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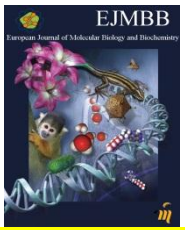

GINGER: PHARMACOTHEREPEUTIC SIGNIFICANCE AS AN ANTIINFLAMMATORY DRUG

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ABSTRACT

Ginger, (*Zingiber officinale* Roscoe, Zingiberacae) is one of the important medicinal plant which naturally occurs in various countries like India, China, South East Asia, West Indies, Mexico and other parts of the world. Ginger is widely used in Chinese, Ayurvedic and Tibb-Unani herbal medicines all over the world for its endless pharmacological activities that include carminative, diaphoretic, antispasmodic, expectorant, peripheral circulatory stimulant, astringent, appetite stimulant, diuretic, digestive aid, antiemetic, antipyretic, analgesic and antiarthritic. It is also used to relieve muscular aches, rheumatism, pains, coughs, sinusitis, sore throats, diarrhea, cramps, indigestion, loss of appetite, motion sickness, fever, flu, chills and infectious diseases. Gingerol and shogaol are two most active constituents of ginger based preparations. Characterized in traditional Chinese medicine as spicy and hot, ginger is claimed to warm the body and treat cold extremities, improve a weak and tardy pulse, address a pale complexion, headaches, nausea, and strengthen the body after blood loss. Ulcer, diabetes, impotency, stroke, hypertension, atherosclerosis and hepatitis are other areas where use of ginger has proved beneficial. The Ginger has a long history of medicinal use dating back 2,500 years in China and India for anti-inflammatory activities. Inflammation is mainly, culprit in various disorders (Pulmonary diseases, Cardiovascular diseases, Diabetes Type-2, cancer, Arthritis, Alzheimer, Neurological diseases and Autoimmune diseases) and anti-inflammatory action of ginger has been confirmed by various scientists. The potent antiinflammatory action of ginger is attributed to its action on NF–ƙB, Cox, Phospholipase, Lox and TNF-α. This review summarizes various actions of ginger as an anti-inflammatory drug and its possible uses in associated ailments.

INTRODUCTION

The use of plants to treat various diseases in India dates back to the times of Rig-Veda (3500 to 1800 B.C.). Later, the monumental Ayurvedic works like Charak samhita and Sushruta samhita followed by other Ayurveda and Siddha treatises have incorporated nearly 700 plant drugs entering into several medicinal preparations used in the management of health care. In fact these systems have been in practice even in remote areas for centuries [1,2].

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Medicinal plants play an important role in pharmacology and medicine for and it is estimated that about 80% of the world population relies on botanical preparations as medicine to meet their health needs [3]. Herbs and spices are generally considered safe and proved to be effective against various ailments. They are extensively used in many Asian, African and other countries and in view of their beneficial effects, use of spices/ herbs has been gradually increasing worldwide. Spices and herbs are widely used in phytotherapy, which is using plants and their chemical constituents to eliminate certain health problems.

Ginger (*Zingiber officinale* Rosc.) is a creeping perennial on a thick tuberous rhizome, which spreads

under ground. In the first year, a green, erect reed like stem about 60 cm high grows from this rhizome. The plant has narrow; lanceolate to linear-lanceolate, 15-30 cm long leaves which die of each year. The o dour and taste are characteristic, aromatic and pungent [4]. It is cultivated in areas of abundant rainfall. Even though it is native to southern Asia, ginger is cultivated in tropical areas also such as Jamaica, China, Nigeria and Haiti too. It is an important spice crop in India. Ginger is cultivated in most of the states in India. However, states namely Karnataka, Orissa, Assam, Meghalaya, Arunachal Pradesh and Gujarat together contribute 65 per cent to the country's total production [5].

The English botanist William Roscoe (1753-1831) gave the plant the name *Zingiber officinale* in an 1807 publication. The ginger family consisting of more1200 plant species in 53 genera. The genus Zingiber includes about 85 species of aromatic herbs from East Asia and tropical Australia. The name of the genus, Zingiber, derives from a Sanskrit word denoting "horn-shaped," in reference to the protrusions on the rhizome [6,7]. In Sanskrit, ginger is known as Sringavera which has given way to Zingiberi in Greek and to the Latin Zingiber. Ginger has been used as medicine from vedic period and is called “maha aushadhi”, means the great medicine. In traditional medicine, it was used as a carminative or antiflatulent. The Greek physician Galen used ginger as a purificant of body. He used ginger to treat conditions caused by imbalances in body [5].

Ginger is also extensively consumed as a flavoring agent it is estimated that in India, the average daily consumption is 8 -10 g of fresh ginger root. The German Commission E has also approved the use of ginger root as a treatment for dyspepsia and prophylactic against motion sickness [8]. Fresh ginger contains 80.9% moisture, 2.3% protein, 0.9% fat, 1.2% minerals, 2.4% fibre and 12.3% carbohydrates. The minerals present in ginger are iron, calcium and phosphorous. It also contains vitamins such as thiamine, riboflavin, niacin and vitamin C [9].

The constituents of ginger are numerous and vary depending on the place of origin and whether the rhizomes are fresh or dry. The odor of ginger depends mainly on its volatile oil, the yield of which varies from 1% to 3%. Over 50 components of the oil have been characterized and these are mainly monoterpenoids [b-phellandrene, (+)-camphene, cineole,geraniol, curcumene, citral, terpineol, borneol] and sesquiterpenoids [a-zingiberene (30–70%), b-sesquiphellandrene (15–20%), b-bisabolene (10–15%), (E-E)-a-farnesene, ar- curcumene, zingiberol] [10,11].

The pungency of fresh ginger is due primarily to the gingerols, which are a homologous series of phenols. The most abundant is gingerol, although smaller quantities of other gingerols with different chain lengths are also present. The pungency of dry ginger mainly results from shogaols. The major pharmacological activity of ginger appears to be due to gingerol and shogaol [12]. The Chinese have used ginger for at least 2500 years as a digestive aid and anti nausea remedy, and to treat bleeding disorders and rheumatism; it was also used to treat baldness, toothache, snakebite, and respiratory conditions[13]. In Traditional Chinese Medicine, ginger is considered a pungent, dry, warming, yang herb to be used for ailments triggered by cold, damp weather. Ginger is used extensively in Ayurveda, to block excessive clotting (heart disease), reduce cholesterol and fight arthritis. In Malaysia and Indonesia, ginger soup is given to new mothers for 30 days after their delivery to help warm them and to help them sweat out impurities. In Arabian medicine, ginger is considered an aphrodisiac[14].Some Africans believe that eating ginger regularly will help repel mosquito[13].

Ginger has been found useful in pregnancy related morning sickness. In rheumatoid arthritis and osteoarthritis it is used as a natural pain reliever and an antiinflammatory agent. It is also useful in curing ulcer and preventing heart attack and stroke [4]. Ginger extracts showed different pharmacological effects such as anti-platelet, anti-oxidant, anti-tumour, anti-rhinoviral, anti- hepatotoxicity and anti-arthritic effect [15-17]. Ginger was found to have hypocholesterolaemic effects and cause decrease in body weight, glucose in blood, serum total cholesterol and serum alkaline phosphatase in adult male rats [18,19]. Beside this Hafez [20] reported that intake of ginger roots as a drink may be beneficial for diabetic patients who suffer from sexual impotency as their extracts induce anti diabetic activity and enhance male fertility in diabetic rats. Morakinyo et al., [21] indicated that extract of Z.Officinale possesses pro-fertility properties in male rats which might be a product of both its potent antioxidant properties and androgenic activities. Nassiri et al. [22] reported that treating diabetic rats with ginger for twenty consecutive days significantly increased sperm motility and viability and decreased lipid peroxidation[19].

The health-promoting perspective of ginger is attributed to its rich phytochemistry [23]. Jolad *et al*. grouped fresh ginger into two wide range categories, i.e. volatiles and non-volatiles. Volatiles include sesquiterpene and monoterpenoid hydrocarbons providing the distinct aroma and taste of ginger. On the contrary, non-volatile pungent compounds include gingerols, shogaols, paradols, and zingerone [24].

Ginger has been listed in “Generally Recognized as Safe” (GRAS) document of the United States Food and Drug Administration (FDA) [25]. It is categorized by the U.S. Food and Drug Administration as a food additive but has been studied as a treatment for nausea and vomiting, as well as for arthritis [26]. Ginger has been extensively studied for its broad spectral pharmacological properties in the form of dried powder, ginger juice and extracts of organic solvents. The prominent nonvolatile pungent components of ginger include gingerol, shogaol and zingerone. These active principles are known to have the ability to suppress the hyperproliferative, inflammatory and transformative processes of several disorders [27]. In

the coming sections various evidences of ginger as an anti inflammatory drug has been summarized which project it as an potent pharmacological target in disorders where inflammation plays a crucial role.

Anti-inflammatory activities of ginger

Most agents derived from spices have antioxidant and anti-inflammatory activities. The antioxidant activities of spice extracts were retained even after boiling for 30 min at 100°C, indicating that the spice constituents were resistant to thermal denaturation. The antioxidant activities of the dietary spices suggest that, besides imparting flavor to foods, they possess potential health benefits [28] and a A number of these botanical supplements have been used for centuries in Ayurvedic medicine, and it has been proposed that they have anti-inflammatory actions [29].

Nowadays, the search for new anti-inflammatory and anti-allergic agents from the huge array of medicinal plant resources is intensifying [30]. In fact, a variety of bioactive components have been shown to modulate inflammatory responses [31]. The inflammatory response is a critical protective reaction to irritation, injury, or infection, characterized by redness, heat, swelling, loss of function and pain [32]. Redness and heat result from an increase in blood flow, swelling is associated with increased vascular permeability, and pain is the consequence of activation and sensitization of primary afferent nerve fibres [33].

Ginger (*Zingiber officinale*) is a non-toxic highly promising natural antioxidant compound having a wide spectrum of biological functions (antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, anticarcinogenic). Safety evaluation studies indicate that *Zingiber officinale* is well tolerated even at a very high dose without any toxic effects [34] and its bioactive components have the potential for development of modern medicine in the treatment of inflammation associated diseases [35].

A great number of inflammatory mediators including kinins, platelet-activating factor (PAF), prostaglandins, leukotrienes, amines, purines, cytokines, chemokines and adhesion molecules, has been found to act on specific targets, leading to the local release of other mediators from leukocytes and the further attraction of leukocytes, such as neutrophils, to the site of inflammation [31]. The potential anti inflammatory action of any bioactive compound must be able to modulate release and activation of these inflammatory mediators.

The anti-inflammatory properties of ginger have been known for centuries. There are over 1,800 studies that shows that ginger has immunomodulatory, anti-tumorigenic, anti-inflammatory, anti-arthritic, anti-apoptotic and anti-hyperglycemic actions. It is helpful for metabolic syndrome, diabetes, cardiovascular disease, dementia, arthritis, osteoporosis, and cancers. It has analgesic, anti-inflammatory and hypoglycemic effects against enzymes linked to Type 2 diabetes, as well as inhibition of COX-2, 5-LOX, NF-kB, and it acts as a strong antioxidant [36].

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 [35].

It has been also shown that ginger (and some of its constituents) is effective against cytokines synthesized and secreted at sites of inflammation[37]. Cytokines are small proteins secreted at sites of inflammation by lymphocytes, macrophages, fibroblasts and other cells, and act as chemical messengers between cells involved in immune and inflammatory responses.

At relatively high mM concentrations, ginger constituents such as gingerols, shogaols, and diarylheptanoids have been reported to weakly inhibit components of proinflammatory signal transduction pathways in vitro, such as NF-kB, protein kinase C, and MAPKs. Moreover, ginger constituents have been shown to inhibit inducible NO synthase, cyclooxygenase (COX)-1/-2, and lipoxygenase in vitro too [38].

It was also discovered that a ginger extract derived from *Zingiber officinale* (and Alpina galanga) inhibits the induction of several genes involved in the inflammatory response, including 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 [12].

Volatile oil of ginger has the capability to modulate the function of lymphocytes and cellular immune response. These results suggest that the volatile oil of ginger influences both cell-mediated immune response and nonspecific proliferation of T lymphocytes, and may exert beneficial effects in a number of clinical conditions such as chronic inflammation and autoimmune diseases [39].

The activation of the TNF-α gene causes the release of pro-inflammatory cytokines, and this would activate the transcription 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 [35]. The 6-gingerol and 6-paradol have been reported to possess a strong anti-inflammatory activity and to suppress the TNF-α production in rats[40,41].

The role of inflammation on diabetes has been reported in numerous studies [42]. Cytokines are associated with the pathogenesis of both type 1 and type 2 diabetes through accelerating beta-cell apoptosis and death. Besides, evidence have shows that insulin resistance as a

pro-inflammatory status may have existed for years before the occurrence of type 2 diabetes [43]. Moreover, increased CRP, IL-6 and TNF-α are associated with nephropathy, retinopathy and cardiovascular disease in both types of diabetes [44].

An animal study on the anti-inflammatory effects of ginger extract on diabetic rats reported the reduced level of TNF-α consequent to ginger extract treatment [45]. Chronic hyperglycemia increases circulating levels of inflammatory biomarkers such as IL-6 (IL6), tumor necrosis factor-α (TNF-α) and C- reactive protein (CRP). TNF-α and IL-6, as the major cytokines, initiate inflammatory responses and cause the production of CRP as an acute-phase reactant. Moreover, lots of evidences showed that low-grade inflammation, a common feature in type 2 diabetes mellitus (DM2), play a major role in pathogenesis of its secondary complications such as atherothrombosis [46].

In a recent study, oral ginger supplementation ameliorated inflammation through reduction in levels of TNF-α and hs-CRP concentrations in blood samples of the patients with type 2 diabetes mellitus. Regarding negligible side effects of ginger, it may be a good remedy for diabetic patients to diminish the risk of some secondary chronic complications [47].

In studies related to neurodegenerative disorders where inflammation is the main culprit It has shown encouraging results eg, in Alzheimer's disease(AD) which a common fatal neurodegenerative disorder , manifested by progressive memory impairment, visuospatial decline, aphasia, agnosia, loss of executive function and severe neuropsychiatric changes like hallucinations and depression [48]. In the AD brain the Aβ proteins, neurofibrillary tangles and neuronal degeneration seem to be the most likely sources of inflammation. Further, findings of reactive glial cells (i.e., microglia and astrocytes) at sites of amyloid plaques have suggested that AD is a neuroinflammatory cascade [49].

In a recent study, Alzheimer's disease induced rats treatment with ginger in doses of 108 or 216 mg/kg, exhibited a significant improvement in Alzheimer's like disease status in rats as evidenced by increases in cholinergic activity, brain Ach level and significant decreases in time (seconds) taken by rats to reach food in T-Maze test, as well as reduction in brain AchE activity. However the high dose of Ginger (216 mg/kg) exhibited a better effect than the low dose (108 mg/kg). Histopathological findings showed that amyloid plaques disappeared [50].

Wattanathorn et al. who demonstrated that alcohol extract of ginger could reduce cognitive deficits and protect against brain damage in rats. Also, the protective and therapeutic effects of ginger aqueous infusion on AD are attributed to its polyphenolic ingredients which are gingerols and gingerol analogs as shogaols and paradols that directly inhibit prostaglandins and leukotriene synthesis [51]. These results might have been due to the antinflammatory effect of ginger which had been previously described by Hassan Abbad et al. [52] in their study that revealed that the addition of aqueous extract of ginger to drinking water reduced inflammation in diabetic mice, as well as Tripathi et al. [53] who indicated that several doses of 6-gingerol selectively inhibited production of pro-inflammatory cytokines such as tumour necrosis factor (TNF-α) and interleukins (IL-1, and IL-12).

In another study where effects of ginger were studied in a model of Parkinson disease it has shown encouraging results. In MPP (+)-treated rat mesencephalic cultures, 6-shogaol significantly increased the number of neurons and suppressed TNF-α and NO levels. In C57/BL mice, treatment with 6-shogaol reversed MPTP induced changes in motor coordination and bradykinesia. Furthermore, 6-shogaol reversed MPTP induced reductions in cell number in the substantia nigra pars compacta (SNpc) and neuronal intensity in stratum. Moreover, 6-shogaol significantly inhibited the MPTP-induced microglial activation and increases in the levels of TNF-α, NO, iNOS, and COX-2 in both SNpc and Striatum [54].

All these activities of Ginger on inflammation are mailny because of its action on nuclear factor kappa B (N*f*kB).The NF-kB molecule is a transcription factor discovered by David Baltimore in 1986, is a ubiquitous factor that resides in the cytoplasm but, when activated, is translocated to the nucleus, where it induces gene transcription. NF-kB is activated by free radicals, inflammatory stimuli, carcinogens, tumor promoters, endotoxin, gamma radiation, ultraviolet (UV) light, and x-rays. On activation, NF-kB induces the expression of more than 200 genes that have been shown to suppress apoptosis, induce cellular transformation, chemo-resistance, radio-resistance, and inflammation.

The activated form of NF-kB has been known to mediate cancer, atherosclerosis, myocardial infarction, diabetes, allergy, Crohn's disease, multiple sclerosis, Alzheimer's disease, osteoporosis, psoriasis, septic shock, AIDS and other inflammatory diseases including Parkinson's disease. Thus, agents that can suppress NF-kB activation, in principle, have the potential to prevent or delay onset or treat NF-KB-linked diseases. Gingerols and shogoals have been reported to inhibit the activation of NF-KB [55] which leads to inhibition of enzymes nitric oxide synthase (NOS) and cyclooxygenase (COX-2) which are known to be regulated through NF-kB.

Furthermore, Nuclear factor-kappa B (NF-*K*B) is the master regulator the hepatic inflammatory response. Under basal conditions, NF-*K*B is present in the cytoplasm of hepatocytes in a latent form, bound to the NF-KB inhibitory protein, inhibitor kappa B (IKB). Upon exposure to pro-inflammatory stimuli, the IkB kinase (IKK) complex is activated and catalyses the phosphorylation of IkB. Phosphorylated IkB is then targeted for degradation by the 26S proteosome complex, thereby liberating NF-KB to migrate to the cell nucleus and direct transcription of target genes [56].

The key finding of study was that *Zingiber officinale* suppresses increased cytokine expression in the liver of high fat diet fed (HFD-fed) rats. The decrease in cytokines correlated with the ability of *Zingiber officinale* to decrease NF-KB activation, the master regulator of inflammation. Th suppression of NF-jB led to a decrease in a number of NF-KB-target genes expressed in hepatocytes [55].

CONCLUSION

Spices have been used as traditional medicine against chronic diseases for thousands of years. Numerous preclinical study results suggest that spices and spice-derived nutraceuticals are associated with a decreased risk of inflammation-regulated chronic diseases. Ginger as a botanical drug has a great acceptance in the population, and might therefore be used as a physically and mentally well-tolerated augmentation to conventional antiinflammatory medication in cases where first-line therapy is not sufficient.

In particular, treatment of inflammatory conditions like arthritis, cancer, hepatitis, diabetes and Alzheimer's disease could be novel therapeutic applications of ginger. Ginger act as an anti-inflammatory agent by NF-κB inhibitory action which suppresses the expression of COX, 5-LOX, iNOS and TNF aplha.

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