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Revisiting old drugs and drug combinations for polycythemia vera and related neoplasms

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Polycythemia Vera (PV) and related myeloproliferative neoplasms (MPNs) require long-term management to minimize thrombotic complications, disease progression, and improve quality of life. While interferon-alpha (IFN- α) offers disease-modifying potential, disease symptoms and side effects often persist, necessitating the exploration of complementary therapeutic strategies. This review examines established drugs and lifestyle interventions for their potential to improve PV/MPN outcomes. We synthesize evidence from preclinical models, clinical trials in non-MPN populations, and observational studies in MPN patients, focusing on interventions targeting MPN-related pathways like JAK/STAT signaling, inflammation, and oxidative stress. We highlight the potential benefits of cardiovascular drugs like ACE inhibitors and statins; anti-diabetic medications such as metformin and pioglitazone; and readily available agents like colchicine, rapamycin, leukotriene modifiers, and N-acetylcysteine (NAC). Additionally, we review the evidence supporting natural compounds like green tea, curcumin, fish oil, alpha-ketoglutarate, beta-alanine, vitamin C, vitamin D3, and probiotics like *Clostridium butyricum*, to identify their potential for symptom management and disease control. We review evidence supporting lifestyle interventions like the Mediterranean diet, weight management, yoga and exercise. We share two case studies that highlight the potential for combination therapies. Finally, we suggest a two-pronged approach: incorporate readily applicable interventions into clinical practice based on biomarkers, while conducting rigorous research to validate emerging combination strategies. The combination therapy approach aims to improve both survival and quality of life for PV and MPNs.

KEYWORDS

cardiovascular drugs, combination therapy, drug repurposing, interferon, lifestyle interventions, myeloproliferative neoplasms, natural compounds, polycythemia vera

1 Introduction

The optimal management of PV has dual objectives: extending survival and maintaining quality of life (QoL). Key therapeutic goals include preventing thrombotic and cardiovascular complications, delaying progression to myelofibrosis (MF) and acute myeloid leukemia (AML), and mitigating the elevated risk of secondary diseases associated with MPNs (1–5). Treatment strategies must simultaneously address disease symptoms—including fatigue and depression—while minimizing therapeutic side effects (6, 7).

IFN- α has emerged as a paradigm-shifting therapy in PV management, demonstrating potential for disease modification (8, 9). Clinical evidence shows it can reduce the JAK2V617F allele burden, preserve healthy hematopoietic stem cell function, induce minimal residual disease in some patients (10, 11), and potentially normalize life expectancy (8, 12–14). However, treatment adherence remains a significant challenge, with substantial discontinuation rates reported in clinical trials primarily due to side effects (15).

Recent advances in understanding PV and MPN pathobiology suggest the need for combination treatment strategies (8). Modern approaches should ideally target not only the malignant hematopoietic clone but also address the systemic inflammatory and metabolic dysregulation associated with MPNs (3, 8, 16–18). Growing evidence supports the repurposing of established medications, the integration of natural compounds and lifestyle modifications as complementary therapeutic modalities (6, 8). The proposed therapeutic framework integrating these approaches is summarized in Figure 1. These interventions target key molecular pathways implicated in MPN pathogenesis—including JAK/STAT signaling, chronic inflammation, oxidative stress and mTOR activation—potentially improving both survival and QoL outcomes. In this review, we synthesize evidence from multiple sources: cellular models, mouse experiments, randomized controlled trials in non-MPN patients, and observational studies in MPN populations. We evaluate treatments based on their demonstrated ability to reduce mortality in clinical settings or exhibiting robust effects in preclinical models, with an emphasis on targeting MPN-specific pathways. By combining insights from cellular and animal studies, clinical trials, and population-based data, we identify promising existing drugs (Tables 1, 2), natural compounds (Table 3), and lifestyle modifications (Table 4) that deserve further study for improving PV and MPN outcomes.

2 Harnessing the benefits of cardiovascular drugs in PV and MPNs

MPN patients face an elevated risk of cardiovascular disease (CVD) (19–27). This section reviews clinical studies that evaluate various CVD drugs to prolong life for MPN patients and highlight preclinical research demonstrating their potential anti-cancer benefits in combating MPNs and other malignancies.

A promising approach to incorporating these drugs into MPN and cancer management involves aggressively addressing CVD risk factors. This can be achieved by encouraging MPN patients to work closely with a cardiologist, who is ideally well-versed in the relevant research. Alternatively, a primary care physician or hematologist can take a proactive approach in addressing the following CVD factors.

2.1 Controlling blood pressure (ACE inhibitor)

Elevated blood pressure is the most frequently observed coexisting condition in MPNs, affecting both the incidence of blood clots and patient survival rates (28). Beyond its systemic role in regulating blood pressure and fluid balance, a localized renin-angiotensin system (RAS) is highly active within the bone marrow microenvironment itself (29). A dysregulated local RAS can have profoundly harmful consequences, directly influencing hematopoiesis (30) and contributing to cardiovascular risk via atherosclerosis and kidney damage.

2.1.1 RAS inhibition in MPNs: breaking a pathological feedback loop?

The local bone marrow RAS is crucially linked to the hyperactive JAK/STAT signaling that drives MPNs (31). Evidence

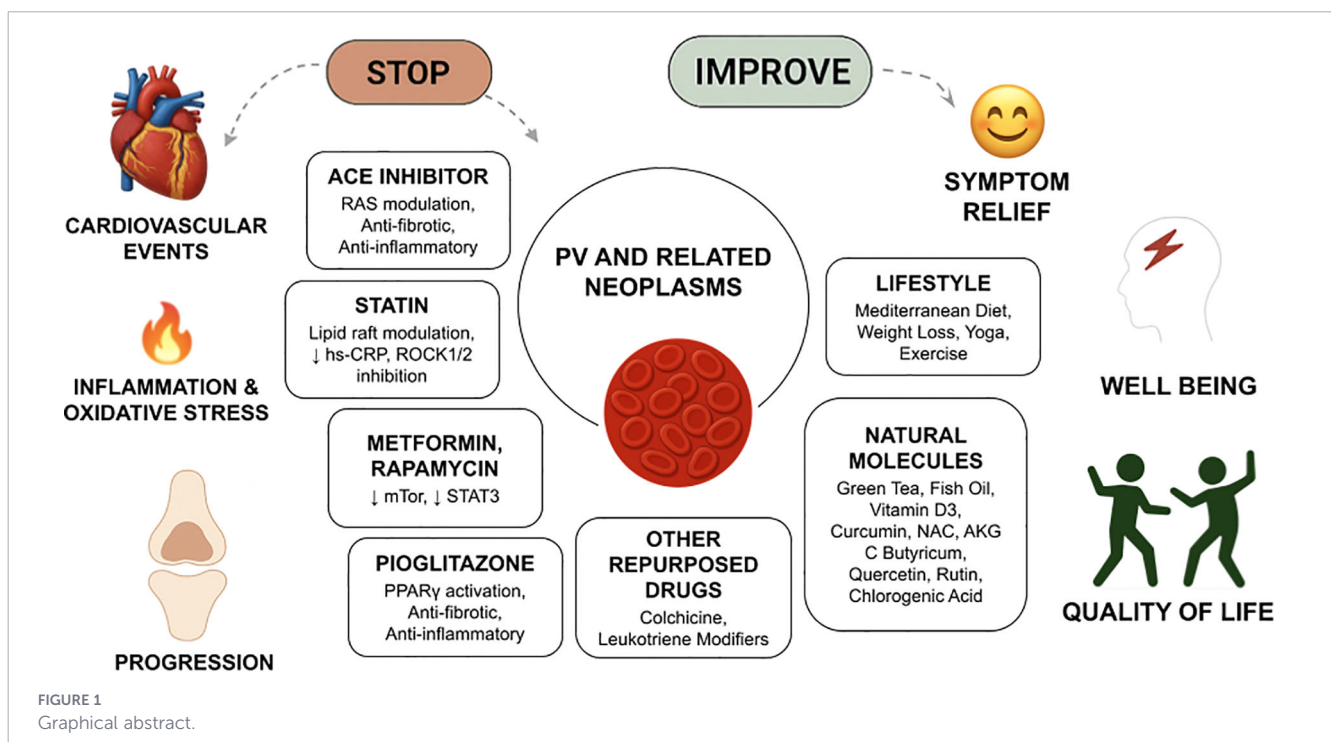


TABLE 1 Cardiovascular and metabolic drugs.

Intervention	Examples	Mechanism
ACE Inhibitor	Captopril, Lisinopril	RAS modulation; Anti-fibrotic; Anti-inflammatory
Statin	Simvastatin, Atorvastatin, Rosuvastatin	JAK2 disruption via lipid raft modulation; Anti-fibrotic; Anti-inflammatory; ROCK1/2 inhibition
Metformin	-	AMPK activation; mTOR inhibition; Anti-inflammatory (NF-κB inhibition); STAT3 inhibition
PPAR-γ activation	Pioglitazone	Anti-fibrotic; Anti-inflammatory; STAT5 inhibition
Colchicine	-	Anti-inflammatory (NLRP3 inflammasome disruption); Anti-thrombotic (↓ NETosis); Anti-proliferative (mitotic inhibitor)

suggests a pathological positive feedback loop: the inflammatory state driven by the MPN clone upregulates the local RAS, and the resulting increase in Angiotensin II (Ang-II) further stimulates the already overactive JAK/STAT pathway, amplifying the oncogenic signal (31). Ang-II acts as a direct mitogen, stimulating the proliferation of hematopoietic stem cells and erythroid progenitors (32, 33). By inhibiting the conversion of Angiotensin I to Ang-II, ACE inhibitors may help break this cycle. They potentially dampen the proliferative stimulus on the malignant clone.

2.1.2 Therapeutic potential beyond blood pressure

ACE inhibitors offer multi-faceted benefits that address several core components of MPN pathology.

- **Anti-Inflammatory Effects:** ACE inhibitors reduce levels of pro-inflammatory cytokines such as IL-6 and TNF-α while inhibiting NF-κB activation, a critical mediator of inflammation in MPNs (34). Additionally, they attenuate oxidative stress through downregulation of NADPH oxidase activity (35).
- **Anti-Fibrotic Properties:** These medications suppress TGF-β signaling, a primary driver of bone marrow fibrosis (36), while simultaneously decreasing tissue fibrosis through reduced angiotensin II production (37). Additionally, ACE inhibitors interact with JAK/STAT pathway across various tissues (38). The anti-fibrotic effects of other old drugs have recently been thoroughly reviewed elsewhere (39).

TABLE 2 Repurposed drugs.

Intervention	Examples	Mechanism
Leukotriene Modifier	Montelukast, Zileuton	5-LO inhibition; Anti-inflammatory
mTOR Inhibitor	Rapamycin, Everolimus	Direct mTOR inhibition; STAT3 suppression; Geroprotective effects

TABLE 3 Natural supplements.

Intervention	Examples	Mechanism
Fish Oil	EPA/DHA supplements	Anti-inflammatory; ↓ IFN-α side effects
Green Tea	Traditional green tea, EGCG supplements	JAK2/STAT inhibition; Antioxidant; Anti-inflammatory
Alpha-ketoglutarate (AKG)	Ca-AKG	PI3K/AKT/mTOR inhibition; MAPK pathway modulation; Epigenetic regulation; Reduced Platelet Hyperreactivity
NAC	-	Antioxidant; ↓ ROS accumulation
Beta-Alanine	-	Carnosine precursor (antioxidant, pH-buffering); Desensitization of skin itch pathways
Vitamin C	Ascorbic acid	Epigenetic regulation (TET2 cofactor); Promotes DNA demethylation
Vitamin D3	-	STAT1/STAT3 modulation; Immunomodulation
Probiotic	C. butyricum	↑ Butyrate production; HDAC inhibition; Immunomodulation
Curcumin	-	JAK2/STAT3 inhibition; mTORC1 suppression; Anti-inflammatory
Quercetin	Quercetin-rich foods (e.g., capers, onions), supplements	JAK2/STAT inhibition; ↓ TGF-β levels; Hecpudin modulation; Anti-inflammatory
Rutin	Buckwheat, asparagus, supplements	JAK2/STAT inhibition; Hecpudin modulation; Anti-inflammatory
Chlorogenic Acid	Coffee (light roast), supplements	JAK2/STAT inhibition
Orientin and Vitexin	Rooibos tea	JAK2/STAT inhibition
Ellagitannin-rich food extracts	Strawberry, Pomegranate, supplements	JAK2/STAT inhibition

↑, increase / upregulation; ↓, decrease / downregulation / reduction.

- **Cardiovascular Protection:** ACE inhibitors enhance endothelial function (40), reduce thrombotic risk through improved fibrinolysis (41), and slow atherosclerosis progression (42). These effects are particularly significant given the cardiovascular complications common in MPNs.

TABLE 4 Lifestyle modifications.

Intervention	Examples	Mechanism
Mediterranean Diet	Mediterranean dietary pattern	Anti-inflammatory foods; Microbiome modulation
Weight Management	GLP-1 RAs, Metformin, Lifestyle modification	↓ Inflammation; Metabolic improvement
Physical Activity	Online yoga programs; Structured exercise rehabilitation; Pedometer-based walking interventions	Stress reduction; Anti-inflammatory effects; Immunomodulation; Improved physical capacity

2.1.3 Clinical and preclinical evidence in MPNs

- In PV: Treating PV patients with ACE inhibitors has been shown to be associated with a reduced need for cytoreductive medications (43). Both enalaprilat (an ACE inhibitor) and losartan (an Angiotensin Receptor Blocker [ARB]) decreased erythroid precursor cell levels, suggesting that RAS inhibition could aid in managing hematocrit levels (44). This is supported by a randomized trial in altitude polycythemia, where the ACE inhibitor enalapril effectively reduced hematocrit and hemoglobin levels (45).
- Thrombotic Risk Reduction: In a large cohort of ET and PV patients with hypertension, the use of RAS inhibitors was associated with a significant reduction in thrombotic events (46).
- In MF: In mouse models of MF, the ACE inhibitor captopril reduced both spleen size and the degree of bone marrow fibrosis (47).
- Kidney Function: ACE inhibitor use was associated with improved estimated glomerular filtration rates (eGFR) in PV patients (48).
- Symptom Burden: It is important to note, however, that ACE inhibitor therapy was not associated with an improvement in the systemic MPN symptom burden (49).

2.1.4 Broad impacts of ACE inhibitors

While the cardiovascular benefits of RAS inhibition are well-established, a meta-analysis of 158,998 patients notably found that ACE inhibitors—but not ARBs—were associated with a significant 10% reduction in all-cause mortality (50). This distinction is relevant for MPN clinicians when selecting an antihypertensive agent. Furthermore, in the context of malignancy, RAS inhibitors have been associated with improved overall and progression-free survival in a large meta-analysis of cancer patients (51), suggesting benefits beyond blood pressure control alone.

2.2 Controlling lipids (statin)

Dyslipidemia is the second most common cardiovascular risk factor in MPNs after hypertension (52). Statins, cornerstone drugs in lipid management (53), effectively lower low-density lipoprotein (LDL) and have demonstrated broad benefits, including reducing all-cause mortality (54, 55). The rationale and perspectives for using statins in the treatment of MPNs were first described 20 years ago (56), and their therapeutic potential extends far beyond cardiovascular risk mitigation, stemming from a combination of direct anti-neoplastic mechanisms and broader pleiotropic effects.

2.2.1 Mechanistic rationale in MPNs

The primary pharmacological action of statins is the inhibition of HMG-CoA reductase (57). While this effectively reduces cholesterol synthesis, it also depletes essential non-sterol isoprenoid intermediates required for the post-translational

prenylation of key signaling proteins like Ras and Rho (58). The disruption of these pathways underlies the broad anti-proliferative, pro-apoptotic, and potent anti-inflammatory effects of statins (59).

More compellingly, a direct, disease-specific mechanism has been identified. The constitutively active JAK2V617F preferentially localizes to cholesterol-rich membrane microdomains known as lipid rafts, which are essential for its signaling activity (60). By depleting cellular cholesterol, statins disrupt the structural integrity of these rafts, displacing JAK2V617F from its signaling platform and thereby inhibiting its function. The lipid raft hypothesis is supported by preclinical work showing that statins selectively induce apoptosis in malignant cells from MPN patients while sparing healthy ones (60).

Extensive evidence from other organ systems demonstrates that statins possess significant anti-fibrotic properties, primarily by suppressing key pro-fibrotic signaling pathways like TGF- β and RhoA/ROCK (61). While not yet specifically demonstrated in bone marrow, this creates a powerful hypothesis for their potential use in mitigating the progressive fibrosis in MF.

High circulating LDL and impaired cholesterol homeostasis exert direct, detrimental effects on hematopoietic stem and progenitor cells (HSPCs). In mouse models, elevated LDL levels drive HSPC proliferation and differentiation toward inflammatory monocytes and granulocytes (62). This dysregulation is linked to mechanisms including defective cholesterol efflux, which enhances HSPC proliferation and mobilization (63), and the induction of significant oxidant stress, which accelerates HSC aging and impairs long-term regenerative capacity (64). This process “tunes” HSPCs toward a myeloid-biased, pro-inflammatory state (65, 66) and may create a persistent pro-inflammatory epigenetic memory (67). Conversely, HDL cholesterol exerts opposing, protective effects by suppressing HSPC proliferation and inhibiting this LDL-driven myeloid differentiation (62).

2.2.2 From prevention to combination therapy

The clinical rationale for using statins in MPNs has been repeatedly highlighted (1, 3, 39, 68, 84) and is supported by evidence across the disease spectrum.

- Cancer Prevention: A large, nationwide Danish case-control study found that long-term statin use was associated with a significantly reduced risk of developing an MPN, particularly PV and MF (69).
- Outcomes in Established Disease: In large retrospective studies of older PV and ET patients, statin use was associated with significantly better overall survival and reduced thrombotic risk (70, 71). While this may partly reflect effective lipid control, distinct disease-modifying activity is suggested by findings that statin use is associated with a reduced need for phlebotomies in PV patients (72). Additionally, a case report described a remarkable molecular response in a PV patient on simvastatin and alendronate (73). Conversely, general population meta-analyses regarding statins' effect on non-MPN cancer mortality remain mixed (74–76).

- Synergy with IFN- α : A recent Danish retrospective study demonstrated a powerful synergistic effect: patients on a statin and IFN- α had significantly higher rates of achieving complete hematologic and partial molecular responses (77). Crucially, these superior responses were achieved with a significantly lower and more tolerable weekly dose of IFN- α , positioning statins as a potential dose-sparing agent that can enhance the efficacy and safety profile of a disease-modifying therapy (77). A potential mechanism for this synergy involves the inhibition of the RhoA/ROCK pathway. Overexpression of ROCK1/2 is seen in MPNs and its inhibition enhances the anti-neoplastic effects of IFN- α (78); notably, atorvastatin and rosuvastatin have been shown to reduce ROCK activity (79, 80).
- Combination with Ruxolitinib: In contrast, the rationale for combining statins with JAK inhibitors is less clear. While promising in *in vitro* cell-line studies, the combination failed to demonstrate any benefit on disease progression in an *in vivo* mouse model of MPN (81).
- Combination with Hydroxyurea (HU): A Bolivian pilot study of 10 high-risk PV patients — including five who were HU-refractory — found that adding atorvastatin to low-dose HU and aspirin reduced hematocrit, leukocyte, and platelet counts with no thrombotic events over a median 2.6-year follow-up (82). A subsequent 13-year prospective follow-up of 14 high-risk PV patients on the same triple regimen (atorvastatin, low-dose HU, aspirin) demonstrated sustained hematologic control with no progression to MF or acute leukemia (83). However, the Danish retrospective cohort study found that while statin co-administration significantly enhanced responses to IFN- α , no such benefit was observed with HU (77), suggesting the statin–HU interaction may be less synergistic than statin–IFN- α .

2.3 Metformin

Metformin, a first-line oral therapy for type 2 diabetes, has garnered significant attention for its pleiotropic anti-cancer effects, making it a compelling candidate for drug repurposing in MPNs (85–87).

2.3.1 Mechanistic rationale

Metformin's primary anti-cancer properties are attributed to its ability to activate AMP-activated protein kinase (AMPK) (85). By inhibiting mitochondrial respiratory chain complex I, metformin increases the cellular AMP: ATP ratio, which in turn activates AMPK (86, 88). This activation suppresses a key pro-survival pathway, mTORC1 signaling, creating bioenergetic stress that leads to cytostatic effects like reduced protein synthesis (89, 90). Since the hyperactive JAK-STAT signaling in MPNs engages the PI3K/AKT/mTOR axis, metformin provides a crucial downstream brake on these pro-proliferative signals (91–93). Furthermore, metformin exerts potent anti-inflammatory activity, including the reduction of key cytokines like IL-6 and TNF- α through AMPK-linked inhibition of NF- κ B (94, 95).

2.3.2 Preclinical evidence in MPNs

Metformin's effects on JAK2V617F-positive MPNs were investigated in comparison to ruxolitinib (92). Metformin significantly reduced cell viability, proliferation, and other cellular functions, while the combination with ruxolitinib showed greater effectiveness. Metformin reduced JAK2V617F tumor burden and splenomegaly in JAK2V617F knock-in-induced MPN mice and spontaneous erythroid colony formation in primary cells from PV patients. Metformin reduced tumor burden, extramedullary hematopoiesis, and clonogenic capacity of hematopoietic stem cells in a mouse model of MPNs (96). Metformin treatment significantly reduced tumor burden in JAK2V617F murine models, effectively reducing splenomegaly (97).

2.3.3 Impact of metformin use in PV and MPNs

Small scale clinical trials have explored metformin's therapeutic potential in MPNs. In an open-label phase II trial, metformin was found to be safe and well-tolerated in patients with primary myelofibrosis (PMF) (98, 99). Although metformin did not reverse established bone marrow fibrosis in PMF, it significantly downregulated the JAK-STAT pathway and reduced cytokine secretion, suggesting potential benefits with an earlier stage disease.

Epidemiological evidence supports metformin's protective role against MPNs. In a Danish cohort study involving 3,816 cases and 19,080 matched controls, metformin users had a significantly reduced risk of developing MPNs (100). Ever-users of metformin had an adjusted odds ratio (aOR) of 0.70 (95% CI, 0.61–0.81), while long-term users had an aOR of 0.45 (95% CI, 0.33–0.63). This protective effect was consistent across genders, age groups, and MPN subtypes, indicating a potential inverse association between metformin use and MPN risk, particularly with long-term use.

2.3.4 Combination potential with interferon

Metformin showed promising QoL enhancements when combined with interferon alpha. Reeves et al. reported that metformin facilitated the reintroduction of ropeginterferon alfa-2b (Ropeg) in 82% (9/11) of previously intolerant patients (101, 102). All patients who tolerated metformin maintained Ropeg therapy, with over half achieving complete hematologic response. Grade 2 diarrhea led to metformin discontinuation in two patients (18% or 2/11). The overall safety profile appears favorable, particularly given the clinical importance of maintaining MPN patients on interferon-based therapy.

This clinical observation is particularly interesting given preclinical data suggesting metformin may inhibit the transcription of certain interferon-stimulated genes, highlighting the need for additional studies to fully understand this interaction (103).

2.3.5 Combination potential with ruxolitinib

Preclinical evidence supports pharmacological synergism between metformin and ruxolitinib, with Combination Index (CI) values significantly less than 1.0 in JAK2V617F-positive cell lines

(HEL and SET-2) (92, 104). The mechanistic basis is complementary: While ruxolitinib blocks JAK-STAT signaling, metformin inhibits mitochondrial Complex I, activating AMPK and suppressing mTORC1 to force G0/G1 cell cycle arrest (92). Additionally, metformin reactivates PP2A—a tumor suppressor inactivated by JAK2V617F phosphorylation at Tyr307—thereby facilitating dephosphorylation of JAK2, STAT5, and ERK1/2, and potentially resensitizing cells to ruxolitinib (104). *In vivo*, metformin monotherapy (125 mg/kg) significantly reduced splenomegaly and neoplastic erythroid progenitors (CD71+/Ter119+) in Jak2V617F knock-in mice (92, 97). The *in vivo* combination with ruxolitinib has not yet been tested, representing a promising avenue for future preclinical investigation.

2.4 Pioglitazone

The thiazolidinedione (TZD) pioglitazone, best known as an anti-diabetic medication, is emerging as a promising agent to target the malignant clone, inflammatory milieu, and fibrotic bone marrow microenvironment implicated in MPN pathogenesis (105–107).

2.4.1 Therapeutic potential of pioglitazone in MPNs

The preclinical evidence for pioglitazone's anti-MPN effects is compelling across multiple experimental models. In mouse models of MF (including JAK2V617F, TPOhigh, and CALRdel52), pioglitazone significantly reduced key disease markers — decreasing spleen size, preserving bone marrow cellularity, reducing reticulin fiber formation, and preventing osteosclerosis (105). The drug showed efficacy in reducing myeloproliferation, with notable reductions in hematocrit values in PV models and platelet counts in ET models.

In human cell line studies and patient samples, pioglitazone demonstrated direct anti-neoplastic effects (105). At 10 μ M concentration, it reduced viable cells by 4-fold in JAK2V617F cell lines, decreased CD34⁺ progenitor cells from PV and MF patients by >3-fold, and increased apoptosis by >3-fold. The mechanism involved reduced STAT5 phosphorylation and decreased cell proliferation through G0/G1 cell cycle arrest (105).

Beyond targeting the malignant clone, pioglitazone also addressed the inflammatory microenvironment. It decreased key inflammatory markers such as TGF- β and interfered with profibrotic pathways by competing for the p300 transcriptional cofactor, resulting in lower expression of fibrosis-related genes (105). Plasma levels achieved in mice (13.6 \pm 3.4 μ M) were sufficient to produce these therapeutic effects, supporting potential clinical translation.

Furthermore, pioglitazone demonstrated immunomodulatory properties by activating PPAR γ in monocytes, which enhanced their differentiation into anti-inflammatory M2 macrophages under IL-4 stimulation (108). This process suppressed the production of inflammatory cytokines, including IL-6, IL-1 β , and TNF- α , underscoring its potential to modulate both neoplastic and inflammatory drivers of MPN pathogenesis.

2.4.2 Evidence from other hematologic malignancies

Pioglitazone's potential as a therapeutic agent in blood cancers is being investigated in clinical trials. In a study of chronic myeloid leukemia (CML) patients who had not reached MR4.5 on imatinib alone (109), adding pioglitazone to their existing imatinib treatment showed promise in deepening molecular response. Within this group, 56% of patients converted to MR4.5 at 12 months. This conversion rate appears favorable when compared to a historical estimate of 23% in a similar patient population treated with imatinib alone. Pioglitazone also boosted complete remission rates by 20% when combined with induction chemotherapy in acute myeloid leukemia (AML) (110), though the difference was not statistically significant, possibly due to limited sample size (40 patients).

2.4.3 Anti-thrombotic and anti-inflammatory effects

Beyond its metabolic effects, pioglitazone offers established cardiovascular protection, reducing major adverse cardiovascular events (MACE) by approximately 20% in large meta-analyses (111). Perhaps more relevant to the chronic inflammatory nature of MPNs is its potent systemic anti-inflammatory effect; pioglitazone treatment has been shown to reduce hs-CRP levels by an average of 27% across diabetic and non-diabetic populations (112). Given that elevated CRP correlates with symptom burden and disease progression in MPNs, these pleiotropic effects support its potential utility in this cohort.

2.5 Colchicine

Colchicine is an ancient drug with proven efficacy in gout and, more recently, cardiovascular disease (113–116). The rationale and perspectives for using colchicine in the treatment of MPNs were described earlier in (8). Its broad-spectrum anti-inflammatory, anti-thrombotic, and anti-neoplastic properties make it an appealing candidate for repurposing in MPNs, where it may simultaneously target the malignant clone, the inflammatory microenvironment, and the elevated thrombotic risk.

2.5.1 Mechanistic rationale in MPNs

- **Targeting Inflammation:** Colchicine potently dampens inflammation by disrupting the assembly and activation of the NLRP3 inflammasome (117–119), thereby reducing release of the pro-inflammatory cytokines IL-1 β and IL-18 (120–122). It further inhibits neutrophil adhesion and chemotaxis (113), potentially attenuating the persistent inflammatory signaling that drives MPN pathobiology (1–3, 18, 123–132).
- **Mitigating Thrombotic Risk:** Colchicine exerts anti-thrombotic effects by suppressing the formation of neutrophil extracellular traps (NETs) (133), which is particularly relevant, as NETosis is markedly elevated in

MPNs and is a significant contributor to the high rate of thrombotic complications (134).

- **Direct Anti-Neoplastic Effects:** Colchicine exerts direct cytotoxic effects against malignant cells. It acts as a mitotic inhibitor by binding tubulin and preventing microtubule polymerization, leading to mitotic spindle disruption, cell cycle arrest, and apoptosis in rapidly dividing cells (113, 135–138). The anticancer potential of colchicine has been demonstrated pre-clinically across many malignancies (139–147). Several studies found that colchicine exerts its anticancer effects at clinically acceptable concentrations (142, 145, 146). Some hematopoietic malignancies may be especially sensitive; for instance, lymphocytes from patients with chronic lymphocytic leukemia (CLL) underwent apoptosis at colchicine concentrations up to 10,000-fold lower than those affecting normal lymphocytes, suggesting a potential for selective targeting of malignant clones (148, 149).

2.5.2 From clinical evidence to combinations

The rationale for using colchicine in MPNs is supported by compelling data from pre-malignant and cardiovascular settings.

- **Slowing Pre-Malignant Clonal Expansion:** The most direct evidence comes from an exploratory substudy of the LoDoCo2 cardiovascular trial. Low-dose colchicine (0.5 mg/day) dramatically slowed the annual expansion of TET2-mutated clonal hematopoiesis (CH)—a common MPN precursor—from 29.6% in the placebo arm to just 9.1% (150). This is the first clinical evidence that a well-tolerated oral agent can favorably alter the trajectory of a pre-malignant myeloid state. These findings are supported by a mouse model where colchicine prevented accelerated atherosclerosis driven by TET2-mutant CH (151).
- **Cardiovascular and Anti-Thrombotic Benefits:** The landmark COLCOT and LoDoCo2 trials established that low-dose colchicine significantly reduces major adverse cardiovascular events in patients with coronary artery disease (114–116). Unlike standard anti-platelet agents, colchicine targets the inflammatory drivers of thrombosis. Given the profound thrombotic burden in MPNs is driven by thrombo-inflammation and NETosis, these general population findings appear mechanistically translatable and highly relevant for MPN management.
- **Cancer Prevention:** Observational data suggest colchicine use is associated with reduced risk of developing MDS and AML, while no significant differences were found in MPN risk (152). Furthermore, a 12-year cohort study of male gout patients found that those treated with colchicine had a significantly lower incidence of any cancer compared to non-users (153).
- **Combination with IFN- α :** Despite its promise, caution is warranted when considering combination therapies. A randomized trial in chronic hepatitis C patients showed

that adding colchicine to IFN- α unexpectedly worsened outcomes, with sustained virologic response rates dropping from 21% to 3% (154). This unexpected antagonism highlights the necessity of careful preclinical and clinical evaluation before combining mechanistically plausible agents.

2.5.3 Safety considerations and future directions

Colchicine has a narrow therapeutic index, with dose-dependent toxicities that must be carefully considered. At therapeutic doses, gastrointestinal adverse effects (diarrhea, nausea) are common. At higher doses, severe myelosuppression can occur (155). Additionally, colchicine is metabolized by CYP3A4 and is a P-glycoprotein substrate, creating potential for significant drug-drug interactions with commonly prescribed agents (138, 156).

Accumulating evidence from cardiovascular and CH trials shows that clinically meaningful effects can be achieved at low, anti-inflammatory doses (0.5 mg daily) where toxicity is minimal and tolerability is excellent (115, 150). This low-dose paradigm may be particularly suitable for MPN patients requiring long-term therapy.

Many patients with PV develop hyperuricemia and gout, for which colchicine is standard therapy (157, 158). Retrospective analyses of these patients may present an immediate opportunity to assess colchicine's impact on MPNs.

3 Emerging frontier: other promising drugs and therapies

MPNs, including PV, are driven by the dysfunction of cellular signaling pathways. The hyperactivation of the JAK/STAT pathway is pivotal in the onset and advancement of MPNs, alongside the overstimulation of the PI3K/AKT/mTOR and MAPK pathways (91). Chronic inflammation and oxidative stress further characterize these disorders, exacerbating their progression and complications. In this section, we explore promising interventions that target these dysregulated cellular growth, inflammation, and oxidation pathways, with the potential to effectively manage and treat MPNs. As PV and ET treatments can last many decades, we focus on interventions that can be safe and effective even at lower doses with few known adverse effects from lifelong treatment.

3.1 Fish oil (natural anti-inflammatories)

The Survey of Integrative Medicine in Myeloproliferative Neoplasms (SIMM) study (159) highlights a correlation between the consumption of omega-3, turmeric, and green tea supplements and a decrease in the symptom burden in MPN patients. The MPN-SAF Total Symptom Score (TSS) served as the measure of symptom burden. The data reveals that patients using these supplements had lower TSS, signifying a reduction in symptom severity compared to

those not taking these supplements. Specifically, omega-3 users reported a TSS of 24.4 (\pm 16.5), significantly lower than the 27.8 (\pm 18.0) TSS of non-users (p -value = 0.03). Both turmeric and green tea supplement users also registered lower TSS, 24.2 (\pm 16.4) and 24.1 (\pm 17.7) respectively, in comparison to 27.5 (\pm 17.9) for non-users of either supplement. Although the p -values for turmeric (0.079) and green tea (0.08) were marginally above the 0.05 threshold, this trend suggests a potential statistical significance. Given the recognized anti-inflammatory properties of these supplements and the dysregulated inflammatory response characterizing MPN, the reduction in symptom burden aligns with scientific expectations. Omega-3 fatty acids, curcumin (active ingredient in turmeric), and catechins (present in green tea) are known to exert anti-inflammatory effects mainly through inhibiting the NF- κ B pathway and decreasing the production of pro-inflammatory cytokines. Hence, these supplements could feasibly moderate the inflammatory etiology of MPN.

IFN- α treatment has a high dropout rate associated with side effects, including depression. Su et al. (160) addressed the depressive symptoms associated with IFN- α in chronic hepatitis C patients. Through a randomized, double-blind, placebo-controlled trial involving 162 participants completing the 24-week IFN- α treatment, the study revealed that Eicosapentaenoic Acid (EPA) treated patients (3.5 g/day) demonstrated a significant decrease in the incidence of IFN- α -induced depression, with rates falling to 10% compared with the 30% seen in placebo patients (p = 0.037). Docosahexaenoic Acid (DHA) treatment, however, did not yield a similar result, maintaining a depression incidence rate of 28%. Both EPA and DHA delayed the onset of IFN-induced depression, but it was notable that EPA emerged as an effective preventive measure against depression. A 2019 meta-analysis (161) came to the same conclusion: EPA-rich fish oil was found effective against depression, while DHA-rich or DHA-pure formulations did not demonstrate efficacy.

A comprehensive meta-analysis of RCTs in 2021 (162) showed that supplementation with omega-3 fatty acids (FAs) led to significant reductions in several key markers of cardiovascular health. Specifically, the study found that omega-3 FAs decreased cardiovascular mortality (RR, 0.93 [0.88–0.98]; p = 0.01), instances of non-fatal myocardial infarction (MI) (RR, 0.87 [0.81–0.93]; p = 0.0001), coronary heart disease (CHD) events (RR, 0.91 [0.87–0.96]; p = 0.0002), major adverse cardiovascular events (MACE) (RR, 0.95 [0.92–0.98]; p = 0.002), and the need for revascularization procedures (RR, 0.91 [0.87–0.95]; p = 0.0001). The cardiovascular risk reduction was more prominent with EPA monotherapy than with EPA+DHA. However, the analysis also uncovered potential drawbacks to omega-3 FA supplementation. It increased the occurrence of atrial fibrillation (AF) (RR, 1.26 [1.08–1.48]). Additionally, when compared with a control group, EPA-only supplementation was associated with a heightened risk of total bleeding (RR: 1.49 [1.20–1.84]) and AF (RR, 1.35 [1.10–1.66]). As such, these potential risks need to be balanced against the cardiovascular benefits.

A small trial (163) of adults diagnosed with leukemia or lymphoma found that fish oil supplementation significantly improved survival rates at 14 months and increased the number of chemotherapy sessions compared to a control group.

3.2 Green tea

Consumption of green tea or its primary catechin, epigallocatechin-3-gallate (EGCG), has been reported to inhibit the JAK/STAT pathway in various preclinical models of blood cancers and autoimmune conditions. Xiao et al. (164) found that EGCG reduces JAK2 expression in chronic myeloid leukemia (CML) cells. EGCG supplementation induced complete molecular remission in a chronic lymphocytic leukemia case (165). Furthermore, EGCG has been found to inhibit specific IFN- γ pathways and JAK2 in alopecia areata patients (an autoimmune disorder that causes hair loss) (166). It also demonstrated potential in vitiligo (an autoimmune skin condition) treatment by inhibiting JAK2 activity (167). Green tea reduced obesity associated inflammation by inhibiting JAK2/STAT3 in mice (168). More recently, a molecular docking analysis found that EGCG has a strong binding affinity to the JH2 pseudo-kinase domain of the mutated JAK2V617F protein, suggesting it could act as a selective inhibitor of JAK2V617F (169).

Willard et al. (170) investigated the effects of green tea (GT) consumption on patients with indolent low-grade B-cell lymphomas and leukemias (LGBCL) and monoclonal gammopathy of undetermined significance (MGUS). The authors were inspired by previous research that demonstrated the beneficial effects of EGCG on patients with asymptomatic CLL. 11 patients with various types of LGBCL and MGUS were advised to drink two bags of GT in hot water daily. The results showed improvements in disease biomarkers and lymphadenopathy across all patients. For example, six CLL patients had reductions in absolute leukocyte count, with percentages ranging from 37% to 74%. Patients with Waldenstrom macroglobulinemia, MGUS, splenic Marginal zone lymphoma, and follicular lymphoma also experienced significant improvements. The study suggested that low-dose EGCG in GT may help delay the onset of therapy for these conditions, reducing the need for immunosuppressive treatment and associated toxicities.

A phase II trial (171) evaluated the clinical efficacy of green tea extract Polyphenon E in patients with early-stage chronic lymphocytic leukemia (CLL). The study included 42 previously untreated patients with asymptomatic, Rai stage 0 to II CLL and an absolute lymphocyte count (ALC) $\geq 10 \times 10^9/L$. Participants received Polyphenon E, containing a standardized dose of EGCG (2000 mg per dose), twice daily for up to six months. The trial reported clinical activity, with 13 patients (31%) experiencing a sustained reduction of $\geq 20\%$ in ALC, and 20 out of 29 patients (69%) with palpable adenopathy experiencing at least a 50% reduction in the sum of the products of all lymph node areas. Overall, 29 patients (69%) met the criteria for a biologic response, exhibiting either a sustained decline $\geq 20\%$ in ALC or a reduction $\geq 30\%$ in the sum of the products of all lymph node areas during the six months of active treatment. The study concluded that daily oral EGCG was well-tolerated by CLL patients, and the majority experienced durable declines in ALC or lymphadenopathy.

Several studies have demonstrated the potential longevity benefits of green tea. Zhao et al. (172) found that green tea intake was inversely associated with all-cause and CVD mortality in Chinese adults, particularly among never-smokers. In a pooled analysis of eight Japanese cohort studies, Abe et al. (173) observed that higher

green tea consumption was associated with a decreased risk of all-cause mortality, heart disease, and cerebrovascular disease mortality. A dose-response meta-analysis by Tang et al. (174) revealed that green tea consumption was significantly inversely associated with CVD and all-cause mortality. Overall, these findings suggest that regular green tea consumption may contribute to a lower risk of mortality due to various causes, particularly CVD.

In animal models of aging, Green tea and its extract, EGCG, extended the lifespan of mice, fruit flies and *C. elegans*, though not every experiment showed statistically significant life extension (175–177).

3.3 Leukotriene modifiers

Leukotriene modifiers reduce inflammation by blocking the action or production of leukotrienes. These medications function by either inhibiting leukotriene-related enzymes (such as arachidonate 5-lipoxygenase or 5-LO) or antagonizing cysteinyl leukotriene receptors. For instance, drugs like zileuton work by inhibiting 5-LO, thereby preventing the formation of leukotrienes (LTB₄, LTC₄, LTD₄, and LTE₄). Conversely, Leukotriene Receptor Antagonists (LTRAs) such as montelukast and zafirlukast disrupt the actions of cysteinyl leukotrienes at the CysLT1 receptor on target cells like bronchial smooth muscle, specifically blocking LTC₄, LTD₄, and LTE₄ through receptor antagonism.

Chen et al. showed that inhibiting 5-LO or deleting the 5-LO gene can significantly reduce the development of JAK2V617F-induced PV in mice (178). Additionally, 5-LO inhibition suppressed colony formation in human JAK2V617F-expressing CD34⁺ cells. The combination of 5-LO inhibitor zileuton and JAK2 inhibitor ruxolitinib demonstrated enhanced antitumor activity in hematopoietic progenitor cells from PV patients, providing conceptual validation for further clinical applications of this combination (179).

Leukotriene over-activation was implicated in numerous cancers including leukemia (180, 181), kidney (182, 183), breast (184), pancreas (185, 186), esophagus (187), prostate (188), etc. LTRA use in asthma patients from Taiwan demonstrated a dose-dependent decrease in cancer risk across all cancers studied, warranting further study of its chemopreventive potential (189). LTRA use in Korea was associated with a decreased cancer risk, especially when used in high doses and for longer durations (190). Leukotriene inhibitor exposure in U.S. veterans with asthma was associated with a reduced risk of lung cancer (191). Montelukast induces apoptosis in lung cancer cells (192). LTRA demonstrated inhibition of tumor growth in a colon cancer xenograft model (193). LTRAs demonstrated potential as chemoprevention candidates in colorectal cancer by reducing aberrant crypt foci formation in a nonrandomized, open-label, controlled trial (194). Leukotriene signaling promotes tumor growth and metastasis, suggesting potential for pharmacological targeting in tumor metastasis treatment (195).

3.3.1 Case study: patient #1

In April 2016, Patient #1 received a diagnosis of PV, accompanied by concerning test results: a JAK2 allele burden of

68%, an unusually elevated hematocrit level at 68%, and a high hemoglobin level of 19 g/dL. To address their high blood count, therapeutic phlebotomies were immediately initiated. In July 2016, the treatment regimen began to include weekly doses of Pegasys at 90 mcg.

Patient #1 responded positively to Pegasys, which led to a systematic reduction in the dosage over time, first to 45 mcg weekly and then to the same dose biweekly. Treatment with Pegasys ended in mid-May 2017 due to a decrease in platelet count to 75 ($\times 10^9/L$), a side effect attributed to the medication.

During treatment with Pegasys, Patient #1, upon reaching the 5th month, introduced montelukast into their medication routine. The patient had learned about research suggesting this leukotriene modifier drug could potentially control the MPN, and they opted to use it as an off-label treatment.

By May 2017, the JAK2 allele burden of Patient #1 had dropped substantially to 6%, indicating a positive response to the treatment. After discontinuing Pegasys due to the dip in their platelet count, the patient continued with daily montelukast and aspirin as their primary treatment. This regimen appeared to work effectively, as the patient's JAK2 levels had fallen to less than 0.5% by June 2018, achieving a minimal residual disease status.

Throughout the treatment period, Patient #1 maintained a vegan diet, which they believed played a significant role in their overall health and recovery.

3.4 Alpha ketoglutarate

Preclinical evidence demonstrates AKG's therapeutic potential in MPNs. In JAK2V617F murine models, oral AKG supplementation significantly improved disease indicators, including reduced splenomegaly and normalized elevated hematocrit, monocyte, and platelet counts (196).

Mechanistically, AKG counteracts MPN platelet hyperreactivity. AKG treatment of MPN patient and JAK2V617F mouse platelets *ex vivo* reduced P-selectin, platelet-leukocyte aggregate (PLA) formation, and oxygen consumption. These effects were linked to PI3K/AKT/mTOR inhibition (196). Independent research showed AKG, as a prolyl-hydroxylase-2 (PHD2) co-substrate, enhances PHD2-mediated hydroxylation and degradation of phosphorylated Akt1 (pAkt1), diminishing platelet aggregation and inflammatory cytokine release (197).

AKG is also a critical epigenetic modulator, acting as an essential cofactor for TET DNA dioxygenases and JmJc histone demethylases. Accordingly, AKG treatment of MPN patient CD34⁺ progenitors reduced megakaryocytic bias (fewer CD41⁺/CD61⁺ cells) and downregulated stemness programs (196).

AKG's favorable safety profile supports its translational potential. Up to 12 g/day arginine-AKG for seven days was well-tolerated in healthy men without significant biochemical changes (198). A review of AKG's metabolic roles and human studies reported no serious adverse events, though oral bioavailability can be limited by its short half-life (199).

In summary, AKG targets four interconnected drivers of MPNs: Platelet hyperreactivity, chronic inflammation, epigenetic dysregulation, and aberrant hematopoiesis. Its multi-targeted

mechanism of action, coupled with its oral bioavailability and established general safety, provides a strong rationale for its clinical investigation in MPNs.

3.4.1 Case study: patient #2

Patient #2, diagnosed with low-risk PV, has been on Pegasys therapy for 3.5 years. Despite achieving hematologic and molecular response under interferon treatment, the patient persistently experienced significant fatigue and depression.

Through systematic self-experimentation with hematologist oversight, Patient #2 developed a complementary symptom management protocol comprising: (1) alpha-ketoglutarate (250 mg daily), reporting substantially increased energy levels; (2) cucumber and celery juice (daily morning intake), noting an additional energy boost; (3) green tea and hibiscus tea (daily), associated with improved mood and alleviated depressive symptoms; and (4) fish oil (2 g EPA/1 g DHA daily), associated with reduced bone pain.

The patient reports achieving a “reasonably normal life” when following this protocol consistently, with significant symptom rebound when components are missed. It should be noted that these improvements were self-reported and not quantified using validated symptom scales such as the MPN-SAF TSS. All interventions were implemented under hematologist supervision, with regular monitoring of blood counts, liver and kidney function, and the protocol has been maintained for over two years with no adverse effects on disease markers.

3.5 N-acetylcysteine

Marty et al. (200) investigated the role of reactive oxygen species (ROS) in the progression of JAK2V617F-mediated MPNs. The study demonstrated that JAK2V617F induced ROS accumulation in the hematopoietic stem cell compartment of a knock-in mouse model and in patients with JAK2V617F MPNs. This ROS elevation was partly mediated by an AKT-induced decrease in catalase expression and led to an increased number of 8-oxo-guanines and DNA double-strand breaks. Mice engrafted with 30% of JAK2V617F knock-in bone marrow cells developed a PV-like disorder. Treatment with the antioxidant NAC significantly restored blood parameters, reduced DNA damage, and decreased splenomegaly with a reduction in the frequency of JAK2V617F-positive hematopoietic progenitors in bone marrow and spleen. The study concluded that overproduction of ROS is a mediator of JAK2V617F-induced DNA damage that promotes disease progression, and targeting ROS accumulation might prevent the development of JAK2V617F MPNs.

Bjørn and Hasselbalch (68) explored the role of ROS in MPN progression and the potential benefits of targeting ROS with NAC. The study suggested that targeting ROS could prevent genomic instability and myelofibrotic or leukemic transformation in MPN patients. Based on the efficacy of NAC in decreasing ROS levels, the researchers recommended investigating the antioxidative potential of other agents such as IFN- α , statins, and JAK inhibitors.

In the Nutrient Survey, PV symptom burden was significantly lower among patients taking NAC (2.4 vs. 3.4; $p=0.02$) and amino

acid supplements (2.8 vs. 3.4; $p=0.02$) (201), suggesting that these supplements may help alleviate symptoms related to MPNs.

Two studies demonstrated that NAC treatment extended the lifespan of JAK2V617F mice without impacting blood counts or splenomegaly (202). NAC reduced thrombus formation similarly to aspirin in an acute pulmonary thrombosis model and reduced thrombin-induced platelet-leukocyte aggregate formation in JAK2V617F mice. Additionally, NAC reduced neutrophil extracellular trap (NET) formation in primary human neutrophils from MPN patients and healthy controls. These findings provide a pre-clinical rationale for investigating NAC as a therapeutic option to reduce thrombotic risk in MPN patients.

3.6 Beta-alanine

Beta-alanine, a non-essential amino acid, has garnered interest for its potential role in the management of MPN symptoms. Its biological significance is derived from being the rate-limiting precursor to dipeptide carnosine (203, 204). Supplementation with beta-alanine effectively elevates intracellular carnosine levels (205). Carnosine itself possesses potent pH-buffering, antioxidant, anti-glycation, and immunomodulatory properties, which are relevant to the inflammatory and metabolic disturbances characteristic of MPNs (206, 207).

The most direct clinical evidence for beta-alanine in MPNs relates to the management of aquagenic pruritus, a potentially debilitating PV symptom. Although formal clinical trials are lacking, case reports have documented significant and rapid relief from severe, refractory aquagenic pruritus with acute dosing of beta-alanine taken shortly before water exposure (208, 209). The mechanism hypothesized by the authors is not directly related to MPN biology but rather to the targeted desensitization of specific histamine-independent itch pathways in the skin. The tingling sensation (paresthesia) commonly associated with beta-alanine is caused by the activation of Mas-related G-protein-coupled receptors on sensory neurons (210). Preemptively stimulating these neurons before a water-induced trigger may blunt the subsequent pathological itch cascade, providing a rationale for why a substance that can cause tingling may also be used to treat itch.

Further preclinical and clinical research into beta-alanine is warranted, focusing on its efficacy in immediate symptom relief (e.g., itching reduction), but also its potential to interact with fundamental aspects of MPN biology. Elevated lactate, chronic inflammation, and oxidative stress sustain both fatigue and disease progression in these disorders (3, 211, 212). Carnosine's pH-buffering and antioxidant actions directly counter these processes, and preclinical studies show it can protect hematopoietic stem cells from metabolic and oxidative stressors (213–215).

3.7 Vitamin C

Vitamin C has attracted increasing attention in myeloid malignancies due to its role as a key epigenetic regulator. It serves as an essential cofactor for the TET family of dioxygenases, which are frequently mutated in conditions such as MDS, AML, and

MPNs (216–218). Loss-of-function mutations in TET2 disrupt the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), resulting in aberrant DNA hypermethylation, silencing of tumor suppressor genes, and impaired cellular differentiation (219). Notably, many patients with myeloid malignancies are vitamin C deficient, providing a rationale for therapeutic supplementation (220, 221).

Preclinical studies provide robust proof-of-concept for this strategy. In TET2-deficient leukemia models, high-dose vitamin C restored residual TET enzymatic activity, promoted DNA demethylation, and suppressed leukemic stem cell self-renewal (219, 222). These effects extend to IDH1-mutant models, where vitamin C counteracts inhibition of TET enzymes by the oncometabolite 2-HG (223).

Importantly, clinical translation has highlighted that vitamin C may be most effective in combination with other targeted agents. Preclinical work has demonstrated synergy with:

- Hypomethylating Agents (HMAs): By promoting active demethylation via TET while HMAs (azacitidine, decitabine) block new methylation, the combination more effectively reverses pathological epigenetic patterns (224).
- PARP Inhibitors: By hyperactivating TET enzymes, vitamin C increases DNA damage, rendering TET2-mutant cells particularly dependent on PARP-mediated repair. Co-treatment with PARP inhibitors induces synthetic lethality and selective leukemia cell death (219).

Early clinical trials are encouraging. A small study in elderly AML patients reported that adding intravenous (IV) vitamin C to decitabine significantly increased complete remission rates (from 44% to 80%) and median overall survival (from 9.3 to 15.3 months) (225). More recently, the randomized phase II EVI-2 trial in low-risk myeloid malignancies (MDS + MDS/MPN) and Clonal Cytopenia of Undetermined Significance (CCUS) found that daily oral vitamin C supplementation was associated with a promising signal for longer overall survival compared to placebo (221). Together, these findings support investigating vitamin C as a low-toxicity adjunct to correct deficiency (oral) and potentially enhance the efficacy of other targeted agents (IV).

3.7.1 Future directions in MPNs

While preclinical and clinical data in classical MPNs are currently lacking, the biologic rationale for investigation is strong. In advanced-stage disease (e.g., post-PV/ET MF, blast phase), MPNs often acquire co-mutations in epigenetic regulators, converging on AML-like biology. Here, adding vitamin C to standard therapies like HMAs or JAK inhibitors could be a logical strategy to target this convergent epigenetic dysregulation.

Second, there may be a role in early-stage MPNs and clonal hematopoiesis for patients with known TET2 mutations or documented vitamin C deficiency. Given that ascorbate depletion accelerates leukemogenesis (222) and that supplementation showed a survival signal in related myeloid conditions (221), a low-toxicity intervention like oral vitamin C could be investigated pre-clinically

to support the function of the remaining TET2 allele and potentially delay disease progression.

As vitamin C enhances nonheme iron absorption (226), its supplementation should be approached cautiously for those PV patients who manage their disease via phlebotomies. And IV vitamin C should be exclusively reserved for clinical trials.

3.8 Vitamin D

Vitamin D deficiency was found to be present in 66.7% of PV patients and 74.2% of ET patients (227). An earlier study by Pardanani et al. (228) found Vitamin D insufficiency in 48% of PMF, 43% of PV, and 28% of ET patients. Vitamin D deficiency was more prevalent in those with JAK2 mutation.

In a meta-analysis of 50 RCTs with a total of 74,655 patients (229), Vitamin D supplementation was associated with a reduced risk of cancer mortality by 15% HR = 0.85 (0.74 to 0.97). There was a trend towards 5% reduction in all-cause mortality from vitamin D3 supplementation HR = 0.95 (0.91 to 1.00, p=0.07).

Pre-clinical research suggests intriguing relationships between the JAK-STAT pathway and vitamin D. Calcitriol (active form of Vitamin D) treatment decreased STAT1 and STAT3 activation and the inflammatory cytokines in T-cell large granular lymphocyte leukemia (T-LGLL) cells (230). Calcitriol significantly decreased the phosphorylation of STAT1 and STAT3 in NKL cells (a model of natural killer cell large granular lymphocyte leukemia) (231). Across hematological cancer cells, vitamin D supplementation promoted apoptosis, induced differentiation, inhibited proliferation, sensitized tumor cells to other anti-cancer therapies, and reduced the production of pro-inflammatory cytokines (232). The doses required to get such therapeutic effects were often supra-physiological.

Interestingly, low vitamin D levels might have beneficial effects in some MPN contexts. In a mouse model of MF (233), a low-vitamin D diet mitigated fibrosis and normalized hematologic parameters. The study found that MF relies on macrophage differentiation influenced by vitamin D receptor (VDR) signaling. Disrupting VDR signaling—through a low-vitamin D diet, VDR deficiency in donor cells, or macrophage depletion—prevented MF in this model, suggesting that low vitamin D levels may inhibit MF progression.

Therefore, the role of vitamin D in MPNs appears complex. While correcting deficiency in PV/ET patients seems prudent based on general health data, the preclinical finding that VDR signaling may drive MF pathogenesis (233) suggests that supplementation in MF patients warrants caution and further investigation. The precise role of vitamin D in MPN subtypes remains to be elucidated.

3.9 mTOR inhibition (rapamycin)

Guglielmelli et al. (234) conducted a phase I/II study of everolimus, an mTOR inhibitor, in 39 high- or intermediate-risk patients with primary or post-PV/post-ET MF. In phase I, no dose-limiting toxicity was observed at doses up to 10 mg/d, and this dose was used for expansion in phase II. Among 30 evaluable patients in phase II, grade ≥ 3 toxicities were infrequent, with grade 1–2 stomatitis being the most common adverse effect. Rapid and

sustained splenomegaly reduction of >50% was achieved in 20% of patients, and > 30% reduction was seen in 44%. Complete resolution of systemic symptoms occurred in 69% of patients, while 80% experienced resolution of pruritus. Responses in leukocytosis, anemia, and thrombocytosis were observed in 15% – 25% of patients. Notably, clinical responses were not associated with a reduction in JAK2V617F allele burden.

JAK2V617F constitutively activates the PI3K/AKT/mTOR cascade alongside STAT5, and JAK2 inhibition alone often fails to fully suppress mTORC1, allowing neoplastic cells to escape apoptosis (91). Preclinical studies combining the dual PI3K/mTOR inhibitor BEZ235 with ruxolitinib demonstrated synergistic reduction in viability of JAK2V617F-mutated cell lines and primary CD34+ progenitors from PV and MF patients, with cell cycle arrest and apoptosis at concentrations where single agents were merely cytostatic (235–237).

The co-targeting rationale is further supported by Mohammadhosseini et al., who showed that mTOR and JAK1/2 pathway inhibition rescued defective hematopoiesis in RUNX1-familial platelet disorder (238). Clinical translation is emerging in acute Graft-versus-Host Disease (aGvHD), where the ruxolitinib–sirolimus combination enhances T-effector suppression while preserving regulatory T-cells (239).

mTOR inhibition has been shown to promote healthy aging by demonstrating robust lifespan extension in yeast, worms, flies, and multiple strains of laboratory mice (240), and by delaying organ aging in mice (241). Rapamycin showed geroprotective effects on human skin (242). Rapamycin improved diastolic and systolic age-related measures of heart function (E/A ratio, fractional shortening, and ejection fraction) in dogs (243). In a human trial, everolimus enhanced participants' immune response to flu vaccinations by about 20% after six weeks (244).

Rapamycin, the first-discovered mTOR inhibitor, exhibits a distinct direct inhibitory effect on STAT3 (245). Rapamycin is a relatively affordable generic medication, and it has a longer half-life compared to everolimus, requiring less frequent and lower dosing. Rapamycin was associated with minimal side effects when dosed up to 1 mg/day in an older human cohort (246). Mechanistically, Rapamycin presents itself as an excellent candidate for addressing MPN symptoms, as suggested by the phase I/II study of its close cousin everolimus. Rapamycin may extend both the lifespan and QoL of PV patients through its anti-cancer and geroprotective effects, and may be complementary to IFN- α , thanks to its diverse mechanisms of action.

To minimize the immunosuppressive side effects of Rapamycin, intermittent dosing strategies have been proposed. Instead of taking 1 mg daily, one can take 1 mg to 6 mg weekly or every other week to get the benefits of mTORC1 inhibition while sparing mTORC2 (~immune suppression) (247). We believe this specific treatment strategy holds promise to maximize the risk-reward ratio of Rapamycin in MPNs, again, perhaps in combination with IFN- α to bring the MPN clone to a state of minimal residual disease.

In kidney and prostate cancer cells, preclinical research has indicated that the combination of IFN- α and mTOR inhibitors may exhibit increased efficacy (248). However, a phase III clinical trial conducted in advanced kidney cancer patients did not corroborate this (249).

3.10 *Clostridium butyricum* (probiotic)

Sodium butyrate (SB) is a histone deacetylase (HDAC) inhibitor and a short-chain fatty acid (SCFA). The effects of SB on JAK2/STAT signaling in MPNs and leukemia was explored in (250). SB inhibited the JAK2/STAT pathway while promoting the expression of suppressors of cytokine signaling (SOCS1 and SOCS3)—feedback inhibitors of this signaling pathway. Mechanistically, SB enhanced histone acetylation at the promoters of SOCS1 and SOCS3, upregulating their expression in leukemia cell lines (K562 and HEL). Increased SOCS1 and SOCS3 expression inhibited cell proliferation, suppressed JAK2/STAT signaling, and reduced the clonogenic activity of hematopoietic progenitors from MPN patients.

Clostridium butyricum, a probiotic strain, has potential for MPN management by improving gut microbiota health and SCFA production. When ingested, *C. butyricum* spores colonize the intestinal tract, increasing SCFAs like butyrate, which exert anti-inflammatory, immunomodulatory, and anti-neoplastic effects (251).

Studies highlight the potential of probiotics like *Clostridium butyricum* (CBM-588) to enhance immune checkpoint inhibitor (ICI) therapies. In metastatic renal cell carcinoma (mRCC), Meza et al. (252) demonstrated that CBM-588 combined with nivolumab/ipilimumab significantly improved response rates (59% vs 11%) and progression-free survival (PFS) compared to ICI alone, without increasing severe toxicities. Similarly, Tomita et al. (253) found that probiotic therapy in advanced non-small cell lung cancer (NSCLC) is associated with prolonged PFS and overall survival, suggesting that microbiota modulation can improve ICI efficacy.

Altered gut microbiota composition may play a critical role in the chronic inflammation observed in PV. Eickhardt-Dalbøge et al. (254) found that PV patients exhibited lower gut microbial diversity and a reduced abundance of Firmicutes taxa compared to healthy controls. Notably, gut microbiota composition varied with different treatments, suggesting potential links between therapeutic interventions and gut health. Lower diversity and shifts in microbial populations may contribute to systemic inflammation and immune dysregulation in PV. Restoring microbial balance, potentially through probiotics like *C. butyricum*, could mitigate these effects, offering a complementary approach to existing treatments.

3.11 Other natural JAK2 inhibitors

Recent research has identified several naturally occurring compounds that demonstrate JAK2 inhibitory activity, potentially offering complementary approaches for managing MPNs. These compounds can be broadly categorized into plant-derived polyphenols and flavonoids, with varying degrees of evidence supporting their therapeutic potential.

3.11.1 Curcumin

Curcumin emerges as a leading natural compound with potent inhibitory effects on the JAK2/STAT3 pathway in contexts ranging

from cancer to inflammation (255–264). In preclinical models of MPNs, curcumin demonstrated the ability to induce apoptosis and suppress cellular proliferation by targeting both the JAK2/STAT3 pathway and mTORC1 signaling (265). Typical anti-inflammatory supplement doses of curcumin range between 500–1000 mg daily; however, patients with advanced MF have reported benefits from higher doses—up to 4 grams per day—under medical supervision (266).

3.11.2 Ellagitannins and fruit-derived compounds

Martin et al. conducted a comprehensive screening of 49 fruit extracts, identifying pomegranate and strawberry extracts as most potent JAK2 inhibitors *in vitro* (267). These findings align with previous research showing anti-inflammatory and anti-proliferative effects of these fruits in various human diseases, e.g. (268–270).

3.11.3 Tomato-derived compounds

Through molecular docking analysis, Rekha (271) and Vaziri-Amjad et al. (272) independently identified five compounds naturally present in tomatoes that show promising JAK2-binding characteristics: rutin, quercetin, naringenin, chlorogenic acid, and kaempferol.

These compounds demonstrated optimal binding features with human JAK2 ATP-binding site, suggesting potential inhibitory effects. Particularly noteworthy is chlorogenic acid, which showed nanomolar-range binding affinity and is abundantly present in lightly roasted coffee.

3.11.4 Quercetin and related flavonoids

Vaziri-Amjad et al. conducted extensive *in silico* molecular docking studies, identifying several quercetin-related compounds and quercetin metabolites as potential natural JAK2 inhibitors, including quercetin, rutin, isoquercitrin, quercetin-3-rhamnoside, and quercitrin (272).

These molecules demonstrated predicted binding affinities in the nanomolar range, suggesting potent JAK2 inhibition potential. Multiple studies have confirmed quercetin's ability to modulate the JAK/STAT pathway across various experimental models (273–286). Quercetin showed anti-AML and anti-MDS effects that aren't mediated by JAK/STAT (287).

A case report described successful management of MF using a multi-component regimen that included quercetin (1000 mg twice daily) (288). Notably, the patient's transfusion dependence decreased significantly after switching to a more bioavailable form of quercetin. The author hypothesized that quercetin's ability to lower TGF- β levels, a key driver of fibrosis, and inhibit the JAK/STAT pathway contributed to the observed improvement.

Quercetin was shown to enhance the anti-proliferative effects of IFN- α in hepatocellular carcinoma cells (289). Quercetin, along with other polyphenols, was found to induce hepcidin, the master regulator of iron homeostasis, in both cell and animal models (290, 291). Quercetin's ability to modulate hepcidin could theoretically help control red blood cell production in PV.

3.11.5 Rooibos tea compounds (orientin and vitexin)

Vaziri-Amjad et al. identified orientin and vitexin as particularly potent JAK2 inhibitors, active at picomolar concentrations (272). These compounds are notably present in Rooibos tea (approximately 4.5 mg orientin per 2 g serving) (292). However, orientin's short half-life (1–2 hours) may limit its therapeutic utility compared to compounds like quercetin, which has a 10–12 hour terminal half-life.

3.11.6 Safety and bioavailability considerations

A 14-week oral toxicity study in mice demonstrated that quercetin, at doses ranging from 62 to 250 mg/kg of diet, did not cause any significant toxicity, organ damage, or alterations in behavior or metabolism (293). The effects of quercetin on lifespan in mice appear to be complex and dependent on dose, sex, and the presence of other dietary factors. A study using a low dose of quercetin (0.125 mg/kg weekly) found improvements in several healthspan markers, including exercise endurance and cardiac function, in aged mice (294). In contrast, an older study reported that a higher dietary dose of quercetin (0.1%) significantly reduced the lifespan of male mice (295). Rutin extended lifespan and health span in mice including positive impacts on liver health (296).

While preclinical evidence demonstrates promising JAK2-inhibitory effects for compounds found in common foods like berries, tomatoes, coffee and Rooibos tea, significant questions remain about their therapeutic potential in humans. The bioavailability of these compounds varies considerably – quercetin's absorption can range from 5–20% depending on its form, while compounds like orientin show very limited bioavailability in humans. Additionally, the concentrations needed to achieve meaningful JAK2 inhibition may exceed what's attainable through diet or even supplementation. Further clinical research is needed to establish whether these compounds, either alone or in combination with conventional therapies, can achieve therapeutically relevant blood and tissue concentrations in MPNs.

4 Lifestyle interventions

4.1 Mediterranean diet

The NUTRIENT trial was a 15-week randomized pilot study examining the feasibility of Mediterranean diet intervention in patients with MPNs (297, 298). The study randomized 31 patients to either Mediterranean diet or standard US dietary guidelines, with 28 completing the study (15 Mediterranean, 13 USDA). Both groups received dietician counseling and educational materials over weeks 3–12. The Mediterranean diet proved as feasible as the USDA diet, with 80% of Mediterranean diet participants meeting feasibility benchmarks versus 77% of USDA participants. Adherence to Mediterranean eating patterns (defined as MEDAS score ≥ 8) was achieved by $\geq 80\%$ of the Mediterranean

diet group at weeks 6 and 9, dropping slightly to 79% at week 12, while the USDA group never exceeded 50% adherence. Notably, >50% reduction in symptom burden (MPN-SAF TSS) was achieved by 53%, 47%, and 53% of Mediterranean diet participants at weeks 9, 12, and 15 respectively, compared to 23%, 17%, and 31% in the USDA group. Changes in Mediterranean diet adherence correlated significantly with symptom improvement ($r=-0.52$, $p=0.007$ at week 9). While the study found no significant changes in inflammatory markers or gut microbiome composition, it demonstrated that Mediterranean diet intervention is feasible in MPN patients and may offer therapeutic benefits, particularly for symptom management, warranting larger trials to assess clinical outcomes.

4.2 Weight management

Weight management is a critical yet often overlooked aspect of comprehensive MPN care. Certain MPN therapies, such as ruxolitinib, are associated with weight gain (299), while obesity itself is linked to a greater MPN symptom burden (300). Interventions that promote weight loss, such as metformin or glucagon-like peptide-1 receptor agonists (GLP-1 RAs), could therefore offer a dual benefit by managing both obesity and MPN symptoms (301).

Among pharmacological options, GLP-1 RAs are particularly compelling. Beyond their established efficacy in inducing weight loss, they also exert systemic anti-inflammatory effects, notably by lowering markers like hs-CRP (302). The potential of this drug class in MPNs has been dramatically highlighted by a recent large-scale, propensity-matched cohort study by Cheema et al. (303). The study analyzed outcomes for 4,119 matched pairs of PV patients, comparing those who received GLP-1 RA therapy with those who did not (303).

Over a three-year follow-up period, the results demonstrated profound clinical benefits associated with GLP-1 RA use (303). The therapy was associated with significantly lower odds of all-cause mortality (OR 0.490), progression to MF (OR 0.548), and venous thromboembolism (OR 0.705) (303). The benefits extended to secondary outcomes as well, with reduced odds of all-cause hospitalizations, ICU admissions, acute kidney injury, and ischemic stroke/TIA (OR 0.831) (303).

The profound clinical benefits observed with GLP-1 agonists may be partly driven by direct antineoplastic mechanisms — preclinical studies in other malignancies have shown that these agents can inhibit key cancer-promoting pathways, including PI3K/AKT/mTOR and ERK/MAPK (304–306). While the retrospective design of the large PV cohort study precludes causal inference, the magnitude and consistency of the observed benefits strongly suggest a therapeutic role for GLP-1 RAs (303). These compelling findings provide a clear rationale for dedicated preclinical studies and randomized controlled trials to formally evaluate their impact on MPN symptoms and disease outcomes.

Beyond the specific context of MPNs, these findings underscore the fundamental importance of metabolic health, as the benefits of intentional weight loss and caloric restriction on longevity and healthspan in the general population are well-established. Even modest weight loss (average of 5.5 kg) in obese individuals achieved

through lifestyle interventions has been shown to produce a 15% reduction in all-cause mortality (307). More significant interventions, such as bariatric surgery in obese populations, are associated with a 38%–41% reduction in all-cause mortality (308, 309).

4.3 Yoga

Emerging research has highlighted the beneficial impact of yoga on improving the QoL in various cancer types (310, 311). Building on this insight, Huberty et al. (312) sought to explore the effectiveness and practicality of an online yoga program specifically designed to mitigate symptoms and enhance QoL for patients with MPNs. Participants were randomized into two cohorts: one that participated in a 12-week online yoga program involving 60 minutes of practice per week, and a wait-list control group that continued their regular activities. Participants in the yoga group had blood tests at the outset and conclusion of the intervention to monitor changes in inflammation levels, specifically IL-6 and TNF- α .

The study engaged 62 MPN patients, with 48 successfully completing the intervention (27 in the online yoga group and 21 in the control group). Through a combination of the Clicky tool and self-reporting, yoga participants were found to average between 40.8 and 56.1 minutes of practice per week.

This research revealed that the yoga intervention led to small to moderate improvements in a variety of health outcomes, such as reductions in sleep disturbance, pain intensity, anxiety, and depression. Furthermore, there was a substantial reduction in TNF- α from the baseline to the 12-week mark (-1.3 ± 1.5 pg/ml) among the yoga group participants. These promising results underscore the potential of online yoga interventions to improve QoL for MPN patients, advocating for more comprehensive, randomized controlled trials in the future to confirm these findings.

4.4 Exercise

Physical exercise exerts well-established anti-inflammatory and immunomodulatory effects, making it a promising non-pharmacological strategy for MPN management (313, 314). While observational studies link physical activity with lower symptom burden, reduced fatigue, and improved QoL in MPN cohorts (159, 315, 316), causal inference remains limited.

Pedersen et al. was the first to investigate an exercise-based rehabilitation intervention for MPNs (317). Forty-eight patients completed a 5-day interdisciplinary program followed by 12 weeks of home-based exercise. Fatigue, QoL, MPN-specific symptoms, and anxiety/depression scores showed no significant improvements. However, physical capacity improved significantly: VO_2 -max increased from 27.2 to 33.6 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, similarly handgrip strength and chair-stand performance improved, despite low adherence (median 14.5 of 42 sessions completed).

The MPN-FIT trial was a 12-week randomized pilot study of a home-based, supervised exercise program in 55 MPN patients (318). The intervention combined 30-minute flexibility, resistance, and aerobic sessions performed 2–3 times weekly with virtual

supervision. All feasibility endpoints were met, with high satisfaction (88%), intention to continue (92%), 81% median adherence, and no adverse events. FIT participants exercised significantly more and at higher intensity than controls (1,280 vs. 120 minutes). LDH decreased significantly in the FIT group compared with controls (-14.5 vs. $+4.0$ U/L; $p = 0.03$). Cytokines trended downward, with some unadjusted significant reductions, though none remained significant after multiple-hypothesis correction. Patient-reported outcomes improved in many FIT participants, but between-group differences were largely non-significant, except for improved global physical health QoL in those with higher baseline symptom burden. Qualitative feedback was uniformly positive.

The road to a standardized, evidence-based exercise protocol for MPN is still being paved (313–327). While we wait for the adequately powered randomized controlled trials to be run, we cannot let “perfect be the enemy of good.” For the person living with PV or MPNs today, the most effective “drug” may well be a pair of walking or running shoes, provided they are used within a framework of clinical safety and individualization. The goal is to move the patient from a state of fragile sedentary behavior to one of resilient, active living, much like any other aging human population.

5 Discussion

This review highlights the compelling potential of a multi-faceted approach to managing PV and related MPNs, integrating established cardiovascular and metabolic therapies, repurposed drugs, natural compounds, and lifestyle interventions alongside conventional treatments like IFN- α . The evidence synthesized herein, spanning preclinical models, clinical trials in non-MPN populations, and observational studies in MPN patients, underscores promising avenues for improving both survival and QoL by targeting key pathways implicated in MPN pathogenesis. These pathways include aberrant JAK/STAT and mTOR signaling, chronic inflammation, oxidative stress, and epigenetic dysregulation.

Taking into account that PV and related neoplasms are chronic blood cancers, which — like any other untreated cancer — will steadily progress due to clonal expansion and evolution, we would like to underscore the urgent unmet need to initiate stem-cell targeting treatment with IFN- α alongside treatment targeting the chronic inflammatory state, which not only drives the malignant MPN-clone but also likely accelerates development of atherosclerosis and accordingly cardiovascular diseases and — important — second cancers in MPNs as well (1, 2, 9, 328).

A central theme emerging from the reviewed studies is the importance of aggressively addressing cardiovascular risk factors in MPN patients. PV inherently confers a heightened thrombotic risk, which is further exacerbated by concurrent metabolic conditions—especially hypertension, dyslipidemia, and insulin resistance. Several well-characterized interventions, already standard of care in general populations, demonstrate not only cardiovascular benefits but also potential anti-inflammatory and anti-fibrotic properties relevant to MPN pathophysiology.

5.1 Prioritizing cardiovascular and metabolic health

The convergence of cardiovascular and MPN-specific benefits supports a proactive approach to managing modifiable risk factors:

- **Blood Pressure Control:** ACE inhibitors represent a particularly valuable therapeutic option for PV patients with hypertension, offering benefits that may extend beyond blood pressure reduction alone. Their anti-inflammatory and anti-fibrotic properties, combined with their modulation of the RAS, make them especially well-suited for the MPN context. We recommend considering ACE inhibitors and other RAS inhibitors for all PV patients with systolic blood pressure exceeding 130 mmHg (329, 330).
- **Lipid Management:** Statins, a cornerstone of cardiovascular risk reduction, possess pleiotropic effects, including anti-inflammatory and potential anti-cancer activities, which further support their role in PV management. We recommend considering statin therapy for all PV patients with LDL cholesterol above 100 mg/dL, and potentially even for those above 70 mg/dL, in line with treatment strategies for other high-risk populations (331). Statins' ability to disrupt lipid rafts, impair JAK2V617F signaling in preclinical data, and be associated with improved survival in PV cohorts underscores their strong potential.
- **Metabolic Health:** Metformin and pioglitazone, both established anti-diabetic agents, have demonstrated promise in preclinical MPN models and may offer benefits beyond glycemic control. Metformin's ability to activate AMPK, inhibit mTOR and STAT3, and potentially facilitate interferon reintroduction, along with pioglitazone's anti-fibrotic and immunomodulatory properties, warrants strong consideration in patients with diabetes, but perhaps also with insulin resistance (HOMA-IR >2) (332), elevated fasting blood glucose (FBG >100 mg/dL), or obesity (301).

5.2 Embracing a holistic approach: lifestyle interventions

Beyond pharmacological interventions, lifestyle modifications offer a safe and potentially synergistic approach to improving MPN outcomes:

- **Mediterranean Diet:** The NUTRIENT trial provides initial evidence supporting the feasibility and potential benefits of Mediterranean diet adoption in MPN patients, particularly for symptom burden reduction. While larger trials are needed to confirm these findings and elucidate the underlying mechanisms, the diet's well-established cardiovascular benefits and safety profile make it a reasonable recommendation for interested patients.
- **Yoga and Exercise:** Pilot trials suggest that structured physical activity and online yoga programs are feasible and

well-received in MPN populations. While their impact on patient-reported outcomes has not consistently shown QoL benefits, encouraging early signals have emerged — including improvements in sleep, pain, anxiety, and depression with yoga (312); significant gains in physical capacity with exercise (317); reduced LDH and favorable trends in inflammatory cytokines with exercise (318). Given these promising early findings, individualized and graduated exercise prescriptions can be recommended as a component of comprehensive MPN care.

- **Weight Management:** The association between obesity and increased symptom burden in MPNs underscores the importance of weight management. For patients on treatments associated with weight gain, such as ruxolitinib, proactive strategies like metformin co-administration or GLP-1 RAs to maintain a healthy weight may be beneficial, potentially mitigating symptom burden and improving cardiovascular health.

5.3 Can targeted supplements help?

A growing body of evidence suggests that specific nutritional supplements may help counteract the chronic inflammation, oxidative stress, and dysregulated signaling characteristic of MPNs. We believe further research is warranted for these interventions based on their preclinical and early clinical data:

- **Fish Oil (EPA-rich):** May help manage MPN symptom burden, particularly depression, bone pain, and cardiovascular risk, potentially through its anti-inflammatory effects.
- **N-acetylcysteine:** May lower reactive oxygen species (ROS), reducing DNA damage and thrombotic risk in preclinical studies. Its potential to improve symptom burden and reduce NET formation supports further investigation.
- **Natural JAK2 Inhibitors:** Compounds like curcumin, quercetin (in onions, tomatoes), EGCG (in green tea), chlorogenic acid (in coffee), and ellagitannins (in berries) demonstrate broad anti-inflammatory and anti-neoplastic properties, with potential synergy when used alongside standard therapies like interferon due to their independent modes of action. Their ability to modulate core signaling pathways implicated in MPN pathogenesis makes them attractive candidates for combination therapies.
- **Alpha-Ketoglutarate:** Shows promise in dampening platelet hyperactivation, rebalancing aberrant epigenetic signaling, and potentially alleviating fatigue, as suggested by the case study of patient #2.
- **Vitamin D3:** Supplementation may be beneficial for deficient PV patients, although caution is warranted in the context of MF, where preclinical data surprisingly suggested that a low-vitamin D environment could mitigate fibrosis.
- **Clostridium butyricum:** This probiotic may help restore gut microbial balance, increase butyrate levels (an HDAC inhibitor with anti-inflammatory and anti-cancer properties), and potentially enhance the efficacy of immunotherapies.

Also, for further research:

- **Leukotriene Modifiers and Rapamycin:** Given their affordability, and strong preclinical evidence, these agents may be beneficial alone or in combination with interferon, as highlighted by the case study of patient #1.

5.4 Combination therapy with ruxolitinib

Ruxolitinib is among the most potent clinically available inhibitors of the JAK1/2-driven inflammatory cascade, and its broad suppressive activity must be carefully considered when designing combination strategies. Agents whose primary mechanism of action substantially overlaps with JAK-STAT suppression may confer limited additional benefit when added to ruxolitinib, as illustrated by the failure of statin-ruxolitinib combinations to improve disease progression in a murine MPN model despite promising *in vitro* activity (81).

However, ruxolitinib does not fully normalize the MPN inflammatory milieu. Fisher et al. showed that plasma cytokine levels in MF patients remained markedly abnormal despite ruxolitinib treatment, with a subset — including TNF- α , IL-6, IL-8, and IL-10 — exhibiting minimal *ex vivo* sensitivity to ruxolitinib, while remaining responsive to NF- κ B and/or MAP kinase inhibition (16, 333). Furthermore, constitutive PI3K/AKT/mTOR activation downstream of JAK2V617F is not fully suppressed by JAK inhibition alone, allowing neoplastic cells to maintain pro-proliferative signaling (235, 237). This incomplete suppression likely contributes to the well-recognized phenomenon of residual disease burden on ruxolitinib therapy.

These observations carry an important lesson for rational drug design: the most promising ruxolitinib-based combinations are those targeting pathways that remain active despite JAK inhibition. Compelling candidates include agents acting on cellular metabolism (e.g., metformin), mTOR signaling (e.g., rapamycin analogs), NF- κ B-driven transcription, stem cell compartment (e.g., IFN- α) etc. This principle has been validated by the MANIFEST trials, in which pelabresib — a BET inhibitor that downregulates NF- κ B-driven gene expression — combined with ruxolitinib produced significantly greater spleen volume reductions than ruxolitinib alone in MF, with a favorable trend in symptom improvement (334, 335). Similarly, the COMBI trials demonstrated that combining ruxolitinib with IFN- α — which targets the malignant stem cell compartment — yielded high rates of hematologic and molecular response in patients with PV or MF who were refractory or intolerant to IFN- α monotherapy (COMBI I) (336, 337), and produced a notably rapid decline in JAK2V617F Variant Allele Frequency in newly diagnosed PV patients (COMBI II) (338), although a comparable benefit was not observed in a retrospective MF cohort (339).

5.5 Brief note on polypharmacy

While the integration of repurposed agents offers a promising avenue for enhancing MPN management, it inevitably increases the

medication burden in a population where polypharmacy (≥ 5 drugs) is already prevalent and associated with inferior survival (340). A critical safety consideration is that adding further drugs on top of standard MPN therapies, specifically ruxolitinib, hydroxyurea, and IFN- α , may elevate iatrogenic risk. Therefore, the addition of repurposed agents must be carefully considered to avoid cumulative pharmacologic toxicities that compound cytopenias, infection susceptibility, and organ stress. Clinicians must weigh these additive risks against potential benefits, recognizing that adverse effects considered minor in the general population can be clinically consequential when superimposed on standard MPN therapies. For an analysis of specific drug-drug interactions and potential safety protocols, please refer to the [Supplementary Appendix](#). Ultimately such signals must come from MPN-specific clinical trials and retrospective analyses, hence further studies are warranted.

5.6 Future directions: a two-pronged strategy

To advance the field towards more effective MPN care, we propose a two-pronged strategy.

- **Immediate Implementation:** Incorporate readily applicable interventions into clinical practice based on individual patient biomarkers and preferences. This includes aggressive management of cardiovascular risk factors through ACE inhibitors and statins, addressing metabolic dysregulation with metformin or pioglitazone, encouraging lifestyle modifications like the Mediterranean diet, yoga, physical exercise and weight management.
- **Rigorous Research:** Conduct rigorous research to validate emerging combination therapies and optimize treatment protocols. This includes:
 - Retrospective analysis of patient data: Determine optimal drugs, combinations, and their effects for initiating cardiovascular and metabolic therapies in MPN patient populations.
 - Large-scale prospective trials: Validate the identified combination options prospectively, assessing their impact on thrombotic risk, disease progression, symptom burden, and QoL.
 - Multi-arm, combinatorial, and adaptive trials: When the JAK pathway is inhibited, TSS changes can be observed in as little as 4 weeks (341). Therefore, a combinatorial multi-arm trial can test numerous possibilities in 4–8 weeks for symptom management.
 - Mechanistic studies: To further elucidate the molecular mechanisms and combination potential.
 - Pharmacokinetic and pharmacodynamic studies: To optimize dosing and delivery strategies for natural compounds, ensuring adequate bioavailability and therapeutic efficacy.

- Longitudinal studies: To assess the long-term safety and efficacy of combination therapies, particularly in the context of lifelong MPN management.

5.7 Conclusion

This review underscores the transformative potential of a multi-faceted approach to PV and MPN management. By integrating established cardiovascular and metabolic therapies, off-label/repurposed drugs, natural compounds, and lifestyle interventions alongside conventional treatments, we can strive to optimize both survival and QoL for MPNs. The case studies presented offer a glimpse into the potential benefits of such personalized combinations, emphasizing the need for continued investigation, collaboration, and a patient-centered approach to advance the field. The convergence of a growing understanding of MPN pathobiology with the availability of safe and potentially synergistic interventions offers a unique opportunity to improve the lives of patients with PV and MPNs.

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Supplementary material

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