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Anti-inflammatory action of ginger: A critical review in anemia of inflammation and its future aspects

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ABSTRACT

Anti-inflammatory action of ginger has been confirmed by various scientists, but there is very few review article published till date on inflammation associated diseases. Inflammation is mainly, culprit of anemia and inflammation associated disorder (like- Pulmonary diseases, Cardiovascular diseases, Diabetes Type-2, cancer, Arthritis, Alzheimer, Neurological diseases and Autoimmune diseases).Since Infection (bacterial/ viral), activate Nuclear factor –-κB, which is a major mediator of inflammation in most of the disease. Zinger has been established potent NF–ƙB inhibitory action via the suppression of pro-inflammatory cytokine, TNF-α and also provides a molecular link between the innate and adaptive immune system. This review takes the Zinger bioactive components, property, Chemical composition, Mechanism of action, function, side effects, current research and their potential application in modern medicine. The present study demonstrates that ginger showed broad spectrum action in which Anti-inflammatory action is one of them. So the present study concludes that ginger and its bioactive components have the potential for development of modern medicine in the treatment of anemia and various diseases in near future.

Keywords: Bioactive component of ginger, Anti-inflammatory action, Anemia, Anemia of inflammation, Modern Medicine.

1. Introduction

Anemia of inflammation is considered a major contributor to anemia observed in developing countries [1] and anemia of inflammation may even be associated with asymptomatic and subclinical infection [2]. The only effective treatment of chronic inflammation is correction of the underlying disorder [3]. NF-κB is a pleiotropic transcription factor. It is involved in the transcriptional activation of numerous genes leading to a cumulative immunogenic response, provides a molecular link between the innate and adaptive immune system, whilst playing regulatory roles in haemapoiesis and lymphoid organogenesis. NF-κB activation seems to be a key early event in a variety of cell & animal model systems developed to elucidate the pathobiology of lung disease including Systemic inflammatory [4].

Ginger is extensively used as a spice & food preservative in India, China and South East Asia and probably originated in India. [5, 58] Ginger obtained from the underground stems of rhizomes of *Zingiber officinale Rosc*.), an herbaceous tropical perennial belonging to the family Zingiberaceae. It has been used in Ayurvedic Medicine since ancient times with various biological applications. Different constituents of ginger has been established its role in medicine to treat various ailments from time immemorial in different parts of the world [6]. Recent years have seen an increased enthusiasm in treating various diseases with natural products. Ginger (*Zingiber officinale*) is a non-toxic highly promising natural antioxidant compound having a wide spectrum of biological function (antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, anticarcinogenic). Safety evaluation studies indicate that *Zingiber officinale* are well tolerated even at a very high dose without any toxic effects [7]. Thus ginger and its bioactive components have the potential for development of modern medicine in the treatment of anemia and inflammation associated diseases

(like- Pulmonary diseases, cardiovascular diseases, Diabetes Type-2, cancer, Arthritis, Alzheimer, Neurological diseases and autoimmune diseases) in near future cost effectively, the main aim of the present review.

2. Review of Literature

2.1 Chemistry of zinger

In the fresh ginger rhizome, the gingerols were identified as the major active components and [6] gingerol [5-hydroxy-1-(4-hydroxy-3-methoxy phenyl) decan-3-one is the most abundant constituent in the gingerol series (Table 1). The powdered rhizome contains 3-6% fatty oil, 9% protein, 60-70% carbohydrates, 3-8% crude fiber, about 8% ash, 9-12% water and 2-3% volatile oil. The volatile oil consists of mainly mono and sesquiter–penes; camphene, beta-phellandrene, curcumene, cineole, geranyl acetate, terphineol, terpenes, borneol, geraniol, limonene, linalool, alpha-zingiberene (30-70%), beta-sesquiphellandrene (15-20%), beta-bisabolene (10-15%) and alpha-farmesene. In dried ginger powder, shogaol a dehydrated product of gingerol, is a predominant pungent constituent upto [8-10].

Table 1: Structure of active component of ginger with IUPAC name

1.	6-gingerol	(*S*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone
2.	8- gingerol	(5S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl) dodecan-3-one
3.	10-gingerol	(E)-1-(4-hydroxy-3-methoxyphenyl) dec-4-en-3-one
4.	6-shogaol	(*E*)-1-(4-Hydroxy-3- methoxyphenyl) dec-4-en-3-one

2.2 Chemical Composition of ginger: Nutritional data for 100 gm. Dry ginger is as follows

Water–9.4 gm, Protein–9.1gm, Fat–6.0gm, Total carbohydrate–70.8 gm, Food energy–374 kcal, Fibre–5.9 gm, ash–4.8 gm, iron–12 mg, magnesium–184 mg, Phosphorous- 148 mg, potassium-1342 mg, sodium-32 mg, zinc–5 mg and niacin-5mg [11].

2.3 The percentage of vitamin in ginger rhizome powder is as follows

Thiamine–0.035%, Riboflavin–0.015%, Niacin–0.045%, Pyridoxin–0.056%, Vitamin C–44%, vitamin A-Traces, vitamin E-Traces, Total-44.15% [12].

2.4 Ginger: safety, dose, side effect and drug interactions

Safety: Ginger is recommended in U.S. Food and Drug Administration's GRAS (generally recognized as safe) list.The British Herbal Compendium documents no adverse effects of ginger [13]. Ginger appears to be relatively safe except in pregnancy [14].

Dose: A dose of 0.5–1.0 g of ginger powder ingested 2-3 times for periods ranging from 3 months to 2.5 years did not cause any adverse effects [15]. Most of the research has been done with 1-2 grams of ginger powder, but in India the average intake is around 8-10 grams per day.

Side effect: Ginger is quite safe in therapeutic doses. For anti-inflammatory purpose, the dose of ginger is 3–6 grams two to three times per day. In experimental animals, the doses of 2.5 gram/kg body weight were tolerated without any mortality. However, when the dose was increased to 3–3.5 gram/kg body weight then there was 10–30 % mortality [16].

Drug interaction: Few ginger–drug interactions have been reported in the literature. Ginger does not interact with the anti-coagulant drug warfarin in rats or man [17- 18].

2.5 Functional property of Ginger: Ginger, as an antimicrobial [19-21], anti-inflammatory [22-29], antioxidant [30--32] and immunomodulatory role [26] have been established.

2.6 Mechanism of action of ginger

Ginger is considered to exert its anti-inflammatory activity by inhibiting COX-2 and LOX pathways [33-34]. Recently, it has been observed that two labdanum-diterpene like dialdehides isolated from Ginger extracts act as *in vitro* inhibitors of the human 5-lipooxygenase [35]. In one study curcumin has been shown to suppress the expression of COX2, 5-LOX, and iNOS, most likely through the downregulation of NF-κB activation [36]. The other study reported that 6-gingerol, a natural analog of curcumin derived from the root of ginger (*Zingiber officinalis*), exhibits a biologic activity profile similar to that of curcumin [37].

2.7 Anti-inflammatory action of ginger

The anti-inflammatory properties of ginger have been known and valued for centuries. The original discovery of ginger's inhibitory effects on prostaglandin biosynthesis in the early 1970s has been repeatedly confirmed. This discovery identified ginger as an herbal medicinal product that shares pharmacological properties with non-steroidal anti-inflammatory drugs. Ginger suppresses prostaglandin synthesis through inhibition of cyclooxygenase-1 and cyclooxygenase-2. An important extension of this early work was the observation that ginger also suppresses leukotriene biosynthesis by inhibiting 5-lipoxygenase. This pharmacological property distinguishes ginger from nonsteroidal anti-inflammatory drugs. This discovery preceded the observation that dual inhibitors of cyclooxygenase and 5-lipoxygenase may have a better therapeutic profile and have fewer side effects than non-steroidal anti-inflammatory drugs. The characterization of the pharmacological properties of ginger entered a new phase with the discovery that a ginger extract (EV.EXT.77) derived from *Zingiberofficinale* (family Zingiberaceae) and Alpinagalanga (family Zingiberaceae) inhibits the induction of several genes involved in the inflammatory response. These include genes encoding cytokines, chemokines, and the inducible enzyme cyclooxygenase-2. This discovery provided the first evidence that ginger modulates biochemical pathways activated in chronic inflammation. The earlier report suggested that in Rheumatoid arthritis (RA) and Osteoarthritis (OA) patients, use of powdered ginger for 3-month to 2.5-year period, reduce pain and inflammation in 75% patients without any adverse effect and suggested ginger is an anti-inflammatory agent [24]. 6-gingerol acts as an anti-inflammatory compound that may be useful to treat inflammation without interfering with antigen presenting function of macrophages [38]. It has been also recently observed that Synergistic effect of Ginger with anti-tuberculosis treatment were more beneficial effect rather than only ATT (anti-tuberculosis treatment) in anemic Pulmonary

tuberculosis Patients and concluded that ginger supplementation in such patients not only increases absorption of iron but also significant decreases in CRP, Ferritin and significant increase in serum iron, total iron binding capacity, which in turn correct anemia [29].

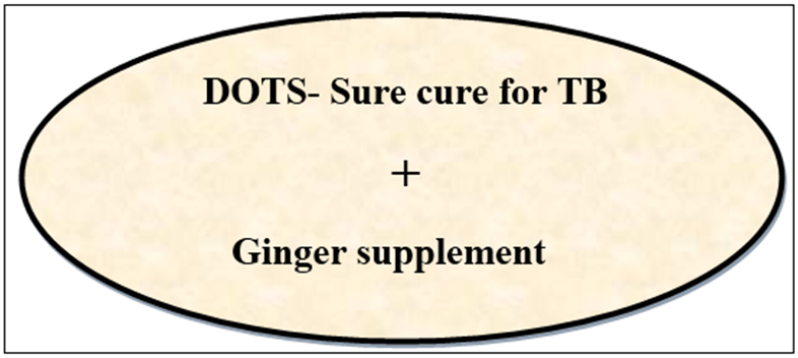

Fig 1: Synergetic effect of anti- tubercular treatment (ATT) with ginger supplementation a new approach to cure TB with better outcome.

2.8 Antimicrobial Action

Investigation of ginger rhizome (*Zingiber officinale*) afforded three lipophilic analogues 6-gingerol [39], 8-gingerol [40] and 10- gingerol [41] that exhibited antimicrobial activity. The lipophilic analogues (8-gengerol and 10 gingerol) were more active, with MIC values of 25–50 µg/ ml exhibited towards *M. tuberculosis* H37Rv and *M. avium* [40, 41].

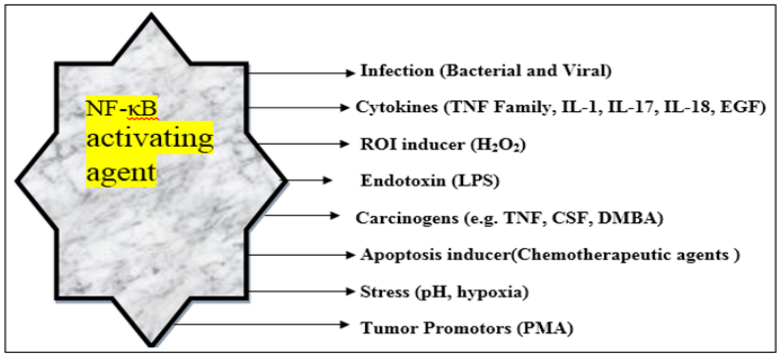

Fig 2: NF-ƙB activating agen

2.9 Pathophysiological Mechanism underlying Anemia of inflammation

Anemia of inflammation Pathophysiology is like Anemia of Chronic disease (ACD) [60]. During inflammation, hepcidin (an acute phase protein) production is stimulated and iron entry into plasma is inhibited, causing the hypoferremia and anemia of inflammation [42]. Acute Phase Proteins are a class of diverse Proteins whose blood plasma concentrations increase (positive acute phase protein), or decreases (negative acute phase protein) during the response to inflammation in the acute phase. They are produced within a few hours by the liver, responding to inflammatory cytokines such as IL-1, TNF-α and in particular IL-6 [43-44, 59]. It has been observed that during infection, there is an increase in cytokine levels (IL-6) which is responsible for activation of NF-κB & endotoxins which in turn increase the synthesis and release of CRP from hepatocytes. Raised level of CRP is marker of inflammation which causes blunted erythropoietin resistance resulting anemia.

2.10 Various disorders linked with anemia of inflammation

Inflammation is considered to play an important role in the Pathophysiology of various disorders. However, when inflammation becomes chronic or lasts too long, it can be harmful. The diagnosis of inflammation and its biomarkers are not fully understood; however, pro-inflammatory cytokines, chemokines, adhesion molecules and the inflammatory enzymes have been linked to chronic inflammation [45]. Chronic inflammation has been found to mediate a wide variety of diseases including cardiovascular diseases, diabetes, arthritis, Alzheimer's disease, pulmonary diseases and autoimmune diseases. Chronic inflammation has also been associated with various steps involved in carcinogenesis as well as cellular transformation, promotion, survival, proliferation, invasion, angiogenesis and metastasis [46-47]. Many pro-inflammatory cytokines can activate the transcriptional factor NF-κB, while some of the effects of pro-inflammatory cytokines may be mediated through the NF-κB pathway [48-50].

2.11 Role of Bioactive component of Zinger

The 6-gingerol and 6-paradol have been reported to possess a strong anti-inflammatory activity and to suppress the TNF-α production in TPA-treated female ICR-mice and rats [51, 52]. The activation of the TNF-α gene causes the release of pro-inflammatory cytokines, and this would activate the transcriptional factor NF-κB. Activation of NF-κB would activate the expression of other inflammatory cytokines such as COX-2, LOX-2, other chemokines and iNOS, which would lead to inflammation and related diseases. Ginger (*Zingiber officinale)* is widely used all over the world as a spice and condiment in daily cooking. It is a natural food component with many active phenolic compounds such as shagaol and gingerol, and it has been shown to have broad anti-inflammatory action. It is apparent that ginger may act as an anti-cancer and anti-inflammatory agent by blocking the activation of NF-κB via the suppression of pro-inflammatory cytokine, TNF-α [53]. Other, similar reports have also shown the inhibitory effect of

ginger on the NF-κB pathway: topical application of 6-gingerol inhibited TPA-induced COX-2 expression and suppressed NF-κB DNA binding activity in mice skin [51, 54]. The 6-gingerol and 6-paradol have been reported to possess a strong anti-inflammatory activity and to suppress the TNF-α production in TPA-treated female ICR-mice and rats [51, 52]. Inhibiting the activity of NF-κB, will subsequently inhibit inflammation and inflammation associated disorder. The natural active compounds in ginger (gingerols and zerumbone) have been found to be potent inhibitors for NF-κB and pro-inflammatory cytokine TNF-a. Ginger may block any one or more steps in the NF-κB signaling pathway, such as the signals that activate the NF-κB signaling cascade, translocation of NF-κB into the nucleus, DNA binding of dimers or interactions with the basal transcriptional machinery [55].

Ginger extract significantly reduced the elevated expression of NF-κB and TNF-α in rats with liver cancer. Ginger may act as an anti-cancer and anti-inflammatory agent by inactivating NF-κB through the suppression of the pro-inflammatory TNF-α [56].

2.12 Zinger future perspective

As a source of potential chemotherapeutic agent continues. Natural products and their derivatives represent more than 50% of all the drugs in clinical use in the world today. Phytomedicine have more beneficial effect than their synthetic counterparts through being safer, acceptable, affordable, culturally compatible and suitable for chronic treatments & finally concluded that although there are some problems limiting the development of phytomedicine, such as lack of standardization, efficacy and quality control of plants used, extinction of some plant species, lack of funds and others, if these problems can be fully addressed, this will help in the future development and harmonization of phytomedicines [57]

3. Discussion & Conclusion

On the basis of above mention review of literature we found that inflammation and acute phase response interact with iron metabolism, which leads to disregulation of iron metabolism resulting anemia. NF-κB activation is a major mediator of inflammation in most of the disease (like- Pulmonary diseases, Cardiovascular diseases, Diabetes Type-2, cancer, Arthritis, Alzheimer, Neurological diseases and Autoimmune diseases), and inhibition of NF-κB activation can suppress inflammation.Over expression of NF-κB, COX2, 5-LOX, and iNOS leads to inflammation and inflammation associated disorder. Since Ginger has potent NF-κB inhibitory action, it suppresses the expression of COX2, 5-LOX, and iNOS, most likely through the downregulation of NF-κB activation.Ginger may act as an anti-inflammatory agent by blocking the activation of NF-κB via the suppression of pro-inflammatory cytokine, TNF-α. (Fig. 3)

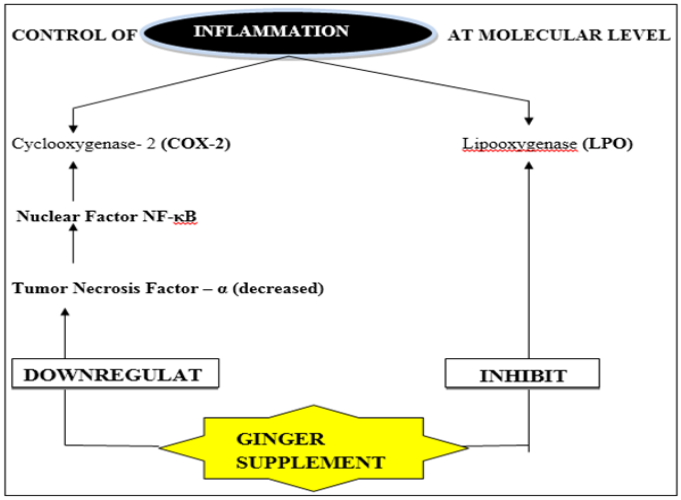

Fig 3: Ginger Supplement inhibits both COX- 2 & LPO expression by suppressing NF- ƙB activity via TNF – α

This review article concludes that ginger and its bioactive components have the potential for development of modern medicine in the treatment of various diseases in near future because it controls the molecular mechanism of inflammation. Further trials in humans are required to determine the efficacy of ginger (one or more of its constituents) and to study what, if any, beneficial or adverse effects are observed if consume over a long period of time.

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