

## Review

## Is 6-Shogaol a beneficial phytochemical for patients with lower-risk myelodysplastic syndrome? A narrative review

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### Abstract

Myelodysplastic syndrome (MDS) evolves due to genomic instability, dysregulated signalling pathway and overproduction of inflammatory markers. Reactive oxygen species contribute to the inflammatory response, which causes gene damage, cellular remodelling and fibrosis. MDS can be a debilitating condition, and management options in patients with MDS aim to improve cytopenias, delay disease progression, and enhance quality of life. High serum ferritin levels, a source of iron for reactive oxygen species production, correlate with a higher risk of progression to acute myeloid leukaemia, and iron overload is compounded by blood transfusions given to improve anaemia. 6-shogaol is a natural phenolic compound formed when ginger is exposed to heat and/or acidic conditions, and it has been shown to possess anti-tumour activity against leukaemia cell lines and antioxidant effects. This narrative review assessed the potential benefits of this phytochemical in lower-risk MDS patients through examining the current evidence on the pharmacological and therapeutic properties of ginger and 6-shogaol.

**Keywords:** *Zingiber officinale*, 6-Shogaol, 6-gingerol, hematopoiesis, hepcidin, anaemia.

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### Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal stem cell disorders characterised by dysplastic and ineffective haematopoiesis and peripheral cytopenias. Anaemia occurs in greater than 85% of MDS patients, while more than 50% are neutropenic, and at least one third have moderate or severe thrombocytopenia (Steensma et al., 2008). The revised International Prognostic Scoring System (IPSS-R) categorises the prognostic risk of the primary untreated adult MDS patients into five levels (Very low, Low, Intermediate, High, and Very High), with the majority of the patients (77%) belonging to the three lower-risk categories (Greenberg et al., 2012). Survival is less than six months for those over 60 years of age who have the most advanced forms of the disease to more than eight years in younger patients with no adverse risk factors (Germing et al., 2013). The only form of curative therapy is allogeneic haematopoietic stem cell transplantation, but most patients are not eligible for this due to advanced age or co-existing medical conditions. Thus, the treatment goals in lower-risk MDS are to improve cytopenias, prolong survival, and enhance health-related quality of life (QoL). Consequently, interventions focus on increasing blood counts, delaying progression to acute myeloid leukaemia and maintaining functional capacities (Steensma et al., 2008).

Compared to a reference population, patients newly diagnosed with lower-risk MDS experience a pronounced reduction in QoL, which is only partly explained by the presence of anaemia. The most debilitating MDS symptom reported was fatigue, but this was poorly correlated with haemoglobin level regardless of whether patients had received any blood transfusions. Fatigue was reported to be associated with significant impairment of both QoL and the ability to work or participate in desired activities (Steensma et al., 2008). In a recent review by Stauder et al. (2018), patients with lower-risk MDS reported moderate to severe impairments to pain/discomfort, mobility, anxiety/depression, and their usual activities. So, improving QoL is an essential management factor for lower-risk MDS patients.

In traditional Chinese medicine, dry ginger is considered a warm herb that can dispel cold and dampness and promote the flow of blood and qi to remove blood stasis and ease weakness and fatigue (Han et al., 2016). Thus, ginger is a choice ingredient in many Chinese herbal remedies for blood circulation, anaemia, and haemorheological conditions. For example, ginger is an ingredient in the Jianpi buxue formula, which has been shown to reverse chemotherapy-induced myelosuppression through increasing haematopoietic stem cells in the bone marrow (Huang et al., 2020). Ginger is also a common ingredient in the blood tonic formulas of Guizhi Tang, Neibu Dangguijianzhong Tang and Zao Tang, which promote the haematopoietic function through stimulation of the protein expressions of erythropoietin via the hypoxia response elements (Lam et al., 2016). In Southern China, the 'ginger vinegar soup' consisting of sweet vinegar, ginger, egg, and pig's trotters is a traditional dietary practice recommended during the early postpartum period for women to recover from blood loss during delivery. Chan et al. (2000) showed that the 'ginger vinegar soup' was rich in iron, with its content comparable to other iron-rich foods. From these traditional usages, it appears that ginger may potentially benefit the haematopoietic function of lower-risk MDS patients to alleviate fatigue and improve QoL.

Shogaols are biologically active constituents of ginger. The most common constituent is 6-shogaol, a promising anti-cancer and anti-inflammatory agent that also possesses hepatoprotective effects (Zhang et al., 2019). A recent study by Golombick et al. (2017) found 6-shogaol supplementation to lower the elevated serum ferritin levels in early-stage, transfusion-independent patients with MDS. In light of the preceding information, it is plausible that ginger extract rich in 6-shogaol, a natural remedy, can potentially benefit lower-risk MDS patients. This article examines the existing literature to explore the therapeutic properties of 6-shogaol as a low-intensity supportive treatment in MDS.

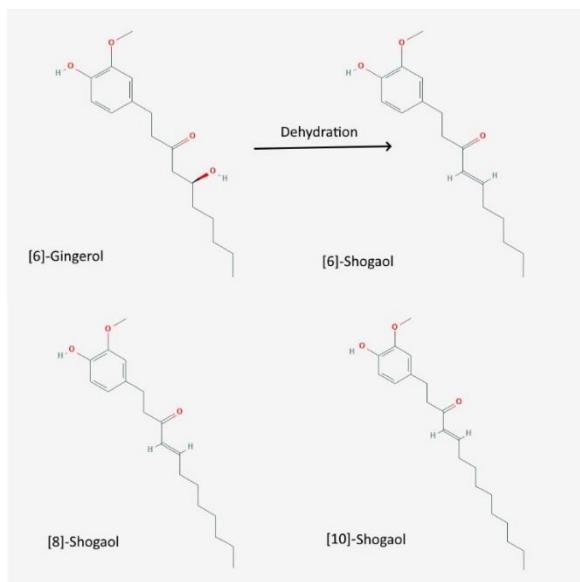
### Ginger and Shogaols

Ginger is the rhizome of *Zingiber officinale* Roscoe, a perennial herbaceous plant of the

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Zingiberaceae family. It has been used as a tonic root and flavouring agent for more than 5000 years by the Indians and Chinese, long before history was formally recorded (Bode & Dong, 2011). Today, ginger is a culinary spice and a herbal remedy widely used around the world. Research to date has demonstrated that ginger possesses many biological activities such as antioxidant, anti-inflammatory, antimicrobial, antiemetic, and anti-cancer activities (Mao et al., 2019). Furthermore, ginger is also proven beneficial in the prevention and management of cardiovascular diseases (Fakhri et al., 2020), obesity (Wang et al., 2017), neurodegenerative conditions (Mohd Sahardi & Makpol, 2019), diabetes mellitus (Huang et al., 2019), respiratory disorders (Townsend et al., 2013) and nausea relief (Nikkhah Bodagh et al., 2018).

Ginger contains both volatile and non-volatile components. The non-volatile components include major biologically active constituents such as shogaols, gingerols, paradols and zingerone (Kiyama, 2020), which are the primary ingredients that give ginger its unique pungent flavour. Through drying, heat or storage, gingerols can dehydrate into shogaols (Ghasemzadeh et al., 2018). Hence, the composition of fresh ginger varies with variety, agronomic conditions, curing and drying methods and storage conditions (Agrahari et al., 2015).



**Figure 1.** Two dimensions structure of 6-gingerol, 6-, 8-, and 10-shogaol. (Source: PubChem) (National Center for Biotechnology Information, 2021a, 2021b, 2021c, 2021d)

The chemical structures of different forms of shogaols are shown in Figure 1. They form due to the unstable beta-hydroxy ketone in gingerols when exposed to heat and/or acidic conditions. Thus, both gingerols and shogaols have different bioactivities, molecular targets and metabolic pathways (Sang et al., 2020). The processing of fresh ginger is essential to produce the most efficacious quantity of non-volatile compounds, especially shogaols. Ho and Su (2016) observed that the optimal temperature in the preparation of 6-shogaol from ginger was 125°C for 40-60 minutes. There was an increase in shogaol content by 9.34-fold at this temperature. Li et al. (2016) also compared the chemical characteristics and antioxidant activities of fresh, dried, stir-fried and carbonised ginger. The highest antioxidant activity, highest phenolic and highest level of shogaols were found in dried ginger. When dried ginger was then carbonised, the amount of 6-shogaol was the most abundant, being around 114-fold higher than in fresh ginger. Moreover, 6-shogaol exhibited the most potent antioxidant and anti-inflammatory properties *in vitro* compared with 6, 8, and 10-gingerol (Dugasani et al., 2010).

## Pharmacokinetics and Toxicity

The pharmacokinetics and toxicity of 6-shogaol have been studied in animal models and humans. Studies in rats show 6-shogaol is well absorbed from the gastrointestinal tract (GIT), with most (64%) excretion occurring via the faecal route through biliary excretion. Urinary excretion is in the order of 20%. 6-shogaol was rapidly and extensively metabolised when given to healthy human subjects; its glucuronic acid conjugates were detected in plasma from 15 minutes to 72 hours post-administration (Asami et al., 2010). In a review by Kou et al. (2018) looking at both animal and human studies, the authors noted that 6-shogaol was extensively metabolised after oral administration and some metabolites were reabsorbed from the GIT. Phase 1 and phase 2 enzymes take part in the first-pass metabolism with the conjugation of glucuronide as the dominant product. 6-shogaol also had inhibitory effects on phase 1 and phase 2 enzymes which could be important in drug-drug interactions. A study by Yu et al. (2011) on the pharmacokinetics of the active ingredients of ginger in humans

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showed that 6-shogaol and its metabolites had short half-lives between one to three hours, and there was no accumulation of these compounds after repeated dosing.

Concerning toxicity, ginger appears to be a safe product. In a systematic review of 109 randomised controlled trials, Anh et al. (2020) found that most adverse effects were GIT related, namely heartburn, nausea, diarrhoea, abdominal pain, bloating, gas and epigastric distress. Moreover, doses ranging from 10 mg/kg to 100 mg/kg of 6-shogaol were administered for 14 days to albino mice (Hassan & Hassan, 2018). No mortality was observed at any dose, and only mild clinical changes were observed at doses of 100 mg/kg. The recommended doses of ginger range from 200 mg to 2.5 g per day of the dried extract, containing between 1-4% shogaols (Cicero & Colletti, 2018). Side effects include mainly GIT symptoms, and there may be potentiation of anticoagulant effects. It is noteworthy that a dose of ginger between 0.5 g and 1.0 g, 2-3 times daily over periods ranging from 3 months to 2.5 years, did not cause any adverse side effects (Kumar et al., 2013). Larger intakes are noted in various populations over the world. In animal models, doses of 2.5 g/kg were tolerated with no mortality, but at doses of 3-3.5 g/kg, mortality rates were 10-30% (Chrubasik et al., 2005). Nota bene, for a 70 kg person, 2.5 g/kg equates to 7 g shogaols per dose based on a 4% content of shogaols.

## Therapeutic Properties

### Anti-inflammatory effect

MDS is the result of genomic instability, dysregulated signalling pathways and overproduction of inflammatory markers. This process is a feature of MDS due to genetic defects within pluripotent stem cell populations, with chronic inflammation causing deoxyribonucleic acid damage, cellular remodelling and fibrosis (Geyer et al., 2015). The pro-inflammatory signalling within the malignant clone and the bone marrow microenvironment, which activate aberrant innate immune responses, are key pathogenic drivers of MDS (Sallman & List, 2019). Symptom development in MDS has been associated with inflammation due to an

abnormal elevation of cytokine expression. Certain inflammatory markers are associated with specific symptoms, for example, ferritin with pruritis and interleukin-8 with elevated blasts. Fatigue is the most debilitating symptom reported to be induced by cytokines (Geyer et al., 2015). Moreover, autoimmune and inflammatory conditions, such as inflammatory arthritis, are common comorbidities in up to 25% of MDS patients (Wolach & Stone, 2016).

Ginger is well-known for its anti-inflammatory effect. The systematic review by Anh et al. (2020) included eight clinical trials that reported the anti-inflammatory effect of ginger supplementation. These studies, primarily conducted among arthritis patients, commonly reported pain relief as a promising benefit. Other observed effects include reducing pro-inflammatory cytokines, promoting forkhead box P3 gene expression, and decreasing ferritin and malondialdehyde levels.

The anti-inflammatory property of 6-shogaol was studied in many *in vivo* and *in vitro* studies. 6-shogaol was shown to attenuate inflammatory process *in vivo* with murine macrophages, microglia cells, epidermal keratinocytes, and oral squamous cell carcinoma through multiple signalling pathways including nuclear factor-kappa B, activator protein 1, mitogen-activated protein kinase cascades, and peroxisome proliferator-activated receptor gamma (Annamalai & Suresh, 2018; Chen et al., 2019; Han et al., 2017; Pan et al., 2008). 6-shogaol also demonstrated its anti-inflammatory effect to lower lung inflammation in a murine asthma model (Yocum et al., 2020), protect against acute lung injury in mice (Wang et al., 2016), downregulate inflammatory markers in hamster buccal pouch carcinogenesis (Annamalai & Suresh, 2018), inhibit monosodium urate crystal-induced inflammation in mice (Sabina et al., 2010), and reduce neuroinflammation in rodent models of dementia (Moon et al., 2014). A recent review of 30 *in vivo* and *in vitro* studies further confirmed 6-shogaol to be a promising anti-inflammatory substance, but conclusive clinical data remained lacking (Bischoff-Kont & Fürst, 2021). Nevertheless, it is reasonable to assume that 6-shogaol can potentially reduce chronic

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inflammation associated with MDS and alleviate inflammation-related comorbidities.

### Antioxidant effect

Chronic inflammation is due to oxidative stress partly related to the free radical production of reactive oxygen species (ROS) generated by iron, an essential but potentially toxic element. The literature shows that ROS, as a result of iron overload, are involved in the pathogenesis of MDS (Pilo & Angelucci, 2018). The high ROS levels within the haemopoietic niche can impact clonal evolution. Oxidative stress affects the self-renewal, proliferation and differentiation of haematopoietic stem cells and impairs cell growth, leading to defective haemopoietic mechanisms in MDS. A study by Saigo et al. (2011) among transfusion-independent MDS patients showed that 85% of them (34 out of 40) had higher than normal ROS levels in serum as measured using derivatives of reactive oxygen metabolites. The study also detected a positive correlation between ROS levels and serum ferritin levels and a negative correlation between ROS levels and haemoglobin levels.

Gonçalves et al. (2015) observed that bone marrow cell types from MDS patients had increased intracellular peroxide levels and decreased glutathione content, compared with control cells. Furthermore, oxidative stress levels were risk group-dependent, with the lower-risk patients having the highest ROS levels characterised by high bone marrow apoptosis. As such, oxidative stress parameters, such as malondialdehyde, were suggested to be predictive biomarkers for treatment response in lower-risk MDS patients (Gonçalves et al., 2021). Hoeks et al. (2021) followed the progress of 256 lower-risk MDS patients over three years and found a progressive increase of malondialdehyde levels in the patients over time. Oxidative stress due to iron toxicity, especially among transfusion-dependent patients, damaged organs and led to inferior outcomes.

The antioxidant effect of 6-shogaol is due to the alpha, beta-unsaturated ketone moiety, which confers increased potency and efficacy to this compound compared to its precursor, 6-gingerol (Dugasani et al., 2010). 6-shogaol possesses a strong metal binding capacity to reduce lipid

peroxidation, scavenge free radicals, and inhibit the action of xanthine oxidase, a generator of oxygen free radicals (Kou et al., 2018). An *in vitro* study with a neuron-like rat pheochromocytoma cell line by Peng et al. (2015) showed that 6-shogaol upregulated a series of phase II antioxidant molecules, such as glutathione, haem oxygenase 1 and thioredoxin 1. 6-shogaol exhibited remarkable cytoprotection against oxidative stress-induced cell damage. The likely mechanism of this cytoprotection is mediated by activating the transcription factor called nuclear factor-erythroid 2-related factor 2 (Nrf2). Consistently, other studies also demonstrated that 6-shogaol was able to enhance cellular antioxidant activities through increasing glutathione levels and antioxidant response element promoter activities via the Nrf2 signalling pathway, *in vivo* and *in vitro* (Bak et al., 2012; Kim & Jang, 2016).

Phenolic compounds have been shown to counter oxidative stress due to free radicals caused by iron overload (Imam et al., 2017). Dried ginger extract was shown to possess free radical scavenging for iron nanoparticles (Mohamed et al., 2020). The water-soluble extracts of red and white gingers were shown to protect against Fe (2+)-induced lipid peroxidation in the rat brain *in vitro* (Oboh et al., 2012). Moreover, another hydroalcoholic ginger extract was shown in rats to protect against ferrous sulphate-induced hepatic and renal toxicity *in vivo* by reducing lipid peroxidation and chelating iron (Gholampour et al., 2017). Currently, there is a lack of direct study on how 6-shogaol may protect against iron-induced oxidative stress in bone marrow cells or MDS. This topic requires further research.

### Haematopoietic effect

Patients with MDS, who have not received blood transfusions, have been shown to have inappropriately low hepcidin levels indicating a blunted hepcidin response to iron overload (Gattermann, 2018; Lyle & Hirose, 2018). This self-sustaining response was driven by ineffective erythropoiesis and caused increased intestinal iron absorption. Adding to this is the effect of growth differentiation factor 15 secreted by mature erythroblasts that suppressed hepcidin production by the liver (Cui et al., 2014).

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Camaschella et al. (2020) also noted a vicious cycle in MDS patients due to the inhibition of hepcidin by erythroferrone released by erythropoietin stimulated erythroblasts. This high serum level of erythroferrone led to high iron levels, which interfered with erythroblast maturation aggravating the anaemia of MDS. The Canadian Consensus Guidelines state that iron overload is defined as a serum ferritin level greater than 1000 micrograms/litre (Leitch et al., 2018). Level II evidence obtained from at least one well-designed randomised controlled study shows that iron overload may worsen overall and leukaemia-free survival in MDS patients. The effect of iron overload is more apparent in low risk or intermediate-1 risk MDS groups, as these patients usually live long enough to experience iron toxicity (Leitch et al., 2018).

The haematopoietic effect of ginger has been studied in a zebrafish embryo model (Ferri-Lagneau et al., 2012). This model looks at tissues in the zebrafish embryo that are equivalent to the mammalian site of haematopoiesis. The bone morphogenetic protein (bmp), a tissue growth factor-beta superfamily member, is involved in a signalling pathway that plays a critical role in haematopoiesis. This pathway regulates the development of human haematopoietic stem cells and early embryonic haematopoiesis during early vertebrate development. The zebrafish embryo model has been used to study the mechanism of haemopoiesis and erythropoiesis *in vivo*. In an inducible haemolytic anaemia model, ginger extract and 10-gingerol were shown to promote haemopoietic recovery via the bmp signalling pathway. Further investigation with the zebrafish model showed that 10-gingerol could rescue the haemogenic endothelium. 10-gingerol was shown to upregulate nitric oxide production crucial for arteriogenesis and haematopoiesis in haematopoietic stem/progenitor cells with genetic defects (Ferri-Lagneau et al., 2019).

Conversely, in an *in vitro* experiment, Alamri et al. (2021) showed that 6-gingerol could stimulate premature death of red blood cells at 100  $\mu$ M concentration. Cell apoptosis was characterised by loss of membrane asymmetry, elevated cytosolic calcium, cell shrinkage, and casein kinase 1 $\alpha$  activation. Since both gingerols are

extensively metabolised after ingestion, such findings are more relevant for intravenous applications of ginger derivatives as anti-cancer agents rather than administration through the oral route.

Ferri-Lagneau et al. (2012) also demonstrated that 6-shogaol is less effective in promoting haemopoiesis than 10-gingerol. Such findings prompted the suggestion that 6-shogaol had no effect on improving anaemia and that fresh ginger (rich in gingerols) was more effective than dried ginger (rich in shogaols) (Sang et al., 2020). However, a cross-sectional study among 4628 residents in China found no significant correlation between daily consumption of fresh ginger as a spice and the prevalence of anaemia (Wang et al., 2017). In contrast, intervention studies among anaemic patients using dried ginger powder did produce promising results.

Table 1 summarised the available human intervention studies with ginger extract on disorders due to ineffective erythropoiesis. Kulkarni et al. (2012) studied the effect of ginger supplementation in anaemic patients requiring iron supplementation. The patients (n=30) who took 250 mg of ginger extract (1.5 g of pure ginger powder) and iron supplements daily had higher percentages rise in haematological and iron-related parameters (iron and ferritin) than the control group (n=32) on iron supplements alone after 30 days. The results showed that dried ginger powder assisted in iron absorption in patients with iron-deficiency anaemia. Similar findings were reported by Kumar et al. (2013) in patients with tuberculosis-associated anaemia. Patients (n=36) who took dried ginger powder supplement (250 mg/day for 30 days) along with anti-tubercular drug had higher percentages increase in haemoglobin, and decrease in ferritin and C-reactive protein (CRP), compared to the control group (n=36) on anti-tubercular drug alone. Hence, the authors concluded that ginger supplementation helped regulate iron metabolism by decreasing systemic inflammation in tuberculosis.

*Is 6-Shogaol a beneficial phytochemical for patients with lower-risk myelodysplastic syndrome? A narrative review***Table 1 Human intervention studies with ginger extract on disorders due to ineffective erythropoiesis**

Study	Study Design	Participants	Interventions	Efficacy Findings
Raza et al. (2008)	Prospective single-arm clinical trial	Patients with low or intermediate-1 risk MDS (N=9).	Gingerol (350 mg twice daily increasing to 1.4 g/day) plus curcumin (starting with 2 g in 4 divided doses/day, increasing to 8 g/day). Duration: > 6 months.	Available data from 6 patients only. 4 out of 6 patients shown overall haematologic improvement, with 3 showing trilineage improvement in Hb, platelets, and ANC.
Kulkarni et al. (2012)	Open-label control trial	Patients with moderate to severe iron deficiency anaemia (N=62). Ginger+iron (n=30). Iron only (n=32).	250 mg of ginger extract (equivalent to 1.5 g of pure ginger powder) twice daily. Iron supplement (dosage not specified). Duration: 30 days.	Ginger+iron group achieved a higher percentage increase in haematological and iron parameters compared to the iron only group. Hb: 8.23% vs 2.3%, Iron: 19.63% vs 5.54%, TIBC: 7.23% vs 4.47%, Ferritin: 45.11% vs 34.11%.
Kumar et al. (2013)	Open-label control trial	Newly diagnosed pulmonary tuberculosis patients having significant anaemia (N=68). Ginger+ATT (n=36). ATT only (n=32).	250 mg of ginger extract (equivalent to 1.5 g of pure ginger powder) twice daily in capsule form. Duration: 30 days.	Ginger+ATT group achieved a higher percentage improvement in CRP (17.52% lower), ferritin (5.08% lower) and Hb (1.39% higher) parameters compared to ATT only group.
Golombick et al. (2017)	Case series	Patients with low or intermediate-1 risk MDS (N=6).	1 gel capsule of 20 mg ginger extract standardised for 20% 6-shogaol once daily. Duration: 6 months + 6 months.	The study detected a decrease in ferritin levels in 3 of the 6 patients whose ferritin levels were elevated at baseline. The decrease in ferritin in the 3 patients was accompanied by an increase in serum hepcidin level in repeat studies in the next 6 months.
<b>Legend:</b> ANC, absolute neutrophil count; TIBC, transferrin and iron-binding capacity; ATT, anti-tuberculosis treatment; CRP, C-reactive protein; Hb, haemoglobin; MDS, myelodysplastic syndrome.				

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Raza et al. (2008) showed promising results in combining curcumin and gingerol to improve lower-risk MDS patients' haematologic parameters. Nine patients with low or intermediate-1 risk MDS took curcumin (2 g/day increasing to 8 g/day) and gingerol (350 mg/day to 1.4 g/day) supplements in incremental doses. Six patients were evaluated for their response after supplementing for a minimum of six months. Four out of six showed overall haematologic improvement, with three of the four showing trilineage improvement.

Golombick et al. (2017) carried out a small investigative study on six patients with low to intermediate-1 risk MDS. Their study investigated the effect of 6-shogaol (20 mg/day of a ginger extract standardised for 20% 6-shogaol) on serum ferritin levels, changes in liver function tests, blood hepcidin levels and blood cell levels in transfusion-independent patients. Results indicated a reduction in serum ferritin level in three patients, improved liver function tests in one patient, and increased serum hepcidin level in two patients. This small investigative study has raised the question of whether 6-shogaol could be beneficial in patients with lower-risk MDS.

### Hepatoprotective effect

The liver is the primary iron store of the body. It regulates the absorption of iron through hepcidin production and synthesises iron metabolism proteins such as transferrin. MDS patients often have lower hepcidin/ferritin ratios than healthy people, a sign of blunted response in hepcidin production in the liver (Santini et al., 2011). Iron overload begins to develop even before a patient becomes transfusion-dependent because of the suppressed hepcidin production, leading to excessive intestinal iron uptake. Regular transfusion to ameliorate anaemia further exacerbates iron overload (Gattermann, 2018). Excessive iron store in the liver is toxic and can lead to cirrhosis, liver failure, and hepatocellular carcinoma (Bonkovsky & Lambrecht, 2000).

The hepatoprotective effects of ginger were seen in ameliorating age-related changes (Mahmoud & Hegazy, 2016), reducing liver injury due to unhealthy diet and alcohol (Leal et al., 2019; Zhuang et al., 2015), and improving chemical-induced hepatotoxicity and liver fibrosis in many

*in vivo* studies (Badawi, 2019; El-Sharaky et al., 2009; Elzwi, 2019; Essawy et al., 2018; Motawi et al., 2011; Mukherjee et al., 2015; Sabina et al., 2011). These studies commonly reported improved aspartate aminotransferase and alanine aminotransferase enzyme levels and preserved hepatocyte structure after ginger administration (Badawi, 2019; Elzwi, 2019; Motawi et al., 2011). More specifically, 6-shogaol has been shown to provide liver protection against aflatoxin B1 induced hepatotoxicity (Vipin et al., 2017) and diclofenac induced liver damage in rats (Alqasoumi et al., 2011). The hepatoprotective effect of 6-shogaol was even more pronounced when it was delivered in nanoparticles. Zhang et al. (2019) demonstrated *in vivo* that 6-shogaol loaded micelles had a 3.2-fold increase in oral bioavailability, improved tissue distribution, and better hepatoprotective effect against carbon tetrachloride-induced hepatic injury than free 6-shogaol. Notwithstanding, Hikino et al. (1985) found gingerols to exert a stronger antihepatotoxic effect *in vitro* than the corresponding shogaols.

### Anti-cancer effect

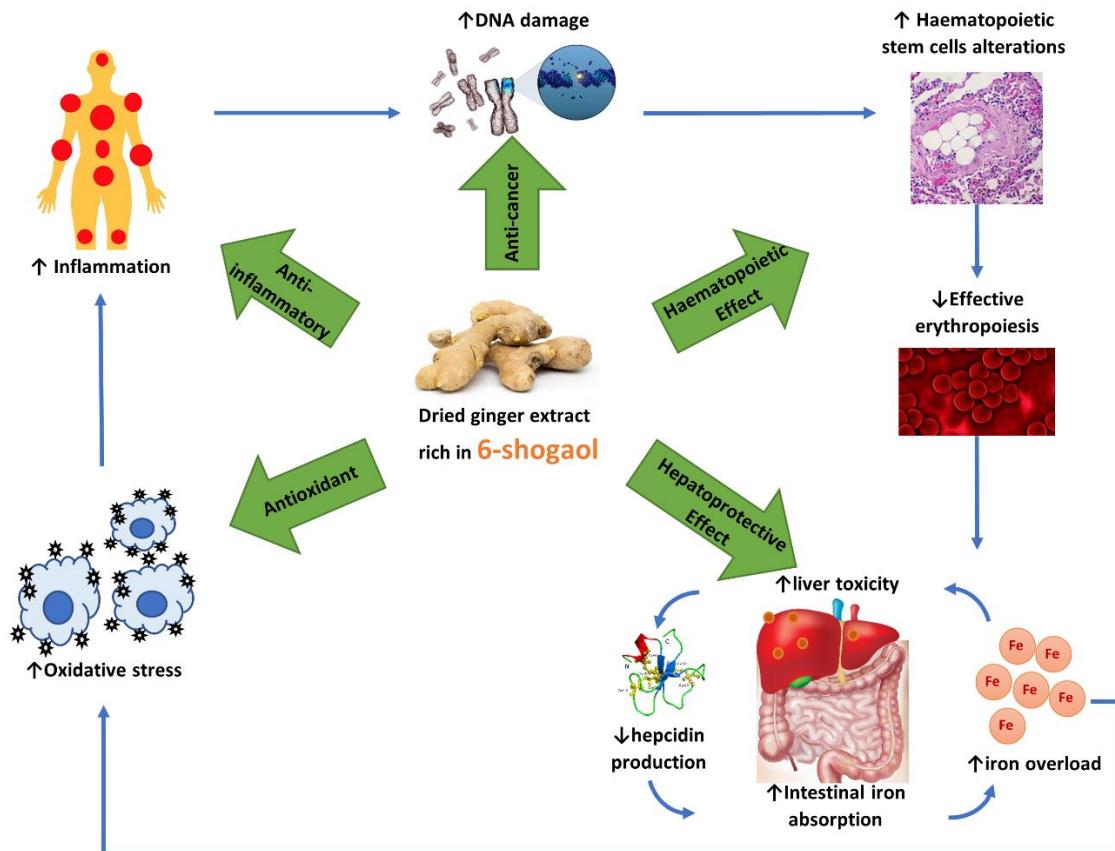
MDS is considered a type of age-related myeloid malignancies. MDS patients also present a higher incidence of malignant tumours than the general population. Prior treatment for other cancers with radiation therapy or chemotherapy also increases the risk of secondary MDS (Sans-Sabrafen et al., 1992; Zeidan et al., 2019). Inability to suppress inflammation and the continuous exposure to inflammatory mediators also increase the rate of transformation and disease progression of MDS to acute myeloid leukaemia (Banerjee et al., 2019).

Ginger and its bioactive constituents have been studied extensively for their anti-cancer effects. Research has shown that ginger protects against aberrant gene expressions and mutations within the transforming cell population. It also reduces inflammation and abnormal gene expressions by the cells within the surrounding lesion (Lechner & Stoner, 2019). Specifically, 6-shogaol has shown anti-cancer activity in prostate, pancreatic and breast cancer via cell arrest and apoptosis (Tuorkey, 2015). Liu et al. (2013) showed that 6-shogaol induces apoptosis in leukaemia cells *in*

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*vitro* and *in vivo*, but not normal cells. The selective toxicity of shogaols for tumour cells appears to be differential activation of the glycosylated metabolites by higher levels of  $\beta$ -glucuronidase in the tumour cells (Lechner & Stoner, 2019). Zhu et al. (2013) examined 12 synthesised metabolites of 6-shogaol and found

that specific metabolites were comparable with 6-shogaol in growth inhibitory effects and discriminatory effects against cancer cells but not causing toxicity towards normal cells. Hence, 6-shogaol could be a potential anti-tumour agent against haematologic malignancies even via oral administration.



**Figure 2.** A schematic depiction of how dried ginger extract rich in 6-shogaol can potentially benefit lower-risk MDS patients. Chronic inflammation leads to genetic aberrations in these patients, altering the haematopoietic stem cells' ability to produce erythrocytes. Ineffective erythropoiesis causes iron overload and accumulation of excess iron in the liver, which lowers the liver's ability to produce hepcidin. Intestinal absorption of iron increases as a result and further exacerbates iron overload. Excess iron is toxic and causing oxidative stress, which worsens inflammation. Dried ginger extract rich in 6-shogaol provides the much-needed antioxidants to scavenge the free radicals and reduce inflammation. It has anti-cancer properties to reduce the spread of malignancies. Ginger also promotes haematopoiesis and protects against liver damage, and preserves hepcidin production to reduce iron overload.

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### Discussion

There is a lack of direct evidence evaluating the use of 6-shogaol in patients with lower-risk MDS, apart from a small investigative study carried out by Golombick et al. (2017). This literature review found evidence that ginger extract, with 6-shogaol as an active constituent, is a safe, natural, phytochemical compound with anti-inflammatory, antioxidant, haematopoietic, hepatoprotective and anti-tumorigenic properties. Evidence has been presented to show a link between MDS development and chronic inflammation secondary to oxidative stress caused by ROS generated by iron overload. Figure 2 is a schematic depiction of how dried ginger extract rich in 6-shogaol can potentially benefit lower-risk MDS patients.

Iron overload measured by elevated serum ferritin is commonly observed in lower-risk MDS patients. Serum ferritin is an acute-phase reactant, and its levels are elevated when inflammation is present, especially during hepatocellular damage. Thus, the anti-inflammatory action of 6-shogaol would be expected to reduce the level of serum ferritin. Moreover, its hepatoprotective effect could reverse the blunted response on hepcidin due to iron overload, resulting in an elevation of hepcidin levels. These effects were seen in Golombick et al. (2017) and warrant further research.

Both traditional use and available clinical evidence suggest that dried ginger extract can potentially improve anaemic conditions. Moreover, Raza et al. (2008) found promising results in improving haematologic parameters of MDS patients with curcumin and gingerol. However, the study by Golombick et al. (2017) did not report improvement in blood cell counts, possibly due to its small sample size. Preclinical evidence of ginger extract and 10-gingerol shows positive effects on haematopoietic recovery in a zebrafish model but not 6-shogaol. Therefore, future research should investigate the haematopoietic effect of 6-shogaol in both preclinical and human studies with a larger

cohort. Furthermore, MDS affects patients' QoL. There is a lack of information on whether ginger or 6-shogaol has any benefits on fatigue and any QoL dimensions of MDS patients, and further studies are needed to clarify this aspect.

6-shogaol is stable in the GIT, rapidly and extensively metabolised, but could potentially involve in drug-drug interactions. In general, ginger extract has been reported in multiple case studies to interact with blood-thinning medication, notably warfarin, increasing bleeding risk. One case reported that consuming 48 mg of a ginger supplement caused a sharp rise in the clotting time of a 76-year-old patient (Rubin et al., 2019). Another two cases with ginger-anticoagulation interaction did not specify the dosage of ginger and its mode of ingestion (Krüth et al., 2004; Lesho et al., 2004). Moreover, a prospective longitudinal study did not find ginger to have a significant risk of increasing clotting time but was associated with an increased risk of self-reported bleeding (Shalansky et al., 2007). However, an open-label, three-way crossover randomised study by Jiang et al. (2005) showed that taking ginger extract at 0.4 g did not affect the pharmacokinetics or pharmacodynamics of either S-warfarin or R-warfarin in humans, nor did it affect coagulation status. Hence, there may exist a dose-dependent relationship between the interaction of ginger and anticoagulant agents. This topic requires further investigation. Given that MDS predominates in the elderly population over 70 years old, many of them also have numerous comorbid conditions that may require blood-thinning agents. Any clinical application or study with 6-shogaol among MDS patients should consider the potential interaction risk with warfarin.

### Conclusion

Based on the evidence presented, the phenolic compound 6-shogaol in ginger appears to have various pharmacological properties, suggesting it would be a beneficial supportive treatment in lower-risk MDS patients. It appears to be safe, well-tolerated, addresses the pathophysiological process driving the cause of MDS, and affects the major risk factor that causes progression to acute myeloid leukaemia. Given the potential

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therapeutic values of 6-shogaol, further studies are needed to evaluate the benefits of this compound to MDS.

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### Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

### Author contributions

The first two authors contributed equally to this work. All authors reviewed and substantially contributed to the final version of the manuscript.

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