some of the anti-parasitic activity of ivermectin could be due to the modulation of host immunity [31]. Ivermectin has the capacity to modulate ion channels in the mammalian nervous system and immune system *in vitro*. However, since the affinity for these channels is far lower than for the invertebrate-specific glutamate-gated chloride channels, the doses required to achieve these off-target effects are far higher than the typical dosing strategy used for its traditional anti-parasitic activity.
An RCT in healthy volunteers (n=12) between the ages of 18 and 65 examined the immunomodulatory effects in peripheral blood mononuclear cells (PBMCs) of a single oral dose of ivermectin (Stromectol® 0.15 mg/kg) [31]. In this study, a standard dose of ivermectin did not have any significant effects on complete blood counts or cytokine levels, though potential differences may have been difficult to detect due to wide variation in pretreatment cytokine levels across participants. Only three out of 770

immunity-related genes showed differential expression four hours post-ivermectin, including platelet-activating factor receptor, prokineticin 2, and histone deacetylase 5, consistent with an anti-inflammatory effect. There were no changes in circulating levels of leukocytes or eosinophils, which have been implicated in mediating anti-helminth immune responses. Additionally, the participant-derived leukocytes did not exhibit enhanced anti-helminth capacity *ex vivo*, based on ability to kill *Brugia malayi* microfilariae. This study suggests that at standard doses, ivermectin does not appreciably modulate host immune function. The doses that could significantly impact immune responses have not been established in humans, but in order to impact mammalian cells in a clinically meaningful manner, these doses would likely fall within the range that results in toxicity.

Preclinical studies indicate that a primary mechanism by which ivermectin could exert immunomodulatory responses is via regulation of the purinergic P2X4 receptor, a ligand-gated ion channel responsive to ATP. In a mouse model of sepsis, the activation of P2X4R by ivermectin (10 mg/kg) augmented bacterial clearance without significantly impacting the profile of inflammatory cytokines [32]. P2X4R has been found to be downregulated in colonic tissues from patients with inflammatory bowel disease, and the loss of P2X4R increases the susceptibility to DSS-induced colitis in mice [33]. Treatment with ivermectin (5 mg/kg) attenuated inflammatory intestinal damage and gut dysbiosis in this colitis model. The potentiation of P2X4R by ivermectin (1 mg/kg) promoted a shift in microglia polarization toward a reparative state in a mouse EAE model [34]. P2X4R potentiation by ivermectin also had a protective effect in the $SOD1^{G93A}$ ALS mouse model [35].
Ivermectin acts as an allosteric modulator of P2X4R by increasing the maximum current activated by a saturating concentration of ATP, and by slowing the rate of current deactivation through the binding to distinct extracellular sites [36]. However, the EC_{50} for the high affinity site is 0.25 µM (~220 ng/mL), which is over four times higher than the peak plasma level at the standard dose (~50 ng/mL). Additionally, human P2X4R may be less sensitive to ivermectin in an *in vivo* setting due to conformational changes impacting binding site accessibility. It is unclear what dose of ivermectin would be needed to impact P2X4R in a clinically meaningful manner, and whether it would be within the tolerable range.

Rosacea: BENEFIT
Ivermectin as a 1% topical cream (SOOLANTRA®) was approved by the FDA for treatment of the inflammatory lesions of rosacea in 2014 [3]. The mechanism of benefit is unclear, but is thought to involve the anti-inflammatory and anti-parasitic properties of ivermectin. The skin mite *Demodex*, particularly *Demodex folliculorum*, has been associated with rosacea. Though, the skin irritation and

inflammatory response may stem more from the bacteria harbored by the mites rather than the mites themselves. Ivermectin may then help quell the mite-associated skin inflammation.
A Cochrane systematic review of 106 RCTs testing interventions for moderate to severe rosacea included two trials using topical ivermectin (n=1,371 participants), both of which reported statistically significant and clinically important improvements on disease-related measures [37]. Participants treated with ivermectin showed greater improvement on health-related quality of life (HRQOL) measures relative to controls (RR: 1.55, 95% CI 1.26 to 1.90). Relative to controls, ivermectin-treated participants exhibited greater participant-assessed (RR: 1.78, 95% CI 1.50 to 2.1) and physician-assessed (RR: 3.30, 95% CI 2.27 to 4.79) improvements in rosacea severity. A network meta-analysis of 19 RCTs testing topical treatment of adult patients with moderate-to-severe papulopustular rosacea conducted mixed treatment comparisons according to Bayesian methodology [3]. Topical ivermectin (1% cream) was assessed in four of the trials (n=3,047). Ivermectin 1 % cream once daily (QD) was associated with a greater likelihood of success compared with azelaic acid 15 % gel twice-daily (BID) (RR: 1.25, 95 % CI 1.14 to 1.37), and metronidazole 0.75 % cream BID (RR: 1.17, 95% CI 1.08 to 1.29) at 12 weeks, though it was comparable to metronidazole 1 % gel QD. Inflammatory lesion count was also significantly reduced with ivermectin 1 % cream QD compared with azelaic acid 15 % gel BID (RR: −8.04, 95% CI −12.69 to −3.43) and metronidazole 0.75 % cream BID (RR: −9.92, 95% CI −13.58 to −6.35) at 12 weeks. Similarly, another meta-analysis including six studies in 3,781 patients with papulopustular rosacea testing ivermectin (1% cream QD) found that ivermectin was associated with a greater percentage of participants achieving complete clearance (OR: 1.72, 95% CI 1.40 to 2.11) and improvement on quality-of-life measures (OR: 1.71, 95% CI 1.34 to 2.18), relative to comparator interventions [38].

Cancer: POTENTIAL BENEFIT IN COMBINATION (Preclinical)
Ivermectin has been found to have anti-cancer properties in preclinical studies, particularly when used in combination with other anti-cancer agents. These effects have primarily been seen *in vitro* or in rodent xenograft model systems, and it is unclear how well these might translate into humans, though more clinically relevant information should be obtained from an ongoing clinical trial (NCT05318469). The anticancer mechanisms identified in these studies include the inhibition of angiogenesis, the production of reactive oxygen species (ROS), the inhibition of AKT/mTOR signaling, the modulation of autophagy, and the induction of apoptosis [39].
Ivermectin induced apoptosis, ROS production, and DNA damage in bladder cancer cells [40]. Ivermectin stimulated autophagy in glioma (U251) cells in a mouse xenograft model, while the combination of ivermectin with chloroquine slowed tumor growth to a greater degree than ivermectin alone [41]. The growth of patient-derived pancreatic cancer organoids was inhibited by ivermectin [39]. The

combination of ivermectin with gemcitabine synergistically inhibited growth in pancreatic cancer cell lines, and slowed tumor growth in a xenograft mouse model [39]. Ivermectin inhibited tumor cell motility in human colorectal cancer cell lines and inhibited metastasis in a xenograft model [42]. In breast cancer cell lines, ivermectin has been shown to induce PAK1-mediated cytostatic autophagy, stemming from the inhibition of AKT/mTOR signaling [43]. The addition of ivermectin potentiated the immunological anti-tumor response of anti-PD1 therapy in a rodent breast cancer model [44]. Ivermectin has also shown promise for mitigating drug resistance via the inhibition of ABC transporters including the ABCG2 transporter and P-gp [45]. Breast cancer resistance protein (ABCG2 transporter) plays a major role in drug resistance in breast cancer [46]. The inhibition of these transporters facilitates the uptake of cytotoxic/chemotherapeutic agents by the cancer cells.
This potentiation effect of ivermectin on other anticancer agents is considered to be the most clinically relevant finding [47]. Unlike other indications, the doses of ivermectin needed for the anticancer effects in preclinical models are low, and thus are not expected to increase the risks for systemic toxicity. Ivermectin is currently being tested in combination with balstilimab, an anti-PD1 antibody, in a Phase 1/2 trial in patients with metastatic triple negative breast cancer (NCT05318469).

Safety: Ivermectin is safely used by millions of people annually in single doses or short-term administration for its anti-parasitic activity. Administration at higher doses could result in visual disturbances, sedation, and other neurological side effects.

Types of evidence:

- 4 meta-analyses/systematic reviews on RCTs testing ivermectin for covid-19
- 3 meta-analyses/systematic review on RCTs testing topical ivermectin for rosacea
- 1 meta-analysis/systematic review on trials testing high dose ivermectin
- 7 well conducted large RCTs of ivermectin for covid-19
- 2 pharmacovigilance studies for use of ivermectin using WHO VigiBase
- Numerous laboratory studies

Ivermectin has been used globally by around 200 to 250 million people per year for the combat of parasitic diseases since it was first administered in 1988 [1; 48]. It is included on the WHO list of essential medicines for the treatment of onchocerciasis, lymphatic filariasis, strongyloidiasis, trichuriasis, ascariasis, ancylostomiasis, hookworm diseases, and scabies. It generally shows excellent safety and tolerability at the standard doses used for its antiparasitic activity (150 to 200 µg/kg). These doses are

designed to impact invertebrate chloride channels without significantly impacting mammalian ion channels, resulting in a good therapeutic index and low incidence of side effects.
The most common adverse events reported in clinical trials and observational studies include headache, pruritus, muscle pain, cough, dyspnea, nausea, vomiting, diarrhea, blurred vision, postural hypotension and confusion [49].
A pharmacovigilance study examined reports of serious adverse events following ivermectin using the WHO Global Individual Case Safety Report (ICSR) database, VigiBase, in comparison to other anti-helminth drugs [49]. The most frequently reported suspected serious adverse events were headache (82 cases), weakness (78 cases), itching (76 cases), and fever (63 cases). Serious adverse events that occurred with ivermectin at a greater frequency relative to other antinematode drugs (benzimidazole drugs) include encephalopathy (55 cases), confusional disorders (22 cases), toxidermia (33 cases), and Mazzotti reactions (42). The cases of encephalopathy and Mazzotti reactions, life-threatening inflammatory reactions, are related to the to the massive death of microfilarie. Encephalopathy has been reported in cases where the individuals are co-infected with a high density of *Loa loa* filarial worms, since these worms are drained into the circulation where they can lead to an embolism in brain capillaries and cerebrovascular inflammation resulting in cases of encephalopathy.

Potential toxicity becomes a concern once doses are high enough to meaningfully impact the function of mammalian channels and receptors. In order to try to achieve antiviral effects, many clinical trials testing ivermectin for covid-19 used higher doses of ivermectin, generally between 400 and 600 µg/kg [25]. The safety and tolerability profile was generally high for ivermectin across these trials with most finding similar incidences of adverse events between ivermectin and placebo arms [17; 24]. A pharmacovigilance study including 1,393 ICSRs from VigiBase associated with ivermectin identified six cases of serious hepatic events, including elevated liver enzymes, in patients taking ivermectin for covid-19 [50]. Neurological adverse events, particularly visual disturbances, a known side effect associated with high dose ivermectin, started to become more frequent in the trials testing ivermectin at 600 µg/kg. In the ACTIV-6 trial testing ivermectin at 600 µg/kg per day for 6 days in US adults ≥ 30 years of age with mild to moderate symptomatic covid-19 (n=1,206), adverse events more common in the high-dose ivermectin group included cognitive impairment (n = 4), blurred vision (n = 5), light sensitivity to eye (n = 5), photophobia (n = 4), and dizziness (n = 5) [30]. Similarly, in the PLATCOV trial testing ivermectin or monoclonal antibodies in patients with early covid-19 (n=205), 6 out of 46 patients receiving high dose ivermectin (600 µg/kg daily for 7 days) reported transient visual disturbances, and three withdrew from treatment [29]. A systematic review and meta-analysis of six studies testing high dose ivermectin (≥200 to 800 µg/kg) found that aside from ocular adverse events, the incidence of

adverse events in different organ classes was not significantly different for high doses of ivermectin compared with standard doses (< 200 µg/kg) (OR: 1.16, 95% CI 0.89 to 1.52) [51].

As a substrate for the P-gp multidrug transporter, ivermectin is generally excluded from the CNS. However, ivermectin is lipophilic in nature, and at high doses ivermectin can inhibit the transporter, allowing it to persist in the CNS and exert effects on brain ion channels, particularly the receptors involved in GABA and glycine-mediated inhibitory neurotransmission [4]. This can lead to neurological side effects including sedation and confusion. Ivermectin enters the brain slowly and is eliminated at an even slower rate, such that evidence of neurological effects may be delayed following systemic administration. Brain concentrations of ivermectin can also increase when it is taken in conjunction with other drugs that are substrates for the P-gp transporter, such as the calcium channel blocker verapamil [4]. Children may also be at higher risk for neurological side effects since they have lower levels of P-gp expression [6]. The potential for neurotoxicity is the main reason that the repurposing of ivermectin for indications that require it to act on mammalian receptors or other targets for which it has a relatively high EC_{50} is generally not considered clinically viable.

Side effects from topical ivermectin (1% cream) used for rosacea are generally rare, mild and transient [37]. They include skin burning, itching, or redness (Drugs.com). A network meta-analysis found that topical ivermectin was associated with a similar or lower incidence of adverse events relative to other topical treatments for inflammatory lesions of rosacea, including metronidazole cream and azelaic acid gel [3].

Drug interactions:

According to Drugs.com, there are 98 known drug interactions with ivermectin, as well as a moderate interaction with alcohol. Due to its potential to modulate the $GABA_A$ receptor if it reaches the CNS at appreciable levels, it may interact with other GABA targeted drugs or anti-epileptics, such as barbiturates, benzodiazepines, and valproic acid (WebMD). Ivermectin may also interact with other drugs that act as P-gp substrates or inhibitors, such as verapamil (P-gp inhibitors listed on Drugbank). One study found that high doses of vitamins E and vitamin A increased the brain exposure of ivermectin in mice, suggesting a possible interaction, though this has not been clinically verified [52].

Sources and dosing:

Oral ivermectin (3 mg) tablets were developed by Merck and marketed under the brand name STROMECTOL®. It is approved for the use in Strongyloidiasis of the intestinal tract and Onchocerciasis. It is also available for use in the treatment of other filarial/helminthic diseases, including lymphatic filariasis, trichuriasis, ascariasis, ancylostomiasis, hookworm diseases, and scabies, in regions where these parasites are endemic, particularly in Africa and South America, as part of the WHO's list of essential medicines. Ivermectin uses weight based dosing, with the standard dose of a single oral dose of 150 µg/kg bodyweight for Strongyloidiasis and 200 µg/kg bodyweight for Onchocerciasis (FDA label).
Topical ivermectin (1% cream) is marketed under the brand name SOOLANTRA™ by Galderma Laboratories and is approved for the use of inflammatory lesions of rosacea. The standard dosing is to apply it to the face once daily (FDA label).
Topical ivermectin (0.5% lotion) is also available OTC for the treatment of head lice (FDA).

Research underway:

According to Clinicaltrials.gov, there are currently over 30 active clinical trials involving ivermectin. These include trials for high dose ivermectin for covid-19, ivermectin in combination with balstilimab for triple negative metastatic breast cancer, mass administration of ivermectin for reducing malaria transmission in Southern and Eastern Africa, ivermectin for scabies in children, annual or biannual doses of ivermectin for onchocerciasis, ivermectin for post-kala-azar dermal Leishmaniasis, ivermectin for rosacea, ivermectin-artemisinin combination for malaria, repeat mass ivermectin administration for malaria control, ivermectin for whipworm in preschool-aged children, and an albendazole-ivermectin coformulation for soil-transmitted helminths.

Search terms:
Pubmed, Google: Ivermectin

- Alzheimer's disease, neurological, cognition, immune modulation, clinical trial, meta-analysis, safety

Websites visited for Ivermectin:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com

- PubChem (Avermectin B1a + Avermectin B1b)
- DrugBank.ca
- ConsumerLab.com

References:

1. Crump A, Ōmura S (2011) Ivermectin, 'wonder drug' from Japan: the human use perspective. *Proceedings of the Japan Academy Series B, Physical and biological sciences* **87**, 13-28https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3043740/.

2. ACS (2016) Discovery of Ivermectin. https://www.acs.org/education/whatischemistry/landmarks/ivermectin-mectizan.html.

3. Siddiqui K, Stein Gold L, Gill J (2016) The efficacy, safety, and tolerability of ivermectin compared with current topical treatments for the inflammatory lesions of rosacea: a network meta-analysis. *SpringerPlus* **5**, 1151https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4956638/.

4. Löscher W (2023) Is the antiparasitic drug ivermectin a suitable candidate for the treatment of epilepsy? *Epilepsia* **64**, 553-566https://pubmed.ncbi.nlm.nih.gov/36645121/.

5. Hayward G, Yu LM, Little P *et al.* (2024) Ivermectin for COVID-19 in adults in the community (PRINCIPLE): An open, randomised, controlled, adaptive platform trial of short- and longer-term outcomes. *The Journal of infection* **88**, 106130https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10981761/.

6. Verscheijden LFM, Koenderink JB, de Wildt SN *et al.* (2021) Differences in P-glycoprotein activity in human and rodent blood-brain barrier assessed by mechanistic modelling. *Archives of toxicology* **95**, 3015-3029https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8380243/.

7. Brownjohn PW, Smith J, Portelius E *et al.* (2017) Phenotypic Screening Identifies Modulators of Amyloid Precursor Protein Processing in Human Stem Cell Models of Alzheimer's Disease. *Stem cell reports* **8**, 870-882https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5390098/.

8. Seyyedabadi B, Babataheri S, Laher I *et al.* (2023) Neuroprotective effects of ivermectin against transient cerebral ischemia-reperfusion in rats. *Metabolic brain disease* **38**, 2807-2815https://pubmed.ncbi.nlm.nih.gov/37755672/.

9. Rahbar A, Shakyba S, Ghaderi M *et al.* (2021) Ivermectin-functionalized multiwall carbon nanotube enhanced the locomotor activity and neuropathic pain by modulating M1/M2 macrophage and decrease oxidative stress in rat model of spinal cord injury. *Heliyon* **7**, e07311https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8247094/.

10. Crump A (2017) Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations. *The Journal of Antibiotics* **70**, 495-505https://doi.org/10.1038/ja.2017.11.

11. Wolstenholme AJ, Rogers AT (2005) Glutamate-gated chloride channels and the mode of action of the avermectin/milbemycin anthelmintics. *Parasitology* **131 Suppl**, S85-95https://pubmed.ncbi.nlm.nih.gov/16569295/.

12. Henriquez-Camacho C, Gotuzzo E, Echevarria J *et al.* (2016) Ivermectin versus albendazole or thiabendazole for Strongyloides stercoralis infection. *Cochrane Database of Systematic Reviews*https://doi.org//10.1002/14651858.CD007745.pub3.

13. Hailu T, Nibret E, Amor A *et al.* (2020) Efficacy of Single Dose Ivermectin Against Strongyloides stercoralis Infection Among Primary School Children in Amhara National Regional State. *Infectious diseases* **13**, 1178633720932544https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7297470/.

14. Rosumeck S, Nast A, Dressler C (2018) Ivermectin and permethrin for treating scabies. *The Cochrane database of systematic reviews* **4**, Cd012994https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6494415/.

15. Sagna AB, Zéla L, Ouedraogo COW *et al.* (2023) Ivermectin as a novel malaria control tool: Getting ahead of the resistance curse. *Acta Tropica* **245**, 106973https://www.sciencedirect.com/science/article/pii/S0001706X23001602.

16. Ekoka Mbassi D, Mombo-Ngoma G, Held J *et al.* (2023) Efficacy and safety of ivermectin for the treatment of Plasmodium falciparum infections in asymptomatic male and female Gabonese adults - a pilot randomized, double-blind, placebo-controlled single-centre phase Ib/IIa clinical trial. *EBioMedicine* **97**, 104814https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10582777/.

17. Popp M, Reis S, Schießer S *et al.* (2022) Ivermectin for preventing and treating COVID-19. *The Cochrane database of systematic reviews* **6**, Cd015017https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9215332/.

18. Caly L, Druce JD, Catton MG *et al.* (2020) The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral research* **178**, 104787https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7129059/.

19. Schmith VD, Zhou J, Lohmer LRL (2020) The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19. *Clinical Pharmacology & Therapeutics* **108**, 762-765https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.1889.

20. Mikamo H, Takahashi S, Yamagishi Y *et al.* (2023) Efficacy and safety of ivermectin in patients with mild COVID-19 in Japan and Thailand. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*https://pubmed.ncbi.nlm.nih.gov/38154616/.

21. Chable-Bessia C, Boullé C, Neyret A *et al.* (2022) Low Selectivity Indices of Ivermectin and Macrocyclic Lactones on SARS-CoV-2 Replication In Vitro. *COVID* **2**, 60-75https://www.mdpi.com/2673-8112/2/1/5.

22. Zhou G, Verweij S, Bijlsma MJ *et al.* (2023) Repurposed drug studies on the primary prevention of SARS-CoV-2 infection during the pandemic: systematic review and meta-analysis. *BMJ open respiratory research* **10**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10462970/.

23. Marko M, Pawliczak R (2023) Assessment of the available therapeutic approaches for severe COVID-19: a meta-analysis of randomized controlled trials. *Scientific reports* **13**, 17114https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10564895/.

24. Marcolino MS, Meira KC, Guimarães NS *et al.* (2022) Systematic review and meta-analysis of ivermectin for treatment of COVID-19: evidence beyond the hype. *BMC infectious diseases* **22**, 639https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9308124/.

25. Wada T, Hibino M, Aono H *et al.* (2023) Efficacy and safety of single-dose ivermectin in mild-to-moderate COVID-19: the double-blind, randomized, placebo-controlled CORVETTE-01 trial. *Frontiers in medicine* **10**, 1139046https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10240959/.

26. Reis G, Silva E, Silva DCM *et al.* (2022) Effect of Early Treatment with Ivermectin among Patients with Covid-19. *The New England journal of medicine* **386**, 1721-1731https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9006771/.

27. Bramante CT, Huling JD, Tignanelli CJ *et al.* (2022) Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. *The New England journal of medicine* **387**, 599-610https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9945922/.

28. Bramante CT, Buse JB, Liebovitz DM *et al.* (2023) Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. *The Lancet Infectious diseases* **23**, 1119-1129https://pubmed.ncbi.nlm.nih.gov/37302406/.

29. Schilling WHK, Jittamala P, Watson JA *et al.* (2023) Pharmacometrics of high-dose ivermectin in early COVID-19 from an open label, randomized, controlled adaptive platform trial (PLATCOV). *eLife* **12**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9988254/.

30. Naggie S, Boulware DR, Lindsell CJ *et al.* (2023) Effect of Higher-Dose Ivermectin for 6 Days vs Placebo on Time to Sustained Recovery in Outpatients With COVID-19: A Randomized Clinical Trial. *Jama* **329**, 888-897https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9941969/.

31. Wilson NE, Reaves BJ, Wolstenholme AJ (2021) Lack of detectable short-term effects of a single dose of ivermectin on the human immune system. *Parasites & vectors* **14**, 304https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8179708/.

32. Csóka B, Németh ZH, Szabó I *et al.* (2018) Macrophage P2X4 receptors augment bacterial killing and protect against sepsis. *JCI insight* **3**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5997389/.

33. Zhong P, Wu H, Ma Y *et al.* (2023) P2X4 receptor modulates gut inflammation and favours microbial homeostasis in colitis. *Clinical and translational medicine* **13**, e1227https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10122071/.

34. Zabala A, Vazquez-Villoldo N, Rissiek B *et al.* (2018) P2X4 receptor controls microglia activation and favors remyelination in autoimmune encephalitis. *EMBO molecular medicine* **10**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6079537/.

35. Andries M, Van Damme P, Robberecht W *et al.* (2007) Ivermectin inhibits AMPA receptor-mediated excitotoxicity in cultured motor neurons and extends the life span of a transgenic mouse model of amyotrophic lateral sclerosis. *Neurobiology of disease* **25**, 8-16https://pubmed.ncbi.nlm.nih.gov/17045808/.

36. Priel A, Silberberg SD (2004) Mechanism of ivermectin facilitation of human P2X4 receptor channels. *The Journal of general physiology* **123**, 281-293https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2217454/.

37. van Zuuren EJ, Fedorowicz Z, Carter B *et al.* (2015) Interventions for rosacea. *The Cochrane database of systematic reviews* **2015**, Cd003262https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6481562/.

38. Husein-ElAhmed H, Steinhoff M (2020) Efficacy of topical ivermectin and impact on quality of life in patients with papulopustular rosacea: A systematic review and meta-analysis. *Dermatologic therapy* **33**, e13203https://pubmed.ncbi.nlm.nih.gov/31863543/.

39. Lee DE, Kang HW, Kim SY *et al.* (2022) Ivermectin and gemcitabine combination treatment induces apoptosis of pancreatic cancer cells via mitochondrial dysfunction. *Frontiers in pharmacology* **13**, 934746https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9459089/.

40. Fan N, Zhang L, Wang Z *et al.* (2024) Ivermectin Inhibits Bladder Cancer Cell Growth and Induces Oxidative Stress and DNA Damage. *Anti-cancer agents in medicinal chemistry* **24**, 348-357https://pubmed.ncbi.nlm.nih.gov/38375808/.

41. Liu J, Liang H, Chen C *et al.* (2019) Ivermectin induces autophagy-mediated cell death through the AKT/mTOR signaling pathway in glioma cells. *Bioscience reports* **39**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6900471/.

42. Jiang L, Sun YJ, Song XH *et al.* (2022) Ivermectin inhibits tumor metastasis by regulating the Wnt/β-catenin/integrin β1/FAK signaling pathway. *American journal of cancer research* **12**, 4502-4519https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9641399/.

43. Wang K, Gao W, Dou Q *et al.* (2016) Ivermectin induces PAK1-mediated cytostatic autophagy in breast cancer. *Autophagy* **12**, 2498-2499https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5173258/.

44. Draganov D, Han Z, Rana A *et al.* (2021) Ivermectin converts cold tumors hot and synergizes with immune checkpoint blockade for treatment of breast cancer. *NPJ breast cancer* **7**, 22https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7925581/.

45. Jiang L, Wang P, Sun YJ *et al.* (2019) Ivermectin reverses the drug resistance in cancer cells through EGFR/ERK/Akt/NF-κB pathway. *Journal of experimental & clinical cancer research : CR* **38**, 265https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6580523/.

46. Dutra JP, Scheiffer G, Kronenberger T *et al.* (2023) Structural and molecular characterization of lopinavir and ivermectin as breast cancer resistance protein (BCRP/ABCG2) inhibitors. *EXCLI journal* **22**, 1155-1172https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10776880/.

47. Juarez M, Schcolnik-Cabrera A, Dominguez-Gomez G *et al.* (2020) Antitumor effects of ivermectin at clinically feasible concentrations support its clinical development as a repositioned cancer drug. *Cancer chemotherapy and pharmacology* **85**, 1153-1163https://pubmed.ncbi.nlm.nih.gov/32474842/.

48. Ashour DS (2019) Ivermectin: From theory to clinical application. *International journal of antimicrobial agents* **54**, 134-142https://pubmed.ncbi.nlm.nih.gov/31071469/.

49. Campillo JT, Boussinesq M, Bertout S *et al.* (2021) Serious adverse reactions associated with ivermectin: A systematic pharmacovigilance study in sub-Saharan Africa and in the rest of the World. *PLoS neglected tropical diseases* **15**, e0009354https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8087035/.

50. Oscanoa TJ, Amado J, Romero-Ortuno R *et al.* (2022) Hepatic disorders associated with the use of Ivermectin for SARS-CoV-2 infection in adults: a pharmacovigilance study in VigiBase. *Gastroenterology and hepatology from bed to bench* **15**, 426-429https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9876768/.

51. Navarro M, Camprubí D, Requena-Méndez A *et al.* (2020) Safety of high-dose ivermectin: a systematic review and meta-analysis. *The Journal of antimicrobial chemotherapy* **75**, 827-834https://pubmed.ncbi.nlm.nih.gov/31960060/.

52. Tras B, Uney K, Parlak TM *et al.* (2023) Vitamins E and A increase the passing of the P-gp substrate ivermectin into the brain in mice. *Canadian journal of physiology and pharmacology* **101**, 475-480https://pubmed.ncbi.nlm.nih.gov/37235885/.

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